Notes

Hydrogenation of Pyridinecarboxylic Acids with Platinum Catalyst

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The inhibiting effect of the pyridine nitrogen and the more basic piperidino nitrogen on the catalyst during hydrogenation is well known.[1] It has been shown that the pyridine compound must be present as a salt or that hydrogenation of the base must be carried out in acidic medium to overcome this catalyst poisoning.[2]

In some recent work in this laboratory[3] we found that uptake of hydrogen proceeded smoothly during conversion of the isomeric pyridinecarboxylic acids in water in the presence of rhodium catalyst. While the yield of 3-piperidinecarboxylic acid was low due to decarboxylation, nevertheless the theoretical amount of hydrogen was absorbed.

Since the carboxyl group should in effect tend to neutralize the inhibitory effect of the basic piperidino nitrogen, it appeared to be of interest to attempt hydrogenation of the same acids with platinum oxide in a neutral medium.

Low pressure reductions were indeed successful with picolinic and isonicotinic acids. Nicotinic acid underwent decarboxylation during hydrogenation as observed by us with rhodium and previously with ruthenium catalyst.[4] In this work, however, uptake of hydrogen was never more than 35% of theory, and only piperidine and starting material were obtained.

The neutralizing effect of the carboxy group was enhanced by the shielding effect in 2-position, picolinic acid being completely reduced in four to five hours compared to isonicotinic acid which was only 50% complete in the same length of time.

This study would suggest then that pyridines containing a carboxyl group, such as the isomeric pyridylacetic acids, could be hydrogenated with platinum oxide catalyst, eliminating the use of the acid medium so necessary with other pyridines.

Experimental

Piperidine-2-carboxylic Acid.—A mixture of 12.3 g. (0.1 mole) of picolinic acid in 150 cc. of water was hydrogenated under 2.5 atm. in the presence of 0.25 g. of platinum oxide. Uptake of hydrogen was complete in 4–5 hr. The solution was filtered and concentrated to dryness. The residue was then treated with absolute alcohol and filtered. On drying 12.7 g. (97%) of material was obtained; It melted at 276°.[5] A mixed melting point with an authentic sample was not depressed.

Piperidine-4-carboxylic acid was obtained in the same manner. Uptake of hydrogen was about 50% in 4–5 hr., but was complete in less than 18 hr. Yield of product melting at 336°[6] was 81.5%. A mixed melting point with isonicotinic acid (m.p. 317°) caused a drop to 230–240°, while a mixed melting point with an authentic sample was not depressed.

Hydrogenation of Nicotinic Acid.—Reduction was carried out in the same manner. However, uptake of hydrogen was about 35%, whether the reaction was carried out at room temperature or at 60°. The mixture was made basic and filtered. The alkaline solution was steam distilled into aqueous hydrochloric acid. The acid solution was then concentrated and the solid isolated. It weighed 2.0 g. (18%) and was identified as piperidine hydrochloride by its melting point and infrared spectrum. The alkaline solution after steam distillation was neutralized to pH 4.1 to recover nicotinic acid.

(1) E. B. Maxted and A. P. Walker, *J. Chem. Soc.*, 1093 (1948).
(2) T. S. Hamilton and R. Adams, *J. Am. Chem. Soc.*, **50**, 2260 (1928).
(3) M. Freifelder, R. M. Robinson, and G. R. Stone, *J. Org. Chem.*, **27**, 284 (1962).
(4) M. Freifelder and G. R. Stone, *ibid*, **26**, 3805 (1961).
(5) R. Willstätter, *Ber.*, **29**, 389 (1896), gives 274.5–275.5°.
(6) K. Freudenberg, *ibid.*, **51**, 1668 (1918), reports 325°.

C-6 Hydroxylated Steroids. III. A New Preparative Method[1]

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Current interest in metabolites having a C-6 hydroxyl function[2] has stimulated our efforts to establish a facile chemical approach to the synthesis of these compounds.

We have previously outlined a preparation of 9α-fluoro-6β,11β,17α,21-tetrahydroxypregn-4-ene-3,20-dione[3] which comprised the reaction of 21-acetoxy-9α-fluoro-11β,17α-dihydroxypregn-4-ene-3,20-dione with trimethyl orthoformate to yield the crude $\Delta^{3,5}$-methyl enol ether. The latter

(1) For the previous paper in this series see, R. Littell and S. Bernstein, *J. Org. Chem.*, **27**, 2544 (1962).
(2) Leading references have been collected in ref. 1.
(3) L. L. Smith, J. J. Goodman, H. Mendelsohn, J. P. Dusza, and S. Bernstein, *J. Org. Chem.*, **26**, 974 (1961).

was then oxidized with monoperphthalic acid to afford the 21-acetate-6β-hydroxy-Δ^4-3-one which on treatment with aqueous methanolic potassium carbonate was converted into the desired tetrol. Extension of the enol ether–peracid reaction sequence to a variety of other compounds has shown (although the yields are low) that this method may have a broader utility than any of the previously described chemical approaches to C-6 hydroxylation.[4] In Table I are summarized the results obtained for representative members of a series of compounds which have been studied. It may be seen (Table I) that the attack of peracid on the enol ether (generally used in the crude form) does not give the 6β-hydroxy epimer exclusively, although this predominates in the reaction mixture. In most cases the isolation of the 6α-hydroxy epimer[5] was achieved by chromatography.

The mechanism involved in the formation of 6-hydroxy-Δ^4-3-ones from $\Delta^{3,5}$-enol ethers is not completely understood and the several possibilities warrant investigation.

Experimental[6]

The following examples are given to illustrate the various methods used in the preparation of compounds that are listed in Table I.

21-Acetoxy-3-methoxypregna-3,5-dien-20-one.—Four drops of 72% perchloric acid were added to a reaction mixture containing 2 g. of 21-acetoxypregn-4-ene-3,20-dione, 20 ml. of dry dioxane, 2 ml. of trimethyl orthoformate and 4 drops of absolute methanol. After 2 min. at room temperature, the reaction was terminated by the addition of 1 ml. of pyridine and then the reaction mixture was poured into water. The solid was collected by filtration and dried to give 2.1 g. of the crude enol ether. A portion (0.25 g.) of this material was crystallized from acetone–petroleum ether and afforded 0.19 g. of an analytically pure sample, m.p. 153–155°.

21-Acetoxy-6β-hydroxypregn-4-ene-3,20-dione.—A solution of 1.85 g. of 21-acetoxy-3-methoxypregna-3,5-dien-20-one in 150 ml. of ether was oxidized with 20 ml. of an ethereal monoperphthalic acid solution (65 mg./ml.). After standing at room temperature for 20 hr., the reaction mixture was washed with a saturated aqueous sodium bicarbonate solution and then with a saturated saline solution. The residue obtained upon evaporation of the dried solution was dissolved in methylene chloride and chromatographed on a synthetic magnesium silicate. The eluates obtained with 6% acetone–methylene chloride (4 × 50 ml.) and 8% acetone–methylene chloride (4 × 50 ml.) were combined and evaporated. The residue was crystallized from acetone–petroleum ether to give 0.33 g. of the 6β-hydroxy compound, m.p. 190–192°.

21-Acetoxy-6β,11β,17α-trihydroxypregn-4-ene-3,20-dione, 21-Acetoxy-6α,11β,17α-trihydroxypregn-4-ene-3,20-dione, and 21-Acetoxy-6β,17α-dihydroxypregna-4,9(11)-diene-3,20-dione.—A suspension of 10 g. of 21-acetoxy-11β,17α-dihydroxypregn-4-ene-3,20-dione in 100 ml. of dioxane, 10 ml. of trimethyl orthoformate, and 0.1 ml. of absolute methanol was stirred rapidly and 8 drops of 72% perchloric acid were added to the reaction mixture. After 2 min. the dark green reaction mixture was rapidly filtered into a flask containing 2 ml. of pyridine. In this manner there was recovered 0.5 g. of unchanged starting material. The filtered solution (now light yellow in color) was poured into water and the precipitated material was collected and dissolved in ether. The solution was washed with a saturated saline solution and dried.

Removal of the ether *in vacuo* gave 9.1 g. of a glass which showed by infrared analysis a small amount of Δ^4-3-one. The addition of 100 ml. of ether to this residue dissolved the enol ether and left undissolved 0.1 g. of hydrocortisone acetate. The ether solution was treated with an ethereal monoperphthalic acid solution (70 ml., 65 mg./ml.) and the reaction mixture was kept at 0° for 68 hr., at which time the solid which had separated was collected by filtration, 0.575 g., m.p. 201–206°. Crystallization from acetone–hexane afforded 0.215 g. of 6β-hydroxyhydrocortisone 21-acetate, m.p. 204–206°, resolidifying and remelting at 222–224°.

The ether filtrate was washed with a saturated sodium bicarbonate solution and then with a saturated saline solution, dried and evaporated to give 7.6 g. of a crude residue. *One half* (3.8 g.) of this material was dissolved in methylene chloride and chromatographed on a synthetic magnesium silicate. The material eluted with 8% acetone–methylene chloride (4 × 100 ml.) was identified as hydrocortisone acetate. A second crystalline fraction was isolated from the late 10% acetone–methylene chloride (3 × 100 ml.) and the early 12% acetone–methylene chloride (6 × 100 ml.) eluates. Crystallization from ethyl acetate–heptane afforded an additional 0.20 g. of 21-acetoxy-6β,11β,17α-trihydroxypregn-4-ene-3,20-dione, m.p. 204–206°, resolidifying then remelting at 219–221°.

A third crystalline fraction was obtained from the late 15% acetone–methylene chloride (4 × 100 ml.), and 20% acetone–methylene chloride (8 × 100 ml.) eluates. Two crystallizations from acetone–hexane yielded 0.245 g. of 21-acetoxy-6α,11β,17α-trihydroxypregn-4-ene-3,20-dione, m.p. 212–214°.

The presence of 21-acetoxy-6β,17α-dihydroxypregna-4,9-(11)-diene-3,20-dione was detected in the above reaction mixture in varying amounts depending on the condition used for enol ether formation. Longer reaction time at this stage led to the formation of increased yields of this stripped product. It appeared in the 8% acetone–methylene chloride and 10% acetone–methylene chloride eluates as a crystalline material, and was eluted before 6β-hydroxyhydrocortisone 21-acetate, but after hydrocortisone acetate. Crystallization from ethyl acetate–heptane yielded the diene, m.p. 214–215°.

6β,11β,17α,21-Tetrahydroxypregn-4-ene-3,20-dione (6β-Hydroxyhydrocortisone).—A suspension of 0.20 g. of 21-acetoxy-6β,11β,17α-trihydroxypregn-4-ene-3,20-dione in 20 ml. of methanol was briskly agitated by a stream of nitrogen. To this was added 0.32 ml. of methanolic 3.15 *N* sodium methoxide solution. Nitrogen agitation was continued for 30 min. and then 0.05 ml. glacial acetic acid was added. The reaction mixture was evaporated *in vacuo* and then refluxed briefly with 75 ml. of acetone and filtered. The acetone was then displaced with petroleum ether and there precipitated 0.12 g. of the tetrol, m.p. 241–243°. Another crystallization from acetone–petroleum ether yielded 0.097 g., m.p. 236–239°.

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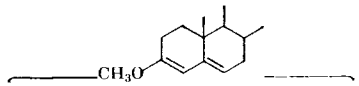
(4) (a) J. Romo, G. Rosenkranz, C. Djerassi, and F. Sondheimer, *J. Org. Chem.*, **19**, 1509 (1954); (b) F. Sondheimer, O. Mancera, and G. Rosenkranz, *J. Am. Chem. Soc.*, **76**, 5020 (1954); (c) S. Bernstein, W. S. Allen, C. E. Linden, and J. Clemente, *ibid.*, **77**, 6612 (1955); (d) S. Bernstein and R. Littell, *J. Org. Chem.*, **25**, 313 (1960); (e) S. Bernstein and R. Littell, *ibid.*, **26**, 3610 (1961).

(5) We have observed that peracid attack on $\Delta^{3,5}$-enol acetates[4a] also may give rise to a mixture of the epimeric 6-hydroxy compounds.

(6) Melting points are uncorrected. The ultraviolet spectra were determined in methanol and the rotations in the solvents specified. The petroleum ether fraction used had a b.p. 60–70°. The authors are indebted to William Fulmor and associates for the infrared, ultraviolet absorption and optical rotation data. We wish also to thank Louis B. Brancone and associates for the analyses.

TABLE I

DATA ON PREPARATION AND CHARACTERIZATION OF 6-HYDROXYLATED STEROIDS



Compound	M.p., °C.	[α]D (1% pyridine in chloroform)	λmax mμ (ε)	Product[b]	Method of isolation[a]	Yield,[c] %	M.p., °C.	[α]D[d]	λmax mμ (ε)
17β-Acetoxyandrost-4-en-3-one	176–180[e]	− 152	234 (19,500)	17β-Acetoxy-6β-hydroxyandrost-4-en-3-one[f]	C	33	210–212	+ 21 (C)	236 (14,600)
				17β-Acetoxy-6α-hydroxyandrost-4-en-3-one[g]		5	225–226	+ 8 (C)	241 (15,700)
17β-Hydroxyandrost-4-en-3-one		Not isolated		17β-Hydroxy-6β-hydroxyandrost-4-en-3-one[h]	C	20	213–215	+ 30 (C)	236 (13,700)
				17β-Hydroxy-6α-hydroxyandrost-4-en-3-one[i]		2	174–175	+ 9 (C)	241 (14,600)
16α,17α-Epoxypregn-4-ene-3,20-dione	192–194[j]	− 49.8	238 (19,800)	16α,17α-Epoxy-6β-hydroxypregn-4-ene-3,20-dione[k]	R	44	269–271		236 (13,500)
11α-Hydroxypregn-4-ene-3,20-dione		Not isolated		6β,11α-Dihydroxypregn-4-ene-3,20-dione[l]	C	8	248–251	+137 (C)	237 (12,800)
				6α,11α-Dihydroxypregn-4-ene-3,20-dione[m]		2	258–261	+162 (C)	242 (14,600)
16α-Hydroxypregn-4-ene-3,20-dione		Not isolated		6β,16α-Dihydroxypregn-4-ene-3,20-dione[n]	C	5	235–236	+ 75 (C)	235 (14,500)
21-Acetoxypregn-4-ene-3,20-dione	153–155[o]	+ 3.6	240 (19,700)	21-Acetoxy-6β-hydroxypregn-4-ene-3,20-dione[p]	C	18	190–192	+107 (C)	236 (13,800)
				6β,21-Dihydroxypregn-4-ene-3,20-dione[q]			*211–212*	*+108 (C)*	*235 (14,900)*
21-Acetoxy-11β-hydroxypregn-4-ene-3,20-dione	201–206[r]	− 10.3	239 (20,900)	21-Acetoxy-6β,11β-dihydroxypregn-4-ene-3,20-dione[s]	R	10	212–216	+190 (P)	235 (16,000)
				6β,11β,21-Trihydroxypregn-4-ene-3,20-dione[t]			*245–248*		*237 (13,000)*
21-Acetoxy-17α-hydroxypregn-4-ene-3,20-dione	188–190[u]	− 91.6	239 (22,500)	21-Acetoxy-6β,17α-dihydroxypregn-4-ene-3,20-dione[p]	R	35	270–272	+ 49 (P)	236 (13,900)
				6β,17α,21-Trihydroxypregn-4-ene-3,20-dione[w]			*229–230*	*+ 39 (P)*	*236 (13,700)*
21-Acetoxy-17α-hydroxypregn-4-ene-3,11,20-trione	190–192[x]	+ 15.4	238 (18,200)	21-Acetoxy-6β,17α-dihydroxypregn-4-ene-3,11,20-trione[y]	R	7	267–268	+130 (P)	231 (15,400)
				6β,17α,21-Trihydroxypregn-4-ene-3,11,20-trione[z]			*241–242*	*+122 (P)*	*231 (14,300)*
21-Acetoxy-11β,17α-dihydroxypregn-4-ene-3,20-dione		Not isolated		21-Acetoxy-6β,11β,17α-trihydroxypregn-4-ene-3,20-dione[aa]	C	7	219–221	+100 (P)	236 (14,100)
				6β,11β,17α,21-Tetrahydroxypregn-4-ene-3,20-dione[bb]			*236–239*	*+ 89 (P)*	*235 (13,800)*
				21-Acetoxy-6α,11β,17α-trihydroxypregn-4-ene-3,20-dione[cc]		4	212–214	+133 (P)	241 (15,400)
				6α,11β,17α,21-Tetrahydroxypregn-4-ene-3,20-dione[dd]			*216–217*		
				21-Acetoxy-6β,17α-dihydroxypregna-4,9(11)-diene-3,20-dione[ee]		..	214–215	+ 57 (C)	235 (14,600)
				6β,17α,21-Trihydroxypregna-4,9(11)-diene-3,20-dione[ff]			*236–238*	*+ 34 (P)*	*235 (14,900)*

TABLE I (*Continued*)

[a] C = chromatography, R = recrystallization of the reaction mixture. [b] Compounds in italics were obtained by hydrolysis of the corresponding 21-acetates. [c] Yields of recrystallized material based on enol ether, except where not isolated, otherwise on Δ^4-3-one. [d] Solvent: C = chloroform, P = pyridine. [e] Calcd. for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.67; H, 9.76. [f] Ref. 2, m.p. 211–212°, $[\alpha]D$ +27°, λ_{max} 236 mμ (log ε 4.14). [g] Calcd. for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.55; H, 9.02. [h] C. Amendolla, G. Rosenkranz, and F. Sondheimer, *J. Chem. Soc.*, 1226 (1954), m.p. 217–218°, $[\alpha]^{20}D$ +34°, λ_{max} 236 mμ (ε 13,800). [i] Calcd. for $C_{19}H_{28}O_3 \cdot {}^1/_2C_3H_6O$: C, 73.91; H, 9.53. Found: C, 73.91; H, 9.30. [j] Calcd. for $C_{22}H_{30}O_3$: C, 77.15; H, 8.83. Found: C, 77.02; H, 8.97. [k] Calcd. for $C_{21}H_{28}O_4$: C, 73.22; H, 8.19. Found: C, 72.63, 72.31; H, 8.26, 8.47. [l] D. H. Peterson and H. C. Murray, *J. Am. Chem. Soc.*, **74**, 1871 (1952), m.p. 245–248°, $[\alpha]^{24}D$ +144°. [m] B. Camerino, C. G. Alberti, A. Vercellone, and F. Ammannati, *Gazz. chim. ital.*, **84**, 301 (1954), m.p. 260–262°, $[\alpha]D$ +164°, λ_{max} 240 mμ (ε 12,220). [n] J. Fried, R. W. Thoma, D. Perlman, J. E. Herz, and A. Borman, *Recent Progr. Hormone Res.*, **11**, 149 (1949), m.p. 230–232°, $[\alpha]D$ +75°. [o] Calcd. for $C_{24}H_{34}O_4$: C, 74.57; H, 8.87. Found: C, 74.23; H, 9.14. [p] S. H. Eppstein, P. D. Meister, D. H. Peterson, H. C. Murray, H. M. Leigh, D. A. Lyttle, L. M. Reineke, and A. Weintraub, *J. Am. Chem. Soc.*, **75**, 408 (1953), m.p. 196–198°, $[\alpha]D$ +113°, λ_{max} 237 mμ (ε 13,900). [q] Ref. *p*, m.p. 198–202°, $[\alpha]^{23}D$ +101°. [r] Calcd. for $C_{24}H_{34}O_5$: C, 71.61; H, 8.51. Found: C, 71.84; H, 8.79. [s] Calcd. for $C_{23}H_{32}O_6$: C, 68.29; H, 7.97. Found: C, 68.05; H, 8.26. [t] R. Neher and A. Wettstein, *Helv. Chim. Acta*, **29**, 2062 (1956), m.p. 225–227°, $[\alpha]^{21}D$ +118°, λ_{max} 237 mμ (log ε 4.13). [u] Calcd. for $C_{24}H_{34}O_5$: C, 71.61; H, 8.51. Found: C, 71.48; H, 8.70. [v] Calcd. for $C_{23}H_{32}O_6$: C, 68.29; H, 7.97. Found: C, 68.08; H, 8.14, ref. *p*, m.p. 258–260°, $[\alpha]^{23}D$ +74°, λ_{max} 237 mμ (ε 14,100). [w] K. Florey and M. Ehrenstein, *J. Org. Chem.*, **19**, 1331 (1954), m.p. 229–230°, $[\alpha]D$ +43.7°, λ_{max} 235 mμ (ε 13,100). [x] A. Ercoli, U. S. Patent 3,009,858, November 21, 1961, m.p. 189–192°, $[\alpha]D$ +20.5°. [y] Ref. 3, m.p. 246–248°. [z] Ref. *y*, m.p. 236–238°, $[\alpha]D$ +117°, λ_{max} 232 mμ (log ε 4.14). [aa] S. Bernstein and R. Littell, *J. Org. Chem.*, **27**, 2544 (1962), m.p. 208–210°, $[\alpha]^{25}D$ +107°, λ_{max} 236 mμ (ε 13,400). [bb] S. Bernstein and R. Littell, *ibid.*, **25**, 313 (1960), m.p. 241–243°, $[\alpha]D$ +90°, λ_{max} 234–235 mμ (ε 12,000). [cc] Calcd. for $C_{23}H_{32}O_7$: C, 65.69; H, 7.67. Found: C, 65.07; H, 7.76. [dd] Ref. *bb*, m.p. 220–222°. [ee] Calcd. for $C_{13}H_{30}O_6$: C, 68.63; H, 7.51. Found: C, 68.91; H, 7.87. [ff] Calcd. for $C_{21}H_{28}O_5$: C, 69.97; H, 7.83. Found: C, 69.56; H, 7.78.

Stereochemistry of Reactions of the Norbornyl Grignard Reagent

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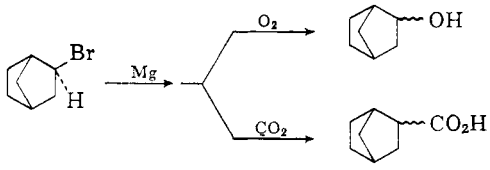
The stereochemistry of reactions of 2-bicycloheptyl Grignard reagents has not been thoroughly investigated. Interpretation of much of the earlier literature on reactions of bornyl Grignard reagents is complicated by the lack of adequate data on the structure and purity of some of the products involved.[2] More recently, Koch and Haaf[3] carbonated the Grignard reagent of norbornyl bromide and apparently obtained mainly *endo*-2-norbornanecarboxylic acid.

We undertook a more systematic study of reactions of the norbornyl Grignard reagent to evaluate the synthetic utility of this reagent. In particular, we studied the oxidation and carbonation reactions at two different temperatures (equation 1). The alcohols and acids (after conversion to methyl esters) were analyzed by gas-liquid chromatography. Table I summarizes the results.



(1)

TABLE I

exo–endo RATIOS OF PRODUCTS FROM REACTIONS OF NORBORNYL GRIGNARD REAGENT

	Reaction	
Temp.	Carbonation	Oxygenation
−78°	90:10	80:20
25°	70:30	79:21

The change in the *exo–endo* ratio of acids with temperature is of some interest. Since the yields at the lower temperature were lower, the possibility exists that carbonation was incomplete and that the *exo* Grignard reagent carbonated faster than the *endo* isomer.[4] A control experiment in which the length of the carbonation period at −78° was doubled led to the same ratio of acids in slightly higher yield. An attractive alternate rationale is that the *exo* and *endo* forms of the Grignard reagent exist in mobile equilibrium. The preponderance of *exo* acid in the product would be due to the fact that the transition state leading to it is of lower energy. Raising the temperature would be expected to shift the equilibrium toward *endo* Grignard as well as decrease the difference in transition state energies, thus leading to a smaller *exo–endo* ratio.

If the above explanation for carbonation is correct, it may be necessary to assume a different type of mechanism for oxidation, since the ratio of *exo–endo* alcohols did not change with temperature. Any possible explanation is complicated by the fact that there are two steps in which carbon–metal

(1) Abstracted from the Bachelor's thesis of G.T.K. (1962).

(2) For a summary and further references see C. Walling and S. A. Buckler, *J. Am. Chem. Soc.*, **77**, 6039 (1955).

(3) H. Koch and W. Haaf, *Ann.*, **638**, 111 (1960).

(4) It is assumed that carbonation is stereospecific with retention of configuration; *cf.* H. M. Walborsky and A. E. Young, *J. Am. Chem. Soc.*, **83**, 2595 (1961).

bonds are broken: formation of the hydroperoxide salt and reduction of the salt.[5] The stereochemistry of the two steps apparently is the same, however.[2] The insensitivity of the product ratio to temperature is suggestive of a free-radical process for these steps. Kooyman and Vegter,[6] for example, obtained the same ratio of *exo–endo* norbornyl chlorides at both 42° and 150° in an investigation of radical-catalyzed chlorination of norbornane.

Experimental

Chromosorb P (35/80) was the solid phase used in the gas chromatographic work. The columns were 1/4-in. o.d. copper tubing of the indicated lengths. Boiling points are uncorrected.

exo-**Norbornyl bromide** was prepared by addition of hydrobromic acid to norbornene[7] and had b.p. 78–80° (19 mm.) (lit.[7] b.p. 82°/29 mm.).

Preparation of the Grignard Reagent of Norbornyl Bromide.—The reagent was prepared in dried apparatus under nitrogen by addition of 5.0 g. (0.029 mole) of the bromide in 20 ml. of dry ether to 1.0 g. (0.041 g.-atom) of magnesium under 15 ml. of ether containing a crystal of iodine. The mixture was refluxed for 1 hr.

Carbonations were carried out by bubbling carbon dioxide from Dry Ice through concentrated sulfuric acid, a calcium chloride drying tower, and into the reaction flask held at 25° or −78°. The mixture was decomposed with 2 *N* hydrochloric acid and extracted with ether. The acidic products were removed by washing with potassium carbonate solution. The yields of acidic and neutral products formed at the two temperatures were as follows: 25°, 1.4 g. (35%) and 1.7 g. −78°, 0.9 g. (22%) and 2.3 g. (1 hr. carbonation); 1.0 g. (25%) and 2.3 g. (2 hr. carbonation).

Analyses of the acids were effected by conversion to methyl esters using boron trifluoride–methanol reagent[8] followed by gas chromatography. The best separation was acheived on a 10 ft. castorwax column (25%) at 142°. The curves were matched with known mixtures of the esters prepared by weighing pure samples. No noticeable epimerization took place during the esterification since the standard samples were also made with the boron trifluoride reagent. The analyses are probably accurate to ±3%. At 25° the *exo:endo* ratio was 70:30; at −78° the ratio was 90:10 in both cases.

Oxygenations were carried out in a similar manner using air in place of carbon dioxide. The reaction mixtures were decomposed with dilute sulfuric acid and extracted with ether. The alcohols were separated from the other neutral products by chromatography on "activated" alumina. Hexane was used to elute everything but the alcohols and methanol was used to remove the alcohols. The analyses were carried out by gas chromatography on an 8 ft. column of carbowax 20M (15%) at 102°. At 25° the yield of mixed norbornanols was 1.8 g. (56%) and 2.4 g. of other neutral products were obtained; the ratio of *exo* to *endo* alcohol was 79:21. At −78° there was obtained 1.9 g. (59%) of alcohols and 2.4 g. of other products; the ratio of *exo* to *endo* alcohols was 80:20. Ratios of peak areas were used to determine these percentages. It was shown that the alumina did not isomerize *exo*-norbornanol.

(5) C. Walling and S. A. Buckler, *J. Am. Chem. Soc.*, **77**, 6032 (1955).

(6) E. Kooyman and G. Vegter, *Tetrahedron*, **4**, 382 (1958).

(7) J. D. Roberts, E. R. Trumbull, W. Bennett, and R. Armstrong, *J. Am. Chem. Soc.*, **72**, 3116 (1950).

(8) Applied Science Laboratories, Inc., State College, Pennsylvania. See L. D. Matcalfe and A. A. Schmitz, *Anal. Chem.*, **33**, 363 (1961), for procedure.

The Synthesis of Bridged Ferrocene Derivatives with Functional Groups on the β-Carbon of the Bridge[1]

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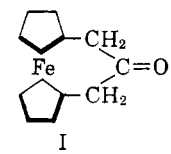
For future mechanistic studies it was desirable to have bridged ferrocene derivatives with functional groups on the β-carbon of the bridge. To this end, the dimethyl ester of ferrocene-1,1′-diacetic acid,[2] was treated with sodium triphenylmethyl in anhydrous ether. The red color of the triphenylmethyl anion soon disappeared and after work-up and chromatography there was obtained in 85% yield 1,1′-(α-carbomethoxy β-ketotrimethylene)ferrocene which was directly hydrolyzed and decarboxylated in glacial acetic acid with hydrochloric acid to 1,1′-(α-ketotrimethylene)ferrocene (I). Reduction of the ketone with sodium borohydride led to 1,1′-(β-hydroxy-trimethylene)ferrocene. The structure of the ketone was proved by desulfurization of its dimethylthioketal derivative with Raney nickel which produced the known 1,1′-trimethyleneferrocene.[3]



I

A principal point of interest in the synthesis is the ease of effecting the Dieckmann cyclization which may suggest that two of the bridging atoms can be planar with considerable double bond character between them. This is further borne out by the smooth preparation of an enol acetate derivative of 1,1′-(α-carbomethoxy-β-ketotrimethylene)ferrocene which possesses a double bond between the α- and β-carbons of the bridge. This is the first reported case of a ferrocene derivative bridged by a three-carbon chain containing a double bond.

NOTE ADDED IN PROOF: Rosenblum[4] has also recently reported bridged ferrocene derivatives with double bonds in the bridge.

A second point of interest is the carbonyl stretching frequency of 1,1′-(β-ketotrimethylene)ferrocene which occurs at 1703 cm.$^{-1}$ in carbon tetrachloride solution. This shift to lower frequencies (*cf.*

(1) Supported in part by a grant from the NSF and from the Paint Research Institute.

(2) K. L. Rinehart, Jr., R. J. Curby, Jr., and P. E. Sokol, *J. Am. Chem. Soc.*, **79**, 3420 (1957).

(3) K. Schlögl and H. Seiler, *Monatsh.*, **91**, 79 (1960).

(4) M. Rosenblum, A. K. Banerjee, N. Danieli, and R. W. Fish, Abstracts of Papers, 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., September 9–14, 1962, p. 2-Q.

acetone 1719 cm.$^{-1}$) may be caused either by a slight opening of the C—CO—C bond angle to 123°[5] or by an interaction of the d-electrons of the adjacent iron atom with the π-electrons of the carbonyl groups.

Experimental

1,1′-(α-Carbomethoxy-β-ketotrimethylene)ferrocene.—To a solution of dimethyl 1,1′-ferrocenediacetate (0.22 g., 0.67 mmole) dissolved in anhydrous ether (20 ml.) was added an ethereal solution of sodium triphenylmethide (0.12 *M*). The reaction was maintained under an atmosphere of nitrogen and the addition was continued until the distinctive red color of sodium triphenylmethide persisted. An orange precipitate immediately formed. The molar ratio (methide/ester) required was 2.9 for several runs. After standing at room temperature for 4 hr., the solution was shaken with water, the orange precipitate dissolving in the ether phase. The ethereal solution was washed with water, dried over anhydrous sodium sulfate, and the ether removed. The residue was chromatographed on a silicic acid–Celite column with hexane–dichloromethane as eluent. The first band of triphenylmethane was followed by the product which was crystallized from heptane yielding 0.17 g. (85%) of orange needles, m.p. 121–121.5°.

Anal. Calcd. for $C_{15}H_{14}O_3Fe$: C, 60.41; H, 4.74; Fe, 18.74. Found: C, 60.34; H, 4.93; Fe, 18.90.

Enol Acetate of 1,1′-(α-Carbomethoxy-β-ketotrimethylene)ferrocene.—1,1′-(α-Carbomethoxy-β-ketotrimethylene)ferrocene (0.1 g., 0.24 mmole) was added to 20 ml. of isopropenyl acetate which contained 0.2 g. of sulfosalicylic acid as catalyst. The mixture was heated to 90° and held at that temperature for 6 hr. The solution (containing a dark red precipitate) was neutralized with sodium bicarbonate solution and then extracted with ether. The ether solution was washed with water, dried over anhydrous sodium sulfate, and the ether removed. The residue was chromatographed on a column of silicic acid–Celite with hexane–chloroform eluent. The product was recrystallized from heptane yielding 0.06 g. (75%) of orange needles, m.p. 149–150°.

Anal. Calcd. for $C_{17}H_{16}O_4Fe$: C, 60.03; H, 4.74; Fe, 16.43. Found: C, 60.22; H, 4.91; Fe, 16.27.

1,1′-(β-Ketotrimethylene)ferrocene.—1,1′-(α-Carbomethoxy-β-ketotrimethylene)ferrocene (0.25 g., 0.84 mmole) was dissolved in a mixture of 20 ml. of glacial acetic acid and 3 ml. of concentrated hydrochloric acid. The mixture was heated at 100° for 30 min. After cooling, the solution was neutralized to pH 8 with sodium hydroxide followed by sodium bicarbonate, extracted with ether, and the ether dried over anhydrous sodium sulfate. After removing the ether, the residue was chromatographed over silicic acid–Celite with hexane–dichloromethane eluent, and the product recrystallized from heptane, yielding yellow-orange needles (0.17 g., 85%) m.p. 154–155°.

Anal. Calcd. for $C_{13}H_{12}OFe$: C, 65.01; H, 5.04; Fe, 23.28. Found: C, 65.12; H, 4.79; Fe, 23.46.

1,1′-Trimethyleneferrocene.—1,1′-(β-Ketotrimethylene)ferrocene (52 mg. 0.22 mmole) was dissolved in 10 ml. of glacial acetic acid and 5 ml. of concentrated hydrochloric acid and 5 ml. of methyl mercaptan were added. The mixture was allowed to stand at 0° for 20 min. and was then neutralized with sodium hydroxide and extracted with ether. After removal of the ether the product was crystallized from octane, yielding 52 mg. (73%) of orange crystals, m.p. 160–162°. Without further purification, the thioketal was refluxed with W-5 Raney nickel in absolute ethanol for 3 hr. with mechanical stirring. The reaction mixture was filtered, acidified, and the product extracted with ether. The ether was evaporated and the residue chromatographed on Merck neutral alumina with hexane as eluent. A yellow solid thus was obtained which after sublimation at 2 mm. at 64° had m.p. 105–106° (lit.,[3] 105–106°). The same product was obtained by Clemmensen reduction of 1,1′-(α-ketotrimethylene)ferrocene.[6]

(5) P. von R. Schleyer and R. D. Nicholas, *J. Am. Chem. Soc.*, **83**, 182 (1961).

(6) K. L. Rinehart, Jr., and R. J. Curby, Jr., *ibid.*, **79**, 3290 (1957).

Formation of an Organotin–Nitrogen Bond

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Tin–nitrogen bonding in triammonotin halides, $Sn(NH_2)_3X$ (where X stands for a halogen atom), are known,[1-3] but the same bonding in organotin compounds has apparently not been described as yet.

The reaction of ammonia or an amine with organotin compounds gives complex addition compounds containing one or two moles of ammonia or amine as coordinating components.[4-8]

It has been discovered that the reaction of diethylaminomagnesium bromide with trialkyltin chlorides gives trialkyl(diethylamino)tins having an organotin–nitrogen bonding (equation 1). The aminotin compounds could be isolated analytically pure by distillation under reduced pressure. The oily product reacted with hydrochloric acid to give trialkyltin chloride and the same amine hydrochloride (equation 2), both compounds being identified by the infrared spectra and the melting points. Upon exposure to air trialkyl(diethylamino)tin compounds were attacked very quickly by atmospheric moisture and carbon dioxide to afford diethylamine and trialkyltin carbonate (equation 3). The infrared spectra of triethyltin carbonate thus obtained coincided in every respect with those of the authentic sample prepared from carbon dioxide and bis(triethyltin) oxide.

$$R_3SnCl + (C_2H_5)_2NMgBr \longrightarrow R_3SnN(C_2H_5)_2 + MgBrCl \quad (1)$$

$$R_3SnN(C_2H_5)_2 + 2HCl \longrightarrow R_3SnCl + (C_2H_5)_2NH\cdot HCl \quad (2)$$

(1) R. Schwalz and A. Jeanmaire, *Ber.*, **64**, 1442 (1932).
(2) E. Bannister and G. W. A. Fowles, *J. Chem. Soc.*, 751 (1958).
(3) E. Bannister and G. W. A. Fowles, *ibid.*, 4374 (1958).
(4) F. Werner and P. Pfeiffer, *Z. anorg. Chem.*, **17**, 82 (1898).
(5) C. A. Kraus and W. N. Geer, *J. Am. Chem. Soc.*, **45**, 2946, 3078 (1923).
(6) K. K. Joshi and P. A. H. Wyatt, *J. Chem. Soc.*, 3825 (1959).
(7) F. Ephraim and T. Schmidt, *Ber.*, **42**, 3856 (1909).
(8) See also R. K. Ingham, S. D. Rosenberg, and H. Gilman, *Chem. Rev.*, **60**, 508 (1960), for further references.

$$2R_3SnN(C_2H_5)_2 + CO_2 + H_2O \longrightarrow (R_3Sn)_2CO_3 + 2(C_2H_5)_2NH \quad (3)$$

(R = C_2H_5, n-C_3H_7, or n-C_4H_9)

Infrared absorptions characteristic to the diethylaminotin grouping, Sn—$N(C_2H_5)_2$, were observed at 1290 (m), 1173 (vs), 1010 (s), 880 (s), and 780 (s) cm.$^{-1}$, all being common to the three trialkyl(diethylamino)tins herein described. These bands completely disappeared on exposure of the sample to air for several minutes on a sodium chloride plate, when characteristic bands of organotin carbonate appeared at 1560–1520 (vs), 1370 (vs), 1070 (m), and 840 (m) cm.$^{-1}$ instead.

These results show that the organotin–nitrogen bonding is rather stable to heating, as indicated by no change upon distillation, but is highly reactive toward proton-containing reagents.

Experimental

Analyses.—A microelementary analysis for carbon and hydrogen was given up because of the too high sensitivity of the sample to air (equation 3). As soon as a sealed ampoule was cut, diethylamine which was recognized by the strong odor vaporized.

Nitrogen was analyzed by titration according to equation 2: an exactly weighed sealed ampoule containing about 2.0 g. of the sample was crushed with a glass rod in 30 ml. of standardized 0.5 N hydrochloric acid, and the excess acid was back-titrated with 0.5 N sodium carbonate with methyl orange as an indicator.

Tin analyses were carried out according to Farnsworth and Pekola.[9] In this case the vaporization of diethylamine has no effect on the analytical values of tin.

Triethyl(diethylamino)tin.—A tetrahydrofuran solution of diethylaminomagnesium bromide prepared from 2.9 g. (0.12 g.-atom) of magnesium, 10.9 g. (0.1 mole) of ethyl bromide, and 7.3 g. (0.1 mole) of diethylamine in 50 ml. of tetrahydrofuran was added dropwise to a solution of 14.5 g. (0.06 mole) of triethyltin chloride[10] (b.p. 86–88°/9 mm.) dissolved in 50 ml. of tetrahydrofuran. An exothermic reaction was observed during this procedure. After refluxing for 4 hr. the solvent was distilled and the reaction product was fractionated under reduced pressure. A fraction boiling at 72–88°/11 mm. was collected; yield, 10.5 g. (63%). Redistillation gave 9.5 g. of an analytically pure fraction boiling at 114–117°/23 mm. All procedures were carried out in a nitrogen atmosphere. This sample gave a negative Beilstein test for halogen. The product was stored in sealed ampoules under nitrogen.

Anal. Calcd. for $C_{10}H_{25}NSn$: Sn, 42.69; N, 5.04. Found: Sn, 42.64, 42.98, 42.45; N, 4.92.

Tri-n-propyl(diethylamino)tin and tri-n-butyl(diethylamino)tin were also obtained in about 70% yields by an analogous way from tri-n-propyltin chloride[10] (b.p. 122–123°/10 mm.) and tri-n-butyltin chloride[10] (b.p. 130–132°/4 mm.), respectively.

Tri-n-propyl(diethylamino)tin had b.p. 118–120°/13 mm.

Anal. Calcd. for $C_{13}H_{31}NSn$: Sn, 36.97; N, 4.36. Found: Sn, 37.41; N, 3.95.

Tri-n-butyl(diethylamino)tin distilled at 124–134°/8 mm.

Anal. Calcd. for $C_{16}H_{37}NSn$: Sn, 32.77; N, 3.87. Found: Sn, 32.62; N, 3.40.

(9) M. Farnsworth and J. Pekola, *Anal. Chem.*, **31**, 410 (1959).

(10) K. A. Kocheskov, *Ber.*, **66**, 1661 (1930).

Attempted Hydrogenolysis of Amines with Triphenyltin Hydride[1]

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It has been reported that allylamine[4] (I) and benzylamine[5] (II), n-butylamine and n-hexylamine[6] are hydrogenolyzed to the parent hydrocarbons, propylene, toluene, butane and hexane, respectively, using triphenyltin hydride (III). Ammonia was claimed as one product of the reactions and hexaphenylditin (IV) was also isolated.

In attempting to repeat these results it was found that I or II with III does give IV and a steady evolution of gas. However, no propylene (using vapor phase chromatography), toluene (using vapor phase chromatography and infrared analysis), or ammonia (Nessler's reagent) could be detected. In the reaction of II with III, a considerable amount of benzene was formed. These results are in direct contrast to the successful reports of van der Kerk and Noltes, who, however, failed to identify positively the expected propylene and ammonia.[7] These results are also in sharp contrast to those of Kupchik and Connolly. The latter reported that a superimposable infrared spectrum of toluene was obtained from the first drops of distillate of the reaction mixture, which is difficult to understand. We were unable to find any trace of toluene. Benzene invariably accompanies the reaction of benzylamine with triphenyltin hydride and therefore should have been present in the first drops of distillate. Again, no positive evidence for ammonia was provided.

In the course of our attempts to hydrogenolyze carbon–nitrogen bonds, we also examined p-toluidine, N-methylbenzylamine, and N,N-dimethylbenzylamine. In these experiments IV and a gas were always obtained, but no hydrocarbon nor ammonia (see Experimental). In the case of p-toluidine and III, which was carried out in a sealed tube, the gas was not condensable at −80°. Qualitatively, the rate of formation of IV

(1) This work was supported by O.O.R. Project No. 2440, Department of the Army Project No. DA-30-069-ORD-2851 and Grant DA-ORD-31-124-61-G39, U. S. Army Research Office (Durham).

(2) Taken from the dissertation submitted to the Faculty of the Polytechnic Institute of Brooklyn in partial fulfillment of the requirements of the degree of Doctor of Philosophy.

(3) To whom inquiries should be sent.

(4) J. G. Noltes and G. J. M. van der Kerk, "Functionally Substituted Organotin Compounds," Tin Research Institute, Middlesex, England, 1958, p. 115.

(5) E. J. Kupchik and R. E. Connolly, *J. Org. Chem.*, **26**, 4747 (1961).

(6) J. G. Noltes and G. J. M. van der Kerk, *Chem. Ind.* (London), 294 (1959).

(7) In a private communication from G. J. M. van der Kerk, J. G. Noltes, and J. G. A. Luijten, the earlier hydrogenolyses are refuted.

decreased in the order of greater substitution of the amine group—*i.e.*, 3° < 2° < 1°. These results suggest that III is being catalytically decomposed to IV and hydrogen.[8,9]

$$Ph_3SnH \xrightarrow{Ar—NH_2} Ph_3SnSnPh_3 + H_2$$

Experimental

Allylamine and III.—To a round bottom flask equipped with a stirrer, reflux condenser, gas inlet tube, and gas exit tube leading from the top of the condenser to a trap containing 95% ethanol kept at −78° were added 32.2 g. (0.092 mole) of triphenyltin hydride and 2.6 g. (0.046 mole) of allylamine. Evolution of a gas was observed on mixing. The reaction mixture was stirred under a nitrogen atmosphere til solidification was complete. The contents of the trap gave a negative test with Nessler's reagent for ammonia, no characteristic brown-red color being observed. The solid in the flask was recrystallized from benzene, m.p. 230–232°. It did not depress the melting point on admixture with an authentic sample of IV.

In a second experiment, using the same procedure as described above, 20 g. (0.057 mole) of III and 1.62 g. (0.029 mole) of I were used. Any possible propylene being evolved was led from the top of the condenser into a trap containing 1-hexene kept at −78°, but no propylene was detected upon running the trap contents into a vapor phase chromatograph.

Benzylamine and III.—The procedure of Kupchik and Connolly was followed. The first few drops of distillate collected showed bands in the infrared (cm.$^{-1}$) at 3077, 3021, 1961, 1815, 1754, 1715, 1529, 1479, 1393, 1247, 1175, 1036, 850, 680, which excludes toluene[10] and confirms benzene. Further distillation and subsequent infrared analyses still showed no evidence for toluene.

In a second experiment, beginning with 22.5 g. (0.064 mole) of triphenyltin hydride and 3.6 ml. (0.032 mole) of II in which ammonia was particularly sought, a water-trap for the evolved gases contained no ammonia, (Nessler's reagent).

***p*-Toluidine and III.**—Beginning with 2.15 g. (0.020 mole) of *p*-toluidine and 8.0 g. (0.023 mole) of III, stirring at 150° for 1 hr. and at 190° for another 2 hr., throughout under a nitrogen atmosphere, evolution of gas was observed and solidification proceeded during the course of the reaction, but no positive test for ammonia was observed throughout this time.

No toluene was determined in the distillate, only benzene. Similar results were obtained in a sealed tube experiment at 80–150°.

***N*-Methylbenzylamine and III.**—In two separate experiments, with 7.00 g. of III and 1.21 g. of *N*-methylbenzylamine each, no methylamine could be determined by means of the Rimini test. It was noted that hydrogen was evolved only at a higher temperature (~100°) for the secondary amine.

***N,N*-Dimethylbenzylamine and III.**—With this amine, using the procedure outlined in detail earlier, no test for secondary amine could be determined from 1.35 g. of *N,N*-dimethylbenzylamine and 7.0 g. of III, by means of the Simon and the nickel dithiocarbonate tests. Again, it was noted that with the tertiary amine, decomposition of III took place at a still higher temperature (~130–150°).

(8) In ref. 7 van der Kerk, Noltes, and Luijten give evidence for the stoichiometry.

(9) We wish to express our gratitude to Drs. van der Kerk, Noltes, and Luijten for making their experimental work known to us prior to publication.

(10) Comparisons were made with spectra as follows: American Petroleum Institute Research Project No. 44, Serial No. 308 (benzene) and No. 498 (toluene).

The Photochemical Preparation of Dimethyl-*N*-(2-cyano-2-propyl)ketenimine from 2,2′-Azobisisobutyronitrile[1]

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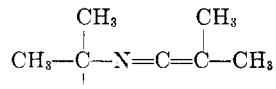
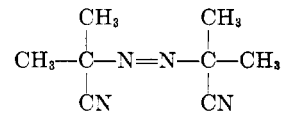
Lately it has been necessary to have a preparative method[3–6] for dimethyl-*N*-(2-cyano-2-propyl)-ketenimine (I). Previously we have employed[5,7]



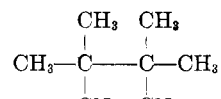
I

a procedure where 2,2′-azobisisobutyronitrile (II)



II

was thermally decomposed in an inert solvent, cyclohexane, at *ca.* 80° until the concentration of I had reached its maximum value,[4,8–10] whereupon the reaction mixture was quenched by cooling to *ca.* 10° and I isolated after filtering off the precipitate, which was largely all the tetramethylsuccinonitrile (III) formed and the undecomposed II.



III

The chief disadvantages of this method are that it gives low yields (*ca.* 15%),[5,7] requires care to keep the reaction under control, and demands a knowledge of the approximate time when the maximum concentration of I is reached.

(1) Supported by grants from Esso Research and Engineering Company and the United States Public Health Service, Division of General Medical Sciences.

(2) In partial fulfilment of the requirements for Graduation with Distinction.

(3) P. Smith, N. Muller, and W. C. Tosch, *J. Polymer Sci.*, **57**, 823 (1962).

(4) P. Smith and S. Carbone, *J. Am. Chem. Soc.*, **81**, 6174 (1959).

(5) P. Smith and A. M. Rosenberg, *ibid.*, **81**, 2037 (1959).

(6) P. E. Miller, J. E. Munzenrider, J. E. Sheats, and P. Smith, unpublished work.

(7) G. S. Hammond, O. D. Trapp, R. T. Keys, and D. L. Neff, *J. Am. Chem. Soc.*, **81**, 4878 (1959).

(8) G. S. Hammond, C.-H. S. Wu, O. D. Trapp, J. Warkentin, and R. T. Keys, *ibid.*, **82**, 5394 (1960).

(9) M. Talât-Erben and A. N. Isfendiyaroğlu, *Can. J. Chem.*, **36**, 1156 (1958).

(10) M. Talât-Erben and S. Bywater, *J. Am. Chem. Soc.*, **77**, 3710, 3712 (1955).

The photolysis of II in inert solvents at room temperature using 365μ also produces I,[4-6] the molar conversion of II into I for a given solvent being essentially the same as for the thermal decomposition at *ca.* 80°. Because I is effectively stable under the conditions of the photodecomposition but is destroyed readily at *ca.* 80° in solution, it was expected that the photodecomposition of II would afford a preparative route for I giving higher yields than the thermal decomposition method with a less complicated procedure. The results obtained supported expectation.

The molar conversion of II into I during the photodecomposition of II is solvent dependent.[6] Benzene was picked as the reaction solvent as a compromise between the aim to obtain the maximum conversion[5,6] of II into I and the wish to carry out the photodecomposition in a convenient, small volume of solvent with moderate volatility.

Experimental

A solution of 164 g. (1.00 mole) of Porophor N (Recrystallized) 2,2′-azobisisobutyronitrile (II) in 0.80 l. of dry reagent grade thiophene-free benzene at *ca.* 45° in 1-l. round-bottom Pyrex flask, through which dry nitrogen (Matheson, Prepurified) bubbled, was placed in a 4-l. Pyrex beaker containing running tap water at 16 ± 2°. After a preliminary purge period of 30 min., during which some II precipitated, the reaction mixture was irradiated for 48 hr. with occasional stirring, by which time all the precipitate had dissolved and the nitrogen evolution had essentially stopped. Irradiation was carried out with the flask and water-jacket inside an aluminum enclosure using two Mazda type ME/D 250 watt extra-high pressure mercury vapor projection lamps of the rectangular metal box variety set *ca.* 20 cm. apart and aimed horizontally at the center of the solution *ca.* 15 cm. away. Each lamp was run with its supplied 6-mm.-thick glass window in place.[11] Following the irradiation, the reaction mixture was concentrated under reduced pressure, filtering off precipitate at intervals, pot temperature 15 ± 5°, the pressure being taken down to 0.5 mm. The precipitate, a total of 55 g., was impure tetramethylsuccinonitrile,[12] III, repeated crystallization from ethanol yielding a pure specimen, m.p. (uncor.) 169–170°, lit.–*e.g.*, 170°,[3] 168.5–169°,[5] and 167–168°.[8] Next the brown filtered concentrate was distilled at 0.2–0.3-mm. pressure, pot temperature 30–45°, yielding 48 g. of colorless liquid I, n^{30}D 1.444$_6$, of 96 ± 1 mole % purity estimated from the refractive index and those of mixtures of I and III with known composition (yield, 35%). Two further distillations of this material at 0.2–0.3-mm. pressure, pot temperature 28–32°, collecting the middle 80% fraction gave a product comparable to that prepared before.[3,5] N.m.r. analysis[3] showed it to contain III as the only impurity and the purity to be at least 99.0 mole %, n^{25}D and n^{30}D, respectively, 1.447$_0$ and 1.444$_9$ (lit., $n^{20.0}$D 1.449$_1$,[3] n^{25}D 1.4470–1.4473,[7] $n^{30.0}$D 1.444$_9$[5]).

An attempt to repeat this photopreparation with similar experimental conditions, but using 0.80-l. of dry reagent grade cyclohexane in place of the benzene and employing vigorous mechanical stirring to keep the crystals of II in suspension, was unsuccessful. After irradiating for 48 hr. and concentrating the reaction mixture as before, the residual amount of I was only a trace. This is not surprising for both II and III are essentially insoluble in cyclohexane at 16 ± 2° and, at a given temperature, II in the solid state is considerably more thermally stable than when dissolved in an inert solvent.[6]

(11) Examination using a Cary Model 11 spectrophotometer showed this window to be optically equivalent to *ca.* 12 mm. of Pyrex glass. Allowing for the water-jacket and reaction flask, the reaction mixture was estimated to be protected by the equivalent of *ca.* 16 mm. of Pyrex. This provides ample protection for the I formed.[8]

(12) Aside from I, this is the chief organic product of the photodecomposition of II in benzene solution at 25° using 365 μ radiation, and the photodecomposition of I under similar conditions yields II as the major product eg (P. E. Miller, N. Muller, P. Smith, and W. C. Tosch, unpublished analyses by the n.m.r. method[3]).

The Preparation of *s*-Triazine Derivatives Containing the N—O Bond. II.[1] Hydroxylamino Derivatives of *s*-Triazine

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A literature search revealed that hydroxylamino-*s*-triazines were only represented by two members: 2,4 - bis(*p* - chlorophenyl) - 6 - hydroxylamino-*s*-triazine[2] and 2,4-bis(trichloromethyl)-6-hydroxylamino-*s*-triazine.[3] The preparation of the latter compound involved the reaction of a chlorotriazine, 2-chloro-4,6-bis(trichloromethyl)-*s*-triazine, and hydroxylamine. This method was found to be quite useful and the compounds shown in Table I were prepared in this fashion. In those reactions where the replaceable chlorine was substituted by the hydroxylamino group, a large excess of hydroxylamine was required to obtain yields greater than 50%. The preparation of the various alkoxyamino derivatives shown in Table I followed well established procedures[4] for the preparation of aminotriazines from the corresponding halotriazines.

As a class, the unsubstituted and N-substituted hydroxylaminotriazines gave purple and sometimes dark green, blue, or black colors with ferric chloride; O-substituted derivatives did not. All of the compounds considered are white to pale lavender solids which usually melt with decomposition. The unsubstituted hydroxylaminotriazines generally showed some solubility in dilute warm acid or base; N- or O-substitution increased the alkali solubility considerably. None of the compounds tested reduced Fehling's or Tollens' reagents.

Experimental[5]

Materials and Methods.—With the exception of cyanuric chloride, which is available from the American Cyanamid

(1) Part I; J. T. Shaw, *J. Org. Chem.*, in press.

(2) C. Grundmann and H. Schroeder, *Chem. Ber.*, **87**, 747 (1954).

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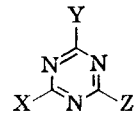
(4) J. T. Thurston, *et al.*, *ibid.*, **73**, 2981 (1951).

(5) All melting points are uncorrected. Microanalyses by Mr. John Kobliska and his staff.

TABLE I

HYDROXYLAMINO-*s*-TRIAZINE DERIVATIVES



Compound	X	Y	Z	M.p., °C.	Yield,[a] %	Method[b]	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
1	HONH—	HONH—	HONH—	218 dec.[c]	27	D	20.7	3.44	48.2	20.4	3.39	47.9
2	HONH—	HONH—	$(C_2H_5)_2N$—	183–185 dec.	57	A	39.2	6.57	39.2	39.5	6.63	39.0
3	HONH—	HONH—	$C_6H_5N(CH_3)$—	172–175 dec.[d]	56	A	48.4	4.84	33.9	48.6	5.19	33.8
4	HONH—	HONH—	CH_3	220 dec.	43	D	30.5	4.48	44.6	30.3	4.60	44.3
5	HONH—	HONH—	*o*-(MeO)C_6H_4[e]	208–209 dec.	78	A	48.1	4.42	28.1	48.3	4.47	28.4
6	HONH—	C_2H_5NH—	C_2H_5NH—	193–196 dec.	86	A	42.4	7.07	42.4	42.1	7.01	42.2
7	HONH—	$C_5H_{10}N$—	$C_5H_{10}N$—[e]	207–209 dec.[f]	31	A	56.2	7.96	30.2	55.9	7.90	30.0
8	HON(CH_3)—	HON(CH_3)—	$(C_2H_5)_2N$—	151–152[g]	82	A-1	44.7	7.44	34.7	45.0	7.76	34.6
9	HON(C_6H_5)—	HON(C_6H_5)—	Cl—[h]	230–232 dec.	87	B	54.7	3.64	21.2	54.7	2.83	21.2
10	CH_3ONH—	CH_3ONH—	CH_3ONH—[i,j]	207–208 dec.	78	C	33.3	5.56	38.9	33.6	5.80	39.2
11	CH_3ONH—	CH_3ONH—	Cl—	167–168	55	B	29.2	3.89	34.1	29.4	3.82	34.1
12	CH_3ONH—	CH_3ONH—	$(C_2H_5)_2N$—	105–108[k]	52	C	44.7	7.44	34.7	44.5	7.39	34.6
13	CH_3ONH—	CH_3ONH—	*p*-Cl-C_6H_4NH—	195 dec.	90	C	44.5	4.39	28.3	44.6	4.77	28.8
14	CH_3ONH—	CH_3ONH—	C_6H_5O—	119–123	69	D	50.2	4.95	26.6	50.0	5.18	26.7
15	C_2H_5ONH—	C_2H_5ONH—	Cl—	164–165 dec.	43	B	36.1	5.19	30.0	36.2	4.28	29.8
16	*n*-C_4H_9ONH—	*n*-C_4H_9ONH—	Cl—	174–175 dec.	74	B	44.6	6.92	24.2	44.3	6.71	23.9
17	CH_3ONH—	Cl—	Cl—[l]	147–151 dec.	78	B	24.6	2.05	28.7	24.8	1.89	28.6
18	CH_3ONH—	H_2N—	H_2N—[m]	248–250 dec.	70	C	30.8	5.13	53.8	30.8	5.16	53.5
19	CH_3ONH	C_2H_5NH—	C_2H_5NH—[n]	88–91 dec.	37	C	45.3	7.55	39.6	45.2	7.24	39.3
20	CH_3ONH—	CH_3O	CH_3O—[o]	136–138	76	C	38.7	5.43	30.1	38.9	5.37	30.0
21	$CH_3ON(CH_3)$—	$CH_3ON(CH_3)$—	$CH_3ON(CH_3)$—	66–67	83	D	41.8	7.00	32.6	41.9	6.98	32.9

[a] The yield of material which was suitable for further reactions. [b] Methods A, A-1, B, and C refer to general methods which are illustrated by representative examples in the Experimental section; method D indicates a method which was sufficiently different to warrant giving the experiment in detail. [c] Recryst. from water. [d] Recryst. from methanol. [e] The product was precipitated by addition of water to reaction mixture. [f] The crude product was purified by extracting impurities away with hot isopropyl alcohol. [g] Recryst. from benzene. [h] Phenylhydroxylamine was added as a solution in dioxane. [i] The product was prepared from 2-chloro-4,6-bis(methoxyamino)-*s*-triazine. [j] Two moles methoxyamine/mole triazine were used; 1 eq. sodium hydroxide/mole triazine was employed to neutralize the acid released. [k] M.p. partially 93–97°, resolidifies and melts entirely 105–108°. [l] Reaction conditions: addition of methoxyamine at −1 to 10° followed by 1 eq. sodium hydroxide (per 1 eq. methoxyamine) at 2–7°, then 2 hr. at 5°; filtration and washing in the cold, and air drying on a porous plate. [m] This product was prepared from 2,4-diamino-6-chloro-*s*-triazine; methoxyamine/triazine = 4; 1 eq. sodium/mole triazine was used to neutralize the acid released. [n] This product was prepared from 2,4-dichloro-6-methoxyamino-*s*-triazine and excess ethylamine; mole ethylamine/mole triazine = 5.5; no sodium hydroxide was used. The aqueous mixture was refluxed 2 hr.; the product is an oil which solidifies on standing. [o] This product was prepared from 2-chloro-4,6-bis-(methoxy)-*s*-triazine; solid sodium carbonate (1 eq./mole triazine) used to neutralize the acid released. The reaction temperature was 75–80° for 0.5 hr.

