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DIBORANE AS A REDUCING AGENT—II[1]

THE REDUCTION OF INDOLE AND PYRROLE CARBONYL DERIVATIVES

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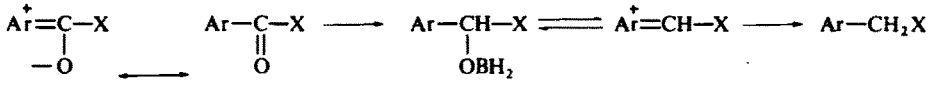
Abstract—Diborane reduction of indole and pyrrole ketones readily affords the corresponding alkyl indoles and pyrroles, even when the nitrogen is substituted. Reduction of 3-formylindoles leads to a mixture of the methylindole, two types of dimeric products and traces of higher polymeric products, whereas 2-formylindole and 2-formylpyrrole give largely polymers. These results are discussed in relation to the mechanisms both of diborane reductions, and of electrophilic substitution in indoles.

PREVIOUS studies of the diborane reduction of simple pyrrole carbonyl derivatives and dipyrroketones,[2] and of other "electronrich" aromatic carbonyl compounds[1] showed that in general the carbonyl group was completely reduced to a methylene group. Elimination of the oxygen formation (from the initially formed alkoxy borane complex) was shown to be facilitated by electron release from the aromatic nucleus (as well as the Lewis-acid character of the borane), and the "methene" or carbonium



ion formed then underwent further reduction by diborane (or possibly by borohydride in "internal reductions".) In so far as pyrrole ketones may be regarded as vinylogous amides the recent demonstration that aliphatic amides may be reduced to amines[3] (see also below) is of some interest in this connection.

The present paper is largely concerned with an extension of our earlier work to carbonyl derivatives of indole partly from an interest in synthetic applications, and partly to compare the reducing properties of diborane (an electrophilic reagent) with those of LAH which has been used extensively in recent years in the indole field.[4,5]

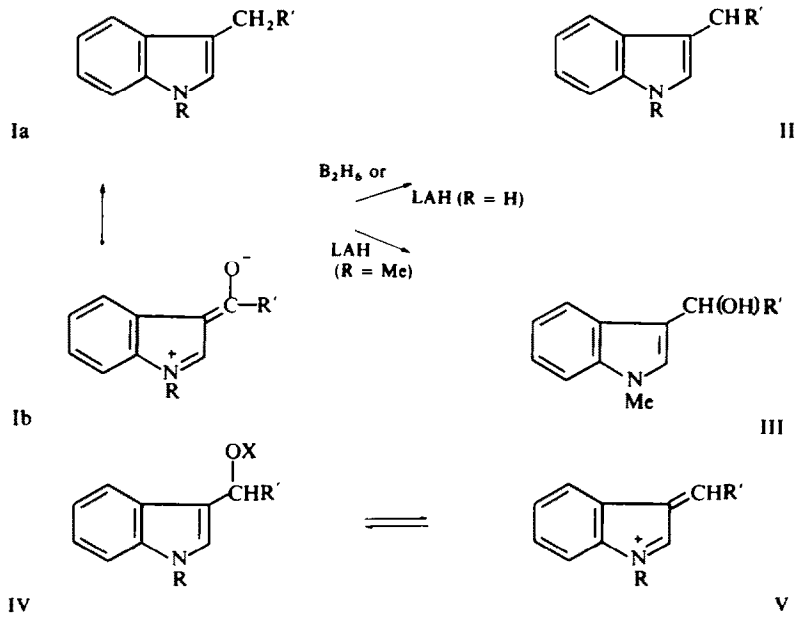
Diborane (generated "externally" or "internally") rapidly reduced 3-acetyl- and 3-benzoyl-indoles, (I) and their N-methyl derivatives, to the corresponding 3-ethyl- and 3-benzyl-indoles (II) in excellent yield (Table 1). In contrast whereas LAH reduction of the 3-acylindoles also affords the corresponding 3-alkylindoles, the N-methyl analogues are only reduced to the corresponding alcohols[4,6] (III). This difference in reactivity presumably reflects the relative difficulty in eliminating the negatively charged aluminate group in the intermediate IV ($X = AlH_3^-$) compared with the corresponding uncharged but electron accepting borate group ($X = BH_2$) formed in a diborane reduction; in the N-unsubstituted series this is perhaps overcome by prior, or further, complexing of the nitrogen with another molecule of LAH. (However LAH–$AlCl_3$ reduction[6] of 3-acetyl-N-methylindole gives the 3-ethylindole

Table 1. Diborane reduction of indole carbonyl derivatives

	Indole (substituents)		Product (substituents)	Yields(%) External reduction[a]	Internal reduction[a]	
Ia	3-COPh	IIa	$3\text{-}CH_2Ph$	80, 95[b], 70[c]	90	
Ib	1-Me, 3-COPh	IIb	$1\text{-Me,3-}CH_2Ph$	85	80	
Ic	3-COMe	IIc	$3\text{-}CH_2CH_3$	85,83[b]	98	
Id	1-Me,3-COMe	IId	$1\text{-Me,3-}CH_2CH_3$	95	78	
	3-COCONHMe		$3\text{-}CH_2CH_2NHMe$	—	78	
	$3\text{-}CH_2CH_2NHCOCH_3$		$3\text{-}CH_2CH_2NHEt$	—	54	
VI	2-COMe,3-Me	VII	$2\text{-}CH_2CH_3\text{,3-Me}$	65	—	
		VIIIa	$2\text{-CH(OH)}CH_3\text{,3-Me}$	14	—	
		VIIIb	$2\text{-CH(OMe)}CH_3\text{,3-Me}$	4	—	
XIa	3-CHO	XIVa	$3\text{-}CH_3$	15	16	
		XVIIa	$R' = R^2 = H$	24	not isolated	
		XVIIIa	$R' = R^2 = H$	55	58	
XIb	1-Me,3-CHO	XIVb	$1\text{-Me,3-}CH_3$	27, 58[b]	7	20[d]
		XVIIb	$R' = Me, R^2 = H$	34, 20[b]	12	—
		XVIIIb	$R' = Me, R^2 = H$	30, 15[b]	70	25[d]
		XIX				25[d]
XIc	2-Me,3-CHO	XIVc	$2\text{-Me,3-}CH_3$	12	49	
		XVIIc	$R' = H, R^2 = Me$	17	5	
		XVIIIc	$R' = H, R^2 = Me$	66	32	
		XX		0·5	2	
	2-CHO		$2\text{-}CH_3$	8		
			$2\text{-}CH_2OH$	32		
			polymer	60		
	$2\text{-}CO_2H$		$2\text{-}CH_3$	5		
			polymer	90		
	$2\text{-}CO_2Et$		$2\text{-}CO_2Et$		100[b]	
	$3\text{-}CH_2NMe_2$		$3\text{-}CH_2NMe_2$	35 (recovered)		
			$3\text{-}CH_3$	trace		
			polymer	65		
	$3\text{-}CH_2\overset{+}{N}Me_3$		$3\text{-}CH_3$		95[e]	
	oxindole		oxindole	64 (recovered)		
			indoline	25	85	
			indole	4		
	indole		indole	51 (recovered)	34	
			indoline	26	35	

[a] 3 moles BH_3 to 1 mole substrate unless otherwise indicated.
[b] 13 moles BH_3 to 1 mole substrate.
[c] 1 mole BH_3 to 1 mole substrate.
[d] LAH-$AlCl_3$ reduction (see Experimental).
[e] $NaBH_4$ reduction (see Experimental).

presumably through the agency of aluminium hydrides generated *in situ*.) Similarly the reduction of pyrrole aldehydes and ketones with LAH yields the corresponding alkyl pyrroles if the nitrogen is unsubstituted, but the alcohols if the nitrogen is substituted,[7] whereas diborane reductions give the alkyl pyrroles whether or not the nitrogen is substituted (Table 3).



The diborane reduction of indole glyoxylamides (I; R′ = $CONR_2''$, R = H or Me) affords the corresponding tryptamines (II; R′ = CH_2NR_2'', R = H or Me) both carbonyl groups suffering hydrogenolysis. This is of considerable value in the synthesis of *ind*-N-methyltryptamines because LAH reductions in this series gives only the 1′-hydroxytryptamines[4,6] (III; R′ = CH_2NR_2'', R = Me).

