date. Formic acid was then titrated with 0.01 *N* sodium hydroxide, with phenolphthalein as indicator. Flasks in which the determinations were made were flushed with carbon dioxide-free nitrogen before adding the test portion and titrations were made in a carbon dioxide-free nitrogen atmosphere. Corrections were applied for acidity found in blanks in which sodium metaperiodate had been reduced with ethylene glycol. These corrections were equivalent to 0.5 to 1.0% of the total formic acid titration.

Heretofore it has been the custom to use methyl red indicator in titrating formic acid in reaction solutions from which excess periodate had[10,17] or had not[22] been removed by ethylene glycol. Our observations, in agreement with statements of Meyer and Rathgeb,[23] showed that in the absence of periodate there is no reason for using methyl red indicator and that its use resulted in low values for formic acid.

The accuracy of the measurements of periodate reduced and of formic acid liberated by the polysaccharides was established by using D-glucosan < 1,5 > β < 1,6 > (levoglucosan)[24] as a reference standard. Prior to use, the levoglucosan was dried over phosphorus pentoxide *in vacuo* at 78°. The results obtained by treating one mole of levoglucosan with 2.2 moles of sodium metaperiodate (Table I) are in close agreement with theory and with previous observations.[25]

Periodate Oxidation Procedure.—Air-dried polysaccharides, of known moisture content,[8] were used.

To prevent oxidation of formic acid, all oxidations with sodium metaperiodate were carried out with concentrations of reactants comparable with those used by Halsall, Hirst and Jones.[10] Tests showed formic acid was not destroyed under these conditions. Duplicate samples of carbohydrate, in amount sufficient to produce about 10 mg. of formic acid per 100 ml., were dissolved or dispersed in freshly boiled distilled water in volumetric flasks. The desired amount of approximately 0.3 *M* sodium metaperiodate was added and the contents were made to volume with freshly boiled distilled water. Since a difference in rate only was observed in preliminary work when dextran was treated with 2.2 or 3.0 moles of sodium metaperiodate per mole of anhydroglucose unit, 3.0 moles was used in all subsequent oxidations of dextran and acid-hydrolyzed dextran. The flasks were placed in a constant temperature room at 25° and aliquots of the solutions were with drawn at intervals for the analytical determinations. Aliquots from dextran solutions were taken usually after seventy-two and ninety-six hours reaction time, when the reaction was found to be complete for the most slowly oxidized dextrans.

The procedure used for oxidation with potassium metaperiodate was that of Halsall, Hirst and Jones,[10] carried out at 25°.

Unlike oxidized waxy corn starch, which is insoluble in the sodium metaperiodate reaction mixture, oxidized dextran is soluble.

(22) Jackson and Hudson, THIS JOURNAL, **61**, 1530 (1939).

(23) Meyer and Rathgeb, *Helv. Chim. Acta*, **31**, 1540 (1948).

(24) We are indebted to Dr. Ivan A. Wolff for this highly purified sample.

(25) Jackson and Hudson, THIS JOURNAL, **62**, 958 (1940).

Summary

1. Conditions have been described for the oxidation of dextran with sodium metaperiodate at 25°, and for measurement of the formic acid produced.

2. The results obtained give a measure of the ratio of 1,4- to 1,6-glycosidically linked anhydropyranose units present and appear to be in good agreement with those from the methylation procedure.

3. Ratios of 1,4- to 1,6-glycosidically linked anhydropyranose units have been observed to vary from 1 to 3 to 1 to 24 for dextrans from different strains of *Leuconostoc mesenteroides*.

4. The primary products of periodate oxidation of dextran and of acid-hydrolyzed dextran are stable to further oxidation by the reagent.

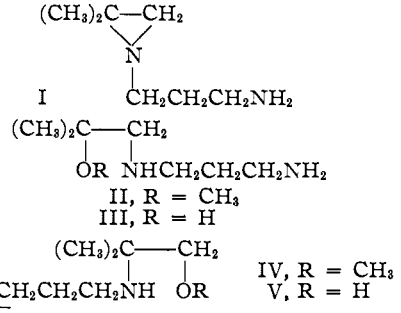
PEORIA, ILLINOIS RECEIVED NOVEMBER 5, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF ROCHESTER]

Acid-catalyzed Ring-opening Reactions of Some Unsymmetrical Ethyleneimine Derivatives

BY D. STANLEY TARBELL AND PAUL NOBLE, JR.

