

Autoxidation of 3,3'-Dimethyl-2,2'-bi-indolyl

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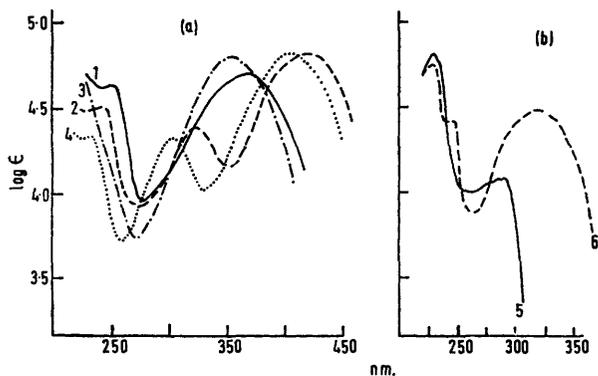
The product obtained during dehydrogenation of 3-methyl-2-(3-methylindolin-2-yl)indole (1) with chloranil is shown to be 3-methyl-2-(3-methylindol-2-yl)-3*H*-indol-3-ol (4), which is produced *via* 3-hydroperoxy-3-methyl-2-(3-methylindol-2-yl)-3*H*-indole (3). The hydroperoxide results from the autoxidation of 3,3'-dimethyl-2,2'-bi-indolyl (2). Further autoxidation of the bi-indolyl (2) produces *NN'*-bis-(2-acetylphenyl)oxamide (10).

IN the dehydrogenation of 3-methyl-2-(3-methylindolin-2-yl)indole (1) with chloranil in boiling xylene, a yellow colour developed on prolonged heating and a small amount of a yellow product (A) was isolated. This material, $C_{18}H_{16}N_2O$, exhibited an intense u.v. absorption (see the Figure, spectrum 1) in neutral ethanol,

Reduction of the compound with sodium borohydride yielded a colourless product (B), $C_{18}H_{18}N_2O$, which contained the NH and OH groups (i.r.) and had a u.v. spectrum in neutral ethanol (Figure, spectrum 5) typical of an indole, and very similar to that of the indole (1). The absorption of compound (B) in acid solution was remarkably different (see spectrum 6). The change was irreversible, and a new product was isolated from the acidic solution. This product, m.p. 156—159°, was identical with 3,3'-dimethyl-2,2'-bi-indolyl (2), obtained from the dehydrogenation of the indole (1) with chloranil in benzene.² The acid-catalysed conversion of the reduced product (B) into the bi-indolyl (2) was accompanied by the loss of 1 mol. equiv. of water from the product, and is readily understood in terms of structure (5) for compound (B). This structure also accounts for the indole-like absorption of the product. Compound (A) therefore appears to be the 3*H*-indole (4).

The conversion of the indolinylindole (1) into the hydroxy-3*H*-indole (4) is unlikely to be a direct process. Since dehydrogenation with chloranil in benzene is known² to yield 2,2'-bi-indolyl (2), it would appear that this is an intermediate, which may be expected to yield the hydroperoxy-3*H*-indole (3) on prolonged heating under reflux, owing to the propensity of 2,3-disubstituted indoles for autoxidation.³ The hydro-

³ (a) R. J. S. Beer, L. McGrath, and H. Robertson, *J. Chem. Soc.*, 1950, 2118, 3283; (b) R. J. S. Beer, T. Donavanik, and A. Robertson, *J. Chem. Soc.*, 1954, 4139; (c) B. Witkop, J. P. Patrick, and M. Rosenblum, *J. Amer. Chem. Soc.*, 1951, **73**, 2188, 2196, 2641; (d) F. McCapra and Y. C. Chang, *Chem. Comm.*, 1966, 522.



