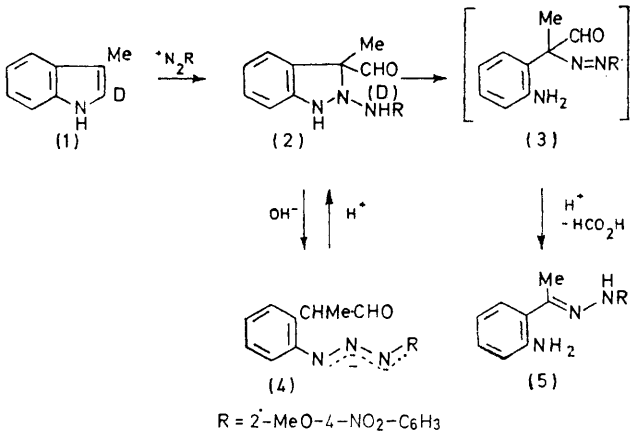
Reaction of 3-Methylindole with a Diazonium Salt

By **Malcolm F. G. Stevens,*** Department of Pharmacy, University of Aston in Birmingham, Birmingham B4 7ET

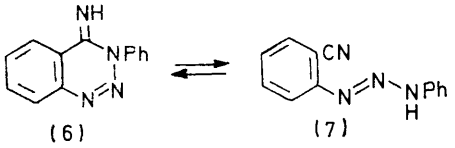
The yellow product isolated from the reaction of 3-methylindole with diazotised 2-methoxy-4-nitroaniline at pH 6—7 is *o*-formamidoacetophenone 2-methoxy-4-nitrophenylhydrazone (9), and not 3-formyl-2,3-dihydro-2-(2-methoxy-4-nitroanilino)-3-methylindazole (2) as originally proposed.

THE reaction of indoles with diazonium salts has recently assumed importance because of evidence suggesting that tryptophan residues of enzymes [1] and antibodies [2] are attacked by diazonium affinity-labelling agents. Spande and Glenner [3] studied the reactions of diazotised 2-methoxy-4-nitroaniline with simple indoles: one of the products isolated from 2-deuterio-3-methylindole (1) at pH 6—7 was assigned structure (2) and described as an ' unusual dihydrotriazene.' Although no mechanism was advanced to explain this transformation it would presumably entail an initial electrophilic attack at the indole nitrogen atom, as is observed in the nitrosation of tryptophan derivatives.[4] Acidic hydrolysis of this coupling product yielded *o*-aminoacetophenone 2-methoxy-4-nitrophenylhydrazone (5), which was envisaged as arising *via* an intermediate arylazoaldehyde (3). Such an intermediate would be expected to undergo a Japp-Klingemann deformylation (Scheme 1).[5]



SCHEME 1

More controversially, compound (2) was claimed to undergo a reversible ring opening in alkali to afford the highly coloured triazene anion (4). Although diaryltriazenes do afford coloured anions (see later) it is difficult to imagine a driving force which would promote recyclisation to the 2-amino-2,3-dihydroindazole (2). Cyclisation of diaryltriazenes normally involves the terminal nitrogen [N(1) or N(3)] of the NNN linkage rather than N(2). For example, 3-phenyl-1,2,3-benzotriazin-4(3*H*)-imine (6) undergoes ring opening to yield the diaryltriazene (7) in piperidine [6] or sodium ethoxide,[7] but recyclises when boiled in (acidic) aqueous ethanol.[8]