The reduction of 2-acetyl-3-methylindole (VI) with diborane affords a mixture of products in which 2-ethyl-3-methylindole (VII) predominates, whilst the hydroxyethyl- and methoxyethylindoles (VIII; R = H and R = Me) are present in smaller amount. (The latter must arise from the methanol used in the work-up to decompose

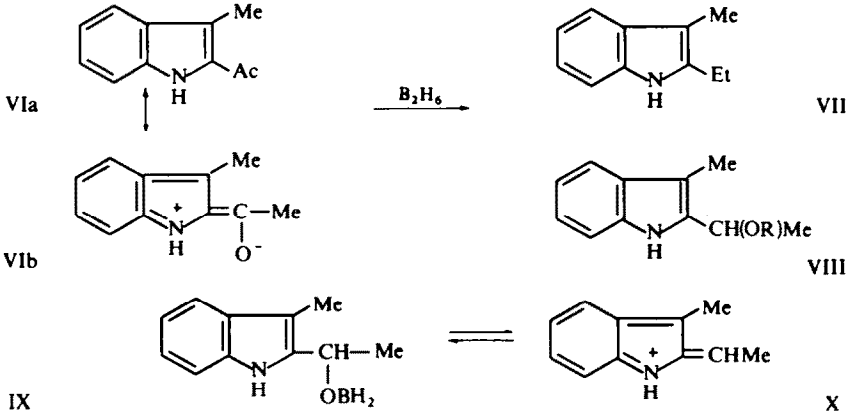
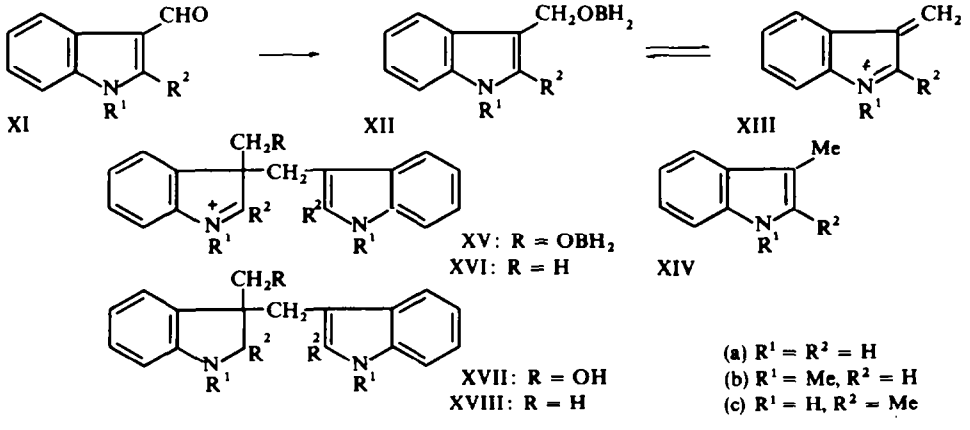


Table 2. UV spectra of 2- and 3-acylindoles

Indole (substituents)	λ_{max}(mμ) (log ε_{max}) In 95% Ethanol	λ_{max}(mμ) (log ε_{max}) In 95% Ethanol containing a little NaOH aq.
3-COMe	240 (4·07), 257 (3·93), 296 (4·08)	229 (3·77) 267 (4·12), 331 (4·15)
3-CHO	242 (4·10), 260 (4·03), 296 (4·09)	228 (3·68) 265 (4·24), 325 (4·25)
3-CHO, 2-Me	223 (4·17), 245 (4·14), 266 (4·04), 302 (4·09)	229 (3·67) 269 (4·21), 329 (4·25)
3-COPh	220 (4·20), 248 (4·25), 272 (4·14), 313 (4·20)	230 (4·07), 245 (3·99), 275 (4·11), 346 (4·19)
3-CHO, 1-Me	219 (4·11), 245 (4·14), 301 (4·16)	no change
3-COPh, 1-Me	249 (4·18) 318 (4·22)	no change
2-COMe, 3-Me	237 (4·16) 311 (4·30)	no change
2-CHO	232 (4·09) 308 (4·35)	230 (4·15), 311 (4·23)
3-COMe, 1-Me	221 (4·05), 243 (4·14) 301 (4·11)	no change

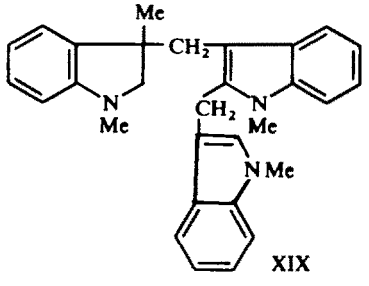
excess diborane, and alkoxy boranes.) This result is of some theoretical interest because it suggests that the intermediate alkoxy borane (IX) shows less tendency to dissociate to the "methane" (X) i.e. that electron release to the 2-substituent is less effective than to a 3-substituent (as in V). This is not unexpected because the former (X) involves disturbance of the π-electrons of the benzene ring whereas the latter (V) does not, and this is reflected in the well-known susceptibility of the 3-position in the indole nucleus to electrophilic attack[8] and to protonation in strongly acidic media.[9,10] Further evidence for this explanation of the difference in behaviour of 2- and 3-substituents is provided by the acetyl indoles (I; R = H, R′ = Me) and VI; the UV spectrum of I (R = H, R′ = Me) shows a pronounced bathochromic shift in alkaline solution[11] (due to ionization of the NH group) whereas the spectrum of VI is unaffected by alkali. (Table 2). This is of practical value in the synthesis of N-methyl-3-acylindoles[10] (see also Experimental).

The diborane reduction of 3-formylindoles (XI) afforded mixtures of products (Table 1) including the corresponding 3-methylindoles (XIV), two types of dimeric products (XVII and XVIII), a trimeric product and traces of other polymeric materials.

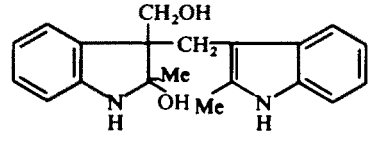


The mixtures were separated chromatographically on columns and plates, and the structures of the dimeric products elucidated by elemental analyses and spectroscopic methods (see below). The 3-formylindole is presumably reduced initially to the alkoxy borane (XII) which then undergoes slow solvolysis to the methylene-indolenine (XIII). The latter can be further reduced by diborane to the 3-methylindole (XIV) or alternatively it may electrophilically attack another molecule of the alkoxy borane (XII) or the 3-methylindole (XIV) to give the indolenines XV and XVI respectively, further reduction of which (followed by the usual methanol work-up) affords the observed products, the indolyl methylindolines (XVII and XVIII). In accord with this mechanism is the fact that greater yields of 1,3-dimethylindole, compared with dimeric products, were obtained by reduction of 3-formyl-1-methylindole with a larger excess of diborane (cf. Table 1), for this would be expected to increase the rate of reduction of the intermediate methylene-indolenine (XIII; $R' = Me$, $R^2 = H$) compared with its dimerization.

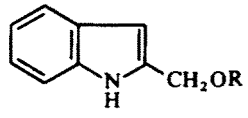
The reduction of 3-formyl-1-methylindole with "mixed hydrides"[12] generated from LAH and $AlCl_3$ was also investigated for comparison with the internal diborane reductions. The same types of products were obtained and it is interesting to note that in one experiment larger amounts of polymeric materials were obtained (see Table 1 and Experimental).



XIX



XX



XXI

3-Formyl-1-methylindole also gave a small amount of a trimeric product in the LAH–$AlCl_3$ reductions which was assigned structure XIX, and was probably formed by electrophilic attack of the "methene" (XIII; $R' = Me$, $R^2 = H$) upon the dimeric product XVIII ($R' = Me$, $R^2 = H$). Repetition of the same type of reactions would account for the formation of higher polymeric products which were also formed. A different type of dimeric product, tentatively assigned structure XX, was also isolated in low yield from the diborane reduction of 3-formyl-2-methylindole, and this may have arisen by addition of water (in the work-up) to residual traces of un-reduced indolenine (XV; $R' = H$, $R^2 = Me$).

