The Synthesis, Reactions, and Spectra of 1-Acetoxy-, 1-Hydroxy-, and 1-Methoxy-indoles

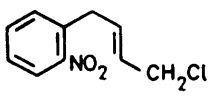
By R. Morrin Acheson,* Paul G. Hunt, David M. Littlewood, Barry A. Murrer, and Howard E. Rosenberg, Department of Biochemistry, South Parks Road, Oxford OX1 3QU

Reduction of 2-nitrophenylacetaldehyde gave the unstable 1-hydroxyindole, trapped as 1-acetoxyindole. Concurrent alkaline hydrolysis with methyl iodide present yielded 1-methoxyindole which was substituted by electrophiles at position 3. The 3-carbaldehyde, from a Vilsmeier reaction, was converted into 1-methoxy-*NN*-dimethyltryptamine. 1,5-Dimethoxyindole underwent the Mannich reaction forming the 3-dimethylaminomethyl derivative. 1-Acetoxyindole with dimethylformamide and phosphoryl chloride yielded 2-chloroindole-3-carbaldehyde and 1-hydroxyindole-3-carbaldehyde, while (1-hydroxyindol-3-yl)glyoxylic acid with hydroxylamine gave 3-cyano-1-hydroxyindole or indole-3-nitrile oxide. The u.v., i.r., n.m.r., and mass spectra of the 1-hydroxyindole derivatives are discussed.

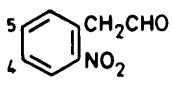
RECENT interest in 1-hydroxyindole derivatives has been stimulated by the isolation from plants of five 1-methoxyindole derivatives, 1,5-dimethoxygramine [5-MeO-(8)],[1] 1-methoxy-*NN*-dimethyltryptamine (28),[2] 1-methoxyindole-3-acetonitrile (10),[3] a derivative of 1-methoxyindole-3-acetic acid called neoglucobrassicin,[4] and oxaline, the major alkaloid of *Penicillium oxalicum*, which is a complex 2,3-dihydro-1-methoxyindole.[5] As secondary aliphatic amines can be oxidised to hydroxylamines by peroxy-acids [6] and in mammals,[7] the possibility that *N*-hydroxylation of indoles could occur *in vivo* needs to be explored, and the biological properties of 1-hydroxy- and similar analogues of tryptophan, serotonin, *etc.* can hardly fail to be of interest. An investigation of the synthesis of compounds of these types has therefore been started, syntheses of 1-acetoxy- and 1-methoxy-indoles have been developed, and the first syntheses of 1,5-dimethoxygramine, briefly reported,[8] and 1-methoxy-*NN*-dimethoxytryptamine are described.

RESULTS AND DISCUSSION

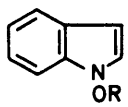
1-Hydroxyindole (3) was first obtained by Mousseron-Canet and Boca [9] by the hydrolysis with sulphuric acid



(1)

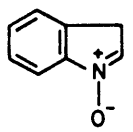


(2)

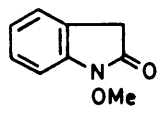


(3) R = H
(4) R = Ac

of ethyl 2-(2-nitrophenylvinyl)carbamate to 2-nitrophenylacetaldehyde (2) (a hydrolysis which has been described [10] as ' très difficile ' and which we have failed to reproduce), followed by a reliable, carefully controlled reduction with zinc–ammonium chloride. Although we [11] obtained 2-nitrophenylacetaldehyde (13% d) by treating 2-nitrobenzenediazonium chloride with ethyl vinyl ether, much nitrobenzene was also produced. A satisfactory route consisted of coupling 2-nitrobenzene diazonium chloride with butadiene to give 1-chloro-4-(2-nitrophenyl)but-2-ene (1) [12] followed by ozonolysis [12] or scission of the olefinic bond with osmium tetraoxide–periodate. The last procedure was successful for (2) and its 4-chloro- and 4- and 5-methoxy-derivatives. Reduction of the aldehyde (2) in a two-phase system gave an ethereal solution of 1-hydroxyindole which on evaporation gave the green substance reported.[9] However, this substance in the mass spectrometer did not show a peak corresponding to the molecular ion, nor a peak [9] at *m/e* 266 which could indicate the presence of a dimer, but behaved as expected of a polymeric mixture. This was confirmed by the absence of resonances expected of (3) or its dimer in the n.m.r. spectrum [$(CD_3)_2$-SO solution], and by a diffuse m.p. When the ether containing the 1-hydroxyindole was replaced, by addition of carbon tetrachloride or deuteriochloroform and partial evaporation, then n.m.r. spectra attributable to the indole were obtainable. In carbon tetrachloride a doublet (τ 3.98, J 3.3), a broad absorption (2.5), and multiplet (2.5—3.3) in the ratios 1 : 1 : 4 are assigned to H-3, OH, and the aromatic protons, respectively; none of the 3*H*-indole tautomer (5) could be detected. In deuteriochloroform the results were similar, but the



(5)



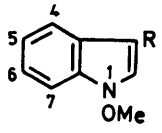
(6)

integrations and some resonance near τ 7 suggested that up to 20% of the 3*H*-indole might be present. The

[1] S. R. Johns, J. A. Lamberton, and J. L. Occolowitz, *Austral. J. Chem.*, 1967, **20**, 1737.
[2] H. Morimoto and H. Oshio, *Annalen*, 1965, **682**, 212; H. Morimoto and N. Matsumoto, *ibid.*, 1966, **692**, 194.
[3] M. Namoto and S. Tamura, *Agric. and Biol. Chem.* (*Japan*), 1970, **34**, 1590.
[4] R. Gmelin and A. I. Virtanen, *Acta Chem. Scand.*, 1962, **16**, 1378.
[5] D. W. Nagel, K. G. R. Pachler, P. S. Steyn, P. L. Wessels, G. Gafner, and G. J. Kruger, *J.C.S. Chem. Comm.*, 1974, 1021.
[6] A. H. Beckett, R. T. Coutts, and F. A. Ogunbona, *J. Pharm. Pharmacol.*, 1973, **25**, 190; A. H. Beckett and F. A. Ogunbona, *ibid.*, Suppl. 170P.
[7] A. H. Beckett, J. M. Van Dyk, H. H. Chissick, and J. W. Gorrod, *J. Pharm. Pharmacol.*, 1971, **23**, 809.
[8] R. M. Acheson, D. M. Littlewood, and H. E. Rosenberg, *J.C.S. Chem. Comm.*, 1974, 671.
[9] M. Mousseron-Canet and J.-P. Boca, *Bull. Soc. chim. France*, 1967, 1296; M. Mousseron-Canet, J.-P. Boca, and V. Tabacik, *Spectrochim. Acta*, 1967, **23A**, 717.
[10] M. Mousseron-Canet, personal communication.
[11] R. M. Acheson and H. E. Rosenberg, unpublished work.
[12] W. E. Noland and J. H. Sellstedt, *J. Org. Chem.*, 1966, **31**, 345.

OH resonance disappeared immediately D_2O was added to the solutions, while the H-3 resonances assigned to both the indole and 3*H*-indole tautomers remained visible for some time. These results are similar to those for 1-hydroxy-2-methylindole,[13] which is a stable crystalline compound, and it therefore appears that the presence of a substituent inhibits polymerisation.

1-Hydroxyindole in ether was acetylated by acetic anhydride with aqueous sodium hydrogencarbonate to give 1-acetoxyindole (4) which was stable to distillation and when pure could be stored essentially unchanged for months at −10 °C. This compound can be used as a source of 1-hydroxyindole, since treatment with methyl iodide and sodium methoxide gives 1-methoxyindole (7). 1-Ethoxyindole, previously obtained in 5% yield from triethyl phosphite and 2-substituted 2-[2-(2-nitrophenyl)vinyl]-1,3-dioxolans,[14] was prepared (77%) in the same way. Reduction of 1-methoxyindol-2-one (6) with $LiAlH_4$ also gave 1-methoxyindole, but a polymeric product was formed from a similar reduction of 1-acetoxyindolone.



