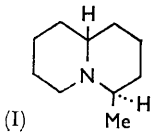
1258. *A Re-examination of the Stereochemistry of Quinolizidine and the Methylquinolizidines through Measurement of their Rates of Quaternisation and those of the Hexahydrojulolidines*

By C. D. Johnson, R. A. Y. Jones, A. R. Katritzky, C. R. Palmer, K. Schofield, and R. J. Wells

The kinetics of quaternisation of quinolizidine, methylquinolizidines, and hexahydrojulolidines by methyl iodide have been studied in acetonitrile and in methanol solutions over the range −20° to +40°. The results, together with pK_a measurements, allow calculation of free-energy differences for *cis–trans*-interconversion for quinolizidine and its methyl derivatives. The findings are discussed, together with literature work on decalins.

A recent joint Paper from our laboratories [1] described a study of the stereochemistry of quinolizidine and the methylquinolizidines, and of their salts and quaternary salts. From the infrared and proton resonance spectra of these bases it was concluded that all of them except one exist predominantly in the *trans*-fused conformations. The exception was *t*-4-methylquinolizidine (I), which according to the criteria adopted appeared to prefer the *cis*-fused conformation.[2]



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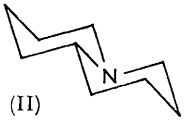

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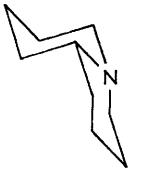


(III)

A weakness in these studies was their inability to provide even semi-quantitative evaluations of the conformational equilibria in these bicyclic amines. Consequently we sought an approach which would permit such evaluation, and this seemed to be provided by measurements of the rates of quaternisation of the bases. The method has been used before to distinguish differing conformational possibilities in quinolizidine derivatives,[3] but for our purpose it was essential to have for comparison compounds which could be regarded as " fixed " models of the *trans*-fused (II) and *cis*-fused (III) quinolizidine conformations.

Such " fixed " models exist in the hexahydrojulolidines, of which the three possible stereoisomeric forms, *c,c*- (IV), *t,t*- (V), and *c,t*-hexahydrojulolidines (VI) are known.[4] Of these, the *t,t*-compound (V) and the *c,t*-compound (VI) represent " fixed " models for the *trans*-fused (II) and *cis*-fused quinolizidine conformation (III), respectively [see (VIII) and (IX)]. *c,c*-Hexahydrojulolidine (IV) is distinguished from its stereoisomers by its very slow quaternisation, caused by the opposition presented in its structure to the approach of the reagent to the nitrogen atom (see VII).[5,6]

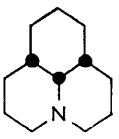
Accordingly, we have measured the rates of reaction of quinolizidine, the methylquinolizidines, and the hexahydrojulolidines with methyl iodide, and used the data to evaluate semi-quantitatively the conformational equilibria in the bicyclic bases. The results show that quinolizidine and all the monomethylquinolizidines exist with the rings *trans*-fused. This confirms our original conclusions [1] except that regarding *t*-4-methylquinolizidine.

Preparation of Materials.—Quinolizidine and the methylquinolizidines were all available from the earlier work.[1] A re-examination of these materials confirmed their purity

[1] T. M. Moynehan, K. Schofield, R. A. Y. Jones, and A. R. Katritzky, *J.*, 1962, 2637.
[2] Throughout this Paper, this *cis*- or *trans*-relationship of the 10-hydrogen atom and the hydrogen atom on the substituted carbon is denoted by *c* or *t*. The prefixes *cis* and *trans* indicate the ring conformation of the bicyclic bases.
[3] M. Shamma and J. B. Moss, *J. Amer. Chem. Soc.*, 1961, **83**, 5038.
[4] F. Bohlmann and C. Arndt, *Chem. Ber.*, 1958, **91**, 2167.
[5] K. Tsuda and S. Saeki, *Chem. and Pharm. Bull.* (*Japan*), 1958, **6**, 391.
[6] S. Saeki, *Chem. and Pharm. Bull.* (*Japan*), 1961, **9**, 226.

and this, together with a new synthesis of *t*-4-methylquinolizidine, will be described elsewhere.[7]

As regards the hexahydrojulolidines, the three stereoisomers were characterised by Bohlmann and Arndt,[4] who hydrogenated julolidine (X) over Raney nickel, so obtaining (IV) and (V) as the major products, and (VI) as a very minor product. Compounds (IV) and (V) were recognised by the presence in their infrared spectra of " Bohlmann bands," [1] and were differentiated by their rates of reaction with mercuric acetate. Isomer (VI) was recognised by the absence from its infrared spectrum of " Bohlmann bands," and by being optically resolved. As mentioned above, the *c,c*-isomer (IV) can also be readily recognised by the slowness of its quaternisation.[5] Recently, reductive cyclisation of the ketone (XI) was found to give 3 : 1 mixture of isomers (IV) and (V) in good yield.[8]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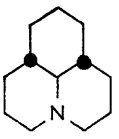
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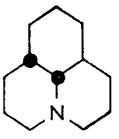
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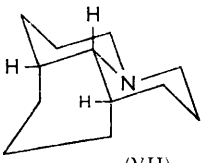
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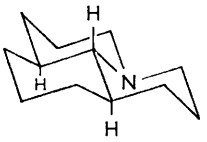
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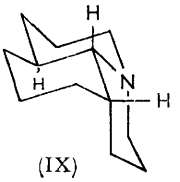
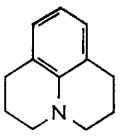

