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SUBSTITUTED OXINDOLES—I

THE PREPARATION AND SPECTRAL CHARACTERISTICS OF SOME SIMPLE OXINDOLE DERIVATIVES

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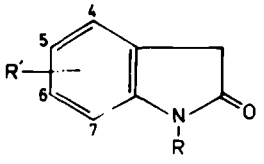
Abstract—A series of oxindole derivatives substituted in the aromatic ring and their N-Me homologues has been prepared. The effects of position and nature of substituents on the IR, NMR and UV spectra have been investigated. Evidence is presented which indicates the presence of an intermolecular hydrogen bond in solutions of oxindole and certain N-unsubstituted derivatives. A relationship between Hammett's σ constant of substituents and the carbonyl frequencies of these oxindoles is reported.

A SERIES of simple oxindole derivatives of types I and II have been prepared, and the IR, NMR and UV spectra examined for correlations which might provide useful corroborative evidence for structural assignments to oxindole alkaloids currently being investigated.[1,2] These derivatives were also required for pharmacological[3] and metabolic[4] studies.

R′	
(a) H	(i) 7-OCH_3
(b) 4-OH	(j) 4-Cl
(c) 5-OH	(k) 5-Br
(d) 6-OH	(l) 5-NO_2
(e) 7-OH	(m) 5-NH_2
(f) 4-OCH_3	
(g) 5-OCH_3	
(h) 6-OCH_3	



I R = H
II R = CH_3

Preparation of the compounds

Oxindole (Ia) was prepared in 80% yield by the partial hydrogenation of isatin.[5] Routes to the remaining compounds, outlined in schemes A and B, are in most instances based on published methods, modified in some cases with improved yields. Noelting's procedure[6] for the preparation of IIIa and IVa has been modified as described in the experimental section to give yields of 90% or more. Replacement of 2-methoxy-6-nitrobenzyl chloride by the bromide VII and potassium cyanide by the sodium salt in the route used by Cook[7] for the preparation of VIII increased the overall yield of the latter when prepared from IIIa, resulting in an ultimate improvement of the yield of If from 3% to 10% overall. The most difficult stage of the routes outlined in scheme A was the condensation of the nitrotoluenes (IVa–d) with diethyl oxalate and the use of a twofold excess of this and potassium ethoxide as described by Stoll *et al.*[8] for the synthesis of bufotenin and related compounds resulted in higher yields of purer products than have been previously reported.[9,10] Although

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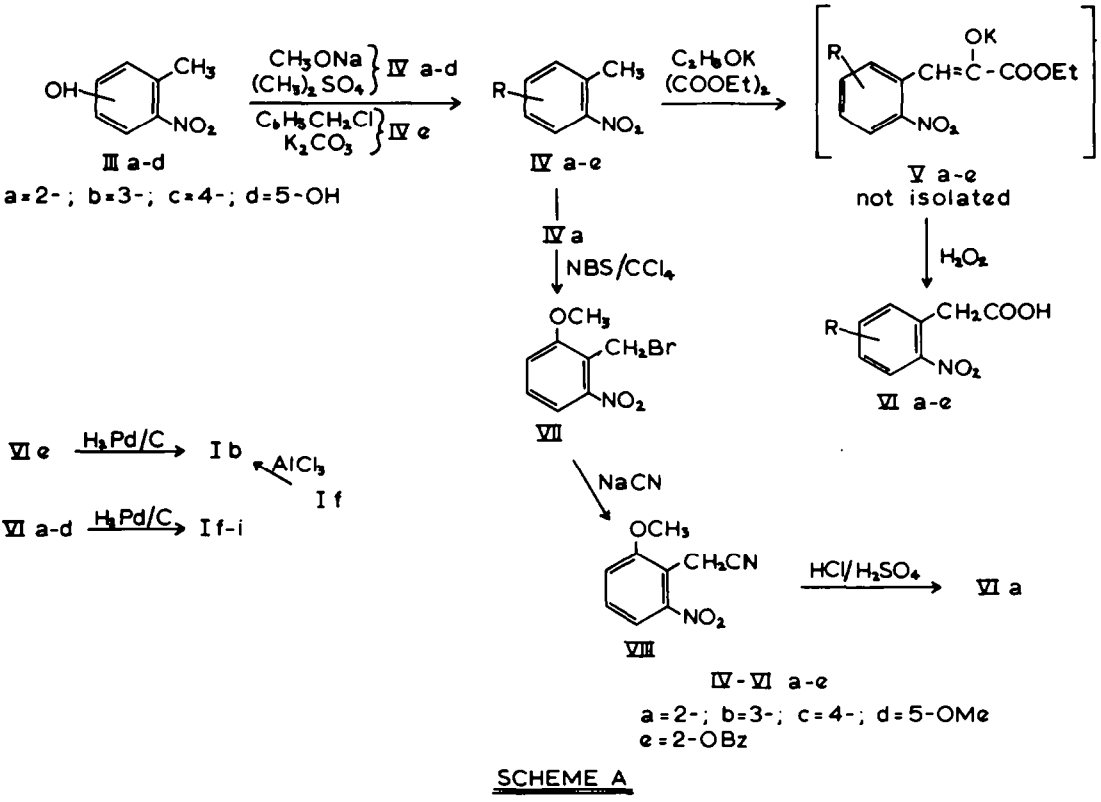
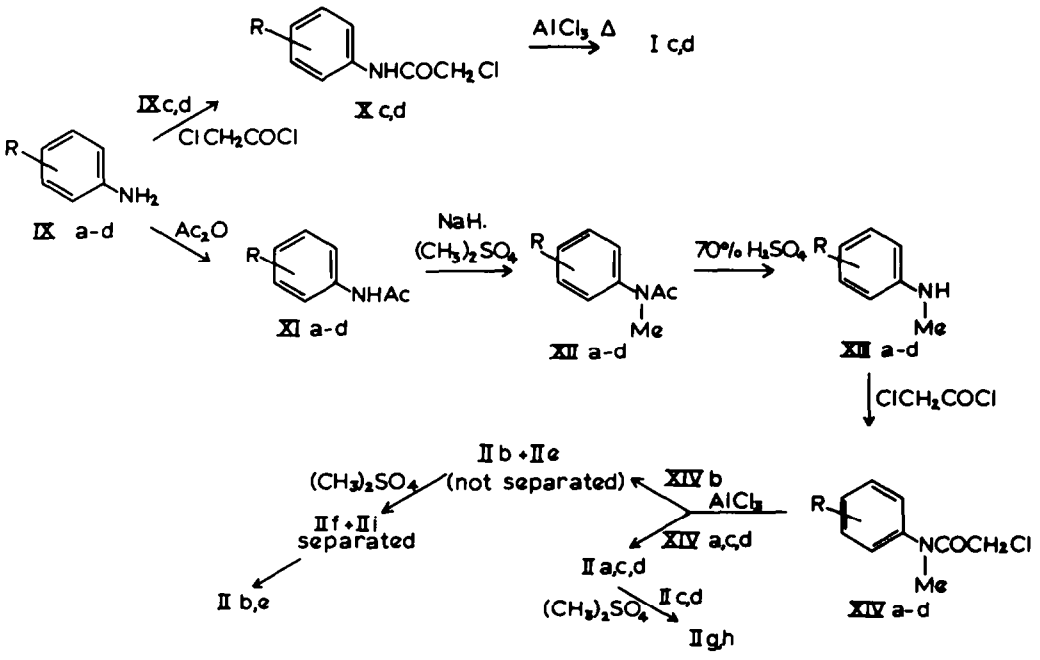
2-benzyloxy-6-nitrophenylacetic acid (VIe) was prepared in only 7% yield, previous workers[8,11] have reported failure in attempts to prepare the compound by the same route. The preparation of 6-hydroxy oxindole (Id) by the cyclization of N-chloroacetyl-*m*-anisidine (IXc scheme B) has not previously been reported. Cyclization of N-methyl-N-chloroacetyl-*o*-anisidine (XIVb scheme B) gave a mixture of the