	R
(7)	H
(8)	CH_2NMe_2
(9)	$CH_2\overset{+}{N}Me_3I^-$
(10)	CH_2CN
(11)	$CH_2C(CO_2Et)_2NHAc$
(12)	CHO
(13)	COMe
(14)	$COCO_2H$
(15)	CH_2CH_2COMe
(16)	$C(CN)=C(CN)_2$
(17)	$CH_2CH(NHAc)CO_2H$
(18)	CH_2NHPr^i
(19)	$CH=C(CO_2H)_2$
(20)	*E*-$CH=CHCO_2H$
(21)	$CH=CHNO_2$
(22)	$CH=CMeNO_2$
(23)	$CH_2CH_2NH_2$
(24)	$CH_2CHMeNH_2$
(25)	$CH_2CH_2NHCO_2Me$
(26)	CH_2CH_2NHMe
(27)	$CH_2CH_2NMeCO_2Me$
(28)	$CH_2CH_2NMe_2$

The ^1H n.m.r. spectra of these 1-substituted indoles are unexceptional (Table 1), resembling those of other indoles, and comparison with the spectrum of 1-(4-chlorobenzoyloxy)-2-methylindole [13] clearly identifies the H-3 resonance at τ *ca.* 3.8. Long-range coupling (0.7 Hz) between H-3 and H-7, as in indoles,[15] occurs with 1-acetoxy-6-chloroindole where the spectrum has been completely analysed, and can be observed for several of the 1-alkoxyindoles. [Eu(fod)$_3$] hardly affected the spectrum of 1-methoxyindole. The ^{13}C spectrum for this last compound is very similar to that of indole,[16] but C-3 and C-7a are more shielded (*ca.* 4 p.p.m.).

The mass spectra of 1-alkoxy- and 1-acyloxy-indoles are similar and show that initial fragmentation occurs on both sides of the 1-oxygen atom, and the u.v. spectra (Table 2) resemble those of the corresponding indoles with small shifts to longer wavelengths. The carbonyl groups of our simple acetoxyindoles have maxima at *ca.* 1 810 cm^{-1}, as reported for more complex derivatives,[17-19] which is significantly higher than that (1760—1765 cm^{-1}) of *O*-acyl-*NN*-dialkylhydroxylamines.[20] 1-Benzoyloxyindoles, however, have maxima at 1 760—1 783 cm^{-1}.[13,19,21]

TABLE 1

60-MHz n.m.r. spectra of substituted indoles (τ; *J* in Hz)

Indole substituents	Proton resonances
1-Acetoxy (4) [a]	$MeCO_2$, 7.72; H-2, H-5, H-6, H-7, 2.76—3.10; H-3, 3.69 (d); H-4, 2.48 (m) ($J_{2,3}$ 3.8)
1-Acetoxy-6-chloro [a]	$MeCO_2$, 7.70; H-2, 2.98 (d); H-3, 3.56 (dd); H-4, 2.53 (dd); H-5, 2.98 (dd); H-7, 2.85 (m) ($J_{2,3}$ 3.7; $J_{3,7}$ <1; $J_{4,5}$ 8.6; $J_{4,7}$ 0.7; $J_{5,7}$ 1.9)
1-Methoxy (7) [a]	MeO, 6.05; H-3, 3.79 (d) ($J_{2,3}$ 3.6); other protons 2.37—3.22 (m)
6-Chloro-1-methoxy [a]	1-MeO, 6.13; H-2, 2.91 (d); H-3, 3.80 (dd); H-4, 2.63 (dd); H-5, 3.05 (dd); H-7, 2.67 (d) ($J_{2,3}$ 3.4; $J_{3,7}$ 0.8; $J_{4,5}$ 8.5; $J_{4,7}$ 0.4; $J_{5,7}$ 1.8)
6-Chloro-3-(dimethylaminomethyl)-1-methoxy [a]	MeO, 6.02; H-2, 2.88; CH_2NMe_2, 6.51; CH_2NMe_2, 7.78; H-4, 2.47 (d); H-5, 3.01 (dd); H-7, 2.66 (d) ($J_{4,5}$ 8.4; $J_{5,7}$ 2.0)
1-Methoxy-3-carbaldehyde (12) [a]	MeO, 5.92; H-2, 2.21; CHO, 0.13; H-4, 1.74 (m); H-5, H-6, H-7, 2.43—2.90 (m)
1-Methoxy-3-methoxycarbonyl [a]	MeO, 5.92; H-2, 2.08; CO_2CH_3, 6.12; H-4, 1.85 (m); H-5, H-6, H-7, 2.5—2.9 (m)
6-Chloro-1-methoxy-3-carbaldehyde [a]	MeO, 5.90; H-2, 2.19; CHO, 0.11; H-4, 1.83 (d); H-5, 2.78 (dd); H-7, 2.58 (d) ($J_{4,5}$ 8; $J_{5,7}$ 2)
1-Hydroxy-3-carbaldehyde (29) [b]	H-2, 1.72; CHO, −0.22; H-4, 1.9 (m); H-5, H-6, H-7, 2.40—2.90 (m)
1-Hydroxy-3-carboxamide [c]	H-2, 1.92; $CONH_2$, H-4, 1.44—1.85; H-5, H-6, H-7, 2.38—2.92 (m)
1-Hydroxy-3-glyoxylic acid (31) [d]	H-2, 1.55; H-4, 1.8 (m); H-5, H-6, H-7, 2.45—3.0 (m)
1-Hydroxy-3-glyoxylamide [c]	H-2, 1.35; H-4, 1.65 (m); H-5, H-6, H-7, 2.4—2.87 (m)
3-Hydroxyimino-3*H*, 1-oxide [a]	H-2, 2.13; NOH, 6.8—7.4 (br); H-4, 1.82 (m); H-5, H-6, H-7, 2.35—2.59 (m)

[a] Solvent $CDCl_3$. [b] Solvent DMSO. [c] Solvent $(CD_3)_2CO$. [d] Solvent CD_3OD.

1-Methoxyindole (7) shows the chemical properties of a weakly deactivated 1-substituted indole, and is readily reduced by hydrogen over palladium–charcoal at room temperature to indole. It did not react with $NaBH_4$ in refluxing propanol, but with $LiAlH_4$ in refluxing ether a 30% conversion to indole occurred over 9 h. This type of demethoxylation has been employed [2] in the identification of the plant 1-methoxyindoles. 1-Methoxyindole slowly ($t_{\frac{1}{2}}$ *ca.* 6 h) decomposes to indole at 150 °C, while

[13] R. M. Acheson, R. G. Bolton, and I. Hunter, *J. Chem. Soc.* (*C*), 1970, 1067.
[14] R. J. Sundberg, *J. Org. Chem.*, 1965, **30**, 3604; 1968, **33**, 487.
[15] J. A. Elvidge and R. G. Foster, *J. Chem. Soc.*, 1964, 981.
[16] LeRoy F. Johnson and W. J. Jankowski, 'Carbon-13 N.M.R. Spectra,' spectrum 283, Wiley–Interscience, New York, 1972.
[17] I. P. Sword, *J. Chem. Soc.* (*C*), 1970, 1916.
[18] J. D. Loudon and I. Wellings, *J. Chem. Soc.*, 1960, 3462.
[19] J. D. Loudon and G. Tennant, *J. Chem. Soc.*, 1960, 3466.
[20] B. O. Handford, J. H. Jones, G. T. Young, and T. F. N. Johnson, *J. Chem. Soc.*, 1965, 6814.
[21] M. Colonna, L. Greci, and L. Marchetti, *Gazzetta*, 1975, **105**, 985; M. Kawana, M. Yoshioka, S. Miyaji, H. Kataoka, Y. Omote, and N. Sugiyama, *J. Chem. Soc. Japan*, 1965, **86**, 526 (*Chem. Abs.*, 1965, **63**, 11479f).

the tryptamine (28) in water at 100 °C decomposes to formaldehyde.[2] Proton abstraction from the methoxy group, and subsequent elimination of formaldehyde leading to the indolyl anion and thence to indole, accounts for these results, and also for the loss of the methoxy group from several 1-methoxyindoles under alkaline conditions. Photolysis of 1-methoxyindole in methanol under nitrogen rapidly gives a tar. Trifluoroacetic acid causes protonation, as with other indoles,[22] and the n.m.r. spectrum of the chloroform-soluble part of the resulting tar strongly suggested that a dimer corresponding to indole dimer [23] had been formed.

TABLE 2

U.v. spectra of substituted indoles in methanol

Indole substituents	$\lambda_{max.}(10^{-3}\varepsilon)$/nm
1-Methoxy (7)	218 (23.44), 270 (4.09), 288 (infl.) (3.44), 296 (2.52)
1,5-Dimethoxy	213 (11.75), 273 (5.69), 303 (2.95), 314 (infl.) (3.17)
1-Methoxy-3-carbaldehyde (12)	214 (15.49), 245 (10.72), 300 (10.38)
1-Methoxy-3-glyoxylic acid (14)	212 (13.95), 253 (4.92), 310 (5.19)
1-Methoxy-3-(tricyanovinyl) (16)	213 (9.95), 286 (2.55), 456 (6.14)
1-Methoxy-3-acrylic acid, (20)	208 (infl.) (5.07), 231 (7.59), 273 (4.34), 321 (7.13)
1-Methoxy-3-nitrovinyl, (21)	225 (9.65), 282 (4.38), 394 (10.52)
1-Hydroxy-3-carbaldehyde, (29)	213 (7.36), 245 (3.63), 255 (3.12), 308 (2.92), 350 (2.22)
1-Hydroxy-3-glyoxylic acid, (31)	222 (20.89), 245 (7.08), 255 (6.76), 313 (5.34), 395 (2.02)
1-Hydroxy-3-carboxamide	218 (13.33), 243 (6.76), 297 (4.33), 340 (1.84)
3-Hydroxyimino-3*H*, 1-oxide	237 (2.29), 302 (2.13)
3-Hydroxyimino-3*H*, 1-oxide *	249 (1.30), 258 (1.46), 295 (0.91), 285 (0.27)

* Basified.

