Anal. Calcd. for $C_5H_{10}O_2N_2S_2$: N, 14.42; S, 33.01. Found: N, 14.43; S, 32.80.

6,7a-Dihydro-*m*-dithiino[5,4-c]pyrazol-7(4H)one (XX).—To a mixture of 10.3 g. (0.05 mole) of IIa and 50 ml. of ethyl alcohol at reflux temperature was added 2.5 g. (0.05 mole) of hydrazine hydrate. A vigorous reaction occurred and the product precipitated in quantitative yield (8.7 g.). After recrystallization from ethyl alcohol, it melted at 233–236° with decomposition beginning at 220°.

Anal. Calcd. for $C_5H_6N_2OS_2$: C, 34.46; H, 3.47; S, 36.80. Found: C, 34.41; H, 3.62; S, 36.96.

6-Thio-*m*-dithiano[5,4-d]uracil (XXI).—A solution of 30 ml. of ethyl alcohol, 0.02 mole of sodium ethoxide, 2.06 g. (0.01 mole) of IIa and 0.76 g. (0.01 mole) of thiourea was refluxed for 4 hours, and poured into water. The solid (0.56 g.) was collected on a filter and purified by dissolving in 1% cold sodium hydroxide, treating with decolorizing carbon and acidifying. It did not melt below 300°.

Anal. Calcd. for $C_6H_6N_2OS_3$: C, 33.01; H, 2.77; N, 12.84; S, 44.06. Found: C, 33.12; H, 2.83; N, 12.83; S, 44.02.

6-Amino-*m*-dithiano[5,4-d]pyrimidin-8-ol (XXII).—A clear solution of 0.035 mole of sodium ethoxide, 2.06 g. of IIa and 1.18 g. (0.01 mole) of guanidinium thiocyanate in 30 ml. of ethyl alcohol was stirred at reflux for 4 hours, poured into a mixture of ice and water, and neutralized with hydrochloric acid. The solid product (1.0 g.) was purified by dissolving in aqueous base, treating with decolorizing carbon, and precipitating by acidification. When heated, the solid began to decompose at 220° but did not melt at temperatures up to 300°.

Anal. Calcd. for $C_6H_7N_3OS_2$: C, 35.80; H, 3.51; S, 31.86. Found: C, 35.89; H, 3.70; S, 31.80.

2-(*o*-Chlorophenyl)-6,7a-dihydro-*m*-dithiino[5,4-c]pyrazol-7(4H)one.—A solution of 19 g. (0.06 mole) of 2-(*o*-chlorophenyl)-4-ethoxycarbonyl-5-*m*-dithianone and 3 g. (0.06 mole) of hydrazine hydrate in 16 ml. of methanol was heated on a steam-bath for about three minutes, and cooled in an ice-bath. The white solid product (17 g.) was collected by filtration and recrystallized from a water–methanol mixture, m.p. 234–238° dec.

Anal. Calcd. for $C_{11}H_9ClN_2OS_2$: Cl, 12.45; S, 22.52; N, 9.84. Found: Cl, 12.90; S, 22.56; N, 9.72.

4-Ethoxycarbonyl-5-*m*-dithianimine (XXIII).—Dry ammonia was passed through a suspension of 61.8 g. (0.3 mole) of IIa in 120 ml. of absolute ethyl alcohol at 25°. The ester dissolved and a crystalline solid suddenly precipitated. The solid was collected by filtration and dissolved in warm ethyl alcohol. The solution was cooled to 30°, rapidly saturated with dry ammonia gas, and cooled to 5° overnight to obtain 29 g. (47%) of product, m.p. 122–123.5°.

Anal. Calcd. for $C_7H_{11}NO_2$: C, 40.95; H, 5.40; S, 31.23; N, 6.82. Found: C, 40.69; H, 5.69; S, 31.19; N, 7.16.

The infrared absorption spectrum has bands at 2.92 and 3.02 μ in the N–H region and at 6.1 μ where carbonyl and imino double bonds show characteristic absorption.

When the product was not isolated from the reaction mixture in a short time, it was converted to 3,5-dithiapimelamide by the water formed in the reaction.

5-Dicyanomethylene-4-ethoxyhydroxymethylene-*m*-dithiane (XXV).—To a solution of 20.6 g. (0.1 mole) of IIa in a mixture of 70 ml. of ethyl alcohol and 40 ml. of water at 60° was added 6.6 g. (0.1 mole) of malononitrile. The mixture was cooled to room temperature to obtain 3 g. of a gummy yellow solid, which melted at 195–197° after it was washed with benzene and recrystallized from a mixture of ethyl alcohol and water. The structure assignment is based on the presence of the OH absorption band in the infrared spectrum at 3.2 μ and the absence of typical ester carbonyl band. Bands at 4.5 μ and at 6.25 and 6.4 μ indicate the presence of a conjugated nitrile group and carbon–carbon unsaturation.

Anal. Calcd. for $C_{10}H_{10}N_2O_2S_2$: C, 47.22; H, 3.96; S, 25.21; N, 11.16. Found: C, 47.35; H, 4.14; S, 25.41; N, 11.16.

1,4-Dioxa-7,9-dithiaspiro[4.5]decane-6-carboxylic Acid Chloride (XXVI).—A stirred mixture of 22.2 g. (0.1 mole) of IVa and 45.3 g. (0.30 mole) of thionyl chloride was heated at 37–39° until sulfur dioxide and hydrogen chloride no longer were evolved. The resulting clear yellow solution was stored overnight at room temperature. Excess thionyl chloride was removed by vacuum distillation to obtain 23.5 g. of product, which, after two recrystallizations from anhydrous benzene, melted at 91–91.5°.

Anal. Calcd. for $C_7H_9ClO_3S$: S, 26.64; Cl, 14.73. Found: S, 26.84; Cl, 14.84.

1,4-Dioxa-7,9-dithiaspiro[4.5]decane-6-carboxamide (XXVII).—A sample of the acid chloride was dissolved in benzene to which was added a large excess of ammonia in ether solution. The mixture was stirred for one-half hour and the solvent removed by evaporation at room temperature. The ammonium chloride was extracted from the residue with water and a portion of the remaining solid was recrystallized from ethyl alcohol, m.p. 179.5–181°.

