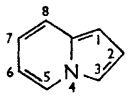
813. *Ionization and Ultraviolet Spectra of Indolizines.*

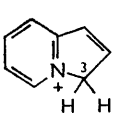
By W. L. F. Armarego.

The ionization constants and ultraviolet spectra of twelve alkylindolizines and of 1,3a-, 2,3a-, and 1,7a-diazaindenes (azaindolizines) were measured. Most of the indolizine cations were found to be protonated predominantly on C-3, but, for steric reasons, the 3-methyl, and the 2,3- and 3,7-dimethyl derivatives were protonated on C-1. However, in 3,5-dimethylindolizine, this steric repulsion of a proton is overcome by another steric effect, *viz.*, overcrowding of the two methyl groups, which permits C-3 protonation. The diazindene cations are protonated on the non-bridgehead nitrogen.

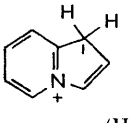
Indolizines were considered [1–3] to be feebly basic because they dissolved slowly in dilute acid. Rossiter and Saxton [4] showed that attack by an electrophilic reagent (*i.e.*, in methylation and formylation) on indolizine takes place first on C-3 then on C-1. It was later shown [5] from reactions of 1,2,3-trimethylindolizine with alkyl iodides that although C-3 alkylation was predominant, C-1 alkylation also occurred to a minor extent. By comparison, it was assumed that protonation of (I) followed the same course and that the indolizine cation possessed the pyridinium structures (IIa) and (IIb) with the former



(I)



(IIa)



(IIb)

predominating.[4–6] Moreover, catalytic reduction of indolizine in 2N-hydrobromic acid gave 1,2-dihydro-3*H*-indolizinium bromide.[3] Recent theoretical calculations [7] are also in agreement with the high reactivity of positions 1 and 3 towards electrophiles. From

[1] Scholtz, *Ber.*, 1912, **45**, 734.
[2] Saxton, *J.*, 1951, 3239.
[3] Lowe and King, *J. Org. Chem.*, 1959, **24**, 1200.
[4] Rossiter and Saxton, *J.*, 1953, 3654.
[5] Holland and Nayler, *J.*, 1955, 1657. Cf. ref. 6.
[6] Robinson and Saxton, *J.*, 1952, 976.
[7] Longuet-Higgins and Coulson, *Trans. Faraday Soc.*, 1947, **43**, 87; Fukui, Yonezawa, Nagata, and Shingu, *J. Chem. Phys.*, 1954, **22**, 1433; see, however, Galbraith, Small, Barnes, and Boekelheide, *J. Amer. Chem. Soc.*, 1961, **83**, 453.

a study of the proton magnetic resonance spectra of several indolizinium perchlorates in 10% w/v trifluoroacetic acid, it was concluded [8] that protonation occurred essentially on C-3 when it carried a hydrogen atom or a substituent similar to that on C-1 (*i.e.*, 1,2,3-trimethylindolizine). These authors also implied that protonation in 2,3-dimethylindolizinium perchlorate takes place on C-1. I have now measured the basic strengths and ultraviolet spectra, under comparable conditions, of indolizine and 12 alkylindolizines and provided evidence that, depending on the position of the substituent, protonation occurs on C-1 or C-3. These results suggested the examination of the position of protonation in all possible monoazaindolizines having the extra nitrogen atom in the five-membered ring.

Basic Strengths of Indolizines.—Ionization constants of indolizine and several methyl derivatives have been measured [9] in 60% alcohol, but the temperature and the method were not stated. These values are unsatisfactory for comparison because the measurements were made in a mixed solvent (for pitfalls in the use of mixed solvents see ref. 10*a*), and also because I found that the neutral species of many of the methyl derivatives were unstable.

The stabilities of the neutral species at pH 10 were examined and are given in Table 1. The more unstable compounds had a methyl group in position 3- (and to a smaller degree in positions 1- and 2-), or when a second methyl group was introduced in the pyrrole ring (*i.e.*, 1,2-dimethylindolizine). The most unstable compound was 1,2,3-trimethylindolizine. During these decompositions, the changes observed in the ultraviolet spectra showed several sharp isosbestic points, indicating the likelihood that a single reaction product was formed. Indeed a detailed kinetic study of the decomposition of 1,2,3-trimethylindolizine

TABLE 1.

