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ELECTROPHILIC SUBSTITUTION IN INDOLES—I

MODEL EXPERIMENTS RELATED TO THE SYNTHESIS OF ECHINULIN

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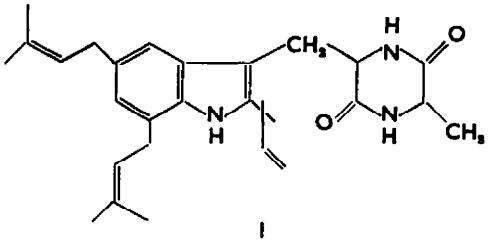
Abstract—3-methylindolyl magnesium iodide reacts with allyl bromide to give a mixture of 1- and 2-allyl-3-methylindoles, and 3-allyl-3-methylindolenine; crotyl- and 3,3-dimethylallyl bromides give 1- and 2-allylic-3-methylindoles only. The structures of the reaction products were confirmed spectroscopically and the mechanisms of the reactions are discussed in relation to possible modes of biogenesis of the mould metabolite echinulin.

THE usual position for electrophilic substitution in simple indoles is the 3-position, although if this is blocked substitution may occur in the 2-position instead.[1] Electrophilic reagents may also effect substitution on nitrogen particularly if the alkali metal salts or Grignard derivatives of the indole are used. However, in most reactions of indolyl Grignard reagents with alkyl halides recorded in the literature substitution takes place at the 3-position and to a lesser extent on nitrogen. Recent NMR studies have shown the largely ionic nature of indolyl magnesium bromides in tetrahydrofuran,[2] but these must presumably be more associated in solution than the corresponding alkali metal salts to account for the greater proportion of the 3-substituted product. Even when the 3-position is already substituted electrophilic attack on indolyl Grignard reagents still occurs largely at the 3-position, and the corresponding 3,3-disubstituted indolenines are formed.[1] On the other hand, it has been suggested that the primary site of electrophilic substitution in 3-methylindole is the 2-position,[3] and thus the present picture is somewhat confusing. This is therefore the first in a series of papers in which various aspects of electrophilic substitution reactions in indoles will be considered and an attempt will be made to define more clearly the conditions under which substitution occurs in the various positions of the indole nucleus.

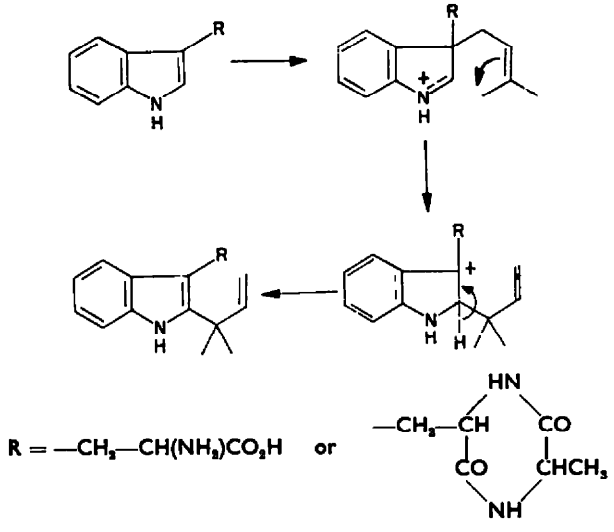
The mould metabolite echinulin (I) is one of the few naturally occurring indole derivatives in which isoprene units are incorporated and dissection of its structure



I

[1] Sumpter and Miller *The Chemistry of Heterocyclic Compounds* Interscience, Chap. 50, Vol 8. (1958).
[2] M. G. Reinecke, A. W. Johnson and J. F. Sebastian, *Tetrahedron Letters* 1183 (1963).
[3] W. E. Noland and D. N. Robinson, *Tetrahedron* 3, 68 (1958).

clearly indicates the probable origin from tryptophan, alanine and three isoprene units. Tracer experiments have shown that L-tryptophan is incorporated[4] by *Aspergillus amstelodarin* into echinulin (I), and that isopentenyl units are incorporated by both *Aspergillus echinulatus* and *Aspergillus amstelodarin*.[5] By analogy with naturally occurring phenolic compounds containing isoprenoid units[6] echinulin is probably formed by electrophilic attack of 3,3-dimethylallyl pyrophosphate on tryptophan, (or the diketopiperazine derived from tryptophan and alanine). From this point of view the most striking feature of echinulin is that the isoprenoid residue at the 2-position of the indole nucleus is reversed relative to those at the 5- and 7-positions. Substitution at the 5- and 7-positions may be regarded as a normal nucleophilic displacement of pyrophosphate from the dimethylallyl pyrophosphate (S_{N_2} type), whereas substitution at the 2-position may involve nucleophilic attack by the indole nucleus at the 3-position in the dimethylallyl pyrophosphate ($S_{N_2'}$ type).[7] The latter seems rather less likely owing to the steric hindrance which may be involved in attack at a tertiary carbon atom.[8] An alternative possibility (which seemed quite attractive to us in view of the propensity of the indole nucleus to substitution at the 3-position), is that the "reversed" isoprenoid unit in the 2-position could arise by an initial substitution at the 3-position followed by a Claisen-like rearrangement as follows:

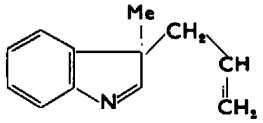


Such an alkylation reaction in nature might well occur through the agency of a metal derivative of the indole and accordingly we have investigated the reactions of some allylic halides with indole Grignard reagents.

