on carbon catalyst. The product, isolated by removing the acetic acid, was recrystallized from isopropyl alcohol.

4-Dimethylamino-3-sulfolanyl diphenylacetate (Compound 23). To a warm solution of 11 g. (0.0615 mole) of 18 in 50 ml. of pyridine was rapidly added 17 g. (0.074 mole) of diphenylacetyl chloride. After the solid had dissolved, the solution was boiled briefly and poured into 200 ml. of water; an oil separated immediately which thickened but would not solidify. The oil was extracted with ether, the ethereal solution dried, filtered, and concentrated, and then the oily residue crystallized on standing (25.0 g.). It was recrystallized from alcohol-ether. The product was insoluble in water and dilute base, was soluble in dilute acid and partially soluble in ether.

4-Trimethylammonium-3-sulfolanol iodide (Compound 24). To a solution of 3 g. of 18 in ethanol was added 4.7 g. (0.034 mole) of methyl iodide in 10 ml. of ethanol; the solution was stoppered and allowed to stand overnight. The resulting white solid was recrystallized from ethanol-water.

trans-3,4-Sulfolanediol diacetate (Compound 25). A solution of 5 g. of 18 in 50 ml. of acetic anhydride was heated on a steam bath for 17 hr.; then the solution was taken to dryness leaving a black solid which was recrystallized from alcohol to give a white crystalline solid.

3-Acetoxymercuri-2-methoxysulfolane (Compound 26). To a solution of 11.8 g. of sulfolene-3 in absolute methanol was added 2.42 g. of benzoyl peroxide, then a solution of 31.9 g. of mercuric acetate and 7.2 cc. of acetic acid in hot methanol. The solution was refluxed overnight, then concentrated at 50–60°. The resulting oil was stirred with acetone and the insoluble white solid was discarded. The solvent was removed at room temperature, the oil was dissolved in chloroform, treated with charcoal, and thrown back out with ether, giving a colorless oil. After several weeks the oil crystallized, m.p. 105°.

3-Chloromercuri-4-methoxysulfolane (Compound 27). To a concentrated aqueous solution of the acetate (26) was added 0.85 g. of sodium chloride. A white precipitate formed rapidly. After being stirred for 0.5 hr., the solid was filtered and rinsed thoroughly with water. It could not be recrystallized without decomposition.

Sulfolene-3 epoxide. Barium carbonate (9.8 g., 0.05 mole) was added to a solution of 17.1 g. (0.1 mole) of 4-chlorosulfolanol-3 dissolved in 200 ml. of hot water. The mixture was stirred and maintained at 85° until all the carbonate went into solution (2 hr.). On chilling, 6 g. of a solid formed and was filtered, m.p. 120–125°. On recrystallization from acetone this material separated into two substances, (*a*) m.p. 123–125°, and (*b*) m.p. 157–159°. The infrared spectra of (a) and (b) in Nujol mulls were identical.

Anal. Calcd. for $C_4H_8SO_4$ (for substance *a*): C, 35.81; H, 4.58. Found: C, 36.23; H, 4.87.

Anal. Calcd. for $C_4H_8SO_4$ (for substance *b*): C, 35,81; H, 4.58. Found: C, 35.92; H, 4.72.

When the dehydrohalogenation was carried out in more dilute solution (500 cc. of water), the only substance isolated was (b).

Substance (b), 5.5 g., was suspended in 25 ml. of water and heated in an autoclave for 2 days at 210°, the autogeneous pressure reaching 200 psig. The resulting brown solution was concentrated to give 5.5 g. of an oil that soon crystallized. It was recrystallized several times from an alcohol-acetone-benzene mixture to give 1 g. of *trans*-3,4-sulfolanediol, m.p. 159–160°. A mixed melting point with the starting epoxide [substance (*b*)] melted at 125–130°. By the same procedure, substance *a* was converted to the identical *trans*-3,4-sulfolanediol.[12]

Anal. Calcd. for $C_4H_8SO_4$: C, 31.57; H, 5.30. Found: C, 31.64; H, 5.40.

