[Contribution from the Department of Chemistry of the University of Wisconsin]

1,4-Diazabicyclo[2.2.2]octanes and 1,5-Diazabicyclo[3.2.2]nonanes from Piperazines and Homopiperazines

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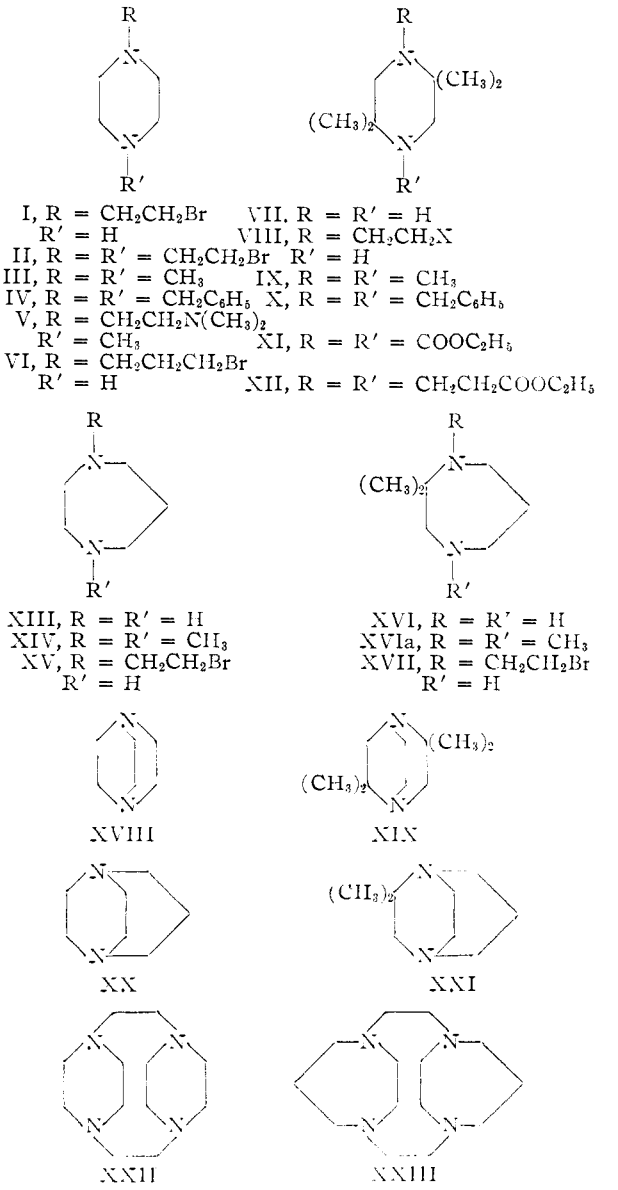
Received September 8, 1953

The introduction of an ethylene bridge between the nitrogens of 2,2,5,5-tetramethylpiperazine, homopiperazine and 2,2-dimethylhomopiperazine to form the bicyclo compounds XIX, XX and XXI has been effected by the pyrolysis of the hydrobromide salts of the 1-(2-bromoethyl) derivatives (VIII, XV, XVII) of these monocyclic compounds. The presence of the *gem*-dimethyl groups in VIII severely hinders this bridging reaction so that the yields are <1%. However, higher yields (*ca.* 13%) are obtained with XVII, which does not have such a hindering group adjacent to the reacting nitrogen. The tricyclic compounds XXII and XXIII are also formed in the pyrolysis of the hydrobromides of 1-(2-bromoethyl)-piperazine (I) and XV. Quaternization bridging of the nitrogens with ethylene bromide, which is quite successful with the 1,4-dimethyl derivatives of piperazine and homopiperazine (III and XIV) fails with those compounds IX and XVIa, which have a *gem*-dimethyl group adjacent to a nitrogen. Indeed, this reaction, as well as quaternization with simple halides, *i.e.*, methyl iodide, also appears to be dependent on the size of the 1,4-substituents, as it fails with 1,4-dibenzylpiperazine (IV). Other attempts to bridge the nitrogens of 2,2,5,5-tetramethylpiperazine utilizing $-CH_2CHO$ and $-CH_2COOC_2H_5$ as 1-substituents and $-CH_2COOC_2H_5$ and $-CH_2CH_2CH_2COOC_2H_5$ as 1,4-substituents were unsuccessful.

Two procedures have been used for the introduction of an ethylene bridge between the nitrogens of piperazine to form the bicyclic triethylene-diamine XVIII. Hromatka and Engel[1] obtained XVIII in 22–25% yields by the pyrolysis of the hydrohalide salts of a 1-(2-haloethyl)-piperazine (I). A large portion of the products of this pyrolysis was piperazine resulting from the loss of the 1-substituent. The second procedure involves the formation of the dimethobromide of XVIII from the reaction of ethylene bromide with 1,4-dimethylpiperazine (III). Mann and Mukherjee[2] reported the formation of this quaternary salt of XVIII in 77% yield. Hromatka and Kraupp,[3] using these authors' procedure obtained only a 50% yield of the quaternary salt of XVIII, but increased the yield to 70% by using ethylene glycol as a solvent for the reactants; they found that this quaternary salt could be demethobrominated by pyrolysis to XVIII in 70% yield. Mann and Mukherjee[2] also reported the preparation of XVIII by the pyrolysis of the amine salt obtained from the reaction of methylamine with tri-(2-chloroethyl)-amine; no yields were given. This bridging reaction doubtless involved the elimination of trimethylamine[4] from the piperazine V. Hromatka and Kraupp[3] obtained the hydrochloride of V from this reaction under the conditions of the earlier work,[2] but made no study of the pyrolysis of this salt.

The present paper reports a study of these bridging reactions with the tetramethylpiperazine VII and the homopiperazines XIII and XVI. In the course of this work a tertiary amine which appears to be the tertramethyl-1,4-diazabicyclo[2.2.2.]octane (XIX) was isolated as the dipicrate in low yields (0.15–0.5%); 1,5-diazabicyclo[3.2.2]nonanes (XX and XXI) were obtained in substantially better yields (30–43% and 13%, respectively).

As a part of this study the work of Hromatka and Kraupp[3] on the preparation of XVIII was repeated. From the pyrolysis of the dihydrobromide of I, XVIII (27–29%) and piperazine (29–51%) were obtained as volatile (with steam) amines; from the non-volatile material an amine picrate whose analyses corresponded to the tetrapicrate of XXII was



(1) O. Hromatka and E. Engel, *Ber.*, **76**, 712 (1943).

(2) F. G. Mann and D. P. Mukherjee, *J. Chem. Soc.*, 2298 (1949).

(3) O. Hromatka and O. Kraupp, *Monatsh.*, **82**, 880 (1951).

(4) For other examples of cyclizations involving the elimination of a tertiary amine see F. F. Blicke, *et al.*, This Journal, **74**, 1844 (1952).

isolated in 10% yield.[5] The dihydrobromide of II was also subjected to pyrolysis; it yielded XVIII (12–26%), piperazine (3–28%) and a non-volatile tertiary amine which was not XXII (m.p. of picrate) and was not further investigated. The dimethobromide of XVIII was obtained from III with ethylene bromide and was demethobrominated to XVIII in substantially the same yields as reported by Hromatka and Kraupp. However, an attempt to extend this quaternization bridging reaction to the 1,4-dibenzylpiperazine (IV) was unsuccessful; the ethylene bromide was dehydrohalogenated and the hydrobromide salt of IV rather than the bridged quaternary salt was obtained.

In an earlier paper,[6] unsuccessful attempts to prepare XIX from certain of derivatives of 2,2,5,5-tetramethylpiperazine (VII) were described. Attempts to effect the cyclodehydration of VIII (X is OH) were unsuccessful; pyrolysis of the hydrohalide salts of VIII (X is Cl or Br) caused the elimination of the 1-substituent as the only observable reaction; the free bases VIII (X is Cl or Br) rapidly passed into polymeric material, probably *via* an intermediate ethylenimonium ion.

The piperazine VII used in the earlier work was prepared in 30% over-all yield from 5,5-dimethylhydantoin *via* α-aminoisobutyric acid and the corresponding diketopiperazine, followed by the hydrogenation of the latter compound. A more convenient route to VII has now been found in the cyclodehydration of the commercially available 2-amino-2-methyl-1-propanol, $H_2NC(CH_3)_2CH_2OH$, which proceeds in 50–60% yields in the presence of Raney nickel or copper–chromium–barium oxide.

The pyrolysis of the dihydrobromide of VIII (X is Br) was reinvestigated and it was found possible to isolate in low yields (0.15–0.50%) the dipicrate of a tertiary amine, whose analyses correspond to XIX. This salt was not obtained in sufficient amount to permit the isolation of the free base, but the steam volatility of the tertiary amine isolated[5] indicated that it was not the octamethyl derivative of XXII. In addition to this salt of XIX, an 80% yield of the dibenzoyl derivative of VII was separated from the pyrolysis mixture.

Attempts were also made to prepare quaternary salts of XIX by bridging the 1,4-derivatives of VII (IX–XII) with ethylene bromide. No quaternary salt was found in any case. The products isolated from the reaction of IX and X with ethylene bromide were the hydrobromides of these tertiary amines and vinyl bromide. With XI the 1-ethyl derivative of VII was isolated in 16% yield.[7] Inasmuch as XII eliminated ethyl acrylate quite rapidly at 100°, it is probable that a considerable amount of this tertiary amine underwent pyrolysis prior to any reaction with ethylene bromide.

After these results were obtained it seemed of interest to determine the susceptibility of the basic nitrogens of the tertiary amines IX, X and XII to quaternization with simple halides. IX readily forms a quaternary salt with methyl iodide at room temperature. However, X does not react with methyl iodide at room temperature and XII showed no reaction when heated in refluxing ethyl iodide. Thus it appears that quaternization is inhibited if not entirely prevented in those derivatives of VII that have N-substituents larger than methyl (*cf.* also the failure of IV to form the dibenzyl quaternary salt of XVIII with ethylene bromide).

The Homopiperazines and the 1,5-Diazabicyclo[3.2.2]nonanes.—The pyrolysis of the dihydrobromide of 1-(2-bromoethyl)-homopiperazine (XV) on a 1-g. scale gave a 43% yield of XX, isolated as the dipicrate, and, an 11% yield of the tetramine XXIII, isolated as the tetrapicrate. The free base XX was obtained as colorless needles, m.p. 89–92°, after sublimation from sodium under diminished pressure, but proved to be too hygroscopic to yield satisfactory analysis. When the pyrolysis of the dihydrobromide of XV was carried out on a 53-g. scale the yields of XX and XXIII dropped to 30% and 3.7%, respectively. From the benzoylated secondary amine fraction of this run a 24% yield of 1,4-dibenzoylhomopiperazine and, surprisingly, a 9% yield of 1,4-dibenzoylpiperazine were obtained. The isolation of the latter compound indicated that some pyrolytic fission of XX to eliminate the trimethylene bridge had occurred. The loss of the 1-bromoethyl substituent of XV to form XIII is analogous to the pyrolytic elimination of this substituent from the hydrohalides of I and VIII. Doubtless the lower yields of XX and XXIII, and the concurrent appearance of the decomposition product of XX, in the larger scale pyrolysis of the salt of XV are associated with the longer heating period as well as with a less even heat distribution in the melt than was obtained in the smaller scale pyrolysis.

Further evidence of the instability of the bicyclic ring system of XX as compared to that of XVIII was obtained from the pyrolyses of the corresponding dimethobromides. Whereas this quaternary salt of XVIII is smoothly demethobrominated to XVIII when heated under diminished pressure, the dimethobromide of XX, which was prepared directly from this tertiary amine or in 43% yield from the reaction of ethylene bromide with 1,4-dimethylhomopiperazine (XIV), failed to yield any of XX under these conditions; the only product isolated was 1,4-dimethylpiperazine (III). In further contrast to the instability of the ring structure of the dimethobromide of XX is the stability of that of the dimethobromide of 1,4-dimethylhomopiperazine (XIV). The latter salt, prepared from the reaction of trimethylene bromide with tetramethylethylenediamine, $(CH_3)_2NCH_2CH_2N(CH_3)_2$, was readily demethobrominated to XIV.

An unsuccessful attempt was made to prepare XX from the pyrolysis of the dihydrobromide of 1-

(5) The general procedure for the separation of these amines and similar mixtures described subsequently involves (a) the separation of secondary from tertiary amines by exhaustive benzoylation by the Schotten–Baumann method,[1,2] and (b) steam distillation from basic solution to remove the volatile diazabicyclo compound from the non-volatile tetrazatricyclo compound.

(6) S. M. McElvain and E. H. Pryde, THIS JOURNAL, **71**, 326 (1949).