	Ionization [a] in water at 20°				Position of predominant protonation	Change in UV spectrum at 20° in pH 10 aqueous buffer		
Indolizine	pK_a	Spread (±)	Concn. 10^4M	λ (mμ) [b]		2 hr.	20 hr.	3 days
Unsubstituted	3·94	0·05	0·8	305	C_3	no	no	v. small
2-Methyl-	5·87	0·05	0·39	325	C_3	v. small	large	complete
2-t-Butyl-	5·60	0·05	0·58	320	C_3	no	v. small	small
3-Methyl-	3·85	0·03	0·25	230	C_1	large	v. large	complete
5-Methyl-	5·04	0·04	0·5	305	C_3	no	no	v. small
6-Methyl-	4·81	0·03	0·8	312	C_3	no	v. small	small
7-Methyl-	5·41	0·03	0·8	300	C_3	no	v. small	small
1,2-Dimethyl-	7·32	0·04	0·5	325	C_3	small	large	v. large
2,3-Dimethyl-	5·43	0·05	0·25	235	C_1	large	v. large	complete
2,5-Dimethyl-	6·83	0·03	0·5	315	C_3	no	v. small	small
3,5-Dimethyl-	6·44	0·05	0·58	310	C_3	large	v. large	complete
3,7-Dimethyl-	5·34	0·04	0·25	270	C_1	small	large	complete
1,2,3-Trimethyl-	6·67	0·05	0·67	325	C_3	v. large	complete	—
1,3a-Diazaindene	6·79	0·04	1·25	300	N_1			
2,3a-Diazaindene	5·54	0·01	2·86	340	N_2			
1,7a-Diazaindene	1·43 [c]	0·03	0·2	223	N_1			

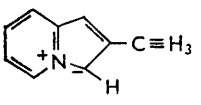
[a] Ionic strength 0·01; for buffers used see Perrin, *Austral. J. Chem.*, 1963, **16**, 572. [b] Analytical wavelength. [c] Measured in aqueous hydrochloric acid.

in pH 9·8 aqueous buffer, and 20°, at $0{\cdot}525 \times 10^{-4}$ M and $0{\cdot}262 \times 10^{-4}$ M showed that it followed first-order kinetics, and that it had a half-life of 39 min. This change is unlikely to involve the formation of a dimer similar to that of indole [11] because it requires the neutral species and is much faster when a methyl group is present in the pyrrole ring—two conditions which retard dimerization of indoles.

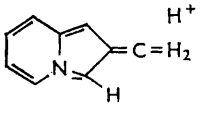
[8] Reid, Malera, Molloy, and Frazer, *J.*, 1962, 3288.
[9] Miller and Brown, Abstracts 130th Meeting, American Chemical Society Atlantic City, N.J., September 1956, 49–**0**.
[10] Albert and Serjeant, "Ionization Constants of Acids and Bases," Methuen, London, 1962. (*a*) p. 66, (*b*) p. 120, and (*c*) p. 69.
[11] Berti and Da Settimo, *Gazzetta*, 1961, **91**, 571.

The cations of all the indolizines studied were stable in dilute acid solutions for at least four hours. The limited stability and solubility of the neutral species in water made it more convenient to use the more stable perchlorates in acid solution, and to neutralise and adjust the pH of the solution to various values. The optical densities were measured within one minute of mixing, during which time decomposition of the neutral species was negligible. All measurements were made at constant ionic strength, and the pK_a values are given in Table 1. To determine if protonation on carbon is unduly slow in this series, a solution of indolizine (neutral species) was acidified to pH 1·0 (using a rapid-reaction apparatus [12]) and it was found that protonation was faster than one second. The reported [1,3] slow solubility of indolizine in dilute acid is therefore not caused by a rate-determining protonation process but by the low solubility of indolizine in water.

