Some Products from Nitrosation of Indoles

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Nitrosation of 1-methylindole with an equimolar amount of nitrous acid gave 5-hydroxy-6,11-dimethylpyrrolo-[2,3-*b*:4,5-*b*']di-indole, and with an excess of nitrous acid 5,11-dimethylpyrazino[2,3-*b*:5,6-*b*']di-indole 6-oxide. Nitrosation of 1-methylindol-3-yl phenyl sulphide gave diphenyl disulphide (23%), 1-methyl-2,3-bis(phenylthio)indole (2.5%), 1-methyl-2-nitroindol-3-yl phenyl sulphide (13%), 1-methyl-3,3-bis(phenylthio)-indolin-2-one (8%), and 1-methyl-3-nitroindole (6%). The formation of these products from nitrosation can be explained by initial electrophilic attack on both free and 3-substituted indoles at the 3-position.

In connection with studies on the deoxygenation of indolyl *o*-nitrophenyl sulphides [1] we were interested in the preparation of indolyl phenyl sulphides bearing a nitroso-group adjacent to the sulphur atom. Whereas nitro-compounds typically require 3 h heating with triethyl phosphite at 160 °C for deoxygenation, the corresponding reaction of nitroso-compounds proceeds rapidly at 0 °C.[2]

It was considered unlikely that the preparation of indolyl *o*-nitrosophenyl sulphides would be successful (*cf.* ref. 3), so we decided to study the nitrosation of the readily available 1-methylindol-3-yl phenyl sulphide (1a) (from 1-methylindole and benzenesulphenyl chloride [4]). Nitrosation of indoles by nitrous acid normally occurs at the 3-position [5] as expected and gives true nitroso-compounds when the 1-position is substituted. Thus nitrosation of 1,2-diphenylindole gives the 3-nitroso-indole,[6] whereas 2-*p*-methoxyphenylindole affords the isonitroso-compound (2); [7] in each case a high yield is obtained.

A number of examples of the displacement of indole 3-substituents by electrophiles [8,9] are known, and since it was considered possible that the phenylthio-group in (1a) might be lost during nitrosation, the nitrosation of 1-methylindole was first reinvestigated. This reaction was originally described by Fischer and Hess,[10] who obtained an uncharacterised greenish-yellow product. In the present work, two products were obtained, the proportions of which were dependent on the amount of nitrous acid used. With approximately equimolar amounts of nitrous acid and indole an emerald green crystalline solid was obtained (*ca.* 40% yield); the mass spectrum showed a molecular ion base peak of *m/e* 289.1209 ($C_{18}H_{15}N_3O$) and an abundant ion (85%) at *m/e* 272.1195 ($C_{18}H_{14}N_3$). The ^1H n.m.r. spectrum showed two non-equivalent NMe groups. The structure (4) was confirmed by synthesis from 2,3'-bi-indole,[11] by treatment of its *NN*-dimethyl derivative with nitrous acid. Formation of the *N*-hydroxypyrrole (4) from 1-methylindole can be explained by nucleophilic attack of unchanged 1-methylindole on 1-methyl-3-nitrosoindole and subsequent oxidation (presumably by nitrous acid) of the intermediate (3).

A second, less soluble yellow crystalline compound ($\lambda_{max.}$ 256, 262, 293infl., 296, and 424 nm) was obtained in very minor amounts. High resolution mass spectrometry revealed the molecular formula $C_{18}H_{14}N_4O$; satisfactory microanalyses were not obtained (possibly

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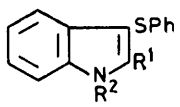
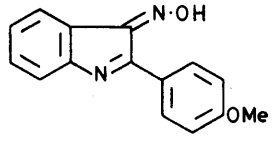
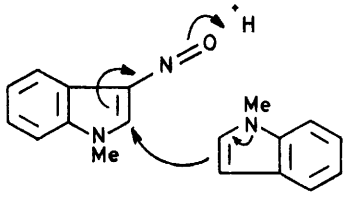
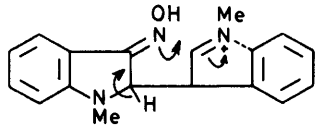