Anal. Calcd. for $C_7H_{11}O_3NS_2$: C, 37.99; H, 5.01; N 6.33; S, 28.98. Found: C, 38.37; H, 5.20; N, 6.33; S, 29.10.

Wilmington 98, Del.

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

2,2,5,5-Tetramethyl-1,4-diazabicyclo[2.2.2]octane Methochloride

By S. M. McElvain and Thomas A. Lies[1]

Received June 1, 1959

The bicyclic structure named in the title was prepared by the intramolecular displacement of the halogen of 2,2,5,5-tetramethyl-1-(2-chloroethyl)-piperazine methochloride (VIII) by the 4-nitrogen. Attempts to demethylate this quaternary salt to yield the bicyclic ditertiary amine IV were unsuccessful.

Earlier work in this Laboratory showed that the formation of the bicyclo structure IV by the establishment of a 1,4-ethylene bridge *via* an intramolecular displacement of the halogen of a 1-(2-haloethyl)-2,2,5,5-tetramethylpiperazine (I) was not feasible. Pryde[2] found that the free base I (X = Cl or Br) preferentially formed the ethylene immonium cation II, which either underwent self-condensation to form polymers or was hydrolyzed to the 1-hydroxyethyl derivative III. Bannister[3] was able to prepare the bicyclic amine IV in only 0.15–0.5% yields by the pyrolysis of the dihydrobromide salt of I (X = Br).

The purpose of the present work was to determine whether an ethylene bridge could be established from a structure of the type of I if the tertiary nitrogen were first quaternized to prevent the for-

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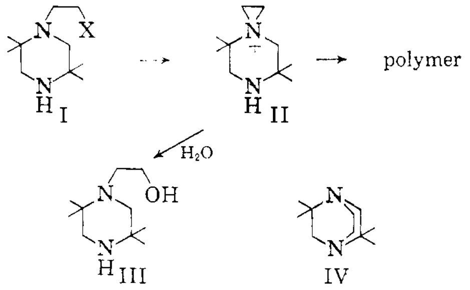
(1) Standard Oil Foundation Fellow 1955–1956; Wisconsin Alumni Research Foundation Research Assistant 1956–1958; du Pont Summer Research Assistant 1957.

(2) S. M. McElvain and E. H. Pryde, This Journal, **71**, 326 (1949).

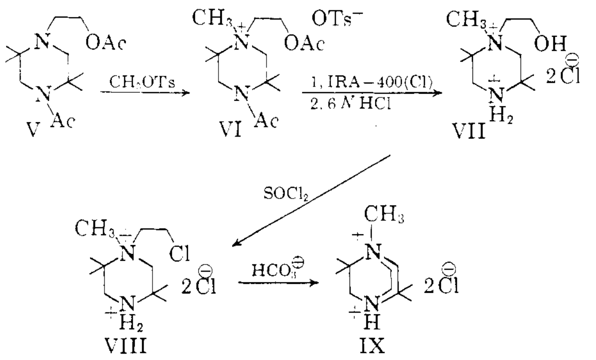
(3) S. M. McElvain and L. A. Bannister, *ibid.*, **76**, 1126 (1954).



mation of the ethylene immonium cation II. The synthetic route to this structure started with the diacetyl derivative (V) of the amino alcohol III. This tertiary amine V proved to be quite hindered as it showed no reaction with an ether solution of methyl iodide after seventy days at room temperature. However, quaternization was accomplished by heating V with methyl *p*-toluenesulfonate at 120° for 24 hours. Methyl bromide, benzyl bromide and benzyl *p*-toluenesulfonate failed to give a significant amount of quaternary salt after long heating with V. Ethyl *p*-toluenesulfonate gave a negligible amount of a quaternary salt under the same conditions that the corresponding methyl ester produced a 50% yield of the salt VI.

The methosulfonate VI was converted by an anion exchange resin to the methochloride, which was hydrolyzed with 6 *N* hydrochloric acid to the hydroxyethyl salt VII. Treatment of this compound with thionyl chloride gave the chloroethyl salt VIII.

When an aqueous solution of the salt VIII was treated with sodium bicarbonate at room temperature, the bicyclic quaternary salt IX was readily formed in high (87%) yields.

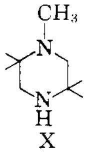


The methochloride hydrochloride salt IX was quite hygroscopic and difficult to recrystallize; the bromide salt was somewhat less hygroscopic; the iodide salt crystallized as a hydrate. The picrate salt was non-hygroscopic and proved to be the most readily purified derivative.

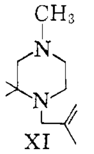
The facile ring closure of VIII to IX is of interest in connection with an earlier attempt to prepare a similar structure. Mann and Senior,[4] when unable to bridge 1,2,2,4,5,5-hexamethylpiperazine with ethylene dibromide (a reaction that has been used successfully to prepare triethylene diamine dimethobromide from 1,4-dimethylpiperazine), suggested that a plausible explanation for their failure is that the hexamethylpiperazine is locked in a chair conformation. Indeed, an X-ray crystal examination of the dinitrate of this amine showed it to have the chair conformation. Mann and Senior, however, recognized that such a conformation might not be retained by the cation in solution or by the liquid free base. It is apparent that the free base from VIII has no difficulty in assuming the boat conformation which is necessary for the formation of IX.

All attempts to demethylate the quaternary salt IX to the ditertiary amine IV were unsuccessful. When heated with potassium sulfide in diethylene glycol[5] at 120°, IX was converted in 61% yield to 1,2,2,5,5-pentamethylpiperazine (X), which doubtless was formed from the corresponding 4-vinyl compound resulting from the rupture of the ethylene bridge of IX. When the salt IX was heated in aqueous alkali, 1,3,3-trimethyl-4-isobutenylpiperazine (XI) was formed in 80% yield. It does not seem likely that the sulfide decomposition was an E_2 reaction while that of the hydroxide reaction was an E_1 process as the methochloride prepared from the salt IX was able to survive refluxing in aqueous solution for 48 hours.

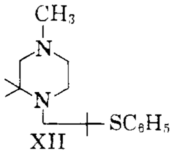
When IX was heated with potassium thiophenolate in diethylene glycol solution, a product containing all of the carbon atoms of the salt together with a sulfur atom and a phenyl group was obtained in 24% yield. It seems likely that this product has the structure XII.



