Reactions of Tryptophols and N^{α}-Acetyltryptamines with Iodine Azide. Formation of 3a-Azido-3,3a,8,8a-tetrahydro-2*H*-furo- and 3a-Azido-1,2,3,3a,8,8a-hexahydropyrrolo-[2,3-*b*]indoles

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Reaction of 2-methyltryptophol (1a) with 1 molar equivalent of iodine azide gives 3a-azido-8a-methyl-3,3a,8,8a-tetrahydro-2*H*-furo[2,3-*b*]indole, which isomerises to 2-azidomethyltryptophol in acetic acid at room temperature. Similar treatment of N^{α}-acetyl-2-methyltryptamine affords two products, 1-acetyl-3a-azido-8a-methyl-1,2,3,3a,-8,8a-hexahydropyrrolo[2,3-*b*]indole and N^{α}-acetyl-2-azidomethyltryptamine; the former does not isomerise to the latter in acetic acid. Tryptophol and N^{α}-acetyltryptamine also give the corresponding 3a-azidofuro- and -pyrrolo-indole derivatives in low yields.

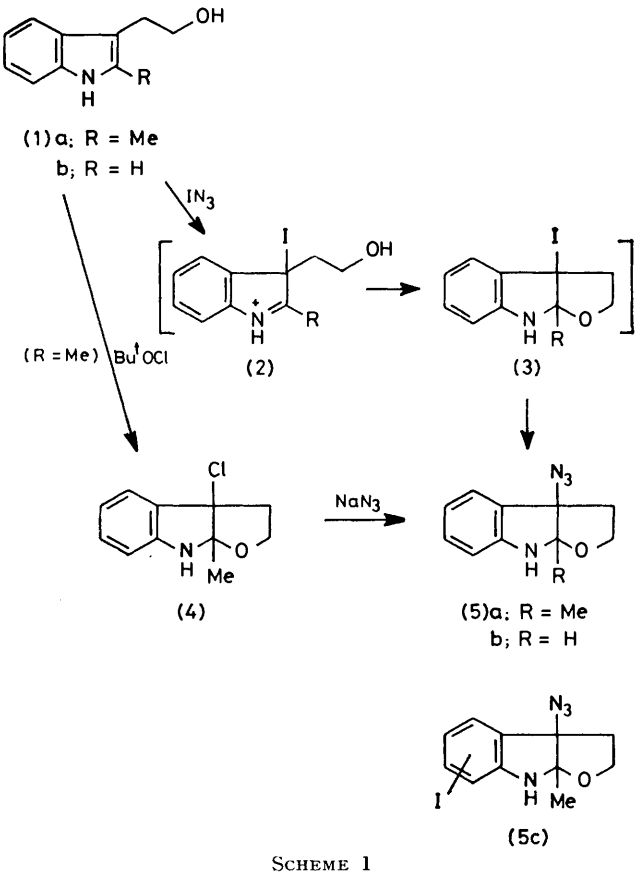
THE transformation of tryptophol and tryptamine derivatives into furo- and pyrrolo-[2,3-*b*]indoles has been the subject of extensive studies.[1] Previously we briefly reported the reaction of 2-methyltryptophol (1a) and N^{α}-acetyltryptamine with iodine azide to afford 3a-azido-3,3a,8,8a-tetrahydro-2*H*-furo- and 3a-azido-1,2,3,3a,-8,8a-hexahydropyrrolo-[2,3-*b*]indoles.[2] We now report on a study of several aspects of this reaction and on the novel tricyclic products.

