Notes

A departmemt for short papers of immediate interest.

The Mechanism of Pyrolysis of β-Hydroxyolefins

R. T. Arnold and G. Smolinsky

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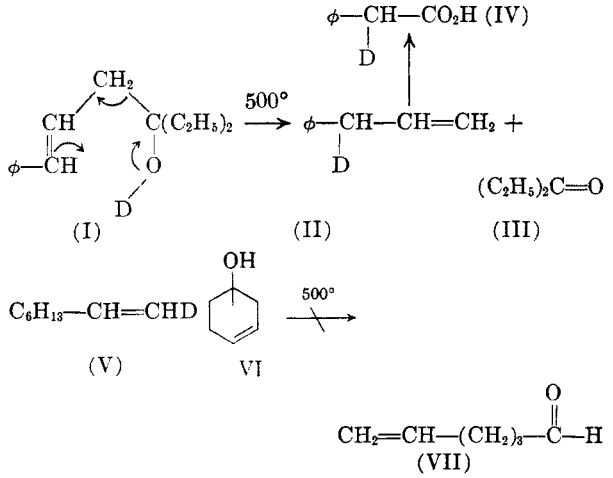
In a previous publication[1] it was demonstrated that the pyrolytic degradation of β-hydroxyolefins at 500° to form new olefinic substances and aldehydes (or ketones) is a general reaction, and that the well known decomposition of ricinoleic acid into heptaldehyde and undecylenic acid is merely a specific example of this transformation.

Two pieces of evidence have now been found to support the proposal[1] that this thermal degradation occurs *via* a six-membered cyclic transition state. The first of these follows from results of a study of the pyrolysis of 1-phenyl-4-ethylhexen-1-ol-4-*d* (I) to give 3-phenylpropen-1-3-*d* (II) and pentanone-3 (III).



No evidence for the presence of excess deuterium in III was found by careful examination of its infrared spectrum.[2] The —C—D stretching frequency at 4.7μ as well as other differences characteristic of the presence of deuterium[3,4] were, however, found in II and IV. That the deuterium atom in II was located at C_3 and not at C_1 was clearly indicated by the fact that the intensity of the $=CH_2$ deformation bands at 10.04μ and 10.91μ in II and in an authentic sample of allylbenzene were indistinguishable. The presence of any appreciable amount of =CHD should markedly reduce the absorption intensities in the 10–11μ region.[5] Further experimental evidence in support of this view was found by an examination of the infrared spectrum of octene-1-1-*d* (V) which showed the normal —C—D stretching frequency (4.5μ), but the intensity of the deformation bands at 10.1μ and 10.9μ were approximately one half of those observed in an undeuterated sample of octene-1 when measured under identical conditions.

The second piece of evidence in favor of a cyclic mechanism follows from geometric considerations. This mechanism requires the β-hydroxyolefin to have at least one readily attainable conformation in which the hydrogen atom of the hydroxyl group can come into close proximity with the π-electrons of the carbon-carbon double bond. An examination of molecular models indicated that such a conformation is not favorable in cyclohexen-3-ol-1 (VI), and it was predicted that VI upon pyrolysis would not be transformed into its "normal" product VII. This, in fact, proved to be the case. When VI was subjected to the usual conditions for the pyrolytic decomposition of β-hydroxyolefins (*i.e.* 500°), there was obtained a condensate whose infrared spectrum showed the absence of carbonyl compounds. Fractionation of this crude product led to a recovery of starting material (73%) plus a low-boiling component (9%) which we regard as a mixture of cyclohexadienes formed by thermal dehydration. Dehydration has been observed invariably as a side reaction during the pyrolytic decomposition of β-hydroxyolefins.

EXPERIMENTAL

Pyrolysis of 1-phenyl-4-ethylhexen-1-ol-4-d (I). The undeuterated alcohol[1] (17 g.) was dissolved in dry ether (25 ml.) and shaken successively with four portions (1 g. each) of essentially pure deuterium oxide. The etheral solution was dried (sodium sulfate) and distilled to give a quantitative yield of product, b.p. 115–117°/1 mm. This material showed extremely weak absorption in the hydroxyl region, but strong absorption in the 3.7–3.9μ region expected for the —O—D stretching vibration.[6] From the ratio of intensities of the absorption bands, it was estimated that the exchange reaction had occurred to the extent of 90–95%. This material was pyrolyzed (500°), as described earlier, for the undeuterated alcohol[1] to give allylbenzene (b.p. 156°) and pentanone-3 (b.p. 101–102°) in 72% yield. The infrared spectrum of the pentanone-3 was identical with that of

(1) R. T. Arnold and G. Smolinsky, *J. Am. Chem. Soc.*, *in press*.

(2) All infrared spectra reported in this paper were measured on CCl_4 solutions.

(3) A. Streitwieser and J. R. Wolfe, *J. Am. Chem. Soc.*, **79**, 904 (1957).

(4) R. D. Shutz and F. W. Millard, *J. Org. Chem.*, **24**, 297 (1959).

(5) R. Breslow, *J. Am. Chem. Soc.*, **80**, 3722 (1958).

(6) A. Weissberger, *Technique of Organic Chemistry*, Interscience Publishers, Inc., New York, Vol. IX, p. 333.

an authentic sample, and no bands attributable to deuterium could be detected. The allylbenzene fraction, however, showed —C—D stretching bands at 4.7μ as well as differences in the 7–13μ region[3,4] when compared with an authentic undeuterated sample of allylbenzene. The strong absorption bands at 10.04μ and 10.91μ[7] were identical in the deuterated and undeuterated samples of allylbenzene indicating the absence of any appreciable =CHD in the former compound. Oxidative degradation of the deuterated allylbenzene (630 mg.) with ozone in ethyl acetate afforded phenylacetic acid (m.p. 74–76°) whose infrared spectrum—compared with authentic undeuterated phenylacetic acid—exhibited differences in the 7–12μ region characteristic of deuterium containing analogs.

Octene-1-1-d (V). Lithium metal (1.38 g.) and 1-bromooctene[8] (20 g.) were allowed to react in ether solution as previously described.[1] The resulting lithium octenyl solution was decomposed with deuterium oxide (4 ml.). The ether solution was dried (sodium sulfate) and fractionated to give octen-1-1-*d*. Yield 7 g. (60%); b.p. 121°; n_D^{25} 1.4078. Reported[9] for 1-octene, b.p. 121–122°; n_D^{19} 1.4085. The intensity of the out-of-plane bending vibrations at 10.1μ and 10.9μ for octen-1-1-*d* were approximately one half of those found in 1-octene. Our sample of octen-1-1-*d* showed the expected —C—D stretching band at 4.5μ.[3]

Pyrolysis of cyclohexen-3-ol-1 (*VI*). The procedure of Owen and Robins[10] was used in the preparation of this unsaturated alcohol. Cyclohexen-3-ol-1 (7.5 g.) was added dropwise to the pyrolysis tube at 500° in an atmosphere of nitrogen using the procedure normally employed.[1] The infrared spectrum of the condensate showed no carbonyl bands. Fractionation of this material gave a small forerun (0.6 g., 9%)—presumably a mixture of cyclohexadienes and starting material (5.45 g., 73%, b.p. 160–163°, n_D^{25} 1.4840). The nonvolatile residue weighed 0.45 g.

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(7) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley and Sons, Inc., New York, 1954, p. 39.
(8) G. B. Bachman, *J. Am. Chem. Soc.*, **55**, 4279 (1933).
(9) M. A. Kirrmann, *Bull. soc. chim. France*, [4] **39**, 990 (1926).
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An Attempt to Synthesize 3,5-Diphenylbenzocyclopentatriene, a Cyclic Allene

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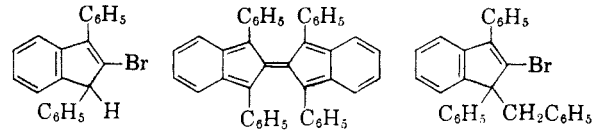
1,2-Cycloheptadiene has been prepared, but attempts to obtain 1,2-cyclohexadiene have led only to polymers.[1]

Considerable distortion, both bending and twisting, would be involved if the allenic system were present in the still smaller five-membered ring. In spite of this, it was considered of interest to discover what would happen if the sodio derivative of 2-bromo-1,3-diphenylindene (I) were prepared, for the heavy substitution might inhibit polymerization of the expected cyclic allene. If the allene



I II III

could not be isolated, it was considered possible that a dimer (II) might be isolated, and this would be of interest since such a dimer has the structure originally proposed for rubrene,[2] and unsuccessful attempts to synthesize a compound having this structure have been reported.[3]

Surprisingly, it has now been found that the anion of 2-bromo-1,3-diphenylindene shows no tendency to eliminate a bromide anion. When the indene was added to sodium *iso*-propoxide in *iso*-propyl alcohol, a bright yellow solution resulted, and no sodium bromide was formed when this solution was boiled for thirty minutes. That the anion was present was shown by addition of benzyl chloride. This caused immediate disappearance of the yellow color and formation of 1-benzyl-2-bromo-1,3-diphenylindene (III) in nearly quantitative yield. The benzyl derivative was identical with the product of bromination of 1-benzyl-1,3-diphenylindene.

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EXPERIMENTAL

2-Bromo-1,3-diphenylindene (I). Bromination of 1,3-diphenylindene has been investigated previously[4] but the 2-bromo derivative has not been reported. It was obtained easily in nearly quantitative yield by adding 3.2 g. of bromine in 5 ml. of carbon tetrachloride to a cooled solution of 5.3 g. of 1,3-diphenylindene in 20 ml. of carbon tetrachloride. The solvent was then removed by distillation and the residue was heated at 100° under reduced pressure for a few minutes. Solution in hexane and chromatography over alumina gave 6.55 g. of colorless oil which solidified completely when it was rubbed with ether-hexane at −70°. Recrystallization from hexane furnished prisms, m.p. 66–68°.

Anal. Calcd. for $C_{21}H_{15}Br$: C, 72.6; H, 4.3. Found: C, 72.5; H, 4.5.

Oxidation of the bromo compound with chromic acid in acetic acid gave *o*-dibenzoylbenzene identified by mixed melting point and infrared spectrum.

(1) A. Favorsky and N. A. Domnin, *Bull. Soc. Chim.*, (4) **3**, 1727 (1936); N. A. Domnin, *J. Gen. Chem.* (*U.S.S.R.*), **15**, 461 (1945); *Chem. Abstr.*, **40**, 4682 (1946); *Vestnik Leningrad Univ.*, **I**, No. 3, 103 (1946); *Chem. Abstr.*, **42**, 3337 (1948).
(2) C. Moureu, C. Dufraisse, and A. Willemart, *Compt. rend.*, **187**, 266 (1928); Dufraisse and Loury, *Compt. rend.*, **194**, 1832 (1932).
(3) J. C. Eck and C. S. Marvel, *J. Am. Chem. Soc.*, **57**, 1898 (1935); C. F. Koelsch and H. J. Richter, *J. Am. Chem. Soc.*, **57**, 2010 (1935).
(4) R. Weiss and S. Luft, *Monatsh.* **48**, 337 (1927); C. Dufraisse and L. Enderlin, *Bull. Soc. Chim.* (5) **1**, 267 (1934).

1-Benzyl-2-bromo-1,3-diphenylindene (III). (a) A solution of sodium *iso*-propoxide from 0.2 g. of sodium in 5 ml. of *iso*-propyl alcohol was treated with 0.7 g. of I and then with 1 g. of benzyl chloride. Volatile materials were removed with steam, and the colorless residue (0.85 g.) was crystallized from ligroin, giving 0.8 g. of prisms, m.p. 117–118°.

(b) A solution of 0.5 g. of 1-benzyl-1,3-diphenylindene[5] in 5 ml. of carbon tetrachloride was treated with 0.2 g. of bromine. The solvent and hydrogen bromide were then removed by short warming at 100° under reduced pressure. Crystallization from ligroin gave 0.5 g. of prisms, m.p. 117–118° alone or mixed with (a); the infrared spectra of the two samples were identical.

Anal. Calcd. for $C_{26}H_{21}Br$: C, 76.9; H, 4.8. Found: C, 76.8; H, 5.1.

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Seven-Membered Ring Compounds. X. Hydroxy- and Methoxybenzosuberones

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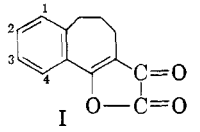
In previous investigations[1] the condensation of benzosuberones with oxalate esters was found to yield cyclic enol esters (I) of the expected glyoxylates, provided that the 4-position of the benzosuberone contained no substituent. In a search for precursors which would be convertible to 4-substituted benzosuberones, we have prepared a number of hydroxybenzosuberones.



I

The condensations of the benzyl ethers of hydroxyaldehydes with diethyl ethylidenemalonate[2] (Table I) proceeded in better yields than the hydroxyaldehydes themselves. Reduction of the cinnamylidenemalonic acids by means of Raney alloy and alkali[3] gave γ-phenylpropylmalonic acids with hydrogenolysis of the benzyl group. The crude malonic acids were heated without purification to obtain the phenylvaleric acids (Table I). As a second usable method, catalytic hydrogenation of several benzyloxycinnamylidenemalonic acids followed by decarboxylation gave benzyl ethers which were hydrolyzed to hydroxyphenyl valeric acids.

The cyclization of hydroxyphenylvaleric acids in polyphosphoric acid (PPA) proceeded in low yield. A cyclization of δ-4-acetoxy-3-methoxyphenylvaleric acid gave material which resisted purification and the attempted cyclization of 4-benzyloxy-3-methoxyphenylvaleric acid gave polymeric material. The cyclization of the benzoates of 2- and 4-hydroxy-3-methoxyphenylvaleric acids by means of PPA gave yields of 51% and 42% respectively.

The assistance of a grant from the National Science Foundation is gratefully acknowledged.

EXPERIMENTAL[5]

4-Benzyloxy-3-methoxycinnamylidenemalonic acid. The following illustrates a convenient modification of the reported method[2] for the condensation of aromatic aldehydes with ethylidenemalonic ester. The cinnamylidenemalonic acids in Table I were obtained by this procedure.

Benzyltrimethylammonium chloride was prepared by the addition of 190 g. of benzyl chloride over a 10 min. period to 350 g. of 25% aqueous trimethylamine at a temperature below 40° maintained by stirring and cooling in an ice bath. After stirring for 3 hr. and standing overnight, the solution was distilled on the water bath at aspirator pressure. The residual solid, after drying for 1 week in a vacuum dessicator, weighed 193 g. (70%).

A solution containing 17 g. of sodium hydroxide in 164 ml. of methanol was added to a flask containing 77.6 g. of benzyltrimethylammonium chloride. After the solution of the salt and standing overnight, the material was filtered by suction and the sodium chloride pressed and washed with a small portion of methanol. To the base was added 23.6 g. (0.0975 mol) of benzylvanillin[6] and 36.6 ml. of ethylidenemalonic ester.[7] The flask was swirled without cooling and stored for 48 hrs. It was diluted with 500 ml. of water, refluxed for 1 hr., cooled, and acidified with 1:1 hydrochloric acid. After standing at 5° for 24 hr. the crystals were filtered, washed with cold water and dried on the steam bath. The orange-yellow solid weighed 26.1 g. (75%) (see Table I).

4-Benzyloxy-3-methoxycinnamylideneacetic acid. A solution of 3.20 g. of the above cinnamylidenemalonic acid in 6.3 ml. of acetic anhydride and 2.7 ml. of pyridine was warmed on the water bath and allowed to stand at room temperature overnight.[8] After dilution with water and decomposition of the acetic anhydride, the solution was extracted with benzene yielding 2.21 g. (79%) of orange-brown crystals m.p. 184–192°. Further purification from ethyl acetate–petroleum ether (b.p. 60–71°) gave fine pale yellow crystals m.p. 203.0–204.0°.

Anal. Calcd. for $C_{19}H_{18}O_4$: C, 73.53; H, 5.85. Found: C, 73.36; H, 5.93.

Phenylvaleric acids. The acids in Table I were obtained by reduction with Raney alloy as described[2,3] with subsequent decarboxylation of the crude malonic acids at 180°. *γ-4-Hydroxy-3-methoxyphenylpropylmalonic acid* was iso-

(1) W. J. Horton, C. E. Hummel, and H. W. Johnson, *J. Am. Chem. Soc.*, **75**, 944 (1953); C. L. Anderson, W. J. Horton, F. E. Walker, and M. R. Weiler, *J. Am. Chem. Soc.*, **77**, 598 (1955).

