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# Synthesis and Stereochemistry of Indolizidine and Pyrrolizidine Methosalts

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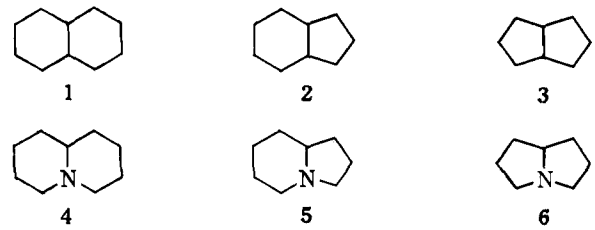
The steric results of three syntheses of indolizidine methobromide and one of pyrrolizidine methobromide have been examined. Methylation of indolizidine produces a 50:50 mixture of the *cis*- and the *trans*-fused methosalts. Cyclization of either N-methyl-2-(3'-bromopropyl)piperidine (**16**) or N-methyl-2-(4'-bromobutyl)pyrrolidine (**22**) affords only *cis*-indolizidine methobromide. Similar cyclization of N-methyl-2-(3'-bromopropyl)pyrrolidine (**30**) leads exclusively to *cis*-pyrrolizidine methobromide. Relative configurations of the salts were assigned from mechanistic arguments in the pyrrolizidine series and from consideration of N-methyl proton chemical shifts in the indolizidine series. Indolizidine and the bromopropylpiperidine **16** were prepared from 2-(3'-hydroxypropyl)pyridine, the former by hydrogenation, treatment with hydrobromic acid, and neutralization, and the latter by methylation, hydrogenation, and treatment with hydrobromic acid. The bromoalkylpyrrolidines **22** and **30** resulted from azeleic and suberic acids, respectively, by conversion to half-ester acyl azides, Curtius rearrangement, lithium aluminum hydride reduction of the isocyanato esters to ω-methylaminoalkanols, photolysis of the corresponding N-chloroamines, and treatment of the resulting hydroxyalkylpyrrolidines with hydrobromic acid. In this sequence, Hofmann–Loeffler photolysis of 8-(N-methyl-N-chloroamino)-1-octanol (**20**) led exclusively to the hydroxybutylpyrrolidine **21**, but similar treatment of the corresponding heptanol **26** gave approximately equal quantities of the hydroxypropylpyrrolidine **29** and 2-(3'-methylaminopropyl)tetrahydrofuran (**31**). The significance of these results is discussed.

Quaternization of a tertiary amine fixes the previously mobile configuration at the nitrogen atom, and thus in systems which have suitable symmetry properties it can lead to either or both of two diastereomeric configurations at nitrogen.[2] The relative amounts of the two salts actually produced in a given instance depend upon the structure of the amine (and perhaps also of the alkylating agent, although adequate evidence on this point is lacking), products ranging from nearly 50:50 mixtures to exclusively one salt having been encountered. When such an N-alkylation is stereoselective, the configuration of the major product often depends upon which N-substituent is introduced in the quaternization reaction, a change in the sequence of N-substitutions at this stage leading to a change in the relative configuration of the predominant quaternary salt. For example, N-ethylnortropine and *n*-propyl iodide give a stereoisomer of the salt obtained from N-propylnortropine and ethyl iodide.[3] With only a few exceptions,[4-11] however, the majority of which are in the tropine series, no consideration has been given to determination of relative configurations of such stereoisomeric pairs. The question is important, for such information might help clarify the structural and mechanistic factors which lead to stereoselectivity in N-alkylations and allow prediction of the configurations of products in future cases. Furthermore, it is not difficult to visualize quaternary salts in which the configuration at nitrogen could influence the conformation of the entire molecule, and if reactions of other functional groups in such a system were conformation dependent, the course they followed might be determined by the configuration at nitrogen. With an eventual view to exploring such stereochemical points, we began a study of the stereochemistry of N-quaternization reactions. This paper reports our results in the indolizidine (**5**) and pyrrolidizine (**6**) series.




Although *cis*- and *trans*-fused isomers of decalin (**1**), hydrindane (**2**), and bicyclo[3.3.0]octane (**3**) and their substituted derivatives are well known, corresponding stereoisomers of quinolizidine (**4**), indolizidine (**5**), and pyrrolizidine (**6**) derivatives cannot be isolated because the rapid inversion of configuration at tricovalent nitrogen interconverts them, producing equilibrium mixtures as the only isolable species.[12] In quaternary salts of these bases, however, the configuration at nitrogen loses such mobility, and the salts should exist in isolable *cis* and *trans* forms, although more than one such salt had not been reported in any of these series prior to initiation of this work. Since the behavior of such a salt might depend upon which diastereomer was in hand, we set out to characterize these isomers and to determine whether any stereoselectivity was exhibited by various methods for their preparation. The problem is of more than academic interest, for these bicyclic systems are structural units in several major classes of alkaloids, and the results of such a study thus could be of importance in connection with the behavior or synthesis of those natural products. During the course of our work we became aware of a similar program in the quinolizidine area by Moynehan, Schofield, Jones, and Katritzky,[11] and thus limited our work to the other systems

(1) Abstracted from the Ph.D. dissertation of N. Sapianchiay, Indiana University, 1963.

(2) W. H. Mills, J. D. Parkin, and W. J. V. Ward, *J. Chem. Soc.*, 2613 (1927).

(3) S. P. Findlay, *J. Am. Chem. Soc.*, **75**, 3204 (1953); compare K. Zeile and W. Schulz, *Chem. Ber.*, **88**, 1078 (1955), and ref. 4–10.

(4) G. Fodor, K. Koczka, and J. Lestyan, *Magy. Kem. Folyoirat*, **59**, 242 (1953); *Chem. Abstr.*, **48**, 10029 (1954).

(5) G. Fodor, *Experientia*, **11**, 129 (1955).

(6) G. Fodor, J. Toth, and I. Vincze, *J. Chem. Soc.*, 3504 (1955).

(7) G. Fodor, O. Kovacs, and M. Halmos, *ibid.*, 873 (1956).

(8) G. Fodor, K. Koczka, and J. Lestyan, *ibid.*, 1411 (1956).

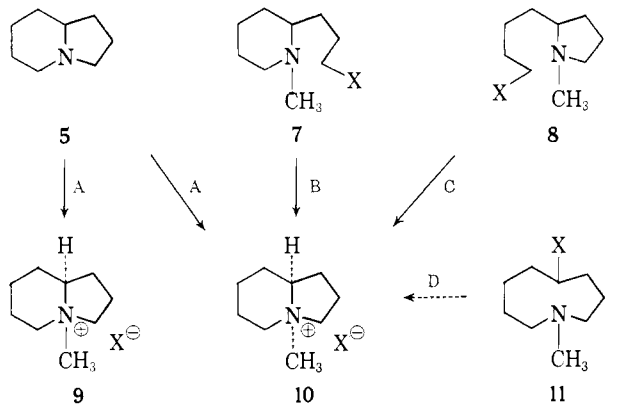
(9) G. Fodor, *Tetrahedron*, **1**, 86 (1957), and further papers.

(10) J. McKenna, J. White, and A. Tulley, *Tetrahedron Letters*, 1097 (1962).

(11) T. M. Moynehan, K. Schofield, R. A. Y. Jones, and A. R. Katritzky, *J. Chem. Soc.*, 2637 (1962).

(12) G. R. Clemo and G. R. Ramage, *ibid.*, 2969 (1932), reported two isomers of indolizidine from Clemmensen reduction of 1-ketoindolizidine, and suggested that they were *cis* and *trans* stereoisomers. Although the structure of one of them still remains undetermined, it is very doubtful that it is such a stereoisomer. It has subsequently been established that such reduction of α-amino ketones often leads to rearranged products; *cf.* V. Prelog and R. Seirverth, *Ber.*, **72**, 1638 (1939), and N. J. Leonard and W. C. Wildman, *J. Am. Chem. Soc.*, **71**, 3089 (1949), *et seq.*

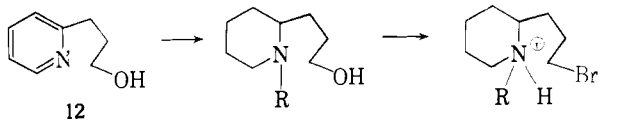
One can envision four different appproaches to preparation of the N-methylindolizidinium ion by an N-alkylation process, the sequences differing in the nature of the final N-substituent which is introduced. These are (A) methylation of the intact bicyclic base, (B) closure of the five-membered ring onto an N-methylpiperidine, (C) cyclization of the six-membered ring onto a N-methylpyrrolidine, and finally (D) formation of both rings by transannular alkylation of an azacyclononane derivative. In the present work the first three of these were examined with reference to the configuration of the resulting methosalt(s). While direct methylation (A) was unselective, giving a 50:50 mixture of the *trans*- and *cis*-fused salts (**9** and **10**), both cyclizations (B and C) were completely stereospecific, producing only the *cis*-salt (**10**).