U.v. spectra: (a) — spectrum 1; ---- spectrum 2; - · - · - spectrum 3; · · · · spectrum 4; (b) — spectrum 5; ---- spectrum 6

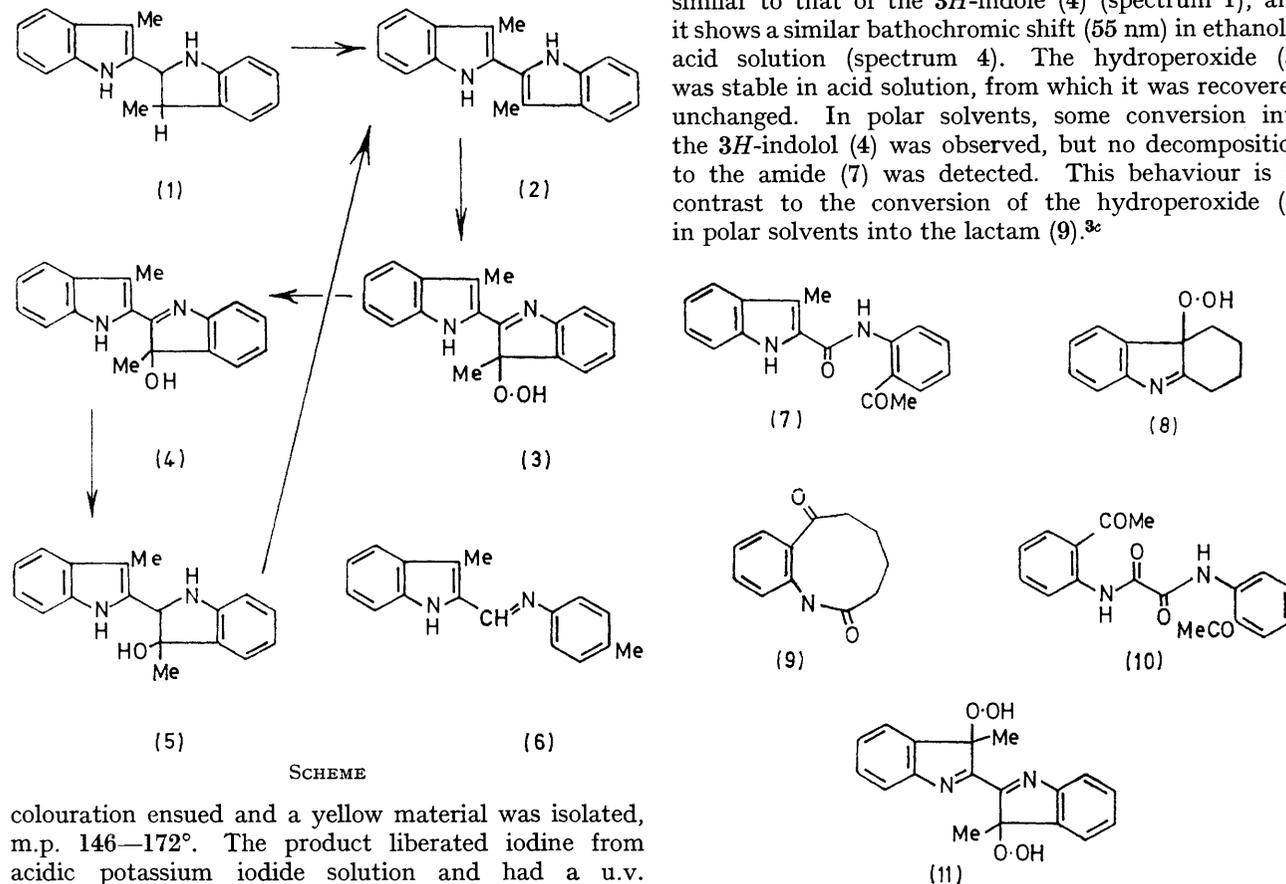
which underwent a bathochromic shift of 50 nm on acidification (spectrum 2). The absorption could not be correlated with any known chromophore. The i.r. spectrum¹ showed the presence of both NH and OH groups.

¹ A. Walters, M.Sc. Thesis, Manchester, 1958.

² G. Berti, A. Da Settimo, and D. Segnini, *Tetrahedron Letters*, 1960, **26**, 13.