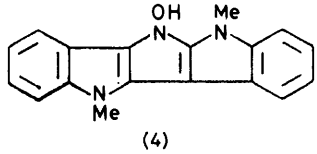
(1) a; R^1=H, R^2=Me
b; R^1=SPh, R^2=Me
c; R^1=NO_2, R^2=Me
d; R^1=NO_2, R^2=H



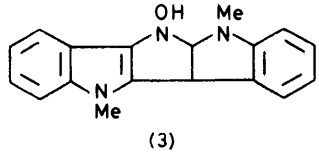
(2)







(4)



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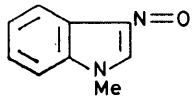
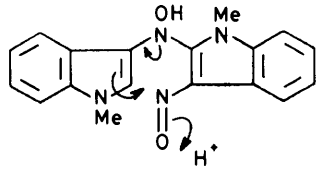
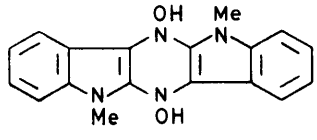
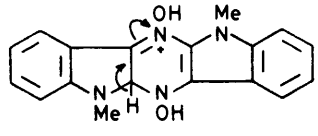
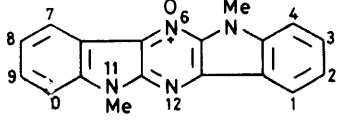




(5)







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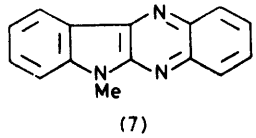
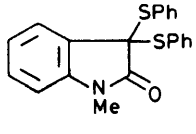


(7)



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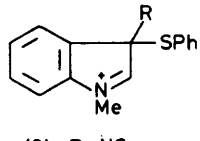
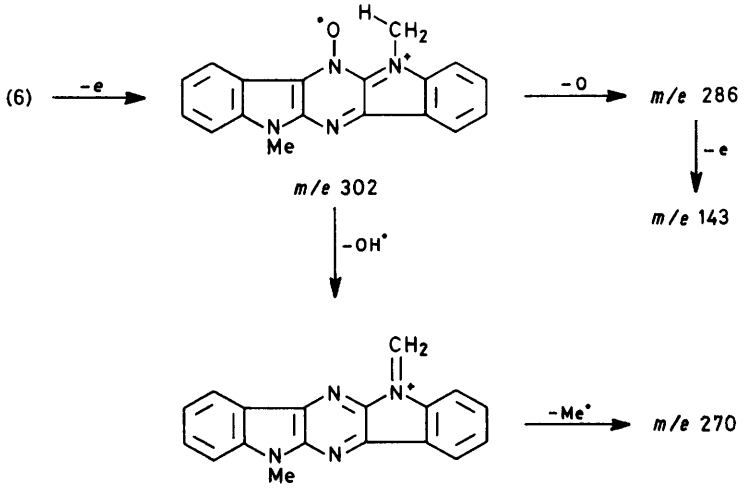


(9) R=NO
(10) R=SPh

owing to the high nitrogen content) but we were satisfied (on the basis of repeated crystallisations and u.v. analyses) of the product's essential homogeneity. The n.m.r. spectrum of a dilute solution in dimethyl sulphoxide showed two singlets at τ 5.53 and 5.50 corresponding to *N*-methyl groups as well as a multiplet for the aromatic protons. The only reasonable structure in view of the mass and n.m.r. spectra and its mode of formation is the pyrazinodi-indole *N*-oxide (6). Symmetrical variations of this structure are ruled out by the occurrence of two different *N*-methyl resonances. These *N*-methyl resonances occur at lower field than those of the *N*-methyl groups of the pyrrolodi-indole (4) (τ 6.02 and 6.09) and of *N*-methylcarbazole (τ 6.08) presumably because of the electron-withdrawing effect of the *N*-oxide group. The electronic spectrum is in accord with structure (6) and