**Methylation of Indolizidine (A).**—Indolizidine (**5**) was prepared by hydrogenation of 2-(3′-hydroxypropyl)pyridine (**12**) as its hydrochloride, treatment of the resulting hydroxypropylpiperidine **13** with hydrobromic acid, and basification of the bromide hydrobromide **15** so produced.

Treatment of the bicyclic base **5** with methyl iodide in ether or ethanol or with methyl bromide in ether produced crystalline methosalts, m.p. 339–341° for the iodide[13] and m.p. 345–346° for the bromide. That these consisted of mixtures of the *cis* (**10**) and *trans* (**9**) racemates[14] in each case was evident from their elemental composition, the presence of two spots on paper chromatograms, and the appearance of two sharp singlet N-methyl resonances at 6.88 and 7.18 $\tau$ in their n.m.r. spectra. Fractional crystallization afforded in each case one isomer in pure form, m.p. 333–334° for the iodide and m.p. 350° for the bromide; n.m.r. spectra of these two products were identical, and contained but one N-methyl singlet, at 6.88 $\tau$. This isomer of the N-methylindolizidinium ion has been assigned the *cis* configuration (**10**) for reasons detailed in the sequel. Although tail fractions from these crystallizations were enriched in the other stereoisomer, as judged from the relative intensities of the 7.18 and 6.88 $\tau$ resonances, in neither case could a pure sample of that salt be isolated.

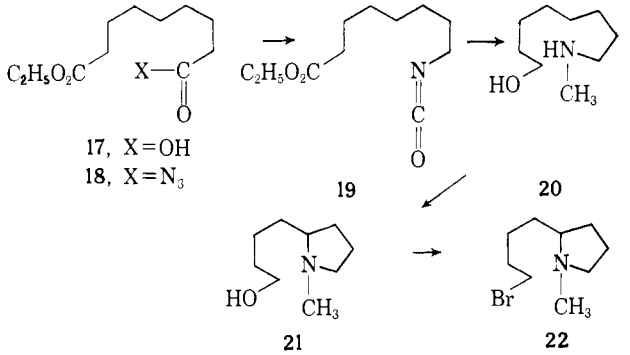
Integration of the N-methyl resonances of the crude methylation product mixture showed that in each instance the *cis*- and *trans*-fused salts were formed in a 50:50 ± 5% ratio. This is clearly the result of a kinetically-controlled alkylation, for both the pure *cis* isomer and a mixture enriched in the *trans* form underwent no change on exposure to the conditions of the methylation.




**Cyclization of N-Methyl-2-(3′-bromopropyl)piperidine (B).**—Synthesis of N-methyl-2-(3′-bromopropyl)-piperidine (**16**), the compound of choice for examining the stereoselectivity of final five-membered ring closure, followed a path analogous to preparation of its desmethyl homolog **15**. The methiodide of the hydroxypropylpyridine **12** was hydrogenated and the resulting tertiary amino alcohol **14** was converted to its bromide hydrobromide **16** by hydrobromic acid, but in this instance the salt was an oil. Consequently, it was not purified but was converted directly to the desired quaternary salt by titration to pH 9 with sodium hydroxide in absolute ethanol.

The indolizidine methobromide produced by this sequence proved to be exclusively the *cis* stereoisomer, identical in all respects with the pure isomer obtained from fractional crystallization of the N-methylation product; n.m.r. examination of even the crude cyclization product showed no 7.18 $\tau$ resonance characteristic of the *trans*-fused salt.

**Cyclization of N-Methyl-2-(4′-bromobutyl)pyrrolidine (C).**—To study formation of the N-methylindolizidinium ion by final closure of the six-membered ring, an N-methyl-2-(4′-halobutyl)pyrrolidine was required, and for preparation of this intermediate we turned attention to the Hofmann–Loeffler pyrrolidine synthesis.[15–19] Ethyl hydrogen azelate[20] (**17**) was converted to the ω-carboethoxy acyl azide **18**, which upon Curtius rearrangement followed by lithium aluminum hydride reduction of the isocyanato ester **19** afforded 8-methylamino-1-octanol (**20**) in excellent yield. Such reduc-




(13) V. Boekelheide and S. Rothchild, *J. Am. Chem. Soc.*, **70**, 864 (1948), reported the m.p. of a crude amorphous sample of this salt, obtained by methylation of indolizidine in benzene solution, to be 280–283° dec. In our hands the dried crude product obtained in this way showed m.p. 337–340° and had infrared and n.m.r. spectra identical with those of the product from methylation in ether. The discrepancy in m.p. may be due to the noncrystalline nature of their sample or to the presence of moisture in it. The salt is extremely hygroscopic, and we have observed m.p.'s more than 20° low for incompletely dried samples.

(14) Although the prefix *dl* is omitted and only one enantiomer of each is depicted in structural formulas, all substances involved in this work were examined only in racemic form.

(15) A. W. Hofmann, *Ber.*, **16**, 558 (1883).

(16) K. Loeffler and C. Freytag, *ibid.*, **42**, 3472 (1909).

(17) S. Wawzonek and T. P. Culbertson, *J. Am. Chem. Soc.*, **81**, 3367 (1959); **82**, 441 (1960).

(18) E. J. Corey and W. R. Hertler, *ibid.*, **82**, 1657 (1960).

(19) M. E. Wolff, *Chem. Rev.*, **63**, 55 (1963).

(20) S. Swann, Jr., R. Oehler, and R. J. Buswell, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 276.

tion of isocyanates has not been widely applied,[21-23] but is in practice an excellent procedure for preparation of N-methyl secondary amines.

The secondary amino alcohol **20** was used directly in the Hofmann–Loeffler sequence without protection of the primary hydroxyl group.[24] The corresponding N-chloroamine, prepared by treatment with N-chlorosuccinimide, was unusually sensitive to heat, light, and atmospheric oxygen, and could not be isolated, but when it was handled only in solution, irradiation in sulfuric acid followed by basification afforded a single tertiary amino alcohol in 70% yield. Since this was different from the N-methylhydroxypropylpiperidine **14,** but isomeric with it, and led to the same N-methylindolizidinium salt, it must indeed be the expected pyrrolidine derivative **21**. The photolytic halogen-transfer step must have been completely specific, for the isomeric piperidine derivative **14** could not be detected in gas chromatograms of even the crude product.

Treatment of the hydroxybutylpyrrolidine **21** with hydrobromic acid produced the corresponding bromobutyl derivative **22,** an oil, which was directly basified to pH 9 with ethanolic sodium hydroxide. As in the previously described cyclization a single indolizidine methobromide was produced, and this again was the *cis*-fused stereoisomer.

**Configurations of the Indolizidine Methiodides.**— Short of X-ray crystallographic analysis, results of which are not yet available, few if any direct and unequivocal methods are available for determination of the relative configurations of the indolizidine methosalts. The stereomechanistic arguments set forth below are best in accord with a *cis* configuration for the isomer formed exclusively by either cyclization process, but additional experimental evidence in support of such an assignment was needed.

The most marked difference in properties of the two isomeric salts is the position of their N-methyl proton resonances, 6.88 and 7.18 $\tau$. During the course of our work the results of Moynehan, Schofield, Jones, and Katritzky[11] from an analogous study in the quinolizidine series became available, and it was of considerable interest to observe that the N-methyl resonances of the two stereoisomeric N-methylquinolizidine salts fell at 6.85 and 7.04 $\tau$, values quite close to those of our indolizidine salts. Further, in that work a number of C,N-dimethylquinolizidinium salts were examined, and in each instance where two ring-fusion stereoisomers were obtained, one of them had N-methyl resonance in the 6.84–6.92 $\tau$ range and the other absorbed between 7.01 and 7.06 $\tau$. When only one of such an isomeric pair was examined, with but one exception it fell into one or the other of these two ranges. The rather striking regularity of these values within the quinolizidine series and the similarity of the indolizidine values to them lent credence to the possibility that this might be a generally useful empirical criterion for assigning configurations to such bicyclic salts, at least when other functional groups are absent. It is not unreasonable that such should be the case and that a change from six- to five-membered rings should not have a profound effect on the relative chemical shifts of N-methyl groups. The N-methyl of a *trans*-fused isomer is axially oriented above both rings, whether they are five or six membered, and thus is slightly differently shielded by them from that of a *cis*-fused compound which is axial to one ring but equatorial to the other.

