510. *The Synthesis and Stereochemistry of Quinolizidine and the Monomethylquinolizidines, and of their Salts and Quaternary Salts.*

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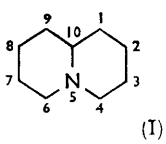
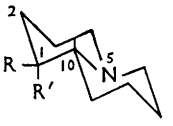
Infrared and proton resonance spectra of quinolizidine and both racemic forms of 1-, 2-, 3-, and 4-methylquinolizidine indicate that in all except one of these compounds the ring system exists predominantly in the *trans*-fused conformation. The exception is that 4-methylquinolizidine in which the 10- and 4-hydrogen atom are "*trans*" with respect to each other; this compound appears to adopt preferentially the conformation in which the rings are *cis*-fused and the methyl group is equatorial. The stereochemistry of the proton salts of these bases is very similar to that of the free bases.

The two possible methiodides of quinolizidine have been obtained, one by quaternisation of quinolizidine, the other by cyclisation of 2-4′-iodobutyl-1-methylpiperidine. Proton resonance spectra of the methiodides indicate that the one formed by direct quaternisation contains the *trans*-fused ring structure, and that formed by cyclisation the *cis*-fused ring structure. Generally, quaternisation of methylquinolizidines which contain in the *trans*-fused conformation an axial methyl group on the same side of the molecule as the nitrogen lone-pair leads to salts with the *cis*-fused ring configuration. The problem of the size of the nitrogen lone-pair is discussed.

The quinolizidine nucleus (I) is a central component of a number of important natural products. The simplest of these are the lupin alkaloids,[1] and it was to lupinine that conformational arguments were first applied in this series. Since lupinine can be epimerised to epilupinine, it carries the hydroxymethyl group in the axial position. By analogy with the decalins the preferred conformation of the quinolizidine structure is expected to be that in which the rings are *trans*-fused, and the hydrogen atom at position 10 must be "*trans*" to the hydroxymethyl group [R′ in (II)], *i.e.*, the 1- and the 10-hydrogen



(I)



(II)

(III)

atom must be "*cis*" * with respect to each other (II; R = H, R′ = CH_2·OH).[2] In epilupinine the equatorial hydroxymethyl group R is associated with the preferred ring conformation (II; R′ = H, R = CH_2·OH). Quinolizidine is thought of as a mixture of the two most important conformations (II; R = R′ = H) and (III), in which the former predominates under ordinary conditions.

The quinolizidines differ from the decalins in the important feature that in them a nitrogen lone-pair takes the place of one of the C–H bonds of the hydrocarbons. The relative space-filling abilities of the lone-pair and the covalently bound hydrogen atom are not certain. Analogy with carbanion stereochemistry led to the suggestion [3] that the nitrogen lone-pair is bulkier than the proton bound to nitrogen, and that, consequently,

* In the remainder of this paper the *cis*- or *trans*-relationship of the 10-hydrogen atom and that on the substituted carbon atom is denoted by *c* or *t*. The prefixes *cis*- and *trans*- indicate a ring conformation, analogous to that in *cis*- or *trans*-decalin, in the bicyclic bases.

[1] Leonard, in Vols. III and VII of "The Alkaloids," ed. R. H. Manske, Academic Press, New York, 1953, 1960.

[2] (*a*) Cookson, *Chem. and Ind.*, 1953, 337; (*b*) Leonard and Ryder, *J. Org. Chem.*, 1953, **18**, 598.

[3] Barton and Cookson, *Quart. Rev.*, 1956, **10**, 44.

in piperidine the conformation with an equatorial lone-pair and an axial N–H bond is preferred. The argument is borne out in the special context of the crystalline state by *X*-ray crystallographic data for acetaldehyde-ammonia.[4] The significance of this example is made even more limited by the presence in the crystals of water molecules, hydrogen-bonded to the nitrogen atoms. Electric polarisability measurements[5] on piperidine, morpholine, and 1-methylpiperidine, in benzene, are interpreted as showing that in these compounds the nitrogen lone-pair is not only more space-demanding than the N–H bond, but is, indeed, almost equal in that respect to $\geq N\text{–}CH_3$.

If this argument can be transferred to the comparison of the nitrogen lone-pair with the C–H covalent bond, it would be expected that the difference in stability between (II; R = R′ = H) and (III) would be smaller than the difference between *trans*- and *cis*-decalin. The lone-pair would be exercising a destabilising influence recalling that of the methyl group in *trans*-9-methyldecalin.[6] If then ring substituents were introduced which in the *trans*-conformation were necessarily axial (*c*-1-, *t*-2-, *c*-3-, and *t*-4-mono-substituted quinolizidines), but in the *cis*-conformation could be equatorial, the balance in favour of the *trans*-conformation would be further reduced.

The position of the conformational equilibrium in quinolizidine is not known. However, Bohlmann[7] has shown that a prominent infrared band at 2800—2700 cm.$^{-1}$ occurs in the spectra of *trans*-fused quinolizidines in which the nitrogen lone-pair is *trans* to at least two axial hydrogen atoms on carbon atoms adjacent to nitrogen. A similar criterion was established by Wenkert and Roychauduri[8] for yohimbine derivatives. A band at 2750 cm.$^{-1}$ occurs in the infrared spectrum of quinolizidine,[7] and the implication is that the *trans*-conformation (II; R = R′ = H) predominates. (−)-Lupinine also shows this characteristic absorption,[9] and so, despite the axial opposition between the hydroxymethyl group, axial hydrogen atoms, and axial lone-pair, the *trans*-conformation (II; R = H, R′ = CH_2·OH) must still be important. In this instance another factor, the intramolecular hydrogen bonding between the nitrogen atom and the hydroxyl group,[1] enters to favour the *trans*-conformation.

We set out to synthesise a series of compounds, the methylquinolizidines, which would be free from the latter complication, and to examine them for conformational preferences by the criteria discussed above and later in this paper. On the assumptions, implicit in the above discussion, that boat forms may be neglected and that an equatorial is more stable than an axial methyl group,[3,6] the possible *trans*/equatorial conformations of *t*-1-, *c*-2-, *t*-3-, and *c*-4-methylquinolizidine would be expected to predominate. With *c*-1-, *t*-2-, *c*-3-, and *t*-4-methylquinolizidine the predominant conformation might be either the *trans*/axial or the *cis*/equatorial.*

We also wished to examine the salts of these bases. The proton salts of these bases will, in solution, comprise a mobile equilibrium between two cations derived from the *cis*- and the *trans*-conformation of the bases (the *cis*-cation will itself exist in two conformations), a kind of prototropic tautomerism. Considerations similar to those outlined above should apply in determining the predominant cation.

The conformational equilibrium in the quinolizidines arises from the stereochemical instability of tervalent nitrogen.[10] Conversion of the quinolizidines into quaternary salts fixes the bicyclic structures in *cis*- or *trans*-configurations. A particular base might

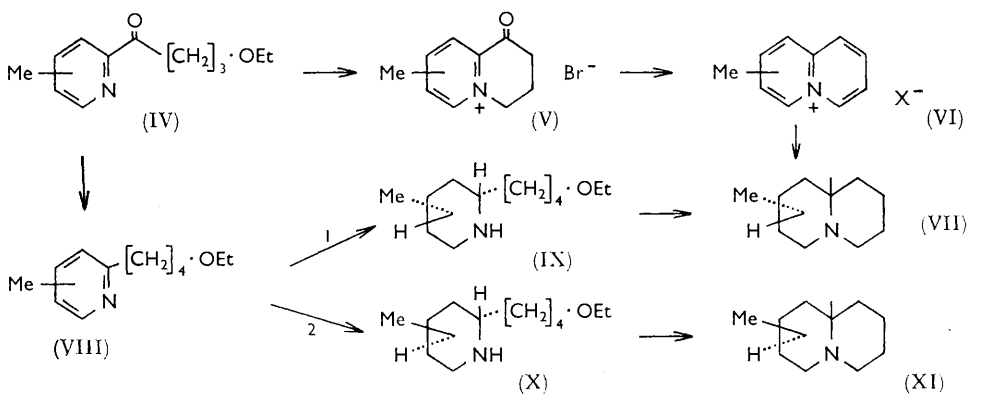
* The steric interactions expected for boat and for chair forms are compared in Table 7. We believe this demonstrates that boat forms will be unimportant.

[4] Lund, *Acta Chem. Scand.*, 1951, **5**, 678.
[5] Aroney and Le Fèvre, *J.*, 1958, 3002.
[6] (*a*) Dauben and Pitzer in " Steric Effects in Organic Chemistry," ed. M. S. Newman, John Wiley and Sons, Inc., New York, 1956; (*b*) Allinger and Coke, *J. Amer. Chem. Soc.*, 1961, **26**, 2096.
[7] Bohlmann, *Chem. Ber.*, 1958, **91**, 2157.
[8] Wenkert and Roychauduri, *J. Amer. Chem. Soc.*, 1956, **78**, 6417.
[9] Thomas, Vipond, and Marion, *Canad. J. Chem.*, 1955, **33**, 1290.
[10] Mann, in " Progress in Stereochemistry," Vol. II, ed. W. Klyne and P. B. de la Mare, Butterworths Scientific Publ., London, 1958.

give mainly a quaternary salt of one configuration, or a mixture of two possible salts, and the kinetic process of formation rather than an equilibrium now becomes important. Thus, methiodide formation by the *trans*/axial conformations (as II; R = H, R′ = Me) of *c*-1- and *c*-3-methylquinolizidine might be prohibitively hindered.

Synthesis of Quinolizidine and the Methylquinolizidines.—Several syntheses of these compounds have been described.[1] Most noteworthy in the present context are the studies of Leonard and his co-workers,[11–13] designed to establish the characteristics of the two racemates of each of the methylquinolizidines. Nesmeyanov and Rybinskaya [14] reduced dehydro-2-methylquinolizinium salts catalytically, as Boekelheide and Ross [15] had earlier done with the 4-isomer. The latter workers established the identity of their product with one of the racemates of 4-methylquinolizidine prepared by Leonard and Nicolaides,[11] and because it arose as the only product of catalytic hydrogenation, over a platinum catalyst, of the cationic aromatic nucleus, they thought it likely to be *c*-4-methylquinolizidine. On the same basis Nesmeyanov and Rybinskaya's product would be *c*-2-methylquinolizidine.

It was our plan to attempt to complete the characterisation of the *c*-1-, -2-, -3-, and -4-methylquinolizidines by using the sequence (IV ⟶ V ⟶ VI ⟶ VII), and at the same time to attempt the preparation of the *t*-isomers by the route (IV ⟶ VIII ⟶ X ⟶ XI). Where catalytic hydrogenation of dehydroquinolizinium compounds (VI), and of the pyridines (VIII) in acid solution, over platinum gave predominantly



Reagents: 1, H_2–Pt–H^+. 2, Na–EtOH.

single products, the weight of evidence [16] made it likely that these would be the *c*-methylquinolizidines (VII) and the *cis*-2-(4-ethoxybutyl)-methylpiperidines (IX), respectively. On the other hand, reduction of the pyridines (VIII) with sodium–ethanol might give mixtures of products, in which, by comparison with (IX), the *trans*-compounds (X) might be recognised. Leonard and Ryder [2b] used a similar approach for synthesising the two racemates of 2-butyl-5-methylpiperidine.

The ketones (IV) were prepared from the 2-cyano-methylpyridines and 3-ethoxypropylmagnesium bromide.[17] 2-Cyano-3-, -5-, and -6-methylpyridine were readily obtained by heating the corresponding 2-bromo-methylpyridines with cuprous cyanide, but this method gave only very poor yields of 2-cyano-4-methylpyridine. The latter was best

[11] Leonard and Nicolaides, *J. Amer. Chem. Soc.*, 1951, **73**, 5210.
[12] Leonard, Hay, Fulmer, and Gash, *J. Amer. Chem. Soc.*, 1955, **77**, 439.
[13] Leonard, Fulmer, and Hay, *J. Amer. Chem. Soc.*, 1956, **78**, 3457.
[14] Nesmeyanov and Rybinskaya, *Doklady Akad. Nauk S.S.S.R.*, 1957, **116**, 93; *Chem. Abs.*, 1958, **52**, 6349.
[15] Boekelheide and Ross, *J. Amer. Chem. Soc.*, 1955, **77**, 5691.
[16] Linstead, Doering, Davis, Levine, and Whetstone, *J. Amer. Chem. Soc.*, 1942, **64**, 1985.
[17] Craig, *J. Amer. Chem. Soc.*, 1934, **56**, 1144.

prepared by the method of Feely and Beavers.[18] The ketones (IV) were smoothly reduced by the Wolff–Kishner method to 2-(4-ethoxybutyl)-methylpyridines (VIII).