Acknowledgment. We are indebted to Drs. A. Kandel, V. Wiebelhaus, and E. Jensen of our laboratories for carrying out the pharmacological evaluation of these compounds, to Mrs. D. Rolston and her staff for carrying out the analyses, and to Mr. K. Snader and Mr. C. Evers for technical assistance.

PHILADELPHIA, Pa.

(12) D. Delfs, Ger. Patent 682079 (1939), b.p. 164° (12.5 mm.).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, LOUISIANA STATE UNIVERSITY]

A New Approach to Polycyclic Bases. II. 1-Azabicyclo[4.3.0]nonanes, 1-Azabicyclo[3.3.0]octanes, and Related Systems[1,2]

ALBERT I. MEYERS AND WILLETTE Y. LIBANO[3]

Received April 12, 1961

The acid-catalyzed condensation of a ditertiary glycol and several ω-chloronitriles has led to a convenient synthesis of 1-azabicycloalkanes. The three-step method involves the formation of an ω-chloroalkyl-1-pyrroline which is reduced with aqueous sodium borohydride to the ω-chloroalkylpyrrolidine and then to the bicyclic base *via* intramolecular alkylation. None of the intermediate products is isolated. The final product is obtained in 60–65% yield based on the glycol.

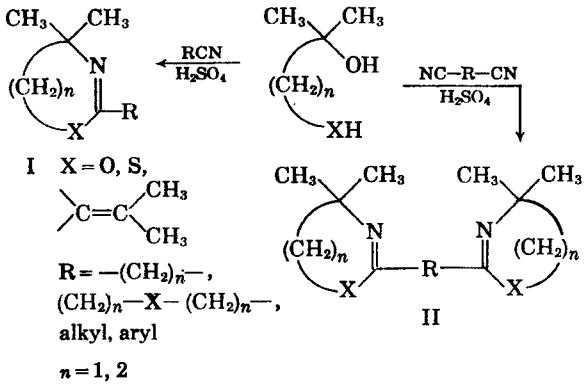
The chemistry of 1-azabicycloalkanes has received considerable attention in the last decade and several comprehensive reviews[4] have appeared during this period. Particular significance has been attributed to the 1-azabicyclo[3.3.0]octanes, more commonly referred to as the pyrrolizidines, because

(1) This work was supported from funds granted by the National Institutes of Health (RG-6248).

(2) Presented before the 16th Annual Southwest Regional Meeting of the American Chemical Society, Oklahoma City, Okla., December 1–3, 1960.

(3) American Cancer Society Summer Research Fellow, 1960.

(4) H. R. Ing, *Heterocyclic Compounds*, Vol. 3, R. C. Elderfield, ed., Wiley, New York, 1952, p. 396; Houben-Weyl, *Methoden der Organischen Chemie*, Band XI 2, G. T. Verlag, Stuttgart, 1958, p. 582; T. S. Stevens, *Chemistry of Carbon Compounds*, Vol. 4, E. H. Rodd, ed., Elsevier, New York, 1957, p. 117.