The overall process and the complex products obtained recall the similar results obtained in the diborane reduction of anisaldehyde in our earlier work.[1] Similar polymeric products will presumably be formed in the diborane reduction of any electron-rich aromatic carbonyl compound if the aromatic nucleus is sufficiently reactive and the rate of electrophilic substitution by the intermediate "methenes"

(e.g. XIII) produced is faster than (or comparable with) the rate of reduction of these methenes.

The formation of the dimeric products is of interest in connection with the mechanism of formation of diindolylmethanes,[13] dipyrrylmethanes[14] and diarylmethanes[15] from the solvolyses of the corresponding alkoxymethyl-, acetoxymethyl-, halomethyl-, or aminomethyl-monomeric compounds ($ArCH_2R$). It is generally accepted that these reactions involve the formation of indolenine type intermediates (e.g. XV; R = OH) followed by elimination of a one carbon fragment (as formaldehyde) to give the diarylmethane ($ArCH_2Ar$), and the present examples confirm this mechanism as the intermediates are trapped by further reduction (e.g. to XVII) and do not undergo elimination. These results in the indole series are also of special interest because they provide good support for our recently formulated proposal that alkylation of 3-substituted indoles at the 2-position involves initial attack at the 3-position, to form a 3,3-disubstituted indolenine followed by rearrangement to the 2,3-disubstituted indole;[16] again, in the diborane reductions the intermediate indolenines are trapped by reduction to indolines (except in the second substitution in the case of the trimeric product XIX).

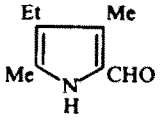
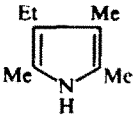
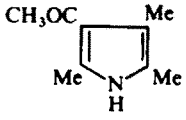
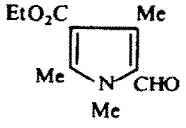
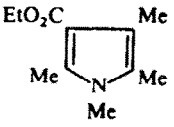
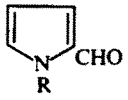
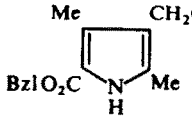
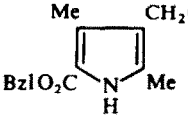
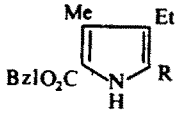
Grammine gives largely polymeric products on attempted diborane reduction, but the methosulphate readily undergoes reduction by borohydride in methanol to give skatole. The intermediate in the latter process (as in many of the nucleophilic substitution reactions of grammine metho-salts) is presumably XIII ($R' = R^2 = H$), and this affords good evidence for our previous suggestion[1] that internal reductions may well be facilitated by the presence of nucleophilic reducing species in solution as well as electrophilic species.

2-Formylindole and indole-2-carboxylic acid both gave largely polymeric products on diborane reduction although some 2-methylindole was also formed, and the former also gave a moderate yield of 2-hydroxymethylindole. The formation of the polymeric compounds is presumably due to the high reactivity of the vacant 3-position in the indole nucleus towards electrophiles,[8] which is enhanced[cf 9] by a 2-alkyl substituent. Polymer formation does not occur to any appreciable extent in the reduction of 3-formylindoles because electrophilic attack during dimer formation takes place at an already occupied position of lower anionoid activity;[cf 9, 10] the intermediate indolenine thus formed is immediately reduced by excess diborane.

2-Formylpyrrole and its N-methyl analogue showed a much greater tendency to form polymer on diborane reduction than 2-formylindole, and this can be attributed to the higher susceptibility of pyrroles to electrophilic attack than indoles, as well as to the larger number of highly reactive vacant positions in the pyrrole nucleus. (The benzene ring in indole is relatively inert to electrophilic attack except under vigorous conditions.) These polymeric indole and pyrrole derivatives may be regarded as heterocyclic analogues of phenolformaldehyde resins and provide another parallel in reactivity between phenols and pyrroles and indoles.

As can be seen from Table 3, pyrrole aldehydes with all the other nuclear carbon atoms substituted did not give polymeric products, and moreover the presence of another electron withdrawing substituent in the ring in direct conjugation with the formyl group diminished its reactivity towards diborane reduction so much so that good yields of the corresponding hydroxymethylpyrrole could be obtained. However, it is interesting to note that the N-methylpyrrole in Table 3 (in which the ester group

TABLE 3. DIBORANE REDUCTION OF PYRROLE CARBONYL COMPOUNDS

No.	Pyrrole	Product	Yield (%)	Remarks
1.			49[a]	External
2.		"	71[a] 80[e]	External Internal
3.			93[a]	Internal
4.	 (R = H or Me)	polymer	100[a]	External
5.			95[b]	External
6.				
	(a) R = CHO	R = CH_2OH	95[c]	External
	(b) R = CHO	R = Me	16[d]	External
	(c) R = CO_2H	R = Me	35[d]	External
	(d) R = $CONMe_2$	R = $CH_2NMe_2BH_3$	40[e]	External
		R = CH_2OH	20[e]	External
		R = CH_3	23[e]	External

[a] 3 moles BH_3 to 1 mole substrate. [b] Large excess BH_3; A. H. Jackson, G. W. Kenner and G. S. Sach, *J. Chem. Soc.* (C) in press. [c] Large excess BH_3: time of reduction 5 min. (Ref. 2). [d] Large excess BH_3: time of reduction 95 min. (Ref. 2). [e] Large excess BH_3: time of reduction 120 min. (Ref. 2).

is not in direct conjugation with the formyl group) gave an excellent yield of the corresponding methyl derivative.

Finally it should be noted that nuclear ester substituents in both pyrroles and indoles are not reduced even by a very large excess of diborane, whereas side-chain (aliphatic type) esters are slowly reduced. The reduction of the aliphatic esters can be inhibited by carrying out reductions in presence of ethyl acetate, and thus diborane has obvious synthetic potential in the specific reduction of indole and pyrrole ketones

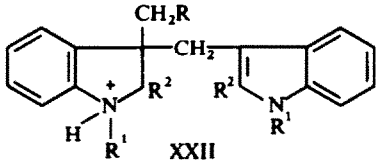
in cases where LAH cannot be used (either because the nitrogen is substituted, or because ester groups are present).

The reduction of indole and oxindole was investigated,[cf 17] and the results are recorded in Table 1; larger amounts of diborane and longer reaction times may well give higher yields of indolines, and thus provide useful synthetic routes to indolines.

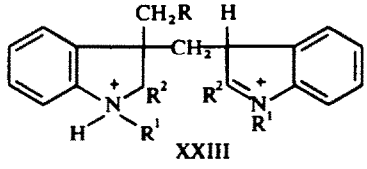
Characterization of the di- and trimeric products obtained from 3-formylindoles

The dimeric products assigned structures XVIIa, b and c and XVIIIa, b and c all gave satisfactory elemental analyses, and mass spectral determinations confirmed their mol. wts. Their UV spectra in ethanol were typical indolic (Table 4) and extinction coefficients showed that each contained only one indole residue, for even in neutral solution the absorptions due to the indoline nuclei (as free bases) are very much overshadowed by those of the indole nuclei except in the N-methyl series. On addition of a small amount of acid to the ethanol solutions the UV spectra showed slight changes, which are probably due to protonation of the more basic indoline moieties to give anilinium type cations (XXII). The latter exhibit only low intensity benzenoid type absorptions which are completely masked by the absorption of the indole nuclei.

