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ELECTROPHILIC SUBSTITUTION IN INDOLES—V[1]

INDOLENINES AS INTERMEDIATES IN THE BENZYLATION OF 3-SUBSTITUTED INDOLES

K. M. BISWAS and A. H. JACKSON
The Robert Robinson Laboratories, The University, Liverpool 3

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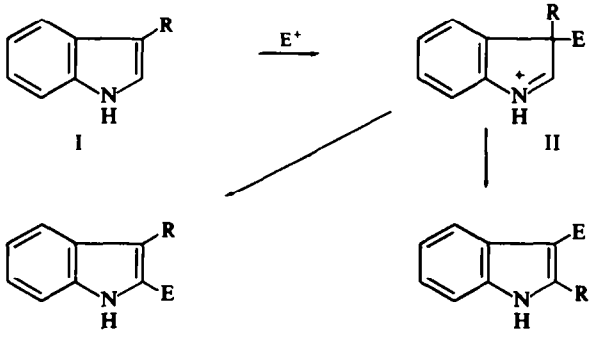
Abstract—3-Benzyl-2-p-methoxybenzylindole is formed either by treatment of the Grignard derivative of 3-benzylindole with *p*-methoxybenzyl chloride, or by benzylation of the Grignard derivative of 3-*p*-methoxybenzylindole. The same intermediate 3-benzyl-3-*p*-methoxybenzyl indolenine must be involved in both reactions.

Cyclization of 3-(*o*-hydroxymethylbenzyl) indole with phosphorous pentoxide in hot benzene affords 1,4-dihydro-2,3-benzcarbazole. The intermediacy of a spirocyclic indolenine in this reaction is supported by the formation of a spirocyclic indoline in a related cyclization which occurs in the diborane reduction of 3(*o*-carboxybenzyl) indole. These results confirm that electrophilic substitution at the 2-position of a 3-substituted indole is an indirect process, and in the light of this work published observations on the reactions of indoles with aromatic aldehydes and ketones are re-interpreted.

PREVIOUS papers[1–4] in this series have provided a considerable body of evidence that electrophilic substitution at the 2-position of 3-substituted indoles is an indirect process involving prior attack at the 3-position to give an indolenine (II), followed by rearrangement to the 2,3-disubstituted indole (III). Which of the two possible products (IIIa or IIIb) is formed will depend on the relative migratory aptitudes of the two groups in the intermediate indolenine (II).[2,4] In our earlier work[2] we encountered one example of an electrophilic substitution in which the incoming group (Me) caused the migration of the more labile substituent already present (I; R = allyl) into the 2-position and gave 2-allyl-3-methyl indole (IIIb; R = allyl, E = Me). We now wish to report a further example of this type of displacement-rearrangement reaction in the benzylation of the Grignard derivatives of 3-benzylic indoles.



Benzylic indoles were chosen for these experiments because of the known high migratory aptitudes of benzylic groups in 1,2-rearrangements of the Wagner–Meerwein type,[5] and also because it was hoped initially that it might be possible to effect Friedel–Crafts type alkylations of indoles with them under relatively mild conditions. Few examples of the direct Friedel–Crafts alkylation of indoles (in the pyrrole ring) have been described in the literature (although a recent report describes the successful alkylation of pyrroles[6]), and the preferred method of alkylation in both indoles and pyrroles has been via their Grignard derivatives. Grignard reactions have three main advantages over Friedel–Crafts reactions (i) reaction occurs under very mild conditions, e.g. in boiling ether, or benzene, (ii) the indole is activated rather than the alkyl halide, and (iii) the active species is destroyed during the reaction whereas the Friedel–Crafts catalyst is still available to catalyse further alkylation of the reactive heterocyclic nucleus, and polyalkylated products or polymers may be obtained. Methylation of indoles with boiling methyl iodide (even in the absence of

TABLE 1. NMR SPECTRA OF BENZYL INDOLES (τ-VALUES)

Indole substituents	2-H	3-H	N-CH_2	2-CH_2	3-CH_2	OCH_3
(a) *In deuterochloroform*						
3-$CH_2C_6H_5$	3·42 *m*	—	—	—	5·98	—
2-$CH_2C_6H_5$	—	3·75 *m*	—	6·02	—	—
3-$CH_2C_6H_4OCH_3$	3·30 *m*	—	—	—	6·01	6·32
1-$CH_2C_6H_4OCH_3$	~3·2	3·51 *d*	4·76	—	—	6·33
3-$CH_2C_6H_5$, 2-$CH_2C_6H_4OCH_3$	—	—	—	5·90	6·03	6·28
3-$CH_2C_6H_4OCH_3$, 2-$CH_2C_6H_5$	—	—	—	5·92	5·92	6·26
3-$CH_2C_6H_5$, 1-$CH_2C_6H_4OCH_3$	3·21 *d*	—	4·93	—	5·93	6·32
3-$CH_2C_6H_4OCH_3$, 1-$CH_2C_6H_5$	3·20 *d*	—	4·80	—	5·97	6·27
3-$CH_2C_6H_5$, 2-$COC_6H_4OCH_3$	—	—	—	—	5·81	6·23
(b) *In trifluoroacetic acid* (3-H-indolium salts)						
3-$CH_2C_6H_5$†	~1·0*	5·6 *m**	—	—	6·96 *d*	—
3-$CH_2C_6H_4OCH_3$‡	~1·0*	5·6 *m**	—	—	6·90 *d*	6·10
1-$CH_2C_6H_4OCH_3$	~1·01 *t*	5·5 *m**	4·30	—	—	6·00
3-$CH_2C_6H_5$, 2-$CH_2C_6H_4OCH_3$	—	5·3 *m**	—	5·54 *m*	6·4 *m**	6·00
3-$CH_2C_6H_4OCH_3$, 2-$CH_2C_6H_5$	—	5·3 *m**	—	5·52 *m*	6·4 *m**	6·00
3-$CH_2C_6H_5$, 1-$CH_2C_6H_4OCH_3$§	—	5·3 *m**	—	5·53 *m*	6·4 *m**	6·01
3-$CH_2C_6H_4OCH_3$, 1-$CH_2C_6H_5$	1·09 *d*	5·3 *m**	4·47	—	6·43 *m*	6·05

Ar-H: in $CDCl_3$, 2·3–3·3 *m*; in TFA, 2·1–3·0 *m*.

* Broad signals.

† Mixture of free indole and 3-H-indolium salt.

‡ Mixture of free indole and 3-H-indolium salt; spectrum changes slowly on standing (see text).

§ Spectrum identical with that of 3-benzyl-2-p-methoxybenzylindole in TFA owing to rearrangement (see text).

