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ELECTROPHILIC SUBSTITUTION IN INDOLES—III[1]

REARRANGEMENT OF 3,3-DIALKYL INDOLENINES

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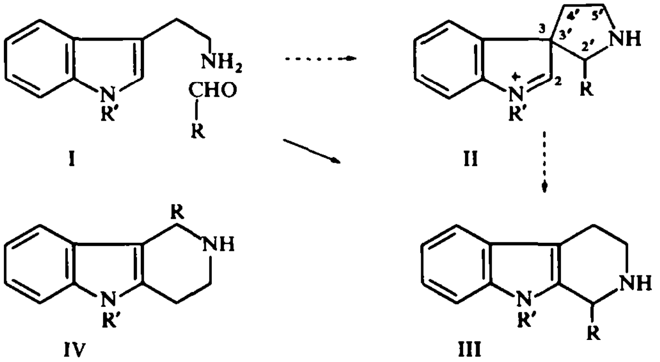
Abstract—A number of 3,3-dialkyl indolenines have been prepared by alkylation of the Grignard derivatives of 3-alkyl indoles. Under acidic conditions these indolenines readily rearrange to 2,3-disubstituted indoles, the structures of which were determined by examination of their NMR spectra in trifluoroacetic acid. In each case a unique product was obtained corresponding to rearrangement of the 3-substituent with the highest migratory aptitude; it was also shown that the rearrangements were first order and intramolecular.

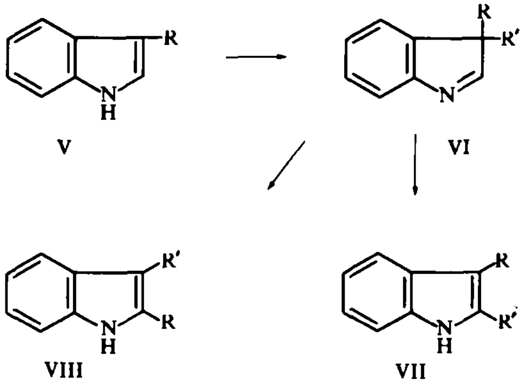
Mass spectra of most of the indoles and indolenines are recorded (together with high resolution data on two compounds); these confirm the partially polymeric character of indolenines deduced from NMR and other studies.

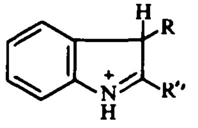
PREVIOUS papers in this series[1, 2] have largely been concerned with electrophilic substitution in 3-substituted indoles, and we suggested that electrophilic substitution at the 2-position did not occur directly but via initial substitution at the 3-position followed by a Wagner–Meerwein type rearrangement. The earlier work provided a certain amount of circumstantial evidence for this hypothesis but it became clear in studies of the cyclization of tryptamines (I) with aldehydes to form β-carbolines (III) that it would not be possible to demonstrate directly the intermediacy of a 3,3-spirocyclic indolenine (II) owing to the great facility with which such compounds (prepared by a different route) rearranged to β-carbolines under mildly acidic conditions.[1] The rearrangements of such intermediates (II) are highly specific giving rise only to β-carbolines (III) and not to the isomeric α-carbolines (IV), and they are presumably facilitated by electron release from nitrogen to the 2′-carbon atom, as well as by any alkyl or aryl substituent at the 2′-position, i.e. the latter carbon has a much higher migratory aptitude than the 4′-methylene group. Earlier experiments[2] had also shown that the rearrangement of 3,3-disubstituted indolenines (VI) to



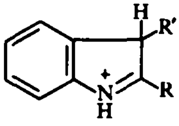
I
II
IV
III

2,3-disubstituted indoles (VII or VIII) involved migration of the group with the greater electron availability, e.g. 3-alkyl-3-methyl indolenine (VI; R = Me, R′ = alkyl) rearranged specifically to 2-alkyl-3-methyl indole (VII; R = Me, R′ = alkyl). The present paper is concerned largely with an extension of this work and preliminary studies of the relative migratory aptitudes of different alkyl groups.





IX



X

Six indolenines (VI) have now been prepared from skatole (V; R = Me) by alkylation of the Grignard derivative, and the products obtained on acid catalysed rearrangement are shown in Table 1. In each case only *one* product was obtained and none of the alternative rearrangement product could be detected. The structures of the products were confirmed by NMR and also in some cases by direct comparison with authentic materials prepared by Fischer indole syntheses. Isomeric indoles (VII and VIII) could not be separated by TLC or VPC, nor could they be satisfactorily distinguished by their NMR spectra in $CDCl_3$. However, in strongly acidic

TABLE 1. ACID CATALYSED REARRANGEMENT OF 3,3-DIALKYL-INDOLENINES

	Indolenine (VI) (substituents)	Indolic rearrangement product (VII) (substituents)	Ref.
a	3,3-di-Me	2,3-di-Me	2
b	3,3-di-Et	2,3-di-Et	present work
c	3-Me, 3-Et	2-Et, 3-Me	present work
d	3-Me, 3-Pr	2-Pr, 3-Me	2
e	3-Me, 3-iPr	2-iPr, 3-Me	present work
f	3-Me, 3-allyl	2-allyl, 3-Me	2
g	3-Me, 3-benzyl	2-benzyl, 3-Me	present work

