Notes

A department for short papers of immediate interest.

Benzocoumarins of Steroid-like Structure

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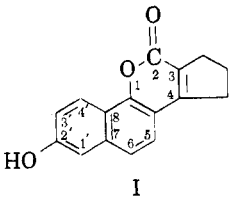
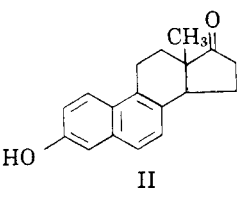
Steroid molecules play an essential role in a wide variety of chemical processes of life, ranging from the control of various endocrine functions and biochemical morphogenesis[1] to the production of cancers. A well-known means of counteracting the effect of hormones and vitamins is to introduce into the body substances with molecular structures similar to those of the hormones or vitamins, but with different biological properties, in order that they may compete with normal metabolites for fixation by the cell receptors. Important steroid metabolites are the estrogens, which are considered as direct or indirect promoters of various cancers; and in view of the growth-inhibiting effects of coumarin on certain tissues,[2] estrogen analogs bearing a coumarin nucleus have been synthesized for biological testing as potential carcinostatic drugs.[3]

1,6-Dihydroxynaphthalene readily condensed with ethyl cyclopentanone-2-carboxylate in ethanol solution in the presence of hydrogen chloride to give 2′-hydroxy-3,4-trimethylene-7,8-benzocoumarin (I) which resembles the natural estrogen equilenin (II)

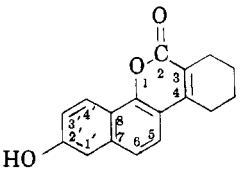


I

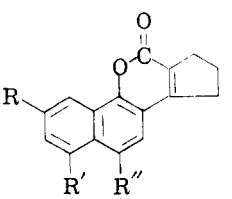


II

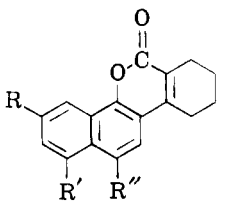
both in molecular shape and in the position of the hydroxyl group. Similar condensation with ethyl cyclohexanone-2-carboxylate afforded 2′-hydroxy-3,4 - tetramethylene - 7,8 - benzocoumarin (III). Under the same conditions, 3′-hydroxy-3,4-trimethylene-(IV) and 3′-hydroxy-3,4-tetramethylene-7,8-benzocoumarin (VII) were obtained from 1,7-dihydroxynaphthalene. The constitution of these four coumarins was deduced from the known fact that α-naphthol reacts with β-keto esters far more easily than does β-naphthol,[4] especially when a weak condensation catalyst such as hydrogen chloride is used. Moreover, 2,6-dihydroxynaphthalene failed to give benzocoumarins with β-keto esters under similar conditions. The same argument applies to naphthoresorcinol (1,3-dihydroxynaphthalene), whose condensation-product with ethyl cyclopentanone-2-carboxylate must have been 5-hydroxy-3,4-trimethylene-7,8-benzocoumarin; with ethyl acetoacetate, 5-hydroxy-4-methyl-7,8-benzocoumarin (X) was obtained.



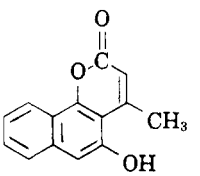
III



IV; R = OH, R′ = R″ = H
V; R′ = OH, R = R″ = H
VI; R″ = OH, R = R′ = H



VII; R = OH, R′ = R″ = H
VIII; R′ = OH, R = R″ = H
IX; R″ = OH, R = R′ = H



X

1,5- and 1,4-Dihydroxynaphthalene condensed with only one molecule of ethyl cyclopentanone- and ethyl cyclohexanone-2-carboxylate to give the corresponding benzocoumarins V, VI, VIII, and IX; cyclic β-keto esters thus behaved like ethyl acetoacetate, which Robinson and Weygand[5] found to react with 1,5-dihydroxynaphthalene in equimolecular amount in the presence of hydrogen chloride. Benzocoumarins V and VIII were also obtained from demethylation with pyridine hydrochloride of their methyl ethers, prepared from 1-hydroxy-5-methoxynaphthalene. From 1-hydroxy-8-methoxynaphthalene, 4′-methoxy-3,4-trimethylene- and 4′-methoxy-3,4-tetramethylene-7,8-benzo-

(1) *Cf.* Needham, *Biochemistry and Morphogenesis*, 2nd Edition, Cambridge University Press, 1950.

(2) Kuhn, Jerchel, Moewus, and Möller, *Naturwissenschaften*, **31**, 468 (1943); Veldstra and Havinga, *Enzymologia*, **11**, 373 (1945).

(3) For experimental inhibition of the carcinogenic activity of hydrocarbons by similarly built inactive polycyclic molecules, see Lacassagne, Buu-Hoï, and Rudali, *Brit. J. Exptl. Pathol.*, **26**, 5 (1945); Kotin, Falk, Lijinsky, and Zechmeister, *Science*, **123**, 102 (1956).

(4) Appel, *J. Chem. Soc.*, 1031 (1935).

(5) Robinson and Weygand, *J. Chem. Soc.*, 386 (1941); Shamshurin, *J. Gen. Chem. U.S.S.R.*, **14**, 885 (1944).

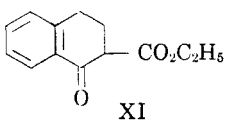
TABLE I

NEW 7,8-BENZOCOUMARINS

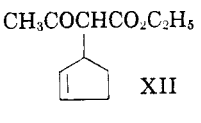
-7,8-Benzocoumarin	No.	Formula	M.P., °C.	Analyses Calc'd C	Calc'd H	Found C	Found H
2'-Hydroxy-3,4-tetramethylene-	III	$C_{17}H_{14}O_3$	330	76.7	5.3	76.6	5.1
3'-Hydroxy-3,4-trimethylene-	IV	$C_{16}H_{12}O_3$	294	76.2	4.8	75.9	4.8
3'-Hydroxy-3,4-tetramethylene-	VII	$C_{17}H_{14}O_3$	311	76.7	5.3	76.5	5.1
3'-Hydroxy-4-methyl-		$C_{14}H_{10}O_3$	285	74.3	4.5	74.0	4.3
1'-Hydroxy-3,4-trimethylene-	V	$C_{16}H_{12}O_3$	341	76.2	4.8	76.0	5.0
1'-Hydroxy-3,4-tetramethylene-	VIII	$C_{17}H_{14}O_3$	304	76.7	5.3	76.4	5.1
6-Hydroxy-3,4-trimethylene-	VI	$C_{16}H_{12}O_3$	206	76.2	4.8	76.0	4.7
6-Hydroxy-3,4-tetramethylene-	IX	$C_{17}H_{14}O_3$	216	76.7	5.3	76.4	5.5
1'-Methoxy-3,4-trimethylene-		$C_{17}H_{14}O_3$	171	76.7	5.3	76.6	5.3
1'-Methoxy-3,4-tetramethylene-		$C_{18}H_{16}O_3$	164	77.1	5.8	77.0	5.6
4'-Methoxy-3,4-trimethylene-		$C_{17}H_{14}O_3$	252	76.7	5.3	77.0	5.5
4'-Methoxy-3,4-tetramethylene-		$C_{18}H_{16}O_3$	188	77.1	5.8	77.3	5.7
5-Hydroxy-4-methyl-	X	$C_{14}H_{10}O_3$	298	74.3	4.5	74.3	4.2

coumarin were likewise readily prepared and dealkylated.

Despite the ease of the above syntheses, the hydrogen chloride-catalyzed condensation of cyclic β-keto esters with dihydroxynaphthalenes to benzocoumarins was not successful in every instance. Thus, ethyl 1-keto-1,2,3,4-tetrahydronaphthalene-2-carboxylate (XI) failed to condense with any of the dihydroxynaphthalenes tried. Nor did ethyl α-Δ^2-cyclopentenylacetoacetate (XII) (prepared



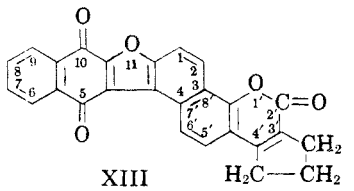
XI



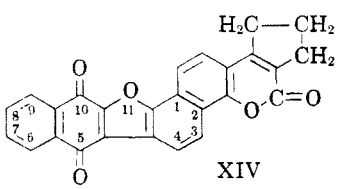
XII

by alkylation of the sodio derivative of ethyl acetoacetate with Δ^2-cyclopentenyl bromide) react with 1,5-dihydroxynaphthalene.

2'-Hydroxy-3,4-trimethylene-7,8-benzocoumarin (I), being a β-naphthol with a free adjacent α-position, reacted with one molecule of 2,3-dichloro-1,4-naphthoquinone in pyridine medium to give a furan



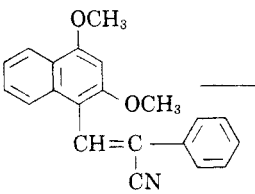
XIII



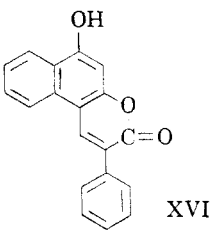
XIV

derivative,[6] 3',4'-trimethylenecoumarino(7',8'-4,-3)brasan-5,10-quinone (XIII), and a similar compound was obtained from coumarin III. From coumarin V, which is an α-naphthol with a free adjacent β-position, 3',4'-trimethylenecoumarino-(7',8'-1,2)brasan-5,10-quinone (XIV) was prepared. These furoquinones represent new types of oxygen-containing heterocycles, with the properties of vat-dyes.

In the course of this work, attention was paid to the chemistry of 1,3-dihydroxynaphthalene. This compound could be readily dialkylated with dimethyl sulfate in aqueous sodium hydroxide to give 1,3-dimethoxynaphthalene, without any appreciable C-methylation. Formylation of this diether with dimethylformamide afforded 2,4-dimethoxy-1-naphthaldehyde; 1-phenyl-2-(2,4-dimethoxy-1-naphthyl)acrylonitrile (XV), prepared by an alkali-



XV



XVI

catalyzed condensation of this aldehyde with benzyl cyanide, was readily converted by pyridine hydrochloride[7] to 7-hydroxy-3-phenyl-5,6-benzocoumarin (XVI).

EXPERIMENTAL

2'-Hydroxy-3,4-trimethylene-7,8-benzocoumarin (I). In a water-cooled solution of 40 g. of 1,6-dihydroxynaphthalene and 58 g. of ethyl cyclopentanone-2-carboxylate in 400 ml. of ethanol, dry hydrogen chloride was bubbled for 3 hours, and the mixture was kept overnight at room temperature. The precipitate which formed was collected, washed with cold ethanol, dried, and recrystallized from nitrobenzene (charcoal), giving shiny, green-tinged, sublimable needles, m.p. 333° (yield, 90–95%). This compound dissolved in aqueous alkalis to give greenish-yellow solutions.

Anal. Calc'd for $C_{16}H_{12}O_3$: C, 76.2; H, 4.8. Found: C, 76.0; H, 4.7.

The other hydroxylated benzocoumarins, listed in Table I, were prepared in the same way and with similar yields.

(6) *Cf.* Buu-Hoï, *J. Chem. Soc.*, 489 (1952); Buu-Hoï and Demerseman, *J. Chem. Soc.*, 4699 (1952).

(7) *Cf.* Buu-Hoï and Lavit, *J. Org. Chem.*, 21, 21 (1956).

The methoxybenzocoumarins were also prepared according to the same procedure, except that they were precipitated from their ethanol solution by means of water, and were recrystallized from ethanol or benzene.

3',4'-Trimethylenecoumarino(7',8'-4,3)brasan-5,10-quinone (XIII). To a solution of 1.5 g. of 2'-hydroxy-3,4-trimethylene-7,8-benzocoumarin in 100 ml. of dry pyridine, 1.4 g. of 2,3-dichloro-1,4-naphthoquinone was added, and the mixture was refluxed for 30 minutes. After cooling, the brown precipitate was collected, washed first with ethanol then with water, dried, and recrystallized from nitrobenzene, giving brown-red sublimable needles (70–75% yield) which did not melt below 360°, and gave a deep violet halochromy in sulfuric acid.

Anal. Calc'd for $C_{26}H_{14}O_5$: C, 76.8; H, 3.5. Found: C, 76.5; H, 3.2.

3',4' - Tetramethylenecoumarino(7',8' - 4,3)brasan - 5,10 quinone, similarly prepared from 2'-hydroxy-3,4-tetramethylene-7,8-benzocoumarin, crystallized from nitrobenzene in brown-red sublimable needles, m.p. above 360°, giving a deep violet halochromy in sulfuric acid.

Anal. Calc'd for $C_{27}H_{16}O_5$: C, 77.1; H, 3.8. Found: C, 76.8; H, 3.6.

3',4'-Trimethylenecoumarino(7',8'-3,4)brasan-5,10-quinone crystallized from nitrobenzene in dark brown needles, which sublimed to brown-red microcrystals, m.p. above 360°. The coloration in sulfuric acid was likewise a deep violet.

Anal. Calc'd for $C_{26}H_{14}O_5$: C, 76.8; H, 3.5. Found: C, 76.6; H, 3.2.

3',4'-Trimethylenecoumarino(7',8'-1,2)brasan-5,10-quinone (XIV). This compound crystallized from nitrobenzene in brown needles, m.p. above 360°; its brown-violet halochromy in sulfuric acid was markedly different from that of the above quinones.

Anal. Calc'd for $C_{26}H_{14}O_5$: C, 76.8; H, 3.5. Found: C, 76.7; H, 3.3.

Ethyl α-Δ²-cyclopentenylacetoacetate (XII). This compound, prepared in 40% yield from the hydrogen chloride adduct with cyclopentadiene, and the sodio derivative of ethyl acetoacetate in toluene medium, was a pale yellow liquid, b.p. 125–126°/13 mm., n_D^{24} 1.4653.

Anal. Calc'd for $C_{11}H_{16}O_3$: C, 67.3; H, 8.2. Found: C, 67.0; H, 8.5.

A cooled solution of 1.5 g. of 1,5-dihydroxynaphthalene and 2 g. of this keto ester in 100 ml. of acetic acid was saturated with hydrogen chloride, and left to stand for 24 hours at room temperature. On dilution with water, 1,5-dihydroxynaphthalene was recovered unchanged. The use of sulfuric acid as condensing agent was also unsuccessful. Ethyl 1-keto-1,2,3,4-tetrahydronaphthalene-2-carboxylate likewise failed to react.

1,3-Dimethoxynaphthalene. This compound (6 g.), prepared from 8 g. of 1,3-dihydroxynaphthalene, 60 ml. of 10% aqueous potassium hydroxide, and 15 g. of dimethyl sulfate, was a pale yellow, viscous oil, b.p. 172–173°/12 mm.

Anal. Calc'd for $C_{12}H_{12}O_2$: C, 76.6; H, 6.4. Found: C, 76.7; H, 6.4.

The *picrate* crystallized from ethanol in brown-red needles, m.p. 141°.

Anal. Calc'd for $C_{18}H_{15}N_3O_9$: C, 51.8; H, 3.6. Found: C, 51.8; H, 3.3.

2,4-Dimethoxy-1-naphthaldehyde. A mixture of 5.5 g. of 1,3-dimethoxynaphthalene, 2.8 g. of dimethylformamide, 5.1 g. of phosphorus oxychloride, and 5 ml. of dry toluene was heated for 3 hours on a boiling water-bath. A saturated aqueous solution of sodium hydroxide was added, and the mixture was refluxed for 30 minutes. The reaction product was taken up in toluene, and the toluene solution was washed with hydrochloric acid, then with water, dried over sodium sulfate, the solvent removed, and the residue vacuum-fractionated. Yield, 2.8 g. of an aldehyde, b.p. 215–235°/13 mm., crystallizing from ethanol in shiny, colorless needles, m.p. 165°, giving a yellow coloration in sulfuric acid.

Anal. Calc'd for $C_{13}H_{12}O_3$: C, 72.2; H, 5.6. Found: C, 71.9; H, 5.2.

The corresponding thiosemicarbazone crystallized from ethanol in pale yellow needles, m.p. 220° (decomp. above 206°).

1-Phenyl-2-(2,4-dimethoxy-1-naphthyl)acrylonitrile (XV). A solution of equimolar amounts of the foregoing aldehyde and benzyl cyanide in warm ethanol was shaken with a few drops of 20% aqueous sodium hydroxide. After addition of water, the precipitate formed was recrystallized from ethanol, giving pale yellow needles, m.p. 151°.

Anal. Calc'd for $C_{21}H_{17}NO_2$: C, 80.0; H, 5.4. Found: C, 80.1; H, 5.6.

7-Hydroxy-3-phenyl-5,6-benzocoumarin (XVI). A mixture of one part of the foregoing nitrile and five parts of redistilled pyridine hydrochloride was refluxed for 10 minutes. Water was added, and the precipitate which formed was recrystallized from benzene, giving pale yellow needles, m.p. 289°, soluble in aqueous sodium hydroxide to give green solutions.

Anal. Calc'd for $C_{19}H_{12}O_3$: C, 79.2; H, 4.2. Found: C, 793.; H, 4.1.

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D-Bis-(*p*-dimethylaminoisopropylphenyl)-carbodiimide

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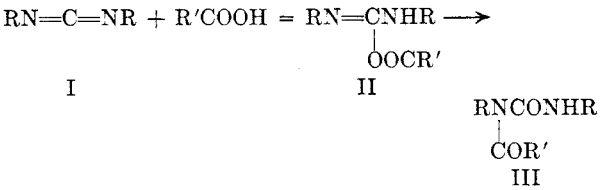
In general, carbodiimides react with carboxylic acids in two ways:[1]

(1) attachment of a proton followed by the attack of the acid anion to form acylurea III:

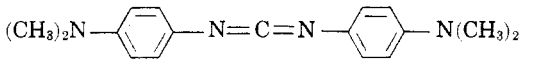


(2) formation of the urea IV and the acid anhydride:

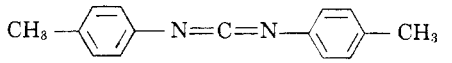
$$I + 2R'COOH = \underset{IV}{RNHCONHR} + (R'CO)_2O$$

The product depends not only on the structure of both reactants but also on the solvent and the temperature. From a study of a large number of carbodiimides, bis-(*p*-dimethylaminophenyl)carbodiimide (V) and bis-(*p*-tolyl)carbodiimide (VI) have been found to react almost exclusively according to (1) and are therefore suggested as the most suitable reagents for the characterization of carboxylic acids.[2]

(1) H. G. Khorana, *Chem. Revs.*, **53**, 145 (1953).
(2) F. Zetzsche and A. Fredrich, *Ber.*, **73**, 1114 (1940).



V

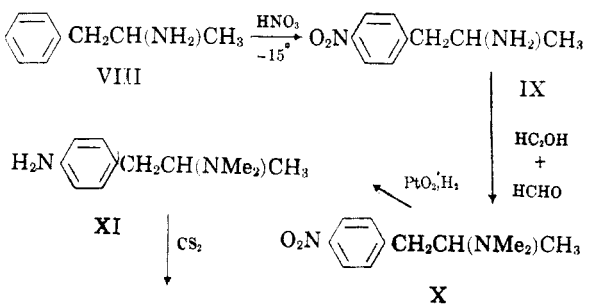


VI

In a previous investigation,[3] the "basic" carbodiimide V was used for the characterization of lipoic acid and some of its derivatives. To study further the reactions of carbodiimides with carboxylic acids, we prepared the optically active compound (XIII) which is, to our knowledge, the first synthesis of an asymmetric diarylcarbodiimide.

Several optically active carbodiimides, *e.g.*, bis-L-menthylcarbodiimide, have been prepared, but their study has shown them to react predominantly according to (2). Analysis of the structures of these substances and of V and VI suggested to us a basic structure for an optically active carbodiimide which is to combine with an organic acid according to (1), namely, a substituted diphenylcarbodiimide, the asymmetric center being located in the side-chain. That this basic structure, represented by XIII, still reacted according to scheme (2) demonstrates the need for more thorough studies of carbodiimides.

In preparing a substituted diphenylcarbodiimide, we started with D-1-phenyl-2-propylamine, commercially available as dexedrine (VIII), since neither 1-(4-nitrophenyl)-1-(N,N-diethylamino)ethane nor 1-(4-aminophenyl)-1-(N,N-diethylamino)ethane (VII) could be resolved. The nuclear nitration was carried out according to[4]; the mixture of nitrobases was fractionated *in vacuo* through a short column and the *p*-isomer was further purified by recrystallization of the hydrochlorides from ethanol:



The carbodiimide (XIII) is an oil, sensitive to moisture by which it is transformed to the urea (XIV); it can be distilled under a pressure of 0.010 mm. in small portions without racemization. Infrared analysis shows a strong band at 2132 cm.$^{-1}$ indicative of the N=C=N grouping. Compound XIII reacts with anhydrous oxalic acid in dry dioxane to form the disubstituted urea (XIV) and a mixture of carbon monoxide and carbon dioxide. With an excess of organic acids in different solvents exclusive formation of the urea (XIV) occurs. Thus, D-bis-(*p*-dimethylaminoisopropylphenyl)carbodiimide falls into that class of carbodiimides which react according to scheme (2) and therefore it is not useful in making derivatives of organic acids.

EXPERIMENTAL

Melting points were taken on the Kofler apparatus and are therefore corrected; analyses by Clark's Microanalytical Lab., Urbana, Ill.

1-(4-Nitrophenyl)-1-(N,N-diethylamino)ethane. 1-(4-Nitrophenyl)-1-bromoethane[5] (16.2 g.) and diethylamine (15 ml.) were heated in a sealed tube in a steam cone for 3 hours. The reaction mixture was taken up in 1 *N* hydrochloric acid and extracted with ether; the aqueous layer was made strongly alkaline and the amine was extracted into ether. The base was purified by distillation *in vacuo:* b.p. (0.4 mm.) 107–109°, yield 11.1 g. or 84%; *picrate* (from methanol): m.p. 152–154°.

Anal. Calc'd for $C_{18}H_{21}N_5O_9$: N, 15.52. Found: N, 15.46.

1-(4-Aminophenyl)-1-(N,N-diethylamino)ethane. Reduction was achieved by refluxing the nitro compound (5.0 g.) with granular tin (5 g.) and 5 *N* hydrochloric acid (400 ml.) for 2 hours. The solution was made strongly alkaline; the amine was collected in ether and purified by distillation *in vacuo.* B.p. (0.4 mm.) 89–91°, yield, 4.1 g. (95%).

Anal. Calc'd for $C_{12}H_{20}N_2$: N, 14.57. Found: N, 14.28.

1-(4-Nitrophenyl)-2-aminopropane (IX). Dexedrine (60.0 g., $[\alpha]_D^{20}$ +34.2°) was nitrated as described.[4] The mixture of nitrobases was fractionated (0.2 mm.) through a Vigreux column (7.5″). Fraction A: 90–95°, 19.2 g.; fraction B: 95–98°, 5.0 g.; fraction C: 98–105°, 53.0 g. Each of these fractions was converted into its hydrochloride by dissolving the substance in absolute ethanol, saturating the solution with dry hydrogen chloride at 0°, and precipitating the salt by addition of absolute ether. By repeated recrystallization from absolute ethanol a total amount of 48.8 g. (51%) of the *p*-isomer hydrochloride was obtained: m.p. 197–199°, $[\alpha]_D^{20}$ +22.0° (*c*, 1.218, water). Further recrystallization did not change the rotation.

Anal. Calc'd for $C_9H_{13}ClN_2O_2$: Cl, 16.36. Found: Cl, 16.25.

The free base was prepared by extracting an alkaline solution of the foregoing hydrochloride with ether and was purified by vacuum-distillation: b.p. (0.5 mm.) 113–114°, $[\alpha]_D^{20}$ +31.4° (*c*, 4.700, methanol), yield 39.0 g. Permanganate oxidation of a sample yielded *p*-nitrobenzoic acid. The hydrochloride and picrate are unsuitable for the isolation of the *o*-isomer from the mother liquor of the *para* compound.

1-(4-Nitrophenyl)-2-(N,N-dimethylamino)propane (X). A mixture of 38.0 g. of IX, 100 ml. of formic acid, and 90 ml. of 35% formaldehyde solution was gently refluxed overnight and then was evaporated to dryness under reduced pressure. The residue was taken up in water, made alkaline, and extracted with ether. The dimethylamino compound was

(3) I. C. Gunsalus, Lois S. Barton, and W. Gruber, *J. Am. Chem. Soc.*, **78**, 1763 (1956).