An alternative route to 2-(4-ethoxybutyl)-methylpyridines, starting from the lutidines, was also examined. 2,6-Lutidine was treated with phenyl-lithium and then with 3-ethoxypropyl bromide to give 2-4′-ethoxybutyl-6-methylpyridine. The yield (32%) was not high, but the method has the advantage of directness. Applied to 2,5-lutidine the method gave a product contaminated with an impurity of high refractive index: the phenyl-lithium may have caused phenylation. More successful with 2,5-lutidine was the reaction in which lithium di-isopropylamide was used instead of phenyl-lithium. When 2,4-lutidine reacted with lithium di-isopropylamide and 3-ethoxypropyl bromide a mixture resulted. From this a compound was isolated, different from, but isomeric with, 2-4′-ethoxybutyl-4-methylpyridine. Presumably the reaction gives mainly 4-4′-ethoxybutyl-2-methylpyridine. The result is surprising, for other work [19] shows that 2,4-lutidine reacts with phenyl-lithium at the 2-methyl group. There is other evidence, however, suggesting that the 4-methyl group is more acidic than the 2-methyl group.[20]

The 2-γ-ethoxybutyryl-methylpyridines (IV) gave the quaternary ketones (V) when boiled with hydrobromic acid. The ketones were converted by hot acetic anhydride into dehydromethylquinolizinium cations (VI), which were isolated as their perchlorates and characterised as their picrates. This synthesis of dehydromethylquinolizinium salts [21] has hitherto been applied to intermediates of type (V) carrying the substituent in the reduced ring.

The dehydromethylquinolizinium perchlorates were hydrogenated in ethanol over Adams catalyst. The 1-, 2-, and 4-methyl compounds each gave good yields of single products, which we take to be *c*-1-, *c*-2-, and *c*-4-methylquinolizidine (see above). The physical evidence given below supports these assignments. In contrast, dehydro-3-methylquinolizinium perchlorate gave a mixture when hydrogenated. Two 3-methylquinolizidines were isolated as their picrates. This different behaviour was unexpected, and at first we doubted the authenticity of our dehydro-3-methylquinolizinium perchlorate. However, its structure seems soundly based on elementary analysis, the ultraviolet absorption spectrum, and the composition and m. p.[21] of the derived picrate.

The hydrogenation of 2-4′-ethoxybutyl-3-methylpyridine over Adams catalyst, in ethanol containing a slight excess of hydrochloric acid, gave a product from which, by recrystallisation, a hydrochloride was isolated in 80% yield. This we regard as *cis*-2-ethoxybutyl-3-methylpiperidine (see above). Reducing the pyridine with sodium–ethanol gave a crude product which retained only a very small degree of unsaturation. This unsaturation was removed by hydrogenation, and crystallisation gave the hydrochloride of a base representing about 66% of the product; it differed from the compound obtained catalytically and is probably *trans*-2-4′-ethoxybutyl-3-methylpiperidine. A little of the hydrochloride of the *cis*-base, as well as mixtures of the two isomers, was also isolated. *cis*- and *trans*-2-4′-Ethoxybutyl-3-methylpiperidine were converted by boiling hydrobromic acid into the 2-bromobutyl-3-methylpiperidines, and the bromides were cyclised, without being isolated, to *c*- and *t*-1-methylquinolizidines by methanolic potassium hydroxide. The method follows one of the first syntheses of quinolizidine.[22] *c*-1-Methylquinolizidine so obtained was identical with the product prepared by hydrogenation of dehydro-1-methylquinolizinium perchlorate.

Equally straightforward was the reduction of 2-4′-ethoxybutyl-6-methylpyridine. The catalytic process gave over 90% of *cis*-2-4′-ethoxybutyl-6-methylpiperidine. The sodium–ethanol reduction also gave more than 60% of this, the thermodynamically more

[18] Feely and Beavers, *J. Amer. Chem. Soc.*, 1959, **81**, 4004.
[19] Cale, McGinnis, and Teague, *J. Org. Chem.*, 1960, **25**, 1507.
[20] Notari and Pines, *J. Amer. Chem. Soc.*, 1960, **82**, 2945.
[21] Glover and Jones, *J.*, 1958, 3021.
[22] Clemo, Ramage, and Raper, *J.*, 1932, 2959.

stable isomer, but the *trans*-base was isolated in 30% yield (as its picrolonate). Cyclisation of these piperidines gave *c*- and *t*-4-methylquinolizidine, the former identical with the compound from dehydro-4-methylquinolizinium perchlorate.[15]

Like the isomers described above, 2-4′-ethoxybutyl-4-methylpyridine gave, on hydrogenation, one piperidine, presumably *cis*-2-4′-ethoxybutyl-4-methylpiperidine, in over 80% yield. However, the reduction with sodium–ethanol presented some difficulties, the crude product retaining a considerable degree of unsaturation. After hydrogenation the mixture provided about 60% of *cis*-2-4′-ethoxybutyl-4-methylpiperidine, and the residue of saturated bases did not give a homogeneous solid derivative. Cyclisation of *cis*-2-4′-ethoxybutyl-4-methylpiperidine gave *c*-2-methylquinolizidine, identical with material obtained from dehydro-2-methylquinolizinium perchlorate. By cyclising the residue of saturated bases mentioned above, a crude product was obtained which, by conversion into the perchlorate and fractional crystallisation, gave a methylquinolizidine distinct from the *c*-2-compound. This we regard as *t*-2-methylquinolizidine.

With 2-4′-ethoxybutyl-5-methylpyridine a different complication arose, for both catalytic hydrogenation and sodium–ethanol reduction produced from this compound mixtures of two saturated bases. The catalytic process gave about 50% of " isomer A " of 2-4′-ethoxybutyl-5-methylpiperidine and about 34% of " isomer B." Sodium–ethanol reduction gave a mixture which again contained a considerable amount of unsaturated material and which, after hydrogenation, gave about 50% of isomer A and 41% of isomer B. The isomeric piperidines were cyclised to 3-methylquinolizidine " A " and 3-methylquinolizidine " B," respectively. The picrate of each of these bases was identical with the picrate of one or other of the bases obtained by hydrogenating dehydro-3-methylquinolizinium perchlorate. For reasons discussed below we believe 3-methylquinolizidine " A " and " B " to be *t*- and *c*-3-methylquinolizidine, respectively.

Quinolizidine itself was prepared from α-picoline. With phenyl-lithium and 3-ethoxypropyl bromide this gave 2-4′-ethoxybutylpyridine, which was cyclised to " tetrahydrodehydroquinolizinium " bromide. Catalytic reduction of the latter gave quinolizidine hydrobromide. Alternatively, 2-4′-ethoxybutylpyridine was converted into 2-4′-ethoxybutylpiperidine, which was cyclised to quinolizidine.

Table 1 summarises the chief properties of our quinolizidine preparations and allows comparison with the reports by other workers, most notably by Leonard and his colleagues.[11–13] It is clear that the racemic 1-methylquinolizidine giving the higher-melting picrate [12] was *c*-1-methylquinolizidine, or *r*-lupinane. The picrates of *r*-α-lupinane and *r*-β-lupinane reported by Schöpf, Thomä, Schmidt, and Braun [23] had m. p.s 187° and 163°.

Agreement is also satisfactory for the 2-methylquinolizidines. Our *c*-2-methylquinolizidine has the lower-melting picrate, and Leonard's [13] racemate with the lower-melting picrate is derived from a base of lower refractive index, as is ours. The results permit the identification of Leonard's base giving the lower-melting picrate as *c*-2-methylquinolizidine, an assignment tentatively suggested by Leonard.[13]

Our preparations of the 3-methylquinolizidines were, as explained above, stereochemically ambiguous. However, the compounds designated 2-4′-ethoxybutyl-5-methylpiperidine " A " and -1,5-dimethylpiperidine " A " and 3-methylquinolizidine " A " all have lower refractive indices than the corresponding " B " compounds. If, then, the usual rule [6a] applies, it follows that the " A " compounds are the more stable isomers, and if the conformational arguments already outlined are accepted, then, in particular, 3-methylquinolizidine " A " and " B " are, respectively, *t*- and *c*-3-methylquinolizidine. The refractive index rule is obeyed by the other pairs of quinolizidines (Table 1), and the assignments in the case of the 3-methylquinolizidines are in agreement with spectroscopic data. It will be seen from Table 1 that the characteristics of the derivatives of our 3-methylquinolizidines differ markedly from those reported by Leonard, Hay, Fulmer,

[23] Schopf, Thomä, Schmidt, and Braun, *Annalen*, 1928, **465**, 97.

TABLE 1.

The methylquinolizidines.

Quinolizidine	Properties (present work)	Leonard *et al.*[11-13]
c-1-Methyl	n_D^{22} 1·4817	" A " racemate, n_D^{20} 1·4740
	Perchlorate, m. p. 193·5—195°	—
	Picrate, m. p. 186·5—187·5°	Picrate, m. p. 192·5—193·5°
t-1-Methyl	n_D^{23} 1·4779	" B " racemate, n_D^{20} 1·4757
	Perchlorate, m. p. 217—219°	—
	Picrate, m. p. 163·5—164·5°	Picrate, m. p. 161—162°
c-2-Methyl	n_D^{22} 1·4718	" A " racemate, n_D^{21} 1·4753 (?) †
	Perchlorate, m. p. 119—121°	—
	Picrate, m. p. 155—157° *	Picrate, m. p. 150°. Picrolonate, m. p. 194—195° ¶
t-2-Methyl	n_D^{22} 1·4784	" B " racemate, n_D^{21} 1·4778
	Perchlorate, m. p. 164—165°	—
	Picrate, m. p. 166—167·5° **	Picrate, m. p. 161—162°. Picrolonate, m. p. 226·5—228° ¶
c-3-Methyl (isomer B) ‡	n_D^{21} 1·4754	" A " racemate, n_D^{20} 1·4757
	Perchlorate, m. p. 184·5—186°	—
	Picrate, m. p. 155—157°	Picrate, m. p. 194·5—195·5°
	Picrolonate, m. p. 220—221·5° §	Picrolonate, m. p. 248—250° ¶
t-3-Methyl (isomer A) ‡	n_D^{21} 1·4723	" B " racemate, n_D^{20} 1·4738
	Perchlorate, m. p. 171—172·5°	—
	Picrate, m. p. 180·5—182°	Picrate, m. p. 183—184°
	Picrolonate, m. p. 229·5—231·5° ¶	Picrolonate, m. p. 208—209° ¶
c-4-Methyl	n_D^{23} 1·4790	" A " racemate, n_D^{20} 1·4794
	Perchlorate, m. p. 274—276° ¶	—
	Picrate, m. p. 197·5—199°	Picrate, m. p. 191—193° ‖
t-4-Methyl	n_D^{23} 1·4882	" B " racemate, n_D^{20} 1·4814
	Perchlorate, m. p. 233—234·5°	—
	Picrate m. p. 198·5—200°	Picrate, m. p. 182—184°

* Nesmeyanov and Rybinskaya [14] give m. p. 154—156°; Clemo *et al.*[2a] give picrate, m. p. 150°, and picrolonate, m. p. 197°. † Leonard *et al.*[13] took this to be the *cis*-compound. ‡ See text. § Decomp. slightly *above* the m. p. ¶ With decomp. ‖ Boekelheide and Ross [15] gave m. p. 192—194°. ** Clemo *et al.*[24] give picrate, m. p. 158°, and picrolonate, m. p. 219°.

and Gash.[12] We cannot explain this situation at present. The physical properties reported below give no cause for us to doubt the character of our products as bicyclic bases. The fingerprint region of the infrared spectra indicated that the two compounds were not contaminated with each other: prominent bands found in only one of the isomers were [cm.$^{-1}$ (ε_A); for details of measurements see below] 1296 (55), 1212 (25), 1152 (55), and 1044 (25) for *c*-3-methylquinolizidine, and 1304 (30), 1222 (35), and 1088 (20) for *t*-3-methylquinolizidine. Proton resonance spectra (see below) also showed that gross contamination was absent.*

In the 4-methylquinolizidine series the picrate of our *t*-compound has a considerably higher m. p. than the picrate of the more refractive *r*-4-methylquinolizidine prepared by Leonard and Nicolaides.[11] The picrates of our two 4-methylquinolizidines have almost identical m. p.s, but show a marked physical difference and a strong mixed m. p. depression. In this series Lukeš and Šorm [25] reported picrates, m. p. 195° and 187°, and Dúbravková, Jezo, Sefcovic, and Voticky [26] gave m. p. 195° and 186—187°. The infrared spectra of our *c*- and *t*-4-methylquinolizidine (see below) are in good agreement with those reported by Leonard and Nicolaides,[11] and identify their racemates " A " and " B " with our *c*- and *t*-4-methylquinolizidine, respectively.

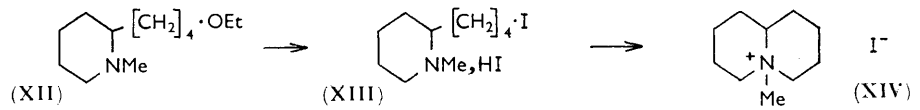
It will be seen (Experimental section) that we give analytical data for all the derivatives of our quinolizidines, but not for the bases themselves. We have done this because

* In a paper which came to hand after our manuscript had been submitted for publication, Bohlmann, Winterfeldt, Studt, Laurent, Boroschewski, and Kleine (*Chem. Ber.*, 1961, **94**, 3151) give m. p. 154° for *c*-3-methylquinolizidine picrate.