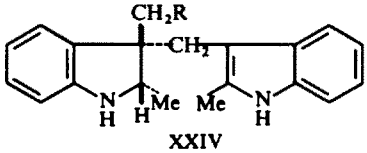
In concentrated sulphuric acid the indole nuclei are also protonated (at the 3-position) to give the 3-H indolium salts (XXIII) and this is clearly shown by the UV spectra which are very similar to those of simple 3-H indolium salts or 3,3-dialkylindolenine salts.[9, 10]



XXII



XXIII



XXIV

TABLE 4. UV SPECTRA OF THE DIMERIC PRODUCTS OBTAINED IN THE REDUCTION OF 3-FORMYLINDOLES

	λ_{max}(mμ) (log ε_{max}) In 95% ethanol	In 95% ethanol + H_2SO_4	In conc H_2SO_4
XVIIa	223 (4·60) 283 (3·90) 290 (3·89)	221 (4·56) 281 (3·79) 290 (3·72)	240 (3·72)245 (3·71) 297 (3·70)
XVIIIa	223 (4·60) 283 (3·92) 290 (3·90)	220 (4·57) 281 (3·80) 290 (3·74)	236 (3·72) 241 (3·71) 300 (3·68)
XVIIb	226 (4·63) 255 (3·99) 293 (3·94)	224 (4·57) 288 (3·83)	239 (3·65) 244 (3·65) 292 (3·73)
XVIIIb	225 (4·57) 257 (3·99) 292 (3·89)	223 (4·54) 288 (3·77)	236 (3·73) 241 (3·73) 288 (3·72)
XVIIc	228 (4·55) 284 (3·95) 290 (3·94)	223 (4·54) 282 (3·89) 289 (3·83)	236 (3·75) 241 (3·75) 290 (3·68)
XVIIIc	229 (4·57) 283 (3·94) 290 (3·92)	224 (4·53) 282 (3·88) 290 (3·81)	236 (3·77) 241 (3·75) 289 (3·66)
XIX	241 (4·20) 294 (3·66)	227 (4·67) 314 (4·34)	
Indoline	241 (3·78) 291 (3·30)	261 (2·81)	

TABLE 5. NMR SPECTRA OF THE DIMERIC PRODUCTS OBTAINED IN THE REDUCTION OF 3-FORMYLINDOLES

Chemical Shifts of Substituents* (τ-values)

Compound	Indoline moiety								Indole moiety					
	Ar—H	N—H	2-H	N—CH_3	2-CH_3	3-CH_3	3-CH_2OH		Ar—H	N—H†	2-H	N—CH_3	2-CH_3	3-CH_2
XVIIIa	2·8–3·5 *m*	6·54	H_A 6·55 *d* H_B 6·93 *d* (J_{AB} = 8·5)	—	—	8·68	—	—	2·4–3·0 *m*	~2·2	3·35 *d* (J = 1)	—	—	7·03
XVIIa	2·7–3·5 *m*	7·43	H_A 6·53 *d* H_B 6·78 *d* (J_{AB} = 8·5)	—	—	—	6·27	7·43	2·3–3·0 *m*	~2·0	3·29 *d* (J = 2)	—	—	H_A 6·80 *d* H_B 6·88 *d* J_{AB} = 14·5
XVIIIb	2·8–3·6 *m*	—	H_A 6·68 *d* H_B 7·22 *d* (J = 8·5)	7·31	—	8·69	—	—	2·4–3·1 *m*	—	3·34	6·34	—	7·05
XVIIb	2·8–3·6 *m*	—	H_A 6·76 *d* H_B 6·93 *d* (J = 8·5)	7·33	—	—	6·31	8·45	2·4–3·1 *m*	—	3·32	6·36	—	H_A 6·78 *d* H_B 7·02 *d* (J = 14)
XVIIIc	2·9–4·0 *m*	~7·4†	6·42 *q* (J = 6·5)	—	8·60 *d* (J = 6·5)	8·73	—	—	2·4–3·1 *m*	~2·5	—	—	8·61	H_A 7·22 *d* H_B 7·42 *d* (J = 14)
XVIIc	2·8–4·1 *m*	~7·3	5·90 *q* (J = 6·5)	—	8·49 *d* (J = 6·5)	—	H_A 6·11 *d* H_B 6·22 *d* (J = 11)	~7·3	2·4–3·1 *m*	2·4	—	—	8·53	7·24

* Singlets unless otherwise indicated by *d* (doublet) *q* (quartet) or *m* (multiplet)

† Broad and concentration dependent.

The NMR spectra of both types of dimers (XVII and XVIII) are all consistent with the proposed structures; in particular the aromatic proton resonances show two sets of superimposed resonances which correspond very closely to those exhibited by simple indoles and indolines respectively. The high field singlet methyl resonance ca. 8·70 in the spectra of the three dimers (XVIIIa, b and c) confirms that the indole and indoline nuclei are linked together at the 3-position of the indoline nucleus, i.e. that the dimerization process involves attack at this position and not elsewhere. In the hydroxymethyl analogues (XVIIa and b) the corresponding methylene resonances are singlets at lower field (ca. 6·3) owing to the deshielding effect of the hydroxyl group; this methylene group must similarly be attached to the quarternary carbon atom at the 3-position of the indoline nucleus because the methylene group in a 3-hydroxymethylindole would be expected to resonate at somewhat lower field (cf. that in 2-hydroxymethylindole which resonates at 5·35 τ). The protons at the 2-position of the indoline moiety give rise in XVIIa and b and XVIIIa and b to AB quartets, as expected, because they are in different environments owing to the asymmetry of substitution at the 3-position; the lower field resonance (XVIIc in Table 5) is presumably due to the proton *cis* to the 3-indolylmethyl substituent as it would be more in the plane of the indole nucleus and hence would experience a slight downfield shift due to the aromatic ring current.

The methylene group linking the indole and indoline nuclei gives rise to a singlet in the dimers XVIIIa, XVIIIb and XVIIc but in the other three compounds an AB quartet is observed. In the first two cases the magnetic environments of the two protons concerned must be virtually equivalent, whereas in the others they are non-equivalent as expected. It is also interesting to note that the two protons of the hydroxymethylene group in XVIIc are magnetically non-equivalent, presumably due to the 2-methyl substituent (in the indoline moiety), whereas they are equivalent in the other two dimers (XVIIa and b) giving rise only to singlets.

One other point of interest is that the spectra of XVIIc and XVIIIc show that only one diastereoisomer is formed in each case, and this must result from stereo-specific reduction of the intermediate indolenines (XVc and XVIc), probably by hydride addition at the 2-position *trans* to the bulky 3-indolymethyl substituent to give XXIV (R = H and OH).

The relatively high field positions of the 2-methyl groups in the indole nuclei of XVIIc and XVIIIc are presumably due to shielding by the benzene ring of the indoline moiety.

Interpretation of some of the spectra was assisted by the addition of small amounts of trifluoracetic acid, or deuterotrifluoroacetic acid, to the deuterochloroform solutions. This caused low field shifts of the indoline N-methyl protons (in XVIIb and XVIIIb) and of the indoline 2-protons (in all the compounds); with higher proportions of acid it was evident that partial protonation of the indole moiety (with formation of the 3H-indolium salts XXIII was occurring.

The mass spectra (Table 6) like the UV and NMR spectra, also reflect the presence of both indole and indoline nuclei in these dimeric products and the fragmentation patterns are shown in the accompanying Schemes I and II. In both series of compounds the major cleavage process involves fission of the bond between the indolylmethyl residue and the 3-position of the indoline moiety. In addition hydrogen transfer from the 2-position of the indoline nucleus may also occur simultaneously

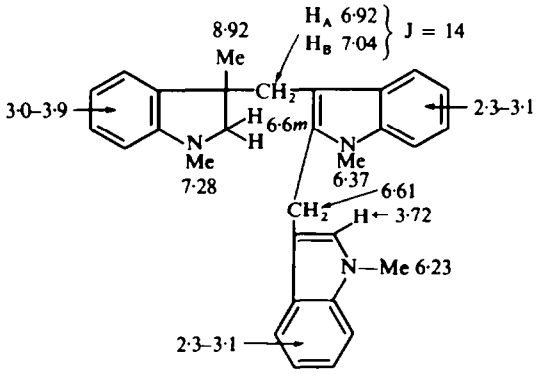
TABLE 6. MASS SPECTRA OF THE DI- AND TRIMERIC PRODUCTS OBTAINED IN THE REDUCTION OF 3-FORMYLINDOLES