(4) T. M. Patrick, Jr., E. T. McBee, and H. B. Hass, *J. Am. Chem. Soc.*, **68**, 1153 (1946).

(5) H. B. Hass and M. L. Bender, *J. Am. Chem. Soc.*, **71**, 3482 (1949).

finally distilled *in vacuo:* b.p. (0.5 mm.) 117–119°, yield 39.0 g. (89%). This base was also converted into its *hydrochloride* which was recrystallized from absolute ethanol-ether until its optical rotation was constant: m.p. 224–226°, $[\alpha]_D^{20}$ +7.8° (*c*, 2.536, water).

Anal. Calc'd for $C_{11}H_{17}ClN_2O_2$: C, 53.89; H, 7.00; Cl, 14.49. Found: C, 54.09; H, 7.15; Cl, 14.40.

The base was set free from a sample of this hydrochloride: $[\alpha]_D^{20}$ 0.0° (*c*, 6.510, methanol), *picrate* (from methanol), m.p. 131–133°, $[\alpha]_D^{20}$ +43.5° (*c*, 0.987, acetone).

Anal. Calc'd for $C_{17}H_{19}N_5O_9$: C, 46.68; H, 4.38; N, 16.01. Found: C, 46.77; H, 4.55; N, 16.17.

1-(4-Aminophenyl)-2-(N,N-dimethylamino)propane (XI). The nitro compound X (35.0 g.) was reduced catalytically with Adams' catalyst (1.4 g.) in methanol (1000 ml.): b.p. (0.3 mm.) 104–106° yield 27.0 g. (94%). Recrystallization of this amine was repeated until a constant optical rotation was reached (ether-hexane): m.p. 78–80°, $[\alpha]_D^{20}$ −13.8° (*c*, 1.210, methanol).

Anal. Calc'd for $C_{11}H_{18}N_2$: N, 15.72. Found: N, 15.62.

4,4'-Di-[2-(N,N-dimethylamino)-propyl-1]-thiocarbanilide (XII). A mixture of 25.0 g. of the amine (XI), carbon disulfide (80 ml.), and benzene (250 ml.) was refluxed for 24 hours and the yellow precipitate was collected on a Büchner funnel (filtrate A). A small portion of this xanthate was further purified for analysis by extracting it with cold acetone: m.p. 103–106°, insoluble in organic solvents, very soluble in water, yellow color reaction with Cu ions, unstable.

Anal. Cal'cd for $C_{23}H_{36}S_2N_4$: S, 14.82. Found: S, 14.49.

The suspension of the xanthate in benzene (500 ml.) was refluxed until the generation of H_2S ceased (3 days). Filtrate A was combined with the yellow benzene solution and then was evaporated to dryness under diminished pressure. After several recrystallizations (ether-hexane) the optical rotation was constant: m.p. 116–118°, $[\alpha]_D^{20}$ −16.4° (*c*, 0.750, methanol); yield, 18.0 g. (64%).

Anal. Calc'd for $C_{23}H_{34}N_4S$: N, 14.06; S, 8.02. Found: N, 13.93; S, 8.24.

Carbodiimide XIII. A mixture of XII (8.0 g.), yellow mercuric oxide (50 g.), and benzene was vigorously stirred and the azeotrope, benzene-water, was distilled off; fresh solvent was added from time to time. After 3 hours the mixture of mercuric sulfide and oxide was filtered and the filtrate was evaporated under reduced pressure. A considerable amount of urea (XIV) was present and was eliminated by repeated addition of hexane to an etheral solution of the mixture. The mother liquor was distilled in small portions, yielding 2.3 g. (31%) of a colorless oil: $[\alpha]_D^{20}$ −6.2° (*c*, 1.499, methanol).

Anal. Calc'd for $C_{23}H_{32}N_4$: C, 75.78; H, 8.85; N, 15.37. Found: C, 75.65; H, 8.80; N, 15.13.

Dipicrate (from methanol-acetone): m.p. 128–130°.

Anal. Calc'd for $C_{35}H_{38}N_{10}O_{14}$: N, 17.03. Found: N, 16.85.

The urea (XIV) was recrystallized from benzene-hexane until the optical rotation was constant: m.p. 181–183° (dimorphous, spontaneous transformation from plates to needles at 150–151°), $[\alpha]_D^{20}$ −6.7° (*c*, 1.128, methanol).

Anal. Calc'd for $C_{23}H_{34}N_4O$: C, 72.38; H, 8.96; N, 14.65. Found: C, 72.61; H, 8.80; N, 14.46.

A mixture of 191 mg. of XIII, 500 mg. of anhydrous oxalic acid, and 5 ml. of absolute dioxane was slowly warmed up to 80°. Evolution of gas bubbles, which apparently were a mixture of carbon monoxide and dioxide, took place. Carbon dioxide was shown to be present by precipitation of $BaCO_3$ from a solution of barium hydroxide. Addition of water to the reacted mixture gave a precipitate shown to be the urea XIV.

To a solution of 382 mg. of XIII in 5 ml. of acetone a solution of 194 mg. of glacial acetic acid in 5 ml. of ether was added. The precipitate formed (acetate of XIII) was redissolved by adding more acetone. After standing at room temperature for 3 days, the organic solvent was evaporated *in vacuo* at 30°, the residue was taken up in dilute sodium bicarbonate solution and benzene. In the benzene layer only the urea XIV was found. Similar results were obtained with caprylic, lipoic, and cinnamic acids in a variety of solvents.

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Synthesis of Dicyclohexylammonium-1-1'-C^{14} Nitrite

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One type of commercial vapor phase corrosion inhibitor is known to be essentially dicyclohexylammonium nitrite. This substance was selected to be synthesized with a radioactive C^{14} atom, in order that the radioactive tracer technique might be applied to obtain certain basic information concerning the application of vapor phase inhibitors to military packaging.

The high pressure catalytic hydrogenation of aniline, as described below, was used to prepare the radioactive corrosion inhibitor. This process was used, since it resulted in the highest percent yield of finished product, required the minimum of personal handling and exposure to radioactivity, and the initial material was readily available as aniline-1-C^{14}.

SYNTHESIS OF DICYCLOHEXYLAMINE-1-1'-C^{14} (Reference 1)

The hydrogenation of aniline-1-C^{14} was performed in a high-pressure autoclave. The catalyst used in this synthesis was prepared by taking 100 g. of nitric acid-washed kieselguhr and mixing it with 100 g. of nickel nitrate [$Ni(NO_3)_2 \cdot 6H_2O$] in 150 ml. of water. This mixture then was ground in a ball-mill until a creamy consistency was obtained. The paste was carefully heated to 70–80° with stirring, and a solution of 60 g. of ammonium bicarbonate ($NH_4HCO_3 \cdot 5H_2O$) in 400 ml. of water was added gradually with continued stirring. The resulting mixture was filtered and washed twice with 75-ml. portions of distilled water. The moist cake was broken up and dried at 100–110°. A 3-g. portion of this dried, impregnated kieselguhr was reduced in a stream of hydrogen at 425–475° for about 70 minutes. The active catalyst thus prepared was immediately used in the hydrogenation.

Freshly distilled aniline (4 g.) (b.p. 184–185°), 51.0 mg. of aniline-1-C^{14} hydrochloride (200 μc of activity), 50 ml. of dioxane, and the active catalyst were placed into the bomb and the whole was assembled. Hydrogen was added to a pressure of 2000 p.s.i. The temperature was raised to 250°, which caused an increase in pressure to 2300 p.s.i. The pressure was maintained at 2300 p.s.i. by the addition of hydrogen periodically, and the whole was heated at 250° for three hours, with stirring. The bomb then was cooled, disassembled, and the reaction mixture was removed with the aid of diethyl ether. The reaction mixture was filtered to re-

(1) U. S. Patent 2,092,525, September 7, 1937, H. Adkins and H. Cramer.

move the catalyst and the filtrate was poured into 50 ml. of a 10% HCl solution, with stirring. The precipitated hydrochloride of dicyclohexylamine was filtered onto a Büchner funnel and washed several times with 25-ml. portions of distilled water. The material from the Büchner funnel was removed and placed into 100 ml. of a 15% solution of NaOH, with stirring. This mixture was cooled and extracted with four 50-ml. portions of ethyl ether. After flash-distilling the ethyl ether, the fraction boiling from 256–257° at atmospheric pressure was collected. Infrared spectrograms of the radioactive material compared to that of a freshly distilled sample of dicyclohexylamine (b.p. 256–257°) at atmospheric pressure) established the identity of the synthesized material and also that it was of a high degree of purity.

SYNTHESIS OF DICYCLOHEXYLAMMONIUM-1-1′-C^{14} NITRITE (Reference 2)

The dicyclohexylamine-1-1′-C^{14} (1.00 g.) was added to 8 ml. of distilled water containing 0.2 ml. of 85% phosphoric acid, and 0.40 g. of sodium nitrite was added at 0°, with stirring. The dicyclohexylammonium-1-1′-C^{14} nitrite precipitated and was filtered onto a Büchner funnel, washed with a 2-ml. portion of cold water, and dried. The material was placed into twice its weight of cold water, and the mixture was stirred. The purified dicyclohexylammonium-1-1′-C^{14} nitrite then was filtered onto a Büchner funnel, washed with a 2-ml. portion of cold water, and dried.

The synthesized material had an activity of 62 microcuries. Thus the radiochemical yield of dicyclohexylammonium-1-1′-C^{14} nitrite was 31%. The material had a melting point of 153.0–154.5° with decomposition. (Literature[3] m.p. 154.5°.)

Acknowledgment. Appreciation is expressed to Dr. N. Rubin of the Philadelphia College of Pharmacy and Science, and to Dr. G. K. Holmes of the Aeronautical Materials Laboratory for their assistance, and to Mr. Philip Fischer of the Aeronautical Materials Laboratory for supplying the infrared data used in this investigation.

The opinions or assertions contained herein are the private ones of the writer, and are not to be construed as official or reflecting the views of the Navy Department, or the Naval service at large.

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(2) U. S. Patent 2,544,245 assigned to Shell Development Company (Preparation of dicyclohexylammonium nitrite).

(3) *Dicyclohexylammonium Nitrite*, A. Wachter, T. Skei, and N. Stillman, Shell Development Company, presented at the symposium on Industrial Use of Corrosion Inhibitors, March 1951, Conference, New York National Association of Corrosion Engineers.

2-N-Alkylaminopyrimidine

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It has been previously reported that 2-aminopyrimidine methiodide warmed with an ethanolic or aqueous solution of sodium hydroxide yields 2-N-methylaminopyrimidine.[2,3] Treatment of the methiodide with a cold aqueous solution of sodium hydroxide has been reported to give 1-methyl-2-iminopyrimidine.[3] Prior to this recent disclosure, it was desirable to determine the alkylation products when 2-aminopyrimidine was treated with ethyl or *n*-butyl iodide. Our results indicate that the major product in both cases is the 2-N-alkylaminopyrimidine and that the 1-N-alkyl products, if formed, are very unstable in dilute sodium hydroxide in the cold. These compounds were synthesized by (A) reaction of 2-chloropyrimidine with ethyl or *n*-butylamine for comparison purposes and (B) reaction of 2-aminopyrimidine with ethyl or *n*-butyl iodide followed by neutralization with cold aqueous sodium hydroxide.

EXPERIMENTAL[4]

2-Chloropyrimidine. The compound was prepared from 2-aminopyrimidine[5] as described by Overberger, Kogon, and Minin,[6] m.p. 64–65°.

Preparation of 2-N-ethylaminopyrimidine. Method A. From 2-chloropyrimidine and ethylamine. A solution of 11.4 g. (0.1 mole) of 2-chloropyrimidine, 9.5 g. (0.21 mole) of ethylamine, and 50 ml. of absolute alcohol was refluxed for 4 hours. The solution was cooled in an ice-bath for one hour. The ethylamine hydrochloride that precipitated was filtered and washed with ether, 7.33 g. (95.5%), m.p. 107–108°. The filtrate was evaporated on a steam-bath and the residue was recrystallized from petroleum ether (b.p. 30–60°), yield 11.0 g. (89.6%), m.p. 50–51°.

Anal. Calc'd for $C_8H_9N_3$: C, 58.5; H, 7.3; N, 34.1. Found: C, 58.7; H, 7.6; N, 34.5.

The *picrate* was prepared by adding an excess of a saturated solution of ethereal picric acid to an ethereal solution of the free base. A yellow crystalline solid precipitated which was recrystallized from ethyl alcohol, m.p. 160–161°.

Anal. Calc'd for $C_{12}H_{12}N_6O_6$: N, 23.8. Found: N, 23.6.

Method B. From 2-aminopyrimidine and ethyl iodide. A mixture of 9.4 g. (0.1 mole) of 2-aminopyrimidine, 31.2 g. (0.2 mole) of ethyl iodide, and 75 ml. of absolute alcohol was refluxed for 24 hours. The resulting solution was concentrated to half the volume and was chilled in an ice-bath for one hour. The iodide (I) that precipitated was filtered and washed thoroughly with ether, 21.5 g. (86.0%). Compound I was recrystallized from ethyl alcohol yielding 21.0 g. (84.0%) of a white crystalline solid, m.p. 154–155°.

Anal. Calc'd for $C_6H_{10}IN_3$: C, 28.7; H, 4.0; N, 16.8. Found: C, 28.4; H, 3.9; N, 16.8.

The free base was obtained by the addition of sufficient cold (10°) aqueous sodium hydroxide solution to neutralize a cold (10°) aqueous solution of compound I. The aqueous solution was extracted with three 25-ml. portions of ether, and the ether then was dried over sodium sulfate for 24 hours. After the removal of the drying agent, the solvent was removed on a steam-bath and the residue was recrystallized from petroleum ether (b.p. 30–60°). The product, 8.5 g.

(1) Present address: Jackson Laboratory, Organic Chemicals Department, E. I. du Pont de Nemours & Co., Deepwater, New Jersey.

(2) Overberger and Kogon, *J. Am. Chem. Soc.*, **76**, 1065 (1954).

(3) Brown, Hoerger, and Mason, *J. Chem. Soc.*, 4035 (1955).

(4) All melting points are uncorrected.

(5) A sample of 2-aminopyrimidine was generously contributed by the American Cyanamid Company.

(6) Overberger, Kogon, and Minin, *Org. Syntheses*, **35**, 35 (1955).

(85%), melted at 50–51°. A mixture melting point with a sample of 2-N-ethylaminopyrimidine prepared by procedure *A* gave no depression, m.p. 50–51°. The picrate prepared from ethereal picric acid and recrystallized from ethyl alcohol melted at 160–161°. A mixture melting point with the picrate prepared from procedure *A* gave no depression, m.p. 159–160°.

Preparation of 2-N-ethylaminopyrimidine picrate from I. To 2.5 g. (0.01 mole) of I dissolved in 5 ml. of ethyl alcohol was added an excess of ethereal picric acid. A yellow crystalline solid precipitated immediately. The picrate was filtered and recrystallized from ethyl alcohol, 3.17 g. 90.0%), m.p. 160–161°. A mixture melting point with 2-N-ethylaminopyrimidine picrate, m.p. 160–161°, prepared from procedure *A* gave no depression, m.p. 160–161°.

Preparation of 2-N-n-butylaminopyrimidine. This compound was prepared by procedure *A* and *B* given for 2-N-ethylaminopyrimidine. The iodide (II) recrystallized from ethyl alcohol was obtained in 55.0% yield and melted at 144–146°.

Anal. Calc'd for $C_8H_{14}IN_3$: C, 34.4; H, 5.0; N, 15.1. Found: C, 34.1; H, 5.2; N, 15.0.

The *free base* was obtained from II in 87% yield, b.p. 75–80° (2 mm.), n_D^{20} 1.5328, and by the reaction of 2-chloropyrimidine with *n*-butylamine in 69.0% yield, b.p. 76–78° (2 mm.), n_D^{20} 1.5330.

Anal. Calc'd for $C_8H_{13}N_3$: C, 63.5; H, 8.6; N, 27.8. Found: C, 63.4; H, 8.4; N, 27.5.

The *picrate* prepared from the free base and II respectively was recrystallized from ethyl alcohol and melted at 126–127°, (128–129°).[7]

MADISON, WISCONSIN

(7) Behnisch and Mietzsch, German Patent 889,445, September 10, 1953 (*Chem. Abstr.*, **48**, 12813[e]). The *picrate* was prepared from the condensation product of propargylaldehyde with *n*-butylguanidine sulfate.

N-Substituted 1-, 2-, and 4-Aminofluorene Derivatives[1]

EUGENE SAWICKI[2] AND BARBARA CHASTAIN[3]

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The procedure for the preparation of 1-aminofluorene usually involves 6 steps starting with fluoranthene.[4,5] In attempting to prepare a large quantity of 1-aminofluorene for cancer research studies it was found that the reduction of 1-fluorenonecarboxylic acid to 1-fluorenecarboxylic acid was the weak link in the synthesis. In our hands difficult-to-purify mixtures and unsatisfactory yields resulted when attempts were made to prepare large quantities of 1-fluorenecarboxylic acid by hydrazine,[4] sodium amalgam,[6] or zinc amalgam reduction.[7] Dissatisfaction with the reduction procedure has also been expressed by Gutmann and Albrecht.[8] Ring-reduced by-products were obtained in the sodium amalgam reduction and 3-hydroxy-1,2-diazofluoranthene[9] was isolated from the hydrazine reduction procedure.

A simplified 5-step preparation resulting in higher yields of 1-aminofluorene has been developed. This method depends on carrying out the reduction at a later stage in the synthesis. As each step has been repeated at least 8 times, the procedure is believed to be reliable. Essentially the sequence consists of fluoranthene → 1-(9-fluorenone)carbonyl azide → 1-acetylamino-9-fluorenone → 1-aminofluorene.

The effect of N-acyl groups on the biological properties of biologically important amines is worthy of more intensive study since 2-trifluoroacetylamino fluorene has been reported to be much more carcinogenic[10] to Buffalo rats than is the well-known 2-acetylaminofluorene.[11,12] For this reason N-substituted fluoroacetyl, difluoroacetyl, trifluoroacetyl, and perfluoropropionyl derivatives of the carcinogenic 2-aminofluorene[11,13] as well as of the 1- and 4-isomers were prepared. Included in Table I are other acyl derivatives and Schiff bases. 4-Aminofluorene was prepared by a six step procedure starting from phenanthrene.[14]

EXPERIMENTAL[15]

1-(9-Fluorenone)carbonyl azide. Reaction between 1-(9-fluorenone)carbonyl chloride, m.p. 130–131°, dissolved in acetone and sodium azide in water solution gave a 90% yield of crude product, dec. 86°. Lit. m.p. 90–91°.[16] Recrystallization from heptane gave a 62% yield of yellow needles, m.p. 148–150°. The infrared spectrum in chloroform had a very strong band at 4.88 μ which is apparently due to the azido group.

1-Acetylamino-9-fluorenone. A solution of 2.49 g. of dry 1-(9-fluorenone)carbonyl azide, m.p. 142–146°, in 33 ml. of acetic anhydride was refluxed for 4 hours and allowed to

(1) This investigation was supported by research grant C-1066 from the National Cancer Institute of the National Institutes of Health, U.S. Public Health Service.

(2) New Address: Robert A. Taft Sanitary Engineering Center, 4676 Columbia Parkway, Cincinnati 26, Ohio.

(3) Taken in part from a thesis to be presented by Barbara Chastain in partial fulfillment of the requirements for the M.S. Degree.

(4) Bergmann and Orchin, *J. Am. Chem. Soc.*, **71**, 1111 (1949).

(5) Weisburger and Weisburger, *J. Org. Chem.*, **18**, 864 (1953).

(6) Fieser and Seligman, *J. Am. Chem. Soc.*, **57**, 2174 (1935).

(7) Forrest and Tucker, *J. Chem. Soc.*, 1140 (1948).

(8) Gutmann and Albrecht, *J. Am. Chem. Soc.*, **77**, 175 (1955).

(9) Campbell and Stafford, *J. Chem. Soc.*, 299 (1952).

(10) Morris, *J. Natl. Cancer Inst.*, **15**, 1535 (1955).

(11) Wilson, DeEds, and Cox, *Cancer Research*, **1**, 595 (1941).

(12) Hartwell, *Survey of Compounds Which Have Been Tested for Carcinogenic Activity*, Fed. Sec. Agency, Washington, 1951.

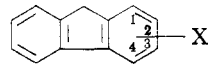
(13) Morris, Dubnik, and Johnson, *J. Natl. Cancer Inst.*, **10**, 1201 (1950).

(14) Sawicki, Ray, and Glocklin, *J. Org. Chem.*, **21**, 243 (1956).

(15) Melting points are uncorrected. Analyses are by Peninsular ChemResearch, Inc., Gainesville, Florida.

(16) Cook and Moffatt, *J. Chem. Soc.*, 1160 (1950).

TABLE I

FLUORENE DERIVATIVES,  —X

X	M.P., °C.	Cryst. Solvent	Yield %	Formula	Analyses Calc'd C	Calc'd H	Calc'd N	Found C	Found H	Found N
1-NHCOOCH$_2$CH$_2$F	123–125	[a]	55	$C_{16}H_{14}FNO_2$			5.17			5.20
1-NHCOCH$_2$F	186–187	[b]	85	$C_{15}H_{12}FNO$			5.81			5.71
1-NHCOCHF$_2$[c]	146–147	[b]	95	$C_{15}H_{11}F_2NO$			5.41			5.28
1-NHCOCF$_3$[c]	154–155	[a]	98	$C_{15}H_{10}F_3NO$			5.05			5.11
1-NHCOC$_2$F$_5$[c]	150–151	[a]	95	$C_{16}H_{10}F_5NO$	58.7	3.05		58.5	3.22	
1-N=CHC$_6$H$_5$	84–86	[d]	80	$C_{20}H_{15}N$			5.20			5.25
1-N=CH(4-C$_6$H$_4$NO$_2$)	198–199	[e]	45	$C_{20}H_{14}N_2O_2$			8.92			9.02
2-NHCO-α-Furyl	198–199	[f]	88	$C_{18}H_{13}NO_2$			5.09			5.13
2-NHCO(4-C$_6$H$_4$OCH$_3$)	236–237	[g]	85	$C_{21}H_{17}NO_2$	80.0	5.40		80.5	5.45	
2-NHCOOCH$_2$CH$_2$Cl	122	[b]	90	$C_{16}H_{14}ClNO_2$	66.7	4.86		66.4	4.92	
2-NHCOCCl$_3$	193–194	[h]	85	$C_{15}H_{10}Cl_3NO$	54.9	3.05		55.2	3.23	
2-NHCO(4-Pyridyl)	223–224	[g]	83	$C_{19}H_{14}N_2O$			9.79			9.60
2-NHCONHC$_2$H$_5$	236 dec	[h]	95	$C_{16}H_{16}N_2O$			11.1			10.7
2-NHCOOCH$_2$CH=CH$_2$	110–111	[b]	38	$C_{17}H_{15}NO_2$	77.0	5.66		77.1	5.72	
2-N=CH(α-Naphthyl)	126–127	[b]	85	$C_{24}H_{17}N$	90.3	5.33		90.1	5.30	
2-N=CHC$_6$H$_3$O$_2$CH$_2$[j]	179–180	[b]	90	$C_{21}H_{15}NO_2$	80.5	4.79		80.7	5.00	
2-N=CH(4-C$_6$H$_4$CH$_3$)	158–159	[b]	85	$C_{21}H_{17}N$	89.0	6.01		88.7	5.90	
2-N=CH(4-C$_6$H$_4$ iso-C$_3$H$_7$)	158–159	[b]	85	$C_{23}H_{21}N$	88.7	6.75		88.4	6.51	
2-N=CH(4-C$_6$H$_4$NHAc)	227–230 dec	[g]	70	$C_{22}H_{18}N_2O$	81.0	5.52		80.7	5.37	
4-NHCOCH$_2$F	175–176	[b]	90	$C_{15}H_{12}FNO$	74.7	4.97		74.5	5.08	
4-NHCOCHF$_2$[c]	172–173	[i]	95	$C_{15}H_{11}F_2NO$			5.41			5.31
4-NHCOCF$_3$[c]	153–154	[a]	97	$C_{15}H_{10}F_3NO$	65.0	3.61		65.1	3.56	
4-NHCOC$_2$F$_5$[c]	144–145	[b]	95	$C_{16}H_{10}F_5NO$	58.7	3.06		58.4	3.14	
4-NHCONHC$_2$H$_5$	253–254	[h]	90	$C_{16}H_{16}N_2O$			11.1			10.8
4-N=CHC$_6$H$_5$	124–125	[a]	88	$C_{20}H_{15}N$	89.2	5.57		89.1	5.40	
4-CONH iso-C$_3$H$_7$	157–158	[b]	78	$C_{17}H_{17}NO$	81.3	6.77		81.5	6.80	
4-CONH-n-C$_4$H$_9$	136–137	[b]	75	$C_{18}H_{19}NO$	81.5	7.17		81.7	7.25	
4-CON(C$_2$H$_5$)$_2$	72–73	[d]	82	$C_{18}H_{19}NO$			5.28			5.35
4-CONHC$_2$H$_5$	138–139	[b]	72	$C_{16}H_{15}NO$	81.0	6.30		81.1	6.38	

[a] Hexane. [b] Heptane. [c] Acid anhydrides were used to prepare these compounds while acid chlorides were used to prepare the remainder of the acylamino derivatives. [d] Pentane. [e] Aqueous Methyl Cellosolve (2-Methoxyethanol). [f] Benzene. [g] Xylene. [h] Methanol. [i] Aqueous methanol. [j] 2-Piperonylideneaminofluorene.

cool. The yellow crystals of *sym*-bis-(9-fluorenonyl) urea[17] m.p. 260–280°, were filtered. The addition of water to the mother liquid gave an approximately 90% yield of a mixture, m.p. 110–118°, probably containing the 1-mono- and 1-di-acetylaminofluorenones. Crystallization of a small amount of this product from aqueous acetic acid gave yellow needles of the monoacetylamino derivative, m.p. 137–138°. Lit. m.p. 138.0–138.3.[18] The infrared spectrum in chloroform showed the presence of a C=O stretching band at 5.89 μ with an inflection at 5.82 μ and an N—H stretching band at 3.0 μ.

