Acknowledgments. The writer wishes to acknowledge the capable assistance of Mr. Tom F. Davenport in conducting this investigation and to express appreciation to Monsanto Chemical Co. for permission to publish the work.

TEXAS CITY, TEX.

[CONTRIBUTION FROM THE WYETH INSTITUTE FOR MEDICAL RESEARCH, WYETH LABORATORIES, AND THE DEPARTMENT OF CHEMISTRY, TEMPLE UNIVERSITY]

Synthesis of Azacycloheptane Derivatives Related to Piperidine Analgesics[1,2]

JULIUS DIAMOND,[3] WILLIAM F. BRUCE, AND FLOYD T. TYSON

Received October 11, 1956

A synthesis of seven-membered ring compounds related to meperidine was effected by the stepwise reaction of 2-phenyl-4-dimethylaminobutyronitrile with trimethylene halides. The initial cyclization products, 1-methyl-4-phenyl-4-cyanoazacycloheptane methohalides, lost methyl halide at elevated temperatures to yield the tertiary aminonitrile, which was converted to the carboxylic acid, amide, ester, ketone, and amine derivatives. *dl*-1-Methyl-4-phenyl-4-carbethoxyazacycloheptane was resolved into its optical antipodes.

Seven-membered ring analogs of the piperidine analgesic meperidine[4] and a number of its derivatives were synthesized in a study of the effect of structure on analgesic activity.[5]

The azacycloheptane ring[6] was formed by the reaction of 2-phenyl-4-dimethylaminobutyronitrile (I) with trimethylene chlorobromide (II), bromide (IIa), or chloride (IIb).[7,8] Highest yields were obtained by a stepwise reaction with the chlorobromide. I was converted to its sodio derivative (Ia) by sodamide in toluene or ether at 35°. When II was added dropwise to the solution of Ia at about −20°, the product was almost exclusively 1-dimethylamino-3-phenyl-3-cyano-6-chlorohexane (III). At temperatures of 0° to +10°, some of the 1,6-aminobromide (IIIa) was also formed. Moreover, at these higher temperatures preferential formation of III was favored by low concentrations of Ia which were obtained by reversing the order of addition of the reactants, *i.e.*, by adding Ia to II. This cumbersome operation was avoided by conducting the "direct addition" alkylation at −20°.

The intramolecular cyclization of III to 1-methyl-4-phenyl-4-cyanoazacycloheptane methochloride (IV) was carried out without isolating III. This was accomplished by replacing the toluene or ether of the alkylation mixture with such polar solvents as nitrobenzene, *o*-nitrotoluene, benzonitrile, or 2-nitropropane, and heating the solution at 100° until no more quaternary salt (IV) precipitated. Use of a high dilution was unnecessary and the yield of IV from I was 65 to 80%. The preferred dilution in the polar solvent for the best yields of pure IV was approximately 1*M*. When the cyclization of III was attempted in toluene at 100° and about 1*M* concentration, an impure preparation of IV was obtained. From those experiments in which Ia was alkylated by II at 0° to +10°, subsequent cyclization led to a mixture of quaternary salts IV and IVa. Trimethylene chloride (IIb) was also used to produce IV from I, but the yield was 24%.

1-Methyl-4-phenyl-4-cyanoazacycloheptane methobromide (IVa) was formed in low yields by the reaction of Ia with trimethylene bromide (IIa). Alkylation of Ia by IIa, even at low temperatures, led to a bis-amine as well as the desired 1,6-aminobromide (IIIa). Formation of the bis-amine was favored when the alkylation was conducted in more concentrated solutions. Cyclization of IIIa to IVa went poorly because IIIa underwent intermolecular polymerization (probably to the linear polymeric salt IVb) more readily than III. To overcome this effect, the cyclization of IIIa required greater dilution. IVa was obtained from I in 26% yield by heating an approximately 0.1*M* solution of IIIa in nitrobenzene at 100° for 1 hr. Longer heating diminished the purity of IVa in the same manner as observed when the cyclization of IIIa was conducted at higher concentrations.

(1) Taken in part from the dissertations of J. Diamond submitted to the Temple University Graduate Council in partial fulfillment of the requirements for the degrees of Master of Arts (1953) and Doctor of Philosophy (1955).

(2) Presented before the Organic Division at the Delaware Valley Regional Meeting of the AMERICAN CHEMICAL SOCIETY, Philadelphia, Pa., February 16, 1956.

(3) Present address: Wallace Laboratories Division, Carter Products, Inc., New Brunswick, N. J.

(4) Generic name for ethyl 1-methyl-4-phenylpiperidine-4-carboxylate.

(5) (a) This portion of our work had been completed when Blicke and Tsao (ref. 5b) reported a similar study in which several of the present compounds were synthesized by modifications of our procedure.

(b) Blicke and Tsao, *J. Am. Chem. Soc.*, **75**, 3999 (1953).

(6) Hexahydro form of azepine, also named hexamethylenimine, Patterson and Capell, *Ring Index*, Reinhold Publishing Corp., New York, N. Y., 1940, p. 60.

(7) Diamond and Bruce, U. S. Patent 2,666,050 (1954) [*Chem. Abstr.*, **49**, 4031 (1955)].

(8) Kaegi and Miescher, *Helv. Chim. Acta*, **32**, 2489 (1949), employed ethylene halides in a synthesis of meperidine and its derivatives.