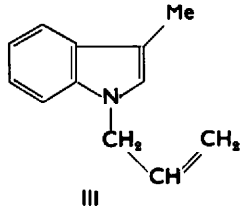
Indolyl magnesium iodide itself reacts straightforwardly with allyl bromide to give

[4] A. J. Birch and K. R. Farrer, *J. Chem. Soc.* 4277 (1963).
[5] A. J. Birch, G. E. Blance, S. David and H. Smith, *J. Chem. Soc.* 3128 (1961).
[6] *Recent Developments in the Chemistry of Natural Phenolic Compounds* Chap. 4. (Edited by D. Ollis) Pergamon Press (1961).
[7] Cf. R. H. DeWolfe and W. G. Young, *Chem. Revs.* **56**, 753 (1956) for a review of the reactions of allylic halides.
[8] Cf. the reaction of indolyl magnesium iodide with t-butyl chloride which gives a very poor yield, G. F. Smith, A. E. Waters, *J. Chem. Soc.* 941 (1961).

3-allyl indole,[9] and the first reaction we investigated was the alkylation of 3-methylindolyl magnesium iodide with allyl bromide. The major product (44%) is 3-allyl-3-methylindolenine (II) as expected, and this may be separated from the other (neutral) products by extraction with 5% hydrochloric acid. The neutral material was shown to be a mixture of 1-allyl-3-methylindole (III; 4% yield) and 2-allyl-3-methylindole (IV; 28% yield), but they were not isolated as such owing to their relative instability to light and air. Instead the mixture was hydrogenated over Pt in methanol to give



II



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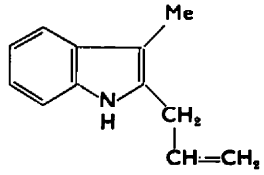
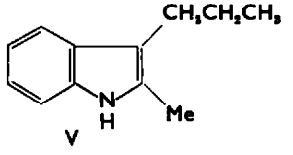
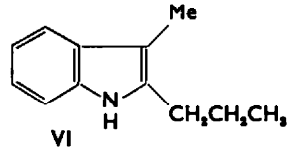


IV

the corresponding propyl indoles which are much more stable and are easily separated chromatographically. The structures of the latter were confirmed by spectroscopic methods and by alternative syntheses, i.e. 1-propyl-3-methylindole may be prepared by alkylation of the sodium salt of 3-methylindole and alkylation of 2-methylindolyl magnesium iodide with allyl bromide followed by catalytic reduction to 2-methyl-3-propylindole (V). The IR spectra of V and the reduction product (VI) of the allyl



V



VI

indole (IV) are quite different from each other in the fingerprint region, but their NMR spectra are almost identical (cf. Table 1). However on standing in air they are both

TABLE 1. PROTON MAGNETIC RESONANCE SPECTRA OF INDOLES IN DEUTEROCHLOROFORM

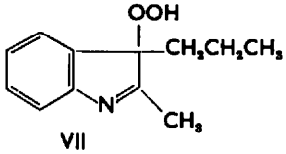
Indole substituents*	τ-Values of protons in substituents†				
	CH_3[s]	—CH_2	—$(CH_2)_n$[m]	—CH_3	2-H[s]
3 Pr	—	7·29[t]	~8·35	9·04[t]	3·11
3 Pr, 2 Me	7·80	7·38[t]	~8·4	9·11[t]	—
2 Pr, 3 Me	7·80	7·38[t]	~8·45	9·09[t]	—
2 Bu, 3 Me	7·77	7·33[t]	8·2–8·9	9·09[t]	—
2 i-Pen, 3 Me	7·82	7·39[t]	8·3–8·7	9·10[d]	—
1 Pr, 3 Me	7·72	6·13[t]	8·1–8·6	9·20[t]	3·26
1 Bu, 3 Me	7·72	6·13[t]	8·2–8·9	9·09[t]	3·30
1 i-Pen, 3 Me	7·70	6·00[t]	8·2–8·6	9·07[d]	3·18
		—CH_2	—CH	=CH_2	
1 allyl, 3 Me	7·71	~5·5[m]	~4·2	~5·0[m]	3·21
3 allyl	—	~6·55[m]	~4·1	~4·9[m]	3·20

* Abbreviations: Me = CH_3, Pr = $CH_3CH_2CH_2$—, Bu = $CH_3CH_2CH_2CH_2$—, i-Pen = $(CH_3)_2CH{\cdot}CH_2CH_2$—

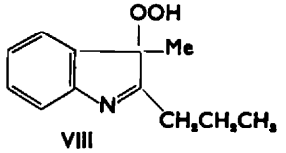
† NH at ~2·3τ, aromatic H as multiplets in the range 2·3–3·1τ. s = singlet, d = doublet, t = triplet, m = multiplet.

[9] J. B. Brown, H. B. Henbest and E. R. H. Jones, *J. Chem. Soc.* 3172 (1952).

converted into isomeric crystalline solids which analyse for $C_{12}H_{15}NO_2$. These were identified as the corresponding hydroperoxyindolenines (VII and VIII) respectively by analogy with similar observations on other 2,3-disubstituted indoles,[10] and their NMR spectra confirm the structures assigned (Table 2), e.g. the 3-methyl group of VIII (attached to a saturated carbon atom) gives rise to a singlet (8·51τ) at higher field than the resonance (7·80τ) of the 2-methyl group of VII (attached to an olefinic carbon atom).