TABLE 2. PMR SPECTRA OF INDOLES (τ-VALUES)

Indole	In deutero-chloroform*		In trifluoroacetic acid†		
(substituents)	2-	3-	2-	3-	3-H
2,3-diMe	$C\underline{H}_3$ 7·72	$C\underline{H}_3$ 7·80	$C\underline{H}_3$ 7·04	$C\underline{H}_3$ 8·21 *d*	5·62 *q*
2,3-di-Et	$C\underline{H}_2C\underline{H}_3$ 7·29 *q*, 8·79 *t*	$C\underline{H}_2C\underline{H}_3$ 7·32 *q*, 8·79 *t*	$C\underline{H}_2C\underline{H}_3$ 6·68 *q*, 8·42 *t*	$C\underline{H}_2C\underline{H}_3$ 7·65 *m*, 9·12 *t*	5·53 *t*
2-Me, 3-Et	$C\underline{H}_3$ 7·97	$C\underline{H}_2C\underline{H}_3$ 7·35 *q*, 8·85 *t*	$C\underline{H}_3$ 7·03	$C\underline{H}_2C\underline{H}_3$ 7·6 *m*, 9·11 *t*	5·57 *t*
2-Et, 3-Me	$C\underline{H}_2C\underline{H}_3$ 7·44 *q*, 8·88 *t*	$C\underline{H}_3$ 7·82	$C\underline{H}_2C\underline{H}_3$ 6·69 *q*, 8·39 *t*	$C\underline{H}_3$ 8·21 *d*	5·57 *q*
2-Me, 3-iPr	$C\underline{H}_3$ 7·85	$C\underline{H}(C\underline{H}_3)_2$ 6·89 *m*, 8·64 *d*	$C\underline{H}_3$ 7·04	$C\underline{H}(C\underline{H}_3)_2$ 7·7 *m*, 8·56 *d* 9·26 *d*	5·61 *d*
2-iPr, 3-Me	$C\underline{H}(C\underline{H}_3)_2$ 6·77 *m*, 8·73 *d*	$C\underline{H}_3$ 7·75	$C\underline{H}(C\underline{H}_3)_2$ 6·67 *m*, 8·38 *d*	$C\underline{H}_3$ 8·22 *d*	5·53 *q*
2-CH_2PH, 3-Me	$C\underline{H}_2C_6\underline{H}_5$ 6·02, 2·80	$C\underline{H}_3$ 7·73	$C\underline{H}_2C_6\underline{H}_5$ 5·44, 2·53	$C\underline{H}_3$ 8·18 *d*	5·54 *q*
2-Ph, 3-Me	C_6H_5 ~ 2·5	$C\underline{H}_3$ 7·58	$C_6\underline{H}_5$ 1·6–2·3 *m*	$C\underline{H}_3$ 8·20 *d*	4·97 *q*
3-sec. octyl	$\underline{H}$ 3·11 *d*	—$C\underline{H}(C\underline{H}_3)(C\underline{H}_2)_5C\underline{H}_3$ 7·0 *m*, 7·65 *d*, 8·0–9·0 *m*, 9·14 *t*			
3-t-butyl	$\underline{H}$ 3·12 *d*	$C(CH_3)_3$ 8·55			

* 4,5,6-$\underline{H}$, 2·85; 7-$\underline{H}$ and N$\underline{H}$ ~ 2·5 *m* (in every spectrum). † 4,5,6,7-$\underline{H}$, ~2·30 (in every spectrum).

TABLE 3. PMR SPECTRA OF INDOLENINES (τ-VALUES)*

Indolenine (substituents)		In deuterochloroform†		In trifluoroacetic acid‡	
		2-$\underline{H}$	3-	2-$\underline{H}$	3-
VIc[a]	C-Me, 3-Et	1·9 (4·95, 5·5, 5·65)	$C\underline{H}_3$ 8·69	0·65	$C\underline{H}_3$ 8·30 $C\underline{H}_2C\underline{H}_3$ 7·72 *q*, 9·22 *t*
VIb[a]	3,3-di-Et	2·19 (5·0, 5·54, 5·73)	$C\underline{H}_2C\underline{H}_3$ 8·17 *q*, 9·46 *t*	0·75	$C\underline{H}_2C\underline{H}_3$ 7·76 *q*, 9·27 *t*
VIe[a]	3-Me, 3-iPr	1·92 (4·87, 5·48, 5·72)	$C\underline{H}_3$ 8·68 $C\underline{H}(C\underline{H}_3)_2$ 7·9 *m*, 9·10 *d*, 9·20 *d*	0·71	$C\underline{H}_3$ 8·25 ($C\underline{H}(C\underline{H}_3)_2$ 7·4 *m*, 8·90 *d*, 8·3 *m*, 8·96 *d*
VIg[b]	3-Me, 3-CH_2Ph	1·88	$C\underline{H}_3$8·64 $C\underline{H}_2C_6\underline{H}_5$ 7·00, 2·7	0·72	$C\underline{H}_3$ 8·26 $C\underline{H}_2C_6\underline{H}_5$ 6·55, 2·6

* Spectra of the other indolenines have been described previously.[2]

† Ar-$\underline{H}$, 2·5–3·5 *m* in each case.