TABLE 2. MASS SPECTRA OF BENZYLINDOLES

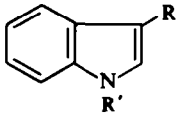
m/e (%)

(i) 3-Benzyl-2-*p*-methoxybenzylindole:	341(11) (3-CH_2Ph, 2-CO—C_6H_4—OMe-*p*), 327(100) (M^+), 250(27) (M − Ph), 236(50) (M − CH_2Ph), 219(27), 218(51), 217(25), 207(25), 206(70) (M − 121), 204(27), 143(51), 135(45), 130(25), 121(61) (*p*-MeO—C_6H_4—CH_2^+), 92(32), 91(72) ($C_7H_7^+$), 78(27), 77(61). m*: 170·4 (327 → 236)
(ii) 2-Benzyl-3-*p*-methoxybenzylindole:	228(30) (M + 1), 327(100) (M^+), 237(15), 236(75) (M − CH_2Ph), 220(26), 219(20), 213(37), 217(14), 206(21) (M − 121), 205(10), 204(16), 192(10), 137(8), 121(15), 118(9), 117(7), 115(7), 91(26), 77(13), m*: 170·4 (327 → 236).
(iii) 3-Benzyl-1-*p*-methoxybenzylindole:	327(22) (M^+), 206(3), 122(10), 121(100) (*p*-MeO-C_6H_4—CH_2^+), 91(5), 78(4), 77(7). m*: 44·8 (327 → 121); 68·4 (121 → 91)
(iv) 1-Benzyl-3-*p*-methoxybenzylindole:	327(63) (M^+), 296(5) (M − OCH_3), 236(32) (M − CH_2Ph), 220(17), 121(11), 92(12), 91(100) (Ph—CH_2^+), 65(14). m*: 170·3 (327 → 236); 46·4 (91 → 65).
(v) 3-Benzyl-2-*p*-methoxybenzoylindole:	342(28) (M + 1), 341(100) (M^+), 340(16), 326(10) (M − CH_3), 324(13), 311(13) (M − CH_2O), 310(44) (M − OCH_3), 233(24), 206(17), 204(14), 135(27) (*p*-MeO—C_6H_4—CO^+), 131·5(14) (M − $C_6H_6^{+}$), 128(10), 92(11), 77(17). m*: 281·9 (341 → 310), 159·3 (341 → 233).

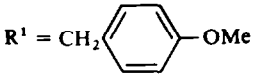
a catalyst) is a complex process leading to polymethylated products,[7] whereas methylation, say, of indole Grignard gives mainly 3-methyl-indole with a small amount of the N-methylindole as a by-product.[8] The cyclization reactions described in the preceding paper[1] are a rather special case because the alkylating group is already attached to the indole, and polyalkylation is precluded (although not polymerization when cyclization is unfavourable). Acylation of indoles[9] (which can often be carried out without a catalyst) leads to mono- rather than poly-acyl indoles because the electron withdrawing effect of the first acyl group introduced inhibits further acylation. (However it should be noted that N-acylation and alkylation of indoles is facilitated under alkaline conditions by an electron withdrawing substituent.[10])

The Grignard derivative of 3-benzylindole (I; R = CH_2Ph) was therefore treated with *p*-methoxybenzylchloride in ether at room temperature, and the product worked up in the usual way under very mild acidic conditions at 0–5°. No basic material was obtained and the neutral fraction was separated chromatographically into three components, which were identified by elemental analysis and spectroscopy (cf. Tables 1 and 2). The first fraction contained 3-benzyl-1-*p*-methoxybenzylindole (IVa), and the second 3-benzyl-2-*p*-methoxybenzylindole (IIIa), both being obtained as high boiling viscous oils which could not be crystallized. The third fraction contained a small amount of 3-benzyl-2-*p*-methoxybenzoylindole (V) which had arisen by autoxidation of the second component during work-up. (Attempts to prepare it in larger quantities by Dolby and Booth's periodate oxidation procedure,[11] which was so successful in the oxidation of tetrahydrocarbazole to the 1-oxo-analogue, failed however). 2-Benzyl-3-*p*-methoxybenzylindole (IIIb) was also prepared by treatment of the Grignard derivative of 2-benzylindole with *p*-methoxybenzylchloride, and this proved to be a crystalline solid, with similar spectroscopic properties

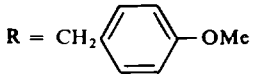
to its isomer, but it had a slightly different R_f on TLC (Experimental). Indirect confirmation of the relative positions of the two benzyl groups in the second fraction from the alkylation of 3-benzylindole was also provided by the spectra of its autoxidation product, i.e. the mass spectrum exhibited a prominent ion corresponding to *p*-MeO—C_6H_4—CO^+ (*m/e* 135), and the UV spectrum did not change on addition of alkali, as would have been expected[12] if the *p*-methoxybenzoyl group had been at the 3- rather than the 2-position. (This was confirmed by the UV spectrum of 3-*p*-methoxybenzoylindole which showed a marked bathochromic shift on addition of alkali.)



IV a: R = CH_2Ph

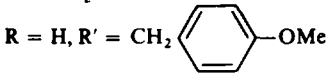


R^1 = CH_2—C$_6$H$_4$—OMe

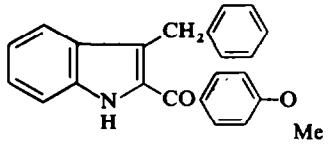


b: R = CH_2—C$_6$H$_4$—OMe

R' = CH_2Ph



c: R = H, R' = CH_2—C$_6$H$_4$—OMe



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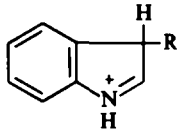
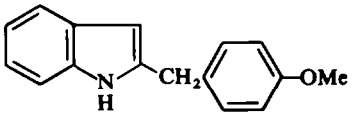
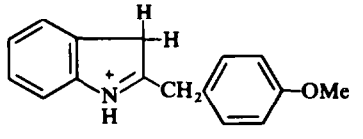