(IX)

We re-examined the hydrogenation of julolidine and separated the products by the method of Bohlmann and Arndt.[4] The results, and the analysis of reaction mixtures by gas–liquid chromatography (g.l.c.) (see Experimental section) showed the need to devise a new route to the *c,t*-isomer (VI) if it were to be obtained in useful amounts.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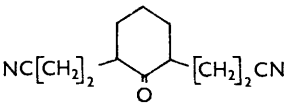
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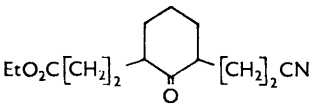
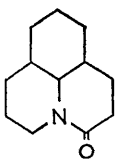

(XII)

Attempts to reduce julolidine methiodide failed, but interesting results obtained in the cyclopentanone series [7] led us to examine the reduction of the keto-ester nitrile (XII), obtained in an overall yield of 60% by reaction of *N*-cyclohex-1-enylpyrrolidine with acrylonitrile and of the product so formed with ethyl acrylate. Hydrogenation of (XII) over Raney nickel gave a mixture containing two major components and shown by infrared spectroscopy to consist mainly of lactams (XIII). Reduction of this mixture with lithium aluminium hydride gave a mixture of hexahydrojulolidines in about 86% yield (based on XII), together with about 2% of an amino-alcohol mixture (XIV). The tertiary-base fraction proved to contain the hexahydrojulolidines (IV), (V), and (VI) in the respective proportions of 60, 2, and 38%. The process of quaternisation with methyl iodide, followed by pyrolysis of the metho-acetate enabled the *c,t*-isomer (VI) to be isolated conveniently, and the method provides a means of preparing this isomer (VI) in reasonable amounts. Cyclisation of the amino-alcohol mixture (XIV) also gave a mixture of the three hexahydrojulolidines.

When this work was already completed the preparation of hexahydrojulolidines by the

[7] K. Schofield and R. J. Wells, in the press.
[8] L. Mandell, J. U. Piper, and K. P. Singh, *J. Org. Chem.*, 1963, **28**, 3440.

hydrogenation of the nitrile-ester (XII) over Raney nickel W-7 was reported.[9] The formation of lactams (XIII) was observed, but reduction of the lactams with lithium aluminium hydride was reported to give the isomers (IV) and (V) in the ratio of about 3 : 2. This result differs markedly from our own findings. The identification by the American workers of their minor product as the *t,t*-isomer (V) appears to depend on the melting point of the derived picrate (186—187°). It should be noticed that the melting points of the picrates of the *c,t*- (VI) and *t,t*-isomers (V) differ only by a few degrees (see Experimental section) and are not alone sufficient for identification. Our own identifications depend on melting points of picrates, infrared spectra, g.l.c., and rates of quaternisation, and comparison of these properties with those of authentic specimens of the hexahydrojulolidines (IV), (V), and (VI) prepared according to Bohlmann and Arndt.[4] Even so, the formation of appreciable



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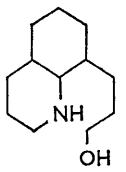

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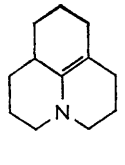


(XV)

quantities of (VI) from (XII) was surprising, and the identification of their products by American authors may be correct and the differences due to the use of differing catalysts.

Under different conditions, involving hydrogenation over platinum in ethanolic hydrochloric acid, followed by lithium aluminium hydride reduction of the product, the keto-ester nitrile (XII) led to a mixture of amines containing (IV) (35%), (V) (25%), (VI) (15%), and (XV) (25%). The use of acetic acid as solvent for the platinum-catalysed hydrogenation of compound (XII) gave only (IV) (50%), (V) (10%), and (VI) (40%).

Experimental

Hydrogenation of Julolidine.—Julolidine (6 g.), methanol (100 ml.), and W-5 Raney nickel (1 teaspoonful) were hydrogenated at 175° and an initial hydrogen pressure of 180 atmospheres, for 16 hr. Worked up by the method of Bohlmann and Arndt,[4] the product gave a mixture of hexahydrojulolidines (4·4 g.; b. p. 90—93°/2·5 mm.) which was analysed by g.l.c. as described below. The results of this and of other experiments are tabulated.