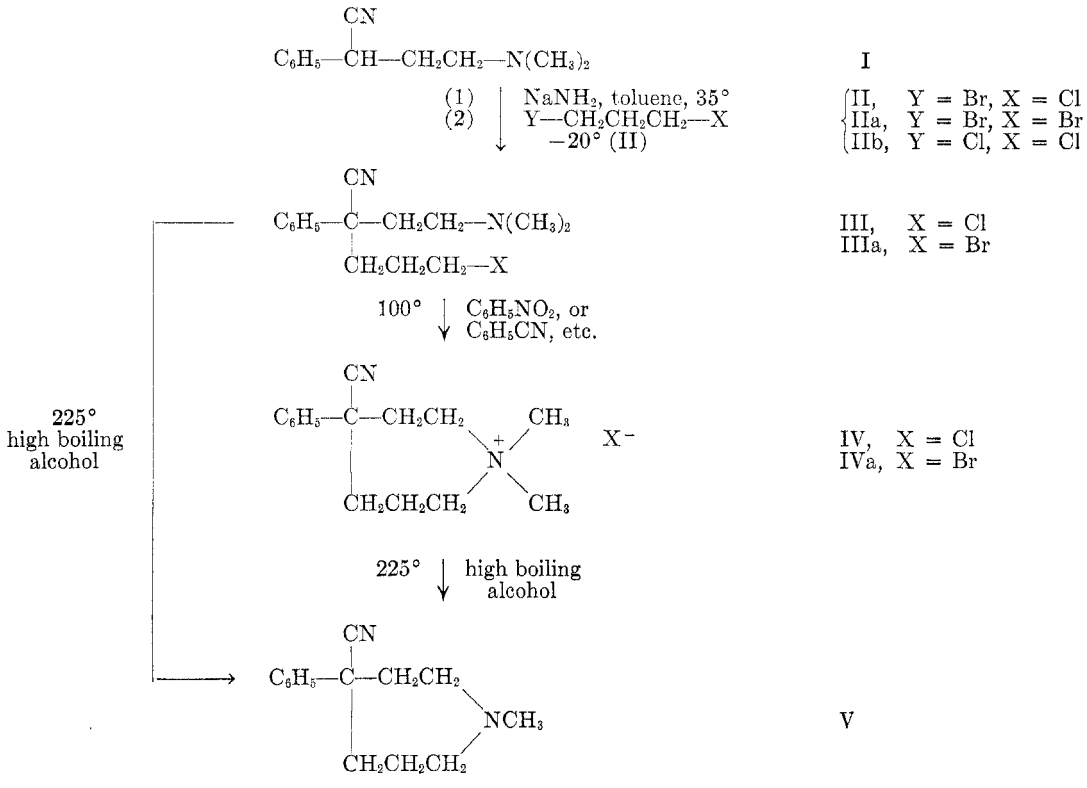


FIG. 1

The structure of IV was confirmed by a modified Hofmann degradation in which IV was treated with sodium methoxide in boiling methanol. Hydrogen chloride was eliminated and ring cleavage occurred yielding an unsaturated alicyclic amine (VI). Catalytic hydrogenation of VI gave a reduction product which was identical with 2-phenyl-2-ethyl-5-dimethylaminovaleronitrile (VII), prepared by an alternative synthesis.

Additional evidence supporting the structure of IV was obtained from microanalytical and molecular weight data. Analysis proved that all the halogen was present in ionic form. The observed molecular weight, determined cryoscopically in water, was

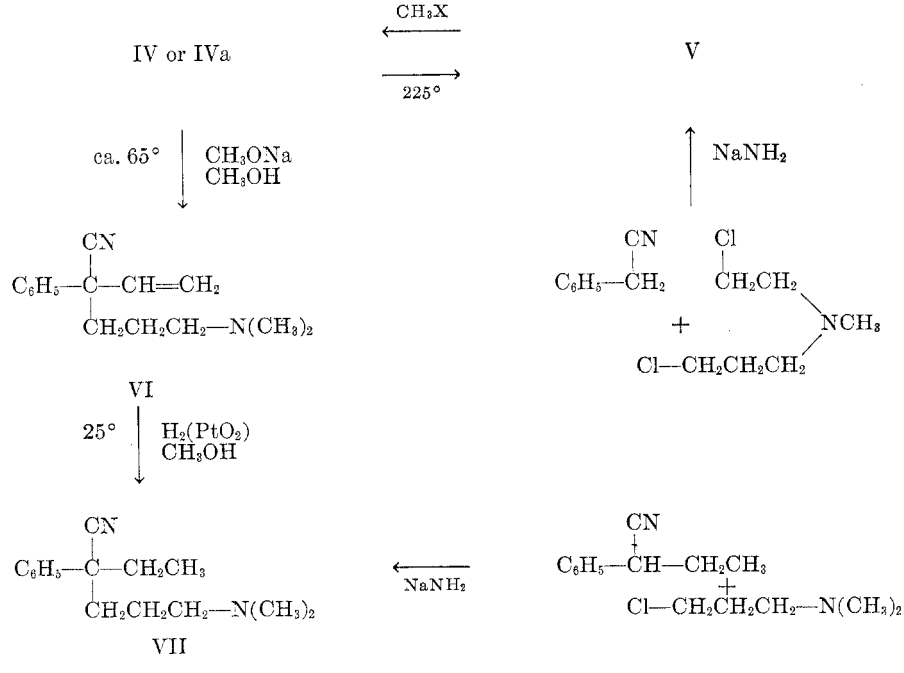


FIG. 2

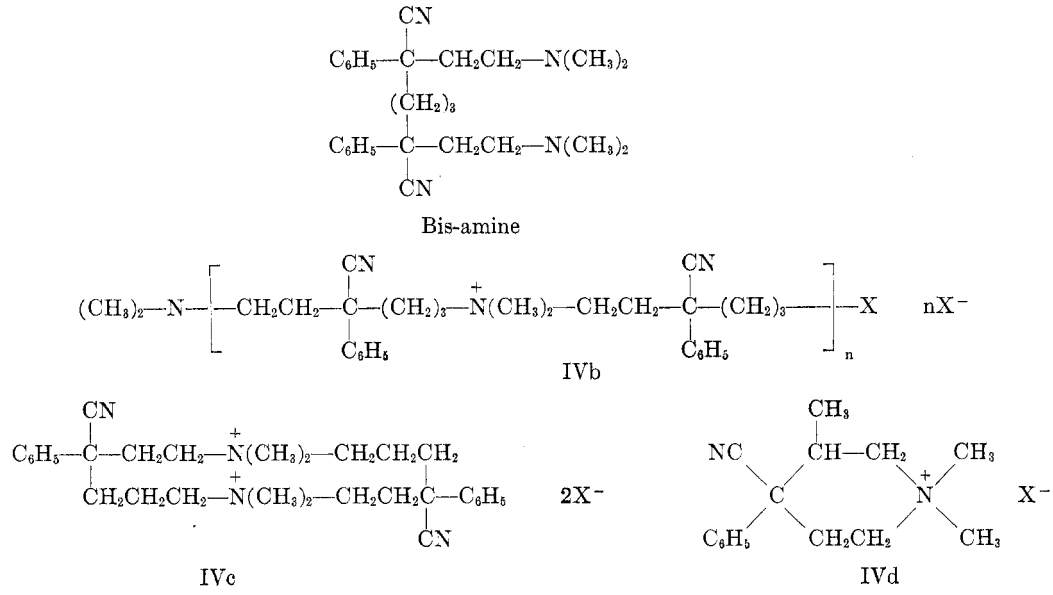


FIG. 3

one half the theoretical value. These facts were only compatible with a cyclic uni-univalent salt, and therefore eliminated the possibilities of a polymeric linear salt (IVb) or a polymeric macrocyclic salt (IVc) structure. Chromic acid oxidation of IV by the Kuhn-Roth method[9] produced no acetic acid, indicating that no C-methyl group was present. This eliminated the further possibility that ring contraction had occurred to give a C-alkylpiperidine (IVd) or other isomeric six- or five-membered ring structure.