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TABLE I

CINNAMYLIDENEMALONIC ACIDS

	Yield, %	M.P.[a]	M.P. (Cor.)[a] for Anal.	Compound	Calcd. C	Calcd. H	Found C	Found H
3-CH_3O	100	189–196	201.6–202.0[b]	$C_{13}H_{12}O_5$	62.91	4.88	62.88	4.72
3-$C_6H_5CH_2O$	89	162–176	192.0[c]	$C_{19}H_{16}O_5$	70.36	4.97	70.71	5.01
2-$C_6H_5CH_2O$-3-CH_3O	95	130–139	162.3–163.9[d]	$C_{20}H_{18}O_6$	67.79	5.12	68.05	5.15
4-$C_6H_5CH_2O$-3-CH_3O	75	140–154	195.0–195.5[e]	$C_{20}H_{18}O_6$	67.79	5.12	68.10	5.03
PHENYLVALERIC ACIDS								
3-HO	81.5	89–112	115.2–117.0[f]	$C_{11}H_{14}O_3$	68.02	7.27	68.21	7.27
3-CH_2O	79	B.p. 200–220 (1 mm.-bath)	B.p. 142–143 (0.17 mm.)	$C_{12}H_{16}O_3$	69.20	7.75	70.22	7.79
2-HO-3-CH_3O	42	81–88	86.2–88.2[g]	$C_{12}H_{16}O_4$	64.27	7.19	64.61	7.24
4-HO-3-CH_3O	74	86–89	90.5–92.5[h]	$C_{12}H_{16}O_4$	64.27	7.19	63.66	7.31
4-$C_6H_5CH_2O$-3-CH_3O	81[i]	93.5–100	100.5–102[j]	$C_{19}H_{22}O_4$	72.59	7.06	72.62	7.17
BENZOSUBERONES								
2-HO	18[k]	156.5–163.5	164.4–166.1[l]	$C_{11}H_{12}O_2$	74.97	6.87	75.06	6.95
2-CH_3O	94	54–58	58.9–60.3[m]	$C_{12}H_{14}O_2$	75.76	7.42	75.81	7.42
1-$C_6H_5CO_2$-2-CH_3O	51	124–139	138.0–141.4	$C_{19}H_{18}O_4$	73.53	5.85	73.39	5.89
1-HO-2-CH_3O	(82)[n]	88–95	98.4–100.6	$C_{12}H_{14}O_3$	69.88	6.84	69.83	6.84
3-$C_6H_5CO_2$-2-CH_3O	42[o]	119–124	126–127.4[p]	$C_{19}H_{18}O_4$	73.53	5.85	73.65	5.68
3-HO-2-CH_3O	30	106–109	112.0–113.2[q]	$C_{12}H_{14}O_3$	69.88	6.84	70.24	7.04

[a] All cinnamylidenemalonic acids melted with gas evolution. [b] From benzene–ethyl acetate, canary yellow. [c] Instantaneous; from benzene–ethyl acetate, canary yellow. [d] From benzene–ethyl acetate, canary yellow. [e] Golden yellow clumps of spears from methanol. [f] From benzene. [g] From cyclohexane–acetone or aqueous methanol; dark green ferric chloride test. The *benzoate* melted at 98–99.6° (cor.). Calcd. for $C_{19}H_{20}O_5$: C, 69.50; H, 6.14. Found: C, 69.39; H, 6.10. [h] From cyclohexane; green ferric chloride test. The *acetate*, from benzene–petroleum ether (b.p. 65–110°) melted at 76.5–78.1° (cor.). Calcd. for $C_{14}H_{18}O_5$: C, 63.14; H, 6.81. Found: C, 63.27; H, 6.85. [i] From the catalytic reduction of the cinnamylidenemalonic acid followed by heating at 180° and extraction with hot cyclohexane. [j] From cyclohexane. [k] Cyclization time 30 min. (95°). [l] From benzene-cyclohexane; identical to the compound obtained (by Mr. Irwin Schmeltz) from 2-methoxybenzosuberone by cleavage with aluminum chloride. The *benzoate* from methanol melted at 60.2–61.2° (cor.). Calcd. for $C_{18}H_{16}O_3$: C, 77.12; H, 5.75. Found: C, 77.24; H, 5.65. [m] From cyclohexane and sublimed at 0.16 mm. (90° bath). The *oxime*, from cyclohexane and sublimed at 0.12 mm. (140° bath) melted at 127.0–128.8° (cor.). Calcd. for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37. Found: C, 70.35; H, 7.55. [n] By saponification of the benzoate; deep green ferric chloride test. [o] Cyclization time 25 mins. (90°). [p] From benzene-petroleum ether (b.p. 60–71°). Saponification of the benzoate gave 3-hydroxy-2-methoxybenzosuberone which was methylated to 2,3-dimethoxybenzosuberone, identical to known material.[4] [q] From benzene-petroleum ether (b.p. 60–71°); green ferric chloride test. The *acetate* from petroleum ether (b.p. 90–110°) melted at 104.8–106.4° (cor.). Calcd. for $C_{14}H_{16}O_4$: C, 67.72; H, 6.50. Found: C, 67.96; H, 6.57.

lated prior to decarboxylation in virtually quantitative yield m.p. 112–119° (gas evol.). From benzene–petroleum ether (b.p. 65–110°) and ethyl acetate–petroleum ether, material melting at 122.8–124.0° (gas evol.) was obtained.

Anal. Calcd. for $C_{13}H_{16}O_6$: C, 58.20; H, 6.01. Found: C, 58.15; H, 6.01.

The catalytic reduction of 4-benzyloxy-3-methoxycinnamylidenemalonic acid in alcohol over platinum gave a malonic acid with retention of the benzyl group. Decarboxylation gave the benzyl ether of the valeric acid (Table I). Debenzylation[9] gave δ-4-hydroxy-3-methoxyphenylvaleric acid (93.2%) identical to the material produced *via* Raney alloy–sodium hydroxide.

δ-4-Benzoyloxy-3-methoxyphenylvaleric acid. The dried mixture of the benzoate and benzoic acid, m.p. 89–102°, obtained by treatment with benzoyl chloride in aqueous sodium hydroxide was either (a) sublimed 24 hr. at 70° (0.3 mm.) to yield material (76%) m.p. 118–123° which depressed the melting point of benzoic acid or (b) digested three times with water at 90°, filtering after each digestion, to yield product (77%) m.p. 121–124°, similarly depressing the melting point of benzoic acid. By repeated crystallization from benzene–petroleum ether (b.p. 90–110°) 1:10, colorless material m.p. 126.0–127.8° was obtained.

Anal. Calcd. for $C_{19}H_{20}O_5$: C, 69.50; H, 6.14. Found: C, 69.51; H, 6.13.

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2,4′-Diphenylbiphenyl

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Of the nine possible $C_{24}H_{18}$ hydrocarbons consisting of four linked benzene rings, eight are recorded.[1–8] We now report the synthesis of the re-

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(6) E. Knoevenagel, *Ann.*, **281**, 72 (1894).

maining compound, 2,4′-diphenylbiphenyl (IV). 2,4′-Dinitrobiphenyl (I)[9] was reduced to 2,4′-diaminobiphenyl (II)[10] and tetrazotized. The tetrazonium hydroxide was decomposed in the presence of benzene[11] to give 2,4′-diphenylbiphenyl (IV), m.p. 209–210° in less than 1% yield. In an alternative synthesis 2,4′-diacetamidobiphenyl (III) was nitrosated and the *N*-nitroso compound was decomposed in benzene solution[12] to give a 3% yield of 2,4′-diphenylbiphenyl.

The availability of 2,4′-diphenylbiphenyl makes possible some further correlations of the ultraviolet absorption characteristics of the quaterphenyls. Ultraviolet absorption data for quaterphenyls and related compounds are recorded in Table I.

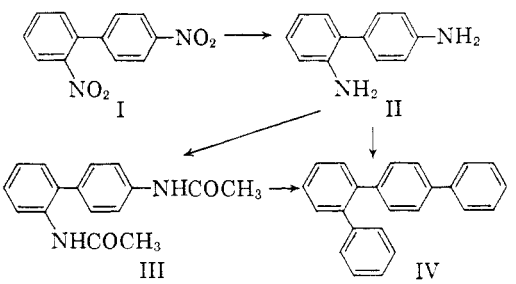
TABLE I
ULTRAVIOLET ABSORPTION DATA FOR QUATERPHENYLS AND RELATED COMPOUNDS

Compound	λ_{max}, mμ	Log ε	Solvent[a]	Ref.
Biphenyl	248	4.3	C	13
p-Terphenyl	276	4.54	H	14
p-Quaterphenyl	292	4.75	H	14
3,4′-Diphenylbiphenyl	~267	4.54	C	3
3,3′-Diphenylbiphenyl	250	4.74	C	3
2,4′-Diphenylbiphenyl	257	4.55	M	
	274	4.55	M	
2,3′-Diphenylbiphenyl	235	4.65	C	3
	255sh.	—	C	3
2,2′-Diphenylbiphenyl	<230	>4.5	E	15
1,3,5-Triphenylbenzene	251	4.76	H	16

[a] The letters stand for the following solvents: C, cyclohexane; H, hexane; M, methanol; E, ethanol.

Two generalizations have been drawn[14] from the spectra of the polyphenyls: For all *p*-polyphenyls, both λ_{max} and ε increase with the number of nuclei present; and for all *m*-polyphenyls, the λ_{max} remains constant (approx. 250 mμ), while ε increases with the number of nuclei present. It has also been observed[3] that an *o*-configuration in a polyphenyl interferes with through-conjugation. The data given in Table I confirm these postulates for the quaterphenyl series. In *p*-quaterphenyl the maximum is at the longest wave length for the series and presumably the chromophore covers the entire molecule. Where *m*- or *o*- configurations are present, the chromophore is broken at that point. Thus, 3,4′-diphenylbiphenyl, in which a *p*-terphenyl structure is found, shows absorption similar to that of *p*-terphenyl, and 3,3′-diphenyl shows absorption at the same wave length as biphenyl, but with almost three times the intensity. 2,4′-Diphenylbiphenyl shows absorption corresponding to both biphenyl and *p*-terphenyl chromophores. 2,3′-Diphenylbiphenyl shows mainly absorption corresponding to single benzene nuclei with a shoulder in the region corresponding to the biphenyl chromophore, and 2,2′-diphenylbiphenyl shows only end absorption in the 230–300 mμ region. 1,3,5′-Triphenylbenzene shows absorption at the same wave length as biphenyl with almost three times the intensity. Presumably each pair of linked rings contributes to the absorption in this case. The spectra of the other two triphenylbenzenes are not recorded.

2,4′-Diphenylbiphenyl shows possibilities as a scintillation solute. It shows a pulse height relative to terphenyl of 1.06 at 3 g./l in toluene[17] and a solubility of 3% in toluene at 27°.



EXPERIMENTAL

2,4′-Diaminobiphenyl. 2,4′-Dinitrobiphenyl, obtained as a by-product from the nitration of biphenyl,[9] was reduced with tin and hydrochloric acid[10] to give the diamine in 65% yield.

2,4′-Diacetamidobiphenyl. Fifteen g. of 2,4′-diaminobiphenyl was heated on the steam bath for 2 hr. with 25 g. of acetic anhydride. The solution was poured into 400 ml. of ice water. The resulting suspension was warmed on a steam bath for 30 min., cooled, and filtered. The crude product was recrystallized from aqueous ethyl alcohol to give 10 g. (61%, from dinitrobiphenyl) of 2,4′-diacetamidobiphenyl, m.p. 198–200°. Reported[10] m.p. 202°.

2,4′-Diphenylbiphenyl. 1. *From 2,4′-diaminobiphenyl.* Six g. of 2,4′-diaminobiphenyl was tetrazotized at 0° in hydrochloric acid. The solution was allowed to warm to 5–6° as 100 ml. of benzene was added. The solution was kept at 5–6° as excess 5*N* sodium hydroxide was added over 1 hr., with rapid stirring. The stirring was continued at 5–6° for 1 hr. and then at room temperature for 20 hr. The benzene layer was separated and dried, and the benzene was removed by distillation to leave 5 g. of a black tar. Sublimation gave 15 mg. of a white solid, m.p. 190–192°. On recrystallization from benzene the m.p. was raised to 208–210°.

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2. *From 2,4'-diacetamidobiphenyl.* Ten g. of 2,4'-diacetamidobiphenyl was dissolved in 150 ml. of glacial acetic acid and 75 ml. of acetic anhydride. Ten g. of anhydrous potassium acetate and 1 g. of phosphorus pentoxide were added, and the solution was cooled to −5°. The solution was stirred and a solution of 5.5 g. of redistilled nitrosyl chloride in 10 ml. of acetic anhydride was added at −20°. Stirring was continued for 15 min., the mixture was poured onto 500 g. of ice and water and the solution was extracted twice with 200 ml. of benzene. The benzene extract was washed twice with 50 ml. of ice water and dried over anhydrous sodium sulfate. The solution was warmed to 35–40° until no more nitrogen was evolved (1 hr.), filtered, and the benzene removed by distillation to leave 10 g. of a black tar. The black tar was chromatographed on acid alumina (Woelm, Grade I), using benzene as eluant. The eluate coming through the column before the colored material was evaporated to dryness to give 0.3 g. (3%) of 2,4'-diphenylbiphenyl, m.p. 209–210° from benzene or toluene. Ultraviolet absorption: λ_{max} 257 mμ (log ε, 4.55); 274 mμ (log ε, 4.55) in methanol (Beckman DK-2 spectrophotometer). Infrared absorption: 1605(w), 1529(w), 1484(m), 1456(w), 1403(w), 1350(w), 1170(w), 1076(w), 1005(m), 908(w), 839(s), 748(v.s.), 686(s) cm.$^{-1}$ All bands attributable to *o*-, *p*- or monosubstituted benzenes. (KBr pellet; Baird recording double-beam spectrometer).

Anal.[18] Calcd. for $C_{24}H_{18}$: C, 94.08; H, 5.92. Found: C, 93.90; H, 6.20.

Acknowledgment. This research was supported in part by the Atomic Energy Commission under Contract No. AT-(40-1)-2162 between the University of Louisville and the Atomic Energy Commission. The authors acknowledge this support and also express their appreciation to the National Science Foundation for Grant NSF-G4074 which provided a recording ultraviolet spectrophotometer. The authors are also indebted to Drs. F. N. Hayes and D. G. Ott, and Miss E. Hansbury of the Los Alamos Laboratories for pulse height measurements.

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(18) Analysis by Micro Tech Laboratories, Skokie, Ill.

Application of the Equilibrium Theory of Solvent Isotope Effects to Deoxymercuration

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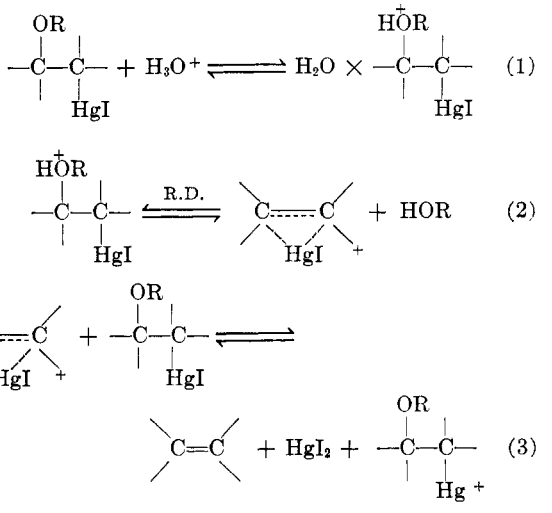
In previous papers[1,2] the mechanism of deoxymercuration induced by nonhalogen acids has been discussed, and evidence favoring a prototropic equilibrium followed by a rate-determining reaction of the protonated substrate was presented. The suggested mechanism is shown in Equations 1–3.



For such a mechanism it would be expected that the equilibrium theory of solvent isotope effects[3] would successfully predict the dependence of rate on solvent deuterium content in partially deuterated water when R is an alkyl group. Although the precision was inadequate for a definite conclusion, the work on 2-methoxy-1-iodomercuripropane (I) suggested that there were systematic differences between observed and predicted rates.[1]

The reason for the lack of precision in the earlier work was that I is deoxymercurated at an inconveniently high rate. The dependence of rate on solvent deuterium content has now been examined for 2-methoxy-1-iodomercuriethane (II). Deoxymercuration of II is slower than deoxymercuration of I by a factor of about 10, so that considerably better precision could be obtained. The present results are in accord with the predictions of the equilibrium theory of solvent isotope effects.[3]

Rates were obtained spectrophotometrically at 25° by following the build-up of the mercuric iodide absorption at 2800 Å. The initial substrate concentration was 3×10^{-5} and the acid was always in large excess. Reactions were followed to 50–80% of completion. With a large excess of acid the mechanism shown in Equations 1–3 leads to the rate law shown in Equation 4,

$$k_1 = \frac{2.303}{2(t - t_0)} \log \frac{(D_\infty - D_0)}{(D_\infty - D_t)} \qquad (4)$$

where k_1 is the pseudo first-order rate constant and D_t is the optical density at time t.[1] The quantity $\log [(D_\infty - D_0)/(D_\infty - D_t)]$ was evaluated from semilogarithmic plots of $(D_\infty - D_t)$ *vs.* t. A typical example of such a plot is shown in Fig. 1. None of the present plots showed the negative curvature mentioned previously,[1] but such curvature was not specifically sought.

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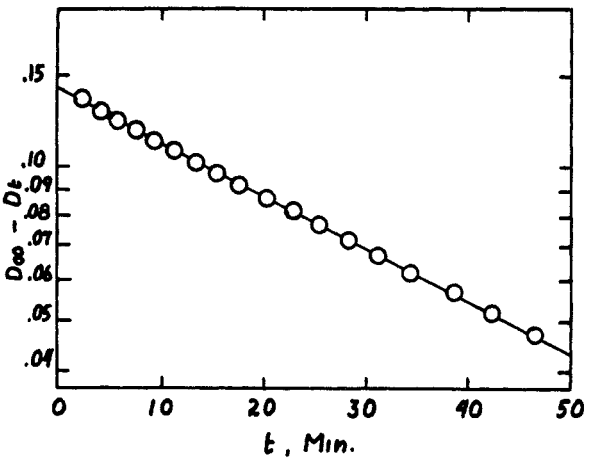

Fig. 1. Typical semilogarithmic plot of $(D_\infty - D_t)$ *vs.* t. The circles are not error circles; they merely identify the points

In undeuterated water, 9 values of k_1 were obtained at acid concentrations ranging from 1.21×10^{-1} to 8.47×10^{-3}. The mean value of $k_2^{H_2O}$ ($k_2 = k_1/(H^+)$) was 3.31×10^{-2}, the average deviation from the mean was 0.07×10^{-2} and the probable error of the mean was 0.02×10^{-2}.[4] No systematic variations in k_2 with acid concentration could be observed. Fourteen determinations of k_2 were made in partially deuterated solutions, the deuterium content ranging up to 98.0 atom %.