VII

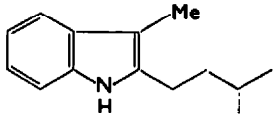


VIII

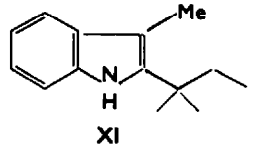
Rearrangement of 3-allyl-3-methylindolenine (II) to 2-allyl-3-methylindole (IV) occurs very readily in acidic solution (e.g. brief warming with 3 N HCl) and even solutions in 0·1 N HCl prepared for UV spectral measurements (Table 3) show evidence of some rearrangement. In contrast, 3-methyl-3-propylindolenine (prepared by catalytic hydrogenation of the allyl indolenine (II) over Pt in MeOH) gives a typical indolenine salt spectrum in 5% ethanolic hydrogen chloride solution, and requires considerably more drastic conditions (e.g. 6 N acid at 80° for 10 min) to cause rearrangement to 3-methyl-2-propylindole (IV). Attempts to rearrange 3-allyl-3-methylindolenine under thermal conditions (e.g. by prolonged refluxing in acetonitrile, or by heating to 200° in a sealed tube) failed completely and only starting material could be recovered from the tarry products.

3-Allyl-3-methylindolenine (II) may also be synthesized by methylation of 3-allylindolyl magnesium iodide but in somewhat lower yield (15%) than by the alternative method described above. The neutral fraction from this reaction was hydrogenated before chromatographic work-up and the only other product isolated was 3-propylindole (70%) derived from unreacted starting material.

3-Methylindolyl magnesium iodide reacts vigorously with 3,3-dimethylallyl bromide at room temperature and it was necessary to cool the mixture in ice during the addition of the allyl halide. In view of the lability of 3-allyl-3-methylindolenine to acid the magnesium complexes were decomposed with Rochelle salt solution instead of acid since the two methyl groups in the γ,γ-dimethylallyl group would be expected to enhance this lability. The crude oily product thus obtained is unstable in air and to facilitate separation of the mixture it was hydrogenated over Pt in methanol to reduce the allylic double bonds before chromatography on alumina in petrol. In addition to a small quantity of 3-methylindole recovered, two major components were isolated (i) 1-isopentyl-3-methylindole (identified by its IR and PMR spectra and comparison with an authentic sample prepared by alkylation of the sodium salt of 3-methylindole with isopentyl bromide) and (ii) 2-isopentyl-3-methylindole (X). The



X



XI

[10] R. J. S. Beer, T. Broadhurst and A. Robertson, *J. Chem. Soc.* 4946 (1952); E. Leete, *J. Amer. Chem. Soc.* **83**, 3646 (1961).

structure of the latter was shown by its PMR spectrum which clearly distinguishes it from its isomer (XI) in which the isopentyl group is reversed. Structure XI would give rise to a singlet (area 6 protons) for the 2 methyl groups and the very characteristic triplet (area 3 protons) and quartet (area 2 protons) for the ethyl group in the isopentyl side chain, whereas a doublet (area 6 protons) and two multiplets (area 3 protons and 2 protons) are actually observed in accord with structure X. The relative positions of the isopentyl and methyl groups were not proved directly but assumed by analogy with the corresponding 2-allyl-3-methylindole as unfortunately aerial oxidation of X to the hydroperoxide can not be achieved and only polymeric products are obtained.

Since allyl bromide gives a mixture of indolenine and indolic products, whereas dimethylallyl bromide gives only indolic products with 3-methylindolyl magnesium iodide, alkylation with crotyl bromide was also investigated. The reaction product was worked up as in the previous case with the dimethylallyl bromide reaction and 1-n-butyl-3-methylindole and 2-n-butyl-3-methylindole were obtained; no trace of indolenine or indoline type products was found.

Thus reaction of all three allyl bromides with 3-methylindolyl magnesium iodide leads to a mixture of 1,2- and 2,3-disubstituted products, and in addition allyl bromide itself also gives a substantial amount of the 3,3-disubstituted indolenine. In view of the lability of the latter to acid it seems reasonable to suppose that the 2-allyl-3-methylindole (IV) arises by partial rearrangement of the indolenine (II) during work-up. If this is accepted then it is very likely that the 2,3-substituted indoles formed from crotyl- and dimethylallyl-bromides arise by rearrangement of the corresponding indolenines during the work-up; the failure to isolate any indolenine in these two cases is attributed to the inductive effects of the extra methyl groups in the allyl side chains which enhance their migratory aptitudes. The rearrangements of the indolenines are clearly 1,2-acid catalysed rearrangements of the Wagner–Meerwein type rather than the Claisen-type rearrangements of the type postulated for the biogenesis of echinulin. It is of course still conceivable that the isoprenoid residue in the 2-position of the indole nucleus of echinulin arises by the type of mechanism we have suggested, although no evidence for it is provided by these experiments. Solvent effects may play a considerable role in these reactions.

Direct substitution may of course occur in nature at the 2-position but another alternative possibility is that isoprenoid substitution takes place first on the nitrogen atom and that this is followed by rearrangement to the 2-position.[11] However, in our hands 1-allyl-3-methylindole could not be induced to undergo rearrangement either under thermal or under acidic conditions, and only partial decomposition or polymerization occurred.

In the course of this work we also had occasion to investigate some aspects of the properties of indolenines. In the literature three different m.ps (170–172°,[12] 152°[13] and 214°[13,14]) have been given for 3,3-dimethylindolenine, and these have been attributed to mono-, di- and tri-meric forms, on the basis of Rast mol. wt. determinations. We observed that 3-allyl-3-methylindolenine also appears to be partially polymeric since Rast determinations give a mol. wt. of 219 whereas the monomeric formula

[11] This possibility has also been considered by other authors cf. Ref. 4, and also Dr. J. D. Bu'Lock—private communication.

[12] K. Brunner, *Monatsh.* **16**, 850 (1895).

[13] R. Robinson and H. Suginome, *J. Chem. Soc.* 298 (1932).

[14] T. Hoshino, *Liebigs' Ann.* **500**, 35 (1933).