In some studies of products obtained from 2,2-dimethylethyleneimine and acrylonitrile, which were initiated with the object of examining the resolvability of the trivalent nitrogen in ethyleneimine, the compound I was obtained by catalytic reduction of the primary addition product.[1]

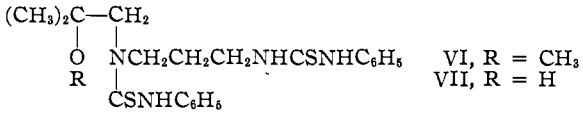


(1) Tarbell and Fukushima, THIS JOURNAL, **68**, 2499 (1946).

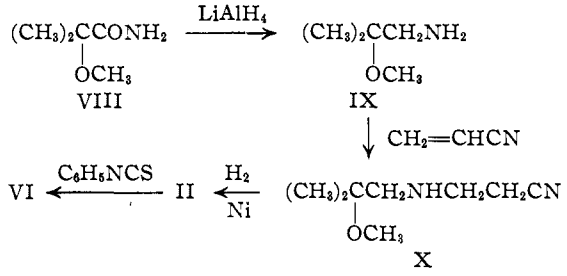
This compound formed an unstable dipicrate, which was converted, by crystallization from methanol, to a new compound, which had the composition expected for the dipicrate of the methanolysis product II or IV. The present paper describes a study of the acid-catalyzed methanolysis and hydrolysis of I, and demonstrates that the product in each case has the structure II (or III); the isomeric compounds IV and V do not appear to be formed.

It was found that the action of acids on the imine I in methanol solution usually led to polymeric materials; this was observed with dry hydrogen chloride, formic acid, ammonium chloride, boron fluoride or acetic acid. The action of picric acid on I in methanol usually led to the contamination of the main product, the dipicrate of the *methanolysis* product II, m. p. 199–200°, with the dipicrate of the *hydrolysis* product III, m. p. 184–187°. This

contamination can be minimized by avoiding the use of dilute methanol in recrystallization or, better, by recrystallization from methanol of the preformed dipicrate of I, as previously described.[1] No evidence was found for the presence of the dipicrate of the isomeric product (IV). The isolation of the free base II from its dipicrate by several methods was not successful; however, a solid bis-phenylthiourea derivative VI was obtained. This derivative had the correct methoxyl content for structure VI.

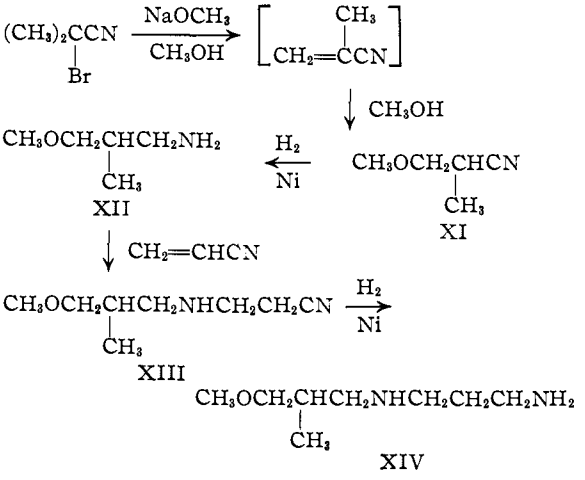


The structure of the methanolysis product II was proved by the following synthesis. Methyl α-methoxyisobutyrate[2] was converted to the amide VIII, which was reduced to β-methoxyisobutylamine (IX) with lithium aluminum hydride[3]; the



amine was then added to acrylonitrile to yield X, and the latter reduced to compound II. The dipicrate obtained from the synthetic material was identical with that prepared by methanolysis of the dipicrate of the imine I, and the synthetic base yielded the same bis-phenylthiourea derivative VI which had been obtained from the methanolysis product.