Several lines of reasoning suggest that in both the six-six- and six-five-fused ring systems the *trans* configuration should be assigned to the isomer which has higher field N-methyl resonance. Calculation of the extent to which the angular methyl protons are shielded by the carbon–carbon bonds of the rings gives this result in each case.[25] Such is known to be the case for the angular methyl groups of steroids, where ring fusion configurations are firmly established; 5$\alpha$-androstanes (A/B *trans*-decalin) have C-19 proton resonance at higher field than do corresponding 5$\beta$- derivatives (A/B *cis*-decalin) and 14$\alpha$-androstanes (C/D *trans*-hydrindane) have C-18 proton resonance at higher field than do analogous 14$\beta$ isomers (C/D *cis*-hydrindane).[26] Likewise in the quaternary salt series, for several reasons Moynehan, Schofield, Jones, and Katritzky[11] assigned the *cis* configuration to those N-methylquinolizidinium salts which had the lower field (6.84–6.92 $\tau$) resonance. Furthermore it has been found that a number of stereoisomeric indole alkaloid methiodides have N-methyl chemical shifts at lower fields if the C/D (quinolizidine) fusion is *cis* than is the case for the *trans*-fused salts,[27,28] and the configurations of at least one of these epimeric pairs are beyond question as the result of X-ray crystallographic analysis.[28] Rather than extrapolate only from these results, however, we felt it would be useful to examine another derivative whose configuration could be assigned with reasonable certainty on independent grounds, to check the validity of the generalization. The compound we chose was pyrrolizidine methobromide (**28**).

Like the indolizidine and quinolizidine methosalts, pyrrolizidine methobromide has not previously been examined from a configurational point of view. Indeed, it has not even previously been reported, although the free base **6** is well known and numerous substituted derivatives of the base occur in the Senecio alkaloids.[29]

(21) A. E. Finholt, C. D. Anderson, and C. L. Agre, *J. Org. Chem.*, **18**, 1338 (1953).

(22) G. Stork, S. S. Wagle, and P. C. Mukharji, *J. Am. Chem. Soc.*, **75**, 3197 (1953).

(23) H. H. Zeiss and W. B. Martin, Jr., *ibid.*, **75**, 5935 (1953).

(24) In contrast J. F. Kerwin, M. E. Wolff, F. F. Owings, B. B. Lewis, B. Blank, A. Magnani, C. Karash, and V. Georgian, *J. Org. Chem.*, **27**, 3628 (1962), found that several N-chloroamines containing a remote secondary hydroxyl group underwent extensive side reactions if photolysis was attempted in sulfuric acid, although the difficulty was alleviated in trifluoroacetic acid.

(25) Calculations were carried out for *cis*- and *trans*-9-methyldecalin, 8-methylhydrindane, and 7-methylbicyclo[3.3.0]octane, using the McConnell equation (H. M. McConnell, *J. Chem. Phys.*, **19**, 1608 (1951)) with $\chi_T - \chi_L$ as $-5.5 \times 10^{-30}$ cm.$^3$/molecule (A. A. Bothner-By and C. Naar-Colin, *Ann. N. Y. Acad. Sci.*, **70**, 833 (1958)) and angles and distances measured from scale models. The four C–N$^+$ bonds of the quaternary salts have the same orientation with respect to the methyl group in each member of a stereoisomeric pair, so their effects cancel in extrapolation of the calculated relative *cis*/*trans* methyl shieldings from the hydrocarbons to the salts. No attempt was made to take into account perturbations of the C–C bond anisotropies by the nearby positively charged nitrogen, although these, of course, would not cancel. These as well as other approximations involved in such a treatment do not allow the results to have more than qualitative significance. However, in each system the angular methyl protons of the *trans* isomer were calculated to be substantially more shielded than those of the *cis* analog. The calculated methyl group shieldings for the three *cis* derivatives differ from one another by much smaller amounts.

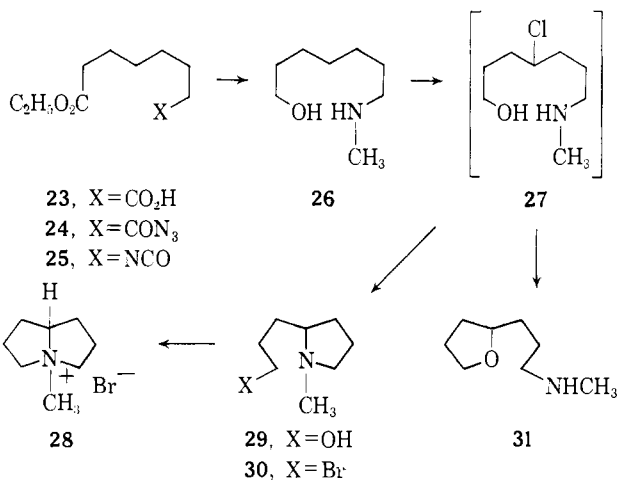
(26) R. F. Zurcher, *Helv. Chim. Acta*, **46**, 2054 (1963); see also J. I. Musher, *J. Am. Chem. Soc.*, **83**, 1146 (1961), for a similar result in the decalin series.

(27) M. Shamma and J. M. Richey, *ibid.*, **85**, 2507 (1963).

(28) M. F. Bartlett, B. Korzun, R. Sklar, A. F. Smith, and W. I. Taylor, *J. Org. Chem.*, **28**, 1445 (1963).

(29) *Cf.* N. J. Leonard in R. H. F. Manske and H. L. Holmes, "The Alkaloids," Vol. 1, Academic Press, Inc., New York, N. Y., 1950, Chapter IV.

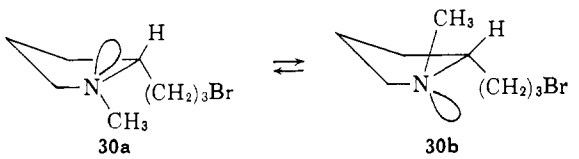
For reasons which will become clear, we chose to prepare the methobromide by a cyclization process, and thus adapted the third (route C) synthesis of indolizidine methobromide to the lower homolog. Ethyl hydrogen suberate (**23**) was converted *via* the acyl azide **24** to ethyl 8-isocyanatoheptanoate (**25**), and lithium aluminum hydride reduction afforded 7-methylamino-1-heptanol (**26**). Surprisingly, while the Hofmann–Loeffler sequence had given a single product when applied to the corresponding methylaminooctanol **20**, in this instance a 50:50 mixture of two products was obtained. One of these was the desired N-methyl-2-(3'-hydroxypropyl)pyrrolidine (**29**), identified both spectrally (n.m.r. and infrared) and by identity of the melting point of its picrate with that reported in the literature.[30] The isomeric coproduct was an N-methyl *secondary* amine in which the hydroxyl group had been lost, for it had 2.8–3.2 $\mu$ (N–H) infrared absorption which disappeared after N-nitrosation, and a 7.65 $\tau$ (N–$CH_3$) proton resonance singlet which shifted to 7.05 $\tau$ in the spectrum of the nitroso derivative. Indeed, the n.m.r. spectrum of the amine was quite similar to those of the secondary amines **20** and **26** except that it had considerably more fine structure, particularly in the 75–120 c.p.s. region. These data, together with the striking similarity of its n.m.r. spectrum to that of tetrahydrofuran and a plausible sequence of events by which it might have arisen, lead us to suggest that the coproduct is 2-(3'-methylaminopropyl)tetrahydrofuran (**31**).




This unexpected result is worth comment. Photolysis of the N-chloroamine in 60% sulfuric acid leads to homolysis of the N–Cl bond, followed by hydrogen abstraction from a sterically accessible C–H bond and attachment of a chlorine atom at the site originally occupied by the hydrogen.[17,18] With open-chain chloroamines, this usually involves hydrogen abstraction from the $\delta$-carbon,[18,19] leading to a $\delta$-halamine, as its ammonium salt, as an intermediate. In the present case this $\delta$-chloramine has structure **27**. Only after basification does intramolecular N-alkylation and pyrrolidine formation occur, for prior to that time the nitrogen is present in its nonnucleophilic protonated form. Even in the acidic medium, however, the hydroxyl oxygen, which in **27** is in the same relative position ($\delta$) with respect to halogen as is the nitrogen, may exist sufficiently as the unprotonated species to carry out nucleophilic substitution of the chlorine.[31] That a corresponding product was not obtained from the higher homolog **20** is not surprising, for one expects displacements involving six-membered ring formation to be slower than those in which five-membered rings are produced.[32] Thus it appears that the same $\delta$-chloroamine leads to both the pyrrolidine **29** and the tetrahydrofuran **31**, the former after basification and the latter before. The obvious corollary of this suggestion is that the yield of tetrahydrofuran could be maximized by increasing the time prior to basification. Since it was the pyrrolidine which we desired, this experiment was not conducted, but rather the mixture was basified as soon as iodide tests indicated that no N-chloroamine remained. However, the synthetic implications of such a process are obvious.