Temp.	Initial pressure (atm.)	Time (hr.)	Scale (g.)	Yield (%)	(IV) (%)	(V) (%)	(VI) (%)
200°	200	10	12	74	60	36	4
200	200	8	9	76	60	36	4
200	200	8	36	75	66	30	4
200[a]	200	16	60	77	50	44	6
175	180	16	6	68	52	43	5

[a] Values in this row are taken from ref. 4.

For separation of the isomers the products (40 g.) from several hydrogenations were used. G.l.c. showed this mixture to contain *c,c*- (60%), *t,t*- (36%), and *c,t*-hexahydrojulolidine (4%). It was dissolved in light petroleum (200 ml.) and added to a column of neutral alumina (Woelm, 1500 g., activity 1). The eluate was collected in 50-ml. fractions and the course of separation followed by g.l.c.

No. of fractions	Eluting solvent	Wt. (g.)	Product
25	Light petroleum	—	—
45	Light petroleum	21·5	*c,c*
27	Light petroleum–1% ether	4·5	*c,c* + *t,t*
23	Light petroleum–2% ether	7·1	*t,t*
20	Light petroleum–10% ether	2·4	*t,t*
25	Light petroleum–50% ether	0·8	*t,t*
26	Ether	1·1	*t,t*
15	Ether	0·7	*t,t* + *c,t*
20	Ether–10% methanol	1·2	*c,t*
	Total recovery	39·3	

[9] L. Mandell, B. A. Hall, and K. P. Singh, *J. Org. Chem.*, 1964, **29**, 3067.

Each pure fraction was converted into its picrate which was recrystallised from ethanol. The free bases were obtained by decomposing the picrates with lithium hydroxide in the usual way. Their characteristics are listed below.

c,c-Hexahydrojulolidine: b. p. 93—95°/2·5 mm., n_D^{20} 1·5142, picrate (yellow prisms from ethanol), m. p. 223—225° (lit.,[4] 225°).

t,t-Hexahydrojulolidine: b. p. 92—95°/2·5 mm., n_D^{20} 1·5050; picrate (yellow prisms from ethanol), m. p. 185—187° (lit.,[4] 186°): methiodide (from ethanol), m. p. 315—317° (decomp.) (Found: C, 48·8; H, 7·6. Calc. for $C_{13}H_{24}IN$: C, 48·6; H, 7·5%); *methopicrate* (yellow needles from ethanol), m. p. 137—137·5° (Found: C, 53·8; H, 6·3; N, 13·25. $C_{19}H_{27}N_4O_7$ requires C, 53·9; H, 6·4; N, 13·25%).

c,t-Hexahydrojulolidine: b. p. 90—92°/2·5 mm., n_D^{20} 1·5124; picrate (yellow needles from ethanol), m. p. 182—183° (lit.,[4] 182°); methiodide (from ethanol), m. p. 321—325° (decomp.) (Found: C, 48·9; H, 7·7%); methopicrate (yellow-orange needles from ethanol), m. p. 158·5—160° (Found: C, 53·8; H, 6·3; N, 13·25%).

Their g.l.c. properties are given below.

2-(2-*Cyanoethyl*)-6-(2-*ethoxycarbonylethyl*)*cyclohexanone*.—This was prepared from cyclohexanone (96 g.) in 65% yield, substantially in the way described by Mandell *et al.*,[8] except that both the first and second stages were done in dioxan. The product was an oil, b. p. 162—164°/0·15 mm., n_D^{18} 1·4738 (Found: C, 66·8; H, 8·3; N, 5·7. Calc. for $C_{14}H_{21}NO_3$: C, 66·9; H, 8·4; N, 5·55%). Hydrolysis with 6N-hydrochloric acid gave cyclohexanone-2,6-dipropionic acid, m. p. 143—144° (lit.,[10] 145°).

Hydrogenation of 2-(2-*Cyanoethyl*)-6-(2-*ethoxycarbonylethyl*)*cyclohexanone*.—(i) The keto-ester nitrile (20 g.), ethanol (100 ml.), and W-5 Raney nickel (1 teaspoonful) were hydrogenated at 60° and 125 atm. Uptake was complete in 20 min. Distillation gave a product (15·4 g.), b. p. 138—140°/2·5 mm., $\nu_{max.}$ 1632s and 1742w cm.$^{-1}$.

(ii) The keto-ester nitrile (20 g.), ethanol (100 ml.), hydrochloric acid (17 ml.), and platinum oxide (0·45 g.) were hydrogenated as above. Uptake of hydrogen was 79% of that expected for saturation, and the product (8·1 g.), b. p. 134—137°/2·5 mm., $\nu_{max.}$ 1634s, 1745w, 3080sh, and 3025sh cm.$^{-1}$, darkened slowly in air.

(iii) The keto-ester nitrile (10 g.), acetic acid (100 ml.), and platinum oxide (0·35 g.) were hydrogenated as above. The product (6·1 g.) was an oil, b. p. 136—139°/2·5 mm., $\nu_{max.}$ 1630s and 1745w cm.$^{-1}$.