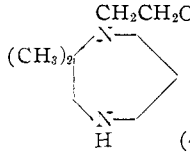
(7) This product is probably formed from XI in a manner analogous to the decarboxylative alkylations of N-carbalkoxypyrazoles and indazoles, *cf.* C. D. Hurd, "The Pyrolysis of Carbon Compounds," American Chemical Society Monograph Series, Chemical Catalog Co., Inc., New York, N. Y., 1929, pp. 563–564.

(3-bromopropyl)-piperazine. Only a 45% yield of piperazine and a small amount (*ca.* 1%) of a tertiary amine, which was not XX, were obtained as steam-volatile amines. The salt used in this pyrolysis was prepared from the corresponding alcohol, which was obtained from the reaction of piperazine with (a) trimethylene chlorohydrin (58%) or with (b) trimethylene oxide (15%).

Since the *gem*-dimethyl groups of VIII and IX had offered such effective steric hindrance to the bridging of the nitrogens, it seemed that the logical starting material for the preparation of XXI would be the hydrobromide salt of XVII. In this compound the *gem*-dimethyl group would have a minimum steric effect on the nitrogen to which the bridge is made. After it was found that the dimethylhomopiperazine (XVI) could be prepared by the cyclodehydration of N-(1-hydroxy-2-methyl-2-propyl) - 1,3 - propanediamine, $HOCH_2C(CH_3)_2NH(CH_2)_3NH_2$, the requisite salt of XVII was prepared by the following sequence of reactions from ethyl cellosolve

$$C_2H_5OCH_2CH_2OH \xrightarrow{HBr} C_2H_5OCH_2CH_2Br \xrightarrow{H_2NC(CH_3)_2CH_2OH} C_2H_5OCH_2CH_2NHC(CH_3)_2CH_2OH\ (55\%) \xrightarrow[2,\ H_2,\ Ni]{1,\ CH_2=CHCN}$$

$$H_2NCH_2CH_2CH_2NC(CH_3)_2CH_2OH\ (89\%) \xrightarrow{CuCrBaO}$$



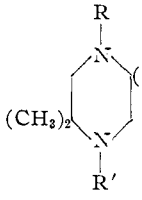
$$\xrightarrow{68\%\ HBr} XVII{\cdot}2HBr\ (89\text{–}92\%)$$

(43%)

The pyrolysis of small portions (*ca.* 1 g.) of this salt of XVII gave a 13% yield of XXI, which was isolated as the dipicrate; none of the dibenzoyl derivative of any secondary amine was obtained in the work-up of the steam-volatile amines. When this pyrolysis was repeated on a 62-g. scale, only a trace of a volatile tertiary amine was obtained, but a 44% yield of a mixture of benzoyl derivatives of secondary amines was separated. The free base XXI is a colorless liquid whose elemental analyses for carbon and nitrogen were somewhat low, due no doubt to its tendency to absorb water and carbon dioxide. However, the dipicrate and the di-2,4-dinitrophenolate salts gave correct elemental analyses.

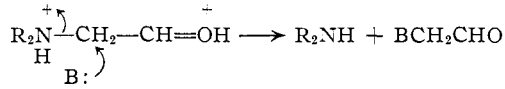
It appears from the above results that (a) the presence of a *gem*-dimethyl group adjacent to the nitrogen of a 1,4-disubstituted piperazine or homopiperazine or (b) the presence of a substituent larger than methyl in the 1- and 4-positions of piperazine effectively prevents the formation of a bridged quaternary salt with ethylene bromide; instead the dihalide is dehydrogenated with the formation of the tertiary amine salt. Similarly, intramolecular bridging *via* pyrolysis of a 1-bromo-ethylpiperazine salt is practically completely prevented by a *gem*-dimethyl group adjacent to the 4-nitrogen. Although it was possible to obtain a low yield of XIX by this latter reaction, the principal reaction involves the elimination of the 1-substituent.

In view of these difficulties, attempts were made to establish a bridge between the nitrogens of 2,2,-5,5-tetramethylpiperazine (VII) with other N-substituents. The aldehyde derived from the acetal XXIV by treatment with hydrochloric acid



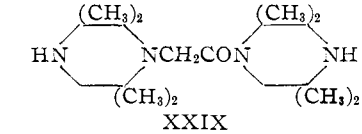
XXIV, R = $CH_2CH(OC_2H_5)_2$, R′ = H
XXV, R = R′ = $CH_2CH(OC_2H_5)_2$
XXVI, R = $CH_2COOC_2H_5$, R′ = H
XXVII, R = R′ = $CH_2COOC_2H_5$
XXVIII, R = R′ = $(CH_2)_3COOC_2H_5$

polymerized too rapidly to yield a 2,4-dinitrophenylhydrazone. An attempt to simultaneously hydrolyze and reduce XXIV to XIX in cold hydrochloric acid with tin, a procedure which has been used for the conversion of γ-benzylaminobutyraldehyde acetal to 1-benzylpyrrolidine,[8] eliminated the 1-substituent to give a quantitative yield of VII. Repetition of the experiment without tin present gave the same result. Similarly, the diacetal XXV was quantitatively converted to VII by 36% hydrochloric acid; the eliminated 1,4-substituents appeared as dark, resinous, insoluble material, which was doubtless the polymerized aldehyde resulting from the cleavage of the protonated intermediate aldehyde from XXIV or XXV by chloride ion or water (B:)



An attempt was made to effect the reductive cyclization of the aldehyde from XXIV with 88% formic acid. The main gases evolved from the reaction were flammable (CO and H_2) with only relatively small amounts of carbon dioxide. No steam-volatile tertiary amine was formed, nor was any tetramethylpiperazine (VII) isolated until the reaction mixture was treated with concentrated hydrochloric acid.

The ester XXVI, as well as 1-carbethoxymethylpiperazine, failed as might be expected[9] to undergo intramolecular aminolysis of the ester. When XXVI was heated at 190–275°, 65% of the theoretical amount of alcohol was collected, but the weight of the residual material indicated a quantitative elimination of alcohol. From this residue were isolated small yields of VII (5.6%), an amine believed to be 1,2,2,5,5-pentamethylpiperazine (12.2%), unchanged XXVI (5%) and the dimeric product XIX (2%); the principal product was a viscous residue of condensation polymer amounting to 52% of the total reaction product.



XXIX

(8) F. E. King, J. R. Marshall and P. Smith, *J. Chem. Soc.*, 239 (1951).

(9) *Cf.* F. S. Fawcett, *Chem. Revs.*, **47**, 258 (1950); N. F. Albertson, THIS JOURNAL, **72**, 2594 (1950); **74**, 249 (1952).

No reductive cyclization of XXVI occurred when it was subjected to 1200–3400 p.s.i. of hydrogen in dioxane at 200–250° over copper–chromium–barium oxide catalyst. The reaction products were tetramethylpiperazine (VII) and 1-(2-hydroxyethyl)-tetramethylpiperazine. It had previously been found[6] that the latter compound did not undergo catalytic cyclodehydration; this failure was not due to the steric effects of the *gem*-dimethyl groups as it has not been possible to convert 1-(2-hydroxyethyl)-piperazine to XVIII by this reaction. Leonard and Shoemaker[10] have reported a similar failure to form atomic-bridged bicyclic structures with a nitrogen bridgehead by this method.

Unsuccessful attempts were made to bridge the nitrogens of VII *via* the esters XXVII and XXVIII. The former ester was recovered unchanged from an attempted Dieckmann cyclization with sodium hydride in benzene, while the ester XXVIII remained unchanged when it was subjected to the conditions of an acyloin condensation.

Experimental

All melting points are corrected.

Materials Used.—2-Amino-2-methyl-1-propanol was generously supplied by the Commercial Solvents Corporation. The picrate of this amine, precipitated from ether as an oil that solidified to a yellow powder on standing, melted at 117–118° after trituration with ether.

Anal. Calcd. for $C_{10}H_{14}N_4O_8$: N, 17.61. Found: N, 17.42.

Ethylenediamine (70–75%) was purchased from Eastman Kodak Co.

N,N,N′,N′-Tetramethylethylenediamine was prepared in 79% yield from ethylenediamine by methylation with formic acid and formaldehyde[11]; it boiled at 120–123° (reported[12] 120–122°). Piperazine was obtained by fractional distillation of its hexahydrate, which was purchased from Chemo Puro Mfg. Corp.

1-(2-Hydroxyethyl)-piperazine and 1,4-Di-(2-hydroxyethyl)-piperazine.—To an ice-cooled solution of 587.5 g. (3.02 moles) of piperazine hexahydrate in 2 l. of methanol was added 62.5 g. (1.42 moles) of ethylene oxide. The reaction flask was immediately stoppered, shaken briefly but thoroughly, and placed in an ice–water-bath so that it warmed up gradually to room temperature as the ice melted. After standing for five days the solution was fractionated through a 20-cm. McMahon packed column to yield, after the forefraction of piperazine, 132.5 g. (72%) of 1-(2-hydroxyethyl)-piperazine, b.p. 118° (9 mm.), $n^{25}D$ 1.5058 (reported[13] b.p. 119.2 (10 mm.), $n^{25}D$ 1.5052).

The distillation residue was dissolved in methanol, partially decolorized with Norit, and concentrated strongly to yield 23.5 g. (19%) of crude crystals of 1,4-di-(2-hydroxyethyl)-piperazine. Recrystallization from methanol afforded colorless plates, m.p. 135.5–136.5° (reported[14] m.p. 135–135.5°).

1-(2-Bromoethyl)-piperazine (I) Dihydrobromide.—Slow distillation of a solution of 1-(2-hydroxyethyl)-piperazine in 48% hydrobromic acid, followed by concentration to dryness under reduced pressure and trituration in acetone yielded 95% of the salt of I, m.p. 233–235° dec., which was suitable for subsequent uses. The pure dihydrobromide of I is reported[1] to melt at 242–243° dec.

1-(3-Hydroxypropyl)-piperazine and 1,4-Di-(3-hydroxypropyl)-piperazine. Method A.—A solution of 101 g. (0.50 mole) of piperazine hexahydrate in 450 ml. of methanol was treated with 10.2 g. (0.176 mole) of trimethylene oxide[15] with shaking and allowed to stand in a glass-stoppered bottle for one month. Fractional distillation through a 30-cm. Vigreux column removed the solvent and piperazine, and the residue was distilled twice from a 10-ml. claisen flask to yield 3.6 g. (13.7%) of the hydroxypropylpiperazine as a yellow, viscous, hygroscopic oil, b.p. 115–120° (0.7 mm.), which gave unsatisfactory analyses.

1-(3-Hydroxypropyl)-piperazine dipicrate was prepared from this oil in aqueous solution. One recrystallization from water afforded a fluffy precipitate of fine, yellow needles, m.p. 252–253° dec.

Anal. Calcd. for $C_{19}H_{22}N_8O_{15}$: C, 37.88; H, 3.68; N, 18.60. Found: C, 38.03; H, 3.73; N, 18.49.

Method B.—A solution of 172.3 g. (2.00 moles) of piperazine in 400 ml. of 95% alcohol was stirred at 75° under reflux while 99 g. (1.05 moles) of trimethylene chlorohydrin was added dropwise during one-half hour. After the reaction mixture had been stirred at reflux for 15 hours, dry potassium carbonate (80 g., 0.58 mole) was added to it, following which water was gradually added at reflux until most of the salts were in solution. Stirring at reflux was continued for another several hours, after which the batch was cooled and filtered. The filtrate was distilled until most of the alcohol had been removed; then, benzene was added and the rest of the water was removed by azeotropic distillation, using a separator to withdraw the water layer and recycle the benzene. The filtered benzene solution was distilled free of solvent and the bulk of the piperazine at atmospheric pressure, and the residue was distilled rapidly through a column packed with 15-cm. of glass helices; 95 g. of a fraction, boiling at 140° (10 mm.)-160° (20 mm.), was collected as 1-(3-hydroxypropyl)-piperazine. Refractionation through a 35-cm. column of glass helices gave 88.5 g. (58.6%) of nearly colorless product, b.p. 132.5–134.0° (10 mm.), m.p. 48.5–49.5°. The dipicrate of this material melted at 252–252.5° dec., and gave no depression of melting point on admixture with the dipicrate of the amine prepared by method A above.

From the distillation residue a total of 27 g. (25.4%) of 1,4-di-(3-hydroxypropyl)-piperazine, m.p. 143–144° (reported[16] m.p. 142–143°), was obtained by recrystallization from methanol.

1-(3-Bromopropyl)-piperazine Dihydrobromide.—A solution of 3.45 g. (0.024 mole) of 1-(3-hydroxypropyl)-piperazine in 160 ml. of 48% hydrobromic acid was slowly distilled from all-glass apparatus until 80 ml. of distillate had been collected. After refluxing overnight the reaction mixture was concentrated to dryness under reduced pressure, and the oily precipitate was triturated in acetone, which rapidly transformed it into a fine, brownish powder; yield 7.65 g. (87%), m.p. 212–214° dec.

