Hypotensives. V. 2,2,6,6-Tetramethylpiperidines and Related Compounds[1]

JERRY E. ROBERTSON,[2] JOHN H. BIEL, AND FRANK DIPIERRO

Research Division, Lakeside Laboratories, Inc., Milwaukee 1, Wisconsin

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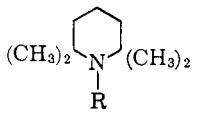
A group of 2,2,6,6-tetramethylpiperidine derivatives has been prepared and evaluated as antihypertensive agents. Some of these compounds incorporate a N-guanidinoalkyl moiety. Others were ring-expanded and variously substituted.

1,2,2,6,6-Pentamethylpiperidine (pempidine, Ia)[3] and certain closely related analogs (*e.g.*, Ib and Ic) are potent and long-acting ganglionic blocking agents with proven clinical efficacy in the treatment of hypertension.[4] In general, these drugs undergo more complete and predictable absorption from the gastrointestinal tract as important advantages over the older diquaternary type of ganglionic blocking compounds.[5] However, the mechanism by which the potent blood pressure lowering activity of pempidine is achieved results in a number of highly undesirable side reactions. The present work represents an attempt at modifying the mechanism of action of pempidine through major structural alterations of the parent molecule, in the hope of



	R
Ia	CH_3
Ib	C_2H_5
Ic	$NHCH_3$

obtaining antihypertensive drugs which might act *via* different mechanisms.

If we assume that pempidine exerts its activity because of high affinity for cell receptor sites that are involved in the control of blood pressure, but that its structural makeup allows it to act only at ganglionic sites, a modification of its structure could conceivably produce a chemical affinity for other receptor sites that are involved in blood pressure regulation, such as the vasomotor centers or the sympathetic postganglionic nerve endings. For these reasons we extended the several structure–activity studies which have already appeared on pempidine[6] by combining 2,2,6,6-tetramethylpiperidine or related amines with selected structural features present in some newer antihypertensive agents as well as through the synthesis of novel derivatives.

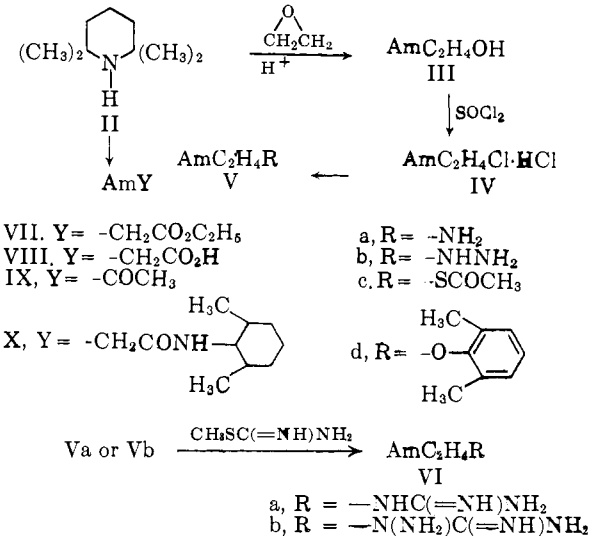


CHART A

The starting material, triacetoneamine, was prepared by modifications of the method of Francis.[7] A cooled mixture of acetone and calcium chloride was intermittently treated with ammonia over a 10-day period. After a suitable workup including a careful distillation, there was obtained approximately a 20% yield of pure triacetoneamine which crystallized at room temperature. Wolff–Kishner reduction of triacetoneamine according to the procedure of Leonard and Nommensen[8] afforded 2,2,6,6-tetramethylpiperidine (II).

Chart A shows the first series of reactions and compounds discussed. Treatment of II with ethylene oxide under acid catalysis gave the primary alcohol (III) in 75% yield. Compound III was converted almost quantitatively with thionyl chloride to the corresponding chloride hydrochloride (IV). A subsequent report of this material by Moffett and Aspergren[9] described a less convenient preparative route. The salt IV was converted readily to the expected amine (Va) and hydrazine (Vb) by addition to large excesses of ammonia and hydrazine, respectively. Reaction of these bases with S-methylisothiourea sulfate furnished the guanidine and aminoguanidine shown (VIa and VIb, respectively). The structure assigned *a priori* to VIb was indirectly verified by analogy to closely related

(1) (a) Presented before the Division of Medicinal Chemistry, 144th National Meeting of the American Chemical Society, Los Angeles, California, March 31–April 5, 1963; (b) Paper IV; J. H. Biel, A. E. Drukker, and T. F. Mitchell, *J. Am. Chem. Soc.*, **82**, 2204 (1960).