[24] Clemo and Metcalfe, *J.*, 1937, 1518; Clemo, Cook, and Raper, *J.*, 1938, 1183.
[25] Lukes and Sorm, *Coll. Czech. Chem. Comm.*, 1947, **12**, 356.
[26] Dubravkova, Jezo, Sefcovic, and Voţický, *Chem. Zvesti*, 1957, **11**, 394.

all the free bases were observed to change rapidly when exposed to air, becoming contaminated with solid matter. Quinolizidine itself changes in 24 hours from a clear liquid to a crystalline mass. Analysis of the material showed it to be quinolizidine hydrogen carbonate, from which the parent base could readily be recovered. Whilst not making analysis of the free bases impossible, this characteristic makes it inconvenient.

Quinolizidine and Methylquinolizidine Quaternary Salts.—Direct quaternisation of quinolizidine with methyl iodide gives a methiodide, m. p. *ca.* 320° (decomp.).[27,28] When we converted this into the quaternary picrate and the quaternary toluene-*p*-sulphonate, we obtained no evidence of heterogeneity. On the other hand, the sequence of reactions (XII ⟶ XIII ⟶ XIV) provided as the major product a quaternary salt distinctly different from the product of direct quaternisation. These compounds are the two expected methiodides of quinolizidine.



In contrast, *c*-1-methylquinolizidine gave a methiodide identical with that obtained by cyclising *cis*-2-4′-ethoxybutyl-1,3-dimethylpiperidine. *trans*-2-4′-Ethoxybutyl-1,3-dimethylpiperidine gave, on cyclisation, material which consisted essentially of the same methiodide as was formed directly from *t*-1-methylquinolizidine, but proton resonance spectra (see below) indicated that the cyclisation product probably contained *ca.* 10% of the isomeric *cis*-fused methiodide.* Similarly, *c*-3-methylquinolizidine and 2-4′-ethoxybutyl-1,5-dimethylpiperidine " B " gave the same quaternary derivatives. In contrast, *trans*-2-4′-ethoxybutyl-1,5-dimethylpiperidine gave, when cyclised, a mixture of quaternary salts. The minor product was identical with that obtained by directly quaternising *t*-3-methylquinolizidine (" *t*-3-methylquinolizidine methiodide 1 "), the major product being the isomeric " *t*-3-methylquinolizidine methiodide 2."

In the 2- and 4-methylquinolizidine series we have, so far, only prepared methiodides by direct quaternisation.

Observations on the homogeneity and stereochemistry of these quaternary salts are made in the Discussion. It should be stressed here that we have attempted in each case to obtain from the two processes, direct quaternisation and cyclisation, the recognisably major product.

Experimental

2-Cyano-3-methylpyridine.—A mixture of 2-bromo-3-methylpyridine [2b] (43 g.) and cuprous cyanide (22 g.) was warmed in a distilling flask, over a flame, until a vigorous reaction began. Immediately the reaction subsided, the flask was evacuated (20 mm.) and the product distilled. It crystallised from light petroleum as plates (21 g.), m. p. 84—85° (Found: C, 71·5; H, 5·2. Calc. for $C_7H_6N_2$: C, 71·2; H, 5·1%) (lit.,[30] m. p. 87—88°).

2-Cyano-5-methylpyridine.—In the same way 2-bromo-5-methylpyridine [2b] (50 g.) gave the nitrile (18 g.), b. p. 134—136°/20 mm., prisms, m. p. 75—77° (from light petroleum) (lit.,[30] m. p. 72—74°) (Found: C, 71·0; H, 5·4%).

2-Cyano-6-methylpyridine.—2-Bromo-6-methylpyridine [31] (33 g.) gave the nitrile (15 g.),

* This modifies the statement made in a preliminary announcement of our work.[29] The confusion arose through an ineradicable m. p. difference (see Experimental section) between the product of direct quaternisation of *t*-1-methylquinolizidine and the product obtained by cyclising *trans*-2-4′-ethoxybutyl-1,3-dimethylpiperidine. Spectroscopic data left no doubt that the major product from both processes was the same quaternary salt.

[27] Leonard and Wildman, *J. Amer. Chem. Soc.*, 1949, **71**, 3100.
[28] Winterfield and Dünwald, *Naturwiss.*, 1956, **43**, 517.
[29] Moynehan, Schofield, Jones, and Katritzky, *Proc. Chem. Soc.*, 1961, 218.
[30] Suzuki, *Pharm. Bull.*, 1957, **5**, 13; see also ref. 18.
[31] Adams and Miyano, *J. Amer. Chem. Soc.*, 1954, **76**, 3168.

b. p. 112—114°/15 mm. It formed needles, m. p. 71—72·5° (Found: C, 71·2; H, 5·4%), from light petroleum (lit.,[30] m. p. 69—71°).

2-*Cyano*-4-*methylpyridine*.—The above procedure, applied to 2-bromo-4-methylpyridine,[32] gave only 10% yields of the nitrile. It was better prepared (40% yield, based on γ-picoline 1-oxide) from 1-methoxy-4-methylpyridinium methyl sulphate.[18]

2-γ-*Ethoxybutyryl*-3-*methylpyridine*.—(*a*) 2-Cyano-3-methylpyridine (22 g.) in ether (600 ml.) was added, during ½ hr. with stirring at −10°, to the Grignard reagent prepared from 3-ethoxypropyl bromide [33] (63 g.) in ether (250 ml.). The mixture was refluxed for 3 hr., cooled in ice, and decomposed with water. The solution obtained by extraction with 4N-hydrochloric acid was heated for 2 hr. on the water-bath, basified, and extracted with ether. The dried (KOH) extract was distilled, giving 2-γ-*ethoxybutyryl*-3-*methylpyridine* (27 g.), b. p. 108—111°/0·5 mm., n_D^{20} 1·5025 (Found: C, 69·8; H, 8·7; N, 7·0. $C_{12}H_{17}NO_2$ requires C, 69·5; H, 8·3; N, 6·8%). The use of benzene or tetrahydrofuran as solvents in which to add the nitrile to the Grignard solution lowered the yield considerably. The ketone reacted with 2,4-dinitrophenylhydrazine in ethanol containing hydrobromic acid, giving a deliquescent hydrobromide. This was shaken with aqueous sodium carbonate and chloroform, and concentration of the chloroform solution gave the 2,4-*dinitrophenylhydrazone*. It formed orange prisms, m. p. 110·5—112° (Found: C, 55·8; H, 5·2. $C_{18}H_{21}N_5O_5$ requires C, 55·8; H, 5·5%), from light petroleum.

(*b*) 2-Bromo-3-methylpyridine (31 g.) in ether (100 ml.) was added during 15 min. to n-butyllithium [from n-butyl bromide (29 g.), lithium (3·5 g.), and ether (100 c.c.)], stirred at −70°. After 10 min. more, γ-ethoxybutyronitrile [34] (21 g.) in ether (50 ml.) was added during 20 min. The mixture was stirred at −70° for 20 min., warmed to −10°, and stirred for 1 hr. more. Water (50 ml.) was added, the mixture was extracted with 4N-hydrochloric acid, and the acid extract was heated on the water-bath for 2 hr. Basification, extraction with ether, and distillation of the dried (KOH) extract gave the ketone (9·2 g.), identical with the compound obtained by method (*a*).

2-γ-*Ethoxybutyryl*-4-*methylpyridine*.—(*a*) Reaction between 2-cyano-4-methylpyridine (31 g.) in tetrahydrofuran (150 ml.), and the Grignard reagent from 3-ethoxypropylbromide (87 g.) was carried through as above, giving the *ketone* (39 g.), b. p. 124—126°/1 mm., n_D^{19} 1·5006 (Found: C, 69·6; H, 8·45%). The 2,4-*dinitrophenylhydrazone*, prepared as above, crystallised from ethyl acetate as pale yellow needles, m. p. 169—171° (Found: C, 55·7; H, 5·3%).

(*b*) By the method used with 2-bromo-3-methylpyridine, 2-bromo-4-methylpyridine (20 g.) was converted through the lithium derivative into 2-γ-ethoxybutyryl-4-methylpyridine (8 g.).

2-γ-*Ethoxybutyryl*-5-*methylpyridine*.—2-Cyano-5-methylpyridine (15 g.), in ether (150 ml.), was converted by the above method into the *ketone* (18·5 g.), b. p. 122—125°/0·8 mm., n_D^{21} 1·5033 (Found: C, 69·4; H, 8·7%), that gave a 2,4-*dinitrophenylhydrazone*, orange plates, m. p. 112·5—114° (Found: C, 55·5; H, 5·3%), from ethanol.

2-γ-*Ethoxybutyryl*-6-*methylpyridine*.—The appropriate nitrile (19 g.), in ether (150 ml.), in the usual way gave the *ketone* (27·5 g.), b. p. 98—100°/0·1 mm., n_D^{20} 1·4980 (Found: C, 70·1; H, 8·6%). The 2,4-*dinitrophenylhydrazone*, prepared as before, crystallised from ethanol as yellow needles, m. p. 150—151·5° (Found: C, 55·9; H, 5·4%). Concentration of the alcoholic liquors gave orange-red plates of an *isomer* which after recrystallisation had m. p. 114—116° (Found: C, 56·0; H, 5·6%).

2-4′-*Ethoxybutyl*-3-*methylpyridine*.—2-γ-Ethoxybutyryl-3-methylpyridine (21 g.), 80% hydrazine hydrate (30 g.), potassium hydroxide (24 g.), and ethylene glycol (150 ml.) were heated at 120—130° for 2 hr. The apparatus was then arranged for distillation, heated to 210° (bath-temp.), and maintained there for 3 hr. Water was added and the mixture was extracted with ether. The dried (KOH) extract was distilled, giving 2-4′-*ethoxybutyl*-3-*methylpyridine* (17 g.), b. p. 94—97°/0·5 mm., n_D^{19} 1·4918 (Found: C, 74·6; H, 9·6. $C_{12}H_{19}NO$ requires C, 74·6; H, 9·9%). The *picrate* formed yellow needles, m. p. 86—87° (Found: C, 51·5; H, 5·5. $C_{18}H_{22}N_4O_8$ requires C, 51·2; H, 5·25%), from ether.

2-4′-*Ethoxybutyl*-4-*methylpyridine*.—The appropriate ketone (25 g.), reduced as above, gave 2-4′-*ethoxybutyl*-4-*methylpyridine* (20·5 g.), b. p. 84—87°/0·2 mm., n_D^{19} 1·4867 (Found: C, 74·6; H, 10·2%) [*picrate*, yellow needles, m. p. 47—48° (Found: C, 50·8; H, 5·0%), from ether].

2-4′-*Ethoxybutyl*-5-*methylpyridine*.—(*a*) Reduction of 2-γ-ethoxybutyryl-5-methylpyridine

[32] Cunningham, Newbold, Spring, and Stark, *J.*, 1949, 2091.
[33] Brown and Gulick, *J. Amer. Chem. Soc.*, 1955, 1079.
[34] Wertheim, *J. Amer. Chem. Soc.*, 1934, **56**, 735.

(17 g.) gave 2-4′-*ethoxybutyl*-5-*methylpyridine* (14·5 g.), b. p. 126—128°/4 mm., n_D^{20} 1·4872 (Found: C, 74·65; H, 10·5%) [*picrate*, yellow plates, m. p. 65·5—67° (Found: C, 51·7; H, 5·4%), from ether].

(*b*) 2,5-Lutidine (58 g.) in ether (100 ml.) was added during 15 min. to phenyl-lithium [from lithium (7·8 g.) in bromobenzene (87 g.), and ether (350 ml.)], stirred at room temperature. The mixture was stirred for 1½ hr. 3-Ethoxypropyl bromide (42 g.) in ether (100 ml.) was added and the mixture was refluxed for 1 hr., cooled, and poured on ice. The aqueous layer was washed with ether, and the combined ether solutions were extracted with 3N-hydrochloric acid. The acid solution was basified and extracted with ether. Distillation of the dried (KOH) extract gave a product (39 g.), b. p. 88—90°/0·2 mm., which had an infrared spectrum very similar to that of material from (*a*) but was yellow and more strongly refractive (n_D^{17} 1·5098). It was converted into the picrate, which was recrystallised to constant m. p. from ethanol and decomposed on alumina, giving pure 2-4′-ethoxybutyl-5-methylpyridine (15 g.).

The following process was more satisfactory. Di-isopropylamine (28 g.) in ether (100 ml.) was added to phenyl-lithium [from lithium (4·5 g.), bromobenzene (44 g.), and ether (200 ml.)], and the mixture was stirred for ½ hr. 2,5-Lutidine (30 g.) in ether (100 ml.) was added, and the mixture was refluxed for 2 hr. 3-Ethoxypropyl bromide (21 g.) in ether (50 ml.) was added and the mixture was refluxed for 1 hr., cooled, poured on ice, and worked up as before, giving 2-4′-ethoxybutyl-5-methylpyridine (16 g.), identical in infrared spectrum, refractive index, and b. p. with the product of the Wolff reduction.

2-4′-*Ethoxybutyl*-6-*methylpyridine*.—(*a*) Wolff reduction of 2-γ-ethoxybutyryl-6-methylpyridine (21 g.) gave 2-4′-*ethoxybutyl*-6-*methylpyridine* (16 g.), b. p. 85—88°/0·8 mm., n_D^{18} 1·4880 (Found: C, 74·6; H, 9·8%) [*picrate*, yellow prisms, m. p. 67—69° (Found: C, 51·2; H, 5·1%), from ether].