With the hydroxypropylpyrrolidine **29** in hand, the remaining steps in preparation of pyrrolizidine methobromide were trivial. Treatment with hydrobromic acid gave the bromopropyl derivative (**30**) as the hydrobromide, and titration of this with alcoholic alkali produced the salt in question. Only one stereoisomeric salt was formed, and this had its N-methyl resonance at 6.88 $\tau$, precisely the same field as did one of the indolizidinium salts.

Two "isomers" of the bromopropylpyrrolidine **30** can be visualized, one in which the N-methyl and bromopropyl groups are *cis* (**30a**) and one in which they are *trans* (**30b**). The *cis*-fused quaternary salt **28** would arise from cyclization of the latter, while the former would lead to a *trans*-locked ion. However, interconversion of the bases **30a** and **30b** is undoubtedly much faster than either alkylation process, for it involves only the inversion of tricovalent nitrogen. Under these circumstances, as has been pointed out by Curtin and Hammett,[33] the relative proportions of the two salts **28** and **32** can be derived solely from the relative energies of the two transition states which lead to them, without reference to the relative energies of the isomers **30a** and **30b** themselves.




Since a single product was formed in the cyclization, the two transition states must differ in energy by at least 1.5–2.0 kcal./mole, for if a smaller energy difference were involved detectable quantities of the other isomer would have been produced. Barrett and Linstead[34] ascertained that the heat of combustion of *trans*-bicyclo[3.3.0]octane (**3**) is approximately 6 kcal./mole greater than that of its *cis* isomer, and this figure, which represents in large measure the strain resulting from *trans* fusion of two five-membered rings, must at least approximate the relative energies of the two N-methylpyrrolizidine salts. Since ring formation is partially

(30) F. P. Doyle, M. D. Mehta, G. S. Sach, and J. L. Pearson, *J. Chem. Soc.*, 4458 (1958).

(31) It is well known that such chlorohydrins form tetrahydrofurans under acidic conditions; *cf.* H. W. Heine, A. D. Miller, W. H. Barton, and R. W. Greiner, *J. Am. Chem. Soc.*, **75**, 4778 (1953).

(32) For example, S. Winstein, E. Allred, R. Heck, and R. Glick, *Tetrahedron*, **3**, 1 (1958), found that 4-methoxybutyl *p*-bromobenzenesulfonate undergoes formolysis with methoxy participation some 15 times more rapidly than does the corresponding amyl derivative.

(33) *Cf.* D. Y. Curtin, *Record Chem. Progr.*, **15**, 111 (1954).

(34) J. W. Barrett and R. P. Linstead, *J. Chem. Soc.*, 611 (1936).

complete in them, it also probably approximates the energy difference between the two transition states in question. Indeed, the difference between the transition states is probably even greater, for although one of the bonds (the N–C being formed) is elongated compared to that in the product, owing to the linear geometry of the SN2 transition state one of the ring angles (that between the nitrogen, the carbon to which it is becoming bonded, and the carbon attached to the newly bonding one) is appreciably less than 109°. Thus under no circumstances does it appear reasonable to imagine that the *trans*-forming transition state is 2 kcal./mole or more *more stable* than the *cis*, in which case the single observed product must be *cis*-N-methylpyrrolizidinium bromide (**28**).

Since the *cis*-pyrrolizidinium salt has its N-methyl proton resonance at precisely the same field as does one of the indolizidinium salts and one of the quinolizidinium salts, the presumption that this resonance position is in fact dependent upon configuration but not upon the size of the rings involved (at least so long as they are five or six membered), as postulated above, is supported. Hence we assign the *cis* configuration to that N-methylindolizidinium salt which has its N-methyl resonance at 6.88 $\tau$, the isomer formed stereoselectively by either cyclization process. The other isomer accordingly is in the *trans*-fused series. It is important to note that these assignments would agree with those made by assuming that the *cis*-fused salt absorbs at lower field, in analogy with the quinolizidinium series,[11,27] and gives independent support to those assignments.

**Stereochemistry of N-Alkylations Leading to Indolizidine Methosalts.**—Both ring-closure reactions by which N-methylindolizidinium bromide was produced gave rise exclusively to the *cis* isomer. As pointed out in connection with the pyrrolizidinium series, this indicates that a *cis*-forming transition state is of appreciably lower energy than that which would lead to the *trans* isomer. When the five-membered ring is being closed onto an intact six-membered ring (*i.e.*, route B), two equatorial bonds of the six-membered system are involved to produce a *trans* fusion, and one axial and one equatorial bond (in either of two conformations) are involved to produce the *cis* isomer. In the process the six-membered ring is distorted to bring these bands somewhat closer to coplanarity than they are in a purely chair piperidine. More strain is introduced in this way when the bonds involved are (e,e) than when they are (a,e), for in the latter case some of the strain can be relieved by rotations in the six-membered ring. This is essentially similar to the argument which has been used to explain the smaller energy difference between *cis*- and *trans*-hydrindane than between *cis*- and *trans*-decalin.[35,36] Although the energy difference between the isomeric hydrindanes, which approximates the magnitude of this effect when a relatively unstrained five-membered ring is fused to a six-membered ring, is very small,[36] it must be remembered that the transition states here under discussion contain a very distorted five-membered ring, particularly with one very compressed angle. This accentuates the importance of the effect, and favors the *cis* form. Indeed, even when a six-membered ring is being closed onto a six-membered ring in the formation of quinolizidine methiodide the *cis* isomer is produced to the exclusion of the *trans*,[11] although the results with C-methylated derivatives suggest that other factors may also be involved there. An analogous situation obtains when the six-membered ring is being closed onto the pyrrolidine (route C), and here, because the intact ring is more rigid, the strain of the *trans*-forming molecule must be even more pronounced.

Methylation of indolizidine produces a 50:50 mixture, a result which in the light of the foregoing type of analysis is perhaps not surprising. This means that the *trans*-like transition state and the *cis*-like transition state are of about equal energy. The rings involved are not undergoing any very serious distortions in these processes, as they are in the cyclizations, and so one might consider that the relative energies of the transition states are more or less approximated by the *cis*- and *trans*-hydrindanes, respectively. These, of course, are also of nearly equal energy.[36] It is important to observe, however, that the results of such an alkylation process reflect *transition state* energies, and, unfortunately, cannot be correlated with the relative energies of *cis*- and *trans*-indolizidine itself.

A significantly smaller proportion of *trans*-fused salt results from angular N-methylation of indolizidine (50% *trans*) than from quinolizidine (100% *trans*[11]). These are, of course, the expected results if the *cis*- and *trans*-N-methylation transition states in each case resemble the corresponding hydrocarbons hydrindane and decalin, with respect to relative energy differences between *cis* and *trans* forms.[36,37] It is also interesting to observe that this result parallels the comparative course of angular C-methylation of 1-keto-2-methylanilinomethylenehydrindane (0% *trans*[38]) and the corresponding decalin (mixture of *cis* and *trans*, the former predominating[39]). In this case, too, more *trans*-fused product is formed from the system with two fused six-membered rings than from the five-six fused ring molecule.

## Experimental[40]

**Methylation of Indolizidine. 2-(3'-Hydroxypropyl)piperidine (13).**—A mixture of 25 g. (0.19 mole) of commercial 2-(3'-hy-

(35) *Cf.* W. G. Dauben and K. S. Pitzer in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p. 37.

(36) N. L. Allinger and J. L. Coke, *J. Am. Chem. Soc.*, **82**, 2553 (1960).

(37) N. L. Allinger and J. L. Coke, *ibid.*, **81**, 4080 (1959).

(38) A. J. Birch, R. Jaeger, and R. Robinson, *J. Chem. Soc.*, 582 (1945).

(39) A. J. Birch and R. Robinson, *ibid.*, 501 (1944).