(2) To whom inquiries regarding this paper should be addressed.

(3) (a) A. Spinks and E. H. P. Young, *Nature*, **181**, 1397 (1958); (b) G. E. Lee, W. R. Wragg, S. J. Corne, N. D. Edge, and H. W. Reading, *Nature*, **181**, 1717 (1958).

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(7) F. Francis, *J. Chem. Soc.*, 2897 (1927).

(8) N. J. Leonard and E. W. Nommensen, *J. Am. Chem. Soc.*, **71**, 2808 (1949).

(9) R. B. Moffett and B. D. Aspergren, *ibid.*, **82**, 1604 (1960).

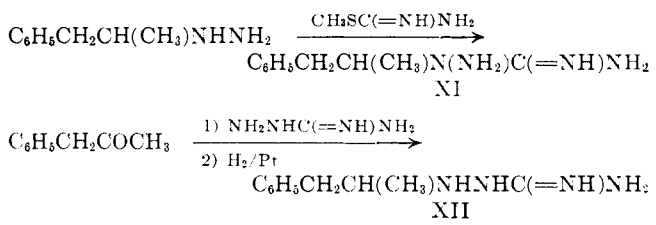

CHART B

reactions which are discussed later. IV was also converted to the thioacetate (Vc) according to the method of Biel and co-workers[10] and to the 2,6-dimethylphenyl ether (Vd) by treatment with sodium 2,6-dimethylphenoxide. Interest in the later material arose from a structural relationship to choline 2,6-xylyl ether.[11]

1-Carboxymethyl-2,2,6,6-tetramethylpiperidine (VII), a novel amino acid, was obtained through the reaction of ethyl chloroacetate with II in the presence of potassium carbonate to yield the anticipated ester (VII) which was hydrolyzed with barium hydroxide. Acylation of II with acetyl chloride gave IX. The lidocaine-like compound X was prepared by treatment of II with ω-chloro-2,6-dimethylacetanilide.

The structures of two aminoguanidines reported here (VIb and XIII) which resulted from guanylation of substituted hydrazines are assigned by analogy to the results obtained by Greer and Smith for guanylation of methylhydrazine[12] and to the results of the following study. β-Phenylisopropylhydrazine[13] was treated with S-methylisothiourea sulfate to afford the aminoguanidine (XI) as shown in Chart B. Displacement of methyl mercaptan by the substituted hydrazino-nitrogen was assumed and is in agreement with the Green and Smith study.[12] To substantiate this point further, the alternative compound, which would result from displacement of methyl mercaptan by the terminal hydrazino nitrogen, was prepared unequivocally. Condensation of phenylacetone with aminoguanidine afforded the expected guanylhydrazone. Catalytic reduction over platinum provided XII which was not identical with the isomeric compound XI (see Experimental).

Chart C shows several series of reactions carried out starting with triacetoneamine. Satisfactory methylation of this base occurred after standing for one week with excess methyl iodide in Skellysolve C. Under these conditions, triacetoneamine hydriodide precipitated and the product remained in solution as expected.[6b] Application of the Schmidt reaction to the product according to the procedure which Dickerman and Lindwall used for the normethyl compound[14] afforded the expected ring-expanded cyclic amide which was reduced with lithium aluminum hydride by a procedure adapted from Michaels and Zaugg[15] to a homopiperazine. Treatment of this material with ethylene oxide gave the anticipated alcohol which was converted to the corresponding chloride. Addition of this chloride to excess hydrazine and guanylation of the product

