8.46 g. (96%), m.p. 210–211° dec., was recrystallized from ethanol–ether to give white needles, m.p. 211–211.5° dec., λ_{max}^{EtOH} 267 mμ (ε 7840).

Anal. Calcd. for $C_{37}H_{35}BP_2$: C, 80.44; H, 6.39; B, 1.96; P, 11.21. Found: C, 80.87; H, 6.34; B, 1.67; P, 11.26.

Acknowledgment.—We wish to thank J. E. Strobel, R. H. Campbell, M. H. Landon, W. T. Cave, and W. S. Coakley for assistance in the spectroscopic investigations.

Reactions of 3-Bromooxindoles. The Synthesis of 3-Methyleneoxindole[1]

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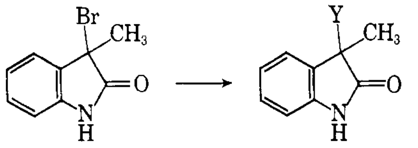
3-Alkyl-3-bromooxindoles underwent facile replacement of the halogen by nucleophiles, including alkoxide, hydroxide, and thiophenoxide ions, and piperidine. With 3-bromooxindole-3-propionic and butyric acids lactone formation took place in the presence of base, but oxindole-3-acetic acid underwent decarboxylation and dehydrobromination to 3-methyleneoxindole. The last compound readily underwent conjugate addition with thiophenol and amines. From hydrolysis of 3-bromooxindole-3-butyric acid in acidic media, the free dioxindole acid was obtained rather than the lactone. Some lactone was obtained from dioxindole-3-propionic acid, but again lactonization under acidic conditions did not take place readily. Attempts to hydrolyze 3-bromooxindole-3-acetic acid to dioxindole-3-acetic acid, under acidic conditions, were unsuccessful. The ultraviolet, infrared, and proton magnetic resonance spectra of a variety of oxindoles and dioxindoles are tabulated and discussed.

In a previous paper a convenient one-step synthesis of 3-bromooxindoles by reaction of the corresponding indoles with N-bromosuccinimide (NBS) was described.[2] The ready accessibility of the 3-bromooxindoles by this new method has led to a study of some aspects of their chemistry, with particular attention to the reactions of the 3-bromooxindole-3-alkanoic acids,[3] and some of the compounds derived therefrom.

Although the 3-bromooxindoles are stable crystalline compounds, the bromine, activated by the adjacent phenyl and carbonyl groups, is very reactive. A precipitate is formed with alcoholic silver nitrate within 3 sec. at room temperature, and replacement of the halogen by nucleophilic agents occurs with ease.[4] Substitution has been effected by nucleophiles of the oxygen, sulfur, and nitrogen series, as shown in eq. 1. 3-Methyldioxindole was also prepared in one over-all step from skatole by addition of sodium bicarbonate to the reaction mixture after formation of I, and treatment of 3-methyloxindole with bromine followed by hydrolysis *in situ* gave 5-bromo-3-methyldioxindole. Structures of the products (II) were confirmed by n.m.r., which showed in all cases a singlet of the proper intensity for the 3-methyl group (Table II). No evidence was found for the presence of the isomeric 3-methylene derivatives, such as 3-(phenylthiomethyl)oxindole (XIII), which could conceivably have been formed by elimination, followed by addition of the nucleophile to the resulting conjugated system (X). In the one case for which both isomers were available (IIc and XIII), they were readily distinguishable by n.m.r. and by the reactivity of isomer XIII towards base (see below).



I

IIa, Y = OH
b, Y = OCH_3
c, Y = SC_6H_5
d, Y = NC_5H_{10}

(1)

Intramolecular nucleophilic displacement by carboxylate ion in the side chain at the 3-position was also observed. In basic solution both 3-bromooxindole-3-propionic acid (IIIa) and 3-bromooxindole-3-butyric acid (IIIb) underwent ring closure to the corresponding lactones (IV). Reference has been made in the previous paper[2] to the direct conversion of indole-3-propionic acid to the lactone IVa by reaction with NBS in the presence of sodium bicarbonate and to the formation of the closely related lactone of α-acetamidodioxindole-3-propionic acid under similar conditions. Since basic conditions promote 3-bromination of an oxindole, reaction of an indole with NBS in a basic hydrolytic medium might serve as a general synthetic route to dioxindoles, similar to the reactions of hypochlorite and lysergic acid derivatives.[2,5,6]

In contrast to the facile lactonization effected by base, hydrolysis of the 3-bromooxindole-3-alkanoic acids (IIIa and IIIb) under acidic conditions, which repress ionization of the carboxyl group, led to the corresponding dioxindole-3-alkanoic acids (VI). Although some lactone was formed along with the dioxindole in the propionic acid case, dioxindole-3-butyric acid was the sole product (76% yield) from IIIb. The reluctance of the dioxindole acids to undergo ring closure was further demonstrated by the following reactions. The dioxindolebutyric acid (VIb) was recovered unchanged after (1) 1 hr. in refluxing 0.05 *M* hydrochloric acid, (2) 30 min. in refluxing glacial acetic acid, or (3) 1 hr. in acetic anhydride at 60°. Ring closure was effected by re-

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[1] Presented in part before the Organic Division of the 144th National Meeting of the American Chemical Society, Los Angeles, Calif., April, 1963.

[2] R. L. Hinman and C. P. Bauman, *J. Org. Chem.*, **29**, 1206 (1964).