(*b*) 2,6-Lutidine (58 g.) with phenyl-lithium and ethoxypropyl bromide, as in (*b*) above, gave the base (34 g.), identical with that from experiment (*a*).

4-4′-*Ethoxybutyl*-2-*methylpyridine*.—With lithium di-isopropylamide, as above, 2,4-lutidine (40 g.) and 3-ethoxypropyl bromide (31 g.) gave a product (18 g.), b. p. 145—155°/15 mm. This was fractionally distilled, and the major fraction (12 g.), b. p. 151—154°/15 mm., was treated with picric acid in ethanol. The product was a mixture which, on recrystallisation from ethanol–ether, gave yellow needles, m. p. 71—72° (Found: C, 51·4; H, 5·3%). It depressed the m. p. of 2-4′-ethoxybutyl-4-methylpyridine picrate and is presumably 4-4′-*ethoxybutyl*-2-*methylpyridine picrate*.

2-4′-*Ethoxybutyl*-3-*methylpiperidine*.—(*a*) The pyridine (10 g.) and platinum oxide (1 g.) were shaken in ethanol (100 ml.), containing a slight excess of concentrated hydrochloric acid, with hydrogen. Uptake was complete in 8 hr. The mixture was filtered, the solvent was removed, and the residue was recrystallised from ethyl methyl ketone, giving cis-2-4′-*ethoxybutyl*-3-*methylpiperidine hydrochloride* (9·8 g.) as needles, m. p. 116·5—118° (Found: C, 60·4; H, 11·1. $C_{12}H_{26}ClNO$ requires C, 61·1; H, 11·0%). The *base*, liberated from the hydrochloride, was a liquid, b. p. 105°/0·8 mm., n_D^{22} 1·4603 (Found: C, 71·9; H, 12·6. $C_{12}H_{25}NO$ requires C, 72·3; H, 12·6%). The *picrolonate* formed yellow prisms, m. p. 104—106° (Found: C, 56·9; H, 7·25. $C_{22}H_{33}N_5O_6$ requires C, 57·0; H, 7·2%), from ethanol.

(*b*) Sodium (36 g.) was added in small portions to a stirred and boiling solution of 2-4′-ethoxybutyl-3-methylpyridine (13 g.) in ethanol (210 ml.). The mixture was refluxed for 4 hr., cooled, diluted with water, and acidified with hydrochloric acid. The ethanol was distilled off, and the residue was basified and extracted with chloroform. Distillation of the dried (K_2CO_3) extract gave a liquid (12·8 g.), b. p. 86—90°/0·4 mm. This was hydrogenated in ethanol (100 ml.) containing hydrochloric acid and platinum oxide. It absorbed only 6% of hydrogen. The solution was filtered, the alcohol removed, and the residue recrystallised from ethyl methyl ketone, giving trans-2-4′-*ethoxybutyl*-3-*methylpiperidine hydrochloride* (10·5 g.) as needles, m. p. 122—123° (Found: C, 61·1; H, 11·25%). Concentration of the mother-liquors gave the *cis*-hydrochloride (0·6 g.) and mixtures of the two. trans-2-4′-*Ethoxybutyl*-3-*methylpiperidine*, liberated from the hydrochloride, had b. p. 88°/0·3 mm., n_D^{22} 1·4574 (Found: C, 71·6; H, 12·3%), and gave a *picrolonate*, yellow prisms, m. p. 171—172·5° (Found: C, 57·1; H, 7·1%) (from ethanol). The *cis*- and *trans*-hydrochlorides gave similar, but not identical, infrared spectra.

2-4′-*Ethoxybutyl*-4-*methylpiperidine*.—(*a*) Hydrogenation of 2-4′-ethoxybutyl-4-methylpyridine (12 g.), as above, gave cis-2-4′-*ethoxybutyl*-4-*methylpiperidine hydrochloride* (12·1 g.),

which formed plates, m. p. 116·5—118° (Found: C, 60·6; H, 11·1%), from ethyl methyl ketone. From it was obtained cis-2-4′-*ethoxybutyl*-4-*methylpiperidine*, b. p. 80—81°/0·15 mm., n_D^{20} 1·4543 (Found: C, 72·4; H, 12·4%) [*picrolonate*, yellow prisms, m. p. 173—175° (Found: C, 57·5; H, 7·2%), from ethanol].

(*b*) The pyridine (35 g.), reduced as before with sodium (84 g.) and ethanol (550 ml.), gave a product, b. p. 83–89°/0·25 mm. A portion of this absorbed 32% of hydrogen when hydrogenated over platinum oxide. The ultraviolet spectrum showed the presence of less than 1% of the parent pyridine, which therefore could not be the cause of the unsaturation. Repetition of the treatment with sodium and alcohol did not change the degree of saturation. The whole of the material was therefore hydrogenated in the usual way, and the product was recrystallised from ethyl methyl ketone, giving the *cis*-hydrochloride (24·5 g., 57·5%). The mother-liquors yielded more of the impure *cis*-hydrochloride (4 g.). No more solid could be isolated, so the residual liquors were basified and extracted with chloroform. The dried extract was distilled, giving a base (8·8 g.), b. p. 93—96°/0·7 mm. This was converted into a picrolonate, but a pure derivative could not be obtained, even after extensive fractional crystallisation.

2-4′-*Ethoxybutyl*-5-*methylpiperidine*.—(*a*) Hydrogenation of the pyridine (10 g.) in the usual way gave, on recrystallisation of the product from ethyl methyl ketone, 2-4′-*ethoxybutyl*-5-*methylpiperidine hydrochloride* " *A* " (6·05 g.), plates, m. p. 151·5—153·5° (Found: C, 61·2; H, 11·05%). *Base* " *A* " had b. p. 79—80°/0·4 mm., n_D^{22} 1·4545 (Found: C, 72·1; H, 12·7%). *Picrolonate* " *A* " formed yellow prisms, m. p. 156·5—158·5° (Found: C, 57·0; H, 7·3%). Concentration of the ethyl methyl ketone liquor gave further material, which could not be purified satisfactorily because of its deliquescence. It was decomposed with alkali and the liberated piperidine was distilled. The product (4·5 g., b. p. 77—80°/1·5 mm.) was treated with picrolonic acid in ethanol. Recrystallisation gave *picrolonate* " *B* " (8·15 g.) as yellow prisms, m. p. 146·5—148 5° (Found: C, 56·9; H, 7·2%) (from ethanol). The corresponding *base* " *B* " had b. p. 82°/0·5 mm., n_D^{22} 1·4568 (Found: C, 71·9; H, 12·5%).

(*b*) The pyridine (16 g.) was reduced with sodium (40 g.) and ethanol (270 ml.) to a product (16·2 g.), b. p. 85—88°/0·5 mm. This was hydrogenated in the usual way, absorbing 21% of hydrogen (again, the absence of ultraviolet absorption showed the unsaturation not to be due to the presence of starting material). Evaporation of the filtered hydrogenation solution, and recrystallisation of the residue from ethyl methyl ketone, gave hydrochloride " A " (9·7 g.). Basification of the mother-liquor, extraction with chloroform, and distillation of the dried (K_2CO_3) extract gave a base (7·8 g.), b. p. 88—92°/1 mm. Conversion into the picrolonate and recrystallisation from ethanol gave picrolonate " B " (15·8 g.).

2-4′-*Ethoxybutyl*-6-*methylpiperidine*.—(*a*) Hydrogenation of 2-4′-ethoxybutyl-6-methylpyridine (8 g.), and recrystallisation of the product from ethyl methyl ketone gave needles of cis-2-4′-*ethoxybutyl*-6-*methylpiperidine hydrochloride* (8·9 g.), m. p. 152·5—154° (Found: C, 61·3; H, 11·3%). The free *base*, b. p. 84—85°/0·5 mm., n_D^{22} 1·4532 (Found: C, 72·0; H, 12·8%), gave a *picrolonate* (yellow prisms from ethanol), m. p. 194—196° (Found: C, 57·1; H, 7·15%).

(*b*) Reduction of the pyridine (25 g.) with sodium (60 g.) and ethanol (420 ml.) gave a product (25·5 g.), b. p. 88—91°/0·8 mm. This was hydrogenated in the usual way in ethanol, and absorbed 5% of hydrogen. Filtration, concentration, and recrystallisation of the residue from ethyl methyl ketone gave *cis*-hydrochloride (19·1 g.). The mother-liquor yielded a deliquescent solid which was decomposed with alkali. Extraction with chloroform and distillation gave a base (9·3 g.), b. p. 76—79°/0·15 mm. This was purified by conversion into the picrolonate and recrystallisation from ethanol. trans-2-4′-*Ethoxybutyl*-6-*methylpiperidine picrolonate*, so obtained (17·8 g.), formed yellow prisms, m. p. 162—164° (Found: C, 57·35; H, 7·3%). The trans-*base*, liberated from the pure picrolonate, had b. p. 70—72°/0·2 mm., n_D^{22} 1·4560 (Found: C, 71·15; H, 13·0%).

Dehydro-1-*methylquinolizinium Salts*.—2-γ-Ethoxybutyryl-3-methylpyridine (4 g.) and 48% hydrobromic acid (25 ml.) were heated under reflux for 2 hr. The solution was concentrated under reduced pressure. A solution of the residue in water (15 ml.) was treated dropwise with potassium carbonate solution and extracted with chloroform after each addition, until the aqueous layer was just alkaline. The chloroform extract was dried ($MgSO_4$) for a few minutes, filtered, and refluxed for 2 hr. Removal of the solvent and recrystallisation of the residue from ethanol–ethyl acetate gave the *ketone bromide* (cf. V) (3·4 g.) as plates, m. p. 211—

212° (Found: C, 49·3; H, 4·9. $C_{10}H_{12}BrNO$ requires C, 49·6; H, 4·9%). This salt (3 g.) was refluxed with acetic anhydride (30 ml.) for 1½ hr. Water (30 ml.) was added and the mixture was kept overnight and then concentrated under reduced pressure. The residue was treated with ethanolic silver perchlorate. Filtration, concentration, and recrystallisation of the product from ethanol gave dehydro-1-methylquinolizinium perchlorate (2·4 g.) as needles, m. p. 173—175° (Found: C, 49·2; H, 4·5. Calc. for $C_{10}H_{10}ClNO_4$: C, 49·3; H, 4·1%). The picrate was obtained from ethanol as yellow needles, m. p. 154°. Glover and Jones [35] recorded m. p. 168—169° for the perchlorate and m. p. 149° for the picrate.

Dehydro-2-methylquinolizinium Salts.—In the same way 2-γ-ethoxybutyryl-4-methylpyridine (4 g.) gave the *ketone bromide* (3·5 g.), prisms, m. p. 197—199° (Found: C, 49·7; H, 5·1%) (from ethanol–ethyl acetate). This salt (3·3 g.) gave dehydro-2-methylquinolizinium perchlorate (2·6 g.), as plates, m. p. 111·5—113·5°, from ethanol. The picrate formed yellow needles, m. p. 162—164°, from ethanol. Glover and Jones [21] gave m. p. 110·5° for the perchlorate and m. p. 162° for the picrate. Richards and Stevens [36] gave m. p. 161° for the picrate.

Dehydro-3-methylquinolizinium Salts.—The *ketone bromide* (4·1 g.), obtained from 2-γ-ethoxybutyryl-5-methylpyridine (5 g.), formed needles, m. p. 186—187·5° (Found: C, 49·6; H, 5·4%), from ethanol–ethyl acetate. The ketone bromide (3·8 g.) gave *dehydro-3-methylquinolizinium perchlorate* (3·0 g.), which formed needles, m. p. 84—86° (Found: C, 49·1; H, 4·1%), from ethanol. The picrate crystallised from ethanol as yellow needles, m. p. 186·5—188°. Glover and Jones [21] recorded m. p. 182° for the picrate. The ultraviolet absorption spectrum of the perchlorate in water closely resembled that of the 1-methyldehydroquinolizinium cation, our figures for which agreed well with those of Glover and Jones.[35]

Dehydro-4-methylquinolizinium Salts.—2-γ-Ethoxybutyryl-6-methylpyridine (4 g.) gave the corresponding *ketone bromide* (3·6 g.) as needles, m. p. 271° (decomp.) (Found: C, 49·1; H, 5·0%). [The "*ketone picrate*" formed yellow needles, m. p. 135—136·5° (Found: C, 49·4; H, 3·5. $C_{16}H_{14}N_4O_8$ requires C, 49·2; H, 3·6%).] The ketone bromide (3·0 g.) was converted into *dehydro-4-methylquinolizinium perchlorate* (2·3 g.), which formed prisms, m. p. 208—210° (Found: C, 49·8; H, 4·0%), from ethanol. The picrate crystallised from ethanol as yellow plates, m. p. 140—141° (lit.,[15,21] m. p. 135°).

c-1-*Methylquinolizidine.*—(*a*) *cis*-2-4′-Ethoxybutyl-3-methylpiperidine (3 g.) was heated under reflux for 2 hr. with 48% hydrobromic acid (30 ml.). The solution was concentrated under reduced pressure and the residue was shaken with aqueous potassium carbonate and chloroform. The residue remaining after concentration of the dried ($MgSO_4$) chloroform solution was heated under reflux for 2 hr. with potassium hydroxide (8 g.) in methanol (40 ml.). The solution was acidified with hydrochloric acid, and the methanol was removed. The residue was basified with aqueous potassium hydroxide and extracted with chloroform. Distillation of the dried (K_2CO_3) extract gave *c*-1-methylquinolizidine (1·4 g.), b. p. 73—74°/16 mm., n_D^{23} 1·4817. The *perchlorate* formed needles, m. p. 193·5—195° (Found: C, 47·2; H, 7·9. $C_{10}H_{20}ClNO_4$ requires C, 47·3; H, 7·9%), from ethanol–ether, and the picrate yellow prisms, m. p. 186·5—187·5° (Found: C, 50·6; H, 5·8; N, 14·35. Calc. for $C_{16}H_{22}N_4O_7$: C, 50·3; H, 5·8; N, 14·65%).