The *urea derivative* was crystallized from benzene to give a 10% yield of yellow needles, m.p. 283–285°.

Anal. Calc'd for $C_{27}H_{16}N_2O_3$: N, 6.73. Found: N, 6.63.

1-Aminofluorene. A solution of 2.79 g. of the crude acetylamino-9-fluorenone, m.p. 110–118°, and 1.4 g. of sodium hydroxide in 35 ml. of ethylene glycol and 4 ml. of 85% hydrazine hydrate was refluxed for 2½ hours. The condenser was removed and the solution was evaporated until its temperature was 205°. The mixture then was refluxed 3 hours longer and finally was poured into excess water. Crystallization from hexane gave a 65% yield (based on 1-(9-fluorenone)carbonyl azide) of colorless needles, m.p. 124–125°. Lit. m.p. 124–125°.[5]

General procedure for the preparation of the acylaminofluorenes. To a warm solution of 0.002 mole of aminofluorene in 10 ml. of benzene and 0.2 ml. of pyridine was cautiously added 0.0022 mole of the acid chloride or acid anhydride. The mixture was warmed for 5–10 minutes and excess water was added. The benzene was steam-distilled and the product was crystallized from the appropriate solvent, Table I. The urethans were prepared in a similar fashion from alkyl chlorocarbonates, Table I.

General procedure for the preparation of the Schiff bases. A hot solution of 0.002 mole of the aldehyde in a small volume of alcohol was added to 0.002 mole of the aminofluorene dissolved in 5 ml. of alcohol. The mixture was refluxed for one hour, excess water was added, and it was allowed to cool. The precipitate was crystallized from the appropriate solvent, Table I.

General procedure for the preparation of 4-carbamoylfluorene derivatives. Two molar-equivalents of an aliphatic amine were added to a solution of a molar-equivalent of 4-fluorenecarbonyl chloride in acetone. The mixture was refluxed for 15 minutes and then excess dilute sulfuric acid was added. The precipitate was crystallized from the appropriate solvent, Table I.

Preparation of 1-(1'- or 4'-fluorenyl)-3-ethylurea. To a 0.01 mole of the aminofluorene dissolved in 20 ml. of ben-

(17) This compound was apparently derived from the rearrangement of a small portion of the carbonyl azide to the isocyanate. Some of the isocyanate reacted with water to give the amine which then reacted with the isocyanate to form the symmetrical urea.

(18) Huntress, Pfister, and Pfister, *J. Am. Chem. Soc.*, **64**, 2845 (1942).

zene was added 0.01 mole of ethyl isocyanate. The mixture solidified. Crystallization from the appropriate solvent gave the pure compound, Table I.

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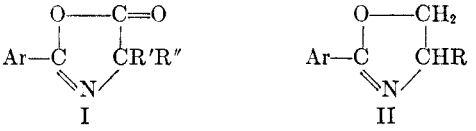
Azidocarbonyl Compounds. IV. Acid Catalysis of α-Azido-Carboxylic Acids and Their Esters[1]

J. H. BOYER AND J. STOCKER

Received April 20, 1956

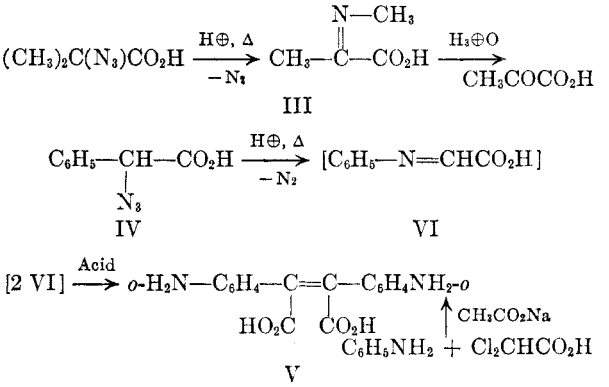
An interest in 5-ketoöxazolines (I) (azlactones) was a natural outgrowth of the discovery of the formation of oxazolines (II) from certain aromatic aldehydes and azidohydrins.[2] In order to determine the possibility of realizing an acid-catalyzed reaction between aldehydes and α-azidoacids, combinations of benzaldehyde containing sulfuric acid with α-azidoacetic, with α-azidoisobutyric, and with α-azido-α-phenylacetic acids were studied. Azlactones were not detected in the reaction products which were investigated not only for the oxazolone itself but also for its hydrolysis products as well as possible condensation products with benzaldehyde, present in excess. Apparently the presence of the aldehyde was unimportant since each azide gave the same product in acid-catalyzed reactions carried out in the absence of benzaldehyde.



I II

Acid catalysis resulted in the evolution of nitrogen with the apparent migration of methyl carbanion from carbon to nitrogen and the formation of the Schiff's base (III) from α-azidoisobutyric acid. Subsequent hydrolysis allowed the formation of pyruvic acid, isolated as its dinitrophenylhydrazone.

Competition between the migration of hydrogen and of the phenyl group apparently favored the latter in the case of α-azido-α-phenylacetic acid (IV) and its ethyl ester.[3] The product, *o,o'*-diaminostilbenedicarboxylic acid (V) (both geometric isomers assumed present) was previously obtained from the anil (VI) of glyoxylic acid upon warming in acetic acid and from treating aniline with dichloroacetic acid in a warm sodium acetate solution.[4]



III

IV VI

V

The infrared spectrum of a sample of the product (V) obtained from α-azido-α-phenylacetic acid was identical with that from a sample obtained from dichloroacetic acid and aniline.

EXPERIMENTAL[5]

Acid decomposition of α-azido-α-phenylacetic acid and its ethyl ester. α-Azido-α-phenylacetic acid[6] (1.02 g., 0.006 mole) or the ethyl ester[3] (1.021 g., 0.005 mole) was dissolved in 20 ml. of warm benzene and added dropwise to a mixture of 1.4 ml. of concentrated sulfuric acid and 15 ml. of benzene, the latter maintained at *ca.* 75° and stirred mechanically. When the reaction appeared complete, the entire mixture was poured into 20–25 g. of ice and water. The mixture was filtered by suction to remove traces of scum, and the aqueous layer was separated. Solid sodium carbonate was added in small portions, with frequent stirring, to adjust the solution to *p*H 2–3 (maximum precipitation). The yellow-brown precipitate was filtered, thoroughly water-washed, and dried in a vacuum for 24 hours. Additional material was obtained by evaporation of the filtrate, crude yield 54%. The m.p. was indeterminate, darkening of the material began about 180°, deepening to a black sintered product about 300°.[4]

The product obtained either by Heller's procedure[4] or by the present procedure was poorly soluble in water, slightly soluble in alcohol, very soluble in aqueous base (0.1 *N* or greater), including pyridine (insoluble in anhydrous pyridine). Solutions in all bases, organic or inorganic, required the addition of acid for reprecipitation. It was very soluble in dimethylformamide from which it was not easily recovered, very slightly soluble or insoluble in ethyl ether, benzene, acetone, and chloroform. Solution of the material, crude or otherwise, in 0.1 *N* sodium hydroxide and reprecipitation with dilute hydrochloric acid yielded a product with apparently unchanged properties.

Anal. Calc'd for $C_{16}H_{14}N_2O_4$: C, 64.41; H, 4.73; N, 9.39. Calc'd for $C_{16}H_{14}N_2O_4 \cdot {}^1/_2H_2O$: C, 62.53; H, 4.92; N, 9.12. Found: C, 62.88; H, 5.51; N, 9.42. Repeat: C, 62.41; H, 4.96; N, 8.80.

The following medium to strong absorption peaks in cm.$^{-1}$ for the product (V) from either aniline and dichloroacetic

(1) A grant from the American Association of Arts and Sciences is gratefully acknowledged.

(2) J. H. Boyer and J. Hamer, *J. Am. Chem. Soc.*, **77**, 951 (1955).

(3) Only hydrogen migration was detected from pyrolysis of ethyl α-azido-α-phenylacetate (J. H. Boyer and D. Straw, *J. Am. Chem. Soc.*, **75**, 1642 (1953)).

(4) G. Heller, *Ann.*, **332**, 268 (1904); **358**, 354 (1907); **375**, 266 (1910).

(5) Melting points are corrected. Elemental analyses by Microtech laboratories, Skokie, Illinois. Infra-red analyses by S. P. Sadtler and Son, Inc., Philadelphia, Pa. and by Mr. R. T. O'Connor, Southern Regional Research Laboratory, New Orleans, Louisiana.

(6) A. Darapsky, *J. prakt. Chem.*, 99, 179 (1919).

acid or from phenylazidoacetic acid are: 3390, 3310, 3018, 1724, 1622, 1590, 1522, 1495, 1362–1350, 1187, 833, 757. These values were obtained from potassium bromide wafers of the samples.

The material did not sublime and was insoluble in camphor. Permanaganate oxidation readily occurred; copious precipitation of manganese dioxide was observed. No organic product was isolated.

Acid decomposition of α-azidoisobutyric acid. α-Azidoisobutyric acid (4.50 g., 0.0349 ml.), a few hundred mg. at a time, was added to 10 ml. of conc'd H_2SO_4 maintained at 65–75°, with stirring. The chemical reaction was very active but easily controlled. When gas ceased to evolve, the reaction mixture was poured into 50 ml. of ice-water. The reaction mixture was placed on the steam-bath overnight, was cooled to room temperature, and filtered from a small amount (0.359 g.) of gray solid. The filtrate was extracted four times with ether. The combined ether extracts were evaporated in an air stream until all ether had been removed. The remaining liquid (1.8 g.) was treated for a ketone derivative. It was dissolved in 5 ml. of 95% EtOH, filtered of a trace of solid, added to 10 ml. of 2,4-dinitrophenylhydrazine reagent, warmed to 50°, and cooled. The DNP of pyruvic acid separated an orange-yellow solid, m.p. 214–218° (mixture m.p. gave no depression), wt. 0.628 g. (7% yield).

Attempts to prepare α-azidodiphenylacetic acid from α-bromodiphenylacetic acid as well as the diethyl acetal of azidoacetaldehyde from the diethyl acetal of bromoacetaldehyde and sodium azide were unsuccessful.

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A New Synthesis of 1-Methyl-3-(4′-dimethylaminobutyl)-piperidine

ARTHUR P. PHILLIPS

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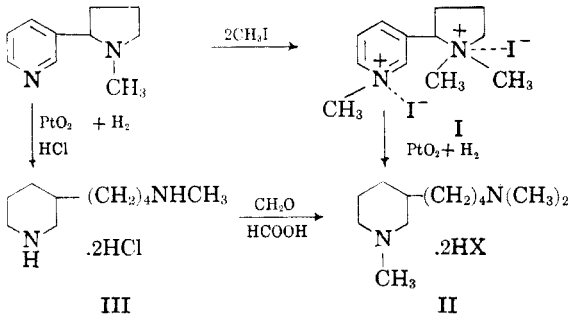
Catalytic hydrogenation of nicotine dimethiodide (I) with Adams catalyst gave good yields of 1-methyl-3-(4′-dimethylaminobutyl)piperidine (II) as its dihydriodide.[1]



Both II and its bis-metho quaternary salts have been found to be potent hypotensive ganglionic blocking agents in laboratory animals.[1,2]

An alternative route has now been devised for the preparation of II. Nicotine dihydrochloride is reduced to octahydrometanicotine (III)[1,3,4] which then is methylated by the Eschweiler[5]-Clarke[6] procedure to yield II.

The new synthesis has several advantages for the larger scale preparations which were necessary in order to obtain enough material for clinical evaluation. One of the limiting factors in larger runs is the amount of nicotine derivative which can conveniently be reduced at one time in the catalytic hydrogenation apparatus. The original route used the relatively costly and heavy methyl iodide which contributes more than half the weight of the intermediate I, as iodide. Since the *dihydriodide* of II is not suitable for clinical purposes, use of iodide was neither necessary nor desirable. Several attempts to circumvent the use of iodide by quaternizing nicotine with methyl chloride in an autoclave under pressure, prior to reduction, gave unsatisfactory results, presumably because of incomplete reaction with the methyl chloride.

The conversion of I to II or of nicotine to III requires, presumably, that the debenzylative-like cleavage of the pyrrolidine ring should *precede* hydrogenation of the pyridine ring. Both the pyrrolidine ring cleavage and the pyridine ring hydrogenation should be accelerated when the nitrogens are cationic. Quaternization seems to favor the preliminary debenzylative-like ring-opening somewhat more efficiently than does the making of the nitrogens cationic through simple salt formation with hydrochloric acid. Thus similar catalytic hydrogenations gave about 90% of II from I and only about 70% of the open chain product,[7] III, from nicotine dihydrochloride.

EXPERIMENTAL

Reduction of nicotine dihydrochloride. Catalytic hydrogenation of 16 g. (0.1 mole) of pure *l*-nicotine in 150 cc. of ethanol containing 0.3 mole of hydrogen chloride and 0.5 g. of Adams catalyst was carried out in a Burgess-Parr type machine at four atmospheres of hydrogen pressure and room temperature. Reduction was rapid and 0.35–0.4 mole of hydrogen was absorbed within three hours. The filtrates were concentrated after removal of the catalyst. The product, octahydrometanicotine dihydrochloride (III), was purified by recrystallizations from ethanol–ethyl acetate, and from isopropyl alcohol. The yield of pure product was 15–17 g. (60–70%); m.p. 202–203°.

Equally successful results were obtained on a much larger scale using a high pressure rocking-bomb hydrogenator.

Methylation of III. A 34-g. portion (0.2 mole) of the free base, liberated from the dihydrochloride, III, was mixed carefully and with cooling with 70 cc. of 98% formic acid.

(1) Phillips, *J. Am. Chem. Soc.*, **76**, 2211 (1954).
(2) Norton and Phillips, *Nature*, **172**, 867 (1953).
(3) Windus and Marvel, *J. Am. Chem. Soc.*, **52**, 2543 (1930).
(4) Harlan and Hixon, *J. Am. Chem. Soc.*, **52**, 3385 (1930).
(5) Eschweiler, *Ber.*, **38**, 880 (1905).
(6) Clarke, Gillespie ,and Weisshaus, *J. Am. Chem. Soc.*, **55**, 4571 (1933).
(7) The authors of references (3) and (4) claim that catalytic hydrogenation of nicotine dihydrochloride gave 75% of octahydrometanicotine (III) and 25% of hexahydronicotine.

After adding 60 cc. of 37% formalin the mixture was heated for four hours at 100°. Another 70 cc. of 98% formic acid and 50 cc. of 37% formalin were added and heating was continued for six hours. The reaction mixture was acidified with 60 cc. of concentrated hydrochloric acid and evaporated to dryness *in vacuo*. The residue was purified by several recrystallizations from isopropyl alcohol and gave 50–52 g. (90–95%) of II dihydrochloride, m.p. 239–240°.

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Steric Factors in the Hydrolysis of Potassium Dinitrochlorobenzenesulfonates

JACK RADELL, LEONARD SPIALTER, AND RICHARD C. JARNAGIN

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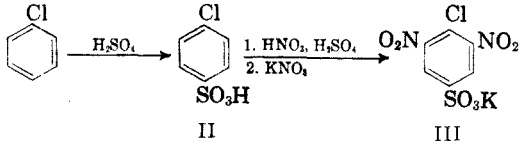
The sulfonate group in potassium 2-chloro-3,5-dinitrobenzenesulfonate, in contrast to its isomer potassium 4-chloro-3,5-dinitrobenzenesulfonate, hydrolyzes readily under nonequilibrium conditions. This was deduced from an examination of the mixture of these isomers obtained by the monosulfonation of chlorobenzene followed by subsequent dinitration. It is suggested that steric factors play an important role in the differential reactivity of these compounds.

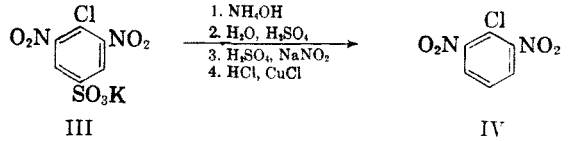
DISCUSSION

An attempt to prepare 2,6-dinitrochlorobenzene (IV) directly from potassium 4-chloro-3,5-dinitrobenzenesulfonate (III)[1] showed that the 4-chloro compound III contained significant amounts of the isomer, potassium 2-chloro-3,5-dinitrobenzenesulfonate (V). Upon refluxing with aqueous sulfuric acid, V but not III could be hydrolyzed under nonequilibrium conditions. However, refluxing under equilibrium conditions resulted in no detectable quantity of either dinitrochlorobenzene isomer.

In the recommended procedure[1,2] for the preparation of potassium 4-chloro-3,5-dinitrobenzenesulfonate (III), the first step involves the sulfonation of chlorobenzene, followed by dinitration and isolation of the potassium salt (III). 2,6-Dinitrochlorobenzene (IV) may be prepared[1,2] from III by the circuitous route involving conversion of the chlorine atom to an amino group, then hydrolysis of the sulfonate function followed by diazotization of the amino group and replacement with a chlorine atom.



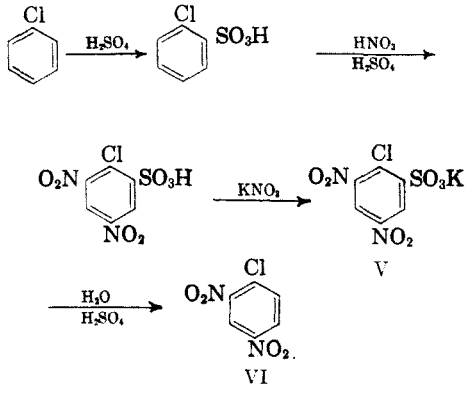
II III



III IV

Since hydrolysis of the sulfonate group in III would lead directly to the desired product, IV, this approach was undertaken. No information is reported on this hydrolysis in the literature.

From the refluxing aqueous sulfuric acid solution of potassium dinitrochlorobenzenesulfonates (I) was steam-distilled a light yellow water-insoluble solid, under nonequilibrium conditions, which was identified as 2,4-dinitrochlorobenzene. Most of the starting material (69.3%) could be accounted for by the recovery of pure III. These results indicate the sulfonation of chlorobenzene resulted in the formation of 2-chlorobenzenesulfonic acid as well as the 4-chlorobenzenesulfonic acid. The reactions converting 4-chlorobenzenesulfonic acid to III, which failed to hydrolyze, have been described above. The 2-chlorobenzenesulfonic acid that formed underwent a similar series of reactions. The latter was nitrated to 2-chloro-3,5-dinitrobenzenesulfonic acid which was isolated as a potassium salt (V). Compound V upon hydrolysis formed 2,4-dinitrochlorobenzene (VI).



The attempt to hydrolyze the same material (I) by simple refluxing with aqueous sulfuric acid failed. This indicated that the equilibrium is far on the side of the sulfonic acid and unfavorable for the hydrolysis of 2-chloro-3,5-dinitrobenzenesulfonate (V). However, under nonequilibrium conditions where the product is removed by steam-distillation as soon as it is formed, complete hydrolysis of V is accomplished. Although the equilibrium is not very favorable it must be established rather readily since the hydrolysis was complete in two hours.

No 2,6-dinitrochlorobenzene (IV) steam-distilled during the 26 hours the aqueous sulfuric acid solution was refluxed, nor could any be isolated from

(1) H. P. Schultz, *Org. Syntheses*, **31**, 45 (1951).
(2) F. D. Gunstone and S. H. Tucker, *Org. Syntheses*, **32**, 23 (1952).

the benzene used to extract the reaction mixture. The failure of compound III to hydrolyze to IV under equilibrium or nonequilibrium conditions must be due to the fact that either the hydrolysis product (IV) is not steam-distillable or the equilibrium in this hydrolysis is both very slow and the position of the equilibrium is very unfavorable in forming IV.

Recrystallization of I from water gave a single pure component which had an x-ray powder diffraction pattern identical with that of unreacted III recovered from the hydrolysis. This indicates that the two samples having the same x-ray powder diffraction patterns are pure III. The latter can be obtained by the hydrolysis or recrystallization of I. This information can be utilized to make a complete separation of a mixture of isomers III and V by exhaustively hydrolyzing isomer V and steam distilling the product, VI.

It appears that electronic considerations cannot be important in explaining the observed behavior. The nitro groups in molecules III and V should exert the same electronic (inductive and resonance) effects on the respective carbon atoms bearing sulfonate substituents. This is true because these groups are in the 3,5-positions in both molecules. The resonance contribution of the chlorine in both molecules might be expected to be the same because of the well-known equivalent $+T$ effect in the *ortho* and *para* positions. However, the chlorine atom in V, because of its proximity, exerts a more pronounced $-I$ effect on the position to which the sulfonate group is attached than does the chlorine atom in III. Experimental evidence[3] indicates that electron-attracting substituents in an aromatic sulfonate retard the hydrolysis of the sulfonate group. Hence, it would be expected that the sulfonate group in III would be hydrolyzed more readily than in V. However, III was recovered unchanged and V was completely hydrolyzed.

The Stuart-Briegleb atomic models show that there is free rotation around the C—S bond of III and restricted rotation around the C—S bond in V. This steric interaction must have weakened the C—S bond in the latter and facilitated the hydrolysis of the sulfonate group. This effect becomes more significant when we realize that the ease of hydrolysis of the sulfonate group in these two isomers is the reverse of what would have been expected from a consideration of inductive effects alone.

EXPERIMENTAL[4]

Potassium dinitrochlorobenzenesulfonates. This mixture was obtained by the procedure in *Organic Syntheses*.[1,2] The unrecrystallized material was isolated after pouring the sulfonation reaction mixture on ice. The mixture of dinitrochlorobenzenesulfonic acids, isolated by filtration after most of the ice had melted, was slowly added to 1.5 l. of water containing 105 g. of anhydrous potassium carbonate. The filtered and air-dried (48 hours) solid (I) weighted 160 g. and was water-soluble.

Equilibrium hydrolysis of potassium dinitrochlorobenzenesulfonates. A solution of 20 g. of I in 525 g. of 75% aqueous sulfuric acid was refluxed for 22 hours at 144°. The refluxed solution after cooling, was continuously extracted with benzene for 24 hours. No detectable solid was isolated from the evaporated benzene extract. When the same procedure was repeated with 85% sulfuric acid, the solution turned black after refluxing at 165° for 23 hours. The black reaction mixture was extracted in the same manner. Evaporation of the benzene extract to dryness left only traces of solid insufficient for characterization.