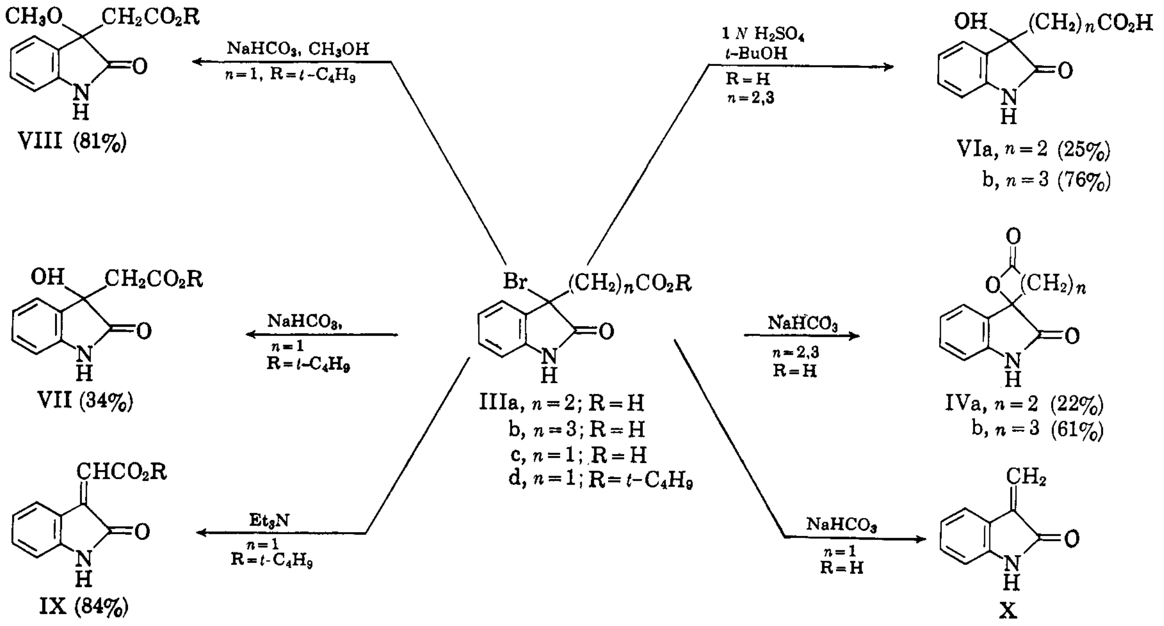
[3] Other methods for preparing 3-bromooxindoles are mentioned in ref. 2. It should be noted in addition that replacement of the dioxindole hydroxyl by reagents such as thionyl chloride is apparently a satisfactory route to 3-halooxindoles [J. M. Bruce and F. K. Sutcliffe, *J. Chem. Soc.*, 4789 (1957); see also P. L. Julian, E. W. Meyer, and H. C. Printy "Heterocyclic Compounds," Vol. III, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1952, p. 247], which has not been used extensively.

[4] A few examples of hydrolysis of 3-halooxindoles have been reported, including the conversion of 3,3-dihalooxindoles to isatin derivatives [E. Fisher and O. Hess, *Ber.*, **17**, 559 (1884); A Michaelis, *ibid.*, **30**, 2811 (1897)] and replacement of the 3-halogen by alkoxide as reported by Bruce and Sutcliffe[3] for 3-chloro-3-phenyloxindole.

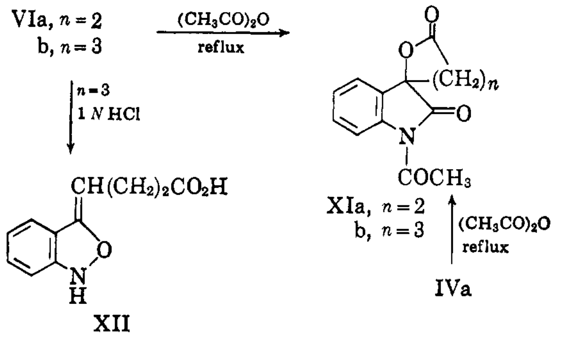
[5] F. Troxler and A. Hofmann, *Helv. Chim. Acta*, **42**, 793 (1959).

[6] The previous paper[2] should be consulted for a discussion of the effect of the medium on the mode of bromination of oxindoles.

CHART I
REACTIONS OF 3-BROMOOXINDOLES



fluxing VIb with acetic anhydride, which gave N-acetyldioxindole-3-butyric acid lactone (XIb) in 75% yield. When VIb was treated with 1 *N* hydrochloric acid for 2 days, including 1 hr. under reflux, a compound with the spectral characteristics of 3-ethylideneoxindole (Table I) was obtained. Isolation of material of this type, presumably XII, indicates that dehydration is preferred to ring closure.



The dioxindolepropionic acid (VIa) cyclized somewhat more readily, as would be expected for formation of a five-membered ring,[7] but even after 4 days at room temperature in 0.2 *M* sulfuric acid in *t*-butyl alcohol only 30% of the lactone (IVa) was isolated and an equal quantity of starting material was recovered. Refluxing acetic anhydride converted VIa to XIa, which was also prepared by acetylation of the lactone IVa.

Although at first sight the resistance of the dioxindole acids to ring closure[8] appeared unusual in view of the facile ring closure of γ- and δ-hydroxy acids of simpler structure, examination of the literature disclosed that a carboxyl adjacent to the hydroxyl inhibits lactonization. Thus, α-hydroxyadipic acid was obtained from its diester by boiling for 10 hr. with concentrated hydrochloric acid.[9] Possibly the electron density of the hydroxyl group is reduced sufficiently by the adjacent carbonyl group to make it relatively unreactive. No evidence of strain or steric hindrance was found in molecular models of the spirolactones (IV).

Attempts to prepare the unknown dioxindole-3-acetic acid by acidic hydrolysis of 3-bromooxindole-3-acetic acid were unsuccessful. A tetrahydropyranyl ester of IIIc was prepared and hydrolyzed by bicarbonate to the dioxindole, but surprisingly, the ester could not be cleaved by acid even under forcing conditions.[10]

In contrast to the behavior of its higher homologs, 3-bromooxindole-3-acetic acid (IIIc) on treatment with base underwent conversion to 3-methyleneoxindole (X)[10] by a process of decarboxylation and dehydrobromination like that which is characteristic of the structurally related β-halo-β-phenylpropionic acids.[11]

The decomposition of 3-bromooxindole-3-acetic acid was more rapid in water than in ethanol and was essentially instantaneous when base-catalyzed. By contrast, *t*-butyl 3-bromooxindole-3-acetate (IIId) reacted with water and with methanol to yield *t*-butyl dioxindole-3-acetate (VII) and *t*-butyl 3-methoxyoxindole-3-acetate (VIII), respectively. In ether in the presence of triethylamine, *t*-butyl isatylidene-3-acetate (IX) was formed.

Although it is unstable in concentrated solutions, we have succeeded in isolating 3-methyleneoxindole as a

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[7] E. L. Eliel, "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p. 116.

[8] Dioxindole-3-propionic acid has been known for some time as a stable substance with no tendency to undergo lactone formation in the presence of acid [P. L. Julian, H. C. Printy, and E. E. Dailey, *J. Am. Chem. Soc.*, **78**, 3501 (1956)], while a closely related malonic acid did readily lactonize [P. L. Julian, E. E. Dailey, H. C. Printy, H. L. Cohen, and S. Hamashige, *ibid.*, **78**, 3503 (1956)]. N-Benzyldioxindole-3-propionic acid has been converted to its lactone by refluxing glacial acetic acid, but the free acid did not lactonize spontaneously [G. Hallmann, *Ber.*, **95**, 1138 (1962)].

[9] C. K. Ingold, *J. Chem. Soc.*, **119**, 305, 951 (1921).