$C_{12}H_{13}N$ requires 171. The NMR spectrum in $CDCl_3$ is also somewhat more complex than expected (Table 2) although it does show a sharp singlet resonance at 2·01τ (area ~0·9 proton) attributed to the 2-proton in the monomeric indolenine form.

TABLE 2. PROTON MAGNETIC RESONANCE SPECTRA OF INDOLENINES

Substituents*	τ-Values†					
	—CH_3[a]	—CH	—CH	—CH	2-H[§]	Aromatic-H
(a) *In Deuterochloroform*						
[a] 3-Me, 3-Allyl	8·66	7·51[d]	4·3–5·1		2·01	2·2–2·9
3-Me, 3-Pr	8·68	~8·2	~9·0	9·18[t]	1·92	2·3–2·8
[b] 3,3-diMe	8·67	—	—	—	2·00	2·3–3·8
‡ 3-Me, 2-Pr, 3-OOH	8·51	7·28[t]	~7·28	8·99[t]	—	2·3–3·1
2-Me, 3-Pr, 3-OOH	7·80	~8·3	~9·0	9·20[t]	—	2·5–3·2
(b) *In Deuterochloroform containing 5–10% trifluoroacetic acid*§						
3-Me, 3-Allyl	8·42	7·25[d]	4·5–5·1		1·24	2·1–2·7
3-Me, 3-Pr	8·36	~7·85	~9·0	9·10[t]	1·05	2·1–2·6
3,3-diMe	8·54	—	—	—	1·53	2·0–2·7
(c) *In Trifluoroacetic acid*						
[c] 3-Me, 3-Allyl	8·25	7·03[d]	4·2–4·9		1·15	~2·2
3-Me, 3-Pr	8·40	7·7[t]	~8·9	~9·1	0·90	~2·2
3,3-diMe	8·25	—	—	—	1·16	2·25[s]

* Abbreviations as in Table 1.

† Multiplets unless otherwise indicated (by s, d, t).

‡ Sparingly soluble in $CDCl_3$. Aromatic H and OOH (−0·7) observed in acetone solution, aliphatic H in pyridine solution.

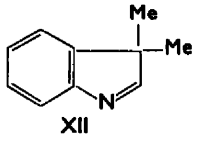
§ Trifluoroacetic acid concentration dependent.

[a] In $CDCl_3$ spectra of most samples of 3-allyl-3-methylindolenine small extra resonances occurred at 5·55, 5·70 and 8·46, but in one sample m.p. 138–140° four singlet peaks of similar intensity were observed in the methyl region (at 8·57, 8·65, 8·67 and 8·70), two doublets (at 7·76 and 7·53), singlets (at 5·55 and 5·75), a very complex pattern in the 2·5–5·5 region, and a low intensity singlet (at 1·98; <0·1 proton).

[b] Additional low intensity singlet resonances occurred at 8·80, 8·65 and 8·41 in the methyl region, and at 5·78, 5·56 and 5·06 in $CDCl_3$ spectra.

[c] Additional low intensity resonances occurred at 8·15 (singlet), and 6·01 (doublet); these may be due to the rearrangement product 2-allyl-3-methylindole.

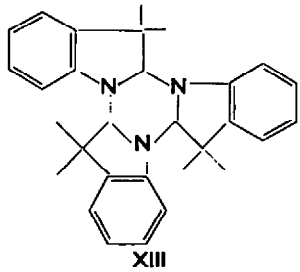
We therefore repeated Hoshino's preparation[14] of 3,3-dimethylindolenine (XII) from 3-methylindolyl magnesium iodide and methyl iodide, and obtained a crystalline



XII

solid m.p. 212° (Rast Mol. wt. 218 whereas $C_{10}H_{11}N$ requires 145). The IR spectrum shows a strong peak at 6·25 μ which could be attributed to the C=N in the monomeric indoline, but on the other hand we have observed that indolines also give strong peaks

in the same region, which are presumably due to ring stretching vibrations. The UV spectrum in 95% ethanol is however similar to those of indolines whereas in 0·5 N HCl it is very similar to that of 2,3,3,-trimethylindolenine methiodide[15] (cf Table 3) and of 3-*H*-indolium salts formed by protonation of indoles at the 3-position in strongly acidic media.[16,17] The NMR spectrum (like that of the 3-allyl-3-methylindolenine) is also more complex than expected, and a singlet at 2·00τ (area <0·1 proton) attributed to the C_2-proton indicates that very little of the compound is present in the monomeric form compared with the allyl analogue. Three weak singlet resonances in the 5–6τ region of the spectrum may be due to protons in a Ph—N—C*H*—N environment (cf. reference 17) e.g. if the trimer has a cyclic structure of type XIII. Since the



XIII

UV studies have shown that the salt form is monomeric, we also determined the NMR spectra of 3,3-dimethylindolenine in $CDCl_3$ containing 5% trifluoroacetic acid, and in 100% trifluoroacetic acid. In both cases much simpler spectra were obtained (Table 2) in accord with the monomeric structure (XII). Similarly the spectrum of 3-allyl-3-methylindolenine in $CDCl_3$ containing trifluoroacetic acid is also in accord with a

TABLE 3. ULTRA-VIOLET SPECTRA OF INDOLENINES

Substituents* 2-	3-	95% Ethanol λ_{max} (log ε max.) (mμ)	Dilute hydrochloric acid λ_{max} (log ε max.) (mμ)
H	Allyl Me	253 (3·83)	225 (3·72), 236^{sh} (3·54), 270 (3·42)§
H	Pr Me	253 (4·11)	233 (3·70), 238^{sh} (3·68), 282 (3·61)
H	Me† Me	256 (4·24), 298 (3·70)	232 (3·72), 236^{sh} (3·69), 280 (3·64)
Pr	Me OOH	218 (4·19), 269 (3·48)	—
Me	P OOH	220 (4·18), 257 (3·48)	—
Me	Me[15] Me	222 (4·22), 255 (3·94)	229 (4·00), 235 (3·95), 275 (3·91) 229 (3·78), 236 (3·73), 273 (3·77)‡
Me	Me OOH[10]	218 (4·29), 249 (3.56)	—

