651. *Nuclear Magnetic Resonance. Part I. The Structure of Indolizinium Salts.*

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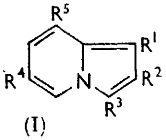
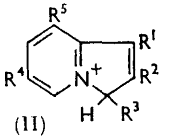
The structures of indolizinium perchlorate and its 2-methyl, 1,2-, 2,6-, and 2,8-dimethyl, and 1,2,3-trimethyl derivatives have been determined by a proton magnetic resonance study of the salts in trifluoroacetic acid. Protonation of indolizines occurs preferentially at position 3.

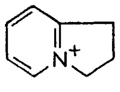
INDOLIZINE (Ia) and its derivatives show well-developed aromatic character, most clearly in that positions 3 and 1 show great reactivity[1] towards electrophilic reagents. Monosubstitution at position 3 has been established for the alkylation, acetylation, benzoylation, formylation, carboxylation, and nitrosation of 2-methylindolizine (Ib). Nitration is exceptional in giving mainly 2-methyl-1-nitroindolizine (62%), with a small amount of the 3-isomer (1·5%). The position of substitution of other alkyl- and aryl-indolizines, and of indolizine itself, is less well-established, and in most cases must be assumed by analogy with the reactions of 2-methylindolizine. Further substitution of indolizines gives in all cases the 1,3-disubstitution product.



(I)



(II) ClO_4^-



(III) Br^-

	R¹	R²	R³	R⁴	R⁵
a	H	H	H	H	H
b	H	Me	H	H	H
c	Me	Me	H	H	H

	R¹	R²	R³	R⁴	R⁵
d	Me	Me	Me	H	H
e	H	Me	H	Me	H
f	H	Me	H	H	Me

The experimental finding of a high reactivity of positions 1 and 3 towards electrophilic reagents agrees with the results of theoretical considerations. A calculation[2] of the π-electron densities of indolizine by the molecular-orbital method gives the positional order of decreasing charge density as $4 \gg 3 > 1 \gg 5 > 2 > 7 > 6 > 8$. Since attack by an electrophile at position 4 cannot result in substitution this order implies that electrophilic substitution should occur first at position 3 or, should this be occupied, at position 1. This conclusion was also reached on the basis of a calculation[3] of the frontier electron densities of indolizine which decrease in the order $3 > 1 \gg 5 > 8 > 7 > 6 > 8a > 4 > 2$. In contrast, the results of a recent calculation[4] of the atom localisation energies of indolizine by the L.C.A.O. molecular-orbital procedure, while confirming the superior reactivity of positions 3 and 1, reverses the order of reactivity of these two positions. It has also been

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[1] See Mosby, " The Chemistry of Heterocyclic Compounds," Interscience Publ. Inc., New York, 1961, Vol. XV (Part I), p. 239.

[2] Coulson and Longuet-Higgins, *Trans. Faraday Soc.*, 1947, **43**, 87.

[3] Fukui, Yonezawa, Nagata, and Shingu, *J. Chem. Phys.*, 1954, **22**, 1433.

[4] Galbraith, Small, Barnes, and Boekelheide, *J. Amer. Chem. Soc.*, 1961, **83**, 453.

inferred [5,6] that electrophilic substitution of indolizine will occur at position 1 or 3 or both, since an intact pyridinium ring is present only in the transition states for substitution at these positions.

Indolizines, though weakly basic (pK_b 8—11),[7] form stable crystalline salts with strong acids. The theoretical considerations previously summarised suggest that protonation, regarded as an electrophilic process, occurs on nitrogen, C-1, or C-3. Rossiter and Saxton [8] consider that the indolizinium cations result from protonation at position 1 or 3, since such structures contain a true pyridine ring. Lowe and King [9] showed that catalytic hydrogenation of indolizine (Ia) dissolved in hydrobromic acid occurs in the five-membered ring, giving the bromide (III). They considered this as evidence that indolizine is protonated in the five-membered ring, at C-1 or C-3. We now describe proton magnetic resonance studies of indolizinium perchlorates which demonstrate that protonation of indolizines occurs preferentially at C-3.

EXPERIMENTAL

M. p.s were determined on a Kofler-type heating stage. Perchloric acid refers to 60% w/w " AnalaR " perchloric acid. Ethanol was dried over sodium ethoxide and diethyl phthalate, then fractionally distilled. Methanol, dried over magnesium methoxide, was fractionally distilled.