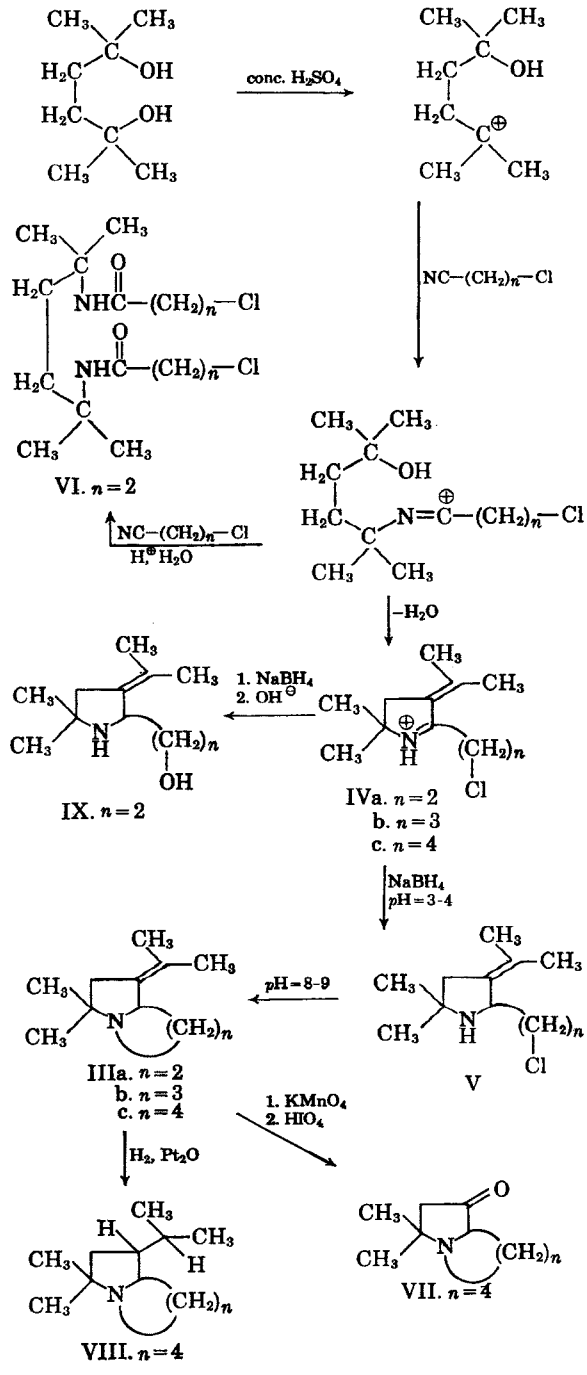
of the occurrence of this ring system in alkaloids of the *Senecio* and *Heliotropium* species.[5]

Leonard and Goode[6] have described a general synthetic route leading to a variety of 1-azabicycloalkanes which relies on the reductive cyclization of oximino diesters in the presence of copper chromite at elevated temperatures and pressures. More recently, Adams and co-workers[7] obtained several pyrrolizidine derivatives by reducing a pyrrolo[1,2a]pyrrole over a rhodium-on-alumina catalyst.

The method described herein for the preparation of 1-azabicycloalkanes is a further extension of a new and general route[8] to heterocyclic compounds from tertiary alcohol derivatives and nitriles. Bis(heterocyclyl)alkanes have also been prepared[9] by this method when dinitriles were employed in one-half the required molar ratio. The use of equimolar amounts of alcohol and dinitrile can, under certain conditions, lead to ω-cyanoalkyl derivatives.[10]

A preliminary communication[11] described the preparation of a derivative of the hitherto unreported bicyclic system, 1-azabicyclo[3.2.0]heptane, IIIa, by the treatment of 2,5-dimethyl-2,5-hexanediol with 3-chloropropionitrile. The pyrrolizidine (IIIb) and octahydropyrrocoline (IIIc) were similarly obtained in 61% and 65% over-all yield from 4-chlorobutyronitrile and 5-chlorovaleronitrile respectively without isolation of the intermediate 1-pyrrolines (IV) and pyrrolidines (V). The reaction sequence occurred under remarkably mild conditions in a relatively short period of time. The crystalline glycol was merely added in portions to a cold solution of the chloronitrile in concentrated sulfuric acid and afterwards diluted with water and the *p*H of the solution adjusted to 3.5 ± 0.5. An equimolar quantity of aqueous sodium borohydride was added which smoothly reduced the C=N link of the 1-pyrroline and then the *p*H of the resulting solution adjusted further to 8.5 ± 0.5 allowing intramolecular alkylation of the amino group to occur. Subsequently, steam distillation removed the heterocyclic base from the mixture of salts and gummy polymeric material.