Indolizine, although a weak base, is as strong as α-naphthylamine (pK_a 3·9) but a much stronger base than indole [11] (pK_a −2·4). A methyl group in nitrogen heteroaromatic compounds (*e.g.*, pyridine) increases the basic strength by 0·5—0·8 pK_a unit.[13] A methyl group in the 2-position of indolizine, on the other hand, makes an unusual increase of 1·9 pK_a units. Although this value is large, a similar effect was observed in 2-methylindole, which is a stronger base than indole by 2·3 pK_a units.[11] Indole also is known to protonate on C-3.[14] It was thought possible that a 2-methyl group in indolizine might stabilize the cannonical forms (IIIa) and (IIIb) of the neutral species by hyper-



(IIIa)



(IIIb)

conjugation, thus making it more basic than expected. We therefore prepared 2-t-butylindolizine and found that it was a weaker base than 2-methylindolizine by 0·27 pK_a unit. No difference in basic strength was observed between 4-methyl- and 4-t-butyl-pyridine, whereas 3-methylpyridine was a weaker base than 3-t-butylpyridine by 0·14 unit, and in the 2-alkylpyridines a base-weakening effect of 0·24 unit was observed on replacing a methyl by a t-butyl group.[13] The authors concluded that in the 4-alkylpyridines the inductive and hyperconjugative effects cancelled each other, in the 3-alkyl derivatives the inductive effect was operating, and in the 2-alkyl derivatives steric effects might be important.[13] In 2-alkylindolizines the effect observed could be explained by steric hindrance as in 2-alkylpyridines, or alternatively by hyperconjugation because, unlike in pyridine, protonation occurs on a five-membered ring. This may account for a small part of the increase in basic strength in 2-methylindolizine but it does not account for the whole of it because methyl groups in the pyridine ring of indolizine also have a base-strengthening effect rather larger than predicted (see below).

The alkyl group in 3-methylindolizine, paradoxically, *decreases* the basic strength of indolizine by a small amount (0·1 pK_a unit). A similar behaviour has been observed in 3-methylindole where protonation is known to occur on C-3. In 3-methylindolizine the alkyl group inhibits protonation on C-3, and the hydrated proton is thus directed to C-1, which is a weaker basic centre. This must be due to the steric effect of the methyl group, which would be expected to increase the electron density on C-3 and cause an increase in basic strength at this position. The base-weakening effect of the 3-methyl group is also observed in 2,3- and 3,7-dimethylindolizine, which are weaker bases than 2- and 7-methylindolizine by 0·4 and 0·1 pK_a unit, respectively.

Methyl groups in positions 5-, 6-, and 7- are base-strengthening, and in these the effect is large, though smaller than in the 2-methyl derivative (see above). The 6-methyl

[12] Perrin, *J.*, 1962, 645.
[13] Brown and Mihm, *J. Amer. Chem. Soc.*, 1955, **77**, 1723.
[14] Hinman and Whipple, *J. Amer. Chem. Soc.*, 1962, **84**, 2534.

derivative is weaker than either the 5- or 7- isomer; hence the 5-methyl group does not interfere, sterically, with protonation in spite of some provisional claims to the contrary (see ref. 9). The effect of methyl groups is not strictly additive. For example, the pK_a values, predicted from simpler members of the series, for 2,5- and 2,3-dimethyl, and 1,2,3-trimethylindolizines are 6·9, 5·7, and 7·2, whereas the observed values are 6·8, 5·4, and 6·7, respectively. It must be pointed out that there are two possible cations (IIa) and (IIb), and that although the former is favoured, the pK_a values may involve protonation at the two centres to varying degrees depending on the substituent. Thus the recorded pK_a is the macroscopic resultant of two microscopic pK_a values (see ref. 10*b* for the definition). The discrepancies between the predicted and observed pK_a values can thus be accounted for, and it is not possible to exclude a small amount of either C-1 or C-3 protonated species in a cation which is considered to be predominantly protonated on C-3 or C-1, respectively.

The insertion of a 3-methyl group in 5-methylindolizine to give 3,5-dimethylindolizine, on the other hand, results in an *increase* in basic strength of 1·4 pK_a units. Moreover, 3,5-dimethylindolizine is a slightly weaker base than the 2,5-isomer (by 0·4 unit), and the large difference in basic strength previously observed between the methyl group in the 2- and 3-position is not shown here (compare 2- and 3-methylindolizines). This can be explained by intramolecular overcrowding of the *peri* methyl groups. The 5-methyl group would push the 3-methyl group out of the plane of the rings and facilitate protonation on C-3 because C-3 would then become more ready to assume a tetrahedral configuration. Further support for this hypothesis is obtained from spectral data (see below). Also, 3,7-dimethylindolizine, where there is no overcrowding, but where the electronic influences are similar to those in the 3,5-isomer, is a weaker base than the latter by 1·1 pK_a units.