VI a: R = CH_2—C$_6$H$_5$

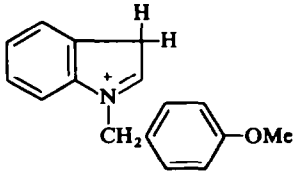
b: R = CH_2Ph



VII



VIII



IX

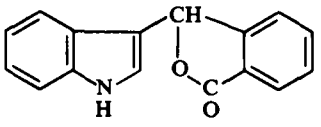
The benzylation of the Grignard derivative of 3-*p*-methoxybenzylindole (I; R = $CH_2C_6H_4OMe$) (prepared by diborane reduction of 3-*p*-methoxybenzoylindole) gave 1-benzyl-3-*p*-methoxybenzylindole (IVb) and 3-benzyl-2-*p*-methoxybenzylindole (IIIa; R = CH_2Ph, E = $CH_2C_6H_4OMe$). The latter was identical in all respects with the product from the first reaction described above, and as in that

case no basic product was obtained even when cold ammonium chloride solution was used in the work-up procedure instead of dilute hydrochloric acid. However, as both experiments gave the same 2,3-disubstituted indole, the same intermediate indolenine (II; R = CH_2Ph, E = $CH_2C_6H_4OMe$) must have been formed in each case; the fact that this could not be isolated is clearly due to the high migratory aptitude of the *p*-methoxybenzyl residue. The NMR spectrum of 3-*p*-methoxybenzylindole in trifluoroacetic acid corresponded to a mixture of the free indole and the 3*H*-indolium salt (VIa), but changed slowly on standing, possibly owing to formation of the 3-*H*-indolium salt (VIII) of the rearrangement product, 2-*p*-methoxybenzylindole (VII). A somewhat more remarkable rearrangement of 3-benzyl-*p*-methoxybenzylindole (IVa) to 3-benzyl-2-*p*-methoxybenzylindole (IIIa; R = CH_2Ph, E = $CH_2C_6H_4OMe$) on dissolution in TFA was also observed (Table 1) and the factors affecting these rearrangements are being investigated. The NMR spectrum of 3-benzylindole showed as expected that only partial protonation (to give VIb) had occurred in TFA, and no change occurred even on standing for three days; polymerization was presumably inhibited by the relatively large bulk of the benzyl group (cf. 4). On the other hand, whilst the spectrum of 1-*p*-methoxybenzylindole (IVc) in TFA corresponded initially to that of the indolium salt (IX) it changed within an hour to give a much less well resolved spectrum indicating that some rearrangement or polymerization process was probably occurring.

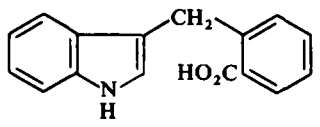
A number of similar reactions in which 3-substituted indoles have been isomerized to 2-substituted indoles under acidic conditions have been recorded in the literature, e.g. the relatively labile t-butyl group migrates from the 3- to the 2-position under moderately acidic conditions,[13] although in boiling hydrobromic acid it can be eliminated and isolated as t-butyl bromide.[14] 3-Benzylindole rearranges to 2-benzylindole on heating with aluminium chloride,[15] and 3-phenylindole rearranges to the 2-isomer on heating with zinc chloride[16] or aluminium chloride.[17] Attempts to rearrange 3-*p*-methoxybenzylindole by heating with aluminium chloride however led only to polymeric material, and it is clear that these conditions are far too vigorous with such a labile substituent as *p*-methoxybenzyl. Friedel–Crafts alkylation of 3-benzylindole with *p*-methoxybenzylalcohol and borontrifluoride etherate under a variety of conditions gave a mixture of polyalkylated products, as shown by TLC, and mass spectral determinations of mol wts.

The results described so far in this paper clearly gave considerable support to our original hypothesis, and we therefore sought to apply a somewhat more rigorous test by investigating the cyclization of *o*-hydroxymethylbenzylindole (XII) under Friedel–Crafts conditions. This compound is an analogue of the indolylbutanol described in the preceding paper, and was readily available by catalytic hydrogenation, followed by LAH reduction, of the adduct (X)[18] of indole and phthalaldehydic acid. Attempts to cyclize this hydroxymethyl derivative (XII) with boron trifluoride etherate (as had been used for the cyclization of the simple indoylbutanol[1]) failed completely and the products were largely polymeric. Treatment with polyphosphoric acid also gave polymer, as did ethereal or ethanolic hydrogen chloride. Attempts to prepare the tosylate of this alcohol also failed. Finally it was discovered that the dihydrobenzcarbazole (XIV) could be obtained in moderate yield by heating the alcohol with phosphorus pentoxide in benzene under nitrogen. If the cyclization was carried out in refluxing xylene (in air) the corresponding benzcarbazole (XV) resulted;

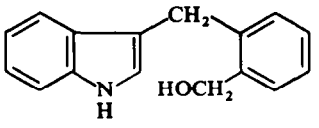
this must have been formed by aerial oxidation of the initially formed dihydro-compound. Little starting material was recovered from these reactions and the remainder of the product was presumably insoluble polymer.



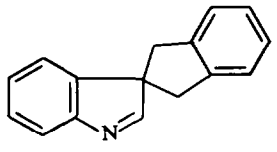
X



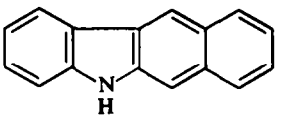
XI



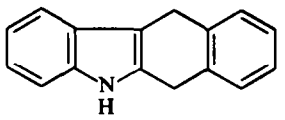
XII



XIII



XV



XIV

During the course of this work the diborane reduction of the carboxybenzyl-indole (XI) was also investigated, but the product was not the expected alcohol (XII) m.p. 79° which had been obtained by LAH reduction. Instead a new compound, m.p. 180°, was produced, which was isomeric with the alcohol (XII), as shown by elemental analysis, and by mass spectral determination of mol wt. (Table 3).

TABLE 3. MASS SPECTRA OF REDUCTION AND CYCLIZATION PRODUCTS FROM 3-PHTHALIDYLINDOLE

m/e (%)

(i) 3-(o-*Hydroxymethylbennzyl*)*indole* (XII):
237(50) (M^+), 219(30) (M − H_2O), 218(90) (M − H_2O—H), 217(35), 204(20), 130(32), 120(60), 119(60), 118(100), 117(20), 91(40), 77(40), m*: 58·7 (237 → 118).

(ii) *Spiroindoline* XVIII; R = H
237(60) (M^+), 219(14), 218(52), 217(15), 130(11), 120(30), 119(44), 118(100), 117(18), 91(25), 77(10), m*: 58·8 (237 → 118).

(iii) 1,4-*Dihydro*-2,3-*benzcarbazole* (XIV):
219(65) (M^+), 218(100) (M − H), 217(47) (M − 2H), 216(17), 189(9), 137(10), 120(10), 108·5(18), 91(11), 77(8).

(iv) 2,3-*Benzcarbazole* (XV):
217(11) (M^+), 87(14), 85(70), 83(100), 49(15), 48(18), 47(35).