[10] Dioxindole-3-acetic acid is a possible intermediate in the enzymatic oxidation of the plant growth hormone indole-3-acetic acid to 3-methyleneoxindole [R. L. Hinman, C. P. Bauman, and J. Lang, *Biochem. Biophys. Res. Commun.*, **5**, 250 (1961)]. Its synthesis by base-catalyzed reaction of dioxindole and chloroacetic acid was also unsuccessful, though this procedure has been used by Hallmann[8] for preparation of the derived ester and nitrile.

[11] H. H. Wasserman, "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p. 364 ff.

TABLE I

SPECTRAL CHARACTERISTICS OF 3-SUBSTITUTED OXINDOLES

No.	Compound	Ultraviolet absorption, $\lambda_{max}^{95\%\ EtOH}$, mμ (ε)			Infrared absorption, μ (KBr)				
					NH region		C=O region		
1	3-Methyloxindole[a]	207 (27,400)	249 (8720)	278 sh (1440)		3.15	5.85	5.97	
2	3-Methyldioxindole	208 (32,500)	252 (6450)	287 (1350)	2.94	3.13	5.80 sh	5.85	
3	3-Methoxy-3-methyloxindole	208 (24,400)	252 (6350)	289 (1390)		3.02	5.72	5.83	
4	3-Bromo-3-methyloxindole[a]	217 (16,900)	229 sh (13,400)	310 (940)		3.12	5.76	5.91	
5	5-Bromo-3-methyloxindole[a]	207 (25,000)	254 (12,200)	288 sh (1290)		3.09	5.78	5.98	
6	6-Bromo-3-methyloxindole[a]	213 (37,200)	254 (7130)	285 (1960) 293 sh (1540)		3.14	5.83	5.91 sh	
7	5-Bromo-3-methyldioxindole	209 (29,400)	258 (10,900)	296 (1420)		3.07	5.79 sh	5.87	
8	3-Methyl-3-(phenylthio)-oxindole	207 (23,600)	230 sh (17,400) 258 sh (16,200)	287 sh (1590)		3.12	5.78	5.95	
9	3-(Phenylthiomethyl)-oxindole[b]	213 (28,000)	251–252 (14,700)	285 sh (2540)		3.17	5.89		
10	3-Methyl-3-(N-piperidino)-oxindole	207 (31,400)	249 (7700)	282 sh (1640)		3.18	5.86 sh	5.91	
11	3-(β-Aminoethyl)oxindole hydrobromide[a]	207 (27,000)	249 (8250)	280 sh (1420)		3.14	5.86 sh	5.91	
12	3-(β-Benzamidoethyl)-oxindole[a]	230 (14,900)		280 sh (1800)		3.04	5.92		
13	Oxindole-3-acetic acid[a]	205 (27,600)	247 (8790)	280 sh (1480)		3.01–3.12	5.83	5.90	
14	Oxindole-3-propionic acid[a]	207	250 (8500)	280 sh (1400)		3.03	5.77–5.81	5.92	
15	Oxindole-3-butyric acid[a]	206 (26,500)	250 (8430)	281 sh (1410)		3.07	5.80	6.00	
16	Dioxindole-3-propionic acid	209 (26,500)	251–252 (6090)	288 (1370)	2.88	3.08	5.80 5.91 sh	5.95	
17	Dioxindole-3-butyric acid	208 (31,300)	253 (5940)	288 (1350)	2.96	3.08	5.70	5.90	
18	3-Bromooxindole-3-acetic acid[a,c]	220 (18,400)	235 sh (13,300)	320 (1000)		3.08	5.75	5.94	
19	3-Bromoxindole-3-butyric acid[a]	217 (16,690)	227 sh (14,110)	310 (1000)		3.14	5.80	5.96	
20	5-Bromooxindole-3-butyric acid[a]	207 (27,900)	255 (13,000)	290 sh (1310)		3.12	5.74	5.93	
21	*t*-Butyl 3-bromooxindole-3-acetate[a]	218 (15,900)	231 sh (13,500)	317 (880)		3.13	5.77	5.87	
22	*t*-Butyl dioxindole-3-acetate	209 (27,400)	253 (6140)	291 (1400)	2.91 sh 2.99	3.09	5.79	5.96	
23	*t*-Butyl 3-methoxyoxindole-3-acetate	208 (27,600)	253 (5620)	293 (1360)		3.15	5.79		
24	Dioxindole-3-propionic acid lactone	209 (33,500)	253 (4990)	297 (1460)		3.08	5.56, 5.75		
25	Dioxindole-3-butyric acid lactone	208 (31,200)	253 (5680)	292 (1510)		3.13	5.72	5.81	
26	α-Acetamido-(dioxindole-3)-propionic acid lactone[a]	*d*	254 (4780)	298 (1460)	3.01	3.14	5.55, 5.74	6.00	
27	3-Methyleneoxindole	*d*	248 (23,500) 254 (23,500)	289 (2760)		3.13		5.80 5.85	6.09
28	3-Ethylideneoxindole	*d*	246 (26,800) 249 (26,700)	255 (31,900) 287 (4420)		3.14		5.84 5.87	6.04
29	3-Isopropylidene oxindole	*d*	250–254 (27,200) 260 (32,000)	291 (6580)		3.17		5.92	6.14
30	*t*-Butyl isatylidene-3-acetate	*d*	252 (22,700) 257 (20,900)	312 (7220)		3.14		5.77 5.84	6.07
31	N-Acetyldioxindole-3-propionic acid lactone	219 (15,800)	231 sh (11,400)	275 sh (500)			5.60 5.67 5.84		
32	N-Acetyldioxindole-3-butyric acid lactone	218 (15,200)	232 sh (11,400)	275 sh (500)			5.70 5.81		

[a] Preparation given in ref. 2. [b] Solvent was dioxane. [c] Solvent was ether. [d] Not measured in this region.

yellow solid of about 90% purity [determined by comparison of the ultraviolet absorption spectrum of an isolated and redissolved sample with that of a solution prepared by decomposing pure IIIc at spectrophotometric concentrations ($\sim 10^{-5}$ *M*)]. In color, ultraviolet spectrum and infrared spectrum, it resembles the known, stable 3-ethylidene- and 3-isopropylideneoxindoles,[10] including the $>C=C<$ band near 6.10 μ in the infrared (Table I). It has been further characterized by the addition of sodium bisulfite or hydrosulfite to its aqueous solutions, an operation which is accompanied by a rapid change of the ultraviolet spectrum to that of a simple oxindole, presumably 3-(β-sulfomethyl)oxindole.[10] 3-Ethylidene- and 3-isopropylideneoxindole were also converted to compounds with oxindolic absorption spectra when treated with aqueous bisulfite. At spectrophotometric concentrations, the reaction with 3-methyleneoxindole was instantaneous, whereas