The Mannich reaction with these 1-methoxyindoles, using the conditions recommended for indole,[24] gave excellent yields of the 3-dialkylaminomethyl derivatives [*e.g.* (8)]. The properties of 5-MeO-(8) were very similar to those reported for the same compound obtained from *Gymnacrantheria paniculata*.[1] The methiodides of (8) and its methoxy- and chloro-derivatives were obtained with 2—3 mol. equiv. of methyl iodide, while corresponding 1-unsubstituted indoles give mainly bis(indol-3-yl)methyl derivatives under these conditions.[25] The lower reactivity of the quaternary nitrogen of the methiodide (9), compared with that of gramine methiodide, to nucleophilic displacement is shown by the failure to prepare 1-methoxyindole-3-acetonitrile (10) from (9) with cyanide under a variety of conditions; instead, preferential loss of the 1-methoxy group took place. However, reaction of (9) with diethyl acetamidosodiomalonate did give (11).

Dimethylformamide and phosphoryl chloride [26] with 1-methoxyindoles gave the corresponding 3-aldehydes [*e.g.* (12)] in good yield, but the yield of the ketone (13) from the reaction with dimethylacetamide was low, and an attempt to form the 3-benzoylated product [27] was unsuccessful. In a similar way to indole,[28] the 1-methoxy-derivative reacted with oxalyl chloride to give (1-methoxyindol-3-yl)glyoxyloyl chloride, which was converted into the free acid (14) and other derivatives. Of many electron-deficient olefins examined only but-2-en-3-one,[29] tetracyanoethylene,[30] and acetamidoacrylic acid [31] reacted as for indole at position 3 and gave (15), (16), and (17), respectively. Attempts to hydrolyse (17) to 1-methoxytryptophan by base also caused elimination of the methoxy group. Bromination of 1-methoxyindole by pyridinium perbromide [32] gave what appeared to be the 3-bromo-derivative, as the resonance due to H-3 in the n.m.r. spectrum had disappeared, but the substance rapidly decomposed to a tar. Methyl iodide did not react with (7) at 100 °C in the presence of potassium carbonate, but in its absence a black tar was obtained which showed no *O*-methyl resonance in its n.m.r. spectrum; possibly a trace of acid produced by decomposition of the iodide caused the decomposition. 1-Methoxyindole was recovered unchanged from attempted coupling with 4-nitrobenzenediazonium chloride [33] and from treatment [34] with β-propiolactone at 110 °C, reagents which attack indole at the 3-position.

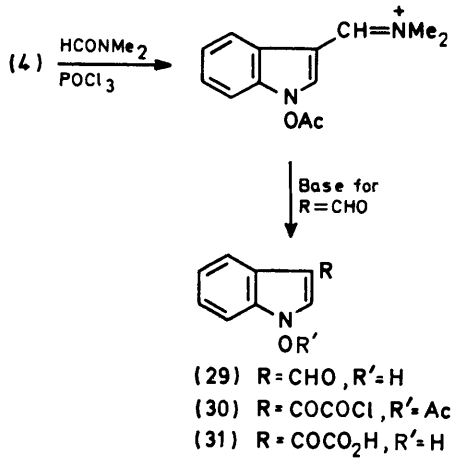
1-Methoxyindole-3-carbaldehyde (12) did not react with methoxy- or methoxycarbonylmethylenetriphenylphosphorane and failed to undergo a glycidic ester condensation, but successive treatments with primary amines and sodium borohydride [35] gave 3-aminomethyl-1-methoxyindoles [*e.g.* (18)]. The aldehyde group combined easily with a number of compounds possessing acidic methylene groups, examples being malonic acid, which can give a mixture of (19) and (20), nitromethane, and rhodanine. The nitrovinyl compounds (21) and (22) were reduced by $LiAlH_4$ to the tryptamines (23) and (24) respectively. Titanium(III) chloride [36] removed the methoxy group of (21). Attempts to oxidise 1-methoxytryptamine (23) to the 3-acetonitrile (10) by silver(II) oxide [37] and nickel peroxide [38] failed.

NN-Dimethyl-1-methoxytryptamine (28), first obtained [2] from *Lespedeza bicolor var. japonica*, was synthesised in 25% overall yield from (23) by conversion

[22] A. H. Jackson and A. E. Smith, *J. Chem. Soc.*, 1964, 5510.
[23] G. F. Smith, *Adv. Heterocyclic Chem.*, 1963, **2**, 300.
[24] H. Kuhn and O. Stein, *Ber.*, 1937, **70**, 567.
[25] T. A. Geissman and A. Armen, *J. Amer. Chem. Soc.*, 1952, **74**, 3916.
[26] G. F. Smith, *J. Chem. Soc.*, 1954, 3842.
[27] W. C. Anthony, *J. Org. Chem.*, 1960, **25**, 2049.
[28] K. N. F. Shaw, A. McMillan, A. G. Gudmundson, and M. D. Amstrong, *J. Org. Chem.*, 1958, **23**, 1171.
[29] J. Szmuszkovicz, *J. Amer. Chem. Soc.*, 1957, **79**, 2819.
[30] G. N. Sausen, V. A. Engelhardt, and W. J. Middleton, *J. Amer. Chem. Soc.*, 1958, **80**, 2815.
[31] H. R. Snyder and J. A. Macdonald, *J. Amer. Chem. Soc.*, 1955, **77**, 1257.
[32] K. Piers, C. Meimaroglou, R. V. Jardine, and R. K. Brown, *Canad. J. Chem.*, 1963, **41**, 2399.
[33] J. H. Binks and J. H. Ridd, *J. Chem. Soc.*, 1957, 2398.
[34] J. Harley-Mason, *J. Chem. Soc.*, 1952, 2433.
[35] G. N. Walker and M. A. Moore, *J. Org. Chem.*, 1961, **26**, 432.
[36] J. E. McMurry and J. Melton, *J. Org. Chem.*, 1973, **38**, 4367.
[37] T. G. Clarke, N. A. Hampson, J. B. Lee, J. R. Morley, and B. Scanlon, *Tetrahedron Letters*, 1968, 5685.
[38] K. Nakagawa and T. Tsuji, *Chem. and Pharm. Bull.* (*Japan*), 1963, **11**, 296.

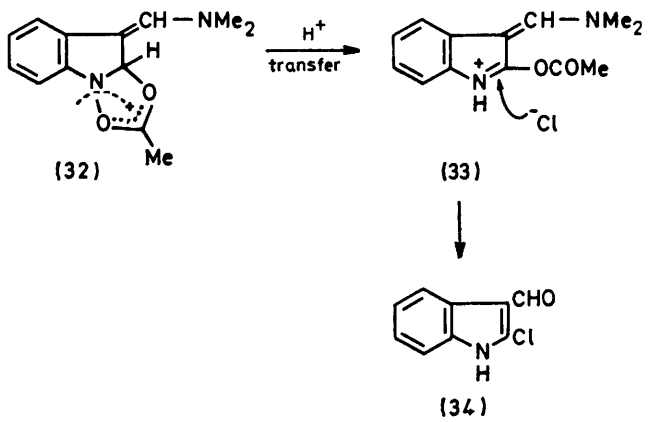
into the carbamate (25) with methyl chloroformate, reduction to (26) by $LiAlH_4$, and repetition of the two steps.