‡ Ar-$\underline{H}$ ~2·30.

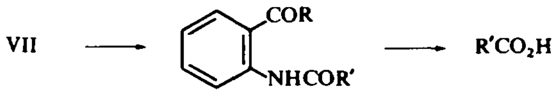
[a] Partially trimeric in $CDCl_3$ (rapidly depolymerized in presence of traces of acid). Positions of 2-$\underline{H}$ in the trimer are given in brackets.

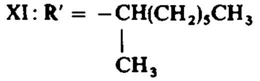
[b] Rearranges rapidly in TFA to the 3-$\underline{H}$-indolium salt of 2-benzyl-3-methylindole; the spectrum of the mixture was run as quickly as possible before all the material had rearranged (ca. 10–15 min.).

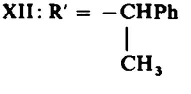
media indoles are protonated at the 3-position, and NMR spectra (Table 2) showed that trifluoroacetic acid was sufficiently strong an acid to effect complete conversion of 2-alkyl- and 2,3-dialkyl indoles into the corresponding 3-H-indolium salts (IX or X). (3-Alkyl indoles are only partially protonated in trifluoroacetic acid solution, but the increased basicity of 2,3-disubstituted indoles was to be expected from earlier UV studies of indole protonation equilibria,[3,4] which showed that 2,3-dimethylindole was more than 100 times as basic as 3-methylindole.) Thus in trifluoroacetic acid solution the 3-alkyl resonances are shifted to high field, and become more complex owing to coupling with the 3-proton introduced (although the latter can be avoided by use of the deuterated acid); on the other hand the 2-alkyl resonances experience a low field shift compared with those of the free bases in $CDCl_3$ owing to the positive charge on nitrogen (Table 2). Hence the two indolium salts (IX and X) can be readily distinguished and consequently the parent indoles (VII and VIII), respectively.

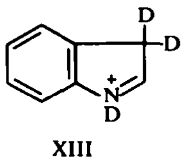
Preliminary studies of the rates of rearrangement in ethanolic hydrochloric acid indicated the following order of migratory aptitudes Me < Et < Pr < i-Pr < allyl < $PhCH_2$ < PhCH-N.[cf. 1] For example, dimethyl indolenine (VI; R = R′ = Me) required heating for 15 min at 80° in 6 M-HCl to effect complete rearrangement, whereas 3-benzyl-3-methylindolenine in $CDCl_3$ rearranged in 15 min at 20° on addition of 10% trifluoroacetic acid (during an attempt to measure the NMR spectra of the salt), and ethanolic acidic solutions rearranged at an appreciable rate at 20°. The migratory aptitude of the 2′-carbon atom in the spirocyclic indolenines (II) is much greater again[cf. 1] than the benzyl group in the present series and this is to be expected as it is flanked both by phenyl and by amino groups (see above).

Kinetic studies indicated that in presence of excess acid (sufficient to fully protonate the indolenines) the rearrangements were first order, but it was clearly desirable also to confirm that the rearrangements were intra-molecular Wagner–Meerwein type 1,2-shifts. A standard procedure for determining the intra molecularity, or otherwise, of a rearrangement reaction is to rearrange two compounds of comparable reactivity in the same medium and determine whether any "cross-over" has occurred. The simultaneous acid-catalysed rearrangement of 3,3-dimethyl- and 3,3-diethyl-indolenine was therefore studied, and VPC determinations showed that only 2,3-dimethyl- and 2,3-diethylindole were obtained. No traces of the possible "cross-over" products (2-ethyl-3-methylindole, or 2-methyl-3-ethylindole) were observed and thus the intra-molecular character of the rearrangements was clearly demonstrated.