X



XI



XII

Cope and Bumgardner[6] were able to demethylate a quaternary salt with lithium aluminum hydride in refluxing tetrahydrofuran. When this procedure was applied to the methochloride prepared from IX, the sole product, obtained in 65% yield, contained all of the original carbon atoms. This product might be formulated as either 1,2,2,5,5-pentamethyl-4-ethylpiperazine or 1,3,3-trimethyl-4-isobutylpiperazine. Attempts were made to prepare these compounds (a) by the reduction of 1,2,2,5,5-pentamethyl-4-(2-bromoethyl)-piperazine dihydrobromide with zinc and hydrochloric acid, and by the action of hydriodic acid on 1,2,2,5,5-pentamethyl-4-(2-hydroxyethyl)-piperazine; and (b) by the catalytic hydrogenation of the 4-isobutenyl derivative XI. In each case the 4-substituent was removed to give, respectively, 1,2,2,5,5-pentamethylpiperazine (X) and 1,3,3-trimethylpiperazine.

When the hydrochloride salt IX was converted to the methochloride and the latter heated at 310–330° under 0.1 mm. pressure, 70% of the weight of the material was obtained as a volatile pyrolysate. Distillation of this material gave a covalent

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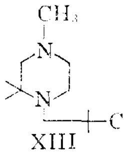
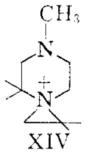
[4] F. G. Mann and A. Senior, *J. Chem. Soc.*, 4476 (1954).

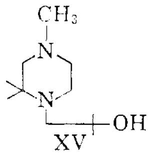
[5] H. R. Snyder and J. C. Speck, THIS JOURNAL, **61**, 668, 2895 (1939).

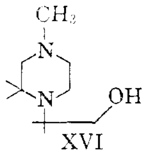
[6] A. C. Cope and C. L. Bumgardner, *ibid.*, **79**, 960 (1957).

chlorine compound formulated as the tertiary chloride XIII, which would result from the thermal scission of the bond between the quaternary nitrogen and the tertiary carbon; however, the absence of other isomers in the pyrolysate could not be conclusively established. In addition to this chloride XIII, a small amount of the isobutenyl derivative XI was obtained as a product of this pyrolysis reaction.


XIII


XIV


XV


XVI

Attempts to establish XIII as the structure of the covalent chlorine compound by dehydrochlorination to the isobutenyl derivative XI were not successful, probably because of the neighboring nucleophilic nitrogen atom. Heating the pyrolysis product with aqueous alkali yielded an alcohol which might be either XV or XVI, formed by the hydrolysis of the intermediate immonium cation XIV. Alcoholic potassium hydroxide and sodium ethoxide in alcohol produced mixtures of products from which none of XI could be isolated.

Experimental

1-(2-Acetoxyethyl)-4-acetyl-2,2,5,5-tetramethylpiperazine (V).—To 42 g. (0.266 mole) of 1-(2-hydroxyethyl)-2,2,5,5-tetramethylpiperazine[2] in a flask equipped with a reflux condenser carrying a calcium chloride tube was added 65 ml. (0.69 mole) of acetic anhydride. The solution was refluxed for 11 hours and then 36 ml. of liquid was distilled from the solution. The hot residue was placed in a separatory funnel and shaken with 25 ml. of water. After the addition of 100 ml. of ether, small portions of sodium carbonate were added cautiously with shaking until the evolution of gas ceased. The organic layer was washed twice with water and dried with sodium sulfate. Evaporation on the steam-bath yielded 56 g. of red-brown oil. This was distilled through a 20-cm. Vigreux column to yield 53.7 g. (88%) of V, b.p. 130–146° (0.15 mm.), n^{25}D 1.4767.

A sample of the compound was fractionated through an 20-cm. Vigreux column to give the following approximately equal fractions: b.p. 140–141° (0.5 mm.), n^{25}D 1.4757; 147–148° (0.8 mm.), n^{25}D 1.4762; 148–148.6° (1.0 mm.), n^{25}D 1.4767; 147–148° (0.8 mm.), n^{25}D 1.4769. Fraction 2 was analyzed.

Anal. Calcd. for $C_{14}H_{26}N_2O_3$: C, 62.18; H, 9.69. Found: C, 61.97; H, 9.58.

1-(2-Acetoxyethyl)-4-acetyl-2,2,5,5-tetramethylpiperazine-1-methotosylate (VI).—A solution of 20 g. (0.074 mole) of 1-(2-acetoxyethyl)-4-acetyl-2,2,5,5-tetramethylpiperazine (V) and 50 g. (0.27 mole) of methyl *p*-toluenesulfonate in a corked erlenmeyer flask was heated in an oil-bath at 120–125° for 25 hr. The red-brown solution was then poured into 300 ml. of magnetically stirred ether and rinsed in with 3 ml. of acetone. The oily precipitate solidified after stirring for 10 hr. The ether was decanted and the residue was dissolved in 50 ml. of boiling absolute ethanol. About 100 ml. of acetone (dried over sodium sulfate) was added, and finally petroleum ether was added slowly to the boiling solution until crystallization commenced. The solid was removed by filtration and dried to yield 18.9 g. (56%) of fluffy tan powder, m.p. 187–190° with previous sintering. A sample of the salt after recrystallization to constant melting point from absolute ethanol–ethyl acetate solution, melted at 188.5–190° with previous sintering. For analysis the sample was dried 10 hr. at 25° and 2 hr. at 50° under 0.15 mm. pressure.

Anal. Calcd. for $C_{22}H_{36}O_6N_2S$: C, 57.87; H, 7.95. Found: C, 58.06; H, 8.24.

A series of experiments were carried out to determine the optimum conditions of the quaternization. The yield was found to increase as the time of heating at 120° was increased from 8 hr. (16%) to 14 hr. (37%) to 24 hr. (42–56% in three runs). When the period of heating was increased to 48 hr. a 49% yield of crude solid was obtained, but the material could not be purified by recrystallization.