Treatment of 2-methyltryptophol (1a) with 1.1 mol. equiv. of iodine azide,† generated *in situ* from iodine chloride and sodium azide in acetonitrile,[3] gave the furoindole (5a) ‡ in 77% yield. The structure of (5a) was assigned mainly on the basis of its spectral data. The u.v. spectrum showed absorption maxima at 245 (log ε 3.70) and 308 nm (3.18), typical of an indoline chromophore. The i.r. spectrum showed an NH band at 3 350 cm^{-1} and a strong azide band at 2 100 cm^{-1}. Its n.m.r. spectrum contained a singlet at δ 1.56 (8a-methyl), a multiplet at δ 2.2—2.4 (3-methylene), a multiplet at δ 3.4—4.1 (2-methylene), a broad singlet at δ 4.44 (NH), and a multiplet (4 H) in the aromatic region. Reduction of (5a) with lithium aluminium hydride gave only (1a) in high yield.

Similarly tryptophol (1b) reacted with iodine azide to give (5b) in 30% yield.

The most likely rationalisation for the formation of (5) would involve 3-iodoindolenine intermediates (2) which may undergo cyclisation to 3a-iodofuroindoles (3). Attack of azide anion on (3) would afford the furoindole (5). Strong support for the proposed scheme was derived from the reaction of the 3a-chlorofuroindole (4) with sodium azide. Thus, treatment of (1a) with 1 mol. equiv. of t-butyl hypochlorite [4] and triethylamine in methylene chloride at −30 to −20 °C for 20 min gave unstable chloro-compound (4), whose n.m.r. spectrum supported the assigned structure (see Experimental section). Compound (4) was transformed into (5a) by stirring with sodium azide in methylene chloride–acetic acid at room temperature.

The furoindole (5a) smoothly rearranged to 2-azidomethyltryptophol (8) when stirred in acetic acid at room temperature. The structure was assigned on the basis of the spectral data: the i.r. spectrum showed a strong azide band at 2 100 cm^{-1} and an indole NH band at

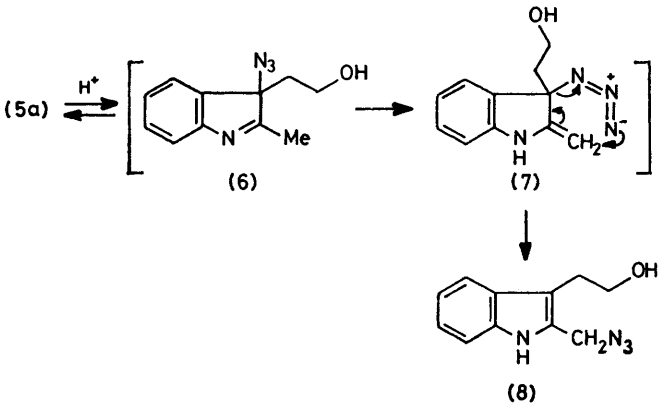


SCHEME 1

3 400 cm^{-1}, while the u.v. spectrum exhibited typical indole absorptions at 228 (log ε 4.32), 282 (3.77), 288 (3.80), and 296 nm (3.72). The final confirmation was given by the n.m.r. spectrum which showed two triplets at δ 2.91 and 3.77 (3-CH_2CH_2OH), a singlet at δ 2.15 (OH), and a singlet at δ 4.34 (2-CH_2N_3). The rearrange-

† Use of 3 mol. equiv. of iodine azide in the reaction of (1a) resulted in the formation of the iodine-containing furoindole (5c) in 48% yield.

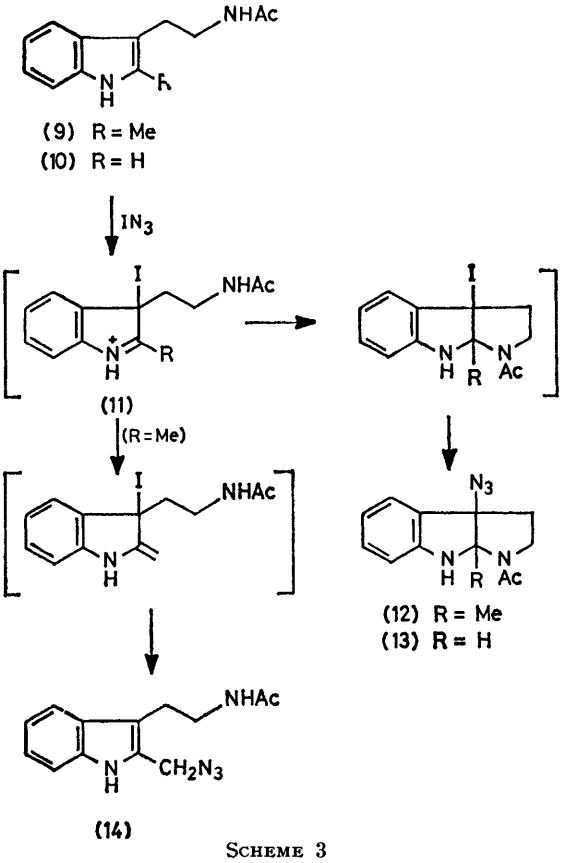
‡ The melting point reported in reference 2 should be revised to 78.5—79.5 °C.



