upon the C=C of an olefin is the rupture of one bond giving rise to a divalent radical Ċ—Ċ. In the examples given above this process is represented by step 1. The splitting of one electron pair of the double bond is doubtless facilitated in the compounds illustrated by resonance involving one of the unpaired electrons (process 2).

The establishment of a covalent bond between β-carbon atoms, as represented in step 3, is to be expected for two reasons. First, the most reactive center in the activated molecule (the di-radical) is the β-carbon atom, since the resonance involving the odd electron associated with the α-carbon atom and the oxygen atom in acrolein or the nitrogen atom in acrylonitrile (process 2) should make any reaction involving that electron less likely. Second, the new di-radicals thus formed can exist in four resonating forms, as partially illustrated by process 4, and hence are stabilized to some extent, whereas, if the initial union were between α-carbon atoms, no such resonance could occur. Similar considerations have been advanced by Koelsch and Boekelheide[8]

(8) Koelsch and Boekelheide, This Journal, **66**, 413 (1944).

to account for the orientations observed in the coupling of aryl radicals with α,β-unsaturated compounds.

The final phase of the reaction (step 5) is a cyclization process. In the case of acrolein a relatively stable six-membered heterocyclic ring is formed. With acrylonitrile, however, the distribution of the odd electrons which would be required for the formation of a six-membered ring produces the linear configuration C=C=N, and the resulting distance between the atoms bearing the odd electrons is too great for electron pairing bond formation. The final electron pairing reaction therefore takes place between the two α-carbon atoms.

## Summary

1. Acrylonitrile has been thermally dimerized to give low yields of 1,2-dicyanocyclobutane.

2. It is proposed that this reaction occurs by an electron pairing mechanism.

3. A similar mechanism is advanced for the thermal dimerization of acrolein and related carbonylenic compounds.

Knoxville, Tennessee Received June 25, 1948

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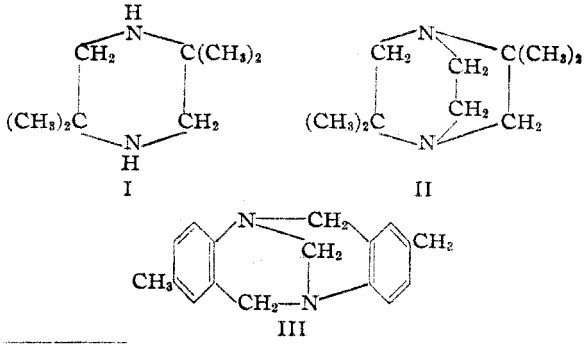
[Contribution from the Laboratory of Organic Chemistry of the University of Wisconsin]

# 2,2,5,5-Tetramethylpiperazine and Derivatives

By S. M. McElvain and Everett H. Pryde[1]

The preparation of 2,2,5,5-tetramethylpiperazine (I) was undertaken in the hope that by bridging its nitrogens with an ethylene radical the bicyclic structure (II), which contains asymmetric nitrogen atoms comparable in structure to those of Troeger's base (III), might be obtained and resolved into its optical antipodes. The resolution of III[2] is the only recorded successful separation of a *dl*-mixture into its component optical isomers, the asymmetry of which is due to trivalent nitrogen atoms. Although the synthesis of II has not been achieved and further work in this direction is in progress in this Laboratory, the preparation of I and the properties of certain of its derivatives seem of sufficient interest to report at this time.



I II

III

The preparation of the dihydrochloride[3] and the N,N′-dinitroso derivative[4] of I in low yields have been reported, but none of these procedures appeared adaptable to the production of substantial quantities of I. For this reason it seemed that 2,2,5,5 - tetramethyl - 3,6 - diketopiperazine (IV), if it could be obtained readily, offered a better approach to I.

The preparation of the diketopiperazine (IV) in 34% yield by heating methyl α-aminoisobutyrate[5] and in 23% yield from the ethyl ester[6] have been reported; however the requisite methyl ester was obtained in yields that left much to be desired.[5] The preparation of IV from N-(α-aminoisobutyryl)-α-aminoisobutyric acid also has been reported.[7] The ester approach[5] to IV was investigated in the present work and, although a method of preparation of methyl α-aminoisobutyrate in good yield was developed, the product resulting from heating this ester contained only about 3% of

(1) S. B. Penick and Company Fellow, 1947-1948.

(2) Prelog and Wieland, *Helv. Chim. Acta*, **27**, 1127 (1944).

(3) (a) Reihlen, *et al.*, *Ann.*, **493**, 20 (1932); (b) Drew and Head, *J. Chem. Soc.*, 49 (1934).

(4) Conant and Aston, This Journal, **50**, 2783 (1928).

(5) Franchimont and Friedman, *Rec. trav. chim.*, **27**, 197 (1908).

(6) Jacobson, This Journal, **68**, 2628 (1946).

(7) Abderhalden and Gebelein, *Z. physiol. Chem.*, **152**, 125 (1926); Levene and Steiger, *J. Biol. Chem.*, **93**, 595 (1931).