Thermal decomposition of IV or IVa occurred at about 225° with loss of methyl chloride or bromide and formation of 1-methyl-4-phenyl-4-cyanoazacycloheptane (V) in 80 to 92% or 65% yield, respectively. The dehalomethylation reaction was effected by dry distillation of IV or IVa under reduced pressure, or by heating IV in a liquid heat transfer medium. The latter method was decidedly superior, especially for more than a few grams of material. Alcohols boiling at about 225°, such as 2,6,8-trimethylnonanol-4, 5-ethylnonanol-2, and decanol-1, were found to be the most suitable heat transfer media. They were partial solvents for the quaternary salt as well as the product. The optimum yield of V was obtained by operating under a nitrogen atmosphere, especially during the cooling period.

Compound V was also produced by a combined cyclization-dechloromethylation procedure in which III was heated at 225° in one of the high boiling alcohols. By this method V was obtained from I in 44% yield.

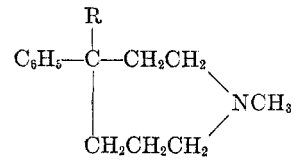
The structure of V was confirmed by the addition of methyl chloride or bromide which produced quaternary salt IV or IVa again. Furthermore, V was synthesized independently (in very poor yield) by condensing phenylacetonitrile with (2-chloroethyl)(3-chloropropyl)methylamine in the presence of sodamide.

V was hydrolyzed to the corresponding carboxylic acid (VIII) by 80% sulfuric acid at 110–120°. Without isolating VIII, it was esterified with ethanol to produce 1-methyl-4-phenyl-4-carbethoxyazacycloheptane (IX), the seven-membered ring analog of meperidine, in 75% yield from V. Esterification of VIII with methanol led to the corresponding methyl ester (X). Pure VIII was obtained from a sample of IX which had been stored without special precaution against inclusion of atmospheric moisture. V was partially hydrolyzed to the amide XI by potassium hydroxide in ethylene glycol–water at 145–160°. Conversion of V to the corresponding ethyl (XII), *n*-propyl (XIII), and phenyl ketones (XIV) was accomplished with the appropriate Grignard reagent. Decyanation of V occurred in excellent yield with sodamide in boiling toluene.[10] Compound V was readily reduced to the corresponding primary amine (XVI) by lithium aluminum hydride in ether.

dl-1-Methyl-4-phenyl-4-carbethoxyazacycloheptane (IX) was resolved into its optical antipodes (IXa and b), confirming the asymmetry of the seven-membered ring structure. This constitutes an outstanding difference between IX and its piperidine analog, meperidine.

(9) Kuhn and Roth, *Ber.*, 66, 1274 (1933).

(10) The decyanation of tertiary nitriles, by heating with sodamide in a hydrocarbon solvent, has been reported by several investigators: (a) Klenk, Suter, and Archer, *J. Am. Chem. Soc.*, **70**, 3846 (1946); (b) Jackman, Bolen, Mackrod, Tuller, and Archer, *J. Am. Chem. Soc.*, **71**, 2301 (1949), **72**, 716 (1950); (c) Ruddy, *J. Am. Chem. Soc.*, **73**, 4096 (1951); (d) Blicke and Tsao, *J. Am. Chem. Soc.*, **75**, 5587 (1953); (e) Sperber, Papa, Schwenk, Sherlock, and Fricano, *J. Am. Chem. Soc.*, **75**, 5752 (1953); and (f) Diamond and Bruce, U.S. Patent **2,740,778** (1956).



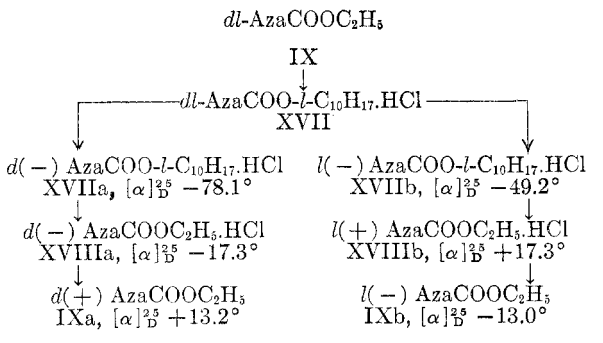
VIII, R = COOH
IX, R = $COOC_2H_5$
X, R = $COOCH_3$

XI, R = $CONH_2$
XII, R = COC_2H_5
XIII, R = COC_3H_7-n

XIV, R = COC_6H_5
XV, R = H
XVI, R = CH_2NH_2

FIG. 4

The resolution of IX was accomplished by two independent procedures. One method was devised in which the alcoholic portion of the ethyl ester (IX) was displaced by the optically active alcohol *l*-menthol. This was carried out by heating a mixture of IX and *l*-menthol at 115–120° under 25 mm. pressure in the presence of sodium methoxide catalyst, and distilling off the displaced ethanol. The two diastereoisomeric *l*-menthyl esters obtained thereby, were readily separated by fractional crystallization of their hydrochloride salts (XVIIa and b). Each diastereoisomer was converted to the corresponding ethyl ester enantiomorph by hydrolysis with 80% sulfuric acid followed by re-esterification with ethanol. The optical antipodes of IX were isolated as their hydrochloride salts (XVIIIa and b) and finally converted to the free bases (IXa and b) by treatment with alkali.



Aza = 4-[1-methyl-4-phenylazacycloheptyl]-; $C_{10}H_{17}$ = menthyl
All specific rotations of solids are for 1% methanolic solutions

FIG. 5

IX was also resolved by conversion to a mixture of the diastereoisomeric acid-*d*-tartrate salts. One of these was separated by fractional crystallization from acetone-water, and this diastereoisomer converted to its respective enantiomorphic base by treatment with alkali.[11] The specific rotations of the optical antipodes obtained by these two independent methods were in close agreement. This is evidence that the resolution was essentially complete. Aqueous and methanolic solutions of the salts of the resolved forms (XVIIIa and b) were found to have signs of rotation opposite that of the corresponding bases (IXa and b).

(11) Muehlmann, private communication.