Surprisingly, the mass spectrum of this new compound was almost identical with that of the alcohol (XII), but mixed m.p. determinations confirmed their non-identity. The UV spectrum of the new compound was not indolic but similar to those of

indolines, and moreover, addition of acid caused the spectrum to become benzenoid in character owing to formation of the corresponding anilinium type cation. Unlike XII this new material was not very soluble in organic solvents but dissolved readily in dilute acid (as would be expected of an indoline) and could be recovered unchanged on basification. The NMR spectrum in deuterotrifluoroacetic acid showed two AB quartets, and a singlet in the aliphatic region of the spectrum, as well as a multiplet for the eight aromatic protons of the two benzene nuclei (Table 4). The

TABLE 4. NMR SPECTRA OF THE SPIROCYCLIC INDOLINE (XVIII; R = H) (τ-values)

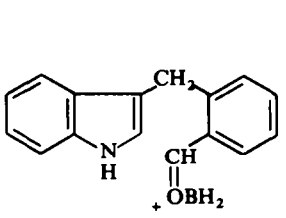
Solvent	Ar-H	2-H†	1'-H	3'-H†
Deuterotrifluoroacetic acid	2·4–3·0	5·89	4·42	6·67
		5·65		6·38
		J = 12		J = 16
Pyridine	*	6·52	4·69	7·02
		6·34		6·40
		J = 9		J = 16
Deuteroacetone	2·5–3·6	6·62	5·07	7·07
		6·53		6·65
		J = 9		J = 16
Deuterodimethyl sulphoxide	2·5–3·6	6·72	4·60	7·10
		6·64		6·72
		J = 8		J = 15

* Obscured by pyridine resonances.
† AB quartets.

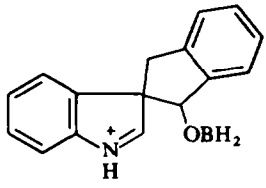
compound was too insoluble in deuterochloroform to determine its NMR spectrum, but the spectra in deuteroacetone, deuterodimethylsulphoxide, and pyridine were slightly more complex though similar to that in DTFA. The IR spectrum showed the presence of OH or NH groups, and on the basis of all the spectral evidence, the new compound was assigned structure (XVIII; R = H). The NMR spectral assignments are shown in Table 4. The similarity of the mass spectra of the alcohol (XII) and the spirocyclic indoline (XVIII) may be explained quite readily on the assumption that the initial loss of water which both exhibit leads to the same ion (*m/e* 219). This is presumably the molecular ion of the spirocyclic indolenine (XIII) because the further fragmentations differ in some respects from those of the isomeric dihydroindolcarbazole (XIV).

The formation of this spirocyclic indoline (XVIII; R = H) may be rationalized by assuming that the primary reduction product (XVI) of the carboxybenzylindole (XI) electrophilically cyclizes at the 3-position of the indole nucleus to give the spirocyclic indolenine (XVII) which is then subsequently reduced by the excess of diborane employed in the reaction to the indoline (XVIII; R = BH_2) ester. The cyclization of XVI, which is at the aldehyde level of oxidation, and the trapping of the spirocyclic indolenine (XVII) by diborane reduction before rearrangement to a 2,3-disubstituted indole (i.e. a benzcarbazole) mechanistically parallel the formation of indolylmethylindolines in the diborane reduction of 3-formylindoles.[12] However it is interesting to note that the reduction of indolylbutyric acid described in the preceding paper[1]

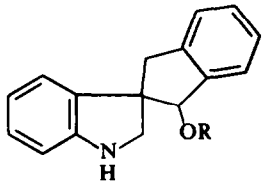
leads directly to the indolyl butanol, and that little cyclized product was found, even though the indolylbutyric acid may be regarded as a simple analogue of the carboxybenzylindole (XI); presumably the intermediate in the reduction of the butyric acid



XVI



XVII



XVIII

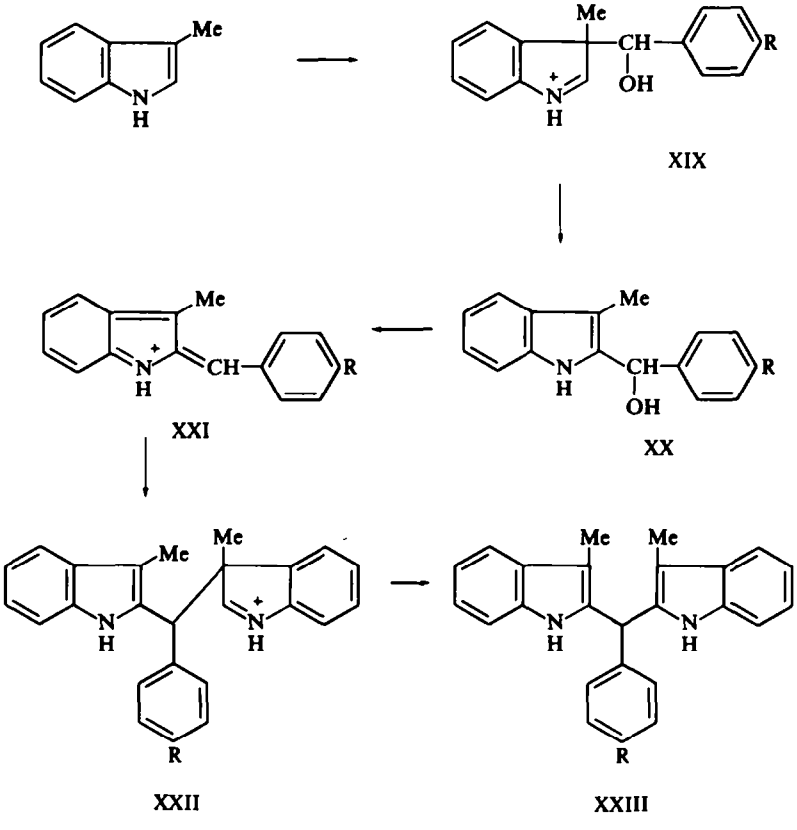
analogous to XVI is reduced much faster than it can cyclize, whereas with XVI the reverse is true owing to stabilization by the benzene nucleus.[cf. 19]

This remarkable cyclization reaction leading to the formation of the spirocyclic indoline (XVIII; R = H) together with the results from the benzylation of indole Grignard reagents clearly provide very good evidence for our hypothesis that electrophilic substitution at the 2-position of 3-substituted indoles is an indirect process. In particular the formation of spirocyclic intermediates such as XIII and XVII in which the benzene ring (D) introduces a further element of strain into ring C (by making it a spiropentene, rather than a spiropentane ring) compared with the spirocyclic indolenine formed in the cyclization of indolylbutanol[1]; even so cyclization at the 3-position is still favoured rather than at the 2-position of the indole nucleus.