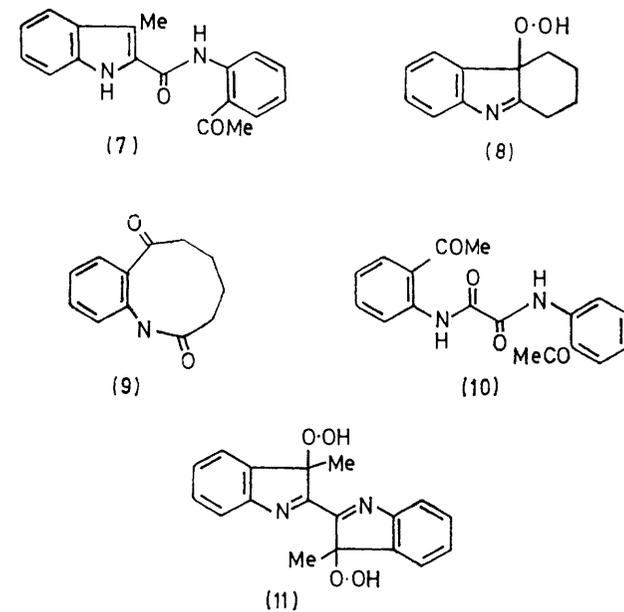
peroxide would then decompose into the hydroxy-3*H*-indole (4), the isolated product (see the Scheme). This reaction scheme was verified as follows.

When a solution of the 2,2'-bi-indolyl (2) in light petroleum was boiled under reflux for 4 h, a yellow



colouration ensued and a yellow material was isolated, m.p. 146–172°. The product liberated iodine from acidic potassium iodide solution and had a u.v. absorption identical with that of the alcohol (4), the proposed dehydrogenation product. Further heating produced another yellow product, m.p. 164–180°, which although possessing the same u.v. absorption as the first material, no longer liberated iodine. Treatment of 2,2'-bi-indolyl (2) with oxygen in the presence of a platinum catalyst gave a yellow product, m.p. 146–155°, which liberated iodine but which after attempted recrystallisation showed a larger melting range and no longer liberated iodine readily. The hydroperoxide (3) was successfully synthesised when a solution of the 2,2'-bi-indolyl (2) in ethyl acetate–light petroleum containing a crystal of benzoyl peroxide was left open to the atmosphere. After 6 h, a quantitative yield of the hydroperoxide (3) was isolated. The i.r. spectrum of (3) showed the presence of an NH and a strongly hydrogen bonded OH group, and the u.v. absorption was identical with that of compound (A) (Figure, spectrum 1). An iodometric titration confirmed the presence of one hydroperoxy-group. Catalytic hydrogenation gave the hydroxy-indoline (5), which produced the 2,2'-bi-indolyl (2) on treatment with acid. Mild reduction of the hydroperoxide with sodium

dithionite gave a product identical with the hydroxy-3*H*-indole (4). The identity of the chromophore in (4) was established by the synthesis of *N*-(3-methylindol-2-ylmethylene)-*p*-toluidine (6), whose u.v. absorption in neutral solution (Figure, spectrum 3) is seen to be similar to that of the 3*H*-indole (4) (spectrum 1), and it shows a similar bathochromic shift (55 nm) in ethanolic acid solution (spectrum 4). The hydroperoxide (3) was stable in acid solution, from which it was recovered unchanged. In polar solvents, some conversion into the 3*H*-indole (4) was observed, but no decomposition to the amide (7) was detected. This behaviour is in contrast to the conversion of the hydroperoxide (8) in polar solvents into the lactam (9).^{3c}



The production of the 3*H*-indole (4) by direct autoxidation of the indolinylindole (1) is unlikely on theoretical grounds, and this was confirmed by recovering (1) unchanged after 2 days from a solution in ethyl acetate–light petroleum containing benzoyl peroxide. This is in agreement with the results of Berti *et al.*,² who recovered the indolinylindole (1) unchanged after treatment with oxygen. The inertness of compound (1) to autoxidation, though surprising in view of the reported ease³ of autoxidation of 2,3-disubstituted indoles, is not exceptional. Both 2-methyl-3-phenyl- and 2,3-diphenyl-indole^{3b} and also 2-(4-hydroxyphenyl)-3-methyl- and 2-(2-methoxyphenyl)-3-methyl-indole⁴ are resistant to autoxidation.