Professor L. M. Jackman has kindly measured the n.m.r. spectrum of 3,5-dimethylindolizinium perchlorate in trifluoroacetic acid and found that protonation had occurred on C-3. The protons of the 3-methyl group are split into a doublet (τ 8·19, J 7·0 c./sec.) by the 3-hydrogen atom (a quartet: τ 4·22, J 7·0 c./sec.). The protons on the 5-methyl group appear as a singlet (τ 6·97).

The positions in which protonation predominates are summarised in Table 1 for each indolizine.

Ultraviolet Spectra of Indolizines.—The absorption spectra of the neutral species and cations of the indolizines examined are given in Table 2. All the neutral species have very similar spectra which consist of three bands: an intense band at 225—240 mμ, a second band of medium intensity at 270—310 mμ which has two or sometimes three peaks, and a third, broad band, also of medium intensity, at 330—360 mμ (*cf.* Figure).

No interaction between the neutral species and water takes place because the spectra of indolizine in water and in cyclohexane [15] are closely similar. The spectra of the cations of indolizines are markedly different from those of the neutral species, whereas normally only small shifts are obtained when heteroaromatic compounds are protonated.[16] The spectrum of the indolizinium cation is the same in water at pH 1·0 as in sulphuric acid at H_0 −4·0. In contrast, the spectrum of the quinazoline cation at pH 1·0, which is different from that of the neutral species because it is (covalently) hydrated, alters drastically on decreasing the H_0 value of the medium. At H_0 −4·0 it becomes very similar to the spectrum of the neutral species because of the formation of the "anhydrous" quinazoline cation.[17] The spectrum of indolizinium cation consists of two main bands of medium intensity and is like the spectrum of 2-vinylpyridinium cation. These large changes in spectra observed on protonation are consistent with the changes in electron distribution between (I) and (IIa) or (IIb).

Holland and Nayler [5] pointed out that it should be possible to distinguish between

[15] Bower, *J.*, 1957, 4510.
[16] Osborn, Schofield, and Short, *J.*, 1956, 4191.
[17] Albert, Armarego, and Spinner, *J.*, 1961, 2689.

the cations (IIa) and (IIb) because the long wavelength band of 1-ethyl-1,2,3-trimethylindolizinium cation absorbed at shorter wavelengths (~235 mμ) than that of 3-ethyl-1,2,3-trimethylindolizinium cation (~325 mμ). A close examination of the spectra of the indolizinium cations revealed that they can be divided into two groups: (*a*) those unsubstituted on C-3 (except 3,5-dimethyl- and 1,2,3-trimethyl-indolizines) and (*b*) those with a

TABLE 2.

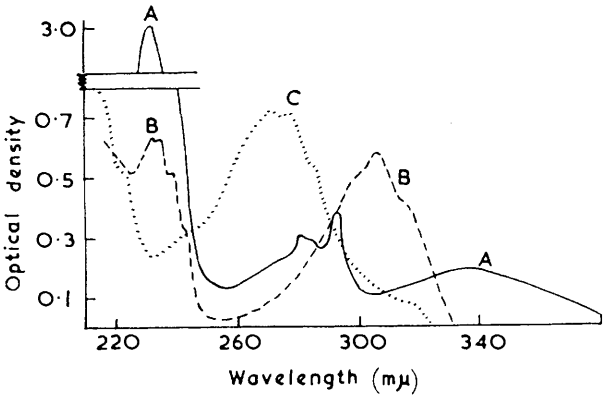
Ultraviolet spectra [a] in water at 20°.