SCHEME A

4- and 7-hydroxy-N-methyloxindoles (IIb and e) which were more readily separable after conversion to the methoxy derivatives (IIf and i), the 7-methoxy isomer (IIi) being more soluble in ether than the 4-methoxy compound (IIf). Subsequent demethylation of these compounds yielded IIb and e.[7,12] Similarly, cyclization of compounds XIVa, c, d (scheme B) furnished IIa, c, d and methylation of IIc and d gave IIg and h. Of the remaining compounds, Ij, k, m and IIk, l have been prepared by methods reported in the literature. 5-Amino-oxindole (Im) and its N-methyl homologue (IIm) were prepared in almost quantitative yield by catalytic hydrogenation of the corresponding nitro derivatives, instead of by the previously reported methods using tin and hydrochloric acid.[37,41]



IX - XIV, a-d

	R
(a)	H
(b)	o CH_3O
(c)	m CH_3O
(d)	p CH_3O

SCHEME B

NMR spectra

Comparison of the NMR spectra of the methoxy-substituted oxindoles (I and IIf–i) with those of rotundifoline, isorotundifoline[1a,b] and javaphylline[2b] showed certain similarities in the aromatic proton signals (Table 1). 4-Methoxy-N-methyloxindole (IIf) showed two apparent triplets (τ 2·72, J = 8·0 c/s, one proton; τ 3·43, J = 7·7 c/s, two protons). The signals due to the two protons at C_5 and C_7 have been shifted upfield through shielding by the *ortho* O and N atoms. The third proton H_6 is split almost equivalently (i.e. J $H_5 \cdot H_6 \simeq$ J H_6H_7) producing the downfield triplet. At 100 mc the higher triplet is resolved into two doublets (τ 3·42, J = 8 c/s; τ 3·55, J = 7·8 c/s) whereas the lower triplet remains virtually unaltered. 4-Methoxyoxindole (If) showed certain similarities, with a triplet (τ 2·75, J = 8·0 c/s) and two doublets (τ 3·30, J = 6·0 c/s; τ 3·45, J = 5·8 c/s) each integrating for one proton. Since $\Delta\nu$ H_6H_7 is still large compared with J H_6H_7 the H_6 pattern appeared as a triplet,[13] but the upfield triplet was resolved into two doublets, H_6 and H_7 not being exactly equivalent in this case. The upfield doublet is probably due to H_5, the shielding at H_7 having been reduced by the absence of the N-Me group. The aromatic proton

TABLE 1. NMR AROMATIC PROTON DATA FOR THE ISOMERIC METHOXY- AND METHOXY-N-METHYLOXINDOLES AND OF SOME OXINDOLE-TYPE ALKALOIDS

Compound	Solvent	Aromatic protons (τ)					
		τ	No. of protons	τ	No. of protons	τ	No. of protons
4-Methoxy oxindole	D_6DMSO	2·75 triplet	1	3·30 doublet	1	3·45 doublet	1
4-Methoxy-N-methyloxindole	$CDCl_3$	2·72 triplet	1	3·43 triplet	2		
Rotundifoline[1]	$CDCl_3$	2·91 triplet	1	3·5 triplet	2		
Rotundifoline[14] (100 mc)	$CDCl_3$	2·55 triplet	1	3·42 doublet	1	3·54 doublet	1
Isorotundifoline[1]	$CDCl_3$	2·98 triplet	1	3·48 triplet	2		
5-Methoxyoxindole	D_6DMSO	Signals overlap; multiplet at τ 3·15					
5-Methoxy-N-methyloxindole	$CDCl_3$	Signals overlap; multiplet at τ 3·24					
6-Methoxyoxindole	D_6DMSO	2·82 doublet	1	3·36 slanting doublet	1	3·47 slanting doublet	1
6-Methoxy-N-methyloxindole	$CDCl_3$	2·84 doublet	1	3·35 quartet	1	3·53 quartet	1
Gelsemicine[15]	$CDCl_3$	2·74 quartet	1	3·45 quartet	1		
Javaphylline[2]	$CDCl_3$	2·90 doublet	1	3·40 multiplet	2		
7-Methoxyoxindole	D_6DMSO	3·04 singlet	3	2 small signals at τ 2·9 and 3·17			
7-Methoxy-N-methyloxindole	$CDCl_3$	3·08 singlet	3				

All spectra determined at 60 mc unless otherwise stated.

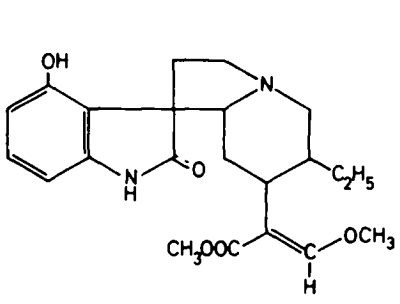
signals of 5-methoxy-N-methyloxindole (IIg) were shifted upfield, all being *ortho* to either a N or O atom. A multiplet (τ 3·12) and an unsymmetrical triplet (τ 3·24, $J = 2·6$ c/s) occurred the spectrum being complex, with overlapping signals. The spectrum of 5-methoxyoxindole (Ig) was similar.