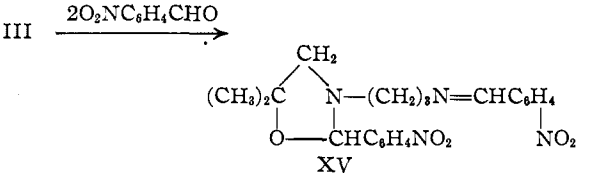
An isomer (XIV) of II was also prepared, by a synthesis which was expected to lead to II. α-Bromoisobutyronitrile was treated with sodium methoxide in methanol,[4] and, since we believed that the product was the α-methoxyisobutyronitrile, the compound was reduced to the amine, added to acrylonitrile, and the nitrile group reduced. The product was different from the methanolysis product, and the discrepancy was traced to the sodium methoxide "replacement" step. This was found to be an elimination reaction, presumably giving α-methylacrylonitrile, which then added methanol to give XI. The structure of XI was established by preparing it from α-methylacrylonitrile and methanol; the identity of the samples of the nitrile prepared by



the two different methods was established through the crystalline phenylthiourea derivatives obtained from the amine XII prepared from both samples of nitrile.

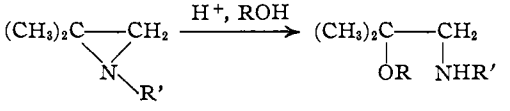
Some experiments on the synthesis of β-methoxyisovaleric acid by the haloform reaction on 4-methoxy-4-methyl-2-pentanone are described in the experimental part.

Hydrolysis of the imine I by hot aqueous sulfuric acid yielded III, the isomer with the tertiary hydroxyl group, which was isolated in good yield as the bis-phenylthiourea derivative VII; it was also characterized by condensation with *p*-nitrobenzaldehyde, the product of which was shown by its percentage composition to be the oxazolidine XV. The structure of III was proved by synthesis from 1-amino-2-methyl-2-propanol and acrylo-



nitrile, followed by reduction of the nitrile group. The derivatives VII and XV obtained from the synthetic sample were identical with those prepared from the hydrolysis product of I.

It is therefore clear that the imine ring in I undergoes both hydrolysis and methanolysis by cleavage of the tertiary carbon–nitrogen bond.



The reactions thus follow the same course as the acid hydrolysis of dimethylethyleneimine,[5] of diphenylmethylethyleneimine[6] and of substituted ethylene oxides.[7] Several examples have been

(2) Weizmann, Sulzbacher and Bergmann, THIS JOURNAL, **70**, 1153 (1948); *cf.* McElvain and Stevens, *ibid.*, **69**, 2667 (1947).

(3) *Cf.* Uffer and Schlittler, *Helv. Chim. Acta*, **31**, 1397 (1948).

(4) Kohlrausch and Kaharec, *Monatsh.*, **74**, 114 (1942), treated ethyl α-bromoisobutyrate with sodium methoxide in methanol and assumed, without comment, that the product was ethyl α-methoxyisobutyrate. Our results indicate that they probably obtained the β-methoxyisobutyrate instead; *cf.* Bischoff, *Ber.*, **32**, 1755 (1899).

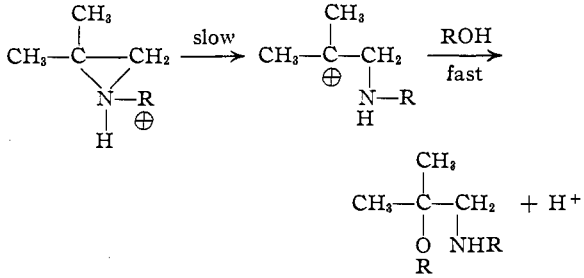
(5) Cairns, THIS JOURNAL, **63**, 871 (1941).

(6) Campbell, Campbell, McKenna and Chaput, *J. Org. Chem.*, **8**, 103 (1943).

(7) Kadesch, THIS JOURNAL, **68**, 41 (1946); Bartlett and Ross, *ibid.*, **70**, 926 (1948).

reported, however, in which the cleavage of an unsymmetrically substituted imine ring under acid conditions breaks the bond between the primary carbon and the nitrogen. The best described case of this is the action of amines in liquid ammonia plus ammonium chloride on substituted ethyleneimines.[8]

The reactions observed by us can best be explained on the basis of a S_N1 mechanism in which the tertiary carbonium ion is formed, and reacts with the solvent to form the observed products; the carbonium ion can be stabilized by solvation and hyperconjugative resonance, and its formation is favored by the positive charge on the nitrogen due to the acid catalyst.