1-(2-Hydroxyethyl)-2,2,5,5-tetramethylpiperazine-1-methochloride Hydrochloride Dihydrate (VII).—A solution of 87 g. of 1-(2-acetoxyethyl)-1-methotosylate-4-acetyl-2,2,-5,5-tetramethylpiperazine (VI) in 200 ml. of water was stirred for 0.5 hr. with 460 g. (wet) of cation exchange resin IRA-400 (Cl) prepared by stirring the basic resin with two 1.5-l. portions of saturated aqueous sodium chloride solution and washing the resin with portions of water until the washings showed no precipitate with silver nitrate solution. The supernatant solution was decanted from the resin and the resin washed repeatedly with 100-ml. portions of water. The last portion of water gave a negligible precipitate with silver nitrate solution. The aqueous solution was evaporated to a thick sirup on the steam-bath. The sirup was dissolved in 130 ml. of 6 *N* hydrochloric acid and the solution was refluxed for 19 hr. Most of the solvent was removed by distillation at atmospheric pressure; the remainder was removed under reduced pressure with gentle heating. A heavy sirup was obtained. A 100-ml. portion of absolute methanol was added and removed by distillation. Another 100-ml. portion of absolute methanol was added and the solution was transferred to a 250-ml. erlenmeyer flask. The methanol solution was evaporated on the steam-bath to give a light sirup and 100 ml. of absolute ethanol added. The solution deposited good crystals when the flask was scratched. The solid was separated by filtration and washed with absolute ethanol. The colorless solid weighed 54.5 g. and lost water and sintered at 207–210° when inserted in the melting point bath at 200°. A sodium fusion test for sulfur was negative. From the mother liquor a second crop of 1.4 g. of colorless crystals losing water at 207–210° was obtained. The total yield of 1-(2-hydroxyethyl)-2,2,5,5-tetramethylpiperazine-1-methochloride hydrochloride dihydrate was 55.9 g. (95%). A sample of the salt was recrystallized from ethanol to yield material which lost solvent at 205–206° when inserted at 200°. The melting point tube was removed from the bath and cooled. On reinsertion at 200° the sample decomposed at 275–285° with considerable previous sintering. The sample was recrystallized twice more from ethanol to yield colorless needles which lost water of hydration on insertion at 195°, and contained 22.8% chlorine. Another recrystallization yielded the analytical sample which lost water on insertion at 200° and decomposed at *ca.* 278–285° with considerable previous sintering. For analysis the sample was dried at 25° for 7 hr. at 1 mm. pressure.

Anal. Calcd. for $C_{11}H_{26}ON_2Cl_2 \cdot 2H_2O$: C, 42.71; H, 9.78; Cl, 22.9. Found: C, 42.65; H, 10.04; Cl, 22.2.

An attempt was made to obtain a sample of the dehydrated material for analysis by inserting a portion of the analytical sample in an oil-bath heated at 200°. The sample lost water, but the residue turned brown and appeared to be unsuitable for analysis.

1-(2-Chloroethyl)-2,2,5,5-tetramethylpiperazine-1-methochloride Hydrochloride (VIII).—To 54 g. (0.175 mole) of 1-(2-hydroxyethyl)-2,2,5,5-tetramethylpiperazine-1-methochloride hydrochloride dihydrate (VII) in a dry 500-ml. flask equipped with a reflux condenser sealed with a calcium chloride tube was added 15 g. (0.19 mole) of pyridine dried over and distilled from barium oxide. The reagents were mixed by shaking, and 180 ml. (2.5 moles) of freshly purified thionyl chloride was added slowly through the condenser. When the vigorous reaction had subsided the resulting gelatinous mass was refluxed for 4 hr. to give an orange solution. The excess thionyl chloride was then removed by distillation under reduced pressure. The pot temperature was not permitted to rise above 100°. When the solution began to foam distillation was stopped and 150 ml. of absolute methanol was added to the hot sirup. A vigorous reaction occurred and solid began to precipitate. (If precipitation did not occur at this point it was necessary to start crystallization from methanol–isopropyl alcohol or methanol–absolute alcohol solution by scratching the walls of the container.) About 350 ml. of dry isopropyl alcohol was added and the stoppered flask cooled. The precipitated solid was removed by filtration and washed with isopropyl alcohol. The solid was dried in a vacuum desiccator over calcium chloride to yield 52 g. of colorless, hygroscopic VIII. For analysis a sample was dried two hours at 70–80° under 1.0 mm. pressure.

Anal. Calcd. for $C_{11}H_{25}N_2Cl_3$: total Cl, 36.5; ionic Cl, 24.3. Found: total Cl, 34.7; ionic Cl, 23.0.

In six preparations of the compound total chlorine values ranged from 32.6 to 34.7% and ionic chloride values from 21.4 to 23.6%, while the various preparations gave material melting between 229 and 237° with decomposition and previous slight sintering. Yields ranged from 72–98%.

2,2,5,5-Tetramethyl-1,4-diazabicyclo[2.2.2]octane Methochloride Hydrochloride (IX).—A mixture of 664 mg. (containing 32.8% total Cl) of 1-(2-chloroethyl)-2,2,5,5-tetramethylpiperazine-1-methochloride hydrochloride (VIII) and 176 mg. (1.1 equivalents) of sodium bicarbonate in a 25-ml. volumetric flask was diluted to the mark with water. Samples were withdrawn at intervals and titrated by the Volhard method to determine the chloride ion present. The following values were obtained:

Time in hours	Ionic chloride, %
0 (dry sample)	22.6
0 (after mixing)	26.2
0.5	27.3
1.15	30.1
1.8	30.8
6.3	31.7
18.3	32.9

The solution was evaporated to dryness and the residue was partially dissolved in absolute alcohol. The solution was filtered to remove inorganic salts, after which it was evaporated to dryness. The residue was recrystallized from absolute ethanol–isopropyl alcohol solution to yield 0.21 g. of crystalline salt IX, m.p. 231–236° dec., and 55 mg., m.p. 228–230° dec.

Anal. Calcd. for $C_{11}H_{24}N_2Cl_2$: Cl, 27.8. Found: Crop 1, Cl, 28.1; Crop 2, Cl, 26.8.

For large-scale preparation of IX the following procedure was used. To a magnetically stirred solution of 50 g. of the crude chloroethyl compound (VIII) in 550 ml. of water contained in a 1-liter erlenmeyer flask was added dropwise a solution of 24 g. (0.33 mole) of sodium bicarbonate in 350 ml. of water over a period of 5 hr. After the solution had stood at room temperature for 36 hr. it was acidified with 25 ml. of concentrated hydrochloric acid and evaporated to a small volume on the steam-bath. The residue was dissolved in absolute ethanol and the filtered solution evaporated to a sirup to which 100 ml. of absolute ethanol was added. After the solution had stood for a few days, the deposit of colorless crystals which had formed was separated and washed with absolute ethanol and dry ether. The extremely hygroscopic solid was dried and stored in a vacuum desiccator over calcium chloride. The dried bicyclic methochloride hydrochloride IX weighed 24.5 g. and melted at 236–242° dec. After being dried 40 min. at 90° under 1 mm. pressure the sample was found to melt at 240–246° dec., and to contain 27.7% chlorine.