Although the borohydride reduction was attempted over the entire *p*H range, reduction in



(5) N. J. Leonard, *The Alkaloids*, Vol. 1, R. H. F. Manske and H. L. Holmes, ed., Academic Press, New York, 1950, p. 107; F. L. Warren, *Progress in the Chemistry of Natural Products*, Vol. 12, Springer and Co., Wien, 1955, p. 198.

(6) N. J. Leonard and W. E. Goode, *J. Am. Chem. Soc.*, 72, 5404 (1950).

(7) R. Adams, S. Miyano, and D. Fles, *J. Am. Chem. Soc.*, 82, 1466 (1960).

(8) E. J. Tillmanns and J. J. Ritter, *J. Org. Chem.*, 22, 839 (1957); A. I. Meyers and J. J. Ritter, *J. Org. Chem.*, 23, 1918 (1958); A. I. Meyers, *J. Org. Chem.*, 25, 1147 (1960).

(9) A. I. Meyers, *J. Org. Chem.*, 25, 2231 (1960).

(10) A. I. Meyers, *J. Org. Chem.*, 25, 147 (1960).

(11) A. I. Meyers and W. Y. Libano, *J. Org. Chem.*, 26, 1682 (1961).

weakly acidic medium was found to produce the highest yield and offered the greatest convenience. When the reductions were performed in solutions having *p*H values greater than 4.5, the 1-pyrroline was present as a separate phase which resulted in extensive foaming when the sodium borohydride was introduced. Poor yields were therefore obtained and extending the reaction time only resulted in a slightly higher degree of reduction. Despite the fact that the rate of decomposition of sodium borohydride becomes excessive in acidic medium,[12] particularly below a *p*H of 3,[13] the rate of reduction of the C=N linkage proceeded rapidly and in good yield when equimolar quantities were employed. Favorable reducing characteristics of sodium borohydride in acid solution are not without precedent in this case. Schechter[14] and Wolfrom[15] have employed acidic conditions in the reduction of various functional groups with sodium borohydride.

As this method for the preparation of the bicyclic bases did not require isolation of the intermediate 1-pyrrolines and pyrrolidines, it was desirable to have each successive step in the synthesis as convenient as possible. With this in mind, an attempt was made to reduce the quantity of concentrated sulfuric acid initially employed in the glycol-nitrile condensation. It has been found in the past[8] that the concentrated sulfuric acid not only functioned as an acid catalyst for the formation of the heterocyclic bases but also served as a convenient solvent. In this particular case, however, it was necessary, after pouring the reaction mixture onto ice (see Experimental) partially to neutralize the acidic solution to a *p*H of 3.5. This required a considerable quantity of 35–40% sodium hydroxide solution which in many cases would cause the precipitation of copious amounts of sodium sulfate. This necessitated the further addition of water to redissolve the precipitated salt so as not to interfere with the stirring during the next step, *i.e.*, the reduction with sodium borohydride. When the glycol-nitrile reaction was performed in half the usual quantity of sulfuric acid, a 64% yield of diamide, VI, was obtained. This product is undoubtedly derived from the Ritter reaction.[16] This reaction represents still a further extension of the Ritter amide synthesis which should lead to a variety of ditertiary alkyldiamines from ditertiary glycols.

Characterization of the 1-azabicycloalkanes (III) prepared herein were made by (a) examining their infrared spectra which exhibited no N—H or C=N[17] stretching bands, (b) performing the Zerewitinoff determination which indicated the absence of any active hydrogen, and (c) examination of their elemental analyses, including the picrate and methiodide derivatives. Further support for the proposed structures is offered by the fact that oxidation of IIIc with neutral potassium permanganate, followed by periodic acid, yielded acetone which was identified through its 2,4-dinitrophenylhydrazone. An attempt to isolate the ketooctahydropyrrocoline, VII, in a pure state was unsuccessful because of its poor thermal stability and decomposition characteristics when exposed to air. Its infrared spectrum, however, did indicate similarities to the starting material in the fingerprint region as well as a strong carbonyl band (5.87 μ). Hydrogenation of IIIc in the presence of platinum oxide, to yield VIII, was very slow and required fifty-seven hours for theoretical hydrogen consumption.