Nonequilibrium hydrolysis of potassium dinitrochlorobenzenesulfonates. To a flask fitted with a 25-ml. Dean and Stark distilling receiver filled with water was added 20 g. of I, 81 g. of water, 240 g. of concentrated sulfuric acid (*sp. gr.* 1.84), and some carborundum boiling chips. During the first 2 hours there steam-distilled from the refluxing solution a yellow solid. No more water-insoluble material collected after an additional 24 hours of refluxing. The yellow solid was filtered and washed with 5 × 20-ml. portions of water on a sintered glass funnel. The last wash was still yellow but neutral to litmus paper. The yield of dinitrochlorobenzene was 1.6 g. (12.7%),[5] m.p. 46.5–47.5°. This material was recrystallized by dissolving in 15 ml. of benzene, with heat, and adding 5 ml. of isopropyl alcohol to the filtered, cooled, and concentrated (to 8 ml.) benzene solution. The crystallized solid was filtered at 0–5° and washed with 5 × 2-ml. portions of low-boiling petroleum ether cooled to 0°. The light yellow solid gave a negative ferric chloride test for phenol, a positive Beilstein test for halogen, and a positive soda lime test for nitrogen. After 18 hours at 25° and 1 mm. over phosphorus pentoxide in an Abderhalden drier, the yellow solid weighed 1.2 g. This was, evidently, the 2,4-isomer since it had an undepressed melting point and an infrared absorption spectrum identical with that of an authentic sample of 2,4-dinitrochlorobenzene.

Anal. Calc'd for $C_6H_3ClN_2O_4$: C, 35.57; H, 1.49; N, 13.83. Found: C, 35.84; H, 1.53; N, 14.02.

The combined aqueous solution of mother liquor and washes was continuously extracted with benzene for 72 hours. No residue was obtained after the benzene was evaporated to dryness. During the extraction a solid formed in the extraction chamber. After filtration and drying it weighed 12.1 g. (69.3%).[5] This material had an x-ray powder diffraction pattern different from I but the same as the product obtained from the recrystallization of I from hot water.

Infrared absorption data. Spectra were obtained on a Perkin-Elmer Model 21 double beam infrared spectrophotometer. Solutions (30 mg. of sample in 1 ml. of $CHCl_3$) in 0.1-mm. cells were examined between 2–15 microns using a sodium chloride prism.

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(3) C. M. Suter, *The Organic Chemistry of Sulfur*, John Wiley and Sons, Inc., New York, N. Y., 1944, pp. 387–393.

(4) All melting points are uncorrected. Analyses were performed by Oakwold Laboratories, Alexandria, Virginia.

(5) These yields are calculated on the assumption that I contains no inorganic salts.

Phenazine Syntheses. VIII.[1] Di-N-Oxides

DONALD L. VIVIAN

Received April 20, 1956

In the course of preparing phenazine derivatives for testing against Sarcoma 37, a number of di-N-oxides were synthesized. The compounds were prepared either (1) by the action on the requisite phenazine of a 10% solution of 30% H_2O_2 in glacial acetic acid at 50–55° for 16–20 hours, or (2) by the action at room temperature for 5–10 days of an equilibrium solution of acetylperoxide. The first is the method of Clemo and McIlwain,[2] and the second that of Pachter and Kloetzel.[3] No significant difference in results was shown between the two methods.

Isolation of the oxides was effected by pouring the solutions into about twice their volume of water. In some instances, especially those of room-temperature reactions, it was necessary to initiate precipitation of the product by the addition of a small amount of sodium carbonate.

Recrystallizations were from absolute ethanol, except for 2-chloro-8-ethoxyphenazine 5,10-dioxide, which was recrystallized from glacial acetic acid. The use of this solvent for general recrystallization, however, was abandoned when it was found that the homologous 2-chloro-8-methoxyphenazine 5,10-dioxide, m.p. 187–188° (d),[4] was converted to a monoxide, m.p. 217–220° (d), by recrystallization from boiling acetic acid, as shown by the analysis (see Table II). This resembles the experience of Yoshioka,[5] who obtained 2-methoxyphenazine from its mono-N-oxide when he refluxed the latter with glacial acetic acid. The same phenomenon was exhibited by 2-bromo-8-ethoxyphenazine 5,10-dioxide, m.p. 191–193° (d), which on recrystallization from acetic acid was likewise converted to a monoxide, m.p. 194–222° (d), as shown by the analysis given in Table II.

It is noticeable that the melting points of all the dioxides, save for the one with a free 2-hydroxyl group, are quite closely grouped, falling within the limits of 187–201°. This is likewise close to the m.p. of the unsubstituted phenazine 5,10-dioxide, which is 204° (d).[2] Too much importance should not be attached to the exact m.p. figures, for, as in the instance of the quaternary phenazines,[8] the temperatures are really those of decomposition, and can be caused to undergo considerable variation by changing the rate of heating.

Results are summarized in the following tables:

TABLE I

PROPERTIES OF PHENAZINE 5,10-DIOXIDES

5,10-Dioxide from:	M.p.,[4] °C.	Form	Yield, %	Empirical Formula	Analyses[6] C Calc'd	C Found	H Calc'd	H Found
2-Bromo-8-ethoxyphenazine[7]	191–193(d)	(*a*)	62	$C_{14}H_{11}BrN_2O_3$	50.2	50.2	3.31	3.50
2-Bromo-7-methoxyphenazine[7]	194–196(d)	(*a*)	65	$C_{13}H_9BrN_2O_3$	48.6	49.0	2.82	3.06
2-Bromo-8-methoxyphenazine[7]	189–191(d)	(*a*)	64	$C_{13}H_9BrN_2O_3$	48.6	48.7	2.82	3.01
2-Chloro-7-ethoxyphenazine[9]	190–191(d)	(*a*)	60	$C_{14}H_{11}ClN_2O_3$	57.8	57.8	3.82	4.12
2-Chloro-8-ethoxyphenazine[9]	193–194(d)	(*a*)	68	$C_{14}H_{11}ClN_2O_3$	57.8	57.8	3.82	4.12
2-Chloro-7-methoxyphenazine[9]	195–197(d)	(*a*)	60	$C_{13}H_9ClN_2O_3$	56.6	56.7	3.26	3.63
2-Chloro-8-methoxyphenazine[9]	187–188(d)	(*a*)	76	$C_{13}H_9ClN_2O_3$	56.6	56.5	3.26	3.48
8-Bromo-2-phenazinol[7,10]	Black by 300°, but not melted	(*b*)	45	$C_{12}H_7BrN_2O_3$	47.0	47.0	2.30	2.72
2-Phenazinecarbonitrile[11]	199–201(d)	(*c*)	64	$C_{13}H_7N_3O_2$	65.8	65.7	2.97	3.14

(*a*) Red-orange microcrystals, or small matted needles. (*b*) Brownish-red leaflets. (*c*) Small orange-red flakes, with a golden luster.

TABLE II

PROPERTIES OF PHENAZINE MONOXIDES

Mono-N-oxide from:	M.p., °C.	Empirical Formula	Analyses C Calc'd	C Found	H Calc'd	H Found	Cl Calc'd	Cl Found	N Calc'd	N Found
2-Chloro-8-methoxyphenazine 5,10-dioxide	217–220(d)[a]	$C_{13}H_9ClN_2O_2$	59.9	59.6	3.48	3.71	13.6	13.4	10.7	10.7
2-Bromo-8-ethoxyphenazine 5,10-dioxide	194–222(d)[a]	$C_{14}H_{11}BrN_2O_2$	52.7	52.4	3.47	3.63				

[a] Both of these compounds form very small, matted orange needles.

(1) Paper VII: *J. Org. Chem.*, **21**, 824 (1956).
(2) Clemo and McIlwain, *J. Chem. Soc.*, 479 (1938).
(3) Pachter and Kloetzel, *J. Am. Chem. Soc.*, **73**, 4958 (1951).
(4) All melting-points are corrected.
(5) Yoshioka, *Jour. Pharm. Soc. Japan*, **72**, 1128 (1952).
(6) Microanalyses by the Microanalytical Laboratory of the National Institutes of Health, under the direction of Dr. W. C. Alford.
(7) Vivian, Hartwell, and Waterman, *J. Org. Chem.*, **19**, 1136 (1954).
(8) Vivian, *J. Org. Chem.*, **21**, 822 (1956).
(9) Vivian, Greenberg, and Hartwell, *J. Org. Chem.*, **16**, 1 (1951).
(10) Purified by solution in KOH, filtration, and reprecipitation. Additional analysis: N, Calc'd: 9.12. Found: 9.03.
(11) Vivian, Hartwell, and Waterman, *J. Org. Chem.*, **20**, 797 (1955).

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The Addition of Alkanols to 1,1,2-Trichloro-3,3,3-trifluoropropene—Some Corrective Data

J. D. PARK, W. M. SWEENEY, AND J. R. LACHER

Received April 27, 1956

We[1] had previously reported the addition of alkanols to $CF_3CCl{=}CCl_2$ in the presence of a base. The principal product was identified as an unsaturated fluorochloroether. However, an examination of the infrared spectrogram taken of these vinyl ethers revealed the presence of an impurity having a characteristic carbonyl absorption peak. This work was repeated in order to obtain pure samples of these vinyl fluorochloroethers and to isolate and identify this carbonyl-containing compound and any other by-products.

Methyl, ethyl, *n*-propyl, and *n*-butyl alcohols were added to $CF_3CCl{=}CCl_2$ in the presence of a base and ethers of the structure of $CF_3CCl{=}CClOR$ were isolated, R being the methyl, ethyl, *n*-propyl, or *n*-butyl group.

Infrared spectrograms of these compounds were quite similar and showed them to be practically free of carbonyl-containing impurities.

As a further proof, the dibromide $CF_3CClBrCClBrOCH_3$ was prepared by the addition of bromine to $CF_3CCl{=}CClOCH_3$. This compound was a solid and easily purified by sublimation at near room temperatures under reduced pressure. The carbon, hydrogen, chlorine, and bromine analyses compared closely with the theoretical values calculated for the above structure.

The dibromides of the higher members of this series of ethers were liquids. No attempts were made to purify and identify them.

As a further proof, these vinyl ethers were hydrolyzed according to the method of Tarrant and Young[2,3] to the corresponding saturated esters by treatment with 90 per cent sulfuric acid. This method is similar to the acid hydrolysis[4] of $CHCl{=}CClOC_2H_5$ to $CH_2ClCO_2C_2H_5$.

The methyl, ethyl, *n*-propyl, and *n*-butyl esters of $CF_3CHClCO_2H$, are new compounds and were identified by analyses and by the conversion of the methyl and ethyl members of the series to the amide, $CF_3CHClCONH_2$ by the usual method.

The carbonyl-containing compounds which were present as impurities in the previous chlorofluorovinyl alkyl ethers[1] were isolated by careful fractionation on a modified Todd precision column with a platinum spiral. These compounds had exactly the same physical and chemical properties as the series of esters prepared by the hydrolysis of the ethers, $CF_3CCl{=}CClOR$ to the corresponding esters $CF_3CHClCO_2R$ where R is the methyl, ethyl, *n*-propyl, and *n*-butyl group. One other by-product proved to be $CF_3CHClC(OCH_3)_3$.

TABLE I

PHYSICAL PROPERTIES OF SUBSTITUTED TRIFLUOROPROPENE DERIVATIVES

Compound	B.p., °C.	Mm.	d_4^{20}	n_D^{20}	M.R. Exptl.	M.R. Calc'd	AF_f	Magnetic Susceptibility[a] Calc'd	Magnetic Susceptibility[a] Obsd.
$CF_3CHClCO_2CH_3$	104.0	628	1.4170	1.3588	27.42	27.19	1.18	− 95.2	− 83.4
$CF_3CHClCO_2C_2H_5$	119.0	620	1.3215	1.3634	32.06	31.81	1.18	−107.1	− 98.2
$CF_3CHClCO_2C_3H_7$	135.0	629	1.2678	1.3733	36.74	36.43	1.20	−118.9	−108.9
$CF_3CHClCO_2C_4H_9$	156.0	627	1.2275	1.3803	41.26	41.03	1.18	−130.8	−118.0
$CF_3CHCl(OCH_3)_2$	150.0	626	1.3311	1.3842	39.09	39.70	0.92	—	—
$CF_3CCl{=}CClOCH_3$	115.0	626	1.4981	1.4070	32.06	31.57	1.26	−100.4	− 93.5
$CF_3CCl{=}CClOC_2H_5$	130.0	612	1.3945	1.4058	36.98	36.19	1.36	−112.3	−106.7
$CF_3CCl{=}CClOC_3H_7$	74.5	43	1.3330	1.4123	41.64	40.81	1.38	−124.1	−121.6
$CF_3CCl{=}CClOC_4H_9$	81.0	29	1.2581	1.4180	47.24	45.70	1.70	−136.0	−138.6

[a] Determined by the Quincke method.

(1) Park, Halpern, and Lacher, *J. Am. Chem. Soc.*, **74**, 4104–4105 (1952).

(2) Young and Tarrant, *J. Am. Chem. Soc.*, **72**, 1860 (1950).
(3) Young and Tarrant, *J. Am. Chem. Soc.*, **71**, 2432 (1949).
(4) Imbert, German Patent 210,502; *Chem. Zent.*, **II**, 78 (1909).

Acid-catalyzed hydrolysis of this *ortho* ester produced the ester $CF_3CHClCO_2CH_3$, a compound previously prepared by the hydrolysis of $CF_3CCl=CClOCH_3$. The amide $CF_3CHClCONH_2$, also prepared from this hydrolysis product, melted at the same temperature as that prepared above.

Acknowledgment: We wish to express our appreciation to the Office of Naval Research and to the Minnesota Mining and Manufacturing Company, St. Paul, Minnesota, for support of this work.

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The Reaction of Perfluoroalkyl Isocyanates with Alcohols

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Received May 2, 1956

Perfluoroalkyl isocyanates have been reported[2] to react in the conventional way with alcohols to form N-perfluoroalkylurethans. This represents the only available synthetic route to these unusual carbamates since the corresponding perfluoroalkylamines are not known.

In the present work, however, initial attempts to use this route as a preparative method led to very low yields of the desired products. A unique reaction of excess alcohol with the perfluoroalkylurethan has been found responsible for these low yields. By treating the isocyanates with a stoichiometric quantity of alcohol, yields of the desired carbamates have been increased to 83–90%.

Proof was readily obtained that alcoholysis of the urethans occurred. Refluxing ethyl N-*n*-perfluoropropylcarbamate with excess alcohol produced 85 mole-% of ethyl carbamate and 52 mole-% of ethyl perfluoropropionate. During the course of the reaction hydrogen fluoride was liberated, for the glass reaction vessel became etched, the odor of hydrogen fluoride was evident, and an inorganic residue containing fluoride and ammonium ions was obtained.

Rigid proof of the mechanism of the reaction with excess alcohol may be difficult to secure. The perfluorourethan can be converted to N-perfluoropropionylurethan by a somewhat analogous mild alkaline hydrolysis.[3] This suggests that reaction with the *alpha* fluorine atoms should precede cleavage of the carbon to nitrogen bond. In fact, perfluoroacylurethans may be produced as intermediates in the present alcoholysis reaction for it has been shown[3] that N-*n*-perfluoropropionylurethan is readily cleaved by ethanol to produce ethyl carbamate and ethyl perfluoropropionate.

In the present system it must be recognized that the fluorine atoms may undergo reaction with either alcohol or water. The water may be produced by reaction of the liberated hydrogen fluoride with alcohol[4] or with the glass flask. Differentiation between these two possible mechanisms of reaction was not considered essential to the synthetic problem involved, and additional experiments are not planned.

EXPERIMENTAL

Ethyl N-n-perfluoropropylcarbamate. To 50 g. (0.236 mole) of *n*-perfluoropropyl isocyanate kept below 5° was slowly added 11.5 g. (0.249 mole, 5% excess) of anhydrous ethanol. After completion of the addition, vigorous stirring was continued for one-half hour after which the mixture was stored in a refrigerator overnight. Distillation *in vacuo* gave 50.7 g. (83% yield) of ethyl N-perfluoropropylcarbamate, b.p. 66–69° (16.5 mm.), n_D^{20} 1.3403, d_{25}^{25} 1.458.

Anal. Calc'd for $C_6H_6F_7NO_2$: C, 28.02; H, 2.33; F, 51.75; N, 5.45. Found: C, 28.19; H, 2.45; F, 51.4; N, 5.50.

Ethyl N-n-perfluoroheptylcarbamate. By an identical procedure, 8.7 g. (0.0212 mole) of *n*-perfluoroheptyl isocyanate[5] and 1.10 g. (0.0240 mole) of anhydrous ethanol gave 8.7 g. (89.8% yield) of ethyl N-perfluoroheptylcarbamate, b.p. 71–74° (1.5 mm.), n_D^{20} 1.3291.

Anal. Calc'd for $C_{10}H_6F_{15}NO_2$: C, 26.27; H, 1.33. Found: C, 26.14; H, 1.20.

Alcoholysis of ethyl N-n-perfluoropropylcarbamate. A solution of 10 g. (0.039 mole) of the urethan in 9 g. (0.20 mole) of anhydrous ethanol was refluxed for 20 hours. At the end of this time the reaction vessel had become etched, but nothing had condensed in a Dry Ice trap attached to the reflux condenser. Distillation at atmospheric pressure gave Fraction I (8.7 g.), b.p. 62–78°, and ethanol (4.5 g.). Continued distillation *in vacuo* of the residual material gave 2.97 g. (85% yield) of quite pure ethyl carbamate, m.p. 48–51°, and 0.58 g. of an inorganic residue. Recrystallization of the distilled ethyl carbamate from carbon tetrachloride gave a pure product, m.p. 50–51°, which did not depress the m.p. of an authentic sample. The inorganic material liberated ammonia upon the addition of alkali and gave a test for fluoride ion. It consisted of more than one substance, however, for sublimation left a substantial residue.

Redistillation of Fraction I through a metal-spiral Todd column gave 7.5 g. of a white liquid, b.p. 63–65°. The infrared absorption curve of the distillate gave the peaks characteristic of ethyl perfluoropropionate. Upon washing the material with 8 ml. of 5% sodium carbonate and 5 ml. of water, followed by distillation from phosphoric anhydride, 3.68 g. (52% yield) of pure ethyl perfluoropropionate, b.p. 74–76° (lit. b.p. 76.5°), was obtained. Treatment with anhydrous ammonia converted the ester to perfluoropropionamide, m.p. 96–97° (lit. m.p. 95–95.5°).[6] The origi-

(1) This paper is based on a portion of the thesis to be submitted by Marvin Lukin in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Graduate School of Western Reserve University. This material was presented in part at the American Chemical Society Meeting, Atlantic City, N. J., September 16–21, 1956.

(2) Reid and Smith, *Abstracts of Papers, 116th Meeting of the American Chemical Society*, Atlantic City, N. J., September 18, 1949, page 9K.

(3) Dannley and Lukin, unpublished work.

(4) Meslans, *Compt. rend.*, 111, 882 (1890).

(5) Haszeldine and Leedham, *J. Chem. Soc.*, 50–51 (1953).

(6) Haszeldine, *Nature*, 166, 192 (1950).

nal fraction, b.p. 63–65°, probably consisted of an azeotrope. The yield of pure ester represents the minimum value for large mechanical losses were sustained in handling the small sample.

Acknowledgment. We are indebted to the Research Corporation for financial aid in the pursuance of this work.

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Triazines. XVI. A New Synthesis for 1,2,4-Triazoles

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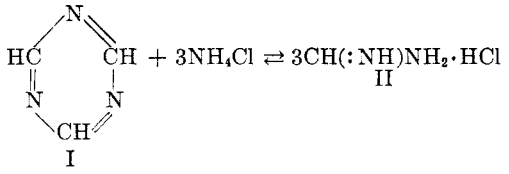
Received May 3, 1956

In our previous work on *s*-triazines it has been found that *s*-triazine (I) reacts with ammonia to form dark intractable resins.[3] However, with ammonium chloride in boiling ethanol a nearly quantitative reaction was observed which leads, with complete ring cleavage, to formamidine hydrochloride (II):[4]

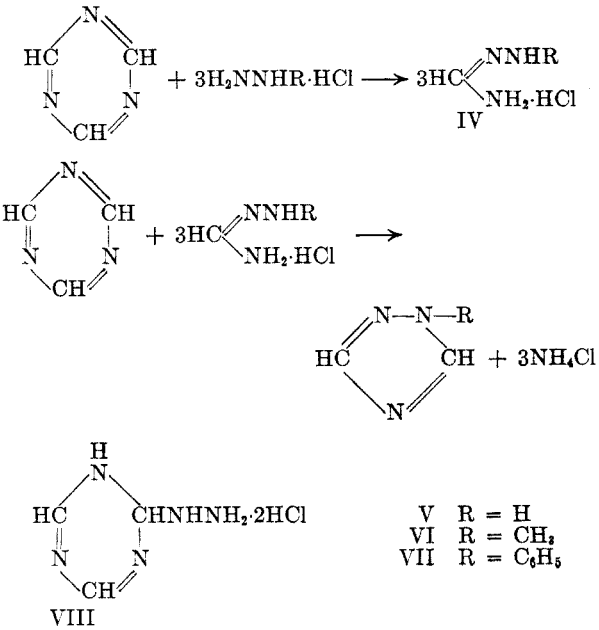


This reaction is essentially the reverse of the previously described formation of *s*-triazine by thermal decomposition of formamidine hydrochloride.[5] In contrast to its formation from *s*-triazine, the reconversion of the formamidine hydrochloride into I is far from being quantitative even in the presence of scavengers for hydrogen chloride.

The above described findings prompted us to attempt the reaction of I with hydrazine monohydrochloride (III) anticipating the formation of the yet unknown formamidrazone hydrochloride (IV, R = H). In boiling absolute ethanol I and III reacted promptly, but instead of IV, 1,2,4-triazole (V) and ammonium chloride were obtained in almost theoretical yields, according to the equation:

$$2C_3H_3N_3 + 3N_2H_4\cdot HCl \longrightarrow 3NH_4Cl + 3C_2H_3N_3$$

This reaction can be explained by a two-step process. First, one molecule of I undergoes the expected ring cleavage to IV. The formamidrazone then will react immediately with another molecule of *s*-triazine, in the same manner as recently described for *ortho*-diamines,[3] to yield 1,2,4-triazole and ammonia. This cyclization reaction seems to be favored since even with an excess of hydrazine monohydrochloride 1,2,4-triazole is the only isolable product.



It seems that this reaction can be generalized in that use of mono-substituted hydrazine monohydrochlorides leads to 1-substituted 1,2,4-triazoles. Thus from methyl hydrazine monohydrochloride, 1-methyl-1,2,4-triazole (VI) is recovered and from phenylhydrazine monohydrochloride, 1-phenyl-1,2,4-triazole (VII) has been obtained. Good yields result in both cases.

Hydrazine dihydrochloride reacts in quite a different manner with I, since the only product isolated was an adduct, $C_3H_3N_3\cdot N_2H_4\cdot 2HCl$ which may tentatively be formulated as the dihydrochloride of 1,2-dihydro-2-hydrazino-1,3,5-triazine (VIII).

EXPERIMENTAL[6]

Formamidine hydrochloride from s-triazine. A mixture of 2.8 g. of *s*-triazine and 3.55 g. of ammonium chloride in 25 ml. of absolute alcohol was gently refluxed. After six hours, all of the NH_4Cl had gone into solution and the formamidine salt could be isolated by addition of an excess of ether. In

(1) This article is based on work performed under Project 116-B of The Ohio State University Research Foundation sponsored by the Olin Mathieson Chemical Corporation, New York, N. Y.

(2) Preceding communication: Grundmann and Kober, *J. Org. Chem.*, **21**, 641 (1956).

(3) Grundmann and Kreutzberger, *J. Am. Chem. Soc.*, **77**, 6559 (1955).

(4) This reaction has been found independently in the laboratories of the American Cyanamid Co. (private communication by I. Hechenbleikner at the 127th A.C.S. meeting in Cincinnati, March–April 1955).

(5) Grundmann, Schroeder, and Ruske, *Chem. Ber.*, **87**, 1865 (1954).

(6) All melting points are determined with the Fisher-Johns apparatus. Microanalyses are by Galbraith Laboratories, Knoxville, Tenn., and Spang Microanalytical Laboratory, Ann Arbor, Michigan.

this way, 90% of the reaction product was isolated. An additional 8% was recovered by vacuum evaporation of the mother liquor. Formamidine hydrochloride was identified by analysis and by the mixture melting point of its picrate with an authentic sample of formamidine picrate.