From the mother liquor of the first crop was obtained a second crop of 6.75 g. of the compound, m.p. 234–239° dec., mixed m.p. with the first crop, 236–243° dec. The total yield was 87.5%.

2,2,5,5-Tetramethyl-1,4-diazabicyclo[2.2.2]octane Methopicrate Picrate.—A solution of 255 mg. of the bicyclic methochloride hydrochloride IX in 5 ml. of water was added dropwise to a hot solution of 2 molecular equivalents of sodium picrate in 10 ml. of water. The mixture was cooled and the precipitate filtered off and dried in air. The dry picrate, m.p. 235–237° dec., weighed 605 mg. (96%). Two recrystallizations from aqueous ethanol yielded the analytical sample, m.p. 236–237° dec., after being dried 5 hr. at 85° and 7 hr. at 25° under 1 mm. pressure.

Anal. Calcd. for $C_{23}H_{28}O_{14}N_8$: C, 43.13; H, 4.40; N, 17.50. Found: C, 43.21; H, 4.40; N, 17.59.

The bromide hydrobromide salt was prepared from IX as follows. A solution of 1.33 g. of IX in 25 ml. of concentrated hydrobromic acid was distilled under 10 mm. pressure until a tan sponge remained, which was allowed to stand under 50 ml. of absolute ethanol. The solidified residue was triturated with isopropyl alcohol, filtered off and washed with isopropyl alcohol. The dried methobromide hydrobromide, m.p. 266° dec., weighed 1.69 g. (94%). Recrystallization from methanol–ethyl acetate solution yielded 937 mg. of the salt, m.p. 263° dec. Another recrystallization from methanol yielded the analytical sample, m.p. 267° dec., after being dried five hours at 60° under 1 mm.

Anal. Calcd. for $C_{11}H_{24}N_2Br_2$: Br, 46.4. Found: Br, 46.2.

The iodide hydroiodide salt was prepared from IX in the following manner. A solution of 1.23 g. of IX and 25 ml. of freshly distilled hydriodic acid was distilled to dryness under 20 mm. pressure and gentle heating. The residue was dissolved in aqueous methanol and the solution diluted with isopropyl alcohol to precipitate 1.94 g. (92%) of the bicyclic methiodide hydriodide, m.p. 225–227° dec. A second precipitation as before yielded a light yellow powder with unchanged melting point. Recrystallization from ethanol gave well-formed light yellow crystals, m.p. 225–232° dec. Another recrystallization from ethanol yielded the analytical sample, m.p. 225–232° dec. after being dried over calcium chloride at 25° under 20 mm. pressure for 1 hr. Analysis showed that the compound contained 1.5 moles of water of hydration.

Anal. Calcd. for $C_{11}H_{24}N_2I_2 \cdot 1.5\ H_2O$: I, 54.6. Found: I, 54.5.

Degradation of IX to 1,3,3-Trimethyl-4-isobutenylpiperazine (XI).—A solution of 4.0 g. of IX in 50 ml. of 40% aqueous potassium hydroxide solution was heated at 120–135° for 4 hr. The mixture was then steam distilled and 200 ml. of distillate collected. The distillate was acidified with hydrochloric acid and evaporated to near dryness. Recrystallization of the residue from ethanol yielded 3.19 g. (80%) of XI dihydrochloride, m.p. 239.5–241.5° dec. For analysis a sample was recrystallized to constant melting point from absolute ethanol. The analytical sample melted at 239–239.5° dec. (inserted at 230°) after being dried for 2 hr. at 60–90° and 12 hr. at 25° (1 mm.).

Anal. Calcd. for $C_{11}H_{24}N_2Cl_2$: C, 51.77; H, 9.48; Cl, 27.8. Found: C, 51.92; H, 9.22; Cl, 27.6.

The infrared spectrum of the dihydrochloride (Nujol mull) showed bands at 6.07 and 11.44 μ (terminal methylene).

A sample of 2.06 g. of the dihydrochloride was decomposed under ether with aqueous potassium hydroxide. The ether layer was washed with water, dried with sodium sulfate, and evaporated to leave 1.20 g. of the free base XI, which was distilled and five equal fractions collected: (1) b.p. to 91°, $n^{25}\text{D}$ 1.4634; (2) 191–199°, 1.4637; (3) 199–203°, 1.4639; (4) 203–205°, 1.4640; (5) 197–205°, 1.4640.

These combined fractions of XI were redistilled under reduced pressure to give the analytical sample, b.p. 87° (5 mm.), $n^{25}\text{D}$ 1.4637.

Anal. Calcd. for $C_{11}H_{22}N_2$: C, 72.47; H, 12.17. Found: C, 72.35; H, 11.90.

The infrared spectrum of the freshly distilled free base (liquid film) showed peaks at 6.10 and 11.22 μ (terminal methylene).

Reaction of IX with the Sulfide Anion.—The procedure of Snyder and Speck[5] was followed for the preparation of the sulfide solution. A solution of 50 g. of potassium sulfide in 50 ml. of water was added to 120 ml. of diethylene glycol and the resulting solution boiled until the boiling point reached 180°. To this brown slurry was added 5.2 g. of IX and the mixture heated at 120° for 7 hr. The slurry was cooled and transferred to a steam distillation apparatus, and 20 g. of sodium hydroxide was added. The solution was steam distilled until 900 ml. of distillate had been collected. The distillate was acidified with hydrochloric acid and evaporated to dryness on the steam-bath. The residue was triturated with isopropyl alcohol and filtered to give 4.19 g. (92%) of colorless 1,2,2,5,5-pentamethylpiperazine (X) dihydrochloride, m.p. sinter 320°, blacken 366°. The salt was dissolved in aqueous alkali and the turbid solution was continuously extracted for 13 hr. The ether extract was dried over sodium sulfate. The ether was distilled off and the higher-boiling residue in the flask was distilled to give 1.92 g. (61.5%) of colorless 1,2,2,5,5-pentamethylpiperazine (X), b.p. 152–175°, $n^{25}\text{D}$ 1.4553. The amine was redistilled from a Claisen flask equipped with a short Vigreux column and collected in five fractions which boiled within the range 176–178° and had the following $n^{28}\text{D}$: (1) 1.4523, (2) 1.4541, (3) 1.4541, (4) 1.4541, (5) 1.4540;

the brown residue remaining from the distillation weighed 0.3 g. Fraction 3 was analyzed. The infrared spectrum (liquid film) showed a band at 3.0 μ (N–H).