The analgesic effectiveness of IX, and several of its derivatives, was first reported by Seifter, *et al.*,[12] and demonstrated clinically by Grossman, *et al.*,[13] and by Lundy.[14] When administered orally to ambulatory and hospitalized patients with pain secondary to a variety of medical and surgical conditions, IX was found to be more potent than codeine, but considerably less toxic, and without the undesirable pharmacologic effects observed with prolonged administration of morphine, meperidine, or codeine.[13] Sedation, depression of respiration, alteration of pulse rate, disturbances in bowel or urinary function, suppression of cough, dryness of mouth, and abnormality in the blood-forming elements were not noted. Eddy[15] has reported that, to date, IX has shown no evidence of addiction liability.

The pharmacologic comparison of the resolved forms (IXa and IXb) of IX is not yet complete.

EXPERIMENTAL[16]

1-Methyl-4-phenyl-4-cyanoazacycloheptane methochloride (IV). *Method A.*[5b] To a stirred solution of 0.70 mole (131.6 g.) of 2-phenyl-4-dimethylaminobutyronitrile (I)[17] in 1 l. of toluene under a nitrogen atmosphere, there was added portionwise 0.90 mole (35.1 g.) of sodamide. The mixture was maintained at 35–40° for 3 hr., then cooled to −30° in a dry ice–acetone bath, and 0.74 mole (116.5 g.) of trimethylene chlorobromide (II) in 200 ml. of toluene added dropwise, while holding the temperature at about −20°. The mixture was allowed to warm to room temperature and stand overnight 0.5 hour after completing the addition. The precipitated sodium bromide and excess sodamide were filtered off, and the toluene and excess II were distilled from the filtrate at 30–35° under reduced pressure leaving a liquid residue of crude 1-dimethylamino-3-phenyl-3-cyano-6-chlorohexane (III).

The liquid residue was diluted to 700 ml. with nitrobenzene and the solution was heated at 100° for 16 hr. to precipitate IV. The cooled mixture was filtered, and the crystalline precipitate was washed repeatedly with acetone yielding 126 g. (68%) of essentially pure methochloride (IV), m.p. 264–265° dec. By diluting the filtrate with an equal volume of acetone and allowing the solution to stand overnight, an

(12) Seifter, Ekfeld, Letchack, Gore, and Glassman, *Fed. Proc.*, **13**, 403 (1954).

(13) Grossman, Golbey, Gittinger, and Batterman, *J. Am. Geriatrics Soc.*, **4**, 187 (1956).

(14) Lundy, Penna, *Med. J.*, **59**, 437 (1956).

(15) Eddy, *J. Am. Geratrics Soc.*, **4**, 177 (1956).

(16) All melting points were taken in an oil bath and are uncorrected.

(17) Kwartler and Lucas, *J. Am. Chem. Soc.*, **68**, 2395 (1946).

additional 13 g. of IV was obtained, m.p. 264–265° dec., which raised the total yield to 139 g. (75%).

Anal. Calcd. for $C_{15}H_{21}ClN_2$: Cl, 13.4; Br, 0.0. Found: Cl, 13.2, Br, 0.67.

Method B. Compound IV was also obtained from 0.26 mole (48.9 g.) of I, 0.31 mole (12.1 g.) sodamide, and 0.30 mole (33.9 g.) of trimethylene chloride (IIb). The alkylation of the sodio derivative of I by IIb was conducted in 300 ml. of toluene, and required a temperature of 100–110° to produce the 1,6-aminochloride (III). After removing the toluene and excess IIb under reduced pressure, the liquid residue containing III was diluted to 260 ml. with *o*-nitrotoluene, and the solution heated at 100° for 19 hr. to precipitate 19.4 g. (24%) of IV, m.p. 269–270° dec.

Anal. Calcd. for $C_{15}H_{21}ClN_2$: C, 68.07; H, 7.99; N, 10.6; Cl (total), 13.4; Cl (ionic), 13.4; mol. wt., 265. Found: C, 67.76; H, 7.91; N, 10.25; Cl (total), 13.6; Cl (ionic), 13.6; mol. wt., 137 (× 2 = 274).

1-Methyl-4-phenyl-4-cyanoazacycloheptane methobromide (IVa).[5b] The methobromide was prepared from 0.35 mole (65.8 g.) of I, 0.45 mole (17.5 g.) of sodamide, and 0.37 mole (74.7 g.) of trimethylene bromide (IIa). The alkylation of the sodio derivative of I by IIa was conducted in 1.8 l. of ether at 2–10°. After removing the ether and excess IIa, the liquid residue containing the 1,6-aminobromide (IIIa) was diluted to 3.5 l. with *o*-nitrotoluene, and the solution heated at 100° for 1 hr. to precipitate 26 g. (26%) of IVa, m.p. 246–247° dec. Longer heating also precipitated a polymeric methobromide.

Anal. Calcd. for $C_{15}H_{21}BrN_2$: C, 58.30; H, 6.84; N, 9.06; Br (total), 25.83; Br (ionic), 25.83; C—CH_3, 0.0; mol. wt., 309. Found: C, 58.36; H, 7.04; N, 8.82; Br (total), 25.25; Br (ionic), 26.0; C—CH_3, 0.0; mol. wt. 152.5 (× 2 = 305).

3,7-Diphenyl-3,7-dicyano-1,9-bis(dimethylamino)nonane (bis-amine). From 0.35 mole (65.8 g.) of I, 0.45 mole (17.5 g.) of sodamide, and 0.37 mole (74.7 g.) of trimethylene bromide (IIa) in a total of 600 ml. of anhydrous ether, a liquid residue was obtained essentially by the procedure described for the preparation of IVa. Samples of this liquid, however, gave negligible amounts of solid either by prolonged heating in the absence of solvent or by heating in a nitrobenzene solution. The liquid residue was therefore redissolved in ether, extracted with 2*N* hydrochloric acid, and the acid extract basified with 4*N* sodium hydroxide solution, and extracted with ether. Removal of the ether from the dried extract left a syrupy residue which solidified on standing overnight. Trituration with *n*-hexane gave 99 g. (60%) of the bis-amine as a yellow powder, m.p. 62–64°. It contained only trace amounts of halogen.

Anal. Calcd. for $C_{27}H_{36}N_4$: N, 13.45; Br, 0.0. Found: N, 13.35; Br, 0.7.

1-Methyl-4-phenyl-4-cyanoazacycloheptane (V).[18] *Method A.* A suspension of 0.30 mole (79.6 g.) of IV in 300 ml. of 2,6,8-trimethylnonanol-4 (b.p. 225°) was heated at its reflux temperature with stirring. The solid slowly dissolved as methyl chloride was evolved. After 2 hr., the clear solution was cooled under a nitrogen atmosphere, and extracted with 2*N* hydrochloric acid. The acid extract was made alkaline with 4*N* sodium hydroxide solution, and extracted with ether. Distillation of the dried ether extract gave 59 g. (92%) of V, b.p. 130–2° (0.35 mm.).