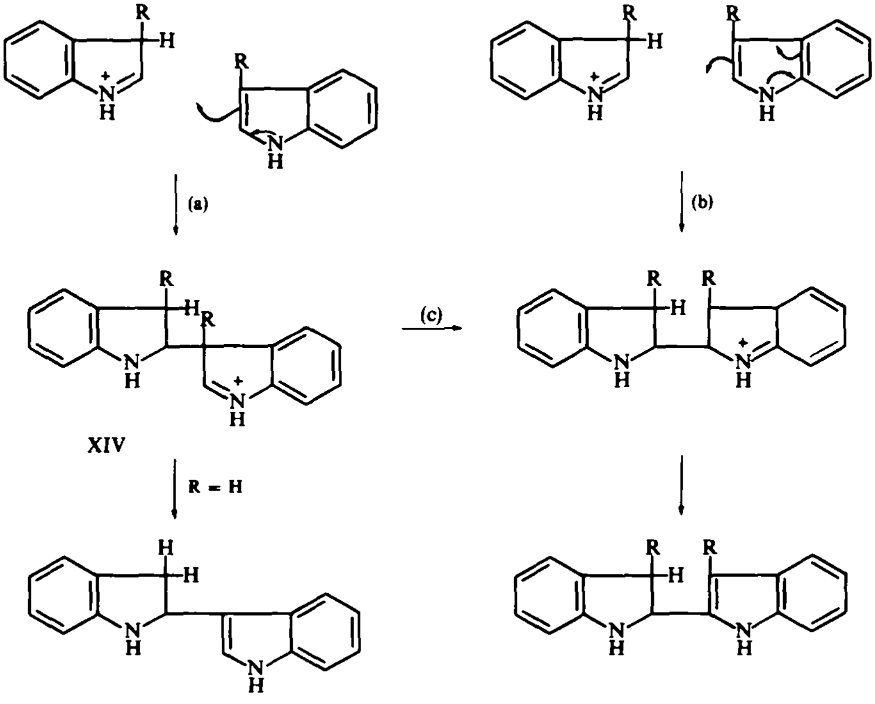

$$\text{XI}: R' = -\underset{\displaystyle CH_3}{CH}(CH_2)_5CH_3$$


$$\text{XII}: R' = -\underset{\displaystyle CH_3}{CH}Ph$$



XIII

Attempts were also made to prepare optically active indolenines (VI; R = Me, R′ = sec-octyl or Ph(CH_3)CH—) which would be expected to rearrange specifically to the indoles (VII; R = Me, R′ = sec-octyl or Ph(CH_3)CH—); the latter could then be degraded by ozonolysis and hydrolysis to the nonanoic, or phenyl propionic acids (XI; or XII) and their optical activity determined. However, whilst 3-sec-octylindole could be prepared in low yield (by alkylation of indole Grignard) its Grignard derivative could not be alkylated with methyl iodide either in ether or in benzene, nor could the Grignard derivative of skatole be alkylated with sec-octyl bromide, or 1-phenylethyl bromide at the 3-position. No basic material was obtained from these reactions and the neutral fractions contained only recovered starting materials together with traces of N-alkylated indoles (as shown by TLC). The failure of these reactions may be attributed largely to steric factors, and in agreement with this we also found that the Grignard derivatives of 3-phenyl- and 3-t-butyl-indole could not be alkylated at the 3-position with methyl iodide. However, 3-t-butyl-indole rearranges[5] to the 2-isomer under acidic conditions and its seems likely that the reaction involves initial formation of a 3-$\underline{H}$-indolium salt (IX; R = t-Bu, R′ = H) followed by migration of the labile t-butyl group. A similar mechanism may well apply in the case of the recently reported rearrangement of 3-phenylindole to 2-phenylindole on heating with aluminium chloride.[6] It is also conceivable that the relatively slow deuterium exchange[4] which occurs at the 2-position (compared with that at the 1-, or 3-positions) in deutero-sulphuric acid involves migration of deuterium from the 3-position of the initially formed 3,3-dideutero-3-$\underline{H}$-indolium salt (XIII), rather than direct substitution at the 2-position.



XIV

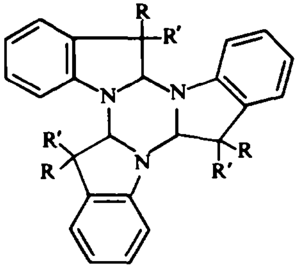
XV

XVI

The mechanism of the acid-catalysed dimerization of indoles[7] is also of some interest in connection with the present work. Dimerization of indole itself almost certainly follows the course (a) shown in the scheme below, i.e. the 3-H-indolium salt generated in presence of acid electrophilically attacks the 3-position of a neutral molecule[cf. 7] to give the dimer (XV). On the other hand skatole and other 3-alkylated indoles give structurally different dimers (XVI). Smith has suggested[7] that formation of the latter dimers is a consequence of direct electrophilic attack at the vacant 2-position of a neutral molecule by the protonated species (i.e. pathway b), and that as 3-isopropyl- and 3-t-butylindoles do not form dimers a bulky 3-substituent sterically hinders this process. However, it is tempting to suggest, in view of our work, that the initial step in the dimerization of a 3-substituted indole is the same as that with indole (i.e. pathway a), but that the initially formed dimer then undergoes rearrangement (pathway c) as it is an indolenine. This rearrangement would be facilitated by the high migratory aptitude of the 2-carbon atom of the indoline moiety in the intermediate (XIV; R = alkyl) as it is flanked by an amino group. The fact that 3-isopropyl- and 3-t-butylindole do not dimerize supports our view, as it seems much more likely that a bulky 3-substituent would inhibit electrophilic attack at the 3-position than at the 2-position.

Polymeric character of indolenines

In the course of this work NMR spectra (Table 3) showed that six of the seven indolenines studied were partially polymerized in $CDCl_3$ solution, whereas in trifluoroacetic acid solution only monomeric species were present. In our earlier paper we suggested that the species present in $CDCl_3$ solution were monomer and trimer (XVII), and this view was confirmed by other workers[8] in variable temperature studies with 3,3-dimethylindolenine; these showed that it was completely dissociated above 120°, whereas at low temperatures it was entirely in the trimeric form. We also suggested[2] that polymerization might well be hindered by bulky substituents at the 3-position and in agreement with this 3-methyl-3-benzylindolenine was the only one of the seven indolenines studied which existed entirely in the monomeric form in deuterochloroform solution (at 30°). These conclusions are now supported by mass spectral measurements (Table 4). At the usual source temperature (200–220°) spectra obtained with the direct inlet showed that only monomeric species were present; however, at lower temperatures (150–200°) appreciable amounts of ions



XVII

derived from di- and trimeric species were observed (except in the case of 3-benzyl-3-methylindolenine) as well as metastable peaks in some cases corresponding to the transitions trimer → dimer, and dimer → monomer.