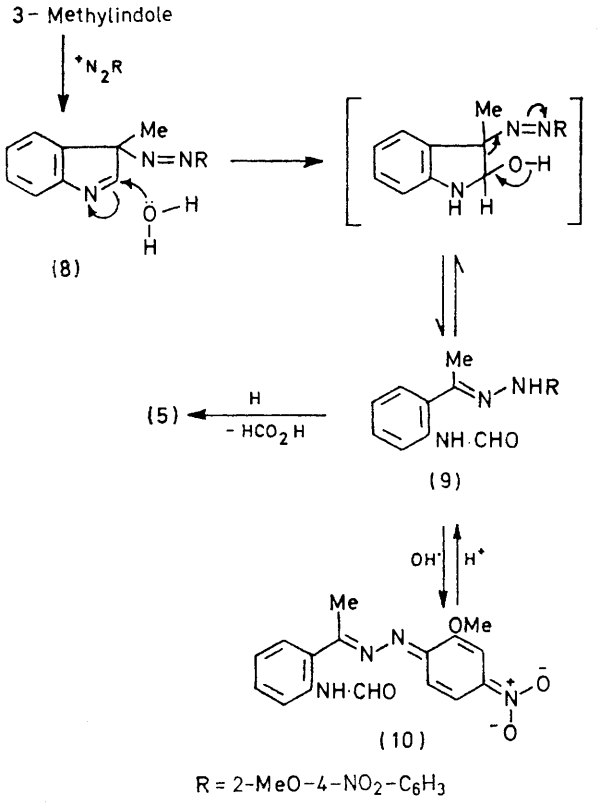


The reaction between 3-methylindole and diazotised 2-methoxy-4-nitroaniline at pH 6—7 was re-examined and a different interpretation put on the result. The initial product was a red gum which contained three components in addition to unchanged 3-methylindole (t.l.c.). When the gum was boiled in aqueous ethanol a yellow product, m.p. 223—225°, was obtained (25%) with physical characteristics in close agreement with those of the product of purported structure (2). The mass spectrum confirmed a molecular formula $C_{16}H_{16}N_4O_4$ and there were substantial fragments at *m/e* 300 (M^+ — CO), 133 (300 — NHR), and 92 (133 — CH_3CN, base peak). The i.r. spectrum (KBr) showed bands at 3 370 (NH), 1 680 (CO), 1 590 (C=N), 1 510, and 1 330 cm^{-1} (NO_2), and the ^1H n.m.r. spectrum [$(CD_3)_2SO$] absorptions at δ 8.3 (s, NH·C*H*O), 8.2—7.0 (7 H, m, aromatic), 3.95 (s, OCH_3), and 2.30 (s, CCH_3).

Structure (9) is assigned to this product since it is identical with the hydrazone formed by heating *o*-formamidoacetophenone and 2-methoxy-4-nitrophenylhydrazine in ethanol containing a trace of toluene-*p*-sulphonic acid. The hydrazone probably arises by initial coupling at C(3) of 3-methylindole to form the arylazo-3*H*-indole (8) (Scheme 2). The 3*H*-indole would be sensitive to hydrolytic ring opening of the pyrrole ring to afford the *o*-formamido-hydrazone (9). The behaviour of this hydrazone in acid and alkali now becomes clear. On acidic hydrolysis it is simply deformylated to (5); in alkali it affords the magenta nitronate anion (10) which re-forms the yellow hydrazone (9) on acidification. These colour changes were accompanied by a shift of the long-wavelength absorption of (9) at 400 nm in 95% ethanol to 506 nm in ethanol containing 5% sodium hydroxide. Similar colour changes were observed with the deformylated product (5) and other model hydrazones (see Experimental section). As observed by Spande and Glenner [3] the

[1] P. Cuatrecasas, *J. Biol. Chem.*, 1970, **245**, 574.
[2] L. Wofsy, J. Kimura, D. H. Bing, and D. C. Parker, *Biochemistry*, 1967, **6**, 1981.
[3] T. F. Spande and G. G. Glenner, *J. Amer. Chem. Soc.*, 1973, **95**, 3400.
[4] R. Bonnett and R. Holleyhead, *J.C.S. Perkin I*, 1974, 962.
[5] R. R. Phillips, *Org. Reactions*, 1959, **10**, 143.
[6] M. S. S. Siddiqui and M. F. G. Stevens, *J.C.S. Perkin I*, 1974, 611.
[7] H. N. E. Stevens and M. F. G. Stevens, *J. Chem. Soc.* (*C*), 1970, 2284.
[8] H. N. E. Stevens and M. F. G. Stevens, *J. Chem. Soc.* (*C*), 1970, 765.

isoelectronic nitrophenyltriazenes also exhibit pronounced bathochromic shifts when converted into their



SCHEME 2

anions. For example, 1-*o*-nitrophenyl- and 1-*p*-nitrophenyl-3-phenyltriazenes show long-wavelength absorptions at 391 and 386 nm in 95% ethanol which are shifted to 500 and 506 nm, respectively, in alkaline ethanol.