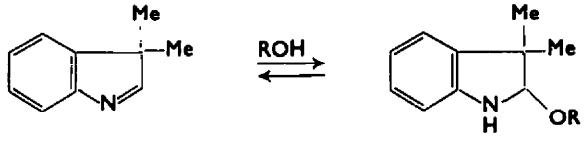
* Abbreviations as in Table 1. † Sample m.p. 212°. ‡ Methiodide in water.[15]
§ Spectrum in 0·1 M HCl. Peaks poorly defined owing to partial rearrangement to 2-allyl-3-methylindole; spectrum changed slowly with time.
sh Shoulder.

[15] R. L. Hinman and E. B. Whipple, *J. Amer. Chem. Soc.* **84**, 2534 (1962).
[16] G. Berti, A. da Settimo and D. Segnini, *Gazz. Chim. Ital.* **90**, 539 (1960).
[17] A. H. Jackson and A. E. Smith, *J. Chem. Soc.* in press.

monomeric structure, as is that of 3-methyl-3-propyl indolenine. From the limited information provided by these experiments it would appear that indolenines exist in polymeric form in the crystalline state or in neutral or alkaline solution, the degree of polymerization to structures such as XIII perhaps being controlled by steric factors (i.e. the size of the substituents).

Attempts to isolate the monomeric 3,3-dimethylindolenine by careful neutralization of a solution of the hydrochloride with ammonium hydroxide gives a solid m.p. 172–176°. The IR spectrum is very similar to that of the earlier product m.p. 212° but not quite identical and the UV spectra of the two samples in ethanol are virtually identical. On standing the m.p. of the freshly prepared sample slowly rises, and changes appreciably within a few hours; after a week or so it was over 200°.

As has already been discussed the allyl group in 3-allyl-3-methylindolenine is readily reduced catalytically in methanol but the ring C=N is not reduced. However if a few drops of concentrated hydrochloric acid are added to the methanol (or alternatively if the hydrogenation is carried out in glacial acetic acid solution) reduction to the corresponding indoline occurs very easily. 3,3-Dimethylindolenine is similarly reduced in acid solution to 3,3-dimethylindoline. The resistance of these indolenines to catalytic hydrogenation in neutral or alkaline solution appears to be a general phenomenon, and may partly be associated with their polymeric nature or may be due to solvation with formation of 2-oxyindolines e.g. (XIV). Reductions by dissolving metals have however been effected in alkaline solution,[12] and indolenine quaternary salts are reduced by sodium borohydride.[18]



XIV

TABLE 4. ULTRA-VIOLET SPECTRA OF INDOLES AND INDOLINES IN 95% ETHANOL

Substituents* 1-	2-	3-	λ_{max} (log ε max) (mμ)
(a) *Indoles*			
Allyl	H	Me	226 (4·53), 288–290 (3·75)
Pr	H	Me	228 (4·49), 290–292 (3·72)
Bu	H	Me	228 (4·44), 290–292 (3·72)
i-Pen	H	Me	228 (4·53), 290–292 (3·69)
H	Pr	Me	229 (4·42), 284 (3·85), 292 (3·82)
H	Bu	Me	227 (4·44), 284 (3·80), 291 (3·75)
H	i-Pen	Me	228 (4·57), 284 (3·85), 292 (3·81)
(b) *Indolines*			
H	H	{Me, Me}	242 (3·85), 291 (3·41)
H	H	{Me, Pr}	243 (3·88), 288 (3·50)

* Abbreviations as in Table 1.

[18] B. Witkop and J. B. Patrick, *J. Amer. Chem. Soc.* **75**, 4474 (1953).

The UV spectra of the various indolines and indoles prepared in the course of this work are recorded in Table 4. In accord with our previous observations[17] these spectra provide further examples of N-substituted indoles which do not show the small peak or inflection ca. 290 mμ usually observed with indoles unsubstituted on nitrogen.

EXPERIMENTAL

Petrol refers to light petroleum ether b.p. 60–80°. In the various small scale distillations described below the temp given refers to the bath temp.

3-*Allyl*-3-*methylindolenine*

(a) 3-Methylindole (6·5 g, 0·05 mole) in dry benzene was added slowly to MeMgI (0·05 mole) prepared from Mg (1·2 g) and MeI (7·8 g) in dry ether (12 ml). The resulting mixture was warmed for 15 min on the water bath, and then cooled in ice and stirred in a N_2 atm. during the slow addition of freshly distilled allyl bromide (6·1 g, 0·05 mole) in ether (10 ml). After standing for a further 2 hr at room temp, the pale red reaction mixture was diluted with ether (50 ml) and poured into ice-cold 5% HCl. The two layers were separated, the acid layer (A) extracted with more ether (30 ml), and the combined ether layers (B) containing the neutral fraction set aside.

The basic fraction was recovered from the acid layer (A) by basification with excess 2 N NaOH and extraction with ether (3 × 40 ml). The combined ether extracts were washed with water (2 × 30 ml), dried (K_2CO_3) and evaporated to dryness under red. press. of N_2. The residual yellow oil was taken up in a little MeOH, and on cooling to 0° chunky white crystals of *3-allyl-3-methylindolenine* (3·8 g, 44%) separated out, m.p. 144°. (Found: C, 83·9; H, 7·7. Rast Mol. wt. 219. $C_{13}H_{15}N$ requires: C, 84·2; H, 7·6%. Mol. wt. 171.) The IR spectrum showed peaks at 6·10 μ and 6·24 μ (mull) in the double-bond region.