TABLE 4. MASS SPECTRA OF INDOLENINES AND INDOLES

Mass spectra were determined with an A.E.I. MS9 spectrometer (at 50 μa and 70 eV), using a direct inlet. Spectra of the indolenines were determined as the source was warming up (ca. 150–200°) in order to detect di- and tri-meric forms (if present), and spectra of indoles were determined at the normal source operating temperature (200–220°).

Indolenines

VIa: 435 (1) M_3^+, 290 (38) M_2^+, 217·5 (0·5) M_3^{++}, 184 (3), 169 (3), 154 (2), 146 (23), 145 (100) M^+, 144 (62), 131 (9), 130 (36), 117 (6), 116 (3), 115 (6), 104 (16), 103 (15), 78 (13), 77 (14).
m*: 193 (435 → 290); 143 (145 → 144); 116·5 (145 → 130); 81·6 (130 → 103); 72·5 (290 → 145); 58·5 (290 → 130).

VIb: 173 (35) M^+, 172 (6), 159 (18), 158 (100), 157 (6), 156 (6), 146 (4), 145 (16), 144 (34), 143 (30), 131 (12), 130 (24), 129 (8), 128 (10), 117 (15), 116 (10), 115 (22), 77 (12).
m*: 144 (173 → 158); 129·4 (158 → 143); 117·5 (146 → 131); 116·5 (145 → 130).

VIc: 477 (0·5) M_3^+, 318 (2) M_2^+, 159 (73) M^+, 158 (21), 144 (100), 131 (16), 130 (26), 117 (7), 115 (7), 104 (6), 103 (7).
m*: 130·3 (159 → 144); 108 (159 → 131); 107·2 (159 → 130); 79·5 (318 → 159).

VId: 346 (1) M_2^+, 173 (45) M^+, 158 (15), 145 (30), 144 (100), 131 (20), 130 (55), 117 (5), 116 (5), 115 (10), 104 (5), 103 (10), 102 (5), 91 (5), 78 (15), 77 (15).
m*: 144 (173 → 158).

VIe: 519 (0·5) M_3^+, 346 (2) M_2^+, 173 (60) M^+, 158 (67), 144 (5), 143 (5), 131 (58), 130 (100), 117 (5), 116 (4), 115 (7), 103 (7), 102 (4), 91 (4), 77 (12), 74 (20).
m*: 144·3 (173 → 158); 130·5 (159 → 144); 129·5 (158 → 143); 99·1 (173 → 131); 86·5 (346 → 173).

VIf: 513 (0·5) M_3^+, 342 (7) M_2^+, 171 (100) M^+, 170 (63), 156 (55), 144 (29), 143 (9), 131 (9), 130 (49), 129 (6), 128 (6), 117 (2), 115 (5), 104 (2), 103 (8), 102 (4), 77 (10).
m*: 228 (513 → 342); 142·3 (171 → 156); 106·7 (?); 85·5 (342 → 171); 81·5 (130 → 103).

VIg: 221 (100) M^+, 220 (11), 206 (2), 178 (2), 165 (1), 144 (5), 130 (8), 91 (50), 85 (36), 83 (57).
m*: 219 (221 → 220); 192 (221 → 206).

Indoles

VIIa: 145 (75) M^+, 144 (100), 130 (58), 117 (4), 116 (3), 115 (8), 104 (7), 103 (7), 77 (16).
m*: 143 (145 → 144); 116·5 (145 → 130); 81·5 (130 → 103).

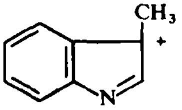
VIIc: 159 (50) M^+, 158 (14), 144 (100), 143 (15), 130 (10), 117 (4), 116 (3), 115 (5), 104 (4), 103 (3).
m*: 130·2 (159 → 144); 106·7 (159 → 130).

VIIg: 221 (100) M^+, 220 (36), 218 (9), 217 (8), 206 (45), 205 (8), 204 (22), 191 (5), 178 (13), 167 (6), 165 (6), 144 (90), 143 (50), 142 (12), 130 (47), 128 (15), 117 (13), 116 (15), 115 (32), 103 (15), 102 (18), 91 (28), 89 (17), 78 (34), 77 (53).
m*: 219 (221 → 220); 192 (221 → 206); 155·5 (204 → 178); 93·8 (221 → 144).

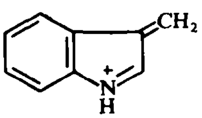
3-sec-octylindole: 229 (18) M^+, 214 (2), 200 (12), 186 (6), 172 (9), 158 (36), 145 (14), 144 (100), 143 (17), 130 (57), 117 (11), 116 (4), 115 (10), 91 (4), 90 (4), 89 (4), 77 (5).
m*: 200 (229 → 214); 175 (229 → 200); 107 (158 → 130); 98·5 (172 → 130); 90·8 (186 → 130); 84·5 (200 → 130).