(*b*) 1-Methyldehydroquinolizinium perchlorate (1 g.), platinum oxide (0·1 g.), and ethanol (50 ml.) were shaken with hydrogen. Uptake was complete in 4 hr. Filtration, concentration, and recrystallisation of the residue from ethanol–ether gave *c*-1-methylquinolizidine perchlorate (0·8 g.), m. p. 193·5—195°, identical with that above.

t-1-*Methylquinolizidine.*—In the same way, *trans*-2-4′-ethoxybutyl-3-methylpiperidine (4·5 g.) gave *t*-1-methylquinolizidine (1·9 g.), b. p. 72—73°/15 mm., n_D^{23} 1·4779 [*perchlorate*, needles, m. p. 217—219° (Found: C, 47·5; H, 8·0%), from ethanol–ether; picrate, yellow needles, m. p. 163—164·5° (Found: C, 50·15; H, 5·8%), from ethanol].

c-2-*Methylquinolizidine.*—(*a*) *cis*-2-4′-Ethoxybutyl-4-methylpiperidine (7 g.), treated as above, gave *c*-2-methylquinolizidine (3·2 g.), b. p. 78—80°/18 mm., n_D^{22} 1·4718 [*perchlorate*, prisms, m. p. 119—121° (Found: C, 47·7; H, 7·9%), from ethanol–ether; picrate, yellow plates, m. p. 155—157° (Found: C, 50·5; H, 5·8; N, 14·3%), from ethanol].

(*b*) Dehydro-2-methylquinolizinium perchlorate (2 g.) was hydrogenated in ethanol (50 ml.)

[35] Glover and Jones, *J.*, 1959, 1686.
[36] Richards and Stevens, *J.*, 1958, 3067.

with platinum oxide (0·2 g.). Reduction was complete in 4 hr., giving *c*-2-methylquinolizidine perchlorate (1·5 g.), m. p. 119—121°, identical with that described above.

t-2-*Methylquinolizidine*.—The base (4 g.) obtained from the crystallisation mother-liquors of the sodium–ethanol reduction product of 2-4′-ethoxybutyl-4-methylpyridine (see above) was cyclised as above, giving a colourless liquid (2·5 g.), b. p. 81—83°/15 mm. This was converted into its perchlorate. Fractional crystallisation from ethanol–ether gave t-2-*methylquinolizidine perchlorate* (2·2 g.) as plates, m. p. 164—165° (Found: C, 48·0; H, 8·1%). The corresponding picrate formed yellow needles, m. p. 166—167·5° (Found: C, 50·5; H, 6·0; N, 14·2%), from ethanol. The base, liberated from pure perchlorate, had b. p. 83—84°/17 mm., n_D^{22} 1·4784.

3-*Methylquinolizidine*.—(*a*) 2-4′-Ethoxybutyl-5-methylpiperidine "A" (4·2 g.) gave, on cyclisation *t*-3-methylquinolizidine (2·1 g.), b. p. 68—69°/15 mm., n_D^{21} 1·4723. This gave a *perchlorate*, needles, m. p. 171—172·5° (Found: C, 47·6; H, 8·1%), from ethanol–ether, *picrate*, yellow needles, m. p. 180·5—182° (Found: C, 50·3; H, 5·9; N, 14·2%), from ethanol, and *picrolonate*, pale yellow needles, m. p. 229·5—231·5° (decomp.) (Found: C, 57·2; H, 6·5. $C_{20}H_{27}N_5O_5$ requires C, 57·5; H, 6·5%), from ethanol.

Similarly, 2-4′-ethoxybutyl-5-methylpiperidine "B" (3 g.) gave *c*-3-methylquinolizidine (1·6 g.), b. p. 72—73°/18 mm., n_D^{21} 1·4754. The *perchlorate* formed plates, m. p. 184·5—186° (Found: C, 47·4; H, 7·9%), from ethanol–ether, the *picrate* yellow prisms, m. p. 155—157° (Found: C, 50·6; H, 6·0%), from ethanol, and the *picrolonate* yellow prisms, m. p. 220—221·5° (Found: C, 57·7; H, 6·5%), from ethanol.

(*b*) 3-Methyldehydroquinolizinium perchlorate (2·5 g.), ethanol (200 ml.), and platinum oxide (0·3 g.) were shaken with hydrogen. Uptake was complete in 3 hr. The product obtained by filtration and concentration was a solid melting over a wide range. The free base obtained from it in the usual way was distilled, giving a liquid (1·35 g.), b. p. 70—72°/15 mm. This was converted into a mixture of picrates, which on recrystallisation from benzene gave yellow needles (0·9 g.), m. p. 180·5—182°, alone and mixed with *t*-3-methylquinolizidine picrate. The mother-liquor was evaporated, and the residue was recrystallised from ethanol, giving yellow prisms (0·55 g.), m. p. 154—155·5°, which did not depress the m. p. of *c*-3-methylquinolizidine picrate.

c-4-*Methylquinolizidine*.—(*a*) *cis*-2-4′-Ethoxybutyl-6-methylpiperidine (2·5 g.) gave *c*-4-methylquinolizidine (1·5 g.), b. p. 82°/17 mm., n_D^{23} 1·4790 [*perchlorate*, needles, m. p. 274—276° (decomp.) (Found: C, 47·4; H, 7·8%), from ethanol–ether; *picrate*, yellow prisms, m. p, 197·5—199° (Found: C, 50·5; H, 5·9; N, 14·3%), from ethanol].

(*b*) Dehydro-4-methylquinolizinium perchlorate (2 g.) in ethanol (100 ml.) with platinum oxide (0·2 g.) was completely hydrogenated in 5 hr. Crystallisation of the product from ethanol–ether gave *c*-1-methylquinolizidine perchlorate (1·5 g.), m. p. 274—276°, identical with that above. When the *crude* reaction product was converted into the picrate this was obtained as prisms, m. p. 194—196°. This m. p. could not be raised, but the specimen did not depress the m. p. of the compound described in paragraph (*a*).

t-4-*Methylquinolizidine*.—Obtained from *trans*-2-4′-ethoxybutyl-6-methylpiperidine (4·2 g.), this liquid (2·6 g.) had b. p. 88°/20 mm., n_D^{23} 1·4822, and gave a *perchlorate*, needles, m. p. 233—234·5° (Found: C, 47·1; H, 7·9%), from ethanol–ether, and a *picrate*, yellow needles, m. p. 198·5—200° (Found: C, 50·4; H, 5·8%), from ethanol.

The crystals of *c*-4-methylquinolizidine picrate, m. p. 197·5—199°, were crisp, those of *t*-4-methylquinolizidine picrate, m. p. 198·5—200°, soft, and a mixture of the two had m. p. 185—192°.

2-4′-*Ethoxybutylpyridine*.—α-Picoline (29·5 g.), in ether (75 ml.), was added during 15 min. to a stirred solution of phenyl-lithium [from lithium (5·0 g.), bromobenzene (55 g.), and ether (250 ml.)], and the mixture was then refluxed for 2 hr. 3-Ethoxypropyl bromide (26·5 g.) in ether (75 ml.) was added dropwise, and the mixture was refluxed for 1 hr. and then decomposed with ice. The ether layer was extracted with 4N-hydrochloric acid, and the extract was basified and extracted with ether. Distillation of the dried (KOH) ether solution gave 2-4′-*ethoxybutylpyridine* (19 g.), b. p. 88—91°/1 mm., n_D^{21} 1·4907 (Found: C, 73·7; H, 9·5. $C_{11}H_{17}NO$ requires C, 73·7; H, 9·6%) [*picrate*, yellow prisms, m. p. 65·5—66·5° (Found: C, 50·7; H, 5·0. $C_{17}H_{20}N_4O_8$ requires C, 50·0; H, 4·9%), from ether].

"*Tetrahydrodehydroquinolizinium*" *Bromide*.—The above base (6 g.) and 48% hydrobromic acid (40 ml.) were heated under reflux for 2 hr. The solution was concentrated and the residue

was dissolved in water (20 ml.). To this solution potassium carbonate solution was added dropwise, followed by repeated extraction with small portions of chloroform, until the aqueous layer was just alkaline. The chloroform solution was dried ($MgSO_4$) for a short time and then refluxed for 1 hr. Removal of the solvent, and recrystallisation of the residue from ethanol–ethyl acetate gave the *bromide* (4·5 g.) as needles, m. p. 235—236° (Found: C, 50·6; H, 6·1. $C_9H_{12}BrN$ requires C, 50·5; H, 5·6%).

2-4′-*Ethoxybutylpiperidine*.—2-4′-Ethoxybutylpyridine (6 g.), ethanol (50 ml.) containing a slight excess of concentrated hydrochloric acid, and platinum oxide (0·5 g.) were shaken with hydrogen. Reduction was complete in 4 hr. Filtration, concentration, basification with aqueous potassium carbonate, and extraction with chloroform, followed by distillation of the dried (K_2CO_3) extract, gave 2-4′-*ethoxybutylpiperidine* (5·4 g.), b. p. 89—90°/1—5 mm., n_D^{20} 1·4575 (Found: C, 71·7; H, 12·3. $C_{11}H_{23}NO$ requires C, 71·3; H, 12·5%) [*picrolonate*, yellow prisms, m. p. 150—152° (Found: C, 56·2; H, 7·1. $C_{21}H_{31}N_5O_6$ requires C, 56·1; H, 6·95%)].

Quinolizidine.—(*a*) 2-4′-Ethoxybutylpiperidine (4 g.) and 48% hydrobromic acid (30 ml.) were heated under reflux for 2 hr. The solvent was removed, and the residue was treated with potassium carbonate solution and extracted with chloroform. The chloroform solution was dried ($MgSO_4$), the solvent was removed, and the residue was boiled for 2 hr. with potassium hydroxide (10 g.) in methanol (40 ml.). The mixture was acidified, the methanol was removed, and the residue was basified and extracted with chloroform. Distillation of the dried (K_2CO_3) extract gave quinolizidine (2·4 g.), b. p. 66—67°/15 mm., n_D^{20} 1·4789. The picrate crystallised from ethanol in plates, m. p. 199—201° (lit.,[28,37] m. p. 198—199° and 197°.)

Like all the methylquinolizidines, the parent base, when kept in an unsealed vessel, very quickly deposited a crystalline solid, the liquid becoming completely solid in 24 hr. Dissolved in water and treated with picric acid the solid gave quinolizidine picrate. Recrystallised from ethanol–ether it gave prisms of *quinolizidine hydrogen carbonate*, m. p. 268° (decomp.) (Found: C, 61·5; H, 9·9; N, 7·3. $C_{10}H_{17}NO_5$ requires C, 59·7; H, 9·5; N, 7·0%).

(*b*) " Tetrahydrodehydroquinolizinium " bromide (4 g.), ethanol (50 ml.), and platinum oxide (0·4 g.) were shaken with hydrogen. Uptake was complete in ¾ hr. Filtration, concentration, and recrystallisation from ethanol gave *quinolizidine hydrobromide* (3·7 g.) as needles, m. p. 287·5—290·5° (Found: C, 49·9; H, 7·9. $C_9H_{18}BrN$ requires C, 49·1; H, 8·2%), identical with a specimen prepared directly from quinolizidine.

Quinolizidine Quaternary Salts.—(*a*) Quinolizidine, an excess of methyl iodide, and ethanol, were heated under reflux for ½ hr. The methiodide " A " crystallised from ethanol in prisms, m. p. 320° (decomp.) (Found: C, 42·2; H, 7·3. Calc. for $C_{10}H_{20}IN$: C, 42·7; H, 7·2%) [lit.,[27,28] m. p. 329—330° (decomp.) and 321°]. Treatment of the methiodide with aqueous sodium picrate, and recrystallisation from ethanol, gave yellow needles of the *methopicrate " A,"* m. p. 241—243° (Found: C, 50·8; H, 6·1. $C_{16}H_{22}N_4O_7$ requires C, 50·3; H, 5·8%). Methiodide " A " in acetonitrile was added to silver toluene-*p*-sulphonate (1 equiv.) in acetonitrile. The mixture was shaken for a few minutes and filtered. Evaporation, and recrystallisation of the residue from ethanol–ethyl acetate, gave small prisms of N-*methylquinolizidinium toluene*-p-*sulphonate " A,"* m. p. 154—157° (Found: C, 62·7; H, 8·2. $C_{17}H_{27}NO_3S$ requires C, 62·75; H, 8·4%). The same compound was obtained when quinolizidine was warmed with methyl toluene-*p*-sulphonate in benzene.