The ether extracts (B) from the above reaction were dried (K_2CO_3) and evaporated to dryness under red. press. of N_2 to give a viscous yellow oil (3·6 g) which rapidly discoloured on exposure to air. To facilitate separation of the components of this oil, it was hydrogenated over Adams PtO_2 catalyst (0·05 g) in MeOH (100 ml). Hydrogen uptake (528 ml) was complete in 2 hr, and filtration and evaporation of the solvent under red. press. afforded a pale yellow oil (3·5 g). The latter was chromatographed on alumina (Spence Grade H) in petrol. The first fraction, eluted with the solvent front, was evaporated to give a colourless oil (0·4 g, 4%) which distilled at 100°/0·1 mm and was shown by its UV and IR spectra, and by comparison with an authentic sample (*vide infra*) to be 1-*n-propyl*-3-*methylindole*. (Found: C, 83·0; H, 8·6. $C_{13}H_{15}N$ requires: C, 83·2; H, 8·7%.) The second fraction gave a pale yellow oil which was distilled at 160°/0·5 mm to give *2-n-propyl-3-methylindole* (2·4 g, 28%). (Found: C, 83·3; H, 8·8. $C_{13}H_{15}N$ requires: C, 83·2; H, 8·7%.) The third fraction contained 3-methylindole (0·4 g, 4%), m.p. 94–96°, undepressed by admixture with an authentic sample.

(b) 3-Allylindolyl magnesium iodide was prepared by addition of 3-allyl indole (3·1 g) in benzene (20 ml) to a previously prepared solution of MeMgI (4·5 g) in ether (20 ml). The ether was distilled off and the solution boiled with MeI (10 g) under reflux for 4 hr. The red solution formed was poured into 5% HCl (50 ml) and the basic and neutral products separated and worked up as in (a) above. The basic fraction (0·5 g, 15%) was recrystallized from MeOH—ether and gave colourless crystals of 3-allyl-3-methylindolenine m.p. and mixed m.p. with the sample prepared as in (a), 144°; the UV and IR spectra of the two samples were also identical. The neutral fraction (2·9 g) was hydrogenated over PtO_2 as in (a), and on chromatography in petrol on alumina was shown to contain only one component. This was distilled at 120°/0·5 mm to give a colourless oil, identified as 3-n-propylindole by IR spectral comparison with an authentic sample prepared by catalytic reduction of 3-allyl indole.

1-*n-Propyl*-3-*methylindole*

3-Methylindole (1·3 g, 0·01 mole) was added to a solution of sodamide (prepared from 0·24 g Na) in liquid ammonia (20 ml). The mixture was stirred for 5–10 min to complete formation of the sodium salt and n-propyl bromide (1·3 g, 0·01 mole) slowly added dropwise with stirring. After allowing the ammonia to evaporate the residue was extracted with ether (50 ml) and the ether washed with water (20 ml) and dried (K_2CO_3). After evaporation of the ether the residual oil was distilled

at 100°/0·1 mm to give 1-n-propyl-3-methylindole (1·5 g, 89%) as a colourless liquid; the IR spectrum (film) was identical with that of the sample isolated in the Grignard reaction above.

2-Methyl-3-n-propyl indole

To MeMgI (4·5 g), prepared from Mg (0·6 g) and MeI (3·9 g), in dry ether (8 ml), was added a solution of 2-methylindole (3·3 g) in dry benzene (10 ml). After warming for 15 min on the water bath to complete formation of the indole Grignard complex, the solution was cooled in ice and stirred during the dropwise addition of freshly distilled allyl bromide (1·8 g) in benzene (10 ml). A mild exothermic reaction occurred and the red-brown reaction mixture was allowed to stand at room temp for 2 hr. The complex was then decomposed by pouring into 10% HCl (100 ml) and the neutral material was extracted into ether (2 × 50 ml). Evaporation of the dried (K_2CO_3) ether extracts afford a yellow oil (3·2 g) which darkened rapidly on exposure to air. It was therefore hydrogenated immediately in MeOH (100 ml) over PtO_2 (0·05 g) at atm. press. and room temp. Hydrogen uptake (390 ml) was complete in 3 hr, and after filtration of catalyst and evaporation of solvent, the residual oil (3·1 g) was chromatographed on alumina in petrol (as the IR spectrum showed evidence of some 2-methylindole in the product). The desired product was eluted first and on evaporation of solvent, followed by distillation at 115°/0·1 mm, 2-methyl-3-n-propylindole. (2·6 g, 60%) was obtained as a pale yellow oil (lit.[19] b.p. 200°/60 mm). (Found: C, 83·5; H, 8·8 Calc. for $C_{12}H_{15}N$: C, 83·2; H, 8·7%.)

3-Hydroperoxy-3-methyl-2-n-propylindolenine

A petrol solution (10 ml) of 3-methyl-2-n-propylindole (0·1 g) in a 25 ml conical flask was left exposed to air for 18 hr. The crude crystalline product formed was recrystallized from ethyl acetate–petrol to give *3-hydroperoxy-3-methyl-2-n-propylindolenine* (0·07 g, 54%) m.p. 126–128°. (Found: C, 70·0; H, 7·3. $C_{12}H_{15}O_2N$ requires: C, 70·2; H, 7·4%.) The IR spectrum (mull) showed a broad band between 2·9 and 4·0 μ due to a bonded hydroxyl group.