Anal. (Stepanow) Calcd. for $C_7H_{17}N_2Br_3$: Br, 64.98. Found: Br, 65.1.

1,4-Di-(2-bromoethyl)-piperazine (II) Dihydrobromide.—After slow distillation of 100 ml. of acid from a solution of 12.00 g. (0.0688 mole) of 1,4-di-(2-hydroxyethyl)-piperazine in 200 ml. of 48% hydrobromic acid, the remaining solution was refluxed overnight in the all-glass apparatus and then concentrated to dryness under reduced pressure. Trituration of the residue in acetone yielded 28.3 g. (89%) of crude, but essentially colorless salt, which in a m.p. tube decomposed gradually from 240–360°.

Anal. Calcd. for $C_8H_{18}N_2Br_4$: Br, 69.20. Found: Br, 64.5.

The bromine determination was made by the Volhard method after the sample had been in solution for 40 hours.

1,4-Dibenzylpiperazine (IV).—A mixture of 97.1 g. (0.50 mole) of piperazine hexahydrate, 126.6 g. (1.00 mole) of benzyl chloride, 450 ml. of absolute alcohol, and 54 g. (0.51 mole) of anhydrous sodium carbonate was stirred at reflux for 20 hours. Crude IV was precipitated when the reaction mixture was poured into 2 l. of water; recrystallization from methanol yielded 90 g. (67.5%) of white plates, m.p. 91–92° (reported[17] m.p. 92°).

2,2,5,5-Tetramethylpiperazine (VII).—A number of small-scale experiments were made to determine the optimum con-

(10) N. J. Leonard and G. L. Shoemaker, THIS JOURNAL, **71**, 1876 (1949).

(11) H. T. Clarke, H. B. Gillespie and S. Z. Weisshaus, *ibid.*, **55**, 4571 (1933).

(12) L. Knorr, *Ber.*, **37**, 3510 (1904).

(13) L. J. Kitchen and C. B. Pollard, *J. Org. Chem.*, **8**, 338 (1943).

(14) D. E. Adelson, L. G. MacDowell and C. B. Pollard, THIS JOURNAL, **57**, 1988 (1935).

(15) C. R. Noller, *Org. Syntheses*, **29**, 92 (1949).

(16) J. H. Gardner and J. H. Schneider, THIS JOURNAL, **55**, 3823 (1933).

(17) H. T. Clarke, *J. Chem. Soc.*, 1927 (1911).

ditions for the catalytic cyclodehydration of 2-amino-2-methyl-1-propanol to VII. The amount of product formed was determined by acidification of the reaction mixture with hydrochloric acid, steam distillation of the organic solvent (if any), and treatment with sodium nitrite solution at 0–10° to precipitate the insoluble 1,4-dinitroso-2,2,5,5-tetramethyl piperazine,[18] m.p. 208–210°. Thus it was found that a temperature of 250° and a hydrogen pressure (hot) of 5000–5700 p.s.i. (2700–3000 p.s.i. cold pressure) for 8 hours over Raney nickel gave the best yields (50–63%) of VII, which could be recovered from the nitroso derivative by refluxing for 24 hours in 10% hydrochloric acid. Copper–chromium–barium oxide[19] instead of Raney nickel gave similar results when the reaction was run in dioxane, but the yields dropped below 50% when this solvent was omitted.

For the large scale preparation of VII the following procedure was adopted. A mixture of 450 g. of the amino alcohol and 45 g. of Raney nickel was placed in a bomb and shaken under the above conditions for 6 hr. After cooling, the reaction products were washed from the bomb with benzene and filtered. Three such runs were combined and distilled. After removal of the benzene and water, the higher boiling distillates were collected, cooled to 0–10° and filtered. The solid VII so obtained melted at 77–80° and amounted to a 26% yield; it could be purified readily by recrystallization from ether.[6] The filtrates from the isolation of VII were recycled through the cyclodehydration step to yield an additional 17% of VII. Further recycling of the resulting filtrate would increase the total yield of VII to above 50%.

2,2,5,5-Tetramethylpiperazine dipicrate was prepared and recrystallized from water as orange-yellow needles, m.p. 287–288° dec.

Anal. Calcd. for $C_{20}H_{24}N_8O_{14}$: N, 18.66. Found: N, 18.88.

1,2,2,4,5,5-Hexamethylpiperazine (IX).—A 500-ml. flask containing a solution of 28.4 g. (0.20 mole) of 2,2,5,5-tetramethylpiperazine (VII) and 150 ml. of 88% formic acid was attached to a reflux condenser, and 60 ml. (0.8 mole) of 37% formalin was then added. When the initial evolution of carbon dioxide subsided, the reaction mixture was heated on the steam-bath for 40 hours, treated with 50 ml. of 37% hydrochloric acid and evaporated to dryness. The residue was dissolved in the minimum of water, made alkaline with potassium carbonate, and extracted with ether. The dried ether extracts were distilled to yield a single fraction of IX as a colorless oil, b.p. 74–78° (23 mm.), $n^{25}D$ 1.4555. The yield was 24 g. (70.5%).

Anal. Calcd. for $C_{10}H_{22}N_2$: N, 16.45. Found: N, 16.05.

1,2,2,4,5,5-Hexamethylpiperazine dihydrochloride was prepared by dissolving IX in an excess of hydrochloric acid, evaporating to dryness, and recrystallizing the residue once from methanol, m.p. > 250°.

Anal. Calcd. for $C_{10}H_{24}Cl_2N_2$: Cl, 29.15. Found: Cl, 29.15.

1,2,2,4,5,5-Hexamethylpiperazine dipicrate was prepared in water and recrystallized once from water, yellow prisms, m.p. 264.5–265° (dec. with extensive previous sintering).

Anal. Calcd. for $C_{22}H_{28}N_8O_{14}$: N, 17.83. Found: N, 17.47.

1,2,2,4,5,5-Hexamethylpiperazine Mono- and Dimethiodides.—To 0.95 g. of (0.0058 mole) of IX in a bomb tube was added 10 ml. of methyl iodide. A salt, presumably the monomethiodide, precipitated quite rapidly; nevertheless, the tube was sealed and heated 40 hours at 100° in a steel bomb. The total reaction product of 2.01 g. was extracted with hot absolute alcohol; from the alcohol solution colorless plates of the monomethiodide of IX separated, m.p. 311–312° dec.

Anal. Calcd. for $C_{11}H_{25}IN_2$: C, 42.31; H, 8.07; I, 40.65. Found: C, 42.30; H, 8.04; I, 40.76.

The solid that failed to dissolve during the hot alcohol extraction was twice recrystallized from aqueous alcohol to give the dimethiodide of IX as a fine, colorless powder, also melting at 311–312° dec.

Anal. Calcd. for $C_{12}H_{28}I_2N_2$: C, 31.73; H, 6.21; I, 55.89. Found: C, 31.37; H, 6.27; I, 55.76.

A mixture of the mono- and dimethiodides showed no depression of decomposition point. The total yield of monomethiodide was 0.94 g. (54%) while that of dimethiodide was 0.625 g. (24.7%).

1,4-Dibenzyl-2,2,5,5-tetramethylpiperazine (X).—A mixture of 250 ml. of benzene, 27.0 g. (0.19 mole) of 2,2,5,5-tetramethylpiperazine (VII), 50.6 g. (0.40 mole) of benzyl chloride and 28 g. (0.02 mole) of anhydrous potassium carbonate was refluxed with stirring for 14 hours. The cold mixture was thoroughly extracted with 5% hydrochloric acid, and the acid extracts were made alkaline with potassium carbonate. The crude precipitate was collected on a filter and crystallized from 60–68° petroleum ether to yield 39.7 g. (63%) of colorless prisms of X, m.p. 162.5–163.5°. One recrystallization from alcohol gave material which melted at 163.5–164.5°.

Anal. Calcd. for $C_{22}H_{30}N_2$: N, 8.69; mol. wt., 322.48. Found: N, 8.40; mol. wt. (Rast), 321.

A solution of 0.2 g. of X in 10 ml. of ether was treated with 10 drops of methyl iodide (an excess) and allowed to stand for 2 weeks. No salt precipitated; moreover, an extraction with water and Volhard titration of the aqueous extract showed no titratable iodide, indicating that quaternization had not taken place.

1,4-Dicarbethoxy-2,2,5,5-tetramethylpiperazine (XI).—To a stirred mixture of 15.5 g. (0.109 mole) of 2,2,5,5-tetramethylpiperazine (VII), 5.8 g. of anhydrous sodium carbonate and 200 ml. of benzene, 23.9 g. (0.22 mole) of ethyl chloroformate was added dropwise over a one-hour period without cooling. The reaction mixture was stirred for another 3 hours, 125 ml. of water was added, and the layers were separated. The aqueous layer was saturated with potassium carbonate and extracted twice with 200-ml. portions of benzene. After drying over Drierite, the combined benzene solutions were distilled to give 25.3 g. (81%) of crude XI, b.p. 154–160° (1.5 mm.). Fractionation of the crude product through a 30-cm. Vigreux column yielded (1) 4.1 g. of forerun, b.p. 120–139° (0.75 mm.), and (2) 17.3 g. of XI, b.p. 139–141° (0.75 mm.). After long standing, fraction 2 crystallized into colorless plates, m.p. 38–39°. The monohydrochloride was prepared by treatment with one equivalent of hydrogen chloride in ethanol; it was recrystallized from carbon tetrachloride as white plates, m.p. 187–189°.

Anal. Calcd. for $C_{14}H_{27}ClN_2O_4$: Cl, 11.00. Found: Cl, 10.85.

1,4-Di-(2-carbethoxyethyl)-2,2,5,5-tetramethylpiperazine (XII).—A solution of 25.8 g. (0.181 mole) of 2,2,5,5-tetramethylpiperazine (VII) in 150 g. (1.5 moles) of ethyl acrylate was refluxed gently for a week and allowed to cool for two days. Excess ethyl acrylate was removed by distillation through a 30-cm. Vigreux column at 23 mm.; the oil-bath temperature did not exceed 80° during the distillation. The residue was cooled and scratched to induce crystallization, and after two days 50 g. (80.5%) of crude crystals of XII were obtained by filtration. Two recrystallizations from alcohol gave white plates, m.p. 56.8–57.8°.

Anal. Calcd. for $C_{18}H_{34}N_2O_4$: N, 8.18; OC_2H_5, 26.32. Found: N, 7.82; OC_2H_5, 25.80.

When 1 g. of XII was heated in a 10-ml. distilling flask placed in an oil-bath, a haziness began to appear on the sides of the flask as the oil-bath temperature reached 100°, and definite droplets could be seen on the sides at 115°. By the time the oil-bath had heated to 155° the vapor temperature was 101°, the boiling point of ethyl acrylate. This experiment indicates that XII is not stable above 100°.

A solution of 1.92 g. of XII in 10 g. of ethyl iodide was warmed at 70–80° under reflux for 24 hours. It was cooled and diluted with 40 ml. of ether; no precipitation occurred. Evaporation of the solution yielded 1.92 g. of unchanged XII, indicating that no quaternization had occurred.

1-(2,2-Dimethoxyethyl)-2,2,5,5-tetramethylpiperazine (XXIV) and 1,4-Di-(2,2-diethoxyethyl)-2,2,5,5-tetramethylpiperazine (XXV).—Bromoacetal (84.7 g., 0.43 mole) was added dropwise over a period of five hours to a stirred, refluxing mixture of 122.5 g. (0.86 mole) of 2,2,5,5-tetramethylpiperazine (VII), 23.4 g. (0.22 mole) of anhydrous sodium carbonate, and 730 ml. of dry benzene. The mixture was stirred at reflux for another 40 hours, during which an additional 12 g. of sodium carbonate was added. After thorough shaking of the reaction mixture with 1 l. of water,

(18) J. B. Conant and J. G. Aston, This Journal, **50**, 2783 (1928).

(19) Catalyst HJS2, H. Adkins, E. E. Burgoyne and H. J. Schneider, *ibid.*, **72**, 2626 (1950).

layers were separated, and the benzene layer was washed twice with small amounts of water; the aqueous solutions contained the bulk of unchanged VII, which was recovered. Distillation of the benzene solution yielded 61.2 g. of a light yellow oil, b.p. 100–145° (1–2 mm.). Fractionation of this oil through a 20-cm. McMahon packed column gave: (1) 1.4 g., b.p. 52–100° (1.7 mm.); (2) 47.3 g. (42%) of XXIV as a colorless oil, b.p. 79–84° (0.3 mm.), $n^{25}D$ 1.4515, d^{25}_4 0.9312; (3) 1.9 g., b.p. 84–107° (0.4 mm.), $n^{25}D$ 1.4522; and (4) 5.8 g. (7.2%) of crude, yellow XXV, b.p. 129-133° (0.5 mm.), $n^{25}D$ 1.4517. A sample of XXIV, fraction 2, was analyzed.