The possibility of autoxidation of the 2,2'-bi-indolyl (2) to give the dihydroperoxide (11) was investigated. No such compound could be isolated, but passage of a rapid stream of oxygen into a solution of the bi-indolyl (2) in boiling xylene for 4 h produced a colourless crystalline product. This compound, obtained in

⁴ B. Robinson and M. V. Zubair, *J. Chem. Soc. (C)*, 1971, 976.

quantitative yield, was identical with authentic *NN'*-bis-(2-acetylphenyl)oxamide (10), which was also produced from 3,3'-dimethyl-2,2'-bi-indolyl ozonide by treatment with acetic or sulphuric acid.²

EXPERIMENTAL

M.p.s were determined on a Kofler hot-stage apparatus. All solutions were dried with potassium carbonate unless otherwise stated. U.v. spectra were recorded for ethanolic solutions (unless otherwise stated) with a Unicam SP 500 spectrophotometer. I.r. spectra were recorded with a Perkin-Elmer model 21 double-beam apparatus. Light petroleum refers to that fraction with b.p. 60–80°.

3-Methyl-2-(3-methylindol-2-yl)-3H-indol-3-ol (4).—3-Methyl-2-(3-methylindolin-2-yl)indole (640 mg) was heated under reflux with chloranil (610 mg) in redistilled xylene (75 ml) for 24 h. The mixture was cooled, filtered, and evaporated to dryness. The residue was taken up in ether (100 ml) and extracted with 0.2N-sodium hydroxide (3 × 30 ml) to remove tetrachlorohydroquinone. The ethereal solution was dried and evaporated to dryness. The residue was chromatographed on an alumina column. Elution with benzene gave yellow needles (224 mg, 35% [the yields varied with the time of reaction over 20–40%; other products included the bi-indolyl (2) and the hydroperoxide (3)]), m.p. 180–182°C (from ethyl acetate–light petroleum) (lit.,¹ 182°), λ_{\max} 251 (log ϵ 4.66) and 365 nm (4.70), in ethanolic 0.1N-HCl λ_{\max} 246 (log ϵ 4.53), 320 (4.41), and 415 nm (4.80).

3-Methyl-2-(3-methylindol-2-yl)indolin-3-ol (5).—The indolol (4) (250 mg) was dissolved in methanol (15 ml) with a drop of alkali and potassium borohydride (400 mg). The solution was gently heated under reflux until the yellow colour had disappeared, then diluted with water (20 ml) and extracted with ether (3 × 5 ml). The extract was dried and evaporated under reduced pressure to yield the colourless amorphous *indolinol* (5) (240 mg, 96%), fusing at 75–126°. The compound would not recrystallise and yielded no crystalline derivatives (Found: C, 77.0; H, 6.4. $C_{18}H_{18}N_2O$ requires C, 77.7; H, 6.5%), λ_{\max} 229 (log ϵ 4.8) and 292 nm (4.12), λ_{\max} (ethanolic 0.1N-HCl) 246 (log ϵ 4.41) and 318 nm (4.45). These latter absorptions are the same as for the 2,2'-bi-indolyl (2).

3,3'-Dimethyl-2,2'-bi-indolyl (2).—The *indolinol* (5) (70 mg) was dissolved in methanol (4 ml) and dilute hydrochloric acid (0.05 ml) was added. The solution was diluted with water and the solid which separated was filtered off to give colourless crystals (68 mg), m.p. 156–159° (from light petroleum) undepressed on admixture with authentic 3,3'-dimethyl-2,2'-bi-indolyl (m.p. 163–164°). The i.r. and u.v. absorptions of this product are identical with those of the authentic material.