Indolizines	Species [b]	$\lambda_{max.}$ (mμ)	log $\varepsilon_{max.}$	pH
Unsubstituted	0	232; *274* + 281 + 292·5; 337	4·47; *3·33* + 3·49 + 3·58; 3·26	7·0
	+	*228* + 231·5 + 234·5 + 238·5 + *242*; *297* + 305 + *316*	*3·75* + 3·79 + 3·79 + 3·71 + *3·50*; *3·68* + 3·76 + *3·61*	1·0
2-Methyl- [c]	0	237·5; *227* + 287 + 297; 338 [d]	4·50; *3·62* + 3·71 + 3·75; 3·63	10
	+	240 + *248*; 317 + *332*	3·97 + *3·82*; 3·75 + *3·51*	1·0
2-t-Butyl- [c]	0	237; *278* + 287 + 296; 337 [d]	4·50; *3·32* + 3·42; 3·31	10
	+	241 + *249*; 318·5 + *332*	4·07 + *3·91*; 3·86 + *3·68*	2·0
3-Methyl- [c]	0	231; *275* + 281 + 293; 348 [d]	4·89; *3·45* + 3·57 + 3·62; 3·28	10
	+	*215* + *222*; *245* + 270 + 276 + *284* + *316*	*3·88* + *3·71*; *3·49* + 3·86 + 3·85 + *3·74* + *2·80*	1·7
5-Methyl- [c]	0	223·5; 282 + 293·5; 330 [d]	4·54; 3·62 + 3·71; 3·39	10
	+	232 + *235* + *239·5* + *244*; 305 + *316*	3·85 + *3·84* + *3·74* + *3·45*; 3·87 + *3·76*	2·0
6-Methyl- [c]	0	235; *276* + 284·5 + 296·5; 335 [d]	4·54; *3·38* + 3·50 + 3·55; 3·38	10
	+	211 + *216*; 283 + *242* + *248* + *251*; *302* + 311 + *324*	4·38 + *4·34*; 3·82 + *3·79* + *3·58* + *3·42*; *3·69* + 3·78 + *3·59*	2·0
7-Methyl- [c]	0	233·5; *274* + 283 + 294; 337 [d]	4·54; *3·46* + 3·62 + 3·66; 3·25	10
	+	213 + *216* + *232*; 300 + *310·5*	4·50 + *4·46* + *3·70*; 3·78 + *3·69*	2·0
1,2-Dimethyl- [c] ...	0	239·5; *284* + 292 + 303; 349 [d]	4·44; *3·27* + 3·36 + 3·38; 3·28	10
	+	245; 325	4·06; 3·73	5·0
2,3-Dimethyl- [c] ...	0	235; *278·5* + 285 + 297; 348 [d]	4·45; *3·43* + 3·48 + 3·49; 3·33	10
	+	229 + 241 + *249*; *282* + 290	3·79 + 3·78 + *3·67*; *3·69* + 3·72	2·0
2,5-Dimethyl- [c] ...	0	235; 287 + 298; 331	4·48; 3·53 + 3·61; 3·40	10
	+	240 + *244* + *248*; 316 + *328*	4·04 + *3·97* + *3·84*; 3·89 + *3·77*	2·0
3,5-Dimethyl- [c] ...	0	232; *276* + 286·5 + 298; 343 [d]	4·48; *3·47* + 3·64 + 3·68; 3·39	10
	+	236 + *243* + *246*; *298* + 310 + 320·5	3·82 + *3·66* + *3·46*; *3·66* + 3·84 + 3·75	2·0
3,7-Dimethyl- [c] ...	0	234; *273* + 283 + 295; 348	454; *3·53* + 3·69 + 3·71; 3·24	10
	+	272 + *312*	3·88 + *2·95*	2·0
1,2,3-Trimethyl- [c] ...	0	240; *283* + 291 + 302; 360 [d]	4·46; *3·37* + 3·41 + 3·37; 3·31	10
	+	246; 325	4·05; 3·71	2·0
1,3a-Diazaindene ...	0	219 + *225*; *267* + 278 + 292	4·43 + *4·23*; *3·53* + 3·61 + 3·54	9·0
	+	211 + *215*; 275	4·37 + *4·28*; 3·84	1·0
2,3a-Diazaindene ...	0	211 + *239*; *262* + 271 + 282 + 308	4·32 + *3·26*; *3·66* + 3·81 + 3·76 + 3·38	8·0
	+	224 + *230* + *239*; *259* + 268·5 + 279 + 295	3·44 + *3·40* + *3·28*; *3·65* + 3·82 + 3·82 + 3·55	2·0
1,7a-Diazaindene ...	0	219 + 223; *280* + 286 + *293*	4·59 + 4·54; *3·61* + 3·65 + *3·61*	7·0
	+	*210* + 213·5 + 218; *272* + 292 + *300*	*4·41* + 4·51 + 4·42; *3·59* + 3·77 + *3·63*	−1·1 [e]
2-Vinylpyridine [f] ...	0	234 + *241*; 278 + *284* + *294*	4·05 + *3·98*; 3·75 + *3·69* + 3·32	9·0
	+	233 + *240* + *250*; 286	3·80 + *3·73* + *3·39*; 3·98	1·0