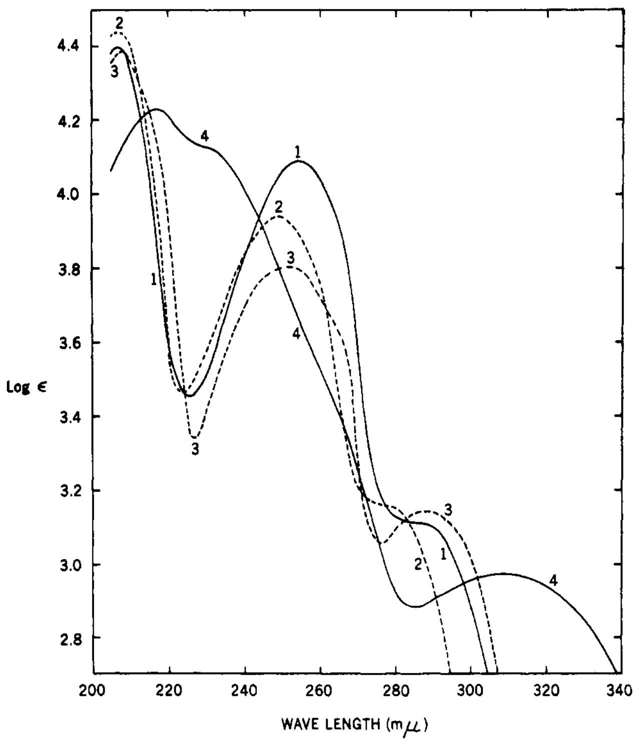
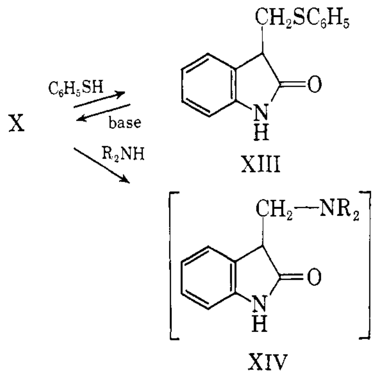


Fig. 1.—Ultraviolet spectra of 3-methyloxindole derivatives in 95% ethanol: 1, 5-bromo-3-methyloxindole; 2, 3-methyloxindole; 3, 3-methoxy-3-methyloxindole; 4, 3-bromo-3-methyloxindole.

reactions of the two higher homologs were complete in 5–10 min. and about 2.5 hr., respectively.[12]

Solid 3-methyleneoxindole underwent no appreciable change during prolonged periods of storage, and the ultraviolet spectra of its solutions in aqueous or ethanolic media underwent very little change over a 24-hr. period if the concentration of methyleneoxindole was 10^{-4} *M* or less. At concentrations above 10^{-2} *M*, however, its solutions in a variety of solvents rapidly deposited a high-melting white solid, probably a dimer or higher polymer of 3-methyleneoxindole. The ultraviolet spectrum of this material was that of a simple oxindole while the existence of two peaks near 3 μ in the infrared correspond to those of the OH and NH of a dioxindole (Table I). In these respects it resembled the material obtained in earlier attempts to carry out the Mannich reaction with oxindole,[12-14] in which 3-methyleneoxindole was presumably formed. Melting points of different preparations of the amorphous solid varied considerably, and elemental analyses indicated products containing 1 mole of water/unit of X. Similar spectral and analytical properties were found in products from oxindole and formaldehyde. Products of Diels–Alder dimerization of X analogous to those derived from 2-methylenecyclohexanone,[15] are ruled out by the analysis and the requirement that they contain an indolic chromophore.

As would be expected from its behavior with bisulfite, 3-methyleneoxindole is reactive towards nucleophiles generally. For example, it reacted smoothly with thiophenol in the presence of a trace of piperidine, a reaction which has been observed with other 3-alkylideneoxindoles,[16] yielding 3-(phenylthiomethyl)oxindole (XIII), isomeric with IIc. This product was very sensitive to base and at spectrophotometric concentrations was easily reconverted to 3-methyleneoxindole.



The success of this reaction prompted us to re-examine the problem of the preparation and stability of Mannich bases of oxindole. Although Mannich bases derived from 3-alkyloxindoles are well known,[17] the few attempts[12,13] to prepare these derivatives of oxindole itself have led invariably to amorphous material of the type described above from the spontaneous reaction of 3-methyleneoxindole. Our experiments with compound XIII indicate that a Mannich base would not survive the treatment with a strong base used in the isolation procedures. Accordingly, we have attempted to prepare Mannich bases derived from oxindole by the reaction of 3-methyleneoxindole with a variety of amines, including piperidine and N-methylaniline, with and without a trace of acid present. In all cases the characteristic double-spiked maximum near 250 mμ in the ultraviolet absorption spectrum of 3-methyleneoxindole[10] was replaced by a spectrum characteristic of a simple oxindolic chromophore. Despite considerable care in working up the reaction mixtures, however, no product corresponding to a Mannich base (XIV) could be isolated. Since the products themselves are amines, they may catalyze their own decomposition. These results do indicate, however, that Mannich bases derived from oxindole can exist in solution and they suggest that, by the proper choice of amine, it may be possible to isolate certain members of the class.

A few experiments were also carried out in attempts to prepare the Mannich bases directly from oxindole itself using milder conditions than those of the earlier work. The ultraviolet spectra showed that transformation to a new oxindole had occurred in the reaction mixture, but again no simple product could be isolated.

Spectral Characteristics of Oxindoles.—In the course of the work described in this paper and the preceding one[2] the spectra of a wide variety of oxindoles and di-

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[12] The reaction of sodium bisulfite with 3-methoxymethylene-1-methyloxindole can also be explained by addition to the exocyclic double bond. It has been suggested that the product is simply a complex with the inorganic salt [E. Wenkert, A. K. Bose, and T. L. Reid, *J. Am. Chem. Soc.*, **75**, 5514 (1953)], but it seems more likely from our experiments that bisulfite addition to this class of α,β-unsaturated carbonyl compounds is a general reaction.

[13] (a) H. Hellmann and E. Renz, *Ber.*, **84**, 901 (1951); (b) E. Wenkert, J. H. Udelhofen, and N. K. Bhattacharyya, *J. Am. Chem. Soc.*, **81**, 3763 (1959).

[14] A dimer of 3-methyleneoxindole was also reported by L. Horner [*Ann.*, **548**, 117 (1941)], but, since the melting point of the starting material, originally presumed to be oxindole-3-acetic acid, agrees in fact with that of 3,4-dihydroquinolone-3-carboxylic acid, this result must be disregarded.