6-Methoxy-N-methyloxindole (IIh) showed a spectrum having a broad doublet downfield (τ 2·84, $J = 7·6$ c/s, one proton) due to the unshielded proton on C_4 and two upfield quartets (τ 3·35, $J = 3·2$, 6·3 c/s, one proton; τ 3·53, $J = 2·3$, 4·2 c/s, one proton) due to the C_5 and C_7 protons, the latter, being *ortho* to both a N and O atom giving the most upfield signal. These quartets were typical of ABX spectra, although the spacing of the peaks was slightly unequal. 6-Methoxyoxindole (Ih) similarly showed a broad doublet (τ 2·82, $J = 8·5$ c/s, one proton) and two slanting doublets (τ 3·36, $J = 3·1$ c/s, one proton; τ 3·47, $J = 2$ c/s, one proton).

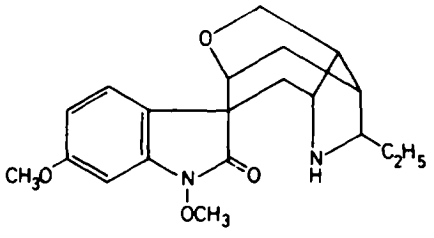
The spectrum of 7-methoxy-N-methyloxindole (IIi) was unusual in that the aromatic proton signals appeared as a singlet (τ 3·08). A previously reported singlet (τ 2·18),[14]

not observed on the present spectrum, is difficult to explain, since a strong deshielding effect would be required in order to account for such a large downfield shift. The unusual equivalence of these protons may be due to the mesomeric influence of the 7-methoxy group on protons at C_4 and C_6 and of the amide group on the proton at C_5. In 7-methoxyoxindole (Ii) however the aromatic protons are not all equivalent, and in addition to the main singlet (τ 3·04, 3 protons) two small singlets appear (τ 2·9, τ 3·17).

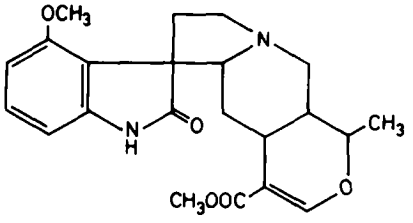
A comparison of the above spectra with those of certain oxindole alkaloids possessing hydroxy or methoxy substituents on the aromatic ring reveals certain similarities (Table 1). Rotundifoline (XV) and its stereoisomer isorotundifoline both show aromatic proton patterns similar to those of 4-methoxyoxindole (If) and 4-methoxy-N-methyloxindole (IIf). Gelsemicine (XVI) has an aromatic proton spectral pattern similar to that of 6-methoxy-N-methyloxindole (IIh) and has been formulated with the aromatic methoxy group in the position shown by comparison of its spectrum with those of certain 11-methoxyindole alkaloids.[15] A recently isolated alkaloid Javaphylline,[2] with an aromatic proton pattern resembling that of 4-methoxyoxindole, has been shown to be a stereoisomer of 9-methoxy-mitraphylline (XVII).



XV



XVI

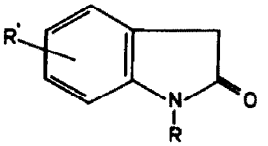


XVII

IR spectroscopy

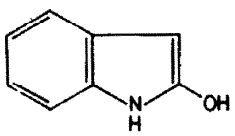
Elucidation of the structure of oxindole alkaloids has been assisted by an examination of the IR spectra of both alkaloids and their degradation products.[16–21] Due to the lack of comprehensive reference data, the IR spectra of the oxindoles I and IIa–m were investigated during the course of the present work.

TABLE 2. PRINCIPAL INFRARED ABSORPTION BANDS OF SUBSTITUTED OXINDOLES (10^{-2} M in $CHCl_3$)

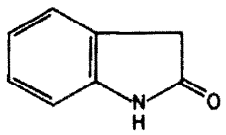


Compound	R	R′	Wavenumber cm^{-1}				$\nu_{C=O}$				No. of carbonyl peaks
Ia	H	H	1472			1642	1710 s	1736 sh	1754 sh	3444	3
b	H	4-OH	very insoluble								
c	H	5-OH					1705 w				
d	H	6-OH			1602 m		1715 w				
e	H	7-OH									
f	H	4-OCH_3	1470 s		1610 sh	1621 s	1698 m	1726 s	1752 w	3446 w	3
g	H	5-OCH_3	1492 s		1606 w		1707 s	1749 w		3446 w	2
h	H	6-OCH_3	1507 m		1600 w	1636 m	1711 s	1739 s		3443 w	2
i	H	7-OCH_3	1460 w		1600 m	1638 w	1700 s	1727 s	1738 s	3446 w	3
j	H	4-Cl	1454 m	1592 w		1622 m		1725 s	1749 m	3440 w	2
k	H	5-Br	1480 m			1621 m	1711 s	1735 s	1760 sh	3442 w	3
l	H	5-NO_2	1454 w, 1486 w	1539 w	1604 m	1628 m	1723 m	1738 m	1757 s	3438 w, 3608 w	3
IIa	CH_3	H	1476	1499 w		1618 m	1705 s				1
b	CH_3	4-OH		1534 m		very insoluble					
c	CH_3	5-OH	1475 w	1502 m	1609 w		1700 s				1
d	CH_3	6-OH	1464 sh, 1482 w	1515 w	1612 sh	1629 s	1708 s				1
e	CH_3	7-OH				very insoluble					
f	CH_3	4-OCH_3	1477 s	1502 w	1610 s		1707 s				1
g	CH_3	5-OCH_3	1475 w	1500 s	1606 w		1701 s				1
h	CH_3	6-OCH_3	1476 w	1504 s		1629 s	1708 s				1
i	CH_3	7-OCH_3	1470 m	1492 w	1610 m		1690 s				1
k	CH_3	5-Br	1468 w	1491 s		1624 w	1711 s				1
l	CH_3	5-NO_2	1470 w	1500 s		1621 s	1728 s				1
m.	CH_3	5-NH_2	1478 w	1503 s	1605 w	1618 m	1697 s				1

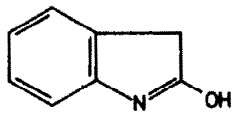
Of the three possible structures (Ia, XVIII, XIX), it has been concluded that oxindole and its derivatives exist in the amide form (Ia).[22] The spectra of all the compounds



XVIII



I a



XIX

examined showed intense absorption in the 1690–1752 cm^{-1} region assigned to the carbonyl stretching frequency ($\nu_{C=O}$) this being the most interesting feature. Compounds Ia, f, i, k, m showed three carbonyl bands in chloroform solution (Table 2). In previous reports of the IR spectra of 1,3 unsubstituted oxindoles, only two carbonyl bands have been reported.[21,22] Compounds Ig, h, j exhibited two bands in this region but Ic and Id which were very sparingly soluble in chloroform showed only one band. Of the N-Me homologues examined under comparable conditions, all showed only one carbonyl band (Table 2). 4- and 7-Hydroxyoxindole (Ib, e) and their N-Me homologues (IIb, e) were too insoluble in chloroform for spectra to be determined in this solvent. The absence of the additional carbonyl bands in solutions of the N-substituted homologues suggested the formation of hydrogen bonded molecules as an explanation of the presence of at least one of the three carbonyl bands in the N-substituted compounds.