TABLE 5. R_f VALUES OF BENZYLINDOLES ON THIN LAYER CHROMATOGRAPHY ON SILICA GEL IN BENZENE-LIGHT PETROLEUM (B.p. 60–80°) (4:1/v:v)

Indole (substituents)	R_f
1-*p*-$CH_2C_6H_4OMe$	0·75
1-CH_2Ph, 3-*p*-$CH_2C_6H_4OMe$	0·70
1-*p*-$CH_2C_6H_4OMe$, 3-CH_2Ph	0·65
2-CH_2Ph	0·55
3-CH_2Ph	0·50
2-CH_2Ph, 3-*p*-$CH_2C_6H_4OMe$	0·45
2-*p*-$CH_2C_6H_4OMe$, 3-CH_2Ph	0·40
3-*p*-$CH_2C_6H_4OMe$	0·35
2-*p*-CoC_6H_4OMe, 3-CH_2Ph	0·05

The work reported in this paper is also of interest in connection with the acid catalysed reactions of indoles with aromatic aldehydes and ketones. Some years ago Noland[20] confirmed that skatole condenses with benzaldehyde to give the 2,2'-diindolylphenylmethane (XXIII), apparently involving direct substitution at the 2-position of the indole nucleus. However our results and particularly those described in this paper would support the alternative possibility that initial substitution occurs first at the 3-position to give an intermediate such as (XIX). Rearrangement to XX followed by elimination of water and reaction with a further mole of skatole would then lead to the 2,3'di-indolylmethane (XXII). A final rearrangement would then give the observed product (XXIII) as shown in the accompanying scheme. The migratory aptitude of the hydroxybenzyl moiety in XIX is to be expected not only on

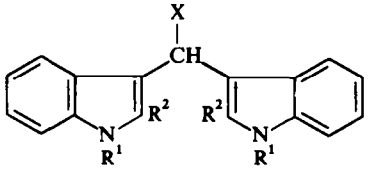


a: R = H
b: R = NMe_2

the basis of the migratory ability of benzyl groups in benzylindolenines described in this and an earlier paper,[4] but also because of the enhancing effect of electron release from the OH group (cf. the migration of an aminobenzyl group in the cyclization of benzylidene tryptamines[3]). Similarly the indolylbenzyl moiety in XXII would also be expected to have a very high migratory aptitude. Noland has recently

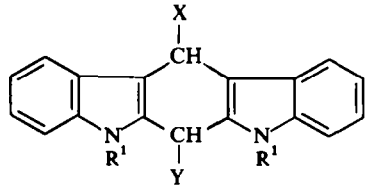
suggested* a somewhat similar pathway for this reaction, and his work on the condensation of 3-substituted indoles with quinones[21,22] provides very good support for the intermediacy of indolenines in electrophilic substitution reactions of indoles.

Other workers[23–26] have also studied the reactions of 3-substituted indoles with aldehydes to give 2,2′-diindolylmethanes, and in particular Dobeneck and Maas[23] have shown that 3,3′-diindolylmethanes (XXIV a–e) give rise to dihydroindolcarbazoles (XXV a–e) respectively. It seems reasonable to assume that formation of the latter follows a similar pattern to that already described for skatole, i.e. substitution at the 3-position, migration, substitution at the 3′-position and a further migration of the incoming group. In suitable cases it seems possible that the group bridging the 3- and 3′-positions (in XXIV) may rearrange into the 2-2′-position if the incoming group has a lower migratory aptitude; experiments to test this prediction are in progress. It is interesting to note that if the 2 and 2′-positions are blocked by methyl groups as in XXIVf, then fission of the 3,3′-methane bridge occurs on treatment with *p*-dimethylaminobenzaldehyde (Ehrlich's reagent) in acidic



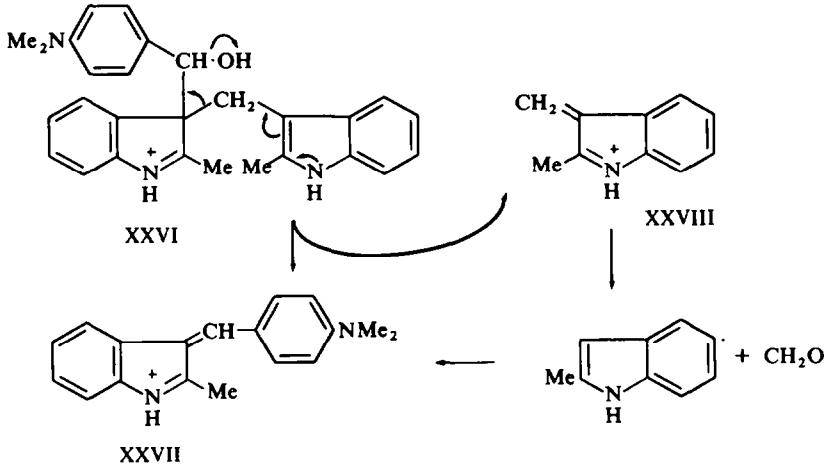
XXIV

a: $R' = R^2 = X = Y = H$
b: $R' = Me, R^2 = X = Y = H$
c: $R^1 = R^2 = X = H, Y = Ph$



XXV

d: $R^1 = R^2 = X = H, Y = p\text{-}C_6H_4NMe_2$
e: $R^1 = R^2 = H, X = Y = p\text{-}C_6H_4NMe_2$
f: $R^1 = X = H, R^2 = Me$



XXVI XXVIII XXVII

* cf. Footnote 45 in Ref. 21.

solution and the Ehrlich derivative (XXVII) of 2-methylindole is formed in high yield.[23] The 2- and 2'-Me groups not only inhibit rearrangement but they also markedly enhance the basicity of the indole nucleus,[27] and hence facilitate electrophilic attack at the 3-position. The initial substitution product (XXVI) undergoes acid catalysed clearage to give the Ehrlich derivative (XXVII), and the other product (XXVIII) may then be hydrolysed to formaldehyde and 2-methylindole; the latter can then react with a further mole of the Ehrlich's reagent. The alternative possibility that direct acid catalysed cleavage of the diindolylmethane (XXIVf) occurs seems less likely, because if the 2- and 2'-Me groups are absent, as in XXIVd, then formation of dihydroindolcarbazole (XXVd) is observed, and secondly the conditions under which XXIVf is cleared by reaction with Ehrlich's reagent are the same as those used in its preparation.

EXPERIMENTAL

M.ps are uncorrected. UV spectra were determined with Unicam SP-500 and SP-800 spectrometers, and NMR spectra with Varian A-60 and HA-100 instruments. Mass spectra were determined with an A.E.I. MS9 spectrometer operating at 50 μA and 70 3V, using a direct inlet heated to 200°. Light petroleum refers to the fraction b.p. 60–80° unless otherwise stated.

p-Methoxybenzylchloride was prepared in 88% yield following Vickrars' procedure[28] by treating the corresponding alcohol in light petroleum with HCl gas. B.p. 71–72°/0·1 mm (Lit.[28] b.p. 80°/0·2 mm). NMR in $CDCl_3$: Ar—H, 3·00 *q*; —CH_2—Cl, 5·57 *s*; —OCH_3, 6·38 *s*.

Preparation according to the procedure described by Muller *et al.*[29] using anisole, formaldehyde and HCl, followed by distillation of the product at 115–120°/16 mm was found to give a mixture of 30% *o*- and 70% *p*-methoxybenzylchloride by NMR in $CDCl_3$ (*o*-methoxybenzylchloride, Ar—H, 3·0 *q*; —CH_2—Cl, 5·42 *s*; O—CH_3, 6·30 *s*).