3-t-butylindole: 173 (27) M^+, 158 (100), 157 (3), 130 (12), 118 (11), 117 (11), 116 (3), 115 (10), 91 (4), 77 (4).
m*: 144·5 (173 → 158); 107 (158 → 130).

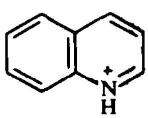
Details of the mass spectra of the seven indolenines studied are recorded in Table 4 together with those of related simple alkylindoles. The monomeric parts of the indolenine spectra are very similar to those of the isomeric 2,3-disubstituted indoles, and it is quite likely that rearrangement occurs under electron impact to give the same ions. With the exception of 3-benzyl-3-methylindolenine all the indolenine mass spectra may be divided into two parts (i) above *m/e* 130 ions corresponding to fragmentation of the alkyl groups are observed, and (ii) ions at *m/e* 130, 117, 116, 115, 104, 103, 78 and 77 common to all the spectra. The base peaks (*m/e* 130) in the spectra of the isopropyl and allyl indolenines (VIe and VIf) correspond to cleavage of the whole alkyl group to give the ion *a* (or a rearrangement product *a*′ or *a*″), whereas the major fragmentation product *b* (or *b*′) in the spectra of the other indolenines is derived by partial cleavage of the alkyl group; this is probably a reflection of the relative stabilities of the isopropyl and allyl radicals expelled compared to the other radicals. 3-Benzyl-3-methylindolenine (VIg) exhibits a very simple spectrum in which the major fragment peak *m/e* 91 clearly corresponds to the benzyl (or tropylium) cation.



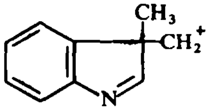
a (*m/e* 130)



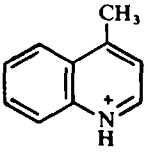
a′



a″



b (*m/e* 144)



b′

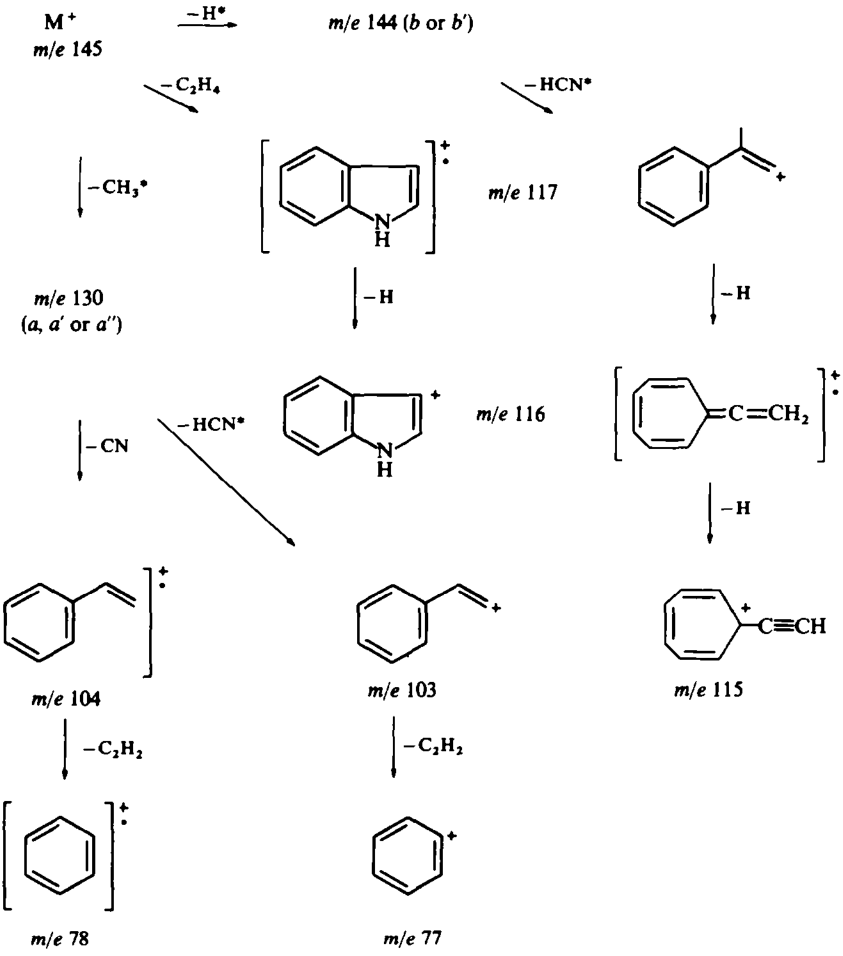
TABLE 5. HIGH RESOLUTION MASS SPECTRA

m/e	Observed: 3,3-dimethyl-indolenine	Observed: 2,3-dimethyl-indole	Calculated:	
	Accurate mass			
130	130·0648	130·0656	C_9H_8N	130·0657
117	117·0687[a]	117·0692	C_9H_9	117·0704
	117·0573	117·0574[a]	C_8H_7N	117·0578
116	116·0612[a]	116·0612[a]	C_9H_8	116·0626
	116·0475	116·0498	C_8H_6N	116·0500
115	115·0549	115·0541	C_9H_7	115·0548
104	104·0610	104·0603[a]	C_8H_8	104·0626
	—	104·0500	C_7H_6N	104·0500
103	103·0538	103·0541	C_8H_7	103·0548

[a] Major peak in each doublet.