Anal. Calcd. for $C_{14}H_{30}N_2O_2$: C, 65.07; H, 11.70; N, 10.34; OC_2H_5, 34.88; *MR*, 75.50. Found: C, 64.89; H, 11.74; N, 10.81; OC_2H_5, 34.6; *MR*, 74.92.

Crystallization of fraction 4 was induced by spot cooling with Dry Ice. The crystals of XXV were recrystallized four times from 60–68° petroleum ether to colorless plates of a constant melting point of 40–41°.

Anal. Calcd. for $C_{20}H_{42}N_2O_4$: C, 64.13; H, 11.30; OC_2H_5, 48.12. Found: C, 64.10; H, 11.40; OC_2H_5, 47.65.

When it was desired to prepare XXV as the main product, the procedure was essentially the same, except that 1.08 moles of bromoacetal was used with 0.50 mole of VII. It was found advisable at the end of the reaction to shake the organic layers thoroughly with 10% sodium hydroxide solution in order to prevent decomposition of the product during distillation. Then distillation and recrystallization yielded 49% of purified XXV.

1-Carbethoxymethyl-2,2,5,5-tetramethylpiperazine (XXVI) and 1,4-Dicarbethoxymethyl-2,2,5,5-tetramethylpiperazine (XXVII).—A mixture of 1500 ml. of dry benzene, 142.2 g. (1.00 mole) of 2,2,5,5-tetramethylpiperazine (VII), and 26.5 g. (0.25 mole) of anhydrous sodium carbonate was stirred at a gentle reflux while 62.0 g. (0.506 mole) of ethyl chloroacetate was added dropwise over a one-hour period. After having been stirred at reflux for another 20 hours, the reaction mixture was cooled to room temperature and stirred with 700 ml. of dilute sodium carbonate solution. The aqueous layer was saved for recovery of VII, and the benzene layer was fractionated through a 30-cm. Vigreux column to yield: (1) some unchanged VII; (2) 64.9 g. (56.2%) of XXVI, b.p. 115–123° (7 mm.), n^{25} 1.4604, d^{25}_4 0.9727; and (3) 18.7 g. (23.5%) of XXVII, b.p. 126–130° (0.2 mm.). The latter fraction solidified and was twice recrystallized from aqueous alcohol, colorless plates, m.p. 62.2–63.2°.

Anal. Calcd. for $C_{16}H_{30}N_2O_4$ (XXVII): C, 61.12; H, 9.62; OC_2H_5, 28.66. Found: C, 61.05; H, 9.66; OC_2H_5, 28.39.

The distilled XXVI could be further purified *via* the monohydrochloride as follows: a solution of 11.4 g. (0.050 mole) of distilled product in absolute alcohol was treated with 12 ml. (0.051 mole) of 4.26 *N* ethanolic hydrogen chloride and evaporated to dryness. Extraction of the crude hydrochloride with two 75-ml. portions of hot carbon tetrachloride and cooling of the extracts afforded 10.7 g. (80.8%) of the monohydrochloride of XXVI, m.p. 178–179.5°. Two recrystallizations from carbon tetrachloride (with Norit) gave an 82% recovery of very small, colorless crystals, m.p. 181.3–182.3°.

Anal. Calcd. for $C_{12}H_{25}ClN_2O_2$: Cl, 13.22. Found: Cl, 13.24.

The pure monohydrochloride (12 g.) was dissolved in 50 ml. of water, and the free amine was released by the addition of an excess of sodium carbonate. The free XXVI was taken up in ether, dried over anhydrous calcium sulfate (Drierite), and distilled (after removal of the drying agent and the ether) from a 50-ml. modified claisen flask. A single fraction of colorless oil was obtained, b.p. 67–67.5° (0.18 mm.), $n^{25}D$ 1.4599, d^{25}_4 0.9710.

Anal. Calcd. for $C_{12}H_{24}N_2O_2$ (XXVI): C, 63.12; H, 10.59; *MR*, 64.63; neut. equiv., 228.33. Found: C, 62.95; H, 10.64; *MR*, 64.39; neut. equiv., 232.

1,4-Di-(3-carbethoxypropyl)-2,2,5,5-tetramethylpiperazine (XXVIII).—A mixture of 14.24 g. (0.10 mole) of 2,2,5,5-tetramethylpiperazine (VII), 40.3 g. (0.207 mole) of ethyl γ-bromobutyrate, 10.6 g. (0.10 mole) of anhydrous sodium carbonate and 100 ml. of absolute alcohol was stirred at reflux for 3 days. After cooling, the reaction mixture was poured into 300 ml. of dilute potassium carbonate solution and extracted with 500 ml. of benzene. After drying over Drierite, the benzene was distilled through a Vigreux column and the residue was fractionated from a 50-ml. modified Claisen flask. After about 2 g. of forerun, 25.4 g. (69%) of XXVIII distilled at 160–163° (0.3 mm.) as an essentially colorless oil, which solidified upon cooling, m.p. 42.5–43.5°.

Anal. Calcd. for $C_{20}H_{38}N_2O_4$: C, 64.83; H, 10.34; OC_2H_5, 24.32. Found: C, 64.67; H, 10.14; OC_2H_5, 23.93.

Homopiperazine (XIII).—The dibenzenesulfonyl derivative of XIII was prepared in 74% yield by alkylating the disodium salt of the dibenzenesulfonyl derivative of ethylenediamine with trimethylene bromide, according to the directions of Bleier.[20] The sulfonamide was then hydrolyzed as follows: 137.8 g. (0.36 mole) of the sulfonamide was heated with 475 g. of 80% sulfuric acid at 170° for 18 hours. The hydrolysis mixture was diluted to five liters and filtered free of the small amount of insoluble material; the clear, nearly colorless filtrate was then stirred into a solution of 200 g. of picric acid in 6 l. of water, digested and cooled. A small amount of the homopiperazine dipicrate which precipitated was twice recrystallized from water to a constant melting point of 267.5–268.5° dec. (reported[20] m.p. 265°).

The remainder of the picrate was converted to the hydrochloride by treatment with 1700 g. of 15% hydrochloric acid, extraction of the picric acid by ether in a continuous liquid–liquid extractor, and evaporation of the hydrochloric acid solution to near-dryness. Trituration with acetone, followed by prolonged drying in a vacuum desiccator, afforded 57.8 g. (0.334 mole) (93.5%) of greenish, hygroscopic crystals of homopiperazine dihydrochloride.

This hydrochloride was dissolved in a small amount of water and treated cautiously with a concentrated solution of 35 g. (0.87 mole) of sodium hydroxide. The alkaline solution was then distilled from a 500-ml. round-bottomed flask, which was attached by a spray trap to a condenser, the last part of the distillation being carried out under reduced pressure. Acidification of the distillation residue and subsequent treatment with picric acid yielded a recovery of 10.6 g. (0.019 mole) of homopiperazine picrate. Therefore, the aqueous distillate is believed to have contained 0.315 mole of homopiperazine; it was used directly in the preparation of the 1-(2-hydroxyethyl) derivative described subsequently.

1,4-Dimethylhomopiperazine (XIV). Method A.—Homopiperazine (11 g.) was methylated by the general procedure,[11] using 100 ml. of 88% formic acid and 75 ml. of 37% formalin. After 16 hours at mild reflux the reaction mixture was treated with 50 ml. of 37% hydrochloric acid and evaporated to dryness. The free base was released with potassium hydroxide solution and extracted with ether. Distillation of the ether solution afforded 11 g. (78%) of XIV as a colorless liquid, b.p. 158–161° (738 mm.), $n^{25}D$ 1.4582.

Anal. Calcd. for $C_7H_{16}N_2$: N, 21.85. Found: N, 21.72.

1,4-Dimethylhomopiperazine dipicrate, prepared in water and recrystallized once from water, separated as stout, orange-yellow needles, m.p. 262–263° dec. with previous sintering.

Anal. Calcd. for $C_{19}H_{22}N_8O_{14}$: C, 38.91; H, 3.78; N, 19.1. Found: C, 38.99; H, 3.61; N, 19.27.

1,4-Dimethylhomopiperazine di-2,4-dinitrophenolate was precipitated by mixing ether solutions of XIV and 2,4-dinitrophenol. Recrystallization from aqueous alcohol gave orange-yellow prisms, m.p. 184–185°.

Anal. Calcd. for $C_{19}H_{24}N_6O_{10}$: C, 45.97; H, 4.87; N, 16.93. Found: C, 46.02; H, 4.87; N, 16.96.

Method B.—1,4-Dimethylhomopiperazine dimethobromide was prepared in the following manner: A solution of 178.2 g. (0.88 mole) of trimethylene bromide and 101 g. (0.87 mole) of N,N,N′,N′-tetramethylethylenediamine in 250 ml. of ethylene glycol was stirred under a reflux condenser. Brief heating at 60° caused an exothermic reaction to set in, accompanied by precipitation and an internal temperature rise to 105°. When the temperature fell below 100°, heating was applied and the temperature was maintained at 100° for another two hours. After cooling the slurry to 0°, it was diluted with 250 ml. of absolute alcohol and filtered. The filter cake of the dimethobromide was

(20) L. Bleier, *Ber.*, **32**, 1825 (1899).

thoroughly triturated with another 325 ml. of absolute alcohol and again collected on a filter; it amounted to 176 g. (63.6%), m.p. 286–286.5° dec. A portion of this salt was crystallized from 95% alcohol as white plates of unchanged m.p.

Anal. Calcd. for $C_9H_{22}Br_2N_2$: Br, 50.28. Found: Br, 50.35.

A 1.00-g. sample of this quaternary salt was placed in an upright 15-cm. test-tube, attached by its sidearm to a U-tube which was immersed in Dry Ice–acetone; the opposite arm of the U-tube was connected to a vacuum pump. The reaction tube was placed under high vacuum and heated by an oil-bath; at 250° bath temperature the pressure in the system rose from an initial 0.05 to 0.10 mm., and as the bath temperature was raised to 275° over the next 45 minutes the pressure increased to 0.15 mm. At the end of two hours at this temperature the pressure had dropped to 0.03 mm. and essentially all of the salt had decomposed.

The U-tube was then rinsed several times with ether, and the ether solutions were extracted with 2% hydrochloric acid. Treatment of the acidic extracts with 65 ml. of 0.1 *N* sodium picrate solution precipitated the dipicrate of 1,4-dimethylhomopiperazine (XIV), which was recrystallized once from water as orange-yellow needles, m.p. and mixed m.p. (with the picrate described under method A) 262–263° dec. The yield was 1.115 g. (60.5%), but solubility relationships indicate that another 6.7% was left in the mother liquors. A sample of XIV from another demethobromination was converted to the di-2,4-dinitrophenol salt (67%), m.p. 184.5–185°, unchanged by admixture with the di-2,4-dinitrophenolate of XIV described under method A.

1-(2-Hydroxyethyl)-homopiperazine.—An aqueous solution of 0.315 mole of homopiperazine (XIII), the preparation of which is described above, was diluted with an equal volume of methanol, cooled to 0° in a glass-stoppered bottle, and treated with 15 ml. (13.3 g., 0.30 mole) of ethylene oxide with immediate shaking. The tightly stoppered bottle was stored at 0° for 12 hours and then allowed to stand at room temperature for 3 days. Fractionation of the aqueous methanol solution through a 20-cm. McMahon packed column yielded: (1) some XIII, b.p. 65–70° (19 mm.), and (2) 21.90 g. (50.6%) of 1-(2-hydroxyethyl)-homopiperazine, b.p. 86.5–87° (0.15 mm.), $n^{25}D$ 1.5060. The distillation residue, which doubtless contained some 1,4-di-(2-hydroxyethyl)-homopiperazine, was not investigated. Analyses of fraction 2 were unsatisfactory due to its hygroscopic nature.

The dipicrate of 1-(2-hydroxyethyl)-homopiperazine was formed in aqueous solution and recrystallized from water as orange-yellow plates, m.p. 216.5–217.5° dec.

Anal. Calcd. for $C_{19}H_{22}N_8O_{15}$: C, 37.88; H, 3.68; N, 18.60. Found: C, 37.95; H, 3.55; N, 18.53.

1-(2-Bromoethyl)-homopiperazine (XV) Dihydrobromide.—A solution of 21.5 g. (0.149 mole) of 1-(2-hydroxyethyl)-homopiperazine in 300 ml. of 48% hydrobromic acid was heated in an all-glass apparatus and 200 ml. of the acid slowly distilled. The remaining liquid was refluxed overnight and then evaporated to dryness under reduced pressure. The residue, after trituration with acetone, weighed 54.5 g. (98%), m.p. 220–222° dec.