Hexahydrojulolidines.—(*a*) The hydrogenation product from (i) above (15·4 g.) in ether (100 ml.) was added during 1 hr. to a stirred solution of lithium aluminium hydride (2·7 g.) in ether (300 ml.). After addition, stirring was continued for 1 hr. and the solution was decomposed by the addition of ethyl acetate and sufficient water to coagulate the inorganic precipitate. The ethereal layer was decanted, the residue was extracted with ether (3 × 100 ml.), and the combined ether solutions were dried (K_2CO_3). Distillation gave a mixture of hexahydrojulolidines (12·2 g.), b. p. 101—104°/3 mm., and decahydro-8-(3-hydroxypropyl)quinoline (0·2 g.), b. p. 160—172°/3 mm. G.l.c. (see below) showed the tertiary amine mixture to contain *c,c*- (60%), *t,t*- (2%), and *c,t*-hexahydrojulolidine (38%).

To the mixed tertiary bases (12 g.) in ether (150 ml.) was added methyl iodide (10 ml.). The progress of quaternisation (which was very rapid) was followed by g.l.c. When the ether solution contained only 5% of *c,t*- and 1·5% of *t,t*-hexahydrojulolidine the precipitated methiodide was collected and recrystallised from ethanol–ethyl acetate. *c,t*-Hexahydrojulolidine methiodide (7 g.) separated as prisms, m. p. 318—320° (decomp.). Pyrolysis of the metho-acetate (prepared by shaking the methiodide with silver acetate in water, filtering, and concentrating the filtrate *in vacuo*) at 300°/20 mm. for 1 hr. gave *c,t*-hexahydrojulolidine, b. p. 97—100°/2·5 mm. Gas chromatography revealed the presence of *c,c*-(0·5%) and *t,t*-hexahydrojulolidine (0·5%). The picrate formed yellow needles, m. p. 181—182°, from ethanol.

(*b*) Similar reduction with lithium aluminium hydride of the hydrogenation product from (ii) above gave a mixture of tertiary amines, b. p. 101—108°/3 mm., and no amino-alcohol. G.l.c. showed the mixture to consist of *c,c*- (35%), *t,t*- (25%), and *c,t*-hexahydrojulolidine (15%), and tetrahydrojulolidine (XV) (25%). The solution of the amines in ether–ethanol (9 : 1) was treated with perchloric acid and the product was recrystallised four times from ethanol. A low yield of $\Delta^{4(13)}$-tetrahydrojulolidinium perchlorate, m. p. 270—274° (decomp.) [lit.,[4] 277° (decomp.)], resulted.

[10] N. J. Leonard and W. J. Middleton, *J. Amer. Chem. Soc.*, 1952, **74**, 5114.

(*c*) Reduction of the product from hydrogenation (iii) with lithium aluminium hydride gave a mixture of hexahydrojulolidines (b. p. 102—105°/3 mm.) containing the *c,c*- (50%), *t,t*- (10%), and *c,t*-isomers (40%).

Cyclisation of Decahydro-8-(3-*Hydroxypropyl*)*quinoline*.—The amino-alcohol (0·15 g.), xylene (5 ml.), and a trace of iodine were heated under reflux for 5 hr. G.l.c. showed the product to contain *c,c*- (30%), *t,t*- (10%), and *c,t*-hexahydrojulolidine (60%).

G.l.c. of Hexahydrojulolidines.—Chromatography was carried out in a Pye Argon Chromatograph using a column (44 × 0·25 in.) of 0·5% of silicone grease on 80-mesh glass beads (29 g. of packing) at 100°. With a flow rate of 42 ml./min. the retention times for *c,c*-, *t,t*-, and *c,t*-hexahydrojulolidine were 13·0, 10·5, and 16·7 min., respectively. The specimens used for kinetic runs were 100% pure. Under the same conditions the retention time for tetrahydrojulolidine (XV) was 14·7 min.

Kinetic Measurements.—The free base (methylpiperidine, pyridine, or quinolizidine; 20—40 mg.) was dissolved in acetonitrile or methanol and made up to 10·0 ml. in the conductivity cell. This was allowed to attain the temperature of the thermostat bath which was maintained to ±0·1°. Methyl iodide in excess (1·00 ml.) was added, the cell vigorously shaken, and the rate of quaternisation then followed using a resistance bridge and an oscilloscope.

In the case of the methylquinolizidines, which were in the form of the perchlorates, the salt was dissolved in about 0·5 ml. of acetonitrile, converted into the free base by addition of the exact amount of N-NaOH solution with a micro-syringe, and the mixture then taken up in acetonitrile and measured as above. The picrate salts of the hexahydrojulolidines were measured similarly. Calculations of pseudo-first-order rate constants were made as by Shamma and Moss.[3] These may be converted into second-order rate constants by dividing by 1·46 mole $l.^{-1}$. For pyridine and quinolizidine, measurements were made both on the free base and on perchlorate and picrate salts. The volumetric additions were frequently checked by weighing the cell empty, after addition of solvent together with the base itself, and finally after addition of methyl iodide when the reaction was complete. The results obtained by the different methods agreed to within experimental error (±3%).