Co., the various aminochlorotriazine intermediates were prepared by methods given in the literature.[4] Methoxyamine hydrochloride (E. G. Sargent Co.) and N-methylhydroxylaminehydrochloride (Aldrich Co.) were used without further purification, while 0,N-dimethylhydroxylamine hydrochloride,[6] ethoxyamine hydrochloride,[7] and butoxyamine hydrochloride[7] were prepared by methods given in the literature. Wherever possible, general methods (A, B, or C) were used for the preparation of the hydroxylamino and substituted hydroxylamino-*s*-triazine derivatives shown in Table I. Experiments illustrating each of these methods are given. Experiments falling outside these general methods are reported separately (D).

Where ambiguity might arise as to what halotriazine starting material was used in a particular synthesis, the one employed is given in the footnotes to Table I. All hydroxylamino and N-substituted hydroxylamino-*s*-triazines were prepared from the corresponding chlorotriazines in one step by reaction with hydroxylamine or a substituted hydroxylamine. Many of the compounds prepared did not require recrystallization; where recrystallization was necessary, the solvent used is given in the footnotes to Table I.

2-Diethylamino-4,6-bis(hydroxylamino)-*s*-triazine, Method A: Hydroxylamine/Replaceable Chlorine = 4.—A solution of 469 g. (6.75 moles) of hydroxylamine hydrochloride in 560 ml. of water was neutralized at a temperature below 22° with a solution of 250 g. (6.25 moles) of 97% sodium hydroxide in 560 ml. of water. (The system was kept free of air as much as possible to avoid oxidation of the hydroxylamine.) The aqueous solution of hydroxylamine was then treated dropwise at 2–6° with 177 g. (0.80 mole) of 2,4-dichloro-6-diethylamino-*s*-triazine dissolved in 720 ml. of dioxane. After completion of the addition (70 min.), the mixture was heated for 1.5 hr. at 55–60°, refluxed at 90° for 3.5 hr., and then chilled; the product was precipitated by adding 1 l. of water. After having been filtered and dried at 65° for 24 hr., the product weighed 98.4 g.

Method A-1.—Method A is essentially followed with these exceptions: hydroxylamine/replaceable chlorine = 2; after refluxing 0.5 hr., 1 mole of aqueous sodium hydroxide per atom of replaceable chlorine is added over a 0.5-hr. period followed by 3 hr. of additional reflux; precipitation of the compound is aided by the addition of sodium chloride.

2-Chloro-4,6-bis(methoxyamino)-*s*-triazine, Method B.—An aqueous dioxane slurry of cyanuric chloride was prepared by adding in portions a solution of 27.7 g. (0.15 mole) of cyanuric chloride in 60 ml. of dioxane to 200 ml. of ice water at 0–10°. To the vigorously stirred slurry was added dropwise at 0–5° a solution of methoxyamine prepared by neutralizing a solution of 25 g. (0.3 mole) of methoxyamine hydrochloride in 73 ml. of water with 12.5 g. (0.3 mole) of 97% sodium hydroxide in 33 ml. of water at a temperature less than 25°. The addition required 43 min., the final pH being 4: the mixture was allowed to warm to 24° (a little heat finally being required); the pH was now 1. A solution of 12.5 g. (0.3 mole) of 97% sodium hydroxide in 37 ml. of water was added dropwise over a 15-min. period during which the temperature rose to 43° and the pH finally was 8. The mixture was allowed to cool to 35° over a 20-min. period, then chilled in ice for 1 hr. and filtered; the cake was washed well with water. The dry cake weighed 16.8 g. and melted partially at 167–168°.

2-Diethylamino-4,6-bis(methoxyamino)-*s*-triazine, Method C.—A slurry of 5 g. (0.025 mole) of 2-chloro-4,6-bis(methoxyamino)-*s*-triazine in 20 ml. of water was treated with 1.77 g. (0.0243 mole) of diethylamine and the mixture was slowly heated to reflux. Addition of 24.3 ml. of 1 *N* sodium hydroxide then followed at such a rate as to keep the mixture neutral or slightly alkaline. The pale yellow oil which formed became a hard plastic-like solid on cooling. The aqueous phase was decanted and the solid residue, after stirring and breaking up with fresh water, was allowed to air dry: 3.0 g., m.p. 97–104°. An amount of 2.7 g. of this material was recrystallized from 80 ml. of hexane and about 1.5 ml. benzene. The oven-dried (52°) material weighed 1.21 g. and gave a negative Beilstein test. The material was soluble in 3 *N* caustic and reprecipitated on acidification with acetic acid. (Caution—below pH 4 the material redissolves.)

2,4-Bis(hydroxylamino)-6-methyl-*s*-triazine.—An intimate mixture of 68 g. (0.976 mole) of hydroxylamine hydrochloride and 77.6 g. (0.73 mole) of sodium carbonate, when added to 400 ml. of ether, formed a slurry. To this stirred slurry was added 40 ml. of water and then the mixture was cooled to −10°, stirred for 10 min., and then treated dropwise at −10 to −5° with a solution of 40 g. (0.244 mole) of 2,4-dichloro-6-methyl-*s*-triazine in 400 ml. of ether. After completion of the addition which took 0.75 hr., the mixture was stirred at −10 to 0° for 1.5 hr. and then allowed to warm to room temperature and stirred for 4 days. The ether was decanted and the residue was stirred vigorously with 500 ml. of water, filtered, and after air drying several hours, was placed in a 60° oven and dried to constant weight; 41.3 g. of a white solid which gave a violet color with ferric chloride, m.p. 213° dec. Recrystallization of 20 g. from water acidified to pH 5 with acetic acid gave 8 g.

2,4,6-Tris(hydroxylamino)-*s*-triazine.—A solution of 167 g. (2.4 mole) of hydroxylamine hydrochloride in 200 ml. of water was cooled to −10° and neutralized by dropwise addition of a solution of 96.7 g. of 99.2% sodium hydroxide (2.4 moles), the temperature being maintained at −10 to −5°. To the resultant stirred solution at −10 to 0° was added dropwise a solution of 36.9 g. (0.2 mole) of cyanuric chloride in 100 ml. of dioxane over a period of 0.5 hr. The mixture was stirred at 0–5° for 1 hr., followed by 50–60° for 2 hr., followed by a final reflux (91°) for 1 hr. A clear violet solution formed, final pH 6. After cooling overnight and then chilling the next morning to 0°, the mixture was filtered, 15.3 g., m.p. > 300°; recrystallization of 8 g. from 120 ml. of water gave 3.5 g., m.p. 207° dec. (vigorous). Analysis of this material was 98% of theory. It was found that an analytical sample could be obtained in the following way. An amount of 6.5 g. of the crude material was stirred with 50 ml. of water at 30° for 5 hr.; after filtering and drying, there was obtained 4 g. of a pale lavender solid.

2,4-Bis(methoxyamino)-6-phenoxy-*s*-triazine.—To a solution of 2.4 g. of (0.0255 mole) of phenol and 1.02 g. (0.0255 mole) of 97% sodium hydroxide in 25 ml. of water was added 5.0 g. (0.0243 mole) of 2-chloro-4,6-bis(methoxyamino)-*s*-triazine. The mixture was refluxed for 4 hr., cooled, and the aqueous phase decanted from the taffy-like material which was placed *in vacuo* over phosphorus pentoxide. The dry material was ground up and weighed 4.4 g.

2,4,6-Tris(N-methyl-N-methoxyamino)-*s*-triazine.—A solution of 4.72 g. (0.0256 mole) of cyanuric chloride in 20 ml. of dioxane was added dropwise at 2–5° to 30 ml. of water (containing a little ice). The slurry which formed was treated dropwise at 0–5° with an aqueous solution of O,N-dimethylhydroylamine [prepared by neutralizing 10 g. (0.112) of O,N-dimethylhydroxylamine hydrochloride in 30 ml. of water with 4.22 g. (0.112) of 97% sodium hydroxide in 20 ml. of water]. The mixture was allowed to warm at 19°, a few drops of phenolphthalein added, and then an aqueous solution of 3.13 g. (0.076 mole) of 97% sodium hydroxide in 20 ml. of water was added dropwise until the solution was alkaline (4/5 of the total caustic was required). The mixture was slowly heated to reflux during which time the remaining caustic was added, and was refluxed for 15 min. after completion of the addition. The mixture was cooled, evaporated at room temperature to one third volume, and the crystals filtered and air dried, 5.5 g. This material, after recrystallization from 25 ml. of water (forms an oil which solidifies on cooling), weighed 4.1 g.

(6) (a) L. W. Jones, *Am. Chem. J.*, **20**, 38 (1898). (b) R. T. Major and E. E. Fleck, *J. Am. Chem. Soc.*, **50**, 1479 (1928).

(7) A. T. Fuller and H. King, *J. Chem. Soc.*, 963 (1947).

Some Substituted Pyrrolizidines

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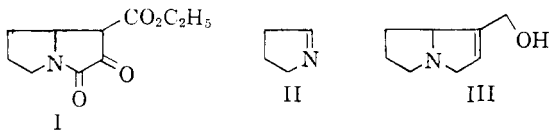
As part of an investigation of a general synthetic approach to the alkamine moiety of *Senecio* alkaloids[3] 1-carboethoxy-2,3-dioxopyrrolizidine (I) was prepared by allowing 1-pyrroline (II) to react with ethyl oxosuccinate. The analysis, infrared spectrum, and subsequent chemical transformations confirmed the structure of I; and recently Adams, Miyano, and Nair[4] synthesized I by the condensation of ethyl 2-pyrrolidylacetate with diethyl oxalate in the presence of sodium ethoxide.

It was envisaged that stepwise reduction and dehydration of I would produce *dl*-supinidine (III). Catalytic reduction of I gave in near quantitative yield 1-carboethoxy-2-hydroxy-3-oxopyrrolizidine (IV). Adams[4] and his co-workers also catalytically reduced I to IV.

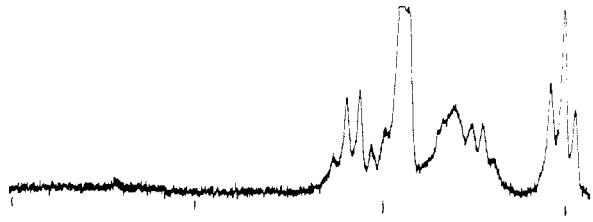


I II III

Attempts to dehyrate 1-carboethoxy-2-hydroxy-3-oxopyrrolizidine (IV) were unsuccessful. Upon treatment of IV with phosphorus oxychloride in pyridine an oil was obtained which was probably 1-carboethoxy - 2 - chloro - 3 - oxopyrrolizidine. Attempted pyrolytic dehydrations as well as acid- and iodine-catalyzed dehydrations of IV yielded starting material.

The lability of the hydroxy group in IV was increased by conversion to the tosylate (V), a transformation which was readily accomplished. The structure of V was confirmed by analysis, as well as infrared and ultraviolet spectra.

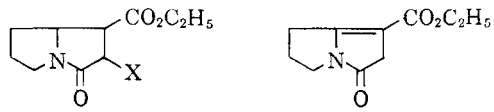
Treatment of V with one equivalent of potassium *t*-butoxide in *t*-butyl alcohol resulted in the facile elimination of *p*-toluenesulfonic acid and the formation of compound VI. Compound VI reacted instantly with bromine and precipitated manganese dioxide upon addition of a potassium permanganate solution. The required formula ($C_{10}H_{13}O_3N$) was indicated by analysis. With 10% palladium on charcoal as a catalyst, compound VI took up one mole of hydrogen. All these experiments and the method of preparation were consistent with the formulation of VI as 1-carboethoxy-3-oxopyrrolizid-1,2-ene. Nair and Adams[5] isolated VI after allowing 1-carboethoxy-2-hydroxy-3-oxopyrrolizidine (IV) to react with *p*-toluenesulfonyl chloride in pyridine. They firmly established the gross structure of VI as they reduced it to the known *dl*-isoretronecanol (1-hydroxymethylpyrrolizidine).[5]



−100 c.p.s. 0 c.p.s. 100 c.p.s. 200 c.p.s.

Fig. 1.—Nuclear magnetic resonance spectrum of 1-carboethoxy-3-oxopyrrolizid-1,8-ene (VI).

Nair and Adams[5] considered compound VI to be 1-carboethoxy-3-oxopyrrolizid-1,2-ene, though they were unable to obtain *dl*-supinidine (III) by stepwise reduction of VI. On the basis of the following evidence, we have concluded that VI is the isomeric 1,8-ene. The ultraviolet spectrum of VI had two peaks, one at 288 mμ (ϵ 12,000) and the other at 218 mμ (ϵ 4600). If VI were the 1,2-ene, it would probably have only one peak of higher intensity in the 220-mμ region as fumarates and related compounds have.[6] A nuclear magnetic resonance spectrum[7] (Fig. 1) of VI showed the hydrogens of one ethyl ester and also methylene hydrogens, but no vinyl hydrogen was detected. The ratio of ethyl ester hydrogens to methylene hydrogens was that expected for VI, 5:8. This evidence allows us to conclude that VI is 1-carboethoxy-3-oxopyrrolizid-1,8-ene not the corresponding 1,2-ene as previously suggested.[5]



IV. X = OH
V. X = OTs

VI

Experimental[8]

1-Carboethoxy-2,3-dioxopyrrolizidine (I).—Ethyl oxosuccinate (22.1 g., 0.117 mole) was added to a solution of 1-pyrroline in ethanol–ethyl ether. (The maximum amount of 1-pyrroline was 0.250 mole; this is based on the amount of pyrrolidine used in the preparation of 1-pyrroline *via* N-

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(2) The author is indebted to Professor E. E. van Tamelen for suggesting this problem and advising and encouraging the author throughout this work.

(3) (a) N. J. Leonard, "The Alkaloids Chemistry and Physiology," Vol. I, R. H. F. Manske and H. L. Holmes, ed., Academic Press, New York, 1950, p. 108. (b) N. J. Leonard, *ibid.*, Vol. VI, R. F. Manske, ed., 1960, p. 35.

(4) R. Adams, S. Miyano, and M. D. Nair, *J. Am. Chem. Soc.*, **83**, 3323 (1961).

(5) M. D. Nair and R. Adams, *J. Org. Chem.*, **26**, 3059 (1961).

(6) (a) H. Ley and H. Wingchen, *Ber.*, **67**, 501 (1934); (b) A. Smakula, *Angew. Chem.*, **47**, 657 (1934).

(7) The n.m.r. spectrum of VI was taken on a Varian Associates Instrument at 40 Mc. and 14,000 gauss with benzene as an internal reference and carbon tetrachloride as the solvent (20%).

(8) All melting points are uncorrected. Microanalyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Michigan.

chloropyrrolidine.[9] This solution was refluxed for 3.5 hr., cooled, and acidified with aqueous hydrochloric acid. The volume of solution was reduced to *ca.* 100 ml. by reduced pressure distillation. The solution was then extracted with three 100-ml. portions of benzene. The benzene extract was washed with three 30-ml. portions of water saturated with sodium chloride. The washings were discarded and the benzene solution dried over sodium sulfate. After the benzene was removed, 15.7 g. (64.0%) of crude solid I was obtained. The solid was dissolved in warm benzene and charcoal was added. This solution was warmed on a steam bath for 10–15 min.; Filter-Cel was added and the solution filtered. After removal of the benzene, the solid was recrystallized from ethyl ether-purified petroleum ether (b.p. 90–100°). The recrystallized white solid was sublimed, m.p. 123–125°.

Anal. Calcd. for $C_{10}H_{13}O_4N$: C, 56.86; H, 6.20; N, 6.63. Found: C, 56.92; H, 6.33; N, 6.71.

1-Carboethoxy-2-hydroxy-3-oxopyrrolizidine (IV).—Six grams (0.0285 mole) of sublimed I was dissolved in 50 ml. of 95% ethanol and placed in a hydrogenation bomb, and 3 g. of W-2 Raney nickel was added. At 100° and 2000 p.s.i. the theoretical amount of hydrogen was taken up in 4 hr. The solution was allowed to cool to room temperature and brought to atmospheric pressure. The solution was then filtered. After removal of the solvent the solid was recrystallized from ethyl acetate-purified petroleum ether (b.p. 60–68°) and sublimed, m.p. 128.2–132.1°.

Anal. Calcd. for $C_{10}H_{15}O_4N$: C, 56.32; H, 7.09; N, 6.57. Found: C, 56.24; H, 7.01; N, 6.54.

1-Carboethoxy-2-hydroxy-3-oxopyrrolizidine Tosylate (V).—A 0.153-g. (2.31 mmoles) sample of IV was dissolved in 10 ml. of anhydrous pyridine, and 1.11 g. (5.71 mmoles) of recrystallized *p*-toluenesulfonyl chloride was added. The solution was stored at 0° for 17 hr. and then poured onto crushed ice. Within 0.5 hr., a copious white precipitate formed. This was filtered, washed with water, and after being dried, 0.634 g. (67.8%) of V was obtained, recrystallized from ethyl acetate, m.p. 123.1–124.2°.

The infrared spectrum of V in 10% chloroform solution had no absorption bands in the 3.0-μ region and had peaks at 5.80 and 6.24 μ. The ultraviolet spectrum in 95% ethanol had one peak at 226 mμ (ϵ 12,500).

Anal. Calcd. for $C_{17}H_{21}O_6NS$: C, 55.72; H, 5.50; Found: C, 55.63; H, 5.97.

1-Carboethoxy-3-oxopyrrolizid-1,8-ene (VI).—A 0.529-g. (1.43 mmoles) sample of V was placed in a flask and 50 ml. of anhydrous *t*-butyl alcohol was added. The solution was warmed on a steam bath for 5–10 min., and most of the tosylate dissolved. To this warmed stirred solution, 7.49 ml. of 0.193 *N* (1.43 mmole) of potassium *t*-butoxide in *t*-butyl alcohol was added. The solution became bright red as each drop of base was added, but the color then disappeared and only persisted after all the base had been addded. The solution was acidified with dilute hydrochloric acid and then extracted with benzene. The benzene was removed by reduced pressure distillation. The residue was chromatographed on a column packed with Florosil (60/100 mesh, Floridian Co., Tallahassee, Florida). The chromatographed material (over 90%) was sublimed, m.p. 88.9–90.0°.

Anal. Calcd. for $C_{10}H_{13}O_3N$: C, 61.52; H, 6.71; N, 7.18. Found: C, 61.61; H, 6.66; N, 6.55.

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(9) D. W. Fuhlage and C. A. VanderWerf, *J. Am. Chem. Soc.*, **80**, 6249 (1958).

Formylation of *t*-Butylamine and *t*-Octylamine[1,2]

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During studies on isocyanides in these laboratories we have had occasion to prepare large quantities of formo-*t*-butylamide. Neither the formylation of *t*-butylamine by formic acid nor the Ritter reaction on isobutylene or *t*-butyl alcohol[3] is appealing as a routine preparation, the former because mixing the very volatile *t*-butylamine with formic acid is a troublesome and tedious procedure, and the latter because of the obvious hazards of working with hydrogen cyanide. We have found that *t*-butylamine can be formylated conveniently by refluxing and then distilling an equimolar mixture of ethyl formate and *t*-butylamine. The high rate of this reaction is in striking contrast with the negligible rate of acetylation of *t*-butylamine by methyl acetate[4] at 25°. Similarly *t*-octylamine (2,4,4-trimethyl-2-pentylamine) is formylated at approximately the same rate.

Experimental[5]

Equimolar quantities of ethyl formate and *t*-butylamine were refluxed in tared flasks, the excess reagents and ethanol were distilled on the water bath, and the residual formo-*t*-butylamide was weighed. The procedure was checked by distilling several batches. Typical yields for 4,16,32, and 48 hr. of reflux were 29.4, 66.8, 79.2, and 84.0%, respectively. Similarly, a mixture of 120 g. (1.0 mole) of *t*-octylamine and 150 g. (2.0 moles) of ethyl formate was refluxed 12 hr. and then distilled. The formo-*t*-octylamide was obtained in a yield of 98 g. (62%), b.p. 245–248°. This material is slightly amber in color and may be better purified by vacuum distillation.

(1) Abstracted from the M.S. theses of Marvin K. Newton and Gerald J. Papenmeier, University of Kansas City, 1960.

(2) The authors gratefully acknowledge support of this work by the National Science Foundation under Grant No. G10031.

(3) J. J. Ritter and J. Kalish, *J. Am. Chem. Soc.*, **70**, 4048 (1948).

(4) E. McC. Arnett, J. G. Miller, and A. R. Day, *ibid.*, **72**, 5635 (1950).

(5) A gift of *t*-octylamine from the Rohm & Haas Corporation is gratefully acknowledged. The other chemicals were purchased.

Bridged Polycyclic Compounds. XVIII. Addition of Dialkyl Azodicarboxylates to Norbornadiene[1]

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Recent reports have established that norbornadiene (I) exhibits unusual chemical reactivity as

compared with ordinary unconjugated dienes.[2] Of particular interest are the observations that I will give 1:1 adducts with dienophiles by a homoconjugate Diels-Alder type addition across the 2,6-position.[2f,g,i,j] In connection with another study, we had occasion to examine the reaction of I with dialkyl azodicarboxylates. Since the latter are well known dienophiles, it was anticipated that analogous 2,6-adducts might be reaction products. This is the case, but in addition, a structurally different 1:1 adduct is also formed.

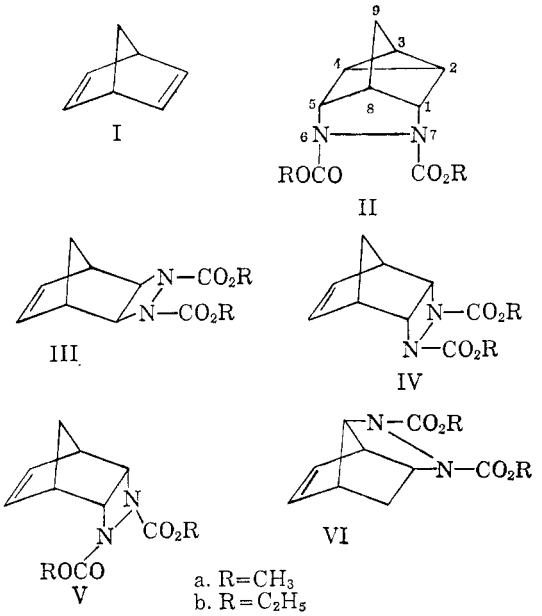
Methyl azodicarboxylate and norbornadiene (I) were heated at 150–160° for twenty-four hours. Distillation of the reaction mixture, followed by chromatography of the distillate on alumina resulted in separation into two fractions. The first fraction, m.p. 59–60.5°, and the second fraction, m.p. 109.5–110°, were in the ratio of *ca.* 1.8:1, respectively.

Molecular weight determinations and elemental analyses clearly established both products as 1:1 adducts.

Chemically the two fractions behaved differently. Acetone solutions of the 60° product reacted instantly with aqueous potassium permanganate and more slowly with bromine in carbon tetrachloride, while acetone solutions of the 110° product reacted only very slowly with potassium permanganate and not at all with bromine at room temperature. Catalytic hydrogenation of the 60° product with palladium-on-charcoal catalyst in ethanol at room temperature led to rapid absorption of one mole of hydrogen per mole of compound and to the formation of a new product. On the other hand, treatment of the 110° product under identical hydrogenation conditions resulted in recovery of unchanged starting material.

The evidence described above is consistent with structure IIa for the 110° product and either IIIa, IVa, Va, or VIa for the 60.5° isomer.

Spectra and Structure.—The infrared spectra of the 60° and 110° products show over-all similarity, but there are some significant differences. The 110° isomer has split carbonyl absorptions of nearly equal intensity at 5.72 and 5.80 μ while the 60° compound has a sharp, single absorption at 5.95 μ. No absorption peak was noted in the 12.3-μ region for the 60° product, a region presumed to be characteristic of the nortricyclene system.[2c,3] An absorption peak was apparent at 12.25 μ for the 110° product. Further evidence that a three-membered ring is present in the latter compound is revealed by the spectral features of the carbon–hydrogen stretching region. This material has a peak at 3.27 μ, a value diagnostic of hydrogen atoms attached to three-membered rings.[3b,4] A similar absorption band at 3.25 μ for the other isomer may be ascribed to the ethylenic hydrogen.



An examination of the proton n.m.r. spectra of the two adducts is of value. The observed resonance frequencies and relative peak intensities are summarized in Table I.

TABLE I

N.M.R. SPECTRAL DATA[a]

60° Product		110° Product	
τ	Relative peak areas	τ	Relative peak areas
8.29	2	8.49	3
6.89	2	8.21	2
6.26[b]	7	7.97	1
5.65[c]	1	6.26	6
3.72[d]	2	5.57	2

[a] All values are p.p.m. referred to tetramethylsilane (internal standard) as 10.00 [see G. V. D. Tiers, *J. Phys. Chem.*, **62**, 1151 (1958)]; only multiplet centers are indicated. Spectra were obtained from *ca.* 7% solutions in carbon tetrachloride at room temperature. [b] This number refers to the value of the singlet band for the six methoxyl protons. Somewhat upfield there is another proton which is partially concealed by the methoxyl proton signal. [c] This number refers to the center of a doublet. [d] This number refers to the center of an eight-line spectrum of two nonequivalent vinyl protons.

(1) Previous papers in series: S. J. Cristol, J. R. Douglas, W. C. Firth, Jr., and R. E. Krall, *J. Org. Chem.*, **27**, 2711 (1962).

(2) (a) H. Bluestone, S. B. Soloway, J. Hyman, and R. E. Lidov, U.S. Patent 2,730,548 (January 10, 1956); U.S. Patent 2,738,356 (March 13, 1956); U.S. Patent 2,782,238 (February 19, 1957); (b) S. Winstein and M. Shatavsky, *J. Am. Chem. Soc.*, **78**, 592 (1956); (c) L. Schmerling, J. P. Luvisi, and R. W. Welch, *ibid.*, **78**, 2819 (1956); (d) S. J. Cristol, R. P. Arganbright, G. D. Brindell, and R. M. Heitz, *ibid.*, **79**, 6035 (1957); (e) S. J. Cristol, G. D. Brindell, and J. A. Reeder, *ibid.*, **80**, 635 (1958); (f) E. F. Ullman, *Chem. Ind.* (London), 1173 (1958); (g) A. T. Blomquist and Y. C. Meinwald, *J. Am. Chem. Soc.*, **81**, 667 (1959); (h) F. Joy and M. F. Lappert, *Proc. Chem. Soc.*, 353 (1960); (i) H. K. Hall, Jr., *J. Org. Chem.*, **25**, 42 (1960); (j) C. J. Krespan, B. C. McKusick, and T. L. Cairns, *J. Am. Chem. Soc.*, **83**, 3428 (1961).

(3) (a) J. D. Roberts, E. R. Trumbull, Jr., W. Bennett, and R. Armstrong, *ibid.*, **72**, 3116 (1950); (b) E. R. Lippincott, *ibid.*, **73**, 2001 (1951); (c) A. Winston and P. Wilder, Jr., *ibid.*, **76**, 3045 (1954).

(4) S. J. Cristol and R. L. Snell, *ibid.*, **80**, 1950 (1958).

The n.m.r. data are entirely consistent with the assignment of structure methyl 6,7-diazaquadricyclo[3.2.1.1^{3,8}.0^{2,4}]nonane 6,7-dicarboxylate (IIa) to the 110° product. The fact that no resonance signals occur below $\tau = 5.57$ rules out the presence of any vinyl protons.[5] The six protons observed at $\tau = 6.26$ are at the proper position for the two methoxyl groups.[5c] The additional bands at $\tau = 8.49$, 8.21, 7.97, and 5.57 may correspond to protons at ring positions 3 and 9, 2 and 4, 8, and 1 and 5, respectively, based on the relative peak areas and the chemical shifts.[6] Another possible assignment is $\tau = 8.49$ (2, 3, and 4) and $\tau = 8.2$ (9).

The n.m.r. spectrum of the 60° isomer shows more complexity. Two vinyl protons are observed at $\tau = 3.72$, the proper chemical shift for the bicyclo[2.2.1]heptyl system.[5] These appear as two bands which are essentially identical unsymmetrical quartets with underlying fine multiplet structure. It is interesting to note that each quartet represents a proton and that these two protons are non-equivalent. This latter point was shown clearly by determination of the spectrum at field strengths of 40 and 60 Mc., the separation of the two four-line patterns being *ca.* 14 and 20 c.p.s., respectively. The separation of the lines within each quartet remains constant at *ca.* 3 c.p.s. with change of field strength. The doublet at $\tau \sim 5.65$ corresponds to one proton ($J \sim 7$ c.p.s.). At $\tau \sim 6.4$ there appears to be another proton multiplet (probably a doublet with $J \sim 7$ c.p.s.) partially hidden by the six methoxyl protons at $\tau = 6.26$. The broad unresolved peak at $\tau = 6.89$ and the single peak at $\tau = 8.29$ each correspond to two protons. Especially pertinent to the assignment of structure is the occurrence of two non-equivalent vinyl protons. This fact apparently rules out structures like III and IV since in such structures the two vinyl protons see identical proton environments and consequently they would have the same chemical shift. Presumably either the conformation V or the structure VI would furnish the molecular asymmetry necessary for non-equivalent vinyl protons.

Treatment of I with ethyl azodicarboxylate also gave two materials separable by column chromatography. The first fraction, b.p. 128–131° (0.4 mm.), and the second fraction, b.p. 126–127° (0.1 mm.), were in the ratio of *ca.* 1.6:1, respectively. On the basis of the order of elution and on chemical tests for unsaturation, the structures of the first and second fractions correspond to the structures of the 60° and 110° products, respectively.

(5) Signals for vinyl protons in the norbornene system occur in the range of *ca.* 3.3 to 4.4τ. (a) H. E. Simmons, *J. Am. Chem. Soc.*, **83**, 1657 (1961); (b) K. B. Wiberg and B. J. Nist, *ibid.*, **83**, 1227 (1961); (c) "NMR Summary," G. V. D. Tiers, Minnesota Mining and Manufacturing Co., St. Paul, Minn., private communication.

(6) E. F. Ullman,[2f] reports a very similar n.m.r. spectrum for the adduct formed from I and maleic anhydride.

Experimental[7]

Dimethyl and diethyl azodicarboxylate were obtained by the procedure of Rabjohn.[8] These were purified by repeated washing with cold 3% aqueous sodium carbonate as directed by Wright and co-workers.[9]

Reaction of Norbornadiene (I) with Methyl Azodicarboxylate.—A solution of 43 g. (0.29 mole) of methyl azodicarboxylate, 54 g. (0.59 mole) of freshly distilled I (Shell Chemical Co.), and 0.1 g. of *p-t*-butylcatechol was heated in a sealed, thick-walled Pyrex glass tube for 24 hr. at 150–160°. The cooled reaction mixture was flash-distilled under reduced pressure to give a recovery of 24 g. (0.26 mole) of (I) (*ca.* 90% of theoretical excess). The remaining very viscous residue was dissolved in ether, washed with cold 5% sodium hydroxide solution, and finally dried with anhydrous magnesium sulfate. Removal of the solvent followed by simple vacuum distillation of the concentrate yielded 21 g. (30%) of a viscous liquid, b.p. 120–135° (*ca.* 0.1 mm.). Elution chromatography of the distillate on Merck aluminum oxide (reagent grade, no. 71707) resulted in a clean separation into two different fractions. The first fraction, which was eluted with petroleum ether (b.p. 35–60°)–benzene solvent mixtures amounted to 12.5 g. Recrystallization of this residue from petroleum ether, b.p. 35–60°, afforded pure product, m.p. 59.0–60.5°. The second fraction was readily eluted with ether and amounted to 6.9 g. Pure product was obtained by recrystallization of the latter concentrate from petroleum ether, b.p. 60–70°, m.p. 109.5–110.0°.

Anal. Calcd. for $C_{11}H_{14}O_4N_2$: C, 55.45; H, 5.92; N, 11.76; mol. wt., 238. Found for the 60° fraction: C, 55.35; H, 5.74; N, 11.72; mol. wt., 232. Found for the 110° fraction: C, 55.24; H, 5.99; mol. wt., 228.

The 60° product in acetone solution instantly decolorized 2% aqueous potassium permanganate. A solution of the product in ethyl acetate decolorized a solution of bromine in carbon tetrachloride quite rapidly. When 346 mg. of the product in 40 ml. of absolute ethanol was subjected to hydrogenation over 33 mg. of 10% palladium-on-charcoal catalyst at one atmosphere pressure, one mole of hydrogen per mole of compound was absorbed in *ca.* 10 min. No more hydrogen was adsorbed during another 7 hr. Catalyst and solvent removal gave saturated product, m.p. 70–72°.

Anal. Calcd. for $C_{11}H_{16}O_4N_2$: C, 54.99; H, 6.71; N, 11.66. Found: C, 54.75; H, 6.81; N, 11.62.

The 110° product in acetone solution did not appreciably decolorize 2% aqueous potassium permanganate. Treatment of an ethyl acetate solution of this material with bromine in carbon tetrachloride showed little decolorization, even after standing for a long period of time. When the product was subjected to the hydrogenation conditions described in the preceding paragraph, only unchanged starting material was recovered; mixed m.p. 109.5–110.0°; identical infrared spectrum.

Reaction of Norbornadiene (I) with Ethyl Azodicarboxylate.—This reaction was carried out exactly as described for the reaction with methyl azodicarboxylate, except that the

(7) Elemental analyses and molecular weight measurements (Rast procedure) were performed by Galbraith Microanalytical Laboratories, Knoxville, Tennessee. All melting points were taken on a Fisher-Johns melting point apparatus and are corrected. Boiling points are uncorrected. Infrared spectra were determined on a Beckman IR-5 double-beam spectrophotometer equipped with sodium chloride optics. Spectra were obtained in potassium bromide disks except that the 3-μ region data were taken in tetrachloroethylene solution. The proton n.m.r. spectra were obtained using a Varian high-resolution n.m.r. spectrometer and electromagnet at a frequency of 60 Mc. Relative proton intensities were obtained by means of a voltage integrator.

(8) N. Rabjohn in E. C. Horning, Organic Syntheses, Coll. Vol. III, John Wiley & Sons, Inc., New York, N. Y., 1955, p. 375.

(9) J. C. J. MacKenzie, A. Rodgman, and G. F. Wright, *J. Org. Chem.* **17**, 1666 (1952).

temperature was 165–169°. Vacuum distillation of the reaction residue resulted in collection of a 31% yield of a viscous liquid, b.p. 122–140° (*ca.* 0.2 mm.). Elution chromatography on Merck aluminum oxide gave a separation into two fractions. The first fraction was eluted with benzene and benzene–ether mixtures and the second fraction was eluted with methanol. The ratio of first to second fraction was *ca.* 1.6:1. Both fractions were further purified by vacuum distillation: first fraction, b.p. 128–131° (0.4 mm.), $n^{25}D$ 1.5036; second fraction, b.p. 126–127° (0.1 mm.), $n^{25}D$ 1.4966. Neither product could be made to crystallize. The analytical results show both products to be somewhat impure. However, it is clear that they are 1:1 adducts.

Anal. Calcd. for $C_{13}H_{18}O_4N_2$: C, 58.63; H, 6.81; N, 10.52; mol. wt., 266. Found for the first fraction: C, 59.27; H, 7.35; N, 10.38; mol. wt., 271. Found for the second fraction: C, 58.96; H, 7.34; N, 10.40; mol. wt. 270.

A solution of the first fraction product in carbon tetrachloride rapidly decolorized a solution of bromine in carbon tetrachloride. The second fraction product decolorized bromine much more slowly.

Acknowledgment.—E. L. A. is indebted to the National Science Foundation for a post-doctoral fellowship under which this research was initiated. D. L. W. was a recipient of a National Science Foundation grant for teacher training through research participation. The n.m.r. spectra were kindly determined by Mr. Bernard J. Nist of the University of Washington.

Studies in Thiazinoquinazolines

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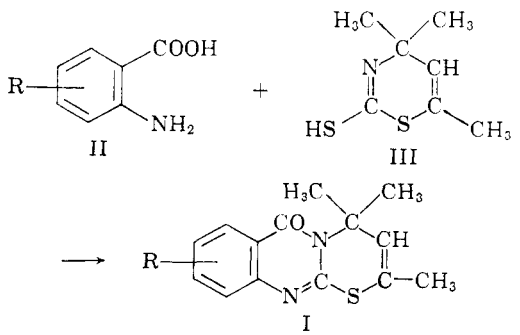
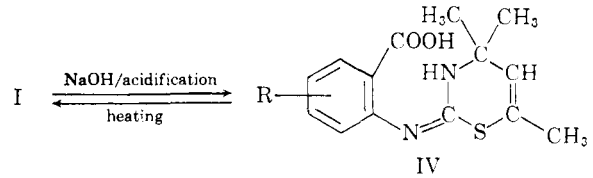
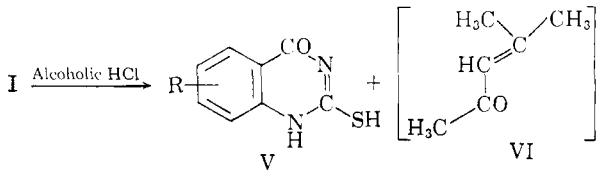
Thiazinoquinazolines (I), a new heterocyclic system which incorporates the physiologically active rings as thiazine and quinazoline present in febrifugine and methylene blue, respectively, have been prepared by a very simple method, which involves a condensation between 2-mercapto-4,4,6-trimethyl 4H-1,3-thiazine (III)[1] and the requisite anthranilic acids (II). This new ring system is quite stable towards cold alkali and remains unaffected for a number of days in 5% sodium hydroxide. The quinazoline ring opens to furnish IV on prolonged heating with 5% sodium hydroxide at 60–70°. The acid (IV) is transformed back to I on either heating in the dry state or refluxing in alcohol.



II III I

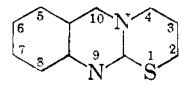


IV



V VI

These thiazino-quinazolines are also insoluble in aqueous hydrochloric acid and undergo a degradation to V and VI on refluxing in alcoholic hydrochloric acid.



VII

The parent ring system (VII) can be named 1,3-thiazino[2,3-b]quinazoline and thus I will be 2,4,4-trimethyl-4H,10H-1,3-thiazino[2,3-b]quinazoline-10-one.

Antibacterial Results.—On preliminary testing the compounds no. 1, 2, 3, 4, 5 (Table I) have proved bacteriosidal to the strains of proteus vulgaris at a dilution of 1:5000.

Experimental

1. **1,3-Thiazino[2,3-b]quinazolines (Table I).**—An equimolar mixture of 2-mercapto-4,4,6-trimethyl-4H-1,3-thiazine and the requisite anthranilic acid was heated in an oil bath at 120–125° for 4 hr.; the completion of the reaction is indicated when hydrogen sulfide no longer evolves. The slurry was cooled, neutralized with sodium carbonate, filtered, and the residue thoroughly washed with water. In all cases it could be crystallized from dilute ethanol or acetic acid.

2. **Treatment of I with Alkali and Isolation of IV.**—Thiazinoquinazoline (I) (R = H) was taken in 5% sodium hydroxide and heated at 60–70° for 5 hr. The solution was acidified with acetic acid and the resulting precipitate purified by dissolving in sodium hydroxide and reprecipitation and finally crystallization from dilute ethanol. The product melted at 290°.

Anal. Calcd. for $C_{14}H_{16}N_2O_2S$: C, 64.61; H, 6.1; N, 10.77. Found: C, 64.23; H, 5.9; N, 10.90.

3. **Treatment of I with Alcoholic Hydrochloric Acid; Isolation of 2-Thio-4-keto-tetrahydroquinazoline (V).**—I (R = H) was dissolved in ethanol and saturated with dry hydrochloric acid. The solution then refluxed over a steam bath for 8 hr. The solvent was removed by dis-

(1) J. E. Jansen and R. A. Mathes, *J. Am. Chem. Soc.*, **77**, 5431 (1955)

TABLE I

1:3-THIAZINO[2:3-b]QUINAZOLINES

S. no.	Anthranilic acid used	Compound formed	Yield, %	M.p., °C.	Molecular formula		Calcd., %	Found,[a] %
1	Anthranilic acid	2,4,4-Trimethyl-4H,10H-1,3-thiazino[2,3-b]quinazoline 10-one	77	247–248	$C_{14}H_{14}N_2OS$	C	65.19	65.52
						H	5.51	5.60
						N	10.85	10.42
						S	12.40	12.15
2	3-Methylanthranilic acid	2,4,4,8-Tetramethyl-4H,10H-1,3-thiazino[2,3-b]quinazoline-10-one	56	227	$C_{15}H_{16}N_2OS$	N	10.30	10.30
3	4-Methylanthranilic acid	2,4,4,7-Tetramethyl-4H,10H-1,3-thiazino[2,3-b]quinazoline-10-one	44	188	$C_{15}H_{16}N_2OS$	N	10.29	10.53
						S	11.76	12.10
4	5-Methylanthranilic acid	2,4,4,6-Tetramethyl-4H,10H-1,3-thiazino[2,3-b]quinazoline-10-one	58	267	$C_{15}H_{16}N_2OS$	N	10.29	10.43
5	4-Chloroanthranilic acid	7-Chloro-2,4,4-trimethyl-4H,10H-1,3-thiazino[2,3-b]quinazoline-10-one	50	243	$C_{14}H_{13}Cl_2N_2OS$	N	9.57	9.30

[a] N tested by Dumas method.

tillation and the residue crystallized from glacial acetic acid. It melted at 285° and was confirmed to be 2-thio-4-keto-tetrahydroquinazoline by comparison with an authentic sample.[2]

Acknowledgment.—The authors are thankful to Dr. K. S. Narang, reader, Panjab University, Chemistry Department, for his valuable guidance and the Director, Central Drug Research Institute, for testing the compounds.

(2) H. Rupe, *Ber.*, **30**, 1097 (1897).

1,2,4-Substituted 5(4H)-Imidazolones[1]

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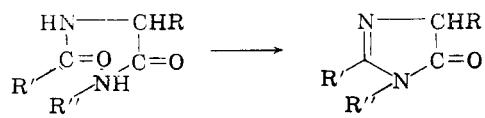
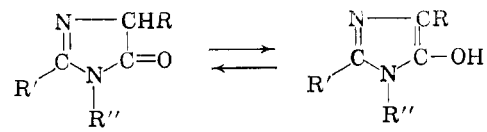
The possible presence of five-membered heterocycles, oxazolones, oxazolines, and imidazolones in proteins has been suggested as being important to the biological activity of proteins. Oxazolones are internal anhydrides of acyl amino acids, oxazolines are lactones involving serine, and 5(4H)-imidazolones are internal condensation products of tripeptides (or acyl amino acid amides).



I

The resemblance of these latter compounds to imidazole, which is thought to be somehow involved in the activity of hydrolytic enzymes, is of some theoretical interest. 5(4H)-Imidazolones are tautomeric with 5-hydroxyimidazoles and under favorable circumstances the enolic form may be stable. This appears to be the case for corresponding oxazolones when R′ = *p*-nitrophenyl.



The enolate anion may be an active nucleophile. It was of interest to prepare imidazolones of the general structure I, of which no members had previously been reported.

Until recently all methods for the preparation of imidazolones applied mostly to those which are not substituted in the position one (R″ = H).[2] Another type of imidazolonscribe deed in the literature contains a side chain linked to carbon four *via* a double bond. These "unsaturated" imidazolones correspond to the "unsaturated" oxazolones which are more stable than the "saturated" derivatives. These compounds do not form enols and are not derivatives of natural amino acids.

Karrer and Granacher[3] prepared "unsaturated imidazolones" and an imidazolone derived from hippurylamide by direct dehydration, but the method did not work with hippuryl ethylamide.

In 1956 a method was devised for the easy preparation of N-substituted 5(4H)-imidazolones. Brunken and Bach[4] condensed ortho esters with substituted glycine amides. The amides were prepared from glycine ethyl ester hydrochloride and the appropriate amine. When applied in the present instance to N-substituted amides of alanine,

(1) This work was supported by the Division of Research Grants and Fellowships of the National Institutes of Health, U.S. Public Health Service, Grants No. B-573 C13 and B-3304.

(2) E. S. Schipper and A. R. Day, "Heterocyclic Compounds," Vol. 5, R. C. Elderfield, ed., J. Wiley & Sons, Inc., New York, N. Y. 1960, p. 248.

(3) P. Karrer and C. Granacher, *Helv. Chim. Acta*, **7**, 763 (1924); C. Granacher and M. Mahler, *ibid.*, **10**, 246 (1927).

(4) J. Brunken and G. Bach, *Ber.*, **89**, 1363 (1956).

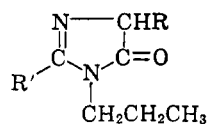
TABLE I

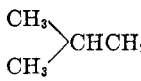
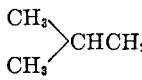
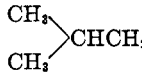
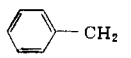
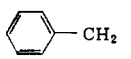
AMINO ACIDS ALKYLAMIDES

Compound	Yield, %	M.p., °C. or b.p., °C.	Mol. formula	—Carbon, %— Calcd.	Found	—Hydrogen, %— Calcd.	Found	—Nitrogen, %— Calcd.	Found
d,l-Alanine *n*-propylamide	74	75/0.03 mm.	$C_6H_{14}N_2O$						
d,l-Alanine *n*-propylamide picrolonate	..	198–199	$C_{15}H_{22}N_6O_6$	48.72	48.82	5.62	5.87	21.31	20.80
l-Leucine *n*-propylamide	81	91/0.1 mm.	$C_9H_2N_2O$						
l-Leucine *n*-propylamide picrolonate	..	238	$C_{19}H_{28}N_6O_6$	52.28	52.37	6.47	6.76	19.26	19.01
d,l-Phenylalanine *n*-propylamide	64	129/0.05 mm.	$C_{12}H_{18}N_2O$	69.86	69.83	8.79	9.41	13.58	13.36
d,l-Phenylalanine *n*-propylamide picrolonate	..	212	$C_{22}H_{26}N_6O_6$	56.16	56.48	5.57	5.77	17.86	17.66

TABLE II

IMIDAZOLONES



R′	R	Yield, %	M.p., °C. or b.p., °C.	Mol. formula	—Carbon, %— Calcd.	Found	—Hydrogen, %— Calcd.	Found	—Nitrogen, %— Calcd.	Found
CH_3CH_2	CH_3[a]	54	76–77/0.2 mm.	$C_9H_{16}N_2O$						
CH_3CH_2	CH_3 Picrolonate	..	181	$C_{19}H_{24}N_6O_6$	52.77	53.01	5.59	5.69	19.44	19.36
CH_3		70	88/0.2 mm.	$C_{11}H_{20}N_2O$	67.30	66.90	10.27	10.25	14.27	13.59
CH_3										
	Picrolonate	..	191	$C_{21}H_{28}N_6O_6$	54.77	54.34	6.13	6.64	18.25	18.03
CH_3										
	5-Enol acetate	68	99/0.1 mm.	$C_{13}H_{22}N_2O_2$	65.51	65.76	9.31	9.58	11.76	12.07
CH_3		55	118/0.3 mm.	$C_{14}H_{18}N_2O$						
CH_3		..	189	$C_{24}H_{26}N_6O_6$	58.29	57.92	5.30	5.68	17.00	16.62
	Picrolonate									

[a] R′ = CH_3. R = CH_3 gave a product, the analytical data of which fell slightly outside analytical limits.

leucine and phenylalanine the reactions proceeded smoothly and gave good yields of imidazolones.

Experimental

Ethyl orthoacetate and propionate are commercially available.

Preparation of Amino Acids Alkylamides.—Amino acid ethyl ester hydrochloride, 0.1 mole, was dissolved in 0.5 mole of the alkylamine (*n*-propylamine in our case), and left at room temperature for 4–6 days. Excess of amine was partly recovered through distillation. The residual mass was dissolved in a minimum amount of methanol and a theoretical amount of a methanolic solution of sodium methoxide added. The reaction mass was concentrated to a thick sirup and the alkylamides extracted into acetone to eliminate sodium chloride. After evaporation of the solvent, the residual oil was distilled in vacuum. Amino acid alkylamides are thick, colorless or slightly colored oils having an amine smell. The results are given in Table I. The compounds were identified through their picrolonates.

Preparation of 5(4H)-Imidazolones.—The general procedure was that used by Brunken and Bach. Amino acid *n*-propylamide, 20 mmoles was mixed with 23 mmoles of an ortho ester and after addition of 1 drop of acetic acid, the solution was gently heated until the reaction started. Temperature was maintained at 110–120° for 1–1.5 hr. The reaction mixture was then fractionally distilled under vacuum. Imidazolones are colorless or slightly yellow oils, very soluble in organic solvents and also soluble in water except for the derivative of phenylalanine.

Preparation of 1-*n*-Propyl-2-methyl-4-isobutyl-5-acetoxyimidazole.—(Enol acetate of imidazolone). Imidazolone, 25 mmoles, was heated on a steam bath with 15 ml. of acetic anhydride for 1.5 hr. Excess acetic anhydride was distilled under water pump vacuum and the residue fractionated, giving a thick almost colorless oil.

The results are given in Table II. The compounds were identified through their picrolonates.

The Infrared Spectrum of Nicotinic Acid

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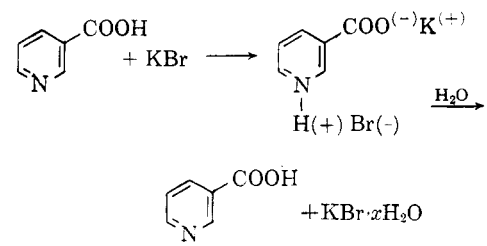
During the course of a synthetic program aimed at making vinyl nicotinate,[1] we routinely measured the infrared spectrum of nicotinic acid in potassium bromide. The spectrum showed abnormal bands at 1640 cm.$^{-1}$ (shoulder at 1620 cm.$^{-1}$) and 1380 cm.$^{-1}$, as well as a normal carbonyl band at 1710 cm.$^{-1}$. A second spectrum on the same disk after several minutes showed no abnormal bands and a more intense carbonyl absorption (see Fig. 1). The initial spectrum also showed an intense band at 3400 cm.$^{-1}$ which decreased in intensity as the disk was allowed to stand. An obvious explanation is that the new bands are due to carboxylate ion C—O asymmetrical and symmetrical stretching and possibly N—H stretching. As the disk picks up moisture from the air, the nicotinic acid reverts completely from a zwitterion to the nonionic form. Preparation of a disk without simultaneous evacuation led to a normal spectrum. Several possible variables were immediately considered and studied in an effort to explain the effect.

The hypothesis that a combination of pressure and vacuum causes zwitterion formation (which is reversed when the sample becomes wet) was first considered. Recent publications on the ultraviolet spectrum of nicotinic acid indicate that in aqueous solution nicotinic acid is a zwitterion but in ethanol is in the undissociated form.[2-4] This would seem to be opposite to our observation since moisture causes a shift to the undissociated form. We have confirmed the ultraviolet study of Stephenson and Sponer with solution infrared measurements of nicotinic acid both in deuterium oxide[5,6] and in ethanol. In the former solvent, no acid carbonyl absorption is shown but bands at 1640 cm.$^{-1}$, 1620 cm.$^{-1}$, and 1380 cm.$^{-1}$ appear. In ethanol a normal carbonyl absorption is shown at 1710 cm.$^{-1}$.

The possibility of a cation exchange between nicotinic acid and potassium bromide was considered since such exchanges with inorganic compounds have been reported.[7] Accordingly solid samples of potassium nicotinate were prepared and measured. The carboxylate ion bands occurred at much lower frequencies, ruling out the possibility of an ordinary cation exchange.

To test the importance of vacuum alone as a variable, thoroughly dried samples of nicotinic acid were measured as mulls in both Nujol and Perfluorolube. No abnormal bands were observed.

After more than forty tests, the important variables were established. The time spent in grinding the sample with potassium bromide under anhydrous conditions was found to be the determining factor, conditioned of course by the initial state of dryness of both the nicotinic acid and the potassium bromide. When preparing the disk after grinding, the importance of evacuation of the system was observed. It was also noted that the spectrum must be run immediately to avoid absorption of moisture from the air. Freshly prepared anhydrous disks placed in dessicators were shown to be stable in terms of abnormal band content but not if allowed to remain in the air. This means then that a reaction occurs which is reversed when the sample becomes wet, since samples purposely wet do not show the new bands (nicotinic acid is only very slightly soluble in water). Such a reaction scheme might be:



Disks, originally showing abnormal bands, show a normal spectrum on exposure to moisture. The abnormal bands cannot be regenerated by drying the discs at 150° over phosphorus pentoxide for forty-eight hours or by repressing. The abnormal bands can be regenerated if a regrinding operation is performed also.

The infrared spectra of various alkali metal carboxylates have been measured and are reported to show shifts in the two carboxylate ion C—O absorptions with a change in cation.[8] Accordingly, dilute deuterium oxide solution measurements of nicotinic acid were made with equivalent amounts of potassium bromide, sodium bromide, and lithium bromide present. The spectra were identical. When, however, the pellet technique was used with both sodium and lithium bromide respectively, the abnormal bands appeared but shifts of 5–10 cm.$^{-1}$ from the potassium bromide values were noted. This points to the formation of a metastable phase of nicotinic acid with the inorganic salt, whose spectrum is shifted with change in cation.

(1) H. C. Haas, N. W. Schuler, and L. D. Taylor, *J. Appl. Poly. Sci.*, **6**, S4 (1962).
(2) H. H. Jaffe, *J. Am. Chem. Soc.*, **77**, 4445 (1955).
(3) R. W. Green and H. K. Tong, *ibid.*, **78**, 4896 (1956).
(4) H. P. Stephenson and H. Sponer, *ibid.*, **79**, 2050 (1957).
(5) R. C. Gore, R. B. Barnes, and E. Petersen, *Anal. Chem.*, **21**, 382 (1949).
(6) E. R. Blout, *Ann. N. Y. Acad. Sci.*, **69**, 84 (1957).
(7) V. W. Meloche and G. E. Kalbus, *J. Inorg. Nucl. Chem.*, **6**, 104 (1958).
(8) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley & Sons, New York, N. Y., 1958, p. 174.

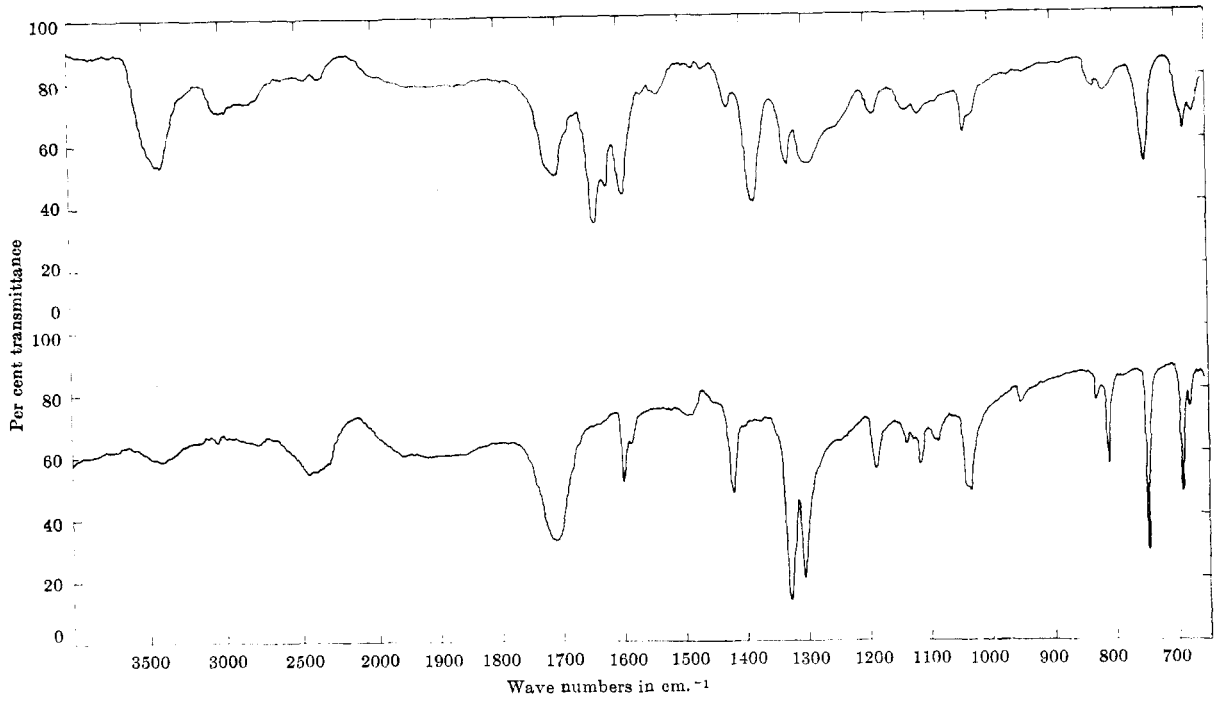


Fig. 1.—The infrared spectrum of nicotinic acid in potassium bromide: upper curve, freshly prepared disk; lower curve, same disc after standing in the air for 12 hr.

To confirm the high values for the carboxylate ion C—O stretching frequencies observed, samples of 1-methylbetaine of nicotinic acid and 1-methylbetaine of isonicotinic acid were measured.[9] These also presented high frequency values. A saturated solution of the latter compound in acetonitrile absorbs at 1630 cm.$^{-1}$.[10] The high frequencies observed are apparently the result of the positive change on the nitrogen atom.

Several experiments were performed with the isomeric picolinic and isonicotinic acids. The effect is again observable and carboxylate ion bands appear and disappear as a function of grinding time and degree of dryness of the system.

Although the potassium bromide technique is extremely valuable for measurements of solid substances, one must be cautious in interpreting a spectrum, as has been pointed out many times by other workers.[7]

Experimental

Materials.—The pyridine carboxylic acids were purest grade Eastman Kodak products and were used after several recrystallizations. The potassium bromide used was obtained from Harshaw Chemical Company. The sodium and lithium bromides were Fisher Chemicals. Both the acids and halides were heated at 100° under full vacuum for several days. They were stored in a desiccator prior to use.

Spectrophotometric Equipment.—Measurements were made with either a Perkin-Elmer infrared spectrophotometer, Model 21, or Perkin-Elmer Infracord, Model 137. The grinding apparatus used was a commercial "Wig-l-bug" manufactured by Crescent Dental Manufacturing Company. The die used for pressing disks was the Perkin-Elmer Model which is equipped for evacuation of the sample.

Measurement of Spectra.—Samples of nicotinic acid were ground with potassium bromide and pressed. Because of the sensitivity of the pellet to moisture, the spectrophotometer was preset to the region of 1750 cm.$^{-1}$, and as soon as the pellet was released from the press and vacuum, this critical region was immediately run. A typical set of conditions would be: grinding time, 1 min.; pressure, 23,000 lb., gage; evacuation, 10 min. by mechanical pump; time under pressure, 6 min.; conc., 0.3 mg. acid per 125 mg. potassium bromide. Changing these variables independently showed the following: (1) pressure, no apparent effect; (2) vacuum, very important but only a necessary condition and not the cause of the bands; (3) length of time under pressure and/or vacuum, no striking effects; (4) dryness of reagents, extemely important; and (5) grinding time, the determining variable.

The reaction of a solid with a solid would be expected to be dependent on the degree of grinding. Large differences were noted among samples ground for 0.5, 1.0, 1.5, and 2 min. It was found that the more grinding performed, the more intense the carboxylate bands. However, this trend is readily reversed if moisture gets into the grinding capsule.

Acknowledgment.—The author wishes to thank Marianne Taylor, Elizabeth Thomas, Walter Legsdin, and especially Judy Shannon, a Thayer Academy National Science Foundation summer science student, for performing the many measurements required for this study.

(9) E. M. Kosower and J. W. Patton, *J. Org. Chem.*, **26**, 1318 (1961).

(10) E. M. Kosower, University of Wisconsin, private communication. 1961.