Purlee[3] has recently reworked the equilibrium theory of solvent isotope effects, introducing modern values for the various parameters. From his work the rate constant, k_2^n, in a solvent containing 100 n atom % deuterium, is given by Equation 5.

$$\frac{k_2^n}{k_2^{H_2O}} = \frac{1}{Q'(n)}\left[1 - n\left(\frac{k_2^{D_2O}}{3.32k_2^{H_2O}} - 1\right)\right] \qquad (5)$$

In Equation 5, $Q'(n)$ is an empirically determined function of n, tabulated by Purlee,[3] and $k_2^{D_2O}$ is the rate constant in pure D_2O. It has been customary[3] to plot calculated and observed values of $k_2^n/k_2^{H_2O}$ against n. This procedure has two disadvantages: (1) $k_2^{D_2O}$ is not usually available from direct measurements and must be obtained by a short extrapolation; (2) the resulting plots are nonlinear. In the present work it seems desirable to rearrange Equation 5 to get Equation 6, which gives the quantity $Q'(n)k^n$ as a linear function

$$Q'(n)k_2^n = k_2^{H_2O} + n\left(\frac{3.32k_2^{H_2O} - k_2^{D_2O}}{3.32}\right) \qquad (6)$$

of n with intercept k^{H_2O} and slope $(3.32\ k_2^{H_2O} - k_2^{D_2O})/3.32$.[5] Fig. 2 shows the plot of $Q'(n)k_2^n$ *vs.* n obtained from the present data.

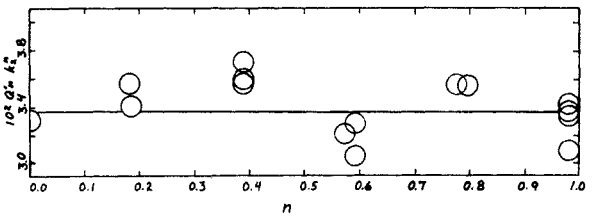

Fig. 2. A plot of $Q'(n)k_2$ *vs.* n. The circles show the error that would be introduced into $Q'(n)k_2^n$ by an uncertainty of ~2% in k_2^n. The latter is the average deviation from the mean for rate constants in H_2O. The point for $n = 0$ is the mean of nine determinations. The line is the least-squares slope

The best straight line, obtained by the method of least squares from all 23 pieces of data, has a slope of 0.000 (apparently accidental) and an intercept, $k_2^{H_2O}$, of 3.37×10^{-2} 1. mole^{-1} sec.$^{-1}$ From the zero slope and the least-squares value of $k_2^{H_2O}$, $k_2^{D_2O}$ has a value of 11.2×10^{-2} 1. mole^{-1} sec.$^{-1}$, and $k_2^{D_2O}/k_2^{H_2O}$ is 3.32. This value is similar to and more accurate than solvent isotope effects previously reported for closely related reactions.[1,2]

The average deviation of the points from the line corresponds to a 5% uncertainty in the quantity $Q'(n)k_2^n$. This is somewhat larger than the average deviation from the mean value of the rate constants in H_2O, but the deviations are not systematic and the fraction D is involved here as an additional variable, because $Q'(n)$ is a function of n. This result is in accord with the expectations following from the suggested mechanism and gives further support to that mechanism.

EXPERIMENTAL

2-Methoxy-1-iodomercuriethane was prepared by the method of Schroeller, Schrauth, and Essers,[6,7] and had a m.p. of 42.5° (uncorr.). Its m.p. has previously been reported to be 42°.[7] Its infrared spectrum was about what one would expect of an aliphatic ether.

Deuterium oxide was obtained from Stuart Oxygen Co. and was certified to be >99.5% D. Three determinations of its deuterium content were made during the course of the kinetic measurements, by determining its density.[8] The results indicated 98.3, 97.5, and 99.7 atom % D, and the D_2O used was all assumed to be 98.5 atom % D, the average of the three.

Methods of making up standard acids and solvents, and the technique of measuring rates have been described previously.[1] The substrate, II, was handled as a stock solution in methanol, with the result that all solutions in which rates were measured contained 2% of methanol by volume. It has been shown, however, that small quantities of methanol have little or no effect on the rate of reactions of this type.[1]

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The Kolbe Electrolysis in Dimethylformamide

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Previous reports[1] from this laboratory have indicated the efficacy of *N,N*-dialkylamides in encouraging the dimerization of cathodically generated organic free radicals. This note describes an extension of the principle to anodic syntheses and presents the results of attempts to improve the yield of dimer in the Kolbe electrolysis[2] of two organic acids.

The most commonly used solvents for the Kolbe electrosynthesis are methanol and water. To a varying degree the Kolbe dimer is accompanied by ethers, alcohols, esters, and monomeric paraffins and olefins.[3] The failure to isolate higher yields of dimer in many of the reactions can be ascribed in part to diversion of the intermediate by reaction with the solvent. To obviate this difficulty a nonreacting, highly polar solvent, dimethylformamide, was used as the electrolysis medium.

The electrolysis of diphenylacetic acid in methanol has been studied previously by Riccobini[4] and by v. d. Hoek and Nauta.[5] In methanol-pyridine mixtures, these workers obtained 6% and 8.9% respectively of tetraphenylethane. Among other products, the latter workers obtained 42.6% of methyl benzhydryl ether. In our hands the electrolysis of diphenylacetic acid in methanol with triethylamine added as the base afforded an 80% yield of methyl benzhydryl ether identified by infrared comparison with authentic material. No tetraphenylethane could be isolated. Likewise, Linstead, Shephard, and Weedon[6] obtained a 73% yield of benzhydrol on saponification of the acetate formed from the electrolysis of diphenylacetic acid in acetic acid.

When the electrolysis medium was changed to dimethylformamide, a 24% yield of tetraphenylethane was obtained. This experiment was conducted for the isolation of only the Kolbe dimer and no attempt was made to find other products.

No description of the Kolbe electrolysis of hydratropic acid could be found in the literature and it was studied in somewhat more detail. Triethylamine again served as the base and the electrolysis was performed in methanol and in dimethylformamide.

In methanol the products obtained in minor amounts included styrene, α-phenethyl alcohol and acetophenone. The major products were 21% of 2,3-diphenylbutane (*meso* and *dl*) and 20% of methyl α-phenethyl ether. The products were analyzed and identified through infrared spectroscopy, vapor phase chromatography and formation of derivatives.

All of the products can be readily explained by the intermediate formation of an α-methylbenzyl radical which can dimerize, react with the solvent or with radicals generated from the solvent, be oxidized, or lose a hydrogen atom.

In dimethylformamide as the solvent the amount of dimer was doubled. 2,3-Diphenylbutane (*meso* and *dl*) was isolated in 41% yield and α-phenethyl alcohol was obtained in 8.2% yield. The latter product could arise from the reaction of the intermediary radical with water present in the dimethylformamide.

It thus appears that dimethylformamide is a good solvent in which to perform the Kolbe electrosynthesis to the relative exclusion of the common side products.

EXPERIMENTAL

All melting points and boiling points are uncorrected. A Perkin-Elmer *154B* vapor fractometer with a "K" column and helium as the carrier gas was used for analysis.

Electrolysis procedure. The electrolysis cell consisted of a 150 ml. tall-form beaker containing the appropriate solution. The cell was cooled with an ice water bath and the cell contents were mixed with a magnetic stirrer. The electrodes were pieces of smooth platinum, 2 cm. × 3 cm., 1 cm. apart and totally immersed in the solution. Current was supplied by a voltage regulated D.C. power supply. An ammeter was connected in series. The initial and final applied voltages for each experiment are indicated. The current was 0.4 amp. and did not vary more than 10% during any of the electrolyses. In each case a solution of 0.1 mol. of the acid, 3 ml. of triethylamine, and 100 ml. of the solvent was used.

Electrolyses. Diphenylacetic acid in methanol. The solution was electrolyzed for 20 hr. and the voltage was increased from 95 volts to 135 volts during the electrolysis. The methanol was partially evaporated at room temperature and the dark residue was poured into a liter of salt water and extracted four times with chloroform. The extract was washed twice with saturated sodium bicarbonate solution and several times with water. It was dried over magnesium sulfate and the chloroform was distilled, leaving a dark tar which would not crystallize. Distillation at 3 mm. gave 16 g. (80%) of methyl benzhydryl ether. Redistillation afforded 15 g., b.p. 86–90° at 0.3 mm., n_D^{28} 1.5623 (reported[7]

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(7) C. C. Price and G. Berti, *J. Am. Chem. Soc.*, **76**, 1207 (1954).

n_D^{20} 1.5685). The infrared spectrum of an authentic sample was identical with that of the electrolysis product.

Diphenylacetic acid in dimethylformamide. The solution was electrolyzed for 17.8 hr. and the voltage was increased from 130 volts to 220 volts during the electrolysis. The reaction mixture was poured into water and extracted three times with ether. Some organic material remained suspended in the ether layer and it was filtered, air dried, and crystallized from chloroform. The ether extract was washed with water, sodium bicarbonate solution, and again with water. The ether was distilled *in vacuo* and the residue was crystallized from chloroform. A further crop of crystals was obtained on concentration of the combined chloroform mother liquors.

A total of 4 g. (24%) of crude product was obtained and was recrystallized from chloroform, m.p. 207–208°. A mixed m.p. with authentic tetraphenylethane[8] was undepressed at 206–207°.

Hydratropic acid[9] *in methanol.* The solution was electrolyzed for 10.7 hr. and the voltage was increased from 80 volts to 120 volts during the electrolysis. The reaction mixture was poured into a liter of salt water and was extracted three times with ether. The ether was washed successively with water, saturated sodium bicarbonate solution, water, 1:1 hydrochloric acid, water, sodium bicarbonate solution, and again with water. After drying over magnesium sulfate the ether was distilled through a Vigreux column and the yellowish residue was distilled at 19 mm. A clear liquid, 3.1 g., b.p. 56–60°, n_D^{26} 1.4950 (reported[10] for methyl α-phenethyl ether n_D^{25} 1.4911) was obtained as the first fraction. Analysis by vapor phase chromatography showed it to consist of 87% of α-phenethyl methyl ether, 3% of styrene (dibromide, m.p. 70–71°, reported[11] m.p. 73°) and a third unidentified component.

The residue was a tan oil, 5.9 g., which solidified on cooling. Crystallization from methanol afforded 721 mg. (6.9%) of solid, m.p. 122–123°, mixed m.p. with authentic *meso*-2,3-diphenylbutane, 122–123°.

The methanol mother liquor was distilled at 0.08 mm. through a short path still. Two fractions were collected: (1) 2.262 g., n_D^{28} 1.5408 and (2) 1.042 g., n_D^{28} 1.5523. Analysis by vapor phase chromatography indicated the following total yield: *meso* and DL-2,3-diphenylbutane, 2.2 g. (21%); α-phenethyl methyl ether, 2.7 g. (19.9%); α-phenethyl alcohol, 0.18 g. (1.5%); and acetophenone, traces.

The infrared spectra of fractions (1) and (2) confirm the presence of the identified substances. A pair of bands at 5.88μ and 7.96μ seem to indicate that the unisolated and unidentified substance retained by the column is an ester.

Hydratropic acid in dimethylformamide. The solution was electrolyzed for 10.3 hr. and the voltage was increased from 130 volts to 260 volts during the electrolysis. The reaction mixture was poured into a liter of salt water and extracted four times with 150-ml. portions of ether. The ether extract was washed successively with water, 1:1 hydrochloric acid, water, saturated sodium bicarbonate solution, again with water, and dried over magnesium sulfate. The ether was distilled through a Vigreux column and the residue was taken up in methanol. Cooling afforded 1.32 g. of *meso*-2,3-diphenylbutane, m.p. 116–120°. The methanol mother liquor was distilled *in vacuo* and three fractions were obtained: (1) 0.7 g., b.p. 96–112° at 15 mm., n_D^{25} 1.5170; (2) 0.4 g., b.p. 112–145° at 15 mm., n_D^{25} 1.5238; (3) 2.8 g., b.p. 115–145° at 0.8 mm., n_D^{25} 1.5455; a further 0.1 g. of *meso*-2,3-diphenylbutane was obtained as a solid in the distillation apparatus. Fractions (1), (2), and (3) were analyzed by vapor phase chromatography.

The total yield of *meso* and *dl*-2,3-diphenylbutane was 4.3 g. (41%) and of α-phenethyl alcohol, 1 g. (8.2%).

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(8) F. J. Norris, R. Thomas, and B. M. Brown, *Ber.*, **43**, 2959 (1910).

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Palladium Catalysts. IX.[1] Kinetic Studies

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Previous papers report that the qualitative character of palladium-on-carbon catalysts may be influenced by such factors as the presence of other metals,[4] the ratio of metal to carrier,[5] and by the nature of the anion present when the metal is deposited on the carrier.[1,6] There is also evidence that a product formed during the hydrogenation reaction may inhibit the catalytic reaction.[7] Results of further studies along these lines are now presented.

In order to control external variables during the hydrogenation reaction the apparatus shown schematically in Fig. 1 was designed. With it one may maintain a constant pressure of hydrogen within the vicinity of one atmosphere throughout the entire course of the reaction; the rate of agitation is constant; the temperature may be controlled to within 0.2°. Results obtained with this apparatus permit the observation of the kinetic order of the reaction and allow for more valid comparison of one reaction with another and, it is hoped, contribute to a better understanding of the catalytic mechanisms.

In Fig. 2 are shown graphically the effects of temperature variation on the reduction of nitrobenzene. In all instances the rate of hydrogen absorption with respect to substrate is zero order as was previously observed by Rampino and Nord.[8]

The phenylcarbonyl compounds with one molecule of hydrogen form the corresponding carbinols, and with two molecules of hydrogen undergo

(1) For number VIII see W. D. Cash, F. T. Semeniuk, and W. H. Hartung, *J. Org. Chem.*, **21**, 999 (1956).

(2) Sharp and Dohme Fellow 1952–1955. Present address: Polychemicals Department, E. I. du Pont de Nemours and Company, Wilmington, Del.

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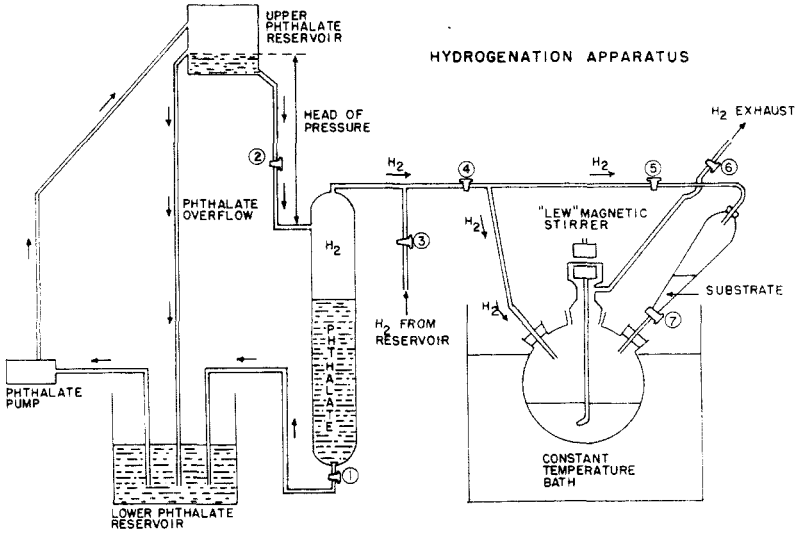

Fig. 1. Scheme of hydrogenation apparatus. The upper phthalate reservoir may be adjusted up or down, depending on the barometric reading and the vapor pressure of the solvent at the temperature of the reaction. Di-*n*-butyl phthalate, because of its negligible vapor pressure, is used to displace the hydrogen in the gas buret. The air in the apparatus may be swept out and displaced by hydrogen through stopcock 3 and out at stopcock 6. The pressure is measured by attaching a manometer at stopcock 3. Constant rate of stirring is maintained by a constant voltage regulator and the speed is measured with a hand tachometer

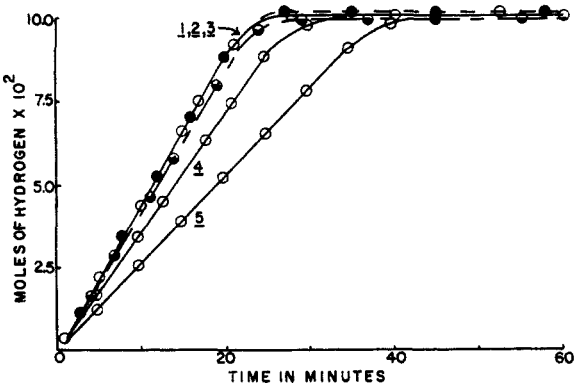

Fig. 2. Reduction of nitrobenzene. Solvent: ethanol. Total volume: 100 ml. 0.033 mol. nitrobenzene. 2 g. of catalyst, 20 mg. $PdCl_2$ per gram. Curves 1, 2, and 3 at 35°; curve 4 at 30°; curve 5 at 25°

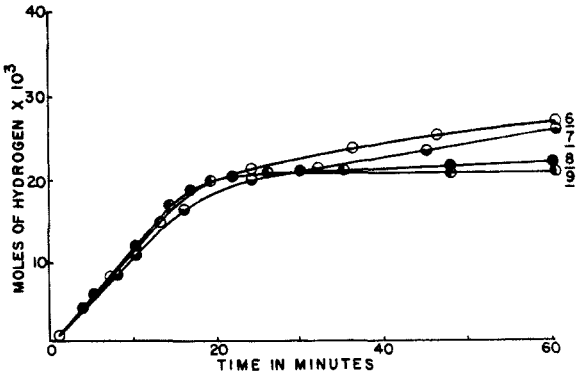

Fig. 3. Reduction of propiophenone. Solvent: ethanol. Total volume: 100 ml. 0.02 mol. propiophenone. 2.0 g. of catalyst, 50 mg. $PdCl_2$ per gram. Curve 6: no propylbenzene; curve 7: 0.040 mol. propylbenzene; curve 8: 0.060 mol. propylbenzene; curve 9: 0.10 mol. propylbenzene

hydrogenolysis to form the hydrocarbon. Hartung and Crossley,[9] reported that propiophenone was reduced to propylbenzene without evidence of forming the intermediate carbinol; presumably during a single contact of the substrate with the catalyst two molecules of hydrogen were transferred.[10] The palladium then employed regrettably is no longer available.[11] Subsequent studies have been carried out with catalysts prepared from pure palladium.[12] The results now point to a reduction in two steps, first to the carbinol and then hydrogenolysis to the hydrocarbon. Typical results are shown graphically for propiophenone in Fig. 3. The first half of the reaction is zero order; the second half is indeterminate, the hydrogenolysis of the carbinol being progressively inhibited by the hydrocarbon as it forms in increasing amounts. Thus curve 6 of Fig. 3, for example, had the reaction been continued (as observed in other experiments) would have approached with decreasing slope the value of hydrogen uptake calculated for complete conversion to propylbenzene. Curve 7, showing the reduction of 20 millimoles of propiophenone in the presence of 40 millimoles of propylbenzene, slopes off much earlier; and curves 8 and 9, with 60 and 100 millimoles, respectively, of propylbenzene, become substantially parallel with the time axis when the ketone is reduced to carbinol.