Acetonitrile (minimum assay 98%) was dried over a molecular sieve and twice distilled, the second time through a fractionating column. Methyl iodide was g.l.c. pure and stored over mercury. Methanol was AnalaR grade.

Proton Magnetic Resonance Spectra.—These were measured in deuterium oxide, with HDO (τ taken as 5·2) as internal standard, on a Perkin-Elmer 40-Mc./sec. permanent-magnet spectrometer with sample spinning. *t,t*-Hexahydrojulolidine methiodide showed peaks at τ 6·60 (ring CH adjacent to N), 6·90 (N–Me), and 8·25 (remaining CH). The *c,t*-hexahydrojulolidine methiodide showed the corresponding bands at τ 6·50, 6·73, and 8·25, respectively. As expected the N^+–CH_3 peak for the *trans*-ring junction is at appreciably higher field than that for the *cis*-fused isomer.[1]

Discussion of Kinetic Results

Measured rate constants for acetonitrile runs are recorded in Table 1 and Arrhenius parameters in Table 2. Rate constants recorded from methanol solution are presented in Table 3. We have calculated the energy of activation for the formation of pyridine methiodide as 14·9 kcal./mole. The rate constant for this reaction in benzonitrile at 25°, as obtained by Hinshelwood and his co-workers,[11] is very similar to our value in acetonitrile at 24·5°. The only other direct comparison between our results and those of other workers concerns the rate constant for the reaction of *t,t*-hexahydrojulolidine with methyliodide in methanol solution. The value obtained by Saeki [6] exceeds that which we report by a factor of about 5 (making an approximate allowance for temperature difference). We can offer no explanation for this discrepancy.

The rate constants allow the following deductions regarding the conformational equilibria.

(*a*) Quinolizidine itself, and the *t*-1-, *c*-2-, and *t*-3-methyl derivatives (cf. XVI) all show essentially the same quaternisation rates as those for the *t,t*-hexahydrojulolidine. The latter is fixed in the *trans*-ring form (XVII), both as free base and as methiodide. The

[11] N. J. T. Pickles and C. N. Hinshelwood, *J.*, 1936, 1353; R. A. Fairclough and C. N. Hinshelwood *J.*, 1937, 1573.

TABLE 1

Pseudo-first-order rate constants (sec.$^{-1}$ × 10^4) for methiodide formation in acetonitrile solution

Compound	Rate const.	Temp.	Rate const.	Temp.	Rate const.	Temp.	Rate const.	Temp.
Pyridine	4·72 (9)	24·5°	8·01 (1)	30°	11·2 (2)	35°	16·0 (1)	40°
N-Methylpiperidine	54·1 (1)	−22	66·8 (1)	−20	148 (2)	−11·5	318 (2)	0
Quinolizidine	8·38 (1)	0	18·6 (2)	9	64·2 (8)	24·5	103 (3)	32·5
c-1-CH_3	9·60 (1)	0	26·6 (2)	13	61·1 (2)	24·5	110 (1)	35
t-1-CH_3	29·0 (1)	15·5	64·2 (3)	24·5	117 (1)	34·5		
c-2-CH_3	22·5 (2)	12	63·1 (3)	24·5	98·1 (3)	33		
t-2-CH_3	36·9 (2)	8·5	115 (3)	24·5	212 (2)	32·75		
c-3-CH_3	9·33 (2)	0	35·0 (2)	16·5	60·4 (7)	24·5	99·2 (3)	34
t-3-CH_3	13·9 (2)	7·5	55·1 (3)	24·5	118 (2)	32·5		
c-4-CH_3	7·48 (2)	17·5	12·3 (5)	24·5	26·2 (2)	35		
t-4-CH_3	4·35 (3)	0	31·3 (2)	24·5	62·6 (1)	34		
9-CH_3	26·5 (1)	24·5						
t,t-Hexahydrojulolidine	10·9 (1)	0	37·1 (1)	16·5	63·6 (3)	24·5	83·3 (2)	32·0
c,c-Hexahydrojulolidine	0·024 (1)	28·2						
c,t-Hexahydrojulolidine	58·9 (1)	−23	329 (1)	−8	663 (2)	0	6151 *	24·5

Numbers in parentheses indicate the number of measurements from which the rate constant was determined.

* This value was obtained by a statistical extrapolation of the values measured at lower temperatures.