SCHEME 2

ment of (5a) would involve reversible acid-induced ring-opening [5] to give a transient indolenine intermediate (6) which may tautomerise to (7) by either a thermal or acid-catalysed process.[6] This step is then followed by a [3, 3] sigmatropic rearrangement to give the product (8). A similar rearrangement has been observed with 4a-azido-2,3,4,4a-tetrahydro-1*H*-carbazole which affords 1-azido-1,2,3,4-tetrahydrocarbazole.[7] In addition, [3,3] sigmatropic rearrangements involving azide groups have recently been reported.[8,9]

In contrast to the reaction of 2-methyltryptophol (1a) treatment of N^{α}-acetyl-2-methyltryptamine (9) with 1 mol. equiv. of iodine azide gave a mixture of two products. Column chromatography afforded (12) and (14) in 48 and 19% yields respectively. The structures of (12) and (14) were readily confirmed by comparison of their spectra with those of (5a) and (8) respectively. Since (12) proved to be stable under the acidic conditions (AcOH or trifluoroacetic acid), (14) must arise directly from (9). A plausible mechanism is shown in Scheme 3. Apparently intramolecular cyclisation of the possible intermediate (11) can compete with isomerisation of the double bond, perhaps because of the lower nucleophilicity of the acetamido-group compared with the hydroxy-group in tryptophol (1a).



SCHEME 3

The reaction of N^{α}-acetyltryptamine (10) with iodine azide gave a mixture of at least three products, from which the 3a-azidopyrroloindole (12) was isolated in 20% yield.

EXPERIMENTAL

I.r. spectra were recorded with a Hitachi EPI-G2 spectrophotometer and u.v. spectra with a Hitachi 124 instrument. N.m.r. spectra were determined with a Hitachi R-20A (60 MHz) or R-22 (90 MHz) spectrometer (tetramethylsilane as internal standard).

3a-*Azido*-8a-*methyl*-3,3a,8,8a-*tetrahydro*-2H-*furo*[2,3-b]-*indole* (5a).—(a) *Using iodine azide.* A solution of 2-methyltyptophol (1a) (300 mg, 1.71 mmol) in dry acetonitrile (5 ml) was added dropwise to a stirred solution of iodine azide [prepared *in situ* from iodine chloride (310 mg, 1.89 mmol) and sodium azide (450 mg, 6.92 mmol) at −10 to 0 °C] in dry acetonitrile (5 ml) at −30 to −20 °C. After stirring at the same temperature for 2 h, the mixture was diluted with water and extracted with ether. The extract was washed with aqueous $Na_2S_2O_3$ and water. After drying ($MgSO_4$), the solution was evaporated under reduced pressure to afford the crude material, which was purified by preparative t.l.c. on silica gel [n-hexane–ether (1 : 1) as eluant] to give the *furoindole* (5a) (284 mg, 77%), m.p. 78.5—79.5 °C (from n-hexane) (Found: C, 60.8; H, 5.6; N, 25.8. $C_{11}H_{12}N_4O$ requires: C, 61.0; H, 5.6; N, 25.9%); $\nu_{max.}$ ($CHCl_3$) 3 380 (NH) and 2 080 cm^{-1} (N_3); δ (90 MHz; $CDCl_3$) 6.5—7.3 (4 H, m, arom.), 4.44 (1 H, br, NH), 3.4—4.1 (2 H, m, 2-methylene), 2.2—2.4 (2 H, m, 3-methylene), and 1.56 (3 H, s, 8a-CH_3); $\lambda_{max.}$ (EtOH) 245 and 308 nm (log ε 3.77 and 3.21).