Anal. Calcd. for $C_7H_{17}N_2Br_3$: Br, 64.98. Found: Br, 64.30.

This bromide determination was made by the Volhard procedure after the sample had been in solution for 40 hours.

2,2-Dimethylhomopiperazine (XVI).—A charge of 173.5 g. (1.19 moles) of N-(1-hydroxy-2-methyl-2-propyl)-1,3-propanediamine,[21] 200 ml. of purified dioxane and 45 g. of copper–chromium–barium oxide catalyst[19] was placed in a 1300-ml. steel bomb, the bomb was filled to 500 p.s.i. of hydrogen, and the reaction was carried out at 200° with shaking for 8 hours. Filtration removed the catalyst, and the blue filtrate was distilled through a 30-cm. Vigreux column. The fraction collected at 50–130° (13 mm.) was worked up for XVI, while the fraction collected at 130–140° (13 mm.) contained 10 g. of recovered starting amine. Concentrated hydrochloric acid (170 ml.) was added to the first fraction, the solution evaporated to near-dryness, triturated with acetone, and filtered. Recrystallization of these crude crystals from alcohol yielded (in two crops) 61.75 g. (25.9%) of stout white needles of the **dihydrochloride of XVI**, m.p. 269–271.5° dec.

Anal. Calcd. for $C_7H_{18}Cl_2N_2$: Cl, 35.25. Found: Cl, 35.08.

The residue obtained by evaporation of the mother liquors was combined in aqueous solution with the oil previously removed by filtration. This solution was cooled to 10° and treated with an excess of cold sodium nitrite solution to yield, after cooling overnight, 7.90 g. (3.6%) of **1,4-dinitroso-2,2-dimethylhomopiperazine**, m.p. 75–83°. Recrystallization from water afforded pale cream-colored crystals, m.p. 85–86°.

Anal. Calcd. for $C_7H_{14}N_4O_2$: C, 45.15; H, 7.58. Found: C, 45.12; H, 7.54.

The total hydrochloride and nitroso derivatives of XVI amounted to a 29.5% yield.

1,2,2,4-Tetramethylhomopiperazine (XVIa).—2,2-Dimethylhomopiperazine (XVI) dihydrochloride (18.24 g., 0.0907 mole) was allowed to react for 45 hours with 75 ml. of 88% formic acid and 30 ml. (0.4 mole) of formalin by the general method of Clarke, Gillespie and Weisshaus.[11] A yield of 12.65 g. (89.1%) of XVIa, b.p. 74–76° (20 mm.), $n^{25}D$ 1.4628, as a colorless oil was obtained.

Anal. Calcd. for $C_9H_{20}N_2$: C, 69.17; H, 12.90. Found: C, 69.10; H, 12.82.

By treating the distillation residue and column washings with picric acid 0.9 g. (1.6%) of **1,2,2,4-tetramethylhomopiperazine dipicrate** was obtained. One recrystallization from 50% alcohol gave short, yellow needles, m.p. 229–230° dec. with previous sintering.

Anal. Calcd. for $C_{21}H_{26}N_8O_{14}$: N, 18.24. Found: N, 17.90.

1,2,2,4-Tetramethylhomopiperazine dihydrochloride was prepared by evaporating a hydrochloric acid solution of XVIa and twice recrystallizing the residue from alcohol containing a small amount of water; it was obtained as white prisms, m.p. 275–276° dec.

Anal. Calcd. for $C_9H_{22}Cl_2N_2$: Cl, 30.94. Found: Cl, 30.4.

2-(2-Ethoxyethylamino)-2-methyl-1-propanol.—A mixture of 437 g. (2.86 moles) of 2-ethoxyethyl bromide[22] and 479.5 g. (5.38 moles) of 2-amino-2-methyl-1-propanol was heated on a steam-bath for 60 hours. The cooled semi-solid material was treated with a solution of 120 g. (3 moles) of sodium hydroxide in 210 ml. of water and was then freed of water by azeotropic distillation with benzene. Salts were removed by filtration and the filtrate was fractionally distilled through a 20-cm. McMahon packed column to give the following fractions: (1) b.p. 76–78° (17 mm.), 320 g. of recovered 2-amino-2-methyl-1-propanol; (2) b.p. 76–112° (17 mm.), 72.5 g. of intermediate; and (3) b.p. 112–117° (17 mm.), 230 g. (50%) of product. A high-boiling residue was not investigated. Refractionation of fraction 3 yielded essentially pure material as a colorless, viscous oil, b.p. 97–100° (8 mm.), $n^{25}D$ 1.4464.

Anal. Calcd. for $C_8H_{19}NO_2$: C, 59.59; H, 11.88; neut. equiv., 161. Found: C, 59.38; H, 12.03; neut. equiv., 164.

Another 23 g. (5%) of this product was obtained by refractionation of fraction 2.

N-(2-Ethoxyethyl)-N-(1-hydroxy-2-methyl-2-propyl)-1,3-propanediamine.—A mixture of 40.1 g. (0.755 mole) of freshly distilled acrylonitrile and 121.8 g. (0.755 mole) of 2-(2-ethoxyethylamino)-2-methyl-1-propanol was heated under reflux at 95–100° for 48 hours. The crude adduct so formed was dissolved in 200 ml. of ether. This solution was chilled in an ice–salt-bath and then placed in a 1300-ml. steel bomb which had been precooled in Dry Ice; Raney nickel catalyst (10 g.) and liquid ammonia (75 ml.) were added, the bomb was filled to 1350 p.s.i. with hydrogen, and the reduction was carried out at 100° for three hours.

After removal of the catalyst by filtration, fractionation through a 30-cm. Vigreux column afforded: (1) b.p. 70–76° (0.7 mm.), $n^{25}D$ 1.4463, 44.85 g. of recovered secondary amine; (2) b.p. 76–116° (0.7 mm.), $n^{25}D$ 1.4590, 13.0 g. of intermediate; and (3) b.p. 118–120° (0.75 mm.), $n^{25}D$ 1.4714, 79.2 g. of product as a colorless, viscous oil.

Anal. Calcd. for $C_{11}H_{26}N_2O_2$: C, 60.51; H, 12.00; N,

(21) G. B. Bachman and R. L. Mayhew, *J. Org. Chem.*, **10**, 243 (1945).

(22) G. C. Harrison and H. Diehl, *Org. Syntheses*, **23**, 32 (1943).

12.83; neut. equiv., 109.17. Found: C, 60.49; H, 12.12; N, 12.50; neut. equiv., 110.5.

The intermediate fraction appeared to be a binary mixture of starting material and product, so its refractive index was used to calculate the relative amounts of these constituents. On this basis the total recovery of secondary amine was 51.3 g. (42%) and the total amount of product was 85.7 g. (52% conversion, 89.5% yield, based on unrecovered starting material).

1-(2-Ethoxyethyl)-2,2-dimethylhomopiperazine.—A 1300-ml. steel bomb, in which a charge of 61.8 g. of N-(2-ethoxyethyl)-N-(1-hydroxy-2-methyl-2-propyl)-1,3-propanediamine, 20 g. of copper–chromium–barium oxide catalyst[19] and 250 ml. of purified dioxane had been placed, was filled to 200 p.s.i. with hydrogen and shaken for 8 hours at 200°.

Two such runs were combined, filtered and the catalyst washed with alcohol. Fractionation through a 20-cm. McMahon packed column yielded, after removal of solvent: (1) 34 g. of forerun, b.p. 85–112° (8 mm.), $n^{25}D$ 1.4550; (2) 37.0 g. of product, b.p. 112–114° (8 mm.), $n^{25}D$ 1.4680; (3) 8.0 g. of intermediate fraction, b.p. 114–130° (8 mm.), $n^{25}D$ 1.4620; and (4) residue. A portion of fraction 2 was analyzed.

Anal. Calcd. for $C_{11}H_{24}N_2O$: C, 65.95; H, 12.06; N, 13.99. Found: C, 65.82; H, 12.19; N, 13.75.

Fractions 1 and 3 were dissolved in 10% hydrochloric acid, and this solution was treated at 0° with a cold aqueous solution of excess sodium nitrite. After the nitrosation mixture had stood for 24 hours at 0–5°, it was made basic with sodium carbonate and extracted with ether; the combined dried ether extract was saturated with dry hydrogen chloride, precipitating crude **1-(2-ethoxyethyl)-4-nitroso-2,2-dimethylhomopiperazine hydrochloride**. The crude hydrochloride was triturated in absolute alcohol and then recrystallized from absolute alcohol, giving 9.30 g. of cream-colored prisms, m.p. 215–216° dec.

Anal. Calcd. for $C_{11}H_{24}ClN_3O_2$: C, 49.71; H, 9.10; N, 15.81; Cl, 13.34. Found: C, 49.94; H, 9.26; N, 15.73; Cl, 13.20.

Distillation of the fractionation residue 4 yielded 12.4 g. (10%) of recovered starting material.

1-(2-Bromoethyl)-2,2-dimethylhomopiperazine (XVII) Dihydrobromide.—Prelog's general procedure[23] for cleaving ethers was used. A solution of 2.10 g. of 1-(2-ethoxyethyl)-2,2-dimethylhomopiperazine in 14 ml. of 48% hydrobromic acid was saturated with hydrogen bromide at 5°, sealed in a bomb tube, and heated for 8 hours at 100°. The solvent was removed under reduced pressure and the residue triturated in acetone to yield directly 3.10 g. of grayish-white salt of XVII; another 0.60 g. of this salt precipitated from the acetone upon standing. The m.p. of the latter was 285–286° dec.; the total yield was 3.70 g. (89%).

Anal. Calcd. for $C_9H_{21}N_2Br_3$: C, 27.23; H, 5.33; N, 7.06; Br, 60.39. Found: C, 27.71; H, 5.37; N, 7.04; Br, 60.1.

Bromine was determined by the Volhard method after the sample had been in aqueous solution for 24 hours; samples titrated directly after dissolution in water gave values for bromide which were 4–6% low.

This salt of XVII could be prepared equally readily from the hydrochloride of 1-(2-ethoxyethyl)-4-nitroso-2,2-dimethylhomopiperazine, the procedure varying from the above only in that the nitroso group was hydrolyzed off by heating in 48% hydrobromic acid at 120° for 1 hour before the solution was cooled and saturated with hydrogen bromide. A 92% yield of the salt of XVII, m.p. 289–290° dec., was thus obtained from the nitroso compound.

General Procedure for the Preparation of Diazabicyclo and Tetrazatricyclo Compounds by Pyrolysis of the Hydrobromides of N-(2-Bromoethyl)-piperazines and Homopiperazines.—The salt was pyrolyzed in a flask at a bath temperature slightly above its melting (decomposition) point. To ensure complete reaction, lumps were crushed up with a tamper when necessary; only with the larger batches was mechanical stirring with a Hershberg stirrer used.

When the reaction appeared to be complete (as evidenced by rate of gas evolution) the brown-black mixture was cooled and benzoylated by the following efficient procedure of Hromatka[1,8]: A little water, 100–400 ml. of thiophene-free benzene and a several-fold excess of benzoyl chloride were added to the batch, and the resulting mixture was stirred or shaken vigorously at room temperature while small portions of 10% sodium hydroxide solution were added. Benzoylation was considered complete when a slight excess of the base over that required to maintain alkalinity to phenolphthalein had been added and the odor of benzoyl chloride could no longer be detected.

The benzoylation mixture was then suction-filtered to remove tars, and the filter cake was washed well with water. The filtrate was acidified with slightly more hydrochloric acid than necessary to reach the congo red end-point and, after thorough shaking, the layers were separated. After the aqueous layer had been extracted several times with thiophene-free benzene and/or ether, it was made alkaline, filtered and steam distilled into hydrochloric acid so long as the distillate was basic to litmus (or at least until several hundred milliliters of distillate had been collected). The acidified steam distillate was evaporated to dryness under reduced pressure to leave the hydrochlorides of steam-volatile tertiary amines as *fraction 1*.

Generally, the steam-distillation still residue was diluted, filtered, acidified to congo red, refiltered to remove silicic acid and then heated with an excess of picric acid or sodium picrate solution. Upon cooling, the picrates of non-steam-volatile tertiary amines separated and were collected by filtration as *fraction 2*.

The organic solutions from the benzoylation work-up were combined and thoroughly extracted with dilute sodium hydroxide and water, decolorized by Norit if necessary, and evaporated to dryness on the steam-bath. The residue so obtained was triturated with ether and filtered to collect any dibenzoyl derivatives of piperazines or homopiperazines as *fraction 3*. Such dibenzoyl derivatives are essentially insoluble in ether.