	m/e (%)
XVIIIa	262 (5) (M^+), 133 (23), 132 (200), 131 (100), 130 (49), 117 (48), 103 (13), 90 (9), 77 (21). m*: 103 (132 → 117), 81·6 (132 → 103), 69·2 (117 → 90), 57·5 (103 → 77).
XVIIIb	290 (7) (M^+), 229 (6), 147 (13), 146 (100), 145 (41), 144 (29), 131 (30), 130 (13), 77 (8). m*: 117·5 (146 → 131), 72·5 (290 → 146).
XVIIIc	290 (13) (M^+), 177 (13), 147 (17), 146 (100), 145 (50), 144 (38), 132 (13), 131 (70), 130 (97), 120 (36), 91 (25), 78 (88), 77 (44). m*: 117·5 (146 → 131).
XVIIa	278 (27) (M^+), 246 (9), 245 (8), 210 (19), 149 (10), 148 (78), 147 (17), 131 (92), 130 (100), 119 (21), 118 (100), 117 (400), 91 (29), 72 (22). m*: 94 (148 → 118), 70 (118 → 91), 62 (278 → 131).
XVIIb	306 (40) (M^+), 163 (10), 162 (81), 161 (16), 146 (10), 145 (79), 144 (100), 143 (8), 133 (13), 132 (100), 131 (8), 130 (9), 117 (18), 103 (7), 91 (7), 77 (10). m*: 107·5 (162 → 132), 104 (132 → 117), 69 (306 → 145).
XVIIc	306 (15) (M^+), 162 (32), 161 (9), 149 (18), 145 (67), 144 (100), 143 (13), 132 (65), 130 (15), 117 (14), 91 (9). m*: 108 (132 → 117).
XX	322 (30) (M^+), 304 (5), 177 (8), 161 (7), 160 (18), 159 (6), 158 (18), 146 (45), 145 (100), 144 (85), 143 (18), 136 (9), 135 (27), 130 (19), 120 (16), 118 (10), 117 (8), 116 (7), 115 (8), 105 (6), 103 (5), 92 (8), 91 (15), 77 (16), 65 (8). m*: 117 (145 → 130), 107 (135 → 120), 65·3 (322 → 145).
XIX	433 (5) (M^+), 289 (14), 288 (8), 145 (39), 144 (100), 143 (11), 111 (5), 109 (5), 97 (8), 95 (7), 77 (7). m*: 193 (433 → 289).

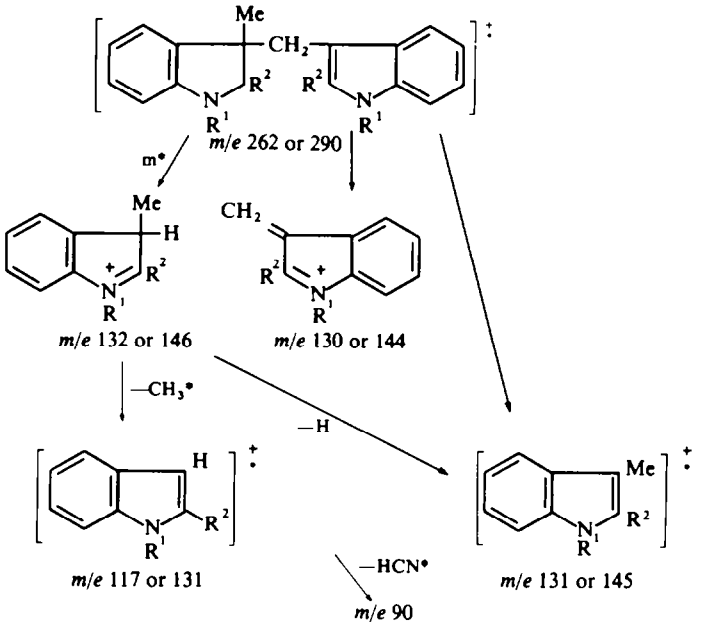
to give the 3-methylindole ions; these ions are much more intense in the hydroxymethyl series and may well be facilitated by hydrogen transfer from the hydroxymethyl group. (In the latter cases the overall process is also substantiated by metastable peaks.)

The structure of the dimeric product (XX) is somewhat tentative and is based largely on elemental analyses and the mass spectrum, as insufficient material was available for NMR studies. The mass spectral mol wt fits this structure, as well as the ready loss of water from the molecular ion, and the major cleavage products *m/e* 144, 145 and 146.

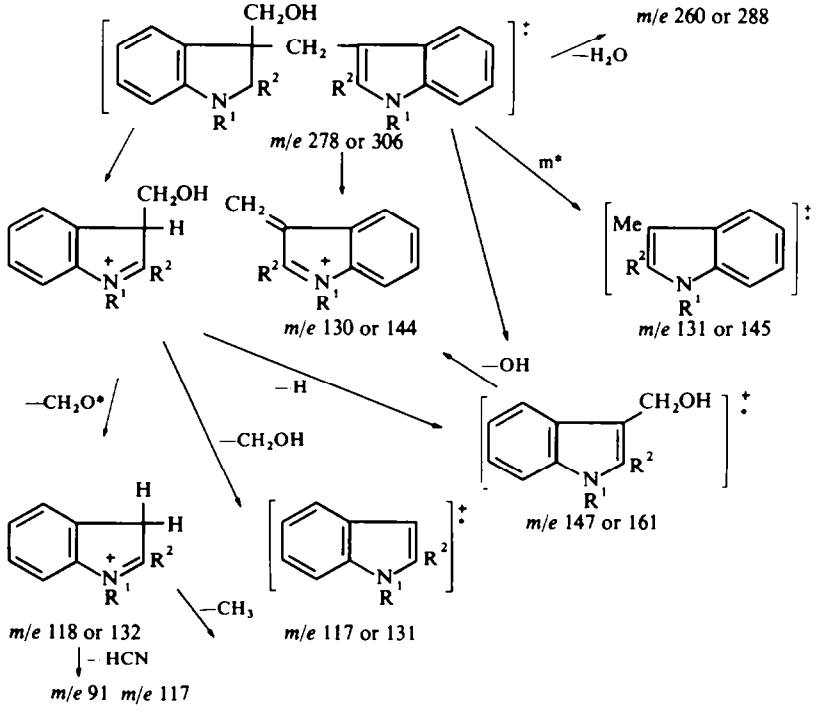
The trimeric compound XIX obtained from 1-formyl-3-methylindole analysed satisfactorily and the mol wt (433) was confirmed by the mass spectrum. The assignment of the NMR spectrum is shown in the accompanying diagram and as can



NMR spectrum of trimer XIX



SCHEME I. *Mass Spectra of Dimers* XVIIIa, b and c.



SCHEME II. *Mass Spectra of Dimers* XVII a, b and c.

readily be seen it shows considerable similarities to those of the dimeric products (Table 5). The mass spectrum is also in accord with the structure and the major ions formed correspond to the 1,3-dimethylindole ion (*m/e* 145) and the 1-methyl-3-indolylmethyl cation (*m/e* 144), although whether these arise from the indoline moiety or from one of the indole groups is not clear. A similar compound was also obtained in the diborane reduction of 3-formyl-1-methylindole in low yield, but although it had a very similar mass spectrum to XIX, the mp and mixed mp were different; insufficient pure material was available for NMR studies or elemental analysis.

EXPERIMENTAL

M.ps are uncorrected. UV spectra were determined with Unicam SP.500 or SP.800 spectrometers, NMR spectra with Varian A-60 or HA-100 instruments and mass spectra with an A.E.I. MS9 spectrometer (at 70 eV and 50 μa) using a direct inlet (heated to 200°).

3-Benzoyl-1-methylindole. 3-Benzoylindole[18] (4·0 g) in acetone (300 ml) and MeI (10·3 g) was heated under reflux over anhyd K_2CO_3 (14 g) for 24 hr. After filtration, and evaporation of the solvents, the residue was crystallized from aqueous MeOH to give the 3-benzoyl-1-methylindole (3·2 g; 75%) as pale yellow needles, m.p. 114° (lit.* m.p. 116–118°). (Found: C, 81·6; H, 5·6; N, 6·1. Calc. for $C_{16}H_{13}NO$: C, 81·7; H, 5·6; N, 5·9%.) NMR spectrum: Ar—H, 2·2–2·7; NCH_3, 6·23; 2-H, 1·5 τ.

3-Acetyl-1-methylindole. This compound was prepared by direct methylation of 3-acetylindole[18,19] in 86% yield using the same procedure as for the analogue above. It formed needles, m.p. 110–111° (lit.[6] m.p. 95°) from ether, benzene or alcohol. (Found: C, 76·0; H, 6·4; N, 8·3. $C_{11}H_{11}NO$ requires: C, 76·3; H, 6·4; N, 8·1%.) NMR spectrum (in $CDCl_3$): 2-H, 2·48; 4-H, 1·6 *m*; 5,6,7-H, ca. 2·7 *m*; N—CH_3, 6·34; $COCH_3$, 7·60 τ.