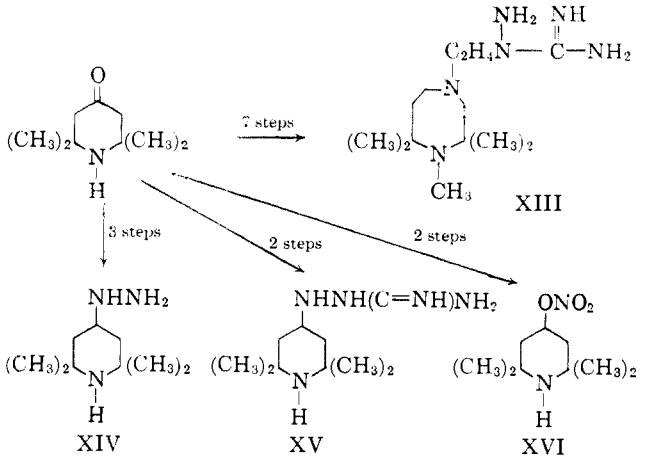

CHART C

provided XIII which perhaps more closely resembles guanethidine than VIa and VIb.

4-Hydrazino-2,2,6,6-tetramethylpiperidine (XIV) was prepared by condensation of triacetoneamine with carboethoxyhydrazine, reduction of the stable adduct over platinum and barium hydroxide hydrolysis to the hydrazine. Triacetoneamine was also condensed with aminoguanidine and the guanylhydrazone catalytically reduced to XV. The novel nitrate ester XVI was prepared by direct nitration of the corresponding alcohol resulting from lithium aluminum hydride reduction of triacetoneamine. The hydrazone of 1-hydrazinophthalazine and triacetoneamine was obtained to evaluate the possibility of hydrolysis, after administration, to two antihypertensives which act by different mechanisms.[16]

All the compounds listed in the preceding discussion were evaluated for hypotensive activity in the normotensive anesthetized dog and rat and for ganglionic blocking activity in the cat nictitating membrane preparation according to the methods described by Buckley and co-workers.[17] A preliminary report of this work has already appeared.[18] Hypotensive agents resulted when a guanidinoalkyl moiety was incorporated into the molecule, such as in VIa, VIb, and XIII. The most potent agent of this class was VIb which resembles pempidine in potency and duration of action at 5 mg./kg. in the rat (intravenous administration) and is also a ganglionic blocking compound.[18] Introduction of groups which decreased basicity of the tetramethylpiperidino nitrogen, as in VII and IX, virtually abolished the hypotensive activity. Bretherick, *et al.*,[6a] reported a similar relationship. The remaining materials mentioned were hypotensive agents of lower potency and shorter duration of action than VIb or pempidine and appeared to act by ganglionic blockade. Detailed pharmacologic results related to the mechanism of action of the more potent antihypertensive drugs will be published elsewhere.[19]

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(12) A. H. Greer and G. B. L. Smith, *J. Am. Chem. Soc.*, **72**, 874 (1950).
(13) CATRON®, pheniprazine hydrochloride.
(14) S. C. Dickerman and H. G. Lindwall, *J. Org. Chem.*, **14**, 533 (1949).
(15) R. J. Michaels and H. E. Zaugg, *ibid.*, **25**, 637 (1960).
(16) Triacetoneamine is an effective ganglionic blocking agent when evaluated in the cat nictitating membrane preparation described in reference 17b; J. P. Buckley, private communication.
(17) (a) J. P. Buckley, M. L. Jacquart, R. K. Bickerton, W. J. Hudak, F. M. Schalit, J. J. Defeo, and J. A. Bianculli, *J. Am. Pharm. Assoc., Sci. Ed.*, **49**, 586 (1960); (b) Z. P. Horovitz, E. C. Reif, and J. P. Buckley, *ibid.*, **47**, 718 (1958).
(18) J. P. Buckley, S. Shanor, J. Gloss, and W. J. Kinnard, Abstracts of Papers, American Pharmaceutical Association Annual Meeting, Miami Beach, Florida, May 12–17, 1963.
(19) J. P. Buckley, private communication.

Experimental[20]

N-(β-Hydroxyethyl)2,2,6,6-tetramethylpiperidine (III).—To 28 g. (0.20 mole) of II in 100 ml. of methanol was added 10 g. of ethylene oxide and 0.5 ml. of concd. hydrochloric acid. The mixture was heated at 100° for 2 hr. in a pressure bottle, cooled, and concentrated to dryness *in vacuo*. The residue was recrystallized from heptane to give 28 g. (76%) of product, m.p. 98–100°, reported[9] m.p. 96–98°.

Anal. Calcd. for $C_{11}H_{23}NO$: N, 7.56. Found: N, 7.55. **Maleate,**[21] m.p. 118–120° dec.