[a] Inflexions are in italics. [b] 0 = Neutral Species, + = Cation. [c] Perchlorates were used. [d] Stock solution in acid was neutralised and the pH adjusted, and the intensities were obtained from the calibrated Spectracord (4000 A) chart within 3 min. of mixing. [e] H_0 in sulphuric acid. [f] pK_a 4·98, Linnell, *J. Org. Chem.*, 1960, **25**, 290.

methyl group on C-3. The absorption maxima of the long wavelength bands in the cations are at longer wavelengths in group (*a*), and at shorter wavelengths in group (*b*) than the longest wavelength peak in the second band of the respective neutral species (see Figure). In group (*a*) protonation is predominantly on C-3 and in group (*b*) on C-1, and this agrees with the above authors and with the ionization measurements. 1,2,3-Trimethylindolizine cation is protonated on C-3 (cf. also ref. 8), and, because of overcrowding of methyl groups,

3,5-dimethylindolizine cation also is protonated predominantly on C-3. By analogy with the latter compound, the spectra of the neutral species and cation (in ethanol) of 1,3,5,8-tetramethylindolizine [2] suggest that the cation is protonated on C-3. Although the spectrum of 3-methyl(and 3,7-dimethyl)indolizium cation is consistent with protonation

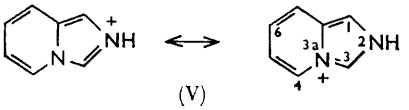


Ultraviolet spectra.
A, Neutral species of indolizine (3-methylindolizine has a very similar spectrum).
B, Cation of indolizine.
C, Cation of 3-methylindolizine.

on C-1, it is conceivable that the weak inflexion at 316 mμ (and 312 mμ) (see Figure) may be due to a small amount of the C-3 protonated species.

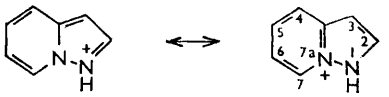
Diazaindenes (*Azaindolizines*).—The pK_a values and ultraviolet spectra of 1,3a-, 2,3a-, and 1,7a-diazaindenes are given in Tables 1 and 2, respectively. Unlike indolizine, protonation in these compounds takes place on the extra nitrogen atom irrespective of its position. The high pK_a value of the 1,3*a*-diaza-compound (6·79) as compared with indolizine (3·94) is undoubtedly due to the amidinium type of stabilization (IV) in the cation. If this were

(IV)



(V)

not so, a very large decrease in basic strength would have resulted from the deactivating influence of the second-ring nitrogen atom. As in 2-aminopyridine,[18] the spectrum of the neutral species is not altered drastically on acidification. Similarly the high basic strength of 2,3a-diazaindenes can be explained by the resonance (V) in the cation. Here also there is a small change in spectrum on acidification.



(VI)

1,7a-Diazaindenes is a much weaker base (pK_a 1·43) than the above two isomers, but its ultraviolet spectrum does not show large changes when the base is protonated. There is no other pK between 3 and 11. By analogy with indolizine, protonation on N-1 would be favoured, and the resonance-stabilized cation (VI) should be possible. The weak basic strength is not altogether surprising because the difference in basic strength between

[18] Steck and Ewing, *J. Amer. Chem. Soc.*, 1948, **70**, 3397; Mason, *J.*, 1960, 219; Albert, *J.*, 1960, 1020.

imidazole (6·95)[19] and pyrazole (2·47)[20] is of the same order as the difference between 2,3a-diaza- and 1,7a-diaza-indene, namely 4·1 pK_a units. The weak basic strength of pyrazole has been attributed to the strong $-I$ effect of the adjacent nitrogen atom[21] (compare[22] isoxazole pK_a −1·96). A similar explanation applies to 1,7-diazaindene, and the strong $-I$ effect appears to mask much of the stabilization gained by resonance in (VI).

Experimental

Microanalyses were made by Dr. J. E. Fildes and her staff.

Evaporations were carried out in a rotary evaporator at 30—40°/15 mm. The materials are examined for purity as before.[23] Indolizine,[1] 2-methyl-[24], 1,2-dimethyl-,[4] 2,3-dimethyl-,[5] 2,5-dimethyl-,[5] and 1,2,3-trimethyl-[4] indolizine; 2,3a-,[25] and 1,7a-diazaindenes[26] were prepared as in the references cited.