2-Formylindole. Ethylindole-2-carboxylate (6·3 g) was reduced in THF soln with LAH (1·58 g) according to the procedure described by Brehm,[20] and gave 2-hydroxymethylindole (4·31 g, 88%) as needles, m.p. 75–77° (lit.[21] m.p. 75–77°), from benzene–n-hexane. NMR spectrum (in $CDCl_3$): Ar—H, 2·4–2·9 *m*; NH, 1·67; 3-H, 3·70; 2-CH_2OH, 5·35, 7·20. (Mass spectrum *m/e* (%): 147 (100), 146 (30), 131 (30), 130 (100), 129 (100), 118 (90), 117 (50), 103 (34), 102 (45), 91 (60), 90 (30), 89 (55), 77 (40). m*: 113 (147 → 129; M-H_2O); 80·7 (103 → 91).

The hydroxymethylindole (2·0 g) was then oxidized with MnO_2[21] by Harley-Mason's method[22] and gave the required 2-formylindole (1·73 g, 88%) as needles, m.p. 140–142° (lit.[22] m.p. 140–142°) from MeOH. The m.p. was raised to 145° by recrystallization from benzene.

Diborane reductions. The reductions of the various indolic and pyrrolic carbonyl compounds were carried out by the two procedures described below, and the yields of the various products are given in Tables 1 and 3. In the previous studies a large excess of borane (13·4 moles) was employed in order to effect rapid and complete hydrogenolysis of the carbonyl groups for preparative purposes. In the course of the present work it was found that the use of 3 moles borane to 1 mole substrate gave equally effective results and these procedures are described below; if only 1 mole borane was employed the reactions took rather longer and slightly lower yields were obtained. Reactions were carried out in a flask with a side-arm fitted with a serum cap, and the progress of most reductions was followed by withdrawal of small samples by means of a syringe followed by UV spectroscopic examination or TLC.

External reductions. Diborane generated externally from $NaBH_4$ (0·85 g, 0·0225 mole) in diglyme (20 ml) by the dropwise addition of BF_3-etherate (4·47 g, 0·03 mole) in diglyme (15 ml) over 30 min was passed into a soln of the carbonyl compound (0·01 mole) in dry THF (100 ml) at 0°. The apparatus was flushed initially with dry N_2 and after completion of the addition, residual diborane was swept out in a slow stream of N_2 into the reaction mixture. The latter was then allowed to stand for 3–6 hr at 20°, and the THF removed by distillation under reduced press. The residue was taken up in MeOH (100 ml) and boiled briefly under reflux to decompose boron complexes. The solvent was then distilled off, and the product crystallized directly from a suitable solvent, or separated chromatographically (if a mixture) and the individual components crystallized. No significant differences in the reaction products and yields

* J. Szmuszkovicz[18] reports that the UV spectrum of 3-benzoylindole is only shifted slightly in alkali; this does not agree with our findings (cf. Table 2 and Ref. 11).

were observed when special care was taken to remove traces of BF_3 in the diborane[23] (e.g. by passage through a trap containing $NaBH_4$ soln in diglyme.)

Internal reductions. BF_3-etherate (4·47 g 0·03 mole) in diglyme (15 ml) was added dropwise with stirring to the carbonyl compound (0·01 mole) and $NaBH_4$ (0·85 g, 0·0225 mole) in diglyme (20 ml). The reaction mixture was stirred for a further 2–3 hr at 20°, and then most of the diglyme was removed by distillation under reduced press at 60°. MeOH (100 ml) was added and the mixture boiled briefly under reflux to decompose excess boron hydrides, boron complexes, etc. The MeOH was then distilled off under reduced press and the residue taken up in ether and water. The ethereal layer was separated, washed with $NaHCO_3$ aq, then with water, dried ($MgSO_4$) and evaporated to dryness. The residue was crystallized, chromatographing first on alumina if necessary.

3-Benzylindole. This compound was produced by either external or internal reduction of 3-benzoylindole, and crystallized from aqueous EtOH as needles, m.p. 110° (lit.[24] m.p. 111°). NMR spectrum (in $CDCl_3$): Ar—H, 2·3–3·0 *m*; indole-2-H, 3·15 *d*; —CH_2— 5·90. The picrate was prepared in ethanolic soln and recrystallized from light petroleum (b.p. 100–120°) to give brick-red needles, m.p. 115° (lit.[24] m.p. 115°).

3-Benzyl-1-methylindole. This compound was prepared by either external or internal reduction of 3-benzoyl-1-methylindole, and after percolation through alumina (grade 3) in light petroleum (b.p. 60–80°) was crystallized from aqueous alcohol to give colourless needles, m.p. 61°. (lit.[25] m.p. 61°). NMR spectrum (in $CDCl_3$): Ar—H, 2·3–3·0 *m*; 2-H, 3·30; —CH_2—, 5·92; N—CH_3, 6·36.

3-Ethylindole. This compound was prepared both by external and internal reduction of 3-acetylindole. The crude oily product (one spot on TLC) was characterized by conversion into its picrate, red hairy needles, m.p. 120–122° (lit.[24] m.p. 120–121°) from light petroleum (b.p. 80–100°), and by its NMR spectrum (in $CDCl_3$): Ar—H, 2·3–3·0; 2-H, 3·14; CH_3CH_2, 8·72 *t*, 7·25 *q*.

3-Ethyl-1-methylindole. This compound was prepared both by external and by internal reduction of 3-acetyl-1-methylindole, and the oily product was extracted into light petroleum (b.p. 60–80°), and characterized as its picrate, red needles, m.p. 97–98° (lit.[26] m.p. 97–98°) from MeOH, and by its NMR spectrum (in $CDCl_3$): Ar—H, 2·5–3·0 *m*; 2-H, 3·18; N—CH_3, 6·30; 3-CH_3CH_2, 8·68 *t*, 7·22 *q*.

External reduction of 2-acetyl-3-methylindole. 2-Acetyl-3-methylindole[19] (1·73 g, 0·01 mole) was reduced externally with diborane, and after work-up gave a yellowish green pasty residue (1·65 g). This product (160 mg) was separated on silica gel thick-layer plates (20 × 20 cm) using light petroleum (b.p. 40–60°)–ether (3/2: v/v) as solvent. Four bands were obtained and each was scraped off the plate, extracted with redistilled AcOEt and the extracts evaporated to dryness:

(i) R_f, 0·57, colourless oil (100 mg) which crystallized from light petroleum (40–60°) to give 2-ethyl-3-methylindole as needles, m.p. 66–68° (lit.[27] m.p. 66°). NMR spectrum (in $CDCl_3$): Ar—H, 2·5–3·0 *m*; 3-CH_3, 7·90; 2-CH_2CH_3, 7·55 *q*, 9·01 *t*.

(ii) R_f, 0·40. A colourless oil (7 mg) which was identified as 2-(1′-methoxyethyl)-3-methylindole by its mass spectrum *m/e* (%): 189 (50) M^+, 174 (50) M—Me, 173 (24), 160 (14), 159 (54), 158 (100) M—OMe, 157 (60) M—MeOH, 156 (52), 149 (38), 144 (50), 143 (30), 130 (70), 77 (36). m*: 130 (159 → 144); 107 (158 → 130).

(iii) R_f, 0·17. An oil (15 mg). The mass spectrum indicated that it was a mixture.

(iv) R_f, 0·07. An oil (23 mg) which was identified from its mass spectrum as 2-(1′-hydroxyethyl)-3-methylindole. *m/e* (%): 176 (32) M + 1, 175 (33) M^+, 160 (35), 159 (30), 158 (74) M—OH, 157 (48) M—H_2O, 156 (45), 149 (35), 144 (35), 143 (27), 132 (100), 130 (55), 117 (40), 77 (30). m*: 107 (158–130), 104 (132–117).

External reduction of 2-formylindole. 2-Formylindole (0·725 g) was reduced externally with diborane and worked up as described above. The crude product was shown to consist of at least 6 components by TLC in benzene, and these were separated on thick plates and extracted with ethyl acetate as before.

(i) R_f, 0·54 (8%). This component was identified as 2-methylindole, m.p. 61°.