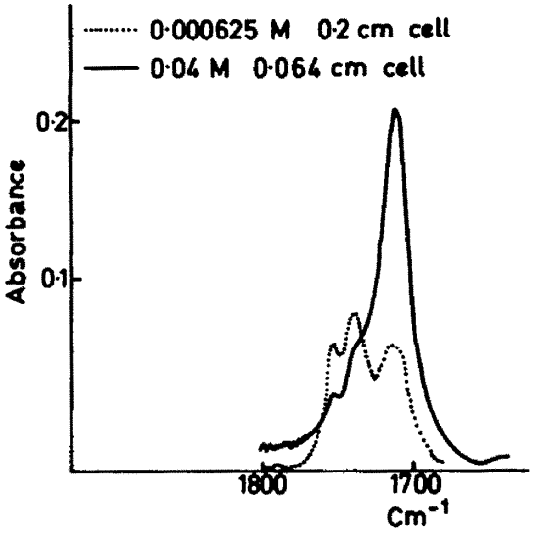


FIG. 1 Concentration dependence of infrared carbonyl absorption bands of oxindole.

A dilution study of oxindole (Ia) in carbon tetrachloride solution over the concentration range 0·04—0·000625M showed that the carbonyl bands were concentration dependent. The 1710 cm^{-1} carbonyl absorption, together with the 3094 and 3194 cm^{-1} hydrogen bond absorptions gradually diminished in intensity on dilution, with a simultaneous increase in the intensity of the 1736 and 1754 cm^{-1}

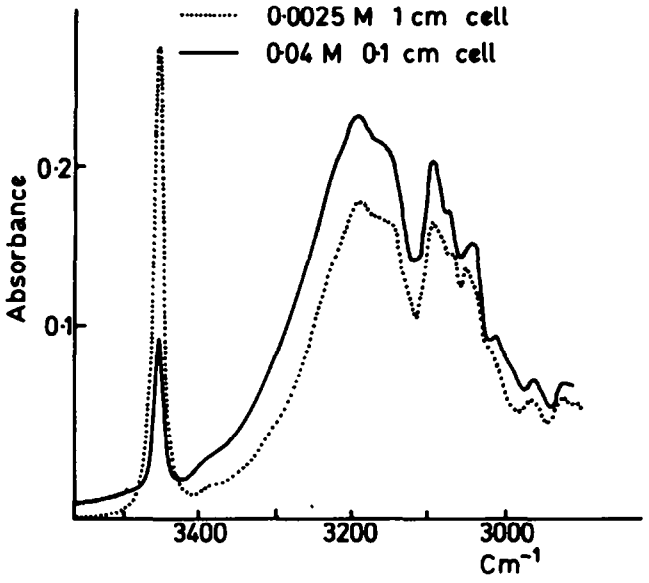
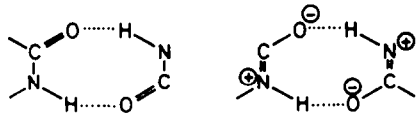


FIG. 2 Concentration dependence of infrared NH absorption bands of oxindole.

(carbonyl) and the 3444 cm^{-1} (free NH) absorption peaks (Figs. 1, 2). Therefore the presence of intermolecular hydrogen bonding is indicated, as suggested by Kellie *et al.*[22] from an examination of the IR spectra of some similar oxindole derivatives.

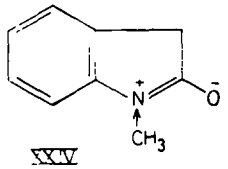


XX XXI

Structures XX and XXI probably represent portions of adjacent molecules contributing to the dimeric hybrid. Some association exists even at high dilution (0·000625M) as indicated by the continued presence of the peak at 1710 cm^{-1} (Fig. 1).

The inductive effect (+I) of the Me group in the N-Me homologues, by reinforcing

the contribution of the polar form of the amide (XXIV) and thus reducing the double-bond character of the C—O bond can account for the shift of the single carbonyl band of these compounds towards the lower portion of its frequency range.[23]

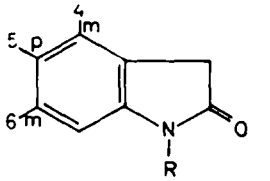


XXV

Split carbonyl bands have been reported for cyclopentanone,[24,25] certain Δ^2-cyclopentenones,[26] substituted-2-indanones[27] and ethylene carbonates[23] and possible reasons for their existence discussed.[23,25–27] In the present instance certain explanations for the presence of the two carbonyl bands at 1736 and 1754 cm^{-1} can be ruled out. Conformational isomerism is impossible and enolisation is unlikely, since except in the case of 5-nitro-oxindole (II) in which a weak band was observed at 3608 cm^{-1}, no absorption attributable to —OH could be detected. The presence of moisture and other impurities was considered, but careful purification and drying of the compounds did not affect the spectra.

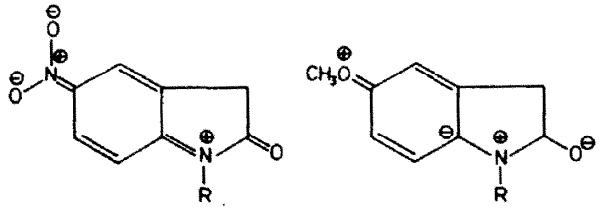
In the examples previously reported,[23–27] Fermi resonance has been postulated as a more likely cause of the carbonyl frequency splitting than a "hot" transition, a conclusion supported in some cases by the spectral changes observed after deuteration. With the present compounds also, Fermi resonance would appear to be the most likely explanation for the presence of the two carbonyl bands, this implying the presence of an overtone of suitable frequency. Since the vibration giving rise to the overtone may be subject to influence by a 3C or aromatic ring substituent this would account for Fermi resonance and the resultant split band not occurring in every case among the examples studied. Also, 3,3 dichloro-oxindole for example has been shown to exhibit only two carbonyl absorption bands (1722 and 1761 cm^{-1}) in chloroform solution.[22]

Kellie *et al.*[22] have shown the existence of a linear relationship between the carbonyl frequency and the Hammett σp value for certain 5-substituted oxindoles (5-NO_2, —Cl, —Br, —CH_3), 4- and 6-substituted derivatives not being available to them. It was decided to extend the examination of this relationship to include various oxindoles substituted in positions 4, 5 and 6. The frequency of the carbonyl absorption (taking the peak of stronger intensity in those examples where two apparent "free" carbonyl bands were present) was plotted against the Hammett σ constant for the given substituent group, using σm for substituents in the 4- and 6-position and σp for those in the 5 position, XXV(R=H), the points being found to lie on a curve