The action of amines in liquid ammonia[8] may not lead to an S_N1 reaction, because the solvent is not as effective as alcohol or water at stabilizing the carbonium ion by solvation, and the acid catalyst is probably not as effective in liquid ammonia solution as in alcohol or water.

Experimental[9]

Methanolysis of 2,2-Dimethyl-1-(γ-aminopropyl)-ethyleneimine (I) to γ-(2-Methoxyisobutylamino)-propylamine (II).—Recrystallization of the dipicrate of I[1] from methanol yielded the dipicrate of II, m. p. 197–198° with decomposition (placed in bath at 195°). The reported m. p.[1] is 201–202° with decomposition, and it varies with rate of heating.

Treatment of the free imine I with picric acid in methanol led to the isolation of the dipicrate of the *hydrolysis* product III, m. p. 184–187°, in addition to the desired dipicrate of the *methanolysis* product II, m. p. 199–200°, which was the main product.

Bis-phenylthiourea Derivative of II (VI).—To 10 g. of the dipicrate of II was added 300 cc. of 2% sodium hydroxide and the resulting solution allowed to stand several days with 2 cc. of phenyl isothiocyanate. The solution was extracted with chloroform, the chloroform evaporated *in vacuo*, and the residue allowed to stand. After several days, about 1.5 g. of yellow crystalline solid was obtained, which, after decolorizing with charcoal and several recrystallizations from methanol, melted at 159–160°.

Anal. Calcd. for $C_{22}H_{30}N_4OS_2$ (VI): C, 61.36; H, 7.02; OCH_3, 7.21. Found: C, 61.15; H, 6.70; OCH_3, 7.04.

α-Methoxyisobutyramide (VIII).—To 150 cc. of concentrated ammonia (sp. gr. 0.9) was added 27 g. of methyl α-methoxyisobutyrate[2] and the minimum amount of methanol to make a homogeneous solution. After standing two days at room temperature, the mixture was evaporated *in vacuo*, and 20.5 g. (86%) of white crystalline solid, m. p. 116–117°, was obtained. Recrystallization from hexane gave long white needles, m. p. 117.5–118.5°.

Anal. Calcd. for $C_5H_{11}NO_2$: C, 51.26; H, 9.47. Found: C, 51.50; H, 9.41.

β-Methoxyisobutylamine (IX).[3]—Ten grams (0.085 mole) of the above amide VIII was placed in a Soxhlet extractor and extracted for twelve hours with 250 cc. of dry ether, which contained 0.17 mole of lithium aluminum hydride. The excess lithium aluminum hydride was destroyed with water, the mixture acidified with dilute sulfuric acid, extracted with ether, and made strongly basic with sodium hydroxide solution. Sodium potassium tartrate (about 250 g. in 400 cc. of water) was added; when almost all of the alumina had dissolved, the solution was extracted thoroughly with ether, the extracts dried over potassium carbonate and the ether evaporated. Distillation of the residue at atmospheric pressure yielded 3.7 g. (42%), b. p. 115–125°. The analytical sample had the following properties: b. p. 121°; $n^{20}D$ 1.4204.

Anal. Calcd. for $C_5H_{13}NO$: C, 58.21; H, 12.70. Found: C, 57.83; H, 12.72.

The phenylthiourea derivative, $(CH_3)_2C(OCH_3)CH_2NHCSNHC_6H_5$, was prepared by heating equal portions of the amine and phenyl isothiocyanate in hexane; the solid which separated on cooling was recrystallized from dilute ethanol and melted at 115–116°.

Anal. Calcd. for $C_{12}H_{18}N_2OS$: C, 60.47; H, 7.61. Found: C, 60.60; H, 7.51.

β-(2-Methoxyisobutylamino)-propionitrile (X).—A mixture of 7 g. of β-methoxyisobutylamine IX and 7 g. of acrylonitrile was stirred at 50° for several hours, and allowed to stand overnight. Fractionation yielded 7.5 g. (71%), b. p. 85° (1 mm.), $n^{20}D$ 1.4438.

Anal. Calcd. for $C_8H_{16}N_2O$: C, 61.50; H, 10.33. Found: C, 61.55; H, 10.06.

The phenylurea derivative, $(CH_3)_2C(OCH_3)CH_2N(CONHC_6H_5)CH_2CH_2CN$, was prepared by heating equal amounts of IX and phenyl isocyanate in hexane. The product was recrystallized from hexane–benzene, and was obtained as white needles, m. p. 116.5–117.5°.