If, after the sodium borohydride reduction and prior to steam distillation, the solution was made too strongly alkaline (*p*H 12) nucleophilic displacement of chloride ion by hydroxyl ion occurs and considerable amounts of the 2-hydroxyalkylpyrrolidine, IX, are obtained. This product, however, is easily converted to IIIa by treatment with thionyl chloride followed by base.

This study has led to a wide variety of 1-azabicyclo compounds containing in some cases, sulfur and oxygen atoms in the ring. Several tricyclic and tetracyclic compounds containing the bridgehead nitrogen atom have already been prepared by this technique and these will be reported in the near future.

EXPERIMENTAL[18,19]

2,2-Dimethyl-4-isopropylidene-1-azabicyclo[3.3.0]octane (IIIb). To a cold solution of 20.8 g. (0.20 mole) of 4-chlorobutyronitrile in 200 g. of concd. sulfuric acid was added, portionwise through a powder funnel, 29.2 g. (0.20 mole) of 2,5-dimethyl-2,5-hexanediol. The addition of the glycol was performed while efficient stirring was maintained and the temperature of the mixture was kept below 10°. The time required for the complete addition of the glycol at these conditions was approximately 2 hr. The orange colored reaction mixture was stirred at 3–5° for an additional 2 hr. and then poured over 300–400 g. of chipped ice in a 2-l. beaker.[20] The resulting acid solution was freed of polymeric material by several extractions with chloroform or methylene chloride, and then partially neutralized (*p*H = 2–4) with 35% sodium

(12) R. E. Davis and C. G. Swain, *J. Am. Chem. Soc.*, 82, 5950 (1960), and earlier references cited therein.

(13) N. G. Gaylord, *Reduction with Complex Metal Hydrides*, Interscience, New York, 1956, p. 33, and references cited therein.

(14) H. Schechter, D. E. Ley, and L. Zeldin, *J. Am. Chem. Soc.*, 74, 3664 (1952).

(15) M. L. Wolfrom and H. B. Wood, *J. Am. Chem. Soc.*, 73, 2933 (1951); M. L. Wolfrom and K. Anno, *J. Am. Chem. Soc.*, 74, 5583 (1952).

(16) J. J. Ritter and P. P. Minieri, *J. Am. Chem. Soc.*, 70, 4045, 4048 (1948).

(17) A. I. Meyers, *J. Org. Chem.*, 24, 1233 (1959).

(18) All boiling points and melting points are uncorrected.

(19) Microanalyses were performed by Alfred Bernhardt, Mulheim (Ruhr), West Germany, and Drs. Weiler and Strauss, Oxford, England.

(20) The two successive reactions—*i.e.*, the sodium borohydride reduction and the intramolecular cyclization—were performed in this vessel.

hydroxide. Care was exercised during the neutralization to keep the temperature below 50°. The volume of the solution at this stage was approximately 1 l. The electrodes of a Beckman Zeromatic *p*H meter were inserted and the *p*H of the solution adjusted to 3.5 with 4*M* sulfuric acid or 6*M* sodium hydroxide. The clear solution was cooled to room temperature and a freshly prepared solution of sodium borohydride (7.6 g. (0.20 mole) in 30 ml. of water containing 1–2 drops of 35% sodium hydroxide) was added dropwise while efficient stirring was supplied by a magnetic stirrer. The *p*H of the reaction, during the borohydride addition, was maintained between the limits of 3–4 by the addition of 4*M* sulfuric acid and 6*M* sodium hydroxide which were contained in dropping funnels suitably situated above the beaker. The sodium borohydride addition was complete within 20–25. min. After stirring the partially cloudy solution for 30 min. 500 ml. of water was added, the *p*H raised to 8.5 ± 0.5, and heated for an additional hour at 50°. The two-phase mixture was directly steam distilled and the product essentially recovered in the first 500–600 ml. of distillate. The organic layer was taken up in ether, the aqueous layer extracted twice with ether, and the extracts combined and dried over potassium carbonate. Distillation of the residual light yellow oil, after the removal of ether, yielded 21.5 g. (60%) of the bicyclic base, b.p. 69–70° (1.5 mm); n_D^{30}, 1.4846.