TABLE 2

Arrhenius parameters for methiodide formation in acetonitrile solution

Compound	E (kcal. mole^{-1})	$\Delta H^{\ddagger}$ (kcal. mole^{-1})	$\log_{10} A$ (sec. units)	$\Delta S^{\ddagger}$ (cal. mole^{-1} deg.$^{-1}$)	$\Delta G^{\ddagger}$ (kcal. mole^{-1})	log k_2 × 10^4 (24·5°)
Pyridine	14·9	14·3	7·6	−26·4	22·1	3·34
Quinolizidine	12·8	12·2	7·2	−28·0	20·6	43·1
N-Methylpiperidine	10·7	10·1	7·1	−29·0	18·7	1100
t-1-CH_3	12·9	12·3	7·2	−28·1	20·7	41·4
c-2-CH_3	12·1	11·5	6·6	−30·8	20·7	40·6
t-3-CH_3	14·3	13·7	8·3	−23·4	20·7	40·9
c-4-CH_3	12·8	12·2	6·5	−32·3	21·8	8·43
t,t-Hexahydrojulolidine	10·5	9·9	5·5	−34·2	20·7	40·9
c,t-Hexahydrojulolidine	14·3	13·8	10·3	−13·85	17·9	4230

Values of E and $\Delta H^{\ddagger}$ are generally accurate to ±300 cal., of log A to ±0·1.

The second-order rate constants in this Table are calculated from E and log A and are not the exact values obtained directly from pseudo-first-order rate constants in Table 1.

Arrhenius parameters cannot be calculated for the *c*-1-CH_3-, *t*-2-CH_3-, *c*-3-CH_3-, and *t*-4-CH_3-compounds, all of which form methiodides either entirely in the *cis*-configuration or as mixtures of *cis* and *trans*, because such calculations require a knowledge of the temperature-variation of the *cis–trans*-conformational equilibria of the free bases.

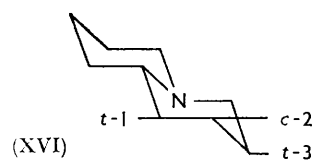
TABLE 3

Pseudo-first-order rate constants (sec.$^{-1}$ × 10^4) for methiodide formation in methanol at 24·5°

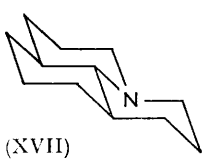
Compound ...	*c*-1-CH_3	*t*-2-CH_3	*c*-3-CH_3	*t,t*-Hexahydrojulolidine	*c,t*-Hexahydrojulolidine
Rate const....	1·86 (2)	2·07 (3)	3·13 (2)	1·64 (3)	40·8 (3)

Numbers in parentheses indicate the number of measurements from which the rate constant was determined.

former compounds yield *trans*-fused methiodides,[1] and the present results confirm the conclusion that they exist as free bases predominantly with *trans*-fused rings. There is somewhat more variation in the $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values (Table 2), but the variations of the two parameters are largely self-compensating.



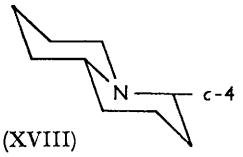
(XVI)



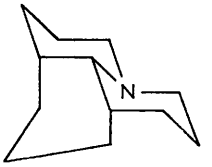
(XVII)

(*b*) *c*-4-Methylquinolizidine also both exists itself as, and forms its methiodide *via*, the *trans*-fused form (XVIII). The somewhat slower rate is explained by a moderate amount of F-strain. *c*,*c*-Hexahydrojulolidine (XIX) is fixed with a *trans*-junction of the hetero-rings, its very slow rate is explained by severe F-strain in the transition state for methiodide formation.

(*c*) *c*-1-Methyl- and *c*-3-methyl-quinolizidine were earlier concluded to exist predominantly *trans*-fused (XX) but to form their methiodides *via* a small proportion of the *cis*-fused form (XXI). *c*,*t*-Hexahydrojulolidine (VI) is constrained to exist with a fixed *cis*-

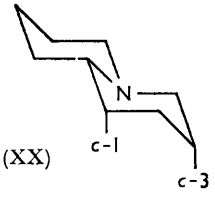


(XVIII)

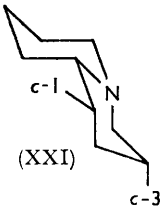


(XIX)

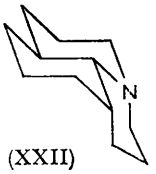
fusion of the hetero-rings, and the rate of its methiodide formation can reasonably be taken as a model for the rate at which the *cis*-conformer (XXI) forms its methiodides. Hence,



(XX)

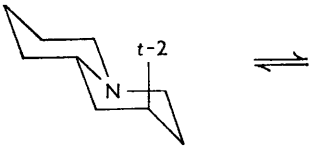


(XXI)



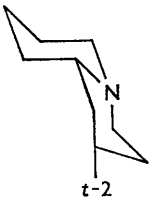
(XXII)

by simple proportion, we calculate that *c*-1- and *c*-3-methylquinolizidine contain about 1% of the *cis*-ring-fused conformer at room temperature. The present results are not considered accurate enough to attempt to find the temperature variation of this equilibrium.