3-Hydroperoxy-2-methyl-3-n-propylindolenine

This compound was prepared from 2-methyl-3-n-propylindole in an exactly analogous fashion to the foregoing compound in 61% yield, and after recrystallization from ethyl acetate–petrol had m.p. 116–118°. (Found: C, 70·4; H, 7·3. $C_{12}H_{15}O_2N$ requires: C, 70·2; H, 7·4%.) IR spectrum (mull) showed a broad band at 3·5–4·1 μ.

3-Methyl-3-n-propylindolenine

3-Allyl-3-methylindolenine (0·1 g) in MeOH (20 ml) was hydrogenated over PtO_2 (0·01 g) at 1 atm. and 20°. When the theoretical amount of H_2 (13 ml, 1 mole) had been taken up, uptake ceased. The catalyst was filtered off and evaporation of the solvent gave a waxy white solid, which was highly soluble in all organic solvents. On distillation at 100°/0·1 mm *3-methyl-3-n-propylindolenine* (0·09 g, 90%) was obtained as a colourless viscous oil. (Found: C, 82·9; H, 8·9. $C_{12}H_{15}N$ requires: C, 83·2; H, 8·7%.) The IR spectrum (film) showed a peak at 6·22 μ (C=N).

3-Methyl-3-n-propylindoline

3-Methyl-3-n-propylindolenine (0·1 g) in EtOH (10 ml) and conc. HCl (0·2 ml) was hydrogenated over PtO_2 (0·01 g) at 25°/1 atm. Hydrogen uptake (13 ml, 1 mole) was complete in 15 min and removal of the catalyst followed by evaporation of solvent gave a gummy solid. The latter was treated with 2 N Na_2CO_3 (2 ml), extracted with ether (2 × 10 ml), and the ether layers dried (K_2CO_3). The ether was evaporated under red. press. and the residual yellow oil was distilled at 60°/0·3 mm to give *3-methyl-3-n-propylindoline* (0·09 g, 90%) as a colourless viscous oil. (Found: C, 82·6; H, 9·5; N, 8·1. $C_{12}H_{17}N$ requires: C, 82·2; H, 9·8; N, 8·0%.) The picrate was prepared in benzene, and recrystallized from benzene to give yellow needles m.p. 164°. (Found: C, 53·7; H, 4·9; N, 14·0. $C_{12}H_{17}N—C_6H_3O_7N_3$ requires: C, 53·5; H, 5·0; N, 13·9%.) This indoline was also prepared by carrying out the hydrogenation of the indolenine in glacial acetic acid.

[19] B. Oddo and C. Alberti, *Gazz. Chim. Ital.* **63**, 236 (1933).

Rearrangement of 3-*Allyl*-3-*methylindolenine*

(a) *Thermal.* The indolenine (0·1 g) in redistilled acetonitrile (5 ml) was heated under reflux for 24 hr in N_2, but no change occurred as shown by IR and UV measurements. Evaporation of the solvent gave an oil which crystallized from MeOH and gave the original indolenine (0·085 g, 85%) m.p. 142°.

The indolenine was also heated at 200° in a sealed tube under N_2 for 3 hr. However, although some charring occurred, starting material m.p. 142–144° was recovered in 75% yield on recrystallization of the crude product from MeOH.

(b) *Acid-catalysed.* The indolenine (0·5 g) in 3 N HCl (40 ml) was warmed on a steam bath for 3 min and the turbid mixture formed poured into water (100 ml). The neutral material was extracted with ether (2 × 30 ml), and the extracts dried (K_2CO_3) before evaporation of the solvent. The residual red oil (0·4 g) had λ_{max} 227, 288 and 294 (typically indolic) and darkened on exposure to air. It was therefore hydrogenated in MeOH (10 ml) over PtO_2 (0·02 g) at 20°/1 atm. Hydrogen uptake (42 ml) was rapid, and removal of catalyst and solvent afforded a yellow oil, which was distilled at 110°/0·4 mm to give 3-methyl-2-n-propylindole (0·24 g, 50%). The IR spectrum of the latter was identical with that of the compound obtained earlier from the Grignard reaction, and was further characterized by conversion into the corresponding hydroperoxyindolenine, m.p. 126°, undepressed by admixture with the previously prepared sample.

Rearrangement of 3-*methyl*-3-*n-propylindolenine*

3-Methyl-3-n-propylindolenine (0·1 g) in 6 N HCl (20 ml) was heated on the water bath at 80° for 10 min and the turbid solution poured into water (100 ml). Ether extraction (2 × 30 ml) followed by evaporation of the dried (K_2CO_3) extracts and distillation of the residual oil at 150°/0·5 mm gave 3-methyl-2-n-propylindole (0·063 g, 63%) as a pale yellow oil, the IR spectrum (film) of which was identical with those of the other samples previously obtained.

1-*Allyl*-3-*methylindole*

This compound was prepared from 3-methylindole (3·9 g) with Na (0·72 g), liquid ammonia (50 ml) and allyl bromide (3·6 g) by the same procedure as utilized in the synthesis of 1-methyl-3-propylindole from 3-methylindole and n-propyl bromide. 1-*Allyl*-3-*methylindole* (4·9 g, 92%) distilled at 110°/0·5 mm as a colourless oil but satisfactory analytical values could not be obtained. (Found: C, 83·1; H, 8·1. $C_{12}H_{13}N$ requires: C, 74·2; H, 7·6%.) (Similar difficulties with the analysis of 3-allylindole were reported by Brown *et al.*[9]) However the UV spectrum was typically indolic (cf. Table 3).

On hydrogenation over PtO_2 in MeOH, 3-methyl-1-n-propylindole was obtained in virtually quantitative yield, and gave an IR spectrum (film) identical with the earlier product obtained by direct alkylation of the sodium salt of 3-methylindole with n-propyl bromide.