Anal. Calcd. for $C_{15}H_{21}N_3O_2$: C, 65.43; H, 7.69. Found: C, 65.46; H, 7.41.

γ-(2-Methoxyisobutylamino)-propylamine (II).—The nitrile X (6.5 g.) was reduced, in 30 cc. of alcohol saturated with ammonia, with hydrogen and Raney nickel at 90° and 1600 lb.; the theoretical amount of hydrogen was absorbed in thirty minutes. The catalyst was removed by filtration, and the reaction yielded 3.3 g. (50%) of product, b. p. 70° (1 mm.); $n^{20}D$ 1.4512.

Anal. Calcd. for $C_8H_{20}N_2O$: C, 59.95; H, 12.58. Found: C, 60.10; H, 12.36.

The bis-phenylthiourea derivative VI was identical, as shown by mixed m. p., with that obtained from the methanolysis of I, and the dipicrates also were apparently identical.

α-Bromoisobutyryl Chloride.—To 70 g. of phosphorus pentachloride was added portionwise 50 g. of dry α-bromoisobutyric acid. When the reaction had subsided, the solution was filtered through glass wool and fractionated; after a forerun of phosphorus oxychloride, the main fraction (50 g., 90%), b. p. 45–53° (30 mm.) was collected. A pure sample had these properties: b. p. 52° (30 mm.), $n^{23}D$ 1.4750.

β-Methoxyisobutyronitrile (XI). A. From α-Bromoisobutyronitrile.—To a solution of 1.6 g. (0.07 mole) of sodium in 50 g. of absolute methanol was added in one portion 10 g. (0.07 mole) of α-bromoisobutyronitrile.[10] The solution was refluxed for four to five hours, about one-fourth of the solvent was evaporated, the remainder was poured into 700 cc. of water and was extracted four times with 200-cc. portions of ether. The combined ether extracts were dried, the solvent removed and the residue fractionated at atmospheric pressure; the product (3.8 g.,

(8) Clapp, THIS JOURNAL, **70,** 184 (1948).

(9) Melting points corrected; analyses by Micro-Tech laboratories and Mrs. G. Sauvage.

(10) Prepared from both α-bromoisobutyryl chloride and isobutyronitrile according to the procedures of Stevens (THIS JOURNAL, **70,** 165 (1948)).

57%) was obtained with b. p. 157–163°. The analytical sample had b. p. 160.5°, $n^{20}D$ 1.4038.

Anal. Calcd. for C_6H_9NO: C, 60.58; H, 9.15. Found: C, 60.36; H, 8.97.

B. From Methacrylonitrile.[11]—Methacrylonitrile[12] (67 g.) was added slowly with stirring at room temperature to a solution of 0.4 g. of sodium in 50 g. of methanol. The solution, after stirring an additional three hours and standing overnight, was poured into 600 cc. of water, extracted with ether, the extracts dried and distilled. The main portion, 27.2 g. (28%), had the following properties: b. p. 159–162°, $n^{23}D$ 1.4028.

γ-Methoxyisobutylamine (XII).—The above nitrile (XI) was reduced with hydrogen and nickel in ammoniacal ethanol, as described above; the product was obtained in 59% yield, and the analytical sample had the following properties: b. p. 128°, $n^{23}D$ 1.4192.

Anal. Calcd. for $C_6H_{13}NO$: C, 58.21; H, 12.70. Found: C, 57.93; H, 13.10.

The phenylthiourea derivative, $CH_3OCH_2CH(CH_3)CH_2NHCSNHC_6H_5$, was prepared in dry ether, and recrystallized from dilute ethanol, m. p. 74.5–75.5°.

Anal. Calcd. for $C_{12}H_{18}N_2OS$: C, 60.47; H, 7.61. Found: C, 60.22; H, 7.35.

Samples of this derivative, prepared from the amine obtained from the nitrile prepared by methods A or B above, were found to be identical.

β-(3-Methoxy-2-methylpropylamino)-propionitrile (XIII).—A mixture of 13.7 g. of γ-methoxyisobutylamine (XII) and 13.7 g. of acrylonitrile was heated at 50° with stirring; there was a slight rise in temperature, and the solution was allowed to cool to room temperature. After standing overnight, the mixture was fractionally distilled, yielding 18.9 g. (91%) of product, b. p. 90–91° (2 mm.). The analytical sample had b. p. 91° (2 mm.), $n^{23}D$ 1.4421.