XXV R = H or CH_3

of the type shown (Fig. 3). This non linear relationship may be explained by the assumption that the electronic effects of the substituents in the aromatic ring of oxindole are transmitted to the carbonyl group via both the amide nitrogen and the 3-methylene group. For example, with 5-nitro-oxindole (II) the —I and —M effect of the nitro group will presumably favour structure XXII (R=H) with a rise



XXII XXIII

R = H or CH_3

in $\nu_{C=O}$ and in the case of 5-methoxyoxindole (Ig) the electron donating (+M) effect of the 5-substituent will favour a tendency to structure XXIII (R=H) increasing the polarity of the C—O bond and decreasing $\nu_{C=O}$. The opposing —I effect of the group however apparently predominates, resulting in a reduction in the polarity of the C—O bond with an increase in $\nu_{C=O}$. Hammett's σ value takes into account

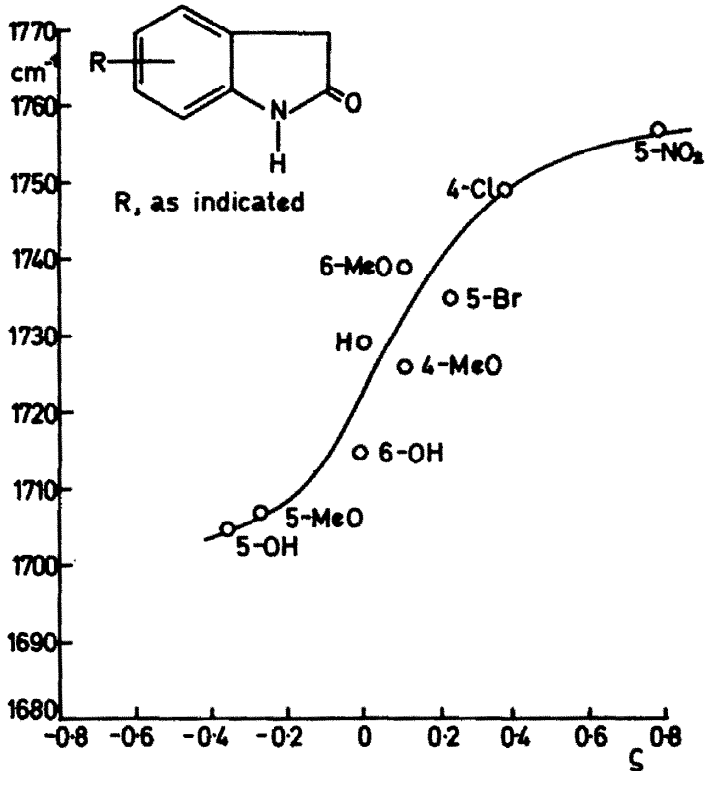


FIG. 3 Carbonyl frequency vs. σ for substituted oxindoles.

these effects. Examination of NMR spectra indicates that the 3-methylene position is one of appreciably lowered electron density,[29] suggesting that the transmission of the electronic effects to the carbonyl group occurs in part via this path, accounting for the non-linear relationship between $\nu_{C=O}$ and the Hammett σ values. The N-Me homologues showed a similar relationship between σm or σp and $\nu_{C=O}$ for low σ values. At higher σ values the steady rise in $\nu_{C=O}$ did not substantially diminish as with the N-unsubstituted series, but continued to rise, producing the smooth curve shown in Fig. 4.

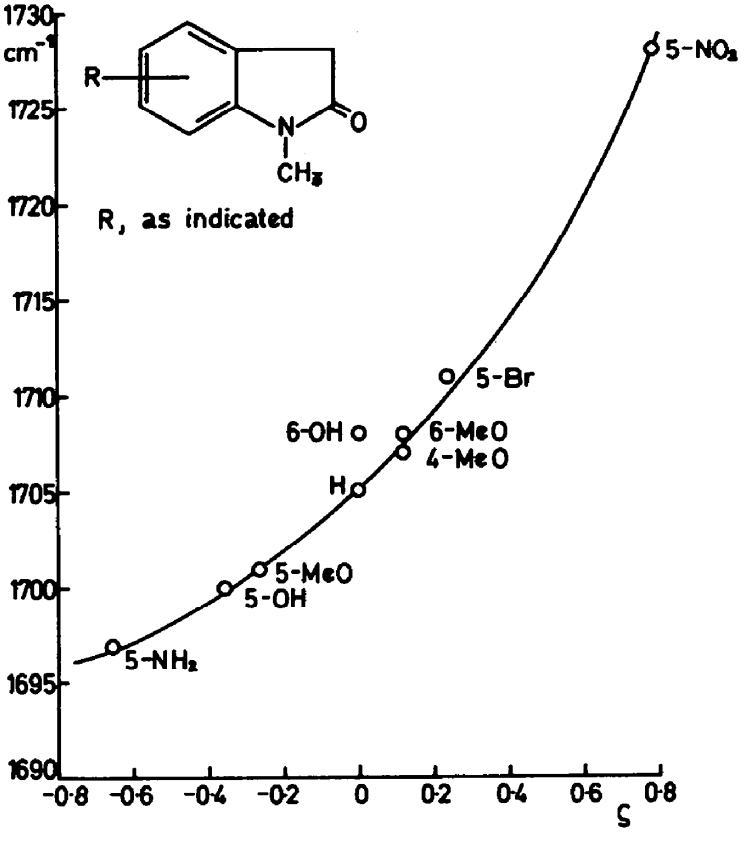


FIG. 4 Carbonyl frequency vs. σ for N-methyl oxindoles.

The linear relationship between Hammett's σ value and $\nu_{C=O}$, described by Kellie for a series of 5-substituted oxindoles does not appear to have a wider applicability. Table 3 shows the principal IR absorption bands of compounds I and IIb–e, determined from Nujol mulls, owing to the insolubility of the compounds in suitable solvents. These spectra have recently been used[4a] to identify 5-hydroxyoxindole (Ic) as the principal metabolite of Ia, IIa and 3-methyloxindole in the rat, guinea pig and rabbit.