Anal. Calcd. for $C_{11}H_{23}NO \cdot C_4H_4O_4$: N, 4.65. Found: N, 4.69.

N-(β-Chloroethyl)-2,2,6,6-tetramethylpiperidine Hydrochloride (IV).—To 40 g. (0.22 mole) of III in 100 ml. of dry benzene was added 30 g. (0.25 mole) of thionyl chloride in 100 ml. of dry benzene. The mixture was stirred at reflux for 2 hr. and then concentrated to dryness *in vacuo*. The residue was dissolved in 100 ml. of methanol, treated with charcoal, filtered, and the filtrate diluted with ether to the cloud point. Cooling gave a solid which was collected and dried to afford 48 g. (91%) of product, m.p. 220–222°. Reported,[9] m.p. 219–220°.

Anal. Calcd. for $C_{11}H_{22}ClN \cdot HCl$: N, 5.83; Cl, 29.58. Found: N, 5.86; Cl, 29.70.

[β-(2,2,6,6-Tetramethylpiperidino)-ethylguanidine] Sulfate (VIa).—To 36 g. (0.15 mole) of IV in a 1 l. autoclave was added 500 ml. of 10% ethanolic ammonia. The mixture was heated to 125° for 2.5 hr. then concentrated to dryness under vacuum. The residue was dissolved in about 200 ml. of water, excess potassium hydroxide was added, and the mixture was extracted with three 100 ml. portions of tetrahydrofuran. The combined organic layers were dried over potassium carbonate. After separation of the drying agent, the solvent was removed under vacuum to give a solid residue which amounted to 24 g. of crude Va, m.p. 55–58°. Without further purification, 19.2 g. (0.050 mole) of Va in 25 ml. benzene was added to 7.0 g. (0.025 mole) of S-methylisothiourea sulfate in 100 ml. of 70% ethanol and the mixture was refluxed and stirred for 6 hr. After standing overnight at room temperature, the solid which formed was collected, triturated with ether, and recrystallized from ethanol to afford 13 g. (82%) of product, m.p. >275° dec.

Anal. Calcd. for $(C_{12}H_{26}N_4)_2 \cdot H_2SO_4$: C, 52.32; H, 9.81; N, 20.31; S, 5.81. Found: C, 51.80; H, 9.95; N, 20.10; S, 5.66.

β-(2,2,6,6-Tetramethylpiperidino)-ethylhydrazine (Vb).—To 500 ml. of refluxing 85% hydrazine hydrate was added 60 g. (0.25 mole) of IV in 100 ml. of water. After stirring and refluxing for 20 hr., excess potassium hydroxide was added, and the cooled mixture was then extracted with three 150-ml. portions of ether. The separated and combined organic layers were dried over potassium carbonate. After removal of the drying agent and the solvent, the residue was fractionated to afford 10 g. (20%) of product, b.p. 85–90° (0.4 mm.).

Anal. Calcd. for $C_{11}H_{25}N_3$: N, 21.07. Found: N, 21.32. **Dihydrochloride salt,** m.p. 202° dec.[21]

Anal. Calcd. for $C_{11}H_{25}N_3 \cdot 2HCl$: Cl, 26.05; N, 15.43. Found: Cl, 25.75; N, 15.49.

N-Amino-N-[β-(2,2,6,6-tetramethylpiperidino)-ethyl]guanidine Sulfate (VIb).—To 4.9 g. (0.025 mole) of Vb in 60 ml. of 70% ethanol was added 3.9 g. (0.014 mole) of S-methylisothiourea sulfate. The mixture was refluxed overnight, concentrated to dryness, and the residue recrystallized from methanol to afford 6.0 g. (83%) of product, m.p. 227–230°.

Anal. Calcd. for $(C_{12}H_{27}N_5)_2 \cdot H_2SO_4$: C, 49.63; H, 9.71; S, 5.52. Found: C, 49.35; H, 9.80; S, 5.31.

β-(2,2,6,6-Tetramethylpiperidino)-ethylthioacetate Hydrochloride (Vc).—To 41 g. (0.17 mole) of IV suspended in 450 ml. of 2-propanol was added 15.2 g. (0.20 mole) of thioacetic acid and the mixture was stirred and refluxed for 15 hr. After concentrating *in vacuo* to near dryness, 300 ml. of ethyl ether was added, and the solid which formed was collected and recrystallized from 2-propanol to provide 46.8 g. (98%) of product, m.p. 130–133°.