(40) Infrared spectra were obtained on Perkin-Elmer Models 21, 137, and 137G spectrometers; n.m.r. spectra were obtained from dilute solutions using a Varian A-60 spectrometer. Tetramethylsilane was used as an internal standard with carbon tetrachloride solutions and dioxane with deuterium oxide solutions, the factor 3.70 p.p.m. (see R. A. Y. Jones, A. R. Katritzky, J. N. Murrell, and N. Sheppard, *J. Chem. Soc.*, 2576 (1962)) being used to convert the latter values to the $\tau$-scale. Spectra are described by the use of abbreviations, (s) for singlet, (d) for doublet, (t) for triplet, (q) for quartet, and (m) for multiplet too complicated to be described by the other symbols. Gas chromatograms (g.l.c.) were run on a Perkin–Elmer Model 154D fractometer with helium as the carrier gas and a thermal conductivity detector or an F and M Model 609 linear programmed temperature gas chromatograph equipped with a hydrogen flame ionization detector using nitrogen as a carrier gas. A 6-ft. 20% Carbowax column, designated C, or a 2-m. 9% silicone gum SE30 on Chromosorb W column, designated Z, or a 2-m. 10% silicone gum SE30 on Chromosorb W column, designated W, was used. The compositions of mixtures were estimated as the ratios of the individual peak areas. Melting points were taken in open capillary tubes unless stated otherwise and are corrected for stem exposure. Melting (decomposition) points of all ammonium salts were determined at a heating rate of 1° per minute. Boiling points are uncorrected. Microanalyses were obtained from Spang Microlab, Ann Arbor, Mich. (indicated S); Midwest Microlab, Inc., Indianapolis 20, Ind. (indicated M); and Alfred Bernhardt Mikroanalytisches Laboratorium, Mulheim, Germany (indicated B).

droxypropyl)pyridine (12) (Aldrich Chemical Co., b.p. 96° (0.5 mm.)), 16 ml. of concentrated hydrochloric acid, and 2 g. of platinum oxide (Englehard Industries, Inc.) in 160 ml. of absolute ethanol was shaken for 3 hr., under 3 atm. of hydrogen. The solid obtained by filtration of the catalyst and evaporation of the solvent *in vacuo* was taken up in 100 ml. of 50% potassium hydroxide solution, sodium chloride was added to the saturation point, and the oily base was extracted with ether. The ether was dried over potassium carbonate and distilled *in vacuo* leaving 26.8 g. (98%) of a pale yellow oil which was distilled to afford 23.7 g. (91%) of the amino alcohol **13** as a colorless oil, b.p. 110° (2.4 mm.), $n^{25}D$ 1.4874; $\lambda_{max}^{film}$ 2.8–3.3 $\mu$ (broad) (reported[13] b.p. 101–102° (3 mm.), $n^{21.5}D$ 1.4882). The hydrochloride, recrystallized from acetone–alcohol, had m.p. 130–131° (reported[13] m.p. 128–129°).

**2-(3′-Bromopropyl)piperidine Hydrobromide** (**15**).—The procedure used by Pearlman in another series[41] was applied to a 52.2-g. (0.365 mole) sample of 2-(3′-hydroxypropyl)piperidine (**13**), b.p. 110° (2.4 mm.). Cold 48% hydrobromic acid (155 ml.) was added with cooling and stirring to the amine, and the resulting mixture was distilled through a Vigreux column until the boiling point was constant at 99°. The residue was cooled and further evaporated by storage overnight in a desiccator evacuated to 20 mm. The resulting slurry was filtered and the solid was recrystallized from absolute ethanol to yield 75 g. (72%) of the bromide hydrobromide **15** as colorless needles, m.p. 173.5–175°. Recrystallization from acetone–ethanol afforded colorless needles, m.p. 176–178° dec.; $\lambda_{max}^{CHCl_3}$ 3.55, 6.32 $\mu$.

*Anal.* Calcd. for $C_8H_{17}Br_2N$: C, 33.47; H, 5.93; Br, 55.72; N, 4.88. Found (S): C, 33.27; H, 5.85; Br, 55.81; N, 5.01.

**Indolizidine** (**5**).—The procedure was a modification of one used by Loeffler.[42] 2-(3′-Bromopropyl)piperidine hydrobromide (**15**, 64 g., 0.22 mole), m.p. 176–178°, was warmed with 250 ml. of 2 *N* sodium hydroxide for 0.5 hr. The light oil which separated was steam distilled. The distillate was basified with sodium hydroxide, saturated with sodium chloride, and extracted with ether, which was then dried over potassium carbonate. Solvent was removed *in vacuo* to yield 18.7 g. (67%) of a light oil, which after distillation afforded indolizidine as a colorless mobile liquid, b.p. 81° (44–45 mm.), $n^{25}D$ 1.4697 (reported b.p. 65–67° (18 mm.)[12] $n^{20}D$ 1.4700[43]); $\lambda_{max}^{CCl_4}$ 3.36, 3.4, 3.48, 3.58, 3.62, 3.66, 3.72, and 3.76 $\mu$. The base turned yellow on standing. The picrate was prepared in ethanol, and recrystallization from this solvent yielded bright yellow prisms, m.p. 228–230° dec. (reported m.p. 226°[12] and 228.5–230°[43]).

**Indolizidine Methiodide.**—To a solution of 0.954 g. (0.00763 mole) of freshly distilled indolizidine, b.p. 81° (44–45 mm.), in 10 ml. of anhydrous ether was added 6 g. (0.05 mole) of purified[44] methyl iodide. White solid separated after 0.5 hr. at room temperature. Centrifugation and removal of the solvent left 1.765 g. (87%) of the salt, m.p. 339–341° (dec., evacuated capillary) (reported[13] m.p. 280–283° dec. from benzene); $\lambda_{max}^{CHCl_3}$ 6.82 and 6.94 $\mu$; n.m.r. ($D_2O$) 6.88 (s), 7.18 $\tau$ (s), relative areas 50:50 ± 5%. A paper chromatogram on Whatman No. 1 filter paper with *n*-butyl alcohol–acetic acid–water (2:1:1) at 25–26° showed two gray spots, with $R_f$ 0.29 and 0.35, respectively, after development with silver nitrate and photographic developer.

*Anal.* Calcd. for $C_9H_{18}IN$: C, 40.46; H, 6.74; I, 47.55; N, 5.25. Found (M): C, 41.11; H, 6.87; I, 47.25; N, 4.95.

An identical product mixture resulted from similar reaction in absolute ethanol as solvent.

Fractional crystallization from acetone afforded two forms of crystals, needles and leaflets. After five crystallizations, the head fraction contained only needle-shaped crystals of the *cis* isomer **10**, m.p. 333–334° (sealed capillary, sublimed at 323°), n.m.r. ($D_2O$) 6.88 $\tau$ (s).

*Anal.* Calcd. for $C_9H_{18}IN$: C, 40.46; H, 6.74; I, 47.55; N, 5.25. Found (M): C, 40.28; H, 6.92; I, 47.78; N, 5.01.

The tail fraction, m.p. 337° (sealed capillary), from the fifth crystallization contained a mixture in a 2:3 ratio (n.m.r.), richer in the *trans* isomer **9**.

**Indolizidine Methobromide.**—To a cooled solution of about 5 ml. of methyl bromide in 10 ml. of anhydrous ether was added a solution of 0.8373 g. (0.0067 mole) of indolizidine, b.p. 70–71° (41–42 mm.), in 10 ml. of anhydrous ether. The mixture was kept protected from moisture at 0° for 7 hr. It was then allowed to warm to room temperature while excess methyl bromide distilled. The white precipitate (1.499 g., 84%) was washed with ether and dried in an evacuated desiccator. The n.m.r. spectrum of this mixture ($D_2O$) was identical with that of the crude methiodide described above, which indicated that it was a 50:50 ± 5% mixture of the two stereoisomers.

The mixture was fractionally crystallized by the technique used with the methiodide. After four crystallizations, the head fraction yielded pure needles, m.p. 350° (sealed tube), n.m.r. ($D_2O$) 6.88 $\tau$ (s).

*Anal.* Calcd. for $C_9H_{18}BrN$: C, 49.11; H, 8.19; N, 6.37. Found (M): C, 49.38, H, 8.19; N, 6.19.