Nitrosation of 1,3-dimethylindole gave a complex mixture from which no pure products were isolated. 1-Methylindol-3-yl phenyl sulphide, however, on nitrosation gave five products which were separated by chromatography. The least polar was shown to be diphenyl disulphide by comparison with an authentic sample. Next was eluted 1-methyl-2,3-bis(phenylthio)-indole (1b), characterised from its indole-like u.v. spectrum, strong molecular ion peak at *m/e* 347 and base peak at *m/e* 238 (*M* — SPh) in the mass spectrum.

The mass spectrum of the third (orange) product indicated (M^+ 284) that it was a nitro-derivative of 1-methylindol-3-yl phenyl sulphide. The n.m.r. spectrum showed no signals below τ 2.56, whereas the lowest field signal in the spectrum of the starting material (1a) is at τ 2.43. This revealed that the nitro-group was on neither of the



SCHEME

the complexity is reminiscent of many other polycyclic aromatic compounds. No precise model was found in the literature but the yellow quinazolinoindole [12] (7) prepared from *N*-methylisatin and *o*-phenylenediamine by Mr. P. W. Taylor in our laboratories has a similarly complex and intense spectrum ($\lambda_{max.}$ 272, 278, 340, 354, and 402 nm) and the *N*-methyl resonance is at τ 6.07. The mass spectral fragmentations of the pyrazine *N*-oxide (6) are also in accord with the structure assigned. The base peak at *m/e* 285 corresponds to loss of OH and this could be accounted for by the cyclic fragmentation process shown in the Scheme.

The pyrazine *N*-oxide (6) is probably derived from dimerisation of 1-methyl-3-nitrosoindole, by initial electrophilic attack at the indole 3-position followed by migration of the 3-hydroxyaminoindolyl group to give the intermediate (5), which subsequently undergoes cyclisation and dehydration. In keeping with this is the fact that the pyrazine *N*-oxide (6) was obtained as the sole indolic product (3.5%) when 1-methylindole was treated with a large excess of nitrous acid, the major product being *N*-methylanthranilic acid.

benzene rings nor in the indole 3-position, since the latter would be expected to result in a marked low-field shift [13] of the indole 4-proton resonance. This product was therefore identified as 1-methyl-2-nitroindol-3-yl phenyl sulphide (1c).

Indol-3-yl phenyl sulphide on treatment with benzoyl nitrate (*cf.* ref 14) gave 2-nitroindol-3-yl phenyl sulphide (1d), whose u.v. spectrum ($\lambda_{max.}$ 347 nm) showed a bathochromic shift to 389 nm in alkali. This shift was very similar to that shown by 3-methyl-2-nitroindole [14] ($\lambda_{max.}$ 347—390 nm) kindly provided by Professor Da Settimo. The indole (1d), on *N*-methylation gave (1c), identical with the product obtained by nitrosation of (1a).

The fourth product from nitrosation of (1a) showed an oxindole-like u.v. spectrum. Its mass and other spectra were consistent with its identification as 1-methyl-3,3-bis(phenylthio)indolin-2-one (8), confirmed by an alternative synthesis from benzenesulphenyl chloride and 1-methyloxindole.

The most polar product from the chromatography was 1-methyl-3-nitroindole, having properties identical with those reported.[9]

[12] S. M. Badger and P. J. Nelson, *J. Chem. Soc.*, 1962, 3926.
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[14] G. Berti, A. Da Settimo, and E. Nannipieri, *J. Chem. Soc.* (*C*), 1968, 2145.