3-Benzylindole. To the Grignard reagent prepared from EtBr (21·8 g) and Mg (3·6 g) in ether, indole (11·7 g) in ether (25 ml) was added and the mixture heated under reflux for 2 hr. The soln was cooled in ice and redistilled benzylbromide (17·1 g) in ether (25 ml) was added in small portions with stirring. The mixture was finally heated under reflux for 1 hr. After cooling 10% NH_4Cl aq was added, the organic material was extracted with ether, dried ($MgSO_4$) and then the solvent removed to give 3-benzylindole as an oil. This oil, after percolation through a column of silicagel in benzene light-petroleum ether (2/3:v/v) and crystallization from aqueous alcohol gave 3-benzylindole (12·4 g; 60%) as colourless needles, m.p. 110° (Lit.,[30] m.p. 111°).

3-Benzylindole was also prepared by reducing 3-benzoylindole with diborane.[12]

2-Benzylindole. A mixture of 3-benzylindole (2 g), anhyd $AlCl_3$ (2 g) and NaCl (0·2 g) was heated at 240° for 20 min and worked up as described by Clemo and Seaton.[15] The product crystallized from EtOH and was recrystallized from light petroleum to give 2-benzylindole (1 g; 50%) as colourless needles, m.p. 84–85° (Lit.[15] m.p. 84°) NMR spectrum in $CDCl_3$: Ar—H, 2·5–3·0 *m*; C-H, 3·75 *b.s.*, 2-CH_2—Ph, 6·02 *s*.

An attempted rearrangement of 3-benzylindole (0·50 g) with conc H_2SO_4 (1 ml) at 20° for 20 hr gave only the starting material (0·3 g).

3-(p-Methoxybenzoyl)indole was prepared from indolyl magnesium bromide and anisoyl chloride in 68% yield following Buu-Hoi's method.[31] It had m.p. 208° (Lit.[31] 208); λ_{max} (log ε_{max}) in EtOH: 221 (4·21), 272 (4·25), 314 (4·18) mμ; in EtOH + NaOH aq: 230 (4·03), 274 (4·27), 348 (4·23) mμ. NMR (TFA): Ar—H, 1·65–2·8 *m*; —OCH_3, 5·94 *S*.

3-(p-methoxybenzyl)indole. 3-*p*-Methoxybenzoylindole (15·0 g; 0·06 mole) was reduced "internally" with diborane (0·12 mole) generated from $NaBH_4$ (6·8 g) in THF (100 ml) and BF_3Et_2O (36 g) in THF (100 ml) according to our previously described procedure. After standing overnight excess diborane was decomposed by addition of a little MeOH, and the solvent was removed *in vacuo*. The residue was taken up in MeOH (100 ml), boiled for 30 min to decompose boron complexes, and then evaporated to dryness. Ether and water were then added and the product extracted with ether, washed with $NaHCO_3$ aq then with water and dried ($MgSO_4$). Evaporation of the ether afforded the crude 3-*p*-methoxybenzylindole (14·2 g) as an off-white crystalline solid, which was purified by percolation through a short column of silica gel in

benzene, and crystallized from benzene light petroleum. The 3-*p*-methoxybenzylindole (11·5 g; 81%) obtained formed shiny needles, m.p. 89° (Lit.[32] 87–88°).

Reduction of 3-*p*-methoxybenzylindole with "externally" generated diborane, gave similar results, although the product was slightly less pure and the final purification resulted in a lower yield.

2-p-*Methoxybenzyl-3-benzylindole and* 1-p-*methoxybenzyl-3-benzylindole.* To a suspension of Mg (1·2 g; 0·05 mole) in dry ether (30 ml) at 0° was added redistilled EtBr (7·6 g; 0·07 mole) in dry ether 20 ml with stirring over 30 min. The mixture was refluxed until all the Mg dissolved (30 min). Dry benzene 30 ml was added to the clear soln and excess EtBr was distilled off.

3-Benzylindole (8·3 g; 0·04 mole) in dry ether 150 ml was slowly added to the reaction mixture and heated under reflux for 15 min. The mixture was cooled in ice and stirred in an atmosphere of N_2 during the slow addition of freshly distilled *p*-methoxybenzylchloride (6·3 g; 0·04 mole) in dry ether 10 ml. After stirring for a further 2 hr at 20°, the mixture was diluted with ether 200 ml and poured onto ice-cold 1·5N HCl. The ethereal layer, after drying ($MgSO_4$) and removal of solvent afforded a brown, viscous oil (13·6 g). The aqueous acidic layer, after basification and extraction with ether, gave practically nothing.

10 g of the crude product was chromatographed on alumina in light petroleum/benzene.

Fraction 1 (0·83 g) was a colourless, viscous oil (eluted by light petroleum) which could not be crystallized and did not form a picrate or picrolonate. It was obtained as a colourless oil by distillation (in a tube) at 174°/0·07 mm and characterized as 1-p-*methoxybenzyl-3-benzylindole* by NMR (Table 1) and mass spectrum (Table 2). (Found: C, 85·5; H, 6·8; N, 4·4. $C_{23}H_{21}NO$ requires: C, 84·4; H, 6·5; N, 4·3%). The IR spectrum showed no NH band. λ_{max} (in EtOH): 227, 278, 284 mμ.

Fraction 2 (2·4 g) after crystallization from aqueous alcohol gave 3-benzylindole, m.p. 84°.

Fraction 3 (5·2 g) contained 2-p-*methoxybenzyl-3-benzylindole* (one spot on TLC). Distillation in a tube at 190–198°/0·06 mm gave a viscous, buff coloured oil. (Found: C, 83·5; H, 6·5; N, 4·55. $C_{23}H_{21}NO$ requires: C, 84·4; H, 6·5; N, 4·3%); ν_{max} 3400 cm^{-1}; (s)(NH); λ_{max} (EtOH): 226, 280–284, 291 (sh) mμ.

Further purification by repeated column chromatography or preparative TLC followed by work-up under N_2 atmosphere did not give better analytical results. Attempts to prepare a picrate or picrolonate derivative also failed. The NMR and mass spectra are recorded in Tables 1 and 3. Fraction 4 (0·61 g) after two crystallizations from benzene gave 2-p-*methoxybenzoyl-3-benzylindole* as needles, m.p. 136°. (Found: C, 80·8; H, 5·6; N, 4·0. $C_{23}H_{19}NO_2$ requires: C, 80·9; H, 5·6; N, 4·1%); ν_{max} (Nujol): 3345 s (NH), 1620 s (C═O), 1600 s (C═C) cm^{-1} λ_{max} (log ε_{max}) in EtOH: 220 (4·51), 327 (4·30) mμ unchanged on addition of alkali.