IV; the major reaction product was α-aminoisobutyric acid.

Recently Sannié[8] reported the preparation of certain diketopiperazines in 60–70% yields by heating α-amino acids in ethylene glycol; however, he found that such amino acids as α-aminoisobutyric acid, in which the amino group is on a tertiary carbon, gave negative results. In the present work it was found that the latter amino acid could be made to undergo this cyclization in the higher boiling diethylene glycol, and a procedure has been developed for the preparation of IV in 40% yield.

The reduction of certain diketopiperazines to the corresponding piperazines in low yields (15–17%) by sodium in amyl alcohol has been effected[9]; however, much higher yields (57–86%) of pyridines and pyrrolidines have been obtained from the reduction of 2-piperidones and 2-pyrrolidones with sodium in butyl alcohol, using a 10:1 ratio of sodium to reductant.[10] Following the latter procedure yields of 24% of I and 40% of half reduced product V were obtained from IV in the present work. The yield of I was improved somewhat by the use of higher ratios of sodium to IV, but with such ratios the manipulation of the reaction mixtures became more difficult. The hydrogenation of IV to I over a copper–chromium oxide catalyst was much more successful. In spite of the insolubility of IV in all of the ordinary solvents, it could be hydrogenated in a dioxane suspension to I in 87% yield.

Attempts to prepare the bicyclic structure II by the catalytic intramolecular alkylation[11] of the 4-nitrogen of VI—obtained together with some of the 1,4-di-(β-hydroxylethyl) derivative, VIa, from the reaction of I with ethylene oxide—with the 1-hydroxyethyl substituent were unsuccessful. At temperatures up to 200°, VI was recovered unchanged; at 250° some of VI was recovered, but the major portion of it lost the 1-substituent and reverted to the original piperazine I.

The bicyclic compound, 1,4-diazobicyclo-(2,2,-2)-octane, the unmethylated homolog of II, has been prepared in low yields by heating (a) diethanolamine hydrochloride (2%)[12] and (b) 1-(β-chloro- (or-bromo)-ethyl)-piperazine dihydrohalides (20–25%)[13]; and by treatment of 1-(β-chloroethyl)-piperazine with aqueous alkali.[13] However, an attempt to effect a similar cyclization of 1-(β-bromoethyl)-piperazine by the latter procedure was unsuccessful.[14]

When the corresponding 1-(β-bromoethyl) derivative of I (VIIa) was added to an aqueous sodium hydroxide solution, it dissolved immediately, but within a few seconds a precipitate began to separate. The amount of this precipitate was dependent upon the dilution of the solution with respect to VIIa, *i. e.*, the more dilute the solution the less the amount of precipitate. This insoluble material was separated into the dimer (IX, $n$ is 1), m. p. 123–125, the trimer (IX, $n$ is 2), m. p. 160–167°, and a higher melting (above 260°), insoluble material, which is, presumably, a more complex polymer (IX, $n > 2$). From the aqueous alkaline solution only VI was isolated; the yields of this compound increased, as those of the insoluble products (IX) decreased, with the dilution of the solutions of VIIa.

The chloro derivative (VII) showed an interesting and significant variation in behavior. When an aqueous alkali solution was added to an aqueous solution of VII, there was an immediate precipitation of the free base, due to the neutralization of the hydrochloride functions. This precipitate, however, rapidly returned to solution and from the resulting clear solution the polymers IX began to separate. All of these changes occurred within approximately one minute after the salt VII was added to the alkaline solution.

This behavior indicates that the free bases of VII and VIIa are preferentially converted into the ethyleneimmonium ion[15] (VIII) rather than the bicyclic structure II; VIII then reacts with water to produce VI (if the solution is sufficiently dilute) or intermolecularly to produce the polymer IX. In the case of the bromo derivative (VIIa), the formation of VIII is so rapid that there is no evidence of the intermediate free base; but with the less reactive chloro compound, the free base of VII is momentarily precipitated before it cyclizes to the soluble ion (VIII) that undergoes the subsequent reactions.

When the salts VII and VIIa were heated alone or in suspension in Stanolind oil, 77–88% of one equivalent of hydrogen halide was evolved at 220–240°. However, investigation of the remaining salt in a search for the bicyclic compound II yielded only the piperazine I. Whether or not the formation of this product involved the quaternary ion VIII could not be determined; it is possible that a salt of I could form from VII by dehydrohalogenation followed by the loss of acetylene.

## Experimental

**Methyl α-Aminoisobutyrate.**—A mixture of 51.5 g. (0.5 mole) of α-aminoisobutyric acid, prepared by the hydrolysis of 5,5-dimethylhydantoin,[16] and 600 ml. (15.3 mole) of methanol was treated with hydrogen chloride until 30 g. (0.82 mole) had been absorbed. The resulting solution was refluxed on a steam-bath for sixteen hours, after which time 150 g. of Drierite was added. Throughout this experiment, the solutions were protected from atmospheric moisture with calcium chloride drying tubes.

(8) Sannié, *Bull. soc. chim.*, [5] **9**, 487 (1942).