Analyses are given in Table 3.

5-, 6-, *and* 7-*Methylindolizines*.—The respective lutidines (*i.e.*, 2,6-, 2,5-, and 2,4-) (15 ml.) and acetic anhydride (80 ml.) in a sealed tube were heated in a Carius oven at 210—220° for 5 hr. Two such batches were combined (cooling of the tubes in a dry-ice–acetone bath for ½ hr. was necessary before opening), boiled with water (1½ l.), filtered through kieselguhr, cooled, and the crystalline solid filtered off. When no solid separated, the solution was extracted with chloroform, and the dried (Na_2SO_4) extract evaporated. The oily residue was diluted with light petroleum (b. p. 40—60°), and the solid filtered off, sublimed at 150—160°/0·5 mm. and recrystallised from methanol or light petroleum (b. p. 60—80°). 1,3-*Diacetyl*-5-, 6-, *and* 7-*methylindolizines* were thus obtained in 28, 5·5, and 2·7% yields with m. p.s 161—162°, 150—151°, and 175°, respectively (lit.,[27] 4·7% and m. p. 161—162° for the 5-isomer). The diacetyl derivatives (1·4 g.) and concentrated hydrochloric acid (50 ml.) were refluxed for 1½ hr. The solution was cooled, basified to pH 11 with 5 N-sodium hydroxide, extracted with chloroform, and the dried (Na_2SO_4) extract evaporated. The residue in benzene was purified through an alumina column (6 in. × 1 in.; B.D.H.), and evaporation of the eluates gave a residue which was distilled or sublimed at 40—50°/0·2 mm. The 5-, 6-, *and* 7-*methylindolizines*, obtained in 40, 64, and 67% yields, had b. p. 66—67°/15 mm. (lit.,[27] 82—83/4 mm.), m. p. 51—52°, and 60—61°, respectively.

The corresponding *methylindolizinium perchlorates*, decomp. > 145°, m. p. 71—73°, and 100—102°, were prepared in over 80% yield by adding 70% w/w perchloric acid (1·3 ml.) to an ice-cooled solution of the base (200 mg.) in ethanol (5—10 ml.). The perchlorate crystallised out on immediate addition of excess of ether, and was filtered off and dried in a vacuum desiccator (P_2O_5) for 24 hr.

3,5-*Dimethylindolizine*.—When 2,6-lutidine (15 ml.) and propionic anhydride (80 ml.) were heated in a sealed tube at 220—240° for 9 hr. and then boiled with water (1 l.) as above, a 6·8% yield of 1-*propionyl*-3,5-*dimethylindolizine* was obtained as yellow needles after recrystallisation from light petroleum (b. p. 60—80°). Acid hydrolysis as above gave a 60% yield of 3,5-*dimethylindolizine*, m. p. 76—77° after sublimation, and the *perchlorate* had m. p. 159—160°.

A similar reaction with 2,4-lutidine gave a 0·05% yield of 1-*propionyl*-3,7-*dimethylindolizine*, m. p. 111—112°, which was hydrolysed and converted into 3,7-*dimethylindolizinium perchlorate* (51% yield), m. p. 89—91°. When α-picoline was used, 1-propionyl-3-methylindolizine, m. p. 85—86° (lit.,[28] m. p. 86°) was obtained in 15% yield, and was hydrolysed to 3-methylindolizine (59% yield), b. p. 52—54°/0·6 mm. (lit.,[29] b. p. 230°, also obtained by decarboxylation of

[19] Kirby and Neuberger, *Biochem. J.*, 1938, **32**, 1146; Walba and Isensee, *J. Amer. Chem. Soc.*, 1955, **77**, 5488.
[20] Dedichen, *Ber.*, 1906, **39**, 1831.
[21] Albert, "Ionization Constants," in "Physical Methods in Heterocyclic Chemistry," Vol. 1, ed. Katritzky, Academic Press, 1963, p. 45.
[22] Boulton and Katritzky, *Tetrahedron*, 1961, **12**, 41.
[23] Armarego, *J.*, 1962, 561.
[24] Borrows, Holland, and Kenyon, *J.*, 1946, 1069.
[25] Bower and Ramage, *J.*, 1955, 2834.
[26] Bower and Ramage, *J.*, 1957, 4506.
[27] Boekelheide and Windgassen, *J. Amer. Chem. Soc.*, 1959, **81**, 1456.
[28] Scholtz and Fraude, *Ber.*, 1913, **46**, 1069.
[29] Bragg and Wibberly, *J.*, 1963, 3277; see also Ochiai and Tsuda, *Ber.*, 1934, **67**, 1011.