The formation of most of these products may be rationalised in terms of an intermediate species (9) resulting from electrophilic attack at the indole 3-position, which undergoes loss of the benzenesulphenium ion or 3 ⟶ 2 migration of the N=O group. Thus, 1-methyl-3-nitroindole and 1-methyl-2-nitroindol-3-yl phenyl sulphide respectively result directly after oxidation. The benzenesulphenium ion, released from (9), may attack the starting material (1a) leading to a second intermediate (10), rearrangement of which leads directly to (1b) or, after attack by water and oxidation, affords the oxindole (8).

EXPERIMENTAL

U.v. spectra were determined with a Unicam SP 800 or Cary 17 instrument, n.m.r. spectra with a Perkin-Elmer R14 or R32 instrument, and mass spectra with a Varian CH5D instrument (electron impact at 50 μA and 70 eV, and field desorption with a carbon fibre-coated tungsten emitter at wire currents in the 10—20 μA range and source temperatures 50—150 °C). M.p.s were determined with a hot-stage apparatus.

Nitrosation of 1-*Methylindole.—Method A.* 1-Methylindole (0.65 g, 5 mmol) in glacial acetic acid (6 ml) was added to sodium nitrite (3.5 g, 50 mmol) in water (5 ml) and glacial acetic acid (25 ml) at −2 °C. The solution was allowed to warm to 25 °C and kept at this temperature for 17 h. Water was added dropwise to precipitate a solid, which was recrystallised from dimethyl sulphoxide to give 5,11-*dimethylpyrazino*[2,3-b:5,6-b′]*di-indole* 6-*oxide* (6) (20 mg, 3.5%), m.p. 292—297°, $\lambda_{max.}$ (EtOH) 256 (ε 19 400), 262 (18 600), 293infl. (47 600), 296 (47 800), and 424 nm (13 100), τ [$(CD_3)_2SO$] 5.43 (s, NMe) and 5.50 (s, NMe), *m/e* 302 (M^+, 22%), 286(60), 285(100), 270(15), and 143(23) [Found: *m/e* 302.1156 and 285.1129. $C_{18}H_{14}N_4O$ requires *M*, 302.1168, $C_{18}H_{13}N_4$ (*M* − OH) requires 285.1140].

Method B. 1-Methylindole (2.6 g, 20 mmol) in glacial acetic acid (100 ml) was treated with stirring with sodium nitrite (1.6 g, 23 mmol) in water (2 ml) at 20 °C. After 15 min the solution was poured into water (600 ml) and extracted with ether (6 × 100 ml) then chloroform (3 × 100 ml). The ethereal extract was washed with sodium hydrogen carbonate solution (saturated; 2 × 50 ml) and water (50 ml), and allowed to evaporate slowly to give a light green solid (0.27 g); recrystallisation (×4 from pyridine) afforded a small quantity (22 mg) of the *N*-oxide (6), m.p. 292—297° (decomp.). The chloroform extract was washed with water (3 × 200 ml), dried, and evaporated to give a solid, which was washed with ethanol and dried at 60 °C giving 5-*hydroxy*-6,11-*dimethylpyrrole*[2,3-b:4,5-b′]*di-indole* (4) as a bright green solid (0.7 g, 28%), m.p. 242°, $\lambda_{max.}$ 282 (ε 22 000), 368 (12 000), and 399infl. nm (10 400), τ [$(CD_3)_2SO$] 1.73—1.95 (1 H, m, ArH), 1.81 (1 H, s), 2.20—2.39 (3 H, m, ArH), 2.52—2.87 (4 H, m, ArH), 6.02 (3 H, s, NMe), and 6.09 (3 H, s, NMe), *m/e* 289 (M^+, 100%), 272(85), and 257(33) (Found: *M*, 289.1209. $C_{18}H_{15}N_3O$ requires *M*, 289.1215).