(9) Gavrilov, *ibid.*, [4] **37**, 1651 (1925); Abderhalden, *et al.*, *Z. physiol. Chem.*, **135**, 180 (1924).

(10) Koelsch, THIS JOURNAL, **65**, 2093 (1943).

(11) *Cf.* Adkins, *et al.*, *ibid.*, **60**, 1033 (1938); *ibid.*, **61**, 3499 (1939).

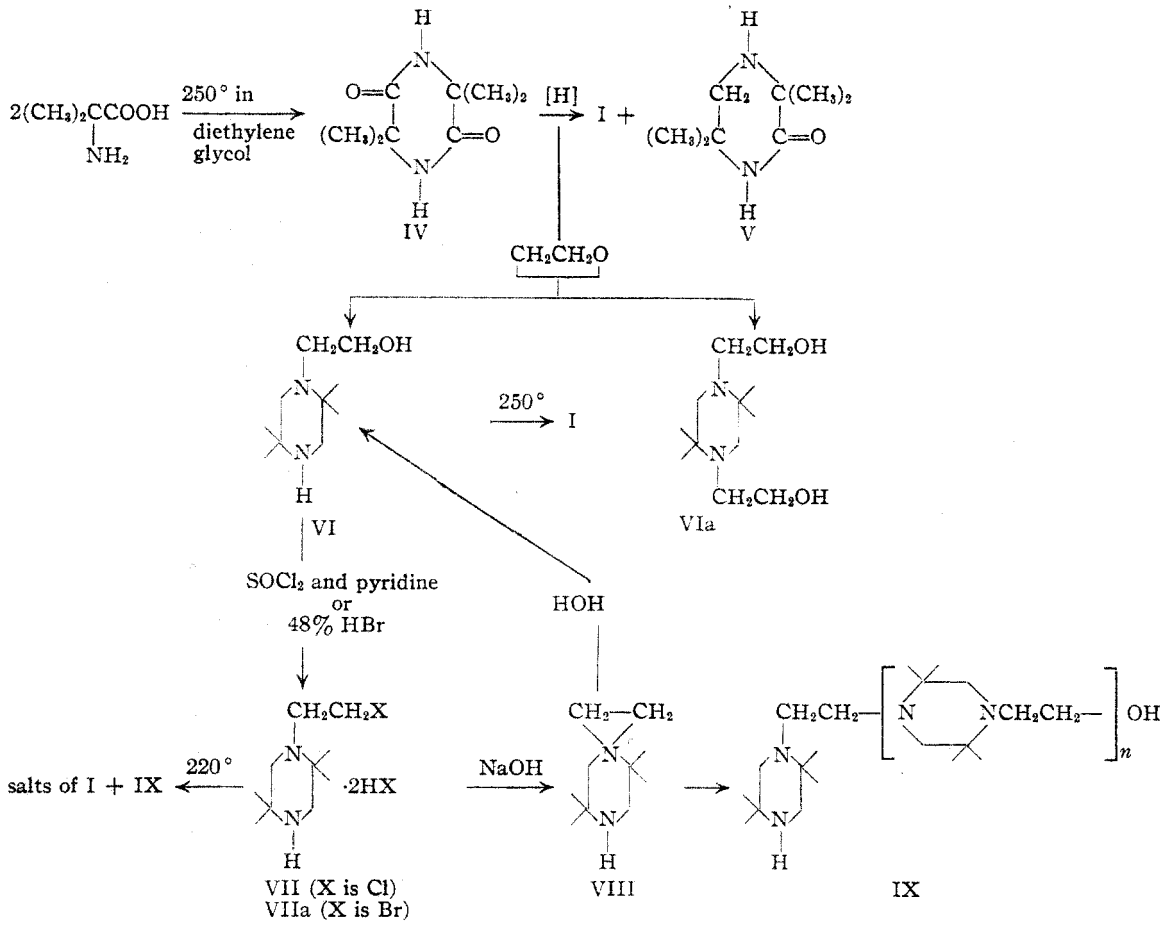
(12) Hromatka, *Ber.*, **75**, 1302 (1942).

(13) Hromatka and Engel, *ibid.*, **76**, 712 (1943); in procedure (b) a loss of the 1-substituent occurred and piperazine formed to the extent of 12–60%.

(14) Prelog, *et al.*, *Ann.*, **535**, 37 (1938).

(15) *Cf.* Bartlett, Ross and Swain, THIS JOURNAL, **69**, 2971 (1947); Cohen, Artsdalen and Harris, *ibid.*, **70**, 281 (1948).

(16) Bucherer and Steiner, *J. prakt. Chem.*, **140**, 305 (1934).