Anal. Calc'd for CH_5ClN_2: N, 34.80; Cl, 44.10. Found: N, 34.43, 34.24; Cl, 43.63, 43.48.

Anal. Calc'd for *formamidine picrate* $C_7H_7N_5O_8$: C, 30.75; H, 2.56; N, 25.61. Found: C, 30.76, 30.90; H, 2.56, 2.66; N, 25.53, 25.57.

1,2,4-Triazole (V). To a solution of 16.2 g. (0.2 mole) of 1,3,5-triazine in 600 ml. of absolute alcohol (previously distilled from metallic sodium), there was added 20.55 g. (0.3 mole) of well-powdered hydrazine monohydrochloride. The mixture then was refluxed for eight hours. After cooling, 9 g. of ammonium chloride was filtered off. An additional amount (7 g.) was precipitated upon addition of ether to the filtrate, thus resulting in an almost quantitative yield (Calc'd 16.35 g.). The red-colored alcohol-ether filtrate was evaporated *in vacuo* to dryness. The remainder, 21 g., was recrystallized from chloroform yielding pure 1,2,4-triazole (95%). A mixture melting point with an authentic sample was without depression.

Anal. Calc'd for $C_2H_3N_3$: N, 60.87. Found: N, 60.80, 60.70.

1-Methyl-1,2,4-triazole. To a solution of 3.24 g. of *s*-triazine in 30 ml. of absolute ethanol 4.95 g. of methyl hydrazine hydrochloride was added. The reaction started immediately with evolution of heat and was completed by refluxing for eight hours. The precipitated ammonium chloride (2.2 g.) then was filtered off and the alcohol was removed through an efficient column. The oily residue was extracted with ether and an additional 0.9 g. of ammonium chloride which remained undissolved was removed by filtration. From the ethereal filtrate the ether was distilled leaving behind 4.0 g. of a yellowish oil which was almost pure 1-methyl-1,2,4-triazole. By distillation under atmospheric pressure the base was obtained colorless; b.p. 175–176°; m.p. 20°; yield: 81%.

Anal. Calc'd for $C_3H_5N_3$: N, 50.57. Found: N, 50.12, 50.10.

1-Phenyl-1,2,4-triazole (VI). A mixture of 16.2 g. of *s*-triazine and 43.4 g. of phenylhydrazine hydrochloride in 200 ml. of absolute alcohol was refluxed for 12 hours. After cooling, 12.5 g. of ammonium chloride was filtered off and the filtrate was distilled to remove the alcohol. There remained 36 g. of a light colored oil which crystallized upon storage in an icebox and consisted of almost pure 1-phenyl-1,2,4-triazole. By distillation under atmospheric pressure the base was obtained pure; b.p. 268–270°; m.p. 47°; yield: 83%.

Anal. Calc'd for $C_8H_7N_3$: N, 28.95. Found: N, 28.63, 28.68.

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Some Derivatives of Dihydroxyacetone

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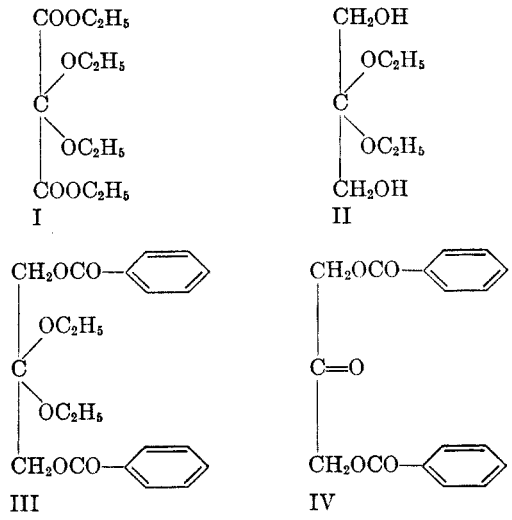
Received May 7, 1956

In connection with a study on carbohydrates it was necessary to prepare the diethyl acetal of dihydroxyacetone. Various methods of ketalation of dihydroxyacetone were investigated without success. However it was found that reduction of diethoxy diethyl malonate (I) with lithium aluminum hydride, afforded the desired acetal (II) in very good yield.



This acetal is a crystalline substance which can be stored for long periods without decomposition. It does not reduce Fehling's solution. Mineral acids immediately cause hydrolysis and the resulting solution reduces Fehling's solution, even at room temperature.

The diethyl acetal can be benzoylated very easily to the corresponding dibenzoate (III) and the hydrolysis of the acetal grouping in III gave dibenzoxyacetone (IV) in almost quantitative yield.

EXPERIMENTAL[1]

We would like to thank Mrs. A. González from Syntex, S. A., for the microanalyses and Mr. F. Casas for technical assistance.

Diethoxy diethyl malonate was prepared from dibromo diethyl malonate according to Bischoff.[2]

Diethyl acetal of dihydroxyacetone (II). Diethoxy diethyl malonate (I) (50 g.) was dissolved in 400 ml. of anhydrous ether. The solution was added at room temperature during 2 hours with mechanical stirring to a slurry of 10 g. of lithium aluminum hydride in 300 ml. of ether, the mixture was refluxed 15 minutes, and the excess of hydride was destroyed with ethyl acetate; 20 ml. of a saturated solution of sodium sulfate was added with stirring and then enough anhydrous sodium sulfate until a clear solution was formed. The inorganic solids were filtered and thoroughly washed with ethyl acetate. The combined liquors were evaporated and the oily residue was crystallized by addition of hexane giving 27 g. of diethyl acetal (II) (81% yield) m.p. 79–80°. The analytical sample was obtained by repeated crystallization from ether-hexane. The product appears as long needles, m.p. 87–89°.

Anal. Calc'd for $C_7H_{16}O_4$: C, 51.20; H, 9.81. Found: C, 51.40; H, 9.83.

(1) The melting points are uncorrected.
(2) Bischoff, *Ber.*, **30**, 487 (1897).

The diethyl acetal (II), does not reduce Fehling's solution. It is very soluble in water and in most organic solvents. If the diethyl acetal is dissolved in 0.1 *N* hydrochloric acid, hydrolysis takes place very rapidly and the resulting dihydroxyacetone reduces Fehling's solution at room temperature.

Diethyl acetal of dibenzoxyacetone (III). The diethyl acetal (II) (8 g.) was dissolved in 50 ml. of pyridine and 14 g. of benzoyl chloride was added slowly, maintaining the temperature below 30°. The mixture then was heated on the steam-bath for 80 minutes and poured onto powdered ice. After standing for 2 hours the oil was extracted with ether and the ethereal extract was washed with dilute hydrochloric acid, sodium carbonate solution, and water. The ether solution was dried with sodium sulfate and the solvent was evaporated. The oily residue was crystallized from methanol furnishing 15.5 g. of thick prisms, m.p. 79–80° (85% yield).

Anal. Calc'd for $C_{21}H_{24}O_6$: C, 67.63; H, 6.50. Found: C, 67.25; H, 6.61.

Dibenzoxyacetone (IV). A solution of 10 g. of the diethyl acetal of dibenzoxyacetone (III) and 8 g. of *p*-toluenesulfonic acid in 500 ml. of methanol and 30 ml. water was refluxed 4 hours and then was concentrated to one-third its volume, diluted with water, and extracted with ether. The ethereal extract was washed with a sodium carbonate solution and water, dried over sodium sulfate, and concentrated. By addition of hexane there crystallized 7.2 g. of long needles m.p. 118–119° (90% yield). This product gave no depression in a mixture m.p. with a sample of dibenzoxyacetone obtained by benzoylation of dihydroxyacetone.[3]

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(3) Fischer, Taube, and Baer, *Ber.*, **60**, 479 (1927).

Studies in *cis*- and *trans*-Stilbazoles[1]

LESTER HORWITZ

Received May 24, 1956

This study was initiated to see if the methods previously used to form *cis*- and *trans*-2-styrylquinolinium salts[2] would be successful in the stilbazole series. Only *cis*- and *trans*-*o*-nitrostilbazole, obtained by fractional crystallization, has so far been reported.[3]

With one exception, identical stilbazolium salts were formed, either by way of a piperidine-catalyzed condensation of the picolinium salt with an aromatic aldehyde (Method A) or by quaternation of stilbazoles, obtained by the condensation of 2 (and 4)-picolines with aromatic aldehydes in acetic anhydride (Method B). These are all presumably the stable *trans* structures.

When *o*-hydroxybenzaldehyde and 2(and 4)-picoline were refluxed with acetic anhydride, *o*-acetoxy-2(and 4)-stilbazoles, were formed (XXI, XXIV). Heating to 95° with methyl iodide in a sealed vessel gave 1-methyl-*o*-hydroxy-2(and 4)-stilbazolium iodides (VIII B, XII B), deacetylation having occurred during quaternation. The piperidine-catalyzed condensation of *o*-hydroxybenzaldehyde with 2(and 4)-picoline methiodides gave different 1-methyl-*o*-hydroxy-2(and 4)-stilbazolium iodides (VIII A, XII A). A *trans* structure is assigned to these latter salts based on their longer wavelength absorption in the ultraviolet. Heating either *cis*- or *trans*-1-methyl-*o*-hydroxy-2(and 4)-stilbazolium iodides with acetic anhydride gave the identical 1-methyl-*o*-acetoxy-2(and 4)-stilbazolium iodides (IX A, IX B, XIII A, XIII B), isomerization accompanying acetylation. It may be inferred that it is only an *o*-hydroxy group which assists in stabilizing the *cis* configuration since no *cis* compounds were isolable with *p*-hydroxy groups (VII A, VII B).

That a Chugaev-type acetate decomposition probably gives rise to the *cis* configuration is evidenced by the fact that six-hour refluxing of *o*-hydroxybenzaldehyde with 4-picoline in acetic anhydride gave *cis*-*o*-acetoxy-4-stilbazole (XXIV A), whereas 72-hour refluxing gave the *trans* compound (XXIV B), which absorbs some 45 mμ longer in the ultraviolet.

Heating *p*-hydroxybenzaldehyde with 4-picoline in acetic anhydride for six hours gave *p*-acetoxy-4-stilbazole (XXV), while, after 72 hours, the deacetylated *p*-hydroxy-4-stilbazole (XXVI) was obtained.

EXPERIMENTAL[4,5]

Piperidine-catalyzed condensation of picolinium salts with aromatic aldehydes. Method A. To a solution of 5 g. (0.02 mole) of the 2(or 4)-picoline methiodide and 5 g. (0.03–0.04 mole) of aromatic aldehyde in 25 cc. of methanol was added 10 drops of piperidine. After refluxing for four hours, the reaction mixture was cooled, and the product was collected and purified.

Condensation of picolines with aromatic aldehydes in acetic anhydride. Method B. All the 2(and 4)-stilbazoles were prepared in this manner by refluxing a mixture of 0.1 mole of 2(or 4)-picoline, 0.1 mole of aromatic aldehyde, and 0.2 mole of acetic anhydride for six hours. At the end of the reflux period the major portion of the acetic acid and

(1) Presented in part before Division of Organic Chemistry, American Chemical Society, Atlantic City, N. J., September 1956.
(2) Horwitz, *J. Am. Chem. Soc.*, **77**, 1687 (1955).
(3) Räth and Lehmann, *Ber.*, **55**, 342 (1925).

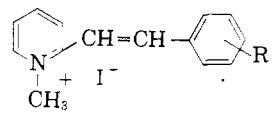
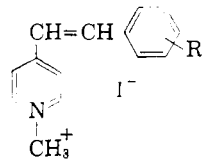
(4) All melting points are corrected. For the salts, the samples were rapidly heated to within 30° of melting and then proceeding at a rate of 3° per minute to melting. Boiling points are uncorrected.
(5) Ultraviolet spectra are on 10^{-5} *M* solutions in methanol.

TABLE I[a]

2(AND 4)-STILBAZOLE METHIODIDES

A compounds are from the piperidine-catalyzed condensation of 1,2-dimethylpyridinium iodide with aromatic aldehydes (Method A).

B compounds are from the quaternation of 2(or 4)-stilbazoles obtained by acetic anhydride condensation (Method B).

Compound	R	Yield, (%)	M.P. (°C.)	Formula	Carbon Calc'd	Carbon Found	Hydrogen Calc'd	Hydrogen Found	Nitrogen Calc'd	Nitrogen Found	λ, mμ	ε
				 2-Stilbazole methiodides								
IA	H	72	230–231[b]	$C_{14}H_{14}IN$	52.01	51.98	4.37	4.41	4.33	4.27	338	30,650
B					52.01	51.43	4.37	4.23	4.33	4.27		
IIA	*3,4*-CH_2O_2	69	274–275[c]	$C_{15}H_{14}INO_2$	49.08	49.01	3.84	3.78	3.81	3.69	282	16,650
B					49.08	48.88	3.84	3.89	3.81	3.82		
IIIA	*o*-NO_2	40	229–230	$C_{14}H_{13}IN_2O_2$	45.66	45.60	3.56	3.48	7.61	7.44	322	18,150
B					45.66	45.79	3.56	3.51	7.61	7.66		
IVA	*m*-NO_2	53	251–253[d]	$C_{14}H_{13}IN_2O_2$	45.66	45.83	3.56	3.44	7.61	7.64	265	8,790
B					45.66	45.75	3.56	3.35	7.61	7.71	326	29,870
VA	*p*-NO_2	59	253–254	$C_{14}H_{13}IN_2O_2$	45.66	46.05	3.56	3.43	7.61	7.54	335	29,300
B					45.66	45.80	3.56	3.38	7.61	7.61		
VIA	*o*-Cl	52	230–231	$C_{14}H_{13}ClIN$	47.01	46.94	3.67	3.57	3.92	3.98	331	24,140
B					47.01	46.95	3.67	3.63	3.92	3.91		
VIIA[e]	*p*-CH_3COO		230–231	$C_{16}H_{16}INO_2$	50.42	50.43	4.23	4.25	3.67	3.61	372	17,200
B					50.42	50.45	4.23	4.29	3.67	3.84		
VIIIA	*o*-OH	75	253–254[f]	$C_{14}H_{14}INO$	49.56	49.42	4.16	4.17	4.13	3.92	375	17,800
B[g]			184–185		49.56	49.63	4.16	4.33	4.13	4.03	333	13,570
IXA[h]	*o*-CH_3COO		201–202	$C_{16}H_{16}INO_2$	50.42	50.45	4.23	4.27	3.67	3.70	329[j]	9,930
B[i]					50.42	50.25	4.23	4.30	3.67	3.75		
				 4-Stilbazole methiodides								
XA	H	64	209–210[k]	$C_{14}H_{14}IN$	52.01	51.88	4.37	4.40	4.33	4.33	342	13,000
B					52.01	51.99	4.37	4.22	4.33	4.52		
XIA	*m*-NO_2	62	299–300[l]	$C_{14}H_{13}IN_2O_2$	45.66	45.70	3.56	3.36	7.61	7.56	330	25,770
B					45.66	45.85	3.56	3.38	7.61	7.50		
XIIA	*o*-OH	61	235–236	$C_{14}H_{14}INO$	49.56	49.49	4.16	4.12	4.13	4.13	383[m]	18,570
B[n]			224–225		49.56	49.57	4.16	4.22	4.13	3.89	325[j]	7,450
XIIIA[o]	*o*-CH_3COO		228–229	$C_{16}H_{16}INO_2$	50.42	50.15	4.23	4.35	3.67	3.71	334[j]	17,200
B					50.42	50.39	4.23	4.24	3.67	3.70		

[a] Solvent of recrystallization was methanol in all cases. [b] Phillips [*J. Org. Chem.*, 12, 333 (1947)] records m.p. 230–231°. [c] Above reference *b* reports m.p. 295°. [d] Above reference *b* reports m.p. 258–260°. [e] Prepared by refluxing 1-methyl-2-*p*-hydroxystilbazolium iodide in acetic anhydride for two hours. The hydroxy salt was prepared by Method A, yield 68%; m.p. 279–280° (reference *b* reports m.p. 269–270°). *Anal.* Calc'd for $C_{14}H_{14}INO$: C, 49.56; H, 4.16; N, 4.13. Found: C, 49.40; H, 4.26. [f] Above reference *b* reports m.p. 253–254°. [g] Obtained by heating 2-*o*-acetoxystilbazole (XXI) with methyl iodide at 95° for three hours in a sealed container. [h] Prepared by refluxing 1-methyl-2-*o*-hydroxystilbazolium iodide in acetic anhydride for two hours. The hydroxy salt was prepared by Method A; 82% yield; m.p. 257–258° (reference *b* reports m.p. 253–254°). *Anal.* Calc'd for $C_{14}H_{14}INO$: C, 49.56; H, 4.16; N, 4.13. Found: C, 49.49; H, 4.42; N, 4.13. [i] From VIIIB by refluxing in acetic anhydride for two hours. [j] Estimated from broad band. [k] Phillips [*J. Org. Chem.*, 14, 302 (1949)] reports m.p. 220–221°. [l] Reference *j* records no melting up to 290°. [m] Inflection point at 322 mμ, 11,730. [n] Obtained when 4-*o*-acetoxystilbazole (XXIVA) was quaternated with methyl iodide by heating in a sealed vessel for three hours on the steam-bath. [o] A compound from XIIA and B compound from XIIB, by refluxing in acetic anhydride for two hours.

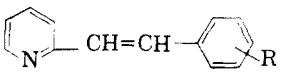
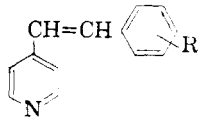
acetic anhydride was removed by distillation and the residue was drowned in water (200 cc.). The mixture was made basic and, if the product crystallized out, it was collected and purified by recrystallization. If the product oiled out it was recovered by extraction with ether and purified by distillation.

Quaternation of the stilbazoles was accomplished by heating with methyl iodide in a closed vessel for three hours on the steam-bath.

Acknowledgment is made of a grant by Midwest Research Institute which made this study possible.

TABLE II[a]

2(AND 4)-STILBAZOLES OBTAINED BY THE CONDENSATION OF AROMATIC ALDEHYDES WITH 2(AND 4)-PICOLINE IN ACETIC ANHYDRIDE (METHOD B)

Compound	R	Yield, %	M.p. or B.p., °C.	Mm.	Formula	Carbon Calc'd	Carbon Found	Hydrogen Calc'd	Hydrogen Found	Nitrogen Calc'd	Nitrogen Found
					2-Stilbazoles						
XIV	H	52	91–92[b]		$C_{13}H_{11}N$	86.17	86.17	6.12	6.07	7.73	7.78
			140–142	2.5							
XV	3,4-CH_2O_2	61	111–112		$C_{14}H_{11}NO_2$	74.66	74.51	4.92	4.82	6.22	6.20
			180–181	2							
XVI	o-NO_2	57	102–103[c]		$C_{13}H_{10}N_2O_2$	69.17	69.10	4.45	4.42	12.39	12.34
XVII	m-NO_2	94	131–132[d]		$C_{13}H_{10}N_2O_2$	69.17	69.01	4.45	4.39	12.39	12.24
XVIII	p-NO_2	91	140–141[e]		$C_{13}H_{10}N_2O_2$	69.17	69.05	4.45	4.36	12.39	12.74
XIX	o-Cl	57	76–77		$C_{13}H_{10}ClN$	72.38	72.29	4.67	4.57	6.49	6.28
			108–110	2							
XX	p-CH_3COO	76	114–115		$C_{15}H_{13}NO_2$	75.28	75.27	5.47	5.60	5.85	5.69
XXI	o-CH_3COO	58	180–181	3.5	$C_{15}H_{13}NO_2$	75.28	75.45	5.47	5.48	5.85	5.98
					4-Stilbazoles						
XXII	H	92	129–130[f]		$C_{13}H_{11}N$	86.17	86.00	6.12	5.99	7.73	7.57
XXIII	m-NO_2	97	144–145[g]		$C_{13}H_{10}N_2O_2$	69.17	69.05	4.45	4.49	12.39	12.61
XXIVA[h]	o-CH_3COO	74	118–119		$C_{15}H_{13}NO_2$	75.28	75.44	5.47	5.51	5.85	5.76
B	o-CH_3COO	67	197–198		$C_{15}H_{13}NO_2$	75.28	75.35	5.47	5.81	5.85	6.10
XXV	p-CH_3COO	68	167–168		$C_{15}H_{13}NO_2$	75.28	75.19	5.47	5.37	5.85	5.67
XXVI[i]	p-OH	90	264–265[j]		$C_{13}H_{11}NO$	78.77	78.47	5.60	5.79	7.07	6.87

[a] Solvent of recrystallization was methanol for XVII, XVIII, XXIII, and XXVI; isopropyl alcohol for XXII; low-boiling petroleum ether for XVI, XX, XXIVA; 1,4-dioxane for XXIVB; and acetonitrile for XXV. [b] Blout *et al.* [*J. Am. Chem. Soc.*, **67**, 1315 (1945)] reports m.p. 89°. [c] Reference 2 reports m.p. 101° for the *trans* isomer. [d] Feist [*Ber.*, **34**, 465 (1901)] reports m.p. 127°. [e] Reference *d* reports m.p. 125–126°. [f] Reference *b* reports m.p. 130°. [g] Friedländer [*Ber.*, **38**, 2838 (1905)] reports m.p. 138°. [h] Ultraviolet spectra: XXIVA, λ 298 mμ; ε 26,580; XXIVB, λ 287, 332 mμ; ε 21,140, 19,220. [i] Obtained by 72-hour refluxing. [j] Chiang and Hartung [*J. Org. Chem.*, **10**, 21 (1945)] reports m.p. 215–217°.

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The Acetylation of Organic Hydroxy Compounds with Ketene

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The use of ketene in acetylating glycols, Cellosolves, carbohydrates, and other polyhydroxy organic compounds appears to be rather limited. Van Alphen[2] reports an unsuccessful attempt to acetylate glucose with ketene, while Hurd[3] and his associates, using acetone, dioxane, and pyridine as solvents and a trace of sulfuric acid as catalyst, obtained syrups which defied purification. Gwynn and Degering[4] report that ketene reacts with acetone and pyridine and this fact may have been a serious complication in the final purification. In addition Rice and Greenburg[5] have studied the rate of polymerization of ketene in various solvents and found this tendency to be a serious complication in many instances. Acetone was a rather serious offender in this regard. However, the rate of polymerization of ketene in carbon tetrachloride was the lowest of the twenty different solvents tested. The reaction constant calculated according to the bimolecular law was 0.0000465 for carbon tetrachloride and 0.0146 for acetone, both at 0°. This means that at 0° ketene polymerizes approximately 300 times faster in acetone than in carbon tetrachloride. This may offer a plausible explanation for the greater difficulty encountered in purifying the acetylation product when acetone was used as solvent.

Significant contributions to carbohydrate and other hydroxy compound acetylations with ketene

(1) Present address: Minneapolis-Honeywell Regulator Company, Plastics Laboratory, Minneapolis, Minnesota.

(2) J. Van Alphen, *Rec. trav. chim*, **43**, 823 (1924).

(3) C. D. Hurd, S. M. Cantor, and A. S. Roe, *J. Am. Chem. Soc.*, **61**, 426 (1939).

(4) B. H. Gwynn and E. F. Degering, *J. Am. Chem. Soc.*, **64**, 2216 (1942).

(5) F. O. Rice and J. Greenburg, *J. Am. Chem. Soc.*, **56**, 2132 (1934).

have been made by several other investigators.[6-9] Ketene has now been used to acetylate ethylene glycol, propylene glycol, diethylene glycol, triethylene glycol, Methyl Cellosolve,[10] Cellosolve,[10] Butyl Cellosolve,[10] glycerol, sorbitol, mannitol, and D-glucose. For this particular study ketene was prepared by the pyrolysis of acetone using a modified ketene lamp[11] and all acetylations were conducted in a type of absorption apparatus previously described.[12] Carbon tetrachloride, not previously reported, has been found to be a suitable solvent for acetylating the solid polyhydroxy compounds. The two hydroxy groups in each of the glycols were acetylated and glycerol produced the triacetate. The ether linkage in diethylene glycol, triethylene glycol, and the several Cellosolves was not ruptured by ketene under the experimental conditions used, even though the Cellosolves were each in turn treated with twice the theoretical amount of ketene.