Anal. Calcd. for $C_8H_{16}N_2O$: C, 61.50; H, 10.33. Found: C, 61.70; H, 10.35.

The phenylurea derivative, $CH_3OCH_2CH(CH_3)CH_2N(CONHC_6H_5)CH_2CH_2CN$, was prepared in dry ether, and recrystallized from hexane as white needles, m. p. 101–101.5°.

Anal. Calcd. for $C_{16}H_{21}N_3O_2$: C, 65.43; H, 7.69. Found: C, 65.66; H, 7.75.

γ-(3-Methoxy-2-methylpropylamino)-propylamine (XIV).—The nitrile XIII (17 g.) was reduced as above with hydrogen and nickel in ammoniacal ethanol; the yield of material of b. p. 70–71° (2 mm.) was 40%. The product was very hygroscopic, and to obtain a good analysis it was necessary to distil the sample from solid potassium hydroxide. The analytical sample had the following properties: b. p. 70° (2 mm.); $n^{20}D$ 1.4513.

Anal. Calcd. for $C_8H_{20}N_2O$: C, 59.95; H, 12.58. Found: C, 60.32; H, 12.60.

The bis-phenylthiourea derivative, $CH_3OCH_2CH(CH_3)CH_2N(CSNHC_6H_5)CH_2CH_2CH_2NHCS\text{-}NHC_6H_5$, was prepared in ether and recrystallized from ethanol, m. p. 114–115°.

Anal. Calcd. for $C_{22}H_{30}N_4OS_2$: C, 61.36; H, 7.02. Found: C, 61.51; H, 7.00.

The dipicrate was prepared in methanol, and was obtained after several crystallizations from methanol as orange needles, m. p. 152–154°.

Anal. Calcd. for $C_{20}H_{26}N_8O_{15}$: C, 38.84; H, 4.24. Found: C, 38.50; H, 4.11.

γ-(2-Hydroxyisobutylamino)-propylamine (III) by Hydrolysis of I. A. Isolation as the Bis-phenylthiourea Derivative.—The imine I (3 g.) was refluxed for fifteen minutes with 20 cc. of 2 *M* sulfuric acid. The solution was made weakly alkaline, 3 cc. of phenyl isothiocyanate was added, the mixture was shaken without heating for a few minutes, and was extracted with chloroform. The chloroform was evaporated *in vacuo*, and the residue, after crystallization from benzene, yielded 7.0 g. (72%) of the **bis-phenylthiourea derivative VII,** m. p. 143–144°.

Anal. Calcd. for $C_{21}H_{28}N_4OS_2$: C, 60.54; H, 6.77; N, 13.45. Found: C, 60.71; H, 6.59; N, 13.11.

The dipicrate was prepared in the usual manner and recrystallized from methanol as yellow needles melting with decomposition at 184–187°, depending upon the rate of heating.

Anal. Calcd. for $C_{19}H_{24}N_8O_{15}$: C, 37.75; H, 4.00. Found: C, 38.03; H, 4.00.

B. Isolation as the *p*-Nitrobenzaldehyde Derivative (XV).—The hydrolysis was carried out as above, and after addition of the sodium hydroxide, 1 g. of *p*-nitrobenzaldehyde was added. After refluxing for one hour, the solid material was collected and recrystallized from ethanol; the product was a yellow solid, melting at 124–125°.

Anal. Calcd. for $C_{21}H_{24}N_4O_5$ (XV): C, 61.15; H, 5.86. Found: C, 61.08; H, 5.76.

β-(2-Hydroxyisobutylamino)-propionitrile.[13]—This compound was prepared by addition of 1-amino-2-methylpropanol-2[12] to acrylonitrile in 87% yield; the properties agree with the reported ones. **The picrate** (not previously reported) was prepared and recrystallized from ethanol, m. p. 135–135.5°.

Anal. Calcd. for $C_{13}H_{17}N_5O_8$: C, 42.05; H, 4.62. Found: C, 42.14; H, 4.52.

The nitrile yielded a crystalline **oxazolidine** when refluxed with *p*-nitrobenzaldehyde in ethanol for thirty minutes. The product melted at 67.5–68° after recrystallization from ethanol.