TABLE 3. IR SPECTRA OF HYDROXYOXINDOLES AND HYDROXY-N-METHYLOXINDOLES IN NUJOL

Wavenumber cm^{-1}									
Ia	Ib	Ic	Id	Ie	IIa	IIb	IIc	IId	IIe
675	722	675	690	725	660	720	672	720	670
707	772	708	725	763	719	770	690	768	708
745	842	758	795	874	730	832	760	824	772
800	1050	817	818	940	760	872	798	860	830
850	1170	854	855	958	866	835	850	960	898
912	1210	905	898	1018	910	990	910	1060	950
943	1232	940	960	1152	957	1050	940	1094	1033
1018	1290	1140	972	1205	1012	1098	1068	1176	1054
1088	1340	1210	1110	1300	1080	1130	1098	1200	1094
1140	1380	1260	1150	1350	1096	1214	1135	1298	1160
1168	1610	1280	1180	1380	1126	1265	1200	1375	1203
1195	1632	1340	1203	1593	1194	1310	1222	1592	1227
1235	1672	1380	1305	1650	1210	1332	1240	1604	1280
1270	3180	1660	1350	1670	1264	1373	1278	1678	1312
1300	3240	3150	1380	1680	1318	1398	1332		1330
1330			1610	3200	1350	1599	1380		1376
1384			1630		1380	1630	1418		1510
1618			1672		1500	1672	1494		1608
1688			3180		1618		1597		1670
3180					1700		1666		

UV absorption spectra (*Table* 4)

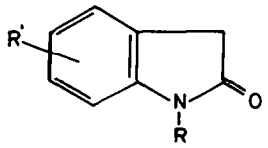
All compounds showed two main absorption bands, a primary band circa 250–260 mμ (ε, 4000–10,000), and a secondary bond varying between 277 and 303 mμ (ε, 1300–3650), both bands in some instances possessing secondary peaks or inflections, the N–Me isomers showing a slight bathochromic shift of the primary band due to the participation of the lone pair nitrogen electrons being enhanced by the electron release of the $N–CH_3$ group.

The 4, 6 and 7 aromatic substituted oxindoles (I and IIb, d, e) exhibited similar spectral patterns. The primary band of the 6-isomers occurred at a longer wavelength but lower intensity than that of the 4-isomers, and both the 4- and 6-isomer showed split secondary absorption, the 6-isomer again absorbing at longer wavelengths, but with greater intensity in this instance. The 5-isomers all showed greatly increased intensity of the primary band, and a bathochromic shift of the secondary band (7–15 mμ) with lowered intensity. The primary band of the 7-isomers (Ie, i, IIe, i) occurred at a lower wavelength than in the case of the 4,5 or 6-isomers with intensity higher than that of either the 4- or 6-isomer and lower than that of the 5-isomers. With the exception of Ie which showed a split secondary band, all the 7-isomers gave a shoulder (circa 260 mμ).

The marked difference of the 5-isomers can be attributed to the reinforcing effect of a hydroxyl or methoxyl para to the nitrogen, a similar pattern occurring with the methoxy acetanilides.[30]

A comparison of these spectral patterns with the UV spectral data quoted for certain oxindole alkaloids currently being investigated in these laboratories[1a–d, 2a, b] offers additional evidence in support of the structures assigned.

TABLE 4. PRINCIPAL ULTRAVIOLET ABSORPTION PEAKS OF SUBSTITUTED OXINDOLES



Compound	R	R′	Absorption maxima or inflections*					
			λ	ε	λ	ε	λ	ε
Ia	H	H	249	9400	277*	1800		
b	H	4-OH	249	4950	283	1800	288	1750
c	H	5-OH	257·5	9000			303	1500
d	H	6-OH	257	4300	288	2800	294·5*	2300
e	H	7-OH	248	6200			249	3650
			257*	4200				
If	H	4-OCH_3	252	4650	283	1550	289	1500
g	H	5-OCH_3	257	10,800			303	1300
h	H	6-OCH_3	257·5	4300	284*	2600	293·5*	2200
i	H	7-OCH_3	249	7000			292	2450
			257·5	4950				
IIa	CH_3	H	252·5	8800	279*	1300		
b	CH_3	4-OH	253	5550	282·5	2000	289·5	1950
c	CH_3	5-OH	260	9100			302	1600
d	CH_3	6-OH	259	4400	288	3400	294·5*	2800
e	CH_3	7-OH	249·5	6000	285·5	2450	290·5	2540
IIf	CH_3	4-OCH_3	254	4800	282	1700	288·5	1600
g	CH_3	5-OCH_3	258	8950			302	1600
h	CH_3	6-OCH_3	258	3850	286	2800	293·5*	2250
i	CH_3	7-OCH_3	253	5750			291	1650
			261·5*	4250				

EXPERIMENTAL

NMR spectra. All values quoted were recorded on a Perkin–Elmer R10 Spectrometer in 20% soln in $CDCl_3$ or deuterodimethylsulphoxide (99·5% Ciba) with TMS (1%) as internal standard. The accuracy of measurement was estimated as ±0·2 c/s.

IR spectra. All soln spectra were recorded on a Unicam SP100 Spectrophotometer and the Nujol spectra on a Unicam SP200 Spectrophotometer.

UV spectra. All spectra were recorded on a Beckmann DK2 recording Spectrophotometer.

Micro analyses are by Mr. Crouch, School of Pharmacy, University of London and Drs. Weiler and Strauss of Oxford.

Oxindole Ia. Finely powdered isatin (29·4 g) suspended in EtOH (500 ml) was hydrogenated at room temp and press in the presence of 10% Pd-C (2 g) and conc HCl (15 ml) until the calculated volume of H_2 had been absorbed. The product was adjusted to pH 7 by the addition of AcONa, the catalyst and inorganic salts removed by filtration and the filtrate evaporated to dryness (reduced press). The resulting reddish brown solid, purified by vacuum distillation gave oxindole 21·8 g, 82%, b.p. 178–179° 0·3 mm, m.p. 125–126°; Lit.[31,32] m.p. 120° and 126°.

2-Hydroxy-6-nitrotoluene (IIIa). A soln of 2-amino-6-nitrotoluene[6] (150 g) in conc H_2SO_4 (550 g) was slowly added to crushed ice (5 kg) and to this was added dropwise a soln of $NaNO_2$ (75 g) in water (100 ml) with stirring and continued cooling (0–5°). When the addition was complete, stirring was continued

for a further 2 hr and 10% w/v. H_2SO_4 (2 l.) containing 0·1% w/v. of $CuSO_4$ added to the mixture, which was then heated to 75–80° until evolution of N_2 ceased (12 hr approx). Traces of a red oily impurity were removed by filtration and yellow needles of 2-hydroxy-6-nitrotoluene crystallized on cooling, 135 g, 90%, m.p. 140–143° (raised to 145–146° on recrystallization from aqueous EtOH); Lit.[6] m.p. 145°.

2-Methoxy-6-nitrotoluene (IVa). A soln of IIIa (15·3 g) in MeOH (75 ml) was added to a soln prepared by dissolving Na (4·6 g) in MeOH (50 ml). Me_2SO_4 (25·2 g) was added dropwise with vigorous stirring and the mixture boiled under reflux for 1 hr. Most of the MeOH was removed by evaporation, the soln diluted with water (100 ml) and extracted with ether (3 × 50 ml). The ether soln was washed successively with 5% w/v NaOH aq (50 ml) and water (2 × 50 ml), dried, filtered and evaporated to dryness (water pump). Vacuum distillation of the residue yielded 2-methoxy-6-nitrotoluene as a pale yellow solid, 15·2 g, 91%, b.p. 94–96°/0·5 mm, m.p. 52°; Lit.[6] m.p. 51°.