The Lead Tetraacetate Oxidation of 1- and 2-Benzenesulfonamido- and Benzamidonaphthalenes[1]

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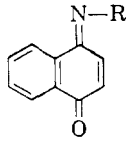
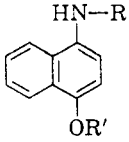
A study of the lead tetraacetate oxidation of 5-benzenesulfonamidoacenaphthene now in progress, produced a number of unknown products.[2]

The oxidation under similar conditions, of selected amides of 1- and 2-naphthylamine where many reference compounds are known,[3] was studied since the results may provide information helpful in elucidating the structures of the products obtained from the amide of 5-aminoacenaphthene. This study has led to a simple method for preparing some 1,4-naphthoquinonemonoimides and 2-substituted 1,4-naphthoquinones.

1-Benzenesulfonamidonaphthalene was oxidized by lead tetraacetate to produce 1-benzenesulfonimido-1,4-naphthoquinone (I). This substance exhibited physical properties similar to the compound previously prepared by Adams and co-workers[4] by the oxidation of 4-benzenesulfonamido-1-naphthol (II). Catalytic reduction of I gave the substituted naphthol II.



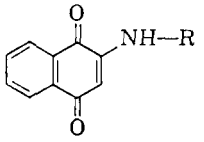
I. R = $SO_2C_6H_5$
III. R = $SO_2C_6H_4$-4-$NHCOCH_3$



II. R = $SO_2C_6H_5$; R′ = H
IV. R = $SO_2C_6H_4$-4-$NHCOCH_3$, R′ = H
V. R = COC_6H_5, R′ = $COCH_3$
VI. R = COC_6H_5; R′ = H

The oxidation of 1-benzamidonaphthalene was found to give somewhat different results. Treatment of this compound with lead tetraacetate gave a white fibrous substance, m.p. 194–195°, for which the infrared spectrum and elemental analysis required the introduction of one acetoxyl group into the original benzamide giving a benzamidonaphthol acetate. Since oxidation had been shown to occur at the 4-position in the sulfonamide I, the oxidation product was compared with a sample of 4-benzamido-1-naphthol acetate (V) prepared from 4-amino-1-naphthol. The samples were identical in all respects. Acid hydrolysis of V gave 4-benzamido-1-napthol (VI), which has been characterized by Witt and Dedichen.[5]

A similar oxidation of 2-benzenesulfonamidonaphthalene failed to give a quinonemonoimide. Yellow needles, m.p. 254–256°, were obtained which showed an absorption at 3220 cm.$^{-1}$ indicating that the N—H group was still intact.[6a] Chemical analysis required the introduction of two atoms of oxygen and chromic acid oxidation of the yellow product gave phthalic acid as shown by a positive fluorescein test.[7a] These facts are accommodated by oxidation at the 1- and 4-positions to give 2-benzenesulfonamido-1,4-naphthoquinone (VII).



VII. R = $SO_2C_6H_5$
VIII. R = H
IX. R = COC_6H_5
X. R = $SO_2C_6H_4$-4-$NHCOCH_3$

Further evidence for structure VII was obtained by acid hydrolysis which formed 2-amino-1,4-naphthoquinone (VIII), previously prepared by F. Kehrmann *via* a five-step synthesis starting from 1-naphthol.[8]

The oxidation of 2-benzamidonaphthalene proceeded in an analogous manner to give IX, which was hydrolyzed to VIII.

The oxidation of 1-(4-acetamidobenzenesulfonamido)naphthalene by lead tetraacetate gave 1-(4-acetamidobenzenesulfonimido)-1,4-naphthoquinone (III), which was reduced to 4-(4-acetamidobenzenesulfonamido)-1-naphthol (IV) identical with the product prepared from 4-amino-1-naphthol and 4-acetamidobenzenesulfonyl chloride. An attempt to obtain the substituted sulfanilamides, 1-(4-aminobenzenesulfonimido)-1,4-naphthoquinone and 2-(4-aminobenzenesulfonamido)-1,4-naphthoquinone through acid hydrolysis of III and X resulted in destruction of the quinoid system and failed to yield an identifiable product.

Experimental[9]

1-Benzenesulfonimido-1,4-naphthoquinone (I).—A suspension of 14.2 g. (0.05 mole) of 1-benzenesulfonamidonaphthalene in 100 ml. of glacial acetic acid was stirred while 46.5 g. of lead tetraacetate was added in small portions over a period of 45 min. The temperature of the mixture was kept under 35° by occasional cooling. After 90 min. 3 ml. of ethylene glycol was added, and stirring was continued for 10 min. The mixture was cooled to 15° in an ice bath. The yellow-green product (6.3 g., 42%)

(1) This work was supported by Research Grant CY-2997 from the National Cancer Institute, National Institute of Health, U. S. Public Health Service.

(2) This is to be the subject of a subsequent paper.

(3) For a review of quinonemonoimides see R. Adams and W. Reifschneider, *Bull. soc. chim. France*, 23 (1958).

(4) R. Adams and R. Wankel, *J. Am. Chem. Soc.*, **73**, 131 (1951); R. Adams and L. Whitaker, *ibid.*, **78**, 658 (1956).

(5) O. N. Witt and J. Dedichen, *Ber.*, **29**, 2954 (1896).

(6) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed., John Wiley & Sons, Inc., New York, N. Y., 1958, (a) p. 205, (b) p. 179, (c) p. 136, (d) p. 150.

(7) L. F. Fieser, "Experiments in Organic Chemistry," 3rd ed., D. C. Heath and Co., Boston, Mass., (a) p. 224, (b) p. 238.

(8) F. Kehrmann, *Ber.*, **27**, 3337 (1894).

(9) All melting points are uncorrected.

was collected, washed first with 10 ml. of cold glacial acetic acid and then thoroughly with water. Crystallization from ethanol gave orange plates, m.p. 154–156° (lit.,[4] 152–154°).

4-Benzenesulfonamido-1-naphthol (II).—Two grams (0.0067 mole) of 1-benzenesulfonimido-1,4-naphthoquinone (I) suspended in 100 ml. of absolute ethanol was reduced catalytically with 0.10 g. of 10% palladium on charcoal and hydrogen at 37 p.s.i. Evaporation of the solvent gave 2.0 g. (99%) of crude tan product. Crystallization from glacial acetic acid gave white crystals, m.p. 201–203° (lit.,[4] 193–194°). A mixed melting point determination with an authentic sample showed no depression and the infrared spectra of the two samples were identical.

4-Benzamido-1-naphthol Acetate (V).—A stirred suspension of 6.17 g. (0.025 mole) of 1-benzamidonaphthalene in 100 ml. of dry ether was treated with 23.25 g. of lead tetraacetate. The mixture was stirred at ambient temperature for 4 hr. giving a dark brown solution in which a white solid was suspended. After adding 2 ml. of ethylene glycol, the white solid was collected, dissolved in 50 ml. of chloroform, and the solution washed with several portions of water. Evaporation of the chloroform gave 5.2 g. (68%) of crude product. Crystallization from benzene gave a mass of interlocking white fibrous solid, m.p. 194–194.5°; ν_{max} 3240 cm.$^{-1}$ (N—H^{6a}), 1750 cm.$^{-1}$ (acetate C=O^{6b}), 1640 cm.$^{-1}$ (amide C=O^{6a}).

Anal. Calcd. for $C_{19}H_{15}NO_3$: C, 74.74; H, 4.95; N, 4.59. Found: C, 74.38; H, 5.07; N, 4.41.

A mixture of 4-benzamido-1-naphthol (VI) (0.35 g., 0.0013 mole), 1g. of sodium acetate, and 3 ml. of acetic anhydride was heated to the boiling point and then cooled. Trituration of the resulting mixture with water left 0.28 g. (69%) of white crude product. A mixed melting point determination with the substance prepared from 1-benzamidonaphthalene showed no depression and the infrared spectra were identical.

One-half gram of the acetate V was heated on the steam bath for 24 hr. with 10 ml. of concentrated hydrochloric acid. On cooling 0.35 g. (81.3%) of crude 4-benzamido-1-naphthol (VI) was obtained. Crystallization from ethanol gave white needles, m.p. 229–231° (lit.,[5] 228–229°) which were identical with the product obtained on treating 4-amino-1-naphthol with benzoyl chloride in the presence of pyridine.

2-Benzenesulfonamido-1,4-naphthoquinone (VII).—2-Benzenesulfonamidonaphthalene (14.15 g., 0.05 mole) was suspended in 45 ml. of glacial acetic acid, and 70.0 g. of lead tetraacetate was added in *ca.* 3-g. portions over a period of 15 min. with continuous stirring. The temperature of the mixture was kept below 30° by occassional cooling in an ice–water bath. The mixture was stirred for 75 min. during which time the product precipitated. One milliliter of ethylene glycol was added and stirring was continued for 5 min. The mixture was cooled at 15° for 45 min., and the crude yellow product (11.4 g., 73%) was collected, washed with cold glacial acetic acid followed by water. Crystallization from acetone with decolorizing carbon gave yellow needles, m.p. 254–256°; ν_{max} 3220 cm.$^{-1}$ (N—H^{6a}), 1670 cm.$^{-1}$ and 1650 cm.$^{-1}$ (quinone C=O^{6d}).

Anal. Calcd. for $C_{16}H_{11}NO_4S$: C, 61.33; H, 3.54; N, 4.47. Found: C, 61.33; H, 3.46; N, 4.48.

Acid hydrolysis of VII according to the procedure described by Fieser[7b] for the acetamido analog gave 2-amino-1,4-naphthoquinone (VIII) in 94.5% yield. A sample crystallized from ethanol, m.p. 206–208° (lit.,[7b] 206°), showed no depression of melting point when mixed with an authentic sample.

2-Benzamido-1,4-naphthoquinone (IX).—To a suspension of 6.17 g. (0.025 mole) of 2-benzamidonaphthalene in 50 ml. of glacial acetic acid was added 35 g. of lead tetraacetate while the mixture was stirred at ambient temperature. After 2 hr. 5 ml. of ethylene glycol was added to the orange solution and stirring was continued for 5 min. The mixture was poured into cold water giving a viscous red tar which subsequently turned green on standing in water. The tar was dissolved in hot ethanol, treated with decolorizing carbon, and on cooling gave 2.72 g. (39%) of yellow-green plates, m.p. 137–138°.

Anal. Calcd. for $C_{17}H_{11}NO_3$: C, 73.64; H, 4.00; N, 5.05. Found: C, 73.71; H, 4.15; N, 5.01.

Acid hydrolysis by the procedure referred to for VII gave 2-amino-1,4-naphthoquinone (VIII) in 97.5% yield.

1-(4-Acetamidobenzenesulfonimido)-1,4-naphthoquinone (III).—To a stirred suspension of 3.49 g. (0.01 mole) of 1-(4-acetamidobenzenesulfonamido)naphthalene[10] in 25 ml. of glacial acetic acid was added 8.95 g. of lead tetraacetate. After 70 min. the excess lead tetraacetate was decomposed with 0.5 ml. of ethylene glycol. The mixture was cooled thoroughly and the crude yellow product (1.61 g., 45%) was collected, washed once with cold glacial acetic acid, and then with water. Crystallization from dry chloroform gave yellow needles, m.p. 207–208°; ν_{max} 3300 cm.$^{-1}$ (N—H^{6a}), 1660 cm.$^{-1}$ (doubly conjugated C=O^{6c}), 1525 cm.$^{-1}$ (doubly conjugated C=N^{11}). Attempts to crystallize the crude product from ethanol, acetone, benzene, or acetic acid led to decomposition.

Anal. Calcd. for $C_{18}H_{14}N_2O_4S$: C, 61.00; H, 3.98; N, 7.90. Found: C, 61.15; H, 4.03; N, 7.89.

An attempt to obtain 1-(4-aminobenzenesulfonimido)-1,4-naphthoquinone by hydrolysis of the acetamido group using 10% hydrochloric acid under reflux resulted in the formation of a red-brown solid, m.p. 150–157°, which could not be crystallized and was not characterized. The infrared spectrum indicated that the quinoid structure had been destroyed.

4-(4-Acetamidobenzenesulfonamido)-1-naphthol (IV).—One-half gram (0.0014 mole) of 1-(4-acetamidobenzenesulfonamido)-1,4-naphthoquinone (III) and 0.4 g. of zinc dust were suspended in 20 ml. of glacial acetic acid. The mixture was heated to 80° and stirred until the orange coloration of the quinonemonoimide was discharged (*ca.* 1 hr.). The white product which separated during the reaction was dissolved by adding additional acetic acid (75 ml. total), and the excess zinc dust was filtered from the mixture. On cooling 0.47 g. (96%) of the white crystalline product was obtained. Recrystallization from ethanol plus several drops of acetic acid gave white plates, m.p. 235–236°.

Anal. Calcd. for $C_{18}H_{16}N_2O_4S$: C, 60.66; H, 4.53; N, 7.86. Found: C, 60.46; H, 4.62; N, 7.85.

The product was identical with that obtained in 74% yield on treating 4-amino-1-naphthol with 4-acetamidobenzenesulfonyl chloride in the presence of pyridine. A mixed melting point determination showed no depression and the infrared spectra were superimposable.

2-(4-Acetamidobenzenesulfonamido)-1,4-naphthoquinone (X).—2-(4-Acetamidobenzenesulfonamido)naphthalene[10] (3.4 g., 0.01 mole) was suspended with stirring in 35 ml. of glacial acetic acid, and 13.5 g. of lead tetraacetate was added. After 20 min. the yellow-orange product started separating, and after 30 min., 1 ml. of ethylene glycol was added and stirring continued for an additional 5 min. The crude product (2.6 g., 70%) was collected and washed thoroughly with water. Attempts to crystallize this material from ethanol, acetone, acetic acid, or chloroform led to decomposition. Crystallization was achieved by suspending the crude product in boiling benzene and adding dimethylformamide dropwise until all solid had dissolved. Upon cooling, the pure substance was obtained as yellow microcrystals, m.p. 256–257°; ν_{max} 3300 cm.$^{-1}$ (N—H^{6a}), 1670 cm.$^{-1}$ and 1640 cm.$^{-1}$ (quinone C=O^{6d}), 1530 cm.$^{-1}$ (amide C=O^{6a}).

Anal. Calcd. for $C_{18}H_{14}N_2O_5S$: C, 58.37; H, 3.81; N, 7.56. Found: C, 58.32; H, 3.69; N, 7.42.

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(10) P. Gelmo, *J. pract. Chem.*, [2] **77**, 380, 381 (1908).

(11) R. Adams and E. L. De Young, *J. Am. Chem. Soc.*, **79**, 705 (1957).

Attempts to obtain 2-(4-aminobenzenesulfonamido)-1,4-naphthoquinone by hydrolysis of X using (a) refluxing concentrated hydrochloric acid, or (b) refluxing 50% sulfuric acid, gave unchanged starting material as the only isolable material.

When the product X was subjected to acid hydrolysis as described for the quinones VII and IX, 2-amino-1,4-naphthoquinone (VIII) was obtained in 90% yield.

The Formation of 1,5,7,11-Tetrathiaspiro[5.5]-undecane in the Reaction of Cyclic Trimethylene Trithiocarbonate with 2,2′-Iminodiethanol[1]

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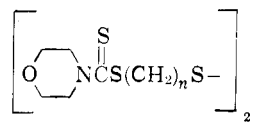
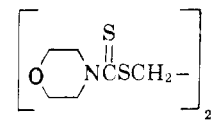
Received April 30, 1962

Ammonium dithiocarbamate and certain of its derivatives, including some with *S*-substitution, have been reported[2,3] to be effective in protecting mice from radiation-induced injury; Foye and Mickles[4] recently reported that a number of dithiocarbamates afforded significant protection to mice exposed to sub-lethal radiation dosage. Therefore, the products of the nucleophilic attack by secondary amines on cyclic ethylene trithiocarbonate—2-mercaptoethyl dithiocarbamates[5] and the corresponding disulfides[6]—should be evaluated as antiradiation agents. The corresponding propyl dithiocarbamates, which should be obtainable from cyclic trimethylene trithiocarbonate, are also of potential interest.

Attempting to use the literature procedures[6] described in general terms, we were unable to obtain the reported high yields (about 95%) of the dithiodiethylene *N,N*-disubstituted dithiocarbamates from the reaction of ethylene trithiocarbonate with dimethylamine and morpholine. The only pure product that we isolated from the reaction of equivalent amounts of ethylene trithiocarbonate and morpholine was not the expected dithiodiethylene 4-morpholinecarbodithioate (I) but ethylene 4-morpholinecarbodithioate (II). Ethylene esters such as II were previously identified as by-products of this general reaction and were obtained in increased yields by modifications of the original procedure; for example, by the addition of base.[7] The anomalous formation of these ethylene esters has been rationalized[7] as involving the base-catalyzed elimination of ethylene sulfide from 2-mercaptoethyl dithiocarbamates.[8] Durden, *et al.*,[9] apparently unaware that the products originally described as thiols[6] were later identified as disulfides,[5] recently demonstrated that the product they isolated in 40% yield from the reaction of ethylene trithiocarbonate with morpholine was the disulfide I. These observed variations in products and yields are apparently due in part to differences in isolation procedure. To make the disulfides in high yield we resorted to the alkylation of sodium dithiocarbamates with bis(2-chloroethyl) disulfide, an alternative procedure mentioned by Delaby, *et al.*[5]

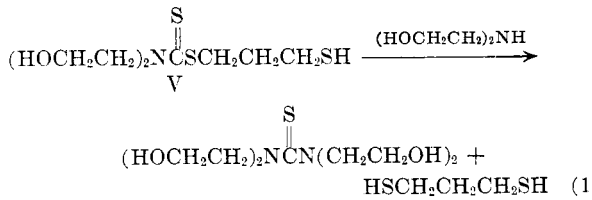


I. $n=2$
IV. $n=3$



II

Cyclic trimethylene trithiocarbonate (III) was opened with morpholine without difficulty to give 3-mercaptopropyl 4-morpholinecarbodithioate (92% pure by iodometric titration), which was subsequently oxidized by iodine to dithiodi(trimethylene) 4-morpholinecarbodithioate (IV). An attempt to prepare 3-mercaptopropyl bis(2-hydroxyethyl)dithiocarbamate (V) from III and 2,2′-iminodiethanol, however, led to the isolation in appreciable yield of a white crystalline compound, which has been identified as 1,5,7,11-tetrathiaspiro[5.5]undecane (VI) on the basis of elemental analysis, molecular weight, and the n.m.r. spectrum shown in Fig. 1. This spectrum, in conjunction with that of the starting material III, confirms the proposed structure as it shows two band systems in the region expected from methylene proton absorption (between 1.5 and 3.5 p.p.m.) whose areas are in a 2:1 ratio. The complex multiplet structure of each band system indicates strong spin coupling among adjacent methylene groups. The following sequence of reactions is proposed to explain the formation of VI:



(1)

(1) This investigation was supported by the U.S. Army Medical Research and Development Command (Contract No. DA-49-193-MD-2028).

(2) P. Alexander, Z. M. Bacq, S. F. Cousens, M. Fox, A. Herve, and J. Lazar, *Radiation Res.*, **2**, 392 (1955).

(3) A. Phil and L. Eldjarn, *Pharmacol. Rev.*, **10**, 437 (1958).

(4) W. O. Foye and J. Mickles, Abstracts of the 141st National Meeting of the American Chemical Society, Washington, D.C., March, 1962, p. 30-N.

(5) R. Delaby, C. Warolin, P. Chabrier, and P. Piganiol, *Compt. rend.*, **232**, 1676(1951).

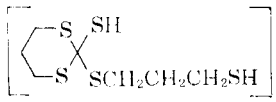
(6) R. Delaby, P. Piganiol, and C. Warolin, *ibid.*, **230**, 1671 (1950).

(7) C. Warolin and R. Delaby, *ibid.*, **240**, 204 (1955).

(8) *Cf.* the mercaptoethylation of amines by the use of 2-mercaptoethyl carbamates [D. D. Reynolds, D. L. Fields, and D. L. Johnson, *J. Org. Chem.*, **26**, 5116 (1961)].

(9) J. A. Durden, Jr., H. A. Stansbury, Jr., and W. H. Catlette, *J. Am. Chem. Soc.*, **82**, 3082 (1960).

$$HSCH_2CH_2CH_2SH + III \longrightarrow$$



$$\longrightarrow VI + H_2S \qquad (2)$$

The proposed formation of a thiourea in equation 1 finds support in the recently described preparation of 1,3-dibutyl-2-thiourea from ethylene trithiocarbonate and butylamine.[9] Although alkyl[10] and aryl[11] tetrathioorthocarbonates are known, VI is apparently the first example of a simple bicyclic tetrathioorthocarbonate, the tetracyclic 2,2′-spirobi(1,3-benzodithiole) has recently been described[12] as the probable product of a thermal decomposition of 1,2,3-benzothiadiazole in the presence of carbon disulfide.

Experimental

Dithiodiethylene Dimethyldithiocarbamate.—A solution of 670 mg. (4.40 mmoles) of sodium dimethyldithiocarbamate hemihydrate[13] in 4 ml. of ethyl alcohol was added to a solution of 380 mg. (2.10 mmoles) of bis(2-chloroethyl) disulfide[14] in 1 ml. of ethyl alcohol. The resulting mixture was stirred for 8 hr. and then allowed to stand for 2 days. The lower oily layer that had separated solidified when the sides of the flask were scratched with a glass rod. The mixture was poured into 75 ml. of water, and the solid that had formed was collected, washed with water and with ethyl alcohol, and dried *in vacuo* over phosphorus pentoxide; yield 662 mg. (92%), m.p. 86–87°[15] (lit.,[6] m.p. 86°).

Dithiodiethylene 4-Morpholinecarbodithioate (I).—A solution of 510 mg. (2.75 mmoles) of sodium 4-morpholinecarbodithioate[16] in 4 ml. of *N*,*N*-dimethylformamide was added to a solution of 240 mg. (1.25 mmoles) of bis(2-chloroethyl) disulfide[14] in 1 ml. of *N*,*N*-dimethylformamide; a solid precipitated within 1 min. The resulting mixture was stirred for 16 hr. at room temperature and then poured into 50 ml. of water. The gum initially formed slowly solidified on stirring to a white amorphous mass, which was collected, washed with water, and dried *in vacuo* over phosphorus pentoxide; yield 550 mg. (99%), m.p. 104–105°,[15] 105°.[17] Recrystallization of a 250-mg. sample from acetone gave 179 mg. of I as a white solid, m.p. 109°[17] (lit.,[6] m.p. 102°).

Anal. Calcd. for $C_{14}H_{24}N_2O_2S_6$: C, 37.81; H, 5.44. Found: C, 37.88; H, 5.44.

Ethylene 4-Morpholinecarbodithioate (II).—A solution of 3.00 g. (22.0 mmoles) of ethylene trithiocarbonate[18] in 1.92 g. (22.0 mmoles) of morpholine was stirred at 40° for 7 hr., the reaction mixture gradually solidifying. The crude solid thus formed was recrystallized from 1.1 l. of acetone with charcoal treatment to give 1.25 g. (32%) of white crystals, m.p. 230°,[17] after being dried *in vacuo* over phosphorus pentoxide. Recrystallization of a sample from 2-methoxyethanol afforded analytically pure II, m.p. 231°.[17,19]

Anal. Calcd. for $C_{12}H_{20}N_2O_2S_4$: C, 40.88; H, 5.72; S, 36.38. Found: C, 40.91; H, 5.86; S, 36.76.

In another experiment the same amounts of reactants were stirred at room temperature for 5 days under nitrogen. The resulting solid reaction mass was dissolved in 15 ml. of boiling 2-methoxyethanol. When cooled, the solution deposited 780 mg. (20%) of II as a white fluffy solid, m.p. 230°.[17]

3-Mercaptopropyl 4-Morpholinecarbodithioate and Dithiodi(trimethylene) 4-Morpholinecarbodithioate (IV).—A solution of 10.5 g. (70 mmoles) of trimethylene trithiocarbonate[20] and 6.1 g. (70 mmoles) of morpholine in 500 ml. of ethyl alcohol was refluxed under nitrogen for 5 hr. The solvent was removed by evaporation *in vacuo*, and the residual clear yellow viscous oil gave a 92% iodometric titer as 3-mercaptopropyl 4-morpholinecarbodithioate; yield 15.2 g. (85%, cor.).

A 7.70-g. sample of the crude thiol was dissolved in ethyl ether and titrated with 1 *N* iodine–potassium iodide solution to an iodine color end point. The yellow solid that precipitated was collected, washed with ether and then ethyl alcohol,

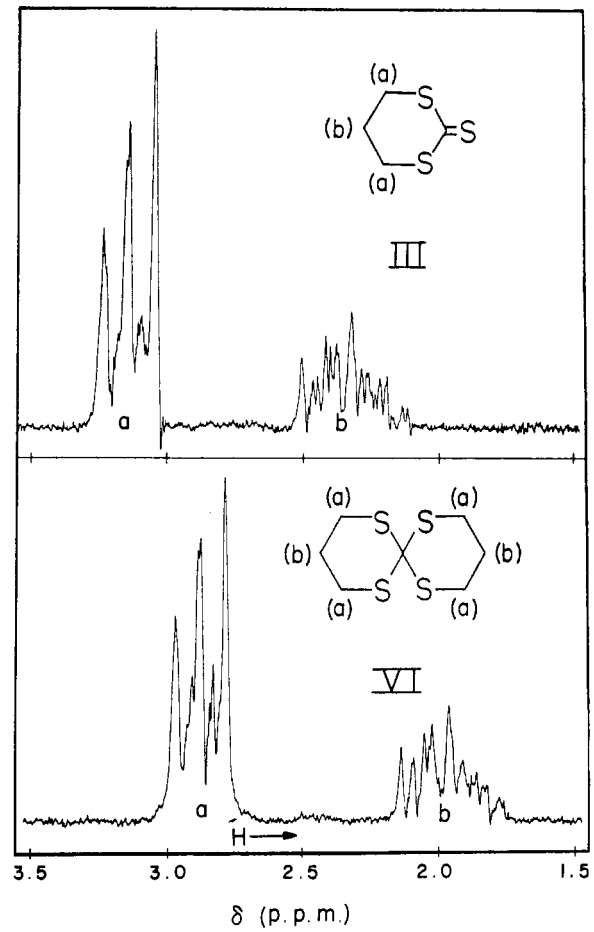


Fig. 1.—N.m.r. spectra of III and VI in carbon disulfide solution [*ca.* 20% (w./v.)] with δ in p.p.m. downfield from tetramethylsilane as internal reference; 60 Mc./sec.; R. F. field 0.06 milligauss.

(10) H. J. Backer and P. L. Stedehouder, *Rec. trav. chim.*, **52**, 923 (1933).

(11) H. J. Backer and P. L. Stedehouder, *ibid.*, **52**, 1039 (1933).

(12) R. Huisgen and V. Weberndörfer, *Experientia*, **17**, 566 (1961).

(13) M. Delépine, *Bull. soc. chim. France*, [4] **3**, 650 (1908).

(14) R. C. Fuson, C. C. Price, D. M. Burness, R. E. Foster, W. R. Hatchard, and R. D. Lipscomb, *J. Org. Chem.*, **11**, 487 (1946).

(15) Determined in a capillary and is uncorrected.

(16) This compound was prepared from morpholine, carbon disulfide, and aqueous sodium hydroxide in the conventional manner; the reaction mixture was evaporated to dryness *in vacuo* and the residue recrystallized from a concentrated aqueous solution and dried to constant weight *in vacuo* over phosphorus pentoxide at room temperature.

(17) Determined on a Kofler Heizbank.

(18) Cyclic ethylene trithiocarbonate was prepared from 1,2-dibromoethane by an adaptation of the method of W. Coltof [U.S. Patent 2,193,415 (March 12, 1940)]. Some of the ethylene ester used was purchased from L. Light and Co., Ltd., Colnbrook, Bucks, England.

(19) Warolin and Delaby[7] obtained II, m.p. 229°, by refluxing a benzene solution of 2-mercaptoethyl 1-piperidinecarbodithioate and morpholine.

(20) W. H. Mills and B. C. Saunders, *J. Chem. Soc.*, 537 (1931).

and dried *in vacuo*, and recrystallized from 900 ml. of ethyl alcohol; yield of IV as a pale yellow solid 6.84 g. (76%), m.p. 94–95°.[15]

Anal. Calcd. for $C_{16}H_{28}N_2O_2S_6$: C, 40.64; H, 5.97; S, 40.69. Found: C, 40.40; H, 5.88; S, 40.96.

1,5,7,11-Tetrathiaspiro[5.5]undecane (VI).—A solution of 2.1 g. (20 mmoles) of freshly distilled 2,2′-iminodiethanol in 50 ml. of ethyl alcohol was added to a solution of 3.0 g. (20 mmoles) of trimethylene trithiocarbonate[20] in 150 ml. of the same solvent. The resulting solution was evaporated under reduced pressure at 55–60° to a yellow oil, which was kept at this temperature for 3 hr. *in vacuo*. The white crystals that formed were collected, washed with cold propyl alcohol, and dried *in vacuo* over phosphorus pentoxide; yield 0.73 g. (33%),[21] m.p. 116°,[17] nitroprusside test for thiol negative (even after boiling briefly in dilute acid or base). Recrystallization from ethyl alcohol afforded a sample of VI for analysis as white crystals, m.p. 116–117°,[15] 117°;[17] ν_{max}^{KBr} (major bands) 2905 (s.), 1410 (s.), 1270 (s.), 1000 (m.), 905 (m.), 880 (s.), 770 (m.-s.), 740 (s.) cm.$^{-1}$. The n.m.r. spectrum (Fig. 1) was measured on a Varian A 60 n.m.r. spectrometer.

Anal. Calcd. for $C_7H_{12}S_4$: C, 37.46; H, 5.39; S, 57.15; mol. wt., 224. Found: C, 37.66; H, 5.39; S, 57.10; mol. wt., 230.

Acknowledgment.—The authors are indebted to Dr. W. C. Coburn, Jr., for determination and interpretation of the n.m.r. spectra; and to the Analytical Section of Southern Research Institute for the analyses reported.

(21) Additional crystals, not included in the yield figures, were deposited in the oily residue obtained by evaporation of the filtrate *in vacuo;* the residual oil gave a positive nitroprusside test. The crude oily thiols obtained from other runs also deposited crystals on long standing when seeded with VI.

The Structure of Ceanothic Acid[1]

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Received May 3, 1962

The medicinal plant *Ceanothus americanus*, fam. *Rhamnaceae* (Jersey Tea), has until quite recently escaped thorough chemical investigation although it has been known to contain numerous compounds of unknown structure.[2] During the last two years four groups have reported work on this plant.[1,3–5] Roscoe and Hall[3] have noted the presence of eight alkaloids in the root bark while others[1,4,5] have investigated the nonalkaloid fractions of the plant.

De Mayo[4] as well as this writer,[1] have been able to confirm the presence of ceanothic acid as first reported by Julian, Pikl, and Dowson[6] in 1938. Ceanothic acid was described by Julian as a hydroxy dicarboxylic acid in which both carboxyl groups were hindered. On melting it lost one equivalent of carbon dioxide and also one of water.

In this paper experiments are reported leading to structure Ia for ceanothic acid. For the sake of simplicity the entire discussion will be presented in terms of the eventually established structure.

An improved extraction procedure led to the easy separation of ceanothic acid, m.p. 356–358°, $[\alpha]_D$ +38°. Dimethyl ceanothate (Ib) showed an average molecular weight of 503 (Rast). Equivalent weight value of 248 was obtained for the free acid by titration using alkali; ceanothic acid is therefore dibasic. The infrared spectra of Ia and of Ib suggested the presence of a vinylidene group (1642 and 885 cm.$^{-1}$). On catalytic hydrogenation Ib absorbs one mole of hydrogen giving dimethyl dihydroceanothate (II) in which these two bands have disappeared. Repeated analyses of all compounds fitted a $C_{30}H_{46}O_5$ formula for ceanothic acid. Such an empirical formula requires a pentacyclic skeleton. On boiling with acid[7] followed by esterification of the remaining free carboxyl group Ia gave III which has a five-membered lactone (ν_{max} 1770 cm.$^{-1}$) but no vinylidene group. A reaction of this type is well known in the lupeol series.[7] In view of the empirical formula, the presence of the vinylidene group and the nature of the lactonization reaction (Ia → III) it seemed plausible that ceanothic acid is a triterpene of the lupeol group. The hydroxyl group, known to be present in the molecule, was assumed, on the basis of rather abundant analogies, to occupy the C-3 position. One of the carboxylic groups could be placed at C-17, in view of the lactonization reaction.

The simultaneous dehydration and decarboxylation occurring at the melting point of ceanothic acid[6] suggested that the second carboxyl group is located beta to the hydroxyl group. Indeed oxidation of the hydroxyl group to a ketone, gave a keto monocarboxylic acid (IVa), presumably obtained on decarboxylation of a labile β-keto acid intermediate. The infrared spectrum of this substance showed the presence of the vinylidene group (1640 and 882 cm.$^{-1}$) and of two bands in the carbonyl region at 1740 and 1720 cm.$^{-1}$. The 1740-cm.$^{-1}$ band suggested a five-membered ring ketone.

The triterpene emmolic acid was isolated in 1958 by Simes and coworkers[8] from *Emmenospermum alphitonioides* F. *Muell* (fam. Rhamnaceae)

(1) Preliminary communication: R. Mechoulam, *Chem. Ind.* (London), 1835 (1961).

(2) For leading references to work prior to 1960 see ref. 3 and 5.

(3) C. W. Roscoe and N. A. Hall, *J. Am. Pharm. Assoc., Sci. Ed.*, **49**, 108 (1960).

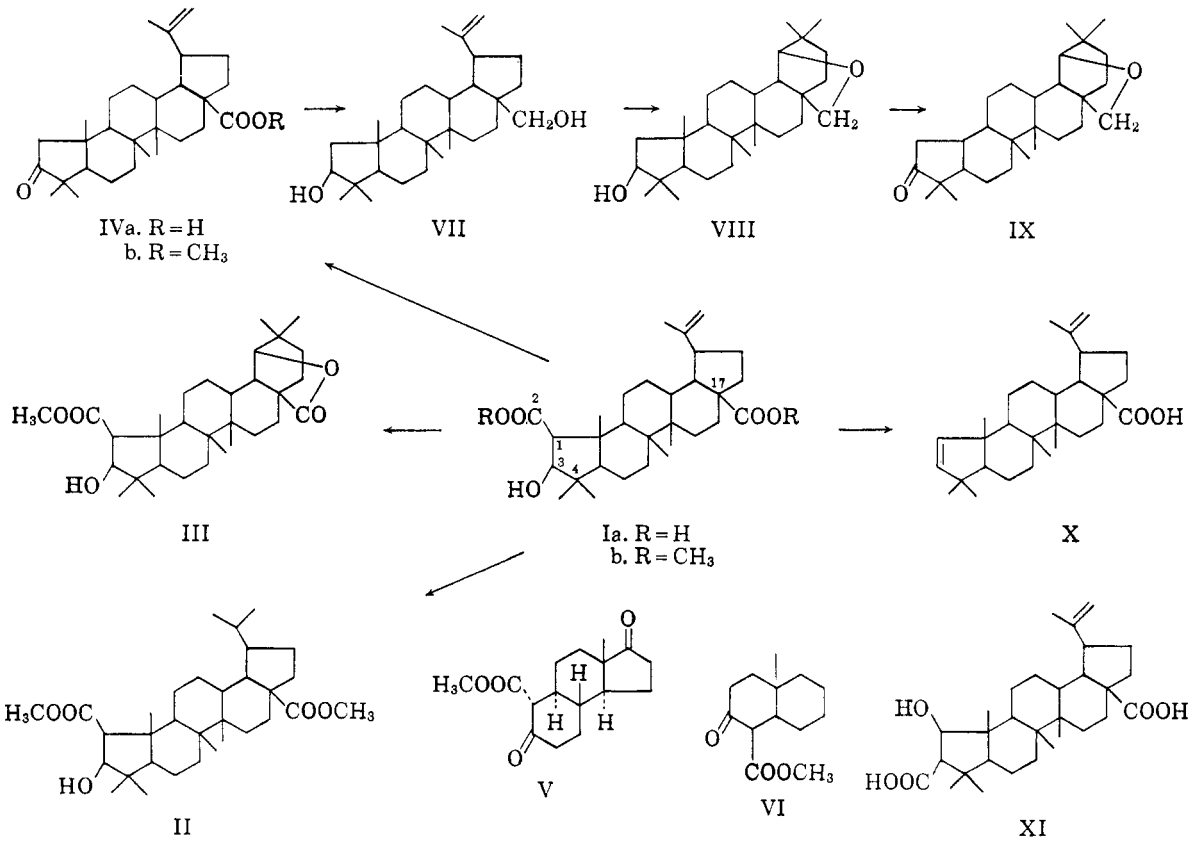
(4) P. de Mayo and A. N. Starratt, *Tetrahedron Letters*, **7**, 259 (1961).

(5) R. A. Abramovitch and G. Tertzakian, *Can. J. Chem.*, **39**, 1733 (1961).

(6) P. L. Julian, J. Pikl, and R. Dowson, *J. Am. Chem. Soc.*, **60**, 77 (1938).

(7) *Cf.* V. Bruckner, J. Kovács, and I. Koczka, *J. Chem. Soc.*, 951 (1948); G. S. Davy, T. G. Halsall, and E. R. H. Jones, *ibid.*, 2696 (1951).

(8) J. P. Boyer, R. A. Eade, H. Locksley, and J. J. H. Simes, *Austr. J. Chem.*, **11**, 236 (1958).



and in 1960 by Birch *et al.*[9] from *Alphitonia excelsa* of the same family. The similarity of the physical constants of this triterpene and of its derivatives with ceanothic acid as well as their botanical relationship intimated that they could be identical. A sample of dimethyl emmolate kindly supplied by Dr. J. J. H. Simes was identical with dimethyl ceanothate (mixed melting point and infrared spectra comparison).[10]

On the basis of experiments similar to those reported above, the Australian group[8] have reached the conclusion that emmolic acid contains two hindered carboxylic groups, one double bond in an isopropenyl group and a secondary hydroxyl group on a five-membered ring in a beta position to one of the carboxyl groups. They concluded that the latter is on a quaternary carbon atom as there was no evidence of enolisation in dimethyl ketoemmolate and dimethyl dihydroketoemmolate. They also suggested that emmolic acid is probably pentacyclic with a carbon skeleton different from that of any of the naturally occurring triterpenes.

The argument for the tertiary position of the carboxyl group to the hydroxyl group seems untenable. It has been shown[11] that compounds such as V and VI have also no enolic properties.

A most important point of the above conclusions was the placing of the hydroxyl group on a five-membered ring. This had been assumed on the basis of the infrared spectra of a number of keto derivatives (1750 cm.$^{-1}$ in Nujol). As in these derivatives the ketone is located beta to a carboxylic ester group; such a high frequency in the carbonyl region, which is usually due to a ketone on a five-membered ring, could be due in this case to a ketone beta to an *equatorial* carboxylic ester on a six-membered ring. Such ketones have been reported to absorb in the 1740-cm.$^{-1}$ region.[12]

To clarify this point, ceanothic acid was oxidized to IVa which was then reduced to the diol VII. Boiling with acid converted the diol into VIII. Such a rearrangement has been described in similar compounds in the lupeol series.[13] On oxidation of VIII compound IX was obtained. This monoketone has only one group absorbing in the carbonyl region—at 1740 cm.$^{-1}$, indicative of a ketone on a five-membered ring, proving thereby that the hydroxyl group is on such a ring.

On melting ceanothic acid loses one mole of carbon dioxide and one of water giving, not a lactone as previously assumed,[6] but a monocar-

(9) A. J. Birch, E. Ritchie, and R. N. Speake, *J. Chem. Soc.*, 3593 (1960).

(10) Prof. E. R. H. Jones and Dr. T. G. Halsall of Oxford University have also reached the same conclusion (personal communication).

(11) F. Sondheimer, R. Mechoulam, and M. Sprecher, *Tetrahedron Letters*, **22**, 38 (1960); G. Stork, P. Rosen, and N. Goldman, *J. Am. Chem. Soc.*, **83**, 2965 (1961); see also R. Hanna and G. Ourisson, *Bull. Soc. Chim. France*, 1945 (1961).

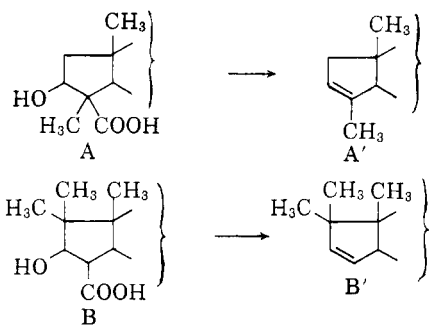
(12) P. A. Stadler, A. Nechvatal, A. J. Frey, and A. Eschenmoser, *Helv. Chim. Acta*, **40**, 1373 (1957); N. A. Nelson and R. N. Schut, *J. Am. Chem. Soc.*, **80**, 6630 (1958).

(13) *Cf.* W. Lawrie, J. McLean, and G. R. Taylor, *J. Chem. Soc.*, 4303 (1960).

boxylic acid (X) which has retained the isopropenyl group (ν_{max}, 1640 and 890 cm.$^{-1}$) and has also an additional *cis* double bond (758 cm.$^{-1}$). A comparison between the n.m.r. spectra of X and of dimethyl ceanothate (Ib) shows that each of them has only one vinylic methyl group (CH_3—C = CH_2) with τ values of the methyl protons of 8.32 and 8.38, respectively. This indicates that in ceanothic acid there is no methyl group alpha to the carboxyl group which is eliminated on melting. If such a methyl group were present, it would have appeared as a second methyl vinyl group after the decarboxylation (see A → A′). In addition to the vinyl protons of the isopropenyl group (5.26 τ and 5.40 τ), X has also two vinyl hydrogens, which appear as two doublets centered at 4.52 τ and 4.02 τ. The splitting to doublets only shows that each vinylic hydrogen is split by the adjacent vinylic hydrogen only and that there are probably no hydrogens on the carbon atoms next to the double bond (C-4 and C-10). These observations show that at least two of the carbon atoms of the cyclopentane ring A are tertiary, while the carboxyl and hydroxyl groups on this same ring are secondary.

If no further skeletal rearrangements have occurred, the preceding data indicate that ceanothic acid has structure Ia or the less probable structure XI.

Structures A and B have to be excluded since the pyrolysis product should then have structures A′ and B′ respectively which are incompatible with the n.m.r. data.



At this point of the investigation, the publication of de Mayo *et al.*[4] appeared These authors reached the same conclusions as presented in this paper concerning the structure of ceanothic acid and were able to ascertain them by comparing one of their degradation products with a known compound. In a later paper, published after the present manuscript was submitted for publication, de Mayo[14] established the full stereochemistry of ceanothic acid. Thus the C-1 carobxyl group is beta, as previously suggested by us,[1] while the C-3 hydroxyl group is alpha, showing that the stereochemical assignment for this asymmetric center previously proposed by us[1] was incorrect.

(14) P. de Mayo and A. N. Starratt, *Can. J. Chem.*, **40**, 788 (1962); see also R. A. Eade, G. Kornis, and J. J. H. Simes, *Chem. Ind.* (London), 1195 (1962)

Experimental

Melting points are uncorrected. Rotations were determined at 20–25° in chloroform solution. Infrared spectra were measured on a Perkin-Elmer model 137 Infracord recording infrared spectrometer. N.m.r. spectra were determined at 56.4 Mc. on a Varian V-4300-C spectrometer in deuteriochloroform solution with tetramethylsilane as internal standard.

Isolation of Ceanothic Acid.—The finely powdered, dried root bark (1 kg.) of *Ceanothus americanus* (purchased from Meer Corp., New York) was extracted twice with boiling petroleum ether (b.p. 60–80°). The defatted plant material was continuously extracted with boiling ether for 40 hr. The ether extract was concentrated to a volume of *ca.* 200 cc. and shaken with 100 cc. of 3% sodium hydroxide solution. The aqueous layer was twice extracted with ether, then acidified with ice cold 5% hydrochloric acid solution. The acidic aqueous layer was extracted several times with ether. The ethereal solution was evaporated to dryness and the residue was crystallized four times from methanol giving long fibrous needles of ceanothic acid, m.p. 353–355° (dec.). The total yield was 1.65 g. The analytical sample showed m.p. 356–358°, $[\alpha]_D$ +37° (in ethanol).

Anal. Calcd. for $C_{30}H_{46}O_5$: C, 74.03; H, 9.53. Found: C, 73.68; H, 9.66.

Dimethyl ceanothate (Ib), dimethyl dihydroceanothate (II), and dimethyl 3-oxoceanothate (XI) were obtained as described by Boyer, *et al.*,[8] for the identical derivatives of emmolic acid. All physical constants obtained correspond to those given by the Australian authors.

Lactone (III) from Ceanothic Acid.—Ceanothic acid (100 mg.) was dissolved in a solution of 10 cc. of acetic acid and 7 cc. of hydrochloric acid and heated under reflux for 2 hr. The reaction mixture was poured into water and extracted with ether. The organic layer was washed with water and evaporated to dryness. The residue was dissolved in 10 cc. of ethanol and water was added until a permanent cloudiness persisted. This mixture was heated on a water bath for 2 hr. After cooling, the solution was extracted with ether. The ether solution was concentrated and excess diazomethane in ether was added. The material obtained was boiled with 5% methanolic sodium hydroxide for 1 hr. After the usual work-up 43 mg. of lactone III were obtained. Crystallizations from petroleum ether–benzene (1:1) gave crystals, m.p. 255–257°, $[\alpha]_D$ +90°. J. J. H. Simes and coworkers[8] report m.p. 258–260°, $[\alpha]_D$ +91.

Oxidation of Ceanothic Acid. Methyl 3-Oxo-2-decarboxyceanothate (IVb).—Ceanothic acid (110 mg.) was dissolved in 10 cc. of acetone. Chromic acid (0.2 cc. of a 8 *N* solution in sulfuric acid) was added under nitrogen with stirring over a period of several minutes. Methanol was added to destroy excess reagent. Water and ether were added. The organic layer was washed with water, dried over magnesium sulfate, and the ether evaporated. The residue was dissolved in a 2% solution of potassium hydroxide in ethanol. After boiling under reflux for 2 hr., water and ether were added. The mixture was acidified with 10% hydrochloric acid. The organic layer was washed with water, dried over sodium sulphate, and evaporated to dryness. The solid material obtained (IVa) was not crystallized. On titration with 0.01 *N* sodium hydroxide solution, only one carboxyl group was shown to be present. The amorphous IVa was dissolved in ether and treated with an ethereal solution of diazomethane. The solution was left at room temperature for 12 hr., after which it was evaporated to dryness. The residue was crystallized from methanol, giving 41 mg., IVb, m.p. 118–121°. The analytical sample showed m.p. 123–125°, $[\alpha]_D$ +95°, ν_{max} 1740 cm.$^{-1}$ and 1725 cm.$^{-1}$.

Anal. Calcd. for $C_{30}H_{48}O_3$: C, 79.24; H, 10.20. Found: C, 79.60; H, 10.11.

Ether (IX) from Methyl 3-Oxo-2-decarboxyceanothate (IVb).—A solution of IVb (250 mg.), m.p. 123°, in dry ether was added to a slurry of lithium aluminum hydride (250 mg.) in ether (30 cc.). The reaction mixture was refluxed for 5 hr. A saturated solution of sodium sulfate was added dropwise until a clear ether solution was obtained. Evaporation to dryness yielded 206 mg. of an oil which was used without further purification. The oil (VII) showed ν_{max} 1640 and 886 cm.$^{-1}$ (terminal methylene group).

A solution of 150 mg. of oil VII in ethanol (45 cc.) and hydrochloric acid (7.5 cc.) was boiled under reflux for 5 hr. The solution was cooled with ice and sodium hydroxide (7 gr.) in water (25 cc.) was added. The organic material was extracted with ether. Evaporation of the ether gave 140 mg. of an amorphous compound (VIII), which was used directly for the next stage. Compound VIII showed no absorption bands for terminal methylene or ketone in the infrared spectrum.

Compound VIII (140 mg.) was dissolved in 20 cc. of acetone and oxidized with 0.4 cc. of a 8 *N* solution of chromic acid in sulfuric acid. After 2 min. methanol (5 cc.) was added and the mixture poured over ice. The organic material was extracted with ether. The ether solution was washed with water, dried over sodium sulfate, and evaporated to dryness. The oil obtained was chromatographed on 16 g. of F-20 (basic Alcoa) alumina. The material eluted with petroleum ether: benzene (2:1) was crystallized with methanol giving 57 mg. of compound IX, m.p. 220–224°. The analytical sample showed m.p. 224–226°, $[\alpha]_D$ +155°, ν_{max} 1740 cm.$^{-1}$ (ketone on a five-membered ring).

Anal. Calcd. for $C_{29}H_{46}O_2$: C, 81.63; H, 10.87. Found: C, 81.76; H, 10.70.

Pyrolysis of Ceanothic Acid.—Compound X was obtained on pyrolysis of ceanothic acid as described by Julian.[6] Complex X showed m.p. 230–232° (rep. 234°), ν_{max} 758 cm.$^{-1}$, 886 cm.$^{-1}$, and 1700 cm.$^{-1}$.

Acknowledgment.—The author is indebted to Professor F. Sondheimer for his interest and to Professor J. J. H. Simes of N.S.W. University of Technology, Sydney, Australia, for a sample of dimethyl emmolate.

Syntheses of 9-Keto- and 10-Hydroxy-*trans*-2-decenoic Acids and Related Compounds

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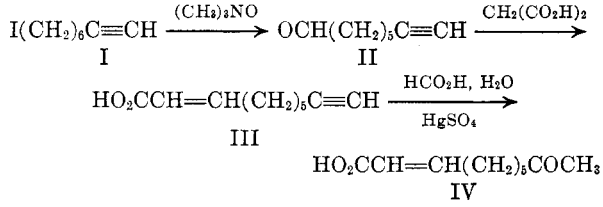
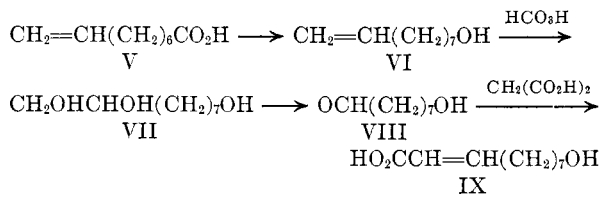
The syntheses of 9-keto- and 10-hydroxy-*trans*-2-decenoic acids noted for Queen Substance[1] and Royal Jelly acid,[2] respectively, of the honey bee have been described. A new synthesis of the keto acid as outlined below was found to be satisfactory:



The oxidation of 8-iodo-1-octyne (I) with trimethylamine oxide was effected as described for octanal by Franzen and Otto[3] with a yield of 69%, and the 7-octynal (II) obtained was condensed with malonic acid under Doebner's conditions[4] to afford 9-decyne-*trans*-2-enoic acid (III) in 65% yield. When the latter was hydrated by means of formic acid in the presence of mercuric sulfate,[5] 9-keto-*trans*-2-decenoic acid (IV) was obtained in almost quantitative yield. Observed physical constants including infrared spectra as well as analyses supported the constitution.

10-Hydroxy-*trans*-2-decenoic acid was prepared according to the following scheme:



Since the condensation of 8-hydroxyoctanal (VIII) with malonic acid has been reported by Fujii and his collaborators,[2c] the description will be confined to the preparation of VIII.

8-Nonenoic acid (V) was prepared by double Barbier-Wieland degradations of 10-undecenoic acid in 25% yield based on the ethyl ester. The preparation of V starting from tetrahydrofurfuryl alcohol[6] required several steps and proved impractical. An alternative method described by Stetter and Dierichs[7] was unsuitable because positive evidence for the migration of the terminal double bond was obtained.

Reduction of the ethyl ester of V with lithium aluminum hydride gave 8-nonenol (VI), which was successively dihydroxylated by means of performic acid[8] to give *dl*-1,2,9-trihydroxynonane (VII) in 80% yield.

Treatment of the triol with periodate[9] gave VIII.[10]

(1) (a) R. K. Callow and N. C. Johnston, *Bee World*, **41**, 152 (1960); (b) M. Barbier and M-F. Hugel, *Bull. Soc. Chim. France*, 951 (1961); M. Barbier, E. Lederer, and T. Nomura, *Compt. rend.*, **261**, 1133 (1960); (c) R. H. Jaeger and R. Robinson, *Tetrahedron*, **14**, 320 (1961); (d) J. Kennedy, N. J. McCorkindale, and R. A. Raphael, *J. Chem. Soc.*, 3813 (1961); (e) K. Eitar, *Angew. Chem.*, **73**, 618 (1961).

(2) (a) G. I. Fray, R. H. Jaeger, E. D. Morgan, R. Robinson, and A. D. B. Sloan, *Tetrahedron*, **15**, 18 (1961); G. I. Fray, R. H. Jaeger, and R. Robinson, *Tetrahedron Letters*, No. 4, 15 (1960); (b) S. A. Barker, A. B. Foster, D. C. Lamb, and L. M. Jackman, *Tetrahedron*, **18**, 177 (1962); (c) M. Fujii, N. Koga, Y. Osawa, and K. Chuma, *J. Chem. Soc. Japan*, Pure Chem. Sect., **81**, 1782 (1960).

(3) V. Franzen and S. Otto, *Chem. Ber.*, **94**, 1360 (1961).

(4) *Cf.* L. Crombie, *J. Chem. Soc.*, 2999 (1952).

(5) A. Mondon, *Ann.*, **585**, 43 (1954).

(6) P. Gaubert, R. P. Linstead, and H. N. Rydon, *J. Chem. Soc.*, 197 (1937).

(7) H. Stetter and W. Dierichs, *Chem. Ber.*, **85**, 1061 (1952).

(8) D. Swern, *Org. Reactions*, **VII**, 378 (1953).

(9) G. King, *J. Chem. Soc.*, 1827 (1938).

(10) C. D. Hurd and W. H. Saunders, Jr., *J. Am. Chem. Soc.*, **74**, 5324 (1952).

Preparations of other triols which gave VIII upon glycol fission have been explored as follows:

Ethyl 9-undecynoate[11,12] prepared by treating 10,11-dibromoundecanoic acid with concentrated alkali[13] followed by esterification was degradated by the Barbier-Wieland method to 8-decynoic acid, whose ethyl ester was converted to *cis*-8-decenol by hydrogenation over the Lindlar's catalyst[14] followed by reduction with lithium aluminum hydride. This unsaturated carbinol was dihydroxylated to afford *threo*-1,8,9-trihydroxydecane in 75% yield. This triol gave VIII when treated with periodate.

9-Decenoic acid[13,15] was isomerized by heating over 200° with potassium hydroxide in diethylene glycol to afford 8-decenoic acid, presumably in a form of an equilibrium mixture of *cis*- and *trans*-isomers.[16] Oxidation with chromic acid gave suberic acid in 70% yield. Ethyl 8-decenoate was converted similarly to 8-decenol and to the nonvolatile 1,8,9-triol.

The preparation of other homologous hydroxyaldehydes and of ω-hydroxy-α,β-unsaturated acids therefrom will be described below.

Trihydroxyoctadecane[17] prepared from commercial oleyl alcohol was cleaved by periodate to afford 9-hydroxynonanal.[18]

Aleuritic acid, 9,10,16-trihydroxyhexadecanoic acid, obtained from shellac resin[19] was subjected to the glycol fission and 7-hydroxyheptanol[20] was secured as a sole neutral product.

Performic acid oxidation of 10-undecenol[21] gave 1,2,11-trihydroxyundecane in 91.8% yield, and the successive glycol fission resulted in the formation of 10-hydroxydecanal.[10]

All these ω-hydroxyaldehydes were exceedingly unstable and polymerized to rubberlike or gelatinous materials on standing in the air. Crude hydroxyaldehydes, however, afforded ω-hydroxy-α,β-unsaturated acids in no less than 40% yields when used immediately after isolation in the subsequent condensation with malonic acid. Thus 9-hydroxy-*trans*-2-nonenoic acid, 11-hydroxy-*trans*-2-undecenoic acid and 12-hydroxy-*trans*-2-dodecenoic acid[22a] were obtained from 7-hydroxyheptanal, 9-hydroxynonanal, and 10-hydroxydecanal, respectively.

(11) W. W. Myddleton and A. W. Barrett, *J. Am. Chem. Soc.*, **49**, 2258 (1927).

(12) The nonterminal triple bond could be assigned on the basis of the infrared spectra. See R. G. Ackman, R. A. Dytham, B. J. Wakefield, and B. C. L. Weedon, *Tetrahedron*, **8**, 239 (1960); E. Stenhagen, *Arkiv Kemi*, **1**, 99 (1940); E. R. H. Jones, G. H. Whitman, and M. C. Whiting, *J. Chem. Soc.*, 3201 (1954). *Cf.* D. J. Cram and G. S. Hammond, "Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p. 408.

(13) H. Black and B. C. L. Weedon, *J. Chem. Soc.*, 1785 (1953).

(14) H. Lindlar, *Helv. Chim. Acta*, **35**, 446 (1952).

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(17) J. T. Scanlan and D. Swern, *J. Am. Chem. Soc.*, **62**, 2307 (1940).

(18) I. Ribas and E. Seoane, *Anales Real Soc. Espan. Fis. Quim.* (Madrid), **50B**, 971 (1954).

(19) H. Rautnitz and F. Petru, *Chem. Ber.*, **68**, 1675 (1935).

(20) S. Fujise and S. Sasaki, *J. Chem. Soc. Japan*, Pure Chem. Sect., **74**, 579 (1953).

(21) W. F. Huber, *J. Am. Chem. Soc.*, **73**, 2730 (1951).

Experimental[22]

8-Iodo-1-octyne (I).—A solution of 22 g. of 8-chloro-1-octyne[23] and 34 g. of sodium iodide in 300 ml. of acetone was heated under reflux for 24 hr. and precipitates were removed by filtration. Evaporation of the filtrate followed by distillation *in vacuo* afforded 18.6 g. (60%) of 8-iodo-1-octyne as a colorless liquid b.p. 115–117° (19 mm.), $n^{16}D$ 1.5078.

Anal. Calcd. for $C_8H_{13}I$: C, 40.69; H, 5.55. Found: C, 40.07; H, 5.68.

7-Octynal (II).—To a solution of 15 g. (0.2 mole) of trimethylamine oxide[3] in 200 ml. of chloroform was added 16.1 g. (0.068 mole) of I under ice-cooling over a period of 45 min. After refluxing for 1 hr. the reaction mixture was decomposed with 60 ml. of 2 *N* hydrochloric acid. The organic layer was separated, washed with water, and dried ($MgSO_4$). Evaporation of chloroform followed by distillation *in vacuo* gave 5.8 g. (69%) of II, b.p. 82–85° (16 mm.) $n^{14}D$ 1.4658, ν_{max} (liquid film) at 3300, 2760, 2160, 1758, cm.$^{-1}$. Since II was quite unstable, its 2,4-dinitrophenylhydrazone, m.p. 93.5–95.5° (from ethanol) was analyzed.

Anal. Calcd. for $C_{14}H_{16}O_4N_4$: C, 55.25; H, 5.30. Found: C, 55.58; H, 5.43.

9-Decyne-*trans*-2-enoic Acid (III).—To an ice-cooled solution of 4 g. (0.04 mole) of malonic acid in 16 ml. of pyridine was added 3.2 g. (0.025 mole) of II in a course of 10 min. After adding 1 ml. of piperidine to the solution the mixture was kept in the dark at 50° for 33 hr. and at room temperature for an additional 28 hr. The reaction mixture was poured into 60 ml. of water and the product was extracted with ether. The ethereal solution was washed with dilute hydrochloric acid and water and dried ($MgSO_4$). Recrystallizations of the evaporation residue from petroleum ether (b.p. 40–60°) gave 2.8 g. (65%) of III as colorless prisms, m.p. 47.5–48.5°, ν_{max} (Nujol) at 3260, 2099, 1691, 1635, 990 cm.$^{-1}$.

Anal. Calcd. for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 71.97; H, 8.45.