Preparation of Indolizines.—Indolizine (Ia) was prepared by the method of Boekelheide and Windgassen.[10] 2-Methylindolizine (Ib) and 1,2-dimethylindolizine (Ic) were prepared as described by Holland and Nayler.[11]

1,2,3-*Trimethylindolizine* (Id). A solution of lithium aluminium hydride (2 g.) in ether (200 ml.) was added during 20 min. to one of 3-formyl-1,2-dimethylindolizine (2 g.), also in ether (200 ml.). The mixture was boiled for 2·5 hr., then left at room temperature for 2 days before being hydrolysed with a slight excess of dilute sulphuric acid. The ether phase was washed free from acid, dried (K_2CO_3), and evaporated. Distillation of the residue gave 1,2,3-trimethylindolizine (1·04 g., 56%), b. p. 142°/10 mm. (Holland and Nayler [11] give b. p. 135—137°/13 mm.; Rossiter and Saxton [8] give b. p. 85—87°/0·095 mm.).

2,6-*Dimethylindolizine* (Ie). Bromoacetone (16·8 ml., 0·2 mole) was added slowly to 2,5-dimethylpyridine (22·6 ml., 0·2 mole) in acetone (20 ml.). When the initial vigour of the reaction had abated the turbid mixture was boiled for 20 min., while crystals began to be deposited. Filtration of the cold mixture gave 1-*acetonyl*-2,5-*dimethylpyridinium bromide* (37·7 g., 77%) which, after recrystallation from ethanol, formed prisms, m. p. 196—198·5° (Found: N, 5·4. $C_{10}H_{14}BrNO$ requires N, 5·7%).

Sodium hydrogen carbonate (60 g.) was added portionwise to the foregoing bromide (35 g.) in water (150 ml.). When effervescense had largely ceased the mixture was steam-distilled. The oily distillate, dissolved in ether, was washed with 0·2N-hydrochloric acid and water. The dried (K_2CO_3) solution was evaporated, and the residual oil was distilled at 10 mm., to give 2,6-*dimethylindolizine* (14·7 g., 70%) which crystallised as waxy plates, m. p. 72·5—74·5° (Found: C, 82·9; H, 7·2; N, 10·0. $C_{10}H_{11}N$ requires C, 82·7; H, 7·6; N, 9·7%).

2,8-*Dimethylindolizine* (If). The preparation was identical with that of 2,6-dimethylindolizine, with 2,3- in place of 2,5-dimethylpyridine. Quaternisation of 2,3-dimethylpyridine (17·3 ml., 0·15 mole) in acetone (25 ml.) with bromoacetone (12·6 ml., 0·15 mole) gave 1-*acetonyl*-2,3-*dimethylpyridinium bromide* (25 g., 65%), colourless needles (from ethanol), decomp. >232° (Found: N, 5·6%). Cyclisation of the bromide (24·4 g.) in water (200 ml.) with sodium hydrogen carbonate (20 g.) afforded 2,8-*dimethylindolizine* (4·32 g., 30%), b. p. 121°/20 mm. (Found: N, 9·6%). 2,6- and 2,8-Dimethylindolizine become brown rapidly in air.

Preparation of Indolizinium Perchlorates.—Perchloric acid (1·5 ml., 37% excess) was added to a solution of the indolizine (1 mmole) in ethanol (10—15 ml.) at room temperature. The

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[5] Dewar, " The Electronic Theory of Organic Chemistry," Oxford Univ. Press, London, 1949, pp. 161, 191.

[6] Borrows and Holland, *Chem. Rev.*, 1948, **42**, 611.

[7] Miller and Brown, American Chemical Society, 130th National Meeting, 1956; Abstract, p. 49.

[8] Rossiter and Saxton, *J.*, 1953, 3654.

[9] Lowe and King, *J. Org. Chem.*, 1959, **24**, 1200.

[10] Boekelheide and Windgassen, *J. Amer. Chem. Soc.*, 1959, **81**, 1459.