Attempts to rearrange 1-allyl-3-methylindole thermally, as described for 3-allyl-3-methylindolenine failed completely and only starting material was obtained as shown by spectral comparisons. Neither did rearrangement occur on allowing an aqueous ethanolic solution of the 1-allyl-3-methylindole saturated with HCl to stand at room temp overnight.

Reaction of 3-*methylindolyl magnesium iodide with* 3,3-*dimethylallyl bromide*

The reaction was carried out in an exactly similar fashion to the analogous reaction with allyl bromide (see above) starting with 3-methylindole (6·5 g), MeMgI (9·0 g) and 3,3-dimethylallyl bromide (7·5 g). The reaction product was worked up by dilution with ether (50 ml), and 5% aqueous Rochelle salt (50 ml). After separation of the two layers, the aqueous layer was further extracted with ether (2 × 50 ml), and the combined extracts dried (K_2CO_3). After evaporation of the ether the residual yellow oil (9·2 g), which darkened rapidly on exposure to air, was taken up in MeOH (100 ml) and hydrogenated over PtO_2 (0·05 g) at atm. press. Hydrogen uptake was slow and ceased when 934 ml had been absorbed (theoretical uptake based on the quantity of dimethylallyl bromide used was ca. 1100 ml). Removal of catalyst and solvent afforded a pale yellow oil (8·8 g) which was chromatographed on alumina in petrol, and separated into three fractions.

(i) The first fraction, eluted with the solvent front, was evaporated and distilled at 120°/0·4 mm to give 1-*isopentyl*-3-*methylindole* (1·85 g, 18%) as a colourless mobile oil. (Found: C, 83·4; H, 9·4.

$C_{14}H_{19}N$ requires: C, 83·5; H, 9·5%.) The IR spectrum (film) was identical with that of a sample prepared by the alternative method described below.

(ii) The second fraction, after removal of solvent, was distilled at 170°/0·1 mm to give *2-isopentyl-3-methylindole* (3·6 g, 36%) as a pale yellow oil, which solidified to a waxy solid. The latter was very soluble in all organic solvents and could not be recrystallized satisfactorily because of its low m.p. (<45°). (Found: C, 83·2; H, 9·4. $C_{14}H_{19}N$ requires: C, 83·5; H, 9·5%.)

(iii) The third component was 3-methylindole (0·8 g, 8%) m.p. 94–96° after recrystallization from petrol.

1-Isopentyl-3-methylindole

This compound was prepared from 3-methylindole (1·3 g), Na (0·24 g), liquid ammonia (50 ml) and isopentyl bromide (1·5 g) using the same procedure as described above for 1-n-propyl-3-methylindole. The product was a colourless oil (1·74 g, 87%) b.p. 120°/0·4 mm and the IR spectrum was identical with the sample prepared in the Grignard reaction above.

Reaction of crotyl bromide with 3-methylindole magnesium iodide

This reaction was carried out (0·046 molar scale) in precisely the same fashion as the foregoing reaction with dimethylallyl bromide. The crude product was hydrogenated as above (uptake 980 ml, theoretical 1030 ml) and finally chromatographed in petrol on alumina to give three fractions:

(i) *1-n-butyl-3-methylindole* (1·6 g, 17%) b.p. 100°/0·1 mm was obtained as a colourless mobile liquid. (Found: C, 83·5; H, 9·2; N, 7·6. $C_{13}H_{17}N$ requires: C, 83·4; H, 8·2; N, 7·5%.) The IR spectrum was identical with that of an authentic sample (b.p. 130°/0·5 mm) prepared by direct alkylation of the sodium salt of 3-methylindole in liquid ammonia with n-butyl bromide, and obtained in 96% yield.

(ii) *2-n-butyl-3-methylindole* (4·2 g, 44%) distilled as a pale yellow oil, b.p. 140°/0·2 mm. (Found: C, 83·3; H, 9·5. $C_{13}H_{17}N$ requires: C, 83·4; H, 9·2%.) With hot Ehrlich's reagent it gave only a pale green coloration.

(iii) *3-Methylindole* (1·2 g, 12%) m.p. 94–95° was undepressed by admixture with starting material.

3,3-Dimethylindolenine

This compound was prepared by Hoshino's method[14] and after recrystallization several times from benzene had m.p. 212° (lit.[18] m.p. 214°) (Rast mol. wt. 218 Calc. for $C_{10}H_{11}N$: 145). A solution of this indolenine (0·1 g) in 2 N HCl (5 ml) was basified by addition of 2 N NH_4OH (5·5 ml). The white ppt was crystallized from benzene, and gave colourless crystals m.p. 172–176°; after 1 hr the m.p. had risen to 180–184°, and after one week it had risen to over 200°.

3,3-Dimethylindoline

3,3-Dimethylindolenine (0·1 g) in glacial acetic acid (10 ml) (or in EtOH containing a few drops of conc. HCl) was hydrogenated over PtO_2 (0·01 g) at atm. press. and 20°. (Uptake of H_2 16 ml: theoretical 15·5 ml). After filtration and evaporation of the solvent, the residual indoline salt was basified with a little 2 N Na_2CO_3, and the product extracted into ether (2 × 10 ml). The dried (K_2CO_3) extracts were evaporated to dryness and the residual gum on crystallization from petrol afforded 3,3-dimethylindoline (0·08 g, 80%) as needles m.p. 34° (lit.[20] m.p. 34°).

3,3-Dimethylindolenine was recovered unchanged from attempts to reduce it catalytically in ethanolic solution without addition of acid.

[20] M. Kates and L. Marion, *Canad. J. Res.* **29**, 37 (1951).