(9) W. H. Hartung and F. S. Crossley, *J. Am. Chem. Soc.*, 56, 158 (1934).

(10) E. W. Reeve (unpublished) later repeated these experiments and was able to detect, by interrupting the reaction, traces of carbinol in the mixture comprised principally of unreduced propiophenone and propylbenzene. This is felt to establish only that with the catalyst then available only a small amount of product was desorbed after the transfer of one molecule of hydrogen into the ketone.

(11) W. H. Hartung and Y.-T. Chang, *J. Am. Chem. Soc.*, 74, 5927 (1952).

(12) *Cf.* footnote 8 in ref. (11).

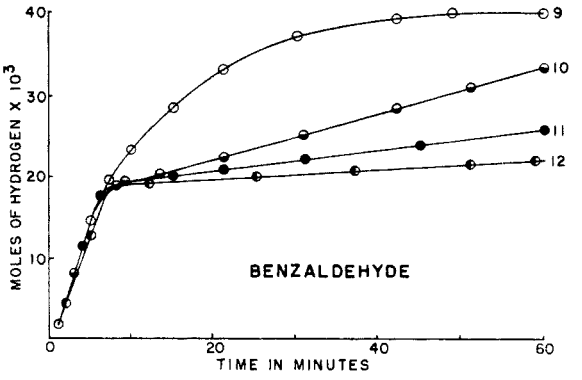

Fig. 4. Reduction of benzaldehyde. Solvent: ethanol. Total volume: 100 ml. 0.020 mol. benzaldehyde. 2 g. of A-50 catalyst.[1] Curve 9: no toluene; curve 10: 0.05 mol. toluene; curve 11: 0.1 mol. toluene; curve 12: 0.30 mol. toluene

[1] For explanation see ref. (1)

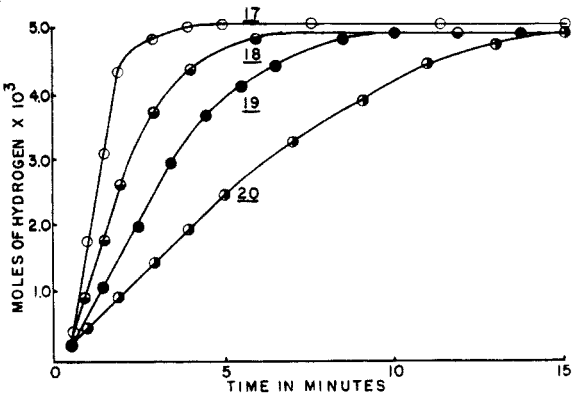

Fig. 6. Reduction of benzyl acetate. Solvent: ethanol. Total volume: 100 ml. 0.005 mol. benzyl acetate. Curve 17: 2 g. of A-100 catalyst; curve 18: 1 g. of A-100 catalyst; curve 19: 0.5 g. of A-100 catalyst; curve 20: 0.25 g. of A-100 catalyst

A similar phenomenon is seen with benzaldehyde, Fig. 4. The reduction to benzyl alcohol proceeds at zero order, and even large amounts of toluene in the solvent have no significant effect on this rate. However, the presence of increasing amounts of toluene have increasing inhibitory effect on the hydrogenolysis of benzyl alcohol.

Other phenylcarbonyl compounds show similar behavior. Desoxybenzoin is rapidly reduced to the carbinol, and the hydrogenolysis of the carbinol then proceeds at a progressively decreasing rate; if diphenylethane is added at the start of the reaction, it has no observable effect on the rate at which the ketone reduces, but has a marked retarding effect on the hydrogenolysis of the carbinol. Acetophenone behaves in an analogous manner.

The hydrogenolysis of benzyl acetate yields interesting results, Figs. 5 and 6. In ethyl acetate solvent the inhibitory effect of the toluene formed during the reaction is sufficiently pronounced to modify the initial zero order to a progressively slowing and indeterminate rate. The addition of toluene at the beginning of the reaction causes earlier deviation. In ethanol solvent the inhibitory effect of the toluene is less pronounced and is absent if adequate catalyst is employed; as the amount of catalyst is decreased, the inhibitory effect becomes correspondingly more pronounced.

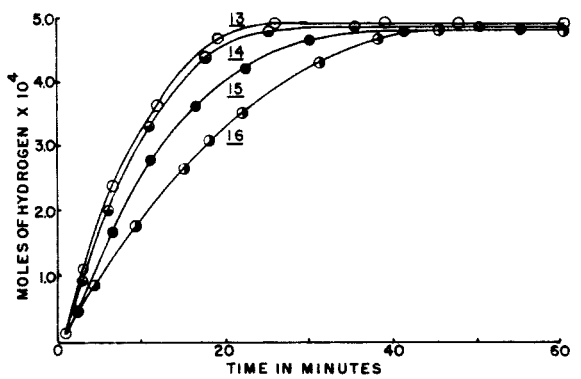

Fig. 5. Reduction of benzyl acetate. Solvent: ethyl acetate. Total volume: 100 ml. 0.005 mol. benzyl acetate. 2 g. of A-100 catalyst.[1] Curve 13: no toluene; curve 14: 0.01 mol. toluene; curve 15: 0.02 mol. toluene; curve 16: 0.04 mol. toluene

[1] For explanation see ref. (1).

A mechanism for the inhibitory effect of propylbenzene in the reduction of the corresponding carbinol is proposed in Fig. 7.

It is not suggested, however, that all deviations from zero order reaction rates are to be attributed to inhibition such as here observed. Another factor that is expected to show similar kinetic results is the erosion or inactivation of the catalyst. A discussion of such phenomena will be delayed until more data become available.

The two-stage hydrogenation as observed with the conversion of phenylcarbonyl compounds to the corresponding hydrocarbon poses an interesting question as to the character of the active sites in the palladium-on-carbon catalysts, especially in view of the observation by Beamer and co-workers[13] that these catalysts have centers which appear to be substrate-specific. It will be observed from Fig. 3 that propylbenzene does not compete with propiophenone for the active sites but does compete with the carbinol; and toluene does not compete with benzaldehyde but does inhibit benzyl alcohol. Does this signify that in the catalyst there are different sites for the carbonyl compound than for the carbinol? This question is all the more interesting since once there was available a catalyst[9] with quite different properties. Further studies are projected.

EXPERIMENTAL

All reagents were carefully purified, and all substrates were "detoxified" by standing in contact for 24 hr. or more with unused Pd-C catalyst.

(13) R. L. Beamer, J. D. Smith, J. Andrako, and W. H. Hartung, *in press*.

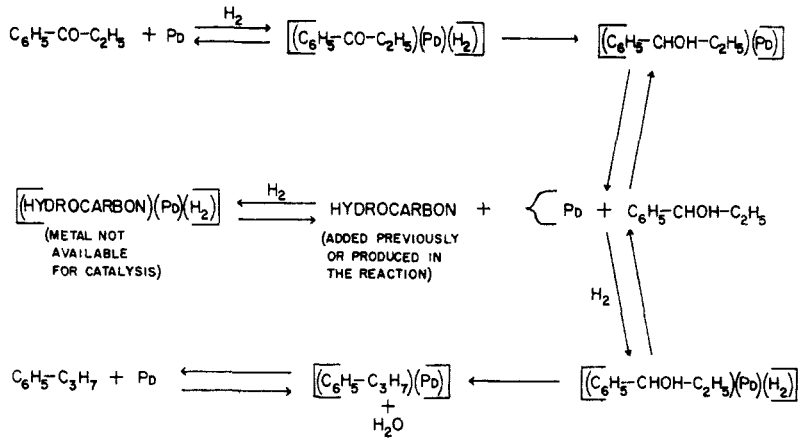

Fig. 7. Mechanism of inhibition

The catalysts were prepared as described in earlier papers of this series.

Acknowledgment. The authors are grateful to the American Platinum Works, now part of Engelhard Industries, Inc., for graciously supplying pure $PdCl_2$.

DEPARTMENT OF CHEMISTRY AND
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o-Hydroxyphenylphosphonic Acid

LEON D. FREEDMAN, G. O. DOAK, AND EDWARD L. PETIT

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Although a number of hydroxy-substituted arylphosphonic acids are known,[1] the preparation of *o*-hydroxyphenylphosphonic acid, the phosphorus analog of salicylic acid, has not previously been accomplished. Kennedy, Lane, and Willans[2] have investigated two possible methods for the synthesis of this phosphonic acid. They found that attempts to demethylate *o*-methoxyphenylphosphonic acid caused cleavage of the carbon-phosphorus bond; and they reported that the diazo reaction could not be used to convert *o*-benzyloxyaniline to *o*-benzyloxyphenylphosphonic acid (which they planned to debenzylate by hydrogenation). The present study was undertaken in the hope of developing a satisfactory method for the preparation of *o*-hydroxyphenylphosphonic acid and related compounds.

As noted by Kennedy, Lane, and Willans,[2] the demethylation of *o*-methoxyphenylphosphonic acid is not a promising route to the synthesis of the corresponding hydroxy compound. In this laboratory we found that after the *o*-methoxy compound was refluxed with 42% hydrobromic acid for 24 hr., over 90% of the phosphorus had been converted to inorganic phosphate. Attempts to replace the bromine in *o*-bromophenylphosphonic acid with the hydroxyl group were also unsuccessful. Thus, heating the *o*-bromo compound with 4*N* sodium hydroxide in an autoclave at 120° resulted in splitting little or no bromine from the ring. In the presence of cuprous oxide the bromine could be replaced by the hydroxyl group. In the process, however, a certain amount of phosphorus was also cleaved from the ring, and we were never able to isolate any *o*-hydroxyphenylphosphonic acid from the reaction mixture. In brief, the results we obtained in trying to convert *o*-methoxy- or *o*-bromophenylphosphonic acid into the hydroxy compound were similar to those reported[3] for the corresponding *para*-substituted acids.

We were successful, however, in obtaining *o*-hydroxyphenylphosphonic acid by the catalytic hydrogenolysis of *o*-benzyloxyphenylphosphonic acid. Several methods for preparing the latter compound were examined. We first investigated the preparation of the acid from the corresponding diazonium fluoborate. Although the diazonium compound could not be prepared by diazotizing *o*-benzyloxyaniline in fluoboric acid, the amine was readily diazotized in hydrochloric acid and the diazonium fluoborate precipitated by the addition of sodium fluoborate. The diazonium salt was then suspended in ethyl acetate and treated with phosphorus trichloride and cuprous bromide under the usual conditions.[4] Steam distillation of the reaction mixture in the customary manner, however, resulted in cleavage of the ether linkage. Accordingly, the conditions were modified to avoid debenzylation; details of the procedure used for iso-

(1) (a) G. B. Arnold and C. S. Hamilton, *J. Am. Chem. Soc.*, **63**, 2637 (1941); (b) G. O. Doak and L. D. Freedman, *J. Am. Chem. Soc.*, **74**, 753 (1952); (c) R. W. Bost and L. D. Quin, *J. Org. Chem.*, **18**, 358 (1953); (d) G. O. Doak and L. D. Freedman, *J. Am. Chem. Soc.*, **75**, 6307 (1953).

(2) J. Kennedy, E. S. Lane, and J. L. Willans, *J. Chem. Soc.*, 4670 (1956).

(3) V. L. Bell, Jr., and G. M. Kosolapoff, *J. Am. Chem. Soc.*, **75**, 4901 (1953).

(4) G. O. Doak and L. D. Freedman, *J. Am. Chem. Soc.*, **73**, 5658 (1951).

lating the desired acid are described in the Experimental section.

We also were able to obtain *o*-benzyloxyphenylphosphonic acid by the reaction between *o*-bromophenylphosphonic acid, benzyl alcohol, and anhydrous potassium carbonate. The desired compound was obtained in only 10% yield. However, we were able to isolate from the reaction mixture a second phosphonic acid in 32% yield. The analysis and ultraviolet absorption spectrum (*cf.* Table I) of this unknown phosphonic acid indicated that it was either 2,2′-diphosphonodiphenyl ether[5] or a hydrate of 2,2′-biphenylenediphosphonic acid. The second possibility was effectively eliminated when we found that the compound lost no weight when heated to 200° for 1 hr. When the compound was heated to 240°, it decomposed to give a 69% yield of diphenyl ether (identified by its b.p. and ultraviolet absorption spectrum) and a residue of inorganic phosphate.[6] There seems little doubt, therefore, that the unknown phosphonic acid must be 2,2′-diphosphonodiphenyl ether.

TABLE I

ULTRAVIOLET ABSORPTION MAXIMA

Compound	λ_{max}, mμ	ϵ_{max}
Phenyl ether[a]	221–225[b]	10,000
	265	1,570
	271	1,850
	278	1,630
o-Phenoxyphenylphosphonic acid[c]	229	9,110
	278.5	3,410
o-Biphenylylphosphonic acid[d]	237	8,220
	274.5	2,030
Unknown phosphonic acid[e]	235.5	7,840
	278.0	3,920

[a] Reagent grade material (Eastman Kodak Co. 104). [b] Shoulder. [c] Prepared as described by L. D. Freedman and G. O. Doak, *J. Org. Chem.*, **23**, 769 (1958). [d] Taken from L. D. Freedman, *J. Am. Chem. Soc.*, **77**, 6223 (1955). [e] Shown to be 2,2′-diphosphonodiphenyl ether (see text). The ε values were calculated on this basis.

o-Hydroxyphenylphosphonic acid at a concentration of 0.01*M* showed significant activity (*i.e.*, at least 50% inhibition compared to the controls) *in vitro* against one strain of *Escherichia coli* and three strains of pathogenic *Staphylococcus aureus:* slight activity at this concentration was found against one strain of *Aerobacter aerogenes.*[7]

EXPERIMENTAL[8]

o-Benzyloxyphenylphosphonic acid. A. From the diazonium fluoborate and phosphorus trichloride. *o*-Nitrophenyl benzyl ether[9] (23.0 g.) was dissolved in 200 ml. of 95% ethanol and shaken for about 2 hr. with Raney nickel and hydrogen at 40 lb. pressure. After the catalyst was removed by filtration, the amine was isolated by evaporating the filtrate to about 20 ml. and cooling in the deep freeze at −25°. The crystals obtained were washed with 5 ml. of petroleum ether and dried *in vacuo*. The yield of *o*-benzyloxyaniline was 87%; m.p. 36.5–37° (lit.[9] 39–40°).

A mixture of 0.2 mol. of the above amine and 150 ml. of 6*N* hydrochloric acid was boiled, with stirring, for about 5 min. to form the amine hydrochloride. The resulting suspension was quickly cooled to 0° and then diazotized with a solution of sodium nitrite. During this reaction, the temperature was kept below 5°. The diazonium fluoborate was then precipitated with a cold solution of sodium fluoborate.[10] The yield was 87%, decomposition temperature about 135°.

o-Benzyloxybenzenediazonium fluoborate (149 g., 0.5 mol.) was suspended in dry ethyl acetate and treated with phosphorus trichloride and cuprous bromide in the usual manner.[4] No evolution of nitrogen occurred until the mixture was warmed to about 55°. After nitrogen evolution had ceased, the reaction mixture was cooled to 5° and hydrolyzed by the dropwise addition of 200 ml. of water. The solution was then concentrated to 400 ml. *in vacuo* at a temperature below 45° and extracted with four 200-ml. portions of ether. The combined ether solutions were then extracted with 1 l. of 10% sodium carbonate solution. The aqueous alkaline solution was then treated with Darco and acidified with concentrated hydrochloric acid to *p*H 0.4, whereupon crude *o*-benzyloxyphenylphosphonic acid crystallized from solution. After recrystallization from aqueous acetone, the yield was 21%; m.p. 156–157°.

Anal. Calcd. for $C_{13}H_{13}PO_4$: C, 59.10; H, 4.96; P, 11.72. Found: C, 59.11; H, 5.25; P, 11.97.

B. From o-bromophenylphosphonic acid and benzyl alcohol. An intimate mixture of 10.0 g. of *o*-bromophenylphosphonic acid,[11] 20 ml. of redistilled benzyl alcohol, 10.0 g. of anhydrous potassium carbonate, and 0.2 g. of copper powder was heated under reflux for a period of 16 hr. The reaction mixture was then diluted with about 35 ml. of water, and the excess benzyl alcohol was removed by steam distillation. The residual liquid[12] from the steam distillation was treated with Darco and then acidified to *p*H 0.4 to obtain crude *o*-benzyloxyphenylphosphonic acid. The yield of the pure acid, after recrystallization, was 1.1 g. (10%).

The original filtrate from the crude *o*-benzyloxyphenylphosphonic acid was acidified further with 10 ml. of concentrated hydrochloric acid and then evaporated to dryness on a steam bath. The residue was further dried in a desiccator over sodium hydroxide. The solid thus obtained was pul-

(5) This possibility was first suggested to us by Professor Robert L. McKee of the University of North Carolina.

(6) It has been known for a long time that heating phosphonic acids at relatively high temperatures may result in splitting of the carbon-phosphorus bond. Thus, A. Michaelis and C. Mathias [*Ber.*, **7**, 1070 (1874)] found that phenylphosphonic acid decomposes at 250° into benzene and metaphosphoric acid. More recently, H. Z. Lecher, T. H. Chao, K. C. Whitehouse, and R. A. Greenwood [*J. Am. Chem. Soc.*, **76**, 1045 (1954)] have reported that 2-naphthylphosphonic acid, when heated in a sealed tube at 275° for 24 hr., gives naphthalene and metaphosphoric acid. Unpublished work from this laboratory indicates that phenylphosphonic acids containing alkyl, aryl, alkoxy, phenoxy, or halogen substituents undergo a similar type of decomposition at 240°.