1-Acetoxyindole (4) with dimethylformamide and



(29) R = CHO, R' = H
(30) R = COCOCl, R' = Ac
(31) R = $COCO_2H$, R' = H

phosphoryl chloride lost the acetyl group and yielded mainly 2-chloroindole-3-carbaldehyde (34) along with some of the 1-hydroxyaldehyde (29). The chloroaldehyde might be formed as outlined in Scheme 1;



SCHEME 1

indolin-2-one gives [39] 2-chloroindole with phosphoryl chloride, possibly *via* an intermediate similar to (33). A cyclic intermediate (32) is preferred to an alternative 1,2-shift, as 1-chloroindole rearranges to 3-chloroindole [40] and treating ethyl 3-cyano-1-hydroxyindole-2-carboxylate with tosyl chloride and triethylamine causes rearrangement to the 3-tosyloxy-3*H*-indole.[41]

Oxalyl chloride, and chloroglyoxylic esters, attacked 1-acetoxyindole at the 3-position [to give *e.g.* (30)] and after aqueous acid work-up the acid (31) was obtained. Attempts to reduce this acid, or the amide, with $LiAlH_4$, gave unstable products. The acid, with hydroxylamine hydrochloride in methanol, gave the nitrile (36) in high yield in 6 h, but it decomposed to a green solid at 60 °C. In the presence of sodium hydrogencarbonate the reaction took 36 h, the nitrile (36) was now a minor product, and the major product was indole-3-carbonitrile oxide (40). A concerted decarboxylation of the oxime (35) *via* a cyclic transition state would give (36) while decomposition of the anion (39) as indicated (Scheme 2) leads to a product which by proton exchange gives the nitrile oxide (40). These reactions correspond to the decarboxylation of acetoacetic acid where the acid decomposes about fifty times faster than the anion.[42] Although nitrile oxides are very reactive and usually dimerise on attempted isolation, structure (40) could be stabilised by resonance (38) and this is consistent with the low value (2 240 cm^{-1}) for ν(CN) in the i.r. compared with other nitrile oxides [43] (2 290 cm^{-1}). The i.r. spectrum shows no OH stretch, and the u.v. and n.m.r. spectra are consistent with structure (40). The mass spectrum of (40) showed remarkable similarities with that of 1-acetoxyindole-3-carbonitrile (37), obtained as an unstable light-sensitive oil from (4) with chlorosulphonyl isocyanate and triethylamine.[44] The 1-acetoxy-compound (37) lost the fragment CH_2CO, confirmed by a metastable transition, to give the base peak at *m/e* 158, which was also the base peak and molecular ion of (40). From this point the fragmentation patterns were almost identical, the first significant losses being those of O and OH. Alkaline hydrolysis of the nitrile oxide (40) gave indole-3-carboxylic acid; had the compound been indol-3-yl cyanate indigo would have been expected and indol-3-yl isocyanate has different properties [45] from (40).

Hydrolysis of the nitrile (37) by hydrogen peroxide, or aqueous M-sodium hydroxide gave 1-hydroxyindole-3-carboxamide, while 10M-sodium hydroxide gave 1-hydroxyindole-3-carboxylic acid. The n.m.r. and i.r. spectra of a freshly prepared sample of the acid were consistent with the formulation proposed. The compound decomposed rapidly at room temperature, in contrast to 1,4-dihydroxyquinolin-2(1*H*)-one,[13] once thought [46] to be this acid, to give a green solid suspiciously like that formed from 1-hydroxyindole, but the freshly prepared acid with diazomethane gave methyl 1-methoxyindole-3-carboxylate.

1-Acetoxyindole with pyridinium perbromide gave a very unstable product, the n.m.r. spectrum of which was consistent with it being 3-bromo-1-hydroxyindole, while with pentyl nitrite and sodium ethoxide 3-hydroxyimino-3*H*-indole 1-oxide was obtained and identified from its spectra.

It may be concluded that while 1-methoxyindoles, as a group, can be fairly easily handled in the absence of alkali, or fairly strong acid, this is not the case for 1-

[39] J. C. Powers, *J. Org. Chem.*, 1966, **31**, 2627.
[40] M. De Rosa, *J.C.S. Chem. Comm.*, 1975, 482.
[41] P. G. Gassman, G. A. Campbell, and G. Mehta, *Tetrahedron*, 1972, **28**, 2749.
[42] E. M. P. Widmark, *Acta Med. Scand.*, 1920, **53**, 393.
[43] R. H. Wiley and B. J. Wakefield, *J. Org. Chem.*, 1960, **25**, 546.
[44] H. Vorbrüggen, *Tetrahedron Letters*, 1968, 1631.
[45] N. N. Suvorov, V. S. Velezheva, A. V. Yarosh, Yu. V. Erofeev, and T. N. Kozik, *Khim. geterotsikl. Soedinenii*, 1975, **11**, 1099 (*Chem. Heterocyclic Compound*, 1975, **11**, 959).
[46] V. Askam and R. H. L. Deeks, *J. Chem. Soc.* (*C*), 1968, 1243.

hydroxyindoles unless some stabilising factor is available. This can be an alkyl or aryl group at position 2 (which can sterically inhibit polymerisation), intramolecular hydrogen bonding as in 1-hydroxyindole-2-carboxylic acid, or a firmly attached electron-attracting group in the five-membered ring.

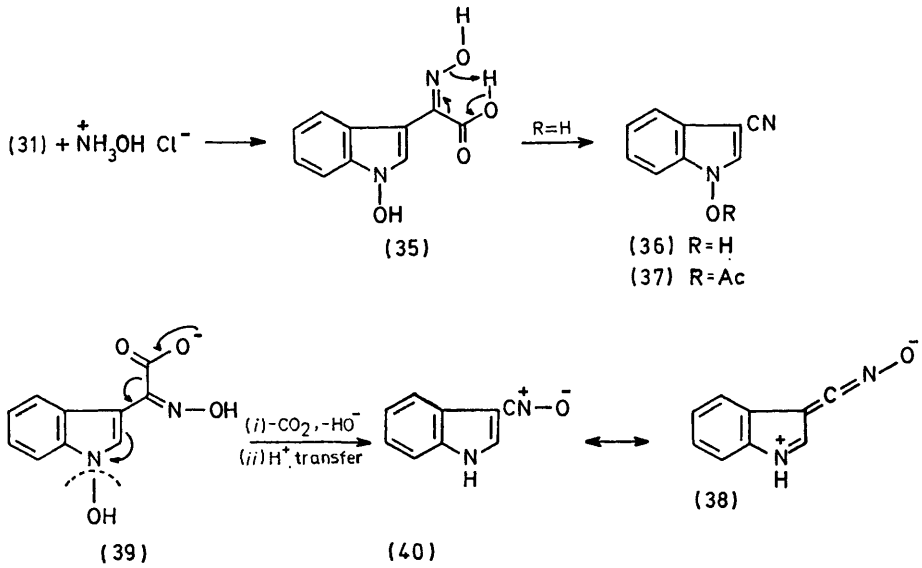
EXPERIMENTAL

The instruments and general procedures employed here have been noted earlier.[47] U.v., mass, and n.m.r. spectra and analytical data for new compounds not noted in the paper are available in Supplementary Publication No. SUP 22287.*

5'-Methoxy-2'-nitroacetanilide.—The following method gave a much better yield than that previously reported.[48] Nitric acid (*d* 1.42; 50 ml) dissolved (30 min) in acetic anhydride (250 ml) at 0 °C was added over 1 h to a vigorously stirred ice-cooled suspension of 3'-methoxyacetanilide (100 g) in acetic anhydride (400 ml) kept below 18 °C. After 5 min the mixture was poured into crushed ice (*ca.* 2 kg), and after 2 h the precipitate (64—81 g) was filtered off and dried. Repeated extraction with boiling light petroleum (b.p. 100—120 °C) gave 5'-methoxy-2'-nitroacetanilide (42—50 g) as long yellow needles, m.p. 121—123 °C (lit.,[48] 125 °C). This was refluxed (3 h) in 12M-hydrochloric acid (600 ml); addition of water (1 l) then precipitated 5-methoxy-2-nitroaniline (51 g), m.p. 126—128 °C (lit.,[48] 129 °C), of sufficient purity for the next stage.

1-Chloro-4-(2-nitrophenyl)but-2-ene (1).—This was obtained as described [12] in 85—95% yield, and was essentially pure (n.m.r.) and could be used in the next stage without distillation; on one occasion the compound exploded towards the end of a distillation (b.p. 112—114 °C at 0.05 Torr); τ(CDCl$_3$) 6.35(d) (ClCH$_2$); 3.85—4.70(m) (CH=CH); 6.00(d) (CH$_2$); 2.60(m) (3-H); and 2.4—2.8(m) (4-, 5-, 6-H$_3$). By the same procedure the following were prepared from the appropriate nitroanilines: *1-chloro-4-(4-chloro-2-nitrophenyl)but-2-ene* (89—98% yield), b.p. 116—118 °C at 0.03 Torr, yellow plates, m.p. 38.5 °C (from methanol); 1-chloro-4-(4-methoxy-2-nitrophenyl)but-2-ene (52%), b.p. 148—152 °C at 0.05 Torr, which could not be obtained analytically pure; *1-chloro-4-(5-methoxy-2-nitrophenyl)but-2-ene* (80%), which decomposed on attempted distillation, but after elution from alumina with toluene was obtained pure (n.m.r.) as a yellow oil, m.p. 20 °C (from methanol, at −70 °C); 2-chloro-5-(2-nitrophenyl)hex-3-ene (from hexa-2,4-diene [49] and 2-nitroaniline) (28%), b.p. 130—140 °C at 0.05 Torr, which was not obtained analytically pure.