2-*p*-Methoxybenzyl-3-benzylindole on long exposure to air, was found to give very small quantities of 2-*p*-methoxybenzoyl-3-benzylindole. Refluxing in benzene did not enhance the apparent rate of formation of the ketone.

3-*Benzyl*-2-p-*methoxybenzylindole and* 1-*Benzyl*-3-*methoxybenzylindole.* To a Grignard reagent prepared from Mg (2·16 g; 0·09 mole) and EtBr (19·6 g; 0·018 mole) in benzene as before, was added slowly 3-*p*-methoxybenzylindole (7·11 g; 0·03 mole) in dry benzene 150 ml with stirring and the mixture refluxed for 1 hr. After cooling the mixture in ice, redistilled benzylbromide (5·13 g; 0·03 mole) in dry benzene 10 ml was added with stirring under an atmosphere of N_2. TLC examination of the reaction mixture after stirring for 2 hr at 20° indicated the presence of some starting material. (In a preliminary experiment using benzyl chloride in ether as solvent over 2 hr at 20°, mainly starting material was recovered).

After heating the mixture under reflux for 2 hr the starting material had almost completely disappeared and 10% NH_4Cl aq (200 ml) was added to the cooled reaction mixture. The organic layer was separated, the aqueous layer re-extracted with benzene and the combined extracts dried ($MgSO_4$). After removal of the solvent a pale yellow viscous oil (12·6 g) was obtained.

This product was chromatographed on alumina in light petroleum and benzene and gave two main fractions:

(i) Elution with light petroleum–benzene (4/5: v/v) gave a colourless oil (1·6 g), which crystallized from light petroleum (b.p. 40–60°) to give 1-*benzyl*-3-p-*methoxybenzylindole* as needles, m.p. 78·5°. (Found: C, 84·1; H, 6·35; N, 4·3. $C_{23}H_{21}NO$ requires; C, 84·4; H, 6·5; N, 4·3%). No NH in the IR spectrum.

(ii) Further elution with light petroleum–benzene (1/1; v/v) gave an oil (7·59 g), which on rechromatography on silica gel in light petroleum–benzene (2/3: v/v) afforded 3-benzyl-2-*p*-methoxybenzylindole (7·0 g) as a viscous oil, which distilled (with some dec) onto a cold finger at 155–140°/0·001 mm. It was shown to be identical on TLC, and by comparison of its UV, IR, NMR and mass spectra with the product prepared by treatment of 3-benzylindole Grignard derivative with *p*-methoxybenzylchloride.

(iii) Elution with benzene gave a small amount of 3-*p*-methoxybenzylindole, and elution with EtOAc

gave a small amount of an unknown product (M.wt. 357—mass spectra), λ_{max} (EtOH): 218, 227 sh. 260 sh., 269, 278, 285 mμ, unchanged by addition of acid.

3-p-*Methoxybenzyl-2-benzylindole.* To the Grignard reagent prepared from Mg (0·37 g; 0·015 mole) in dry ether (20 ml) and redistilled EtBr (2·18 g; 0·02 mole) was added 2-benzylindole (1·88 g; 0·0 9 mole) in ether (25 ml) and the mixture was refluxed under dry N_2 for 2 hr. After cooling, freshly distilled *p*-methoxy benzylchloride (1·57 g; 0·01 mole) in ether (25 ml) was added slowly with stirring. TLC examination of the mixture indicated the presence of a small amount of 2-benzylindole even after 15 hr at 20°. More *p*-methoxybenzylchloride (0·78 g; 0·005 mole) in ether (25 ml) was then added and the mixture stirred at 20° for another 4·5 hr. After adding 2N HCl (100 ml), the organic material was extracted into ether, dried ($MgSO_4$) and then the ether distilled off under reduced press to leave a pale brown, viscous oil (3·72 g). This was percolated through silicagel in benzene-pet. ether (4·1 : v/v) and crystallized once from light petroleum and then from EtOH to furnish 3-p-*methoxybenzyl-2-benzylindole* (0·9 g; 30%) as transparent plates, m.p. 127°. (Found: C, 84·5; H, 6·6; N, 4·35. $C_{23}H_{21}NO$ requires: C, 84·4; H, 6·5; N, 4·30%) ν_{max} (Nujol): 3240 (NH) cm^{-1}.

N-p-*Methoxybenzylindole.* This compound was prepared following the method described by Plieninger[33] for the synthesis of N-benzylindole.

Sodamide was prepared from liquid ammonia (400 ml), metallic Na (3·45 g; 0·15 mole) and ferric nitrate (0·1 g). Indole (17·6 g; 0·15 mole) was added to the mixture followed by freshly prepared *p*-methoxybenzyl chloride (23·48 g; 0·15 mole) and worked up as described by Plieninger[33] for the analogue to give 35·4 g of a pale yellow oil. This, on distillation at 178–192°/0·8 mm, followed by crystallization from alcohol, furnished N-p-*methoxybenzylindole* (32 g; 90%) as colourless needles, m.p. 37°. (Found: C, 81·0; H, 6·4; N, 6·0. $C_{16}H_{15}NO$ requires: C, 81·0; H, 6·4; N, 5·9%).

Rearrangement of 1-p-*methoxybenzyl-3-benzylindole to* 2-p-*methoxybenzyl-3-benzylindole.* Compound LXXIV (0·3 g) was stirred with trifluoroacetic acid (0·5 ml) at 20° under N_2 for 15 min. The mixture was then treated with cold water and extracted with ether (3 × 20 ml). After washing the extract with $NaHCO_3$ aq and drying ($MgSO_4$) the solvent was removed under reduced press to give 2-*p*-methoxybenzyl-3-benzylindole (0·235 g; 95%) as a pale yellow, viscous oil. Its IR, UV, NMR and mass spectra and behaviour on TLC plates were exactly identical with those of the samples prepared by Grignard reactions.

3-*Phthalidylindole.*[18] Indole (5·85 g; 0·05 mole) and phthaladehydic acid (7·5 g; 0·05 mole) in benzene (190 ml) were refluxed allowing the benzene to percolate through a Soxhlet apparatus containing molecular sieves type 4A (10 g) for 2 hr. After concentration and cooling the resulting white crystals were separated and recrystallized from alcohol to give 3-phthalidylindole (10·53 g; 85%), m.p. 177° (Lit.[18] m.p. 177°); ν_{max} (Nujol): 3330 (NH), 1735 (C=O) cm^{-1}; NMR (acetone): Ar—H, 2·1 – 3·1 *m*; N—H, −0·03 *b.s.*; 3-CH, 3·19 *s*.