[11] Holland and Nayler, *J.*, 1955, 1657.

perchlorate, which crystallised at once, was filtered off, washed with a small volume of ethanol followed by dry ether, and dried at reduced pressure over phosphoric anhydride. The purity was checked by recrystallisation. In all cases the m. p. remained unaltered. The following salts, all forming colourless needles, were prepared by this procedure: 2-methylindolizinium perchlorate (IIb) (96%), m. p. 92·5—94·5° (lit.,[12] 92—93·5°); 1,2,3-trimethylindolizinium perchlorate (IId) (98%), m. p. 127—130·5° (lit.,[8] 126—128°); 1,2- (IIc) (98%), m. p. 131—133° (lit.,[11] 128—129°), 2,6-*dimethylindolizinium perchlorate* (IIe) (88%), m. p. 145° (Found: N, 5·7. $C_{10}H_{12}ClNO_4$ requires N, 5·7%), and 2,8-*dimethylindolizinium perchlorate* (IIf) (98%), m. p. 166·5—168° (Found: N, 5·8%), all stable for several months if stored in a desiccator.

Indolizinium perchlorate (IIa), colourless needles, m. p. 183—185° (decomp.) (Found: N, 5·8. $C_8H_8ClNO_4$ requires N, 6·4%), is best prepared by addition of perchloric acid (1·2 ml., 10% excess) to indolizine (1 mmole) in methanol (20 ml.), and recrystallised from methanol (charcoal). It is unstable and begins to decompose 1—2 days after preparation.

Proton Magnetic Resonance Spectra.—The indolizinium perchlorates were examined in trifluoroacetic acid (~10% w/v solutions) at about 30°. The spectra were measured with a Varian A-60 spectrometer operating at 60 megacycles per sec., at a sweep rate of 1 cycle per sec. per sec. The intensities of the signals were measured by the built-in integrator. Tetramethylsilane was used as the internal reference. Chemical shifts are given on the τ scale, the absolute values being accurate to $\pm 0{\cdot}015$ p.p.m. on the precalibrated 500 c./sec. scale. *J* values were measured on the 500 c./sec. scale and are accurate to $\pm 0{\cdot}3$ c./sec. Signal positions quoted in c./sec. are downfield relative to the tetramethylsilane line. The values were independent of concentration in the range 5—15% (w/v).

RESULTS AND DISCUSSION

None of the spectra of the indolizinium perchlorates (II) shows a broad band or triplet which would arise from a proton bonded to nitrogen. Protonation at carbon must therefore occur with the formation of a methylene or substituted methylene group. The site of protonation was determined by studying the effect of substitution in the five-membered ring on the occurrence of signals and their multiplicity due to spin–spin coupling.

We compare first the spectra of indolizinium perchlorate (IIa), 2-methylindolizinium perchlorate (IIb), 1,2-dimethylindolizinium perchlorate (IIc), and 1,2,3-trimethylindolizinium perchlorate (IId) (Fig. a—d). Substitution in either ring by methyl groups in most cases increases the shielding of the ring protons by a small amount (0—0·3 p.p.m.). The spectrum of the parent salt (IIa) shows three features: (*a*) A single peak occurs at τ 4·45. This is assigned to the protons of a methylene group on the basis of its spectral position. (*b*) Two doublets with equally spaced components occur at τ 2·49 and 2·81 ($J = 6$ c./sec.) and clearly arise from an AB system of two protons. (*c*) The remaining signals occur at low-field in three groups comprising a doublet centred at τ 1·02 ($J = 6{\cdot}5$ c./sec.), a triplet at τ 1·53 ($J \sim 7$ c./sec.), a complex signal consisting of a triplet at τ 2·16 ($J \sim 7$ c./sec.), and a doublet at τ 1·96 ($J = 7{\cdot}5$ c./sec.). Integration of the spectrum shows unequivocally that the single peak is equivalent to two protons, the AB quadruplet to two protons, and the low-field signals together to four protons.

Two features of the spectrum of the salt (IIa) are also found in the spectra of 2-methyl- (IIb) and 1,2-dimethyl-indolizinium perchlorate (IIc). (i) The spectra of (IIb and c) show single peaks at τ 4·60 and 4·68, respectively, corresponding to the signal at τ 4·45 assigned to the methylene group of indolizinium perchlorate. (ii) They also show three groups of low-field signals, identical in pattern with those in the spectrum of indolizinium perchlorate. The integral curves of the spectra of (IIb and c) confirm the view that in each case the single peak corresponds to two protons and the low-field groups together to four protons, as in the spectrum of indolizinium perchlorate. The spectrum of 1,2,3-trimethylindolizinium perchlorate (IId) shows one feature common to the spectra of (IIa—c), namely, the three groups of low-field signals. These also are found from the integral curve to correspond to four protons. The three low-field groups of signals of the four

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[12] Borrows, Holland, and Kenyon, *J.*, 1946, 1069.

salts (IIa—d) all occur in the same spectral region and, in each spectrum, are distinctly separated from all other peaks.