Nitrosation of 1,1′-*Dimethyl*-2,3′-*bi-indole.*—2,3′-Biindole [11] (1.2 g, 0.005 mol) was added under nitrogen to a stirred suspension of powdered potassium hydroxide (2.4 g, 0.04 mol) in dimethyl sulphoxide (30 ml), giving a deep green solution which turned deep blue on exposure to air. After ¼ h methyl iodide (2.8 g, 0.04 mol) was added and the resulting solution poured into water (100 ml) and extracted with ether (4 × 25 ml). The extract was washed with water (4 × 20 ml), dried ($CaCl_2$), and evaporated. The residual oil, in glacial acetic acid (40 ml), was cooled to −2 °C before dropwise addition of sodium nitrite (0.35 g, 5 mmol) in water (3 ml) with stirring. The resultant blood-red solution was allowed to warm to 20 °C and maintained at this temperature for ½ h before the acetic acid was removed under reduced pressure. The residue was stirred with methanol for 2 h at 20 °C, filtered off, and washed with methanol until the washings were pale yellow. Recrystallisation from dimethyl sulphoxide–water gave 5-hydroxy-6,11-dimethylpyrrolo-[2,3-*b*:4,5-*b*′]di-indole (4) (0.88 g, 61%), m.p. 237—238°, identical with samples prepared by nitrosation of 1-methylindole.

1-*Methylindol*-3-*yl Phenyl Sulphide* (1a).—1-Methylindole (2.62 g, 0.02 mol) in dry ether (50 ml) and pyridine (1.58 g, 0.02 mol) was treated with benzenesulphenyl chloride [from benzenethiol [4] (2.2 g, 0.02 mol)] with stirring at 25 °C. Water (50 ml) was added and the ether layer separated, dried (Na_2SO_4), and evaporated. The residue was recrystallised from ethanol–water giving 1-*methylindol*-3-*yl phenyl sulphide* (1a) as crystals (2.2 g; 94%), m.p. 91°, $\lambda_{max.}$ 284 (ε 6 700) and 290 nm (5 700), τ($CDCl_3$) 2.37 (1 H, d, *J* 11 Hz, indole 4-H), 2.67—3.37 (9 H, m, ArH), and 6.32 (3 H, s, NMe), *m/e* 239 (M^+, 100%) (Found: C, 75.7; H, 5.6; N, 5.8. $C_{15}H_{13}NS$ requires C, 75.3; H, 5.5; N, 5.85%).

Nitrosation of the Sulphide (1a).—1-Methylindol-3-yl phenyl sulphide (1a) (2.39 g, 10 mmol) in glacial acetic acid (50 ml) was cooled and stirred during dropwise addition of sodium nitrite (0.83 g, 12 mmol) in water (1.2 ml) so that the temperature remained between 0 and 5 °C. The temperature was kept at 5 °C for 1 h then at 20 °C for a further 1 h. Nitric oxide was evolved. Ether (150 ml) was added and the solution washed with water (4 × 100 ml), saturated sodium hydrogen carbonate solution (3 × 50 ml), and water (100 ml) before drying (Na_2SO_4) and removal of the solvent. The residual red oil was extracted with ether (20 ml) and light petroleum (150 ml) and the solvent removed under reduced pressure to give an orange-red oil (2.6 g), which was chromatographed on alumina (150 g). Elution with ether–light petroleum (1 : 9) gave (*a*) diphenyl disulphide (0.25 g, 23%), m.p. 61° (lit.,[15] 61°); (*b*) 1-methyl-2,3-bis(phenylthio)indole (1b) (60 mg, 2.5%), m.p. 107°, $\lambda_{max.}$ 243infl. (ε 39 600), 298 (19 000), and 307 nm (15 600), τ($CDCl_3$) 2.24—3.42 (14 H, m, ArH) and 6.22 (3 H, s, NMe), *m/e* 347 (M^+, 79%), 238(100), and 223(83). Elution with ether–light petroleum (1 : 3) afforded 1-*methyl*-2-*nitroindol*-3-*yl phenyl sulphide* (1c) (370 mg, 13%), m.p. 105°, $\lambda_{max.}$ 250 (ε 12 400), 347 (8 300), and 416 nm (4 500), τ($CDCl_3$) 2.56—3.25 (9 H, m, ArH), and 6.10 (3 H, s, NMe), *m/e* 284 (M^+, 100%), 237(26), 222(73), 219(24), 205(54), and 191(20) (Found: C, 63.5; H, 4.05; N, 9.6. $C_{15}H_{12}N_2O_2S$ requires C, 63.4; H, 4.25; N, 9.85%). Ether–light petroleum (9 : 11) eluted 1-*methyl*-3,3-*bis*(*phenylthio*)*indolin*-2-*one* (8) (300 mg, 8%), m.p. 120.5—121°, identical with a sample prepared from 1-methyloxindole (see below). Ether–light petroleum (4 : 1) eluted 1-methyl-3-nitroindole (70 mg, 6%), m.p. 155.5—156.5° (lit.,[9] 156—157°).