(XXIII)

$\rightleftharpoons$



(XXIV)

(*d*) *t*-2-Methylquinolizidine forms a mixture of methiodides, derived from its *trans*- (XXIII) and *cis*-fused (XXIV) form. If [XXIV]/[XXIII] = K and k_t and k_c refer to rate constants for the *trans*- and *cis*-forms, then, using the hexahydrojulolidines as models, we obtain from the values at 24·5°,

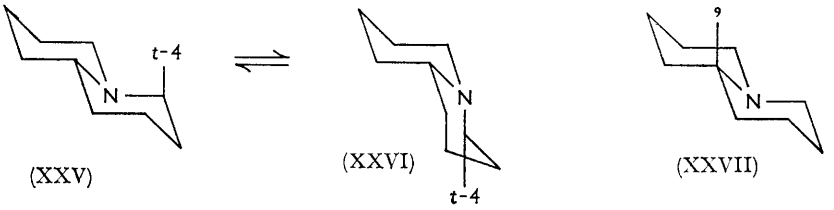
$$\text{rate of methiodide formation} = (k_t + Kk_c)/(K + 1)$$

$$\textit{i.e.},\ 115 = (64 + 6151K)/K + 1, \text{ whence } K = 0{\cdot}0087.$$

Further, the methiodides should be formed in a ratio of 1 of *cis* : 1,2 of *trans*; intensity measurements on the proton resonance spectrum of the mixed methiodides produced indicated that the ratio was indeed $1{\cdot}2 \pm 0{\cdot}2$.

(*e*) *t*-4-Methylquinolizidine (XXV $\rightleftharpoons$ XXVI) was earlier considered to exist principally in the *cis*-ring-fused conformation (XXVI). The kinetic results indicate that this conclusion was erroneous. The equatorial methyl group in (XXVI) will show a small steric effect, and we may estimate that (XXVI) will be slower than (XXII) by a factor of about 5, this being the factor by which (XVIII) is slower than (XVII). Now nuclear

magnetic resonance experiments confirm that the *cis*- and *trans*-methiodides are formed in approximately equal amounts in acetonitrile solution.



Hence, if $k_t' \times 10^4$ is the first-order rate constant (in sec.$^{-1}$) for formation of the *trans*-methiodide, and x is the percentage of *cis*-form in the equilibrium mixture of the free base at 24·5°, then:

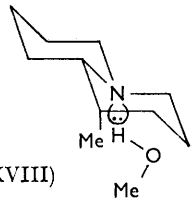
$$k_t'[(1 - x)/100] + 6151x/500 = 31 \quad (1)$$

$$k_t[(1 - x)/100] = 6151x/500 \quad (2)$$

whence $x = 1{\cdot}3\%$ and $k_t = 16$

Hence the rate of formation of the *trans*-methiodide from (XXV) is 16×10^{-4} sec.$^{-1}$. The lower value from that of quinolizidine itself is most easily explained by B-strain. This explanation is supported by the similar slow rate shown by 9-methylquinolizidine (XXVII) (Table 1).

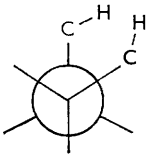
(*f*) Using the two hexahydrojulolidines as models, some of the compounds were examined in methanol solution. Similar calculations indicate that the percentages of the *cis*-fused conformer are 4, 7, and 1% for the *c*-1-, *c*-3-, and *t*-2-methylquinolizidines, respectively. We believe the increase of *cis* over the values for acetonitrile solution may be significant for the first two compounds, and could be a result of steric interaction in the *trans*-fused conformer of the hydrogen-bonded lone pair with the axial methyl-group (cf. XXVIII). This supports other work indicating that a hydrogen-bonded lone pair has greater steric requirements than the unsolvated lone-pair.[12] For the *t*-2-derivative, no such interaction occurs, and the proportion of the *cis*-form does not change appreciably.



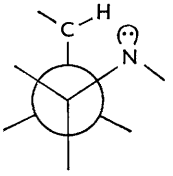
(XXVIII)

General Discussion

The results are conveniently described in terms of *gauche*-butane (XXIX) and *gauche*-n-propylamine (XXX) interactions. The numbers of such interactions, neglecting those between ring carbon atoms in the same ring, are shown in Table 4. These results indicate



(XXIX)



(XXX)

that (i) there is little difference between a *gauche*-butane and a *gauche*-n-propylamine interaction for acetonitrile solutions, but that, for methanol solutions, the *gauche*-n-propylamine interaction is appreciably greater [see also (*f*) above] and (ii) that some other factor is stabilising the *trans*-fused quinolizidine ring.

For a *gauche*-butane interaction at 25°, ΔG values of *ca.* 0·8 kcal./mole have been found experimentally in the methyl- and dimethyl-cyclohexane series.[13] For quinolizidine itself

[12] K. Brown, A. R. Katritzky, and A. J. Waring, *J.*, to be published.

[13] See discussion in E. L. Eliel, " Stereochemistry of Carbon Compounds," McGraw-Hill, New York, 1962, p. 208 ff.