Anal. Calcd. for $C_{13}H_{25}NO_5 \cdot HCl$: Cl, 12.67; N, 5.01; S, 11.46. Found: Cl, 12.64; N, 5.04; S, 11.61.

β-(2,6-Dimethylphenoxy)-2,2,6,6-tetramethylpiperidinoethane Hydrochloride (Vd).—To a solution prepared from 2.3 g. (0.10 mole) of sodium in 100 ml. of ethanol was added 6.1 g. (0.050 mole) of 2,6-dimethylphenol and then 12.0 g. (0.050 mole) of IV with stirring and cooling. After 24 hr. at reflux the cooled mixture was treated with potassium hydroxide and extracted twice with ether. The combined organic extracts were dried over potassium carbonate and, after separation of the drying agent, excess dry hydrogen chloride was introduced. The crude product separated and was recrystallized from ethyl acetate to provide 6.2 g. (38%), m.p. 232–234°.

Anal. Calcd. for $C_{19}H_{31}NO \cdot HCl$: Cl, 10.87; N, 4.30. Found: Cl, 11.10; N, 4.26.

1-Carbethoxymethyl-2,2,6,6-tetramethylpiperidine (VII).—A mixture of 42 g. (0.30 mole) of II, 39 g. (0.27 mole) potassium carbonate, and 40 g. (0.33 mole) ethyl chloroacetate was refluxed in 200 ml. ethanol for 6 hr. After cooling, the precipitated salt was collected and discarded and the filtrate was concentrated to dryness. This residue was fractionated to provide 45 g. (65%) of product, b.p. 110–115° (15 mm.).

Anal. Calcd. for $C_{13}H_{25}NO_2$: N, 6.05. Found: N, 6.08. **Maleate,**[21] m. p. 155–156°.

Anal. Calcd. for $C_{13}H_{25}NO_2 \cdot C_4H_4O_4$: C, 58.80; H, 8.41; N, 4.03. Found: C, 58.68; H, 8.53; N, 4.01.

1-Carboxymethyl-2,2,6,6-tetramethylpiperidine (VIII).—A mixture of 11.3 g. (0.49 mole) of the above ester and 15.8 g. (0.50 mole) of barium hydroxide octahydrate in 100 ml. of water was refluxed for 12 hr. After cooling, carbon dioxide was added until barium carbonate precipitation was completed. The solid was collected and washed with water. The combined filtrate and washings were reduced to dryness and dissolved in about 100 ml. of acetonitrile. This solution was diluted with an excess of anhydrous ether and cooled. The solid which formed was collected and dried to provide 4.5 g. (46%) of product, m.p. 124–126°.

Anal. Calcd. for $C_{11}H_{21}NO_2$: N, 6.89; neut. equiv., 203. Found: N, 6.97; neut. equiv., 202.

1-Acetyl-2,2,6,6-tetramethylpiperidine (IX).—To 28 g. (0.20 mole) of II dissolved in 100 ml. of benzene was added 7.9 g. (0.10 mole) of acetyl chloride in 100 ml. of benzene over 1.5 hr. at 20–25°. After stirring overnight at this temperature, the mixture was filtered and the filtrate was concentrated *in vacuo*. Distillation of the residue provided 9.0 g. (50%) of product, b.p. 120–123° (0.2 mm.).

Anal. Calcd. for $C_{11}H_{21}NO$: C, 72.08; H, 11.53; N, 7.65. Found: C, 71.86; H, 11.53; N, 7.62.

ω-(2,2,6,6-Tetramethylpiperidino)-2,6-dimethylacetanilide Hydrochloride (X).—A mixture of 9.7 g. (0.050 mole) of ω-chloro-2,6-dimethylacetanilide, 15 g. (0.10 mole) of sodium iodide, and 21.5 g. (0.15 mole) of II in 100 ml. of dimethylformamide was stirred on the steam bath for 10 hr. After cooling and dilution with water, a solid formed which was collected and recrystallized from dimethylformamide–water to provide 5.5 g. (37%) of the free base, m.p. 235–237° dec., which was converted to a hydrochloride, m.p. 245–247° dec.