Pyrolysis of 1-(2-Bromoethyl)-piperazine (I) Dihydrobromide, Triethylenediamine (XVIII) and Hexaethylenetetramine (XXII).—(a) Pyrolysis of 0.56 g. of this dihydrobromide for one-half hour at 235–265°, benzoylation with 3 ml. of benzoyl chloride and work-up of the benzoylation mixture were carried out according to the general procedure.

Fraction 1 was made basic with 50% sodium hydroxide solution and extracted with four 15-ml. portions of ether. The dried ether extract was filtered into an ether solution containing a slight excess of *p*-nitrophenol; the resulting slurry of crystals was concentrated to near-dryness, triturated in a little ether, filtered and washed with ether to yield 0.182 g. (29.5%) of light yellow triethylenediamine di-(*p*-nitrophenolate), m.p. 182.5–184° (reported[3] m.p. 184–185°).

No attempt was made to obtain a fraction 2 from this experiment, but a fraction 3 of 0.24 g. (51%) of 1,4-dibenzoylpiperazine, m.p. 193–194° (reported[1] m.p. 194°), was isolated.

(b) To test the efficiency of pyrolysis of larger amounts of the salt of I, 11.2 g. was pyrolyzed with mechanical stirring at 240–250° for one-half hour; it changed to a brown-black gum. Benzoylation with two 12-ml. portions of benzoyl chloride and work-up of the benzoylation mixture were conducted by the general procedure.

Fraction 1 was processed as above to yield 3.34 g. (27.1%) of triethylenediamine (XVIII) di-(*p*-nitrophenolate), m.p. 182.5–183.5°. Fraction 3 consisted of 2.7 g. (29%) of 1,4-dibenzoylpiperazine, and fraction 2 was recrystallized once from water to give 1.8 g. (10%) of **hexaethylenetetramine (XXII) tetrapicrate**, m.p. 275° dec. with extensive previous sintering, reported[2] m.p. 277° dec. Part of this tetrapicrate after two recrystallizations from water was obtained as yellow-orange needles that melted at 275° dec.

Anal. Calcd. for $C_{36}H_{36}N_{16}O_{28}$: C, 37.90; H, 3.18; N, 19.65. Found: C, 37.50; H, 3.31; N, 19.28.

Pyrolysis of 1,4-Di-(2-bromoethyl)-piperazine (II) Dihydrobromide.—The thermal decomposition of 38.5 g. of this salt was initially conducted with mechanical stirring at 255–260°, but after 90 minutes the melt had resolidified to a hard glass, causing the stirrer to break. After an additional two hours of heating at 260–275° without stirring the dark mixture was benzoylated with 85 ml. of benzoyl chloride by the general procedure and worked up.

From fraction 1 5.34 g. (17%) of triethylenediamine (XVIII) di-(*p*-nitrophenolate), m.p. 182–183°, was obtained.

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

Fraction 2 consisted of 2 g. (4.3%) of the picrates of non-steam-volatile amines; this picrate sample melted at 250–252° dec. and its melting point was not raised by recrystallization from water, which indicates that it is not hexaethylenetetramine tetrapicrate (reported[2] m.p. 277° dec., found in this work 275°).

Fraction 3 proved to be 1,4-dibenzoylpiperazine, m.p. 191–192°, raised to 192–193° upon admixture with an authentic sample. The yield was 6.80 g. (28.5%).

Pyrolysis of 1-(2-Bromoethyl)-2,2,5,5-tetramethylpiperazine (VIII) Dihydrobromide; 2,2,5,5-Tetramethyl-1,4-diazabicyclo[2.2.2]octane (XIX).—Pyrolysis of 3.05 g. of this salt for 1 hour at 290–297°, during which the melt was crushed once with a glass rod, benzoylation with 10 ml. of benzoyl chloride, and work-up of the benzoylation mixture were carried out by the general procedure.

Fraction 1 was rebenzoylated with 9 ml. of benzoyl chloride by the same procedure and worked up in the same way. The new fraction 1 was treated with 10 ml. of 0.1 *N* sodium picrate solution, and the resulting picrate was crystallized from 40 ml. of water to yield 7 mg. (0.15%) of yellow platelets of 2,2,5,5-tetramethyl-1,4-diazabicyclo[2.2.2]octane (XIX) dipicrate, m.p. 250.5° dec.

Anal. Calcd. for $C_{22}H_{26}N_8O_{14}$: C, 42.17; H, 4.18; N, 17.89. Found: C, 42.39; H, 4.52; N, 17.88.

No fraction 2, *i.e.*, no picrate of a non-steam-volatile tertiary amine, could be isolated.

The total yield of 1,4-dibenzoyl-2,2,5,5-tetramethylpiperazine,[6] m.p. 281–282° (uncor.), from fraction 3 and from benzene extraction of the benzoylation insolubles was 2.08 g. (80%); this compound is sparingly soluble in benzene.

Several other small-scale pyrolyses of the dihydrobromide of VIII, conducted under essentially the same conditions, gave yields of 0.1–0.5% of the dipicrate of XIX.

Pyrolysis of 1-(2-Bromoethyl)-homopiperazine (XV) Dihydrobromide; 1,5-Diazabicyclo[3.2.2]nonane (XX) and 1,4,8,11-Tetrazatricyclo[9.3.2.2^{4,8}]octadecane (XXIII).—During the first part of the pyrolysis of 53.3 g. of this salt of XV at 235–245° mechanical stirring was necessary to prevent frothing out of the sticky melt, but after 90 minutes the melt had again become quite hard and was caked against the sides of the flask so that stirring no longer was effective. Nevertheless, the pyrolysis was continued for another 3.5 hours since hydrogen bromide was still being evolved. Benzoylation with 72 ml. of benzoyl chloride and work-up of the benzoylation mixture were conducted by the general procedure.

Fraction 1 was triturated in water to give 8.64 g. (30%) of colorless **1,5-diazabicyclo[3.2.2]nonane (XX) dihydrochloride**; one recrystallization from water gave analytically pure material, m.p. 308° dec.

Anal. Calcd. for $C_7H_{16}Cl_2N_2$: C, 42.22; H, 8.10; Cl, 35.61; N, 14.07. Found: C, 42.29; H, 7.83; Cl, 35.49; N, 14.18.

Fraction 2 consisted of 3.1 g. (3.7%) of the crude **tetrapicrate of XXIII**; one recrystallization from water gave fine, yellow crystals, m.p. 236.5–237.5° dec. with previous sintering.

Anal. Calcd. for $C_{36}H_{40}N_{16}O_{28}$: C, 39.05; H, 3.45; N, 19.18. Found: C, 39.07; H, 3.37; N, 18.93.

Systematic fractional crystallization of fraction 3 from alcohol eventually yielded 3.82 g. (9%) of 1,4-dibenzoylpiperazine, m.p. and mixed m.p. with an authentic sample, 193–194°, and 10.63 g. (23.8%) of 1,4-dibenzoylhomopiperazine, m.p. 96–103°. A portion of the latter compound was recrystallized from water to give white plates, m.p. 106–108° (reported[20] m.p. 108°, after loss of water at 103°), after drying over sulfuric acid.

The free base XX was obtained from a concentrated aqueous solution of its hydrochloride by treatment with an excess of strong potassium hydroxide solution and extraction with five 35-ml. portions of thiophene-free benzene. After the benzene had been removed from the extract through a 20-cm. McMahon packed column, a distillation of the residue was attempted; at a bath temperature of 110–140° and 22 mm. pressure the product distilled up into the still head, where it solidified on the cold finger. The yield of XX thus obtained amounted to 45%. After resublimation from sodium at 45–70° (22 mm.), it was obtained as stout, white needles, m.p. 89–92°.

Anal. Calcd. for $C_7H_{14}N_2$: C, 66.62; H, 11.18; mol. wt., 126.20. Found: C, 64.96; H, 10.82; mol. wt., 119 (cryoscopic in benzene).

This base is extremely hygroscopic, a fact which probably explains the poor elemental analyses.

1,5-Diazabicyclo[3.2.2]nonane (XX) di-*p*-nitrophenolate was prepared by adding an ether solution of XX to an excess of *p*-nitrophenol in ether solution. Most of the ether was evaporated from the crystals of the *p*-nitrophenolate, which were then collected on a filter and washed with ether, m.p. 116.5–117°. One recrystallization from absolute alcohol gave stout, yellow prisms of unchanged melting point.

Anal. Calcd. for $C_{19}H_{24}N_4O_6$: C, 56.43; H, 5.98; N, 13.85. Found: C, 56.34; H, 5.86; N, 13.72.

In like manner an ether solution of XX was added to an ether solution of excess 2,4-dinitrophenol to form a precipitate of **1,5-diazabicyclo[3.2.2]nonane di-2,4-dinitrophenolate.** The ether was decanted and the precipitate was recrystallized once from absolute alcohol, giving orange prisms, m.p. 169–170°.

Anal. Calcd. for $C_{15}H_{22}N_6O_{10}$: C, 46.15; H, 4.49; N, 17.00. Found: C, 45.75; H, 4.54; N, 16.92.

1,5-Diazabicyclo[3.2.2]nonane dipicrate was prepared from both XX and its hydrochloride, crystallizing from water as bright yellow prisms. Four recrystallizations from water raised the m.p. from 258.5–259.5° to 260–261° dec.

Anal. Calcd. for $C_{19}H_{20}N_8O_{14}$: C, 39.05; H, 3.45; N, 19.18. Found: C, 39.04; H, 3.60; N, 19.02.

1,5-Diazabicyclo[3.2.2]nonane Dimethobromide—. Methyl bromide (2 ml.) was added to a bomb tube containing an ice-cold solution of 0.2 g. of XX in 95% alcohol; the tube was sealed and heated for 10 hours at 80°. The residue obtained by evaporating the contents of the tube was twice recrystallized from alcohol to yield colorless, hygroscopic prisms, m.p. 252–253° dec.; a mixture melting point with a sample prepared from ethylene bromide and 1,4-dimethylhomopiperazine (see below) was unchanged.

The dimethobromide was converted to the dimethopicrate of XX by treatment with 0.1 *N* sodium picrate solution. Recrystallization from water gave yellow platelets, m.p. 279–280° dec., which melted without depression upon admixture with the **1,5-diazabicyclo[3.2.2]nonane dimethopicrate** described below.

A pyrolysis of 1 g. of the dihydrobromide of XV at 235–245° for only 2 hours afforded 43% of the dipicrate of XX and 11% of the tetrapicrate of XXIII.

Pyrolysis of 1-(2-Bromoethyl)-2,2-dimethylhomopiperazine (XVII) Dihydrobromide; 6,6-Dimethyl-1,5-diazabicyclo[3.2.2]nonane (XXI) Dipicrate.—Four equivalent portions of the salt of XVII, totaling 3.9 g., were separately pyrolyzed for an hour at 280–295°. They were then combined and benzoylated with 10 ml. of benzoyl chloride and worked up by the general procedure.

Fraction 1 was heated with 50 ml. of water and 100 ml. of 0.1 *N* sodium picrate solution, but the resulting picrate did not entirely dissolve. This slurry of crystals was cooled and filtered, giving a picrate, m.p. 241–242° dec. One recrystallization of this material from 300 ml. of water gave 0.640 g. (10.6%) of **6,6-dimethyl-1,5-diazabicyclo[3.2.2]nonane dipicrate** (XXI) as small, lemon yellow prisms, m.p. 241.5–242.5° dec.

Anal. Calcd. for $C_{21}H_{24}N_8O_{14}$: C, 41.18; H, 3.95; N, 18.30. Found: C, 41.48; H, 3.87; N, 18.05.

Since a second crop of this picrate proved to be less pure, it and all of the picrate mother liquors were combined, made basic and steam distilled into hydrochloric acid. The amine hydrochloride which was obtained from this steam distillate by evaporation was rebenzoylated and worked up. Fraction 1 from this rebenzoylation was treated with sodium picrate solution, and the resulting picrate was recrystallized from water: two crops, totaling 0.145 g. (2.4%) of the dipicrate of XXI, m.p. 241.5–242.5° dec., were collected. The total yield of this picrate salt amounted to 0.785 g. (13.0%).

No crystalline fraction 2 or 3 could be obtained from this experiment.

When 62.5 g. of this salt of XVII was pyrolyzed with stirring at 290–310° for 90 minutes and worked up in a manner similar to the small-scale run, only about 0.5% of a steam-volatile tertiary amine was obtained; furthermore, the picrate of this amine was not the picrate of XXI (de-

pressed melting point), although repeated recrystallizations from water did raise its m.p. to 241.5–242.5° dec. and probably would have raised it even higher had such recrystallizations been continued). In contrast to the small-scale runs, also, a 44% yield of (uncharacterized) dibenzoyl derivatives, m.p. 125–130°, was obtained.