Anal. Calcd. for $C_9H_{20}N_2$: C, 69.16; H, 12.90. Found: C, 69.02; H, 12.45.

A sample of the amine was dissolved in 5 *N* hydrochloric acid and the solution was evaporated to dryness on the steam-bath. The colorless residue was dissolved in methanol, filtered and the solution was evaporated to dryness on the steam-bath. The colorless 1,2,2,5,5-pentamethylpiperazine (X) dihydrochloride, m.p. sinter to 360°, was dried 2 hr. at 100° under 0.1 mm. pressure. The infrared spectrum of this dihydrochloride (Nujol mull) was essentially identical with that of the crude dihydrochloride obtained from steam distillation of the reaction mixture.

Anal. Calcd. for $C_9H_{22}N_2Cl_2$: Cl, 31.0. Found: Cl, 30.7.

Degradation of IX to 1,3,3-Trimethyl-4-(2-phenylthio-2-methylpropyl)-piperazine (XII).—A mixture of 4 g. of potassium thiophenolate, 360 mg. of IX and 10 ml. of redistilled diethylene glycol was heated at 110–120° for 7 hr. Some of the potassium thiophenolate remained undissolved. The mixture was cooled and then steam distilled. The distillate was acidified and filtered to remove oily droplets. The filtrate on evaporation to dryness left 170 mg. of a brown solid, which after recrystallization from ethanol yielded 122 mg. (24%) of colorless crystals of the dihydrochloride of XII, m.p. 277–278° dec. For analysis the sample was recrystallized from ethanol. The analytical sample melted at 276–278° dec. after being dried 8 hr. at 60° and 11 hr. at 30° (0.1 mm.).

Anal. Calcd. for $C_{17}H_{30}N_2SCl_2$: C, 55.88; H, 8.28; Cl, 19.4. Found: C, 56.25; H, 8.23; Cl, 19.1.

Reduction of IX with Lithium Aluminum Hydride.—To a solution of 500 mg. of lithium aluminum hydride in 100 ml. of dry tetrahydrofuran was added 500 mg. of 2,2,5,5-tetramethyl-1,4-diazabicyclo[2.2.2]octane methochloride, prepared from IX as described below. The mixture was allowed to stir at room temperature for 3 days. A condenser fitted with a calcium chloride tube was then added and the mixture refluxed for 2 days. Addition of 2 ml. of water to the ice-cold stirred solution decomposed the remaining lithium aluminum hydride. The precipitated inorganic salts were filtered off and washed with ether, and the filtrate was dried with sodium sulfate and then saturated with hydrogen chloride. The vacuum-dried precipitate weighed 444 mg. A sample sublimed at *ca.* 330° leaving a residue which was unchanged at 360°. The inorganic salts were dissolved in aqueous potassium hydroxide solution and the solution steam distilled. The distillate was acidified with hydrochloric acid and evaporated to dryness to yield 74 mg. of a solid, which sublimed and decomposed, leaving a tan residue when heated from 320–350°.

Recrystallization of these two crops from aqueous ethanol solution gave 383 mg. (65%) of a crystalline solid subliming at 335–342°, which was formulated as 1,3,3-trimethyl-4-isobutylpiperazine dihydrochloride. This product was recrystallized twice from aqueous ethanol to give an analytical sample that sublimed at 330°. For analysis the sample was dried 4 hr. at 60–115° and 12 hr. at 25° (1 mm.).

Anal. Calcd. for $C_{11}H_{26}N_2Cl_2$: C, 51.35; H, 10.19; Cl, 27.6. Found: C, 51.68; H, 9.88; Cl, 27.3.

1-(2-Hydroxyethyl)-2,2,4,5,5-pentamethylpiperazine.—To a solution of 20 g. of 1-(2-hydroxyethyl)-2,2,5,5-tetramethylpiperazine in 85 ml. of 88% formic acid contained in a 250-ml. flask equipped with a reflux condenser was added 65 ml. of 37% formalin. When the initial reaction had subsided the solution was heated at 100° for 40 hr. After the addition of 50 ml. of concentrated hydrochloric acid the solution was evaporated to dryness. The residue was dissolved in the minimum amount of water and sodium hydroxide pellets were added to give the free base, which was taken up in ether. The ethereal solution was washed with water, dried with sodium sulfate and evaporated to yield 21 g. of a brown oil. Distillation yielded 12.8 g. (60%) of colorless 1-(2-hydroxyethyl)-2,2,4,5,5-pentamethylpiperazine, b.p. 115–120° (5–10 mm.), $n^{25}D$ 1.4738. A sample of the base was distilled through a short Vigreux column in a nitrogen atmosphere and six equal fractions, all boiling at 114° (5 mm.), were collected; the $n^{25}D$ of these fractions were 1.4737–1.4742. The fifth fraction, $n^{25}D$ 1.4742, was analyzed.

Anal. Calcd. for $C_{11}H_{24}ON_2$: C, 65.96; H, 12.08. Found: C, 66.01; H, 11.70.

Attempted Reduction of 1-(2-Hydroxyethyl)-2,2,4,5,5-pentamethylpiperazine with Hydriodic Acid.—A solution of 0.8 g. of the hydroxylethyl compound in 100 ml. of colorless concentrated hydriodic acid was refluxed for 67 hr. The dark red hydriodic acid was removed by distillation, the last 10 ml. of the acid being distilled under reduced pressure. The residue was dissolved in aqueous potassium hydroxide and steam distilled. The distillate was acidified with hydrochloric acid and evaporated to dryness. The residue was dissolved in aqueous ethanol, and isopropyl alcohol and ether were added to precipitate 0.61 g. of a powder, m.p. >360°. Three recrystallizations from aqueous ethanol–ethyl acetate solution gave the analytical sample, which was dried for 9 hr. at 80° (1 mm.). Analyses indicated that the compound isolated was 1,2,2,5,5-pentamethylpiperazine dihydrochloride.