(7) We are grateful to Dr. J. D. Thayer, Chief of the Biology Section of our laboratory, for testing this compound.

(8) Melting points were taken as previously described; *cf.* ref. 4. Phosphorus was determined by the method of B. C. Stanley, S. H. Vannier, L. D. Freedman, and G. O. Doak, *Anal. Chem.*, **27**, 474 (1955).

(9) A. Sieglitz and H. Koch, *Ber.*, **58B**, 78 (1925).

(10) A. Roe, *Org. Reactions*, **V**, 203 (1949).

(11) G. O. Doak and L. D. Freedman, *J. Am. Chem. Soc.*, **75**, 683 (1953).

(12) Bromide ion analyses on aliquots of this liquid showed that all the bromine had been split from the ring.

verized and then extracted for several hours with 250 ml. of ether in a Soxhlet apparatus.[13] The material in the thimble was then extracted for 8 hr. with 250 ml. of absolute ethanol. The alcoholic solution was evaporated to dryness, and the residue was recrystallized from 6*N* hydrochloric acid. The yield of pure *2,2'-diphosphonodiphenyl ether* was 2.0 g. (32%); m.p. 233–235°.

Anal. Calcd. for $C_{12}H_{12}O_7P_2$: C, 43.65; H, 3.66; P, 18.76; neut. equiv. (for two ionizable hydrogens per molecule), 165.1. Found: C, 43.46; H, 3.96; P, 18.50; neut. equiv. (to *p*H 4.3), 168.2.

o-Hydroxyphenylphosphonic acid. A solution of 5.28 g. of *o*-benzyloxyphenylphosphonic acid in 50 ml. of 95% ethanol was shaken with 5.0 g. of 10% palladium-on-carbon[14] under an initial hydrogen pressure of 40 lb. After the uptake of hydrogen ceased, the catalyst was removed by filtration and the solvent distilled off under vacuum. The resulting sirup solidified when dried in a desiccator over calcium chloride. The crystals obtained were further dried *in vacuo* at 100°. The yield was quantitative, m.p. 124–127°.

Anal. Calcd. for $C_6H_7O_4P$: C, 41.39; H, 4.05; P, 17.79. Found: C, 41.17; H, 4.27: P, 17.51.

Absorption spectra measurements. The ultraviolet absorption spectra were determined in 95% ethyl alcohol by the procedure previously described.[15]

Acknowledgment. The authors wish to acknowledge the assistance given by Mrs. Betty Pegram Herring throughout the course of this research.

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(13) This step served to remove a small amount of colored material.

(14) R. Mozingo, *Org. Syntheses*, **Col. Vol. III,** 687 (1955).

(15) H. H. Jaffé and L. D. Freedman, *J. Am. Chem. Soc.*, **74,** 1069 (1952).

9-Substituted-9-hydroxy-Δ^{10}-ergolenes

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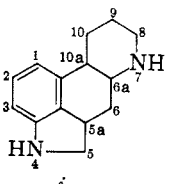
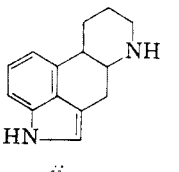
Received August 7, 1959

Numerous times during the course of our work on the total synthesis of lysergic acid[1] we found it appropriate to submit certain of the intermediates for pharmacological evaluation. On one such occasion we became interested in some 9-substituted-9-hydroxy-7-methyl-Δ^{10}-ergolenes (I).[2]



i



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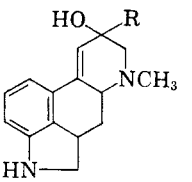

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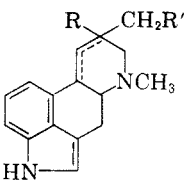

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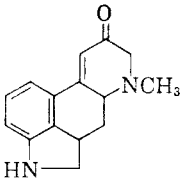
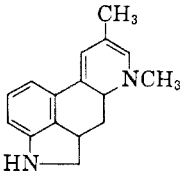


III

We were further intrigued by the possibility of synthesizing several new alkaloids which have been obtained by other workers during their studies on the fermentation of various strains of the ergot fungus.[3] Several members of this group of alkaloids are agroclavine (II, Δ^9, R′ = H), elymoclavine (II, Δ^9, R′ = OH), penniclavine (II, Δ^{10}, R = R′ = OH), and setoclavine (II, Δ^{10}, R = OH, R′ = H). The desired synthetic compounds, I (R = methyl, ethyl, allyl, phenyl), were prepared by the action of the appropriate organo-lithium compound or Grignard reagent on 9-keto-7-methyl-Δ^{10}-ergolene (III).[1] Except in the case of the phenyl substituted compound, it was necessary to employ an extremely large excess of reagent in order to obtain the product. Subsequent efforts to convert I (R = CH_3) to setoclavine by dehydrogenation were unrewarding.

The dehydration of I (R = CH_3) to 7,9-dimethyl-$\Delta^{8,10}$-ergoladiene (IV) was accomplished by the use



IV

of boron trifluoride. Evidence for the endocyclic position of the newly introduced double bond was the absence of terminal methylene absorption in the infrared spectrum.

Pharmacologically, these materials are characterized by their oxytocic, hypothermic, and central nervous system activity. Details of these studies will be published elsewhere.

(1) E. C. Kornfeld, E. J. Fornefeld, G. B. Kline, M. J. Mann, D. E. Morrison, R. G. Jones, and R. B. Woodward, *J. Am. Chem. Soc.*, **78,** 3087 (1956).

(2) In order to avoid the cumbersome nomenclature of this multi-ring system, we have assigned the generic name ergolane to 4, 5, 5a, 6, 6a, 7, 8, 9, 10,10a-decahydroindolo-[4,3-*fg*]quinoline (*i*). The name ergoline has geen assigned to the corresponding Δ^5-compound (ii) by W. A. Jacobs and R. G. Gould, Jr., *J. Biol. Chem.*, **120,** 142 (1937).

(3) M. Abe, T. Yamano, Y. Kozu, and M. Kusumoto, *J. Agr. Chem. Soc. Japan*, **25,** 458 (1952); **29,** 364, 697 (1955); M. Abe, and S. Yamatodani, *J. Agr. Chem. Soc. Japan*, **28,** 501 (1954); *Bull. Agr. Chem. Soc. Japan*, **19,** 92, 94, 161 (1955); M. Pöhm, *Die Pharmazie*, **11,** 110 (1956); A. Stoll, A. Brack, H. Kobel, A. Hofmann, and R. Brunner, *Helv. Chim. Acta*, **37,** 1815 (1954); A. Hofmann, R. Brunner, H. Kobel, and A. Brack, *Helv. Chim. Acta*, **40,** 1358 (1957).

EXPERIMENTAL

Melting points were determined in soft glass capillary tubes and are uncorrected.

9-Hydroxy-7,9-dimethyl-Δ^{10}-ergolene. Methyllithium in ether solution was prepared by dropwise addition of methyl iodide (148 g., 1.04 mol.) to a stirred suspension of 14.6 g. (2.08 mol.) of lithium ribbon in 350 ml. of dry ether. The solution was stirred for 0.5 hr. after the addition was complete and then with ice-bath cooling there was added slowly a solution of 10 g. (0.042 mol.) of 9-keto-7-methyl-Δ^{10}-ergolene in 200 ml. of warm anisole. The reaction mixture was stirred for several hours at room temperature, allowed to stand overnight, and then decomposed by slow addition of 150 ml. of ice water. Part of the product which was insoluble in both the organic and aqueous phases separated at this point and was removed by filtration and crystallized from methanol; yield, 3.72 g., m.p. 206–208°. Another crop was obtained from the ether-anisole layer by extraction with dilute hydrochloric acid, neutralization of the extract with sodium bicarbonate and extraction with chloroform. The chloroform extract on evaporation gave 0.63 g. of the methyl carbinol. The total yield was 4.35 g. (41%). A sample was recrystallized from methanol for analysis, m.p. 209–212°.

Anal. Calcd. for $C_{16}H_{29}N_2O$: C, 74.96; H, 7.86; N, 10.93. Found: C, 75.01; H, 7.98; N, 10.82.

9-Ethyl-9-hydroxy-7-methyl-Δ^{10}-ergolene. Ethylmagnesium bromide was prepared in the usual fashion in a 1 l. 3-necked flask using 113 g. of ethyl bromide, 25.4 g. of magnesium, and 350 ml. of ether. After addition of the ethyl bromide was complete, the solution was stirred for 30 min. and then cooled in an ice bath. A solution of 10 g. of 9-keto-7-methyl-Δ^{10}-ergolene in 200 ml. of warm anisole was then added during 20 min. and the reaction mixture was allowed to stir for 2 hr. at room temperature and then to stand overnight. Decomposition of the complex was carried out by the addition of 140 ml. of saturated aqueous ammonium chloride solution at 0°. The organic layer was decanted and the sludge was extracted with chloroform. About 25 ml. of 50% aqueous sodium hydroxide was added and the sludge was again extracted with chloroform. The combined chloroform extract was washed with water and then extracted with three portions of dilute hydrochloric acid, each containing 5 ml. of the concentrated acid. The acid extracts were carboned and neutralized with an excess of sodium bicarbonate and then extracted with four 75 ml. portions of warm chloroform. The extracts were warmed to keep the product in solution, dried quickly over magnesium sulfate, and concentrated *in vacuo*. The residue was taken up in a little methanol, and the ethyl carbinol was filtered and washed with methanol and ether; yield, 2.67 g. (24%). A sample for analysis was recrystallized from methanol containing a little water, m.p. 204–206° (dec.).

Anal. Calcd. for $C_{17}H_{22}N_2O$: C, 75.52; H, 8.20; N, 10.36. Found: C, 75.80; H, 8.77; N, 10.29.

9-Allyl-9-hydroxy-7-methyl-Δ^{10}-ergolene. The allyl Grignard reagent was prepared in a 3 l. 3-necked flask by the addition during 5–6 hours of a solution of 126 g. (1.1 mol.) of allyl bromide in 625 ml. of dry ether to a stirred suspension of 76 g. (3.1 mol.) of magnesium in 250 ml. of ether. Stirring was continued for 15 min., after which the reaction mixture was cooled in an ice bath. A solution of 10 g. of 9-keto-7-methyl-Δ^{10}-ergolene in 200 ml. of warm anisole was then added during 10 min. Stirring was continued at room temperature for 3 hr., and the mixture was allowed to stand overnight. It was then cooled and decomposed by addition of 140 ml. of saturated aqueous ammonium chloride solution. Ethyl acetate (300 ml.) was added and the organic layer was decanted. The sludge was extracted with ethyl acetate and then with chloroform. Fifty milliliters of 50% aqueous sodium hydroxide was then added, and the sludge was again extracted with chloroform. The chloroform extracts were combined and extracted five times with dilute hydrochloric acid (each portion containing 5 ml. of concentrated acid). The combined acid extract was neutralized with an excess of sodium bicarbonate and the allyl carbinol was extracted with three 200 ml. portions of chloroform. The combined extract was dried over magnesium sulfate and evaporated *in vacuo*. The product was digested with methanol, filtered and washed with methanol and ether; yield, 6.64 g. (62%). A sample was recrystallized from ethanol containing a little water, m.p. 198–202° (dec.).

Anal. Calcd. for $C_{18}H_{22}N_2O$: C, 76.56; H, 7.85; N, 9.92. Found: C, 76.75; H, 8.34; N, 9.59.

9-Hydroxy-7-methyl-9-phenyl-Δ^{10}-ergolene. Phenylmagnesium bromide was prepared in the usual way from 15.7 g. (0.1 mol.) of bromobenzene and 2.9 g. (0.12 mol.) of magnesium in 200 ml. of absolute ether. A solution of 4.8 g. (0.02 mol.) of 9-keto-7-methyl-Δ^{10}-ergolene in 50 ml. of pure dioxane was then added with stirring during 10 min. Stirring was continued for 2 hr. and then the solution was allowed to stand at room temperature overnight. Saturated aqueous ammonium chloride solution (27 ml.) was added to decompose the complex and the ether layer was decanted. The residual sludge was extracted once with ether and twice with chloroform, and the combined extract was dried over magnesium sulfate and concentrated *in vacuo*. The residual phenyl carbinol, 0.7 g. (11%), was crystallized from ethanol, m.p. 219–220° (dec.).

Anal. Calcd. for $C_{21}H_{22}N_2O$: C, 79.21; H, 6.96; N, 8.80. Found: C, 79.12; H, 7.05; N, 8.67.

7,9-Dimethyl-$\Delta^{8,10}$-ergoladiene. 7,9-Dimethyl-9-hydroxy-Δ^{10}-ergolene, 0.5 g., was mixed with 20 ml. of acetonitrile and 5 ml. of boron trifluoride–etherate. The solution was allowed to stand at room temperature for 24 hr. and then poured into an excess of ice and water. The mixture was neutralized with sodium bicarbonate and extracted with chloroform. The extract was dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The residue was crystallized from methanol containing a little ethyl acetate; yield, 0.34 g. (74%), m.p. 122–126°.

Anal. Calcd. for $C_{16}H_{18}N_2$: C, 80.63; H, 7.61; N, 11.76. Found: C, 80.21; H, 7.60; N, 12.09.

Ultraviolet absorption maxima are at 253, 293 and 306 mμ (neutral) and 213, 222, 230, 238, 288, and 309 mμ (acidic).

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Biologically Active 2,4-Dichlorophenoxyacetylated Amino Acids

CHARLES F. KREWSON AND JOHN W. WOOD[1]

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This report on amino acid derivatives of 2,4-dichlorophenoxyacetic acid, designated 2,4-D, is an extension of previous studies[2–8] which have dem-

(1) Present address, Laboratory of Chemical Pharmacology, National Cancer Institute, National Institutes of Health, Bethesda, Md.

(2) W. A. Gentner and W. C. Shaw, 1957 Field Results, Crops Research Division, ARS, U. S. Dept. Agr., Beltsville, Md., Processed Rept. CR-25-58 (January 1958).

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TABLE I

PHYSICAL AND ANALYTICAL DATA OF AMINO ACID DERIVATIVES OF 2,4-DICHLOROPHENOXYACETIC ACID

N-(2,4-Dichlorophenoxyacetyl)-	M.P., °C. (Corr.)[a]	Yield, %		Formula	Analyses[b]					
					Cl, %		N, %		Optical rotation	
		Crude	Refined		Calcd.	Found	Calcd.	Found	$[\alpha]_D^{25}$	C, g./100 ml[c]
D-alanine	203.7–204.7	73.8	51.6	$C_{11}H_{11}Cl_2NO_4$	24.28	24.24	4.80	4.84	−12.8 ± 0.4	5.77
β-alanine	172.8–174.0[d]	82.5	72.6		24.28	24.27	4.80	4.79		
L-asparagine	186.4–187.4	73.2	57.1	$C_{12}H_{12}Cl_2N_2O_5$	21.15	21.14	8.36	8.27	+17.4 ± 0.5	4.46
D-asparagine	183.3–184.3	82.6	60.6		21.16	21.24	8.36	8.14	−18.5 ± 0.4	4.56
DL-asparagine	180.2 181.3[e]	82.8	47.1		21.16	21.21	8.36	8.11		
D-glutamic acid	184.0–185.0[f,g]	17.1	12.4	$C_{13}H_{13}Cl_2NO_5$	20.25	20.10	4.00	4.09	−12.5 ± 1.5	0.89
Glycylglycine	184.0–185.0[g]	74.4	48.8	$C_{12}H_{12}Cl_2N_2O_5$	21.16	20.80	8.36	8.11		
L-isoleucine	143.4–143.9	71.7	41.4	$C_{14}H_{17}Cl_2NO_4$	21.22	21.23	4.19	4.21	+10.0 ± 0.3	7.80
D-isoleucine	143.9–145.1	71.1	59.9		21.22	21.19	4.19	4.22	−10.1 ± 0.3	8.96
D-leucine	155.7–156.7	82.4	70.6		21.22	21.14	4.19	4.21	+16.0 ± 0.4	5.19
L-serine	180.0–183.0[h]		19.5	$C_{11}H_{11}Cl_2NO_5$	23.02	23.07	4.55	4.51	+22.2 ± 0.4	2.00[i]
D-serine	171.8–172.8[j]	58.7	13.6		23.02	22.38	4.55	4.67	−25.3 ± 0.4	5.29
L-threonine	131.0–132.5[k]		20.0	$C_{12}H_{13}Cl_2NO_5$	22.01	21.82	4.34	4.62	+13.8 ± 0.6	2.00
D-threonine	131.0–132.0[f]	62.2	42.6		22.01	21.92	4.34	4.32	−13.1 ± 0.4	5.47
L-tryptophane	152.2–153.4	98.9	70.1	$C_{19}H_{16}Cl_2N_2O_4$	17.40	17.32	6.88	6.88	−13.0 ± 0.3	8.22
D-tryptophane	177.2–178.2	89.2	79.2		17.40	17.41	6.88	6.86	+13.0 ± 0.3	9.09
L-valine	164.2–164.7	79.8	69.4	$C_{13}H_{15}Cl_2NO_4$	22.15	22.14	4.38	4.40	+13.8 ± 0.4	5.15
D-valine	164.2–164.7	80.0	70.6		22.15	22.15	4.38	4.39	−14.3 ± 0.4	5.33
N,N'-bis-(2,4-Dichlorophenoxyacetyl)-										
D-cystine	217.0–220.0[h]		32.8	$C_{22}H_{20}Cl_4N_2O_8S_2$	21.94	21.85	4.33	4.30	+109.2 ± 0.4	1.00[l]
DL-cystine	214.0–217.0[h]		40.0		21.94	21.64	4.33	4.35		

[a] Recrystallized twice from 50% ethanol unless otherwise indicated. [b] The authors are indebted to J. S. Ard of this laboratory for the analyses. [c] In 10% molar excess of sodium hydroxide. [d] Recrystallized once from 50% ethanol. [e] Sample sealed under nitrogen. [f] Recrystallized twice from ethyl acetate–hexane. [g] Prepared by C. H. H. Neufeld. [h] Prepared by J. F. Carmichael. [i] In pyridine. [j] Recrystallized twice from methyl ethyl ketone–hexane. [k] Prepared by T. F. Drake. [l] In dimethyl formamide.

onstrated that amino acid coupling can have a marked effect upon the growth-regulating properties of a compound. Such properties are also modified by combination with inexpensive protein hydrolyzates prepared from animal and vegetable sources.[9]

A previous report on the synthesis of 28 amino acid derivatives of 2,4-D appeared in 1952;[10] this note extends the 2,4-D series to 48 amino acid derivatives. The 20 new derivatives were prepared to elucidate further the mode of action and specificity of aryloxyalkylcarboxylic acids as plant growth regulators, as well as to investigate further the use of amino acids as bioactive formulating agents. Many of the compounds from the various series have been submitted to various cooperating agencies for evaluation as plant growth regulators, herbicides, fungicides, anticancer agents, insect repellents, and nematocides. One report[2] on herbicidal evaluation describes *N*-(2,4-dichlorophenoxyacetyl)-D-asparagine as effective in killing pigweed, mustard, and broadleaf weeds without effect on corn and gladiolus in postemergence sprays at $^1/_2$ to 1 pound per acre application rates. Details on the specific biological properties of these compounds will be reported elsewhere.