6,6-Dimethyl-1,5-diazabicyclo[3.2.2]nonane (XXI) was prepared from 0.952 g. of its picrate in the following manner. The picrate was placed in a 125-ml. erlenmeyer flask with 15 ml. of 37% hydrochloric acid and 25 ml. of water, and this mixture was extracted repeatedly with ether until essentially all of the picric acid had been extracted. The aqueous solution was then evaporated to dryness, the residual hydrochloride of XXI was treated with concentrated potassium hydroxide solution and extracted with three 10-ml. portions of ether. After thorough drying over potassium hydroxide pellets the ether solution was decanted into a 20-cm. test-tube, several small pieces of sodium were added, and the ether was removed by slow distillation (maximum bath temperature 110°). Evaporative distillation of the residue at 80–100° (20 mm.) gave XXI as a colorless, viscous oil, which was quite hygroscopic.

Anal. Calcd. for $C_9H_{18}N_2$: C, 70.07; H, 11.76; N, 18.17; mol. wt., 154.25. Found: C, 69.37; H, 11.66; N, 17.46; mol. wt., 176 (micro-Rast).

6,6-Dimethyl-1,5-diazabicyclo[3.2.2]nonane (XXI) di-2,4-dinitrophenolate was prepared by dissolving the remainder of the free base (XXI) in ether and adding this solution to an ether solution of 0.5 g. of 2,4-dinitrophenol. The precipitated 2,4-dinitrophenolate was recrystallized twice from absolute alcohol as small, yellow-orange prisms, m.p. 138–140°.

Anal. Calcd. for $C_{21}H_{26}N_6O_{10}$: C, 48.27; H, 5.02; N, 16.09. Found: C, 48.58; H, 4.91; N, 16.14.

Pyrolysis of 1-(3-Bromopropyl)-piperazine (VI) Dihydrobromide.—Pyrolysis of 3.5 g. of this salt at 220–237° for 5 hours, subsequent benzoylation with 10 ml. of benzoyl chloride, and the processing of the benzoylation mixture were conducted by the general procedure.

Thus, a fraction 3 was obtained, which consisted of 1.25 g. (45%) of 1,4-dibenzoylpiperazine, m.p. and mixed m.p. 193–194°.

Fraction 1, containing the hydrochlorides of steam-volatile tertiary amines, was recycled through the benzoylation and benzoylation work-up step; the reprocessed fraction 1 was then heated with 10 ml. of 0.1 *N* sodium picrate solution and sufficient water to effect solution. Cooling yielded 31 mg. (0.56%) of picrate, m.p. 240–241° dec., and concentration afforded a smaller second crop of the same melting point. The two crops were combined and recrystallized twice from water, giving small, yellow needles, m.p. 241.5–242° dec.; the melting point on admixture with authentic 1,5-diazabicyclo[3.2.2] nonane dipicrate of m.p. 260.5–261° dec. was not significantly raised. It appears doubtful, therefore, that any of the latter compound is present in the picrate from this experiment.

Fraction 2, containing the picrates of non-steam-volatile tertiary amines, was twice recrystallized from water to yield 1 g. (18%) of yellow platelets of constant m.p. 268.5–269.5° dec., which were thought to be the tetrapicrate of the dimer corresponding to XXIII. Analyses, however, did not verify this conclusion. Nothing further was done with this picrate.

Anal. Calcd. for $C_{38}H_{40}N_{16}O_{28}$: C, 39.05; H, 3.45; N, 19.18. Found: C, 37.68, 37.77; H, 3.52, 3.65; N, 19.34.

Reaction of 1,4-Disubstituted Piperazines and Homopiperazines with Ethylene Bromide. (a) 1,4-Dimethylpiperazine. Dimethobromide of XVIII and Its Demethobromination.—Heating 4.15 g. of 1,4-dimethylpiperazine[24] and 6.83 g. of ethylene bromide in 10 g. of ethylene glycol at 100°, according to the procedure of Hromatka and Kraupp,[3] yielded, after one recrystallization from alcohol, 66% of the quaternary salt, m.p. 298–300° dec., compared with the 70% yield of product that these authors reported. Demethobromination of 1 g. of this salt by the method of Hromatka and Kraupp[3] gave 60% of triethylenediamine (I), isolated as the dipicrate, m.p. 297–298° dec.

(b) **1,4-Dibenzylpiperazine (IV).**—A mixture of 6.66 g. (0.025 mole) of IV, 4.70 g. (0.025 mole) of ethylene bromide, and 15 ml. of distilled ethylene glycol was heated at 110° under reflux for 44 hours; the dibenzylpiperazine initially melted to a lower, immiscible layer, and the reaction mixture did not become homogeneous until it had been heated overnight. The red reaction mixture was then cooled, and, since no crystallization took place, it was poured into 60 ml. of absolute alcohol, causing an immediate precipitation. The colorless crystals (3.44 g.) thus formed were collected on a filter, washed with alcohol and dried. Elemental analysis of this material and regeneration of pure IV, m.p. 90.8–91.3°, from it in 93% yield by neutralization at room temperature indicated that it was the partially solvated dihydrobromide of IV; the yield of this dihydrobromide thus was 31%.

Anal. Calcd. for $C_{18}H_{24}Br_2N_2 \cdot {}^1/_3C_2H_5OH$: Br, 36.03. Found: Br, 35.90.

No evidence was found for the presence of any bridged diquaternary salt.

(c) **1,2,2,4,5,5-Hexamethylpiperazine (IX).**—To the top of a reflux condenser was attached a train of three 20-cm. test-tubes: the first of these was cooled by a Dry Ice–acetone-bath, the second served as a safety trap, and the third contained a freshly prepared ammoniacal solution of silver nitrate.

A flask containing a solution of 10.21 g. (0.06 mole) of IX in 11.27 g. (0.06 mole) of ethylene bromide was attached to this reflux condenser and heated at a bath temperature of 150–155° for 8 hours; as the temperature was raised to this point, cloudiness first appeared at 100°. Although there was still considerable liquid left at the end of this time, the reaction mixture was cooled and triturated several times with ether.

From the ether filtrates 9.39 g. (64.4%) of the dihydrochloride of IX was obtained by acidification with hydrochloric acid and evaporation to dryness.

The fine gray solid from the ether trituration, after drying in a vacuum desiccator, assayed 38.3% of bromine (Volhard). It was triturated twice in 50-ml. portions of cold absolute alcohol to leave 3.58 g. (18.0%) of the **dihydrobromide of IX** (Found: Br, 47.89); one recrystallization of this solid from alcohol gave colorless crystals, m.p. > 265°.

Anal. Calcd. for $C_{10}H_{24}Br_2N_2$: C, 36.16; H, 7.28; Br, 48.12. Found: C, 36.21, 36.35; H, 7.33, 7.56; Br, 48.13.

Further proof of the identity of these crystals was afforded by neutralizing a sample, steam-distilling the free amine, and converting it to the dihydrochloride of IX.

Anal. Calcd. for $C_{10}H_{24}Cl_2N_2$: Cl, 29.15. Found: Cl, 29.15.

From the cold trap 1.5 g. of vinyl bromide was obtained, but no precipitate appeared in the tube containing the ammoniacal silver nitrate solution either during the reaction or when the system was finally flushed with nitrogen.

(d) **1,4-Dibenzyl-2,2,5,5-tetramethylpiperazine (X).**—In the same apparatus as described in (c), a mixture of 6.34 g. (0.02 mole) of X and 3.69 g. (0.02 mole) of ethylene bromide was heated under reflux at a bath temperature of 130–140° for 4 days. The reaction mixture, which had lost 0.76 g. in weight, was triturated, successively, with 40 ml. of absolute alcohol, five 40-ml. portions of ether, and several 30-ml. portions of boiling 60–68° petroleum ether. Evaporation of the combined organic solutions yielded 0.48 g. (7.6%) of unchanged X, while the solid from the trituration proved to be the **dihydrobromide of X**, 7.00 g. (73.5%), m.p. 244–246°; one recrystallization from water gave colorless plates, m.p. 246.5–248°.

Anal. Calcd. for $C_{22}H_{32}Br_2N_2$: C, 54.55; H, 6.66; Br, 33.00; N, 5.79. Found: C, 54.55; H, 6.71; Br, 32.84; N, 5.73, 5.54.

Neutralization of a portion of this salt in aqueous solution precipitated X in high yield.

The yield of vinyl bromide from this reaction, if calculated as equivalent to the loss of weight, was 36%. Actually, only 27% of the theoretical yield of vinyl bromide was found in the cold trap, but, since no acetylene was detected by the ammoniacal silver nitrate solution, it seems probable that the entire loss in weight was due to loss of vinyl bromide. No evidence for a bridge diquaternary salt was found.

(e) **1,4-Dicarbethoxy-2,2,5,5-tetramethylpiperazine (XI).**—A flask, containing a mixture of 9.49 g. (0.05 mole) of ethylene bromide and 14.39 g. (0.05 mole) of XI, was attached by a cork stopper to a reflux condenser; the mixture was then heated at reflux for 4 days (maximum bath tem-

(24) H. W. Stuart, *et al.*, *J. Org. Chem.*, **13**, 134 (1948).

perature 187°). During this time the reaction mixture solidified and lost 9.62 g. in weight.

It was then refluxed with 17 ml. of 37% hydrochloric acid for a day, made alkaline with sodium hydroxide solution and steam distilled; the basic steam distillate was acidified with hydrochloric acid and concentrated to dryness under reduced pressure. The residue so obtained was subjected to a Hinsberg separation in which only the fraction which should contain tertiary amines was further investigated; this fraction solidified upon standing and was then recrystallized from alcohol–water to give material of m.p. 67–70°. Three additional recrystallizations from aqueous alcohol gave colorless plates of constant m.p. 72.5–73.5°. Analysis of this material, which included a qualitative test for sulfur, indicated that it was the **benzenesulfonyl derivative** of **1-ethyl-2,2,5,5-tetramethylpiperazine**. The yield was 2.5 g. (16%); it seems very likely that 1,4-diethyl-2,2,5,5-tetramethylpiperazine was also a constituent of the tertiary amine fraction but was lost during the recrystallization of this sulfonamide.

Anal. Calcd. for $C_{16}H_{26}N_2O_2S$: C, 61.96; H, 8.44; N, 9.02. Found: C, 61.90; H, 8.43; N, 8.80, 8.90.

(f) **1,4-Di-(2-carbethoxyethyl)-2,2,5,5-tetramethylpiperazine (XII).**—A mixture of 5.00 g. (0.015 mole) of XII and 2.74 g. (0.015 mole) of ethylene bromide was heated under reflux at 92–98° for 10 days, and the solid residue was pyrolyzed directly at a bath temperature of 230°. The distillate thus obtained weighed 2.91 g., $n^{25}D$ 1.4172, and was estimated on the basis of its refractive index to contain 2.58 g. (88.5%) of ethyl acrylate and 0.33 g. (12%) of unchanged ethylene bromide; fractional distillation indicated that these two compounds were, indeed, the only components of the pyrolysis distillate.

The pyrolysis residue of 4.14 g. was benzoylated by the Schotten–Baumann procedure, giving 1,4-dibenzoyl-2,2,5,5-tetramethylpiperazine, m.p. 274–280°. Distillation of the benzoylation filtrate yielded a non-basic distillate, indicating the absence of the tertiary amine XIX.

(g) **1,4-Dimethylhomopiperazine (XIV); 1,5-Diazabicyclo[3.2.2]nonane Dimethobromide.**—A solution of 2.80 g. (0.022 mole) of XIV and 4.10 g. (0.022 mole) of freshly distilled ethylene bromide in 9 g. of ethylene glycol (b.p. 197°) was heated under a reflux condenser at 100–105° for six hours. Upon cooling, no precipitate formed; dilution with 30 ml. of absolute alcohol also failed to induce crystallization, but further dilution with 250 ml. of acetone did precipitate out a colorless solid. The solid was collected on a filter, but rapidly liquefied as it absorbed water; another crop of oily solid was obtained by diluting the mother liquors with ether, and the two crops were then combined and recrystallized six times from absolute alcohol to give 2.97 g. (43%) of colorless, extremely hygroscopic prisms of the quaternary salt, m.p. 255–256° dec.

Anal. Calcd. for $C_9H_{20}N_2Br_2$: Br, 50.57. Found: Br, 49.73.

1,5-Diazabicyclo[3.2.2]nonane dimethopicrate was prepared by treating an aqueous solution of the dimethobromide with an excess of 0.1 *N* sodium picrate solution. Recrystallization from water gave lemon-yellow platelets, m.p. 278–279.5° dec.

Anal. Calcd. for $C_{21}H_{24}N_8O_{14}$: C, 41.18; H, 3.95; N, 18.30. Found: C, 41.12; H, 3.99; N, 17.97.