9-Keto-*trans*-2-decenoic Acid (IV).—To a solution of 0.2 g. of mercuric sulfate in 15 ml. of 80% formic acid was added 0.49 g. of III with stirring and the mixture was heated on a boiling water bath for 50 min. After cooling, the black precipitate was removed by filtration and the filtrate was dilute with 10 ml. of water and extracted with ether. The ethereal solution was washed with water and dried ($MgSO_4$). Evaporation of the solvent afforded a waxy material, m.p. 49.5–52.0°. Two recrystallizations from a mixture of petroleum ether (b.p. 40–60°) and ethyl ether afforded 0.5 g. (99%) of the keto acid, m.p. 54–55° (reported[10c] m.p. 54–55°) as colorless prisms, which gave correct analyses for carbon and hydrogen, ν_{max} (Nujol) at 1710, 1690, 1640, 993 cm.$^{-1}$ [reported[10c] λ_{max} (Nujol) at 5.83, 5.90, 6.07 μ].

8-Nonen-1-ol (VI) from 9-Decenoic Acid.—Esterification of 57 g. of 9-decenoic acid[13] in the conventional manner gave 65.6 g. (95%) of ethyl 9-decenoate, b.p. 135° (27.5 mm.), $n^{22}D$ 1.4366.

Anal. Calcd. for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 72.72; H, 11.14.

To a Grignard reagent prepared from 54.9 g. (0.35 mole) of bromobenzene and 9.3 g. of magnesium in 110 ml. of ether was added 30 g. (0.302 mole) of ethyl 9-decenoate. Dehydration of the resulting crude carbinol followed by distillation *in vacuo* gave 71.9 g. (81.7%) of 1,1-diphenyl-1,9-decadiene, b.p. 174° (5 mm.), $n^{22}D$ 1.5540.

(22) All temperatures are uncorrected. Microanalyses were performed by Miss Kenko Ogawa.

(23) R. A. Raphael and F. Sondheimer, *J. Chem. Soc.*, 2100 (1950).

Anal. Calcd. for $C_{22}H_{26}$: C, 90.98; H, 9.02. Found: C, 90.58; H, 9.29.

Oxidation of 50 g. of the aforementioned diene dissolved in 500 ml. of glacial acetic acid with 36.2 g. of chromic acid in 40 ml. of water gave 15.7 g. (58%) of 8-nonenoic acid (V), b.p. 113–114° (3 mm.), $n^{20}D$ 1.4492 [reported[5] b.p. 116–118° (1 mm.), $n^{15}D$ 1.4492; b.p. 145° (15 mm.)[24]]. The *p*-phenylphenacyl ester prepared by the usual manner[25] melted at 54.5–55.3° after single recrystallization from ethanol.

Anal. Calcd. for $C_{23}H_{26}O_3$: C, 78.82; H, 7.48. Found: C, 78.86; H, 7.40.

Reduction of 20.2 g. (0.11 mole) of ethyl 8-nonenoate, b.p. 117–118° (20 mm.), $n^{22}D$ 1.4352 [reported[6] b.p. 114–116° (15 mm.)], prepared from V with 2.6 g. of lithium aluminum hydride in 100 ml. of ether gave 15.2 g. (97%) of 8-nonen-1-ol (VI), b.p. 133–134° (20 mm.), $n^{22}D$ 1.4452 [reported[6] b.p. 135° (20 mm.), $n^{23}D$ 1.4450], ν_{max} (liquid film) at 990, 910 cm.$^{-1}$. The sample gave correct analyses.

***dl*-1,2,9-Trihydroxynonane (VII).**—To a solution of 14.2 g. (0.1 mole) of VI in 80 ml. of 99% formic acid was added 11.4 g. of 30% hydrogen peroxide under vigorous stirring at 40°. After 3 hr. at the same temperature, the solvent was removed under diminished pressure. To the residue 107 ml. of 2 *N* alcoholic potassium hydroxide was added and heated under reflux for 1 hr. Ethanol was removed under diminished pressure and the residue was poured into 100 ml. of hot water with vigorous agitation. The oily layer was separated, dissolved into 200 ml. of ethyl acetate, and dried ($MgSO_4$). Evaporation of the solvent furnished 15.0 g. (80%) of crude triol as a colorless liquid. This was refluxed with 66 g. of acetic anhydride in the presence of 7 g. sodium acetate for 2 hr. and triacetate thus obtained was purified by distillation. A fraction (21.6 g.), b.p. 176° (8 mm.), $n^{22}D$ 1.4419, weighed 216 g. (71.5% yield based on VI).

Anal. Calcd. for $C_{15}H_{26}O_6$: C, 59.58; H, 8.67. Found: C, 59.73; H, 8.63.

8-Decen-1-ol from 9-Decenoic Acid.—A mixture of 42.5 g. (0.25 mole) of 9-decenoic acid[13] and 74 g. of potassium hydroxide dissolved in 400 ml. of diethylene glycol was heated under reflux at 200–210° for 15 hr. The hot reaction mixture was poured into 2 l. of water and strongly acidified with concentrated hydrochloric acid. The acid organic layer was extracted with ether and the ethereal solution was washed with water and dried ($MgSO_4$). Evaporation of the ether followed by distillation afforded impure 8-decenoic acid, b.p. 126–127° (6.5 mm.), $n^{28}D$ 1.4490, iodine value (Wijs) 136.8. Esterification in a conventional way followed by distillation gave 45.6 g. (92.3%) of ethyl 8-decenoate, b.p. 135–136° (33 mm.), $n^{27}D$ 1.4379, iodine value (Wijs) 127.9: calcd. 128.5; ν_{max}(liquid film) at 965 cm.$^{-1}$, not at 990 and 910 cm.$^{-1}$. Saponification followed by vacuum distillation afforded pure 8-decenoic acid, b.p. 122–123° (4 mm.), $n^{29}D$ 1.4475 [reported[26] b.p. 155–157° (14 mm.)], iodine value (Wijs) 149.7; calcd. 149.1, yield 36.7 g. or 86.1% as calculated on the basis of the starting acid; ν_{max} (liquid film) at 965 cm.$^{-1}$, not at 990 and 910 cm.$^{-1}$.

The *p*-phenylphenacyl ester of 8-decenoic acid, m.p. 59.0–58.9° (from ethanol) showed a distinct depression of m.p. when admixed with the ester derived from 9-decenoic acid, m.p. 59.0–60.1°.

Anal. Calcd. for $C_{24}H_{28}O_3$: C, 79.09; H, 7.74. Found for 8-isomer: C, 79.23; H, 7.88, for 9-isomer: C, 79.12; H, 7.81.

As given for the preparation of VI, 39.6 g. (0.2 mole) of ethyl 8-decenoate was reduced with 4.8 g. of lithium aluminum hydride in 120 ml. of ether to afford 27.3 g. (87.2%) of 8-decen-1-ol, b.p. 96–97° (7 mm.), $n^{25}D$ 1.4500.

Anal. Calcd. for $C_{10}H_{20}O$: C, 76.86; H, 12.90. Found: C, 76.51; H, 13.04.

***cis*-8-Decen-1-ol from 9-Undecynoic Acid.**—Ethyl 9-undecynoate, b.p. 150° (18 mm.), $n^{18}D$ 1.4508, was prepared according to the published procedure[11] [reported[11] b.p. 197° (49 mm.)] and its infrared spectrum has no absorption maximum in the 3300 and 2140–2100 cm.$^{-1}$ regions. Treatment of 80 g. of ethyl 9-undecynoate with phenylmagnesium bromide prepared from 130 g. of bromobenzene and 20.5 g. of magnesium in 300 ml. of ether followed by usual work-up[13] gave 83 g. (79%) of 1,1-diphenyl-1,9-undeceyne, b.p. 215° (6 mm.) as a viscous oil.

Anal. Calcd. for $C_{23}H_{26}$: C, 91.33; H, 8.67. Found: C, 90.99; H, 8.70.

Oxidation of 82 g. of the 1,1-diphenyl-1,9-undecenyne with chromium oxide in acetic acid in the same manner as described before gave 27 g. (53%) of 8-decynoic acid, b.p. 122° (0.2 mm.), m.p. 38.5–39°.

Anal. Calcd. for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.19; H, 9.51.

Esterification of 27 g. of 8-decynoic acid in the usual way gave 25.3 g. (80.5%) of ethyl 8-decynoate, b.p. 102–104° (3 mm.).

Anal. Calcd. for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.31; H, 10.13.

Partial hydrogenation of 25 g. (0.128 mole) of ethyl 8-decynoate in 130 ml. of ethanol at atmospheric pressure in the presence of 5 g. of the Lindlar's catalyst[14] gave 21.0 g. (80%) of ethyl *cis*-8-decenoate, b.p. 128–130° (23 mm.).

Anal. Calcd. for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 72.60; H, 11.02.

Reduction of 21.0 g. of ethyl *cis*-8-decenoate with 3 g. of lithium aluminum hydride afforded 14.3 g. (86%) of *cis*-8-decen-1-ol, b.p. 130° (29 mm.).

Anal. Calcd. for $C_{10}H_{20}O$: C, 76.86; H, 12 90. Found: C, 76.93; H, 13.02.

1,8,9-Trihydroxydecane.—Hydroxylation of 23.5 g. of 8-decen-1-ol (isomeric mixture) was effected by the same procedure for the preparation of VII and 29.1 g. of crude triol was obtained. Acetylation of the triol gave 33.6 g. (70.9%) of triacetate, b.p. 161.5–162.5° (3.5 mm.), $n^{22}D$ 1.4429.

Anal. Calcd. for $C_{16}H_{28}O_6$: C, 60.74; H, 8.92. Found: C, 60.39; H, 8.97.

1,2,11-Trihydroxyundecane.—As given above 10-undecen-1-ol[21] was dihydroxylated to give 1,2,11-trihydroxyundecane, m.p. 74–75° (from ethyl acetate), in 91.8% yield.

Anal. Calcd. for $C_{11}H_{24}O_3$: C, 64.66; H, 11.84. Found: C, 64.46; H, 11.74.

11-Hydroxy-*trans*-2-undecenoic Acid.—To a solution of 10 g. of *threo*-1,9,10-trihydroxyhexadecane[17] in 400 ml. of ethanol was added a solution of 7.5 g. of potassium periodate in 400 ml. of 1 *N* sulfuric acid under vigorous stirring at 40° in a course of 20 min. After 10 min. the turbid solution was cooled to 15° and diluted with 2 l. of water. The organic layer was extracted with ether and the ethereal solution was washed with water. Evaporation of ether gave an oily residue which was successively steam-distilled in the presence of 0.5 g. of hydroquinone. The nonvolatile portion was extracted with ether and dried ($MgSO_4$). Evaporation of the solvent afforded 4.0 g. (77%) of an oily substance which gradually polymerized to a gelatinous material. The 2,4-dinitrophenylhydrazone from the freshly prepared crude hydroxyaldehyde melted at 66–67° (reported[18] m.p. 69°). A mixture of 14.4 g. of the crude hydroxyaldehyde, 10 g. of malonic acid, and 25 ml. of pyridine was kept at room temperature for 1 week with occasional shaking and then heated

(24) A. Seher, *Fette, Seifen, Anstrichmittel*, **58**, 1077 (1956).

(25) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th ed., John Wiley & Sons, Inc., New York, N. Y., 1956, p. 200.

(26) P. Chuit, F. Boelsing, J. Hausser, and G. Malet, *Helv. Chim. Acta*, **10**, 167 (1927).

on a boiling water bath for 2 hr. After cooling, 50 ml. of water was added and extracted with ether. The ethereal solution was washed with dilute hydrochloric acid and successively extracted three times with 50-ml. portions of 5% aqueous sodium hydroxide. Acidification of the aqueous alkaline solution with dilute hydrochloric acid followed by extraction with ether furnished an oily material which solidified on cooling in Dry Ice–methanol bath. Recrystallizations from a mixture of *n*-hexane and ethyl ether gave 7.2 g. (40%) of colorless crystals, m.p. 66–67.5°.

Anal. Calcd. for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07. Found: C, 65.88; H, 10.04.

The infrared spectrum (Nujol) showed absorption maxima at 3390, 1690, 1685, and 975 cm.$^{-1}$. Reported absorption maxima for natural Royal Jelly acid[27] (Nujol) are at 3390, 1710, 1658, and 976 cm.$^{-1}$ and for the synthetic one[1a] (Nujol), at 2.92, 5.89, and 6.05 μ.

In an analogous way 8-hydroxyoctanal [2,4-dinitrophenylhydrazone, m.p. 64 and 87–96° (double melting points) reported[10] m.p. 91–93°], and 10-hydroxy-*trans*-2-decenoic acid were obtained from *dl*-1,2,9-trihydroxynonane as well as 1,8,9-trihydroxydecane, and 10-hydroxydecanal (2,4-dinitrophenylhydrazone, m.p. 100°; reported[10] m.p. 101–103°) and 12-hydroxy-*trans*-2-dodecenoic acid[1a] were obtained from 1,2,11-trihydroxyundecane.

Migration of the Double Bond in Nonenoic Acid During the Preparation from 2-Allylcyclohexane-1,3-dione.—2-Allylcyclohexane-1,3-dione was treated exactly according to the published procedure[7] and the acid obtained was purified by esterification followed by saponification, b.p. 110–114° (2.5 mm.), iodine value (Wijs) found, 156; calcd. for nonenoic acid, 162.

Oxidation of 5 g. (0.032 mole) of this acid with a solution of 23.5 g. of potassium permanganate in 500 ml. of water under slightly alkaline conditions gave 3.5 g. of a mixture of dibasic acids, m.p. 83–93°. Neutralization value found, 696; calcd. for pimeric acid, 701; for suberic acid, 644. This mixture was fractionally recrystallized from water into suberic acid, m.p. 139–141°, and pimelic acid, m.p. 95–97°; both were identified by mixed melting points with authentic specimens as well as by analyses for carbon and hydrogen.

9-Hydroxy-*trans*-2-nonenoic Acid from Alueritic Acid.—Aleuritic acid, m.p. 99.8–100.1° (reported[28] m.p. 100–101°), was obtained from commercial wax-free shellac resin according to the published procedure.[19] To a solution of 4 g. of potassium periodate in 200 ml. of 1 *N* sulfuric acid was added a solution of 5 g. of aleuritic acid in 400 ml. of ethanol and the mixture was kept at 35–40° for 20 min. with vigorous agitation. The reaction mixture was diluted with 500 ml. of water and extracted repeatedly with ether. The ethereal solution was washed with aqueous sodium bicarbonate and water and dried ($MgSO_4$). Evaporation of ether afforded crude hydroxy aldehyde, the 2,4-dinitrophenylhydrazone of which melted at 82.5–85° and gave correct analyses for carbon and hydrogen (reported[20] m.p. 99.5°). A mixture of the crude hydroxyaldehyde thus obtained, 4 g. of malonic acid, 8 ml. of pyridine, and 1 ml. of piperidine was treated in the same manner as described for 11-hydroxy-*trans*-2-undecenoic acid, and 1 g. of crude hydroxy acid, m.p. 58–60° was obtained. Recrystallizations from a mixture of petroleum ether (b.p. 40–60°) and ethyl ether gave 9-hydroxy-*trans*-2-nonenoic acid, m.p. 64.5–65.5°, ν_{max} (Nujol) at 3365, 1686, 1658, 984 cm.$^{-1}$.

Anal. Calcd. for $C_9H_{16}O_3$: C, 62.76; H, 9.36. Found: C, 62.88; H, 9.45.

(27) W. H. Brown and R. J. Freure, *Can. J. Chem.*, **37**, 2042 (1959).

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Electrolysis of Quaternary Phosphonium Salts

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Horner and co-workers[1,2] have recently reported the formation of tertiary phosphines from the electrolysis of various quaternary phosphonium halides. The present note describes the electrolysis of some other quaternary phosphonium salts under different conditions.

We have found that the electrolysis of several substituted triphenylphosphonium nitrates and trifluoroacetates at an aluminum cathode and a gold or platinum anode in a single-compartment cell yields triphenylphosphine oxide. This is in contrast to the results of Horner who found that, in a divided cell, phosphines were formed at a mercury or lead cathode.

The original purpose of this work was to investigate the use of quaternary phosphonium salts in the dimerization reaction previously described for ammonium salts.[3,4] Although bibenzyl was obtained in 31% yield (along with 35% of triphenylphosphine oxide) from the electrolysis of benzyltriphenylphosphonium nitrate in dimethylformamide, no dimer was obtained from the electrolysis of allyltriphenylphosphonium nitrate or 9-fluorenyltriphenylphosphonium nitrate. Each of these electrolyses afforded substantial amounts of triphenylphosphine oxide. The reaction mixtures were in general much less convenient to work with than those resulting from the electrolysis of quaternary ammonium salts.

It is possible that the quaternary phosphonium salt is first cleaved to a hydrocarbon radical and triphenylphosphine which is then oxidized to triphenylphosphine oxide. In actual fact, the electrolysis of benzyltriphenylphosphonium nitrate in methanol gave 5% of triphenylphosphine in addition to 44% of triphenylphosphine oxide.

Further evidence in support of such a reaction path is obtained from the electrolysis of triphenylphosphine in methanol in the presence of ammonium nitrate. In an undivided cell with an aluminum cathode and a platinum anode a yield of 54% of triphenylphosphine oxide is obtained.

Another possible mechanism for the formation of triphenylphosphine oxide is the oxidation of triphenylphosphine by nitrate ion. That such a reac-

(1) L. Horner, H. Winkler, A. Rapp, A. Mentrup, H. Hoffmann, and P. Beck, *Tetrahedron Letters*, 161 (1961).

(2) L. Horner and A. Mentrup, *Ann.*, **646**, 65 (1961).

(3) M. Finkelstein, R. C. Petersen, and S. D. Ross, *J. Am. Chem. Soc.*, **81**, 2361 (1959).

(4) S. D. Ross, M. Finkelstein, and R. C. Petersen, *ibid.*, **82**, 1582 (1960).

tion is not required is shown by the isolation of 51% of triphenylphosphine oxide (in addition to 14% of toluene) from the electrolysis of benzyltriphenylphosphonium trifluoroacetate in methanol.

Since it has now been shown that triphenylphosphine can be electrolytically oxidized under the same conditions that phosphonium salts are cleaved there appears to be no discrepancy between this work and that of Horner. Horner used an electrolysis cell having separate cathode and anode compartments which effectively prevented diffusion of the initially formed phosphines. In the present work, however, the triphenylphosphine is free to diffuse and undergo anodic oxidation to the phosphine oxide.

Experimental

Electrolysis Procedure.—In the experiments designated (A) the procedure was that previously used for quaternary ammonium compounds.[4]

In the experiments designated (B) the electrolysis cell consisted of a jacketed tall-form beaker 10 cm. high and 5 cm. in diameter with an enlarged top 1 cm. high. The electrodes were attached to a circular piece of Bakelite which fitted in the enlarged top. Two strips of aluminum 2.5 cm. apart served as cathodes with a platinum wire anode centered between them. The immersed area of each cathode was 12.5 cm.^{2} (5c m. high and 2.5 cm. wide) and the anode also was immersed to a depth of 5 cm. Tap water was constantly circulated through the jacket and stirring was provided by a Teflon-covered magnetic bar.

In both procedures the current was provided by a variable voltage-regulated power supply and an ammeter was connected in series with the electrolysis cell. The current was maintained constant at 0.40 amp. throughout each electrolysis and the initial applied voltage was generally about 100 volts.

In each experiment 0.050 mole of salt was dissolved or suspended in 130 ml. of solvent. At the conclusion of each electrolysis the reaction mixture was poured into a liter of water and worked up as described for each compound.

Quaternary Phosphonium Compounds.—The salts were prepared in good yield by refluxing equimolar quantities of triphenylphosphine and the appropriate halide in acetone and subsequent reaction of the phosphonium bromide with either silver nitrate or silver trifluoroacetate.

Electrolyses. Benzyltriphenylphosphonium Trifluoroacetate in Methanol (B).—The solution was electrolyzed for 24 hr. at which time analysis by vapor phase chromatography indicated the formation of toluene in 14% of the theoretical yield. The aqueous mixture was extracted four times with chloroform and twice with hexane. The combined organic layer was washed with water, dried over magnesium sulfate, and the solvents distilled at the water pump under nitrogen. The dark residue was dissolved in benzene and chromatographed on alumina. A total of 7.1 g. (51%) of triphenylphosphine oxide was obtained from the various fractions on elution with benzene. Crystallization from benzene–hexane gave a m.p. 153–154°; mixed m.p. with triphenylphosphine oxide was 153–155°.

Benzyltriphenylphosphonium Nitrate in Methanol (B).—The solution was electrolyzed for 23.5 hr. The aqueous mixture was extracted six times with chloroform and once with hexane. The combined organic layer was washed with water, dried over magnesium sulfate, and the solvents distilled through a Vigreux column. After removal of all of the solvent at the aspirator the dark residue was dissolved in methanol and crystals were obtained as follows. Hexane was boiled with the methanol solution and decanted. The hexane was concentrated with an air jet and periodically decanted from any tar which settled. When no more tar deposited the hexane was completely evaporated to give clean crystals. This procedure was repeated several times to give 5.0 g., m.p. 152–154°. Five more digestions gave another 1.4 g., m.p. 149–153°. The combined crops were washed with a small amount of warm ether, the ether was evaporated, and the residue was crystallized from methanol with cooling by Dry Ice–acetone, 0.6 g. obtained, m.p. 79–80°.

Coincidence of infrared spectra established that the higher melting material was triphenylphosphine oxide (44% yield) and the lower melting was triphenylphosphine (5%).

Benzyltriphenylphosphonium Nitrate in Dimethylformamide (A).—The solution was electrolyzed for 18.7 hr. The aqueous mixture was extracted four times with a total of 1 l. of ether. The ether extract was washed twice with water, dried over magnesium sulfate, and distilled through a Vigreux column. The residue was digested once with hexane, the hexane was evaporated, and the solid was crystallized from methanol (Dry Ice–acetone cooling) to give 1.43 g. (31.4%) of bibenzyl, m.p. 51–52°. The material which was insoluble in the hexane digestion was treated as in the previous experiment to isolate triphenylphosphine oxide. A total of 4.7 g. (35%) was obtained. After crystallization from benzene–hexane the m.p. was 154–155° and a mixed m.p. with triphenylphosphine oxide was 153–154°.

Allyltriphenylphosphonium Nitrate in Dimethylformamide (A).—The solution was electrolyzed for 23.5 hr. The aqueous mixture was extracted four times with ether and twice with hexane. The combined extract was dried over magnesium sulfate and the solvent removed by distillation through a Vigreux column. The solid obtained, 3.2 g. (23%), was crystallized twice from benzene–hexane to give a m.p. 150–152°; mixed m.p. with triphenylphosphine oxide was 151–152°.

9-Fluorenyltriphenylphosphonium Nitrate in Dimethylformamide (A).—The suspension was electrolyzed for 20 hr. The aqueous mixture was extracted twice with ether, twice with hexane, and three times with chloroform. The extracts were combined, dried over magnesium sulfate, and distilled *in vacuo* to remove the solvents. The dark solid was digested repeatedly with hexane to give 2.7 g. of crude triphenylphosphine oxide. The residue after digestion was dissolved in methanol and treated as previously described for the isolation of triphenylphosphine oxide; an additional 4.1 g. was obtained. The total yield was 50%. The combined product was crystallized twice from benzene–hexane to give a m.p. of 153–154° which was undepressed on mixture with triphenylphosphine oxide.

Triphenylphosphine in Methanol (B).—A suspension of 13.1 g. (0.05 mole) of triphenylphosphine in a solution of 8 g. (0.1 mole) of ammonium nitrate in 140 ml. of methanol was electrolyzed for 25 hr. At this time all of the solid had dissolved. The dark electrolysis mixture was poured into a liter of water and extracted four times with 200-ml. portions of chloroform. The combined extract was dried over magnesium sulfate and the chloroform was distilled *in vacuo*. The dark residue was digested repeatedly with boiling ether and boiling hexane until evaporation of the solvent afforded no additional crystals. More solid was obtained, however, by dissolving the residue in methanol and treating it as previously described for the isolation of triphenylphosphine oxide. All of the crystals were combined, washed with a small amount of ether, and filtered to give 7.54 g. (54%) which had a m.p. of 152–154°. The melting point was undepressed on mixture with triphenylphosphine oxide.

Two experiments attested to the stability of triphenylphosphine under the work-up conditions: (1) A solution of triphenylphosphine in hexane was refluxed for 23 hr. and the triphenylphosphine was recovered unchanged. (2) A solution of triphenylphosphine was boiled and concentrated to dryness by an air jet. This was repeated four times and triphenylphosphine was recovered uncontaminated by triphenylphosphine oxide.

Acknowledgment.—The vapor phase chromatographic analysis was performed by Dr. R. C. Petersen and the benzyltriphenylphosphonium trifluoroacetate was prepared by Dr. S. D. Ross.

The Reaction of 2,3-Dichloro-*p*-dioxane with Phenyllithium

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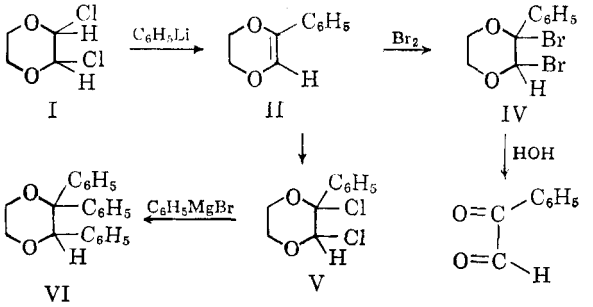
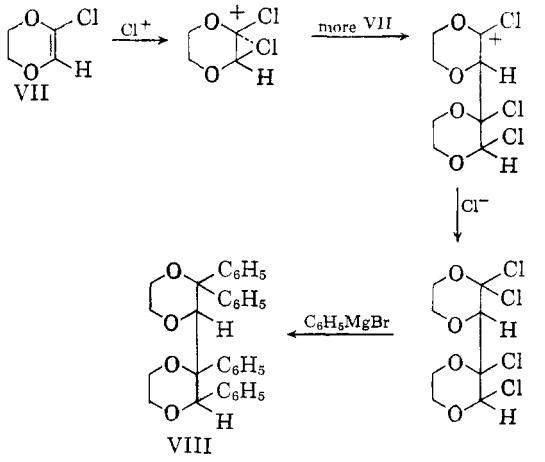
Organometallic compounds react with 2,3-dichloro-*p*-dioxane (I) in a variety of ways. Aryl Grignard reagents give mixtures of isomeric 2,3-diaryl-*p*-dioxanes in excellent yields.[3-5] The dominant isomer was assigned a *cis* structure by Stumpf,[5] but later strong evidence for a *trans* structure was presented.[6] The *trans* product predominates whether the starting material I is *cis* or *trans*.[7] The reaction of compound I with alkyl Grignard reagents is primarily one of dehalogenation,[4] dioxene and disproportionation products of the alkyl group resulting. The very small yields of mixtures of isomeric dialkyldioxanes produced from the alkylmagnesium halides can be markedly increased[8] by employing the Blaise[9] modification of the Grignard reagent utilising unisolated alkylzinc intermediates. Even better yields are obtained from similar alkylcadmium compounds, but dialkylmercury or alkylmercuric halide reagents are inert toward I. In the present study, phenyllithium has been found to react with I in yet another way, the product being 2-phenyl-*p*-dioxene (II).



The unsymmetrical 2-phenyl-*p*-dioxene is an extremely unstable and fugacious substance, in sharp contrast to the closely related, but symmetrical 2,3-diphenyl-*p*-dioxene (III).[6] Samples of III have now been kept for several years in ordinary shelf storage without modification, but II changes from a white crystalline solid to a light green liquid on standing at room temperature, often in a matter of hours. The nature of the change taking place in II is as yet obscure. Some sort of polymerization occurs, as the average molecular weight of a modified sample was found to be about 1400. That the reaction was not simply polymerization was indicated by the change in analysis, the percentages of carbon decreasing as modification proceeds. Addition of one oxygen atom for each phenyldioxene unit would account roughly for the change in composition. The infrared spectra indicate loss of double bond and a slight, but by no means proportional, formation of carbonyl during the transition.

Characterization and proof of structure of the 2-phenyl-*p*-dioxene were complicated by its unstable character but are quite definite. It adds one mole of bromine to yield 2-phenyl-2,3-dibromo-*p*-dioxane (IV). This readily undergoes hydrolysis to phenylglyoxal, which was isolated in the form of the osazone. The chlorine addition product, 2-phenyl-2,3-dichloro-*p*-dioxane (V), was converted by phenylmagnesium bromide to 2,2,3-triphenyl-*p*-dioxane (VI), which was also prepared by an independent synthesis from the known 2,2,3-trichloro-*p*-dioxane.[10]

When 2,2,3-trichloro-*p*-dioxane was treated with phenylmagnesium bromide, two products rather than the expected one were produced. Since the major one had the correct analysis and molecular weight for 2,2,3-triphenyl-*p*-dioxane, it was assigned that structure. The less soluble one, formed in minor amount, was reminiscent of by-products



(1) Present address: United States Naval Academy, Annapolis, Maryland.

(2) National Science Foundation Undergraduate Research Participant, National Science Foundation Grant, 16238, Summer, 1961.

(3) R. Christ and R. K. Summerbell, *J. Am. Chem. Soc.*, **54**, 3777 (1932); **55**, 4547 (1933).

(4) R. K. Summerbell and L. N. Bauer, *ibid.*, **57**, 2364 (1935).

(5) W. Stumpf, *Z. Electrochem.*, **57**, 690 (1953).

(6) R. K. Summerbell and D. R. Berger, *J. Am. Chem. Soc.*, **81**, 633 (1959).

(7) R. K. Summerbell and Hans E. Lunk, *ibid.*, **79**, 6504 (1957).

(8) R. K. Summerbell and L. N. Bauer, *ibid.*, **58**, 750 (1936).

(9) E. E. Blaise, *Bull. soc. chim. France*, 9 (1911).

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(11) R. K. Summerbell and R. R. Umhoefer, *ibid.*, **61**, 3016 (1939).

observed when chloro-*p*-dioxane was treated with alkyl Grignard reagents, methyldioxanyldioxane and butyldioxanyldioxane.[11] A mechanism like that suggested by McElvain and Davie[12] in a similar situation would predict that in the present case a tetraphenyl-*p*-dioxanyl-*p*-dioxane of structure VIII would be expected to result from a by-product formed when the intermediate 2,2,3-trichloro-*p*-dioxane was prepared. The analysis and molecular weight are consistent with this assignment of structure.

Our original work on 2-phenyl-*p*-dioxene was done a number of years ago, but publication was held up because several attempts to repeat or extend the work gave erratic results or were entirely unsuccessful. Even when the compound was obtained, carbon and hydrogen analyses were not satisfactory. Our present success seems to be due to a stringent avoidance of acid at any stage of the preparation or storage, all apparatus being rinsed with alkali carbonate or ammonia before contact with the product. Hydrolysis of the organometallic–chloro ether reaction mixture was with water, not with dilute acid. The traces of acid present in the atmospheres of desiccators charged with sulfuric acid or calcium chloride were sufficient to cause a noticeable increase in the rate of deterioration over that which took place in the open air of the laboratory. Obtaining a satisfactory analytical sample was achieved by Dry Ice temperature crystallization from pentane, followed by drying at room temperature in a desiccator charged with paraffin chips.

Experimental

2-Phenyl-*p*-dioxene (II).—Lithium (12.5 g., 1.8 g.-atoms) was cut into 300 ml. of absolute ethyl ether while the flask was continuously flushed with pure nitrogen. A solution of 141 g. (0.9 mole) of bromobenzene dissolved in 225 ml. of absolute ether was added dropwise at a rate to maintain ether reflux. A solution of 41.7 g. (0.3 mole) of *trans*-2,3-dichloro-*p*-dioxane (I) dissolved in 150 ml. of absolute ether was added, again at a rate to maintain ether reflux. The solution was heated to reflux, stirred for an additional 2 hr., and allowed to stand, with stirring, for 12 hr. It was then hydrolyzed with water and the ether collected and combined with two additional 100-ml. portions of ether used to extract the hydrolysis mixture. The ether was stripped and the resulting liquid distilled rapidly at 2 mm. through a 6-in. Vigreux column. The material, boiling at 97–103°, weighing 15.5 g., readily solidified on cooling. When crystallized from pentane, it melted sharply at 43°, yield 31%. An attempt was made to prepare an analytical sample by crystallization from ether and drying in a vacuum desiccator over sulfuric acid, but the sample (a) showed marked signs of deterioration in less than 0.5 hr. A second sample (b), recrystallized from pentane and dried in a vacuum desiccator over paraffin shavings, gave a satisfactory analysis.

Anal. Calcd. for $C_{10}H_{10}O_2$: C, 74.04; H, 6.21. Sample (a): C, 73.21; H, 5.81. Sample (b): C, 73.77; H, 6.04.

Mol. wt: Calcd.: 162. Found: 160, by micro-Rast method. Titrations in triplicate showed the addition of 0.96 mole of Br_2 per mole of phenyl-*p*-dioxene.[13]

2-Phenyl-2,3-dibromo-*p*-dioxane (IV).—Bromine dissolved in carbon tetrachloride was added in slight excess to a dilute carbon tetrachloride solution of II. After standing in the dark for 30 min., the solution was washed with a sodium thiosulfate solution, evaporated, and the residue recrystallized rapidly from methanol without prolonged heating, m.p. 118.5–119°.

Anal. Calcd. for $C_{10}H_{10}O_2Br_2$: Br, 49.64. Found: Br, 49.58.

A similar sample was prepared by adding bromine in chloroform solution to 1 g. of II, the solvent was removed, and the residue treated with 20 ml. of water containing 1 drop of conc. hydrochloric acid. Heating on the water bath for an hour produced a homogeneous solution which was allowed to react with a water solution of phenylhydrazine hydrochloride. The osazone, recrystallized from ethanol, melted at 150–151°. Lit. for osazone of phenylglyoxal: 152°.[14]

Properties of Modified 2-Phenyl-*p*-dioxene.—Crystals of 2-phenyl-*p*-dioxene could be kept indefinitely if stored at Dry Ice temperature; however, after standing at room temperature for a few hours, a coating of light green oil invariably formed, and the entire sample would liquefy in a matter of days. A sample of this oil (2 months old) was dried at 1-mm. pressure and 100° for 3 hr. and was then analyzed.

Anal. Found: C, 65.80; H, 6.46.

Infrared spectra differed from that of unmodified 2-phenyl-*p*-dioxene in that the prominent olefin band at 6.04 μ had almost disappeared, and new small probably carbonyl bands at 5.8 and 5.9 μ were evident. Molecular weight, cryoscopic, using benzene, was 1388, equivalent to about eight $C_{10}H_{10}O_2$ units.

2,2,3-Triphenyl-*p*-dioxane (V).—A solution of 1.62 g. (0.01 mole) of II in 50-ml. of pentane was cooled in ice and chlorine bubbled in until color persisted. It was added dropwise to 0.05 mole of phenylmagnesium bromide and the resulting mixture stirred and heated for 15 min. After hydrolysis, the residue which resisted crystallization was placed on an alumina column by means of hexane and eluted with a 25% solution of ether in hexane. After 0.1 g. of biphenyl, a single product, 1.71 g., m.p. 128°, identical in mixed melting point and infrared spectrum with 2,2,3-triphenyl-*p*-dioxane was obtained. Yield, 54%. The comparison sample which had been made earlier in connection with another study was prepared as described below.

To a solution of phenylmagnesium bromide prepared from 39.3 g. (0.25 mole) of bromobenzene and 6.1 g. (0.25 g.-atom) of magnesium in 150 ml. of dry ether was added, dropwise and with stirring, a solution of 10.1 g. (0.053 mole) of 2,2,3-trichloro-*p*-dioxane[7] in 50 ml. of ether. After refluxing for 15 min., the mixture was hydrolyzed by pouring onto ice–sulfuric acid, the layers separated, the aqueous layer washed with ether, and the combined ether solutions washed with dilute aqueous sodium bicarbonate and water. The ether was removed and the residual syrup was steam-distilled until no more biphenyl was present in the distillate. The residue was extracted in ether and dried over magnesium sulfate; crystallization gave 0.1 g. of a compound, m.p. 201°. The ether was removed and the residue taken up in hexane. Several evaporations of the hexane were done in order to remove the remaining traces of ether, and the hexane solution was separated into its components by chromatography, using a column of 80–200-mesh alumina packed in hexane. The column was eluted with a solution of one part ether and three parts pentane. A large amount of material was collected in the early fractions, melting, after recrystallization from ethanol, at 128°. The next compound isolated was the same compound, m.p. 201°, obtained above. The combined samples of the 201° compound were recrystallized from hexane.

(12) S. M. McElvain and W. R. Davie, *J. Am. Chem. Soc.*, **74**, 1816 (1952).

(13) H. S. Davis, G. S. Crandall, and W. E. Higbee, *Ind. Eng. Chem., Anal. Ed.*, **3**, 108 (1931).

(14) R. L. Shriner and R. C. Fuson, "Identification of Organic Compounds," John Wiley & Sons, New York, N. Y., 1956, p. 284.

The major product, the compound melting at 128°, was assigned the structure of 2,2,3-triphenyl-*p*-dioxane on the basis of its analysis, molecular weight, and method of synthesis. The compound, m.p. 201°, has not been positively identified, but it is probably a tetraphenyl-*p*-dioxanyl-*p*-dioxane (VIII).

Compound, m.p. 201°. Yield: 0.3 g. *Anal.* Calcd. for $C_{32}H_{30}O_4$: C, 80.5; H, 6.3. Found: C, 80.86, 80.26; H, 6.30, 6.30. Compound, m.p. 128°. Yield: 2 g. Anal. Calcd. for $C_{22}H_{20}O_2$: C, 83.51; H, 6.37. Found: C, 83.51; H, 6.09. Molecular weight: Calcd.: 316. Found: 306 (Rast camphor).

The Structure of the Thiocytosine Analog of Nitrogen Mustard[1]

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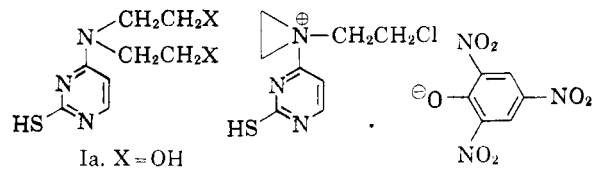
Recently the synthesis of 4-[bis(2-chloroethyl)-amino]-2-pyrimidinethiol (Ib, the thiocytosine analog of nitrogen mustard) by the chlorination of 2,2′-[(2-mercapto-4-pyrimidinyl)imino]diethanol (Ia) with thionyl chloride has been claimed[2] but no evidence was offered that both chlorine atoms of this compound are in fact covalent. Further, the conversion of Ib to 1-(2-chloroethyl)-1-(2-mercapto-4-pyrimidinyl)aziridinium picrate (II) by treatment with hot ethanolic picric acid is described. Since the true structure of a nitrogen mustard such as Ib is important to the evaluation of biological data obtained with it, and since it has been established that attempts to prepare the purin-6-yl analog of nitrogen mustard by thionyl chloride chlorination of the corresponding iminodiethanol gave only the tricyclic purine III,[3] we have studied the chlorination of Ia as recently described.[2] We have obtained conclusive evidence that the product of this reaction is actually the hydrochloride of the bicyclic 1-(2-chloroethyl)-2,3-dihydromidazo[1,2-*c*]-pyrimidine-5(1*H*)-thione (IV)[4] and, therefore, that the reported picrate is the picrate of the dihydromidazopyrimidine IV and not of the ethyleneimonium form of the nitrogen mustard.

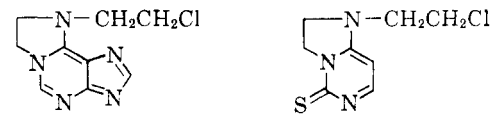
Chlorination of Ia gave a material which resembled the reported compound,[2] but about half of its chlorine content was ionic. This material could, by careful neutralization, be converted to its free base whose ultraviolet spectrum is practically identical with that of the chloride and quite different from that of Ia (whose spectrum should be very similar to a structure such as Ib). The free base, which must have the structure IV, was then converted back to its hydrochloride by treatment with dry hydrogen chloride in chloroform. An anhydrous sample of the hydrochloride was thus obtained.

The rather low toxicity reported[2] for the chlorination product of Ia is more in keeping with the imidazo[1,2-*c*]pyrimidine (IV) than the nitrogen mustard (Ib) structure.



Ia. X = OH
Ib. X = Cl

II



III IV

Experimental[5]

2-(2-Chloroethyl)-2,3-dihydroimidazo[1,2-*c*]pyrimidine-5(1*H*)-thione (IV). (a) **Free Base.**[6]—2,2′-[(2-Mercapto-4-pyrimidinyl)imino]diethanol (Ia)[2] (2.0 g., 9.3 mmoles) was added to a well stirred solution of 0.3 ml. of thionyl chloride and 0.5 ml. of ethyl alcohol in 22 ml. of bis(2-methoxyethyl) ether. Additional thionyl chloride (4.0 ml.) was slowly added to the mixture and the resulting white suspension stirred at room temperature overnight. The reaction mixture was then evaporated to dryness under reduced pressure to give a tan residue, which was dissolved in hot ethyl alcohol (100 ml.), treated with charcoal, and filtered. The clear filtrate was evaporated to dryness under reduced pressure to give the crude hydrochloride of IV; λ_{max} in mμ ($\epsilon \times 10^{-3}$): pH 1—247 (11.4), 273 (16.9), 320 (4.07); pH 7—232 (12.2), 266 (9.44), 336 (7.10); pH 13–232 (14.5), 266 (9.15), 338 (7.90); EtOH—245 (10.5), 278 (16.8), 326 (3.65).

Anal. Calcd. for $C_8H_{10}ClN_3S \cdot HCl$: Cl (total), 28.12; Cl (ionic), 14.06. Found: Cl (total), 27.0; Cl (ionic), 13.1 (by acid-base titration at 0°).

After several unsuccessful attempts to recrystallize the crude hydrochloride, it was dissolved in cold water and the pH carefully brought to 8 by the dropwise addition of 0.1 *N* sodium hydroxide solution. The free base precipitated as a yellow solid, which was recrystallized from methyl alcohol

(1) This work was carried out at the suggestion of Dr. H. W. Bond and was supported by funds from the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Contract No. SA-43-ph-1740.

(2) H. Segal and C. G. Skinner, *J. Org. Chem.*, **27**, 199 (1962).

(3) T. P. Johnston, A. L. Fikes, and J. A. Montgomery, *ibid.*, **27**, 973 (1962).

(4) Many examples have been reported in which the chlorination of a 2-(4-pyrimidinylamino)ethanol has resulted in the formation of an imidazo[1,2-*c*]pyrimidine [G. R. Ramage and G. Trappe, *J. Chem. Soc.*, 4410 (1952); R. H. Martin and J. Mathieu, *Tetrahedron*, **1**, 75 (1957); J. Clark and G. R. Ramage, *J. Chem. Soc.*, 2821 (1958); J. H. Lister, *ibid.*, 899 (1960); P. R. Brook and G. R. Ramage, *ibid.*, 896 (1955)].

(5) Melting points were determined on a Kofler Heizbank and are corrected. The ultraviolet spectra were determined in alcoholic and aqueous solutions with a Cary Model 14 spectrophotometer. Paper chromatography was done by the descending technique on Whatman No. 1 paper; spots were viewed in ultraviolet light. R_{Ad} values were determined by locating spots relative to adenine arbitrarily assigned an R_f value of 1.00. Solvent systems: A, water-saturated butyl alcohol; B, butyl alcohol–acetic acid–water (5:2:3 by vol.); C, isopropyl alcohol–concentrated ammonium hydroxide–water (14:1:5 by vol.); D, acetate buffer (pH 6.1).

(6) The first part of this procedure is practically identical with that described by Segal and Skinner.[2]

and dried *in vacuo* over phosphorus pentoxide at 60° for 8 hr.; yield 1.05 g. (53%); m.p. 178–180°, the melt solidifying and remelting > 260° dec.; λ_{max} in mμ ($\epsilon \times 10^{-3}$): pH 1—248 (15.5), 274 (23.6), 320 (6.55); pH 7—234 (17.5), 268 (13.2), 338 (12.5); pH 13—232 (17.9), 267 (12.7), 338 (12.6); R_{Ad}: A—1.23; B—0.94 and 1.16; C—1.48; D—2.26.

Anal. Calcd. for $C_8H_{10}ClN_3S$: C, 44.54; H, 4.68; N, 19.49. Found: C, 44.66; H, 4.72; N, 19.47.

(b) **Hydrochloride.**—A well stirred suspension of 1-(2-chloroethyl)-2,3-dihydromidazo[1,2-*c*]pyrimidine-5(1*H*)-thione (IV) (500 mg., 2.33 mmoles) in 20 ml. of chloroform was cooled in an ice bath to 0° and anhydrous hydrogen chloride slowly bubbled through the suspension for 2 hr. The volatiles were removed under reduced pressure to give a thick syrup, which formed a white crystalline residue on repeated *in vacuo* evaporations with additions of ethyl alcohol. The residue was recrystallized from a small volume of ethyl alcohol and dried over phosphorus pentoxide *in vacuo* at 60° for 18 hr.; yield 450 mg. (76%); m.p. 196–198°; λ_{max} in mμ ($\epsilon \times 10^{-3}$): pH 1—247 (14.3), 273 (21.9), 320 (6.00); pH 7—233 (16.4), 267 (12.3), 338 (12.0); pH 13—233 (16.4), 267 (11.9), 338 (12.0); EtOH—244 (13.4), 277 (23.4), 329 (5.56); R_{Ad}: A—1.34; B—1.03 and 1.17; C—1.50; D—2.14.

Anal. Calcd. for $C_8H_{10}ClN_3S \cdot HCl$: C, 38.10; H, 4.40; N, 16.67. Found: C, 38.34; H, 4.52; N, 16.60.

The picrate was prepared in ethyl alcohol and recrystallized from methyl alcohol; m.p. 176–178° dec.; λ_{max} in mμ ($\epsilon \times 10^{-3}$): pH 1—245 (16.0), 274 (15.7), 335 (9.06); pH 7—232 (17.4), 260 (10.9), 344 (14.7); pH 13—232 (17.7),; 260 (10.9), 345 (15.0); R_{Ad}: A—1.47; B—1.22; C—1.59 and 1.94; D—1.49.

Anal. Calcd. for $C_{14}H_{13}ClN_6O_7S$: C, 37.80; H, 2.94; N, 18.90. Found: C, 38.02; H, 3.21; N, 18.59.

Acknowledgment.—The authors are indebted to the members of the Analytical Section of Southern Research Institute who, under the direction of Dr. W. J. Barrett, performed the spectral and microanalytical determinations reported and to Miss Mary Broadaway for the chromatographic work reported.

Methylaminomethylsuccinic Acid

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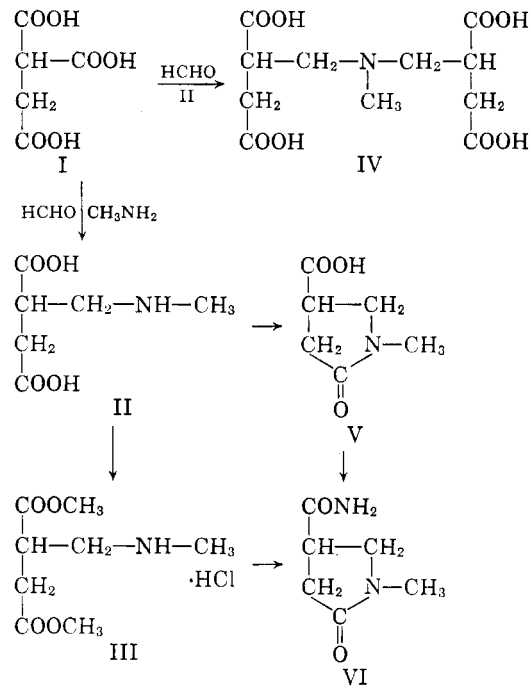
Some years ago the preparation of a methylaminodicarboxylic acid designed as an intermediate for a projected synthesis of lysergic acid was mentioned in a preliminary communication.[1] Experimental details, together with newer results, are given in the present report.

Carboxysuccinic acid (I) was allowed to react with aqueous methylamine and formaldehyde under Mannich conditions[2] to afford methylaminomethylsuccinic acid (II). Esterification of II with methanolic hydrogen chloride in the presence of 2,2-dimethoxypropane,[3] or with methanol and thionyl chloride,[4] gave 85% of nicely crystalline, nonhydroscopic dimethyl methylaminomethylsuccinate hydrochloride (III). Esterification of II with ethanolic hydrogen chloride furnished the less stable diethyl methylaminomethylsuccinate hydrochloride. The methylamino acid and its dimethyl and diethyl esters were characterized as *N*-p-toluenesulfonyl derivatives.



Brief pyrolysis of II at the melting point, or prolonged boiling of its aqueous solution, gave 1-methyl-5-oxo-3-pyrrolidinecarboxylic acid (V).[5] Treatment of dimethyl methylaminomethylsuccinate hydrochloride (III) with concentrated aqueous ammonia at 0° afforded 1-methyl-5-oxo-3-pyrrolidinecarboxamide (VI). Reaction of diethyl bromomethylsuccinate with ethanolic methylamine provided the ethyl ester of V. Hydrogen chloride ethanolysis of the ethyl ester at reflux temperature opened the pyrrolidone ring to give the diethyl ester hydrochloride of II.

Condensation of methylaminomethylsuccinic acid (II) with carboxysuccinic acid (I) and formaldehyde gave the methylamino tetracarboxylic acid IV. Esterification of IV with methanol and thionyl chloride afforded the tetramethyl ester hydrochloride.

(1) F. C. Uhle, *J. Am. Chem. Soc.*, **73**, 2402 (1951).

(2) C. A. Mannich and E. Ganz, *Ber.*, **55**, 3486 (1922).

(3) For introduction of this excellent general procedure see N. B. Lorette and J. H. Brown, Jr., *J. Org. Chem.*, **24**, 261 (1959).

(4) For other examples of this method see M. Brenner and W. Huber, *Helv. Chim. Acta*, **36**, 1109 (1953); F. C. Uhle and L. S. Harris, *J. Am. Chem. Soc.*, **78**, 381 (1956).

(5) This compound has also been prepared (70%) from itaconic acid with 25% aqueous methylamine at reflux temperature during forty minutes: P. L. Southwick, E. P. Previc, J. Casanova, Jr., and E. H. Carlson, *J. Org. Chem.*, **21**, 1092 (1956).

Reaction of dimethyl methylaminomethylsuccinate with various heterocyclic α-bromo ketones will be described elsewhere.

Experimental[6]

Methylaminomethylsuccinic Acid (II).—To a solution of 1.62 g. (0.01 mole) of carboxysuccinic acid (I)[7] in 1 ml. of water was added dropwise, with cooling, 1 ml. (0.011 mole) of 11 *N* aqueous methylamine, followed by 0.825 ml. of 37% aqueous formaldehyde (equivalent to 0.33 g. or 0.011 mole of formaldehyde). A brisk evolution of carbon dioxide began within a few minutes. After 2 days at 25°, the solution was heated under reflux for 15 min., cooled, and diluted with 10 ml. of methanol. After 20 hr. at 0°, the precipitate was collected by filtration to give 700 mg. (43%) of prismatic needles; m.p. 110–115°. Recrystallization, accomplished by dissolution in 1 ml. of warm water, followed by dilution with 10 ml. of methanol, gave material melting at 133–137°.

Although the compound crystallizes exceedingly well, the melting point is not a reliable index of identity or purity, varying considerably from one preparation, and from one crystallization, to the next; samples melting as high as 145–155° have been obtained. A satisfactory infrared spectrum in potassium bromide could not be secured.

Anal. Calcd. for $C_6H_{11}NO_4$ (161.16): C, 44.71; H, 6.88; N, 8.69. Found: C, 44.81; H, 6.91; N, 8.82.

***N*-Methyl-*p*-toluenesulfonamidomethylsuccinic Acid.**—To a solution of 161 mg. (0.001 mole) of methylaminomethylsuccinic acid (II) and 336 mg. (0.006 mole) of potassium hydroxide in 1.5 ml. of water was added 384 mg. (0.002 mole) of finely powdered *p*-toluenesulfonyl chloride. When the mixture had been stirred magnetically for 20 hr. at 25°, the clear solution was diluted with 1 ml. of water and acidified with 1 ml. of 6 *N* aqueous hydrochloric acid. After 20 hr. at 0°, the precipitate was collected by filtration, washed with water, and recrystallized from water to give 220 mg. (70%) of needles; m.p. 141–144°; infrared spectrum: 5.95 (carboxyl), 7.50, 8.65 μ (—SO_2N—).

Anal. Calcd. for $C_{13}H_{17}NSO_6$ (315.35): C, 49.51; H, 5.44; N, 4.44. Found: C, 49.57; H, 5.47; N, 4.51.

Dimethyl Methylaminomethylsuccinate Hydrochloride (III).—(a) To a solution of approximately 3% methanolic hydrogen chloride (prepared by addition of 1 ml. of acetyl chloride to 20 ml. of methanol) was added 322 mg. (0.002 mole) of methylaminomethylsuccinic acid (II) and 832 mg. (0.008 mole) of 2,2-dimethoxypropane. After 45 hr. at 25°, the solution was concentrated under reduced pressure to give a remainder from which 20 ml. of toluene was vacuum distilled. A solution of the residue in a few drops of methanol was diluted with ethyl acetate (in which product is sparingly soluble) to give, after 20 hr. at 0°, 385 mg. (85%) of dense, long needles, m.p. 107–110°. The analytical sample, from methanol–ethyl acetate, melted at 111–113°; the crystals were stable under atmospheric conditions; infrared spectrum: 3.70, 3.75, 3.80, 4.00 (w), 4.25 (w) (substituted ammonium), 5.85 μ (ester), twenty prominent bands in finger print region.

Anal. Calcd. for $C_8H_{16}NO_4Cl$ (225.68): C, 42.57; H, 7.15; N, 6.21. Found: C, 42.38; H, 7.09; N, 6.28.

(b) To 4 ml. of methanol at 0° was added dropwise, with cooling, 715 mg. (0.44 ml.) (0.006 mole) of thionyl chloride; after 1 hr. at 0°, 322 mg. (0.002 mole) of methylaminomethylsuccinic acid (II) was added. After 45 hr. at 0°, followed by 25 hr. at 25°, the solution was concentrated under reduced pressure to give a remainder from which 20 ml. of toluene was vacuum distilled. A solution of the residue in a few drops of methanol was diluted with ethyl acetate to give 360 mg. (80%) of needles, m.p. 96–99°; recrystallization from methanol–ethyl acetate brought the melting point to 111–113°.

Dimethyl *N*-Methyl-*p*-toluenesulfonamidomethylsuccinate.—To a solution of 77 mg. (0.0004 mole) of *p*-toluenesulfonyl chloride in 1 ml. of anhydrous pyridine at 0° was added 68 mg. (0.0003 mole) of dimethyl methylaminomethylsuccinate hydrochloride (III). After 20 hr. at 0°, the mixture was diluted with water to give a precipitate which was collected by filtration, washed with water, and dried. Recrystallization from a mixture of ethyl acetate and petroleum ether (b.p. 30–60°) gave 55 mg. (53%) of dense, crystalline kernels, m.p. 63–64°. The analytical sample melted at 64–66°; infrared spectrum: 5.80 (ester), 7.50, 8.60 μ (—SO_2N—).

Anal. Calcd. for $C_{15}H_{21}NSO_6$ (343.40): C, 52.46; H, 6.17; N, 4.08. Found: C, 52.41; H, 5.94; N, 4.22.

Diethyl Methylaminomethylsuccinate Hydrochloride.—To a solution of approximately 6% ethanolic hydrogen chloride (prepared by addition of 2 ml. of acetyl chloride to 20 ml. of absolute ethanol) was added 403 mg. (0.0025 mole) of methylaminomethylsuccinic acid (II). After 20 hr. at 25°, the solution was concentrated under reduced pressure to give a residue from which three successive portions of 10 ml. of benzene were vacuum distilled. The ethanolic hydrogen chloride treatment (20 hr.) and evaporation with benzene were repeated. The residue was recrystallized from ethyl acetate to give 530 mg. (83%) of plates; m.p. 60–70°. The analytical sample, from ethyl acetate, melted at 70–71°; infrared spectrum: 3.65, 4.10 (w) (substituted ammonium), 5.80 μ (ester).

Anal. Calcd. for $C_{10}H_{20}NO_4Cl$ (253.73): C, 47.33; H, 7.95; N, 5.52; Cl, 13.97. Found: C, 47.08; H, 7.90; N, 5.86; Cl, 13.94.

Although the ester hydrochloride crystallizes well from ethyl acetate, the isolated solid is rather hygroscopic and must be stored in a desiccator; extended exposure to humid atmosphere leads to liquefaction and decomposition.

The compound was also prepared from ethyl 1-methyl-5-oxo-3-pyrrolidinecarboxylate with ethanolic hydrogen chloride at reflux temperature[8]; the reaction was worked up as was the esterification of II.

Diethyl *N*-Methyl-*p*-toluenesulfonamidomethylsuccinate.—To a solution of 77 mg. (0.0004 mole) of *p*-toluenesulfyl chloride in 1 ml. of anhydrous pyridine at 0° was added 51 mg. (0.0002 mole) of diethyl methylaminomethylsuccinate hydrochloride. After 2 days at 0°, the solution was diluted with water to give a precipitate which was collected by filtration, washed with water, dried, and recrystallized from a mixture of ethyl acetate and petroleum ether (b.p. 30–60°) to give 65 mg. (87%) of dense, crystalline kernels; m.p. 51–52°; infrared spectrum: 5.80 (ester), 7.50, 8.60 μ (—SO_2N—).

Anal. Calcd. for $C_{17}H_{25}NO_6S$ (371.45): C, 54.97; H, 6.78; N, 3.77. Found: C, 54.61; H, 6.69; N, 4.02.

1-Methyl-5-oxo-3-pyrrolidinecarboxylic Acid (V).—(a) Pyrolysis of methylaminomethylsuccinic acid (II) at the melting point during 5 min., followed by recrystallization from ethyl acetate, gave 70% of dense crystals; m.p. 155–156°[5]; infrared spectrum: 5.85 (carboxyl), 6.15 μ (cyclic tertiary amide).

Anal. Calcd. for $C_6H_9NO_3$ (143.14): C, 50.34; H, 6.34; N, 9.79. Found: C, 50.27; H, 6.26; N, 9.79.

(b) A solution of 161 mg. (0.001 mole) of methylaminomethylsuccinic acid (II) in 3 ml. of water was heated under

(6) Melting points were observed on a calibrated micro hot stage. Microanalyses were performed by Dr. S. M. Nagy, Massachusetts Institute of Technology, Cambridge, Massachusetts. Infrared spectra, in potassium bromide, were recorded with a Perkin-Elmer spectrophotometer, Model 137; only those maxima of significance in interpretation are noted.

(7) C. A. Bischoff, *Ann.*, **214**, 40 (1882).

(8) *Cf.* the ethanolysis of 5-oxo-2-pyrrolidinecarboxylic acid with ethanolic hydrogen chloride under reflux to give diethyl glutamate hydrochloride: R. B. Angier, C. W. Waller, B. L. Hutchings, J. H. Boothe, J. H. Mowat, J. Semb, and Y. SubbaRow, *J. Am. Chem. Soc.*, **72**, 74 (1950).

reflux for 15 hr.[9] The solution was concentrated under reduced pressure to give a residue (freely soluble in absolute ethanol) which was recrystallized from ethyl acetate to afford 105 mg. (74%); m.p. 145–155°.

Ethyl 1-methyl-5-oxo-3-pyrrolidinecarboxylate was prepared by vacuum distillation (after filtration of methylamine hydrobromide) of the product from treatment of diethyl bromomethylsuccinate[10] with 3 equivalents of 3.5 *N* ethanolic methylamine at 0°; b.p. 167–168°/20.5 mm.[11]; d_{20}^{20} 1.1170; $n^{25}D$ 1.4620; M_D calcd.: 42.43; M_D found: 42.13.