Anal. Calcd. for $C_{14}H_{17}N_3O_3$: C, 61.07; H, 6.23. Found: C, 60.95; H, 6.24.

γ-(2-Hydroxyisobutylamino)-propylamine (III).—Reduction of the above nitrile in the usual way[13] yielded the amine in 56% yield, b. p. 72° (1 mm.), $n^{20}D$ 1.4698. The properties agree with those reported.[13] The bis-phenylthiourea derivative VII and the *p*-nitrobenzaldehyde derivative XV prepared from this material were identical with those from the hydrolysis product, as shown by mixed melting points.

β-Methoxyisovaleric Acid.[14]—To a cold solution of sodium hypobromite, prepared from 160 g. of sodium hydroxide, 320 g. of bromine and 600 g. of ice and water, was added with stirring 65 g. of 4-methoxy-4-methyl-2-pentanone[12] keeping the temperature below 20°. After addition of the ketone was completed, the reaction mixture was stirred an additional three hours, the bromoform layer was removed, and the aqueous layer washed repeatedly with ether to remove bromoform. The aqueous layer was acidified with dilute sulfuric acid, and a little sodium bisulfite added to destroy excess bromine. The acid was isolated by ether extraction, and purified by vacuum distillation; the yield of material of b. p. 93–110° (3 mm.) was 25 g. (38%). The analytical sample had b. p. 88° (2 mm.), $n^{22}D$ 1.4348; these agree with those reported.[14]

The *p*-phenylphenacyl ester was prepared in the usual manner and melted, after recrystallization from dilute ethanol, at 54–55°.

Anal. Calcd. for $C_{20}H_{22}O_4$: C, 73.60; H, 6.80. Found: C, 73.60; H, 6.49.

A second fraction in the distillation (28 g., b. p. 110–130° (3 mm.)) solidified, and, after two crystallizations from petroleum ether, melted at 70–74°. It was probably

(11) *Cf.* Carpenter, U. S. Patent 2,372,624; *C. A.*, **39**, 3541 (1945).

(12) We are indebted to the Shell Development Co., Emeryville, Calif., for this material.

(13) Reported after our work was completed by Steck, Hallock and Suter, THIS JOURNAL, **70**, 4063 (1948), who used procedures similar to ours.

(14) This preparation is described briefly, without characterization of the product, by Hoffman, THIS JOURNAL, **49**, 530 (1927). Preparation of the acid by other methods is reported by (a) Wagner, *ibid.*, **71**, 3214 (1949), and (b) Farmer and Kracovski, *J. Chem. Soc.*, 2321 (1926).

α-bromo-β-methoxyisovaleric acid, which is reported to melt at 77°.[15]

Methyl β-Methoxyisovalerate.—This ester was prepared in 45% yield by esterification of the acid with methanolic hydrogen chloride, but it was found advantageous to esterify the mixture from the haloform reaction directly without isolation of the acid.

The ether residue, obtained from the haloform reaction as described above, was refluxed for eight hours with 100 g. of dry methanol containing 10% of dry hydrogen chloride; about two-thirds of the methanol was removed under reduced pressure, the residue poured into water and the solution neutralized with solid sodium carbonate. The ester layer was separated, the water layer washed with three portions of ether, and the combined ester-ether solutions dried and distilled. The ester was obtained in 29% yield (based on the methyl ketone); b. p. 57–64° (15 mm.), $n^{22}D$ 1.4158; the values agree with those of Wagner.[14]

(15) Schrauth and Geller, *Ber.*, **55**, 2788 (1922).

The second fraction, b. p. 70–85 (15 mm.), when redistilled, yielded 17% of what appeared from the analysis to be methyl α-bromo-β-methoxyisovalerate. The analytical sample boiled at 86° (15 mm.), $n^{23}D$ 1.4618.

Anal. Calcd. for $C_7H_{13}BrO_3$: C, 37.35; H, 5.82. Found: C, 37.62; H, 6.01.

Summary

The acid-catalyzed methanolysis and hydrolysis of 2,2-dimethyl-1-(3-aminopropyl)-ethyleneimine led in each case to cleavage of the bond between the tertiary carbon and the nitrogen of the imine ring. The structure of the products has been proved by synthesis, and the possible causes for the course of the cleavage reaction have been discussed.