Anal. Calcd. for $C_9H_{22}N_2Cl_2$: Cl, 31.0. Found: Cl, 30.5.

The analytical sample was redried for infrared analysis for one hour at 150° under 0.1 mm. pressure. Its infrared spectrum (Nujol mull) was identical with that of the 1,2,2,5,5-pentamethylpiperazine dihydrochloride obtained from the treatment of 1-(2-bromoethyl)-2,2,4,5,5-pentamethylpiperazine dihydrobromide with zinc and hydrochloric acid (see below).

1-(2-Bromoethyl)-2,2,4,5,5-pentamethylpiperazine Dihydrobromide.—A solution of 3.25 g. of 1-(2-hydroxyethyl)-2,2,4,5,5-pentamethylpiperazine in 100 ml. of concentrated hydrobromic acid was slowly distilled through a 25-cm. Vigreux column for 5 hr. until the residue in the pot was almost to dryness. All of the distillate was returned to the pot and slow distillation continued until a precipitate began to form. After the addition of 50 ml. of concentrated hydrobromic acid the solution was refluxed for 11 hr. The flask was cooled in Dry Ice and the precipitated solid filtered off and washed with 100 ml. of ethanol. The yield of crude bromoethyl compound was 4.3 g. (62%). For analysis a sample of the compound was dried for 6 hr. at 50–110° under 1 mm. pressure. The analytical sample blackened when heated to 360°.

Anal. Calcd. for $C_{11}H_{25}N_2Br_3$: total Br, 56.3; ionic Br, 37.6. Found: total Br, 57.1; ionic Br, 49.3.

Reduction of 1-(2-Bromoethyl)-2,2,4,5,5-pentamethylpiperazine Dihydrobromide.—To a mixture of 4.2 g. of the bromoethyl salt and 3.7 g. of zinc which had previously been treated with aqueous copper sulfate solution and washed with water was added 30 ml. of 5 *N* hydrochloric acid. After the initial reaction had subsided 30 ml. of water was added and the mixture was stirred. After 1 hr., 30 ml. of 5 *N* hydrochloric acid was added and after 2 hr., 20 g. of zinc was added and stirred vigorously for 2 hr. The solution was filtered, neutralized with sodium hydroxide and extracted with ether. The ether extract was dried with sodium sulfate and saturated with hydrogen chloride. The resulting precipitate weighed 1.89 g. and a sample sintered and sublimed when heated to 360°. Three recrystallizations from aqueous ethanol yielded the analytical sample which was dried at 190° for 0.5 hr. and 110° for 4 hr. (1 mm.).

The chlorine content (30.4%) indicated that the compound isolated was 1,2,2,5,5-pentamethylpiperazine dihydrochloride.

A sample of this salt weighing 528 mg. was decomposed with sodium hydroxide solution and extracted with ether. The ether solution was dried over sodium sulfate and evaporated to leave 166 mg. of the free amine which was distilled to give a main fraction of 65 mg., $n^{25}D$ 1.4543. The infrared spectrum of the free base (liquid film) was identical to that of a sample of 1,2,2,5,5-pentamethylpiperazine (X), $n^{25}D$ 1.4557, prepared by the hydrosulfide degradation of IX.

Hydrogenation of 1,3,3-Trimethyl-4-isobutenylpiperazine (XI) Dihydrochloride.—A solution of 0.10 g. of this salt in 10 ml. of 40% aqueous ethanol was hydrogenated at atmospheric pressure and room temperature over 10% palladium-on-carbon. The reaction consumed 10 ml. of hydrogen. The catalyst was filtered off and washed with ethanol. The filtrate was acidified with 5 drops of 5 *N* hydrochloric acid and evaporated to dryness. The residue was triturated with isopropyl alcohol and filtered off. The tan crystalline powder, m.p. 286–293° dec., weighed 65 mg. Repeated recrystallization from ethanol–ethyl acetate solution gave the analytical sample, m.p. 290–291.5° after being dried 3 hr. at 80° under 1 mm. pressure. Analysis indicated this product to be 1,3,3-trimethylpiperazine dihydrochloride.

Anal. Calcd. for $C_7H_{18}N_2Cl_2$: C, 41.81; H, 9.03; Cl, 35.3. Found: C, 41.97; H, 8.76; Cl, 34.6.

2,2,5,5-Tetramethyl-1,4-diazabicyclo[2.2.2]octane Methochloride.—To a mixture of 2.35 g. of the methochloride hydrochloride IX and 774 mg. of sodium bicarbonate in a 125-ml. erlenmeyer flask was added 10 ml. of water. The solution was evaporated to a small volume on the steam-bath and 30 mm. of isopropyl alcohol was added. The resulting solution was filtered and the filtrate evaporated to a sirup. Ether was added to the sirup to precipitate the methochloride, which was filtered off and dried under reduced pressure. The colorless hygroscopic powder, m.p. 286–287° dec., weighed 1.93 g. (96%).

Anal. Calcd. for $C_{11}H_{23}N_2Cl$: Cl, 16.2. Found: Cl, 16.4.

A solution of this methochloride salt prepared from 479 mg. of IX and 158 mg. (one molecular equivalent) of sodium bicarbonate in 25 ml. of water was refluxed for 48 hr. The solution was then acidified with 1 ml. of 5 *N* hydrochloric acid and evaporated to near dryness. From the residue was obtained 325 mg. of a colorless solid, m.p. 237–243° dec., by recrystallization from ethanol–benzene solution, and 78 mg. of a pink powder, m.p. 233–250°, by evaporation of the mother liquor from the first crop. The melting point of the first crop was not depressed on admixture with authentic methochloride hydrochloride IX and the infrared spectra (Nujol mulls) of both crops were essentially identical to that of IX. The yield of recovered starting material was 84%.