3-Methoxy-6-nitrotoluene (IVb). *m*-Cresol (108 g) was first converted to IIIb (via 3-hydroxy-6-nitrosotoluene as described by Koelsch[10]), which was then methylated by the procedure described for the preparation of IVa to yield 3-methoxy-6-nitrotoluene as a pale yellow solid 55 g, 33% (from *m*-cresol), b.p. 125–135°/0·4–0·5 mm, m.p. 57°; Lit.[10] m.p. 55°.

2-Methoxy-6-nitrobenzylbromide (VII). A mixture of IVa (3·24 g), N-bromosuccinimide (3·4 g) and benzoyl peroxide (0·07 g) in CCl_4 (20 ml) was stirred and irradiated from a 250 watt tungsten filament bulb for 12 hr, at 60–70°. The product was then filtered and the filtrate evaporated to dryness under reduced press. The residual pale yellow oil slowly crystallized, and recrystallization from EtOH/water gave slender almost colourless needles of *2-methoxy-6-nitrobenzyl bromide* 4·2 g, 85%, m.p. 74°. (Found: C, 39·45; H, 3·6; N, 5·9. $C_8H_8NO_3Br$ requires: C, 39·05; H, 3·3; N, 5·7%).

2-Methoxy-6-nitrobenzyl cyanide (VIII). Compound VII (4·0 g) was dissolved in EtOH (6·5 ml) and heated under reflux for 4 hr with a soln of NaCN (1·6 g) in water (2 ml). The product was then cooled, diluted with water (10 ml) and extracted with ether (3 × 50 ml). The ether layer was washed with water (2 × 10 ml), dried and evaporated to dryness. Crystallization of the residue from aqueous EtOH yielded pale yellow prisms of 2-methoxy-6-nitrobenzyl cyanide 2·7 g, 70%, m.p. 77–78°; Lit.[7] m.p. 78–79°.

2-Methoxy-6-nitrophenylacetic acid (VIa). Compound VIII (2·7 g) was heated under reflux with conc HCl (50 ml) and conc H_2SO_4 (5 ml) for 3 hr. On cooling, pale yellow crystals appeared which when recrystallized from water gave almost colourless needles of 2-methoxy-6-nitrophenylacetic acid 1·4 g, 43%, m.p. 172–173°; Lit.[7] m.p. 171–172°, yield 20%.

Methoxy-6-nitrophenylacetic acids (VIa–d). These were prepared via the phenylpyruvates according to the methods described by Stoll[8] *et al.* from the appropriate methoxy-6-nitrotoluenes (16·7 g).

Compound	Position of MeO substituent	Recrystallisation solvent	Yield g.	% yield	m.p.	Lit. m.p.
VIa	2	water	15·5	74	170–172°	172°[34]
VIb	3	1:1 H_2O/CH_3COOH	17·6	83	175–177°	176°[34]
VIc	4	1:1 H_2O/CH_3COOH	15·1	73	160–161° (d)	157–158°(d)[33]
VId	5	water	18·0	85	138–139°	137–138°[34]

2-Benzyloxy-6-nitrophenylacetic acid (VIe). To a suspension of KOEt (prepared from K (1·07 g) and abs EtOH (1·2 ml) in dry ether (25 ml), a soln of 2-benzyloxy-6-nitrotoluene (6·5 g) and diethyl oxalate (4 g) in dry ether (30 ml) was added dropwise. The resulting dark red soln was allowed to stand at room temp for 16 hr, and finally boiled under reflux for a further 2 hr. The subsequent procedure was that used for the preparation of the methoxy-6-nitrophenylacetic acids[8] and the crude product recrystallized from aqueous EtOH yielded *2-benzyloxy-6-nitrophenyl acetic acid* as small yellow needles 0·52 g, 7%, m.p. 141–142°. (Found: C, 62·4; H, 4·4; N, 4·95. $C_{13}H_{13}O_5N$ requires: C, 62·7; H, 4·55; N, 4·9%).

4-Hydroxyoxindole (Ib). (a) Compound VIe (0·5 g) in glacial AcOH (60 ml) was hydrogenated at room temp and press in the presence of 10% Pd-C (0·05 g). The product was filtered, and the filtrate when evaporated to dryness under reduced press gave a residue which after two recrystallizations from water furnished white needles of 4-hydroxyoxindole 0·18 g, 72%, m.p. 264–265°; Lit.[9] m.p. 267°.

(b) 4-Methoxyoxindole (0·5 g) was demethylated with anhydrous $AlCl_3$ as described by Wieland,[9] yield 0·25 g, 53%, m.p. 265°.

N-*Chloroacetylanisidines* (Xc, d). Chloroacetyl chloride (0·1 mole) in dry benzene (40 ml) was added dropwise to a stirred and cooled soln of the anisdine (0·1 mole) in dry benzene (100 ml) and anhydrous pyridine (0·1 mole). The mixture was allowed to stand overnight at room temp and then heated on a boiling water bath for 30 min. When cool, the product was treated with water (80 ml) to dissolve precipitated salts, the benzene layer separated and extracted with 1·5% HCl (20 ml) followed by successive portions of water (30 ml) until the aqueous layer was neutral. The benzene layer was dried ($MgSO_4$), filtered and evaporated under reduced press to yield the crude chloroacetyl derivative which was used without further purification.

Methoxyoxindoles (If–i). The appropriate methoxy-6-nitrophenylacetic acid (2·11 g) was dissolved in glacial AcOH (50 ml) and hydrogenated at room temp and press in the presence of 10% Pd-C (0·1 g). Filtration and subsequent evaporation of the solvent under reduced press yielded the crude methoxyoxindole. (N.B. During the isolation of 5-methoxyoxindole it was noticed that excessive heating caused considerable discoloration of the product).

Compound	Recrystallization solvent	Yield g	Yield %	m.p.	Lit. m.p.
If 4-MeO	Ethanol/water	1·1	66	197°	196–197°[7]
Ig 5-MeO	Ethanol	1·5	92	153–154°	152–154°[10]
Ih 6-MeO	Toluene	1·18	72	161–162°	158°[9]
Ii 7-MeO	Toluene	1·22	75	148–149°	146°[9]

N-*Methylaniline* (XIIIa) *and* N-*methylanisidines* (XIIIb–d). N-Acetylaniline or the appropriate N-acetylanisidine (0·2 mole) prepared by standard methods was slowly added to a suspension of NaH (10 g of 50% dispersion in oil) in boiling xylene (400 ml). The thick white suspension resulting was boiled under reflux and stirred vigorously for 1 hr. Me_2SO_4 (28·0 g, 0·22 mole) was then added dropwise to the boiling mixture and boiling continued for 1 hr, after which time the soln was filtered free of inorganic salts and the xylene removed under reduced press. The residue was boiled under reflux for 6 hr, with 50% w/v H_2SO_4 (250 ml) and the acid soln when neutralized with 20% w/v NaOH aq yielded the crude base which was extracted with ether (3 × 100 ml). The ethereal soln was dried ($MgSO_4$), filtered evaporated under reduced press and the residue distilled under vacuum.