After filtering off the Drierite, the methanol and excess hydrogen chloride were removed under vacuum until the residue was solid; it then was placed in a vacuum desiccator over potassium hydroxide until completely dry. A quantitative yield of methyl α-aminoisobutyrate hydrochloride, m. p. 179–182° dec., and which contained 23.2% chlorine (calcd. 23.1%), was obtained. The ester hydrochloride after recrystallization from absolute alcohol and ether melts at 182–183° dec.[5]

The free ester was liberated from its salt by adding a solution of sodium methoxide in dry methanol (from 14 g. of sodium and 200 ml. methanol) to a sirup of the ester hydrochloride in methanol until the solution was alkaline to phenolphthalein. After filtering off the sodium chloride, the methanol solution was distilled in a modified Claisen flask at atmospheric pressure. A 64% yield of methyl α-aminoisobutyrate, b. p. 133–134°, was obtained.

**2,2,5,5-Tetramethyl-3,6-diketopiperazine (IV).**—To 200 ml. of diethylene glycol contained in an open 500-ml. long-neck, round-bottom flask was added 100 g. of crystalline α-aminoisobutyric acid, which had been ground and passed through a 20-mesh screen (a larger crystal size caused prolongation of the heating time). The glycol was refluxed at such a rate that the water formed in the reaction was driven out as steam. During four hours of heating, the temperature at reflux gradually increased from 210 to 234°, and all the acid had gone into solution. The diketopiperazine crystals which formed when the solution was allowed to cool to room temperature were collected on a filter and washed with methanol until free from glycol; the yield was 16 g.

To the filtrate was added another 100 g. of α-aminoisobutyric acid and the mixture heated as above. After five hours, the temperature of the vapors above the refluxing glycol had increased to 249°, and only a small amount of insoluble material remained. After the solution had cooled, 47.5 g. of IV was collected. Two repetitions of this procedure, using 75 g. and 50 g. of acid in the same glycol filtrate, yielded 31.5 g. and 16.5 g. of diketopiperazine, respectively. Smaller quantities of acid were employed in these latter runs to insure complete solution of the acid in the glycol. After these four runs, the diethylene glycol solution was dark brown and viscous, and not suitable for further use. The total yield of the diketopiperazine (IV) from 325 g. of α-aminoisobutyric acid was 111.5 g. (41.6%).

Undoubtedly, some acid and diketopiperazine are lost through sublimation from the diethylene glycol. In an effort to determine the fate of the remainder of the acid not recovered as IV, the diethylene glycol solution from the above runs was diluted with methanol and benzene. No precipitate separated; any acid or diketopiperazine that was in solution would have been precipitated by this change in solvent. When the diethylene glycol solution was distilled, 7% of its weight was recovered as methyl α-aminoisobutyrate; 42% as diethylene glycol, b. p. 75–120° (0.4 mm.), $n^{25}D$ 1.4483; 27% as material, b. p. 160–198° (0.3 mm.), $n^{25}D$ 1.4630–1.4760; and 16% remained as residual tar. The latter two materials were not investigated further. The methyl ester was formed from the methanol used to wash the diketopiperazine crystals and which was added to the diethylene glycol filtrate. That portion of the acid not recovered probably was in the form of glycol esters.

The diketopiperazine (IV) does not melt, even in a sealed capillary tube, below 400°, but sublimes in the temperature range 360–370° (cor.) in an open capillary and at about 390° in a sealed capillary. Many sublimation tem-

peratures have been reported,[6] varying from 210 to 260°, all of which are much lower than those found for IV in the present work. The diketopiperazine is much less volatile than α-aminoisobutyric acid (sublimation temperature 300–320°). The sublimation temperatures now reported for these compounds are those ranges in which the rate of sublimation suddenly increases as the compounds are heated. The diketopiperazine (IV) is insoluble in water, and relatively insoluble in most organic solvents. It dissolves to the extent of about 0.2% in hot 95% ethyl alcohol, 0.4% in hot butanol, 3% in hot glacial acetic acid, 10% in diethylene glycol at 250°, but less than 0.5% at room temperature. Recrystallization from this latter solvent, followed by leaching with hot water, gives a very pure product.

*Anal.* Calcd. for $C_8H_{14}N_2O_2$: C, 56.47; H, 8.23; N, 16.47; mol. wt., 170. Found: C, 56.66; H, 8.33; N, 15.96; mol. wt. (in acetic acid), 170, 177.

When α-aminoisobutyric acid was heated in diphenyl ether or diphenyl amine, the acid sublimed from the liquid and no diketopiperazine was found. Apparently, a polar solvent such as diethylene glycol, is necessary to keep the acid from volatilizing at the temperature required for its condensation to IV.

When methyl α-aminoisobutyrate hydrochloride was heated in a distilling flask, only a small amount of a semi-solid distillate, from which was recovered some of the original acid, was obtained. No trace of diketopiperazine was found. When methyl α-aminoisobutyrate was heated in a glass lined bomb at 200° it was converted to a solid, only 3% of which (IV) was insoluble in water. Evaporation of the aqueous solution yielded only α-aminoisobutyric acid.