(*b*) 2-4′-Ethoxybutylpiperidine (3 g.), 40% aqueous formaldehyde (4 ml.), and 98% formic acid (4·5 ml.) were kept at room temperature for 4 hr., then heated under reflux for 4 hr. The solution was basified with aqueous potassium carbonate and extracted with chloroform. Distillation of the dried (K_2CO_3) extract gave 2-4′-*ethoxybutyl*-1-*methylpiperidine* (3 g.), b. p. 83—85°/0·7 mm. (Found: C, 73·0; H, 12·6. $C_{12}H_{25}NO$ requires C, 72·3; H, 12·6%) [*picrate*, yellow prisms, m. p. 76—77·5° (Found: C, 50·7; H, 6·6. $C_{18}H_{26}N_4O_8$ requires C, 50·7; H, 6·15%)].

This base (1 g.) and constant-boiling hydriodic acid (10 ml.) were heated under reflux for 2 hr. The solution was concentrated and the residue was shaken with chloroform and water. The dried ($MgSO_4$) chloroform layer was concentrated, and the residue was recrystallised from ethanol–ethyl acetate, giving prisms of 2-4′-*iodobutyl*-1-*methylpiperidine hydriodide* (1·4 g.), m. p. 108—110° (Found: C, 30·0; H, 5·4. $C_{10}H_{21}I_2N$ requires C, 29·4; H, 5·2%) [*picrate*,

[37] Leonard and Hay, *J. Amer. Chem. Soc.*, 1956, **78**, 1984.

yellow prisms, m. p. 105—107° (Found: C, 37·9; H, 4·7. $C_{16}H_{23}IN_4O_7$ requires C, 37·6; H, 4·5%), from ethanol]. The hydriodide (1 g.) in chloroform was shaken with aqueous potassium carbonate. The chloroform layer was dried ($MgSO_4$), the solvent was removed, and the residue was recrystallised from ethanol, giving needles of quinolizidine methiodide "*B*" (0·4 g., 58%), m. p. 314° (decomp.) (because of a typing error, this m. p. was given wrongly as 214° in our original communication [29]) (Found: C, 42·2; H, 7·2%). The *methopicrate* "*B*," yellow needles, had m. p. 289—291° (decomp.) (Found: C, 49·95; H, 5·9%) (from ethanol). *N-Methylquinolizidinium toluene-p-sulphonate* "*B*" formed plates, m. p. 142—144° (Found: C, 61·5; H, 8·4%).

The mother-liquor from the recrystallisation of methiodide "B," when treated with sodium picrate, gave a picrate which after recrystallisation from alcohol had the apparently constant m. p. 260·5—263·5° (Found: C, 50·6; H, 5·6%). From another experiment the corresponding material had m. p. 275—277°. These substances must be mixtures of the methopicrates "A" and "B."

c-1-*Methylquinolizidine Quaternary Salts*.—The base gave directly, as above, a *methiodide*, which formed needles, m. p. 311° (decomp.) (Found: C, 45·3; H, 7·7. $C_{11}H_{22}IN$ requires C, 44·75; H, 7·5%), from ethanol–ethyl acetate. The derived *methopicrate* was yellow prisms, m. p. 231·5—233·5° (Found: C, 51·1; H, 6·4. $C_{17}H_{24}N_4O_7$ requires C, 51·5; H, 6·1%).

cis-2-4′-Ethoxybutyl-3-methylpiperidine (2 g.) gave, by the method described above, cis-2-4′-*ethoxybutyl*-1,3-*dimethylpiperidine* (2 g.), b. p. 95—97°/0·8 mm., n_D^{20} 1·4589 (Found: C, 73·5; H, 12·65. $C_{13}H_{27}NO$ requires C, 73·2; H, 12·8%) [*picrate*, yellow prisms, m. p. 63—65° (Found: C, 52·1; H, 6·9. $C_{19}H_{30}N_4O_8$ requires C, 51·6; H, 6·8%), from ether]. The base (1 g.) and constant-boiling hydriodic acid (10 ml.) were heated under reflux for 2 hr. The solution was concentrated under reduced pressure and the residue dissolved in chloroform. [A portion (10%) of the solution was evaporated to dryness, and the residue was treated with aqueous sodium picrate. Crystallisation of the product from ethanol gave yellow prisms of cis-2-4′-*iodobutyl*-1,3-*dimethylpiperidine picrate*, m. p. 133·5—134·5° (Found: C, 39·4; H, 5·2. $C_{17}H_{25}IN_4O_7$ requires C, 38·95; H, 4·8%).] The remainder of the chloroform solution was shaken with an excess of aqueous potassium carbonate, and the chloroform layer was quickly separated and dried ($MgSO_4$) for a few min. Removal of the solvent and recrystallisation from ethanol–ethyl acetate gave the methiodide, m. p. 311° (decomp.). This and the methopicrate, m. p. 231·5—233·5°, obtained from it, were identical with the products of direct quaternisation.

t-1-*Methylquinolizidine Quaternary Salts*.—The base, quaternised in the usual way with methyl iodide, gave the methiodide, which formed small prisms, m. p. 204—206° (Found: C, 45·1; H, 7·8%), from ethanol–ethyl acetate. This m. p. could not be raised, but infrared and nuclear magnetic resonance spectra showed it to be substantially identical with the higher-melting material described below. A mixture of the two had m. p. 214—218°. The derived methopicrate, after crystallisation from ethanol, had m. p. 192·5—194·5° (Found: C, 51·3; H, 6·4%). A mixture with the compound (m. p. 200—202·5°) obtained by cyclisation had m. p. 195—198·5°.

t-1-Methylquinolizidine (0·7 g.), methyl bromide (10 ml.), and ethanol (5 ml.) were kept in the ice-chest for 5 days. The residue, after removal of the solvent, was deliquescent. With aqueous sodium picrate it gave t-1-*methylquinolizidine methopicrate* (1·1 g.), which formed yellow needles, m. p. 200—202° (Found: C, 51·8; H, 6·1%), from ethanol. This was identical with the methopicrate obtained by cyclisation.

Methylation of *trans*-2-4′-ethoxybutyl-3-methylpiperidine (2 g.) gave trans-2-4′-*ethoxybutyl*-1,3-*dimethylpiperidine* (2·1 g.), b. p. 95—97°/1 mm., n_D^{23} 1·4558 (Found: C, 73·6; H, 12·7%) [*picrate*, yellow prisms, m. p. 84—85° (Found: C, 52·0; H, 7·1%), from ether]. This base (1 g.) was converted in the usual way into *trans*-2-4′-iodobutyl-1,3-dimethylpiperidine [*picrate*, yellow prisms, m. p. 106—107° (Found: C, 38·7; H, 4·5%), from ethanol]. This was not isolated, but its chloroform solution was submitted to the usual cyclisation procedure, giving t-1-*methylquinolizidine methiodide*, which formed needles, m. p. 225—228° (Found: C, 45·0; H, 7·6%), from ethanol–ethyl acetate. The derived methopicrate crystallised from ethanol as yellow needles, m. p. 200—202·5°, alone and mixed with the compound described above.

c-3-*Methylquinolizidine Quaternary Salts*.—The base gave, by direct quaternisation, c-3-*methylquinolizidine methiodide*, which formed needles, m. p. 301° (decomp.) (Found: C, 44·65;

H, 7·5%), from ethanol. The *methopicrate* formed yellow needles, m. p. 206—208° (Found: C, 51·0; H, 6·3%), from ethanol.

Methylation of 2-4′-ethoxybutyl-5-methylpiperidine " B " (1 g.) gave 2-4′-*ethoxybutyl*-1,5-*dimethylpiperidine* " *B* " (0·9 g.), b. p. 69°/0·2 mm., n_D^{20} 1·4569 (Found: C, 72·3; H, 12·6%) [*picrate*, yellow prisms, m. p. 67—69° (Found: C, 51·7; H, 6·9%), from ether]. Cyclisation of the base (0·7 g.) in the usual way gave a product (0·5 g.) which when crystallised from ethanol gave *c*-3-methylquinolizidine methiodide as needles, m. p. 301° (decomp.). This and the derived methopicrate, m. p. 206—208°, were identical with the compounds described above.

t-3-*Methylquinolizidine Quaternary Salts*.—(*a*) The product of direct quaternisation, after crystallisation from ethanol, had m. p. 255—264°. It was treated with aqueous sodium picrate; recrystallisation of the product from ethanol then gave pale orange needles of t-3-*methylquinolizidine methopicrate* 1, m. p. 159—161° (Found: C, 51·3; H, 6·3%). This was treated with hydriodic acid. Removal of the picric acid with toluene, evaporation to dryness of the hydriodic acid solution, and crystallisation of the residue from ethanol gave needles of t-3-*methylquinolizidine methiodide* 1, m. p. 254—256° (Found: C, 44·6; H, 7·6%). Above the m. p. this compound partly resolidified and remelted at 261—264°.

(*b*) Methylation of 2-4′-ethoxybutyl-5-methylpiperidine " A " (1·6 g.) gave 2-4′-*ethoxybutyl*-1,5-*dimethylpiperidine* " *A* " (1·45 g.), b. p. 69—70°/0·05 mm., n_D^{22} 1·4542 (Found: C, 73·2; H, 12·85%) [*picrate*, yellow prisms, m. p. 103·5—105° (Found: C, 51·7; H, 6·9%), from ether]. This base (1·4 g.) and constant-boiling hydriodic acid (10 ml.) were heated under reflux for 2 hr. The solution was concentrated, and the residue was dissolved in chloroform and shaken with aqueous potassium carbonate. The chloroform layer was dried ($MgSO_4$) for a short time and the solvent was removed. The residue recrystallised from ethanol as colourless needles (1·2 g.), m. p. 269·5—271·5°. This was converted into the picrate. Recrystallisation from ethanol gave a minor fraction (0·15 g.) of pale orange needles, m. p. 159—161°, identical with methopicrate 1 described above, and a major fraction (0·9 g.) of yellow plates, m. p. 131—133° (Found: C, 51·5; H, 6·2%). The major fraction was re-converted into the methiodide, as described above, and recrystallisation from ethanol gave methiodide 2 as needles, m. p. 270·5—272° (Found: C, 44·9; H, 7·8%).

Infrared and nuclear magnetic resonance data indicate the methiodide 2 to be a mixture (see Discussion).

2- *and* 4-*Methylquinolizidine Quaternary Salts*.—Direct quaternisation of *c*-2-methylquinolizidine and crystallisation of the product from ethanol–ethyl acetate gave the methiodide, m. p. 222·5—225·5° (Found: C, 45·3; H, 7·8%). Clemo, Cook, and Raper [24] described a methiodide, m. p. 212°.

Similarly, *t*-2-methylquinolizidine gave material, m. p. 294—295·5° (decomp.) (Found: C, 44·9; H, 7·7%). The products from *c*- and *t*-4-methylquinolizidine showed m. p. 300—301° (decomp.) (Found: C, 45·3; H, 7·6%) and m. p. 314° (decomp.) (Found: C, 44·9; H, 7·5%), respectively. Comments on these materials will be found in the Discussion. Quaternary picrates, probably mixtures, have been described by Lukeš and Šorm.[25]

Physical Measurements.—The quinolizidines, after being obtained analytically pure, as described, were distilled shortly before measurements were to be made, a small middle fraction being collected in each case and sealed in a glass bulb. The salts were recrystallised and dried just before use.

For the conditions of measurement of infrared spectra see Katritzky *et al.*[38] The infrared spectra of the quinolizidines were measured for 0·2M-solutions in carbon tetrachloride. Proton magnetic resonance spectra were obtained at 40 mc./sec. with a Varian Associates V4300B spectrometer and 12″ electromagnet with flux stabilisation and spinning sample tube of 5 mm. outside diameter. Positions of peaks were obtained by interpolation, with sidebands generated by a Muirhead–Wigan D695A decade oscillator, and are given on the τ scale ($SiMe_4 = 10$). For the quinolizidines, proton resonance spectra were measured for *ca.* 0·65M-solutions in carbon tetrachloride, with tetramethylsilane as an internal standard. The protonated quinolizidinium ions were examined as *ca.* 0·65M-aqueous solutions, with dioxan as an internal standard (τ value 6·28). The *N*-methylquinolizidinium ions were used in *ca.* 0·65M-solution, again with dioxan as the internal standard.

[38] Katritzky, Monro, Beard, Dearnaley, and Earl, *J.*, 1958, 2182; Katritzky and Lagowski, *J.*, 1958, 4155.