[15] For leading references, see H. O. House, *J. Org. Chem.*, **26**, 2190 (1961).

[16] T. Wieland and O. Unger, *Ber.*, **96**, 253 (1963).

[17] E. C. Horning and M. W. Rutenberg, *J. Am. Chem. Soc.*, **72**, 3534 (1950).

oxindoles have been determined. These data are summarized in Table I.[18] A point of particular interest in the ultraviolet spectra is the absorption at low wave length (near 208 mμ) of oxindoles, which has not previously been pointed out. This peak is shifted to about 217 mμ by introduction of a bromine at the 3-position (Fig. 1), and the strong absorption here covers the usual oxindole absorption near 250 mμ; the band near 285 mμ is also shifted bathochromically. Oxygen (compound **2**, **3**, **7**, **14**, **15**, **16**, and **17**), nitrogen (**10**), or sulfur (**8**) at the 3-position does not particularly affect the peak at 208 mμ.[19] Acetanilide, which may be considered a parent of the oxindoles, shows peaks at 242 mμ (ε 14,400) and 280 mμ (ε 500), but lacks the peak near 208 mμ. It is interesting that the N-acetyloxindoles (**31** and **32**) show very marked differences from the parent molecules (**24** and **25**), lacking both the peaks at 208–209 and 253 mμ.[3] In this respect the spectra resembled those of the 3-bromooxindoles, but the peak positions at highest wave length do not correspond.

In the infrared spectra, the splitting of the carbonyl peak, observed previously in simple oxindoles,[20] has been noted in a number of examples (**1–10**), and appears to be a general effect. In dioxindoles the OH and NH peaks were clearly distinguishable at about 2.95 and 3.1 μ, respectively (**2**, **11**, and **15**).

The n.m.r. spectra of 3-methyloxindole and its 3-bromo derivative are compared with that of skatole (Table II). The proton resonances show the expected relationship.

TABLE II

N.M.R. SPECTRA OF OXINDOLES[a]

Compound	CH_3	NH	Aromatic	CH at C-3
Skatole[b]	7.70		2.82	
3-Methyloxindole[c]	8.45, 8.57	−0.56	2.97	6.68[d]
3-Bromo-3-methyloxindole	7.93	1.24	3.13	
3-Methyl-3-(N-piperidino)oxindole	8.45		2.85[d]	
3-Methyl-3-(phenylthio)oxindole	8.26		2.76[d]	
3-(Phenylthiomethyl)-oxindole	*e*		2.60[d]	*e*

[a] Chemical shifts are given as τ-values (tetramethylsilane as internal standard). Data were obtained with a Varian A-60 magnetic resonance spectrometer. Solvent was deuteriochloroform except where noted otherwise. [b] Taken from L. A. Cohen, J. W. Daly, H. Kny, and B. Witkop, *J. Am. Chem. Soc.*, **82**, 2184 (1960). [c] CCl_4. [d] Unresolved multiplet. [e] Complex pattern of at least seven principal lines from τ 6.1–6.9. Hydrogens of side-chain CH_2 are apparently nonequivalent.

Experimental[21]

3-Methyldioxindole (IIa).—A mixture of 1.00 g. (4.42 mmoles) of 3-bromo-3-methyloxindole and 0.371 g. (4.42 mmoles) of sodium bicarbonate in 25 ml. of water and 25 ml. of *t*-butyl alcohol was stirred at room temperature for 22 hr. The mixture was then extracted with three 15-ml. portions of ethyl acetate. The extract was dried over sodium sulfate and then concentrated under reduced pressure until a precipitate began to form. After standing overnight at −20°, 0.487 g. of white crystals of 3-methyldioxindole, m.p. 161–162°, were obtained (lit.[22] m.p. 159.5–160.5°). By concentration of the filtrate three additional crops totaling 0.121 g., m.p. 160–162°, were obtained, making the total yield of 3-methyldioxindole 84%.

3-Methoxy-3-methyloxindole (IIb).—A solution of 1.00 g. (4.42 mmoles) of 3-bromo-3-methyloxindole and 0.317 g. (4.42 mmoles) of sodium bicarbonate in a mixture of 10 ml. of water and 100 ml. of methanol was stirred at room temperature for 3 days. The solution was concentrated under reduced pressure until cloudy. After cooling, 0.41 g. of crystals, m.p. 121–123°, were collected by filtration. The filtrate was extracted with three 25-ml. portions of ethyl acetate. The extract was washed with saturated salt solution, dried over sodium sulfate, and evaporated. The residual oil was crystallized from an acetone–hexane mixture, yielding an additional 0.25 g. of product melting at 121–122°. The total yield of 3-methoxy-3-methyloxindole was 85%. An analytical sample was obtained as white crystals, m.p. 124.0–124.5° from an acetone–hexane mixture.

Anal. Calcd. for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.91. Found: C, 67.87; H, 6.33; N, 7.88.

3-Methyl-3-(phenylthio)oxindole (IIc).—To a solution of 2.26 g. (0.01 mole) of 3-bromo-3-methyloxindole in 50 ml. of *t*-butyl alcohol was added 1.10 g. (0.01 mole) of thiophenol followed by 1.0 ml. of 10 *N* sodium hydroxide. After the mixture had been stirred for 15 min. at room temperature, the white solid that had formed was removed by filtration, and the filtrate was evaporated *in vacuo* at room temperature. The residue was taken up in 20 ml. of toluene, and hexane was added until a white precipitate began to form, which was removed by filtration From the filtrate was obtained two crops of white crystals of 3-methyl-3-(phenylthio)oxindole, m.p. 151–158°, totaling 0.52 g., which when recrystallized from a mixture of methanol and water gave two crops (0.44 g.) of white crystals, m.p. 158–162°. An additional 0.78 g. of product, m.p. 160.0–161.5°, was obtained from the toluene–hexane mother liquor, giving a total yield of 1.22 g. (48%). An analytical sample, m.p. 161–62°, was obtained by recrystallization from methanol.

Anal. Calcd. for $C_{15}H_{13}NOS$: C, 70.56; H, 5.13; N, 5.49; S, 12.56. Found: C, 70.49; H, 5.03; N, 5.53; S, 12.36.

3-Methyl-3-piperidinooxindole (IId).—To a solution of 1.13 g. (0.005 mole) of 3-bromo-3-methyloxindole in 75 ml. of anhydrous ether was added 1.0 ml. (0.010 mole) of piperidine. The mixture was stirred at room temperature for 1.5 hr. Two crops of piperidine hydrobromide were removed by filtration. From the filtrate were obtained several crops of 3-methyl-3-piperidinooxindole, m.p. 155–160°, totalling 1.1 g. (91% yield). An analytical sample, m.p. 160–161°, was obtained by recrystallization from ether.