**2,2,5,5-Tetramethylpiperazine (I) and 2,2,5,5-Tetramethyl-3-ketopiperazine (V) (a).**—A mixture of 34 g. (0.2 mole) of IV, 15 g. of copper–chromium oxide catalyst[17] and 50 ml. of dioxane were placed in a steel bomb, which then was filled with hydrogen to 3500 p. s. i. The hydrogenation was carried out at 250° for sixteen hours. The dioxane solution, after separation from the catalyst by centrifuging, was distilled and two fractions, b. p. 85–168° (a liquid) and 168–173° (a crystalline solid), collected. Hydrogen chloride was added to the first fraction, and the dioxane evaporated. The free base (I) was liberated from the remaining salt with 50% sodium hydroxide and extracted with benzene; the benzene solution then was distilled and yielded 10.5 g. of crystalline I, which, when combined with the second fraction, gave a total yield of 22 g. (77%) of I.

After recrystallization from absolute ether, **2,2,5,5-tetramethylpiperazine (I)** is obtained as a white, crystalline, fairly volatile solid, m. p. 85–87° with previous softening at 83°. It boils at 168–171° and has a pleasant ammoniacal odor. It is very soluble in water and all organic solvents. In contrast to the unsubstituted piperazine, the tetramethylpiperazine is not hygroscopic and does not react with carbon dioxide of the atmosphere.

*Anal.* Calcd. for $C_8H_{18}N_2$: C, 67.55; H, 12.75; N, 19.70. Found: C, 67.40; H, 13.13; N, 19.71.

**2,2,5,5-Tetramethylpiperazine dihydrochloride** was prepared by passing hydrogen chloride through a solution of I in dioxane and evaporating the dioxane. This dihydrochloride is very soluble in water, but insoluble in all organic solvents, and no means for recrystallization was found. It does not melt below 350°, but begins to darken at 310°.

*Anal.* Calcd. for $C_8H_{20}Cl_2N_2$: Cl, 32.96. Found: Cl, 32.45.

**1,4-Dibenzoyl-2,2,5,5-tetramethylpiperazine** was prepared from I in 92% yield by the usual Schotten–Baumann procedure. When recrystallized from absolute ethanol, it melted 273–276°.

*Anal.* Calcd. for $C_{22}H_{26}N_2O_2$: C, 75.40; H, 7.48. Found: C, 75.26; H, 7.82.

From the residue, remaining after the distillation of I from the hydrogenation products, was obtained 3.1 g. 5% of **2,2,5,5-tetramethyl-3-ketopiperazine** (V), which after recrystallization from toluene melted at 153–156° and boiled at 250–258°. This compound is soluble in water, ether, alcohol and benzene.

*Anal.* Calcd. for $C_8H_{16}N_2O$: C, 61.50; H, 10.33; N, 17.93. Found: C, 61.17; H, 10.17; N, 18.12.

**2,2,5,5-Tetramethyl-3-ketopiperazine hydrochloride** was prepared by passing hydrogen chloride through a solution of 0.5 g. of V in 30 ml. of dioxane and evaporating the dioxane. After recrystallization from alcohol–ether, 0.5 g. (81%) of the hydrochloride, m. p. 305–308° dec., was obtained.

*Anal.* Calcd. for $C_8H_{17}ClN_2O$: Cl, 18.4. Found: Cl, 18.2.

The hydrogenation of V, as described above for IV, gave the piperazine I in 87% yield.

The yields of I and V varied from 87% and 0% to 36% and 42%, depending on the purity of IV. The former high yield of I was obtained with a sample of IV that had been recrystallized from diethylene glycol. With less pure samples of IV, *i. e.*, those obtained by washing the crude product with methanol or water, the yields of V became significant.

(b) **The Reduction of IV with Sodium in Butanol.**—To 400 ml. of hot, absolute butanol and 25 g. (0.147 mole) of IV, contained in a three-neck, three-liter round-bottom flask equipped with a stirrer and a large bore condenser, was added 90 g. (3.48 mole) of sodium over a period of approximately ten minutes. To prevent the formation of solid sodium butoxide, another 600 ml. of butanol was added portionwise during the reduction. The solution was kept at reflux by heating on sand-bath until all the sodium had reacted. About 300 ml. of water was added then, and, after cooling, the water layer separated and 115 ml. of concentrated hydrochloric acid was added to the butanol solution. The aqueous layer was extracted with benzene to determine if any reduced product remained in it, but only a negligible amount was found. The acidified butanol layer was steam distilled to remove the butanol. To the remaining aqueous acid solution of the piperazine salt (about 750 ml.) was added 200 ml. of 50% sodium hydroxide, and the solution was extracted five times with 100 ml. portions of benzene. From the remaining aqueous layer was recovered 3 g. (12%) of the insoluble diketopiperazine (IV). The benzene solution was distilled to yield 5.0 g. (24%) of I in the fraction boiling at 165–210°, and 9.2 g. (40%) of V in the fraction boiling at 210–250°.

**1-(β-Hydroxyethyl)-2,2,5,5-tetramethylpiperazine (VI).**—In a 10-inch length of 15-mm. Pyrex tubing sealed at one end was placed 11.36 g. (0.08 mole) of I. The neck of the tube was drawn out for sealing, and, after chilling the tube in Dry Ice, 2 ml. (1.85 g., 0.042 mole) of ethylene oxide was added, and the tube sealed. The tube then was heated with shaking for two hours at 150°.