Anal. Calcd. for $C_8H_{13}NO_3$ (171.18): C, 56.12; H, 7.65. Found: C, 56.10; H, 7.55.

1-Methyl-5-oxo-3-pyrrolidinecarboxamide (VI).—To 5 ml. of concentrated aqueous ammonia at 0° was added 113 mg. (0.0005 mole) of dimethyl methylaminomethylsuccinate hydrochloride (III). After 20 hr. at 0°, the solution was concentrated under diminished pressure to give a residue which was triturated with chloroform to discard 22 mg. of insoluble ammonium chloride. The chloroform filtrate was concentrated under reduced pressure to give a residue which was recrystallized from a mixture of methanol and ethyl acetate to afford 60 mg. (85%) of plates; m.p. 140–142°[12]; infrared spectrum: 5.95, 6.05, 6.15, 6.65 μ (amide bands).

Anal. Calcd. for $C_6H_{10}N_2O_2$ (142.16): C, 50.69; H, 7.09; N, 19.71. Found: C, 50.97; H, 7.21; N, 19.88.

Methyliminodi(methylsuccinic) Acid (IV).—To a solution of 483 mg. (0.003 mole) of methylaminomethylsuccinic acid (II) and 486 mg. (0.003 mole) of carboxysuccinic acid (I) in 1 ml. of water was added 0.25 ml. of 37% aqueous formaldehyde (equivalent to 100 mg. or 0.0033 mole of formaldehyde); a brisk evolution of carbon dioxide commenced within a few minutes. A precipitate, which began to form within 1 hr., had completely pervaded the solution after 2 hr. The mixture was kept at 25° for 2 days, diluted with 2 ml. of water, and heated to dissolve the product. After 20 hr. at 25°, followed by 2 days at 0°, the precipitate was collected by filtration and recrystallized from water to afford 255 mg. (29%) of plates; m.p. 180–183°; infrared spectrum: 5.80, 5.85 μ (carboxyl).

Anal. Calcd. for $C_{11}H_{17}NO_8$ (291.26): C, 45.36; H, 5.89; N, 4.81. Found: C, 45.33; H, 5.92; N, 4.85.

Tetramethyl Methyliminodi(methylsuccinate) Hydrochloride.—To 2.5 ml. of methanol at 0° was added dropwise, with cooling, 357 mg. (0.22 ml.) (0.003 mole) of thionyl chloride; after 1 hr. at 0°, 146 mg. (0.0005 mole) of methyliminodi(methylsuccinic) acid (IV) was added. After 2 days at 0°, followed by 2 days at 25°, the solution was concentrated under diminished pressure to give a remainder from which 20 ml. of toluene was vacuum distilled. Two recrystallizations of the residue from ethyl acetate gave 165 mg. (86%) of needles; m.p. 117–121°; infrared spectrum: 4.20, 4.30 (substituted ammonium), 5.80 μ (ester).

Anal. Calcd. for $C_{15}H_{26}NO_8Cl$ (383.83): C, 46.93; H, 6.83; N, 3.65. Found: C, 47.15; H, 6.80; N, 3.57.

Acknowledgment.—The author is indebted to Louis S. Harris for preparative assistance in the early work; to the National Institute of Mental Health (M-2029) and the National Heart Institute (H-2205), National Institutes of Health, United States Public Health Service; and to the Eugene Higgins Trust for financial support.

(9) Cyclization proceeded to a lesser extent during short periods of reflux as shown by incomplete solubility of the reaction residue in absolute ethanol; *cf.* the conversion of aqueous glutamic acid to 5-oxo-2-pyrrolidinecarboxylic acid: J. P. Greenstein and M. Winitz, "Chemistry of the Amino Acids," Vol. 3, J. Wiley & Sons, Inc., New York, N. Y., 1961, pp. 1934–1937.

(10) R. Anschütz and F. Reuter, *Ann.*, **254**, 144 (1889). In the older literature, bromomethylsuccinic acid was known as "itabrompyrotartaric acid."

(11) *Cf.* the preparation from diethyl itaconate with methylamine: Y. H. Wu and R. F. Feldkamp, *J. Org. Chem.*, **26**, 1519 (1961).

(12) *Cf.* the preparation from dimethyl itaconate with one equivalent of methanolic methylamine followed by excess methanolic ammonia: H. C. Scarborough, J. L. Minielli, B. C. Lawes, W. G. Lobeck, Jr., J. R. Corrigan, and Y. H. Wu, *ibid.*, **26**, 4955 (1961).

Acyl Derivatives of 3,4-Dihydro-4-oxobenzo-1,2,3-triazine

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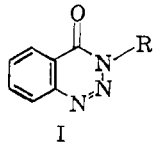
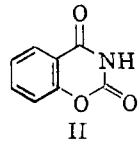
Heller[1] has reported the preparation of an acetyl and a benzoyl derivative of 3,4-dihydro-4-oxobenzo-1,2,3-triazine (I, R = H) by reaction of the sodium or silver salt with the appropriate acid chloride. These compounds were formulated as lactam (*i.e.* *N*-acyl) derivatives rather than lactim (*O*-acyl) derivatives since (i) methylation under similar conditions had been shown to give the *N*-methyl derivative (I, R=Me), and (ii) ethoxycarbonylation had given an ethoxycarbonyl derivative which was degraded by hot hydrochloric acid to (II); the latter compound contains nitrogen linked to two carbonyl groups, thus implying formula (I, R = COOEt) for the ethoxycarbonyl derivative, assuming that no lactim–lactam isomerisation occurs under the influence of acid.



I



II

In two recent reviews of triazine chemistry,[2,3] the possibility that these compounds are *O*-acyl derivatives has been revived, and, without further evidence, the lactim formulation has actually been adopted for purposes of tabulation.

However, the infrared spectra of both the acetyl and the benzoyl derivative show two absorption bands due to carbonyl in the 1750–1650-cm.$^{-1}$ region. In this respect, these compounds resemble the *N*-acylisocarbostyrils, but differ from, *e.g.*, 2-benzoyloxypyridine and 4-acetoxyisoquinoline which show only one such band (at 1740 cm.$^{-1}$).[4] The ultraviolet absorption spectrum of the acetyl derivative is similar to that of the parent compound, though shifted to shorter wave length;

(1) G. Heller, *J. prakt. Chem.*, (2) **111**, 1 (1925).

(2) J. G. Erickson, "The Chemistry of Heterocyclic Compounds," Vol. 10, A. Weissberger, ed., Interscience Publishers, Inc., New York, N. Y., 1956, p. 17.

(3) J. P. Horwitz, "Heterocyclic Compounds," Vol. 7, R. C. Elderfield, ed., J. Wiley & Sons, Inc., New York, N. Y., 1961, p. 787.

(4) M. M. Robison and B. L. Robison, *J. Org. Chem.*, **21**, 1337 (1956).

that of the benzoyl derivative shows the same shift, masked partly, however, by additional absorption due to the benzoyl group.

We conclude, therefore, that, as in the case of isocarbostyril,[4] acylation of 3,4-dihydro-4-oxobenzo-1,2,3-triazine (I, R = H) yields the *N*-acyl derivatives (I, R = COMe, COPh), as originally suggested by Heller.

Experimental

Ultraviolet absorption spectra were determined for ethanol solutions (Higler Unicam spectrophotometer); infrared spectra were measured for Nujol and hexachlorobutadiene mulls (Perkin-Elmer 21 spectrophotometer). Compounds were prepared by Heller's methods; experimental details are given below in cases where his information is incomplete.

3,4-Dihydro-4-oxobenzo-1,2,3-triazine occurred as needles (from ethanol), m.p. 210° dec. (Heller, m.p. 213° dec.), ν_{max} 3140 (N—H) and 1695 cm.$^{-1}$ (C:O), λ_{max} 209 (ϵ 17,100), 225 (ϵ 20,050) and 281 mμ(ϵ 6100), λ_{min} 212 (ϵ 16,670) and 257 mμ (ϵ 3600), λ_{infl} 294 (ϵ 4300) and 305 mμ (ϵ 2750).

3-Acetyl-3,4-dihydro-4-oxobenzo-1,2,3-triazine.—Silver acetate (1.2 g.), dissolved in aqueous ethanol, was added with shaking to the triazine (1.1 g.) in warm ethanol. The silver salt separated as a white solid, was collected, and dried *in vacuo*.

Freshly distilled acetyl chloride (1 ml.) was added to a suspension of the silver salt (1.5 g.) in dry benzene (30 ml.), and the mixture was refluxed for 30 min. After standing overnight at room temperature, the silver chloride was removed, and the filtrate evaporated. The residual orange sirup slowly solidified. The acetyl derivative (0.7 g.) was crystallized from water, dried, and recrystallized from light petroleum (b.p. 100–120°), forming needles, m.p. 165° (Heller, m.p. 165°), ν_{max} 1695 and 1655 cm.$^{-1}$ (C:O) [*cf.* *N*-acetylisocarbostyril,[4] ν_{max} 1705 and 1665 cm.$^{-1}$], λ_{max} 219 (ϵ 23,100), 252 (ϵ 11,360) and 298 mμ (ϵ 4320), λ_{min} 239 (ϵ 9900) and 272 mμ (ϵ 3580), and λ_{infl} 261 mμ (ϵ 8400).

3-Benzoyl-3,4-dihydro-4-oxobenzo-1,2,3-triazine.—The triazine (1.5 g.) in warm ethanol was treated with sodium ethoxide (from 0.24 g. of sodium) in ethanol (30 ml.). After standing overnight at room temperature, ethanol was removed *in vacuo;* trituration of the residue with dry toluene gave the sodium salt (1.8 g.) as a white solid. This was converted to the benzoyl derivative (1 g.), which separated from light petroleum (b.p. 100–120°) as needles, m.p. 132° (Heller, m.p. 132–133°), ν_{max} 1718 and 1690 cm.$^{-1}$ (C:O), λ_{max} 209 (ϵ 26,150) and 227 mμ (ϵ 28,800), λ_{min} 213 mμ (ϵ 24,900), λ_{infl} 249 (ϵ 14,800) and 276 mμ (ϵ 9850).

Equilibration of *cis*- and *trans*-α-Methylstilbene in Presence of Potassium *t*-Butoxide as Catalyst[1]

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Incidental to the study of base-catalyzed reactions of alkenyl-benzenes *cis*- and *trans*-α-methylstilbenes have been equilibrated in the presence of catalytic amounts of potassium *t*-butoxide at 139 ± 1° and 200 ± 1°. The equilibrium mixture consisted, respectively, of 21.0% and 21.2% *cis*-, 76.8 and 74.0% *trans*-α-methylstilbene, and 2.2 and 4.8% 2,3-diphenyl-1-propene.

Cis- and *trans*-α-methylstilbene were synthesized by a modification of the procedure described by Abd Elhafez and Cram[3]. A mixture of the two diastereomers of 1,2-diphenyl-1-propanol was transformed to a solid mixture of two diastereomeric chlorides by the action of thionyl chloride in the presence of pyridine. The chlorides were separated into distinct diastereomeric species by fractional crystallization and subsequently dehydrohalogenated by means of 5% ethanolic potassium hydroxide[4] to give pure *cis*- and *trans*-α-methylstilbenes. Attempted preparation of pure *cis*-α-methylstilbene by the method described by Simamura and Suzuki[5] failed although the *trans* isomer was obtained in pure form. The equilibration reactions were made by refluxing a solution of methylstilbenes in either xylene or decahydronaphtalene in the presence of 0.1 *M* equivalent of potassium *t*-butoxide, based on the stilbenes used.

Starting with *trans* isomer in xylene solution (temp. 139 ± 1°), the equilibrium was reached after twenty-four hours while at 200°, in decahydronaphtalene solution, within one hour equilibrium was achieved. The progress of the reaction was investigated by taking out samples during the reaction and analyzing by gas chromatography. Equilibration reactions were also made using either pure *cis*-α-methylstilbene or a mixture of methylstilbenes enriched in the *cis* isomer.

It was found that 2,3-diphenyl-1-propene was formed in equilibrium concentration shortly after the reflux temperature of the solvent was reached; the double bond migration was much faster than the *cis-trans* isomerization. The composition of 1,2-diphenylpropenes at equilibrium is summarized in Table I. The hydrogenation of the equilibrated mixture produced only 1,2-diphenylpropane, which shows that the compounds present had the same skeleton as the starting α-methylstilbene.

TABLE I

EQUILIBRIUM MIXTURE OF *cis*- AND *trans*-α-METHYLSTILBENE AND 2,3-DIPHENYL-1-PROPENE

Temperature (±1°)	139°	200°
cis-α-Methylstilbene, %	21.0	21.2
trans-α-Methylstilbene, %	76.6	74.0
2,3-Diphenyl-1-propene, %	2.4	4.8

(1) Paper XXIV of the series Base Catalyzed Reaction. For paper XXIII, see J. Shabtai, E. M. Lewicki, and H. Pines, *J. Org. Chem.*, **27**, 2618 (1962).

(2) On leave of absence from Polytechnic Institute, Lodz, Poland.

(3) F. A. Abd Elhafez and D. J. Cram, *J. Am. Chem. Soc.*, **75**, 340 (1953).

(4) E. Ellingboe and R. C. Fuson, *ibid.*, **55**, 2960 (1933).

(5) O. Simamura and H. Suzuki, *Bull. Chem. Soc. Japan*, **27**, 234 (1954).

The structure of 2,3-diphenyl-1-propene was established by means of ozonolysis. Formaldehyde and desoxybenzoin obtained from the ozonolysis by the reductive decomposition of the ozonide afforded final evidence of the position of the double bond in 2,3-diphenyl-1-propene.

The retention volumes of the diphenylpropenes and of some related compounds are summarized in Table II.

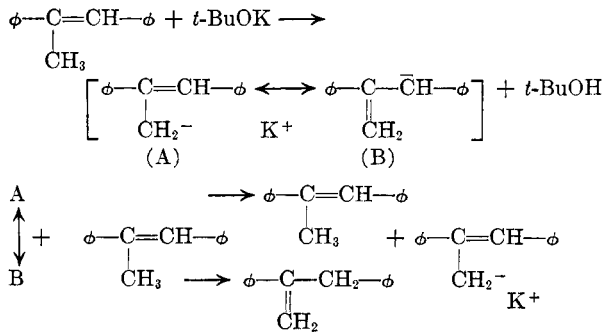
TABLE II

RETENTION VOLUMES TO α-METHYLSTILBENES AND OF RELATED COMPOUNDS RELATIVE TO PHENYLCYCLOHEXANE[a]

Compound	Rv/Rv —Phenylcyclohexane— Temp. 200°	Temp. 220°
cis-α-Methylstilbene	2.95	2.70
trans-α-Methylstilbene	5.35	4.65
2,3-Diphenyl-1-propene	3.44	3.14
1,2-Diphenylpropane	2.79	2.51
cis-1,2-Diphenylcyclopropane	3.68	3.33
trans-1,2-Diphenylcyclopropane	5.44	4.74

[a] 4 m. column filled with 8% silicon (Dow-Corning 550 fluid) on 30–60 mesh chromosorb P; helium flow rate, 75 ml./min.; helium pressure, 35 p.s.i.

The isomerization reaction most probably involves the removal of an allylic proton to form a carbanion and can be presented as follows:



The resonance structure (B) of the carbanion formed is more reactive than the form (A) because of smaller delocalization of the negative charge in the anion. For this reason it can metallate an α-methylstilbene molecule relatively fast, giving rise to the formation of 2,3-diphenyl-1-propene. The reaction explains the rapid appearance of this compound in the mixture. The rotation around the C—C bond in the carbanion (B) followed by its transformation to the form (A) and chain propagation reaction leads to relatively slow *cis-trans* isomerization.

Experimental

1,2-Diphenyl-1-propanol.—This compound was prepared from 100.5 g. (0.75 mole) of 2-phenylproponaldehyde, 21.1 g. (0.9 g.-atom) of magnesium, and 141.3 g. (0.9 mole) of bromobenzene.[6a] Anhydrous ether, 500 ml., was used as solvent. The addition product was decomposed with 400 ml. of cold 20% sulfuric acid, the organic layer was separated, dried over anhydrous magnesium sulfate, and distilled *in vacuo* yielding 79.5 g (50%) of colorless oil, b.p. 170–175°/9 mm. Hg; $n^{25}D$ 1.5707.

1,2-Diphenyl-1-propyl Chloride.—Thionyl chloride, 59.5 g. (0.5 mole), was added over a period of 30 min. to a stirred mixture of 79.5 g. (0.38 mole) of 1,2-diphenyl-1-propanol and 36.4 g. (0.4 mole) of pyridine placed in an ice bath. The resulting thick brown oil was stirred at room temperature for an additional 30 min. and then heated at 60–65° for 1 hr. and at 90–100° for 1.5 hr. until the evolution of sulfur dioxide ceased. The mixture was poured on 200 g. of ice. The reaction product solidified immediately. It was filtered, washed with cold water, and crystallized twice from 100 ml. and 60 ml. of ethanol. In order to resolve the mixture into pure *erythro* and *threo* chlorides, the crystals were extracted with five 100-ml. portions of hot *n*-pentane; the solution was cooled immediately. The insoluble residue and the first crop of crystals were found to be pure *dl-erythro*-chloride, colorless plates (after recrystallization from ethanol-benzene), m.p. 140–141° (reported m.p. 139.5–140.5°).[6b] Yield 10.0 g. (11%). From the mother liquor, 41.0 g. (48%) of *dl-threo*-chloride has been obtained in the form of colorless needles which after recrystallization from ethanol melted at 56.5–57° (reported 54–55°).[6b]

Anal. Calcd. for $C_{15}H_{15}Cl$: C, 78.08%; H. 6.55%. Found: *dl-Threo*-isomer, C, 78.27%: H, 6.43%. *dl-Erythro*-isomer, C, 78.44%; H, 6.34%.

***cis*-α-Methylstilbene.**—*dl-erythro*-1,2-Diphenyl-1-propyl chloride, 5.8 g. (0.025 mole) in 250 ml. of 5% ethanolic potassium hydroxide solution was refluxed for 16 hr. The solvent was then removed *in vacuo*, and the residue washed with cold water. The crude *cis*-α-methylstilbene was recrystallized from 10 ml. of hot methanol. Colorless prisms were obtained melting at 49–50° (reported m.p. 47–48°[6a]), yield, 4.4 g. (90%)

Anal. Calcd. for $C_{15}H_{14}$: C, 92.74%; H, 7.26%. Found: C, 92.33%; H, 6.96%.

***trans*-α-Methylstilbene.**—*dl-threo*-1,2-Diphenyl-1-propyl chloride, 5.8 g. (0.025 mole), was dehydrohalogenated as described above. Yield, 4.5 g. (93%). The *trans*-α-methylstilbene in the form of colorless plates (from ethanol) melted at 82–83°.

Anal. Calcd. for $C_{15}H_{14}$: C, 92.74%; H, 7.26%. Found: C, 92.90%; H, 7.32%.

Equilibration of *cis*- and *trans*-α-Methylstilbenes. General Procedure.—A 1.94-g. sample (0.01 mole) of α-methylstilbene was refluxed in 20.0 g. of the suitable solvent in presence of 0.11 g. (0.001 mole) of potassium *t*-butoxide. Samples were taken periodically and analyzed by gas chromatography.

Hydrogenation of the Equilibrated Mixture.—An equilibrated mixture of diphenylpropenes at 200°, 1.94 g., was hydrogenated at room temperature and at atmospheric pressure in the presence of 0.2 g. of 5% palladium on charcoal. The hydrogenated product was found to be pure 1,2-diphenylpropane.

Ozonolysis.—An equilibrated mixture of diphenylpropenes at 139°, 9.7 g. (0.05 mole) in 50 ml. of carbon tetrachloride was ozonized at −20°. The ozonide was decomposed by refluxing the solution for 2 hr. in the presence of 20 ml. of acetic acid and 20 g. of zinc powder. The gases evolved were passed through a solution of 0.5 g. of dimedone in 25 ml. of water and 10 ml. of ethanol. The solid obtained, 0.2 g., after recrystallization from ethanol melted at 187–188° and did not depress the melting point of an authentic sample produced from the condensation of formaldehyde with dimedone.

The solution obtained after the decomposition of the ozonide was found to consist according to gas chromatographic analysis, of benzaldehyde, acetophenone, and desoxybenzoin.

(6) D. J. Cram and F. A. Abd Elhafez (a) *J. Am. Chem. Soc.*, **74**, 5828 (1952); (b) *ibid.*, **74**, 5851 (1952).

The Synthesis of 6α-Difluoromethyl Steroids[1]

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Certain modifications of the hydrocortisone molecule at C-6, for example the introduction of a 6α-methyl group[2] or a 6α-halogen atom,[2] have resulted in derivatives having valuable therapeutic properties. Recently several 6α-monofluoromethyl steroids[3] and 6α-trifluoromethyl steroids[4] have been synthesized. We now report the preparation of 6α-difluoromethyl corticoids, a study which was facilitated by the availability of a suitable intermediate (I)[3a] for the preparation of a 6-formyl cortical steroid (II), and a mild procedure[5] for the selective replacement of formyl oxygen with fluorine.

Oxidation of the hydroxymethyl derivative I with chromium trioxide in pyridine[6] afforded ketoaldehyde II. Treatment of this aldehyde with a large excess of a reagent comprised of two parts of hydrogen fluoride, ten parts of sulfur tetrafluoride, and one part of tetrahydrofuran afforded a difficultly separable mixture of the desired difluoromethyl derivative IIIa and a product, assigned either the fluoro ether[7] structure IIIb or IIIc, resulting from attack on the bismethylenedioxy grouping.[8] Fortunately the relatively high order of reactivity of the 6-formyl group towards fluorination with sulfur tetrafluoride permitted the use of milder conditions (a lower hydrogen fluoride to sulfur tetrafluoride ratio was employed) which selectively fluorinated the formyl group affording IIIa in over 60% yield. Survival of the bismethylenedioxy group in the presence of the hydrogen fluoride–sulfur tetrafluoride reagent provided another synthetic application for this versatile protective grouping.[9] Reduction of the 6α-difluoromethyl compound (IIIa) with lithium aluminum hydride afforded the diol IV which was oxidized to the monoketone V by the Oppenauer method. Selenium dioxide dehydrogenation,[10] hydrolysis of the bismethylenedioxy protective group and acetylation of the C-21 alcohol function afforded a low yield of 6α-difluoromethylprednisolone 21-acetate (VIII). Removal of the bismethylenedioxy protective group and acetylation prior to the selenium dioxide treatment afforded some improvement in the yield of VIII from V.

(1) Presented in part at the Symposium on Fluorine Containing Compounds of Biological Interest, at the 140th National Meeting of the American Chemical Society, September 6, 1961, Chicago, Ill.

(2) See L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, pp. 685, 686, and 692, 693.

(3) (a) P. F. Beal, R. W. Jackson, and J. E. Pike, *J. Org. Chem.*, **27**, 1752 (1962); (b) A. L. Nussbaum, M. Kirtley, A. V. Maresco, and E. P. Oliveto, *ibid.*, **26**, 2147 (1961).

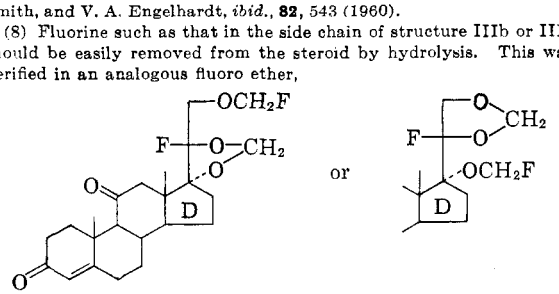
(4) W. O. Godtfredsen, S. African Patent 611049; W. O. Godtfredsen and S. Vangedal, *Acta Chem. Scand.*, **15**, 1786 (1961).

(5) D. G. Martin and F. Kagan, *J. Org. Chem.*, **27**, 3164 (1962) and references cited.

(6) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Am. Chem. Soc.*, **75**, 422 (1953).

(7) An analogous reaction $(HCHO)_x + SF_4 \longrightarrow CH_2F_2$ (49%) + $FCH_2—O—CH_2F$ (21%) has been reported, W. R. Hasek, W. C. Smith, and V. A. Engelhardt, *ibid.*, **82**, 543 (1960).

(8) Fluorine such as that in the side chain of structure IIIb or IIIc should be easily removed from the steroid by hydrolysis. This was verified in an analogous fluoro ether,



obtained from the bismethylenedioxy derivative of cortisone on fluorination under the same conditions (see Experimental). Hydrolysis of a small analytically pure specimen of this difluoro derivative in aqueous formic acid regenerated cortisone (see Experimental).

Experimental[11]

17,20;20,21-Bismethylenedioxy-6α-formyl-3β-hydroxy-5α-pregnan-11-one Acetate (II).—The 6α-hydroxymethyl compound I[3a] (10.0 g.) was dissolved in pyridine (100 ml.) and oxidized for 18 hr. at room temperature with the chromium trioxide–pyridine complex prepared from chromium trioxide (10.0 g.) and pyridine (100 ml.). Isolation was effected by the addition of benzene–ether (1:1) and water followed by filtration through Supercel. The organic layer was separated and the aqueous layer twice re-extracted with benzene–ether. The combined extracts were washed with sodium bicarbonate solution, water, dried (sodium sulfate), and the solvent removed; toluene (200 ml.) was added and the solvent evaporated to remove residual pyridine. This latter operation was repeated twice. The residue was dissolved in methylene chloride (25 ml.) and chromatographed on Florisil[12] (900 g.). The column was eluted with increasing proportions of acetone in Skellysolve B.[13] Elution with 20% acetone–Skellysolve B gave, after combination of the fractions and crystallization from acetone–Skellysolve B, ketoaldehyde II, 2.48 g., m.p. 212–220°. Crystallization from acetone–Skellysolve B gave a sample, m.p. 205–210°; ν_{max} 2710 (—CHO), 2680, 1720, 1702, 1275 sh, 1260, 1250, 1125, 1105, 1085, 1040, 1010 cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{36}O_8$: C, 65.53; H, 7.61. Found: C, 65.19, 65.33; H, 7.69, 8.14.

17,20;20,21-Bismethylenedioxy-6α-difluoromethyl-3β-hydroxy-5α-pregnan-11-one Acetate (IIIa).—In a 100-ml. stainless steel autoclave a mixture of 0.94 g. of 17,20;20,21-bismethylenedioxy - 6α - formyl - 3β - hydroxy - 5α - pregnan-11-one acetate, 0.05 ml. of water, 0.25 ml. of tetrahydrofuran, 20 ml. of methylene chloride, and 46 g. of sulfur tetrafluoride was agitated for 16 hr. at 15°. After venting the autoclave,[5] its contents were diluted with methylene chloride and washed with excess aqueous potassium bicar-

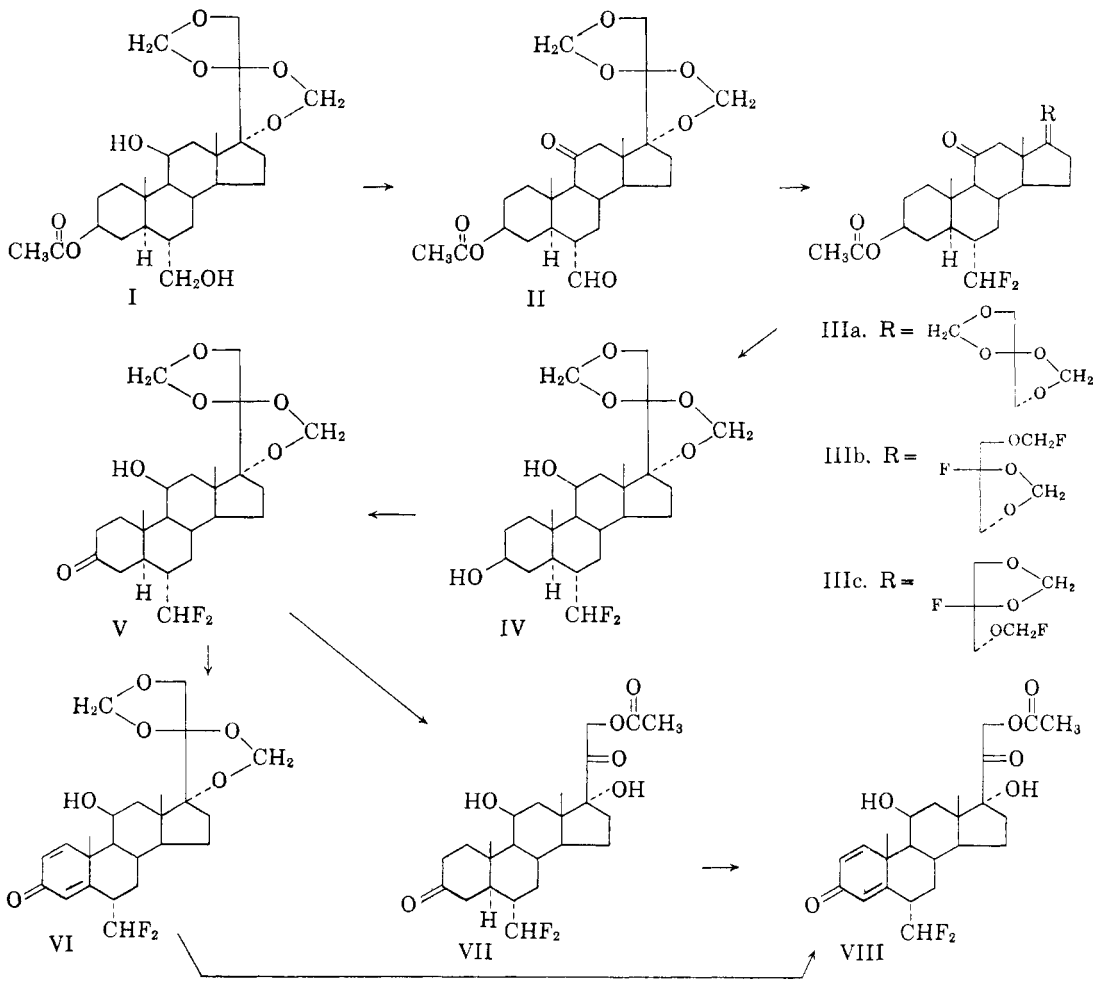
(9) *Cf.* R. E. Beyler, F. Hoffman, L. H. Sarett, and M. Tishler, *J. Org. Chem.*, **26**, 2426 (1961), and prior references.

(10) C. Meystre, H. Frey, W. Voser, and A. Wettstein, *Helv. Chim. Acta*, **39**, 734 (1956).

(11) Melting points are uncorrected. Rotations were observed at 26° on chloroform solutions. Infrared spectra were recorded on a Perkin-Elmer Model 21 spectrophotometer from Nujol mulls. Ultraviolet spectra were taken on 95% ethanol solutions using a Cary Model 14 spectrophotometer.

(12) A synthetic magnesia–silica gel manufactured by the Floridin Co., Warren, Pa.

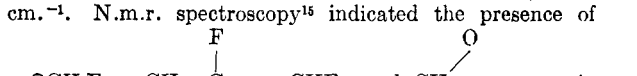
(13) A saturated hydrocarbon fraction, b.p. 60–71°.



bonate. This organic solution was dried (sodium sulfate) and concentrated to dryness. Chromatography on Florisil with increasing percentages of acetone in Skellysolve B gave crystalline material from the 2–5% acetone–Skellysolve B eluates; recrystallization of those fractions melting between 232 and 238° afforded 0.59 g. III (60%), m.p. 233–238°. Further recrystallization from acetone and Skellysolve B gave the analytical sample, m.p. 238–242°; $[\alpha]_D$ ($CHCl_3$) −40°; ν_{max} 1720, 1710, 1280 sh, 1265, 1255, 1133, 1104, 1088, 1045, 1027 cm.$^{-1}$.

Anal. Calcd. for $C_{26}H_{36}F_2O_7$: C, 62.63; H, 7.28; F, 7.62. Found: C, 62.38; H, 7.11; F, 7.44.

17,20-Methylenedioxy-20-fluoro-21-fluoromethoxy-6α-difluoromethyl-3β-hydroxy-5α-pregnan-11-one Acetate IIIb or Alternate Structure IIIc.—A mixture of 17,20;20,21-bismethylenedioxy - 6α - formyl - 3β - hydroxy - 5α - pregnan - 11 - one acetate (1.00 g.), 0.75 ml. of water, 3.50 ml. of tetrahydrofuran, 20 ml. of methylene chloride, and 46 g. of sulfur tetrafluoride was agitated overnight at 15°. The crude product was isolated as described above and chromatographed on 50 g. of Florisil without delay. Elution with 2% acetone in Skellysolve B afforded 297 mg. of a partially crystalline gum which was evidently a mixture[14] of IIIa and IIIb (or IIIc). Continued elution with 2% acetone–Skellysolve B and with 3% acetone–Skellysolve B afforded fractions totalling 404 mg. from which crystalline material was obtained by trituration with ether. Combining and recrystallizing these fractions from ether–Skellysolve B gave 269 mg. of a substance melting 173–174° with decomposition. Three recrystallizations from acetone–Skellysolve B afforded the analytical sample, m.p. 183.5–184° with decomposition; $[\alpha]_D$ 0 (micro determination); ν_{max} 1723, 1703, 1253, 1178, 1147, 1130, 1093, 1078, 1035, 1018 cm.$^{-1}$. N.m.r. spectroscopy[15] indicated the presence of



groups in addition to the angular methyl groups and the acetate function.

Anal. Calcd. for $C_{26}H_{36}F_4O_6$: C, 59.99; H, 6.97; F, 14.60; mol. wt., 520.55. Found: C, 59.42; H, 7.07; F, 14.33; mol. wt.,[16] 519.5.

17,20;20,21-Bismethylenedioxy-6α-difluoromethyl-5α-pregnane-3β,11β-diol (IV).—A solution of 17,20;20,21-bismethylenedioxy-6α-difluoromethyl-3β-hydroxy - 5α - pregnan-11-one acetate (0.86 g.; m.p. 237.5–240°; and 0.59 g.; m.p. 233–238°; total weight 1.45 g.) in benzene (20

(14) Repeat chromatography of these fractions yielded 88 mg. of 111a.m.p. 227–236°, as the only crystalline product. However, the observation that crystalline IIIb or IIIc was not obtained from this repeat chromatography was not surprising since the fluoro ether derivative was not very stable except as a pure crystalline solid.

(15) N.m.r. spectra were determined in deuterochloroform on a Varian DP-60 spectrometer at 60 Mc. and calibrated against internal tetramethylsilane by audio-frequency–side band interpolations. The authors are grateful to Dr. G. Slomp and Mr. F. A. MacKellar of these laboratories for the determination and interpretation of these spectra. These spectra will be included in a forthcoming publication by them.

(16) The authors are indebted to Dr. John W. Shell of these laboratories for the molecular weight determination by the method of X-ray diffraction (J. W. Shell, *J. Pharm. Sci.*, **51**, in press.)

(17) R. E. Beyler, R. M. Moriarty, F. Hoffman, and L. H. Sarett, *J. Am. Chem. Soc.*, **80**, 1517 (1958).

ml.) and ether (10 ml.) was added dropwise to a stirred suspension of lithium aluminum hydride (2.0 g.) in ether (40 ml.) and benzene (80 ml.) under nitrogen. The reduction was allowed to proceed at room temperature for 1.5 hr. Isolation was effected by the successive addition of ethyl acetate and water. Filtration of the inorganic salts with the aid of Supercel, and evaporation of the solvent gave a crystalline residue. Recrystallization from acetone–Skellysolve B gave 990 mg., m.p. 186–188°. Further crystallization from acetone–Skellysolve B gave 17,20;20,21-bismethylenedioxy-6α-difluoromethyl-5α-pregnane-3β,11β-diol, m.p. 186–188°; ν_{max} 3500, 3250, 1198, 1173, 1130, 1100–1080, 1065, 1048, 1030, 1023, 1007, 990 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{36}F_2O_6$: C, 62.88; H, 7.86; F, 8.3. Found: C, 62.95; H, 7.99; F, 8.2.

17,20;20,21-Bismethylenedioxy-6α-difluoromethyl-11β-hydroxy-5α-pregnan-3-one (V).—17,20;20,21-Bismethylenedioxy-6α-difluoromethyl-5α-pregnane-3β,11β-diol (0.625 g., m.p. 186–188°) was stirred and refluxed for 1 hr. in toluene (100 ml.) and cyclohexanone (30 ml.) while removing water as its toluene azeotrope. Aluminum *t*-butoxide (1.3 g.) was added and the solution heated under reflux for 18 hr. The mixture was then cooled and washed successively with Rochelle salt solution, dilute hydrochloric acid, water, and finally dried (sodium sulfate). Removal of the solvent gave an oil which was dissolved in methylene chloride (10 ml.) and chromatographed on Florisil (50 g.). Elution with increasing proportions of acetone in Skellysolve B gave crystalline material from the 10 to 20% acetone–Skellysolve B eluates. Crystallization from acetone–Skellysolve B gave 0.391 g., m.p. 184–188°. Further crystallization from the same solvent gave 17,20;20,21-bismethylenedioxy-6α-difluoromethyl-11β-hydroxy-5α-pregnan-3-one, acetone solvate, m.p. 189–190°; ν_{max} 3510, 1712, 1135, 1100, 1090, 1025 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{34}F_2O_6 \cdot C_3H_6O$: C, 63.02; H, 7.78; F, 7.39. Found: C, 63.18; H, 7.62; F, 7.74.

6α-Difluoromethylprednisolone-B.M.D. (VI).—A mixture of 17,20;20,21-bismethylenedioxy-6α-difluoromethyl-11β-hydroxy-5α-pregnan-3-one (284 mg., m.p. 184–188°) and selenium dioxide (400 mg.) in *t*-butyl alcohol (20 ml.) and acetic acid (0.1 ml.) was heated to reflux for 20 hr. Further selenium dioxide (400 mg.) was then added and the reflux period continued for another 24 hr. After cooling, the insoluble material was removed by filtration through Celite; the filtrate was then evaporated to dryness in a nitrogen stream, and the residue extracted with ethyl acetate. These extracts were washed successively with sodium bicarbonate solution, freshly prepared ice-cold ammonium sulfide solution, dilute aqueous ammonia, dilute hydrochloric acid, sodium bicarbonate solution, and water. After drying over sodium sulfate the solvent was removed *in vacuo* to give an oil which was dissolved in methylene chloride (10 ml.) and chromatographed on Florisil (25 g.). Elution with increasing proportions of acetone in Skellysolve B gave crystalline material from the 20% acetone–Skellysolve B to give 6α-difluoromethylprednisolone-B.M.D., 64 mg., m.p. 248–252°. Further crystallization from acetone–Skellysolve B gave material, m.p. 263–265°; ν_{max} 3370, 1660, 1608, 1182, 1125, 1102, 1082, 1062, 1053, 1038, 1026, 1005 cm.$^{-1}$; λ_{max} 242 mμ (ε 15,550).

Anal. Calcd. for $C_{24}H_{30}F_2O_6$: C, 63.72; H, 6.64; F, 8.41. Found: C, 63.67; H, 6.73; F, 8.43.

6α-Difluoromethylprednisolone 21-Acetate (VIII). Procedure A.—6α-Difluoromethylprednisolone-B.M.D. (480 mg.) was suspended in 20 ml. of 65% aqueous formic acid and the mixture heated in a nitrogen stream on a steam bath for 15 min. The solution was then cooled and poured onto ice water; the organic material was extracted with ethyl acetate. The combined extracts were washed successively with water, sodium bicarbonate solution, water and then dried (sodium sulfate). Removal of the solvent gave an oil which was dissolved in pyridine (35 ml.) and acetic anhydride (5 ml.). After standing 18 hr. at room temperature this mixture was poured onto ice:sodium bicarbonate solution and the organic material extracted with ethyl acetate. The combined extracts were washed with dilute hydrochloric acid, sodium bicarbonate solution, water and dried (sodium sulfate). Removal of the solvent gave an oil which was dissolved in methylene chloride and chromatographed on Florisil (40 g.). Elution with increasing proportions of acetone in Skellysolve B gave crystalline material from the 20–30% acetone–Skellysolve B eluates. Crystallization from acetone–Skellysolve B gave 25 mg., m.p. 210–214° (positive triphenyltetrazolium chloride test). Further crystallization from acetone–Skellysolve B gave 6α-difluoromethylprednisolone 21-acetate, acetone solvate, m.p. 212–215°; ν_{max} 3520, 3240, 1750, 1722, 1650, 1610, 1600, 1260, 1250, 1230, 1180, 1125, 1055, 1040 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{30}F_2O_6 \cdot C_3H_6O$: C, 63.52; H, 7.06; F, 7.45. Found: C, 63.59; H, 6.92; F, 7.19, 7.49.

6α-Difluoromethyl-4,5α-dihydrohydrocortisone 21-Acetate (VII).—17,20;20,21-Bismethylenedioxy-6α-difluoromethyl-11β-hydroxy-5α-pregnan-3-one (250 mg.) was heated on a steam bath in 10 ml. of 65% formic acid in a nitrogen stream for 10 min. Isolation was then effected by cooling and then pouring the reaction mixture onto ice-water, and extracting the organic material with methylene chloride. The combined extracts were washed with dilute sodium bicarbonate solution, water and dried (sodium sulfate). After evaporation of the solvent the residue was dissolved in pyridine (10 ml.) and acetic anhydride (5 ml.). After standing 18 hr. at room temperature, the reaction mixture was poured onto ice–water and extracted with methylene chloride. These extracts were washed with dilute hydrochloric acid, sodium bicarbonate solution, water and dried (sodium sulfate). Evaporation of the solvent gave an oil which was dissolved in methylene chloride (10 ml.) and chromatographed on Florisil (25 g.). Elution with increasing proportions of acetone in Skellysolve B gave crystalline material from the 20–30% acetone–Skellysolve B eluates. These were combined and crystallized from acetone–Skellysolve B to give 86 mg., m.p. 189–192° (positive triphenyltetrazolium chloride test). Further crystallization from acetone–Skellysolve B gave m.p. 192–195°; ν_{max} 3620, 3420, 1755, 1725, 1704, 1277, 1237, 1202, 1125, 1090, 1063, 1050, 1020, 1002 cm.$^{-1}$.

Anal. Calcd. for $C_{24}H_{34}F_2O_6 \cdot C_3H_6O$: C, 63.00; H, 7.78; F, 7.39. Found: C, 62.45; H, 7.78; F, 7.64.

6α-Difluoromethylprednisolone 21-Acetate (VIII). Procedure B.—6α-Difluoromethyl-4,5α-dihydrohydrocortisone 21-acetate (307 mg.) and selenium dioxide (400 mg.) in *t*-butyl alcohol (25 ml.) and acetic acid (1.5 ml.) were heated to reflux for 18 hr. At the end of this time further selenium dioxide (400 mg.) was added and the reflux period extended for another 24 hr. Isolation was effected exactly as described for the corresponding bismethylenedioxy compound. The residual oil was chromatographed on Florisil (25 g.) and crystalline material was obtained from the 20–30% acetone–Skellysolve B to give 24 mg., m.p. 217–220°. A mixed melting point with the previously prepared sample of 6α-difluoromethylprednisolone 21-acetate was not depressed.

Sulfur Tetrafluoride Fluorination of Cortisone B.M.D.—A mixture of cortisone B.M.D.[17] (1.00 g.), 0.75 ml. of water, 3.50 ml. of tetrahydrofuran, 20 ml. of methylene chloride, and 46 g. of sulfur tetrafluoride was agitated overnight at 20°. Volatile materials were evaporated[5] and a solution of the crude product in methylene chloride was washed with 10% potassium bicarbonate solution, dried (sodium sulfate), and concentrated to dryness under reduced pressure at room temperature leaving an amber gum which was chromatographed on 80 g. of Florisil without delay.[18] The polarity of the solvent was gradually and

(18) When allowed to stand as a crude gum the fluoro ether slowly decomposed. A sample of this gum, after standing 1 month, had turned black and etched the flask containing it; chromatography of this black residue afforded a small amount of recovered cortisone B.M.D. as the only crystalline product.

continuously increased from 3–10% acetone in Skellysolve B over 8 l. The first eluates contained negligible amounts of material. When the solvent consisted of approximately 6% acetone–Skellysolve B, gummy fractions totalling 227 mg. were eluted. Chromatography on paper[19] indicated that these fractions contained cortisone B.M.D. and the fluoro ether described below along with a variety of more polar materials presumably arising from degradation of the fluoroether. The first gummy fractions were followed by oils (380 mg.) which were crystallized from acetone–Skellysolve B affording 234 mg., m.p. 147° dec. A sample was recrystallized from the same solvents for analysis, m.p. 149.5–151° (dec.); $[\alpha]_D$ +104°; ν_{max} 1708, 1670, 1615, 1280, 1227, 1205, 1180, 1150, 1123, 1110, 1012, 1006, 993, 970 cm.$^{-1}$. N.m.r. spectroscopy indicated the presence of $-OCH_2F$, $-CH_2-\overset{F}{\underset{|}{C}}-$, and $CH_2\begin{smallmatrix}O\\/\\\backslash\\O\end{smallmatrix}$ groups as well as the angular methyl groups.

Anal. Calcd. for $C_{23}H_{30}F_2O_5$: C, 65.08; H, 7.12; F, 8.95. Found: C, 65.19; H, 7.06; F, 9.09.

Hydrolysis of the Fluoro Ether from Cortisone B.M.D.—A solution of 11 mg. of the fluoro ether described above, m.p. 149.5–151°, in 8 ml. of 60% formic acid which had been previously purged with nitrogen was heated for 16 min. on the steam bath while bubbling nitrogen through the solution. The solution was cautiously poured into excess 10% potassium bicarbonate and extracted with three portions of methylene chloride. The extracts were dried (sodium sulfate) and concentrated to dryness leaving 9 mg. residue. This residue was dissolved in 5 ml. of methanol (previously purged with nitrogen), treated with 2 ml. of aqueous 1% potassium bicarbonate (previously purged with nitrogen), and stirred under nitrogen for 48 hr. After the potassium bicarbonate had been neutralized with acetic acid, the solution was concentrated to dryness under reduced pressure and the organic material isolated by extraction with methylene chloride and a small volume of acetone. The extracts held 8 mg. of gummy residue. Attempts at crystallization were not successful but paper chromatographic analysis[19] indicated that the major constituent of this residue moved with cortisone in two different systems (formamide stationary phase developed with 1:1 benzene–chloroform and the Bush B_5[20]).

Acknowledgment.—The authors are grateful to M. A. Rebenstorf and D. T. Kloosterman for running the sulfur tetrafluoride fluorinations and J. L. Johnson and W. A. Struck and associates for spectral and analytical determinations.

(19) The authors are grateful for Mr. L. M. Reineke of these laboratories for the paper chromatographic analyses.

(20) L. M. Reineke, *Anal. Chem.*, **28**, 1853 (1956).

The Radical Addition of Hydrogen Bromide to Hexafluoropropene

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Contribution No. 792 from the Central Research Department, Experimental Station, E. I. du Pont de Nemours and Company Inc., Wilmington, Delaware

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In an earlier publication,[1] we have shown that free radical additions of thiols to trifluoroethylene and to hexafluoropropene are bidirectional. In view of these results and the fact that hydrogen bromide adds to trifluoroethylene to give both possible adducts,[2] the report[3] that radical addition of hydrogen bromide to hexafluoropropene gives only the single isomer, CF_3CFHCF_2Br, seemed questionable. We have now determined unequivocally that *both* isomers are formed in the X-ray- and ultraviolet-initiated reactions of hydrogen bromide with hexafluoropropene.

$$CF_3CF{=}CF_2 + HBr \longrightarrow \underset{\text{I}}{CF_3CFHCF_2Br} + \underset{\text{II}}{CF_3CFBrCF_2H}$$

The reactions were carried out at room temperature using equimolar amounts of reactants, and the products were analyzed by gas chromatography and nuclear magnetic resonance spectroscopy. The adducts, I and II, were found in a ratio of 58:42 for the X-ray-initiated reaction and 62:38 for the ultraviolet-initiated reaction, when determined by proton n.m.r. analysis. Gas chromatographic analysis of the products from the X-ray reaction showed a ratio of 57:43 for the two isomers, in excellent agreement with the values calculated from the n.m.r. spectrum.

In the absence of irradiation, no reaction occurs between hydrogen bromide and hexafluoropropene under the conditions used here.

Experimental

X-Ray-initiated Addition of Hydrogen Bromide to Hexafluoropropene.—A mixture of 15 g. (0.1 mole) of hexafluoropropene and 8 g. (0.1 mole) of anhydrous hydrogen bromide in a 100-ml. stainless steel reaction vessel at 25–35° was irradiated with X-rays for 5 hr. at an average dose rate of approximately 30,000 rads/min. The reaction vessel was then cooled to −10° and the volatile material removed slowly. The liquid residue (16.5 g.) was distilled through a small spinning-band column to give 12 g. (52% yield) of 1:1 adduct boiling at 34°/760 mm.

Anal. Calcd. for C_3HBrF_6: Br, 34.63; F, 49.35. Found: Br, 34.82; F, 49.16.

The proton n.m.r. spectrum of this product indicated the presence of the isomers I and II in a ratio of 58:42. The spectrum of a portion of the crude reaction product gave a similar result indicating that no fractionation of isomers occurred during distillation.

Examination of a portion of the distilled product by gas chromatography (6-ft × 1/4 in. o.d. column packed with 20% ethyl ester of "KelF" acid No. 8114[4] on "Columnpak"[4]; helium flow rate, 62.5 ml./min.; temp., 0°) showed the presence of two principal constituents with elution times of 18.6 min. and 21.3 min. in the ratio of 43:57, together with some nine minor ones totaling about 2.5% of the sample. The principal constituents were separated for identification by preparative-scale gas chromatography.

(1) John F. Harris, Jr., and F. W. Stacey, *J. Am. Chem. Soc.* **83**, 840 (1961).

(2) R. N. Haszeldine, *J. Chem. Soc.*, 2800 (1957), obtained 58% $BrCHFCHF_2$ and 42% $BrCF_2CH_2F$ in an ultraviolet-initiated reaction of hydrogen bromide with trifluoroethylene. With X-ray irradiation, we have obtained the same products in a nearly identical ratio of 57:43.

(3) R. N. Haszeldine, *ibid.*, 3559 (*1953*).

(4) "KelF" acid no. 8114 was obtained from Minnesota Mining and Manufacturing Co. "Columnpak" was obtained from Fisher Scientific Co.

The A-60 proton n.m.r. spectrum of the 43% constituent consists of a triplet centered at $\delta = 5.7$ (I) $(CH_3)_4Si$ external = 0.0 with J = 53 c.p.s. The components of the triplet are further split to doublets (J = 5 c.p.s.), and at very high resolution, the further splitting of the doublets to quadruplets can be detected (J ≈ 1 c.p.s.). The pattern thus is wholly consistent with that predicted for the previously unreported 2-bromo-1,1,1,2,3,3-hexafluoropropane (II) ($n^{24}D$ 1.3059). The proton spectrum of the other isomer, 3-bromo-1,1,1,2,3,3-hexafluoropropane (I) ($n^{24}D$ 1.3032), consists of a doublet centered at $\delta = 4.7$ with J = 44 c.p.s. The doublet components further resolve to quartet–quadruplet combinations (J1 doublet = 10 c.p.s.; J2 doublet = 5.5 c.p.s.; J quad. = 5.5 c.p.s.) by virtue of the asymmetry of the central carbon atom.[5]

Ultraviolet-initiated Addition of Hydrogen Bromide to Hexafluoropropene.—A mixture of 11.5 g. (0.08 mole) of hexafluoropropene and 6.3 g. (0.08 mole) of anhydrous hydrogen bromide was sealed in a 50-ml. Pyrex Carius tube and irradiated with a G.E. C3-H85 lamp at a distance of *ca.* 6 inches for 6 days. The tube was cooled to −78° and opened. The liquid reaction product was distilled through a small spinning-band column to give 13.5 g. (76% yield) of 1:1 adduct mixture boiling at 34–35°/760 mm. The proton n.m.r. spectrum of this material showed that it consisted of a mixture of isomers I and II in a ratio of 62:38.

(5) (a) P. M. Nair and J. D. Roberts, *J. Am. Chem. Soc.*, **79**, 4565 (1957). (b) J. J. Drysdale and W. D. Phillips, *ibid.*, **79**, 319 (1957).

The Synthesis of Dihydropyrimidines from Benzamidine and α,β-Unsaturated Ketones

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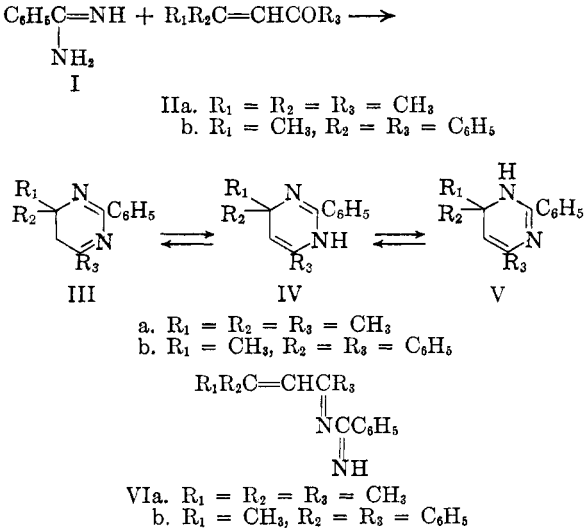
The reaction of amidines (*e.g.*, benzamidine, I) with α,β-unsaturated ketones is an attractive approach to the synthesis of dihydropyrimidines bearing an alkyl or aryl group at the 2-position. Traube and Schwarz[1] treated benzamidine (I) with mesityl oxide (IIa) in the absence of solvent and obtained a product, m.p. 91°, to which they assigned structure IIIa. Ruhemann[2] found that the reaction of benzamidine with 3-benzylidene-2,4-pentanedione at 100° results in the loss of an acetyl group with formation of a dihydromethyldiphenylpyrimidine, to which structure IV (R_1 = H, R_2 = C_6H_5, R_3 = CH_3) was assigned. Dodson and Seyler[3] used the reaction of benzamidine with various α-benzylidene ketones (II, R_1 = H, R_2 = C_6H_5) for the preparation of 6-substituted-2,4-diphenylpyrimidines; the presumed dihydropyrimidine intermediates, to which structure III (R_1 = H, R_2 = C_6H_5) was assigned, were not isolated.



In our hands the reaction of benzamidine with mesityl oxide in ethanol or under Traube and Schwarz's conditions[1] yielded a compound melting several degrees higher than reported[1] and having an analysis consistent with the formula $C_{13}H_{16}N_2$. The infrared spectrum (carbon tetrachloride solution) has a band at 2.89 μ (N—H), which contradicts IIIa but is consistent with the tautomerized structures IVa and Va and the open-chain structure VIa. The proton nuclear magnetic resonance spectrum, taken in carbon tetrachloride solution with tetramethylsilane as internal standard, also rules out IIIa. Absorption occurs at 8.83 τ (*gem*-dimethyl), 8.23–8.25 τ (doublet, methyl), 5.60 τ (vinylic hydrogen), and 2.25–2.79 τ (multiplet, phenyl group) with approximate relative areas of 6:3:1:5. The absorption of the amino hydrogen, which is undoubtedly broad,[4] could not be detected with certainty. Structure VIa can be ruled out by comparing the τ-value of the *gem*-dimethyl groups with those of model compounds, as summarized in Table I. The *gem*-dimethyl grouping absorbs close to that of isopropylamine and at considerably higher τ than that of mesityl oxide, demonstrating that the two methyls are attached to a saturated carbon.

An analogous reaction occurs between benzamidine and dypnone (IIb); the elemental analysis, molecular weight, and infrared and n.m.r. spectra demonstrate that the product is IVb or Vb. The infrared spectrum has an N—H maximum at 2.91 μ, while n.m.r. peaks are present at 8.35 τ (methyl), 4.64 τ (vinylic hydrogen), and 2.00–3.00 τ (multiplet, phenyl) with approximate area ratios of 3:1:15. Structure VIb is ruled out by the data in Table I. The τ-value of the methyl protons of the reaction product is close to those of α-methylbenzylamine (a model for structure Vb) and N-benzylidene-α-methylbenzylamine (a model

(1) W. Traube and R. Schwarz, *Ber.*, **32**, 3163 (1899).
(2) S. Ruhemann, *J. Chem. Soc.*, **83**, 1371 (1903).
(3) R. M. Dodson and J. K. Seyler, *J. Org. Chem.*, **16**, 461 (1951).
(4) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p. 270.

TABLE I

N.M.R. MAXIMA OF METHYL GROUPS IN REACTION PRODUCTS AND MODEL COMPOUNDS

Compound	N.m.r. maxima[a]
Product of benzamidine–mesityl oxide reaction	8.23–8.25,[b] 8.83[c]
Isopropylamine	8.92–9.02[b]
Mesityl oxide	7.89–7.91–7.92,[b] 8.14–8.17[b,d]
Product of benzamidine–dypnone reaction	8.35
α-Methylbenzylamine	8.60 to 8.75[e]
N-Benzylidene-α-methylbenzylamine	8.42–8.53[b]
Dypnone	7.45–7.48[b]

[a] τ-Values, relative to internal tetramethylsilane. [b] Hyphenated numbers indicate multiplets. [c] Area ratio of doublet to singlet: 1:2. [d] Area ratio of triplet to doublet: 2:1. [e] Amino hydrogens absorb in the same region, and methyl bands can not be assigned with certainty.

for IVb), but considerably higher than those of dypnone (a model for VIb).

At present we are unable to decide between structures IV and V for the condensation products. One is tempted to favor V which has conjugated endocyclic double bonds. However, structures similar to both IV[2,5] and V[5a,5b,6] have appeared in the literature.

Experimental

2-Phenyl-4,4,6-trimethyl-1,4(or 3,4)-dihydropyrimidine (IVa or Va).—A mixture of 15.66 g. (0.10 mole) of benzamidine hydrochloride, 9.8 g. (0.10 mole) of freshly distilled mesityl oxide, 6.60 g. (0.10 mole) of potassium hydroxide, and 300 ml. of absolute ethanol was heated at reflux for 3 hr. The mixture was cooled, filtered to remove potassium chloride, and concentrated *in vacuo*, leaving a brown oil which was boiled with 300 ml. of hexane. The mixture was filtered while hot, the filtrate was cooled to room temperature and poured onto an alumina chromatographic column. Elution with hexane yielded 12.6 g. (63%) of yellow solid, m.p. 85–97°. The product was purified by boiling with 700 ml. of petroleum ether (b.p. 30–60°), filtering while hot, and cooling the filtrate in Dry Ice, giving 9.1 g. (45%) of pale yellow crystals, m.p. 97.0–98.5°.

Anal. Calcd. for $C_{13}H_{16}N_2$: C, 78.0; H, 8.1; N, 14.0. Found: C, 78.2, 78.2; H, 8.1, 8.2; N, 14.1, 14.2.

The hydrogen chloride–mercuric chloride double salt, m.p. 183–185° (lit., m.p. 179°), was prepared as previously described.[1]

The reaction of benzamidine with mesityl oxide in the absence of solvent[1] gave a crude product, m.p. 68–82°, which was too soluble in ether[1] to make recrystallization from this solvent practical. Recrystallization from petroleum ether as described above resulted in a 63% yield of yellow solid, m.p. 89.0–94.5°, which had an infrared spectrum identical to that of the product obtained in ethanol. A second recrystallization raised the m.p. to 93.0–95.5°.

4-Methyl-2,4,6-triphenyl-1,4(or 3,4)-dihydropyrimidine (IVb or Vb).—The above procedure was repeated on a 0.05-mole scale, using dypnone instead of mesityl oxide. The brown oil remaining after solvent removal was boiled with 100 ml. of benzene. The mixture was filtered while hot, treated with 300 ml. of hexane, and boiled till the volume was 150 ml. Cooling gave two crops of yellow crystals: 1.15 g., m.p. 117–119°, and 3.54 g., m.p. 109–117°, a total yield of 29%. Recrystallization from hexane raised the m.p. of the first fraction to 121.0–122.5°.

Anal. Calcd. for $C_{23}H_{20}N_2$: C, 85.2; H, 6.2; N, 8.6; mol. wt., 324. Found: C, 85.6, 85.4; H, 6.3, 6.2; N, 8.7, 8.5; mol. wt. (ebullioscopic in benzene), 322, 330.