Anal. Calcd. for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.17. Found: C, 73.33; H, 8.24; N, 11.80.

***t*-Butyl Dioxindole-3-acetate (VII).**—Prepared from IIId[2] by the procedure used for 3-methyldioxindole, this compound melted at 149–149.5° after recrystallization from an acetone–hexane mixture.

Anal. Calcd. for $C_{14}H_{17}NO_4$: C, 63.86; H, 6.51; N, 5.32. Found: C, 64.04; H, 6.68; N, 5.44.

***t*-Butyl 3-Methoxyoxindole-3-acetate (VIII).**—To a solution of 1.00 g. (3.06 mmoles) of *t*-butyl 3-bromooxindole-3-acetate[2] in 25 ml. of water and 5 ml. of methanol was added 0.257 g. (3.06 mmoles) of sodium bicarbonate. The mixture was stirred for 23 hr. at room temperature and then was concentrated under reduced pressure until crystallization began. The white crystals of *t*-butyl 3-methoxyoxindole-3-acetate, which were filtered and washed with water, weighed 0.69 g. (81%) and melted at 150–151°. An analytical sample, which was obtained by recrystallization from ethanol, then from an acetone–benzene mixture, and finally from an acetone–water mixture, melted at 152–153°.

Anal. Calcd. for $C_{15}H_{19}NO_4$: C, 64.96; H, 6.91; N, 5.05. Found: C, 65.15; H, 7.13; N, 5.10.

***t*-Butyl Isatylidene-3-acetate (IX).**—A solution of 2.00 g. (6.12 mmoles) of *t*-butyl 3-bromooxindole-3-acetate[2] and 0.618 g. (6.12 mmoles) of triethylamine in 100 ml. of anhydrous ether was refluxed for 7 hr. and then stirred at room temperature for 48 hr. The cream-colored precipitate of triethylamine hydro-

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[18] For an earlier discussion of ultraviolet and infrared absorption spectra of oxindoles and 3-alkylideneoxindoles, see ref. 12 and E. Wenkert, B. S. Bernstein, and J. H. Udelhofen, *J. Am. Chem. Soc.*, **80**, 4899 (1958).

[19] A bathochromic shift accompanying introduction of a chlorine at the 3-position of 3-phenyloxindole has been reported by Bruce and Sutcliffe.[3]

[20] A. E. Kellie, D. G. O'Sullivan, and P. W. Sadler, *J. Chem. Soc.*, 3809 (1956).

[21] Melting points and boiling points are uncorrected. Ultraviolet absorption spectra were determined with a Beckman DK-2 recording spectrophotometer, using quartz cells of 1-cm. light path. Infrared spectra were obtained with a Perkin-Elmer 21 recording spectrophotometer equipped with sodium chloride optics.

[22] A. S. Endler and E. I. Becker, *J. Am. Chem. Soc.*, **77**, 6608 (1955).

bromide was removed by filtration and washed with ether. The filtrate was evaporated under reduced pressure. The residue was dissolved in methylene chloride, and hexane was added to the saturation point. Orange crystals were obtained, which after recrystallization from cyclohexane gave 0.623 g. (42%) of *t*-butyl isatylidene-3-acetate, m.p. 133–134°. Since there was evidence of incomplete reaction, all materials from the reaction mixture, except the purified product, were treated with an additional 1.24 g. (12.2 mmoles) of triethylamine in 50 ml. of anhydrous ether. After stirring for 22 hr. at room temperature, the mixture was worked up as before. An additional 0.637 g. of product, m.p. 132–133°, was obtained giving a total yield of 1.26 g. (84%). An analytical sample, obtained as orange needles by recrystallization from cyclohexane, melted at 134–135°.

Anal. Calcd. for $C_{14}H_{15}NO_3$: C, 68.55; H, 6.16; N, 5.71. Found: C, 68.99; H, 6.35; N, 5.83.

5-Bromo-3-methyldioxindole.—Bromine was added to a solution of 0.29 g. (0.002 mole) of 3-methyloxindole in 13 ml. of *t*-butyl alcohol until an orange-yellow color persisted. After 3 hr. the solvent was removed by evaporation at room temperature and the residue was stirred with a mixture of 10 ml. of water and 10 ml. of *t*-butyl alcohol for 3 days. The solution was concentrated *in vacuo* until precipitation began. Cream-colored crystals, m.p. 240–242° (70 mg., 14%), of 5-bromo-3-methyldioxindole were obtained. An analytical sample, m.p. 241–242.5°, was obtained by recrystallization from 95% ethanol.

Anal. Calcd. for $C_9H_8BrNO_2$: C, 44.66; H, 3.33; Br, 33.01; N, 5.79. Found: C, 44.43; H, 3.00; Br, 33.01; N, 5.80.

Dioxindole-3-butyric Acid Lactone (IVb).—A solution of 1.00 g. (3.36 mmoles) of 3-bromooxindole-3-butyric acid and 0.565 g. (6.72 mmoles) of sodium bicarbonate in a mixture of 25 ml. of water and 55 ml. of methanol was stirred for 2 hr. at room temperature, then acidified to pH 2 with dilute hydrochloric acid, and concentrated under reduced pressure until a precipitate began to form. Two crops of crystals of dioxindole-3-butyric acid lactone were collected, totaling 0.45 g. (61%), m.p. 132–134°. An analytical sample, obtained by recrystallization from water, melted at 134–135°.

Anal. Calcd. for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.12; N, 6.45. Found: C, 65.97; H, 5.16; N, 6.63.

Dioxindole-3-butyric Acid (VIb).—A solution of 2.00 g. of 3-bromooxindole-3-butyric acid in a mixture of 4 ml. of 3 *M* sulfuric acid and 20 ml. of *t*-butyl alcohol (final acid concentration = 0.5 *M*) was stirred for 8 days at room temperature. The solution was diluted with 10 ml. of water, concentrated under reduced pressure until the mixture became cloudy, and then was extracted with three 25-ml. portions of ethyl acetate. The extract was evaporated, and the residue was crystallized from an acetone–benzene mixture. Several crops of dioxindole-3-butyric acid were obtained totaling 1.20 g. (76%), m.p. 169–173°. An analytical sample, m.p. 172–173°, was obtained by recrystallization from an acetone–benzene mixture.

Anal. Calcd. for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.96. Found: C, 61.58; H, 5.53; N, 6.42.