The pattern of the low-field group of signals is thus not altered by the progressive introduction of methyl groups into positions 2, 1, and 3. A small diamagnetic displacement only is observed. Therefore, for all four salts, the four protons responsible for the low-field signals must be those at positions 5, 6, 7, and 8. These salts must consequently have resulted from protonation of the corresponding indolizines in the five-membered ring. In the case of 1,2-dimethylindolizinium perchlorate (IIc), in which positions 1 and 2 are substituted, a methylene group can develop on protonation only at position 3. Also, since the signals from the methylene protons of (Ia and b) occur in the same narrow spectral range (τ 4·45—4·68) as that from the methylene protons of 1,2-dimethylindolizinium perchlorate, we conclude that indolizinium perchlorate and 2-methylindolizinium perchlorate are also protonated at position 3. The signal of a methylene group resulting from protonation at position 1 would intuitively be expected to show a substantial upfield shift relative to the signal from a 3-methylene group, since the latter group is directly attached to the positively charged nitrogen atom.* The chemical shifts of the methylene protons of compounds (IIa—d) are consistent with direct linking of the methylene group to a positively charged nitrogen atom. The progressive upfield shift of the methylene signal in this series is the expected result of the introduction of the electron-releasing methyl groups.

The interpretation of the remaining features of the spectra of perchlorates (IIa—c) agrees with the foregoing. The AB quadruplet in the spectrum of (IIa) arises from the spin–spin coupled pair H-1 and H-2. Although individual assignments cannot be made with certainty on the basis of the available results, the high-field components of the quadruplet are tentatively assigned to H-1 on the basis of a comparison with the H-1 signals of the salts (IIb, e, and f). The single peak at τ 3·17 in the spectrum of (IIb) arises from the isolated 1-proton. The observed slight (~1 c./sec.) splitting of the 2-methyl signal is attributed to weak coupling with H-1 through four bonds.

We next consider again the spectrum of 1,2,3-trimethylindolizinium perchlorate (IId). An evenly spaced quadruplet occurs at τ 4·71 (J = 7 c./sec.) in place of the methylene singlets in the spectra of compounds (IIa—c) and is shown from the integral curve to correspond to one proton. The multiplicity arises from the spin–spin coupling of this proton with those of a methyl group linked to the same carbon atom. This is confirmed by the presence of a doublet centred at τ 8·19, showing the same splitting (J = 7 c./sec.) and equivalent to three protons. The multiplicity of the single proton signal is independent evidence that protonation of 1,2,3-trimethylindolizine occurs in the five-membered ring. It strengthens also the conclusion that protonation occurs in the five-membered ring of all four salts (Ia—d).

From the occurrence of the quartet in the same spectral region as the methylene signals of (IIa—c) it is concluded that 1,2,3-trimethylindolizine also is protonated at position 3. The 1- and 2-methyl protons of salt (IId) have identical chemical shifts, giving together a single sharp signal at τ 7·73, and the doublet centred at τ 8·19 arises from the 3-methyl group.

We consider finally the three low-field groups of signals in the spectra of salts (IIa—d). Since the patterns are identical in all four cases we shall examine the representative spectrum of indolizinium perchlorate only. Recent work [13] has shown that the order of increased shielding of the pyridinium ion is H-2 < H-4 < H-3. By analogy, we assign the low-field doublet centred at τ 1·02 in the spectrum of indolizinium perchlorate to H-5, the low-field triplet centred at τ 1·53 to H-7, and the complex signal (quadruplet) to H-6 + H-8. The ratio (1 : 1 : 2) of the integrated intensities of these three groups of signals