Anal. Calcd. for $C_{12}H_{21}N$: C, 80.44; H, 11.73; N, 7.82. Found: C, 8.45; H, 11.69; N, 7.72.

The methiodide, from methanol–ether acetate, melted at 245–246°.

Anal. Calcd. for $C_{13}H_{24}NI$: C, 48.62; H, 7.48; N, 4.35; I, 39.55; Found: C, 48.41; H, 7.59; N, 4.41; I, 39.21.

The picrate, from ethanol, had a m.p. of 212–213°.

Anal. Calcd. for $C_{18}H_{24}N_4O_7$: N, 13.72. Found: N, 13.60.

2,2-Dimethyl-4-isopropylidene-1-azabicyclo[4.3.0]nonane (IIIc). A cold solution of 23.4 g. (0.20 mole) of 5-chlorovaleronitrile in 200 g. of cond. sulfuric acid was treated with 29.2 g. of 2,5-dimethyl-2,5-hexanediol as described above. Distillation of the residue from the ethereal solution afforded 25.2 g. (65%) of a colorless oil which darkened on exposure to air; b.p. 91–92° (2 mm.); n_D^{30}, 1.4861.

Anal. Calcd. for $C_{13}H_{23}N$: C, 80.82; H, 11.92; N, 7.25. Found: C, 80.97; H, 11.59; N, 7.48.

The methiodide, from methanol–ether acetate, had a m.p. of 233–234°.

Anal. Calcd. for $C_{14}H_{26}NI$: C, 50.14; H, 7.76; H, 4.17; I, 37.91. Found: C, 50.26; H, 7.96; N, 4.03; I, 37.69.

The picrate, from ethanol, had a m.p. of 152–153°.

Anal. Calcd. for $C_{19}H_{26}N_4O_7$: N, 13.27; Found: N, 13.14.

2,2-Dimethyl-4-isopropylidene-1-azabicyclo[3.2.0]heptane (IIIa). The preparation of this compound was accomplished in essentially the manner described above and its physical constants were reported in an earlier communication.[11]

2,2-Dimethyl-4-isopropyl-1-azabicyclo[4.3.0]nonane (VIII). *By catalytic hydrogen of* IIIc. A solution of 8.9 g. of IIIc in 100 ml. of glacial acetic acid containing 0.2 g. of platinum oxide was subjected to 3 atm. of hydrogen pressure in a Paar apparatus at 25°. Approximately one-third of the theoretical quantity of hydrogen was absorbed after 24 hr. at which point a fresh portion of catalyst (0.2 g.) was added. This operation was repeated again after 24 hr. and continued until no further uptake of hydrogen was observed. After several similar experiments the minimum time necessary for theoretical hydrogen uptake was found to be 57 hr. The catalyst was removed by filtration and the major portion of the acetic acid distilled *in vacuo*. Fifty milliliters of 10% sodium hydroxide was added to the residue, the resulting oil taken up in ether, and dried with potassium carbonate. Concentration of the ethereal solution and subsequent distillation of the residue gave 8.1 g. of a colorless oil, b.p. 82–83° (1 mm.); n_D^{30}, 14680.

Anal. Calcd. for $C_{13}H_{25}N$: C, 80.00; H, 12.82; N, 7.18. Found: C, 80.21; H, 12.69; N, 7.27.

The methiodide, from absolute ethanol, had a m.p. of 284° dec.

Anal. Calcd. for $C_{14}H_{28}NI$: I, 37.68. Found: I, 37.52.

The picrate, from ethanol, had a m.p. of 138°.