The *picrate*, m.p. 174–175°, did not depress the melting point of the picrate of the product obtained by method (B) below.

The *methochloride*, m.p. 270° dec., was prepared in acetone. Its melting point was not depressed when mixed with a sample of IV.

Method B.[5b] Compound IVa (0.02 mole, 6.2 g.) was placed in a small Claisen flask. The pressure was reduced to 2–3 mm., and the mixture heated in an air bath. At a bath temperature of 230–250° the methobromide melted with decomposition, and 2.8 g. (65%) of distillate was obtained. Redistillation gave V, b.p. 125–127° (0.3 mm.), n_D^{26} 1.5362, d_4^{26} 1.029.

Anal. Calcd. for $C_{14}H_{18}N_2$: C, 78.42; H, 8.46; N, 13.07; C—CH_3, 0.0; MR_D, 64.92. Found: C, 78.35; H, 8.49; N, 12.74; C—CH_3, 0.0; MR_D, 65.00.

The *picrate*, m.p. 174–175°, was formed in methanol.

Anal. Calcd. for $C_{20}H_{21}N_5O_7$: C, 54.20; H, 4.77; N, 15.80. Found: C, 54.18; H, 5.19; N, 15.41.

The *acid sulfate*, m.p. 158–160°, was formed in 80% sulfuric acid and precipitated by the addition of acetone.

Anal. Calcd. for $C_{14}H_{20}N_2O_4S$: C, 53.80; H, 6.45; N, 8.97; S, 10.3. Found: C, 53.87; H, 6.52; N, 9.24; S, 10.4.

The *methobromide*, m.p. 248–249° dec., was formed in ether. A mixture with IVa melted at 246–248° dec., establishing their identity.

Method C. Crude compound III was obtained in the manner described under method A for the preparation of IV. The liquid residue containing III was diluted to 1.4 liters with 2,6,8-trimethylnonanol-4. This solution was added, during 2 hr., to 700 ml. of refluxing and stirred 2,6,8-trimethylnonanol-4. The temperature was maintained 2 hr. after the addition was completed, then the solution was cooled under a nitrogen atmosphere, and extracted with 2*N* hydrochloric acid. The acid extract was basified with 4*N* sodium hydroxide solution, and extracted with ether. Distillation of the dried ether extract gave 66 g. (44%) of V, b.p. 131–5° (0.4 mm.). The picrate, m.p. 175–176°, prepared from redistilled material, did not depress the melting ing point of the picrate of the base obtained by method B.

Method D. Sodamide (0.77 mole, 30 g.) was added portionwise at 50–60° to a stirred solution of 0.35 mole (41 g.) of phenylacetonitrile and 0.36 mole of (2-chloroethyl) (3-chloropropyl)methylamine.[19] After the addition was completed, the mixture was stirred at 50° for 1 hr., then at its reflux temperature for 1 hr. The cooled mixture was treated with 2*N* hydrochloric acid. A 3-phase system resulted, composed of an upper toluene layer, a middle clear aqueous acid layer, and a brown syrupy bottom layer. The two lower layers were drawn off, basified together with 4*N* sodium hydroxide solution, and extracted with ether. Vacuum distillation of the dried ether extract gave only 13.2 g. of distillate, leaving the bulk of the material in the still pot as resin. Redistillation gave 8 g. of forerun, b.p. 65–70° (760 mm.), followed by 5 g. of yellow liquid, b.p. 120–140° (0.6 mm.). The second fraction was redistilled as follows: (1) 1 g., b.p. 80–100° (0.25 mm.), n_D^{22} 1.5250; (2) 2 g., b.p. 100–119° (0.25 mm.), n_D^{22} 1.5302; and (3) 2.2 g., b.p. 119–121° (0.25 mm.), n_D^{22} 1.5341, d_4^{22} 1.030, MR_D (obs.) 64.66, MR_D (calcd.) 64.92. The physical properties of the last fraction were in fair agreement with those of V.

The *picrate*, m.p. 172–4°, of the last fraction was formed in methanol. A mixture with the picrate of the base obtained by method B melted at 171–173°, proving their identity.

2-Vinyl-2-phenyl-5-dimethylaminovaleronitrile (VI). A solution of sodium methoxide was prepared by dissolving 0.1 g.-atom (2.3 g.) of sodium metal in 100 ml. of methanol. Compound IV (0.1 mole, 26.5 g.) was added, and the mixture heated at its reflux temperature with stirring for 1 hr. The mixture was cooled, and the precipitated sodium chloride filtered off. Distillation of the filtrate gave 8.4 g. (36.8%) of VI, b.p. 113–115° (0.3 mm.), n_D^{28} 1.5074, d_4^{28} 0.9479.

Anal. Calcd. for $C_{15}H_{20}N_2$: C, 78.90; H, 8.83; N, 12.27; MR_D, 71.3. Found: C, 78.70; H, 9.10; N, 11.89; MR_D, 71.8.

The *picrate*, m.p. 123–125°, was formed in methanol.

Anal. Calcd. for $C_{21}H_{23}N_5O_7$: C, 55.15; H, 5.95; N, 15.31. Found: C, 55.28; H, 5.50; N, 15.53.

2-Ethyl-2-phenyl-5-dimethylaminovaleronitrile (VII). *Method A.* A mixture of 0.05 mole (11.4 g.) of VI and 0.001 mole (0.23 g.) of platinum oxide catalyst in 100 ml. of methanol was shaken with hydrogen gas at 25° under 50 lb. pressure. The theoretical amount of hydrogen was ab-

(18) The analogous piperidine compound was first synthesized by Eisleb, *Ber.*, 74B, 1433 (1941).

(19) Jones and Wilson, *J. Chem. Soc.*, 547 (1949).

sorbed within 4 min., after which the uptake of hydrogen ceased. After filtering off the catalyst, the filtrate was distilled to give 9.4 g. (82.5%) of VII, b.p. 115–120° (0.3 mm.), n_D^{28} 1.5000, d_4^{28} 0.937.

Anal. Calcd. for $C_{15}H_{22}N_2$: C, 78.30; H, 9.62; N, 12.17; MR_D, 71.74. Found: C, 78.54; H, 9.86; N, 12.14; MR_D, 72.25.

The *picrate*, m.p. 127–128°, was formed in methanol.