EXPERIMENTAL

The compounds listed in Table I were prepared by Schotten-Baumann techniques in accordance with descriptions outlined in previous publications. No special directives are necessary here in view of earlier descriptions and the absence of any particular preparative difficulties.

Some of the D-amino acids used in this work were obtained through the courtesy of the late Dr. Jesse P. Greenstein of the National Institutes of Health, Bethesda, Md.; others, and the 2,4-D used, were purchased from commercial sources and utilized without further purification. The 2,4-D was converted to its acyl chloride by the method of Freed[11] and also described by us.[10]

In general the yields of reaction products were fairly high but appreciably losses were taken in the purification processes because it was essential that traces of free acid be removed from the derivatives and that optical purity be obtained. The optical values received were essentially equal and opposite for the D- and L-isomeric compounds. The special variations used in the purification techniques are indicated in the footnotes of Table I.

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The Structure of the Addition Product from Hydrogen Cyanide and a 2-Vinyldihydro-1,3-oxazine

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A recent article[1] described the preparation of several 2-alkenyl-4,6,6-trimethyldihydro-1,3-oxazines from unsaturated nitriles and 2-methyl-2,4-pentanediol and the reaction of one of these dihydro-1,3-oxazines with hydrogen cyanide. The heterocyclic bases were prepared according to the general method first described by Tillmanns and Ritter[2] who condensed a series of nitriles with 2-methyl-2,4-pentanediol in cold 92% sulfuric acid.

Treatment of I with hydrogen cyanide in glacial acetic acid yielded an addition product which could possess structure II or III as a result of either 1,4- or 3,4- addition, respectively. On the basis of the infrared spectrum of the adduct, II was concluded to represent the true structure. This reaction has now been re-examined and III is claimed to be the correct structure of the adduct. This claim is based upon an alternate synthesis of III, alkaline hydrolysis of the addition product, and a revised interpretation of the infrared spectrum in the light of recent studies.[3]

The alternate method of synthesis of the addition compound was accomplished by treating 2-methyl-2,4-pentanediol with succinonitrile in cold concentrated sulfuric acid. Comparison of this product with that obtained by treating I with hydrogen cyanide according to the method of Lynn[1] showed that both compounds were identical in every respect. This method of obtaining III is one which is currently under investigation in our laboratory for the preparation of a wide variety of *N*-heterocycles of the type, IV. It has been found possible, however, to limit the reaction of the dinitriles to only one of the nitrile groups, thus enabling the facile preparation of III. Other *N*-heterocycles such as 1-pyrrolines, 2-thiazolines, and dihydropyridines have already been reported.[4] Extension

(1) J. W. Lynn, *J. Org. Chem.*, **24**, 711 (1959).

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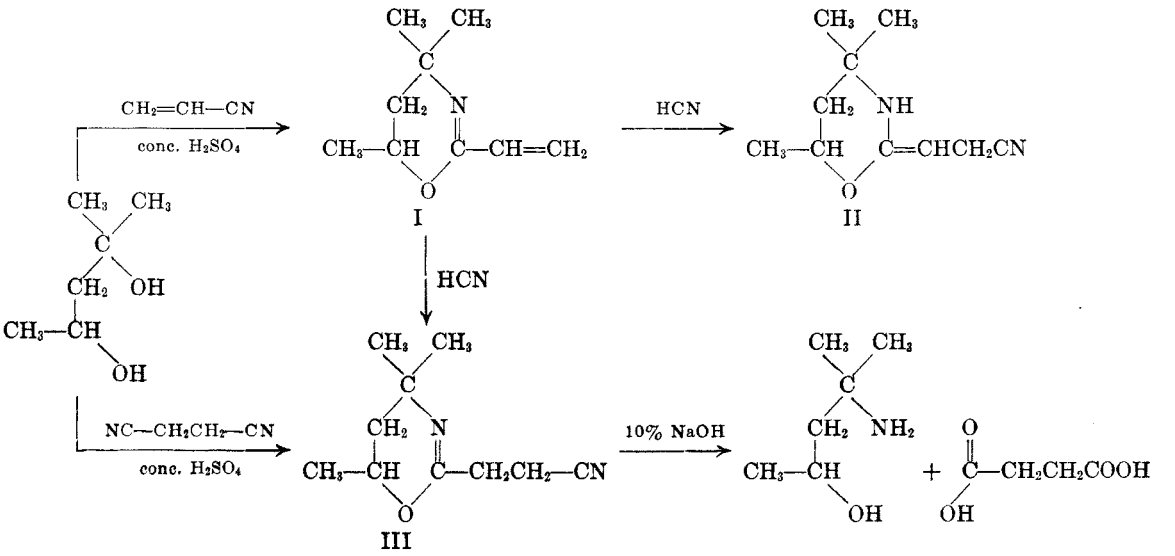

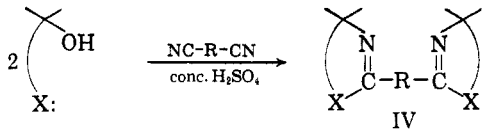

X = S, O, N; R = alkylene, arylene

of this ring closure reaction to dihydro-1,3-thiazines, dihydro-1,3-oxazines, and benzothiazines will be reported in the near future.

Additional proof in support of III was obtained by refluxing the hydrogen cyanide addition compound with 10% aqueous sodium hydroxide[5] for 24 hr. and isolating 4-methyl-4-amino-2-pentanol and succinic acid in quantitative yield. This mode of hydrolysis strongly supports the presence of the C=N link rather than the exocyclic C=C link in the molecule.

With regard to the infrared spectrum of the hydrogen cyanide addition compound, examination of the 6μ region reveals a single intense band at 6.00μ which had originally been assigned[1] to the stretching frequency of the C=C link. This intense band (not at all typical of the cyclic unconjugated C=C link) has recently been the subject of a study[3] on the spectral position of the C=N link in nitrogen heterocycles. It has been found, as a result of this study, that unconjugated 1-pyrrolines, 2-thiazolines, and more recently dihydro-1,3-thiazines[6] containing a 2-alkyl substituent exhibit a sharp intense band in the 6.00–6.10μ region. Two additional dihydro-1,3-oxazines containing a 2-alkyl substituent were prepared and their absorption in the 6μ region were compared (Table I). The moderately strong band in the 6.88–6.92μ region is due to —CH_2— deformation frequencies.[7] Examination of the 3μ region showed a weak band at 3.00μ which did not reappear when the oxazines were dried in benzene over potassium hydroxide pellets. Thus, it was concluded that a trace of water was responsible for the absorption in the 3μ region and not the presence of the N—H link. Furthermore, the structure of the 2-methyldihydro-1,3-oxazine, whose spectrum was used as a comparison, is well known.[5]

TABLE I

ABSORPTION OF 2-ALKYL-4,6,6-TRIMETHYLDIHYDRO-1,3-OXAZINES IN THE 6μ REGION

2-Alkyl Substituent	Absorption in 6μ Region (%T)
$-CH_3$	6.00 (4.0); 6.90 (39.4)
$-CH_2CH_3$	6.01 (4.0); 6.88 (42.6)
$-CH_2CH_2CN$	6.00 (3.5); 6.92 (27.0)

An additional study on the infrared spectra of *N*-heterocycles containing the C=N link is presently in progress and a communication in this respect is forthcoming.

EXPERIMENTAL[8,9]

The infrared spectra were performed in a Perkin-Elmer Model 21 recording spectrophotometer employing a sodium chloride prism. The samples were studied in a 5–6% carbon tetrachloride solution utilizing a cell with 0.48 mm. spacing.

2-(2-Cyanoethyl)-4,6,6-trimethyldihydro-1,3-oxazine (III). (a). Prepared by the addition of hydrogen cyanide in glacial acetic acid to 2-vinyl-4,6,6-trimethyldihydro-1,3-oxazine according to the method of Lynn.[1]

(b). To 40 g. (0.50 mol.) of succinonitrile in 100 ml. of concentrated sulfuric acid previously cooled to 3° in an ice bath was added with stirring 39.6 g. (0.25 mol.) of 2-methyl-2,4-pentanediol during a 3-hr. period. The temperature during the addition was maintained between 7–10°. The orange mixture was stirred for an additional hour at 3–5° and then poured over 300 g. of chipped ice. The aqueous

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(6) A. I. Meyers, unpublished observation.

(7) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley & Sons, New York, 1958, p. 20.

(8) All melting points and boiling points are uncorrected.

(9) Microanalyses were performed by Dr. Alfred Bernhardt, Mulheim (Ruhr), West Germany.

acid solution was extracted with three 75-ml. portions of chloroform and then cautiously neutralized by the addition of a sufficient amount of 35% sodium hydroxide solution. The red oil that appeared was taken up in ethyl ether and the alkaline solution further extracted with three 75-ml. portions of ether. The ethereal extracts were combined and dried over potassium carbonate. After the ether was removed at atmospheric pressure, the residual oil was distilled *in vacuo*. There was obtained 17.8 g. (40%) of a colorless oil b.p. 104–106°/3.5 mm., n_D^{30} = 1.4544 (lit.[1] b.p. 87°/1.3 mm.; n_D^{30} = 1.4542). Picrate (from ethanol) m.p. 282° dec.

Alkaline hydrolysis of III. Ten g. (0.055 mol.) of III were added to 100 ml. of 10% aqueous sodium hydroxide and refluxed for 24 hr. The colorless oil which was present was taken up in ether and the remaining aqueous layer was saturated with sodium chloride and extracted twice with an equal volume of ether. The ether extracts were combined and dried over anhydrous sodium carbonate. After removal of the ether, distillation of the residue yielded 6.3 g. of 4-amino-4-methyl-2-pentanol, b.p. 71–72°/12 mm., n_D^{20} = 1.4345 (lit.[5] b.p. 74–75°/15 mm., n_D^{20} = 1.4335).

Acidification of the alkaline aqueous solution yielded succinic acid, m.p. 272–274° dec. Admixture with an authentic sample of succinic acid showed no depression in the melting point.

2,4,4,6-Tetramethyldihydro-1,3-oxazine. This compound was prepared according to the method of Tillmanns and Ritter.[2] B.p. 58°/25 mm., n_D^{25} = 1.4355.

2-Ethyl-4,6,6-trimethyldihydro-1,3-oxazine. Prepared in the same manner as the 2-methyl derivative. B.p. 67°/20 mm., n_D^{25} = 1.4385.

Anal. Calcd. for $C_9H_{17}ON$: C, 69.67; H, 10.96. Found: C, 69.62; H, 10.91.

Acknowledgment. The author wishes to express his gratitude to the Research Corporation and the National Institutes of Health (DGMS-6248) for funds granted to support a study of which the present work is a part. Thanks are due to Mr. R. T. O'Connor and his staff at the Southern Regional Research Laboratory, United States Department of Agriculture, for determining the infrared spectra.

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Synthesis of 5-Alkyl-2-iminohexahydro-*s*-triazine-1-carbonitriles and 3,3′-Ethylenebis-(6-iminohexahydro-*s*-triazine-1-carbonitrile)

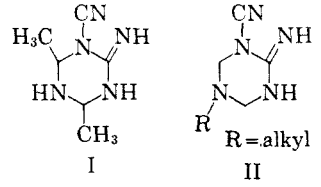
EDWARD H. SHEERS

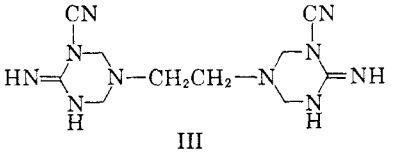
Received August 5, 1959

The condensation of primary alkylamines with one mol. of urea or thiourea and 2 mol. of formaldehyde to give 5-alkylhexahydro-*s*-triazinones and 5-alkylhexahydro-*s*-triazinethiones[1] suggested that cyanoguanidine might react in a similar fashion to form a cyclic derivative.

Pohl[2] showed that cyanoguanidine condenses with acetaldehyde-ammonia to give 2-imino-4,6-dimethylhexahydro-*s*-triazine-1-carbonitrile (I). This reaction has not been reported with any aldehyde-ammonia above C_2. This, together with the fact that the higher aliphatic aldehydes are not readily available, somewhat limits the scope of Pohl's reaction.

Cyanoguanidine reacted readily with one mol. of alkylamine and 2 mol. of formaldehyde to give high yields of 5-alkyl-2-iminohexahydro-*s*-triazine-1-carbonitriles (II), a new series of colorless, solid hexahydro-*s*-triazine derivatives. With 0.5 mol. of ethylenediamine and 1 mol. of formaldehyde cyanoguanidine yielded the expected 3,3′-ethylenebis(6-iminohexahydro-*s*-triazine-1-carbonitrile) (III). This condensation appears to be quite general in nature.





EXPERIMENTAL

The cyanoguanidine used was American Cyanamid Company's commercial grade (purity 99%+). All other compounds used were Eastman White Label grade. All melting points are uncorrected.

Typical procedure for 5-alkyl-2-iminohexahydro-s-triazine-1-carbonitriles: 5-Butyl-2-iminohexahydro-s-triazine-1-carbonitrile. To 400 ml. water, there were added 43 g. cyanoguanidine, 37 g. *n*-butylamine, and 81 ml. formalin while stirring vigorously. The temperature rose to 54°. Stirring was continued for 1 hr. after the addition was complete. A colorless oil deposited which crystallized on standing overnight. This product was collected by filtration and recrystallized from 95% ethanol. The yield was 80% of theory and consisted of colorless platelets having a melting point of 149–150°.

Anal. Calcd. for $C_8H_{15}N$: C, 53.01; H, 8.34; N, 38.64. Found: C, 52.89; H, 8.45; N, 38.80.

3,3′-Ethylenebis(6-iminohexahydro-s-triazine-1-carbonitrile). To a solution of 43 g. cyanoguanidine in 200 ml. water, there were added 20 g. ethylenediamine and 81 ml. formalin while stirring vigorously. The temperature rose to 72°. The hot, clear solution was stirred, and white crystals of the product, m.p. 225–226°, deposited within 1 hr. in 75% yield.

Anal. Calcd. for $C_{10}H_{16}N_8$: C, 48.37; H, 6.50; N, 45.13. Found: C, 48.54; H, 6.47; N, 45.11.

(1) Burke, W. J., *J. Am. Chem. Soc.*, **69**, 2136 (1947); U. S. Patent **2,304,624** (1942); *cf.* also Paquin, A. M., *Angew. Chem.*, **A60**, 267 (1948).

(2) Pohl, F., *J. prakt. Chem.*, **77**, 538–539 (1908).

TABLE I

5-ALKYL-2-IMINOHEXAHYDRO-s-TRIAZINE-1-CARBONITRILES

Alkyl	Yield, %	M.P., °C.	Analysis					
			Calculated			Found		
			% C	% H	% N	% C	% H	% N
Methyl	92	196–197	43.15	6.52	50.33	43.20	6.58	50.30
Butyl	80	149–150	53.01	8.34	38.64	52.89	8.45	38.80
Isobutyl	88	177–178	53.01	8.34	38.64	52.96	8.35	38.71
Allyl	86	172–173	50.89	6.71	42.40	51.00	6.69	42.30
Cyclohexyl	84	172–173	57.94	8.28	33.79	57.91	8.29	33.69
n-Decyl	94	160–161	63.36	10.25	26.39	63.27	10.29	26.35
n-Dodecyl	92	157–158	65.48	10.65	23.87	65.54	10.59	23.82
n-Octadecyl	92	132.3	69.97	11.48	18.55	69.94	11.42	18.51

Acknowledgment. The author wishes to thank the Microanalytical Laboratory of the Stamford Laboratories for the microanalyses and Stanley E. Polchlopek for the infrared curves and their interpretation.

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Studies in Purine Chemistry. VII. An Improved Synthesis of Hypoxanthine[1,2]

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Received August 6, 1959

The desulfurization of a mercapto or alkylmercapto substituent is often a critical step in heterocyclic synthesis, particularly in pyrimidine and purine chemistry. The most commonly employed desulfurization method is to reflux the compound with an excess of Raney nickel under what are commonly termed "Mozingo conditions,"[3] and this procedure[4] has been employed in syntheses of both hypoxanthine[5] and adenine[6–8] derivatives. Other methods for replacement of the mercapto group by hydrogen include oxidation with nitric acid[9] or with hydrogen peroxide in acidic solution.[9–11]

An attractive alternative has more recently been described which involves oxidation of the mercapto group in alkaline solution with hydrogen peroxide to a sulfinic acid, followed by decomposition with strong acid, and has been applied to the synthesis of 4,5,6-triaminopyrimidine from 2-mercapto-4,5,6-triaminopyrimidine[12,13] and of 4,6-diaminopyrimidine from 2-mercapto-4,6-diaminopyrimidine.[13] By application of this method to the preparation of 4-hydroxy 5,6-diaminopyrimidine from 2-mercapto-4-hydroxy-5,6-diaminopyrimidine, and by means of certain other modifications, we have been able to effect significant improvements in the conventional synthesis of hypoxanthine from thiourea and ethyl cyanoacetate. Details are given in the Experimental.