Anal. Calcd. for $C_{19}H_{28}N_4O_7$: N, 13.21. Found: N, 13.07.

Oxidative cleavage of VIIIc. A suspension of 2.6 g. of VIIIc in 200 ml. of 5% potassium permanganate was stirred at room temperature for 6 hr. The manganese dioxide was collected on filter and 3% hydrogen peroxide was added to the violet filtrate to discharge its color. A 5-ml. portion of the clear colorless solution was added to 5 ml. of the 2,4-dinitrophenylhydrazine reagent and immediate precipitation was observed. After collection on a filter, recrystallization from 50% aqueous ethanol, and drying it melted at 125.5–126.5°. Admixture of this product with an authentic sample of acetone 2,4-dinitrophenylhydrazone did not depress the melting point.

The manganese dioxide, collected above, was added to 50 ml. of ether and digested for several hours. The ether extract was dried with magnesium sulfate and concentrated. A dark viscous oil was obtained whose infrared spectrum exhibited a strong hydroxyl band (3.04 μ) and a medium carbonyl band (5.87 μ), both of which were absent in the starting material. When this oil was treated with a solution of 100 ml. of 1*N* sulfuric acid, 3.5 g. of potassium periodate, and 150 ml. of ethanol for 30 min. at 40°, a viscous brown oil was again obtained. This material exhibited no hydroxyl band but only a strong carbonyl band (5.87 μ). Various attempts to purify this viscous material were unsuccessful.

2-(2-Hydroxyethyl)-3-isopropylidene-5,5-dimethylpyrrolidine (IX). This compound was obtained when the solution following the borohydride reduction was adjusted to *p*H 12, or higher. The following describes the method employed to obtain IX specifically:

After the addition of sodium borohydride at *p*H 3–4, the solution was stirred for 1 hr., and then it was made strongly alkaline and stirring continued for an additional hour at 50–60°. After cooling to room temperature, the solution was extracted four times with ether, dried over potassium carbonate and concentrated. Upon distillation, a viscous, colorless oil was obtained, b.p. 148–151°, (0.5 mm.); n_D^{30}, 14796.

Anal. Calcd. for $C_{11}H_{20}NO$: C, 72.53; H, 10.99; N, 7.69. Found: C, 72.39; H, 10.81; N, 7.71.

The infrared spectrum of this compound exhibited a strong, broad band at 3.07 μ, indicative of the hydroxyl group.

Intramolecular cyclization of IX *to* IIIa. The hydroxyethylpyrrolizidine was converted to the chloroethylpyrrolidinium chloride and cyclized to the 1-azabicyclo[3.2.0]heptane (IIIa) according to the method described by Lavagnino *et al.*[21] Comparison of the bicyclic base obtained by both methods showed them to be identical in all respects.

2,5-Dimethyl-2,5-bis(N-3-chloropropionyl)hexane (VI). 2,5-Dimethyl-2,5-hexanediol (29.2; 0.2 mole) was added portionwise to a stirred cold solution of 17.9 g. (0.20 mole) of 3-chloropropionitrile in 55 ml. of cond. sulfuric acid. After addition was complete, the mixture was stirred at ice-temperatures for 3 hr., and then poured over 300 g. of chipped ice. The precipitate which was present was removed by filtration, washed with water, sodium bicarbonate solution, and again with water. Recrystallization from chloroform-hexane yielded 23.1 g. of a crystalline colorless material (63.5%); m.p. 158°.

Anal. Calcd. for $C_{14}H_{26}N_2O_2Cl_2$: C, 51.69; H, 8.00; N, 8.62. Found: C, 51.71; H, 7.95; N, 8.87.

The infrared spectrum exhibited C=O, N—H, stretching bands at 5.96 μ and 3.01 μ, respectively.

New Orleans 22, La.

(21) E. R. Lavagnino, R. R. Chavette, W. N. Cannon, and E. C. Kornfeld, *J. Am. Chem. Soc.*, **82**, 2609 (1960).