**Ring Closure of N-Methyl-2-(3′-bromopropyl)piperidine. N-Methyl-2-(3′-hydroxypropyl)piperidine** (**14**).—To a solution of 20 g. (0.15 mole) of 2-(3′-hydroxypropyl)pyridine (**12**), b.p. 96° (0.5 mm.), in 30 ml. of ether was added 22.2 g. (0.16 mole) of purified[44] methyl iodide. The salt which precipitated as an oil and then crystallized was centrifuged and the solvent was removed. The product was washed twice with ether and dried in an evacuated desiccator to a weight of 36.7 g. (92%), m.p. 85–90°. Two recrystallizations did not improve the m.p., apparently owing to the very hygroscopic nature of the yellow prisms, and thus the material was hydrogenated directly. A solution of 14.4 g. (0.0516 mole) of the methiodide in 250 ml. of absolute ethanol was warmed slightly to produce a clear solution, 0.7 g. of platinum oxide was introduced, and the mixture was hydrogenated under 3 atm. pressure for 3 hr. The oil obtained by filtration of the catalyst and evaporation of solvent *in vacuo* was basified with 50% potassium hydroxide solution and extracted with ether. Vacuum distillation gave 7.0 g. (86%) of the amino alcohol **14** as a colorless viscous oil, b.p. 111° (2.9 mm.), $n^{25}D$ 1.4812; $\lambda_{max}^{film}$ 2.7–3.2 $\mu$ (broad); n.m.r. ($CCl_4$) 5.2 (s, broad, OH), 6.53 (t), 7.77 $\tau$ (s).

The hydrochloride was prepared in methanol and recrystallized from acetone–ethanol as white needles, m.p. 137–138°; $\lambda_{max}^{CHCl_3}$ 2.9 (broad), 3.7–4.1 $\mu$ (broad).

*Anal.* Calcd. for $C_9H_{20}ClNO$: C, 55.83; H, 10.34; Cl, 18.33; N, 7.24. Found (M,S): C, 56.18, 55.61; H, 10.56, 10.27; Cl, 18.89; N, 7.27, 7.43.

The methiodide was prepared in 91% yield from 0.5 g. of the amino alcohol and 2 g. of methyl iodide in 10 ml. of ether. It crystallized from acetone–ethanol as colorless prisms, m.p. 145–146°, $\lambda_{max}^{KBr}$ 2.88 $\mu$.

*Anal.* Calcd. for $C_{10}H_{22}INO$: C, 40.14; H, 7.36; I, 42.45; N, 4.68. Found (M): C, 40.10; H, 7.24; I, 42.66; N, 4.59.

**N-Methyl-2-(3′-bromopropyl)piperidine Hydrobromide** (**16**).—Treatment of 10.0 g. (0.0637 mole) of N-methyl-2-(3′-hydroxypropyl)piperidine (**14**), b.p. 111° (2.9 mm.), with 27.5 g. (0.163 mole) of 48% hydrobromic acid in the manner[41] described for the desmethyl derivative **13** afforded 23 g. of the corresponding bromide hydrobromide **16** as a viscous oil which was used directly for the ring closure.

***cis*-Indolizidine Methobromide.**—The crude hydrobromide **16** was dissolved in 60 ml. of absolute ethanol, cooled in ice, and titrated with sodium hydroxide in absolute ethanol to a pH of about 9 (phenolphthalein). The solvent was removed *in vacuo* leaving a semisolid. This was washed with ether and dried leaving 20 g. of a biege solid consisting of sodium bromide and indolizidine methobromide, the n.m.r. of which ($D_2O$) showed only one N-methyl singlet, 6.88 $\tau$. The product was dissolved in absolute ethanol, sodium bromide was removed by filtration, and the filtrate was evaporated to dryness. The salt was crystallized thrice from acetone–ethanol, which afforded fine white needles of the *cis*-fused methobromide **10**, m.p. 348–349° (sealed tube, sublimed at 320°), $\lambda_{max}^{film}$ 6.72 and 6.88 $\mu$. Infrared and n.m.r. spectra were identical with those of the crude product.

*Anal.* Calcd. for $C_9H_{18}BrN$: C, 49.11; H, 8.19; N, 6.37. Found (M): C, 49.23; H, 8.05; N, 6.41.

***cis*-Indolizidine Methiodide.**—To a solution of 3.2 g. of the crude mixture of sodium bromide and indolizidine methobromide described above in 8 ml. of absolute ethanol was added a solution of 2.2 g. of sodium iodide in 6 ml. of absolute ethanol. A white precipitate of sodium bromide separated. After several hours sodium bromide was removed by filtration and the filtrate was evaporated to dryness *in vacuo*. After three crystallizations of the residue from acetone–ethanol, white needles of *cis*-indolizidine methiodide (**10**), m.p. 331–334° dec., were obtained. An in-

(41) W. M. Pearlman, *J. Am. Chem. Soc.*, **70**, 871 (1948).

(42) K. Loeffler and M. Flugel, *Ber.*, **42**, 3420 (1909).

(43) V. Boekelheide, W. J. Linn, P. O'Grady, and M. Lamborg, *J. Am. Chem. Soc.*, **75**, 3243 (1953).

(44) L. F. Fieser, "Experiments in Organic Chemistry," 3rd Ed., D. C. Heath and Co., Boston, Mass., 1955, p. 304.

frared spectrum was identical with that of the pure product obtained by fractional crystallization of the mixture of the two isomers from methylation of indolizidine; n.m.r. also indicated that this sample contained only one isomer, the N-$CH_3$ singlet falling at 6.88 $\tau$.

**Ring Closure of N-Methyl-2-(4'-bromobutyl)pyrrolidine. Diethyl Azelate.**—Following the procedure described by Micovic[45] for diethyl adipate, reaction of 94.0 g. (0.50 mole) of azelaic acid (Eastman Organic Chemicals), m.p. 104.5–106.5°, with 180 ml. (1.5 mole) of absolute ethanol in 90 ml. of toluene and 0.4 ml. of concentrated sulfuric acid afforded 112.42 g. (93%) of diethyl azelate as a colorless oil, b.p. 140–145° (1.8–2.0 mm.) (reported[46] b.p. 140° (1 mm.)), $\lambda_{max}^{film}$ 5.76 $\mu$; g.l.c. (Z, 200°) showed only one peak.

**Ethyl Hydrogen Azelate (17).**—The general method employed was that of Swann.[20] Reaction of 94.0 g. (0.50 mole) of azelaic acid, m.p. 104.5–106.5°, 70.5 g. (0.289 mole) of diethyl azelate, b.p. 148° (7.5 mm.), 25 ml. of di-*n*-butyl ether, 12.5 ml. of concentrated hydrochloric acid (sp. gr. 1.19), and 30 ml. followed after 2 hr. by another 10 ml. of 95% ethanol afforded after fractional distillation 54.7 g. (50%) of pure ethyl hydrogen azelate, b.p. 178–195° (6 mm.) (reported[46] b.p. 170° (1 mm.)); $\lambda_{max}$ 2.85–3.2, 5.76, and 5.86 $\mu$. Earlier fractions contained the diester together with some additional half-ester, and the residue in the distilling flask contained unchanged azelaic acid.

**Ethyl 8-Isocyanatooctanoate (19).**—The acid chloride was prepared from 21.6 g. (0.100 mole) of ethyl hydrogen azelate (**17**), b.p. 185–195° (6 mm.), and 20.5 g. (0.15 mole) of thionyl chloride following the technique of Helferich and Schaefer.[47] Vacuum distillation afforded 21.28 g. (91%) of ethyl 8-chloroformyloctanoate, b.p. 140–141° (6–6.5 mm.) (reported[46] b.p. 155° (14 mm.)); $\lambda_{max}^{film}$ 5.56, 5.76 $\mu$. Conversion of this to the isocyanate followed the procedure of Allen and Bell.[48] To an ice-cold solution of 5.2 g. (0.078 mole) of sodium azide in 15 ml. of water was added dropwise with stirring a solution of 11.97 g. (0.051 mole) of the distilled acid chloride in 15 ml. of acetone, the temperature being kept below 15°. The mixture was held at 0° for 2 hr., the aqueous layer was removed, and the acyl azide layer was added dropwise to 50 ml. of dry benzene held at 65–70°. When nitrogen evolution had subsided, 30 ml. of benzene was added, the mixture was filtered, and benzene was evaporated under reduced pressure leaving 10.6 g. of a yellow oil. Distillation afforded 8.0 g. (74%) of the isocyanate **19** as a colorless liquid, b.p. 106° (1 mm.), $\lambda_{max}^{film}$ 4.4 and 5.76 $\mu$. The gas chromatogram (Z, 200°) showed one major peak of about 97% purity. After two more fractional distillations, an analytical sample, b.p. 111° (1.4 mm.), was obtained.

*Anal.* Calcd. for $C_{11}H_{19}NO_3$: C, 61.97; H, 8.92; N, 6.57; O, 22.54. Found (B): C, 61.97; H, 9.00; N, 6.71; O, 22.70.