The combined contents of three of such tubes was distilled through an eight-inch Vigreux column to yield 18.8 g. of I and 15.5 g. (66% based on the ethylene oxide) of VI, b. p. 240–247°, which after recrystallization from petroleum ether (b. p. 60–68°), melted at 78–83°.

*Anal.* Calcd. for $C_{10}H_{22}N_2O$: C, 64.47; H, 11.90; N, 15.04. Found: C, 64.21; H, 11.91; N, 14.63.

From the residue (4.5 g.) of this distillation, after treatment with Norit and recrystallization from toluene, was isolated 1.83 g. (13% based on the ethylene oxide) of **1,4-di-(β-hydroxyethyl)-2,2,5,5-tetramethylpiperazine** (VIa), m. p. 110–115°. After a second recrystallization from toluene, VIa melted at 113–116°.

*Anal.* Calcd. for $C_{12}H_{26}N_2O_2$: C, 62.56; H, 11.38; N, 12.16. Found: C, 62.21; H, 11.42; N, 12.55.

When a ratio of 1.5 moles of I to one mole of ethylene oxide was used in one experiment, 54% of VI and 41% (based on the ethylene oxide) of VIa were obtained.

**1-(β-Hydroxyethyl)-2,2,5,5-tetramethylpiperazine Dihydrochloride.**—Hydrogen chloride was passed through a

(17) Adkins, "Reactions of Hydrogen," The University of Wisconsin Press, Madison, Wis., 1937, p. 112.

solution of 5 g. of VI in 100 ml. of dioxane until no further precipitate was formed. The dioxane was evaporated in a stream of air, and the residue dried overnight in a vacuum desiccator. This dihydrochloride had no definite melting or decomposition point, but began to darken at about 200°. As it is very soluble in water but insoluble in organic solvents, it was not possible to recrystallize it. However, analysis showed the compound to be quite pure.

*Anal.* Calcd. for $C_{10}H_{23}ClN_2O$: Cl, 27.36. Found: Cl, 27.18.

**1-(β-Chloroethyl)-2,2,5,5-tetramethylpiperazine Dihydrochloride (VII).**—In a 200-ml. round-bottom flask were placed 5.0 g. of the dihydrochloride of VI, 5.8 ml. of freshly distilled thionyl chloride, 2.2 ml. of pyridine, and 50 ml. of benzene. The flask was attached to a condenser fitted with a calcium chloride tube, and the solution heated to gentle reflux. After the first two to three hours of refluxing the flask was removed, and the large lumps which had formed were crushed to a powder. The flask then was replaced, and the refluxing continued for twenty hours. At the end of this time, the solution was filtered while hot. The solid on the filter was washed with benzene and absolute ethanol, after which it was placed in a 200 ml. flask, 25 ml. of absolute ethanol added, and any large lumps were broken into a powder. The alcoholic suspension was refluxed for fifteen minutes and filtered. The solid on the filter was washed with absolute ethanol and then absolute ether. After drying in a vacuum desiccator for several hours, the weight of the white powder was 5.57 g. (74.6%).

*Anal.* Calcd.: ionic Cl, 25.55; total Cl, 38.31. Found: ionic Cl (Volhard), 25.11; total Cl (Stepanow), 37.83.

**1-(β-Bromoethyl)-2,2,5,5-tetramethylpiperazine Dihydrobromide (VIIa).**—To a 50-ml. round-bottom flask were added 5 g. of VI and 25 ml. of 48% hydrobromic acid. An all-glass still head and condenser was attached to the flask, and the solution was distilled slowly for three to four hours, during which time the distilled material was replaced by hydrobromic acid. The solution then was allowed to reflux for sixteen hours, after which it was slowly distilled until the residue was a sludge. Acetone was added, and the insoluble product filtered off. After drying in a vacuum desiccator, the resulting white salt (VIIa) weighed 8.8 g. (80%).

*Anal.* Calcd. for $C_{10}H_{23}Br_3N_2$: Total Br, 58.32. Found: Br, 55.5.

The Volhard procedure gave the same halogen values as those obtained with the Stepanow procedure.

**Attempted Preparation of 2,2,5,5-Tetramethyl-1,4-diazabicyclo-(2,2,2)-octane (II). (a) By Catalytic Intramolecular Alkylation of VI.**—In a 150-ml. glass-lined bomb were placed 5.0 g. of VI, 2.0 g. of copper–chromium oxide catalyst and 20 ml. of dioxane. The bomb was filled with hydrogen and heated in various experiments at temperatures ranging from 200 to 250° for two to four hours. At the end of the heating period, the catalyst was removed from the dioxane solution by centrifuging, and the solution distilled. The recovery of VI varied from 63 to 78%; in the case of the lower recovery of VI (250°), a 13% yield of I was obtained. Repetition of the experiment at 250° using nitrogen instead of hydrogen in the bomb gave 62% of VI and 30% of I. With a nickel catalyst at 150°, 90% of VI was recovered; at 250° a 51% yield of I was obtained. There was no evidence that any di-tertiary amine (II) had formed in any of these experiments.