(ii) R_f, 0·30 (3%). Mass spectrum, *m/e* (%): 268 (30), 149 (100), 117 (60), 105 (50), 104 (60), 91 (80), 78 (60), 77 (60). This may be 2-hydroxymethylindoline (mol. wt. 149) contaminated with polymeric material.

(iii) R_f, 0·16, and (iv) R_f, 0·10 were very similar and probably dimeric since the mass spectra showed a molecular ion at *m/e* 368.

(v) R_f, 0·05 and (vi) R_f 0·0. NMR and mass spectral measurements showed that these fractions contained 2-hydroxymethylindole and polymeric material, and the former was separated by further TLC on thick-plates in benzene–AcOEt (3/2: v/v) and characterized spectroscopically and by mixed m.p.

Reduction of N(*b*)-*acetyltryptamine*

N-Acetyltryptamine (1·5 g) in THF (50 ml) was reduced internally at 0° with diborane generated from $NaBH_4$ (0·85 g) in diglyme (20 ml) and BF_3-etherate (4·47 g) in diglyme (5 ml). After 3 hr the mixture was evaporated to small bulk, heated briefly with MeOH and then evaporated again. The residue was taken up in dil H_2SO_4 and ether, the aqueous layer separated, basified with dil NaOH and the product extracted into ether. After washing with water, drying ($MgSO_4$) and evaporation of the solvent it gave a colourless oil (2·1 g) which was chromatographed on alumina in benzene–ether. Collection of the appropriate fractions gave N-(b)-ethyltryptamine (0·76 g, 54%) which crystallized from light petroleum (b.p. 60–80°) as needles, m.p. 81–82° (lit.[28a] b.p. 151–156°/0·06 mm). The orange red picrate crystallized from alcohol as needles, m.p. 191–192° (lit.[28b] m.p. 187–189°). NMR spectrum: Ar—H, 2·3–2·8 m, 2-H, 3·05 *s*, N-(a)-H, 1·3, N-(b)-H, 8·58; 3-CH_2—CH_2, 7·05, N-(b)-CH_2—CH_3, 7·3 *q*, 8·93 *t*.

Reduction of indole 3-(N-*methylglyoxamide*). The glyoxamide (14·1 g) in THF (200 ml) was reduced internally with $NaBH_4$ (12 g) in diglyme (300 ml) and BF_3-etherate (63 g) in diglyme (180 ml). After 12 hr the solvents were evaporated, the residue boiled for 1 hr with MeOH and the MeOH removed. The residue was taken up in ether, and washed with water, dried ($MgSO_4$), and chromatographed on alumina in benzene, $CHCl_3$ and $CHCl_3$–MeOH. The first fractions gave the borane complex of N(b)-methyltryptamine (3·5 g) which crystallized as shining needles, m.p. 95°. ν_{max} 3330 (s), 3175 (s), 2375 (s), 2300 (s), 2250 (s), 1280 (s), 805 (m) and 742 (s) cm^{-1}. NMR spectrum: Ar—H, 2·3–2·95 *m*, N-(a)-H, 1·83, 3-CH_2—CH_2, 6·9 (broad s), N-(b)-CH_3, 7·55 (*d*). Later fractions gave N(b)-methyltryptamine (6·5 g) which crystallized from benzene as colourless needles m.p. 90° (lit.[29a] m.p. 89°). NMR spectrum:[cf. 29b] Ar—H, 2·3–2·8 *m*, 2-H, 3·05 *s*, N-(a)-H, 1·1, 3-CH_2—CH_2, 7·04 *s*; N-(b)-CH_3, 7·58 *s*, N-(b)-H, 8·58.

The borane complex was decomposed by heating for several hr with methanolic NaOH (but was stable to boiling MeOH) and gave a further 3 gm of the desired N-(b)-methyltryptamine; total yield 9·5 g (78%).

Reduction of grammine. Grammine was reduced externally in boiling THF for 15 hr and after the usual work-up, an insoluble borane compoex was obtained. The latter was decomposed on taking up in methanolic HCl, and after basification and extraction with ether grammine (35%) was recovered. The remainder of the product was largely polymeric, but traces of skatole were detected (by TLC and its characteristic odour).

Reduction of grammine methosulphate with sodium borohydride. $NaBH_4$ (0·76 g) in MeOH (30 ml) containing a few drops of dil NaOH was added to grammine methosulphate (3·0 g) in MeOH (30 ml) over 30 min with stirring. Me_3N evolution occurred during the addition and after a further 30 min the mixture was acidified cautiously with dil HCl, evaporated to remove most of the MeOH and then extracted with AcOEt. The extracts were dried ($MgSO_4$), evaporated to dryness and the residue crystallized from light petroleum (b.p. 40–60°) to give skatole (1·1 g, 84%) as needles, m.p. 95°.

External reduction of indole 2-*carboxylic acid.* Indole-2-carboxylic acid (1·61 g) was reduced externally and gave a crude oily product (1·46 g) from which 2-methylindole (0·1 g, 5%) was obtained by extraction with light petroleum (b.p. 60–80°). TLC examination of the crude product showed that several other components were also present, and preliminary experiments on their separation by use of thick-layer plates, followed by NMR and mass spectrometry confirmed that they were largely polymeric, and similar to those obtained from 2-formylindole.

Reduction of indole. Indole (3·51 g) in THF (100 ml) was treated externally with excess diborane (3 mole equiv BH_3) and the mixture allowed to stand for 4½ hr. After work-up in the usual manner the crude product was taken into ether and dil HCl. The acid layer yielded indoline (0·91 g, 26%) on basification, etc. (picrate, yellow needles, m.p. 174°, (lit.[30] m.p. 174°)), and indole (1·78 g, 52%) was recovered from the ether layer.

In a similar experiment indole (1·75 g) was reduced internally (using $LiBH_4$ (0·73 g) and BF_3-etherate (6·7 g) in THF to facilitate work-up) over 5 hr at 20°. After work-up as above indoline (0·61 g, 35%) and indole (0·60 g, 34%) were obtained.

Reduction of oxindole.[cf. 17] Oxindole (0·27 g) was reduced externally in THF for 6 hr at 20° with diborane generated from BF_3-etherate (1·34 g) in diglyme (4 ml) and $NaBH_4$ (0·26 g) in diglyme (6·6 ml). After work-up and thick-layer chromatography in benzene–$CHCl_3$ (7/3: v/v) indole (R_f 0·55; 4%), indoline (R_f 0·30; 25%) and recovered oxindole (R_f 0·04; 64%) were obtained. An internal reduction of oxindole (5·32 g) in THF (200 ml) with $LiBH_4$ (1·98 g) in THF (88 ml) and BF_3-etherate (17·9 g) in THF (52 ml) for 6½ hr at 20° gave a light brown oil (5·04 g) after work-up. TLC showed this to be mainly indoline with a trace of oxindole. Acidic extraction etc. in the usual manner gave indoline (4·06 g, 85%) (one spot by TLC), identified by NMR and conversion to the yellow picrate needles m.p. 174°. (lit.[30] m.p. 174°).

Reduction of 3-formylindole. 3-Formylindole (8·7 g) was reduced externally and gave an oily product (7·9 g) which was chromatographed on alumina and eluted successively with light petroleum (b.p. 60–80°), light petroleum–benzene, benzene and AcOEt.

Skatole (1·03 g, 15%) m.p. 95° was eluted first, and the petroleum–benzene fractions then gave an oil (3·0 g) which rapidly crystallized. This was recrystallized from MeOH and afforded *3-(3'-indolylmethyl)-3-methylindoline*, m.p. 132–134°. (Found: C, 82·6; H, 7·0; N, 10·4. $C_{18}H_{18}N_2$ requires: C, 82·4; H, 6·9; N, 10·7%.) The benzene fractions contained a mixture of compounds (TLC) which were rechromatographed on alumina in benzene, and benzene–ether. Early fractions contained further quantities of the foregoing indoline, and later fractions gave *3-hydroxymethyl-3-(3'-indolylmethyl) indoline* as a brittle solid, m.p. 100° after sublimation at 210–220°/0·07 mm. (Found: C, 77·1; H, 6·55; N, 9·8. $C_{18}H_{18}N_2O$ requires: C, 77·7; H, 6·5; N, 10·1%.)