Pyrolysis of 2,2,5,5-Tetramethyl-1,4-diazabicyclo[2.2.2]-octane Methochloride.—(a) A mixture of 480 mg. of the bicyclic methochloride and 10 volumes of sand was placed in a 2.5 × 20 cm. Pyrex test-tube having a side arm 8 cm. from the top. The tube was stoppered and the side arm connected to one end of a U-tube. The apparatus was evacuated to 0.1 mm. through the other end of the U-tube and the test-tube was placed vertically in an electric heater at 310° at the same time as the U-tube was immersed in an acetone–Dry Ice-bath. The tube was heated at 310–330° for 45 min. The congealed material in the U-tube was dissolved in ether and the solution saturated with hydrogen chloride to precipitate 415 mg. of a tan powder, m.p. 258–261° dec. The solid was steam distilled from an alkaline solution and the distillate acidified with hydrochloric acid and evaporated to dryness. The residue was recrystallized from aqueous ethanol to give 168 mg. of a tan powder, m.p. 278° dec., and 42 mg. of solid which melted at 255° dec. and contained 23.6% chlorine.

The first crop was recrystallized from aqueous ethanol to give 97 mg. of an off-white powder which melted at 282° dec. and contained 25.7% chlorine and was recrystallized from aqueous ethanol to give the analytical sample, which was dried for 3 hr. at 70° (0.1 mm.). The analytical values obtained correspond to those calculated for 1,3,3-trimethyl-4-(2-hydroxy-2-methylpropyl)-piperazine dihydrochloride.

Anal. Calcd. for $C_{11}H_{26}ON_2Cl_2$: C, 48.34; H, 9.59; Cl, 26.0. Found: C, 47.99; H, 9.12; Cl, 26.3.

(b) A sample of 1.05 g. of the methochloride salt was placed in the same apparatus used in (a) above and a plug of Pyrex glass wool was pressed down on top of it to prevent spattering. The pyrolysis was carried out as before at 310° for 1.5 hr., after which only a small amount of a brown solid remained of the original sample. The yellow pyrolysate which had collected in the cold U-tube weighed 731 mg. The liquid product was distilled to give a light yellow liquid, b.p. 40–54° (0.1–0.2 mm.), $n^{25}D$ 1.4734. Analysis (found Cl, 11.1%) showed the liquid to be a mixture of the chloro compound (calcd. Cl, 16.2%) from which the alcohol obtained in (a) was derived, and at least one chlorine-free product. The total chlorine value was not changed by a threefold increase in the reflux time in the Stepanow procedure.

A sample of the crude pyrolysate was transformed from an ether-soluble liquid to an ether-insoluble solid by heating a short time at 280°.

(c) In a repetition of procedure b, 1.92 g. of the methochloride salt was pyrolyzed and the crude pyrolysate dissolved in ether. The ethereal solution was saturated with hydrogen chloride and the resulting precipitate filtered off and dried. The crude solid product, which weighed 2.0 g., was allowed to stand in isopropyl alcohol for 12 hr. The solid was then filtered off and dried to give 1.68 g. of a colorless powder, m.p. 278–280° dec. (viscous melt). The filtrate was evaporated to a small volume and from this concentrated solution 80 mg. of a solid, m.p. 222–224° dec., was obtained. Two recrystallizations of this product from ethanol–ethyl acetate solution yielded 43 mg. of a solid, m.p. 239.5–240.5°. A mixture of this material with authentic 1,3,3-trimethyl-4-isobutenylpiperazine (XI) dihydrochloride melted at 238.5–239.5° dec. and their infrared spectra (Nujol mulls) were identical.

The first crop 1.68 g. of solid material above was recrystallized from aqueous ethanol–isopropyl alcohol solution to give 1.20 g. of a solid, m.p. 288° dec. (viscous melt), and 0.20 g. of a solid, m.p. 275–278° dec. The first crop was recrystallized from aqueous ethanol–isopropyl alcohol solution to yield the analytical sample, which weighed 0.82 g. and melted at 290° (viscous melt) after being dried 8 hr. at 45° (1 mm.). The chlorine values obtained indicated that the material was an impure sample of 1,3,3-trimethyl-4-(2-methyl-2-chloropropyl)-piperazine (XIII) dihydrochloride.

Anal. Calcd. for $C_{11}H_{25}N_2Cl_3$: total Cl, 36.5; ionic Cl, 24.3. Found: total Cl, 32.4; ionic Cl, 25.9.

A sample of the above chloro dihydrochloride compound weighing 0.75 g. was decomposed with aqueous sodium bicarbonate solution and the free base was taken up in ether. The ethereal solution was washed with water, dried with sodium sulfate, and evaporated to leave 0.32 g. of an oil, which was distilled to give 0.23 g. of impure 1,3,3-trimethyl-4-(2-methyl-2-chloropropyl)-piperazine (XIII), b.p. *ca.* 59° (0.15 mm.), $n^{25}D$ 1.4726. The infrared spectrum (liquid film) of this distilled free base, which analysis indicated to be 89% pure, had a weak band at 11.25 μ which indicated the presence of traces of an unsaturated compound.

Anal. Calcd. for $C_{11}H_{22}N_2Cl$: total Cl, 16.2. Found: total Cl, 14.5.

Attempted Dehydrochlorination of XIII.—(a) To a solution of 2 g. of potassium hydroxide in 20 ml. of absolute ethanol was added 400 mg. of the dihydrochloride of XIII and the mixture was refluxed for 10 hr. Steam distillation of the mixture, and evaporation of the acidified distillate yielded a mixture of partly crystalline hydrochlorides. This material was dissolved in isopropyl alcohol and ether added to precipitate 333 mg. of a colorless powder, m.p. 239–245° (viscous melt). The solid was recrystallized from ethanol–isopropyl alcohol solution to give 229 mg. of a powder which melted at 240–245° after being dried for 2 hr. at 80° (1 mm.). The infrared spectrum (Nujol mull) of this sample showed a band at 2.95 μ (OH) and a weak band at 11.44 μ which indicated the presence of traces of an unsaturated compound.

(b) To a solution prepared from 1.3 g. of sodium in 50 ml. of absolute ethanol in a dry flask equipped with a reflux condenser stoppered with a calcium chloride tube was added 0.43 g. of the dihydrochloride of XIII. The mixture was refluxed for 36 hr. and then water was added to bring all of the salts into solution. After the resulting solution had been refluxed for 3 hr., the solution was steam distilled. The distillate was acidified with hydrochloric acid and evaporated to dryness. The residue, m.p. 233–243°, weighed 390 mg., the solid was recrystallized twice from ethanol–isopropyl alcohol solution and once from ethanol ethyl acetate solution to yield 0.21 g. of a colorless powder, m.p. 244–254° dec.

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