Oxidation of 3,3'-Dimethyl-2,2'-bi-indolyl.—(a) The bi-indolyl (2) (80 mg) was dissolved in an excess of light petroleum and left to reflux, open to the atmosphere. After 4 h, a yellow solid, m.p. 146–175°, was isolated from the pale yellow solution. The solid liberated iodine from acidified iodide solution. After a further 8 h under reflux, the yellow solid no longer gave the iodide test, and had m.p. 164–180°. Three recrystallisations of this second yellow product gave a small amount of material

(12.3 mg), m.p. 180–182°, with spectral characteristics¹ of the indolol (4).

(b) The bi-indolyl (2) (72 mg) was dissolved in hot ethyl acetate–light petroleum (25 ml) and a crystal (0.01 mg) of benzoyl peroxide was added. The solution was left at room temperature, open to the atmosphere. After 6 h, the product (68 mg, 94%) was filtered off, washed with ethyl acetate, and dried to yield fine yellow needles of 3-hydroperoxy-3-methyl-2-(3-methylindol-2-yl)-3H-indole, m.p. 153–154.5° [Found: C, 73.65; H, 5.35%; *M* (iodometric titration), 292.5. $C_{18}H_{18}N_2O_2$ requires C, 73.95; H, 5.5%; *M*, 292], λ_{\max} 250 (log ϵ 4.50) and 365 nm (4.68).

Reduction of the Hydroperoxide (3).—(a) The hydroperoxide (3) (24.4 mg) was dissolved in ethyl acetate (5 ml) containing Adams catalyst (10 mg) and hydrogen was passed through. Absorption ceased after uptake of 2.1 mol of hydrogen. The solution was filtered, dried, and evaporated to yield a colourless, amorphous solid (24.01 mg), which would not crystallise, fusing at 75–122°. The absorption spectra were identical with those of the *indolinol* (5). Treatment with acid gave the bi-indolyl (2).

(b) The hydroperoxide (28.9 mg) was dissolved in 2N-sodium hydroxide (4 ml) and ethanol (1 ml). Sodium dithionite (60 mg) was added and the solution was kept on a steam-bath for 1 h, diluted with water (15 ml), and extracted with ether (3 × 3 ml). The ethereal solution was dried and evaporated to yield a yellow oil (25 mg, 86%), which crystallised on scratching as yellow needles, m.p. 178–182° (from light petroleum–ethyl acetate), undepressed by admixture with authentic *indolinol* (4) (m.p. 180–182°).¹ The spectra were identical with those of (4).

N-(3-Methylindol-2-ylmethylene)-p-toluidine (6).—3-Methylindole-2-carbaldehyde (11 mg) was heated under reflux with *p*-toluidine (7.5 mg) in methanol (0.5 ml). On cooling, pale yellow crystals of the *toluidine* (6) separated out (15 mg, 87%), m.p. 137–138° (from benzene) (Found: C, 82.0; H, 6.4. $C_{17}H_{16}N_2O$ requires C, 82.3; H, 6.45%), λ_{\max} 350 nm (log ϵ 4.78), λ_{\max} (ethanolic 0.1N-HCl) 237 (log ϵ 4.35), 307 (4.37), and 4.05 nm (4.79).

Oxidation of 3-Methyl-2-(3-methylindolin-2-yl)indole (1).—The indole (1) (126 mg) was dissolved in light petroleum–ethyl acetate (50 ml) and a crystal of benzoyl peroxide (0.023 mg) was added. The solution was left open to the atmosphere. After 2 days, unchanged indole (1) (123 mg), m.p. 126°, was recovered from the solution. Berti *et al.*² report that no peroxides are formed when oxygen is bubbled through a solution of the bi-indolyl.

Action of Oxygen on 3,3'-Dimethyl-2,2'-bi-indolyl (2).—The bi-indolyl (2) (37 mg) was dissolved in redistilled xylene (25 ml). The solution was boiled and a rapid stream of oxygen was passed through it. The solution turned yellow and after 6 h a colourless solid separated out. The solid was collected, dried, and recrystallised from morpholine to yield colourless needles of *NN'*-bis-(2-acetylphenyl)oxamide (10) (30 mg, 81%), m.p. and mixed m.p. 261–264° (lit.,² 267°).

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