N-Acetyldioxindole-3-butyric Acid Lactone (XIb).—A solution of 0.50 g. (2.13 mmoles) of dioxindole-3-butyric acid in 3 ml. of acetic anhydride was refluxed for 2.5 hr. The solution was diluted with 12 ml. of water and cooled. The solid which formed was recrystallized from an acetone–water mixture, yielding 0.414 g. (75%) of N-acetyldioxindole-3-butyric acid lactone, m.p. 148–151°. An analytical sample obtained by recrystallization from an acetone–water mixture melted at 149–151°.

Anal. Calcd. for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05; N, 5.40. Found: C, 64.64; H, 5.27; N, 5.52.

Hydrolysis of 3-Bromooxindole-3-propionic Acid under Acidic Conditions.—To a solution of 4.73 g. (0.025 mole) of indole-3-propionic acid in 162 ml. of *t*-butyl alcohol, which had been dried over sodium sulfate and treated with Darco (see previous paper[2] for significance of this treatment), was added with stirring under nitrogen at 23–25°, 8.90 g. (0.05 mole) of N-bromosuccinimide over a period of 45 min. After 3 hr. the solution was concentrated *in vacuo* at room temperature to a sirupy residue which was mixed with 100 ml. of anhydrous ether. Two crops of succinimide were removed by filtration. The filtrate was evaporated at room temperature, and the residual sirup was stirred with a mixture of 16 ml. of 1.5 *M* sulfuric acid and 80 ml. of *t*-butyl alcohol for 24 hr. Water (25 ml.) was added, and the mixture was concentrated *in vacuo* until a precipitate began to form. The solid was filtered and upon recrystallization from a benzene–hexane mixture gave two crops totaling 0.98 g. (19%) of impure dioxindole-3-propionic acid lactone, m.p. 120–123° (lit.[2] m.p. 134°), identified by its absorption spectra (Table I). The filtrate from the sulfuric acid–*t*-butyl alcohol solution was then extracted with ethyl acetate, the extract was dried and evaporated, and the residue taken up in a mixture of acetone, benzene, and hexane. A tan solid formed which upon recrystallization from a mixture of acetone, benzene, and methanol gave 1.36 g. (25%) of dioxindole-3-propionic acid, m.p. 182–185° dec. Recrystallization from a methanol–benzene mixture and then from a methanol–acetone mixture raised the melting point to 189–190° (lit.[8] m.p. 195–196°). Although the melting point did not agree with the reported value, the spectra and the reactions described below left no doubt about the structure.

Lactonization of Dioxindole-3-propionic Acid in Sulfuric Acid–*t*-Butyl Alcohol.—A solution of 0.221 g. (1.0 mmole) of dioxindole-3-propionic acid in a mixture of 0.64 ml. of 3 *M* sulfuric acid and 8.2 ml. of *t*-butyl alcohol was stirred at room temperature for 3 days. Then 6 ml. of water was added, and the mixture was concentrated *in vacuo* at room temperature until cloudy. Upon cooling, 0.058 g. of a white solid, m.p. 115–117°, was obtained, which was crude dioxindole-3-propionic acid lactone, as indicated by its ultraviolet spectrum. The filtrate was extracted with three 10-ml. portions of ethyl acetate, and the extract was shaken with three 10-ml. portions of 5% sodium bicarbonate. The quantity of dioxindole-3-propionic acid in the sodium bicarbonate extract was estimated by ultraviolet absorption to be 0.063 g. (29%). The quantity of lactone in the ethyl acetate layer was estimated by ultraviolet absorption to be 0.0039 g., which when added to the crude lactone isolated above gave a total yield of 30% of the lactone. The lactone did not react appreciably with bicarbonate under these conditions.

N-Acetyldioxindole-3-propionic Acid Lactone.—A solution of 0.50 g. of dioxindole-3-propionic acid lactone in 3 ml. of acetic anhydride was refluxed for 2 hr. After cooling and dilution with 12 ml. of water, 0.56 g. (92%) of N-acetyldioxindole-3-propionic acid lactone, m.p. 134–135°, was obtained. An analytical sample, m.p. 134–135° (resolidified and melted at 146–147°), was obtained by recrystallization from a mixture of acetone and water.

Anal. Calcd. for $C_{13}H_{11}NO_4$: C, 63.67; H, 4.52; N, 5.71. Found: C, 63.93; H, 4.65; N, 5.91.

The same product was obtained in 88% yield by treating dioxindole-3-propionic acid with acetic anhydride by the above procedure.

3-Methyleneoxindole (X).—3-Bromooxindole-3-acetic acid (0.587 g., 2.17 mmoles) was dissolved in 15 ml. of 95% ethanol and 260 ml. of water. The solution was immediately extracted with four 50-ml. portions of chloroform. The chloroform extract was washed with water, dried over sodium sulfate, and evaporated *in vacuo*. The yellow solid remaining was further dried in a vacuum desiccator, yielding 0.22 g. (69%) of material which decomposed at 218–232°. The purity was determined to be 91% by comparing the ultraviolet spectrum of a quantitatively prepared solution of the material in 95% ethanol with that of a solution prepared from pure 3-bromooxindole-3-acetic acid (10^{-5} *M*) and a trace of triethylamine. Further purification was not feasible because of the instability of the material in solution.

Anal. Calcd. for C_9H_7NO: C, 74.46; H, 4.86; N, 9.65. Found: C, 69.41; H, 4.84; N, 7.79.

3-(Phenylthiomethyl)oxindole (XVI).—To a solution of one drop of piperidine in 1 ml. of thiophenol was added 0.290 g. of 3-methyleneoxindole, which was 80% pure as determined by ultraviolet spectrum. The thick slurry was stirred under nitrogen for 3.5 hr. at room temperature. After dilution with 5 ml. of *n*-hexane a white solid formed. This solid was isolated by suction filtration and dissolved in 50 ml. of toluene. A small amount of insoluble material was removed by filtration, and to the filtrate *n*-hexane then was added to the saturation point. Two crops of white crystals were obtained, which upon recrystallization from toluene and then from a methanol–water mixture yielded four crops of 3-(phenylthiomethyl)oxindole, totaling 0.24 g. (60%), m.p. 128.0–129.5°. An analytical sample, m.p. 129–130°, was obtained by recrystallization from a methanol–water mixture.

Anal. Calcd. for $C_{15}H_{13}NOS$: C, 70.56; H, 5.13; N, 5.49; S, 12.56. Found: C, 70.16; H, 5.19; N, 5.94; S, 12.52.