N-methyl-*o*-anisidine 17·7 g, 65%, b.p. 92–94°/0·1 mm; Lit.[7] b.p. 228/230°/760 mm. N-methyl-*m*-anisidine 18·3 g, 67%, b.p. 108°/0·35 mm; Lit.[36] b.p. 131°/17 mm. N-methyl-*p*-anisidine 16·4 g, 60%, b.p. 120°/10 mm; Lit.[37] b.p. 120–122°/14 mm.

N-*Chloroacetyl*-N-*methylaniline and anisidines* (XIVa–d). These were prepared from the appropriate secondary amine (0·1 mole) by a method similar to that described for the preparation of N-chloroacetylanisidines and were isolated and used without further purification.

4- *and* 7-*Methoxy*-N-*methyloxindoles* (IIf and Ii). N-Methyl-N-chloroacetyl-*o*-anisidine XIVb (12 g) was cyclized according to the method of Cook[7] to give a mixture of crude 4- and 7-hydroxy-N-methyloxindoles (8·2 g). This mixture of isomers was dissolved in MeOH (12 ml) and added to a soln of Na (2·3 g) in MeOH (25 ml). Me_2SO_4 (12·6 g) was added dropwise with vigorous stirring and the product boiled under reflux for 1 hr. The resulting soln was reduced to small bulk by evaporation of most of the MeOH, diluted with water (100 ml) and extracted with EtOAc (4 × 50 ml). The bulked EtOAc was washed with 5% NaOH aq (20 ml), water, (2 × 20 ml) and dried ($MgSO_4$), filtered, and evaporated under reduced press to yield a semi-solid residue which was distilled under high vacuum; 6·3 g, b.p. 132–134°/0·8 mm; Lit.[7] b.p. 118–123°/0·25 mm. This when treated according to the method of Cook *et al.*[7] gave IIi as pale yellow prisms from ether, 3·5 g, m.p. 101°, and IIf as long white needles from water, 2·5 g, m.p. 136–137°; Lit.[7] m.ps 102° and 137° respectively.

6-*Hydroxy*-N-*methyloxindole* (IId). An intimate mixture of XIVc (6 g) and powdered anhyd $AlCl_3$ (10 g) was warmed at 50° for 10 min and subsequently at 200° for 1 hr. When cool the black solid was decomposed with ice (50 g), the crude product removed by filtration and recrystallized twice from water to yield 6-hydroxy-N-methyloxindole 4 g, 87%, m.p. 210–211° (d); Lit.[38] m.p. 209–210°.

6-Methoxy-N-methyloxindole (IIh). Compound IId (1 g) was dissolved in 7·5% NaOH aq (4 ml). Me_2SO_4 (0·7 ml) was added dropwise, with shaking and cooling between the additions. When addition was complete, the mixture was heated on a steam bath for 30 min, adding 7·5% NaOH aq as necessary, to maintain alkalinity. The product was cooled, extracted with ether (3 × 20 ml) and the ether extract dried ($MgSO_4$), filtered and evaporated to dryness under reduced press. The residue recrystallized from pet. ether (80–100°) yielded large pale yellow prisms of *6-methoxy-N-methyloxindole*, 0·76 g, 70% m.p. 99–100°. (Found: C, 67·7; H, 6·4; N, 8·0. $C_{10}H_{11}O_2N$ requires: C, 67·8; H, 6·3; N, 7·9%).

5-Amino-oxindole (Im). 5-Nitro-oxindole II (1·78 g) in dry EtOH (50 ml) was hydrogenated at room temp and press in the presence of 10% Pd-C (100 mg). Filtration, evaporation of the EtOH under reduced press and crystallization of the residue from benzene yielded white needles of 5-amino-oxindole 1·2 g 79%, m.p. 212–214°; Lit.[41] m.p. 213–214°.

5-Amino-N-methyloxindole (IIm). Catalytic hydrogenation of III (1·92 g) as described for the preparation of Im gave 5-amino-N-methyloxindole after recrystallization from pet. ether (60–80°), 1·36 g, 84%, m.p. 117–118°; Lit.[37] m.p. 112–115°.

The remaining compounds, tabulated below, were synthesized by methods reported in the literature.

Compound	Method of prepn Ref.	Crystallization solvent	Yield %	B.p. or m.p.	Lit. b.p. or m.p.
4-Methoxy-6-Nitrotoluene IVc	33		94	b.p. 150°/18 mm	150°/20 mm[33]
3-Methoxy-2-Nitrotoluene IVd	Commercial sample*			m.p. 50–51°	54°[44]
2-Benzyloxy-6-Nitrotoluene IVe	from IIIa 11	ethanol/water (after vac. distn)	75	b.p. 161°/0·1 mm m.p. 62–63°	m.p. 62[11]
5-Hydroxyoxindole Ic	(from Xd) 35	water	48	m.p. 265–266°(d)	265 (d)[35]
6-Hydroxyoxindole Id	(from Xc) 35	water	30	m.p. 244–246°(d)	243°[9]
7-Hydroxyoxindole Ie†				m.p. 251°	251°[45]
4-Chloro-oxindole Ij	42	ethanol/water	31	m.p. 217–218°	216–218°[42]
5-Bromo-oxindole Ik	43	ethanol	35	m.p. 219–220°	220–221°[43]
5-Nitro-oxindole Il	40	Acetic acid/water	76	m.p. 239–241°	240–241°[40]
N-Methyloxindole IIa	39	Pet. ether (80–100°)	84	b.p. 106°/0·01 mm	89°[39]
4-Hydroxy-N-methyloxindole IIb	12	water	80	m.p. 230–231°	230–232°[12]
5-Hydroxy-N-methyloxindole IIc	37	water	80	m.p. 187–188°	186·5°[37]
7-Hydroxy-N-methyloxindole IIe	(from IIi) 12	water	58	m.p. 274–276°	275–276°[12]
5-Methoxy-N-methyloxindole IIg	37	Pet. ether 80–100°	55	m.p. 98°	92°[37]
5-Bromo-N-methyloxindole IIk	41	ethanol/water	77	m.p. 130–132°	132–133°[41]
5-Nitro-N-methyloxindole III	41	ethanol/water	64	m.p. 198°	194–195°[41]

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