Anal. Calcd. for $C_{21}H_{25}N_5O_7$: C, 54.90; H, 5.49; N, 15.25. Found: C, 55.15; H, 5.57; N, 15.04.

Method B. A solution of 0.20 mole (29 g.) of 2-phenyl butyronitrile[20] in 50 ml. of toluene was added dropwise at 30–40° to a stirred suspension of 0.25 mole (9.7 g.) of sodamide in 100 ml. of toluene under a nitrogen atmosphere. After 2 hr. at 35°, 0.3 mole (36 g.) of 3-dimethylaminopropyl chloride[21] in 50 ml. of toluene was added dropwise at 30–40°, then the mixture was heated at its reflux temperature for 15 min. The cooled mixture was washed with water, extracted with 3*N* hydrochloric acid, and the acid extract was basified with 4*N* sodium hydroxide solution, and extracted with ether. Distillation of the dried ether extract gave 17.5 g. (38%) of VII, b.p. 118–120° (0.3 mm.), n_D^{28} 1.4994, d_4^{28} 0.937.

The *picrate*, m.p. 126–127°, was formed in methanol. A mixture with the picrate of VII obtained by method A melted at 126–128°, establishing their identity.

1-Methyl-4-phenyl-4-carboxyazacycloheptane (VIII).[18] A sample of the ethyl ester (IX) prepared below, which had been stored without special precaution against inclusion of atmospheric moisture, deposited crystals of the carboxylic acid (VIII). The mixture was triturated with acetone and filtered to give VIII, m.p. 222–223°.

Anal. Calcd. for $C_{14}H_{19}NO_2$: C, 72.05; H, 8.21; N, 6.00. Found: C, 71.82; H, 8.70; N, 6.33.

The *sulfate* melted at 250–251° dec.

Anal. Calcd. for $C_{14}H_{19}NO_2 \cdot {}^1/_2\ H_2SO_4$: C, 59.52; H, 7.14; N, 4.96; S, 5.68. Found: C, 59.27; H, 7.30; N, 5.00, S, 5.30.

1-Methyl-4-phenyl-4-carbethoxyazacycloheptane (IX).[5b,18] A mixture of 0.244 mole (52.3 g.) of V, 66 g. of 98% sulfuric acid, and 16.2 g. of water was heated at 110–120° for 3 hr. The mixture, which contained the carboxylic acid (VIII), was cooled somewhat, and 300 ml. of absolute ethanol was added. After refluxing the solution for 16 hr., the excess ethanol was distilled off at atmospheric pressure. The cooled residue was poured into an ice cold saturated solution of sodium carbonate, and extracted with ether. Distillation of the dried ether extract gave 49.1 g. (75.4%) of IX, b.p. 128–130° (0.3 mm.), n_D^{28} 1.5220, d_4^{26} 1.038.

Anal. Calcd. for $C_{16}H_{23}NO_2$: C, 73.51; H, 8.86; N, 5.36; MR_D 76.06. Found: C, 73.66; H, 8.89; N, 5.67; MR_D, 76.30.

The *hydrochloride*,[5b] m.p. 151–153°, was formed in diisopropyl ketone–ether and recrystallized from ethyl acetate–ether.

Anal. Calcd. for $C_{16}H_{24}ClNO_2$: C, 64.55; H, 8.12; N, 4.71; Cl, 11.91. Found: C, 64.75; H, 8.16; N, 4.78; Cl, 12.15.

The *picrate*, m.p. 169–170°, was formed in methanol.

Anal. Calcd. for $C_{22}H_{26}N_4O_9$: C, 53.90; H, 5.35; N, 11.43. Found: C, 54.18; H, 5.39; N, 11.41.

The *methobromide*, m.p. 215–217° dec., was formed in ether.

Anal. Calcd. for $C_{17}H_{26}BrNO_2$: C, 57.33; H, 7.36; N, 3.93; Br, 22.4. Found: C, 56.99; H, 7.07; N, 3.76; Br, 22.3.

1-Methyl-4-phenyl-4-carbomethoxyazacycloheptane (X).[18] Compound X was prepared in a manner analogous to that described for IX. From 0.04 mole (8.6 g.) of V, 10.6 g. of 98% sulfuric acid, 2.6 g. of water, and 75 ml. of methanol, there was obtained 7.3 g. (73.4%) of X, b.p. 124–125° (0.3 mm.), n_D^{28} 1.5278, d_4^{28} 1.062.

Anal. Calcd. for $C_{15}H_{21}NO_2$: C, 72.82; H, 8.55; N, 5.66; MR_D, 71.44. Found: C, 72.55; H, 8.75; N, 5.74; MR_D, 71.65.

(20) Bodroux and Taboury, *Compt. rend.*, **150**, 531 (1910).

(21) Marxer, *Helv. Chim. Acta*, **24**, 209 (1941).

The *hydrochloride*, m.p. 174–176°, was formed in diisopropyl ketone.

Anal. Calcd. for $C_{15}H_{22}ClNO_2$: C, 63.52; H, 7.82; N, 4.94; Cl, 12.5. Found: C, 63.08; H, 7.67; N, 5.19; Cl, 12.7.

1-Methyl-4-phenyl-4-carbamylazacycloheptane (XI).[18] A mixture of 0.715 mole (153 g.) of V, 2.86 moles (160 g.) of potassium hydroxide, and 1.43 moles (25.7 g.) of water in 100 ml. of ethylene glycol was heated at 145–160° for 3 hr. with stirring. The cooled mixture was diluted with 350 ml. of water, and the precipitated product filtered off. The solid was ground under cold water, refiltered, and air dried overnight. It was then ground under *n*-hexane and filtered to give 115 g. (64.6%) of crude XI as a monohydrate, m.p. 81–86°. Recrystallization from benzene-*n*-hexane gave white crystals, m.p. 95–96°, of XI monohydrate.

Anal. Calcd. for $C_{14}H_{20}N_2O.H_2O$: C, 67.15; H, 8.86; N, 11.20. Found: C, 67.11; H, 8.87; N, 10.76.

1-Methyl-4-phenyl-4-propionylazacycloheptane (XII). Ethylmagnesium bromide was prepared from 0.082 mole (9.0 g.) of ethyl bromide and 0.075 g-atom (1.8 g.) of magnesium turnings in 100 ml. of anhydrous ether. Compound V (0.05 mole, 10.7 g.) in 50 ml. of ether was added to the first solution during 1 hr. The mixture was heated at its reflux temperature with stirring for 5 hr., then treated with 120 ml. of 2*N* hydrochloric acid, and heated on a steam bath for 1 hr., allowing the ether and excess ethyl bromide to distill off. The cold aqueous solution was basified with ammonium hydroxide, and extracted with ether. Distillation of the dried ether extract gave 10.4 g. (85%) of XII, b.p. 132–136° (0.35 mm.), n_D^{26} 1.5302, d_4^{26} 1.014.