TABLE 4

gauche-Butane (gb) and *gauche*-n-propylamine (ga) interactions

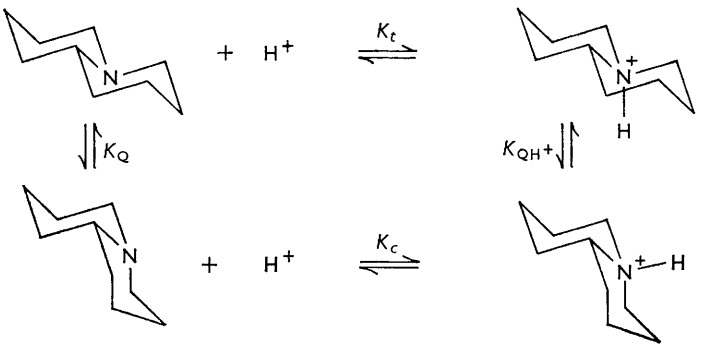
Compound	*trans*-Form	*cis*-Form	Difference	ΔG CH_3CN	ΔG MeOH
c-1-Methylquinolizidine.....	2gb + ga	4gb	2gb-ga	2·71	1·87
t-2-Methylquinolizidine.....	2gb	3gb	gb	2·80	2·80
c-3-Methylquinolizidine	gb + ga	3gb	2gb-ga	2·71	1·53
t-4-Methylquinolizidine.....	3gb	4gb	gb	2·81	—

ΔG values refer to 25° and were calculated from equilibrium constants.

there is a difference of three *gauche*-butane interactions between the *cis*- and *trans*-ring-fused conformers, *i.e.*, two more than for the compounds of Table 4. Hence, ΔG at 25° for quinolizidine should be *ca.* 4·4 kcal./mole, corresponding to $K = 1600$.

For the decalins, ΔH has been estimated as 2·7 kcal./mole [14] or as 3·1 kcal./mole,[15] and ΔS measured as −0·55 cal./deg.[14] These figures yield $\Delta G_{25°}$ of 2·55—2·95 kcal./mole. However, for comparison with quinolizidine, it must be taken into account that *cis*-decalin has a symmetry number of 2, and $\boldsymbol{R} \ln 2 = 0{\cdot}42$ kcal./mole must be added to these figures to give 3·0—3·4 kcal./mole for a hypothetical equilibrium involving a single *cis*-decalin conformer.

It appeared possible that the extra stabilisation of *trans*-ring-fusion in the quinolizidine series might be a result of the smaller size of the lone pair on the nitrogen atom compared to the corresponding angular hydrogen atom in *trans*-decalin. We have therefore measured the pK_a value of quinolizidine, *t,t*-hexahydrojulolidine, and *c,t*-hexahydrojulolidine, by potentiometric titration in aqueous solution, and found 10·19 ± 0·07, 10·10 ± 0·05, and 11·12 ± 0·06, respectively. The protonation of quinolizidine involves the equilibria shown in Scheme 1. Although K_t and K_c cannot be measured directly, the pK_a values of *t,t*-, and *t,c*-hexahydrojulolidine, respectively, afford approximations of them. Hence, knowing



Scheme 1

K_Q to be 1600, we can estimate $K_{QH}+$ to be 160 at 25°; *i.e.*, ΔG for protonated quinolizidine to be 3·0 kcal. This value is in good agreement with that for *cis*/*trans*-decalin quoted above.

The agreement between protonated quinolizidine and decalin is reassuring. The simplest explanation for the greater stabilisation of the *trans*-isomer for the quinolizidine free base appears to be that there is less 1,3-diaxial repulsion (or greater attraction) between the lone pair and hydrogen than between two axial hydrogen atoms. However, the magnitude of the effect is surprising, and further work is needed to define the role of (*a*) changing bond angles and/or lengths on protonation, and (*b*) solvation in the quinolizidinium ion.

[14] N. L. Allinger and J. L. Coke, *J. Amer. Chem. Soc.*, 1959, **81**, 4080.
[15] D. M. Speros and F. D. Rossini, *J. Phys. Chem.*, 1960, **64**, 1723.

In our previous work we had concluded that *t*-4-methylquinolizidine existed predominantly in the *cis*-ring-fused conformation because of the absence of infrared absorption peaks near 2800 cm.$^{-1}$. Our present results show that this conclusion was incorrect, and therefore that the absence of such peaks is not sufficient evidence to exclude the predominance of the quinolizidine in a *trans*-ring-fused form. We are at present investigating the limitations of this infrared criterion.[16]

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(K. S., R. J. W.) The Washington Singer Laboratories, The University, Exeter.
(C. D. J., R. A. Y. J., A. R. K., C. R. P.) The School of Chemical Sciences,
University of East Anglia, Norwich. [*Received, April 23rd,* 1965.]

[16] Cf. M. Wiewiorowski and J. Skolik, *Bull. Acad. polon. Sci., Ser. Sci. chim.*, 1962, **10**, 1.