Anal. Calcd. for $C_{19}H_{30}N_2O \cdot HCl$: C, 67.70; H, 9.27; Cl, 10.53; N, 8.32. Found: C, 67.41; H, 9.18; Cl, 10.49; N, 8.27.

N-Amino-N-(1-methyl-2-phenethyl)guanidine Hydrochloride (XI).—A mixture of 60 g. (0.40 mole) of β-phenylisopropylhydrazine and 27.8 g. (0.10 mole) of S-methylisothiourea sulfate in 200 ml. of ethanol was refluxed for 1 hr. A precipitate formed on cooling which was collected and thoroughly washed with ethanol to provide, after drying, 45 g. of the product as a sulfate salt, m.p. 191–193° dec. A mixture of 2.41 g. (0.0050 mole) of the sulfate salt and 1.22 g. (0.0050 mole) of barium chloride dihydrate in 200 ml. of water was refluxed and stirred for 15 hr. After cooling, the solid was collected and the filtrate concentrated to dryness. The residue was recrystallized from acetonitrile–ether to afford 2.0 g. (43%) of product, m.p. 114–116°.

Anal. Calcd. for $C_{10}H_{16}N_4 \cdot HCl$: C, 52.54; H, 7.50; Cl, 15.51. Found: C, 52.57; H, 7.21; Cl, 15.41.

N-Guanidino-α-methyl-β-phenethylamine Hydrochloride (XII).—A solution of 13.4 g. (0.10 mole) of phenylacetone, 13.6 g. (0.10 mole) of aminoguanidine bicarbonate, and 10 ml. of concd. hydrochloric acid in 200 ml. of ethanol was refluxed 15 hr., cooled, and reduced under 3 atm. of hydrogen in the presence of 0.6 g. of platinum dioxide over several days. The catalyst was collected and the filtrate concentrated to dryness. The residue was crystallized from acetonitrile–ether to afford 8.5 g. (36%) of product, m.p. 124–126°.

(20) Melting points are corrected; boiling points are uncorrected. Analyses were performed under the direction of Mr. E. Kluchesky in this Laboratory; Manser Laboratories, Germany; and by Illini Microanalytical Laboratories.

(21) Salts were prepared and recrystallized from ethanol or ethanol–ether.

Anal. Calcd. for $C_{10}H_{16}N_4 \cdot HCl$: Cl, 15.51; N, 24.50. Found: Cl, 15.43; N, 24.40.

A mixture of XI and XII melted at 100–115°. Infrared spectra of chloroform solutions of XI and XII were not identical.

N-Methyltriacetoneamine.—A solution of 56 g. (0.40 mole) of methyl iodide and 31 g. (0.20 mole) of triacetoneamine in 100 ml. of Skellysolve C was allowed to stand at room temperature for 1 week. The solution was decanted from the crude triacetoneamine hydriodide which precipitated, the solvent removed *in vacuo*, and the residue distilled to afford 13 g. (39%) of product, b.p. 97–102° (14 mm.). Reported,[6b] b.p. 100–102° (15 mm.).

Anal. Calcd. for $C_{10}H_{19}NO$: N, 8.28. Found: N, 8.34.

1,2,2,7,7-Pentamethyl-4-(β-chloroethyl)-1,4-diazacycloheptane Dihydrochloride.—To a solution of 70 g. (0.41 mole) of the above ketone in 200 ml. of chloroform was added 150 ml. of concd. sulfuric acid at 0–5° followed by 58 g. (0.89 mole) of sodium azide in small portions with stirring. The mixture was heated to 45° for 1 hr., cooled, and poured over a mixture of ice and excess potassium hydroxide. The resulting emulsion was filtered and allowed to stratify. The layers were separated and the aqueous phase was extracted twice with chloroform. The combined organic layers were dried over sodium sulfate. After separating the drying agent, the solvent was removed under vacuum and the residue collected and thoroughly washed with hexane to afford, after drying, 55 g. of 1,2,2,7,7-pentamethyl-1,4-diazacycloheptane-2-one. To 22 g. (0.58 mole) of lithium aluminum hydride in 500 ml. of tetrahydrofuran at reflux was added 55 g. (0.30 mole) of the cyclic amide in 300 ml. of tetrahydrofuran and the resulting mixture was stirred and refluxed for 20 hr. Water (50 ml.) followed by 100 ml. of 40% potassium hydroxide was added slowly and the precipitate which formed was collected and washed with tetrahydrofuran. The combined filtrates were dried over potassium carbonate. The drying agent and solvent were removed and the residue was fractionated to afford 30 g. of 1,2,2,7,7-pentamethylhomopiperazine,[22] b.p. 46–48° (0.2 mm.).