Evans *et al.*[13] pointed out that the decomposition of 4,6-diaminopyrimidine-2-sulfinic acid to 4,6-diaminopyrimidine required much stronger acid than the analogous decomposition of 4,5,6-triaminopyrimidine-2-sulfinic acid to 4,5,6-triaminopyrimidine and that weaker acid led predominately to the 2-hydroxy derivative. This was attributed to the weaker basicity of the former pyrimidine, coupled with the requirement that diprotonation precede heterolytic cleavage of the C—S bond. We have found that oxidation of 2-mercapto-4-hydroxy-6-aminopyrimidine, a still weaker base, leads directly to 2,4-dihydroxy-6-aminopyrimidine; the 2-sulfinic acid could not even be isolated.

(1) This investigation was supported in part by a grant (C-2551) to Princeton University from the National Cancer Institute of the National Institutes of Health, Public Health Service.

(2) For the previous paper in this series, see E. C. Taylor and C. C. Cheng, *Tetrahedron Letters*, No. 12, 9 (1959).

(3) R. Mozingo, D. E. Wolf, S. A. Harris and K. Folkers, *J. Am. Chem. Soc.*, **65**, 1013 (1945).

(4) For examples of the utilization of this method, see M. P. V. Boarland, J. F. W. McOmie, and R. N. Timms, *J. Chem. Soc.*, 4691 (1952); M. P. V. Boarland and J. F. W. McOmie, *J. Chem. Soc.*, 4942 (1952); L. F. Cavalieri and A. Bendich, *J. Am. Chem. Soc.*, **72**, 2587 (1950); E. A. Falco and G. H. Hitchings, *J. Am. Chem. Soc.*, **78**, 3143 (1956); R. K. Robins and G. H. Hitchings, *J. Am. Chem. Soc.*, **78**, 973 (1956); E. C. Taylor, *J. Am. Chem. Soc.*, **74**, 2380 (1952); C. C. Cheng and R. K. Robins, *J. Org. Chem.*, **23**, 852 (1958); D. J. Brown, *J. Soc. Chem. Ind.*, **69**, 353 (1950); H. Getler, P. M. Roll, J. F. Tinker, and G. B. Brown, *J. Biol. Chem.*, **178**, 259 (1949).

(5) G. B. Elion, E. Burgi, and G. H. Hitchings, *J. Am. Chem. Soc.*, **74**, 411 (1952).

(6) A. Bendich, J. F. Tinker, and G. B. Brown, *J. Am. Chem. Soc.*, **70**, 3109 (1948).

(7) G. A. Howard, B. Lythgoe, and A. R. Todd, *J. Chem. Soc.*, 556 (1945).

(8) E. C. Taylor, O. Vogl, and C. C. Cheng, *J. Am. Chem. Soc.*, **81**, 2442 (1959).

(9) W. Traube, *Ann.*, **331**, 64 (1904).

(10) H. Andersag and K. Westphal, *Ber.*, **70**, 2035 (1937).

(11) G. W. Kenner, B. Lythgoe, A. R. Todd, and A. Topham, *J. Chem. Soc.*, 574 (1943).

(12) M. Hoffer, "Jubilee Volume Dedicated to Emil C. Barrell," Basel, 1946, p. 428.

(13) R. M. Evans, P. G. Jones, P. J. Palmer, and F. F. Stephens, *J. Chem. Soc.*, 4106 (1956).

EXPERIMENTAL

2-Mercapto-4-hydroxy-6-aminopyrimidine.[14] To a solution of sodium ethoxide (prepared by dissolving 9 g. of sodium in 200 ml. of ethanol) was added 22.6 g. of ethyl cyanoacetate. A white precipitate formed immediately. After 15 min., 15.2 g. of thiourea was added with shaking, and the mixture was allowed to stand at room temperature for 1 hr. with occasional shaking. It was then heated under reflux for 2 hr., cooled and filtered. The collected solid was dissolved in boiling dilute potassium hydroxide and reprecipitated by the addition of glacial acetic acid to give 28.4 g. (99%) of white crystals.

2-Mercapto-4-hydroxy-5-nitroso-6-aminopyrimidine.[14] To a solution of 20 g. of 2-mercapto-4-hydroxy-6-aminopyrimidine in 500 ml. of water containing 5.5 g. of sodium hydroxide and 10 g. of sodium nitrite and maintained at room temperature was added dropwise 15 g. of glacial acetic acid. The reaction mixture was stirred overnight and then filtered to give a brownish-red solid in 90% yield. The crude product was extracted with boiling acetone and then with boiling ethanol (thus removing a small amount of colorless impurity) and was then suitable for further reaction.

2-Mercapto-4-hydroxy-5,6-diaminopyrimidine. The procedure used was essentially the same as previously described by Albert *et al.*,[15] except that the temperature of the reduction mixture was maintained below 30° rather than below 50°, and the sodium hydrosulfite was added very slowly rather than all at once. Furthermore, the reduction mixture was stirred for 20 hr. at room temperature following addition of all of the hydrosulfite and was then decolorized with charcoal. The diaminopyrimidine was obtained in 96.5% yield.

4-Hydroxy-5,6-diaminopyrimidine-2-sulfinic acid. To a solution of 1 g. of 2-mercapto-4-hydroxy-5,6-diaminopyrimidine in 90 ml. of water containing 0.6 g. of sodium hydroxide and precooled to −3° was added dropwise 1.8 ml. of 30% hydrogen peroxide in 17 ml. of water. During the addition the temperature was carefully maintained below 0°. The reaction mixture was allowed to stir for 1.5 hr. following addition of the peroxide and was then acidified with glacial acetic acid. Filtration yielded 0.8 g. of a colorless solid, m.p. 188–190°.

4-Hydroxy-5,6-diaminopyrimidine hydrochloride. A mixture of 1.5 g. of 4-hydroxy-5,6-diaminopyrimidine-2-sulfinic acid and 30 ml. of ethanolic hydrogen chloride was stirred at room temperature for 20 hr. in a flask protected from atmospheric moisture by a calcium chloride tube. The reaction mixture was evaporated to dryness, the residue dissolved in water, filtered and the filtrate again evaporated to dryness to give 1.3 g. of a colorless solid, m.p. 249–251°d., identical in all respects with an authentic sample of 4-hydroxy-5,6-diaminopyrimidine hydrochloride prepared by Raney nickel desulfurization of 2-mercapto-4-hydroxy-5,6-diaminopyrimidine.[16]

Decomposition of 4-hydroxy-5,6-diaminopyrimidine-2-sulfinic acid with concentrated hydrochloric acid yielded 2,4-dihydroxy-5,6-diaminopyrimidine hydrochloride rather than the desired product.

Hypoxanthine. A mixture of 2 g. of 4-hydroxy-5,6-diaminopyrimidine hydrochloride and 30 ml. of an equimolar mixture of ethyl orthoformate and acetic anhydride was heated under reflux for 4 hr. and then evaporated to dryness. Recrystallization of the residual solid from aqueous ethanol gave 1.6 g. (95.5%) of pure hypoxanthine, identical in all respects with an authentic sample.

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(14) This preparation is a slight modification of the original method described by Traube (Ref. 9).

(15) A. Albert, D. J. Brown, and G. Cheeseman, *J. Chem. Soc.*, 474 (1951).

(16) R. O. Roblin, Jr., J. O. Lampen, J. P. English, Q. P. Cole, and J. R. Vaughan, Jr., *J. Am. Chem. Soc.*, **67**, 290 (1945).

Potential Anticancer Agents.[1] XXVIII. Synthesis of 5-(Chloromethyl)uracil

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Both 5-fluorouracil[2] and 5-[bis(2-chloroethyl)-amino]uracil[3] have been shown to inhibit the growth of various tumors. Matthews[4] reported that all of the 5-halogenated uracils were incorporated into phage DNA, giving mutants. Hitchings *et al.*,[5] have shown 5-bromouracil to be a competitive thymine antagonist.

Efforts to find new anticancer agents could, therefore, be logically directed toward the preparation of various thymine derivatives such as 5-(fluoromethyl) uracil, 5-[bis(2-chloroethyl)aminomethyl]uracil, and other uracil derivatives containing potential alkylating groups attached to a 5-methyl grouping. The key intermediate to the synthesis of these agents would be 5-(chloromethyl)-uracil (IV). This compound has now been synthesized in 57% yield by the choromethylation of uracil (I).

Early attempts in this laboratory to prepare IV by the chlorination of thymine using *N*-chlorosuccinimide and benzoyl peroxide, as reported by West and Barrett,[6] failed to yield IV. Instead, a compound melting at 224.5–225.5° was obtained. West reported a similar melting point of 222–224° and an empirical formula of $C_5H_5ClN_2O_4$. The failure of this compound to react with alcoholic silver nitrate solution upon heating, its stability toward water (being recrystallized without change from hot water), its lack of absorption in the ultraviolet, and its liberation of iodine from an acetic acid solution of potassium iodide, are convincing

(1) This work was carried out under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, Contract No. SA-43-ph-1892. For the preceding paper in this series, *cf.* E. J. Reist, R. R. Spencer, and B. R. Baker, *J. Am. Chem. Soc.*, in press.

(2) C. Heidelberger, L. Greisbach, B. J. Montag, D. Mooren, O. Cruz, R. J. Schnitzer, and E. Grunberg, *Cancer Res.*, **18**, 305 (1958); R. Duschinsky, E. Pleven, and C. Heidelberger, *J. Am. Chem. Soc.*, **79**, 4559 (1957).

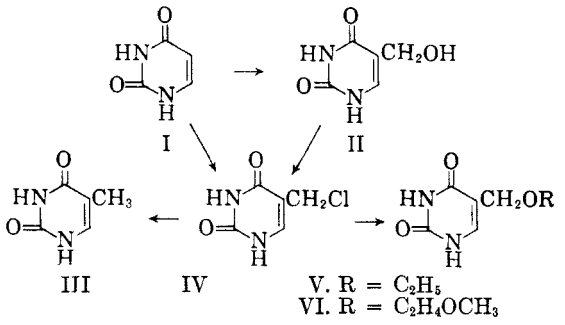
(3) D. A. Lyttle and H. G. Petering, *J. Am. Chem. Soc.*, **80**, 6459 (1958).

(4) R. E. F. Matthews, *Pharm. Reviews*, **10**, No. 3, 359 (1958).

(5) G. H. Hitchings, E. A. Falco, and M. B. Sherwood, *Science*, **102**, 251 (1945).

(6) R. A. West and H. W. Barrett, *J. Am. Chem. Soc.*, **76**, 3146 (1954).

evidence that it was not IV. The absence of absorption in the ultraviolet would suggest that the uracil ring had been either ruptured or else saturated. The iodide test indicates *N*-chlorination.



Efforts were shifted to the chlorination of 5-(hydroxymethyl)uracil (II), which was prepared by the method of Cline *et al.*[7] Attempts to chlorinate II in pyridine with thionyl chloride resulted in the formation of a compound that appeared to be the quaternary salt formed from IV and pyridine. When chlorination in dichloromethane with thionyl chloride was attempted, no reaction occurred, probably due to the limited solubility of II in that solvent.

Crude IV was prepared in 37% yield by heating 5-(hydroxymethyl)uracil (II) in concentrated hydrochloric acid. Although an analytical sample of IV could not be obtained by this procedure, the infrared absorption spectrum and paper chromatographic[8] behavior indicated that a product different from thymine (III), uracil (I), and 5-(hydroxymethyl)uracil (II) had been obtained. This crude IV was reduced to thymine in 62% yield by means of tin and hydrochloric acid. The thymine produced was identical with that of an authentic sample in its infrared absorption and paper chromatographic behavior.

Schmeds[9] reported the chloromethylation of 3,6-dimethyluracil to yield 3,6-dimethyl-5-(chloromethyl)uracil by heating the former in aqueous formaldehyde with excess concentrated hydrochloric acid. Attempts to prepare IV from uracil (I) using that procedure resulted in only a 13% yield of crude 5-(chloromethyl)uracil (IV). It was found, however, that extraction of crude IV with warm 1,2-dimethoxyethane and concentration of the extracts yielded a more pure sample of IV, as evidenced by paper chromatographic[8] behavior (disappearance of spots near the origin) and chloride analyses (closer to theoretical for IV).

It was then found that the best conditions for the synthesis of IV were continuous passage of hydrogen chloride through a solution of uracil and paraformaldehyde in concentrated hydrochloric acid while heating to 70–80°. The product was isolated in 57% yield and analyzed closely to the theoretical chlorine value for IV without extraction with 1,2-dimethoxyethane. Only a trace spot still remained at the origin on paper chromatographic[8] investigation. Proof that chloromethylation had occurred at the 5-position of uracil was shown by reduction of IV to thymine (III) in 82% yield by means of tin and hydrochloric acid. The thymine was characterized by the identity of its infrared absorption spectrum and paper chromatographic behavior[8] with those of an authentic sample of thymine. In addition, IV differs from West's compound[3] in that IV gives an immediate precipitate of silver chloride on treatment with alcoholic silver nitrate solution, and 5-(hydroxymethyl)-uracil (II) is produced upon reaction with water. The identity of II was proven by its agreement in behavior on paper[8] (R_f 0.19) and by its identical infrared absorption spectrum with that of II prepared by the method of Cline.[7]

5-(Chloromethyl)uracil (IV) also reacted readily with alcohols to yield ethers. A similar reaction has been reported by Cline[7] to occur with 5-(hydroxymethyl)uracil (II) and alcohols under somewhat more vigorous reaction conditions. The product obtained by heating IV with 2-methoxyethanol was isolated as a crystalline solid, m.p. >300°, and shown by analysis to be 5-[(2-methoxyethoxy)-methyl]uracil (VI). This material was homogeneous on paper chromatography,[8] showing only one spot, R_f 0.39.

EXPERIMENTAL

5-(Chloromethyl)uracil (IV). A suspension of 40 g. (0.36 mol.) of uracil (I) and 13.4 g. (0.44 mol.) of paraformaldehyde in 350 ml. of concentrated hydrochloric acid was stirred while gaseous hydrogen chloride was passed through the reaction mixture, which was then heated to 80°. When that temperature was reached, complete solution had been attained. The heat source was removed; the reaction temperature remained spontaneously at 80° for 0.5 hour, then subsided. After 4 hr. total time, the now heterogeneous reaction mixture was filtered through a glass sintered funnel and the precipitate dried over phosphorus pentoxide at 1 mm. pressure; yield, 32.6 g. (57%), m.p. >300°; $\lambda_{max\ (\mu)}^{Nujol}$ 3.05, 3.20 (NH), 5.70, 5.98 (uracil C=O), 6.70, 6.96, 8.24, 8.48 (uracil ring). The compound moved as two spots (R_f 0.70, 0.18)[8] provided the compound was dissolved in 1,2-dimethoxyethane for spotting on the paper. Uracil has R_f 0.28; thymine, R_f 0.42; and 5-(hydroxymethyl)uracil, R_f 0.19 in this system.[8] When IV was spotted in warm ethanol, the compound had R_f 0.53, and in warm methyl Cellosolve, R_f 0.39, corresponding to V and VI, respectively. In warm 1-butanol an R_f of 0.70 was obtained due to the formation of 5-(butoxymethyl)uracil.

Anal. Calcd. for $C_5H_5ClN_2O_2$: C, 37.5; H, 3.14; Cl, 22.1. Found: C, 37.7; H, 3.54; Cl, 21.1.

The compound is very sensitive to moisture, fuming in air, thus making an accurate analysis difficult.

5-[(2-Methoxyethoxy)methyl]uracil (VI). Crude IV (1 g.; Cl, 13.2%), prepared from uracil (I), was extracted with 2-methoxyethanol by heating to 70° and filtering hot.

(7) R. E. Cline, R. M. Fink, and K. Fink, *J. Am. Chem. Soc.*, **81**, 2521 (1959).

(8) Paper chromatograms were run by the descending technique on Whatman No. 1 paper with 1-butanol–water, unless otherwise indicated. Spots were detected by their ultraviolet absorption.

(9) K. Schmeds, *Ann.*, **441**, 192 (1925).

The filtrate upon concentration *in vacuo* yielded 0.46 g. of VI, m.p. >300°, silver nitrate test negative; λ_{max}^{Nujol} (μ) 3.12, 3.25 (NH), 5.72, 5.44 (C=O of uracil), 9.00, 9.10 (C—O—C of ether).

Anal. Calcd. for $C_8H_{12}N_2O_4$: C, 48.0; H, 6.05; N, 14.0. Found: C, 47.7; H, 6.00; N, 14.0.

Reduction of 5-(chloromethyl)uracil (IV) *to thymine* (III). A suspension of 5.00 g. (0.03 mol.) of 5-(chloromethyl)uracil (IV), prepared by chloromethylation of uracil, in 150 ml. of concentrated hydrochloric acid was heated to 60°. The reaction mixture was kept at 60° and 35.0 g. of tin was added over a period of 20 min. with stirring. After being stirred and heated for 3 hr., the reaction mixture was decanted to remove the excess tin. The solution was evaporated to one third its volume under reduced pressure on a water bath at 60°. The solution was diluted with 750 ml. of hot, distilled water and filtered. The filtrate was treated with hydrogen sulfide for 15 min., then heated for 30 min. at 80°, the mixture cooled to room temperature, and the tin sulfide removed by filtration. The filtrate yielded 3.49 g. of white crystals when concentrated *in vacuo*. This crude thymine was recrystallized from dilute aqueous ethanol to give 3.2 g. (82%) of thymine; λ_{max}^{Nujol} (μ) 3.15 (NH), 5.68, 5.94 (C=O of uracil), 6.65, 7.00 (ring). The spectrum was identical with that of an authentic sample of thymine.