Anal. Calcd. for $C_{16}H_{23}NO$: C, 78.32; H, 9.44; N, 5.71, MR_D, 74.42. Found: C, 78.56; H, 9.64; N, 5.67; MR_D, 74.78.

The *hydrochloride*, m.p. 122–125°, was formed in diisopropyl ketone–ether.

Anal. Calcd. for $C_{16}H_{24}ClNO$: C, 68.20; H, 8.58; N, 4.98; Cl, 12.6. Found: C, 67.94; H, 9.05; N, 5.03; Cl, 13.2.

1-Methyl-4-phenyl-4-n-butyrylazacycloheptane (XIII). Compound XII was prepared in a manner analogous to that described for XII. From 0.082 mole (10.1 g.) of *n*-propyl bromide, 0.075 g-atom (1.8 g) of magnesium turnings, and 0.05 mole (10.7 g.) of V in 150 ml. of anhydrous ether, there was obtained 8.8 g. (67.9%) of XIII, b.p. 132–133° (0.3 mm.) n_D^{26} 1.5300, d_4^{26} 0.995.

Anal. Calcd. for $C_{17}H_{25}NO$: C, 78.80; H, 9.71; N, 5.40; MR_D, 79.05. Found: C, 79.02; H, 9.57; N, 5.83; MR_D, 80.21.

1-Methyl-4-phenyl-4-benzoylazacycloheptane (XIV). Compound XIV was prepared essentially by the procedure described for XII. From 0.225 mole (35.3 g.) of bromobenzene, 0.21 g-atom (5 g.) of magnesium turnings, and 0.15 mole (32.1 g.) of V in 500 ml. of ether-toluene (the temperature of the mixture was finally raised to 95°), there was obtained 32 g. (72.8%) of XIV as a yellow viscous syrup, b.p. 180–190° (0.2 mm.).

Anal. Calcd. for $C_{20}H_{23}NO$: C, 82.00; H, 7.89; N, 4.78. Found: C, 81.97; H, 7.88; N, 4.89.

The *hydrochloride*, m.p. 226–228° dec., was formed in ether.

Anal. Calcd. for $C_{20}H_{24}ClNO$: C, 72.82; H, 7.33; N, 4.25; Cl, 10.75. Found: C, 72.25; H, 7.27; N, 4.30; Cl, 10.95.

1-Methyl-4-phenylazacycloheptane (XV). A mixture of 0.5 mole (107.1 g.) of V and 1.1 mole (42.9 g.) of sodamide in 750 ml. of toluene was heated at its reflux temperature with stirring for 6 hr. The cooled mixture was washed with water, then extracted with 2*N* hydrochloric acid. The acid extract was basified with 4*N* sodium hydroxide solution, and extracted with ether. Distillation of the dried ether extract gave 85 g. (90%) of XV, b.p. 88–90° (0.25 mm.), n_D^{29} 1.5288.

The *hydrochloride*, m.p. 144–146°, was formed in methyl ethyl ketone–ether.

Anal. Calcd. for $C_{13}H_{20}ClN$: C, 69.15; H, 8.93; N, 6.20; Cl, 15.70. Found: C, 68.90; H, 9.09; N, 5.92; Cl, 15.78.

The *methiodide*, m.p. 146–147°, was formed in acetone.

Anal. Calcd. for $C_{14}H_{22}IN$: C, 50.75; H, 6.70; N, 4.23; I, 38.31. Found: C, 50.78; H, 6.80; N, 4.01; I, 38.30.

The *picrate*, m.p. 149–150°, was formed in methanol.

Anal. Calcd. for $C_{19}H_{22}N_4O_7$: C, 54.55; H, 5.30; N, 13.38. Found C, 54.52; H, 5.03; N, 13.20.

1-Methyl-4-phenyl-4-aminomethylazacycloheptane (XVI). A solution of 0.20 mole (42.9 g.) of V. in 100 ml. of anhydrous ether was added dropwise to a suspension of 0.148 mole (6.0 g.) of lithium aluminum hydride in 300 ml. of ether. The mixture was heated at its reflux temperature with stirring for 3 hr., then allowed to stand overnight, and decomposed with 12 ml. of ice water. It was filtered, the precipitate washed with ether, and the washings and filtrate combined, dried, and distilled. Compound V was collected at 120–122° (0.3 mm.), n_D^{21} 1.5496; yield 32.5 g. (74.5%).

Anal. Calcd. for $C_{14}H_{22}N_2$: C, 77.00; H, 10.15; N, 12.83. Found: C, 77.27; H, 10.14; N, 12.74.

Resolution of IX. l-Menthyl dl-1-methyl-4-phenylazacycloheptane-4-carboxylate hydrochloride (XVII). A mixture of 0.6 mole (156.6 g.) of IX, 0.9 mole (140.4 g.) of *l*-menthol, and 0.03 mole (1.6 g.) of sodium methoxide was heated at 110–115° under 25 mm. pressure for 6 hr. About 30 ml. of distillate was collected in a dry ice trap. The cooled mixture was diluted with 1 l. of acetone, filtered, and a slight excess of dry hydrogen chloride passed into the filtrate. The precipitated product (XVII) was filtered off, and washed with acetone; yield 137.8 g., m.p. 246–247° dec., $[\alpha]_D^{25}$ −64.6° (C = 1, CH_3OH).

l-Menthyl d(−) 1-methyl-4-phenylazacycloheptane-4-carboxylate hydrochloride (XVIIa).[22] Compound XVII (137.8 g.) was dissolved in a boiling mixture of 1.2 l. of 2-propanol and 2 l. of methanol. The solution was concentrated on a steam bath until crystallization began, then the mixture was allowed to cool. The crystalline precipitate was filtered off and washed with cold 2-propanol; yield 75.6 g., m.p. 271.5–272° dec., $[\alpha]_D^{25}$ −74.8° (C = 1, CH_3OH).

This material was recrystallized from 500 ml. of 2-propanol and 1.9 l. of methanol to give 58.8 g. of essentially pure XVIIa, m.p. 275–275.5° dec., $[\alpha]_D^{25}$ −78.1° (C = 1, CH_3OH).