3-methylindolizine-2-carboxylic acid). It solidified at 0°, darkened rapidly, but gave a stable *perchlorate* (decomp. >140°).

2-t-Butylindolizine.—α-Picoline (1·43 g.) and 1-bromo-3,3-dimethylbutan-2-one [30] (2·6 g.) were heated at 100° for 3 hr. The crystalline solid was treated with water (50 ml.) and sodium hydrogen carbonate (6 g.) and heated at 100° for 2 hr. The cooled solution was extracted with chloroform and the dried extract (Na_2SO_4) evaporated. The residue in benzene was purified through an alumina column (6 in. × 1 in.; B.D.H.), and the eluate (white, fluorescent under Hg lamp, 365 mμ) gave, after evaporation and sublimation of the residue at 50°/0·5 mm., *2-t-butylindolizine* (393 mg., 16%), m. p. 49—50°, as highly volatile plates with a strong aromatic odour. The *perchlorate* had m. p. 125—126°.

TABLE 3.

	Found (%)				Requires (%)		
Indolizine	C	H	N	Formula	C	H	N
1,3-Diacetyl-6-methyl	72·6	5·8	6·6	$C_{13}H_{15}NO_2$	72·5	6·1	6·5
1,3-Diacetyl-7-methyl	72·7	6·0	6·4	$C_{13}H_{15}NO_2$	72·5	6·1	6·5
3,5-Dimethyl-1-propionyl	77·9	7·4	6·7	$C_{13}H_{15}NO$	77·6	7·5	7·0
3,7-Dimethyl-1-propionyl	77·9	7·7	7·0	$C_{13}H_{15}NO$	77·6	7·5	7·0
2-t-Butyl	83·3	9·0	8·0	$C_{12}H_{15}N$	83·2	8·7	8·1
3-Methyl	82·7	7·2	11·1	C_9H_9N	82·4	6·9	10·7
6-Methyl	82·0	7·2	10·7	C_9H_9N	82·4	6·9	10·7
7-Methyl	82·0	7·2	10·2	C_9H_9N	82·4	6·9	10·7
3,5-Dimethyl	82·6	7·7	9·6	$C_{10}H_{11}N$	82·7	7·6	9·65
3-t-Butyl(perchlorate)	—	—	4·8	$C_{12}H_{16}NO_4Cl$	—	—	5·1
5-Methyl(perchlorate)	—	—	6·1	$C_9H_{10}NO_4Cl$	—	—	6·05
6-Methyl(perchlorate)	—	—	6·1	$C_9H_{10}NO_4Cl$	—	—	6·05
7-Methyl(perchlorate)	—	—	5·9	$C_9H_{10}NO_4Cl$	—	—	6·05
2,5-Dimethyl(perchlorate)	—	—	5·7	$C_{10}H_{12}NO_4Cl$	—	—	5·7
3,5-Dimethyl(perchlorate)	—	—	5·5	$C_{10}H_{12}NO_4Cl$	—	—	5·7
3,7-Dimethyl(perchlorate)	49·3	4·9	5·6	$C_{10}H_{12}NO_4Cl$	48·9	4·9	5·7

1,3a-Diazaindene, b. p. 72—73°/1 mm. (lit.,[15] b. p. 109°/2 mm.) was prepared in 56% yield by oxidation of 2,3-dihydro-1,3a-diazaindene [31] with alkaline ferricyanide as described,[13] except that it was shaken at room temperature for 4 hr. (heating at 90—100° gave very poor yields, cf. ref. 15).

Physical Properties.—Ionization constants were determined by the spectroscopic method used in this Department.[10c] Ultraviolet spectra were measured with a Perkin-Elmer Spectracord, model 4000 Å, and the maxima checked with an Optica manual instrument unless otherwise stated.

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[30] Boyer and Straw, *J. Amer. Chem. Soc.*, 1952, **74**, 4506.
[31] Brenner, *Annalen*, 1936, **521**, 286.