2-Nitrophenylacetaldehyde (2).—(i) 1-Chloro-4-(2-nitrophenyl)but-2-ene (10 g) in ethyl acetate (100 ml) was cooled to −78 °C and ozonised (4—5%) oxygen bubbled (18 l h^{-1}) through for 135 min. The brown solution became pale green after 2 h. Oxygen was then bubbled through (15 min) to remove ozone, sodium iodide (28 g) in glacial acetic acid (28 g) was added, the cold bath was removed, and stirring was continued until room temperature was reached. Saturated aqueous sodium thiosulphate (*ca.* 150 ml) was added until the iodine colour had disappeared. The combined organic layer, and ether extracts (3 × 50 ml) of the aqueous phase, were washed with saturated aqueous sodium hydrogencarbonate until effervescence ceased, then with saturated sodium chloride, dried, and evaporated (precipitated sulphur being filtered off), to give 2-nitrophenylacetaldehyde as an orange oil (7.5 g) which showed no impurities in its n.m.r. spectrum. (ii) 1-Chloro-4-(2-nitrophenyl)but-2-ene (53 g) in ether (500 ml) and water (500 ml) was treated with osmium(VIII) oxide (0.5 g) in ether (*ca.* 20 ml) and powdered sodium periodate (118 g). The mixture was stirred vigorously (*ca.* 24 h) until a sample from evaporation of the ether layer showed no i.r. band at 1 250 cm^{-1} (due to NO$_2$) or doublets in the n.m.r. corresponding to the methylene protons of the butene. The mixture was filtered and the residue washed with ether. The ether layer and the ether



SCHEME 2

* See Notice to Authors No. 7 in *J.C.S. Perkin I*, 1977, Index issue.

[47] R. M. Acheson and D. F. Nisbet, *J. Chem. Soc.* (*C*), 1971, 3291.

[48] F. Reverdin and K. Widmer, *Ber.*, 1913, **46**, 4066.

[49] R. Adams and T. A. Geissman, *J. Amer. Chem. Soc.*, 1939, **61**, 2083.

washings of the residue and aqueous layer were combined, washed with saturated aqueous sodium hydrogencarbonate (250 ml), water (250 ml), and saturated brine (250 ml), dried ($MgSO_4$), and evaporated *in vacuo* to give 2-nitrophenylacetaldehyde (2) as a brown oil (38 g), which decomposed on attempted distillation *in vacuo*; $\tau(CDCl_3)$ 0.31 (CHO), 5.98 (CH_2), 2.0(m) (3-H), and 2.1—2.9(m) (4-,5-,6-H_3); $\nu_{max.}$ 1 730s, 1 615, 1 580, 1 525s, 1 350s, 940, 860, and 790. The 2,4-dinitrophenylhydrazone, yellow crystals (from MeOH–EtOH) had m.p. 150—152 °C (lit.,[50] 150—153 °C). *4-Methoxy-2-nitrophenylacetaldehyde* [4-MeO-(2)] was prepared by the above method, but with an oxidation time of 48 h (60% yield): the *2,4-dinitrophenylhydrazone*, orange crystals (90% aqueous EtOH), had m.p. 145—149 °C. *5-Methoxy-2-nitrophenylacetaldehyde* [5-MeO-(2)] was obtained by method (ii) above (24 h) in *ca.* 60% yield; the *2,4-dinitrophenylhydrazone*, orange crystals (from ethanol), had m.p. 166—169 °C. *4-Chloro-2-nitrophenylacetaldehyde* [4-Cl-(2)] was obtained by method (ii) above (*ca.* 65% yield) after 24 h; the *2,4-dinitrophenylhydrazone*, orange crystals (from ethanol) had m.p. 155—160 °C.

1-Acetoxyindole (4).—(*a*) Unpurified 2-nitrophenylacetaldehyde (15.6 g) in ether (500 ml) was added to zinc powder (40 g), ammonium chloride (7 g), and water (100 ml) in a 2-l three-necked flask. Careful stirring initiated reaction (ether refluxed), and the reaction rate was controlled by reducing the stirring rate and/or adding ice. Samples (5 min intervals) of the ether layer were evaporated to dryness, and when the residues no longer showed a carbonyl absorption at 1 730 cm^{-1} the reaction was stopped (*ca.* 45 min). After filtration the ether layer (containing 1-hydroxyindole) was combined with ether washings (400 ml) of both the residue and aqueous layer and added to a mixture of sodium hydrogen carbonate (100 g) and water (100 ml). Acetic anhydride (40 ml) was added, and the mixture was shaken occasionally over 12 h, and filtered. The ether layer was washed with 10% aqueous sodium hydrogencarbonate (6 × 25 ml), then saturated aqueous sodium chloride, and dried ($MgSO_4$). Distillation gave *1-acetoxyindole* as an orange oil, b.p. 75—77 °C at 0.015 Torr (6.8—12.6 g), *m/e* 176 (10%), 175 (50), 147 (11), 146 (10), 145 (12), 144 (13), 135 (10), 134 (32), 133 (84), 132 (48), 131 (84), 130 (86), 129 (22), 128 (24), 127 (26), 119 (10), 118 (94), 117 (100), 116 (86), 115 (18), 114 (12), 105 (36), 104 (68), 103 (46), 102 (30), 101 (10), 93 (16), 92 (10), 91 (60), 90 (72), 89 (66), 88 (28), 87 (27), 86 (20), 85 (10), 78 (60), 77 (72), 76 (36), 75 (29), 74 (26), 66 (10), 65 (42), 64 (60), 63 (77), 62 (68), 61 (28), and 60 (40); $\nu_{max.}$ 1 810s, 1 450m, 1 368m, 1 321m, 1 220w, 1 170s, 1 120m, 1 075m, 1 032m, 835m(br), and 740s, best results being obtained when the distillation was carried out in minimum light, and when the aldehyde had been prepared by ozonolysis. An ethereal solution (10 ml) containing 1-hydroxyindole (*ca.* 0.5 g) was added to 4-chlorobenzoyl chloride (0.9 g) in pyridine (7.5 ml); after stirring (12 h) saturated aqueous sodium hydrogen carbonate (100 ml) was added and stirring was continued (2 h). Filtration, extraction with ether, and evaporation of the washed and dried extract gave as the first fraction 4-chlorobenzoyl chloride (0.2 g) followed by *1-(4-chlorobenzoyloxy)indole*, beige crystals (0.44 g) (from ether), m.p. 110—111 °C. *1-Acetoxy-6-chloroindole*, b.p. 110—114 °C at 0.04 Torr, plates (from aqueous 5% ethanol), m.p. 70—71 °C, was obtained (52%) from crude 4-chloro-2-nitrophenylacetaldehyde as described above; 5-methoxy- and 6-methoxy-1-acetoxyindole, obtained similarly but as red oils, were not purified since the latter compound decomposed vigorously on attempted distillation.

(*b*) Acetic anhydride (2.4 ml) was added to 1-hydroxyoxindole (1.67 g)[51] in pyridine (2 ml); the mixture was stirred (12 h), treated with ice (8 g), and brought to pH 6 (2-M HCl). Extraction with ether, evaporation of the washed (aqueous $NaHCO_3$) dried extract, and recrystallisation (from aqueous ethanol) of the residue gave *1-acetoxyoxindole* (1.56 g) as prisms, m.p. 100—101 °C. Reduction with $LiAlH_4$, as for 1-methoxyoxindole, gave a polymeric green solid.

1-Methoxyindole (7).—(*i*) 1-Acetoxyindole (1.75 g) dissolved in a solution of sodium methoxide [from sodium (0.23 g)] in methanol (50 ml) at room temperature was stirred for 30 min, methyl iodide (1.5 g) in methanol (5 ml) being added over 20 min. After 12 h water (2 J ml) was added, the mixture was extracted with ether (4 × 150 ml), and the extracts were washed with brine, dried, and distilled to give *1-methoxyindole* (1.04 g) as a yellow oil, b.p. 47—48 °C at 0.035 Torr; ^{13}C n.m.r. ($CDCl_3$; p.p.m. from internal $SiMe_4$) OCH_3, 65.5; C-2, 122.3; C-3, 97.9; C-3a, 124.3; C-4, 121.2; C-5, 122.3; C-6, 120.0; C-7, 108.2; and C-7a, 131.8 (all assignments were confirmed by off-resonance experiments); $\nu_{max.}$ 1 530s, 1 450m, 1 350m, 1 323m, 1 220m, 1 075m, 1 035s, 960m, and 740s; *m/e* 147 (100%), 132 (78), 118 (27), 117 (78), 116 (70), 90 (35), 89 (47), 77 (27), 63 (25), and 43 (20). Higher-boiling fractions of large-scale preparations contained indole. In a similar way *6-chloro-1-methoxyindole* (67% yield), b.p. 55—56 °C at 0.03 Torr; 1,5-dimethoxyindole [5-MeO-(7), 19%], b.p. 75—85 °C at 0.04 Torr; and *1,6-dimethoxyindole* [6-MeO-(7), 17%], b.p. 75—85 °C at 0.04 Torr, were obtained. Using ethanol and ethyl iodide under similar conditions gave 1-ethoxyindole (77%), b.p. 55—56 °C at 0.035 Torr, and *6-chloro-1-ethoxyindole* (79%), b.p. 64—65 °C at 1.01 Torr.