The mass spectra of several alkyl indoles have been discussed by Beynon and Williams,[9a] and our results largely confirm their findings. The precise structure of the fragmentation products below *m/e* 130 is a matter of speculation,[9b] but accurate mass measurements have been carried out with two compounds (Table 5) and a number of possibilities are included in the accompanying scheme.

Mass Spectral fragmentation of
2,3-Dimethylindole and 3,3-Dimethylindolenine



EXPERIMENTAL

M.ps are uncorrected. UV spectra were determined with a Unicam SP800 spectrophotometer, NMR spectra with a Varian A-60 instrument, and mass spectra with an A.E.I. MS9 spectrometer (operating at 50 μa, 70 eV and with a direct inlet at 200–220° unless otherwise indicated). TLC was carried out on silicagel (for indoles) or alumina (for indolenines) in benzene–light petroleum (b.p. 60–80°) mixtures.

Indoles

These were prepared by the Fischer indole synthesis using a method adapted from that described by Snyder and Smith.[10] Phenylhydrazine hydrochloride (140 g) and sodium acetate (82 g) were dissolved in water (1·2 l.) and filtered. The resulting soln was treated with the appropriate aldehyde or ketone (1·0 mole) in water (750 ml; or MeOH, if the ketone was immiscible in water) when a yellow oil formed rapidly and was separated. The aqueous layer was extracted with ether, and the combined extracts washed with water, dried ($MgSO_4$) and evaporated to give a yellow oil. The latter was fractionally distilled under reduced press and afforded the desired phenylhydrazone.

(a) Boron trifluoride-etherate (0·5 mole) was added to a soln of the phenylhydrazone (0·6 mole) in glacial AcOH (180 ml) when rapid evolution of heat occurred and the mixture boiled under reflux. The soln was finally heated for a further 15 min under reflux, cooled and poured into ice-water. The latter was extracted thrice with ether, and the extracts washed twice with water, dried ($MgSO_4$) and evaporated to dryness. The crude product was then distilled under reduced press, or recrystallized from light petroleum (b.p. 40–60°) as appropriate.

(b) One of the phenylhydrazones was cyclized by heating for 30 min at 150° with $ZnCl_2$ (0·1 mole equiv). After cooling the tarry mass was poured into ether and water and worked up as above.

Ketone	Cyclizing agent	Indole (substituents)	Overall yield (%)	M.p. or b.p.	Lit.* m.p. or b.p.
EtCOMe	BF_3/Et_2O	2,3-di-Me	48	106°	107°
EtCOEt	BF_3/Et_2O	2-Et, 3-Me	72	65–66°	66°
PrCOMe	BF_3/Et_2O	2-Me, 3-Et	66	120°1·0 mm	156°/12 mm
Me_2CHCH_2COMe	BF_3/Et_2O	2-Me, 3-iPr	64	120°/0·8 mm	173°/15 mm
PhCOEt	BF_3/Et_2O	2-Ph, 3-Me	64	58°	59°
$PhCH_2CHO$	BF_3/Et_2O	3-Ph	70	88°	88–89°
PrCHO	$ZnCl_2$	3-Et	40	100°/0·8 mm	282°/760 mm

* cf. Beilstein. Vol. XX.

3-*sec*-*Octylindole*

Excess EtBr (8·2 g, 0·075 mole) was added slowly to Mg turnings (1·2 g, 0·05 mole) in dry ether (30 ml) and when all the Mg had reacted dry benzene (30 ml) was added and the ether and excess EtBr distilled out. Indole (5·9 g, 0·05 mole) in benzene (20 ml) was then added slowly and the resulting yellow soln heated for 15 min under reflux. sec-Octyl bromide (9·7 g, 0·05 mole) was added and the mixture heated for 2 hr under reflux before pouring onto ice-cold 2N HCl (50 ml). The organic layer was separated, and the aqueous layer extracted with ether (50 ml). The combined extracts were washed with water, dried ($MgSO_4$), evaporated to dryness and the residual oil distilled at 150°/0·1 mm to give 3-*sec-octylindole* (2·28 g, 20%) as a viscous yellow oil. (Found: C, 84·0; H, 10·3; N, 6·3. $C_{16}H_{23}N$ requires: C, 83·8; H, 10·1; N, 6·1%); NMR spectrum see Table 2.

3,3-*Dialkyl-indolenines*

The 3-alkyl-indole (0·05 mole) in benzene was converted into its Grignard derivative and alkylated with the appropriate alkyl halide by the same procedure as that described above for the preparation of 3-sec-octylindole. The product was poured into cold 2NHCl as above and neutral materials extracted with ether. The aqueous layer was then basified with 2N NaOH and extracted with ether (3 × 50 ml). The combined extracts were washed with water (2 × 20 ml), dried ($MgSO_4$) and evaporated to dryness to give the crude indolenine, which was crystallized from alcohol or distilled.