Anal. Calcd. for $C_{10}H_{22}N_2$: N, 16.44. Found: N, 16.40.

To 30 g. (0.18 mole) of the base obtained from the above procedure was added 10 g. of ethylene oxide in 100 ml. of methanol in a pressure bottle. Concd. hydrochloric acid (0.5 ml.) was added and the bottle quickly stoppered and then heated to about 100° for 2.5 hr. The solvent was removed *in vacuo* and the residue fractionated to give 33 g. of 1,2,2,7,7-pentamethyl-4-(β-hydroxyethyl)-1,4-diazacycloheptane, b.p. 156–158° (20 mm.).

Anal. Calcd. for $C_{12}H_{26}N_2O$: N, 13.08. Found: N, 12.81.

Excess hydrogen chloride gas was added to 35 g. (0.16 mole) of the alcohol obtained previously in 250 ml. of chloroform. To this mixture was then added 40 g. (0.33 mole) of thionyl chloride dropwise over 1 hr. The mixture was stirred and refluxed for 8 hr., the solvent and excess thionyl chloride were removed under vacuum, the residue was dissolved in about 500 ml. of hot ethanol, and excess dry ether was added to induce precipitation of the product. The precipitate was collected, washed with ether, and dried to afford 41 g. of product, m.p. 235–237° dec.

Anal. Calcd. for $C_{12}H_{25}ClN_2 \cdot 2HCl$: N, 9.17; Cl^-, 23.20. Found: N, 9.11; Cl^-, 23.23.

4-{β-(N-Amino-N-guanyl)aminoethyl}-1,2,2,7,7-pentamethyl-1,4-diazacycloheptane Sulfate (XIII).—To 300 ml. of refluxing 85% hydrazine hydrate was added a solution of 15 g. (0.050 mole) of the above chloride hydrochloride in 500 ml. of cold water over 3.5 hr. with stirring. After refluxing an additional 16 hr., the mixture was concentrated *in vacuo* to an emulsion. After saturating with sodium hydroxide, 3 extractions with 150-ml. portions of tetrahydrofuran were carried out and the organic layers combined and dried over potassium carbonate. The drying agent and solvent were removed and the residue fractionated to give 10.5 g. of crude 1,2,2,7,7-pentamethyl-4-(β-hydrazinoethyl)-1,4-diazacycloheptane, b.p. 96–100° (0.01 mm.). The hydrazine (4.6 g., 0.020 mole) was added without further purification to 2.8 g. (0.010 mole) of S-methylisothiourea sulfate in 25 ml. of 70% ethanol and the mixture was refluxed for 16 hr. The solvent was removed under vacuum and the residue was recrystallized from ethanol to afford 6.3 g. (28%) of product, m.p. 193–197° dec.

Anal. Calcd. for $C_{13}H_{30}N_6 \cdot H_2SO_4$: N, 26.28; S, 5.01. Found: N, 26.06; S, 5.22.

(22) References 4 and 6a list this compound without physical data.

4-Carbethoxyhydrazino-2,2,6,6-tetramethylpiperidine Dihydrochloride.—A mixture of 52 g. (0.50 mole) of carbethoxyhydrazine and 77 g. (0.50 mole) of triacetoneamine in 25 ml. of 2-propanol was refluxed for 12 hr. The solvent was removed *in vacuo* and the residue was recrystallized from Skellysolve B to provide 83 g. of crude triacetoneamine carboethoxyhydrazone, m.p. 102–105°. A mixture of 43 g. (0.18 mole) of this material, 1 g. of platinum dioxide, and 24 g. of acetic acid in 200 ml. of ethanol was treated with hydrogen at 3 atm. The theoretical amount of hydrogen was taken up in 20 hr. The catalyst was separated and washed and the combined filtrate and washings were concentrated to dryness *in vacuo*. The residue was dissolved in a small amount of water and this solution was treated with excess potassium hydroxide then extracted with 3 portions of ether. The combined and dried organic layers were concentrated to dryness to provide about 40 g. of crude base. Conversion of this material to the hydrochloride gave 43 g. (52%) of product, m.p. 236–238° dec.