(*ii*) 1-Methoxyoxindole (6) (0.5 g) was stirred into a suspension of $LiAlH_4$ (0.117 g) in ether (10 ml) during 10 min; stirring was continued for 15 min, and water (10 ml) was added carefully. After filtration the ether layer, and ether extracts of the solid and aqueous phases, were dried and the ether was evaporated off *in vacuo* to give a red oil containing (n.m.r.) only indole and 1-methoxyindole. Chromatography on silica gel and elution with toluene gave 1-methoxyindole (0.27 g), identical (n.m.r. and i.r.) with that described under (*i*).

1-(2-Diethylaminoethoxy)indole.—1-Acetoxyindole (1.75 g), followed by *NN*-diethyl-2-chloroethylamine hydrochloride (1.72 g), was added with stirring to a solution of sodium ethoxide [from sodium (0.46 g)] in ethanol (50 ml) below 18 °C, and stirring was continued (18 h). The product was dissolved in water (200 ml), the pH was adjusted to 7.8 with HCl, and the mixture was extracted with ether. The aqueous phase was basified (pH 12—13) and extracted with ether (4 × 150 ml) and the combined ether extracts washed (aqueous NaCl), dried, and distilled to give 1-(2-diethylaminoethoxy)indole (1.58 g, 68%) as a red-brown viscous oil, b.p. 80—82 °C at 0.005 Torr; the *dipicrate* (from methanol) had m.p. 122—123 °C. The 6-chloro-analogue, prepared similarly (71%) had b.p. 90—92 °C at 0.05 Torr, and formed a *picrate* (from methanol), m.p. 132—133 °C.

Mannich Reactions with 1-Methoxyindoles.—3-Dialkyl-

[50] H. Bredereck, G. Simchen, and R. Wahl, *Chem. Ber.*, 1968, **101**, 4048.

[51] W. B. Wright, jun., and K. H. Collins, *J. Amer. Chem. Soc.*, 1956, **78**, 221.

aminomethyl-1-alkoxyindoles were obtained from the appropriate indoles with formaldehyde and the secondary amine using the procedure of Kuhn and Stein [24] on a 0.5—5.0 g scale (Table 3). The methiodides were obtained by refluxing with methyl iodide in methanol. Characterisable products were not obtained from attempted Mannich reactions with 1-acetoxyindole and its 6-chloro-derivative.

Diethyl 2-Acetamido-2-(1-methoxyindol-3-ylmethyl)malonate (11).—Finely powdered sodium (0.35 g) was stirred overnight with dry dioxan (25 ml) and diethyl acetamidomalonate (3.4 g) in an oil-bath at 105 °C. 3-Dimethylaminomethyl-1-methoxyindole methiodide (9) (5.0 g) was added and the mixture stirred at 110 °C (20 h) and then at 125—130 °C (6 h). After cooling, the combined filtrate, and dioxan washings of the insoluble material gave, on evaporation *in vacuo*, a red oil which slowly solidified at 0 °C. Recrystallisation (50% aqueous EtOH) gave *diethyl 2-acetamido-2-(1-methoxyindol-3-ylmethyl)malonate* (11) (2.95 g) as plates, m.p. 127—130 °C.

1-Methoxyindole-3-carbaldehyde (12).—Freshly distilled $POCl_3$ (5 ml) was added dropwise to a stirred, ice-cooled flask containing dry dimethylformamide (17.5 ml). 1-Methoxyindole (7.35 g) in dry dimethylformamide (5 ml) was added (1 h); the mixture was kept at 45 °C for 1 h and treated with ice–water (*ca.* 100 ml). The resulting orange solution was extracted with ether (3 × 50 ml); the extracts were discarded, and the stirred aqueous layer treated with sodium hydroxide (9.5 g) in water (50 ml) during 10 min. Heating to *ca.* 80 °C (1—2 min), cooling, extraction with ether (4 × 100 ml), and distillation of the washed and dried extract gave *1-methoxyindole-3-carbaldehyde* (12) (7.0 g, 80%) as a pale orange oil, b.p. 109—110 °C at 0.06 Torr; the *thiosemicarbazone*, pale brown needles from 60% aqueous ethanol, had m.p. 187—188 °C (decomp.); the *oxime*, white needles from 50% aqueous ethanol, had m.p. 140—143 °C (sublimes).

6-Chloro-1-methoxyindole-3-carbaldehyde [6-Cl-(12)].—The above reaction on a one-fifth scale using 6-chloro-1-methoxyindole gave a solid mixture which did not dissolve in ice–water; boiling with sodium hydroxide had no visible effect, but filtration gave crude *6-chloro-1-methoxyindole-3-carbaldehyde* (86%), off-white needles (from EtOH), m.p. 150—151 °C; the *thiosemicarbazone*, pale buff plates from 60% aqueous ethanol, had m.p. 190—192 °C (decomp.).

3-Acetyl-1-methoxyindole (13).—Using the literature conditions [27] for the preparation of 5-benzyloxy-3-acetylindole but with 1-methoxyindole (7.35 g) instead of 5-benzyloxyindole, and the same work-up as for 1-methoxyindole-3-carbaldehyde, 1-methoxyindole (4.0 g) was obtained in the first ether extract while the second yielded a brown oil (3.5 g). Chromatography on alumina (100 ml) (eluant toluene) gave *3-acetyl-1-methoxyindole* (13) as off-white crystals (1.8 g), which after recrystallisation from ethyl acetate–toluene (1 : 1) had m.p. 76—79 °C; the *thiosemicarbazone*, pale brown needles from 50% aqueous ethanol, had m.p. 186—188 °C (decomp.).

N-Acetyl-1-methoxytryptophan (17).—This compound was prepared exactly as described for *N*-acetyltryptophan [52] using 1-methoxyindole (1.47 g), except that as the final acidified solution gave no precipitate it was extracted with chloroform (5 × 50 ml) and the extracts were dried and evaporated to give a brown oil (1.3 g). This was left *in vacuo* over NaOH until the odour of acetic acid had disappeared (2 days), and then dissolved in hot chloroform (*ca.* 2 ml); ether (10 ml) was added and the process repeated on the resultant solid to give *N-acetyl-1-methoxytryptophan* (17) (0.7 g) as pale brown crystals, m.p. 156—159 °C.

1-(1-Methoxyindol-3-yl)butan-3-one (15).—Methyl vinyl ketone (90%; 2.5 g) was added to 1-methoxyindole (1.47 g) in acetic acid (6 ml) and acetic anhydride (2 ml). The mixture was heated to 100 °C (5 h), cooled, poured into water, and extracted with ether. Evaporation of the washed (aq. M-NaOH), dried extract gave an oil which was chromatographed on deactivated alumina. Elution with toluene gave the ketone, b.p. 130—140 °C at 0.05 Torr, as a yellow oil, pure by n.m.r. and t.l.c., but neither a good analysis nor a crystalline derivative could be obtained.

1-Methoxy-3-(1,2,2-tricyanovinyl)indole (16).—1-Methoxyindole (0.73 g) and tetracyanoethylene (0.64 g) were swirled in acetone (5 ml), whereupon the solution rapidly blackened. After several days at room temperature the acetone had evaporated to give a dark brown solid, which after recrystallisation (acetic acid, then ethanol) gave *1-methoxy-3-(1,2,2-tricyanovinyl)indole* (16) as dark brown crystals (0.8 g), m.p. 147.5—150.5 °C.