3-(o-*Carboxybenzyl)indole* was prepared by hydrogenating 3-phthalidylindole over 10% Pd–C following Rees and Sabet's procedure[18] and was obtained in 70% yield as white needles, m.p. 214–215° (Lit.[18] m.p. 214–215°); ν_{max} (Nujol): 3475 (NH), 267 w, 926 (acid OH), 1695 cm^{-1} (acid C=O); NMR (acetone): Ar—H, 1·95–3·08 *m*; N—H, 1·5 *b.s.* —COO—H, 0·1. *b.s.*; 3-CH_2—, 5·45 *s*.

Reduction of 3-(o-*carboxybenzyl)indole*

(a) *With lithium aluminium hydride.* 3-(o-carboxybenzyl) indole (7·53 g; 0·03 mole) in dry THF (100 ml) was added carefully to LAH (2·74 g; 0·072 mole) in THF (100 ml). After refluxing for 2·5 hr, water was added carefully, followed by a saturated aqueous soln of sodium potassium tartrate. The organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 100 ml). The combined extracts were dried ($MgSO_4$) and then the solvent distilled off. The crystalline residue on recrystallization from benzene gave 3-(o-*hydroxymethylbenzyl)indole* (6·4 g; 90%) as colourless, hairy needles, m.p. 79°. (Found: C, 80·8; H, 6·45; N, 6·16. $C_{16}H_{15}NO$ requires: C, 81·0; H, 6·37; N, 5·90%); ν_{max} (Nujol): 3400(s), 3375(s), 3265(s) (NH, OH), 1600(w) (C=C), 1055(s), 1000(m), 800(m), 762(s), 751(s), 742(s), cm^{-1}; NMR spectrum in $CDCl_3$: Ar—H, 2·4–2·9 *m*, N—H, 2·1 *b.s.*; 2-H, 3·48 *s*; 3-CH_2—, 5·93 *s*; CH_2—OH, 5·4 *s*, 8·15 *b.s.* (exchanged with D_2O); λ_{max} (log ε_{max}) in EtOH: 223 (4·56), 275 (3·76), 282·5 (3·78), 292 (3·72) mμ.

(b) *With Diborane.* (i) Borane (0·03 mole) generated from $NaBH_4$ (0·85 g; 0·0225 mole) in diglyme (22 ml) and BF_3OEt_2 (4·47 g; 0·03 mole) in diglyme (13 ml) was passed into a soln of 3-(o-carboxybenzyl)indole (2·51 g; 0·01 mole) in THF (100 ml). The mixture was left at 20° for 24 hr and then refluxed for 5 hr. (IR and TLC examinations indicated the presence of a small quantity of the acid even after refluxing for 5 hr). The reaction mixture was worked up in the usual manner. The crude product, which showed 4 spots on TLC plates, after two crystallizations from alcohol and two crystallizations from ethylacetate gave the *spiroindoline* (XVIII; 0·5 g; 21%) as prisms, m.p. 182°. Mixed m.p. with the product from LAH reduction:

shrank at 78° and melted from 140–170°. (Found: C, 81·0; H, 6·4; N, 5·9. $C_{16}H_{15}NO$ requires: C, 81·0; H, 6·4; N, 5·9%); ν_{max} (Nujol): 3325 (s) (broad, NH, OH), 1610 (m) (C=C), 1039 (s), 782 (m), 762 (s) cm^{-1}; λ_{max} (log ε_{max}) in EtOH: 244 (3·76), 272 (3·34), 295 (3·43); in EtOH + H_2SO_4: 263 (3·04), 267 (3·04), 272 (2·98) mμ. NMR: see Table 4.

(ii) Borane (0·090 mole) generated from $NaBH_4$ (3·57 g; 0·0942 mole) in diglyme (60 ml) and I_2 (114 g; 0·0898 mole) in diglyme (36 ml) was passed through a soln of $NaBH_4$ (0·30 g) in diglyme (15 ml) into a soln of 3-(*o*-carboxybenzyl)indole (3·765 g; 0·015 ml) in THF (200 ml). The mixture was left at 20° for 24 hr, refluxed with MeOH (100 ml) and then the solvents removed. The residue was taken up in EtOAc, extracted with 5% Na_2CO_3 aq (3 × 25 ml), dried ($MgSO_4$) and then EtOAc was removed to give a crystalline residue. After three crystallizations from EtOAc and one crystallization from alcohol, it gave the spirocyclic indoline (0·78 g; 21%) as white prisms, m.p. 182°. The aqueous phase, on acidification afforded 265 mg 3-(*o*-carboxybenzyl)indole.

1,4-*Dihydro*-2,3-*benzcarbazole*. A mixture of 3-(*o*-hydroxymethylbenzyl)indole (1·66 g; 0·007 mole) in benzene (200 ml) and P_2O_5 (4 g; 0·028 mole) was refluxed for 2·5 hr under N_2 filtered hot and the residue washed repeatedly with hot benzene. The combined filtrates were concentrated and cooled to give colourless hairy needles (0·70 g). This material was sublimed at 200°/0·001 mm and gave 1,4-*dihydro*-2,3-*benzcarbazole* (0·4 g; 26%) as shining crystals, m.p. 317°. (Found: C, 88·07; H, 6·2; N, 6·5. $C_{16}H_{15}N$ requires: C, 87·64; H, 6·0; N, 6·4%); ν_{max} (Nujol): 3390 (NH), 1620 (C=C), cm^{-1}; λ_{max} (log ε_{max}) in EtOH: 225 (4·52), 272 (4·26), 282 (4·19), 292 (4·03) mμ. NMR ($CDCl_3$); C$\underline{H}_2$, 5·89; Ar-$\underline{H}$, 2·3–3·0 *m*; N$\underline{H}$, ~2·2 *b*, (T.F.A.): C$\underline{H}_2$, 5·34; Ar-$\underline{H}$, 2·62 *s* (4H), 2·27 *m* (4H) τ.

2,3-*Benzcarbazole*. A mixture of 3-(*o*-hydroxymethylbenzyl)indole (0·4 g) and P_2O_5 (1 g) in redistilled xylene (50 ml) was heated under reflux for 1 hr, filtered hot, and the residue washed with hot xylene. The solvent was distilled off from the combined filtrates under reduced press. The residual solid thus obtained furnished 2,3-benzcarbazole (0·14 g; 40%) after crystallization from benzene, as colourless needles, which shrank at 210° and melted at 335° (Lit.[3,4] m.p. 330–331°). (Found: N, 6·5; Calc. for $C_{16}H_{11}N$: N, 6·45%); NMR ($CDCl_3$): Ar—$\underline{H}$, 1·49 *s* (1H), 1·7–2·2 *m* (4H), 2·38 *s* (1H), 2·5–3·0 *m* (4H) τ.

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* Present address: Natural Drugs Research and Development Institute, P.C.S.I.R., P.O. Chittagong Cantonment, Chittagong, E. Pakistan.

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