N-Benzylidene-α-methylbenzylamine.—This compound was prepared by the method of Nerdel, Becker, and Kresze.[7]

Infrared spectra were run in carbon tetrachloride solution on a Perkin-Elmer Infracord, Model 137B.

N.m.r. spectra were determined on a Varian A60 spectrometer, using 0.6 *M* solutions in 5:1 carbon tetrachloride–tetramethylsilane.

(5) (a) W. H. Hill, U. S. Patent 2,628,716 (1953); (b) Wellcome Foundation Ltd., British Patent 734,842 (1955); (c) G. E. McCasland, E. Blanz, Jr., and A. Furst, *J. Org. Chem.*, **24**, 999 (1959).

(6) W. H. Hill, British Patent 633,353 (1949); T. D. Heyes and J. C. Roberts, *J. Chem. Soc.*, 328 (1951).

(7) F. Nerdel, K. Becker, and G. Kresze, *Ber.*, **89**, 2862 (1956).

The Reaction of Benzilic Acid with Benzonitrile

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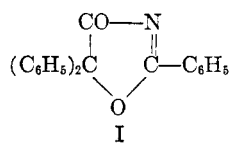
Only one example of a 4-oxazolone is reported in the literature.[1] From the treatment of benzilic acid and benzonitrile with concentrated sulfuric acid there was obtained a compound A, $C_{21}H_{15}NO_2$, readily hydrolyzed to a compound B, $C_{21}H_{17}NO_3$. By analogy with prior work[2] on the formation of oxazoles from benzoin and nitriles under the same conditions, compounds A and B were assigned the structures I and II, respectively. These formula-



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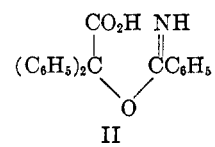

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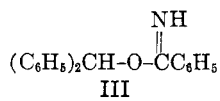


III

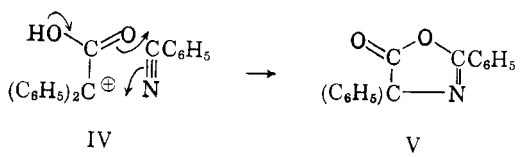
tions apparently were confirmed by subsequent transformations. Thus compound B was converted back into compound A by refluxing with acetic anhydride. Both compounds A and B, on reduction with hydriodic acid, gave benzamide and diphenylacetic acid. Further, compound A, on heating either alone or with strong alkali, was decarboxylated to a neutral compound C, $C_{20}H_{17}NO_3$. This was identical to the product obtained by treating benzonitrile and benzhydrol with hydrogen chloride gas and thus thought to be III.

The marked stability of compounds B and C to

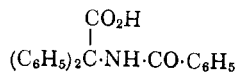
(1) F. R. Japp and A. Findlay, *J. Chem. Soc.*, **75**, 1027 (1899).

(2) F. R. Japp and T. S. Murray, *ibid.*, **63**, 469 (1893).

hydrolysis, as commented upon by the original authors, appeared remarkable for compounds having imino-ether structures as in II and III. Reinvestigation fully confirmed the reported transformations. It also was found that B was decarboxylated almost quantitatively to C by heating in quinoline. Consideration of the mode of formation of A suggested that the reaction was that of benzonitrile with the $(C_6H_5)_2{}^+CCO_2H$ carbonium ion, which is known[3] to be the main species present, as in IV leading to formulation of compound A as the azlactone V. Compound B then would be VI and



IV V



VI

compound C should be N-diphenylmethylbenzamide. This latter conclusion was confirmed by comparison of compound C with an authentic sample.[4] The formation of C from benzonitrile and benzhydrol must result from a reaction of the Ritter type.[5]

These revised structures obviously are equally compatible with the previously reported transformations, and also are supported by the infrared spectra in Nujol. Thus, in keeping with structure V, compound A shows a high frequency carbonyl band at 1820 cm.$^{-1}$ and a strong band at 1650 cm.$^{-1}$ characteristic of the —O—C=N— grouping. Compound B, apart from bands at 3350 (N—H), *ca.* 2450 and *ca.* 2600 cm.$^{-1}$ (carboxyl O—H), has two bands at 1705 cm.$^{-1}$ and 1625 cm.$^{-1}$ attributable to carbonyl groups.

Experimental

Compound A, namely 2,4,4-triphenyl-5-oxazolone, and compound B, α-benzamidodiphenylacetic acid, were obtained as previously described[1] and had the reported melting points.

Decarboxylation of α-Benzamidodiphenylacetic Acid.—The acid (0.9 g.) was heated under reflux in quinoline (5 ml.) for 1 hr. The cooled solution was poured into excess water and acidified. The solid product (0.7 g.) was isolated by chloroform extraction and crystallized from ethyl acetate m.p. 172–173°. This compound was shown by mixed melting point and infrared spectra to be identical to an authentic specimen of N-diphenylmethylbenzamide.

(3) C. M. Welch and H. A. Smith, *J. Am. Chem. Soc.*, **75**, 1412 (1953).

(4) G. W. H. Cheeseman and R. C. Poller, *Analyst*, **87**, 366 (1962).

(5) J. J. Ritter and P. P. Minieri, *J. Am. Chem. Soc.*, **70**, 4045 (1948).

Biosynthesis of Bacterial Pigments. II.[1] Chlororaphin

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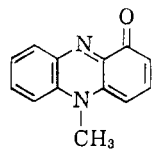
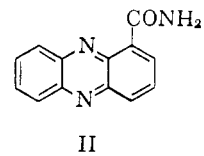
A review[2] of the chemistry of phenazines gives neglibible information on biosynthetic pathways of the bacterial phenazine pigments. However, several reports on the biosynthesis of two bacterial pigments, pyrocyanine[3] (I) and chlororaphin (a 3:1 molecular compound of phenazine-1-carboxamide (II) and its 5,10-dihydro derivative)[4] have been helpful in speculating on possible biosynthetic intermediates.



I



II

Recent observations that anthranilic acid, an intermediate in the biosynthesis of tryptophan in microörganisms,[5] has been incorporated into chlororaphin in trace amounts (0.002% incorporation) prompted us to study simulated biosyntheses of phenazine pigments through the dimerization of substituted anilines by symmetrical carbon–nitrogen pairing.

Biogenetic implications of phenol oxidation and the biosynthesis of dimeric and polymeric phenols are available in excellent laboratory analogies—*e.g.*, usnic acid,[6] gossypol,[7] griseofulvin,[8] and picrolichenic acid.[9] The oxidative dimerization examples can be regarded as either the pairing of radicals (C· → ·O and/or C· → ·C) or the substitution of one radical into a neutral phenol molecule followed by further oxidation. Coupling of radicals derived from amino phenols (C· → ·C and/or

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(3) M. V. Burton, J. J. R. Campbell, and V. A. Eagles, *Can. J. Res.*, **26C**, 15 (1948); A. C. Blackwood and A. C. Neish, *Can. J. Microbiol.*, **3**, 165 (1957); N. Grossowicz, P. Hayat, and Y. S. Halpern, *J. Gen. Microbiol.*, **16**, 567 (1957); L. H. Frank and R. D. DeMoss, *J. Bact.*, **77**, 776 (1959).

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(5) J. C. Yanofsky in "Amino Acid Metabolism," W. D. McElroy and H. B. Glass, ed., Johns Hopkins Press, Baltimore, Md., 1955, pp. 930–939; J. C. Yanofsky, *J. Biol. Chem.*, **224**, 783 (1957).

(6) D. H. R. Barton, A. M. Deflorin, and O. E. Edwards, *J. Chem. Soc.*, 530 (1956).

(7) J. D. Edwards, Jr., *J. Am. Chem. Soc.*, **80**, 3798 (1958).

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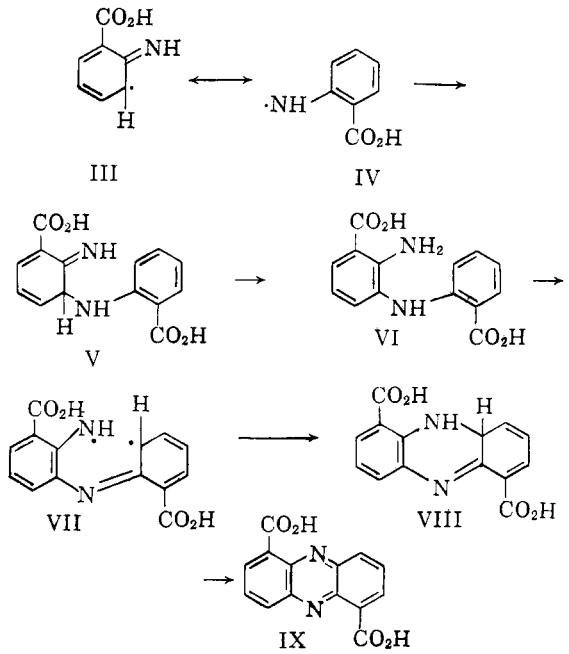
C· → ·N) can also be considered in the biogenesis of *Amaryllidaceae* alkaloids—*e.g.*, galanthamine.[10]

One possible explanation for biosynthesis of II involves dimerization of anthranilic acid with the loss of a carboxyl carbon.[4] Oxidative dimerizations of aromatic amines by pairing of radicals (C· → ·N) rather than substitution of one radical into a neutral molecule followed by further oxidation suggests a plausible biosynthetic pathway for phenazine-1-carboxamide (II) and its dihydro derivative from anthranilic acid (see structures III–IV). Presence for such a scheme is found in the radical coupling theory for oxidation of anilines to polymeric products—*e.g.*, nigraniline dyes[11] as well as concepts of the radical coupling theory of biogenesis.[10] To obtain II from IX would require two additional steps, decarboxylation and amination.

An interesting synthesis of phenazine through low temperature irradiation of aniline[12] gave support to the plan to investigate one-electron oxidizing agents on aniline and derivatives. We chose anthranilic acid for initial investigations with the goal in mind of finding pertinent information leading to a chemical model for the bacterial synthesis of phenazine pigments.

The effectiveness of manganese dioxide and lead dioxide as one-electron-transfer oxidizing agents for phenols has been attributed to coupling of radicals on a solid surface.[13] Presumably this explains the similar success now observed in the oxidation of anthranilic acid by each of these reagents. Active lead dioxide and manganese dioxide[13] were freshly prepared and used in dry benzene or chloroform under a nitrogen atmosphere. After shaking anthranilic acid in benzene or chloroform for several hours at 40° under nitrogen (oxygen-free) with either lead or manganese dioxide, phenazine-1,6-dicarboxylic acid (IX) was isolated (up to 16%). Apparently dihydro intermediates—*e.g.*, VIII—if produced are oxidized to IX. Extensive polymerization accompanying the formation of IX was not unexpected since intermolecular coupling of *para* isomers of III and IV leads to linear polymers incapable of forming IX. Oxidation of anthranilic acid with alkaline potassium ferricyanide resulted in unidentified polymers.

Decarboxylation of phenazine-1,6-dicarboxylic acid in refluxing diphenyl ether containing copper powder under nitrogen (oxygen-free) affords a mixture of phenazine and phenazine-1-carboxylic acid from which the amide, II, was prepared by standard procedure with thionyl chloride and ammonia.[14]



Experimental[15]

Oxidation of Anthranilic Acid with Manganese and Lead Dioxide.—A solution of 5.0 g. (0.036 mole) of anthranilic acid in chloroform or benzene (50 ml.) was shaken with active manganese dioxide[16] at 40° for 3 hr. under nitrogen (oxygen-free). The manganese dioxide was removed by filtration and the dark solution extracted with 50 ml. of 5 *N* potassium hydroxide. The dark alkaline extract was concentrated to a volume of about 25 ml. and allowed to stand at 0° for several days. The resulting brown microcrystals of the dipotassium salt of phenazine-1,6-dicarboxylic acid were collected. Neutralization of the salt with 0.5 *N* hydrochloric acid afforded phenazine-1,6-dicarboxylic acid, charring without melting 300–320°, 16% yield.

Anal. Calcd. for $C_{14}H_8N_2O_4$: C, 62.69; H, 3.01; N, 10.44. Found: C, 62.77; H, 3.21; N, 10.29.

A similar experiment with active lead dioxide[17] gave phenazine-1,6-dicarboxylic acid (5%) which proved difficult to purify.

Ethyl Ester of Phenazine-1,6-dicarboxylic Acid.—A solution of 1.5 g. (0.0056 mole) of phenazine-1,6-dicarboxylic acid in 20 ml. of concentrated sulfuric acid was quickly added to 125 ml. of absolute ethanol. The solution was allowed to cool slowly to room temperature and made basic (pH 9) with 1 *N* sodium hydroxide. Several extractions with moist ether afforded a 63% yield of the diethyl ester of phenazine-1,6-dicarboxylic acid, recrystallized from ethanol as greenish yellow needles, m.p. and mixture m.p. 143°.[18]

Pyrolysis of Phenazine-1,6-dicarboxylic Acid.—Phenazine 1,6-dicarboxylic acid (2 g., 0.0075 mole) was dissolved in 500 ml. of hot diphenyl ether and refluxed at 260° for 3 hr. with 25 g. of copper powder under nitrogen (oxygen-free). After cooling to room temperature, the dark solution was filtered

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(12) B. K. Malaviya and S. Dutt, *Proc. Acad. Sci. United Provinces Agra and Oudh, India*, **4**, 319 (1935); *Chem. Abstr.*, **30**, 1956 (1936).

(13) For previous uses of solid oxidants for effecting phenol coupling see ref. 6, 8, 9, and 10.

(14) F. Kögl and B. Tönnis, *Ann.*, **486**, 497 (1932).

(15) Semimicro analyses by Alfred Bernhardt, Max Planck Institute Microanalytisches Laboratorium, Mülheim (Ruhr), Germany. Melting points are uncorrected.

(16) S. Ball, T. W. Goodwin, and R. A. Marton, *Biochem. J.*, **42**, 576 (1948).

(17) R. Kuhn and I. Hammer, *Ber.*, **83**, 413 (1950).

(18) L. Birkofer and A. Widmann, *ibid.*, **86**, 1295 (1953).

and extracted with 0.1 *N* sodium hydroxide. The organic layer was neutralized with 0.1 *N* hydrochloric acid, and chromatographed over alumina (grade III). Elution of the column with methanol afforded brownish needles of phenazine (33%) which recrystallized from ethanol as yellow needles, m.p. and mixture m.p. 171–171.5°.

The alkaline fraction was neutralized with 0.1 *N* hydrochloric acid and the precipitate isolated and recrystallized from acetone–water as yellow needles of phenazine-1-carboxylic acid (25%), m.p. and mixture m.p. 242–244°.

Phenazine-1-carboxamide (II) was prepared in 42% yield from phenazine-1-carboxylic acid according to the procedure of Kögl and Postowsky[19] employing thionyl chloride and ammonium hydroxide.

Acknowledgment.—This work was supported in part by Grant CA 06566 from the National Cancer Institute, U. S. Public Health Service.

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The Nef Reaction of 1,2,3,4,5,6,7,8,9,10,11,14-Dodecahydro-9-nitrophenanthrene

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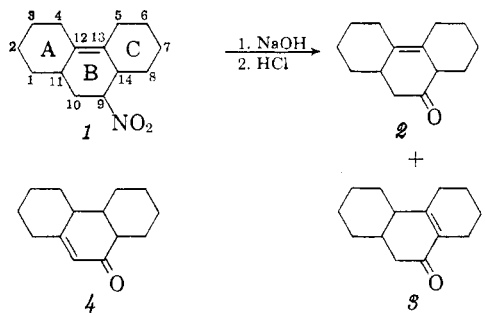
Recently it was reported that 1,2,3,4,5,6,7,8,9,-10,11,14 - dodecahydro - 9 - nitrophenanthrene (*1*) under Nef reaction conditions afforded a pair of isomeric ketones, 1,2,3,4,5,6,7,8,9,10,11,14-dodecahydro - 9 - ketophenanthrene (*2* and *3*, respectively, Fig. 1).[1] The conjugated ketone *3* also was



1 2 3 4

Figure 1

obtained by heating the Nef ketone *2* in an acidic medium. The assignment of the position of the olefinic linkage in the conjugated ketone *3* was based on the ultraviolet spectral characteristics of both the α,β-unsaturated ketone and the 2,4-dinitrophenylhydrazone derivative. The absorption contants of the ketone *3* were reported to consist of maxima at 235 mμ (ϵ 3880) and 280 mμ (ϵ 940) in isoöctane.

Interest in this problem was aroused when it was noted that the above maxima and extinction values were not consistent with structure *3*. In particular, the application of the usual correction factor for solvent change (isoöctane → ethanol, + 7 mμ) implied that the K-band for the ketone *3* was in the area of 242 mμ. A trisubstituted α,β-unsaturated ketone similar to *3* would be expected to absorb at about 247 mμ (Woodward's rules).[2] This discrepancy in the K-band's observed absorption maxima, as compared to the calculated value and the unusually low extinction sum, led to a reconsideration of the structure previously formulated for compound *3*. An interesting alternative to *3* was ketone *4* which was expected to possess an absorption around 240 mμ. If *4* was the correct structure for the conjugated ketone, then an abnormal reaction pathway must be invoked to rationalize the rearrangement of the double bond into the $\Delta^{10,11}$ position.

The nitro olefin *1* was resynthesized by a modification in the literature route. Specifically, bi-1-cyclohexen-1-yl was condensed with nitroethylene which was generated simultaneously *in situ* from 2-nitroethyl acetate and sodium acetate.[3] The well known disadvantages of pure nitroethylene were avoided by this indirect sequence. The presence of the double bond at $\Delta^{12,13}$ in compound *1* was assigned in the original work by ozonolysis experiments as well as by infrared arguments.

The n.m.r. spectrum of *1* revealed the proton on C-9 at 4.60 δ. This signal appeared to consist of a pair of doublets with couplings of 7 and 12 c.p.s., presumably due to spin-spin interaction with the two protons at C-10 as well as the proton at C-14. This information was used in an attempt to ascertain the preferred state of ring B and whether the nitro group existed in either the axial or equatorial configuration. If one assumed that the hydrogens C-11 and C-14 were *cis* to each other (*cis* addition *via* a Diels–Alder reaction) and were in the axial position, then the nitro group must be either in the axial or equatorial conformation. First, it may be said that any boat or half-boat form for ring B as visualized by Dreiding models appeared to be unstable and would collapse into the more rigid chair or half-chair form. More importantly, if the dihedral angles for the couplings between $J_{9,10}$ and $J_{9,14}$ were measured for the various axial or equatorial nitro configurations, then reference to the literature curve relating dihedral angle to $J_{H,H'}$ provided theoretical coupling values which were incompatible with the observed pattern.[4] Thus, the boat form of ring B was eliminated from further consideration.

Four possible chair or half-chair representations of ring B must be considered now. Number one of

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the chair set had the nitro group axial and *trans* to the C_{14} proton; a coupling of about 3 c.p.s. was predicted here. The second example possessed the nitro group axial and *cis* to the C_{14} proton; a coupling constant of some 7 c.p.s. was visualized for this model. It appeared clear at this point that the axial configuration of the nitro group produced coupling sums far below the actual data. The third form contained an equatorial nitro which was *cis* to H_{14}. The dihedral angles were as follows: $\phi(H_{9a,14e}) = 180°$; $(H_{9a,10a}) = 175°$; and $(H_{9a,10e}) = 60°$. The equivalent theoretical couplings were therefore 10, 10, and 2 c.p.s., respectively. The total amounts to 22 c.p.s. and would give a pattern similar to the observed one. Experimental error in measuring the couplings and angles would account for the slight differences. The fourth and final state contained an equatorial nitro that was *trans* to H_{14}. The tabulated dihedral angles were found to be: $\phi(H_{9a,14a}) = 15°$; $(H_{9a,10a}) = 180°$; and $(H_{9a,10e}) = 60°$. The coupling constants would be 7, 10, and 2 c.p.s. Here, the sum is 19 c.p.s. and the actual pattern is not far from this predicted set. It was felt that both of the last two models fitted the real data; therefore, the only conclusion drawn was that ring B was in the chair or half-chair form and the nitro group was in the equatorial position.

An interesting phenomenon was noted in the n.m.r. spectrum in the area between 2.35 and 3.00 δ. One absorption was centered at 2.81 δ, whose integrated area was equivalent to one hydrogen, and a second peak was located at 2.62 δ with an area equal to two hydrogens. It was believed that the two equatorial protons located at C-8 and C-10 were shifted downfield by the long-range deshielding effects of the nitro group and thus appeared at lower field values than the allylic protons in compound *1*. The third proton was tentatively assigned as H_{14}, which is both allylic and near the nitro group and therefore was expected to appear even further downfield. The recognization of long-range shielding effects by the nitro group was noted only recently and may be of great importance to future structure proof work in alicylic nitro chemistry.[5]

The nitro olefin *1* was isomerized under Nef conditions to yield a mixture of β,γ-ketone *2* and α,β-ketone *3* (or *4*) as determined by infrared techniques. Gas chromatography of the crude product revealed that some starting nitro olefin *1* was still present as well as other unidentified materials. Various abortive efforts were made to separate and purify the two ketones by crystallization and liquid–solid chromatography. During an attempted vacuum distillation of *2* and *3* (or *4*), it was observed that compound *2* was being thermally isomerized into *3* (or *4*). A resulting slow evaporative distillation of the ketone mixture afforded an almost pure sample of *3* (or *4*). The ultraviolet spectrum of the α,β-unsaturated ketone in ethanol contained a maximum at 248 mμ (ϵ 12,470), which was completely consistent for structure *3*, but not for *4*. The n.m.r. spectrum contained no olefinic proton absorption and thereby confirmed the presence of a tetrasubstituted double bond in *3*. It was concluded that the previous spectroscopic properties associated with ketone *3* were in error and were due apparently to the low purity of the described compound. The new data obtained here fully support a direct isomerization of *2* into *3*.

In the latter stages of this work, a Communication appeared concerning the acid-catalyzed hydrolysis of 2-nitrooctane to 2-octanone.[6] Compound *1* was treated therefore with hydrochloric acid in various solvent combinations for extended periods of time. On work-up, the crude oil was shown to be a mixture of *1*, *2*, *3*, and other materials. No significant change in final product composition was observed in these experiments, as compared to the usual Nef sequence.

Experimental

Melting points were read on a Kofler block and are not corrected; boiling points are uncorrrected, also. The ultraviolet spectra (recorded in mμ) were obtained in ethanol, unless otherwise stated, on a Cary Model 14 recording spectrophotometer. Infrared spectra (recorded in μ) were determined in pressed potassium bromide disks or as neat films using a Perkin-Elmer Model 421 double beam grating instrument. Isothermal gas–liquid chromatograms were measured on the Wilkens Instrument A-600 and the A-90 devices. Thin-layer chromatoplates were coated with Merck (Darmstadt) silica gel containing calcium sulfate as a binder. Ceric sulfate was utilized as a visualization agent. All n.m.r. measurements were conducted in deuterochloroform solution using tetramethylsilane as an internal reference on the Varian Associates A-60 machine. Proton n.m.r. signals were noted in p.p.m. as δ-values [c.p.s. (relative to tetramethylsilane)/60]. The microanalyses were performed by the Microanalytical Laboratory, Department of Chemistry, Stanford University.

Bicyclohexyl-1,1′-diol.—The bimolecular reduction of cyclohexanone with aluminum amalgam gave consistent 33–35% yields of the desired compound. The diol melted at 123.0–124.0° [lit.,[7] 123–124°] and exhibited $\lambda\lambda_{max}$ 2.93 (hydroxyl) and 10.38 (cyclohexyl).

Bi-1-cyclohexen-1-yl.—The diene was produced by the dehydration of bicyclohexyl-1,1′-diol in 80–82% yields by use of phosphorus oxychloride and pyridine.[8] The material was a colorless oil which boiled at 48.4–49.3° (0.09 mm.) [lit.,[7] b.p. 95–96° (3 mm.)] and gave a single peak on gas phase chromatography using a 20% SE-30 on a base-washed Chromosorb P column at 173°; thin-layer chromatography showed a single peak at the solvent front with ether–benzene (1:4) as the eluant. The diene exhibited $\lambda\lambda_{max}$ 232 (shoulder) (log ϵ 4.18), 238 (log ϵ 4.23), and 245 (shoulder) (log ϵ 4.11) [lit.,[9] $\lambda\lambda_{max}^{n\text{-hexane}}$ 231 (log ϵ 4.25) and 238 (log ϵ 4.26)]; $\lambda\lambda_{max}^{film}$ 3.30 (aliphatic olefin) and 12.55 (trisubstituted olefin); and $n^{25}D$ 1.5341. Occasionally, the diene crystallized on standing in the cooler night air to afford long, colorless needles that melted at about 26°.

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(8) D. Greidinger and D. Ginsburg, *J. Org. Chem.*, **22**, 1406 (1957).

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2-Nitroethanol.—This material was purchased from Columbia Organic Chemicals, Columbia, S. C.

2-Nitroethyl Acetate.—The acetate was prepared by sulfuric acid-catalyzed esterification with acetic anhydride.[10a,b] The ester boiled at 68–69° (1.2 mm.) [lit.,[10b] b.p. 62–64° (1.3 mm.)]; yield, 83–85%. The compound possessed $\lambda\lambda_{max}^{film}$ 5.72 (carbonyl), 6.40 and 6.92 (nitro), and 8.10 (acetate).

1,2,3,4,5,6,7,8,9,10,11,14-Dodecahydro-9-nitrophanenthrene (*1*).—In a typical preparation, 2-nitroethyl acetate (19.6 g., 0.148 mole) was added dropwise over a 30-min. period to a stirred suspension of sodium acetate (12.4 g., 0.150 mole) and a solution of bi-1-cyclohexen-1-yl (24.0 g., 0.148 mole) in benzene (155 ml.). Afterwards, the two-phase mixture was refluxed for 16 hr.; previous model experiments had shown that a maximum yield was obtained at the end of this period. The cooled reaction mixture was filtered through a sintered funnel and the inorganic salts were washed with hot benzene (2 × 10 ml.). The combined organic phases were treated with Norit, were refiltered, and were evaporated to dryness *in vacuo* to leave a red oil. This material was twice crystallized from alcohol and then was sublimed readily at 60° (0.1 mm.); yield, 14.2 g. (40.9%); m.p. 72.5–73.4° (lit.,[1] m.p. 74.0–74.8°); the solid produced a single peak on gas phase chromatography using a 20% SE-30 on an acid-washed Chromosorb P column at 178°; thin-layer chromatography showed a single spot near the solvent front with pentane as the eluent. The nitro olefin exhibited no selective absorption in the ultraviolet above 210 mμ; $\lambda\lambda_{max}$ 3.41 and 3.51 (aliphatic olefin), 6.52 and 7.25 (nitro), and 12.95 (ring methylene). The n.m.r. spectrum contained signals centered at 4.60 (the hydrogen attached to the carbon holding the nitro group), 2.80 and 2.60 (integrated area equivalent to one and two hydrogens, respectively), and a series of overlapping peaks stretching from 1.98 to 1.47 (miscellaneous aliphatic hydrogens).

Anal. Calcd. for $C_{14}H_{21}NO_2$: C, 71.45; H, 9.00; N, 5.95. Found: C, 71.48; H, 9.15; N, 5.73.

1,2,3,4,5,6,7,8,9,10,11,12-Dodecahydro-9-ketophenanthrene (*3*).—A cold solution of sodium hydroxide (5.00 g., 0.125 mole) in ethanol (100 ml.) was slowly added to a chilled stirred solution of nitro olefin *1* (10.9 g., 0.0424 mole) in ethanol (100 ml.). The combined liquids were held at 0–2° under a nitrogen atmosphere for 30 min. and were then poured into a cold, dilute hydrochloric acid solution (2 *N*, 300 ml.). The resulting mixture was stirred at 5° for 2 hr. and was allowed to warm to room temperature over a day. The organic material was extracted with ether (3 × 300 ml.) and the combined extracts were dried over magnesium sulfate and were taken to dryness *in vacuo* to leave a brown oil, wt. 9.5 g. Thin-layer chromatography with benzene as the eluent revealed the presence of four components. The infrared spectrum exhibited two carbonyl bands—5.85 (β,γ-ketone *2*) and 6.01 (α,β-ketone *3*); some starting material was noted, also (6.49 and 7.25). Gas phase chromatography using a silicone rubber on an acid-washed Firebrick column at 150° produced four separable peaks: unknown material, β,γ-ketone *2*, α,β-ketone *3*, and nitro olefin *1*. It was not possible to separate the two ketones by column chromatography with silicic acid and petroleum ether.

An effort to distil the ketone mixture revealed that the application of heat was isomerizing compound *2* into the desired *3*; therefore, the impure brown oil (1.0 g.) was distilled slowly at 70° (0.12 mm.) to yield a pale yellow oil (0.46 g.). This latter product gave a major peak (95%) and a minor, trailing peak (5%) on gas phase chromatography using a 20% SE-30 on an acid-washed Chromosorb P column at 202°; thin-layer chromatography showed a single spot with benzene as the eluent; λ_{max} 248 (log ε 4.09); $\lambda\lambda_{max}^{film}$ 6.03 (carbonyl) and 6.19 (double bond); and $n^{23}D$ 1.5472. The n.m.r. spectrum did not contain any olefinic proton absorptions. The physical constants of *3* were not further improved by preparative gas chromatography.

Anal. Calcd. for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 81.10; H, 9.82.

The brilliant red 2,4-dinitrophenylhydrazone was crystallized from ethyl acetate–grain alcohol (1:1) and then from ethanol; m.p. 231.0–231.5° (lit.,[1] 233.5–234.1°); $\lambda\lambda_{max}^{CHCl_3}$ 258 (log ε 4.25), 290 (shoulder) (log ε 3.42), and 393 (log ε 4.46 [lit.,[1] $\lambda\lambda_{max}^{CHCl_3}$ 260 (log ε 4.31) and 293 (inflection)].

Anal. Calcd. for $C_{20}H_{24}N_4O_4$: C, 62.48; H, 6.29; N, 14.58. Found: C, 62.46; H, 6.36; N, 14.58.

The white semicarbazone was crystallized from methanol–ether (1:1), m.p. 181.5–182.0°; $\lambda_{max}^{CH_3OH}$ 268 (log ε 4.52).

Anal. Calcd. for $C_{15}H_{23}N_3O$: C, 68.93; H, 8.87; N, 16.08. Found: C, 68.66; H, 9.05; N, 15.80.

Acid Hydrolysis of 1,2,3,4,5,6,7,8,9,10,11,14-Dodecahydro-9-nitrophenanthrene.—The nitro olefin *1* (0.253 g., 0.0011 mole) was refluxed with grain alcohol (100 ml.) containing concentrated hydrochloric acid (0.20 ml.) for 15 days. The solvent was removed *in vacuo* to afford a brown oil which was analyzed by gas chromatography using a 5% SE-30 on an acid-washed Chromosorb W column at 212°. The composition of the crude product was as follows (arranged in order of increasing retention time): other products (4%), β,γ-ketone (30%), α,β-ketone (25%), and starting material (41%).

A second reaction involved nitro olefin (0.520 g., 0.0022 mole) and a mixture of ethanol (80 ml.) and dilute hydrochloric acid (1 *N*, 170 ml.) which was boiled for 12 days. Work-up of the crude oil produced a similar result: unknown materials (8%), β,γ-ketone (41%), α,β-ketone (33%), and starting compound (18%).

Finally, nitro olefin (0.520 g.) was heated with dilute hydrochloric acid (1 *N*, 250 ml.) for 15 days. The oil (0.283 g.) was comprised of other compounds (5%), β,γ-ketone (40%), α,β-ketone (35%), and nitro olefin (20%).

Acknowledgment.—The authors are indebted to Mrs. Dalia Aguilar for the infrared and ultraviolet absorption spectra, to Dr. Lois J. Durham for discussions concerning the n.m.r. data, and to Mr. Erich H. Meier for the microanalyses.

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The Synthesis of (+)-3-Methyl-β-citronellal

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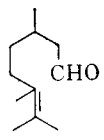
The synthesis of DL-3-methyl-β-citronellal (DL-V) has been accomplished[1] by the selective hydrogen-

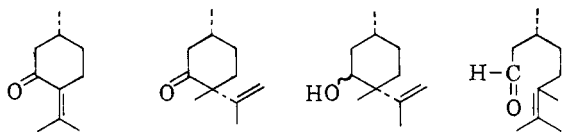


I

(1) Y. R. Naves, *Bull. soc. chim. France*, 519 (1952).

ation of 3-methyl-β-citral (I). The preparation of optically active V or any other active 3-alkyl or aralkyl substituted β-citronellals has not as yet been reported. Since these compounds have potential use as aroma and vitamin intermediates we wish to report a three-step synthesis of (+)-3-methyl-β-citronellal[2] (V) by a synthetic route that is useful for preparing other 3-alkyl or aralkyl derivatives.

The sodium *t*-amylate-catalyzed methylation of (+)-pulegone (II) by the procedure of Conia[3] gave a 71.5% yield of methylisopulegone fraction. The ultraviolet spectrum of this material gave a maximum at 254 mμ indicating the presence of pulegone or possibly a 2-methylated pulegone isomer.[4] A gas liquid chromatograph (GLC), revealed three components, A (12.3%), B (51.4%), and C (36.3%), in order of elution.

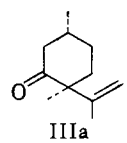


II III IV V

Component C was identified as unchanged pulegone by matching its GLC retention time with authentic pulegone. Evidence that II was the only system causing the 254-mμ absorption in these fractions was established by the comparison of % pulegone calculated from GLC (36.3%) with that obtained from ultraviolet data (37.5%). The good agreement of these values rules out any more than trace amounts of a 2-methylisopulegone[4] isomer.

The major constituent B was shown to be the desired (−)-4-methylisopulegone (III) by matching its retention time with a pure sample obtained through the semicarbazone separation procedure of Conia.[3a]

The first component A was thought to be isopulegone[5] on the basis of its elution time in reference



IIIa

to pulegone and on the observation of Conia[3a] that when pulegone was treated for a few minutes with sodium *t*-amylate[5] the recovered "pulegone" had a lower ultraviolet absorption, presumably due to the presence of isopulegone. However, comparison with a known sample proved this to be incorrect. Since the presence of 2-methylated pulegone has been ruled out it is assumed that A is the other 4-methyl isomer IIIa. Recent work by Djerassi[6] and co-workers lend additional support to the assignment of A as IIIa since they report that the base catalyzed methylation of pulegone gave an 83:17 ratio of III and IIIa while in the present work an 81:19 ratio was obtained.

The lithium aluminum hydride reduction of pure III gave 4-methylisopulegol (IV) that was shown by GLC to be 43:57 mixture of two isomers. Since axial alcohols are known[7] to be eluted earlier than their equatorial isomers in chromatographic separations our earlier eluted isomer (43%) is presumably the axial alcohol while the other isomer (57%) contains an equatorial hydroxyl group.

The pyrolysis of isopulegol has been reported by Grignard[8] and Doeuvre to give a good yield of β-citronellal. Using a modification of their procedure we pyrolyzed IV at 500° in an inert atmosphere. The resultant pyrolysate was treated with isobutyl borate to remove some unchanged alcohol. A 65% yield of (+)-3-methyl-β-citronellal (V) was isolated.

Experimental

Elemental analyses were determined by the Schwarzkoff Microanalytical Laboratory, Woodside 77, New York.

Gas Chromatography.—Six-foot copper tubes (0.25 in. o.d.) packed with sucrose acetate isobutyrate[9a] (SAIB; 20% by wt.) deposited on 60/80 mesh Chromosorb[9b] or Hyprose SP-80[9c] (20% by wt.) on Chromosorb were used as analytical columns. Detection was carried out on an Aerograph Model A-90[9d] equipped with a thermal conductivity cell and a speedomax Model G recorder.[9e]

(+)-Pulegone (II).—The fractional distillation of European Oil of Pennyroyal[10] afforded (+)-pulegone of b.p. 81° (5.0 mm.), $n^{25}D$ 1.4861, λ_{max}^{EtOH} 253 mμ, log ε 3.84, $[\alpha]^{22}D$ +23.56 (neat, 1 dm.). A GLC spectrum on SAIB and Hyprose revealed only one component in both cases. A 2,4-dinitrodiphenylhydrazone had m.p. 148.7–149°. The lit.[11] reports b.p. 102–102.5° (17 mm.), $n^{24.8}D$ 1.4853, $[\alpha]^{26.5}D$ +22.47 (neat, 1 dm.). λ_{max}^{EtOH} 252 mμ, log ε 3.85, 2,4-dinitrophenylhydrazone m.p. 148–149°.

(2) All structural formulas used in this paper signify absolute configuration since the absolute configuration of (−)-4-methylisopulegone (III) has been established by E. J. Eisenbraun, F. Burian, J. Osiecki, and C. Djerassi, *J. Am. Chem. Soc.*, **82**, 3476 (1960).

(3) (a) J. M. Conia, *Bull. soc. chim. France*, 943 (1954); (b) J. M. Conia, French Patent 1,113,274 (March 26, 1956).

(4) It has been reported that the sodium amide-catalyzed methylation of pulegone produces the 2-methyl isomer. *Cf.* A. Haller and P. Ramart, *Compt. rend.*, **179**, 121 (1924).

(5) It is interesting to note that 25% alcoholic sodium ethoxide has been reported to isomerize an isopulegone–pulegone mixture to pure pulegone. C. Black, G. L. Buchanan, and A. W. Jarvie, *J. Chem. Soc.*, 2971 (1956).

(6) C. Djerassi, J. Osiecki, and E. J. Eisenbraun, *J. Am. Chem. Soc.*, **83**, 4433 (1961).

(7) S. Winstein and N. J. Holness, *ibid.*, **77**, 5562 (1955); D. H. R. Barton, A. das Campos-Naves, and R. C. Cookson, *J. Chem. Soc.*, 3500 (1956).

(8) V. Grignard and J. Doeuvre, *Compt. rend.*, **190**, 1164 (1930).

(9) (a) Eastman Chemical Products Inc., Kingsport, Tennessee; (b) F. & M. Scientific Corp., New Castle, Delaware; (c) The Dow Chemical Co., Midland, Michigan; (d) Wilkens Instrument and Research Inc., Walnut Creek, California; (e) Leeds & Northrup, Philadelphia, Pennsylvania.

(10) Obtained from Ungerer and Co., New York, N. Y.

(11) E. J. Eisenbraun and S. M. McElvain, *J. Am. Chem. Soc.*, **77**, 3383 (1955).

(−)-**4-Methylpulegone** (III).—The procedure of Conia[3a] was followed. From (+)-pulegone (154 g., 1.0 mole), methyl iodide (200 g., 1.4 moles), 1.9 *N* sodium *t*-amylate (550 ml.), and diethyl ether (750 ml.), there was obtained 120.5 g. (71.5%) of a methylisopulegone fraction of b.p. 72–74° (2.0 mm.), $n^{27}D$ 1.4738–1.4741, λ_{max}^{EtOH} 253 mμ, log ε 3.44. A GLC analysis on the SAIB column showed three bands, A (12.3%), B (51.4%), and C (36.3%) in order of elution.

Treatment of this material with semicarbazide reagent[12] gave a semicarbazone of m.p. 201–205°, which after one recrystallization from ethanol melted at 204–205°. The semicarbazone of (−)-4-methylisopulegone is reported[3a] to have m.p. 203–205°. The steam distillation of the semicarbazone in the presence of 5% aqueous hydrochloric acid gave (−)-4-methylisopulegone (III) of b.p. 60° (1.0 mm.), $n^{20}D$ 1.4698, $[\alpha]^{23}D$ −116.5°, lit.[3a] reports b.p. 86–88° (8 mm.) $n^{19}D$ 1.4711, $[\alpha]^{20}$ 578 −118.88°.

The retention time of III was found to be identical with component B in the original ketone mixture.

Component C matched the retention time of (+)-pulegone. The % pulegone calculated from the ultraviolet value (log ε 3.44) was 37.5%. This is in excellent agreement with the 36.3% calculated from the GLC data.

Component A failed to match the retention time of isopulegone.

4-Methylisopulegol (IV).—A solution of 4-methylisopulegone (7.0 g., 0.042 mole) in diethyl ether (50 ml.) was added dropwise to a slurry of lithium aluminum hydride (4.0 g., 0.105 mole) in diethyl ether (100 ml.). After hydrolysis with 10% sodium hydroxide there was obtained 6.3 g. (88%) of 4-methylisopulegols, b.p. 58–61° (1 mm.), $n^{20}D$ 1.4790, infrared spectrum, 2.96, 6.11, and 11.27 μ. A gas-liquid chromatograph on Hyprose gave two bands, 43 and 57%, in order of elution. These isomers presumably correspond to the axial (43%) and equatorial (57%) hydroxyl isomers.

Anal. Calcd. for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found: C, 78.39; H, 11.92.

(+)-**3-Methyl-β-citronellal** (V).—An 18-in. Pyrex tube (0.75 in. i.d.) was packed loosely to a depth of 12 in. with 0.25-in. o.d. Pyrex-helices. The tube was placed in a vertically mounted electric muffle furnace so that all the packed area was in the heating zone. The system was heated so that the outer surface of the glass tube was maintained at 490–500°. 4-Methylisopulegol (28 g.) in the presence of a slow stream of nitrogen was dropped onto the heated glass helices. The pale yellow pyrolysate (24.5 g., 87.5% recovery) was collected in an ice-cooled receiver. Infrared analysis of this material showed the presence of some alcohol. To remove this the mixture was treated with excess isobutyl borate and a mixture of isobutanyl alcohol, isobutyl borate, and V was distilled. The distillate was treated with 10% sodium bicarbonate and extracted with hexane. The hexane layer was dried and distilled. There was obtained 18.5 g. (65%) of (+)-3-methyl-β-citronellal, b.p. 64–66° (2 mm.), $n^{20}D$ 1.4564, $[\alpha]^{22}D$ +10.62° (neat. 1 dm.), infrared 3.69, 5.81, and 7.25 μ. A GLC spectrum on SAIB showed the material to be better than 98.5% pure. The literature[1] reports for the DL-isomer, b.p. 63–64° (1 mm.), d^{20}_4 0.8261, $n^{20}D$ 1.4549.

Anal. Calcd. for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found: C, 78.47; H, 11.87.

Acknowledgment.—The author wishes to thank Mr. Aaron Kossoy and his associates for GLC determinations.

(12) R. L. Shriner and R. C. Fuson, "Identification of Organic Compounds," 3rd ed., J. Wiley & Sons, Inc., New York, N. Y., 1900.

Preparation of Some Bis(nitrophenyl) Ethers, Bis(aminophenyl) Ethers, and Some Derived Azo Compounds[1]

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Contribution from the American Cyanamid Co., Organic Chemicals Division, Bound Brook Laboratories, Bound Brook, New Jersey

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As part of a program to prepare unusual azo compounds, we decided to investigate the chemistry of bis(2-aminophenyl) ether (III). The reaction between 2-nitrochlorobenzene and potassium 2-nitrophenoxide to produce bis(2-nitrophenyl) ether (I), a compound which may be easily reduced to the diamine, has been known for many years.[2–4] However, yields were either very low (<6%)[2,3], or the procedure unspecified[4] (23% yield).

We found that a 72% yield of I was obtained when equimolar quantities of reactants were heated at reflux overnight in dimethylformamide. Dimethylacetamide and dimethyl sulfoxide were similarly effective as reaction solvents. The use of dimethylformamide as solvent for preparing the other bis(nitrophenyl) ethers was investigated. Table I shows the results of allowing the potassium salt of the nitrophenol in the first column to react with the nitrochlorobenzene of the second column to give the bis(nitrophenyl) ether in the yield shown. The last column gives reported yields.

TABLE I

PREPARATION OF BIS(NITROPHENYL) ETHERS

Nitrophenoxide	Nitrochlorobenzene	Reaction time (hrs.)	Yields, % Found[a]	Yields, % Reported
o	*o*	18	72,[b] 33,[c] 65[d]	23[f]
p	*o*	4.5	61	30[g]
p	*p*	16	79	85[g]
m	*p*	1	73	87[h]
m	*o*	5	60	..
m	*m*	18	0[e]	23[i]

[a] After one recrystallization. [b] Dimethylformamide. [c] Dimethyl sulfoxide. [d] Dimethylacetamide. [e] A reduction product, 3,3′-dichloroazobenzene, was isolated. [f] See ref. 4. [g] M. J. Rarick, R. Q. Brewster, and F. B. Dains, *J. Am. Chem. Soc.*, **55**, 1289 (1933). [h] R. Q. Brewster and F. Strain, *Ibid.*, **56**, 117 (1934). [i] M. Julia and G. Tchernoff, *Bull. soc. chim. (France)*, 546 (1952).

When potassium 3-nitrophenoxide was allowed to react with 3-nitrochlorobenzene, none of the dinitrodiphenyl ether was obtained. A small quantity of an orange material was isolated which proved to

(1) Presented in part at the Metropolitan Regional Meeting, New York and North Jersey Section, American Chemical Society, New York, N. Y., January 22, 1962.

(2) C. Haeussermann and E. Bauer, *Ber.*, **29**, 2083 (1896).

(3) N. M. Cullinane, H. G. Davey, and H. J. H. Padfield, *J. Chem. Soc.*, 719 (1934).

(4) N. L. Allinger and G. A. Youngdale, *J. Am. Chem. Soc.*, **84**, 1020 (1962).

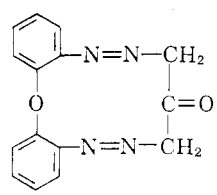
be 3,3′-dichloroazobenzene.[5] This compound could have come only from reduction of the 3-nitrochlorobenzene, and the only possible reducing agent is dimethylformamide. There is no precedent for such a reduction in the literature. We hope to do further work on this reaction.

The reaction to give dinitrophenyl ethers does have certain limitations. The sodium phenoxide may not be substituted for the potassium salt and the potassium salt may not be prepared *in situ* from potassium hydroxide and the phenol, but must be prepared and dried before use.

The reduction of I to III and of bis(4-nitrophenyl) ether to bis(4-aminophenyl) ether (V) in methanol with 10% palladium-on-charcoal catalyst goes in high yield. When acetic acid–acetic anhydride solvent is substituted for methanol in the reduction of I, a good yield of bis(2-acetamidophenyl) ether is obtained.

A standard method for nitrating acetanilide[6] applied to the bis(2-acetamidophenyl) ether gave bis(2-acetamido-5-nitrophenyl) ether which, when treated with refluxing concentrated hydrochloric acid, gave bis(2-amino-5-nitrophenyl) ether (VI).

It is known that two equivalents of diazonium salt react with acetonedicarboxylic acid to give a bisarylazo acetone.[7] The bis(2-aminophenyl) ether could be easily tetrazotized in dilute hydrochloric acid solution, but when allowed to react with acetone dicarboxylic acid it gave only polymeric material, no IV. Fischer–Hirschfelder models show

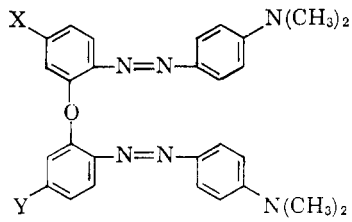


IV

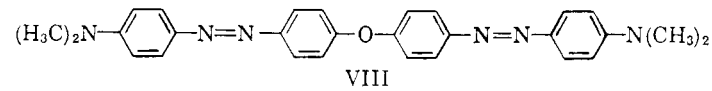
IV to be free of strain, indicating that it could have formed. High dilution techniques were not attempted. Other reactions of III with various difunctional compounds are being investigated.

VII, VIII, IX, and X are typical disazo compounds derived from the diamines III, V, and VI. Other derivatives, differing only in that other coupling components were substituted for dimethylaniline, are described in the experimental section. X was prepared by allowing *p*-nitrobenzene diazonium chloride to couple into III, then tetrazotizing the monoarylazo diamine, and allowing it to couple with dimethylaniline.

Table II gives the absorption maxima and molar extinction coefficients for the azo derivatives having a dimethylaniline moiety and for the monoazo compounds which were prepared for comparison purposes.



VII. X = Y = H
IX. X = Y = NO_2
X. X = *p*-Nitrophenylaze
Y = H



VIII

TABLE II

VISUAL SPECTRAL DATA FOR DIMETHYLANILINE AZOS

Compound	λ_{max} (mμ)	ε
p-(*p*-Methoxyphenylazo)-*N*,*N*-dimethylaniline[a] (XIII)	408	27,400
p-(*p*-Phenoxyphenylazo)-*N*,*N*-dimethylaniline[b]	415	29,200
4,4′-[Oxybis(*p*-phenyleneazo)]bis(*N*,*N*-dimethylaniline) (VIII)	420	39,700
p-(*o*-Methoxyphenylazo)-*N*,*N*-dimethylaniline (XI)	418	25,100
p-(*o*-Phenoxyphenylazo)-*N*,*N*-dimethylaniline (XIV)	425	26,800
4,4′-[Oxybis(*o*-phenyleneazo)]bis(*N*,*N*-dimethylaniline) (VII)	422	47,900
p-(2-Methoxy-4-nitrophenylazo)-*N*,*N*-dimethylaniline[c] (XII)	493	30,000
4,4′-[Oxybis(4-nitro-*o*-phenyleneazo)]bis(*N*,*N*-dimethylaniline) (IX)	468	54,300
p-{2-[*o*-(*p*-Dimethylamino)phenylazophenoxy]-4-(*p*-nitrophenylazo)phenylazo}-*N*,*N*-dimethylaniline (X)	472	60,900

[a] E. Sawicki and D. Gerber, *J. Org. Chem.*, **21**, 410 (1956). [b] A. Mailhe, *Comp. rend.*, **154**, 1241 (1912). [c] J. T. Hewitt and W. Thomas, *J. Chem. Soc.*, 1297 (1909).

The curves for these compounds show only a single absorption peak in the visible region and have molar extinction coefficients normal for such compounds.

Experimental

Intermediates were obtained commercially or were prepared by standard literature methods. Melting points are corrected. Microanalyses, given only for new compounds, were by the Research Services Section of these laboratories.

Bis(2-nitrophenyl) Ether (I).—A solution of 9 g. (0.05 mole) of potassium *o*-nitrophenoxide and 8 g. (0.05 mole) of *o*-nitrochlorobenzene in 30 ml. of dimethylformamide was heated at reflux for 18 hr., cooled, and poured over ice. Filtration, air drying, and recrystallization from ethanol gave 9.3 g., 71.5%, of yellow crystals melting at 114.5–116° (lit. m.p. 114.5°,[2] 116°[3]). The reactions in dimethyl sulfoxide and dimethylacetamide were carried out similarly.

The same procedure yielded the 2,3′-isomer as orange

(5) A. Laubenheimer, *Ber.*, **8**, 1625 (1875).

(6) R. Adams and J. R. Johnson, "Laboratory Experiments in Organic Chemistry," The Macmillan Company, New York, N. Y., 1940, p. 335.

(7) H. v. Pechmann and K. Jenisch, *Ber.*, **24**, 3257 (1891).

needles of m.p. 78–80° after recrystallization from ethanol.

Anal. Calcd. for $C_{12}H_8N_2O_5$: C, 55.4; H, 3.1; N, 10.8. Found: C, 55.8; H, 3.1; N, 10.4.

3,3′-Dichloroazobenzene.—A solution of 42 g. (0.24 mole) of potassium *m*-nitrophenoxide and 47 g. (0.30 mole) of *m*-nitrochlorobenzene in 170 ml. of dimethylformamide was heated at reflux overnight. The reaction mixture was poured on ice, and the solid filtered off, dissolved in ethanol, treated with Darco, and partially evaporated. Cooling of this concentrated solution yielded 9.5 g. of brown crystals melting at 95.5–99°. Three recrystallizations from ethanol gave orange crystals of m.p. 99–102° (lit.,[5] 101°) and infrared spectrum and microanalysis consistent with the assigned structure.

Bis(2-aminophenyl) Ether (III).—A suspension of 52 g. (0.20 mole) bis(2-nitrophenyl) ether and 0.1 g. of palladium-on-charcoal catalyst in 125 ml. of methanol was hydrogenated in the Parr apparatus until hydrogen uptake ceased. The catalyst was removed by filtration and the filtrate drowned in ice–water to recover tan-yellow needles which, when dried, melted at 62.5–63.5° (lit.[8] m.p. 60° from water). The yield was 38 g., 95%.

Bis(2-acetamidophenyl) Ether.—Bis(2-nitrophenyl) ether (I) (50 g., 0.19 mole), 90 ml. of acetic anhydride, 60 ml. of acetic acid, and 0.1 g. of 10% palladium-on-charcoal catalyst were hydrogenated in the Parr apparatus until hydrogen uptake ceased. After removal of the catalyst by filtration, 150 ml. of methanol was added and the excess acetic anhydride destroyed by heating at reflux for a few minutes. Water (400 ml.) was added and the product slowly crystallized. The yield was 41 g., 75%, m.p. 182.5–185° after one recrystallization from methanol.

Anal. Calcd. for $C_{16}H_{16}N_2O_3$: C, 67.6; H, 5.7; N, 9.9. Found: C, 67.7; H, 5.6; N, 9.6.

Bis(2-acetamido-5-nitrophenyl) Ether.—Bis(2-acetamidophenyl) ether (26 g., 0.092 mole) was dissolved in 39 ml. of hot acetic acid and poured slowly into 60 ml. of cold concentrated sulfuric acid. A nitrating mixture of 18 ml. of concentrated nitric acid and 24 ml. of concentrated sulfuric acid was slowly added while the temperature was maintained below 10°. The reaction solution was then allowed to warm to room temperature and was poured over ice. The product was filtered, washed with water, and recrystallized from Methyl Cellosolve to give yellow crystals, m.p. 258–259°.

Anal. Calcd. for $C_{16}H_{14}N_4O_7$: C, 51.4; H, 3.8; N, 15.0. Found: C, 51.4; H, 3.8; N, 15.2.

Bis(2-amino-5-nitrophenyl) Ether (VI).—Bis(2-acetamido-5-nitrophenyl) ether (9.2 g., 0.025 mole), 30 ml. of concentrated hydrochloric acid, and 30 ml. of water were heated to reflux and sufficient Methyl Cellosolve was added to give an homogeneous solution. After 1 hr. at reflux, the solution was poured over ice and neutralized with ammonia; the product was filtered and air-dried. The yield was 7.1 g., 91%, of brown material decomposing at 221–231°. Three recrystallizations from Methyl Cellosolve yielded golden crystals melting at 248–250° with decomposition.

Anal. Calcd. for $C_{12}H_{10}N_4O_5$: C, 49.7; H, 3.5; N, 19.3. Found: C, 50.0; H, 3.6; N, 19.3.

4,4′-[Oxybis(4-nitro-*o*-phenyleneazo)]bis(*N*,*N*-dimethylaniline) (IX).—Bis(2-amino-5-nitrophenyl) ether (1.1 g., 0.0038 mole) was dissolved in 10 ml. of 5 *N* hydrochloric acid and cooled to 0–5° by adding ice. Sodium nitrite solution (0.1 *N*, 8 ml., 0.008 mole) was added slowly at 0–5° and stirring was continued for 1 hr. Dimethylaniline (1 g., 0.0083 mole) was dissolved in dilute hydrochloric acid and added in one portion, the pH was adjusted to about 5 with sodium acetate, and the product was filtered after an "R salt" test showed the solution to be free of diazonium salt. The nearly quantitative yield of product was air dried, and recrystallized from toluene, giving red crystals, m.p. 217–219° (dec.).

Anal. Calcd. for $C_{28}H_{26}N_8O_5$: C, 60.7; H, 4.7; N, 20.2. Found: C, 60.3; H, 4.4; N, 20.2.

When *N*-(2-cyanoethyl)-*N*-methylaniline was substituted for dimethylaniline, the product was 4,4′-[oxybis(4-nitro-*o*-phenyleneazo)]bis[*N*-(2-cyanoethyl)-*N*-methylaniline], giving red crystals from ethyl acetate, m.p. 208–209.5°.

Anal. Calcd. for $C_{32}H_{26}N_{10}O_5$: C, 60.7; H, 4.5; O, 22.3. Found: C, 61.2; H, 4.9; O, 2.0.

4,4′-[Oxybis(*p*-phenyleneazo)]bis(*N*,*N*-dimethylaniline) (VIII).—Bis(4-aminophenyl) ether (V) (2 g., 0.01 mole) was dissolved in 20 ml. 5 *N* hydrochloric acid and the solution diluted to 100 ml. with ice and water. Sodium nitrite solution (0.1 *N*, 200 ml., 0.02 mole) was added rapidly and after a few minutes a negative starch–iodide test was obtained. Dimethylaniline (2.5 g. 0.02 mole) in 30 ml. ethanol was added and the pH brought up to 5 with sodium acetate. After the coupling reaction was complete, the product was filtered, air dried, and recrystallized from *n*-propyl alcohol. The yield was nearly quantitative of yellow crystals which sintered at 183°, and had m.p. 186–188.5°.

Anal. Calcd. for $C_{28}H_{28}N_6O$: C, 72.4; H, 6.1; N, 18.1. Found: C, 70.8; H, 6.1; N, 17.2.

When the coupling component was 2-naphthol, the product was 1,1′-[oxybis(*p*-phenyleneazo)]bis(2-naphthol), a red solid which, after two recrystallizations from toluene, melted at 223.5–224.5° (dec.).

Anal. Calcd. for $C_{32}H_{23}N_4O_3$: C, 75.3; H, 4.3; N, 11.0. Found: C, 75.5; H, 3.9; N. 11.1.

When the coupling component was *N*-(2-cyanoethyl)-*N*-methylaniline, the product was **4,4′-[oxybis(*p*-phenyleneazo)bis[*N*-(2-cyanoethyl)-*N*-methylaniline]**, an orange solid which melted at 166–168° after two recrystallizations from *n*-propyl alcohol.

Anal. Calcd. for $C_{32}H_{30}N_8O$: C, 70.8; H, 5.57; N, 20.7. Found: C, 71.0; H, 5.68; N, 20.4.

Tetrazotization of Bis(2-aminophenyl) Ether (III) was carried out in the same manner as the tetrazotization of V.

Reaction with Acetonedicarboxylic Acid.—Acetonedicarboxylic acid (1.46 g., 0.1 mole) in 20 ml. of ethanol was added and the pH adjusted to 5 with sodium acetate. The red precipitate which formed was filtered off and washed with warm ethanol. No solvent for recrystallization could be found. When heated, the material began darkening at 240° and decomposed at 260–270°. There was no evidence even of microcrystallinity, and some absorption in the infrared at 5.9 and 7.9 μ indicated that carboxylic acid end groups, which would be expected if the material were polymeric, were present.

Anal. Calcd. for cyclic structure $C_{15}H_{12}N_4O_2$: C, 64.3; H, 4.3; N, 20.0. Found: C, 64.9; H, 4.9; N, 19.5.

When the coupling component was dimethylaniline, the product was **4,4′-[oxybis(*o*-phenyleneazo)]bis(*N*,*N*-dimethylaniline) (VII)**, a dark red material which, after two recrystallizations from toluene, melted at 206–210° with decomposition.

Anal. Calcd. for $C_{28}H_{28}N_6O$: C, 72.4; H, 6.1; N, 18.1. Found: C, 72.5; H, 6.0; N, 17.9.

When the coupling component was 2-naphthol, the product was **1,1′-[oxybis(*o*-phenyleneazo)]bis(2-naphthol)**, an orange material which melted at 164–266°, after two recrystallizations from toluene.

Anal. Calcd. for $C_{32}H_{22}N_4O_3$: C, 75.3; H, 4.3; N, 11.0. Found: C, 75.6; H, 4.0; N, 10.9.