EXPERIMENTAL

Acetylation of liquid hydroxy compounds. Weighed quantities, 30 to 50 g., respectively of ethylene glycol, propylene glycol, diethylene glycol, triethylene glycol, glycerol, Methyl Cellosolve, Cellosolve, and Butyl Cellosolve, were each acetylated in turn at room temperature by placing the weighed sample in the absorption apparatus[12] together with one or two drops of 18 *molar* sulfuric acid. Ketene then was passed into the apparatus for a period of time slightly in excess of that theoretically required to acetylate the hydroxy groups known to be present in the compound. The several acetates were purified by treatment with anhydrous sodium carbonate and vacuum distillation. The results are summarized in Table I.

Acetylation of solid hydroxy compounds. After studying the solvent effect of numerous organic compounds, carbon tetrachloride was found to be a suitable solvent for the acetylation of sorbitol, mannitol, and D-glucose. The final technique developed was to saturate the solvent with 18 *molar* sulfuric acid. A suspension of 5 g. of solid hydroxy compound in 40 ml. of prepared solvent was placed in the absorption apparatus.[12] A micro-burner was placed under the absorption apparatus and enough heat was supplied to keep the solvent refluxing gently. Ketene then was passed through the solution as long as absorption took place. The completion of the reaction was easily detected since the acetylation product was completely soluble in the hot carbon tetrachloride, whereas the initial hydroxy compound was only slightly soluble.

After acetylation the carbon tetrachloride solution was shaken with dilute sodium carbonate solution to neutralize the acid catalyst and any acid substances formed during acetylation. The carbon tetrachloride solution then was washed twice with water and the solvent was removed by distillation on a steam-bath. This treatment left a brown oily residue to which water was added and the last traces of carbon tetrachloride were removed by boiling. A sufficient quantity of ethanol then was added to dissolve the product when the solution was hot, and the solution was decolorized with Norit, filtered hot, and allowed to crystallize. If necessary the product was recrystallized from water-ethanol with a second Norit treatment. This treatment yielded sharp-melting products which then were dried in a vacuum desiccator. The products were characterized by their melting points, combustion analysis, and acetyl values. The results are again summarized in Table I.

No difficulty was encountered in obtaining a crystalline product from the acetylation of D-glucose in carbon tetrachloride. However, Hurd[3] reports that he obtained a syrup which defied all crystallization attempts when he acetylated D-glucose in acetone solution. His procedure was repeated and a similar syrup was obtained. However, on standing for several days, long crystals appeared in the syrup. Varying the procedure somewhat, the acetone was distilled off and the product was dissolved in carbon tetrachloride. The resulting solution was washed with a large quantity of sodium carbonate solution, then twice with water, and the solvent was distilled off on a steam-bath. The brown syrup remaining was recrystallized five times from a water-ethanol solution before a sharp-melting product was obtained.

The saponification equivalents were determined by standard published methods.[13] A modified procedure was developed for the semi-micro determination of acetyl groups, the fundamental principle of which was to hydrolyze the ester, and then to distill the acid quantitatively into a known amount of standard alkali. A weighed sample (0.2–0.4 g.) of the acetate was gently refluxed in a 50-ml. Claisen flask with 5 ml. of approximately 6 *molar* sulfuric acid for 1 hour. The contents of the flask were cooled and partially neutralized with 5 ml. of 6 *N* sodium hydroxide solution. The apparatus then was arranged for a traditional vacuum distillation so that the distillate was collected under the surface of a known amount of standard sodium hydroxide solution. Water was repeatedly added to the hydrolysis mixture to compensate for distillation loss until all volatile acetic acid was distilled. At this point 10 ml. of saturated barium hydroxide solution was added to the distillate to precipitate any sulfuric acid present, and the excess alkali was titrated with standard acid, allowance being made for the added barium hydroxide. The acetyl values, in general, were consistently high. This may be due to the reduction of some sulfuric acid during the initial hydrolysis of the acetate, and subsequent distillation of the more volatile reduction products. Blank runs were made in some cases, using an amount of the original hydroxy compound equivalent to the acetate taken in the determination. When this correction for the blank determination was subtracted from the original values, more satisfactory results were obtained, as shown in the case of sorbitol pentaacetate.

DISCUSSION

The selection of a suitable solvent is evidently of major importance in acetylating solid polyhydroxy compounds with ketene. Such a solvent should not react with ketene to form objectionable by-products, but should have suitable solvent character-

(6) C. S. Vestling and M. C. Rebstock, *J. Biol. Chem.*, **152**, 585 (1944).

(7) G. H. Morey, *Ind. Eng. Chem.*, **31**, 1129 (1939).

(8) C. A. Burkhard and E. F. Degering, *Rayon Textile Monthly*, **23**, 340 (1942).

(9) E. A. Talley and L. T. Smith, *J. Org. Chem.*, **10**, 101 (1945).

(10) "Methyl Cellosolve, Cellosolve, and Butyl Cellosolve" are trade names of Carbide and Carbon Chemicals Corp. "Cellosolve" is 2-ethoxyethanol; "Methyl Cellosolve" is 2-methoxyethanol; "Butyl Cellosolve" is 2-butoxyethanol.

(11) R. E. Dunbar and L. L. Bolstad, *J. Org. Chem.*, **9**, 219 (1944).

(12) L. L. Bolstad and R. E. Dunbar, *Ind. Eng. Chem., Anal. Ed.*, **15**, 498 (1943).

(13) Shriner and Fuson, *The Systematic Identification of Organic Compounds*, John Wiley and Sons, Inc., New York, N. Y., 1948, p. 134.

TABLE I

PHYSICAL CONSTANTS OF ORGANIC ACETATES

Organic Hydroxy Compounds Acetylated	Acetyl Groups Introduced	Boiling Point, 0°/mm.		Density 20/4		Index of Refraction	Molecular Refraction		Sapon. Equiv.		Acetyl, %		Analysis C		Analysis H	
		Lit.	Obsv'd.	Lit.	Obsv'd.		Theor.	Calc'd	Theor.	Obsv'd.	Theor.	Obsv'd.	Calc'd	Found	Calc'd	Found
Ethylene glycol	2	188–190[a]	88–89/5 185.6/733	1.108[a] (14/4)	1.1053	1.4146	33.22	33.08	73.1	70.9	—	—	49.31	49.18	6.90	6.85
Propylene glycol	2	188/758[a]	182/739	—	1.0547	1.4121	37.83	37.69	80.1	79.58	—	—	52.49	52.26	7.55	7.51
Diethylene glycol	2	245–251[b]	199/732	—	1.1144	1.4285	44.10	43.95	95.1	94.9	—	—	50.52	50.37	7.42	7.38
Triethylene glycol	2	300[b]	275.6/740	—	1.1172	1.4368	54.97	54.91	117.12	117.2	—	—	51.27	50.87	7.74	7.66
Glycerol	3	258–259[a]	256/720	1.160	1.1596	1.4298	48.72	48.59	72.37	72.37	—	—	49.54	49.41	6.46	6.38
Methyl Cellosolve	1	144.5/762[b]	141/732	1.0090[b] (14/14)	1.0062	1.4011	28.59	28.53	—	—	36.43	41.11	50.83	50.96	8.53	8.73
Cellosolve	1	158[b]	152–153/733	—	0.9751	1.4038	33.21	33.12	132.16	129.3	—	—	54.53	54.28	9.21	9.11
Butyl Cellosolve	1	—	185.5/740	—	.9425	1.4121	42.44	42.29	—	—	26.88	29.04	59.97	60.13	10.06	10.32
		Melting Point														
Mannitol	6	123–124[c]	123–124	—	—	—	—	—	—	—	59.42	61.73	49.76	50.06	6.03	5.97
Sorbitol	6	95[d]	98–99	—	—	—	—	—	—	—	59.42	59.36	49.76	49.62	6.03	6.14
D-Glucose (in CCl_4)	5	112–113[a]	112	—	—	—	—	—	—	—	52.56	56.85	49.20	49.42	5.64	5.87
D-Glucose (in Acetone)	5	112–113[a]	111–112	—	—	—	—	—	—	—	52.56	55.53	49.20	49.66	5.64	5.81

[a] Lange, *Handbook of Chemistry*, Fourth Ed., Handbook Publishing Co., Sandusky, Ohio (1941). [b] Beilstein's *Handbuch der Organischen Chemie*, Vierte Auflage. [c] R. M. Man- and C. S. Hudson, *J. Am. Chem. Soc.*, **64**, 926 (1942). [d] E. Pacsu and F. V. Rich, *J. Am. Chem. Soc.*, **55**, 3022 (1933).

istics for the polyol and its acetylated derivative. Solvents given preliminary attention were chloroform, carbon tetrachloride, ether, dioxane, ethyl acetate, acetic acid, benzene, and absolute ethanol. Of these carbon tetrachloride appeared to be most satisfactory.

Acetylation of D-glucose in carbon tetrachloride was found to be superior to acetylation in acetone in several respects. In the first place fewer steps are involved in the isolation of the final product. Secondly, a purer product is formed. Evidently the acetone solution is compatible with undesirable acidic side reactions as is indicated by the greater amount of sodium carbonate required in washing. The work of Rice and Greenburg[5] further substantiates this conclusion.

All available hydroxy groups in four typical glycols, glycerol, three Cellosolves, D-glucose, sorbitol, and mannitol were completely acetylated with ketene in the presence of a trace of sulfuric acid. Available ether linkages were not ruptured under similar treatment. Carbon tetrachloride was found to be a suitable solvent for the acetylation of solid polyols and definitely superior to acetone.

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The Addition of Trichlorosilane to Pentene-1 with Peroxide Initiators

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The addition of organosilicon hydrides and tribromosilane to olefinic double bonds in the presence of peroxide initiators has recently been described.[1] In continuing this work, using trichlorosilane, certain factors influencing the addition were observed.

The addition proceeds by a free radical mechanism, very likely as it is described by Sommer, *et al.*[2]

$$A\cdot + HSi\equiv \longrightarrow AH + \cdot Si\equiv$$
$$RCH{=}CH_2 + \cdot Si\equiv \longrightarrow R\dot{C}HCH_2Si\equiv$$
$$R\dot{C}HCH_2Si + HSi\equiv \longrightarrow RCH_2CH_2Si\equiv + \cdot Si\equiv$$

In this mechanism A· is the free radical initiating the chain reaction. The manner in which the chain terminates is not known.

Burkhard and Krieble[3] have pointed out that mixtures containing methyldichlorosilane gave relatively poor yields of adduct per mole of initiator (peroxide efficiency). Trichlorosilane gave much better results and peroxide efficiencies as high as 17 were obtained with pentene-1 with diacetyl peroxide. We have found that this value may under favorable conditions rise considerably, for example, reaching 300 (Table III).

In order to find some of the factors influencing yields and peroxide efficiencies, a series of experiments were carried out in which pentene-1, trichlorosilane, and *tert*-butyl perbenzoate were mixed and sealed into small Claisen flasks. After a period of heating, the flasks were opened and the contents were distilled from them. Very good material balances and a fairly accurate estimate of yields were obtained in this way. To these flasks were also added miscellaneous components thought likely to have an effect on the yields. Such materials as silicone stopcock grease, traces of water, alcohol, nickel, lead, zinc, air, nitrogen, or carbon dioxide had little or no effect. Certain other materials had very obvious effects. Table I summarizes some results obtained in this way.

Metals and their salts may either hinder or aid the reaction. Iron and its salts were outstanding in preventing the formation of adduct. Tin was a promoter for the reaction, causing successful addition, at temperatures lower than those normally effective. Tin and its salts showed no catalytic activity alone, however, but presumably through some action on the peroxide acted as an effective promoter. Tin mixed with stannic chloride caused the addition to become violent even at room temperature.

Three samples of tin were tested and found to possess greatly differing effects as promoters. Granular tin (No. 1) used in Table II was 20 mesh, lot 15, from Baker and Adamson Co. A sample (No. 2) from J. T. Baker Co., 20 mesh, reagent grade, lot 3787, was less effective. A third sample (No. 3) filed from a bar of commercial tin of uncertain origin proved to be far the best. Addition of small amounts of it to the mixtures at room temperature caused violent reactions. Each sample of tin was analyzed spectroscopically and showed increasing activity with increasing amounts of impurities although the trace elements responsible could not be identified.

Experiments using various initiators showed appreciable differences as might be expected. Benzoyl peroxide was very active and gave high peroxide efficiencies, but in certain mixtures tended to react so rapidly as to make control difficult. Table III summarizes some data concerning initiators and the effects of temperature. Higher temperatures than employed here would be likely to improve the yields from some of the initiators.

The pentyltrichlorosilane obtained as the product from all these experiments was examined closely to establish its identity beyond question. Sommer[2] has found that octene-1 and trichlorosilane formed *n*-

[a] Now at Dow Corning Corporation, Midland, Michigan.
[b] Now at Monsanto Chemical Co., Dayton, Ohio.

(1) J. L. Speier, Ruth Zimmerman, and J. A. Webster, *J. Am. Chem. Soc.*, **78**, 2278 (1956).
(2) L. H. Sommer, E. W. Pietrusza, and F. C. Whitmore, *J. Am. Chem. Soc.*, **69**, 188 (1947).
(3) C. A. Burkhard and R. H. Krieble, *J. Am. Chem. Soc.*, **69**, 2687 (1947).

TABLE I

EFFECTS OF VARIOUS MATERIALS ON ADDITION OF Cl_3SiH TO PENTENE-1 WITH *tert*-BUTYL PERBENZOATE AS INITIATOR

moles Cl_3SiH / moles pentene-1	Added Material	moles pentene-1 / moles initiator	T., °C.	Hours	Yield,[a] %
3	Steel wool	70	80–85	15	0
3	Fine copper wire	50	80–85	18	52
3	None	70	80–85	16	88
2	Chromium chips	50	80–90	16	34
3	Nickel chips	50	80–90	16	100
2	None	50	80–90	16	100
2	Lead filings	50	80–90	16	90
2	Lead filings	50	25–30	24	0
2	Zinc dust	50	80–90	16	100
2	Tin granules	50	25–30	1.5	67
2	Tin granules	(b)	25–30	24	0
2	$SnCl_4$	50	25–30	24	11
2	SnO	50	25–30	24	18
2	$SnCl_2$	50	25–30	22	9
2	None	50	25–30	24	0
2	Tin granules + $AlCl_3$	50	25–30	24	0
2	Tin granules + $SnCl_4$	50		flask blew up	
2	Bu_2SnCl_2	50	25–30	24	0

[a] Based upon the pentene-1 charged. [b] No *tert*-butyl perbenzoate.

TABLE II

SPECTROSCOPIC ANALYSES OF TIN SAMPLES

Element	No. 1 Tin	No. 2 Tin	No. 3 Tin
Fe	0.003–0.03	0.003 –0.03	0.01 –0.1
Co	None	None	.003 – .03
Cu	.01 – .1	.0001– .001	.003 – .03
Pb	.003– .03	None	.03 – .3
Bi	None	None	.003 – .03
Si	.01 – .1	.003 – .03	.01 – .1
Cr	.001– .01	.001 – .01	.0003– .003
Ni	.001– .01	None	.001 – .01
In	None	0.01	.01 – .1

octyltrichlorosilane. By analogy Burkhard and Krieble[3] assigned the *n*-pentyl configuration to the product they obtained from pentene-1. Bygden[4] reported the properties of 2-pentyltrichlorosilane as prepared by Melzer[5] but inspection of Melzer's paper showed he had prepared only isopentyltrichlorosilane. No reference giving the properties of 2-pentyltrichlorosilane could be found. Pentene-2 and trichlorosilane were used to form a pentyltrichlorosilane easily distinguished from that obtained with pentene-1. These products proved to be essentially pure *n*-pentyltrichlorosilane from pen-

TABLE III

ADDITION OF TRICHLOROSILANE TO PENTENE-1 USING VARIOUS INITIATORS

$HSiCl_3$[a] / Pentene-1	Initiator[b]	Pentene-1[a] / Initiator	Temp., °C.	Time, hours	Conversion,[c] Percent	Peroxide[d] Efficiency
3	Bz_2O_2	33	55	2.5	Explosion	—
2.5	Bz_2O_2	100	80	0.25	Explosion	—
2	Bz_2O_2	1000	80	16	30	300
3	AZO-I	33	55	18	68	22
2.5	AZO-I	100	80	18	98	98
3	TBPA	33	55	18	0	0
2.5	TBPA	100	80	18	82	82
3	DTBP	33	55	18	0	0
2.5	DTBP	100	80	18	5.6	5.6
3	MAKP	33	55	18	0	0
1	MAKP	50	80	18	72	36
2.5	TBPB	100	80	18	82	82
2	TBPB	100	95	1.4	10	10
2	TBPB	100	95	5	79	79
3	TBPB	65	35	16	0	0
2	TBPA	100	95	1.4	8	8
2	TBPA	100	95	5	71	71

[a] In moles. [b] Bz_2O_2, benzoyl peroxide; AZO-I, N,N'-azo-bis-isobutyronitrile; TBPA, *tert*-butyl peracetate; DTBP, di-*tert*-butyl peroxide; MAKP, methyl amyl ketone peroxide; TBPB, *tert*-butyl perbenzoate. [c] Based on pentene-1. [d] Moles of product/mole of initiator.

(4) A. Bygden, *Inaug. Diss. Upsala, Sweden* (1916).

(5) W. Melzer, *Ber.*, **41**, 3370 (1908).

tene-1 and a mixture of two isomers in the ratio of 70/30 from pentene-2. The isomers are likely to be the 2-pentyl- and 3-pentyl-silanes.

EXPERIMENTAL

Addition of trichlorosilane to pentene-1. Burkhard and Krieble[3] added trichlorosilane to pentene-1 and reported the formation of *n*-pentyltrichlorosilane. *n*-Pentyltrichlorosilane has also been made from the *n*-pentylmagnesium bromide and tetrachlorosilane.[6] The reported properties were not sufficient to indicate with certainty that the pentyltrichlorosilane we obtained was *n*-pentyltrichlorosilane free of isomers. Therefore, the product obtained as described in the discussion was carefully distilled through a column 3 ft. long and 1 inch in diameter packed with 1/16 inch "Helipak" packing. The product was *n*-pentyltrichlorosilane essentially free of isomers: b.p. 171.0° at 742 mm., n_D^{25} 1.4379, d_4^{25} 1.128; R_D 0.2327, Calc'd 0.2320.

Methylation with excess methylmagnesium bromide in ether gave an 80% yield of *n*-pentyltrimethylsilane: b.p. 139.3° at 743 mm., n_D^{25} 1.4069, d_4^{25} 0.7271; R_D 0.3385, Calc'd 0.3382.[7]

n-Pentyltrimethylsilane was prepared by adding a mixture of *n*-amyl chloride and trimethylchlorosilane to molten sodium in refluxing toluene, b.p. 138.9–139.1° at 740 mm., n_D^{25} 1.4069, d_4^{25} 0.7267; R_D 0.3387, Calc'd 0.3382.

The infrared absorption curves of the two samples were identical.

Addition of trichlorosilane to pentene-2. Under the same conditions pentene-2 yielded a pentyltrichlorosilane with properties quite easily distinguishable from those of *n*-pentyltrichlorosilane. From pentene-2 one might expect 2-pentyl- or 3-pentyl-trichlorosilane or a mixture of the two.

A gas-phase chromatographic analysis was performed on a 15 microliter sample on a six-foot Celite column impregnated with didecyl phthalate as the liquid substrate at 80°. Nitrogen was used as the carrier gas with an inlet pressure of 2 p.s.i. at a flow rate of 10 ml. per minute. Two peaks were obtained. The first had a retention time of 21.2 min. and amounted to 70% of the sample. The second at 23.1 min. contained about 30% of the sample. Because standard samples were not available it is impossible to ascertain the structures of the two components[8] at this time. The product had the properties: b.p. 165–167°, n_D^{25} 1.4455, d_4^{25} 1.145; R_D 0.2327, Calc'd 0.2320. An adduct prepared in this way has been reported[3] to boil at 164–168°.

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(6) F. C. Whitmore, *et al.*, *J. Am. Chem. Soc.*, **68**, 475 (1946).

(7) F. C. Whitmore, *et al.*[6] report b.p. 139° at 760 mm., n_D^{20} 1.4096, d_4^{20} 0.7313.

(8) This analysis was carried out in the Department of Research in Physical Chemistry at Mellon Institute.

Preparation of 6-Quinolyl- and 6-Quinolylmethyl-phosphonic Acids

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Although several phosphonic acids, in which the phosphono group is attached to a heterocyclic ring, have been prepared in recent years by various procedures, there is still a decided paucity of data about the phosphonic acids with the simple, more common nitrogen-bearing heterocyclic rings. In view of the fact that the classical Skraup reaction does not appear to have been applied to the readily available aminoarylphosphonic acids, it was felt that this application of the Skraup reaction should be examined. In order to avoid the separation of isomeric phosphonic acids the present synthesis was confined to amino derivatives which can give only one compound by the Skraup reaction.

EXPERIMENTAL

6-Quinolylphosphonic acid. *p*-Nitrophenylphosphonic acid was prepared according to Doak and Freedman[1] and was hydrogenated to *p*-aminophenylphosphonic acid over a palladium-charcoal catalyst in aqueous solution at room temperature and atmospheric pressure. The amino acid (3.0 g.), 13 ml. of 70% sulfuric acid, 4.0 g. of dry glycerol, and 3.5 g. of nitrobenzene were mechanically stirred and refluxed gently for 1.5 hours. The dark mixture was diluted with 20 ml. of water, steam-distilled, cooled, and filtered from tarry material. The filtrate was adjusted to the Congo Red endpoint with 20% sodium hydroxide and the crude product which precipitated was collected. The precipitate was dissolved in 15% hydrochloric acid and re-precipitated by the addition of sodium hydroxide solution. It was finally dissolved in 10% sodium hydroxide solution and precipitated by the addition of 15% hydrochloric acid. At each step of the purification the solution was treated with charcoal. There was obtained 2.0 g. (56%) of 6-quinolylphosphonic acid, in the form of colorless, stubby flat needles which melted to a bright red liquid at 303–304°. Titration of the material with 0.1 *N* sodium hydroxide yielded a curve with inflections near *p*H 5 and 10.5, the latter inflection being the more clearly defined of the two.

Anal. Calc'd for $C_9H_8NO_3P$: P, 14.85; Equiv. wt. 209. Found: P, 14.7, 14.8; Equiv. wt. 210.

6-Quinolylmethylphosphonic acid. The procedure described above was followed, with 6.0 g. of *p*-aminobenzylphosphonic acid,[2] 26 ml. of 70% sulfuric acid, 8.0 g. of glycerol, and 7.0 g. of nitrobenzene. There was obtained, after three acid-base re-precipitations, 3.9 g. (54%) of 6-quinolylmethylphosphonic acid, in the form of light-tan colored, fine plates which decomposed to a red liquid at 328–329°.

Anal. Calc'd for $C_{10}H_{10}NO_3P$: P, 13.9; Equiv. wt., 223. Found: P, 13.8, 13.75; Equiv. wt., 219, 220 (inflection points on the titration curve occurred at approximately *p*H 5.8 and 11).

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

(2) G. M. Kosolapoff, *J. Am. Chem. Soc.*, **69**, 2112 (1947).

The Geminal Alkyl Effect on the Rates of Ring Closure of Bromobutylamines

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In view of the temporary interruption of an investigation[1] of the profound effect which geminal

(1) R. F. Brown and N. van Gulick, *J. Am. Chem. Soc* **77**, 1079, 1083, 1089 (1955).

alkyl substitution exerts upon ring closure, it seems advisable to present our preliminary kinetic data as well as some interesting conclusions to be drawn therefrom.

It is a well known rule that geminal alkyl substitution strikingly enhances the tendency of a suitably chosen bifunctional compound to cyclize.[2] The cyclization of substituted 4-bromobutylamines to the corresponding pyrrolidines with elimination of hydrogen bromide was selected as being conveniently amenable to kinetic investigation and because it would afford adequate information as to the effect of the nature and position of substitution. Furthermore, as demonstrated by Freundlich[3] for the parent compound, 4-bromobutylamine, the reaction is virtually quantitative, being free from side reactions, and is completely irreversible. The short half-life of approximately one second which Freundlich established for 4-bromobutylamine suggested that the reaction should be run in a buffered acidic medium, as the concentration of the reactive free base could be controlled to afford observed rates in an easily measurable region.