(b) via *the intermediate* (4). To a solution of 2-methyltryptophol (1a) (200 mg, 1.14 mmol) and triethylamine (125 mg) in dry methylene chloride (5 ml) was added dropwise t-butyl hypochlorite (125 mg, 1.14 mmol) at −30 to −20 °C with stirring. After stirring at the same temperature had been continued for 20 min, sodium azide (150 mg, 2.3 mmol) and glacial acetic acid (1 ml) were added and the mixture was stirred at room temperature for a further 3 h. The mixture was neutralised with 10% w/v sodium carbonate–water and the organic layer was washed with water, dried ($MgSO_4$), and evaporated under reduced pressure. The residue was purified by preparative t.l.c. on silica gel [n-hexane–ether (1 : 1) as eluant] to give the furoindole (5a) (182 mg, 74%), m.p. 78.5—79.5 °C.

In a separate experiment, the intermediate 3a-*chloro*-8a-*methyl*-3,3a,8,8a-*tetrahydro*-2H-*furo*[2,3-b]*indole* (4) was isolated as an unstable oil by preparative t.l.c. on silica gel [ether—n-hexane (3 : 1) as eluant] of the crude mixture

obtained from the reaction of (1a) with t-butyl hypochlorite; δ (60 MHz, $CDCl_3$) 6.5—7.4 (4 H, m, arom.), 4.75 (1 H, br, NH), 3.3—4.2 (2 H, m, 2-methylene), 2.55—2.85 (2 H, m, 3-methylene), and 1.72 (3 H, s, 8a-CH_3). Treatment of (4) with sodium azide, as described above, gave (5a).

Lithium Aluminium Hydride Reduction of (5a).—A solution of the furoindole (5a) (150 mg) in dry ether (5 ml) was added dropwise to a stirred suspension of lithium aluminium hydride (100 mg) in dry ether (5 ml) and the mixture was refluxed for 1.5 h. The excess of hydride was decomposed by addition of ethyl acetate and water, and the mixture was extracted with ether. The extract was washed with water and dried ($MgSO_4$), and concentrated to give 2-methyltryptophol (1a) (115 mg, 95%).

3a-*Azido*-3,3a,8,8a-*tetrahydro*-2H-*furo*[2,3-b]*indole* (5b).—Using the procedure (a) for the preparation of (5a), the *furoindole* (5b) (86.6 mg, 31%) was obtained from tryptophol (1b) (220 mg) and iodine azide [prepared from iodine chloride (210 mg) and sodium azide (220 mg)] and had m.p. 66—67 °C [from light petroleum (b.p. 30—60 °C)] (Found: C, 59.4; H, 5.0. $C_{10}H_{10}N_4O$ requires C, 59.4; H, 5.0%); $\nu_{max.}$ ($CHCl_3$) 3 430 (NH) and 2 090 cm^{-1} (N_3); δ (60 MHz; $CDCl_3$) 6.5—7.4 (4 H, m, arom.), 5.48 (1 H, s, 8a-H), 4.71 (1 H, br, NH), 3.4—4.2 (2 H, m, 3-methylene), and 2.2—2.5 (2 H, m, 3-methylene); $\lambda_{max.}$ (EtOH) 242 and 304 nm (log ε 3.81 and 3.36); *m/e* 202 (M^+).