***p*-{2-[*α*-(*p*-Dimethylamino)phenylazophenoxy]-4-[(*p*-nitrophenylazo)phenylazo}-*N*,*N*-dimethylaniline (X).**—To a solution of *p*-nitrobenzenediazonium chloride prepared from 3.5 g. (0.025 mole) of *p*-nitroaniline was added a solution of 5 g. (0.025 mole) of III in 30 ml. of acetic acid. When the coupling was completed, the product was filtered and air dried to yield 4.5 g., 50%, of material melting at 95–110°. This diamine (3.5 g., 0.01 mole) was tetrazotized in the

(8) C. Haeussermann and E. Bauer, *Ber.*, **30**, 738 (1897).

same manner as was III. Dimethylaniline (2.54 g., 0.02 mole) in 30 ml. of acetic acid was added. When the solution had come to room temperature, the product was filtered off, dried, and recrystallized three times from toluene. Only a few hundred milligrams of yellow-brown product melting at 196–197.5° remained.

Anal. Calcd. for $C_{34}H_{31}N_9O_3$: C, 66.5; H, 5.1; N, 20.5. Found: C, 65.2; H, 6.3; N, 19.3.

***p*-(2-Methoxy-4-nitrophenylazo)-*N*,*N*-dimethylaniline (XII).**—2-Methoxy-4-nitroaniline (3.3 g., 0.02 mole) was diazotized in a standard way and allowed to couple with 2.4 g. (0.02 mole) of dimethylaniline to give a nearly quantitative crude yield. Recrystallization from ethanol gave violet crystals, m.p. 173.5–175°.

Anal. Calcd. for $C_{15}H_{16}N_4O_3$: C, 60.0; H, 5.4; N, 18.7; O. 16.0. Found: C, 59.7; H, 6.0; N, 18.4; O, 15.7.

***p*-(*o*-Phenoxyphenylazo)-*N*,*N*-dimethylaniline (XIV)** was prepared in the usual way.

Anal. Calcd. for $C_{20}H_{19}N_3O$: C, 75.7; H, 6.0; N, 13.2; O, 5.0. Found: C, 75.5; H, 5.9; N, 13.2; O, 5.0.

The Tetraphenylphenols

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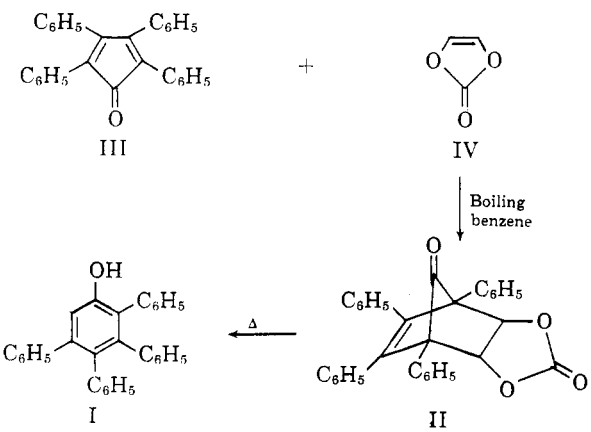
Received June 18, 1962

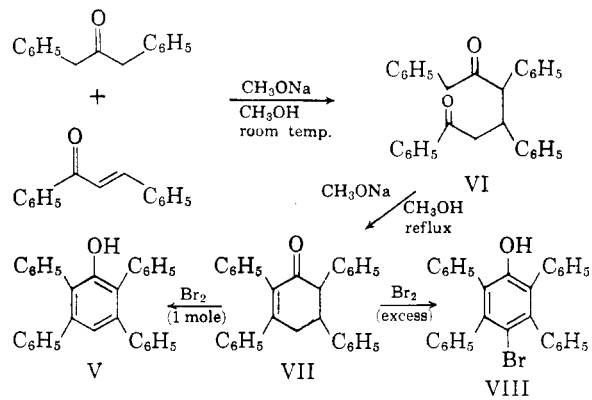
In connection with another investigation we have had occasion to synthesize the three tetraphenylphenols.

2,3,4,5-Tetraphenylphenol (I) was prepared by the following route:



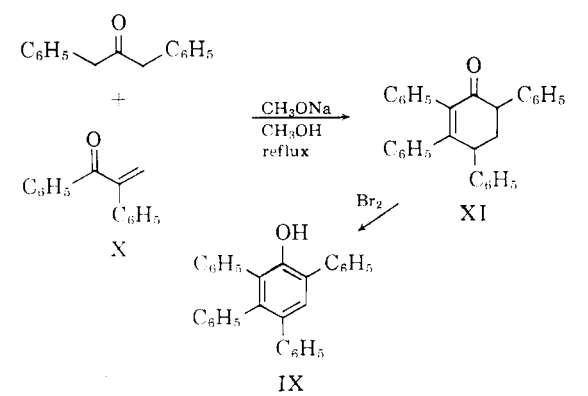
A Diels–Alder adduct II, of undetermined stereochemistry, was obtained when tetracyclone (III) and vinylene carbonate (IV)[2] were heated together in boiling benzene. The adduct has bands in its infrared spectrum at 5.50 and 5.59 μ; these can be assigned to the stretching vibrations of the carbonate[3] and ketonic[4] carbonyl groups, respectively. When II was heated at its melting point, gas evolution occurred and it was converted to a compound, $C_{30}H_{22}O$, which in its infrared spectrum shows no carbonyl band but a sharp hydroxyl band at 2.81 μ. On the basis of its genesis and spectrum this compound is assigned structure I. It was also obtained together with the adduct II when the Diels–Alder reaction was carried out in refluxing xylene.

2,3,5,6-Tetraphenylphenol (V) was prepared by the following route:



Michael addition of dibenzyl ketone to benzalacetophenone gave the δ-diketone VI (infrared bands at 5.84 and 5.93 μ) when carried out with methanolic sodium methoxide at room temperature. The same reagent at reflux effected the aldolization and dehydration of VI to give the cyclohexenone VII. This shows in its infrared spectrum a band at 6.00 μ and in its ultraviolet spectrum a maximum at 295 mμ (log ϵ 3.86) in accord with expectation.[5] Oxidation of VII with one molar equivalent of bromine gave 2,3,5 6-tetraphenylphenol (V) (infrared band at 2.83 μ). When excess of bromine was used for the oxidation, a brominated product, $C_{30}H_{21}OBr$, was obtained which is considered to have structure VIII on the basis of its ultraviolet spectrum (*vide infra*).

The remaining tetraphenylphenol, IX, was prepared by the following route, analogous to that used for the synthesis of V, although in this case the intermediates were not characterized (X → XI → IX).



(1) Present address: Department of Chemistry, University of Toronto.

(2) M. S. Newman and R. W. Addor, *J. Am. Chem. Soc.*, **77**, 3789 (1955).

(3) *Cf.* C. L. Angell, *Trans. Faraday Soc.*, **52**, 1178 (1956).

(4) *Cf.* C. F. H. Allen, T. Davis, D. W. Stewart, and J. A. VanAllan, *J. Org. Chem.*, **20**, 306 (1955).

Michael addition of dibenzyl ketone to methylenedeoxybenzoin (X)[6] gave a viscous oil from which no crystalline product was obtained directly. The infrared spectrum of the oil—bands at 6.01 and 6.29 μ—showed that it was rich in the cyclohexenone XI; the spectrum was similar to, but not identical with, that of the cyclohexenone VII.[7] Treatment of the oil with bromine in carbon tetrachloride gave crystalline 2,3,4,6-tetraphenylphenol (IX) (infrared band at 2.81 μ).[8]

The melting points and ultraviolet spectra of the tetraphenylphenols are listed in Table I. It may

TABLE I

	M.p., °C.	λ_{max},[a] mμ	log ϵ
2,3,4,5-Tetraphenylphenol (I)	183–184	243	40,200
		300	5,900
2,3,5,6-Tetraphenylphenol (V)	277–278	239	31,600
		304	4,850
2,3,4,6-Tetraphenylphenol (IX)	244–245	247	43,200
		308	7,200
4-Bromo-2,3,5,6-tetraphenylphenol (VIII)		249	19,800

[a] In cyclohexane.

be noted that the isomer assigned the structure of the highest symmetry (V) has the highest melting point. Detailed discussion of the ultraviolet spectra is not possible because of the complexity of the absorbing systems and the unavailability of closely related model compounds. However, it may be pointed out that the K-band of V, which has no phenyl group in the *para* relationship to the hydroxyl group, occurs at a somewhat shorter wave length and is of appreciably weaker intensity than the K-bands of I and IX, each of which has a phenyl group in the *para* position on the phenolic ring. This may be compared with the case of the phenylphenols,[9] where the K-bands of the *ortho* and *meta* isomers occur at lower wave length and are of weaker intensity than the K-band of the *para* isomer. The large hypochromic effect observed on bromination of V suggests strongly that the bromine attacks the phenolic ring to give VIII, the intensity of whose K-band is reduced relative to that of the K-band of V largely because of increased steric hindrance to coplanarity of the peripheral phenyl groups and the phenolic ring. Attack of bromine at the *para* position of one of the peripheral rings would not be expected to give rise to a large hypochromic effect, while preferential attack at the *ortho* position of a peripheral ring appears unlikely.

(5) *Cf.* 2,3,4,5-tetraphenyl-2-cyclopentenone, λ_{max} 295 mμ (log ϵ 4.13): E. D. Bergmann, *Bull. soc. chim. France*, 703 (1952).

(6) H. Fiesselmann and J. Ribka, *Chem. Ber.*, **89**, 27 (1956).

(7) Reaction of dibenzyl ketone with methylenedeoxybenzoin in the presence of methanolic sodium methoxide in the cold also gave an oil from which no crystalliue product was obtained; the infrared spectrum of this product, with bands at 5.83 and 5.94 μ, resembled that of the diketone VI.

(8) Professor D. G. Farnum, Cornell University, has informed us that he has prepared the tetraphenylphenol IX by an alternative route and has established the identity of his product with that obtained by us. He has also corroborated the structural assignment V by oxidation of this compound to a quinone. We are grateful to him for his kindness in informing us of these results. *Cf.*, also, D. G. Farnum and M. Burr, *J. Am. Chem. Soc.*, **82**, 2651 (1960).

(9) A. Burawoy and J. T. Chamberlain, *J. Chem. Soc.*, 2310 (1952); V. Prelog, O. Metzler, and O. Jeger, *Helv. Chim. Acta*, **30**, 675 (1947).

Experimental[10]

5,6-Dihydroxy-1,2,3,4-tetraphenylbicyclo[2.2.1]hept-2-en-7-one Carbonate (II).—Tetracyclone (2.00 g.) and vinylene carbonate[2] (1.00 g.) were heated together in refluxing benzene (20 ml.) for 24 hr. The solvent was removed under reduced pressure and the residue was crystallized from benzene–petroleum ether to give the adduct II (1.5 g., 60%), m.p. 208–209° dec., $\lambda_{max}^{CHCl_3}$ 5.50, 5.59 μ.

Anal. Calcd. for $C_{32}H_{22}O_4$: C, 81.68; H, 4.71. Found: C, 81.66; H, 4.81.

When the Diels–Alder reaction was carried out on the same scale in boiling xylene, the product was found to be a mixture of II and the phenol I by infrared spectral comparison.

2,3,4,5-Tetraphenylphenol (I).—The adduct II (0.50 g.) was heated at 215° for 5 min., after which time gas evolution had ceased. The residue was recrystallized from benzene–petroleum ether to give the phenol I (0.40 g., 95%) as plates, m.p. 183–184°, $\lambda_{max}^{CHCl_3}$ 2.81 μ.

Anal. Calcd. for $C_{30}H_{22}O$: C, 90.42; H, 5.57. Found: C, 89.83, 90.70; H, 5.60, 6.01.

1,3,4,6-Tetraphenyl-1,5-hexanedione (VI).—Benzalacetophenone (5.00 g.) and dibenzyl ketone (5.00 g.) were dissolved in methanol (50 ml.) and saturated methanolic sodium methoxide (1 ml.) was added to the solution. After 5 min. a crystalline deposit began to appear after 1 hr. the mixture was cooled in an ice bath and the product filtered. This was recrystallized from methanol to give VI as cubes (7.56 g., 75%), m.p. 195–196°, $\lambda_{max}^{CHCl_3}$ 5.84, 5.93 μ.

Anal. Calcd. for $C_{30}H_{26}O_2$: C, 86.09; H, 6.26. Found: C, 86.13; H, 6.35.

2,3,5,6-Tetraphenyl-2-cyclohexenone (VII).—A suspension of VI (5.05 g.) in methanol (50 ml.) was treated with saturated methanolic sodium methoxide (5 ml.), and the mixture was boiled under reflux in a nitrogen atmosphere for 24 hr. The tan solid which separated when the reaction mixture was cooled was filtered and recrystallized from benzene–petroleum ether to give the cyclohexenone VII (3.70 g., 75%), m.p. 159–160°, $\lambda_{max}^{CHCl_3}$ 6.00, 6.27 μ, λ_{max}^{EtOH} 295 mμ (log ϵ 3.86).

Anal. Calcd. for $C_{30}H_{24}O$: C, 89.89; H, 6.04. Found: C, 89.89; H, 5.78.

2,3,5,6-Tetraphenylphenol (V).—A solution of VII (1.08 g., 0.0027 mole) in acetic acid (20 ml.) was treated with bromine (0.43 g., 0.0027 mole). After all of the bromine had been consumed, water was added to the reaction mixture, and the precipitated product was filtered and recrystallized from benzene–petroleum ether to give the phenol V as needles (0.85 g., 80%), m.p. 272–273°, $\lambda_{max}^{CHCl_3}$ 2.83 μ.

Anal. Calcd. for $C_{30}H_{22}O$: C, 90.42; H, 5.57. Found: C, 90.54; H, 5.77.

4-Bromo-2,3,5,6-tetraphenylphenol (VIII).—A solution of VII (1.03 g.) in acetic acid (20 ml.) was treated with successive small portions of bromine until the color of the latter persisted when the reaction mixture was heated on the steam bath. Water was added to the reaction mixture and the precipitated product was filtered and recrystallized from benzene–petroleum ether to give VIII as rhombs (0.75 g., 60%), m.p. 329–330° ($\lambda_{max}^{CHCl_3}$ 2.81 μ.

Anal. Calcd. for $C_{30}H_{21}OBr$: C, 75.47; H, 4.43; Br, 16.74. Found: C, 75.95; H, 4.39; Br, 16.42.

2,3,4,6-Tetraphenylphenol (IX).—A solution of methylenedeoxybenzoin[6] (5.01 g.) and dibenzyl ketone (5.01 g.) in methanol (40 ml.) was treated with saturated methanolic sodium methoxide (12 ml.). The mixture was boiled under

(10) Melting points are uncorrected.

reflux for 3 hr., then cooled and poured into water (100 ml.). The resulting mixture was extracted with three 50-ml. portions of dichloromethane and the combined extracts were washed with water, dilute hydrochloric acid, water, and saturated brine, and dried over anhydrous sodium sulfate. Removal of the solvent under reduced pressure left the crude product as a viscous, brown oil (8 g.), $\lambda_{max}^{CHCl_3}$ 6.01, 6.29 μ. A solution of 0.8 g. of this oil in carbon tetrachloride (30 ml.) was treated with a solution of bromine (1.5 g.) in carbon tetrachloride (10 ml.) and the mixture was boiled under reflux for 1 hr. It was then cooled and treated with aqueous sodium bisulfite to discharge the excess of bromine. The organic layer was separated and washed with water, aqueous sodium bicarbonate, water, and saturated brine. It was dried over anhydrous sodium sulfate and stripped of solvent under reduced pressure. The residue was crystallized from benzene–petroleum ether to give the phenol IX, m.p. 244–245°, $\lambda_{max}^{CHCl_3}$ 2.81 μ.

Anal. Calcd. for $C_{30}H_{22}O$: C, 90.42; H, 5.57. Found: C, 90.47; H, 5.61.

Isocyanide Bond Refraction

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Extensive tabulations of bond refractions have been made by Vogel[1] and by Gillis.[2] The isocyanide bond refraction, which has not previously been determined, is now reported for comparison with that of the cyanide bond. The new value is based on the properties of four alkyl isocyanides shown in Table I.

TABLE I

PROPERTIES OF ALKYL ISOCYANIDES

R	B.P.	d^{20}_4	$n^{20}D$	R^aD	(N≡C)[a]	(Mn^{20}D)[a]
Me	59–60	0.7497	1.3466	11.68	5.10	29.16
Et	78–79	0.7478	1.3658	16.49	5.27	28.51
n-Pr	99–100	0.7665	1.3832	21.04	5.17	28.27
n-Bu	129–130	0.7818	1.3976	25.64	5.12	28.26
				Mean	5.17	28.55

[a] The symbolism is Vogel's.[1]

(N≡C) determined from each of these alkyl isocyanides is greater than (C≡N) determined from the corresponding alkyl cyanide,[1] and the difference of the means is significant at the 0.01 level. (The bond refraction coefficients 28.55 for isocyanides and 29.91 for cyanides[1] are also significantly different.) This result is in contrast with the low bond refractions normally associated with systems containing dative bonds.[2–4] It is probably owing to the effect of the lone pairs of electrons on the nitrogen and carbon atoms, because the bond refraction as determined is a measure of the polarizability of the six electrons in the bond plus that of the lone pair in each case. Linnett[5] has suggested that these pairs are in some way connected with the lower value for the N≡C force constant in methyl isocyanide as compared with that of C≡N in methyl cyanide.

Methyl isocyanide has a lower boiling point and smaller dipole moment[6] than methyl cyanide. These facts are compatible with the terminal lone pair in isocyanide being less strongly bound than in cyanides. Further evidence is being sought from retention data on various donor and acceptor stationary phases in gas chromatography.

Experimental

The isocyanides were prepared from the corresponding iodide and silver cyanide by the method of Jackson and McCusick.[7] It was advantageous to dilute the reaction mixture with a little ethylene glycol which made the pasty complex easier to stir. The products were fractioned in a column packed with helices, and physical properties were determined[2,3] on fractions shown to be homogeneous by gas chromatography.

Acknowledgment.—This paper is published by the permission of the Chief Scientist, Australian Defence Scientific Service, Department of Supply, Melbourne, Victoria, Australia.

(1) A. I. Vogel, W. T. Cresswell, G. H. Jeffery, and J. Leicester, *J. Chem. Soc.*, 514 (1952).
(2) R. G. Gillis, *Rev. Pure and Appl. Chem.*, **10**, 21 (1960).
(3) C. C. Price and R. G. Gillis, *J. Am. Chem. Soc.*, **75**, 4750 (1953).
(4) R. G. Gillis, J. F. Horwood, and G. L. White, *J. Am. Chem. Soc.* **80**, 2999 (1958).
(5) J. W. Linnett, *J. Chem. Phys.*, **8**, 91 (1940).
(6) S. N. Ghosh, R. Trambarulo, and W. Gordy, *ibid.*, **21**, 308 (1953).
(7) H. L. Jackson and B. C. McCusick, *Org. Syn.*, **35**, 62 (1955).

Chlorination of Phenyl Ether

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Previous studies of phenyl ether (I) chlorination are very sparse in the chemical literature, possibly due to the difficulty in separating the liquid or low melting products. Vapor phase chromatography has allowed us to examine this system in a much more precise way. We were particularly anxious to check some previously reported results[1] which we considered anomalous. They are (a) monochlorination of I in acetic acid yields no detectable amounts of 2-chlorophenyl ether (II), and (b) chlorination of 4-chlorophenyl ether (III) yields a significant amount of 3,4-dichlorophenyl ether (IV). Although the first seemed not too improbable, the second would require some revision of our concept of electrophilic substitution.

(1) R. Q. Brewster and G. Stevenson, *J. Am. Chem. Soc.*, **62**, 3144 (1940).

Discussion and Results

Compounds I, II, and III were chlorinated under a wide variety of conditions and the results are recorded on Tables I, II, and III.

TABLE I
PHENYL ETHER CHLORINATION

Chlorinating system	% 2-	% 4-
No catalyst, Cl_2,CCl_4, R.T.	8.4	91.6
No catalyst, Cl_2, HOAc, 0°	11.0	89.0
$SnCl_4$, Cl_2, CCl_4, 0°	25.2	74.8
$FeCl_3$, Cl_2, CCl_4, 0°	17.0	83.0
$AlBr_3$, Cl_2, CCl_4, 0°	7.7	92.3

TABLE II
2-CHLOROPHENYL ETHER CHLORINATION

Chlorinating system	% 2,6-	% 2,4-	% 2,2'-	% 2,4'-
No catalyst, Cl_2, HOAc, 0°	...	0.9	10.7	88.4
$SnCl_4$, Cl_2, CCl_4, 0°	Trace	1.4	23.1	75.5
$FeCl_3$, Cl_2, CCl_4, 0°	Trace	2.0	22.9	75.1
$AlBr_3$, Cl_2, CCl_4, 0°	1.2	5.4	21.5	72.0

TABLE III
4-CHLOROPHENYL ETHER CHLORINATION

Chlorinating system	% 2,4-	% 2,4'-	% 4,4'-
No catalyst, Cl_2, HOAc, 0°	...	8.8	91.2
$SnCl_4$, Cl_2, CCl_4, 0°	0.3	23.2	76.5
$FeCl_3$, Cl_2, CCl_4, 0°	1.0	20.2	78.8
$AlBr_3$, Cl_2, CCl_4, 0°	3.7	19.6	76.7

Examination of Table I provides some explanation of why II was not found in previously reported noncatalytic chlorinations since it is formed in relatively minor amounts. The most interesting feature of Table I is the manner in which the *ortho/para* ratio rises and falls with increasing activity of the chlorinating species. A possible explanation for this is discussed elsewhere.[2,3] Briefly, we believe the increase in *ortho/para* ratio is due to a decrease in steric interactions in the transition state as more reactive chlorinating species are used. We feel the *ortho/para* ratio passing through a maximum is also correlated with increasing activity of the chlorinating species, since the dipolar interaction between the ether group (-I) and the incoming partially positive chlorine atom increases.

Tables II and III show the same general trend to a lesser extent, which is somewhat puzzling.[4] They also show that some substitution takes place in the already chlorinated nucleus and this increases as the activity of the chlorinating species increases. The data in Table III clearly demonstrate that IV[5] is not formed in measurable amounts nor is any product of meta substitution produced in any of the systems[5] in measurable amounts.

(2) H. Weingarten, *J. Org. Chem.*, **26**, 4347 (1961).

(3) J. R. Knowles, R. O. C. Norman, and G. K. Radda, *J. Chem. Soc.*, **4885** (1960).

(4) Treatment of II under much more severe conditions (30 min. at 140° with aluminum chloride or aluminum bromide and no solvent) produced no detectable isomerization.

(5) Standard samples of the possible *meta* substituted compounds were prepared for comparison by usual Ullmann methods.

Experimental

General Chlorination Method.—A solution of 0.01 mole of I, II, or III in 10 ml. of solvent (acetic acid or carbon tetrachloride) was prepared and cooled in an ice bath. To this solution was added 0.01 g. of catalyst (stannic chloride, ferric chloride, or aluminum bromide), if any. The resulting mixture was combined with a cold solution of 0.003 mole of chlorine in 4 ml. of solvent. The reaction mixture was allowed to stand in an ice bath for 1 hr. (The noncatalytic chlorination of I in carbon tetrachloride was carried out at room temperature and stored in the dark for 48 hr.) At the end of the reaction period, the mixture was poured into water, carbon tetrachloride added if necessary, the organic layer dried, evaporated, and the oily residue used directly for vapor phase chromatographic analysis.

Analytical Procedure.[6] The analyses were performed on a Barber-Colman Model 20 gas chromatograph equipped with a 200-ft. apiezon "L" capillary column and an argon ionization detector. Although areas were found to be nearly proportional to mole per cent, any deviation from linearity was corrected for by use of calibrated standard samples.

(6) Details of the analytical procedure are identical to those reported by H. Weingarten, W. D. Ross, J. M. Schater, and G. Wheeler, Jr., *Anal. Chim. Acta*, **26**, 391 (1962).

The Synthesis and Properties of N,N-Dialkylaminovinylindoles

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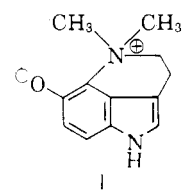
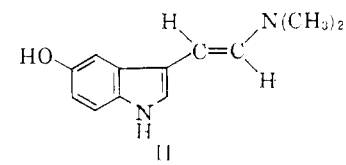
Recently the structure of dehydrobufotenine, isolated from the parotid gland of the South American toad, *Bufo marinus*, has been established as the tricycle I[1,2] superseding the old enamine formula II.[3] Because of interest in the hallucinogenic ac-



I



II

tivity of alkylated tryptamines[4] we are reporting here the synthesis and some properties of enamines of type II.[5,6]

The starting materials, namely 3-indoleacetaldehyde[7] and 5-benzyloxy-3-indoleacetaldehyde were prepared by the oxidation of the corresponding tryptophans according to the method of Gray.[7]

(1) F. Märki, A. V. Robertson, and B. Witkop, *J. Am. Chem. Soc.*, **83**, 3341 (1961).

(2) B. Robinson, G. F. Smith, A. H. Jackson, D. Shaw, B. Frydman, and V. Deulofeu, *Proc. Chem. Soc.* (London), 310 (1961).

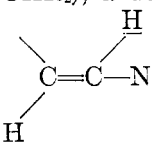
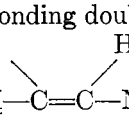
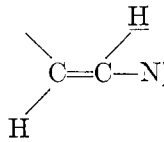
(3) H. Wieland and T. Wieland, *Ann.*, **528**, 234 (1937).

(4) St. Szara, *Experientia*, **12**, 441 (1956).

The aldehydes were then condensed with secondary amines using the technique of Herr and Heyl.[8]

The two dimethylaminovinylindoles, 3-(2′-dimethylaminovinyl)indole and 5-benzyloxy-3-(2′-dimethylaminovinyl)indole, were isolated as unstable oils of roughly 80% purity as judged from infrared analysis. They hydrolyzed readily to dimethylamine and apparently polymeric material. Piperidinovinylindole likewise was obtained as an unstable oil which was characterized by infrared and ultraviolet spectra. Condensation of the appropriate aldehydes with dibenzylamine afforded the crystalline enamines, 3-(2′-dibenzylaminovinyl)indole and 5-benzyloxy-3-(2′-dibenzylaminovinyl)indole. In addition 3-(2′-diisopropylaminovinyl)indole was obtained as a relatively stable crystalline solid.

These three enamines gave satisfactory n.m.r. spectra[9] whereas the spectra of the N,N-dimethyl analogs were indicative of extensive polymerization and decomposition.

The diisopropylamino compound (III) (Fig. 1) showed the following assignable n.m.r. peaks: a doublet at 1.20 δ (—CH_3) (tetramethylsilane = 0.0 δ), a septet at 3.72 δ (—$NCHR_2$), a doublet (J = 14.5 c.p.s.) 5.41 δ (*trans* ) and the corresponding doublet (J = 14.5 c.p.s.) at 6.88 δ (*trans* ). The data for 3-(2′-dibenzylaminovinyl)indole (IV) and for 5-benzyloxy-3-(2′-dibenzylvinylamino)indole (V) are presented in Fig. 1. The 3-(2-piperidinovinylamine)indole gave less satisfactory n.m.r. spectrum due to polymerization but showed a doublet at 5.53 δ (J = 14 c.p.s., *trans* ).

For comparison the data for 3-indole-β-acrylic acid (VI) are presented in Fig. 1 and establish the *trans* relationship of the ethylenic protons.

The infrared spectra of the indolevinyl amines showed a sharp N—H absorption at 2.80 μ and a sharp intense C=C peak at 6.07–6.10 μ which

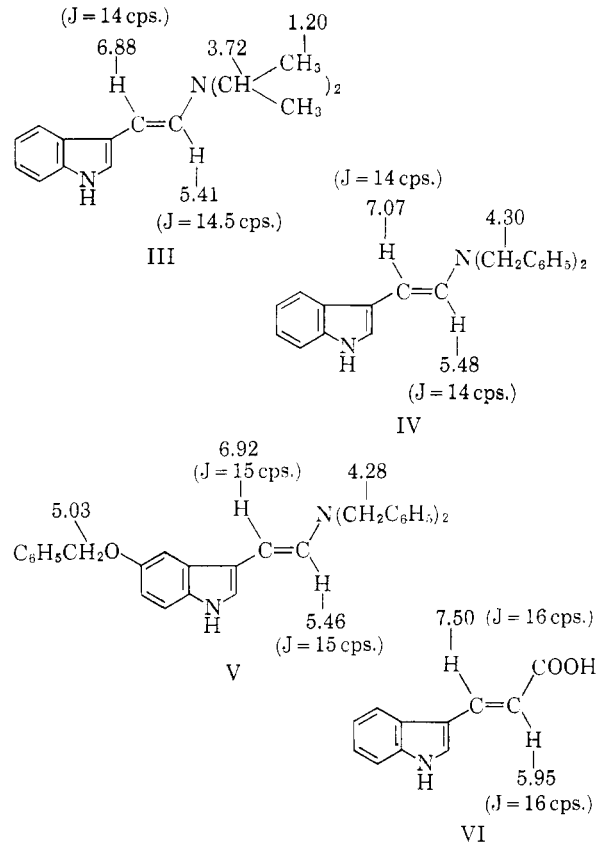
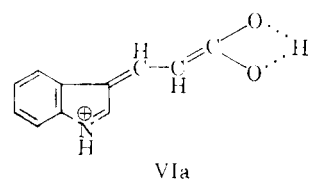


Fig. 1.—N.m.r. data for vinylindoles, expressed in δ units, tetramethylsilane = 0.0 δ. Solvent: deuteriochloroform for III–V, deuteroacetone for VI.

compares well with the enamine absorption reported for N,N-dimethyl-β-methyl-β-phenylvinylamine (6.10 μ vs)[6] and for di-β-β-diphenylvinylamine (6.08 μ vs).[6]

The ultraviolet spectra of the various indolevinylamines showed only end absorption in the 290–340-mμ region in contrast to 3-indole-β-acrylic acid[10] which shows a strong absorption peak (λ_{max}^{EtOH} 3186, ϵ_{max} 12,500) in this region.

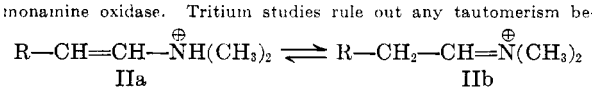
This result is due to the fact that in the photoexcited state the two nitrogens oppose or cancel each other's contributions, whereas the excited state VIa of indoleacrylic acid leads to a considerable bathochromic effect. The ultraviolet absorption spectrum of 3(2′-diisopropylvinylamine)indole is shown in Fig. 2.



VIa

3-(2′-Dimethylaminovinyl)indole was converted to a methiodide by treatment of a benzene solution of the enamine with methyl iodide but even after

(5) The isomeric iminonium structure (IIb) has been implied as an intermediate in the degradation of N,N-dimethyltryptamine by monamine oxidase. Tritium studies rule out any tautomerism between the imine and enamine: T. E. Smith, H. Weissbach, and S. Udenfriend, *Biochem.*, **1**, 137 (1962).



(6) B. Witkop, *J. Am. Chem. Soc.*, **78**, 2873 (1956).

(7) R. A. Gray, *Arch. Biochem. Biophys.*, **81**, 480 (1959).

(8) M. E. Herr and F. W. Heyl, *J. Am. Chem. Soc.*, **74**, 3627 (1952).

(9) We thank Mr. Robert Bradley for the n.m.r. spectra obtained with a Varian A-60 instrument.

(10) J. S. Moffatt, *J. Chem. Soc.*, 1442 (1957).

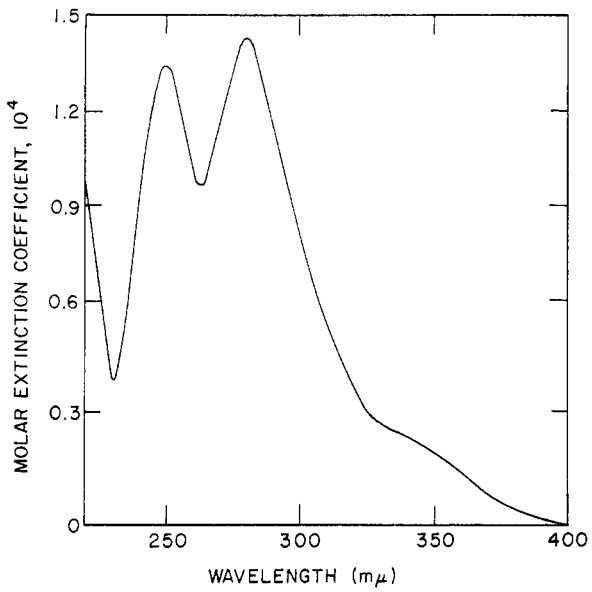


Fig. 2.—Ultraviolet absorption spectra of 3(2′-diisopropylvinylamino)indole in acetonitrile.

recrystallization from methanol–ether and dry acetone, analysis indicated contamination with trimethylammonium iodide and the compound was not investigated further. All other attempts to prepare stable salts from these enamines were unsuccessful.

Attempts to reduce 3-(2′-dimethylaminovinyl)-indole by catalytic hydrogenation to N,N-dimethyltryptamine were unsuccessful, but reduction with sodium borohydride in methanol or with lithium aluminum hydride in ether resulted in the formation of N,N-dimethyltryptamine which was identified by comparison of R_f values on thin layer chromatography (Silica Gel-G), color reaction (Ehrlich's) and infrared spectrum with those of authentic N,N-dimethyltryptamine.

Catalytic debenzylation of 5-benzyloxy-3-(2′-dimethylaminovinyl)indole in benzene with palladium on charcoal and hydrogen did not lead to the desired product (II).

Experimental[11]

5-Benzyloxy-3-indoleacetaldehyde was prepared by the method of Gray[7] from 5-benzyloxytryptophan.[12] A benzene solution of the aldehyde was mixed with a saturated sodium sulfite solution. The resulting bisulfite addition compound was recrystallized from water–ethanol. Liberation of the aldehyde with sodium carbonate solution gave a yellow oil (infrared absorption spectrum (neat): NH 2.85 μ, C=O 5.80 μ) which was characterized as the semicarbazone, m.p. 150–151°, recrystallized from methanol–water.

Anal. Calcd. for $C_{18}H_{18}N_4O_2$: C, 67.05; H, 5.61; N, 17.38. Found: C, 67.07; H, 5.78; N, 16.80.

Preparation of 3-(2-Disubstituted Aminovinyl)indoles.—The free aldehydes were prepared directly before use by liberation from the bisulfite addition compounds with sodium carbonate, and simultaneous extraction into ether. The ether was dried over sodium sulfate and then removed *in vacuo*. To 0.01 mole of aldehyde in 30–50 ml. of dry thiophene-free benzene in a reflux apparatus containing a Bidwell-Sterling moisture trap[7] and magnetic stirrer was added a solution of 0.012–0.02 mole of amine in 15 ml. of benzene. The reaction was warmed slowly and then refluxed for 2–3 hr. The benzene was evaporated and the residue purified as described under the individual amines. The amines were stored in a desiccator, preferably under nitrogen.

3-(2′-Dimethylaminovinyl)indole was obtained as an unstable oil after treatment of a benzene solution of the condensation product with Norit followed by evaporation of the benzene *in vacuo*.

Infrared absorption spectrum ($HCCl_3$): N—H 2.84 μ, C=C 6.07 μ vs. $\lambda_{max}^{acetonitrile}$ 245 mμ, 276 mμ, 325 mμ shoulder; ϵ_{max} 10,000; 9400; 3500.

5-Benzyloxy-3-(2′-dimethylaminovinyl)indole was obtained as an unstable brown oil. Infrared absorption spectrum (neat): N—H 2.78 μ, C=C 6.08 μ vs. $\lambda_{max}^{acetonitrile}$ 248 mμ shoulder, 278 mμ, 315 mμ shoulder; ϵ_{max} 7600; 8100; 3400.

3-(2′-Piperidinovinyl)indole was obtained as an unstable light brown oil. Infrared absorption spectrum (neat): N-H 2.79 μ, C=C 6.09 μ vs. $\lambda_{max}^{acetonitrile}$ 245 mμ shoulder; 278 mμ, 325 mμ shoulder; ϵ_{max} 10,100; 10,800; 3400.

3-(2′Dibenzylaminovinyl)indole was recrystallized from dry ether containing a trace of triethylamine yielding white crystals, m.p. 128.5–130°; yield 12%. The crystals turned tan within a week. Infrared absorption spectrum (KBr): N-H 2.80 μ C=C 6.10 μ vs. $\lambda_{max}^{acetonitrile}$ 246 mμ, 272 μ, 310 mμ shoulder; ϵ_{max} 12,00; 9600; 5030.

Anal. Calcd. for $C_{24}H_{22}N_2$: C, 85.17; H, 6.55; N, 8.28. Found: C, 85.06; H, 6.76; N, 7.91.

5-Benzyloxy-3-(2′-dibenzylaminovinyl)indole was recrystallized from ether containing a trace of trimethylamine as white crystals, yield 15%, m.p. 139–141°, which became tan on standing. Infrared absorption spectrum ($CHCl_3$): N-H 2.70 μ C=C 6.10 μ vs. $\lambda_{max}^{acetonitrile}$ 245 mμ, 258 mμ, 279 mμ, 330 mμ shoulder; ϵ_{max} 15,400; 95,400; 16,100; 5100.

Anal. Calcd. for $C_{31}H_{28}N_2O$: C, 83.75; H, 6.36; N, 6.30. Found: C, 83.24; H, 6.53; N, 5.98.

3-(2′-Diisopropylaminovinyl)indole was recrystallized from dry ether containing a trace of triethylamine as light tan crystals, m.p. 129–132°, yield 25%. Infrared absorption spectrum ($HCCl_3$): N-H 2.82 μ. C=C 6.09 μ vs. $\lambda_{max}^{acetonitrile}$ 250 mμ, 280 mμ, 338 shoulder; ϵ_{max} 11,600; 13,200; 2800.

Anal. Calcd. for $C_{16}H_{22}N_2$: C, 79.34; H, 9.09; N, 11.57. Found: C, 78.93; H, 8.45; N, 11.37.

(11) The skillful cooperation of the Regis Chemical Co. under a Psychopharmacology Service Center Contract is gratefully acknowledged.

(12) A. Ek and B. Witkop, *J. Am. Chem. Soc.*, **75**, 500 (1953).

Photochemical Reactions. XI. Diphenylacetylene[1-3]

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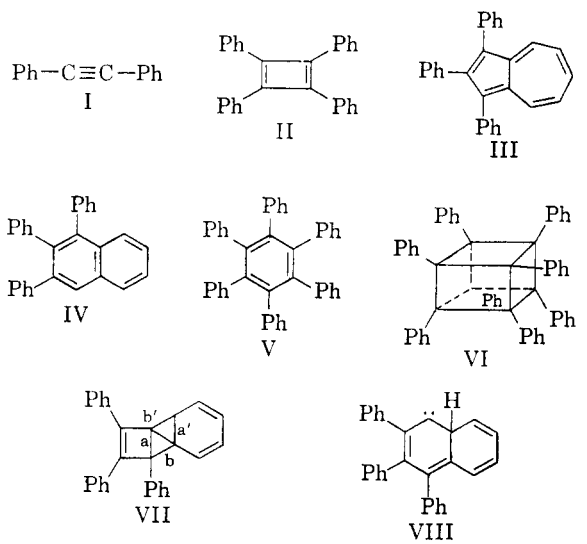
Photochemical dimerization of substituted olefins represents a convenient method for the preparation of certain cyclobutanes. In analogy, sub-

(1) Part of a program of research supported by a grant from the Godfrey L. Cabot Fund, Publication No. 75, M.I.T. Solar Energy Conversion Project.

stituted acetylenes should be susceptible to dimerization and give cyclobutadienes or their transformation products. Irradiation of diphenylacetylene (I) in hexane solution with a Hanau "Labortauchlampe S81" gave 1,2,3-triphenylazulene[4] (III), 1,2,3-triphenylnaphthalene[5] (IV), hexaphenylbenzene[6] (V), and a colorless, extremely insoluble compound, m.p. 427–429°. The infrared spectrum of this substance was identical to that of a hydrocarbon, m.p. 425–427°, prepared later in far superior yield by thermal decomposition of (4-bromo-1,2,3,4-tetraphenyl-*cis*,*cis*-1,3-butadienyl)dimethyltin bromide[7] and by reaction of I with phenylmagnesium bromide.[8] It seems to be a tetramer of diphenylacetylene and expression VI has been proposed.[9] The following, *purely speculative* scheme accounts for the formation of the various photoproducts. Photodimerization of I may produce tetraphenylcyclobutadiene[10] (II) which according to theoretical considerations is a triplet in the ground state.[11]



This intermediate may subsequently dimerize to yield VI, combine with starting material to give hexaphenylbenzene (V), and finally undergo bond redistribution. The resulting substituted bicyclobutane[12] (VII) is not expected to be stable at room temperature and of the various bond breaking processes those producing strain free rings should be favored. Homolysis at a and a′ gives the azulene (III) while an alternate process at b and b′ regenerates tetraphenylcyclobutadiene (II). Cleavage of geminal bonds in the bicyclobutane (VII) results in the generation of carbenes and of the four isomers formally possible only one, VIII, contains no small ring. Conversion to the naphthalene (IV) is terminated by hydride shift. The feasibility of the bond redistribution reaction leading to VII is being investigated experimentally.

Experimental[13]

Diphenylacetylene, m.p. 60–61° (17 g.) dissolved in pure hexane (50 ml.) was irradiated for 1 week. "Prepurified" nitrogen was bubbled through the solution and the apparatus was cooled to 15–30° using a water bath. The reaction mixture was filtered to remove insoluble material (A, 92 mg.) and the filtrate was concentrated to a green solid. Recrystallization from ethanol (50 ml.) removed the bulk of unchanged starting material and the mother liquor was chromatographed in hexane solution over a column of "Davison 923" silica gel. Elution with the same solvent gave I (total recovery 16.0 g.). Further elution with hexane containing 5% benzene yielded 1,2,3-triphenylnaphthalene (IV) (172 mg.), m.p. 151–153° pure and mixed with an authentic sample (superimposable infrared spectra in potassium bromide pellets). Later fractions contained a blue substance (151 mg.) which after recrystallization from ether–pentane had m.p. 214–216°. A mixture of it and an authentic sample of 1,2,3-triphenylazulene (III) m.p. 216–217° melted at 214–217° and the infrared spectra (in potassium bromide) of the two samples were superimposable. The insoluble material (A) mentioned above was washed on a filter with chloroform and then with hot nitrobenzene. A colorless, crystalline compound (6 mg.), m.p. 437–439°, remained on the filter whose infrared spectrum (in potassium bromide) was identical with that of authentic hexaphenylbenzene (V), m.p. 439–441°, and a mixture of the two had m.p. 439–440°. When the nitrobenzene filtrate was poured into benzene (30 ml.), a colorless substance (11 mg.) precipitated which had m.p. 427–429°. Its infrared spectrum was different from that of hexaphenylbenzene (V) and a mixture of the two had m.p. 400–430°. As mentioned in the discussion section, this new hydrocarbon is identical with a substance prepared by a different route and believed to be octaphenylcubane (VI).

Acknowledgment.—The authors are indebted to the National Science Foundation (Grant G22547) for financial support.

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(4) S. J. Assony and N. Kharasch, *J. Am. Chem. Soc.*, **80**, 5978 (1958); R. Breslow and M. Battiste, *ibid.*, **82**, 3626 (1960); N. R. Slobotkin, *J. Org. Chem.*, **25**, 273 (1960). We wish to thank Professor N. Kharasch for an authentic sample of this substance.

(5) L. I. Smith and H. H. Hoehn, *J. Am. Chem. Soc.*, **63**, 1184 (1941).

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(8) M. Tsutsui, *Chem. Ind.* (London), 780 (1962).

(9) H. H. Freedman and D. R. Petersen, *J. Am. Chem. Soc.*, **84**, 2837 (1962).

(10) Tetraphenylcyclobutadiene iron tricarbonyl [W. Hubel, *et al.*, *J. Inorg. Nucl. Chem.*, **9**, 204 (1959); R. P. Dodge and V. Schomaker, *Nature*, **186**, 798 (1960)] and nickel bromide complexes[7] are known but there is no published evidence to support the suggestion [A. T. Balaban, *Tetrahedron Letters*, **5**, 14 (1959)] that a hydrocarbon m.p. 154–155° prepared by Kharasch (ref. 4) is tetraphenylcyclobutadiene.

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(12) A few bicyclobutanes are known: K. B. Wiberg and R. P. Ciula, *J. Am. Chem. Soc.*, **81**, 5262 (1959); W. R. Moore, H. R. Ward, and R. F. Merritt, *ibid.*, **83**, 2019 (1961).

(13) Melting points are uncorrected.

The Reduction of 22,26-Oxido-$\Delta^{17(20)}$-cholestene-3β,22-diol-16-one with Lithium Aluminum Hydride

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In 1952, Nussbaum, *et al.*,[2] converted 5,6-dihydrokryptogenin diacetate through a series of reactions to 22,26-oxido-$\Delta^{17(20)}$-cholestene-3β,22-diol-16-one (Ia). Reduction of Ia with lithium aluminum hydride was reported[2] to yield IVa. Compound IVa appeared to us to be an appropriate starting material for the partial synthesis of 5,6-dihydropennogenin of structure V, proposed by Marker and associates.[3] An alternate formulation VI has been sugested by Heusler and Wettstein.[4]

We attempted to prepare IVa from 5,6-dihydrokryptogenin by carrying out the sequence of reactions as previously reported.[2] The intermediates leading to IVa were in regard to physical properties and yields in complete agreement with the published data.[2] While the physical properties of the final product, supposed to be the IVa, were also in full agreement with those reported, the analytical data of IIa and its derivatives, particularly of the acyl derivatives showed clearly that in the reduction of Ia a dialcohol of the structure of 22,26-oxido-$\Delta^{17(20)}$-cholestene-3β,16ξ-diol (IIa)[5] had been formed. Esterification gave readily diesters (acetate, dinitrobenzoate). Oxidation of IIa with chromic acid led to the diketone III. Its ultraviolet spectrum showed a band at 237 mμ practically identical with that of Ia. The strong bands at 1706 and 1666 cm.$^{-1}$ also indicated α,β-unsaturated carbonyl. The 3- and 16-ketone absorption bands overlap because of the shift of the 16-ketone band to lower frequency (conjugation with the C-$^{17(20)}$-double bond). Compound III gave a crystalline monooxime which exhibited strong bands at 1706 and 1666 cm.$^{-1}$ indicating that only the 3-ketone was involved in oxime formation.[6] Lithium aluminum hydride reduction of III gave IIa in a yield of 60%.

An analogous sequence of reactions was carried out in the Δ^5-series starting from kryptogenin.[7] The results were entirely analogous.

Experimental[8]

22,26-Oxido-$\Delta^{17(20)}$-cholestene-3β,22-diol-16-one (Ia).—The isomerization of 5,6-dihydrokryptogen diacetate (10.0 g.) with refluxing acetic anhydride containing a small amount of *p*-toluenesulfonic acid proceeded as described.[2] Three recrystallizations from methanol gave 6.0 g of $\Delta^{16,20(22)}$-allofurostadiene-3β,26-diol 3β,26-diacetate, m.p. 94–96°, $[\alpha]^{20}D$ +10°, λ_{max} 226 mμ(ϵ 10,500)[lit.,[2] m.p. 96–98°, $[\alpha]^{20}D$ +10°, λ_{max} 226 mμ (log ϵ 4.05)]. The free diol, m.p. 187–189°, $[\alpha]^{20}D$ + 30°, λ_{max} 228 mμ(ϵ 10,100)[lit.,[2] m.p. 189–191°, $[\alpha]^{20}D$ +31°, λ_{max} 227 mμ (log ϵ 4.03)].

We observed that the pseudokryptogenins and their derivatives exhibit two bands of moderate intensity in chloroform solution at 1623 and 1572 cm.$^{-1}$. The presence of these bands may be used for the detection of a $\Delta^{16,20(22)}$-furostadiene system.

The $\Delta^{16,20(22)}$-allofurostadiene-3β,26-diol 3β,26-diacetate (5.0 g.) was oxidized with an excess of chromic acid in acetic acid at room temperature and the mixture worked up as reported.[2] The crude oily product, λ_{max} 246 mμ (ϵ 11,000), was immediately saponified by refluxing for 1 hr. with 2% methanolic potassium hydroxide solution and extracting with a large volume of ether. The product crystallized from the dried ether extracted in a yield of 3.0 g.; spears m.p. 204–206°. Recrystallization from ethyl acetate gave 2.8 g. of Ia as rods, m.p. 205–206°, $[\alpha]^{20}D$ −106°, λ_{max} 237 mμ (ϵ 13,300) ν_{max}^{Nujol} 3390, 1712, and 1672 cm.$^{-1}$ [lit.,[2] m.p. 205–206°, $[\alpha]^{20}D$ −105°, λ_{max} 237 mμ (log ϵ 4.19)].

Anal. Calcd. for $C_{27}H_{42}O_4$: C, 75.30; H, 9.83. Found: C, 75.18; H, 9.79.

22,26-Oxido-$\Delta^{5,17(20)}$-cholestadiene-3β,22-diol-16-one (Ib).—This product was obtained from kryptogenin diacetate by repeating the sequence of reactions used in the preparation of Ia.[7]

The intermediate $\Delta^{5,16,20(22)}$-furostatriene-3β,26-diol 3β,26-diacetate was obtained in a yield of 60%, m.p. 94–95°, $[\alpha]^{20}D$ −44°, λ_{max} 226 mμ (ϵ 12,000)[lit.,[7] m.p. 94–95°, $[\alpha]^{20}D$ −44°, λ_{max} 226 (log ϵ 4.16)]. Oxidation of 5.0 g. of the $\Delta^{5,16,20(22)}$-furostatriene-3β,26-diol 3β,26-diacetate and immediate saponification of the oxidized product with 2% methanolic potassium hydroxide solution gave after isolation and purification 3.1 g. of Ib, m.p. 220–223°, $[\alpha]^{20}D$ −178°, λ_{max} 237 mμ (ϵ 13,100), ν_{max}^{Nujol} 3367, 1706, and 1669 cm.$^{-1}$ [lit.,[7] m.p. 225–226°, $[\alpha]^{20}D$ −173°, λ_{max} 236 mμ (log ϵ 4.17)].

22,26-Oxido-$\Delta^{17(20)}$-cholestene-3β,16ξ-diol (IIa).—A solution of 2.0 g. of 22,26-oxido-$\Delta^{17(20)}$-cholestene-3β,22-diol-16-one (Ia), 1.5 g. of lithium aluminum hydride, and 150 ml. of tetrahydrofuran was refluxed for 1 hr. Decomposition of the excess reagent with ethyl acetate, followed by addition of water and dilute sulfuric acid, filtration of the precipitate, and recrystallization from methanol gave 1.2 g. of elongated needles, m.p. 228–230°, $[\alpha]^{20}D$ −11°, no selective absorption

(1) Department of Chemistry, University of Delaware, Newark, Delaware.

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(4) K. Heusler and A. Wettstein, *Chem. Ber.*, **87**, 1301 (1954).

(5) The configuration at C-22 as shown in the structural formulas Ia, IIa, and III is arbitrary.

(6) A compound of similar structure to III was observed to exhibit considerable hindrance at C-16, I. Scheer, M. J. Thompson, and E. Mosettig, *J. Am. Chem. Soc.*, **79**, 3218 (1957).

(7) A. Sandoval, J. Romo, G. Rosenkranz, St. Kaufmann, and C. Djerassi, *ibid.*, **73**, 3820 (1951).

(8) All melting points were determined on Kofler block. Rotations were determined in approximately 1% solutions in chloroform and ultraviolet spectra in absolute ethanol with a Cary Model 11 recording spectrophotometer. Infrared spectra were obtained with a Perkin-Elmer Model 21 double beam spectrophotometer with sodium chloride prism and cells. Microanalyses are by the Analytical Service Laboratory of this Institute under the direction of Dr. William C. Alford. Infrared spectra were determined by Mr. H. K. Miller and ultraviolet spectra by Mrs. A. Wright of this laboratory.

in the ultraviolet, free hydroxyl in the infrared but no carbonyl (lit.,[2,9a] m.p. 226–228° $[\alpha]^{20}D$ −12°).

Anal. Calcd. for $C_{27}H_{44}O_3$: C, 77.83; H, 10.65. Found: C, 77.64; H, 10.38.

The diacetate (acetic anhydride–pyridine, steam bath, 2 hr.) was obtained as plates from methanol, m.p. 218–220°, $[\alpha]^{20}D$ −9°, acetate but no free hydroxyl bands in the infrared (lit.,[2,9b] m.p. 223–225°, $[\alpha]^{20}D$ −8°.

Anal. Calcd. for $C_{31}H_{48}O_5$: C, 74.36; H, 9.66; acetyl, 17.1. Found: C, 74.29; H, 9.56; acetyl, 16.3

The bis-3,5-dinitrobenzoate (3,5-dinitrobenzoyl chloride–pyridine, 3 hr., steam bath) was obtained as plates from acetone–methanol, m.p. 186–187°, $[\alpha]^{20}D$ +35°.

Anal. Calcd. for $C_{41}H_{48}O_{13}N_4$: C, 61.18; H, 6.01; N, 6.96. Found: C, 61.29; H, 6.14; N, 6.85.

22,26-Oxido-$\Delta^{5,17(20)}$-cholestadiene-3β,16ξ-diol (IIb).—The lithium aluminum hydride reduction of 22,26-oxido-$\Delta^{5,17(20)}$-cholestadiene-3β,22-diol-16-one (Ib) carried out exactly as in the preparation of IIa gave IIb in a yield of 65% as needles after recrystallization from methanol, m.p. 236–237°, $[\alpha]^{20}D$ −80° (lit.,[7,9c] m.p. 236–237°, $[\alpha]^{20}D$ −81.3°).

Anal. Calcd. for $C_{27}H_{42}O_3$: C, 78.21; H, 10.21. Found: C, 78.28; H, 10.10.

The diacetate (acetic anhydride–pyridine, 2 hr., steam bath) was obtained as rectangular plates from chloroform–methanol, m.p. 258–260°, $[\alpha]^{20}D$ −71° (lit.,[7,9d] m.p. 260–262° $[\alpha]^{20}D$ −70.7°).

Anal. Calcd. for $C_{31}H_{46}O_5$: C, 74.66; H, 9.29; acetyl, 17.3. Found: C, 74.53; H, 8.99; acetyl, 17.1.

The bis-3,5-dinitrobenzoate (3,5-dinitrobenzoyl chloride–pyridine 3 hr., steam bath) was obtained as thin plates from acetone–methanol, m.p. 206–207°, $[\alpha]^{20}D$ −1°.

Anal. Calcd. for $C_{41}H_{46}O_{13}N_4$: C, 61.34; H, 5.77; N, 6.97. Found: C, 61.52; H, 5.72; N, 6.77.

22,26-Oxido-$\Delta^{17(20)}$-cholestene-3,16-dione (III).—To a stirred solution of 300 mg of 22,26-oxido-$\Delta^{17(20)}$-cholestene-3β,16ξ-diol (IIa) in 200 ml. of acetone at 20°, was added dropwise, an 8 *N* solution of chromic acid in dilute sulfuric acid (*ca.* 40%) until a persistent orange-brown coloration indicated oxidation was complete. The mixture was diluted with water and the crystalline precipitate was collected, washed with water, and dried to yield 280 mg. of III, m.p. 182–188°. Recrystallization from ethanol raised the melting point to 195–197°, $[\alpha]^{20}D$ −78°, λ_{max} 236 (ϵ 10,400), ν^{CHCl_3} 1706 cm.$^{-1}$ strong (3-ketone and 16-ketone) and 1666 cm.$^{-1}$, strong (double bond in conjugation with a carbonyl).

Anal. Calcd. for $C_{27}H_{40}O_3$: C, 78.59; H, 9.77. Found: C, 78.82; H, 9.54.

The monoöxime (hydroxylamine hydrochloride, methanol–pyridine, water, steam bath, 2 hr.) was obtained as plates from ethanol, m.p. 234–237°, with slight decomposition.

Anal. Calcd. for $C_{27}H_{41}O_3N$: C, 75.83; H, 9.67, N, 3.28. Found: C, 75.70; H, 9.50; N, 3.33.

Reduction of III with lithium aluminum hydride gave the original diol IIa in a yield of 60%.

Acknowledgment.—We are indebted to Dr. G. Rosenkranz, Syntex, S.A., Mexico, for a generous supply of kryptogenin.

(9) (a) Considered previously to be IVa; (b) acetate of IVa; (c) considered previously to be IVb; (d) acetate of IVb.

Furazan Oxides. II. Evidence for Equilibria of Benzofurazan Oxides with *o*-Dinitrosobenzenes[1]

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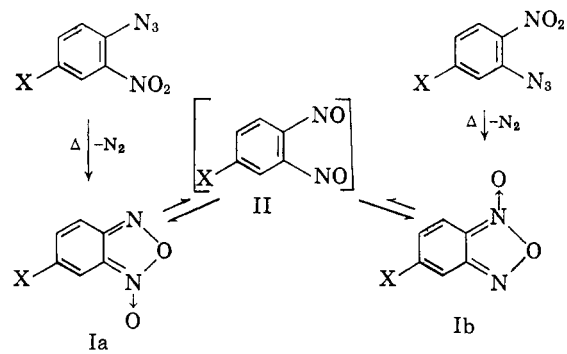
Received July 2, 1962

The fact that the pyrolysis of either of the substituted nitroazides of the type shown below yields a single compound X—$C_6H_3N_2O_2$ rather than two separate isomeric benzofurazan oxides such as Ia and Ib was originally thought[2] to indicate a



symmetrical configuration of the N_2O_2 grouping. However, recent n.m.r.[3,4] and X-ray[5] results have demonstrated the validity of the unsymmetrical *N*-oxide formulation I for this class of compound. These results require the existence of an equilibration Ia ⇌ Ib such that only the more stable isomer is isolated. This type of equilibration was originally postulated by Hammick[6] and has recently been demonstrated by n.m.r. studies.[3,4] For example, the proton resonance pattern of the parent benzofurazan oxide (I with X = H) is a complicated ABCD type at low temperatures but changes to a symmetrical A_2B_2 pattern at higher temperatures when the rate of the Ia ⇌ Ib interconversion is sufficiently rapid that only the average proton environments are detected. Similarly, the two peaks of the O^{17} n.m.r. spectrum of I (X = H) at room temperature coalesce to a single peak above 45°.[4]

(1) Presented before the Organic Division at the National Meeting of the American Chemical Society, Atlantic City, N. J., Sept. 13, 1962.

(2) M. O. Forster and M. F. Barker, *J. Chem. Soc.*, **103**, 1918 (1913).

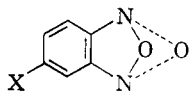
(3) G. Englert, *Z. anal. Chem.*, **181**, 447 (1961); F. B. Mallory and C. S. Wood, *Proc. Natl. Acad. Sci.*, **47**, 697 (1961); G. Englert, *Z. Naturforsch*, **16b**, 413 (1961); A. R. Katritzky, S. Øksne, and R. K. Harris, *Chem. Ind.* (London), 990 (1961).

(4) P. Diehl, H. A. Christ, and F. B. Mallory, *Helv. Chim. Acta*, **45**, 504 (1962).

(5) D. Britton and W. E. Noland, *Chem. Ind.* (London), 563 (1962).

(6) D. L. Hammick, W. A. M. Edwards, and E. R. Steiner, *J. Chem. Soc.*, 3308 (1931).

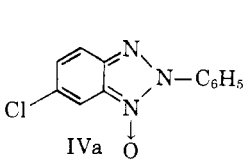
This type of interconversion has been assumed[3,4,6] on plausibility grounds to proceed by way of an *o*-dinitrosobenzene[7] such as II. However, it is conceivable, although less likely, that the equilibration occurs by way of a bicyclic configuration of heteroatoms, such as in III.[8]



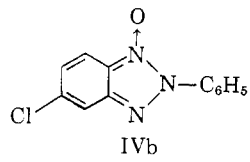
III

Two pieces of evidence are now available to help distinguish between these two mechanisms. First, from the results of the recent kinetic study[4] which was based on the temperature dependence of the proton and O^{17} n.m.r. spectra of benzofurazan oxide a value of 10 ± 4 e.u. can be calculated for the activation entropy of the process Ia ⇌ Ib (with X = H). Although there is considerable uncertainty in the magnitude of this value there is reasonable assurance that the sign is positive, which is in accord with the mechanism of ring opening to *o*-dinitrosobenzene as a transient intermediate (or transition state). On the other hand, the Ia ⇌ III ⇌ Ib mechanism would be expected to have a negative activation entropy.