The kinetics may be set up on the basis of a fast equilibrium between the salt of the bromoamine and the free base, followed by the irreversible rate determining S_N2 displacement of bromide ion by the free amino group. Employing the steady state convention, the kinetic expression for a strongly buffered system is

$$k_{obs.} = \frac{k K_a}{(H^+)} = \frac{2.303}{t} \log \left[\frac{(A)}{(2(A) - (Br^-)_t)}\right], \quad (1)$$

where k is the *p*H-invariant cyclization rate constant for the free base, K_a is the dissociation constant for the 4-bromobutylammonium ion, (A) is the initial concentration of bromobutylamine hydrobromide, and $(Br^-)_t$ is the bromide ion concentration at time t. Formulated in terms of the analytical method, this becomes

$$k_{obs.} = \frac{k K_a}{(H^+)} = \frac{2.303}{t} \log \left(\frac{V_o - V_\infty}{V_t - V_\infty}\right), \quad (2)$$

where V_o, V_t, and V_∞ represent the volumes of potassium thiocyanate titrant required in the Volhard determination of bromide ion at the times indicated by the subscripts. Precise determination of rate constants in unbuffered systems is difficult as the corresponding kinetic expression,

$$k'_{obs.} = \frac{k K_a}{(Br^-)_0} = \frac{2.303}{t} \log \left(\frac{V_o - V_\infty}{V_t - V_\infty}\right) - \frac{1}{t}\left(\frac{V_o - V_t}{V_o - V_\infty}\right), \quad (3)$$

involves a small difference between large terms. Results for runs at 30.00 ± 0.01°C. with acetate-acetic acid and formate-formic acid buffers are summarized in Table I.

TABLE I

SUMMARY OF RATE STUDIES AT 30°

Run No.	Substances as Hydrobromides	Buffer, Moles per liter NaAc	HAc	NaFo	HFo	KNO_3	$k_{obs} \times 10^6$ (sec.$^{-1}$)	k_{rel}
5[a]	4-Bromobutylamine	2.0	0.5				6.7	
12	4-Bromobutylamine	0.5	.25				2.66 ± 0.05	1.00
13[a]	4-Bromo-1,1-dimethylbutylamine	.5	.25				5.5	
17	4-Bromo-1,1-dimethylbutylamine	.5	.25				5.84 ± .25	2.19
1	4-Bromo-2,2-dimethylbutylamine	1.0	1.0				204 ± 6	
7	4-Bromo-2,2-dimethylbutylamine	1.0	1.0				204 ± 2	
3	4-Bromo-2,2-dimethylbutylamine	1.0	1.0			1.0	203 ± 2	
6	4-Bromo-2,2-dimethylbutylamine	0.5	0.5			0.5	180 ± 1	
9	4-Bromo-2,2-dimethylbutylamine	.25	.25			.75	171 ± 3	
11	4-Bromo-2,2-dimethylbutylamine	.25	.25				210 ± 5	158
2	4-Bromo-2,2-dimethylbutylamine	.5	1.0			.5	96.3 ± 1.4	
10	4-Bromo-2,2-dimethylbutylamine	.25	0.5			.75	87.8 ± 1.0	
16	4-Bromo-2,2-dimethylbutylamine			0.5	1.0		7.96 ± 0.08	
8	4-Bromo-2,2-dimethylbutylamine	None					0.47 ± .05[b]	
19	4-Bromo-2,2-diethylbutylamine			.5	1.0		29.9 ± 1.7	594
4[a]	4-Bromo-2,2-diisopropylbutylamine	0.5	1.0			.5	56	9190
18[a]	4-Bromo-2,2-diphenylbutylamine	.5	0.25				140	5250
14[a]	4-Bromo-3,3-dimethylbutylamine	.5	.25				0.42	0.158

[a] These runs should be regarded as preliminary results. [b] This is k'_{obs} in which $(Br^-)_0 = 9.59 \times 10^{-3}$ *M*.

Comparison of runs 1 and 7 illustrates the excellent reproducibility of the system. Inspection of run 3 shows that, at an acetate concentration of 1 *M*, addition of an inert salt, potassium nitrate, has no further effect upon the rate. However, by maintaining a constant buffer ratio of 1 and using potassium nitrate to maintain constant ionic strength, runs 7, 6, and 9 demonstrate a definite trend of increasing rate with increasing buffer concentration. The same phenomenon is evident in runs 2 and 10 at the same ionic strength but with a buffer ratio of ½. Offhand, this would appear to result from oper-

(2) See, for example, G. W. Wheland, *Advanced Organic Chemistry*, 2nd ed., J. Wiley and Sons, Inc., New York, N. Y., 1949, pp. 373–374.

(3) H. Freundlich, *et al.*, *Z. physik. Chem.*, **122**, 29 (1926).

ation of a mild Brønsted general acid catalysis. However, comparison of runs 9 and 11 shows that removal of the inert salt allows $k_{obs.}$ to increase. Also, since runs 9 and 11 show a faint tendency to slow down as the reaction proceeds, 0.25 *M* acetate was considered to be the lower limit of successful buffer action.

A rate *versus* buffer concentration plot at the two buffer ratios gives two lines with different slopes. These facts fail to support general catalysis as the only explanation. An understanding is rather to be sought in the complex *p*H–composition behavior of the acetate-acetic acid buffer system.[4] The rates of runs 2 and 10 would be $^1/_2$ those of runs 6 and 9 if hydrogen ion concentration were determined only by the buffer ratio. Such discrepancies preclude using buffer ratios to determine relative *p*H's among runs. In extending the work, it will be necessary to determine *p*H's to three places in the mantissa, a bothersome task it was originally hoped to avoid. Until this is done, it will be impossible to ascertain the magnitude of the primary and secondary salt effects on the reaction *per se*. On the other hand, once standardized, a very sensitive method would be available for the determination of *p*H.

The effect of change of position of geminal methyl substitution is seen to be large. For substitution at the first carbon, the rate is only doubled as compared to the parent molecule, but, at the second carbon, the maximum effect appears, the rate being 158 times faster. Substitution at the third carbon decreases the rate which is only about $^1/_6$ as fast as the parent. However, the bromine occupies a neopentyl position in this case and the observed rate represents a marked acceleration for such a hindered displacement reaction.

The remarkable effect of size of the geminally substituted group at the 2-position is shown by the observation that ethyl is 594 times better than the parent, isopropyl is 9190 times better, and phenyl is 5250 times better in promoting ring closure. This would seem to exclude electronic effects of the substituents as exerting anything other than a minor influence on the rates, as phenyl and isopropyl have opposite electronic effects but similar steric requirements. A consideration of the intimate cyclization process suggests that geminal alkyl substitution profoundly affects the distribution of rotational configurations by reason of nonbonded interactions with the chain, favoring coiled configurations over what would be the energetically preferred extended configuration of the parent molecule. While it is difficult to predict how this would affect activation energies *a priori*, the effect upon activation entropies is more clearly evident. The decrease in entropy for a rotationally restricted coiled molecule upon going into the transition state would be less than that for the parent molecule, thus increasing the cyclization probability. It is expected that activation energies and entropies made available from rate data at other temperatures will provide valuable quantitative information concerning rotational conformations which would otherwise be difficultly accessible for such relatively complex molecules.

With these preliminary data in hand, it is possible to advance an explanation for the puzzling behavior of 4-phenoxy-2,2-diarylbutylamines and 4-methoxy-2,2-diisopropylbutylamine in boiling concentrated hydrobromic acid.[1] The expected 4-bromobutylamine hydrobromides were formed in yields of 3% (48 hour reflux period) and 47% (*ca.* 30 min. reflux period), respectively. Surprisingly, the corresponding pyrrolidine hydrobromides accounted for the remainder of the starting material. That the pyrrolidine salts were formed by cyclization of the bromoamine hydrobromides produced by hydrolysis of the amino ethers was considered completely untenable at the time as the concentration of the reactive free bromoamine must be negligible in such a highly acidic reaction medium. However, it now appears that such negligible concentrations are sufficient to explain the results.

It is reasonable to assume that $K_{a(BrRNH_3^+)} \simeq K_{a(BuNH_3^+)}$ and $\Delta H_{(BrRNH_3^+)} \simeq \Delta H_{(NH_4^+)}$, where ΔH refers to the heat of dissociation of the corresponding aqueous ammonium ions, and it can be seen that for a one *molar* solution in boiling 48% hydrobromic acid, the concentration of the free bromoamine is on the order of 10^{-9} *M*, if K_a is still reasonably valid under these conditions. Despite this tiny concentration, ring closure will occur at an easily measurable rate by virtue of the inordinate cyclization tendency conferred by geminal or isopropyl substitution. This is easily shown by a simple approximate calculation. Using the observed cyclization rate of 4-bromo-2,2-diphenylbutylamine hydrobromide at 30°, and, assuming that the heat of dissociation of this salt in aqueous solution is 12 kcal., the value for the aqueous ammonium ion, and that $\Delta H^{\mp}$ is 20 kcal., a reasonable value for most organic reactions, then $(k\ K_a)_{126°} \simeq 10^{-1}$ sec^{-1}. The observed value from the preparative data[1] is on the order of 10^{-4} sec^{-1}. The main reason for the discrepancy is to be found in the implicit assumption that hydrolysis of the phenoxyamine is rapid compared to cyclization of the bromoamine so produced. This condition is not actually fulfilled as the insolubility of the phenoxyamine in the reaction medium precludes rapid hydrolysis. If this could be taken into account, the correction would be in the right direction. On the other hand, 4-methoxy-2,2-diisopropylbutylamine is quite soluble in concentrated hydrobromic acid and hydrolysis does appear to be rapid. Consequently, the observed and calculated values agree more closely. Thus, $(k\ K_a)_{126°}$ is calculated to be on the order of 10^{-1} sec^{-1}

(4) W. M. Clark, *The Determination of Hydrogen Ions*, 3rd ed., The Williams and Wilkins Co., Baltimore, Md., 1928, pp. 21, 219.

and the observed value is on the order of 10^{-2} sec^{-1}. Considering the drastic approximations, this agreement is excellent and substantiates the proposed explanation. Further supporting evidence is available in the fact that the 4-bromo-2,2-disubstituted-butylamine hydrobromides melt with dissociative decomposition in the range 170–195°, freely evolving hydrogen bromide with concomitant formation of the corresponding pyrrolidine hydrobromides. In fact, the isopropyl compound is so predisposed to cyclize that solutions of the pure bromoamine salt in carbon tetrachloride begin visibly to evolve hydrogen bromide at 50°. Rate studies of cyclization in 48% hydrobromic acid are planned for the future in order to throw additional light on this unexpected phenomenon.

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The Dimethylamine–1,3,5-Trinitrobenzene Complex in Dioxane

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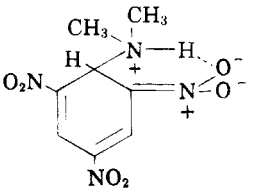
Evidence has been presented[1] that 1,3,5-trinitrobenzene reacts with four molecules of dimethylamine in dioxane solution to form a colored 4:1 complex. The particular treatment used to test this hypothesis assumed that the only species present in the solution were dimethylamine, 1,3,5-trinitrobenzene, and the 4:1 complex. We find that the color produced by dimethylamine and 1,3,5-trinitrobenzene in dioxane is formed instantaneously and is stable with time at constant temperature. It, therefore, seems to us improbable that only a 4:1 complex is formed, particularly since this would necessitate a transition state involving five molecules. Moreover, if 1:1, 2:1, or 3:1 complexes are intermediates for formation of the 4:1 complex, then it seems to us inconsistent with both the chemical nature of the reagents involved and the principle of microscopic reversibility that none of these lower complexes persist at equilibrium. Accordingly, it is our present purpose to offer an alternate hypothesis which fits the available data equally well and which appears to us to be more probable.

Studies of the acidity of aromatic nitro compounds towards amines by Lewis and Seaborg[2] suggest a possible mode of interaction of dimethylamine and 1,3,5-trinitrobenzene. These authors suggest that the attachment of the amine to the nitro compound is *via* the direct addition of the base to one of the ring carbons that is not attached to a nitro group and *via* hydrogen bonding between the amine hydrogen and an oxygen of a nitro group. To illustrate, we have represented one of the contributing structures to the resonance state of the 1:1 complex in the formula below.



Since 1,3,5-trinitrobenzene has three nitro groups and three intervening ring carbon atoms, there are possibilities for forming three complexes, a 1:1, a 2:1, and a 3:1 complex.

For this type of interaction the three equilibria involved are

$$T + A \rightleftharpoons TA$$
$$TA + A \rightleftharpoons TA_2$$
$$TA_2 + A \rightleftharpoons TA_3$$

where T is the trinitrobenzene and A is dimethylamine, and the three associated equilibrium constants are given by

$$K_1 = \frac{TA}{T \cdot A}$$

$$K_2 = \frac{TA_2}{A \cdot TA}$$

and

$$K_3 = \frac{TA_3}{A \cdot TA_2}$$

To relate these equilibrium constants to the spectroscopic data in a manageable form it is necessary to make some assumptions as to the relative amounts of the 1:1, the 2:1, and 3:1 complexes at equilibrium. The simplest assumption we can make is that the relative amounts of the three complexes are determined by purely statistical considerations; *i.e.*, $K_1 = 9\,K_3$ and $K_2 = 3\,K_3$. This assumption is probably justified, since all of the species involved are neutral molecules and no strong electrostatic forces are involved. Further, we assume that

$$A \cong Ao,$$

where A is the equilibrium concentration of amine and Ao is the initial concentration of the amine. This assumption is clearly permissible, since in all of the measurements the amine concentration is at least 200 times as great as the trinitrobenzene concentration. Finally, we assume that

$$TA_3\,\epsilon_{TA_3} \gg TA\,\epsilon_{TA} \text{ or } TA_2\,\epsilon_{TA_2},$$

where the ϵ's are extinction coefficients. This assumption is, we feel, a reasonable approximation based on the qualitative results reported by Lewis and Seaborg.[2]

The resulting equation, which relates the optical data and the equilibria is

(1) Foster, Hammick, and Wardley, *J. Chem. Soc.*, 3817 (1953).

(2) Lewis and Seaborg, *J. Am. Chem. Soc.*, **62**, 2122 (1940).

$$\frac{1}{9}\sqrt[3]{\frac{To}{d_c}} = \frac{1}{K_3\sqrt[3]{\epsilon_{TA_3}}}\left[\frac{1}{3Ao}\right] + \frac{1}{\sqrt[3]{\epsilon_{TA_3}}}$$

where $d_c = d_T - To\epsilon_T - Ao\epsilon_A$ and d_T is the total measured optical density in an absorption cell having a 1-cm. light path. To test this equation, we plot $\frac{1}{9}\sqrt[3]{\frac{To}{d_c}}$ *vs.* $\frac{1}{3Ao}$. The points should fall on a straight line with the slope equal to $\frac{1}{K_3\sqrt[3]{\epsilon_{TA_3}}}$ and the intercept equal to $\frac{1}{\sqrt[3]{\epsilon_{TA_3}}}$. Such a plot, using the data reported by Foster, Hammick, and Wardley,[1] is shown in Figure 1. As can be seen from the figure, the fit is all that can be expected and lends some support to our structural hypothesis.

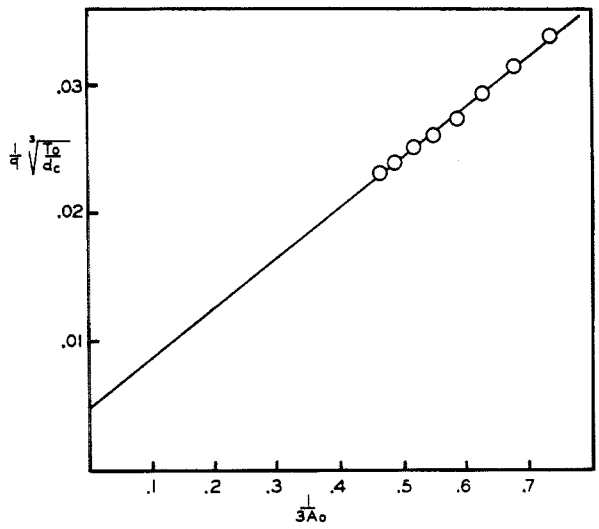


FIG. 1.—A PLOT OF $1/9\sqrt[3]{\frac{To}{d_c}}$ *vs.* $\frac{1}{3Ao}$ WHICH TESTS THE FIT OF THE DATA TO THE PROPOSED HYPOTHESIS OF 3:1 COMPLEXING CO-EXISTING WITH 1:1 AND 2:1 COMPLEXING.

In a similar way and making similar assumptions, it is possible to derive an expression for the case where the complexes present are 2:1 and 1:1.[3] However, when the data are plotted for this case a curve rather than a straight line is obtained. The possibility of simple 1:1 complexing has been adequately eliminated by Foster, Hammick, and Wardley.[1] We have not considered the possibility of a 4:1 complex coexisting with the 1:1, 2:1, and 3:1 complexes, since our structural hypothesis cannot accommodate the fourth amine molecule.

Finally, a dioxane solution which is 0.101 *M* in 1,3,5-trinitrobenzene and 0.043 *M* in dimethylamine shows appreciable cclor formation at 25° (d_c's of about 0.06 from 390 to 440 mμ). At the same temperature, a solution which was 0.021 *M* in trinitromesitylene and 0.043 *M* in dimethylamine showed no additional color formation (d_c's = 0). Similar observations have been reported by Lewis and Seaborg[2] for solutions in petroleum ether. We consider this to be evidence for the proposed hypothesis, since the anticipated effect of the methyl groups in trinitromesitylene is to inhibit resonance of the nitro groups with the ring and prevent formation of the postulated complexes.

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(3) The final equation for this case is

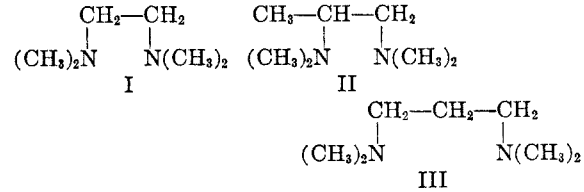
$$\sqrt{\frac{To}{d_c}} = \frac{1}{K_2\sqrt{\epsilon_{TA_2}}}\frac{1}{2\,Ao} + \frac{1}{\sqrt{\epsilon_{TA_2}}}$$

Amines. I. N,N,N′,N′-Tetramethyl-1,2-propanediamine and Its Characterization

ROSS W. MOSHIER AND LEONARD SPIALTER

Received April 16, 1956

The methylation of ethylenediamine to the N,N,N′,N′-tetramethyl derivative, **I**, was first reported by Eschweiler[1] to result from the action of excess formaldehyde on the primary diamine. Subsequently, the Clarke modification, where formic acid is used as the reductant, was introduced[2] in the methylation of 1,4-butanediamine and certain monoamines. Wide application of this method of N-methylation to the synthesis of poly-tertiary amines has been hindered by the unavailability of the starting polyamines. It was, therefore, surprising to find that N,N,N′,N′-tetramethyl-1,2-propanediamine (**II**) had not been previously reported although 1,2-propanediamine is a common commercial chemical,[3] as is also 1,2-dichloropropane,[3] an intermediate for the alternative preparative route *via* condensation with dimethylamine. This latter reaction has been used for the synthesis from 1,3-dichloropropane of the isomeric N,N,N′,N′-tetramethyl-1,3-propanediamine (**III**) and for the preparation of compound **I**.[4]



(1) W. Eschweiler, *Ber.*, **38**, 880 (1905).

(2) H. T. Clarke, H. B. Gillespie, and S. Z. Weisshaus, *J. Am. Chem. Soc.*, **55**, 4571 (1933).

(3) This compound, ethylenediamine and various polyethylenepolyamines are prepared and marketed by Carbide and Carbon Chemicals Corporation, 30 E. 42nd Street, New York 17, N. Y.

(4) (a) L. Knorr and P. Roth, *Ber.*, **39**, 1420 (1906); (b) M. Freund and H. Michaels, *Ber.*, **30**, 1374 (1897); (c) G. F. Grail, L. E. Tenenbaum, A. V. Tolstoouhov, C. J. Duca, J. F. Reinhard, F. E. Anderson, and J. V. Scudi, *J. Am. Chem. Soc.*, **74**, 1313 (1952); (d) I. G. Farbenindustrie A-G, French Patent 802,105 (1936).

The present note describes the synthesis, physical properties, and standard derivatives, which characterize the diamine molecule II.

EXPERIMENTAL[5]

N,N,N',N'-Tetramethyl-1,2-propanediamine (II). To 4060 ml. of 90% formic acid in a 12-l. 3-neck round-bottom flask fitted with a condenser, stirrer, and dropping-funnel was slowly added 1334 g. (17.3 moles) of 1,2-propanediamine[6] with thorough mixing. Then somewhat more rapidly was introduced 5960 ml. of a 37% formalin solution. The uniform evolution of bubbles of carbon dioxide from the body of the solution indicated the progress of the reaction. After the early rapid gas liberation had subsided, the flask was heated at a gentle refluxing temperature for 48 hours. While still boiling, the reaction mixture was carefully treated with 1.0 l. of concentrated sulfuric acid to bind the amine as a salt. The excess formaldehyde, formic acid, and water then were distilled off.

When the still pot residue began to froth badly (after 5600 ml. of distillate had been collected), 900 g. of sodium hydroxide (as a warm 50% aqueous solution) was added. About one liter of amine product distilled over. More was obtained by salting it out from the residue with concentrated aqueous potassium hydroxide. The combined amine fractions were dried over potassium hydroxide pellets and distilled from sodium. The yield of N,N,N',N'-tetramethyl-1,2-propanediamine, b.p. 138–139° at 745 mm. was 1692 g. (76%) of clear colorless liquid with a very strong amine odor. The product was completely miscible with water and organic solvents. It remained a mobile fluid even at −100°. Cooling below this temperature in a liquid nitrogen bath led to a rapid increase in viscosity with ready supercooling to a hard brittle glass. It was not found possible to crystallize this amine.

Other physical properties found include n_D^{25} 1.4230 (Abbe-type refractometer); d_4^{25} 0.7900 (pycnometer); and dielectric constant 2.4 (determined with dielectric constant meter made by Yellow Springs Instrument Co., Yellow Springs, Ohio).

Anal. Calc'd for $C_7H_{18}N_2$: C, 64.56; H, 13.93; N, 21.51; Neut. equiv., 65.1; MR_D, 42.00.[7] Found: C, 64.47; H, 13.75; N, 21.42; Neut. equiv., 65.0; MR_D, 41.98.

II·Dihydrochloride. This compound was obtained by adding dropwise from a hypodermic syringe 5 ml. of diamine II to 15 g. of concentrated hydrochloric acid in a 50-ml. Erlenmeyer flask with shaking and cooling in an ice-bath to remove the high heat of neutralization. The reaction mixture then was concentrated by heating to remove almost all of the water. There resulted a clear colorless viscous resin which set to a glass on cooling to room temperature. Slow crystallization took place over a period of days. A portion of the crystals, removed and washed with a small amount of absolute ethanol, had m.p. 177–179°. Potentiometric titration with base proved the diprotic nature of this compound.

II·Monopicrate.[8] To 10 ml. of a saturated solution of picric acid in anhydrous ethanol was added 1.0 ml. of diamine II. The solution was refluxed for one minute and allowed to cool slowly overnight. The yellow crystalline salt was filtered off and washed well with ethanol. Yield was 0.80 g., m.p. 112–114°.

Anal. Calc'd for $C_{13}H_{21}N_5O_7$: C, 43.45; H, 5.89; N, 19.49. Found: C, 43.75; H, 5.95; N, 19.40.

II·Di(methiodide). To 2.0 ml. of methyl iodide in 10 ml. of methanol in a 25-ml. Erlenmeyer flask cooled in an ice-bath was added dropwise from a hypodermic syringe 1.0 ml. of diamine II. Constant shaking and cooling were required to dissipate the heat of reaction. After addition was complete, the solution was heated to boiling and allowed to cool slowly overnight. Crystallization occurred. The product was filtered off and washed thoroughly with cold methanol. Yield was 2.0 g. (80%), m.p. 222–224° with decomposition and gas evolution. Recrystallization from methanol gave crystals, m.p. 223–225° with decomposition.

Anal. Calc'd for $C_9H_{24}I_2N_2$: C, 26.10; H, 5.84. Found: C, 26.20; H, 5.80.

II·Di(methyl-p-toluenesulfonate). This derivative was prepared by a procedure identical with that described above for the dimethiodide except for the use of 2.0 ml. of methyl *p*-toluenesulfonate instead of the iodide. The yield was 2.4 g. (80%) of the di(methotosylate), m.p. 225–228°. Recrystallization from methanol gave m.p. 228–229° with a little decomposition since the fused material, after crystallization, had m.p. 223–225°.