The following four compounds were prepared using this general procedure, the first three from skatole and the appropriate alkyl bromide, and the last from 3-ethylindole and EtBr or EtI. In the case of 3-benzyl-3-methylindolenine the alkylation of the skatolyl Grignard reagent with benzyl bromide was carried out in ether soln at 0°, and the product was worked up as rapidly as possible using ice-cold solns throughout to avoid rearrangement.

(VIb) 3,3-Diethylindolenine (30%), b.p. 120–125°/2mm (Lit.[11] b.p. 134–135°/30 mm) *Picrate*, yellow needles from alcohol, m.p. 105–106° (Found: C, 53·6; H, 4·5; N, 14·0. Calc. for $C_{12}H_{15}N.\ C_6H_3N_3O_7$: C, 53·7; H, 4·5; N, 13·9%)

(VIc) 3-*Ethyl*-3-*methyl-indolenine* (38%) formed needles, m.p. 163–164°, and gave a *picrate*, as yellow needles, m.p. 148° from alcohol. (Found: C, 52·6; H, 4·3; N, 14·3. $C_{11}H_{13}N$. $C_6H_3N_3O_7$ requires: C, 52·6; H, 4·2; N, 14·4%); λ_{max} (log ε_{max}): in 95% EtOH, 256 (3·91), 297 (3·49); in 95% EtOH/HCl, 232 (3·62), 236 sh. (3·60), 277 (3·48) mμ.

(VIe) 3-*Isopropyl*-3-*methylindolenine* (12%) needles, m.p. 75°. *Picrate*, yellow needles, m.p. 160–161° from alcohol (Found: C, 54·0; H, 4·6; N, 13·7. $C_{12}H_{15}N$. $C_6H_3N_3O_7$ requires: C, 53·7; H, 4·5; N, 13·9%); λ_{max} (log ε_{max}): in 95% EtOH, 257 (3·88); in 95% EtOH/HCl, 233 (3·77), 238 sh (3·78), 280 (3·69) mμ.

(VIg) 3-*Benzyl*-3-*methylindolenine* (35%), needles, m.p. 61°. (Found: C, 86·6; H, 6·8; N, 6·3. $C_{16}H_{15}N$ requires: C, 86·8; H, 6·8; N, 6·3%); λ_{max} (log ε_{max}): in 95% EtOH, 257 (3·86), 292 (3·37); in 95% EtOH/HCl, 229 (3·84), 282 (3·53) mμ.

Rearrangement of indolenines VI *to* 2,3-*disubstituted indoles* (VII) The seven indolenines (cf. Table 1) prepared in this and earlier work[2] were rearranged completely and in nearly quantitative yield (determined by UV spectroscopy) by heating in aqueous ethanolic 6N HCl for 15 min. The resulting 2,3-disubstituted indoles were isolated by dilution with water followed by ether extraction, etc., and crystallization or distillation as appropriate. Some of the products were quite sensitive to antoxidation resulting in low yields on isolation, e.g. 2-benzyl-3-methylindole. The structures of the products were determined by their NMR spectra in trifluoroacetic acid (cf. Table 2) as well as by comparison with authentic materials (available in some cases through Fischer indole syntheses). Preliminary studies of the rates of rearrangement showed that the reactions were first order in 0·5N HCl in aqueous EtOH.

(VIIb) 2,3-Diethyl-indole, b.p. 105–110°/0·1 mm (Lit.[13] b.p. 118–120°/2 mm).

(VIIc) 2-Ethyl-3-methylindole was identical in all respects with material prepared by Fischer synthesis from diethyl ketone phenyl hydrazone.

(VIIe) 2-Isopropyl-3-methylindole, b.p. 140–145°/2 mm (Lit.[12] 175–177°/30 mm).

(VIIg) 2-*Benzyl*-3-*methylindole*, rhombs, m.p. 90–91° from light pet. (b.p. 60–80°) *Picrate*, dark red needles from alcohol, m.p. 140–142°. (Found: C, 59·0; H, 4·2; N, 12·1. $C_{16}H_{15}N$. $C_6H_3N_3O_7$ requires: C, 58·7; H, 4·0; N, 12·4%.)

Gas chromatography of indoles

Indoles were chromatographed on 5% silicon oil on celite at 220° with N_2 as carrier gas (15 lb/in^2). Retention times (relative to benzene as internal standard) are shown in the Table below, and except for N-substituted indoles (which tend to run slightly faster) these show an almost linear dependence on mol wt.

Rearrangement of a mixture of 3,3-dimethyl and 3,3-diethylindolenines in the same solution gave only 2,3-dimethyl- and 2,3-diethylindoles; no traces of methylethylindoles could be detected.

Indole (substituents)	Retention time*
2,3-H	27·5
3-Me	39·5
2-Me	40·3
1,2-di-Me	47·5
2,3-di-Me	59·5
3-Et	59·0
2-Et, 3-Me	75·0
3-Et, 2-Me	54·0
3-t-Bu	88·0
3-i-Pr, 2-Me	90·5

* Relative to benzene as internal standard.

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