(1-Methoxyindol-3-yl)glyoxylic Acid (14).—Freshly distilled oxalyl chloride (1.9 g) was added (20 min) to a stirred, ice-cooled solution of 1-methoxyindole (2.9 g) in dry ether

TABLE 3

1-Alkoxy-3-dialkylaminomethylindole derivatives

Dialkylamino-group	Alkoxy-group	Other substituents	Yield (%)	Derivative	Solvent	Appearance	M.p. (°C)
Me_2N	MeO		86	Picrate	EtOH	Yellow plates	143.5—144.5
				Methiodide	MeOH	Cubes	173—175
Me_2N	MeO	5-MeO	91	Picrate	EtOH	Yellow needles [a]	151—152
Me_2N	MeO	6-Cl	64	Picrate	MeOH	Yellow plates	172
				Methiodide	MeOH	Crystals	195—199 (decomp.)
Piperidino	MeO		*ca.* 100	Methiodide	MeOH	Crystals	164—167 (decomp.)
4-Me-Piperazin-1-yl	MeO		97	Dipicrate	EtOH–MeOH	Powder	200 (decomp.)
				Dimaleate	80% aqueous EtOH	Buff crystals	173—176
Me_2N	EtO			Picrate	EtOH	Yellow	118—122
4-Me-Piperazin-1-yl	EtO		57	Dipicrate [b]		Orange	225—227
4-Me-Piperazin-1-yl	EtO	6-Cl	62	Dipicrate [b]		Yellow	*ca.* 250

[a] Lit.[2] 154—155°; none of the isomorphous red crystals were observed. [b] Too insoluble for recrystallisation. Precipitated from methanolic solutions of the reagents.

[52] H. R. Snyder and C. W. Smith, *J. Amer. Chem. Soc.*, 1944, **66**, 350.

(20 ml) to give the acid chloride, and after stirring (1 h) the mixture was basified to pH 12—13 with M-KOH (*ca.* 100 ml). The aqueous layer was washed with ether (3 × 20 ml), then stirred in an ice-bath with ethyl acetate (70 ml), and acidified to pH 1—2 with 6M-HCl. The organic layer and ethyl acetate (2 × 100 ml) extracts of the aqueous layer were combined, washed with saturated brine, dried, and evaporated. The residue (3.0 g) was dissolved in boiling ethanol (25 ml), and poured into hot water (125 ml); cooling to 0 °C gave (*1-methoxyindol-3-yl)glyoxylic acid* (14) (2.2 g), pale pink needles, recrystallised from acetone–cyclohexane (1 : 2), m.p. 163—165 °C.

Aqueous ammonia (10%; 50 ml) was added dropwise to a stirred solution of 1-methoxyindole-3-glyoxyloyl chloride in ether, prepared as above from 1-methoxyindole (1.47 g). After stirring (15 min) filtration gave (*1-methoxyindol-3-yl)glyoxylamide* (0.83 g), pale buff crystals (from ethanol), m.p. 214—216 °C.

(*1-Methoxyindol-3-yl)glyoxylohydrazide.*— 1-Methoxyindole (0.73 g) and ethyl chloroglyoxylate (0.7 g) were stirred in ether (10 ml) (3 d). Evaporation gave a black tar yielding ethyl 1-methoxyindole-3-glyoxylate as a brown oil (0.9 g), after chromatography on alumina and elution with ethyl acetate. This was boiled in methanol (10 ml) with hydrazine hydrate (0.5 ml) and on cooling gave *1-methoxyindole-3-glyoxylohydrazide* (0.32 g) (fawn plates from methanol), m.p. 190—195 °C (decomp.).

Reaction of 1-Methoxyindole-3-carbaldehyde (12) *with Primary Amines followed by Sodium Borohydride.*—Using a procedure for preparing 3-alkylaminomethylindoles,[35] the following were obtained: 1-methoxy-3-(isopropylaminomethyl)indole (18), red oil (60% yield), the *1-naphthylthiocarbamoyl* derivative, needles (from ethanol), m.p. 157—159 °C; *1-methoxy-3-(2-thiazol-2-ylaminomethyl)indole* (30% yield), off-white crystals (from ethanol), m.p. 143.5—145 °C.

1-Methoxyindole-3-carbaldehyde (12) *with Malonic Acid.*—The aldehyde (0.87 g), malonic acid (1.56 g), and piperidine (0.1 ml) in dry pyridine (8 ml) were maintained at 45 °C (45 h). The residue obtained after removal of solvent *in vacuo* was diluted with water (10 ml), brought to pH 11 with M-NaOH, and extracted with ethyl acetate (3 × 50 ml). The aqueous phase was acidified (to pH 2) with 6M-HCl and the precipitate (0.88 g) was dissolved in boiling ethyl acetate. The solution was filtered and cooled to give (*1-methoxyindol-3-yl)methylenemalonic acid* (19), yellow-brown needles (0.17 g), m.p. 180—185 °C (decomp.). The mother-liquor yielded *1-methoxyindole-3-acrylic acid* (20), yellow crystals [from cyclohexane–ethyl acetate (2 : 1)] (0.47 g), m.p. 145—148 °C. A similar experiment with a heating period of 5 days gave only the acrylic acid (70%).

1-Methoxy-3-(2-nitrovinyl)indole (21).—1-Methoxyindole-3-carbaldehyde (4.0 g), ammonium acetate (0.8 g), and nitromethane (16 ml) were heated at 100 °C (30 min) with occasional swirling. Filtration, evaporation *in vacuo*, and titration with methanol gave *1-methoxy-3-(2-nitrovinyl)-indole* (21), as orange needles from methanol (2.5 g), m.p. 105—106 °C.

1-Methoxy-3-(2-nitroprop-1-enyl)indole (22).—The above method, using nitroethane and heating for 3 h, gave the *nitropropenyl compound* (22) as orange-yellow prisms (52%) (from methanol), m.p. 118—120 °C.

4-(1-Methoxyindol-3-ylmethylene)-2-phenyloxazol-5-one.—This compound was prepared from the 3-carbaldehyde by the literature procedure [53] as yellow *needles* (28%) [from methanol–acetone (1 : 1)], m.p. 192—195 °C.

[(1-Methoxyindol-3-yl)methylene]rhodanine.—This compound was obtained by the above method using rhodanine (1 equiv.) [53,54] and by extracting the diluted reaction mixture with chloroform; orange crystals (15%) (from methanol), m.p. 201—205 °C (decomp.).

3-(2-Aminoethyl)-1-methoxyindole (23).—1-Methoxy-3-(2-nitrovinyl)indole (21) (1.0 g) was extracted from a Soxhlet thimble into a suspension of $LiAlH_4$ (1.0 g) in refluxing ether (300 ml) during 1 h. The mixture was refluxed (1 h), cooled, quenched with water (5 ml), stirred (15 min), filtered, and dried, and the ether was distilled off to give 3-(2-aminoethyl)-1-methoxyindole (0.4—0.7 g) as a colourless, hygroscopic, and slightly fluorescent oil, b.p. 106—112 °C at 0.05 Torr; the *1-naphthylthiocarbamoyl derivative*, white crystals (from methanol), had m.p. 167—168 °C.

3-(2-Aminopropyl)-1-methoxyindole (24).—The above method with 1-methoxy-3-(2-nitropropenyl)indole (22) gave the amine (60%), b.p. 105—115 °C at 0.1 Torr; the *1-naphthylthiocarbamoyl derivative*, off-white crystals (from ethanol), had m.p. 145—146 °C.

1-Methoxy-3-[2-(methylamino)ethyl]indole (26).—Using a known procedure,[55] 3-(2-aminoethyl)-1-methoxyindole (23) (12.4 g) with methyl chloroformate (12.2 g) gave crude methyl *N*-[2-(1-methoxyindol-3-yl)ethyl]carbamate (25) as an orange oil (21 g). This in dry ether (50 ml) was added to $LiAlH_4$ (8.0 g) in dry ether (600 ml) and the mixture was refluxed (11 h), cooled, treated dropwise with water (*ca.* 30 ml), stirred for 20 min, and filtered. The filtrate was dried and distilled. 1-Methoxy-3-(2-methylaminoethyl)-indole (26) was obtained as a colourless oil (5.6 g), b.p. 105—120 °C at 0.05 Torr; the *1-naphthylthiocarbamoyl derivative*, white needles (from ethanol), had m.p. 128—130 °C.

3-[2-(Dimethylamino)ethyl]-1-methoxyindole (28).—The above method [55] applied to 1-methoxy-3-(2-methylaminoethyl)indole (26) (5.1 g) and methyl chloroformate (4.7 g) gave the carbamate (27) as an orange oil (5.94 g); this in dry ether (20 ml) was added to $LiAlH_4$ (3.0 g) in dry ether (250 ml) and the mixture refluxed (2 h). Work-up as above gave 3-(2-dimethylaminoethyl)-1-methoxyindole (28) (3.15 g, 40%) as a colourless liquid with a violet fluorescence, b.p. 100—106 °C at 0.08 Torr (lit.,[2] 113—114 °C at 0.28 Torr); the picrate, orange rhombs from methanol, had m.p. 161—164 °C [lit.,[2] 160—162 °C (decomp.)]; the styphnate, yellow plates (from methanol), had m.p. 170—172 °C [lit.,[2] 169—170 °C (decomp.)].