Results

Before examining our results we must consider the physical criteria which are available. These are:

(*A*) Bohlmann's and Wenkert and Roychauduri's infrared criterion,[7,8] already mentioned. The band involved is probably a C–H stretching mode related to the characteristic N–CH_3 band found in the same region,[39] and the criterion has been amply confirmed.[40]

(*B*) The degree of splitting of *C*-methyl proton resonance peaks. Previous work [41] indicated that splitting by the adjacent hydrogen might generally be less for equatorial methyl groups than for axial groups. For the dimethylcyclohexanes J(H-*ax*/Me-*eq*) was 0—3·7 c./sec., and although the compounds studied did not contain any rigid axial groups, the coupling J(H-*eq*/Me-*ax*) was estimated as 8·1—9·9 c./sec. It has been pointed out to us [42] that there are theoretical grounds for believing that this is only an apparent difference in J, and arises because the observed splitting of the *C*-methyl signal depends, not on the coupling constant J(H/Me) alone, but on the ratio of J to δ, the chemical shift between the *C*-H and *C*-methyl group. When this ratio is small (*i.e.*, $\delta \gg J$), the observed splitting will be equal to J, but when J and δ are of comparable magnitude the observed splitting will be greatly reduced (cf., *e.g.*, ref. 43*a*). However, it seems that the chemical shifts depend on the conformation in a systematic manner (see criterion *C*), so that the apparent coupling constant may still be a useful criterion.

(*C*) The position of the centre of the *C*-methyl proton resonance doublet. Previous work indicates that axial and equatorial groups may cause absorption at different positions: this may be either because of the long-range shielding effects of the magnetically anisotropic carbon–carbon single bonds or because of the diamagnetic anisotropy which arises from electronic ring currents. However, the conformational effect is not always in the same direction. Thus the methyl-protons of an acetoxy-group generally absorb at higher fields when the group is equatorial,[44] whereas equatorial ring-hydrogen atoms absorb at lower fields than their axial analogues.[43*b*] In work on the methylcyclohexanols [45] it was found that those isomers where the methyl group was certainly equatorial absorbed at lower fields than their analogues where either the methyl group or the hydroxyl atom was axial. It was concluded [45] that this was due to the partially axial character of the methyl group in the latter compounds. In contrast, Slomp and McGarvey [46*a*] found that for methyl groups in the 6-position of the steroid nucleus the axial group absorbs at lower fields than the equatorial; however, this does not apply to all the nuclear positions of the steroid ring system.[46*b*] The present work shows that the signals due to axial *C*-methyl groups occur at lower fields than those from their equatorial analogues in the methylquinolizidines and their cations. The present conclusion is also contrary to results of calculations [47] based both on the bond-anisotropy and on the ring-current models, which indicate that the chemical shifts of axial methyl groups should be *ca.* 0·3 p.p.m. to higher field than their equatorial analogues. We cannot explain these discrepancies. However, if the differences in apparent coupling constants are due to chemical shift effects as suggested,[42] then our results require that axial protons have chemical shifts $>$ *ca.* 8·85 and equatorial protons $<$ *ca.* 8·4, which is in reasonable agreement with the calculations [47] that axial hydrogen atoms should absorb at *ca.* 0·4 p.p.m. to higher field than equatorial ones.

(*D*) A new criterion, based on the present work, is that *N*-methyl groups absorb at lower field in *cis*-fused *N*-methylquinolizidine cations than in the *trans*-fused analogues. It was previously established that angular methyl groups in *cis*-decalins absorb at lower field than those in *trans*-decalins.[48]

[39] Hill and Meakins, *J.*, 1958, 760; Braunholtz, Ebsworth, Mann, and Sheppard, *ibid.*, p. 2780.
[40] Bohlmann, *Chem. Ber.*, 1959, **92**, 1798; Ohke and Noike, *Chem. and Pharm. Bull.* (*Japan*), 1959, **7**, 708; Freed and Day, *J. Org. Chem.*, 1960, **25**, 2108; Rosen, *Tetrahedron Letters*, 1961, 481.
[41] Musher, *Spectrochim. Acta*, 1960, **16**, 835.
[42] Personal communication from Dr. A. Moritz and Dr. N. Sheppard.
[43] Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, Oxford, 1959, (*a*) p. 95, (*b*) p. 115, (*c*) p. 56, (*d*) p. 52, (*e*) p. 53.
[44] Lemieux, Kullnig, Bernstein, and Schneider, *J. Amer. Chem. Soc.*, 1957, **79**, 1005; 1958, **80**, 6098; Baggett, Dobinson, Foster, Homer, and Thomas, *Chem. and Ind.*, 1961, 106.
[45] Brownstein and Miller, *J. Org. Chem.*, 1959, **24**, 1886.
[46] (*a*) Slomp and McGarvey, *J. Amer. Chem. Soc.*, 1959, **81**, 2200; (*b*) personal communication from Dr. G. Slomp.
[47] A. Moritz, unpublished work.
[48] Musher, *J. Amer. Chem. Soc.*, 1961, **83**, 1146.

(*E*) Musher and Richards [49] showed that *cis*-decalins give sharp proton-resonance lines for the ring protons, in contrast to the broad signals obtained from *trans*-decalins. Similar effects are found with other saturated bicyclic compounds.[48,50] This behaviour is believed to result from rapid equilibration between the axial and the equatorial protons in the flexible *cis*-compound, which cannot occur in the rigid *trans*-isomer. The success of this method depends on the small chemical-shift differences between the various types of ring proton in decalin derivatives. It might be expected that this criterion would fail in the quinolizidine series where the introduction of the nitrogen atom would result in larger chemical shifts between the various ring protons. The present work shows that this is so.

We now discuss our results in terms of these criteria.

Quinolizidine Free Bases.—In the 3000 cm.$^{-1}$ region (Table 2) * all the compounds showed a prominent band at 2760—2750 cm.$^{-1}$ except one of the 4-methyl compounds. This is therefore identified as *t*-4-methylquinolizidine (in agreement with the chemical evidence, see above) and, in this compound, by Bohlmann's criterion, the *cis*/equatorial conformation must be preferred. All the other compounds exist mainly in the *trans*-fused conformation.

The proton-resonance spectra (Table 3) showed broad peaks at *ca.* 7·3 (often with two maxima) and *ca.* 8·5 and (for the methylquinolizidines) a sharp doublet centred at 8·92—9·18. The broad peaks are assigned to the ring protons, that at lower field to those adjacent

TABLE 2.

Infrared data for quinolizidine and the methylquinolizidines.

Quinolizidine	cm.$^{-1}$	ε_A	cm.$^{-1}$	ε_A	cm.$^{-1}$	ε_A	cm.$^{-1}$	ε_A	cm.$^{-1}$	ε_A	cm.$^{-1}$	ε_A
Parent	2935	340	2855	110	2790	95	2750	115	2675	45	2610 *	15
c-1-Me	2945	320	2865	110	2805	75	2755	115	2680	45	2610 *	15
t-1- ,, ...	2945	320	2865	110	2805	85	2755	130	2685	45	2605	15
c-2- ,, ...	2940	320	2880 *	110	2805	90	2760	105	2675	40	2605	20
t-2- ,, ...	2935	320	2860	90	2800	90	2760	100	2675	35	2600 *	10
c-3- ,, ...	2940	340	2860	110	2795	85	2755	120	2680 *	40	2615 *	20
t-3- ,, ...	2945	340	2860	110	2805	75	2760	120	2685 *	35	2625 *	20
c-4- ,, ...	2950	330	2870	110	2795	110	2760 *	85	—	—	2625	25
t-4- ,, ...	2945	340	2870	110	2805	65	—	—	—	—	—	—

* Prominent shoulder.

TABLE 3.

Proton resonance of quinolizidines.

	Ring CH				Conformation				
	adjacent to N		non-adjacent to N		*C*-Methyl				
					axial		equatorial		Ring fusion
Quinolizidine	τ		τ	½ width (c./sec.)	τ	J *	τ	J *	(from IR)
Parent	7·23	7·43	8·56	17	—	—	—	—	*trans*
c-1-Me	7·25	7·40	8·46	18	9·05	5·8			*trans*
t-1- ,, ...	7·24	7·45	8·41	28			9·16	1·6	*trans*
c-2- ,, ...	7·20	7·44	8·59	22			9·09	2·7	*trans*
t-2- ,, ...	7·82		8·68	26	9·01	6·9			*trans*
c-3- ,, ...	7·41	7·84	8·58	12	8·92	6·6			*trans*
	7·63								
t-3- ,, ...	7·27	7·44	8·57	17			9·18	4·8	*trans*
c-4- ,, ...	6·88	7·75	8·57	11			9·00	5·1	*trans*
t-4- ,, ...	*ca.* 7·7		8·56	11			9·07	6·4	*cis*

* Apparent coupling constant, in c./sec.; see text.

to the nitrogen atom (cf. the value of 7·2—7·4 given for methylene groups adjacent to heterocyclic nitrogen by Jackman [43c]), and that at higher field to the non-adjacent protons (cf. cyclohexane $\tau = 8{\cdot}56$ [43d]). As mentioned under *E* above, the half-width of this peak (see Table 3) is not simply related to the *cis*- or *trans*-arrangement of the rings: it is 11—28 c./sec. for the

* Detailed spectra will be submitted to the D.M.S. scheme. Certain characteristic band sequences could be seen, *e.g.*, at 1449—1447 cm.$^{-1}$ (ε_A = 70—110).

[49] Musher and Richards, *Proc. Chem. Soc.*, 1958, 230.
[50] Moriz and Dixon, *J. Amer. Chem. Soc.*, 1961, **83**, 1671.

rings shown by the infrared evidence to be *trans*-fused and 11 c./sec. for *t*-4-methylquinolizidine. The sharp doublet is assigned to the *C*-methyl group (cf. methylcyclohexane, 9·08 [43d]). Methyl groups at the 4-position are β to the nitrogen atom and this is expected [43e] to cause a deshielding of about 0·1 p.p.m.

Of the pairs of 1-, 2-, and 3-methylquinolizidines, one of each pair shows smaller splitting (1·6—4·8 c./sec.) of the methyl resonance than the other (5·8—6·9 c./sec.). By criterion *B* the compounds showing the smaller splitting have an equatorial methyl group and are *t*-1-, *c*-2-, and *t*-3-methylquinolizidine. This assignment is in agreement with the chemical evidence (see above) for the 1- and the 2-methyl series, and defines the configurations in the 3-methyl series.

The *C*-methyl proton resonance signals for the 1-, 2-, and 3-methyl compounds with equatorial methyl groups (9·09—9·18) are at higher fields than the signals (8·92—9·05) for the compounds with axial methyl groups (cf. criterion *C*).

Infrared evidence (see above) indicates that *t*-4-methylquinolizidine exists in the *cis*-fused form, which must contain an equatorial methyl group. This is supported by the fact that the methyl resonance for the *t*-4-compound is *not* at lower field than that for the *c*-isomer, which must itself have an equatorial methyl group. The splitting in both these compounds is rather high for equatorial groups (cf. criterion C). This may be because the proximity of the nitrogen atom shifts the signal from the adjacent *C*-H proton to lower fields, so that the ratio of coupling constant to chemical shift becomes too small to cause a significant reduction in the splitting of the *C*-methyl signal.

Protonated Quinolizidinium Ions.—The spectra (Table 4) showed broad peaks for the ring-hydrogen atoms adjacent to the nitrogen at 6·6—7·0 (cf. the value for $-CH_2-N^+$ of 6·6 [43c]), and for those not adjacent at *ca.* 8·30. All the compounds showed a sharp methyl doublet, except the *c*-1-methyl isomer which showed two doublets of approximately equal intensity.

If the configurations of the parent bases are assumed as proved, the results show (criteria *B* and *C*) that *t*-1-, *c*-2-, and *t*-3-methylquinolizidine cations (chemical shift 9·08—9·12, splitting 4·3—5·2 c./sec.) have equatorial methyl groups and that the *t*-2- and *c*-3-isomers have axial methyl groups (positions 8·91—8·98, splitting 6·8—7·8 c./sec.). Although direct evidence for the ring fusion is lacking, it can be inferred as *trans* in all these cases—the compounds have

TABLE 4.

Proton resonance of quinolizidinium ions.

	Ring CH			Conformation				
	adjacent to N	non-adjacent to N		*C*-Methyl				
				axial		equatorial		Ring
Quinolizidine	τ	τ	½ width (c./sec.)	τ	*J* [a]	τ	*J* [a]	fusion [b]
Parent	6·61, 7·03	8·31	11					*trans*
c-1-Me	6·60	8·31	11·3	9·02	7·0	9·08	2·3	*trans*/*cis*
t-1- ,, ...	6·59	8·30	18			9·08	4·3	*trans*
c-2- ,, ...	6·62, 7·08	8·33	15			9·12	4·9	*trans*
t-2- ,, ...	6·65	8·32	13	8·98	6·8			*trans*
c-3- ,, ...	6·67	8·30	9	8·91	7·8			*trans*
t-3- ,, ...	6·63, 7·42 7·06	8·34	14			9·12	5·2	*trans*
c-4- ,, ...	7·02	8·30	10			8·68	6·4	*trans*
t-4- ,, ...	6·92	8·29	11			8·68	6·8	*cis*

[a] Apparent coupling constant, in c./sec., see text. [b] Deduced conformation, see text.

configurations corresponding exactly to the conformations of the corresponding free bases.