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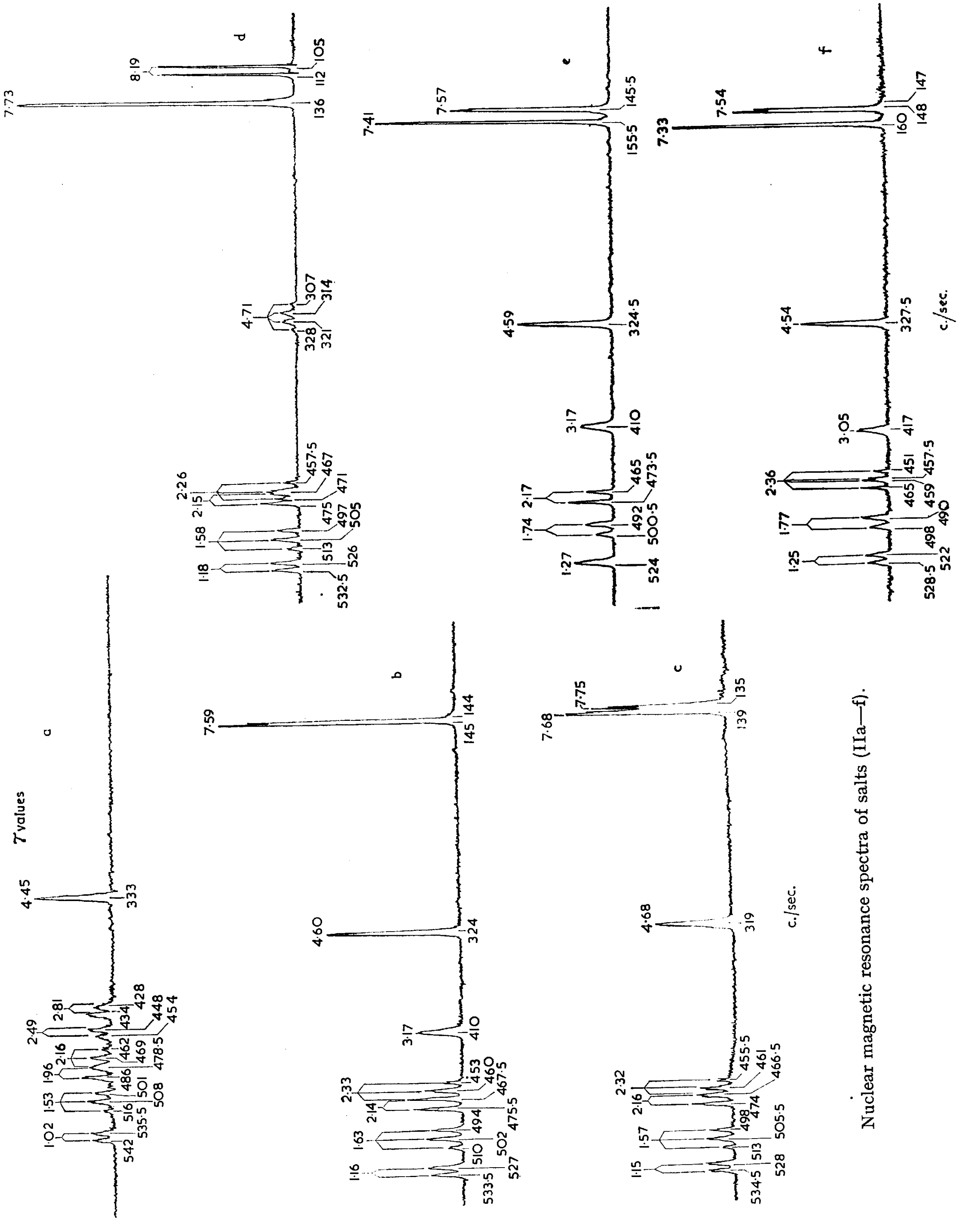
* In a forthcoming paper it will be shown that the 1-methylene signal of 2,3-dimethylindolizinium perchlorate occurs at τ 5·87.

[13] Smith and Schneider, *Canad. J. Chem.*, 1961, **39**, 1158.



Nuclear magnetic resonance spectra of salts (IIa—f).

supports these assignments. The H-5 signal is a doublet due to coupling with H-6. The near equivalence of *H-6 and H-8 results in the H-7 signal's being a triplet.* The triplet* centred at τ 2·16 and the doublet at τ 1·96, constituting the complex signal, are assigned to H-6 and H-8, respectively. These multiplets have one component (478·5 c./sec.) coincident.

The spectra of 2,6- (IIe) and 2,8-dimethylindolizinium perchlorate (IIf) were also recorded. In both a signal corresponding to two protons occurs between the positions of the methylene signals of (IIa and c). We conclude that 2,6- and 2,8-dimethylindolizinium perchlorate also are protonated at position 3. Signals due to H-1 and the 2-methyl group likewise occur at positions expected (see Table and Figs. e and f). The 6- and 8-methyl signals are here shifted downfield relative to the 2-methyl signal of either these salts or 2-methylindolizinium perchlorate, owing to deshielding arising from the positively charged pyridinium structure.