Anal. Calcd. for $C_{24}H_{38}ClNO_2$: C, 70.63; H, 9.38; N, 3.43; Cl, 8.69. Found: C, 70.53; H, 9.38; N, 3.24; Cl, 8.64.

Recrystallization of a sample of the latter material from 2-propanol–methanol resulted in only a slight change in physical properties: m.p. 277–278° dec., $[\alpha]_D^{25}$ −78.8° (C = 1, CH_3OH).

An additional quantity of XVIIa was obtained by evaporating the mother liquor from recrystallized XVIIa (m.p. 275–275.5° dec.) to dryness. The residue weighed 13.9 g., m.p. 254–256° dec. It was combined with 9.5 g. of by-product (m.p. 255–256° dec.), obtained in the preparation of the second crop of XVIIb, described below. Recrystallization of the combined material from 800 ml. of 1:3 2-propanol-methanol gave 18.4 g. of almost pure XVIIa, m.p. 271–272° dec., $[\alpha]_D^{25}$ −76.4° (C = 1, CH_3OH).

The total yield of XVIIa from IX was 77.2 g. (31.5%).

l-Menthyl l(−)1-methyl-4-phenylazacycloheptane-4-carboxylate hydrochloride (XVIIb). The mother liquor and acetone washes from XVII (m.p. 246–247° dec.) were combined and the solvent removed under reduced pressure. On taking up the residue in 1 l. of ether and allowing the mixture to stand 1 hr., a precipitate was obtained. The crude XVIIb was filtered off, then triturated with acetone, refiltered, and washed with acetone to give 33.7 g. of essentially pure XVIIb, m.p. 230–231° dec., $[\alpha]_D^{25}$ −49.2° (C = 1, CH_3OH).

Anal. Calcd. for $C_{24}H_{38}ClNO_2$: C, 70.63; H, 9.38; N, 3.43; Cl, 8.69. Found: C, 70.23; H, 9.65; N, 3.68; Cl, 8.77.

(22) The convention adopted for designating stereoisomers is based on the arbitrary assignment of the (+) antipode of IX to the *d*-series.

An additional quantity of XVIIb was obtained by combining the mother liquor and 2-propanol washes from crude XVIIa (m.p. 271.5–272° dec.), and allowing the solution to stand overnight. After filtering off 9.5 g. of precipitate (m.p. 255–256° dec.), the filtrate was evaporated almost to dryness on a steam bath. The cold residue was triturated with ether, and the precipitated product (XVIIb) filtered off, and washed with ether; yield 45.4 g., m.p. 235–236° dec., $[\alpha]_D^{25}$ −51.3° (C = 1, CH_3OH).

d(−) 1-Methyl-4-phenyl-4-carbethoxyazacycloheptane hydrochloride (XVIIIa). Essentially pure XVIIa (0.14 mole, 57.3 g., m.p. 275–275.5° dec.) was added portion-wise, at 25°, to a solution prepared from 175 ml. of 98% sulfuric acid and 76 ml. of water. Hydrogen chloride gas was evolved. The solution was heated at 70–80° for 1.75 hours, then poured into 1 l. of absolute ethanol, and a water-ethanol mixture distilled off. Fresh absolute ethanol was added and the process repeated until 2 l. of distillate was collected. The concentrated cold residue was poured into 2 l. of ice water, the aqueous solution washed with ether, basified with 40% sodium hydroxide solution, and extracted with ether. The dried ether extract was concentrated under reduced pressure.

The liquid residue was diluted with 100 ml. of acetone, and a slight excess of dry hydrogen chloride passed in to precipitate XVIIIa. The product was filtered off, and washed with acetone; yield 26.9 g., m.p. 166–167°, $[\alpha]_D^{25}$ −17.3° (C = 1, CH_3OH).

Anal. Calcd. for $C_{16}H_{24}ClNO_2$: C, 64.55; H, 8.12; N, 4.71; Cl, 11.91. Found: C, 64.66; H, 8.05; N, 4.41; Cl, 11.88.

The mother liquor from XVIIIa was concentrated under reduced pressure, whereupon crystallization began. The crystalline precipitate was filtered off, and washed with a 1:3 acetone-ether mixture. In this way an additional 6 g. of XVIIIa, m.p. 165.5–166.5°, $[\alpha]_D^{25}$ −17.2° (C = 1, CH_3OH), was obtained.

The total yield of XVIIIa from XVIIa was 32.9 g. (79%); the over-all yield of XVIIIa from IX was 25.9%.

d (+) 1-Methyl-4-phenyl-4-carbethoxyazacycloheptane (IXa). Six grams of XVIIIa was dissolved in water. The solution was basified with 4*N* sodium hydroxide solution, and extracted with ether. Distillation of the dried ether extract gave 5 g. of IXa, b.p. 126° (0.2 mm.), n_D^{29} 1.5198, d_4^{25} 1.04, $[\alpha]_D^{25}$ +13.2° (no solvent).

l(+)1-Methyl-4-phenyl-4-carbethoxyazacycloheptane hydrochloride (XVIIIb). The method of preparation of XVIIIb from XVIIb was analogous to that described for the preparation of XVIIIa from XVIIa. From 0.08 mole (32.7 g.) of XVIIb (m.p. 230–231° dec.), 16.5 g. of XVIIIb, m.p. 164.5–165°, $[\alpha]_D^{25}$ + 17.3° (C = 1, CH_3OH).

Anal. Calcd. for $C_{16}H_{24}ClNO_2$: C, 64.55; H, 8.12; N, 4.71; Cl, 11.91. Found: C, 64.57; H, 8.20; N, 4.59; Cl, 11.73.

Concentration of the mother liquor yielded an additional 2.2 g. of XVIIIb, m.p. 163.5–165°, $[\alpha]_D^{25}$ + 17.0° (C = 1, CH_3OH).

The total yield of XVIIIb from XVIIB was 18.7 g. (78.5%); the over-all yield from IX was 25.4%.

l(−) 1-Methyl-4-phenyl-4-carbethoxyazacycloheptane (IXb). Four g. of XVIIIb was dissolved in water, basified with 4*N* sodium hydroxide solution, and extracted with ether. Distillation of the dried extract gave 3 g. of IXb, b.p. 126° (0.2 mm.), n_D^{29} 1.5197, d_4^{25} 1.04, $(\alpha)_D^{25}$ − 13.0° (no solvent).

Acknowledgment. We are indebted to Mr. Carl Gochman for technical assistance and to Dr. W. Reiss, Dr. G. H. Ellis, and members of the Analytical Department of the Wyeth Institute for Medical Research for the microanalyses, molecular weight determinations, and optical rotations.

PHILADELPHIA, PA.