EXPERIMENTAL

Electronic absorption spectra were measured for solutions in 95% ethanol (A) or 95% ethanol containing 5% sodium hydroxide (B).

o-*Formamidoacetophenone* 2-*Methoxy*-4-*nitrophenylhydrazone* (9).—(i) A solution of 2-methoxy-4-nitroaniline (1.68 g) in 4N-hydrochloric acid (20 ml) was diazotised at 0 °C with sodium nitrite (0.7 g) in water (2 ml); the mixture was neutralised to pH 6—7 with sodium acetate trihydrate, and added in one portion to a vigorously shaken solution of 3-methylindole (1.3 g) in ice-cold dioxan (20 ml). The mixture was kept at 4 °C for 3 days, the pale supernatant layer was decanted, and the red gummy residue was boiled in 60% aqueous ethanol for 1 h. The mixture was cooled (1 h) and a dark brown solid (0.95 g) collected; this was not examined further. Addition of ether (10 ml) to the filtrate precipitated the *nitrophenylhydrazone* (0.82 g, 25%), which crystallised from butan-1-ol as yellow-brown rosettes, m.p. 222—225° (Found: C, 58.8; H, 4.8; N, 16.9. $C_{16}H_{16}N_4O_4$ requires C, 58.5; H, 4.9; N, 17.1%). Spande and Glenner [3] record a double m.p. (192—195 and 218—221°) for the compound assigned structure (2).

(ii) 2-Methoxy-4-nitrophenylhydrazine (1.83 g) (prepared by reduction of diazotised 2-methoxy-4-nitroaniline with sodium sulphite according to the method of Davies [9]) and *o*-formamidoacetophenone (1.63 g) in ethanol (50 ml) containing toluene-*p*-sulphonic acid (0.1 g) were boiled for 15 min. The hydrazone (65%), collected from the cooled solution, was identical (i.r.) with the aforementioned sample. Similarly prepared (from the appropriate hydrazine and acetophenone) were the following: o-*aminoacetophenone* 4-*nitrophenylhydrazone* (80%), red needles (from butan-1-ol), m.p. 195—196° (Found: C, 62.1; H, 5.1; N, 20.9. $C_{14}H_{14}N_4O_2$ requires C, 62.2; H, 5.2; N, 20.7%), $\lambda_{max.}$ 412 (A) and 520 nm (B); p-*aminoacetophenone* 4-*nitrophenylhydrazone* (75%), red crystals, m.p. 220—221° (from ethanol) (Found: C, 62.0; H, 5.1; N, 20.6%), $\lambda_{max.}$ 420 (A) and 504 (B); *o*-aminoacetophenone 2-methoxy-4-nitrophenylhydrazone (5) (45%), brown needles (from ethanol), m.p. 144—145° (lit.,[3] 141—142°), $\lambda_{max.}$ 420 (A) and 482 nm (B); o-*formamidoacetophenone* 4-*nitrophenylhydrazone* (55%), golden needles, m.p. 246—248° (from butan-1-ol) (Found: C, 60.3; H, 4.6; N, 18.9. $C_{15}H_{14}N_4O_3$ requires C, 60.4; H, 4.7; N, 18.8%), $\nu_{max.}$ (KBr) 3 370 (NH), 1 679 (C=O), 1 590 (C=N), and 1 520 and 1 328 cm^{-1} (NO_2), δ [$(CD_3)_2SO$] 8.4 (s, NH·C*H*O) and 2.3 (s, CH_3), $\lambda_{max.}$ 390 (A) and 530 nm (B); p-*formamidoacetophenone* 4-*nitrophenylhydrazone* (68%), yellow-brown needles, m.p. 239—240° (from ethanol) (Found: C, 60.3; H, 4.5; N, 18.6%), $\nu_{max.}$ (KBr) 3 320 and 3 240 (NH), 1 660 (C=O), 1 600 (C=N), and 1 522 and 1 330 cm^{-1} (NO_2), δ [$(CD_3)_2SO$] 8.27 (s, NH·C*H*O) and 2.25 (s, CH_3), $\lambda_{max.}$ 410 (A) and 504 nm (B).

Hydrolysis of o-*Formamidoacetophenone* 2-*Methoxy*-4-*nitrophenylhydrazone*.—The formamide (0.2 g) was boiled in 1N-hydrochloric acid (5 ml) and ethanol (5 ml) for 1 h. The cooled solution was basified with aqueous ammonia; the red product (0.12 g) was identical (i.r.) with the sample of *o*-aminoacetophenone 2-methoxy-4-nitrophenylhydrazone described above. Both *o*- and *p*-formamidoacetophenone 4-nitrophenylhydrazone were similarly hydrolysed to *o*- and *p*-aminoacetophenone 4-nitrophenylhydrazone, respectively, in ethanolic hydrochloric acid.

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[9] W. Davies, *J. Chem. Soc.*, 1922, **121**, 715.