(b) **From 1-(β-Bromoethyl)-2,2,5,5-tetramethylpiperazine Dihydrobromide (VIIa).**—Experiments in which aqueous solutions of VIIa were treated with aqueous sodium hydroxide solutions are listed in Table I.

In experiment A, the solution containing 2.5 g. of VIIa was overlaid with ether, and 5% aqueous sodium hydroxide was added with shaking. The layers were separated, and the ether distilled from a steam-bath. Water was added to the residue from the ether solution, and the insoluble polymer, m. p. 113–120°, was separated by filtration. The filtered aqueous solution was distilled, and the distillate was found to contain 0.0006 mole of base (16% calculated as VI). This titrated solution was evaporated to dryness, treated with benzoyl chloride and 5% sodium hydroxide, and filtered. The filtrate from this treatment was distilled, and the resulting distillate showed no titratable basicity, indicating the absence of any of the di-tertiary amine II.

Table I

Reaction of Aqueous Solutions of VIIa with Alkali

| Experiment | % Solution of VIIa in water Original | Final[a] | Moles NaOH per mole VIIa | Recovery, % as VI | IX |
|---|---|---|---|---|---|
| A | 10 | 6 | >3[b] | 16 | 70 |
| B | 10 | 6 | 3 | 16 | 30 |
| C | 0.3 | 0.3[c] | 3 | 72 | 7 |
| D | 24 | 8 | 3 | .. | 65 |

[a] After addition of the aqueous sodium hydroxide solution. [b] An excess of 5% aqueous sodium hydroxide added. [c] The amount of water added with the alkali in this case did not change the original percentage significantly.

In B and C, the polymer was separated by filtration, after which 50% sodium hydroxide was added to the aqueous filtrate, which then was extracted with benzene. Distillation of the benzene solution gave the quantities of VI listed in Table I. No other amine was present.

In D, 4.8 g. of VIIa (54.6% bromine content) in 15 ml. of water was treated with 46 ml. of 0.706 *N* (three equivalents) sodium hydroxide solution. After four hours, the solution was filtered, and the insoluble material leached with water to remove occluded inorganic salts; no attempt was made to identify the products in the aqueous filtrates. After drying the insoluble product in an oven at 70°, it (1.88 g.) was treated with 75 ml. of absolute ethanol, and 1.12 g. of insoluble material, m. p. above 260°, was separated from the alcoholic solution. The alcoholic solution was evaporated to dryness and treated with petroleum ether (b. p. 60–68°), and 0.1 g. of an insoluble material, m. p. 160–170°, was separated. The petroleum ether solution was concentrated and chilled; 0.47 g. (11%) of the dimer IX ($n$ = 1), m. p. 112–133°, separated. After one recrystallization from petroleum ether, this dimer, **1-β-(2,2,5,5-tetramethylpiperazino)-ethyl-2,2,5,5-tetramethyl-4-(β-hydroxyethyl)-piperazine,** melted at 121–129°. After another recrystallization, it melted at 123–125.5°.

*Anal.* Calcd. for $C_{20}H_{42}N_4O$: C, 67.76; H, 11.94; mol. wt., 354.5. Found: C, 67.54; H, 12.20; mol. wt. (Rast), 346.

The material melting at 160–170°, which was insoluble in petroleum ether, had a molecular weight and gave analytical values corresponding to those calculated for the trimer IX ($n$ is 2). The yield of this product amounted to 2% of the theoretical.

*Anal.* Calcd. for $C_{30}H_{62}N_6O$: C, 68.92; H, 11.95; mol. wt., 522. Found: C, 68.12; H, 12.43; mol. wt. (Rast), 511.

The major portion of the polymer, which was insoluble in ethanol and melted above 260°, was too insoluble in all solvents to permit a molecular weight determination. Although its properties indicated it to be a higher polymer IX, ($n > 2$), its analyses (C, 67.7%; H, 12.7%) were not satisfactory for such a structure (for higher values of $n$ the calcd. values for IX approach the limiting values: C, 71.5; H, 12.5, the calcd. values for IX minus water). Because of its refractory nature, this polymer was not investigated further.

When an aqueous solution of the chloro-dihydrochloride (VII) was treated with alkali in the manner described above, there was a momentary turbidity, indicating precipitation of the free base, but the solution cleared within five seconds. Within one minute a gelatinous precipitate began to separate. From such solutions the polymers

(IX) were obtained in quantities approximating those shown in Table I for the bromo compound, VIIa.

(c) **From Heating 1-(β-Chloroethyl)-2,2,5,5-tetramethylpiperazine Dihydrochloride (VII).**—This salt was heated alone and suspended in Stanolind mineral oil. The results of four such experiments are given in Table II.