Further support for the mechanism involving the dinitroso form II as opposed to the bicyclic form III has been obtained from a study of the analogous benzotriazole oxides IVa and IVb.

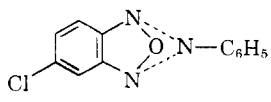


IVa



IVb

In contrast to the substituted benzofurazan oxides, where rapid equilibration precludes isolating both isomers, the corresponding compounds IVa and IVb have each been prepared and shown to be nonidentical crystalline solids. Furthermore, IVa and IVb did not interconvert on heating as liquids at 145°. This indicates that the bicyclic configuration V, which would provide a path for the interconversion IVa ⇌ V ⇌ IVb, is not readily accessible. This negative result lends indirect support to the hypothesis that the analogous bicyclic



V

(7) This assumption is not to be confused with the erroneous assignment of the dinitroso structure as the stable configuration of benzofurazan oxides by Boyer. See J. H. Boyer in "Heterocyclic Compounds," R. C. Elderfield, ed., John Wiley & Sons, Inc., New York, N. Y., 1961, p. 462.

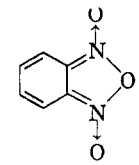
(8) This type of structure also was once mistakenly considered to be the stable configuration of benzofurazan oxides. See A. G. Green and F. M. Rowe, *J. Chem. Soc.*, **103**, 897 (1913), and ref. 2.

form III is not involved in the benzofurazan oxide equilibrations.

In view of the supposition of the transient existence of *o*-dinitrosobenzenes in equilibrium with the corresponding benzofurazan oxides, it is surprising that chemical properties of nitroso groups have not been observed in the studies of these compounds. For example, benzofurazan oxide (I with X = H) does not give an azo compound on treatment with aniline[9] and is not oxidized to *o*-dinitrobenzene by nitric acid,[10] peracetic acid,[11] or performic acid.[11]

These observations may be rationalized by assuming that molecules in the *o*-dinitroso form undergo ring closure to benzofurazan oxides at rates which are much faster than the rates of any reactions characteristic of isolated aromatic nitroso groups. Alternatively, it might be that the two nitroso groups are never free from a strong mutual interaction which could alter the normal properties of such groups.

The one seeming exception to this behavior involves the reported oxidation of I (X = H) with peroxytrifluoroacetic acid to give *o*-dinitrobenzene in low yield.[12] Although this may represent a reaction taking place by way of *o*-dinitrosobenzene, which is presumed to be present in extremely low concentration at equilibrium, it is also possible that this reaction proceeds by oxidation of the furazan oxide to benzofurazan dioxide (VI). This di-



VI

oxide has been shown[13] to be unstable with respect to ring opening to *o*-nitronitrosobenzene which would be oxidized under the reaction conditions to *o*-dinitrobenzene.

Experimental[14]

4-Chloro-2-nitroazobenzene.—A solution of 1.9 g. (0.01 mole) of 4-chloro-2-nitronitrosobenzene[13] and 1.0 ml. (0.9 g., 0.01 mole) of freshly distilled aniline in 50 ml. of glacial acetic acid was stirred magnetically at room temperature in the dark for 5 hr. The solution was diluted with 100 ml. of water, and cooled in an ice bath. The crude brown precipitate was collected by suction filtration, washed with 100 ml. of water, and sublimed[15] at 85° (0.05 mm.) to give 2.4 g. (92%) of dark red crystals, m.p. 91.8–92.5°. The sublimate was recrystallized twice from 95% ethanol in the dark to give orange needles, m.p. 92.2–92.5°.

(9) P. Ruggli and F. Buchmeier, *Helv. Chim. Acta*, **28**, 850 (1945).

(10) P. Drost, *Ann.*, **307**, 49 (1899).

(11) A. S. Bailey and J. R. Case, *Tetrahedron*, **3**, 113 (1958).

(12) J. H. Boyer and S. E. Ellzey, Jr., *J. Org. Chem.*, **24**, 2038 (1959).

(13) F. B. Mallory, K. E. Schueller, and C. S. Wood, *ibid.*, **26**, 3312 (1961).

(14) All melting points are uncorrected. Analyses were carried out by Galbraith Microanalytical Laboratories, Knoxville, Tenn.

(15) F. B. Mallory, *J. Chem. Ed.*, **39**, 261 (1962).

Anal. Calcd. for $C_{12}H_8ClN_3O_2$: C, 55.08; H, 3.08. Found: C, 55.28; H, 3.34.

5-Chloro-2-nitroazobenzene.—The procedure was as described above. From 1.9 g. (0.01 mole) of 5-chloro-2-nitronitrosobenzene[13] and 1.0 ml. (0.9 g., 0.01 mole) of aniline was obtained after sublimation 2.4 g. (92%) of bright red needles, m.p. 92.6–94.2°. The sublimate was recrystallized from 95% ethanol to give 2.2 g. (84%) of orange needles, m.p. 93.6–94.2° (lit.,[16] m.p. 94°).

6-Chloro-2-phenylbenzotriazole Oxide.—A solution prepared by warming 2.6 g. (0.01 mole) of 4-chloro-2-nitroazobenzene in 10 ml. of 95% ethanol was stirred magnetically and a solution of 9.6 g. (0.04 mole) of sodium sulfide nonahydrate in 30 ml. of water was added all at once. After stirring at room temperature for 17 hr. the mixture was cooled in an ice bath and the light tan solid was collected by suction filtration. The crude material was sublimed at 125° (0.05 mm.) to give 2.4 g. (97%) of pale yellow crystals. Two recrystallizations from 95% ethanol (Norit) gave 2.2 g. (90%) of white needles, m.p. 141.6–142.4°. A small sample which had been recrystallized twice more from ethanol melted at 142.2–142.8°.

Anal. Calcd. for $C_{12}H_8ClN_3O$: C, 58.67; H, 3.28. Found: C, 58.91; H, 3.15.

5-Chloro-2-phenylbenzotriazole Oxide.—The procedure was as described above. From 2.6 g. (0.01 mole) of 5-chloro-2-nitroazobenzene and 9.6 g. (0.04 mole) of sodium sulfide nonahydrate was obtained after sublimation 2.3 g. (94%) of light yellow crystals. Two recrystallizations from 95% ethanol (Norit) gave 2.0 g. (82%) of white needles, m.p. 139.8–140.4° (lit.,[16] m.p. 142.5°).

Attempted Isomerization of Benzotriazole Oxides.—Separate 0.1-g. portions of 6-chloro-2-phenylbenzotriazole oxide and 5-chloro-2-phenylbenzotriazole oxide were heated for 2.5 hr. in an oil bath maintained at 145°. The 5-chloro isomer became dark on heating while the 6-chloro compound underwent no visible change. In each case, the infrared spectrum of the sample after heating was identical with that of the pure compound.

(16) C. Willgerodt and L. Ellon, *J. prakt. Chem.*, **44**, 67 (1891).

Naphthalene as a Photoquencher

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Received July 3, 1962

Our interest in a photoadduct between naphthalene and maleic anhydride was intensified by reports of an analogous reaction proceeding with benzene.[1-3] Preliminary evaluation led us to the conclusion the former reaction should proceed in the same manner as the latter and, as a consequence, the reaction would be of lesser significance. However, upon further consideration it was observed that a decision could be made between a 1,2- and a 1,4-addition as the initial reaction of maleic anhydride with naphthlene if the reaction occurred. An analogy could then be made to the benzene photoproduct formation. Two quite different products would be expected depending on the mode of the first addition.

Upon irradiation of naphthalene and excess maleic anhydride in tetrahydrofuran, no photoadduct was found. Naphthalene was recovered quantitatively and the maleic anhydride nearly so with an uncharacterized polymeric material. In an irradiation under identical circumstances without naphthalene, the polymer was obtained exclusively.

On the basis of these results we conclude that naphthalene has a quenching effect on the photoinduced polymerization of maleic anhydride. A similar observation has recently been reported by Moore and Ketchum[4] for the influence of naphthalene on the photoreduction of benzophenone.

Experimental

The following reaction solutions were irradiated simultaneously in identical quartz vessels with a 140-watt Hanovia high pressure mercury arc lamp.

Irradiation of Naphthalene and Maleic Anhydride.—A solution of 5.6 g. (0.057 mole) of maleic anhydride and 1.44 g. (0.011 mole) of naphthalene in 30 cc. of purified tetrahydrofuran was irradiated for 8 hr. Distillation of the reaction mixture provided 4.88 g. (87%) of maleic anhydride. Chromatography of the residue on alumina produced 1.40 g. (97%) of naphthalene. On further elution a gum appeared which was not completely eluted until ether was passed over the column.

Irradiation of Maleic Anhydride.—The above procedure was duplicated omitting the naphthalene. Distillation provided no maleic anhydride and alumina chromatography failed to yield material other than an amorphous gum.

Acknowledgment.—The financial support received from the Research Corporation which made this research possible is gratefully acknowledged.

(4) W. M. Moore and M. Ketchum, *J. Am. Chem. Soc.*, **84**, 1368 (1962).

Formation of Dibenzothiophene by a Disulfide Ring Closure[1]

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Received July 6, 1962

Disulfides, derived by oxidation of β-aryl-α-mercaptoacrylic acids, have been shown in earlier reports[2,3] to undergo cyclization in the presence of a Lewis acid to give the corresponding condensed

(1) E. Grovenstein, Jr., D. V. Rao, and J. W. Taylor, *J. Am. Chem. Soc.*, **83**, 1705 (1961).

(2) G. O. Schenkt and R. Steinmetz, *Tetrahedron Letters*, **21**, 1 (1961).

(3) H. J. F. Angus and D. Bryce-Smith, *J. Chem. Soc.*, 4791 (1960).

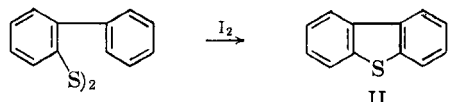
(1) This research was supported in part by the U. S. Army Research Office (Durham) under contract No. DA-33-008-ORD-1916.

(2) E. Campaigne and R. E. Cline, *J. Org. Chem.*, **21**, 39 (1956).

(3) E. Campaigne and W. E. Kreighbaum, *J. Org. Chem.*, **26**, 1326 (1961).

thiophene-2-carboxylic acids. More recently,[4] condensed 2,3-dihydrothiophenes have been obtained from bis(β-arylethyl) disulfides using iodine or aluminum bromide as the catalyst.

During the course of further work on the scope of the disulfide ring-closure reaction, we have found that bis(2-biphenylyl) disulfide (I) will cyclize in good yield in the presence of iodine to give dibenzothiophene (II).



I II

A combination of catalyst and conditions was sought which might be even more favorable for ring closure, and therefore the reaction was repeated, using catalysts other than iodine and varying the solvent and temperature. The results are summarized in Table I.

TABLE I
CYCLIZATION OF BIS(2-BIPHENYLYL) DISULFIDE

Catalyst	Moles catalyst/mole disulfide	Conditions, °C.	Dibenzothiophene, % yield
I_2	1.1	198°, 1 hr.[a]	64
I_2	Excess	101°, 24 hr.[b]	0
I_2	2.0	Reflux, 12 hr.[c]	50
$I_2 + Me_2SO_4$	0.6, 1.2, resp.	Reflux, 5 hr.[b]	0
$I_2 + SnCl_4$	0.6, 2.1, resp.	Reflux, 2.5 hr.[d]	0
$AlBr_3$	1.0	80°, 3 hr.[d]	38
$AlCl_3$	2.0	65°, 3 hr.[d]	35
BF_3	Excess	Reflux, 3 hr.[d]	0
Br_2	1.0	78°, 37 hr.[e]	16
Poly-H_3PO_4	Excess	200°, 24 hr.	0
Conc. H_2SO_4	Excess	25°	0

Solvents: [a] Ethylene glycol. [b] Dioxane. [c] Toluene. [d] Benzene. [e] Carbon tetrachloride.

Iodine was found to be the most effective of the catalysts employed, as the reaction can be run at higher temperatures without significant desulfurization occurring, and it has a further advantage over reagents such as aluminum chloride in that it has the ability to oxidize the thiol[4] (formed as the by-product on cleavage of the disulfide) to starting material. However, even with iodine present, no dibenzothiophene could be isolated when stannic chloride was employed.

With bromine, ring closure was expected to proceed in good yield *via* the formation of the sulfenium bromide. In fact a surprisingly low yield of dibenzothiophene was obtained and 70% of the disulfide was recovered. In contrast, bis(2-biphenylyl) diselenide affords an essentially quantitative yield of dibenzoselenophene under the same conditions.[5]

In addition to dibenzothiophene, a very small amount of a compound, m.p. 163–165°, was isolated when iodine and ethylene glycol were employed as the catalyst and solvent respectively. Its analysis was consistent with $C_{14}H_{12}S$ and it seems probable that the two additional carbon atoms are acquired by reaction with either a solvent molecule or a product of the interaction of solvent and iodine. The infrared spectrum indicated the presence of both aromatic and aliphatic carbon–hydrogen bonds. Furthermore, absorption suggesting aromatic monosubstitution together with 1,2,3-trisubstitution and the absence of C-methyl absorption provide reason for the tentative formulation of the by-product, m.p. 163°, as 2,3-dihydro-7-phenylbenzo[*b*]thiophene, which to our knowledge has not yet been reported in the literature.

(4) E. Campaigne and B. G. Heaton, *Chem. Ind.* (London), 96 (1962).

(5) J. D. McCullough, T. W. Campbell, and E. S. Gould, *J. Am. Chem. Soc.*, **72**, 5753 (1950).

Experimental[6]

Bis(2-biphenylyl) Disulfide (I).—The disulfide I was prepared as previously reported by Campaigne and Osborn[7] from 2-aminobiphenyl and melted at 117–118°.

Dibenzothiophene (II).—The following details exemplify the general work-up procedure for the majority of experiments in Table I and also describe the isolation of the by-product, m.p. 163°.

A solution of I (3.70 g., 0.01 mole), and iodine (2.70 g., 0.011 mole) in freshly redistilled ethylene glycol (300 ml.) was heated under reflux for 1 hr., cooled, and poured slowly into water (1 l.). The small excess of iodine was bleached by the addition of dilute sodium bisulfite solution, and, after cooling overnight, the white solid was collected, washed well with water, and dried under reduced pressure. The solid (3.53 g., m.p. 92–96°) was dissolved in a large volume of boiling ethanol. On cooling the solution, plates (0.1 g.) were obtained which crystallized from benzene–ethanol as fine white needles, m.p. 163–165°. Infrared spectrum: ν_{max}^{KBr} 3049 cm.$^{-1}$ (aromatic C—H); 2920 and 2841 cm.$^{-1}$ (aliphatic C—H); 702(s) and 744 cm.$^{-1}$ (s) (aromatic monosubstitution); and 697(m) and 769 cm.$^{-1}$ (s) (aromatic 1,2,3-trisubstitution).

Anal. Calcd. for $C_{14}H_{12}S$: C, 79.19; H, 5.70; S, 15.10. Found: C, 78.42; H, 5.73; S, 15.35.

The filtrate was partially evaporated and on cooling gave needles, m.p. 97–99° (2.34 g., 64%). Recrystallization afforded white needles m.p. 97.5–99.5°.[8] No melting point depression was observed on admixture with dibenzothiophene prepared by an independent route.

Anal. Calcd. for $C_{12}H_8S$: C, 78.22; H, 4.38; S, 17.40. Found: C, 78.17; H, 4.45; S, 17.27.

(6) All melting points are corrected.

(7) E. Campaigne and S. W. Osborn, *J. Org. Chem.*, **22**, 561 (1957).

(8) H. Gilman and A. Jacoby, *ibid.*, **3**, 108 (1938), report the melting point of dibenzothiophene to be 99°.

On the Color Reaction of Khellin with Alkali

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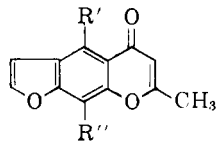
Received July 9, 1962

Khellin (Ia), the main active principle of the fruits of *Ammi visnaga* (L.), has attracted interest,

being antispasmodic and a coronary vasodilator.[1] It is used in the treatment of angina pectoris and as a duiretic.

According to Abd-El-Rahman[2] and Fahmy, Badran, and Messeid[3] khellin gives an intense red-violet color with potassium or sodium hydroxide pellets. The method has been used for colorimetric estimations by Anrep.[4]

Schönberg and Sina[5] showed, however, that this color reaction is not specific for khellin, since visnagin (Ib) among other 2-methylchromones gives the same test.

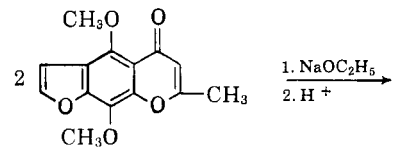


Ia. $R' = R'' = OCH_3$
Ib. $R' = OCH_3$, $R'' = H$

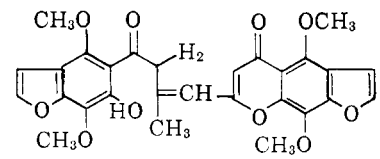
The nature of the violet substance obtained from the reaction of khellin with alkali remained, however, unsettled because of difficulty in its isolation.[5]

We have now found that khellin suspended in dry ether and shaken with dry freshly prepared sodium ethoxide produces a solid deep violet reaction product. Treatment of the violet product with acetic acid yields a yellow crystalline substance which proved to be the dimer of the starting material. The yellow substance when dissolved in ethanol (difficultly soluble) gives at once with 1% aqueous potassium hydroxide the red-violet color. Khellin, on the other hand, develops the color only when treated with moistened alkali pellets.[5] A certain time elapses before the color appears.

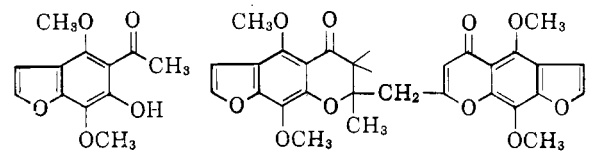
Nature of the Reaction Product of Khellin with Alkali.—Structure II is proposed for the reaction product of khellin with sodium ethoxide. This structure finds confirmation from the following: (a) The molecular weight of the product is double that of khellin. (b) The n.m.r. spectrum of compound II contains signals for an OH—, CH_2—, and CH_3— groups.[6] The resonance of the hydroxyl proton indicates an intramolecular hydrogen bonded OH group. (c) Infrared curves[7] are resolved very poorly around the 3-μ region, a case observed also with khellinone (III), which contains a chelated hydroxyl group. The CO band of compound II lies at 6.05 μ while that of khellin and khellinone lie at 6.00 μ and 6.10 μ, respectively.[7] (d) Pyrolysis of II results in the formation of two molecules of khellin. (e) The similarity of the formation of compound II and that of the dimeric product of 2-methylchromone[8] as well as their thermochromic behavior in piperidine solutions suggests that both compounds are of analogous constitution.



Ia



II



III IV

Compound II could be formed by 1:4 addition of the carbanion to the $\alpha:\beta$-unsaturated system of another molecule, followed by ring opening of the intermediate adduct IV.[8] This mechanism of a Michael condensation reaction is supported by the fact that the methyl group in khellin is strongly activated in alkaline media and undergoes condensation reactions,[9] as do other 2-methylchromones.[10]

Experimental[11]

Action of Sodium Ethoxide on Khellin.—Two grams of khellin was added to ethanol-free dry powdered sodium ethoxide suspended in about 50 ml. of dry ether (E. Merck, peroxide-free). The sodium ethoxide was prepared by dissolving 1 g. of sodium metal in absolute ethyl alcohol, and the excess alcohol was removed under vacuum at 160–170° (bath temperature). The mixture was shaken in a tightly closed vessel for about 1 hr., then kept at room temperature for 48 hr. The deep violet-colored deposit was quickly filtered, washed with ether, then decomposed with ice cold 10% aqueous acetic acid. The reddish yellow substance, which separated, was treated with ethyl alcohol, filtered, washed several times with hot ethyl alcohol, and crystallized from *n*-butyl alcohol to give compound II as pale yellow crystals, m.p. 170–172° (uncorrected); yield, *ca.* 0.2 g.

(1) G. V. Anrep, G. S. Barsoum, M. R. Kenawy, and G. Misrahy, *Brit. Heart J.*, **8**, 171 (1946); *Lancet*, **I**, 557 (1947).

(2) Abd-El-Rahman, Master's thesis, Fouad I University, Cairo, 1943.

(3) I. R. Fahmy, N. Badran, and M. F. Messeid, *J. Pharm. Pharmacol.*, **1**, 529 (1949).

(4) G. V. Anrep, M. R. Kenawy, G. S. Barsoum, and I. Fahmy, *Gazz. Fac. Medicine (Cairo)*, **14**, 1 (1947).

(5) A. Schönberg and A. Sina, *J. Chem. Soc.*, 3344 (1950).

(6) We wish to acknowledge our thanks to Dr. N. S. Bhacca, NMR Applications Laboratory Instrument Division, Varian associates, Palo Alto, Calif., for carrying out the n.m.r. and for helpful discussion.

(7) The infrared absorption spectra were determined in Nujol with a Perkin-Elmer Infracord spectrophotometer Model 137.

(8) A. Schönberg, E. Singer, and M. M. Sidky, *Ber.*, **94**, 660 (1961).

(9) A. Schönberg and A. Sina, *J. Am. Chem. Soc.*, **72**, 1611 (1950).

(10) I. M. Heilbron, H. Barnes, and R. A. Morton, *J. Chem. Soc.*, 2559 (1923); J. Schmutz, R. Hirt, and L. Lauener, *Helv. Chim. Acta.*, **35**, 1171 (1952).

(11) The khellin used was provided by the Memphis Chemical Co., Cairo.

Anal. Calcd. for $C_{14}H_{12}O_5$: C, 64.6; H, 4.6; mol. wt., 520.5. Found: C, 64.9; H, 4.8; mol. wt., 509.0 (in camphor).

Pyrolysis of Compound II.—One-half gram of compound II was heated in a distilling apparatus at 270–280° (bath temperature) under normal pressure. The reaction vessel was left to cool and the substance collected was crystallized from ethyl alcohol and proved to be khellin (m.p. and m.m.p.). Yield, *ca.* 70%.

Thermochromic Behavior in Piperidine.—Compound II dissolved in piperidine (E. Merck), produces a red-violet color at room temperature. The color discharges almost completely on heating. On cooling the red color is regenerated. The phenomenon is reversible for several times, but on standing for a long time at room temperature, the color of the solution fades considerably.

Action of Alumina on II.—When compound II in benzene (thiophene-free and dried over sodium) is treated with a small amount of alumina (Aluminiumoxyd Woelm, alkalifrei, annährend neutral, Akt. Stufe 1, M. Woelm-Eschwege), a red-violet color appears instantaneously on the surface of the inorganic material and the benzene solution remains practically colorless.

The Configurations of Flavan-3,4-diols

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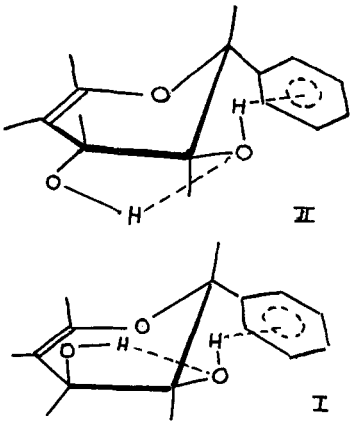
Corey, Philbin, and Wheeler[2] have recently reported proton magnetic resonance studies on the carbonates and benzoates of two flavan-3,4-diols, the results of which allow an unambiguous assignment of configuration to these two materials. The diol, m.p. 145°, prepared by direct reduction of the 4-ketone has the *trans* relationship of the alcohol functions. The diol, m.p. 160°, which was prepared *via* the oxime followed by reduction to the amine and deamination by nitrous acid possesses a *cis* relationship of the alcohol functions. We now report confirmation of these assignments on the basis of infrared study of the intramolecular hydrogen bonding (H-bonding) in the parent diols.[3]

Infrared spectra of the flavandiols were measured in a saturated solution in carbon tetrachloride (about 0.005 *M*) in a pair of matched, one-cm. silica cells and employing a Beckman DK-1 recording spectrophotometer. The material, m.p. 145°, showed a sharp band at 3608 cm.$^{-1}$. The diol, m.p. 160°, showed a pair of maxima of equal intensity at 3606 cm.$^{-1}$ and 3578 cm.$^{-1}$.



II

I

Consideration of the stretching frequencies to be expected for the several OH...O and OH...π H-bonded species as well as for the free hydroxyl functions permits discussion of the stereo arrangement of the two flavandiols. Benzyl alcohol[4] shows a peak associated with the free alcohol at 3632 cm.$^{-1}$ and a H-bonded (OH...π) peak at 3615 cm.$^{-1}$. Similarly, β-phenylethanols have a free peak near 3630 cm.$^{-1}$ and a bonded peak about 25 cm.$^{-1}$ lower in frequency.[5] The shifts ($\Delta\nu = \nu_{free} - \nu_{bonded}$) in cyclic glycols range from about 30 cm.$^{-1}$ to 103 cm.$^{-1}$ as the projection angle (θ) between the C—O bonds is reduced from near 60° to 0°. Thus the cyclohexane diols with θ near 60° for both the *cis*- and *trans*-diols show similar shifts. The tetrahydronaphthalene-1,2-diols reveal a greater strength of the H-bond in the *cis*- than the *trans*-diol. In the less puckered cyclopentane diols the *cis*-diol shows a strong H-bond, but the *trans*-material shows none. In the bicycloheptanediols[6] with $\theta = 0°$ the shift $\Delta\nu$ is 102–103 cm.$^{-1}$.

The presence of a strong intramolecular OH....O bond at 3578 cm.$^{-1}$ in the isomer with m.p. 160° allows an assignment of a *cis*-configuration to the hydroxyl functions. Chemical evidence[7] which has been confirmed by n.m.r studies[1] shows that the 2-phenyl and 3-hydroxyl groups in the flavandiols are equatorial and *trans*. The diol, m.p. 160°, is therefore represented as at I. The isomer m.p. 145° which must be the *trans*-diol is shown at II.

The sharp band 3608 cm.$^{-1}$ in this latter compound must result from two different O—H stretching frequencies. One involves the π-bonding of the hydrogen atom of the 3-hydroxyl group to the phenyl ring; the other relates to the hydrogen

(1) Harrison Fellow at the University of Pennsylvania, 1961–1962.

(2) E. J. Corey, E. M. Philbin, and T. S. Wheeler, *Tetrahedron Letters*, No. **13**, 429 (1961).

(3) For development of the method see (a) A. R. H. Cole and P. Jefferies, *J. Chem. Soc.*, 4391 (1956); (b) L. P. Kuhn, *J. Am. Chem. Soc.*, **74**, 2492 (1952); **76**, 4323 (1954); **80**, 5950 (1958).

(4) P. von R. Schleyer, D. S. Trifan, and R. Bacskai, *J. Am. Chem. Soc.*, **80**, 6691 (1958).

(5) P. von R. Schleyer, G. Wintner, D. S. Trifan, and R. Bacskai, *Tetrahedron Letters*, No. **14**, 1 (1959).

(6) H. Kwart and W. G. Vosburgh, *J. Am. Chem. Soc.*, **76**, 5400 (1954).

(7) R. Bognár, M. Rákosi, H. Fletcher, E. M. Philbin, and T. S. Wheeler, *Tetrahedron Letters*, No. **19**, 4 (1959).

TABLE I

O—H STRETCHING FREQUENCIES OF CYCLIC GLYCOLS AND ARYLALKYL ALCOHOLS (CM.$^{-1}$)

Compound	Free	OH...π	OH...O	Ref.
Benzyl alcohol	3632	3615	...	4
β-Phenylethanol	3631	3604	...	5
cis-Cyclohexane-1,2-diol	3626	...	3587	3b
trans-Cyclohexane-1,2-diol	3634	...	3602	3b
cis-Tetrahydronaphthalene-1,2-diol	...	3618	3575	3b
trans-Tetrahydronaphthalene-1,2-diol	...	3615	3582	3b
cis-Cyclopentane-1,2-diol	3633	...	3572	3b
trans-Cyclopentane-1,2-diol	3620	...	...	3b
exo-cis-Bicycloheptane-2,3-diol	3632	...	3529	6
endo-cis-Bicycloheptane-2,3-diol	3633	...	3531	6
cis-Flavan-3,4-diol (m.p. 160°)	...	3606	3578	
trans-Flavan-3,4-diol (m.p. 145°)	...	3608	...	

atom of the 4-hydroxyl group which is weakly bonded to the oxygen atom in the 3-position. These two frequencies superimpose to give a single sharp band.

Cyanoethylation of Fatty Amines Using Acidic Ion Exchange Catalysis[1]

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The uncatalyzed addition of acrylonitrile to activated hydrogen bearing molecules is employed to yield the corresponding cyanoethyl substituted derivative. Ionic catalysis aids this addition to less activated centers. Cyanoethylation of weakly basic amines (for example secondary amines already bearing a deactivating cyanoethyl group) has been aided by organic acids such as acetic, propionic, benzoic, or *p*-toluenesulfonic.[2] A mixture of acetic and phosphoric acids has been employed in the direct addition of two moles acrylonitrile to primary fatty amines.[3] Reference 2 suggests use of the organic acid to 10–50% of the combined amine–acrylonitrile weight and the product yield varies from 40–70%.

Acidic ion exchange resins have been found effective in the dicyanoethylation of fatty amines. Since they remain insoluble throughout the reaction, simple filtration removes the resin or resin–amine salt from the final reaction solution. Reuse of the resin has been demonstrated, but a moderate decrease in catalytic activity was noted.

The resins were obtained water-wet and several repeated suspensions in absolute methanol removed most of the water leaving a methanol-wet resin. Similar treatment was given the three types of resins used: Dowex 50W (sulfonic acid type); Rohm & Haas XE-89 (carboxylic acid type); and Chemical Process Co. Duolite C-63 (phosphoric acid type).

Table I (p. 4116) indicates that the sulfonic resin was most active in catalyzing this reaction and the phosphoric acid resin least active.

Experiment 6 represents the repeated usage of the Dowex resin. The weight increase from A to B indicates that some amine–resin salt is combined from the first reaction. The recovered resin was washed twice in absolute methanol and reused immediately. A notable decrease in conversion of primary amine to N,N-dicyanoethyl fatty amine was observed—from 84 to 72%. When used still a third time, no further activity decrease was recorded.

The degree of resin cross linking and the mesh size also appear to affect the degree of dicyanoethylation. Dowex 50W cross linked with 1% divinylbenzene is more effective than resin cross linked with 4, 8, or 12% DVB. Likewise the smaller particle size (50–100 mesh) resin aids this reaction.

Experimental

(Table I, Run 5).—The following materials were placed in a 500-ml. three-neck round-bottom flask with mechanical stirrer, thermometer, and reflux condenser: 177 g. (0.64 mole) of octadecylamine (total amine #205, 97% primary and 0.3% secondary amine, IV 3.5, containing approximately 7% hexadecylamine), 75 g. (1.4 mole) of acrylonitrile, 5 g. of absolute methanol, and 20 g. of methanol-wet Dowex 50W-IX (50–100 mesh) H^+ form. An initial exothermic reaction occurred and then external heat was required to maintain the reaction at the reflux temperature of 70–75°. Samples and final reaction mixture were filtered to remove ion exchange resin. The solvent and excess acrylonitrile were removed from the filtrate under reduced pressure and finally at 60° under high vacuum. Nearly quantitative total recovery was achieved.

Hours	Total amine no.	Tertiary amine no.
2	170	22.8
7	161	65
22	157	109
29.5	150	134.7

Theoretical amine no.: dicyanoethyl derivative 149.2; monocyanoethyl derivative 174.0.

(1) Journal Series Number 312, Central Research Laboratories, General Mills, Inc.

(2) G. W. Fowler and J. W. Lynn, U. S. Patent 3,020,310 (February 6, 1962).

(3) R. Nordgren, U. S. Patent 3,028,415, (April 3, 1962).

TABLE I

Run no.	Reactants: Amine Name	Amine no.	Amine G.	Amine Mole	Resin[a] Name	Resin Size	Resin G.	Acrylonitrile G.	Acrylonitrile Mole	MeOH, g.	Reaction Temp., °C.	Reaction Time, hr.	Product Wt., g.	Total amine no.[d]	Tertiary amine no.[e]	Secondary amine no.[f]	Theor. tertiary amine no.	% R—N—(CH₂CH₂CN)₂
1	n-$C_8H_{16}NH_2$	433.7	22	0.17	Dowex 50W-4X	(20–50)	10	21	0.396	4	70–76	22	39	236	234	1.4	238.7	100
2	$C_{12}H_{24}NH_2$	303	91	0.49	Dowex 50W-4X	(20–50)	20	62	1.17	5	70–74	17	132	192.9	182	10.0	192.4	95
3	$C_{18}H_{36}NH_2$	205	276	1.0	Dowex 50W-4X	(20–50)	30	125	2.35	10	72	26	365	155.4	102	50	149.2	65
4	$C_{18}H_{36}NH_2$	205	276	1.0	Dowex 50W-4X	(50–100)	30	125	2.35	10	72	24	352	150.6	125	23	149.2	85
5	$C_{18}H_{36}NH_2$	205	177	0.64	Dowex 50W-1X	(50–100)	20	75	1.41	5	70–75	29	218	150.2	134.7		149.2	90
6a	$C_{18}H_{36}NH_2$[b]	206	273	1.0	Dowex 50W-1X	(50–100)	27	116	2.19	15	70–78	25	346	150.5	126.4		148	84
b	$C_{18}H_{36}NH_2$[b]	206	273	1.0	Dowex 50W-1X	(50–100)	37[c]	116	2.19	15	70–78	24	363	152	110		148	72
c	$C_{18}H_{36}NH_2$[b]	206	233	0.85	Dowex 50W-1X	(50–100)	35[c]	95	1.79	13	70–80	24	311	153.5	109.6		148	71
7	$C_{12}H_{24}NH_2$	303	91	0.49	XE-89		15	62	1.17	5	72	18	136	195.6	167	29	192	85
8	$C_{12}H_{24}NH_2$	303	91	0.49	Duolite C-63		15	62	1.17	5	72	18	132	209	109	100	192	50

[a] Weight-methanol-wet. [b] Mixed tall oil fatty amines. [c] Reused from previous run. [d] Total amine number: mg. potassium hydroxide equiv. to total amine in 1-g. sample (method: potentiometric titration using perchloric acid in glacial acetic acid solvent). [e] Tertiary amine number: mg. potassium hydroxide equiv. to tertiary amine in 1-g. sample (method: potentiometric titration using perchloric acid after sample treated to acetylate primary and secondary amine). [f] Secondary amine number: mg. potassium hydroxide equiv. to secondary amine in 1-g. sample (method: determine secondary + tertiary by titration after addition of salicylaldehyde; subtract tertiary).

3-Pentadienone[1]

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In connection with other studies in progress in this laboratory it was desired to have a source of 3-pentadienone (divinyl ketone). 3-Pentadienone has previously been prepared by the dehydrochlorination of di(β-chloroethyl) ketone[2] and by the thermal cracking of di(β-methoxyethyl)ketone.[3] Both methods were rejected due to a number of inconveniences connected with the various reactions involved. A route which appeared promising was the oxidation of divinylcarbinol under the mild conditions exemplified in the manganese dioxide oxidation of allylic alcohols, a reaction which has been studied in some detail with satisfactory results being reported in numerous instances.[4]

Various factors exert an influence on the rate of the reaction and the ultimate yield of the oxidized product. The type of manganese dioxide employed appears to be the most important single factor. It was found that divinylcarbinol could be oxidized to 3-pentadienone in moderate yields employing manganese dioxide of four different types. Manganese dioxide (type A) was purchased commercially[5] and used as received. Manganese dioxides (types B and C) were prepared according to the procedure of Harfenist[6] by pyrolysis of manganese carbonate (type B) followed by washing with dilute nitric acid and thorough drying (type C). More consistent yields of the ketone were obtained employing a grade of manganese dioxide (type D) prepared by the method of Attenburrow and coworkers.[7]

The oxidations were carried out in chloroform or methylene chloride solutions with equal results employing ratios of divinylcarbinol to manganese dioxide of from 1/5 to 1/15. The yield data is presented in Table I. Although the yields varied considerably even with oxidations carried out using a single type of manganese dioxide a ratio of 1/10 was found to give near optimum yields. The extent of the reaction was followed by infrared spectroscopy which showed in most instances that the reaction was essentially complete within four to

(1) This work was performed under sponsorship of the U. S. Army under Contract No. DA-01-021 ORD-11878.

(2) Johannes Nelles, U. S. Patent 2,105,792 (January 18, 1938).

(3) I. N. Nazarov and I. V. Torgov, *Bull. Acad. Sci. URSS Classe Sci. Chim.*, 495 (1946); *Chem. Abstr.*, **42**, 7735 (1948).

(4) For leading reference see R. M. Evans, *Quart. Rev.*, **13**, 61 (1959).

(5) Leco manganese dioxide obtained from E. H. Sargent and Co.

(6) N. Harfenist, A. Bavley, and W. A. Lazier, *J. Org. Chem.*, **19**, 1608(1954).

(7) J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen, and T. Walker, *J. Chem. Soc.*, 1094 (1952).

TABLE I

MAXIMUM YIELD DATA (%) FOR OXIDATION OF DIVINYLCARBINOL WITH MANGANESE DIOXIDE

Manganese dioxide	Ratio divinyl carbinol/manganese dioxide 1/5	1/10	1/15
Type A	10–20	28–50	30–50
Type B	5–12	15–26	20–27
Type C	5–15	23–41	22–40
Type D	18–20	40–49	39–50

six hours. Extended reaction periods did not greatly improve the yield of the ketone.

The 3-pentadienone was isolated by vacuum distillation in the presence of a polymerization inhibitor, hydroquinone. It was identified by elemental analysis, refractive index, and infrared spectroscopy. Vapor phase chromatography showed the isolated product to be 98–99% pure, containing a small quantity of the carbinol as an impurity in some instances.

In one reaction the ketone was isolated as the 2,4-dinitrophenylhydrazone in a 96% yield indicating that a considerable part of the product may have been lost during its isolation. Attempts to prepare the oxime and dimethyl ketal were unsuccessful using conventional methods due to polymerization of the ketone.

Experimental[6]

Divinylcarbinol was prepared by the method of Ramsden.[9] The oxidation of the carbinol was carried out as follows: To a 200-ml. three-necked flask equipped with mechanical stirrer, condenser, and thermometer (all outlets covered with Drierite tubes) was introduced 10.0 g. (0.12 mole) of divinylcarbinol in 150 ml. of dry chloroform. One hundred grams of manganese dioxide (type A) was added over a period of 15 min. and the mixture stirred rapidly at ambient temperature for 24 hr. The infrared spectrum of the solution indicated a carbonyl-containing compound and only a trace of residual carbinol. The solid material was removed by filtration and the major part of the solvent removed at reduced pressure until the volume was reduced to 25–30 ml. The liquid residue to which 0.25 g. hydroquinone had been added was then distilled through an 18-in. semimicro spinning band column to give 4.97 g. (50%) 3-pentadienone, b.p. 37–38° (50 mm.), $n^{20}D$ 1.4497 [reported[2] b.p. 41–44° (75 mm.), $n^{20}D$ 1.4485]. The infrared spectrum showed absorption at 3050 cm.$^{-1}$ (C—H valence stretching absorption), 1660 cm.$^{-1}$ (C=C stretching vibration absorption) and 1672 cm.$^{-1}$ (C=O). The latter absorption band is consistent with that reported by Bellamy[10] for the carbonyl absorption in vinyl ketones (1685–1665 cm.$^{-1}$). This general procedure was used employing all four types of manganese dioxide.

Anal. Calcd. for C_5H_6O: C, 73.17; H, 7.31. Found: C, 73.10; H, 7.39.

The ketone was examined by vapor phase chromatography[11] and found to be 98–99% pure in all instances.

The 2,4-dinitrophenylhydrazone of 3-pentadienone was obtained by treating a solution of the ketone [from 2.0 g. of divinylcarbinol and 20.0 g. of manganese dioxide (type C) in 50 ml. chloroform] with a solution of 4.0 g. of 2,4-dinitrophenylhydrazine and 8.0 ml. of concentrated sulfuric acid in 90 ml. of methanol. An immediate orange precipitate appeared which was collected by filtration and recrystallized from 95% ethanol, melting with polymerization at 95–102°. The yield was 6.0 g. (96%).

Anal. Calcd. for $C_{11}H_{10}N_4O_4$: C, 50.38; H, 3.81; N, 21.37. Found: C, 50.21; H, 3.71; N, 21.49.

(8) All melting and boiling points are uncorrected.

(9) H. E. Ramsden, *et al.*, *J. Org. Chem.*, **22**, 1602 (1957).

(10) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley & Sons, Inc., New York, N. Y., 1959, p. 136.

(11) Vapor phase chromatography was carried out on an Aerograph Gas Chromatographic Instrument, Model A-100C, employing a 5-ft. dinonylphthalate column at 75°.

Hydroxy Alkylation of Primary Aromatic Amines

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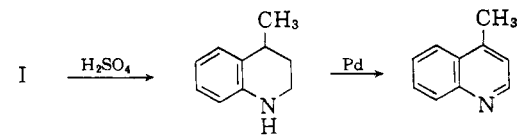
Received May 21, 1962

The one-step reaction of aniline with 1,3-butanediol in the presence of Raney nickel[2] furnished 4-anilino-2-butanol[3] I (R = C_6H_5) in 20% yield.

$$RNH_2 + HOCH_2{-}CH_2CHOHCH_3 \xrightarrow{Ni} RNHCH_2CH_2CHOHCH_3 \quad (I)$$

o-Anisidine, *p*-anisidine, ethyl *p*-aminobenzoate, α-naphthylamine, and β-naphthylamine reacted similarly.[4] The physical properties and analyses of these products are shown in Table I.

Treatment of I (R = C_6H_5) with concentrated sulfuric acid at room temperature gave *dl*-1,2,3,4-tetrahydrolepidine in 90% yield. The latter



was readily dehydrogenated in near quantitative yield to lepidine. 4-*p*-Anisidino-2-butanol I (R = *p*-$CH_3OC_6H_4$) gave *dl*-6-methoxy 1,2,3,4-tetrahydrolepidine in 60% yield.[5] Dehydrogenation furnished 6-methoxylepidine.

4-*p*-Carbethoxyanilino-2-butanol failed to undergo the intramolecular Friedal–Crafts reaction

(1) To whom inquiries should be addressed.

(2) Raney nickel induced alkylation of primary aromatic amines with primary and secondary alcohols is described by G. N. Kao, B. D. Tilak, and K. Venkataraman, *J. Sci. Ind. Res.* (India), **14B**, 624 (1955); R. G. Rice and E. J. Kohn, *J. Am. Chem. Soc.*, **77**, 4052 (1955); C. Ainsworth, *ibid.*, **78**, 1835 (1956); J. Horyna and O. Cerny, *Chem. listy*, **50**, 381 (1956); *Collection Czech. Chem. Commun.*, **21**, 906 (1956); R. G. Rice, E. J. Kohn, and L. W. Daasch, *J. Org. Chem.*, **23**, 1352 (1958).

(3) N. V. Bringi and P. V. Deshmukh, *Hindustan Antibiotics Bull.*, **3**, 66 (1960), report the preparation of 4-anilino-1-butanol from the primary glycol.

(4) J. Lichtenberger and L. Dürr, *Bull. soc. chim. France*, 664 (1956), report the preparation of I (R = C_6H_5, and R = *o*-$CH_3OC_6H_4$) by the reaction of 1,3-butanediol cyclic sulphate and the amine followed by hydrolysis.

(5) This has been prepared previously by catalytic hydrogenation of 6-methoxylepidine; M. Levitz and M. T. Bogert, *J. Org. Chem.*, **10**, 341 (1945).

TABLE I
$RNHCH_2CH_2CHOHCH_3$
I

I, R =	Yield, %	B.p. or m.p./mm.	Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	Infrared spectra[a] μ
C_6H_5—	20	124/1.3 61[b]								2.9, 6.22, 6.65, 7.25, 7.6, 8.9
p-$CH_3OC_6H_4$—	40	162/2[c]	$C_{11}H_{17}NO_2$	67.69	8.71	7.18	67.79	8.50	7.21	2.88, 6.14, 6.55, 7.22, 7.65, 8.8
o-$CH_3OC_6H_4$—	10	152/3[d]								2.88, 6.18, 6.65, 7.25, 7.4, 7.65, 8.8
p-$C_2H_5OCC_6H_4$ (O ‖)	28	104[e]	$C_{13}H_{19}NO_3$	65.81	8.01	5.90	65.81	7.93	6.10	2.88, 5.85, 6.15, 6.5, 7.25, 7.41, 8.95
α-Naphthyl	10	168/1.7[f]	$C_{14}H_{17}NO$	78.13	7.90	6.51	77.73	8.12	6.50	2.9, 6.15, 6.3, 6.55, 7.25, 7.45, 8.95
β-Naphthyl	12	78[g]	$C_{14}H_{17}NO$	78.13	7.90	6.51	77.34[h]	7.81	6.50	2.9, 6.1, 6.22, 6.55, 7.25, 7.4, 8.87

[a] Solids in chloroform and liquids in film. [b] Colorless crystals from hexane; lit.,[4] m.p. 61°. Picrate crystallized from benzene, m.p. 118°. Calcd. for $C_{16}H_{18}N_4O_8$: C, 48.73; H, 4.57; N, 14.21. Found: C, 48.98; H, 4.31; N, 14.20. [c] $n^{25}D$ 1.5501. [d] Lit.,[4] b.p. 158–160°/8 mm., $n^{25}D$ 1.5508. [e] The compound was obtained by chilling the benzene filtrate of the reaction mixture after addition of one volume of ether or by chromatography of benzene solution on ethyl acetate-washed alumina and elution with 2:1 benzene–ether. Crystals from benzene. [f] $n^{25}D$ 1.6553. [g] Colorless crystals from benzene–petroleum ether (b.p. 60–80°). [h] Even though the carbon analysis was low, the infrared spectrum was satisfactory.

and was recovered unchanged on esterification after forty hours at room temperature. Similarly the amino alcohol from α-naphthylamine failed to close either at room temperature or at 80° for four hours.

The synthesis of tetrahydrolepidines in two steps from substituted primary amines is thus a variant from the established methods of synthesis.

Experimental[6]

The following procedure for the preparation of 4-*p*-anisidino-2-butanol served as a general procedure for the alkylation of other primary amines.

A mixture of *p*-anisidine (12.3 g.; 0.1 mole) and 1,3-butanediol (10 g.; 0.11 mole) in benzene (60 ml.) containing 2 drops of 4% aqueous sodium hydroxide was refluxed with Raney nickel[7] (20 g.) for 30 hr. The mixture was filtered, nickel washed with ether, and the filtrate was extracted with 10% hydrochloric acid. The acidic extract was made strongly basic and re-extracted into ether. The product obtained after removal of ether was fractionally distilled (see Table I.).

***dl*-1,2,3,4-Tetrahydrolepidine.**—A solution of the alcohol I (R = C_6H_5) (200 mg.) in concentrated sulfuric acid (1 ml.) was kept at room temperature for 24 hr. The mixture was poured into crushed ice, made alkaline, and extracted with ether. Removal of ether and distillation yielded 160 mg. (90%) of *dl*-1,2,3,4-tetrahydrolepidine, b.p. 106°/7.5 mm. (lit.,[8] b.p. 110°/8 mm.). The infrared spectra of the compound was indistinguishable from the spectra of authentic compound prepared by sodium and alcohol reduction of lepidine.[9] The N-benzoyl derivative crystallized from alcohol and had m.p. and mixed m.p. with authentic specimen 138° (lit.,[8] m.p. 138°).

The picrate derivative, prepared in benzene solution, crystallized from benzene in yellow, feathery needles and had m.p. and mixed m.p. with authentic specimen 138° (reported[10] m.p. 157°).

Anal. Calcd. for $C_{16}H_{16}N_4O_7$: C, 51.06; H, 4.26; N, 14.89. Found: C, 51.20; H, 4.50; N, 14.74.

***dl*-6-Methoxy-1,2,3,4-tetrahydrolepidine.**—The alcohol I (R = *p*-$CH_3OC_6H_4$) (750 mg.) was dissolved in concentrated sulfuric acid (3 ml.) and immediately poured into crushed ice. The solution was made alkaline and extracted with ether. Removal of ether and distillation of the residue yielded 410 mg. (60%) of *dl*-6-methoxy-1,2,3,4-tetrahydrolepidine, b.p. 118–120°/0.9 mm. (lit.,[5] b.p. 114–115°/0.5 mm.).

Dehydrogenation of the above tetrahydrolepidine (400 mg.) in the presence of palladium–charcoal (10%; 150 mg.) and *p*-cymene (5 ml.) under reflux in a nitrogen atmosphere for 10 hr. gave after usual work-up 350 mg. (90%) of 6-methoxylepidine; picrate, m.p. 224° (lit.,[11] m.p. 224–225°).

Acknowledgment.—We thank Dr. M. J. Thirumalachar and Dr. D. S. Bhate for their interest in the work.

(6) Melting points are uncorrected. We are thankful to A. V. Patankar for microanalysis.

(7) Raney nickel was prepared from nickel-aluminum alloy (B.D.H.) according to the method described in A. I. Vogel's "A Textbook of Practical Organic Chemistry," 3rd ed., Longmans, Green and Co., New York, N. Y., 1956, p. 871.

(8) J. C. Sauer and H. Adkins, *J. Am. Chem. Soc.*, **60**, 402 (1938).

(9) A. A. Zata and V. V. Levchenko, *Zh. Obshch. Khim.*, **22**, 2076 (1952); *Chem. Abstr.*, **47**, 9328 (1953).

(10) A. Chichibabin and C. Barkoysky, *Compt. rend.*, **212**, 914 (1941).

(11) A. T. Babayan and N. P. Gambaryan, *Sb. Statei Obshch. Khim., Akad. Nauk SSSR*, **1**, 666 (1953); *Chem. Abstr.*, **49**, 1048 (1955).

Thermal Elimination Reaction of Aliphatic Amine Salts

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Received January 29, 1962

We recently reported[1] the synthesis of highly hindered aliphatic tertiary amine salts of the type

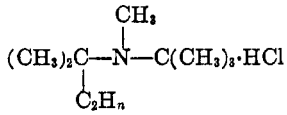
(1) C. Ainsworth and N. R. Easton, *J. Org. Chem.*, **26**, 3776 (1961).

TABLE I

TERTIARY AMINES, $(CH_3)_2CRN(CH_3)C(CH_3)_3$

Compound	R	Hydrocarbon evolved on heating[a] · HCl			· Picrate	
A	C≡CH	70% W[b]	15% X[c]	15% U[d]	80% W	20% X
B	CH=CH$_2$	90% Y[e]	10% W		95% Y	5% W
C	CH$_2$—CH$_3$	80% Z[f]	20% W		80% Z	20% W

[a] Identified by gas chromatography. A concentrated chloroform solution of the salt was injected into a unit with the following operating conditions: injection chamber temp. 190°; detector temp. 170°; 8-ft. column (3/8-in. i.d.) containing 30% Dow Corning silicone oil DC-300 on 30–60 mesh firebrick, column temp. 100°; helium flow rate at 30 p.s.i. and 25° was 200 cc./min. [b] W is isobutylene, retention time 1.0 min. [c] X is 2-methyl-1-buten-3-yne, retention time 1.4 min. The unsaturated hydrocarbon for comparative purpose was prepared from N-isopropyl-N,N,1,1-tetramethylpropargylammonium iodide.[1] [d] U is unidentified, retention time 2.0 min. In addition, there is a small peak at about 4 min. [e] Y is isoprene, retention time 1.9 min. In addition, there are unidentified peaks at 3.8 and 7.5 min. [f] Z is a mixture consisting of equal amounts of 2-methyl-1-butene, retention time 1.5 min., and 2-methyl-2-butene, retention time 1.7 min. The authentic compounds were prepared according to J. F. Norris and R. Reuter, *J. Am. Chem. Soc.*, **49**, 2624 (1927).



illustrated below. It was noted that, on heating, these relatively low melting salts evolved gas, solidified, and remelted at considerably higher temperatures.

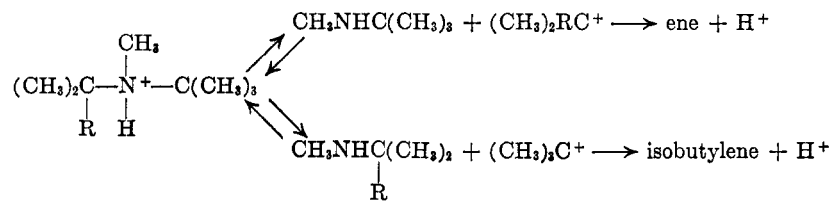
This paper reports a study of the thermal decomposition products of some closely related aliphatic tertiary amine salts of the general formula shown in Table I. It was found that compound A-HCl melted at 140° with gas evolution and quickly solidified to give a higher melting salt that was identified as N,1,1-trimethylpropargylamine hydrochloride. Compound B-HCl behaved in a similar manner when heated, and the new salt was shown by melting point and infrared analysis to be mainly N-methyl-*t*-butylamine hydrochloride. Crystalline compound C-HCl decomposed at its fusion point to give a melt that was not pure but which on recrystallization gave N-methyl-*t*-butylamine hydrochloride.

Next the salts were decomposed in the injection chamber of a gas chromatography unit, and by comparison and combination with known hydrocarbons the products of pyrolysis were determined as shown in Table I. In addition, samples of the gases were collected and identified by infrared analysis.

These observations are consistent with the theory that an E 1 reaction[2] takes place, with the stability of the carbonium ion the chief factor in determining the olefin formed. The carbonium ion $(CH_3)_2RC^+$ is stabilized by a summation of the inductive and the resonance effects, with R = CH=CH$_2$ > C_2H_5 > CH_3 > C≡CH.

The elimination reaction also took place in aqueous medium. When compound B·HCl, dissolved in 6 *N* hydrochloric acid, was heated under reflux for one hour, isoprene polymer and N-methyl-*t*-butylamine hydrochloride were formed. The polymer was the same as that formed from isoprene and 6 *N* hydrochloric acid.

The earliest observation of a tertiary amine hydrochloride undergoing change on heating was recorded by Hofmann.[3] Although isolated observations of amine hydrohalide thermal decomposition are recorded,[4] the problem was not systematically investigated. Actually, it was the thermal treatment of quaternary ammonium compounds that received the attention of Hofmann, and from this work his classical degradation rules evolved.



Certain secondary and even primary amine salts[4b] related to this series have been found to

(2) (a) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, pp. 424–427; (b) D. J. Cram, "Olefin Forming Elimination Reactions," in M. S. Newman "Steric Effects in Organic Chemistry," John Wiley & Sons, Inc., New York, N. Y., 1956, pp. 304–348; (c) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Co., New York, N. Y., 1959, pp. 472–507.

(3) A. W. Hofmann, *Proc. Roy. Soc.*, **10**, 595 (1860), reported the decomposition of trimethylamine hydrochloride into dimethylamine hydrochloride, methyl chloride, and trimethylamine. The reaction once served as a commercial method for the production of methyl chloride from trimethylammonium chloride (by-product of the sugar beet industry) and added hydrogen chloride.

(4) The best sources found that summarize the degradation of amine salts are (a) W. J. Hickinbottom, "Reactions of Organic Compounds," Longmans Green and Co., New York, N. Y., 3rd ed., 1957, p. 416, and (b) C. D. Hurd, "The Pyrolysis of Carbon Compounds," ACS Monograph Series, 1929, p. 310.

undergo thermal fragmentation. Di-*t*-butylamine[5] hydrochloride on melting gave isobutylene and *t*-butylamine hydrochloride. 1,1-Dimethylallylamine hydrochloride[6] heated at 260° decomposed to give isoprene and ammonium chloride.

Important degradation products are obtained by pyrolysis under reduced pressure of certain alkaloid hydrochlorides[7] and we wish to point out that this method might be useful for obtaining degradative compounds from other natural products. Preliminary findings indicate that pyrolysis of N-*t*-butyl-N-methyl tertiary amine hydrochlorides to N-methyl secondary amine salts can be synthetically useful.

Acknowledgment.—The physical data were supplied by H. E. Boaz, D. O. Woolf, Jr. (infrared), and R. R. Pfeiffer and Ann Van Camp (X-ray). W. Hargrove prepared di-*t*-butylamine hydrochloride.

(5) F. Klages and H. Setz, *Ber.*, **92**, 2606 (1959).
(6) Prepared according to the general method of G. F. Hennion and E. G. Teach, *J. Am. Chem. Soc.*, **75**, 4297 (1953).
(7) M. Gorman, N. Neuss, and K. Biemann, *ibid.*, **84**, 1058 (1962).

Communications TO THE EDITOR

Observations on the Acetylation of Carbohydrates in Aqueous Solution

Sir:

In an attempt to prepare disaccharides containing D-glucose linked through the C-2 hydroxyl group, we considered the use of 1,3,4,6-tetra-*O*-acetyl-α-D-glucose. The preparation of this acetate by acetylation of D-glucose in aqueous solution has been described recently.[1,2]

In our hands, several acetylations of glucose by this method all gave a crystalline product in 60–70% yield which had physical constants in good agreement with those reported by Prey and Aszalos[1] (m.p. 98°, $[\alpha]_D$ +63°) although the specific rotation of our product as well as that of the above authors was very different from the value of +145° previously reported.[3]

Acetyl determination[4] indicated that the product contained five acetyl groups per glucose unit, and no hydroxyl absorption could be detected in the infrared. Gas-liquid partition chromatography[5] showed that the product was a mixture of the α- and β-anomers of penta-*O*-acetyl-D-glucopyranose. No other compound was detected. The two anomers are difficult to separate by fractional crystallization but a synthetic mixture, prepared in the ratio indicated by the optical rotation, had the same melting point and infrared absorption spectrum.

We would also like to point out that the physical constants reported[1] for "sorbital pentaacetate" and "mannitol pentaacetate" are in excellent agreement with those of the corresponding hexaacetates; and when we applied the acetylation method to mannitol, the crystalline product contained no free hydroxyl group and did not depress the melting point of mannitol hexaacetate.

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(1) V. Prey and A. Aszalos, *Monatsh. Chem.*, **91**, 729 (1960).
(2) A. Aszalos and V. Prey, *Die Stärke*, **14**, 50 (1962).
(3) R. U. Lemieux and G. Huber, *Can. J. Chem.*, **31**, 1040 (1953).
(4) S. Hestrin, *J. Biol. Chem.*, **180**, 249 (1949).
(5) We would like to thank Dr. M. B. Perry of Queen's University, Kingston, Ont., Can., for the gas chromatographic analysis.
(6) Present address: Corn Products Co., Technical Division, P. O. Box 345, Argo, Ill.

A New Synthesis of Diarylphosphinous Chlorides[1]

Sir:

In spite of the current interest in organophosphorus chemistry, the diarylphosphinous chlorides, Ar_2PCl, remain rather inaccessible and therefore little explored,[2] even though they serve as valuable precursors of other phosphorus compounds. We have devised for these chlorides a new synthesis which appears to have considerable versatility and the potential of making these compounds more readily available.

The reaction of aryldiazonium fluoroborates with arylphosphonous dichlorides is known to give a type of intermediate which may be hydrolyzed to diarylphosphinic acids.[3]

$$ArN_2BF_4 + Ar'PCl_2 \longrightarrow [ArAr'PCl_2{}^+BF_4{}^-] \xrightarrow{H_2O} ArAr'P(O)OH$$

(1) Supported by Research Grant CY-5507 from the National Cancer Institute, Public Health Service.
(2) G. M. Kosolapoff, "Organophosphorus Compounds," John Wiley & Sons, Inc., New York, N. Y., 1950, Chap. 3.
(3) L. D. Freedman and G. O. Doak, *J. Am. Chem. Soc.*, **74**, 2884 (1952).