The signals from the six-membered ring protons of 2,6-dimethylindolizinium perchlorate (IIe) comprise a singlet at τ 1·27 and a AB quadruplet centred at τ 1·74 and 2·17 (J = 8·5 c./sec.), and those of 2,8-dimethylindolizinium perchlorate (IIf) a doublet centred at τ 1·25 (J = 6·5 c./sec.), a doublet centred at τ 1·77 (J = 8 c./sec.), and a quadruplet centred at τ 2·36. The correspondence in position of the singlet of salt (IIe) with the centres of the low-field doublets in the spectra of salts (IIa—d) confirms the previous assignments of these doublets to H-5. The only other six-membered ring proton common to (IIe and f) is H-7, which is adjacent to one other ring proton in each salt. The only doublet still to be accounted for in the spectrum of the salt (IIf) is that at τ 1·77. It must arise from H-7 coupled with H-6. This doublet also corresponds positionally to the low-field pair, centred at τ 1·74, of the quadruplet in the spectrum of (IIe). These components must therefore also arise from H-7 spin-spin coupled with H-8. The high-field pair of the quadruplet centred at τ 2·17, must then arise from H-8. The correspondence in position of the H-7 signals of (IIe and f) with the triplets of (IIa—d) confirms

Chemical shifts in the proton magnetic resonance spectra of the indolizinium perchlorates (IIa—f). (Solutions in trifluoroacetic acid. *J* values refer to protons unless otherwise stated and are in c./sec.)

	Proton signals											
	Five-membered ring			Six-membered ring				Substituent				
Per-chlorate	H-1	H-2	H-3	H-5	H-6	H-7	H-8	1-Me	2-Me	3-Me	6-Me	8-Me
IIa	2·81d *J* (1,2) 6	2·49d *J* (2,1) 6	4·45	1·02d *J* (5,6) 6·5	2·16t	1·53t	1·96d *J* (8,7) 7·5					
IIb	3·17		4·60	1·16d *J* (5,6) 6·5	2·33t	1·63t	2·14d *J* (8,7) 8		7·59d *J* Me-2, H-1) = 1			
IIc			4·68	1·15d *J* (5,6) 6·5	2·32t	1·57t	2·16d *J* (8,7) 7·5	7·75m*	7·68m*			
IId			4·71q *J* (H-3, Me-3) = 7	1·18d *J* (5,6) 6·5	2·26t	1·58t	2·15d *J* (8,7) 8	7·73	7·73	8·19d *J* (Me-3, H-3) = 7		
IIe	3·17		4·59	1·27		1·74d *J* (7, 8) 8·5	2·17d *J* (8,7) 8·5		7·57		7·41	
IIf	3·05		4·54	1·25d *J* (5,6) 6·5	2·36q *J* (6,5) 6·5 *J* (6,7) 8	1·77d *J* (7,6) 8			7·54d *J* (Me-2, H-1) ~ 1			7·33

Unless otherwise indicated, values refer to singlet absorptions. For multiplets, d = doublet, t = triplet, q = quadruplet, m = multiplet. * *J* = 0·5—1 c./sec.

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* In order to simplify our analysis we disregard the fine splitting due to *meta*-couplings ($J \sim$ 1 c./sec.) in face of the much stronger *ortho*-couplings ($J \sim$ 6—8 c./sec.).

the previous assignments of these multiplets to H-7. Also, the position of the quadruplet * at τ 2·36 in the spectrum of (IIf) corresponds well with that of the triplets assigned to H-6 in the spectra of the perchlorates (IIa—d).

The spectra of 2-methylindolizinium perchlorate in deuterotrifluoroacetic acid and trifluoroacetic acid were identical, thus showing that the 3-methylene protons of this salt do not exchange at a detectable rate with the solvent protons. It may be concluded that the cations from 1,2- and 2,6-dimethyl- and 1,2,3-trimethyl-indolizine, which are more basic than 2-methylindolizine,[7] also from 2,8-dimethylindolizine whose basicity, though not determined, is likely to be greater than that of the base (Ib), by virtue of the additional methyl group, also do not exchange in trifluoroacetic acid. The possibility that indolizinium perchlorate exchanges with the solvent, though unlikely, is not excluded with certainty.

We conclude that all the six indolizinium cations examined are protonated in solution exclusively at position 3; further, that 2-methylindolizinium perchlorate, and probably also the other five perchlorates, are protonated at position 3 in the solid state.

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* The inner pair of components are weakly separated (~1·5 c./sec.).