**8-Methylamino-1-octanol (20).**—The reduction was based on the procedure of Stork.[22] To 11.5 g. (0.3 mole) of lithium aluminum hydride in 250 ml. of ice-cold freshly distilled tetrahydrofuran was added dropwise with stirring a solution of 13.2 g. (0.062 mole) of ethyl 8-isocyanatooctanoate (**19**), b.p. 106° (1 mm.), in 100 ml. of tetrahydrofuran. After 23 hr. at reflux the mixture was cooled in ice and a mixture of 16 ml. of water and 14 ml. of tetrahydrofuran was carefully added, followed by just enough 20% sodium hydroxide (75 ml.) to give a loose precipitate. The ether solution was decanted and the precipitate was washed twice with ether. The ether extracts were dried with potassium carbonate, filtered, and evaporated, leaving 9.19 g. (93%) of a heavy oil which upon distillation afforded 7.63 g. (78%) of the amino alcohol **20** as a colorless oil, b.p. 117° (1.3 mm.), $n^{25}D$ 1.4588, $\lambda_{max}^{film}$ 2.85–3.35 $\mu$ (broad); n.m.r. ($CCl_4$) 6.52 (t), 7.28 (s, broad, OH), and 7.62 $\tau$ (s); g.l.c. (C, 200°) showed one peak. The hydrochloride, prepared in ether, was recrystallized from acetone–ethanol as shiny white plates, m.p. 95–96°; $\lambda_{max}^{KBr}$ 2.8–3.1, 7.3, and 7.4 $\mu$.

*Anal.* Calcd. for $C_9H_{22}ClNO$: C, 55.23; H, 11.33; Cl, 18.11; N, 7.16. Found (B): C, 55.39; H, 11.32; Cl, 18.45; N, 7.13.

**N-Methyl-2-(4'-hydroxybutyl)pyrrolidine (21).**—The conditions employed in this experiment were modified from those of Corey[18] and Coleman.[49] To a cold solution of 1.7960 g. (0.01192 mole) of 8-methylamino-1-octanol, b.p. 116° (0.9 mm.), in 125 ml. of anhydrous ether was added 2.41 g. (0.01812 mole) of N-chlorosuccinimide, m.p. 142–146°, and the mixture was stirred for 160 min. It was filtered, washed with 30 ml. of ice-cold water, 30 ml. of 10% sulfuric acid, and 30 ml. of ice-cold water, and dried with magnesium sulfate. A stream of nitrogen was bubbled through the ether solution whereupon the solution became concentrated and cooled. To this solution was added 50 ml. of petroleum ether (b.p. 90–95°). The stream of nitrogen was continued until all ether was swept off. To the residual ice-cold solution was added 25 ml. of ice-cold 60% sulfuric acid and the reaction mixture was allowed to stand for 10 min. and then stirred for 20 min. under nitrogen. The acid layer was separated from petroleum ether by means of a precooled separatory funnel. The acid solution was placed in a 100-ml. quartz flask and a stream of nitrogen was passed through the solution for 5 min. The mixture was immersed in an ice bath and irradiated under nitrogen with a Hanovia 140-watt lamp, Type 30600. The reaction was followed by testing aliquots with aqueous potassium iodide for the presence of positive halogen. After 2.5 hr. no iodine color was produced, irradiation was stopped, and ice and then 100 ml. of 20% sodium hydroxide were added. The pH was adjusted to 10 with solid sodium hydroxide, and the solution was allowed to warm to room temperature overnight. The oil was extracted four times with ether, dried with potassium carbonate, filtered, and ether was evaporated *in vacuo* leaving 1.2475 g. (71%) of a yellow oil. Vacuum distillation afforded the amino alcohol **21** as a colorless liquid, b.p. 110° (0.3 mm.), $n^{25}D$ 1.4710; $\lambda_{max}^{film}$ 2.8–3.3 (broad), 7.3, and 7.4 $\mu$; n.m.r. ($CCl_4$) 5.82 (s, broad, OH), 6.51 (t), 7.76 $\tau$ (s). The gas chromatogram (C, 200°) showed one component different from the starting material.

*Anal.* Calcd. for $C_9H_{19}NO$: C, 68.79; H, 12.10; N, 8.92. Found (B): C, 68.23; H, 11.78; N, 9.10.

**N-Methyl-2-(4'-bromobutyl)pyrrolidine Hydrobromide (22).**—The Pearlman[41] procedure, described above for the bromide **15**, was applied with 0.4120 g. (0.00262 mole) of N-methyl-2-(4'-hydroxybutyl)pyrrolidine (**21**), b.p. 110° (0.3 mm.), and 1.56 g. (0.0062 mole) of 48% hydrobromic acid. The product was a viscous heavy brown oil weighing 0.759 g. which could not be crystallized and thus was used directly for the next step.

***cis*-Indolizidine Methobromide.**—The crude N-methyl-2-(4'-bromobutyl)pyrrolidine hydrobromide (**22**, 0.759 g.) was taken up in 8 ml. of absolute ethanol, titrated to pH 9 (phenolphthalein) with 2% sodium hydroxide in absolute ethanol, and the resulting mixture was left at room temperature for several hours. Solvent was removed leaving 0.7413 g. of pale beige solid, a mixture of indolizidine methobromide and sodium bromide; n.m.r. ($D_2O$) showed only one N-$CH_3$ peak, at 6.88 $\tau$, indicating that only the *cis* isomer **10** of the methobromide was present. After two crystallizations from acetone the product gave white needles of the salt, m.p. 348°, identical in all respects with the product obtained from cyclization of N-methyl-2-(3'-bromopropyl)-piperidine hydrobromide (**16**).

**Pyrrolizidine Methobromide. Diethyl Suberate.**—The procedure[45] described for diethyl azelate was employed. From 60.51 g. (0.348 mole) of suberic acid (Aldrich Chemical Co.), m.p. 140–141°, 130 ml. of absolute ethanol, 60 ml. of toluene, and 0.4 ml. of concentrated sulfuric acid was obtained 74.39 g. (93%) of the diester, b.p. 149–149.5° (10–11 mm.) (reported[50] b.p. 82–84° (0.1 mm.)), $\lambda_{max}^{film}$ 5.76 $\mu$; g.l.c. (Z, 200°) showed only one peak.

**Ethyl Hydrogen Suberate (23).**—A method similar to that[20] described for the azelaic ester **17** was employed. From 87 g. (0.5 mole) of suberic acid, m.p. 140–141°, 67.3 g. (0.3 mole) of diethyl suberate, b.p. 149–149.5° (10–11 mm.), 25 ml. of di-*n*-butyl ether, 12.5 ml. of concentrated hydrochloric acid (sp. gr. 1.19), and 50 ml. (0.5 mole) of 95% ethanol there was obtained 63.4331 g. (63%) of pure ethyl hydrogen suberate (**23**), b.p. 182° (10 mm.) (reported[51] b.p. 181–183° (9–10 mm.)); $\lambda_{max}$ 2.85–3.2, 5.76, and 5.86 $\mu$.

**Ethyl 7-Isocyanatoheptanoate (25).**—The procedure[47,48] was similar to that used with the higher homolog **19**. From 36 g. (0.3 mole) of thionyl chloride and 46.936 g. (0.2343 mole) of ethyl hydrogen suberate (**23**), b.p. 182° (10 mm.), was obtained 49.22 g. (96%) of ethyl 7-chloroformylheptanoate, b.p. 136° (7 mm.), $\lambda_{max}^{film}$ 5.56 and 5.76 $\mu$ (reported[51] b.p. 146° (12 mm.)).

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Reaction of 21.5840 g. (0.1085 mole) of the distilled acid chloride with 12.9247 g. (0.1988 mole) of sodium azide followed by rearrangement of the acyl azide produced 13.2928 g. of the isocyanate as a colorless liquid, b.p. 91–92° (0.1 mm.), $\lambda_{max}^{film}$ 4.4 and 5.76 μ; g.l.c. (Z, 200°) showed a major peak of 85% purity. After two more fractional distillations, a pure sample was obtained, b.p. 98° (1.5 mm.), $n^{25}D$ 1.4374.

*Anal.* Calcd. for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60; N, 7.03. Found (B): C, 60.36; H, 8.44; N, 7.31.