Anal. Calcd. for $C_{12}H_{25}N_3O_2 \cdot 2HCl$: Cl, 22.42; N, 13.28. Found: Cl, 22.47; N, 13.36.

4-Hydrazino-2,2,6,6-tetramethylpiperidine Dimaleate (XIV).—A mixture of 18.2 g. (0.075 mole) of the above carbethoxyhydrazine base and 23.7 g. (0.075 mole) of barium hydroxide octahydrate in 600 ml. of 5:1 water–methanol was refluxed for 2.5 hr. The mixture was filtered and the precipitate was washed with cold water. The combined filtrate and washings were treated with excess sodium hydroxide and this mixture was extracted with 3 portions of ether and one of tetrahydrofuran. The combined and dried organic layers were concentrated *in vacuo* to provide a residue of crude product. Rapid distillation of this material gave 12 g. (94%) of product, b.p. 72–74° (0.05 mm.). The maleate was immediately prepared and melted at 147–149° dec. after one recrystallization.

Anal. Calcd. for $C_9H_{21}N_3 \cdot 2C_4H_4O_4$: C, 50.61; H, 7.25. Found: C, 50.62; H, 7.31.

4-Aminoguanidino-2,2,6,6-tetramethylpiperidine Dihydrochloride (XV).—A mixture of 6.8 g. (0.050 mole) of aminoguanidine carbonate and 7.7 g. (0.050 mole) of triacetoneamine was refluxed for 4 hr. in 100 ml. of ethanol. Platinum dioxide (0.3 g.) was added and the mixture treated with hydrogen at 3 atm. The theoretical amount of gas was taken up in a few hours, the catalyst was separated by filtration, and the filtrate was treated with excess ethereal hydrogen chloride. The solid which formed was collected and recrystallized from ethanol to afford 10 g. (71%) of product, m.p. 244–246° dec.

Anal. Calcd. for $C_{10}H_{23}N_5 \cdot 2HCl$: C, 41.95; H, 8.80; Cl, 24.78; N, 24.60. Found: C, 42.17; H, 8.62; Cl, 24.53; N, 24.46.

4-Nitrato-2,2,6,6-tetramethylpiperidine Maleate (XVI).—To 35 ml. of fuming nitric acid at −5 to −10° was added 4.0 g. (0.25 mole) of 2,2,6,6-tetramethyl-4-piperidinol[23] with stirring. After 2 hr. of cooling, the mixture was allowed to stir at room temperature for 15 hr. After pouring onto ice and slow addition of excess potassium carbonate, the mixture was extracted with 3 portions of chloroform. The combined organic layers were dried over sodium sulfate and then concentrated to dryness *in vacuo*, after separation of the drying agent, to provide 5.0 g. of crude base. This residue was dissolved in ether and a solution of maleic acid in ethanol was added. A solid formed which was collected and recrystallized from ethanol to provide 3.4 g. (43%) of product, m.p. 157–159°.

Anal. Calcd. for $C_9H_{18}N_2O_3 \cdot C_4H_4O_4$: C, 49.07; H, 6.84; N, 8.81. Found: C, 49.14; H, 6.91; N, 8.66.

Triacetoneamine 1-Phthalazinylhydrazone Dihydrochloride.—A solution of 4.8 g. (0.031 mole) of triacetoneamine and 4.7 g. (0.029 mole) of 1-hydrazinophthalazine in 50 ml. of ethanol was refluxed 1 hr. Dilution with water provided a precipitate which was collected and recrystallized from ethanol to afford 6.2 g. (58%) the hydrazone, m.p. 139–142°. The dihydrochloride, m.p. 231–233° dec., was prepared.

Anal. Calcd. for $C_{17}H_{23}N_5 \cdot 2HCl$: C, 55.10; H, 6.18; Cl, 19.19; N, 18.93. Found: C, 55.04; H, 6.87; Cl, 19.51; N, 18.60.

(23) Prepared by lithium aluminum hydride reduction of triacetoneamine in tetrahydrofuran. See reference 6h for a similar procedure.