(h) **1,2,2,4-Tetramethylhomopiperazine (XVIa).**—A solution of 1.88 g. (0.01 mole) of ethylene bromide and 1.56 g. (0.01 mole) of XVIa was refluxed in 30 ml. of absolute alcohol for 16 days. After 10 days of refrigeration had failed to induce crystallization the solution was poured into 400 ml. of ether, whereupon some material separated as an oil; the ether solution was immediately decanted from the oil and allowed to stand. The precipitated oil was treated with picric acid solution, yielding only the dipicrate of XVIa, m.p. 227–228° dec., raised to 228–229° dec. upon admixture with an authentic sample of the dipicrate of XVIa of m.p. 229–230° dec.

After several weeks 0.875 g. (36.7%) of **the** monohydrobromide of **XVIa** had separated from the ether solution. Its identity was shown by conversion of part of it to the dipicrate of XVIa, m.p. and mixed m.p. 229–230°, and by Volhard titration.

Anal. Calcd. for $C_9H_{21}BrN_2$: Br, 33.69. Found: Br, 33.40.

Since treatment of the ether mother liquors with excess picric acid afforded only additional dipicrate of XVIa, making the total recovery 71.7%, there was no evidence, whatsoever, that any bridged diquaternary salt had been formed.

Action of Hydrochloric Acid on 1-(2,2-Diethoxyethyl)-2,2,5,5-tetramethylpiperazine (XXIV).—A solution of 4.5 g. (0.017 mole) of XXIV in 45 ml. of cold 37% hydrochloric acid was allowed to stand at room temperature for 4 hours and was then added to 14 g. (0.12 atom) of granulated tin.[8] This mixture was heated under reflux on the steam-bath for 5 hours, made basic, and steam distilled into hydrochloric acid until the distillate was no longer basic. The acidified distillate was evaporated to dryness and the residue so obtained was benzoylated by the Schotten–Baumann procedure to yield 6.10 g. (100%) of crude **1,4-dibenzoyl-2,2,5,5-tetramethylpiperazine**, m.p. 250–270°; one recrystallization gave the pure benzoyl derivative, m.p. 281–282° (cor.). Distillation of the benzoylation filtrates afforded no basic distillate, thus showing that none of the desired bicyclic amine XIX had been formed.

As it was suspected that the above result was due to an acidic hydrolysis of the intermediate α-amino aldehyde to 2,2,5,5-tetramethylpiperazine (VII), this experiment was repeated point for point except for the addition of tin. Identical results were obtained.

Reaction of XXIV with Formic Acid.—A solution of 4.80 g. of XXIV in 60 ml. of 88% formic acid was refluxed for 9 days, and the evolved gas collected in a calibrated manostat; the rate of gas evolution rose slowly but steadily throughout this period. A total of 1600 ml. of gas was collected at 740 mm. and 25°, compared to the calculated 465 ml. of carbon dioxide for the desired reductive alkylation reaction. The gas did, indeed, give a qualitative test for carbon dioxide (precipitate formed with barium hydroxide solution), and it also burned readily with a blue flame and is believed to have been mainly hydrogen and carbon monoxide, products of the thermal decomposition of formic acid.

Half of the reaction mixture was evaporated with an excess of 37% hydrochloric acid; the residue so obtained was benzoylated and worked up as described above to yield 3.06 g. (94%) of 1,4-dibenzoyl-2,2,5,5-tetramethylpiperazine, m.p. 281–282°. No steam-volatile tertiary amine was found.

The other half of the reaction mixture was evaporated from the steam-bath under a current of air without the addition of hydrochloric acid; the residue thus obtained was subjected to the benzoylation procedure. No 1,4-dibenzoyl-2,2,5,5-tetramethylpiperazine was produced, but some steam-volatile amine was obtained. However, rebenzoylation of this steam-volatile amine gave 0.4 g. (12%) of 1,4-dibenzoyl-2,2,5,5-tetramethylpiperazine and no steam-volatile tertiary amine.

Reaction of 1,4-Di-(2,2-diethoxyethyl)-2,2,5,5-tetramethylpiperazine (XXV) with Hydrochloric Acid.—A solution of 5 g. of XXV in 50 ml. of 37% hydrochloric acid was quantitatively converted to 2,2,5,5-tetramethylpiperazine (isolated as the benzoyl derivative) when heated for 14 hours on the steam-bath. A total of 1.06 g. of a brown-black acid-insoluble powder was isolated from this experiment; this weight approaches that (1.15 g.) of the $-CH_2CHO$ units in the intermediate dialdehyde.

Pyrolysis of 1-Carbethoxymethyl-2,2,5,5-tetramethylpiperazine (XXVI).—This pyrolysis was carried out by heating 22.15 g. of XXVI in a 50-ml. round-bottomed flask, attached by standard taper joint to a 30-cm. jacket-heated Vigreux column and still-head, in a Woods metal-bath; at 190° bath temperature the first bubbling of the ester began. The bath temperature was raised to 260° and later to 275°; 2.90 g. (65%) of alcohol, $n^{25}D$ 1.3627, was collected as distillate over a period of 10 hours. The actual loss in weight of the reaction mixture was 4.48 g., corresponding to a quantitative yield of alcohol, if it is assumed all loss is due to alcohol evolution.

The residue of 17.67 g. of a dark semi-solid gum was distilled under reduced pressure through a straight take-over still-head to yield: (1) 3.0 g., b.p. 50–90° (24 mm.), a semi-solid; (2) 1.1 g. (5%) of unchanged XXVI, b.p. 125–132° (10.5 mm). $n^{25}D$ 1.4632; (3) 2.83 g., b.p. 140–150° (0.1 mm.), a semi-solid; and (4) 1.03 g., b.p. 150–172° (0.1 mm.), a viscous semi-solid (the last two fractions were distilled by heating the flask with a free flame). Residual dark, viscous material, which amounted to 52% of the reaction product, was discarded.

Fraction 1 was filtered, the filtrate (sparingly soluble in water) dissolved in 25 ml. of ether and the ether solution extracted several times with water. The ether solution then was dried over potassium hydroxide pellets. Distillation of the ether left 1.84 g. (12.2%) of a mobile oil which probably was 1,2,2,5,5-pentamethylpiperazine as it formed a viscous benzoyl derivative, which was readily soluble in dilute acid.

The solid part of fraction 1, which had the m.p. of VII, was combined with the alcohol distillate and column washings of the pyrolysis, and this combined solution benzoylated to give 1.90 g. (5.6%) of 1,4-dibenzoyl-2,2,5,5-tetramethylpiperazine, m.p. and mixed m.p. 276–279°.

Fraction 3 was triturated with 90–100° petroleum ether and filtered to give 0.3 g. (2%) of the crude dimeric amide (XXIX), m.p. 95–100°; seven recrystallizations of this material from 90–100° petroleum ether gave small, almost white crystals of constant m.p. 119–120°.

Anal. Calcd. for $C_{18}H_{36}N_4O$: C, 66.62; H, 11.18; N, 17.27. Found: C, 66.66; H, 10.70; N, 17.14.

Attempted Reductive Cyclization of XXVI.—The general method of Leonard and co-workers[10] was used as follows: A solution of 22.8 g. (0.1 mole) of XXVI, $n^{25}D$ 1.5604, and 100 ml. of purified dioxane was charged to a steel bomb with 15 g. of copper–chromium–barium oxide catalyst, and hydrogen was admitted to a pressure of 3100 p.s.i. The reaction was carried out with shaking at 250° for seven hours, during which time the pressure dropped 800 p.s.i. (calcd. for desired reaction: 541 p.s.i.).

The filtered reaction mixture was fractionated through a 20-cm. McMahon packed column at 738 mm. to give (1) 3.64 g. (25.5%) of crude 2,2,5,5-tetramethylpiperazine, b.p. 176–183°; (2) 6.74 g. of crystalline 1-(2-hydroxyethyl)-2,2,5,5-tetramethylpiperazine, b.p. 240–252°; and (3) 2.8 g. of residue.

The non-crystalline portion of fraction 1 was combined with fractions 2 and 3 and exhaustively benzoylated. No volatile tertiary amine was obtained when the benzoylation mixture was subjected to steam distillation, showing that no reductive cyclization of XXVI had occurred.

Attempted Dieckmann Condensation of 1,4-Dicarbethoxymethyl-2,2,5,5-tetramethylpiperazine (XXVII).—A solution of 16 g. (0.05 mole) of XXVII in 50 ml. of dry benzene was added dropwise to a stirred slurry of 4.5 g. (0.18 mole) of sodium hydride in 100 ml. of dry benzene over a period of 90 minutes, first at room temperature and later at reflux. During this time it was attempted unsuccessfully to start a reaction by the addition of small amounts of absolute alcohol. After an additional 5 hours at reflux the batch was cooled to 10° and treated with 10.7 ml. (11.2 g., 0.18 mole) of glacial acetic acid. Later, 100 ml. of water was added, layers were separated, and the water layer was extracted once with 100 ml. of benzene. From the dried benzene solutions a single fraction of 12 g. (75%) of unchanged XXVII was obtained by distillation, b.p. 123–127° (0.3 mm.), m.p. 61–61.5°.

Attempted Acyloin Condensation of 1,4-Di-(3-carbethoxypropyl)-2,2,5,5-tetramethylpiperazine (XXVIII).—A general procedure[25] for the acyloin condensation was used in this experiment. The apparatus consisted of a 3-l. 3-necked round-bottomed flask, equipped with a side-arm separatory funnel, thermometer, reflux condenser and a Hershberg stirrer driven by a high-speed air motor. A slow stream of nitrogen was passed through the apparatus throughout the following operations. One liter of sodium-dried xylene was placed in the reaction flask and about 100 ml. distilled to remove traces of water from the system; then 30.9 g. (0.67 mole) of a 50% emulsion (from National Distillers Chemical Corp., Cincinnati, Ohio) of sodium in xylene was added at a temperature just below reflux.

A solution of 62.0 g. (0.167 mole) of XXVIII in 550 ml. of dry xylene then was added to the vigorously stirred reaction mixture over a period of 90 minutes at 132–137°. After an additional half-hour stirring at this temperature the reaction mixture was cooled to room temperature and 5 ml. of methanol was added to destroy any excess sodium. Then 490 g. of 10% sulfuric acid (0.5 mole) was added gradually with stirring for another half-hour. Finally an excess of potassium carbonate was added and layers were separated; the aqueous layer was well extracted with ether and benzene and the combined organic solution was dried over anhydrous sodium sulfate, filtered and distilled. The only material obtained was 53 g. (85%) of the starting ester (XXVIII), b.p. 148–152° (0.18 mm.), m.p. 39–41°.

(25) M. Stoll and A. Rouve, *Helv. Chim. Acta*, **30**, 1822 (1947).

MADISON, WISCONSIN

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF CALIFORNIA AT LOS ANGELES]

Mold Metabolites. VII. The Constitution and Synthesis of a New Compound Related to Penicillin[1]

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RECEIVED JUNE 3, 1953

Treatment of residues obtained from the commercial production of penicillin with acetic anhydride and pyridine gave a new material, $C_9H_{14}N_2SO_2$. The provisional structure, 2-keto-4-acetyl-3,4,5,4′,3′,2′-(5′,5′-dimethylthiazolido)-piperazine (I), for the substance was derived from degradative experiments, and this structure was confirmed by synthesis of the substance and its degradation products. The probability that this compound is an artifact was demonstrated by its direct preparation from benzylpenilloic acid.

As an extension of earlier studies of compounds produced as by-products of commercial penicillin production,[5] the present investigation reports the isolation, determination of structure and synthesis of a new compound obtained from residues ordinarily discarded in the course of purifying the N-ethylpiperidine salt of penicillin G.[6]

Attempts to obtain crystalline compounds from these residues failed. Since the lack of solubility in organic solvents of the acids free from N-ethylpiperidine made them difficult to manipulate, the amorphous mixture of amine salts was acetylated with acetic anhydride and pyridine to give a mixture that was divided into its neutral, acidic and basic components. When submitted to chromatographic absorption on alumina, the neutral component was split into fractions from which were isolated a number of crystalline compounds, only one of which was obtained in sufficient quantity for further work.[7]

(1) Taken largely from the Ph.D. Dissertation of Russell L. Hodgson presented to the University of California at Los Angeles.

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(5) D. J. Cram and M. Tishler, THIS JOURNAL, **70**, 4238 (1948); D. J. Cram, *ibid.*, **70**, 4240 (1948).

(6) The authors are indebted to Merck and Co., Rahway, N. J., for a supply of this crude, amorphous mixture of N-ethylpiperidine salts of various acids, as well as for DL-penicillamine hydrochloride and sodium salt of penicillin G.

(7) The authors are indebted to Miss Yi-Hsien Sha who carried out preliminary isolation studies on the original mixture of salts.