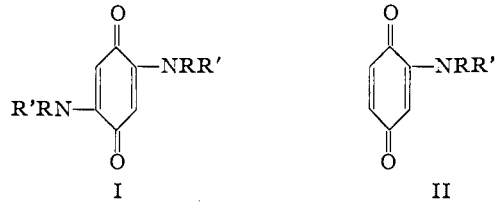
ROCHESTER, N. Y. RECEIVED DECEMBER 5, 1949

[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

Amino- and Ammonium-alkylaminobenzoquinones as Curarimimetic Agents

BY CHESTER J. CAVALLITO, ALBERT E. SORIA AND JAMES O. HOPPE

Recent investigations have led to the view that quaternary salts of known structure with a high curare-like physiological activity require the presence of at least two quaternary groups situated approximately 12 to 14 Å. apart in the molecule.[1,2,3,4] This communication describes a group of mono and bis quaternary derivatives of intense activity as well as the corresponding amines, some of which show unusually high curare-like activity. The active compounds described belong to class I or II in which R is H



and R′ is an alkyl chain containing a tertiary amine or quaternary group.

Quinones (or hydroquinones and oxygen) are known to react with primary or secondary amines to yield mono- and 2,5-bis-substituted quinones, I.[5,6,7,8] These compounds also may be prepared by substitution of halogen or alkoxy groups in quinones by amines.[9,10] In such compounds the nitrogen is amide-like in character. By using amino-substituted acids there have been described the preparations of acidic amino-substituted quinones by these methods.[8,11] No published information was found describing quinone bases such as might be formed from dialkylaminoalkylamines. A few such bases appear to have been prepared in Germany during the last war for study as antibiotic types.[12]

It was found that the reaction of dialkylaminoalkylamines with hydroquinone and oxygen in aqueous or ethanol solutions was not as satisfactory as the reaction of simple amines[7] under these conditions. Yields of 2,5-bis-(dialkylaminoalkylamino)-benzoquinone could be markedly improved by conducting the reaction with amine, quinone and oxygen in dioxane, acetonitrile, benzene or similar solvents. With hydroquinone, the reaction was slower and depended upon prior oxidation to quinone. With a number of amines, the monosubstituted dialkylaminoalkylaminoquinone could be isolated by carrying out the reaction in a concentrated solution from which the product crystallized. The mono- and bis-substituted aminoalkylaminoquinones described were orange or red crystalline substances which formed orange or red quaternary salts that usually crystallized.

An interesting property of the 2-alkylaminoalkylaminoquinones is the ability to undergo disproportionation to the 2,5-bis derivative. In an inert solvent or neutral aqueous solutions, 2-piperidylpropylaminobenzoquinone gave a 90% yield of the 2,5-bis derivative after four days at 25°.

(1) Bovet and Bovet-Nitti, *Experientia*, **4**, 325 (1948).
(2) Barlow and Ing, *Brit. J. Pharmacol.*, **3**, 298 (1948).
(3) Kimura, Unna and Pfeiffer, *J. Pharmacol.*, **95**, 149 (1949).
(4) Paton, *J. Pharmacy and Pharmacol.*, **1**, 273 (1949).
(5) Hofmann, *Proc. Roy. Soc., London*, **13**, 4 (1863).
(6) Suida and Suida, *Ann.*, **416**, 113 (1918).
(7) Harger, THIS JOURNAL, **46**, 2540 (1924).
(8) Martynoff and Tsatsas, *Bull. soc. chim.*, **29**, 52 (1947).
(9) Kehrmann, *J. prakt. Chem.*, [2] **43**, 260 (1891).
(10) Jackson and Torrey, *Am. Chem. J.*, **20**, 395 (1898).
(11) Suchanek, *J. prakt. Chem.*, [2] **90**, 467 (1914).
(12) P. B. Report 981, 33–35 (1945), mentions that the following were prepared for study as antibiotic types: 2,5-bis-(piperidylethylamino)-benzoquinone, 2-hydroxy-5-piperidylethylaminobenzoquinone, 2,5-dichloro-3,6-bis-(diethylaminoethylamino)-benzoquinone and 2,5-bis-[*p*-(diethylaminoethoxy)-phenylamino]-benzoquinone.