3-Formylindole was also reduced internally, and the products were separated on thick layer plates in light petroleum (b.p. 40–60°)/ether (2/3: v/v) to give skatole, and the 3-methylindolines.

Reduction of 3-formyl-1-methylindole. 3-Formyl-1-methylindole[10] (6·36 g) was reduced externally for 3 hr at 20° (test samples removed for UV spectral determinations showed that reduction of the carbonyl group was complete in ca. 2 hr) and gave a crude oily product (6·06 g). The latter was chromatographed on alumina in the same manner as the foregoing experiment and gave 1,3-dimethylindole on elution with light petroleum. The next fractions (petroleum–benzene) gave *1,3-dimethyl-3-(1'-methylindolyl-3'-methyl) indoline* as a colourless viscous oil (one spot on TLC) which slowly crystallized over several months and was recrystallized from EtOH to give needles, m.p. 66°. It was characterized by UV, NMR and mass spectroscopy and by conversion into its *monopicrate*, orange needles from MeOH, m.p. 166–167° (with dec). (Found: C, 60·2; H, 4·9; N, 13·1. $C_{20}H_{22}N_2$. $C_6H_3N_3O_7$ requires: C, 60·1; H, 4·85; N, 13·5%.)

Elution with a higher proportion of benzene gave a trimeric product in very low yield. This crystallized from ether, as needles m.p. 184–185·5°. The mol wt was 433 (mass spectrum—see Table 6).

Elution with pure benzene gave *3-hydroxymethyl-1-methyl-3-(1'-methylindolyl-3'-methyl)indoline* as prisms, m.p. 136–136·5° from ether. (Found: C, 78·2; H, 7·3; N, 9·1. $C_{20}H_{22}N_2O$ requires: C, 78·4; H, 7·2; N, 9·1%).

Similar results were obtained from internal reductions.

Reduction of 3-formyl-1-methylindole with LAH-$AlCl_3$. Anhyd $AlCl_3$ (6·67 g; 0·05 mole) was placed in a 3-necked-flask fitted with a sealed stirrer, condenser and dropping funnel. The flask was cooled to 0° and dry ether (50 ml) added with stirring. After 30 min LAH (0·47 g; 0·0125 mole) suspended in ether (25 ml) was added, and then after a further 30 min 3-formyl-1-methylindole (3·98 g; 0·025 mole) in ether (200 ml) was added dropwise over 40 min. The mixture was stirred for a further 2 hr at 20°, before cautious addition of 10% H_2SO_4 (50 ml) with cooling. The ether was separated, and the aqueous layer and undissolved solid material were basified with 20% NaOH aq and extracted with AcOEt. The combined extracts were dried ($MgSO_4$) and evaporated to dryness to yield a dark oily product (3·18 g). TLC examination of which showed at least 4 components. After chromatography on alumina in the same way as for the diborane reduction products it gave 1,3-dimethylindole (20%), XVIIIb (25%), and a trimeric product identified as XIX (25%) by NMR and mass spectra. The *trimeric product* (XIX) crystallized from ether–alcohol as tiny crystals, m.p. 158–159°, purified for analysis by sublimation at 270–275°/0·05 mm. (Found: C, 83·2; H, 7·1; N, 9·4. $C_{30}H_{31}N_3$ requires: C, 83·1; H, 7·2; N, 9·7%.) λ_{max}(log ε_{max}): 226·5 (4·85), 291 (4·15); in EtOH–dil H_2SO_4: 223·5 (4·86), 288 (4·08).

Reduction of 3-formyl-2-methylindole. 3-Formyl-2-methylindole (6·36 g) was reduced externally and gave a crude pasty product (6·30 g) which was chromatographed on alumina as in the two foregoing examples. The following products were obtained: 2,3-dimethylindole, m.p. 108–109° (eluted by light petroleum); *2,3-dimethyl-3-(2'-methylindolyl-3'-methyl)indoline*, (eluted by light petroleum–benzene (1/1: v/v)) needles m.p. 85° from benzene–light petroleum. (Found: C, 82·8; H, 7·8; N, 9·4. $C_{20}H_{22}N_2$ requires: C, 82·7; H, 7·6; N, 9·65%), picrate, red needles, m.p. 196–197°. Further elution with benzene and benzene–AcOEt gave oily products which were rechromatographed on alumina, eluting with benzene–ether and benzene–AcOEt. The first fractions gave *3-hydroxymethyl-2-methyl-3-(2'-methylindolyl-3'-methyl)indoline*, which crystallized as needles, m.p. 176° from benzene. (Found: C, 78·4; H, 7·4; N, 9·0. $C_{20}H_{22}N_2O$ requires: C, 78·4, H, 7·2; N, 9·1%.) The later fractions gave a crystalline *product*, m.p. 211–213° as plates from ether. (Found: C, 74·4; H, 7·1; N, 9·1. $C_{20}H_{22}N_2O_2$ requires: C, 74·5; H, 6·9; N, 8·7%) tentatively identified as XX on the basis of its mass spectrum (see Table 6).

Internal reduction of 3-formyl-2-methylindole gave similar results and the products were separated by

thick layer chromatography, and compared (TLC, spectra, m.p., etc.) with the materials obtained from the external reductions.

Reduction of 3-acetyl-2,4,5-trimethylpyrrole. The acetylpyrrole (3·0 g) was reduced externally with diborane (3 moles BH_3) over 3 hr (spectroscopic analysis indicated that first stage of reduction was complete in 2 hr). After work-up with MeOH in the usual way the IR spectrum of the crude product indicated that a small amount of residual borane complex was present. The residue was therefore taken up in a little hot AcOEt, poured into $NaHCO_3$ aq and extracted with ether. The dried ($MgSO_4$) extracts gave an oil (2·2 g), which was extracted with light petroleum (b.p. 60–80°), decolourized with charcoal and evaporated to small bulk. 3-Ethyl-2,4,5-trimethylpyrrole (1·94 g) crystallized as needles, and was recrystallized from light petroleum to give needles, m.p. 69° (lit.[31] m.p. 69°). NMR spectrum ($CDCl_3$): 2-$C\underline{H}_3$, 7·88; 3-$C\underline{H}_2C\underline{H}_3$, 7·62, 8·86; 4-$C\underline{H}_3$, 8·08; 5-$C\underline{H}_3$, 7·88 τ. Internal reduction of the acetylpyrrole also gave the same product in slightly higher yield, after work-up by the foregoing procedure.

External reduction of 4-ethyl-2-formyl-3,5-dimethylpyrrole. The formylpyrrole was reduced externally (ca. 1 hr) in the usual manner and the product worked up as in the preparation above. After chromatography of the oily product on alumina in light petroleum 3-ethyl-2,4,5-trimethylpyrrole, needles, m.p. 69° was obtained.

Internal reduction of ethyl 5-formyl-1,2,4-trimethylpyrrole-3-carboxylate. Reduction was complete in ca. 30 min, and after a further 90 min the product was worked-up by the usual MeOH treatment. The crude product crystallized immediately the solvent was removed, and was recrystallized from light petroleum (b.p. 40–60°) to give *ethyl 1,2,4,5-tetramethylpyrrole-3-carboxylate* as needles, m.p. 68–69°. (Found: C, 67·95; H, 8·7; N, 7·3. $C_{11}H_{17}NO_2$ requires: C, 67·7; H, 8·8; N, 7·2%). NMR spectrum (in $CDCl_3$): N—$C\underline{H}_3$, 6·65; 2-$C\underline{H}_3$, 7·54; 4-$C\underline{H}_3$, 7·91; 5-$C\underline{H}_3$, 7·82; $CO_2C\underline{H}_2C\underline{H}_3$, 5·74, 8·67. Mass spectrum, *m/e* (%): 195 (40) M^+, 181 (23), 167 (15), 166 (100) M—Et, 150 (60) M—OEt, 149 (14), 122 (25), 121 (30), 56 (55). m*: 141 (195 → 166).

Reduction of 2-formyl- and 1-methyl-2-formylpyrroles. Both these formylpyrroles gave resinous materials on external reduction with diborane, which were unaffected by treatment with boiling aqueous AcOH, mineral acid or caustic soda, and which were insoluble in most solvents.

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