The two doublets of the *c*-1-methyl cation may be assigned to approximately equal amounts of the *trans*/axial and *cis*/equatorial tautomers of this cation.

For the 4-methyl cations the influence of the positive pole at the β-position is marked. For comparison we measured triethylamine in water (CH_3 signal of NEt_3 at 9·00) and in trifluoroacetic acid (CH_3 signal of $^+HNEt_3$ at 8·57); the shift of *ca.* 0·4 p.p.m. for the methyl resonance is in reasonable agreement with the quinolizidine results. As the methyl group in *c*-4-methylquinolizidine can reasonably only be equatorial, and the *t*-4-methyl signal is not at lower field, the *t*-4-methyl is presumably also equatorial. As with the free bases, the rather

high splitting for these equatorial methyl groups is probably due to the influence of the β-nitrogen atom.

N-*Methylquinolizidinium Ions*.—The spectra (Table 5) consisted of a broad peak at *ca.* 6·6 for ring-protons adjacent to the nitrogen atom, a sharp singlet at *ca.* 6·9 assigned to the *N*-methyl group (cf. the value for CH_3N^+ of 6·7 [43c]), a broad peak at *ca.* 8·3 for the non-adjacent ring protons, and, for the *C*-methyl compounds, a doublet centred at *ca.* 9·0.

TABLE 5.

Proton resonance of *N*-methylquinolizidinium ions.

Parent base of the methiodide	Prepn.[a]	Ring CH adj. to N	*N*-Me *trans*-ring	*N*-Me *cis*-ring	Ring CH not adj. to N		*C*-Methyl axial		*C*-Methyl equatorial	
		τ	τ	τ	τ	½ width (c./sec.)	τ	*J*[b]	τ	*J*[b]
Quinolizidine	M	6·65	7·04	—	8·26	9				
,, ...	RC	6·48, 6·62	—	6·85	8·22	12				
c-1-Me	M/RC	6·56	—	6·84	8·26	14			9·11	6·3
t-1- ,, ...	M/RC	6·64, 6·84[c]	7·03	—	8·26	15			9·10	5·3
c-2- ,, ...	M	6·67	7·06	—	8·28	13			9·01	4·4
t-2- ,, ...	M	v. broad	7·05	6·86	8·24	13	8·93	6·8	9·05	2·4
c-3- ,, ...	M/RC	6·51	—	6·85	8·25	11			9·05	6·3
t-3- ,, ...	M	*ca.* 6·7, 6·86[d]	7·04	—	8·27	10			9·10	5·9
,, ,, ...	RC	(lost)	7·04	6·85	8·26	11			9·09	5·7
c-4- ,, ...	M	6·8	7·31	—	8·29	9			8·72	6·3[e]
t-4- ,, ...	M	(lost)	7·01	6·92	8·27	13	*f*		*f*	

[a] M indicates preparation by reaction with methyl iodide, RC by ring-closure. [b] Apparent coupling constant, in c./sec., see text. [c] If this peak represents admixture of some *cis*-fused ring analogue in the sample, then the relative areas indicate that this component could not exceed 5% in the case of a sample prepared by direct methylation and 15% in the case of the sample prepared by ring-closure. [d] If this peak represents admixture of some *cis*-fused ring analogue in the sample, then the relative areas indicate that it could not exceed 10%. [e] Deduced conformation, see text. *ca.* 8·77, *J ca.* 7.

The methiodides obtained by direct quaternisation of *t*-2- and *t*-4-methylquinolizidine and the methiodide of *t*-3-methylquinolizidine obtained by ring-closure appeared to consist of approximately equal amounts of two isomers; in the last case one of the components of the mixture was identical with the methiodide obtained by direct quaternisation of *t*-3-methylquinolizidine (this identity was confirmed by a detailed examination of the highly characteristic infrared spectra). The methiodides of *t*-1-methylquinolizidine gave essentially the same spectra, but that obtained by ring-closure appeared to contain about 10% of the *cis*-fused isomer (see below).

For compounds of the 1-, 2-, and 3-methyl series, application of criteria *B* and *C* indicates that all the isomers possess an equatorial methyl group, except for one of the components of the mixture obtained by quaternisation of *t*-2-methylquinolizidine. It is clear that criterion *E* is not applicable in this series to determine the *cis*- or *trans*-nature of the ring fusion (as later determined, half band width 9—15 c./sec. for *trans*-fused rings and 11—14 c./sec. for *cis*-fused rings for the non-adjacent ring proton peak). Fortunately, it was possible to develop criterion *D* as an alternative. The *N*-methyl signal (excluding the 4-methyl series) appeared at either 7·03—7·06 or 6·84—6·86; the following considerations indicate that the former range applies to a *trans*-ring fusion and the latter to a *cis*-fusion:

(i) The free bases, quinolizidine, and *t*-1-, *c*-2-, *t*-3-, and *c*-4-methylquinolizidine all exist predominantly in the *trans*-fused ring conformation, with an equatorial methyl group which would not be expected to hinder the approach of a quaternising reagent. Thus the derived methiodides would all be expected to retain the *trans*-ring fusion and the equatorial *C*-methyl group.

(ii) *c*-1- and *c*-3-Methylquinolizidine exist predominantly with a *trans*-ring fusion and axial methyl groups on the same side of the molecule as the nitrogen lone-pair. Models indicate that steric hindrance would be prohibitive to methiodide formation with retention of configuration. These compounds presumably therefore form methiodides in the alternative *cis*-fused configuration with the methyl groups equatorial.

(iii) Formation of quinolizidine methiodide by ring-closure affords a different compound from that formed by direct methylation. The former must accordingly have the rings *cis*-fused.

(iv) The configurations of the *C*-methyl groups in these compounds (as determined by criteria *B* and *C*, see above) strongly support the assignments of the ring fusion.

c-4-Methylquinolizidine exists with a *trans*-ring fusion and an equatorial methyl group and would be expected to form a methiodide retaining these features. This is probably the case: the *N*-methyl signal is at an abnormally high field but this may well be due to the adjacent *C*-methyl to which it is gauche; * the low position of the *C*-methyl signal is explained by the β-positive pole. Quaternisation of *t*-4-methylquinolizidine appears to give a mixture on the *N*-methyl-signal criterion. Little can be deduced from the *C*-methyl peak because of the lowering of its position by the β-positive pole.

Discussion

Results are summarised in Table 6.

Conformational Equilibria of Free Bases.—Chief interest resides in those cases where *trans*-ring/axial-methyl and *cis*/equatorial conformations are alternatives. The 1,3-interactions experienced by the methyl group in these compounds when they are in the *trans*-fused form are given in Table 7, together with the interactions expected for the boat and the *cis*-fused chair forms. All of these compounds exist predominantly with *trans*-ring fusion, with the exception of the *t*-4-methyl compound. This indicates that (*a*) three Me/H interactions are necessary to force the compound into the *cis*-fused form and (*b*) the nitrogen lone-pair is " smaller " than a hydrogen atom.

Table 6.

Summary of results.

Quinolizidine	Conformation of *C*-Me when ring fusion is *trans* [a]	Conformation of free base	Configuration of methiodide by methyln.	Configuration of methiodide by ring-closure	Predominant tautomer of proton salts
Parent	—	*trans*	*trans*	*cis*	*trans*
c-1-Me	*ax*	*trans/ax*	*cis/eq*	*cis/eq*	*trans/ax* + *cis/eq*
t-1- ,, ...	*eq*	*trans/eq*	*trans/eq*	*trans/eq* [b]	*trans/eq*
c-2- ,, ...	*eq*	*trans/eq*	*trans/eq*	—	*trans/eq*
t-2- ,, ...	*ax*	*trans/ax*	*trans/ax* + *cis/eq*	—	*trans/ax*
c-3- ,, ...	*ax*	*trans/ax*	*cis/eq*	*cis/eq*	*trans/ax*
t-3- ,, ...	*eq*	*trans/eq*	*trans/eq*	*trans/eq* + *cis/eq*	*trans/eq*
c-4- ,, ...	*eq*	*trans/eq*	*trans/eq*	—	*trans/eq*
t-4- ,, ...	*ax*	*cis/eq*	*trans/ax* + *cis/eq*	—	*cis/eq*

[a] For *cis*-fused rings both axial and equatorial *c*-Me conformations are always possible. [b] Probably contains *ca.* 10% of the *cis/eq* isomer.

Table 7.

Steric interactions.

Confign.	*trans*/axial (chair)	Conformation *cis*/equatorial (chair)	*trans*/equatorial (boat)
***c*-1**	2 × Me/H Me/N:	3 × H/H Me/H	Me/CH_2 eclipsed 3 × H/H eclipsed H/N (1,4 interaction)
***t*-2**	2 × Me/H	3 × H/H	3 × H/H eclipsed H/N (1,4 interaction)
***c*-3**	Me/H Me/N:	3 × H/H	3 × H/H eclipsed H/N (1,4 interaction)
***t*-4**	3 × Me/H	3 × H/H Me/H	Me/H 3 × H/H eclipsed H/N (1,4 interaction)

In this context " smaller " means that in carbon tetrachloride solution less steric compression occurs between a methyl group and the nitrogen spare pair than between a methyl group and a hydrogen atom attached to carbon. In other solvents, which form hydrogen

* In hydrocarbon derivatives proximity to a bulky group usually displaces the signal to *lower* field,[51] but the introduction of the positively charged nitrogen might well cause the opposite effect.

[51] Brownstein, *J. Amer. Chem. Soc.*, 1959, **81**, 1606.

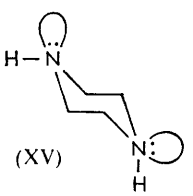
bonds to the spare pair, the effective size may be increased and conceivably become greater than that of a hydrogen atom. Experiments to test this are planned.

C–H – – – – H–C (i)
C–H – – – – :N (ii)
N: – – – – – :N (iii)

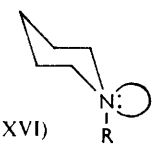
It may well be that the repulsion energy in case (ii) is less than in either case (i) or case (iii)—hydrogen atoms attached to carbon are known to form hydrogen bonds in favourable cases (*e.g.*, chloroform, hydrogen cyanide) and recent infrared work indicates that weak hydrogen bonding involving C–H bonds is more common than had been accepted. We hope to test these speculations.

Tautomeric Equilibria of Quinolizidine Cations.—These equilibria are very similar to those of the free bases. The 1,3-interactions noted in Table 5 apply, except that " N–lone pair " should be replaced by " N–H." The fact that the *c*-1-methylquinolizidine cation exists to a considerable extent with the rings *cis*-fused (as well as the *t*-4-isomer) strongly supports the conclusions (*a*) and (*b*) of the previous paragraph.

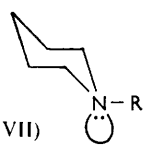
Previous Evidence as to the Size of the Spare Pair.—The dipole moment of piperazine indicates that the compound exists predominantly with one of the spare pairs axial and one equatorial (XV).[52] This is compatible with the spare pair's being smaller than the



(XV)



(XVI)



(XVII)

hydrogen on nitrogen, if the not unreasonable assumption is made that axial–axial hindrance only occurs for groups which are larger than hydrogen: a statistical average would then be expected.

The work of Aroney and Le Fèvre,[5] which led them to conclude that in benzene solution piperidine existed essentially entirely as (XVI; R = H) and that 1-methylpiperidine existed as (XVI; R = Me) and (XVII) in approximately equal amounts, has been mentioned. The conclusion is at variance with the dipole-moment work and with the results of the present study (insofar as C–H may be compared with N–H). We can offer no explanation for this discrepancy. We have measured the infrared spectra of *c*-1-methyl- and *t*-4-methyl-quinolizidine in benzene; the results agree, as expected, with those for carbon tetrachloride solutions.

Formation of Quinolizidine Methiodides by Direct Methylation.—As is discussed above, the free bases with *trans*/equatorial conformation form methiodides with retention of this structure; those which, in the *trans*-conformation, have an axial methyl group on the same side of the molecule as the lone-pair (namely, the *c*-1- and the *c*-3-isomers) form methiodides derived from the *cis*/equatorial conformation. *t*-2-Methylquinolizidine exists in a *trans*/axial conformation in which the methyl group does not directly hinder approach of the methylating agent. However, 1,3-diaxial interactions are probably greater in the methiodides than in the free bases, and the difference appears to be just important enough to cause a mixture of methiodides to be formed in the *trans*/axial and *cis*/equatorial configurations.

t-4-Methylquinolizidine exists in the *cis*/equatorial conformation. By analogy with the *t*-2-isomer, it would at first sight be expected to yield entirely the *cis*/equatorial

[52] Martin, Thesis, London, 1936, p. 134.

methiodide. However, models show that the equatorial 4-methyl group in the *cis*-fused conformation of the free base hinders the approach of the methylating agent. The balance of factors appears to be such that approximately equal amounts of *trans*/axial and *cis*/equatorial methiodides are formed.

We reserve discussion of the cyclisation processes, leading to quaternary salts, until our examination of them is more complete.

This work was made possible by a Special Research Grant from the Department of Scientific and Industrial Research, for which we express our appreciation.

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