The compound had the following R_f values as compared with thymine: in benzene-methanol-water (2:1:6) on Schleicher and Schuell No. 2043B acetylated paper, R_f 0.64 (thymine, 0.64); in 1-butanol–water on Whatman No. 1 paper, R_f 0.45 (thymine, 0.45); in isopropanol–ammonium hydroxide–water (70:5:25), R_f 0.79 (thymine, 0.79); in isopropanol–2*N* hydrochloric acid (65:35), R_f 0.85 (thymine, 0.83).

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New Di- and Tetrahydropyran Derivatives

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In connection with another study, certain di- and tetrahydropyran dibasic acids and amino acids were desired whose preparation is described below.

The dibasic acids were obtained through the addition of phosgene to the requisite 2,3-dihydro-4*H*-pyran derivative, followed by the elimination of the elements of hydrogen chloride, saponification of the acid chloride and, if desired, by hydrogenation. Alternatively, the acid chlorides were converted into amides which, on dehydration, yielded nitriles. An amino acid derivative was also prepared through the addition of *N*-substituted 2-aminoethanol to 5-carbethoxy-2,3-dihydro-4*H*-pyran.

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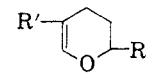
It is known that when a mixture of 2,3-dihydro-4*H*-pyran and phosgene is allowed to react and the resulting addition product is subsequently heated under reduced pressure, hydrogen chloride is eliminated and 2,3-dihydro-4*H*-pyran-5-carbonyl chloride is formed.[2] By adapting this method, Ia was obtained in 42% yield. Attempts to add phosgene to 2-formyl-2,3-dihydro-4*H*-pyran failed to produce an acid chloride, the phosgene reacting instead with the formyl group. However, acid chloride Ig was obtained from compound Ii in which the aldehyde function was masked through formation of the acetal derivative. In the absence of interfering substituents, the addition of phosgene may be a general method for the introduction of a carbonyl chloride group into the dihydropyran nucleus.

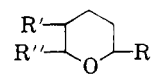
With Raney nickel catalyst, dihydropyran derivatives show a wide variation of susceptibility to hydrogenation, ranging from ready reactions at room temperature[3] to slow hydrogenations at elevated temperatures and pressures.[4,5] 2,5-Dicarbethoxy-2,3-dihydro-4*H*-pyran (Id) was difficult to reduce over Raney nickel at 150° and at 300 atm. pressure. However, over rhodium or palladium catalysts in glacial acetic acid, hydrogenation of Id could be effected with ease at room temperature and ordinary pressure.

Substituted 2,3-Dihydro-4*H*-pyran



Ia. R = $COOC_2H_5$, R′ = COCl; Ib. R = $COOC_2H_5$, R′ = COOH; Ic. R = R′ = COOH; Id. R = R′ = $COOC_2H_5$; Ie. R = $COOC_2H_5$, R′ = $CONH_2$; If. R = R′ = $CONH_2$; Ig. R = $CH(OC_2H_5)_2$, R′ = COCl; Ih. R = $CH(OC_2H_5)_2$, R′ = $COOC_2H_5$; Ii. R = $CH(OC_2H_5)_2$, R′ = H; Ik. R = $CONH_2$, R′ = H; Il. R = CN, R′ = H; Im. R = R′ = CN; In. R = $COOC_2H_5$, R′ = CN.

Substituted Tetrahydropyrans



IIa. R = R″ = H, R′ = $COOC_2H_5$; IIb. R = R″ = H, R′ = COOH; IIc. R = R′ = $COOC_2H_5$, R″ = H; IId. R = CHO, R′ = H, R″ = OC_2H_5; IIe. R = $OCH_2CH_2NHCOCH_3$, R′ = R″ = H; IIf. R = $OCH_2CH_2NHCOCH_3$, R′ = H, R″ = $COOC_2H_5$; IIg. R = $OCH_2CH_2NHCOC_6H_4NO_2$, R′ = R″ = H.

The replacement of the carbethoxy by a carboxamide group occurred easily when dihydropyran derivative Ia was treated with ammonium hydroxide at 0°. The carboxamides were converted to the nitriles by *p*-toluenesulfonyl chloride and

(2) P. A. Hawkins and N. Bennett, British Patent 570,974.

(3) M. Delépine and A. Horeau, *Bull. soc. chim. France*, (5) **5**, 339 (1938).

(4) J. G. M. Bremner and D. G. Jones, British Patent 612,314.

(5) R. R. Whetstone and S. A. Ballard, *J. Am. Chem. Soc.*, **73**, 5280 (1951).

pyridine at 60 to 130°.[6] Several other methods[7] resulted either in the recovery of the starting material or in complete destruction of the molecule.

Owing to its basicity, 2-aminoethanol, not unexpectedly, failed to add to the double bond of dihydropyran under conditions similar to those usually employed for the addition of alcohols.[8] The *N*-acetyl and *N*-nitrobenzoyl derivatives of 2-aminoethanol underwent the desired addition reaction in the presence of catalytic amounts of hydrochloric acid, resulting in compounds IIe, IIf, and IIg, respectively.

EXPERIMENTAL[9]

2-Carbethoxy-2,3-dihydro-4H-pyran-5-carbonyl chloride (Ia). A mixture of 24 g. (0.154 mol.) of 2-carbethoxy-2,3-dihydro-4*H*-pyran[5] and 34 g. (0.342 mol.) of phosgene was maintained for 7 days at 40° in a sealed glass tube. Vacuum distillation of the mixture yielded 9.4 g. (39%) of the initial ester, contaminated with hydrogen chloride, followed by 14.1 g. (42% yield) of compound Ia, b.p. 155–156° (8 mm.). When the reaction was conducted at 15° most of the starting material was recovered unchanged. In the presence of BF_3 the only product obtained was a clear resin.

2-Carbethoxy-5-carboxy-2,3-dihydro-4H-pyran (Ib). Acid chloride Ia was hydrolyzed with water at 5° to give Ib, (m.p. 127–128° from water). Saponification with 10% NaOH under reflux for 1 hr. gave the dicarboxylic acid Ic, (m.p. 237° from water).

Anal. Calcd. for $C_9H_{12}O_5$ (Ib): C, 54.2; H, 6.0; OC_2H_5, 22.5. Found: C, 53.8; 54.3; H, 6.2, 6.3; OC_2H_5, 22.2, 22.2.

2,5-Dicarbethoxy-2,3-dihydro-4H-pyran (Id). Acid chloride Ia, (28 g., 0.128 mol.), was added at 5° with stirring to 50 ml. of ethanol. After 1 hr., 130 ml. of water was added and the diester was extracted with ether (82%, b.p. 161–163° [11 mm.]).

Anal. Calcd. for $C_{11}H_{16}O_5$: C, 58.1; H, 7.1; OC_2H_5, 39.4. Found: C, 58.0; H, 7.3; OC_2H_5, 38.8.

2-Carbethoxy-5-carboxamide-2,3-dihydro-4H-pyran (Ie). Acid chloride Ia, (22 g., 0.1 mol.), was slowly added with stirring at −20° to a mixture of 12 ml. (0.2 mol.) of conc. ammonium hydroxide and 110 ml. of benzene (65%, m.p. 150–151.5° [from water]).

Anal. Calcd. for $C_9H_{13}NO_4$: C, 54.8; H, 6.6; N, 7.1; OC_2H_5, 22.5. Found: C, 54.8; H, 6.7; N, 7.1; OC_2H_5, 22.1.

2,5-Dicarboxamide-2,3-dihydro-4H-pyran (If). Acid chloride Ia, (8 g., 0.037 mol.), was slowly added with stirring at ordinary temperature to a mixture of 12 ml. (0.2 mol.) of conc. ammonium hydroxide and 40 ml. of benzene (48%, m.p. 256–257° dec.).

Anal. Calcd. for $C_7H_{10}N_2O_3$: C, 49.3; H, 5.9; N, 16.4; OC_2H_5, 0.0. Found: C, 49.6, 49.1; H, 6.4, 6.1; N, 16.3, 16.4; OC_2H_5, 0.0, 0.0.

2-Diethoxymethylene-2,3-dihydro-4H-pyran (Ii). Using the method of Fischer and Baer,[10] 44.8 g. (0.4 mol.) of 2-formyl-2,3-dihydro-4*H*-pyran[11] was treated with 72 g. (0.48 mol.) of ethyl orthoformate, 15 ml. of ethanol and 1.5 g. of NH_4NO_3. The yield was 50%, b.p. 94° (12 mm.).

Anal. Calcd. for $C_{10}H_{18}O_3$: C, 64.8; H, 9.7; OC_2H_5, 48.3. Found: C, 64.2, 63.7; H, 10.3, 9.9; OC_2H_5, 49.1, 47.5.

Only 2-formyl-5-ethoxy-tetrahydropyran (IId) was obtained when a few drops of alcoholic HCl were added at −5° to a mixture of 2-formyl-2,3-dihydro-4*H*-pyran and ethanol. The yield was 40%, b.p. 85° (12.5 mm.).

Anal. Calcd. for $C_8H_{14}O_3$: C, 60.8; H, 8.9; OC_2H_5, 28.5. Found: C, 60.4; H, 9.1; OC_2H_5, 28.6.

2-Diethoxymethylene-2,3-dihydro-4H-pyran-5-carbonyl chloride (Ig). Phosgene, 10 g. (0.101 mol.), was condensed into 17 g. (0.092 mol.) of Ii and the mixture kept at ordinary temperature in a closed Erlenmeyer flask for 4 days. Vacuum distillation yielded 4 g. (22%) of unchanged acetal, 6 g. (24%) of acid chloride Ig, b.p. 164° (16 mm.), and 4 g. of resinous residue. When the reaction was run with 2-formyl-2,3-dihydro-4*H*-pyran, the only product was a clear resin.

2-Diethoxymethylene-5-carbethoxy-2,3-dihydro-4H-pyran (Ih). Acid chloride Ig, (3.9 g., 0.0157 mol.), was added with stirring to 7.5 ml. of ethanol. After 1 hr. water was added and the acetal-ester extracted with ether. Vacuum distillation of the ether extract gave Ih (88%, b.p. 162–165° [12 mm.]).

Anal. Calcd. for $C_{13}H_{21}O_5$: C, 60.5; H, 8.5; OC_2H_5, 52.3. Found: C, 60.4; H, 8.9; OC_2H_5, 53.3.

3-Carbethoxytetrahydropyran (IIa). (a) 2,3-Dihydro-4*H*-pyran-5-carboxylic acid,[2] (32 g., 0.250 mol.), in 100 ml. of ethanol was hydrogenated over 5 g. of Raney nickel for 10 hr. at 150° and 200 atm. IIa (18 g., b.p. 89–91° [13 mm.]) and saturated acid IIb (b.p. 142–145° [12 mm.], *p*-bromophenacyl ester, m.p. 98–99° [lit.[4] m.p. 96°]) were obtained.

Anal. Calcd. for $C_8H_{14}O_3$: C, 60.7; H, 8.9. Found: C, 60.8; H, 8.9. Calcd. for $C_6H_{10}O_3$: C, 55.3; H, 7.7. Found: C, 55.7; H, 7.9.

(b) Ester IIa was obtained in 25% yield when 32 g. of 5-carbethoxy-2,3-dihydro-4*H*-pyran[2] was hydrogenated over 4 g. of Raney nickel for 4 hr. at 110° and 150 atm.

2,5-Dicarbethoxytetrahydropyran (IIc). (a) Id, (20 g., 0.088 mol.), in 30 ml. of ethanol was hydrogenated over 3 g. of Raney nickel for 3 hr. at 150° and 300 atm. (82%, b.p. 158–158.5° [12 mm.]).

Anal. Calcd. for $C_{11}H_{18}O_5$: C, 57.4; H, 7.9; OC_2H_5, 39.1. Found: C, 56.4; H, 8.1; OC_2H_5, 38.3.

(b) Id, (5 g., 0.022 mol.) in 25 ml. of glacial acetic acid was hydrogenated at ordinary temperature and pressure over rhodium and palladium catalyst. With 3 g. of Rh catalyst (5% Rh on charcoal), the theoretical amount of hydrogen was taken up after 1 hr.; with 0.5 g. of Pd catalyst (10% Pd on asbestos), 48 hr. were required for complete hydrogen uptake. In both cases hydrogenation was considerably slowed in an ethanol medium. The saturated diester was saponified with 10% aqueous NaOH. The free acid, very water soluble, was isolated as the silver salt and as the *p*-bromophenacyl ester, m.p. 163–165°.

Anal. Calcd. for $C_{15}H_{15}BrO_6$ (monoester): C, 48.5; H, 4.1; Br, 21.53. Calcd. for $C_{23}H_{20}Br_2O_7$ (diester): C, 48.6; H, 3.5; Br, 28.2. Found: C, 48.5; 49.1; H, 3.9, 4.0; Br, 26.9.

2-Carboxamide-2,3-dihydro-4H-pyran (Ik). 2-Carbethoxy-2,3-dihydro-4*H*-pyran (76 g., 0.487 mol.), and 50 ml. of liquid ammonia were heated in an autoclave for 8 hr. at 150° under 50 atm. hydrogen (76%, m.p. 117° [from water and benzene]).

Anal. Calcd. for $C_6H_9NO_2$: C, 56.8; H, 7.1; N, 11.0. Found: C, 57.4; H, 7.4; N, 11.4.

2-Carbonitrile-2,3-dihydro-4H-pyran (Il). Amide Ik, (12.7 g., 0.1 mol.), pyridine, (18 ml., 0.22 mol.) and *p*-toluenesulfonyl chloride (19.1 g., 0.1 mol.) were heated to 60°. The homogeneous solution which formed solidified on cooling. The solid was pulverized and extracted with ether. Vacuum distillation of the ether extract gave the nitrile (40%, b.p. 99–101° [14 mm.]).

Anal. Calcd. for C_6H_7NO: C, 66.0; H, 6.4; N, 12.9. Found: C, 65.4; H, 6.6; N, 12.9.

2,5-Dicarbonitrile-2,3-dihydro-4H-pyran (Im). Diamide If, (3.2 g., 0.019 mol.), pyridine (10 ml., 0.124 mol.) and *p*-toluenesulfonyl chloride (10 g., 0.053 mol.) were heated to

(6) C. R. Stephens, E. J. Bianco, and F. J. Pilgrim, *J. Am. Chem. Soc.*, **77**, 1701 (1955).

(7) D. T. Mowry, *Chem. Revs.*, **42**, 257 (1948).

(8) R. C. Elderfield, *Heterocyclic Compounds*, John Wiley and Sons, Inc., New York, 1950, Vol. 1, p. 344.

(9) All melting points are uncorrected.

(10) H. Fischer and E. Baer, *Helv. Chim. Acta*, **18**, 576 (1935).

(11) K. Alder and E. Rüden, *Ber.*, **74**, 920 (1941).

130°. After cooling, the solid residue was crushed and extracted with ether, m.p. 46–48°.

Anal. Calcd. for $C_7H_6N_2O$: C, 62.7; H, 4.5; N, 20.9. Found: C, 62.1; H, 4.9; N, 20.6.

2-Carbethoxy-5-carbonitrile-2,3-dihydro-4H-pyran (In). Amide-ester Ie (5 g., 0.025 mol.), pyridine (6.3 ml., 0.078 mol.), and *p*-toluenesulfonyl chloride (4.71 g., 0.025 mol.) were heated to 80°, and treated further as under Im. On concentration of the ethereal extract 3 ml. of an oil was obtained.

Anal. Calcd. for $C_9H_{11}NO_3$: C, 60.0; H, 6.1; N, 7.8; OC_2H_5, 24.8. Found: C, 59.5; H, 6.1; N, 8.0; OC_2H_5, 24.7.

2-(2-Acetaminoethoxy)tetrahydropyran (IIe). Equimolecular quantities of 2-acetamino-ethanol[12] and 2,3-dihydro-4*H*-pyran[13] were heated with stirring in the presence of 3 drops of conc. HCl. When the mixture became homogeneous, the solution was cooled, neutralized with aqueous Na_2CO_3, extracted with ether and distilled, (b.p. 180–182° [12 mm.]).

Anal. Calcd. for $C_9H_{17}NO_3$: C, 57.8; H, 9.1; N, 7.5. Found: C, 57.8; H, 9.4; N, 7.4.

2-(2-Acetaminoethoxy)tetrahydro-6-carbethoxypyran (IIf). A mixture of 10.3 g. (0.1 mol.) of 2-acetaminoethanol,[12] 15.6 g. (0.1 mol.) of 2-carbethoxy-2,3-dihydro-4*H*-pyran,[5] and 3 drops of conc. HCl was heated with stirring until a homogeneous solution was formed. It was purified as above (31%), b.p. 150–170° (0.3 mm.).

Anal. Calcd. for $C_{12}H_{21}NO_5$: C, 55.6; H, 8.1; N, 5.4; OC_2H_5, 17.3. Found: C, 54.4; H, 8.0; N, 5.9; OC_2H_5, 18.0.

2-(2-p-Nitrobenzaminoethoxy)tetrahydropyran (IIg). A mixture of 4.5 ml. (0.05 mol.) of 2,3-dihydro-4*H*-pyran,[13] 10 g. (0.05 mol.) of 2-(*p*-nitrobenzamino)-ethanol,[14] 2 drops of conc. HCl and 50 ml. of xylene was heated on a water bath. After cooling, the crystals which formed were filtered, dried, and recrystallized from benzene and ethanol, m.p. 103–106°.

Anal. Calcd. for $C_{14}H_{18}N_2O_5$: C, 57.2; H, 6.1; N, 9.5. Found: C, 56.5; H, 6.4; N, 9.9.

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(13) R. L. Sawyer and D. W. Andrus, *Org. Syntheses*, **Coll. Vol. III**, 276 (1955).

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