1-Acetoxyindole (4) *with Dimethylformamide.*—1-Acetoxyindole (1.75 g) in dry dimethylformamide was added over 30 min with stirring to a mixture of freshly distilled $POCl_3$ (1 ml) and dimethylformamide (3 ml) kept below 10 °C (ice-bath),[56] and the mixture was then heated to 45 °C (1 h), and to 85 °C (1 h). Sodium hydroxide (0.45 g) in water (10 ml) was added, and the mixture was boiled (2—3 min), cooled, and poured onto crushed ice (20 g); extraction with ether (3 × 25 ml) yielded mainly tar. The aqueous phase was acidified (to pH < 1) with concentrated HCl, extracted

[53] A. F. Ames, D. E. Ames, C. R. Coyne, T. F. Grey, I. M. Lockhart, and R. S. Ralph, *J. Chem. Soc.*, 1959, 3388.
[54] *cf.* C. Gränacher, M. Gerö, and V. Schelling, *Helv. Chim. Acta*, 1924, **7**, 575.
[55] J. K. Horner and W. A. Skinner, *Canad. J. Chem.*, 1966, **44**, 315.
[56] K. E. Schulte, J. Reisch, and V. Stoess, *Angew. Chem. Internat. Edn.*, 1965, **4**, 1081.

with ether (3 × 25 ml, extract A), and brought to pH 6—8 with concentrated NaOH; a precipitate (1.51 g) formed which was filtered off, and the filtrate on ether extraction yielded a little more of the solid along with dimethylformamide. The solid yielded 2-chloroindole-3-carbaldehyde (34) (1.04 g), needles (from aqueous ethanol), m.p. 224—226 °C (lit.,[56] 223—225 °C). Extract A was washed (aqueous NaCl), dried, and evaporated to give 1-*hydroxyindole*-3-*carbaldehyde* (29), orange-red crystals (0.1 g) (from acetone–cyclohexane), m.p. 146—150 °C.

1-*Acetoxy*-6-*chloroindole* [6-Cl-(4)] *with Dimethylformamide*.—This acetoxyindole (2.1 g), exactly as above, gave some 6-chloro-1-hydroxyindole-3-carbaldehyde, identified by its n.m.r. spectrum, and 2,6-*dichloroindole*-3-*carbaldehyde*, brown needles (1.41 g) (from aqueous ethanol), m.p. 238—239 °C.

(1-*Hydroxyindol*-3-*yl*)*glyoxylic acid* (31).—Oxalyl chloride (0.9 ml) in ether (5 ml) was dropped into a stirred solution of 1-acetoxyindole (4) (1.75 g) in ether (10 ml) during 10 min in the absence of light. The reaction was set aside overnight, then the pH was adjusted to 11 by the addition of aqueous M-KOH (*ca.* 30 ml) to the suspension of the acid chloride. The ether-extractable material was discarded, and after addition of ethyl acetate (50 ml) the mixture was acidified to pH 2. The ethyl acetate-soluble portion yielded (1-*hydroxyindol*-3-*yl*)*glyoxylic acid* (1.5 g), brick-red needles (from ethanol or water), m.p. 189—191 °C (decomp.). The methyl ester, m.p. 158—160 °C, obtained by addition of methanol to the acid chloride, could not be obtained analytically pure. Ammonia gas was passed through an ether suspension of the acid chloride [from 1-acetoxyindole (1.75 g)] for 15 min. Water (50 ml) was added, the pH was adjusted to 10 (with aqueous NaOH), and ether extracts (2 × 20 ml) were discarded. The aqueous phase, brought to pH 4, was extracted with ethyl acetate (4 × 40 ml); evaporation of the washed (aqueous NaCl), dried extracts gave 1-*hydroxyindole*-3-*glyoxylamide* (1.9 g), yellow needles (from 50% aqueous methanol), m.p. 195—197 °C (decomp.).

(1-*Hydroxyindol*-3-*yl*)*glyoxylic Acid with Hydroxylamine*.—(i) The acid (0.5 g) and hydroxylamine hydrochloride (0.75 g) in methanol (25 ml) were refluxed for 5 h, then cooled; water (50 ml) was added and the solution extracted with chloroform (4 × 20 ml). The washed, dried, extract was evaporated to a red tar (0.6 g) which after chromatography on a silica (50 ml) column and elution with ether gave 1-hydroxyindole-3-carbonitrile (36) as a thick yellow oil (0.34 g). It decomposed to a green solid in a few days at room temperature and rapidly at *ca.* 60 °C.

(ii) The acid (1.0 g), hydroxylamine hydrochloride (0.5 g), and sodium hydrogencarbonate (0.6 g) were refluxed together in methanol (50 ml) for 36 h, the solvent was removed, and the residue dissolved in aqueous 0.05M-NaOH (20 ml). The solution was washed with ether (discarding the washings), acidified, and extracted with ether. The washed (aqueous NaCl), dried extract was evaporated to dryness. Chromatography on silica (eluant ethyl acetate) gave first 1-hydroxyindole-3-carbonitrile (0.13 g), and then *indole*-3-*carbonitrile oxide* (40) (0.32 g), needles (from water), m.p. 124—126 °C; τ H-2, 2.38; H-4, 2.40—2.87(m); $\lambda_{max.}$ (MeOH) 232 (ε 15 000), 251 (7 500), and 340 (3 000). Compound (40) (5 mg) was refluxed in aqueous 10M-NaOH for 12 h; the solution was acidified, and extracted with ethyl acetate. T.l.c. of the evaporated extract gave a substance which was indistinguishable (by t.l.c.) from indole-3-carboxylic acid using EtOAc–AcOH (9 : 1; R_F 0.56), EtOAc–MeOH (9 : 1; R_F 0.60), and EtOAc–PhMe (1 : 1; R_F 0.35); (40) had R_F 0.65, 0.72, and 0.70, respectively.

1-*Acetoxyindole*-3-*carbonitrile* (37).—Chlorosulphonyl isocyanate (0.87 ml) in dry acetonitrile (10 ml) was added dropwise with stirring to 1-acetoxyindole (1.75 g) in acetonitrile (10 ml) at 0 °C; stirring was continued for 4 h. Triethylamine (0.95 g) in acetonitrile (5 ml) was added, and the mixture was stirred at room temperature for 2 h, treated with water, and extracted with ether (3 × 20 ml). The combined, washed (brine), dried, extracts on evaporation gave the nitrile (37) (1.6 g), which slowly solidified at −15 °C. Distillation gave a yellow oil, b.p. 115—117 °C at 0.05 Torr, which solidified (m.p. 82—83 °C). The very light-sensitive compound gave satisfactory spectra, but a good analysis could not be obtained.

1-*Hydroxyindole*-3-*carboxamide*.—(i) Hydrogen peroxide (30%; 1.2 ml) was added dropwise to the nitrile (37) (0.6 g) dissolved in aqueous M-NaOH (7 ml) and ethanol (10 ml) at 0 °C with stirring. After 1 h at 0 °C, and 3 h at 50 °C, water was added, and the mixture was cooled, acidified, and extracted with ether. Evaporation of the washed (brine), dried extracts gave a tar, which on extraction with boiling water (20 ml) followed by concentration gave 1-*hydroxyindole*-3-*carboxamide* (0.21 g), green-brown rods, m.p. 181—182 °C (decomp.) (ii) Refluxing the nitrile (37) with aqueous M-NaOH for 12 h gave a poorer yield of the same carboxamide.

1-*Hydroxyindole*-3-*carboxylic Acid*.—The nitrile (37) (0.8 g) was refluxed with aqueous 10M-NaOH for 12 h, and the cooled solution was washed with ether. The aqueous phase was acidified and extracted with ether. The washed (brine) and dried ether was evaporated off to give 1-hydroxyindole-3-carboxylic acid (0.49 g) as a pale orange solid, m.p. 135—137 °C (decomp.), pure by n.m.r. but rapidly darkening; attempted recrystallisation gave a green solid. The acid (0.1 g) with an excess of diazomethane in ether (12 h) gave *methyl* 1-*methoxyindole*-3-*carboxylate* (0.08 g), as a red oil; t.l.c. gave prisms (from chloroform), m.p. 40—41 °C.

3-*Hydroxyimino*-3H-*indole* 1-*Oxide*.—Pentyl nitrite (0.79 ml) was added to 1-acetoxyindole (1.0 g) in a solution of sodium ethoxide [from sodium (0.14 g)] in ethanol (10 ml) with stirring at 0 °C, and the mixture was set aside overnight at −15 °C. After dilution with water (50 ml) and ether extraction (3 × 50 ml), acidification of the aqueous phase precipitated 3-*hydroxyimino*-3H-*indole* 1-*oxide* (0.8 g), yellow-green needles (from water), m.p. 167—169 °C (sublimes *ca.* 150 °C).

We thank the S.R.C. for a studentship (D. M. L.) and Lady Richards for the ^{13}C spectrum.

[7/1218 *Received*, 11*th July*, 1977]