**7-Methylamino-1-heptanol (26).**—The isocyanato ester **25** was reduced as described for its homolog **19**. Reaction of 11.5602 g. (0.0581 mole) of ethyl 7-isocyanatoheptanoate (**25**, *ca.* 90% pure by v.p.c.) with 11.6 g. (0.303 mole) of lithium aluminum hydride produced 8.5 g. (100%) of a heavy oily crude product. Vacuum distillation yielded 5.7496 g. (69%) of the amino alcohol **26** as a colorless oil, b.p. 94° (0.3 mm.), $n^{27}D$ 1.4562, $\lambda_{max}^{film}$ 2.85–3.3 μ (broad); n.m.r. ($CCl_4$) 6.55 (t), 7.19 (s, broad, OH), and 7.65 τ (s). A gas chromatogram (Z, 175°) showed a major peak (70%) at 4.6 min. and a minor one (30%) at 2.0 min. After two fractional distillations a pure sample as evidenced by g.l.c. was obtained.

The hydrochloride was prepared and recrystallized four times from acetone–ethanol to afford groups of shiny needles, m.p. 74–76°; $\lambda_{max}^{KBr}$ 2.8–3.1 (broad), 7.3, and 7.4 μ.

*Anal.* Calcd. for $C_8H_{20}ClNO$: C, 52.89; H, 11.02; N, 7.71. Found (B): C, 52.97; H, 11.10; N, 7.88.

**Photolysis of 7-Methylamino-1-heptanol (26).**—The conditions employed in this experiment were modified from the procedures of Corey[18] and Coleman.[49] To a solution of 2.3916 g. (0.0165 mole) of 7-methylamino-1-heptanol (**26**, *ca.* 99% pure by g.l.c.) in 130 ml. of anhydrous ether was added 3.1647 g. (0.0237 mole) of N-chlorosuccinimide, m.p. 142–146°. The mixture was cooled in ice and stirred for 1 hr. It was filtered and the precipitate was washed twice with 5-ml. portions of ether. The ether solutions were combined, washed with 30 ml. of ice-cold water, 30 ml. of 10% sulfuric acid, and then 30 ml. of ice-cold water, dried with magnesium sulfate, and filtered. The solvent was partially removed by passing a stream of nitrogen through the solution, 50 ml. of petroleum ether (b.p. 90–95°) was added, and the stream of nitrogen was continued to ensure that all ether had evaporated. The solution was cooled in ice and 31 ml. of cold 60% sulfuric acid was added. The mixture was allowed to stand for 10 min. and stirred for 20 min. under nitrogen. The acid layer was separated by means of a precooled separatory funnel. The organic layer was washed with 5 ml. of 60% sulfuric acid. The acid extracts were combined and placed in a 100-ml. quartz flask and a stream of nitrogen was passed through for 10 min. The flask was immersed in an ice bath and irradiated under nitrogen with a Hanovia 140-watt lamp Type 30600 for 2.25 hr., aliquots being tested with potassium iodide. At the end of this time an aliquot gave a negative test with potassium iodide. The mixture was basified with 100 ml. of 20% sodium hydroxide solution and sodium hydroxide pellets were added to bring the pH to 10. The solution was left standing at room temperature overnight and a brown oil appeared on the top layer. This was extracted with ether, dried with magnesium sulfate, and filtered. Removal of the solvent *in vacuo* yielded 1.8041 g. (77%) of a yellow oil, the gas chromatogram of which (W, 125°) indicated the presence of two components in a ratio of 5:6 in the order of emergence.

Another reaction was carried out under identical conditions to obtain an additional 2.1284 g. of photolyzed product. A gas chromatogram showed it to contain a mixture of the two components in the ratio of about 1:1. The two batches were combined and distilled at 4.5 mm. using a 20-cm. spinning band column. Four fractions were collected: (1) b.p. 72°, g.l.c. (W, 125°) 9.7 min.; (2) b.p. 72–88°, g.l.c. 9.7 min. (90%), 10.8 min. (10%); (3) b.p. 88–98°, g.l.c. 9.7 min. (30%), 10.8 min. (70%); (4) b.p. 98°, g.l.c. 9.7 min. (5%), 10.8 min. (95%).

**2-(3′-Methylaminopropyl)tetrahydrofuran (31).**—Fraction 1 from the above preparation had b.p. 72° (4.5 mm.), $n^{27}D$ 1.4520; $\lambda_{max}^{film}$ 2.8–3.2 (broad), 6.8, 6.92, 7.26, and 7.36 μ; n.m.r. ($CCl_4$) 7.65 τ (s). A picrate was prepared in absolute ethanol. Recrystallization from ethanol afforded canary-yellow needles of the methylaminotetrahydrofuran picrate, m.p. 131–132°.

*Anal.* Calcd. for $C_{14}H_{20}N_4O_8$: C, 45.16; H, 5.41; N, 15.05. Found (B): C, 45.13; H, 5.47; N, 15.09.

The nitroso derivative of 2-(3′-methylaminopropyl)tetrahydrofuran was prepared by the method of Shriner, Fuson, and Curtin.[52] To a cooled solution of 0.400 g. (0.0028 mole) of 2-(3′-methylaminopropyl)tetrahydrofuran (**31**, 100% pure by g.l.c.) in 5 ml. of 10% hydrochloric acid was added with stirring a cooled solution of 3.6 g. (0.0052 mole) of sodium nitrite in 8 ml. of water. The yellow solution was left standing in ice for 1 hr.; no precipitate appeared. The solution was basified with 5 ml. of 20% sodium hydroxide solution and saturated with sodium chloride. It was extracted with ether, dried with magnesium sulfate, and filtered. Evaporation of the solvent afforded 0.41 g. (84%) of a yellow oil. Distillation on a Hickman still afforded the nitroso compound as a pale yellow oil at a bath temperature of 170° (3 mm.); $n^{27}D$ 1.4760; $\lambda_{max}^{CCl_4}$ 3.35, 3.45, 6.95, and 7.5 μ; n.m.r. ($CCl_4$) 7.05 τ (s).

*Anal.* Calcd. for $C_8H_{16}N_2O_2$: C, 55.79; H, 9.36; N, 16.27. Found (B): C, 55.74; H, 9.48; N, 16.16.

**N-Methyl-2-(3′-hydroxypropyl)pyrrolidine (29).**—The fourth fraction from fractional distillation of the photolysis product (1.0083 g.) was dissolved in 10 ml. of 10% hydrochloric acid and cooled in ice. To this solution was added with stirring a solution of 1.2 g. of sodium nitrite in 2.5 ml. of water. It was left standing in ice for 1 hr., then basified with 5 ml. of 20% sodium hydroxide solution. A green precipitate was removed by centrifugation. The aqueous solution was saturated with sodium chloride and extracted five times with ether. The ether solution was dried with magnesium sulfate, filtered, and the solvent was removed *in vacuo* yielding 0.9494 g. of an oil. Distillation on a Hickman still afforded the pyrrolidine **29** as a colorless oil at a bath temperature of 120–130° (3 mm.); $n^{25}D$ 1.4727. A gas chromatogram (W, 125°) showed only one component; $\lambda_{max}^{CCl_4}$ 2.8–3.3 (broad), 6.9, and 7.5 μ; n.m.r. ($CCl_4$) 5.6 (s, broad, OH), 6.56 (t), and 7.72 τ (s).

The picrate was prepared in absolute ethanol. Recrystallization from chloroform–cyclohexane yielded bright yellow needles, m.p. 54° (reported[30] m.p. 54°).

***cis*-Pyrrolizidine Methobromide (28).**—The hydrobromide intermediate (**30**) was prepared by the technique[41] used in the other series. From 0.4921 g. (0.003441 mole) of N-methyl-2-(3′-hydroxypropyl)pyrrolidine (**29**), b.p. 98° (4.5 mm.), and 4.3 g. (0.0255 mole) of cold 48% hydrobromic acid there was obtained 2.7071 g. of the bromide hydrobromide as a brown viscous oil.

The crude N-methyl-2-(3′-bromopropyl)pyrrolidine hydrobromide (**30**) was dissolved in 10 ml. of absolute ethanol and titrated to pH 9 with a saturated solution of sodium hydroxide in absolute ethanol. The solvent was evaporated yielding 2.0686 g. of a yellow solid. This was washed with ether and dried; n.m.r. ($D_2O$) analysis indicated the presence of only one isomer, with its N-methyl resonance at 6.88 τ (s). The salt was very hygroscopic and turned brown in contact with air. After three crystallizations, a white amorphous material was obtained, m.p. 381–382° (sealed capillary), $\lambda_{max}^{CHCl_3}$ 3.40 and 6.90 μ.

*Anal.* Calcd. for $C_8H_{16}BrN$: C, 46.60; H, 7.83; Br, 38.77; N, 6.80. Found (M): C, 47.01; H, 8.08; Br, 37.95; N, 6.55.

**Acknowledgment.**—Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

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