Nitration of Indol-3-*yl Phenyl Sulphide.*—Silver nitrate (8.5 g, 0.050 mol) in dry acetonitrile (50 ml) was treated with stirring at 0 °C with benzoyl chloride (6.4 g, 0.046 mol) over 20 min. To this solution was added indol-3-yl phenyl sulphide [16] (8.6 g, 0.036 mol) in dry acetonitrile (30 ml) at

[15] F. Krafft and W. Vorster, *Ber.*, 1893, **26**, 2813.
[16] P. P. Lynch, Ph.D. Thesis, University of Liverpool, 1970.

−5 °C with stirring. The mixture was allowed to warm to 20 °C and maintained at this temperature for ½ h before being poured into water and extracted with benzene (6 × 50 ml). The extract was washed with saturated sodium hydrogen carbonate solution (50 ml), dried (Na_2SO_4), and concentrated to 10 ml. Ether (100 ml) was added and the mixture extracted with 2M-sodium hydroxide (400 ml). The aqueous layer was washed with ether (4 × 100 ml) and neutralised with 4M-hydrochloric acid, and the resulting yellow emulsion extracted with ether (3 × 100 ml). After drying and removal of solvent the crude product was chromatographed on a column of alumina (type H; 200 g). Elution with ether–light petroleum (3 : 1) gave *2-nitroindol-3-yl phenyl sulphide* (1d) (0.30 g, 3.2%), m.p. 154—155°, $\lambda_{max.}$ 249 (ε 17 200), 347 (13 300), and 415 nm (5 800), $\lambda_{max.}$ (NaOH—EtOH) 256 (ε 20 800) and 389 nm (14 600), τ($CDCl_3$) 0.31 (1 H, s, NH) and 2.43—3.08 (9 H, m, ArH), *m/e* 270 (M^+, 100%), 223(63), 205(38), and 177(50) (Found: C, 62.1; H, 3.8; N, 10.0. $C_{14}H_{10}N_2O_2S$ requires C, 62.2; H, 3.75; N, 10.35%).

Methylation of 2-Nitroindol-3-yl Phenyl Sulphide (1d).—The nitroindolyl sulphide (1d) (0.135 g, 0.50 mmol) and powdered potassium hydroxide (0.13 g, 2.0 mmol) were stirred together in dimethyl sulphoxide (4 ml) for ½ h at 25 °C before addition of methyl iodide (0.14 g, 1.0 mmol) and stirring for a further ¾ h. The mixture was treated with water (20 ml) and extracted into ether (3 × 10 ml). After drying ($CaCl_2$) the solvent was removed and the residue crystallised from ethanol–water to give 1-methyl-2-nitroindol-3-yl phenyl sulphide (1c) (0.12 g, 85%), m.p. 105°, mixed m.p. 105°, identical with the sample from nitrosation of 1-methylindol-3-yl phenyl sulphide (see above).

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