TABLE II

PYROLYSIS OF VII

| Run | Condition | Temp., °C. | Time, min. | Mole HCl/mole VII evolved | I, %, recovered |
|---|---|---|---|---|---|
| 1 | Alone | 230–245 | 30 | 0.82 | 69 |
| 2 | Alone | 210–240 | 35 | .82 | 76.3 |
| 3 | In oil | 180–220 | 80 | .77 | 56.3 |
| 4 | In oil | 213–220 | 80 | .88 | 29.4 |

A typical experiment (run 3) follows: In a 200-ml. three-neck, round-bottom flask fitted with a stirrer, a thermometer, an air inlet and an outlet leading to 50 ml. of water in an erlenmeyer flask were placed 5 g. of VII and 50 ml. of Stanolind mineral oil. The flask was heated in a metal-bath and the hydrogen chloride evolved collected in water and titrated periodically with standard alkali. Above 180° the evolution of hydrogen chloride was steady. After the evolution of hydrogen chloride slowed, the oil suspension was diluted with petroleum ether (b. p. 60–68°), filtered, and the insoluble solid washed with petroleum ether; it weighed 3.48 g. after drying. The solid was dissolved in water, and the solution filtered; 0.06 g. of insoluble material remained. To the aqueous solution was added 5% sodium hydroxide solution; no precipitate formed. The solution was distilled until the distillate was no longer alkaline. Titration of the distillate with standard 1 *N* hydrochloric acid against methyl orange showed the presence of sufficient base to amount to 56.3% of I. Conversion of the salt, remaining from evaporation of the titrated solution, to the dibenzoyl derivative of I, m. p. 273–276°, identified this base as the reaction product. The filtrate from the preparation of the benzoyl derivative was distilled and a non-alkaline distillate obtained, indicating the absence of any of the tertiary, bicyclic amine II.

## Summary

The preparation of 2,2,5,5-tetramethyl-3,6-diketopiperazine (IV) from α-aminoisobutyric acid is described. This diketopiperazine has been converted to 2,2,5,5-tetramethylpiperazine (I) and 2,2,5,5-tetramethyl-3-ketopiperazine (V) by catalytic hydrogenation over copper–chromium oxide as well as by reduction with sodium in butanol.

Attempts to convert the 1-(β-hydroxyethyl)- and the 1-(β-haloethyl)-2,2,5,5-tetramethylpiperazines to the tetramethyl-1,4-diazabicyclo-(2,2,2)-octane (II) were unsuccessful. The hydroxy compound lost the 1-substituent and reverted to I; the 1-haloethyl derivatives in aqueous alkaline solution yielded the 1-hydroxyethyl derivative and polymers (IX) *via* an intermediate ethylene immonium ion, or when heated as salts, lost the 1-substituent to form the piperazine I.

MADISON, WISCONSIN RECEIVED SEPTEMBER 25, 1948

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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF NORTHWESTERN UNIVERSITY]

# The Synthesis of Some Isomeric Dimethyl-hydroxymethylpyridines. 3,4-Didesoxypyridoxin

BY RAYMOND P. MARIELLA AND JOHN L. LEECH[1]

Recent interest in antibiotics has led us to investigate the effect of the variation of the substituents in pyridoxin on possible anti-pyridoxin activity.

It has been shown by Ott[2] that 4-desoxypyridoxin was a powerful competitor to pyridoxin in the chick, and that methoxypyridoxin[3] exhibited similar activity, but to a lesser extent. Recently,[4] 5-deshydroxymethylpyridoxin was shown to be a weak inhibitor of pyridoxin in *Saccharomyces Cerevisiae*, while more recent work with 4-deshydroxymethylpyridoxin[5] has shown that this compound also exhibited very weak anti-pyridoxin properties.[6]

In the present work 2,3-dimethyl-5-hydroxymethylpyridine (VII), and 2,4-dimethyl-5-hydroxymethylpyridine (III) (3,4-didesoxypyridoxin) were synthesized as shown in Fig. 1.

As might be expected, VII exhibited neither pyridoxin nor anti-pyridoxin activity, but III did show weak anti-pyridoxin activity when tested against *Neurospora Sitophila*.[7]

From our work and previously cited work, it would appear that those structures similar to pyridoxin (with one or two groups removed) can exhibit this effect of anti-vitamin activity, and this could be explained on the basis of failure of the organism to differentiate between the vitamin and the similar molecule. With this reasoning, however, it would be difficult to explain why 3-amino-5-aminomethyl-4-ethoxymethyl-2-ethylpyridine has turned out to be the most potent anti-pyridoxin compound yet reported.[4] Work on the synthesis of other compounds related to pyridoxin is continuing in this Laboratory and will be reported soon.

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(1) Taken in part from a Master of Science thesis of John L. Leech.

(2) Ott, *Proc. Soc. Exp. Biol. Med.*, **61**, 125 (1946).

(3) Ott, *ibid.*, **66**, 215 (1947).

(4) Reported by Martin, Avakian and Moss at the April, 1948, meeting of the American Chemical Society.

(5) Perez-Medina, Mariella and McElvain, THIS JOURNAL, **69**, 2574 (1947).

(6) Private communication from Professor S. M. McElvain.

(7) These experiments were conducted by the Biochemical Group of the Lilly Research Laboratories, Indianapolis, Indiana.