Polymer from 3-Methyleneoxindole.—To a solution of 0.20 g. of 3-bromooxindole-3-acetic acid in 2.5 ml. of 95% ethanol was added 47.5 ml. of 0.2 *M* acetate buffer (pH 5.0). After about 10 min., a fine white precipitate began to form. After 6 days, 0.039 g. of a cream-colored solid was removed by filtration, but upon drying in a desiccator the solid decomposed to a dark brown solid. The filtrate was concentrated and the white precipitate was isolated by centrifugation. The solid was mixed with water and centrifuged, the clear solution was decanted, and the tan solid was dried in a desiccator. The product melted from 230–270° with gradual decomposition. The ultraviolet spectrum showed $\lambda_{\max}^{\text{EtOH}}$ 252 mμ; the infrared, $\lambda_{\max}^{\text{KBr}}$ 2.88, 3.1–3.2, 5.78 μ.

Polymer from Oxindole and Paraformaldehyde.—A mixture of 1.00 g. (7.5 mmoles) of oxindole, 0.23 g. of paraformaldehyde (equivalent to 8 mmoles of formaldehyde), 4 drops of piperidine, and 20 ml. of absolute ethanol was refluxed for 24 hr. A tan solid (0.02 g.) was removed by filtration and the filtrate was evaporated to dryness at room temperature. The residue was dissolved in tetrahydrofuran (THF), and benzene was added to the saturation point. Two crops of a cream solid, m.p. 211–213° dec., totaling 0.28 g., were obtained with $\lambda_{\max}^{\text{EtOH}}$ 207 and 251 mμ. The infrared spectrum resembled that of the polymeric product from the decomposition of 3-bromooxindole-3-acetic acid.

A sample of the polymer, m.p. 220–221° dec., which had been recrystallized from tetrahydrofuran–benzene, had the following analysis: C, 67.89; H, 5.99; N, 9.00 ± 1.00.

Notes

The Synthesis and Infrared Spectrum of 3-Deuterioindole

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Whereas exchange of deuterium for hydrogen on the indole nitrogen can be effected in neutral solution by repeated evaporation of solutions of indole and D_2O in a common solvent,[1] exchange at the 3-position requires acid catalysis.[2,3] We have applied this method for convenient syntheses of 1,3-dideuterio- and 3-deuterioindole.[4] Recognition of pronounced differences between the infrared spectra of indole and its 3-deuterio derivatives enabled us to follow the exchange readily and to characterize the isolated products.

Previous work from this laboratory[5] has shown that very rapid exchange of the NH of skatole occurs in dioxane solutions containing 5×10^{-5} *M* sulfuric acid. Very little exchange of the indole NH occurred under comparable conditions during a 2-hr. period. In the presence of 10^{-4} *M* acid, NH exchange occurred but was still slower than exchange in skatole. At this acid concentration no evidence of deuterium at the 3-position of the isolated product was found.[6]

By refluxing a solution of indole in D_2O containing 5×10^{-3} *M* sulfuric acid, exchange of the β-proton was accomplished, yielding 1,3-dideuterioindole. This in turn was converted to 3-deuterioindole by refluxing with water. The last product had an isotopic purity of 87%, as determined by n.m.r. Although the 1,3-dideuterioindole also had a high per cent of deuterium at the 3-position, the nitrogen seldom held more than 60% deuterium, as determined by infrared. Exchange from the nitrogen is a more facile process, and attempts to raise this level by repeated treatments with D_2O were not effective. The same problem was encountered in a recent synthesis of 1,3-dideuterioindole *via* the indole Grignard reagent.[1b] In this case, however, the β-carbon was also only 50% deuterated. The work-up of the Grignard reagent involved basic conditions, which may have promoted exchange[2c] with traces of water inadvertently admitted.

Although the introduction of deuterium produced no visible changes in the CH or CD stretching region near 3.3 μ of the infrared spectrum, probably because the bands are too weak to see with standard equipment, in the C–H bending region deuterium had a very marked effect similar to that reported for other substituents at the 3-position.[7] Of the three characteristic strong peaks at 13.05, 13.45, and 13.85 μ in the indole spectrum, that at 13.05 μ disappeared completely in the deuterated material, and that at 13.85 μ, associated with indoles bearing no substituents at the 2- and 3-positions,[7] was reduced to a weak absorption at 13.70 μ. Had it been possible to obtain isotopically pure product, the last peak would probably have disappeared completely. The band at 13.45 μ, characteristic of indoles unsubstituted in the benzene ring,[7] was unchanged in 3-deuterioindole. New peaks in the deuterated material included a band of moderate intensity at 12.1 μ (830 cm.$^{-1}$), a strong band at 12.4 (808), and what appeared to be an overtone of the former at 6.05 (1660). The absorption at 12.4 μ is in the region characteristic of indoles bearing a substituent at the 3-position.[7]

Thus, the presence of deuterium at the 3-position can be detected by the band at 12.4 μ, and residual C–H at that position can be estimated quantitatively from the

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[1] (a) L. A. Cohen J. W. Daly, H. Kny, and B. Witkop, *J. Am. Chem. Soc.*, **82**, 2184 (1960); (b) R. V. Jardine, and R. K. Brown, *Can. J. Chem.*, **41**, 2067 (1963).

[2] (a) M. Koizumi and T. Titani, *Bull. Chem. Soc. Japan*, **13**, 307 (1938); (b) M. Koizumi, *ibid.*, **14**, 453 (1939). (c) The possibility of base-catalyzed exchange at the 3-position is suggested by recent work with 2-methylindole [B. C. Challis and F. A. Long, *J. Am. Chem. Soc.*, **85**, 2524 (1963)].

[3] The occurrence of considerable exchange at the 3-position upon evaporation of solutions of D_2O and indole or 2-methylindole in acetone or ethanol has been reported.[1b] Although this result would be expected in the latter case,[2b] it is difficult to reconcile the indole result with the earlier studies[2a,b] and our own.

[4] The only reported syntheses of C-deuterated indoles are those for 1,3-dideuterioindole (50% isotopic purity at C-3),[1b] 5-deuterioindole, and 2,3,4,5,6,7-hexadeuterioindole [H. Plieninger, R. Fischer, G. Keilich, and H. D. Orth, *Ann.*, **642**, 214 (1961)].

[5] R. L. Hinman and E. B. Whipple, *J. Am. Chem. Soc.*, **84**, 2534 (1962).

[6] Indole is considerably more basic than skatole in equilibrium protonation where 3-protonation predominates [R. L. Hinman and J. Lang, *Tetrahedron Letters*, **No. 21**, 12 (1960)]. The differences in exchange rates of the NH proton may reflect differences in basicity of the 1-position.

[7] "Physical Methods in Heterocyclic Chemistry," Vol. II, A. R. Katritsky, Ed., Academic Press, New York, N. Y., 1963, pp. 211,212.