Anal. Calc'd for $C_{23}H_{38}N_2O_6S_2$: C, 54.95; H, 7.62. Found: C, 55.11; H, 7.45.

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(5) Analyses were performed by Oakwold Laboratories, Alexandria, Virginia. Melting points were corrected values taken on a Kofler micro hot-stage.

(6) The diamine was the Matheson, Coleman, and Bell technical grade propylenediamine. A representative sample subjected to analysis by fractional distillation indicated 96% purity, b.p. 119–120°. The 1,2-propanediamine forms no azeotrope with water, according to *Synthetic Organic Chemicals Catalog*, Carbide and Carbon Chemicals Corporation, New York, N. Y., 1945, 12th ed., p. 75.

(7) Values for atomic refractivities (sodium D-line) were those of A. I. Vogel, *A Textbook of Practical Organic Chemistry*, Longmans, Green and Co., Inc., New York, N. Y., 1948, p. 898.

(8) One of the referees called our attention to a paper by E. Rothstein, *J. Chem. Soc.*, 1560 (1940), which reports in a small footnote the isolation of a compound presumed to be the bis-quaternary ammonium picrate of the diamine described in the present note. This purported "N,N,N,-N',N',N'-hexamethylpropylenediammonium picrate" was obtained by extended heating of trimethyl-β-chloropropylammonium chloride with potassium hydroxide and then adding picrate ions. The nature of the reaction conditions, lack of structure proof, and the reported m.p. 315–316° make us feel that Rothstein's compound may be tetramethylammonium picrate which fits the analytical data better and has been described as melting at 312–313°, W. Lossen, *Ann.*, **181**, 364 (1876); 318–320°, M. Kohn and F. Grauer, *Monatsh.*, **34**, 1751 (1913); 313°, P. Walden, H. Uhlich, and G. Busch, *Z. physik. Chem.*, **A123**, 429 (1926).

Amines. II.[1] The Preparation and Reduction of Benzo[*c*]cinnoline

JACK RADELL, LEONARD SPIALTER, AND JEROME HOLLANDER[1a]

Received May 7, 1956

An unreported preparation and catalytic reduction product of benzo[*c*]cinnoline have been found. Benzo[*c*]cinnoline (I) also referred to in the literature as 2,2'-azodiphenyl, dibenzopyridazine, phen-

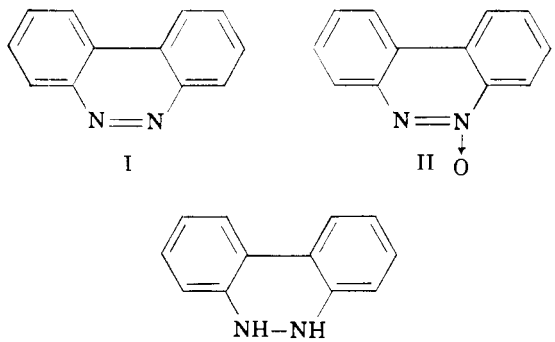
(1) For previous paper in this series, see R. W. Moshier and L. Spialter, *J. Org. Chem.*, 21, 1050 (1956).

(1a) Department of Chemistry, University of North Carolina, Chapel Hill, North Carolina.

azone, diphenazone, diphenylenazone, 3,4-benzocinnoline, and 5,6-naphthisodiazine has been prepared by the reduction of 2,2′-dinitrobiphenyl: electrochemically,[2] chemically with sodium amalgam and methanol,[3] lithium aluminum hydride,[4] ferrous oxide,[5] or iron[6] and catalytically by hydrogenation with platinum oxide[7] or Raney nickel.[8]

The hydrogenation of either I or benzo[*c*]cinnoline oxide (II) with a platinum oxide catalyst reportedly resulted only in the obtaining of I, although there was evidence[7] that hydrazobiphenyl (III) formed and was readily oxidized to I. The hydrogenation of 2,2′-dinitrobiphenyl at an unspecified but presumably lower temperature and lower pressure in the presence of Raney nickel[8] also gave I. In no case was it reported that the catalytic hydrogenation of I yields 2,2′-diaminobiphenyl.

Upon reduction of 2,2′-dinitrobiphenyl with zinc and alkali a 55% yield of I has now been isolated. When I was catalytically hydrogenated with Raney



nickel, it had been expected that III would be formed. Consequently, the hydrogenation product was recovered under an atmosphere of nitrogen to avoid possible oxidation of III to I which occurs readily in air.[2,7] Contrary to our expectation, only 2,2′-diaminobiphenyl was obtained. Its infrared spectrum was identical with those of authentic samples of 2,2′-diaminobiphenyl obtained both by chemical[9,10] and by catalytic[7,11] reductions of 2,2′-dinitrobiphenyl. Melting points of the mixtures of reduction product and the authentic samples were undepressed.

(2) T. Wohlfahrt, *J. prakt. Chem.*, [2] **65**, 295 (1902).
(3) E. Tauber, *Ber.*, **24**, 3085 (1891).
(4) G. M. Badger, J. H. Seidler, and B. Thompson, *J. Chem. Soc.*, 3207 (1951).
(5) H. C. Waterman and D. L. Vivian, *J. Org. Chem.*, **14**, 289 (1949).
(6) P. Z. Slack and R. Slack, *Nature*, **160**, 437 (1947).
(7) S. D. Ross, G. J. Kahan, and W. A. Leach, *J. Am. Chem. Soc.*, **74**, 4122 (1952).
(8) J. L. Everett and W. C. J. Ross, *J. Chem. Soc.*, 1972 (1949).
(9) T. F. Macrae and S. H. Tucker, *J. Chem. Soc.*, 1520 (1933).
(10) S. von Niementowski, *Ber.*, **34**, 3325 (1901).
(11) R. B. Carlin and W. O. Forshey, Jr., *J. Am Chem. Soc.*, **72**, 793 (1950).

EXPERIMENTAL[12]

Benzo[c]cinnoline. In a 200-ml. 3-neck r.b. flask fitted with a reflux condenser, stirrer, and thermometer, 10 g. (0.041 mole) of 2,2′-dinitrobiphenyl, 133.4 ml. of absolute ethanol, and 13.4 ml. of an aqueous solution containing 10 g. of sodium hydroxide were heated on a water-bath. When the temperature of the mixture reached 70–80°, 30 g. of granular (30 mesh) zinc was added gradually over a period of 1/2 hour. Heating with stirring at 70–80° was continued for an additional 1/2 hour. The hot mixture was filtered through a Büchner funnel to remove the zinc oxide. The yellow crystalline material which precipitated from the cooled filtrate, was filtered and washed with absolute ethanol. The combined filtrate and wash solution were boiled with the zinc oxide residue and filtered while hot. From the cooled filtrate a second crop of yellow crystals was obtained. The combined yellow crystals of benzo[*c*]cinnoline (I), after recrystallization from absolute ethanol, weighed 4.1 g., yield 55.4%, m.p. 156–158°.

Anal. Calc'd for $C_{12}H_8N_2$: C, 79.98; H, 4.48; N, 15.55. Found: C, 79.87; H, 4.58; N, 15.79.

Reduction of benzo[c]cinnoline to 2,2′-diaminobiphenyl. A teaspoonful of commercial aqueous Raney nickel paste was washed by decanting with three 50-ml. portions of 95% ethanol. Benzo[*c*]cinnoline (0.53 g., 0.0030 mole) dissolved in 10 ml. of absolute ethanol and 10 ml. of an ethanolic suspension of Raney nickel was hydrogenated with shaking at 34–37° in a glass-lined bomb. The vapor-free space was 65 ml. and the pressure dropped from 98 to 70 p.s.i. The ethanolic solution was filtered and concentrated to 8 ml. in an atmosphere of nitrogen. The white colorless crystals of 2,2′-diaminobiphenyl (V) which separated upon cooling weighed 0.35 g., yield 86%, m.p. 77.5–78.5°.

Preparation of 2,2′-diaminobiphenyl from 2,2′-dinitrobiphenyl (IV) *by two different routes:* (*a*). By reduction with tin and hydrochloric acid[10] as described by Macrae and Tucker.[9]

(*b*). By hydrogenation with a platinum oxide catalyst[11] according to the procedure of Ross, Kahan, and Leach.[7]

Anal. Calc'd for $C_{12}H_{12}N_2$: C, 78.23; H, 6.57; N, 15.21. Found: (a) C, 78.24; H, 6.57; N, 15.38. (b) C, 78.25; H, 6.73; N, 15.44.

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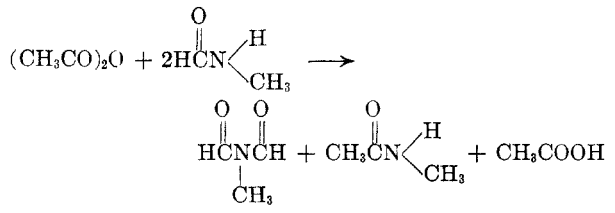
(12) The melting points are uncorrected. The analyses were performed by Oakwold Laboratories, Alexandria, Virginia.

The Preparation of Diformylmethylamine

JAMES D. RAY, HAROLD O. KAMMEN, LAWRENCE H. PIETTE, AND RICHARD A. OGG, JR.

Received March 16, 1956

In the course of investigations of the nuclear magnetic resonance spectra of N-substituted amides in this laboratory, diformylmethylamine was synthesized. This compound, which has not been previously reported, was prepared by the reaction of acetic anhydride with N-methylformamide in accordance with the following equation.



EXPERIMENTAL

A solution of 18 ml. of N-methylformamide (0.31 mole) (b.p. 197°) and 25 ml. of acetic anhydride (0.26 mole)was placed in the pot of a 60 plate fractionating column. Acetic acid was distilled off over a period of 15 minutes without prior reflux. The remaining material was separated into two main fractions (b.p. 183 and b.p. 205° respectively).

N-Methylacetamide was identified by its m.p. 28° and its proton nuclear magnetic resonance spectrum which was identical with that of material prepared by the method of Galat and Elion.[1]

The fraction boiling at 183° with m.p. 13.5 to 14.5° was found to be *diformylmethylamine*. Yield 50%.

Anal. Calc'd for $C_3H_5NO_2$: M.W., 87.14; N, 16.09; Moles formate, 2. Found: M.W. (from vapor density at 240°), 86.8; N, 15.85; Moles formate, 1.98.

The diformylmethylamine was further characterized by its proton nuclear magnetic resonance spectrum which consisted of two sharp lines of area ratio 3:2 which is perfectly compatible with the assigned structure.

Use of a higher ratio of acetic anhydride to N-methylformamide resulted in formation of diacetylmethylamine as by-product. Of the several ratios of reactants tried, the one specified above proved to be the optimum. No ratio of reactants employed resulted in formation of any fraction which could be characterized as formylacetylmethylamine.

Diformylmethylamine was also prepared by fractionation of stoichiometric quantities of N-methylformamide and diacetylmethylamine to produce as a by-product, N-methylacetamide. This exchange reaction proved to be very slow.

It is to be noted that the b.p. of N-methylformamide reported by Gautier[2] (180–185°) is not in agreement with that reported in this paper. Gautier's method of preparation of N-methylformamide involved acetic anhydride as a by-product. Thus his products were exactly the starting materials used in the present study. Apparently Gautier's b.p. for N-methylformamide was actually determined on a somewhat impure sample of diformylmethylamine.

Acknowledgment. The authors gratefully acknowledge the financial support of this study by the Research Corporation.

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(1) A. Galat and G. Elion, *J. Am. Chem. Soc.*, **65**, 1566 (1943).

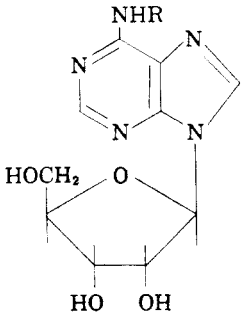
(2) A. Gautier, *Ann.*, **151**, 242 (1869).

Kinetin Riboside and Related Nucleosides

HENRY M. KISSMAN AND MARTIN J. WEISS

Received June 6, 1956

Since Miller and co-workers reported the isolation of kinetin,[1] a cell division factor, from autoclaved DNA samples and its identification as 6-furfurylaminopurine,[2,3] several groups have published on the synthesis of similarly substituted adenine derivatives.[4,5,6] It has been shown[4] that some of these derivatives have kinetin-like activity on plant growth. Because kinetin itself has been isolated from DNA it appeared conceivable that it might actually occur as a riboside or 2-deoxyriboside in nature. In view of our interest in the synthesis of nucleosides and related compounds[7] it seemed pertinent to prepare and test the 9-β-D-ribofuranosyl derivatives (I) of 6-furfurylaminopurine and other substituted adenines.[8] The synthesis of these derivatives, which are listed in Table I, is the subject of this note.



I

A convenient starting material for the preparation of these substituted adenosine derivatives would be a properly blocked 6-chloro-9-β-D-ribofuranosylpurine. The ready replaceability of the 6-chlorine atom in such a nucleoside by ammonia has been demonstrated by Brown and Weliky[9] in their synthesis of adenosine from 6-chloro-9-(2,3,5-tri-*O*-acetyl-β-D-ribofuranosyl)purine.[10] However, for our purposes, we have used the corresponding benzoyl blocked 6-chloronucleoside, *i.e.* 6-chloro-9-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)purine (II), because it had been shown previously[11] that the pre-

(1) Miller, Skoog, von Saltza, and Strong, *J. Am. Chem. Soc.*, **77**, 1392 (1955).

(2) Miller, Skoog, Okumura, von Saltza, and Strong, *J. Am. Chem. Soc.*, **77**, 2662 (1955).

(3) Miller, Skoog, Okumura, von Saltza, and Strong, *J. Am. Chem. Soc.*, **78**, 1375 (1956).

(4) Skinner and Shive, *J. Am. Chem. Soc.*, **77**, 6692 (1955).

(5) Daly and Christensen, *J. Org. Chem.*, **21**, 177 (1956).

(6) Bullock, Hand, and Stokstad, *J. Am. Chem. Soc.*, **78**, 3693 (1956).

(7) See for example paper XI of the Puromycin series.[11]

(8) While this work was in progress, R. H. Hall and R. S. de Ropp of these laboratories reported convincing evidence to the effect that kinetin is actually an artifact formed from adenine and 2-deoxy-D-ribose during autoclaving.[15]

(9) Brown and Weliky, *J. Biol. Chem.*, **204**, 1019 (1953).

(10) L. Goldman, J. Marsico, and R. Angier of these laboratories have successfully effected the reaction of 6-chloro-9-(2,5-di-*O*-benzoyl-3-deoxy-3-phthalimido-β-D-ribofuranosyl)purine with aliphatic amines (to be published).

(11) Kissman, Pidacks, and Baker, *J. Am. Chem. Soc.*, **77**, 18 (1955).

TABLE I

6-(SUBSTITUTED-AMINO)-9-β-D-RIBOFURANOSYLPURINES (I)

R[e]	Starting Amine	Formula	Yield, %	M.p., °C.	Optical Rotation $[\alpha]_D^{25-26}$	c^d	Analyses Calc'd C	H	N	Found C	H	N
Furfuryl	Furfurylamine	$C_{15}H_{17}N_5O_5$	67[a]	148–150	−63.5°	1.13	51.87	4.93	20.17	51.84	5.00	20.28
Benzyl	Benzylamine	$C_{17}H_{19}N_5O_4$	54[b]	177–179	−68.6°	0.55	57.13	5.36	19.60	57.04	5.66	19.70
Thenyl	Thenylamine	$C_{15}H_{17}N_5O_4S$	44[a]	149–150	−60.7°	1.05	49.58	4.72	19.23	49.78	4.91	19.26
3-Pyridylmethyl	3-Pyridylmethylamine[c]	$C_{16}H_{18}N_6O_4$	53[b]	183–184	−66.6°	1.02	53.62	5.06	23.45	53.36	5.31	23.16

[a] Recrystallized from methanol. [b] Recrystallized from ethanol. [c] We would like to thank Dr. M. W. Bullock[6] for a sample of this amine. [d] In ethanol. [e] See formula I.

TABLE II

ULTRAVIOLET SPECTRA[a]

R[b]	Acid λ_{max}	ϵ	λ_{min}	ϵ	Neutral λ_{max}	ϵ	λ_{min}	ϵ	Base λ_{max}	ϵ	λ_{min}	ϵ
Furfuryl	267	18460	236	4580	268	19000	234	3195	269	19140	237	4030
Benzyl	266	20600	235	4140	268	20850	233	2570	269	21300	236	3570
Thenyl	266	18820	240	10310	243	9860	230	9150	270	20880	247	9446
					270	20000	247	9440				
3-Pyridylmethyl	266	20520	233	4300	268	21650	231	3440	268	22230	236	4440

[a] The compounds were dissolved in ethanol. Aliquots were diluted 1:10 with 0.1 *N* hydrochloric acid for the acid spectra and 1:10 with 0.1 *N* sodium hydroxide for the base spectra. [b] See formula I.

cursor sugar, 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (III)[11,12] was more readily available[13] and in two instances[11] gave better yields of ribonucleosides than could be obtained with the corresponding tetra-*O*-acetyl-D-ribofuranose.

The condensation of the 1-chloro sugar derived from III[11] with the chloromercuri derivative of 6-chloropurine[9] was carried out in refluxing xylene and the blocked 6-chloronucleoside (II) was obtained as a fluffed glass after chromatography on acid-washed alumina. The β-configuration of this material was established by its conversion in 61% yield through ammonolysis[9] to a crystalline solid which was shown to be identical with adenosine. It may be noted that the yield of adenosine over-all from 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (III) was 35% whereas the reported yield over-all from tetra-*O*-acetyl-D-ribofuranose was 22%.[9]

The transformation of the 6-chloronucleoside (II) to the compounds described in Table I was carried out in two stages in satisfactory over-all yields. Compound II was heated with the required amine in 2-methoxyethanol solution[6,10] and the crude reaction product—presumably the 6-(substituted-amino)-9-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-purine—was de-*O*-benzoylated with catalytic amounts of sodium methoxide in methanol. The ultraviolet absorption maxima and minima of the final products are given in Table II.

Preliminary testing results[14] indicate that the substituted adenosine derivatives listed in Table I had kinetin-like activity.[15] Details of these tests will be published elsewhere.

EXPERIMENTAL[16]

Chloromercuri derivatives of 6-chloropurine. The chloromercuri derivative of 6-chloropurine[17] was prepared as described by Brown and Weliky[9] except that 4.87 g. of Celite was added to the sodium hydroxide solution of the 6-chloropurine before addition of the mercuric chloride solution.[18]

6-Chloro-9-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)purine (II). A solution of 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride,[11] obtained from 10.33 g. (0.025 mole) of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose,[11,12] in 20 ml. of anhydrous xylene was added to an azeotropically-dried suspension of the 6-chloropurine chloromercuri derivative on Celite [12.46 g. of the mixture containing 7.95 g. (0.024 mole) of the purine salt] in 500 ml. of xylene. The mixture was stirred under reflux for three hours and then was filtered. The filtrate was evaporated under reduced pressure and the

(12) Ness, Diehl, and Fletcher, Jr., *J. Am. Chem. Soc.*, **76**, 763 (1954).

(13) See also Wright and Khorana, *J. Am. Chem. Soc.*, **78**, 811 (1956).

(14) Private communication from Dr. R. S. de Ropp of these laboratories.

(15) Hall and de Ropp, *J. Am. Chem. Soc.*, **77**, 6400 (1955).

(16) Melting points were taken on a Kofler micro hot-stage and are corrected. Ultraviolet absorption spectra were determined on a Cary recording spectrophotometer.

(17) 6-Chloropurine was obtained from The Francis Earle Laboratories Inc.

(18) Baker, Joseph, and Schaub, *J. Org. Chem.*, **19**, 1780 (1954).

residue was dissolved in a mixture of 100 ml. of chloroform and 20 ml. of a 30% aqueous potassium iodide solution. The layers were separated and the organic phase was washed with another 15-ml. portion of the potassium iodide solution and then with 20 ml. of water. The chloroform layer was dried over magnesium sulfate, filtered, and evaporated *in vacuo*. This left 11.3 g. of yellow glassy material, which was dissolved in 12 ml. of benzene and was chromatographed on a column (28 × 3 cm.) of acid-washed alumina.[19] The column was washed with 600 ml. of benzene and these washings were discarded. Elution with 1000 ml. of 20% ethyl acetate in benzene afforded, after evaporation *in vacuo*, a faintly yellow glass which was further purified by solution in ether, filtration through Darco and evaporation *in vacuo*. There was obtained 7.01 g. (57%); $\lambda_{max}^{ethanol}$ 265 mμ (ε 9900).

For analysis, this material was dissolved in hot isopropyl alcohol and was collected as an amorphous solid on cooling. The dried substance showed the following characteristics[20]: λ_{max} 265 mμ (ε 9850 acid); 265 mμ (ε 9620 neutral); 263 mμ (ε 9350 base); $[\alpha]_D^{25}$ −64.0° (*c*, 0.79 in ethanol).

Anal. Calc'd for $C_{31}H_{23}ClN_4O_7$: C, 62.16; H, 3.87; N, 9.35. Found: C, 62.11; H, 4.52; N, 9.03.

Adenosine. A mixture of 1.2 g. of the 6-chloronucleoside (II) and 35 ml. of methanolic ammonia (saturated at 0°) was heated in a stainless steel bomb on the steam-bath for five hours. The bomb contents were evaporated to dryness *in vacuo* and the partially crystalline residue was mixed with 25 ml. of water. The mixture was extracted with three 10-ml. portions of ether and the aqueous phase was evaporated *in vacuo* to a small volume. The solid which crystallized on cooling was collected and dried to yield 0.386 g., m.p. 223–226°. It was recrystallized from a small amount of water and dried *in vacuo* at 100° for four hours; 0.325 g. (61%); m.p. 229–230°; $[\alpha]_D^{24}$ −61.2° (*c*, 1.01 in water). The m.p. was not depressed by admixture of an authentic sample[21] of adenosine. Identity was further confirmed by comparison of the ultraviolet and infrared spectra.

6-(Substituted-amino)-9-β-D-ribofuranosylpurines (I). The compounds which are summarized in Table I were prepared by reacting 6-chloro-9-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)purine (II) with the appropriate amine according to the procedure described below for the 6-furfurylamino derivative.

For the preparation of *6-thenylamino-9-β-D-ribofuranosylpurine* it was necessary, due to the decreased water solubility of the final product, to change the work up slightly as follows. The reaction mixture, after debenzoylation, was evaporated *in vacuo* and the residue was simply triturated with ether, collected by filtration, and then was washed with more ether and finally with a little water. The dried product was recrystallized from methanol.

6-Furfurylamino-9-β-D-ribofuranosylpurine. To a solution of 0.6 g. (0.001 mole) of the 6-chloronucleoside (II) in 15 ml. of 2-methoxyethanol was added 1.5 ml. of freshly distilled furfurylamine and the mixture was heated at the reflux point for one hour. It was then evaporated *in vacuo* and the oily residue was taken up in 20 ml. of chloroform. The solution was washed with saturated aqueous sodium bicarbonate solution and then with water. The organic phase was dried over magnesium sulfate, filtered, and freed from solvents *in vacuo* to leave 0.69 g. of ether-soluble gum. This was dissolved in 20 ml. of anhydrous methanol and after addition of 0.2 ml. of 1 *N* methanolic sodium methoxide solution, the mixture was allowed to reflux for one hour, during which time the solution remained between *p*H 8 and 9. Evaporation *in vacuo* afforded a partially solid mixture to which was added 30 ml. of water. Following extraction with three 10-ml. portions of ether, the aqueous phase was concentrated to a small volume *in vacuo*. The solid, which formed on cooling in the refrigerator overnight, was collected and washed with a small amount of ice-water. The dried substance (0.269 g., m.p. 137–135°) was recrystallized from methanol to afford 0.231 g. (67%) with m.p. 148–150°.

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(19) Reagent Grade alumina (Merck & Co., Inc.) was washed with 1 *N* hydrochloric acid and then with water until neutral. It was dried at 170–180° for 24 hours.

(20) The acid spectrum was determined in methanol:0.1 *N* hydrochloric acid (1:1); the base spectrum was run in methanol:0.1 *N* sodium hydroxide (1:1); the neutral spectrum was run in methanol.

(21) Authentic adenosine, m.p. 228–230°, was obtained from Nutritional Biochemicals Corporation.