3a-*Azido*-5(*or* 6)-*iodo*-8a-*methyl*-3,3a,8,8a-*tetrahydro*-2H-*furo*[2,3-b]*indole* (5c).—Treatment of (1a) (200 mg, 1.14 mmol) with iodine azide [prepared from iodine chloride (558 mg, 3.42 mmol) and sodium azide (336 mg, 5.13 mmol) in dry acetonitrile (5 ml)] gave the *iodofuroindole* (5c) (328 mg, 48%), m.p. 105 °C (from n-hexane) (Found: C, 38.6; H, 3.3; N, 16.6. $C_{11}H_{11}IN_4O$ requires C, 38.6; H, 3.2; N, 16.4%); $\nu_{max.}$ (KCl) 3 350 (NH) and 2 080 (N_3) cm^{-1}; δ (90 MHz; $CDCl_3$) 7.49 (1 H, br s, 7- or 4-H), 7.41 (1 H, dd, *J* 2 and 8 Hz, 5- or 6-H), 6.38 (1 H, d, *J* 8 Hz, 4- or 7-H), 4.5 (1 H, br, NH), 3.3—4.1 (2 H, m, 2-methylene), 2.2—2.5 (2 H, m, 3-methylene), and 1.58 (3 H, s, 8a-CH_3); $\lambda_{max.}$ (EtOH) 256 and 318 nm (log ε 4.26 and 3.38).

2-*Azidomethyltryptophol* (8).—A solution of the furoindole (5a) 150 mg, 0.7 mmol) in glacial acetic acid (3 ml) was stirred at room temperature for 2.5 h. The mixture was neutralised with 10% w/v sodium carbonate–water and then extracted with methylene chloride and dried ($MgSO_4$). The solution was evaporated under reduced pressure and the residue purified by preparative t.l.c. on silica gel [ether–n-hexane (2 : 1) as eluant] to give (8) (120 mg, 80%) as an oil; $\nu_{max.}$ ($CHCl_3$) 3 450 (NH) and 2 090 cm^{-1} (N_3); δ (90 MHz; $CDCl_3$) 8.38 (1 H, br s, NH), 6.9—7.6 (4 H, m. arom.), 4.37 (2 H, s, CH_2N_3), 3.77 (2 H, t, *J* 7 Hz, CH_2CH_2OH), 2.91 (2 H, t, *J* 7 Hz, CH_2CH_2OH), and 2.14 (1 H, br s, OH); $\lambda_{max.}$ (EtOH) 228, 282, 288, and 296 nm (log ε 4.32, 3.77, 3.80, and 3.72); *m/e* 202 (M^+).

1-*Acetyl*-3a-*azido*-8a-*methyl*-1,2,3,3a,8,8a-*hexahydropyrrolo*[2.3-b]*indole* (12) *and* N$^{\alpha}$-*Acetyl*-2-*azidomethyltryptamine* (14)—A solution of (9) (500 mg, 2.3 mmol) in dry acetonitrile (10 ml) was added dropwise to a stirred solution of iodine azide [prepared from iodine chloride (380 mg, 2.3 mmol) and sodium azide (300 mg, 4.5 mmol)] in dry acetonitrile (10 ml) at −30 to −20 °C. Work-up as for the preparation of (5a) gave a crude mixture of (12) and (14), which were separated by chromatography on silica gel. Elution with n-hexane–ethyl acetate gave (12) (286 mg, 48%) and (14) (115 mg, 19%). *Compound* (12) had m.p. 134—135 °C (from n-hexane) (Found: C, 60.7; H, 5.9; N, 27.0. $C_{13}H_{15}N_5O$ requires C, 60.7; H, 5.9; N, 27.2%), $\nu_{max.}$ ($CHCl_3$) 3 360 (NH), 2 070 (N_3), and 1 620 cm^{-1} (C=O); δ (60 MHz; $CDCl_3$) 6.6—7.4 (4 H, m, arom.), 6.1 (1 H, br, NH), 2.9—3.85 (2 H, m, 2-methylene), 2.1—2.6 (2 H, m, 3-methylene), 1.89 (3 H, s, $COCH_3$), and 1.72 (3 H, s, CH_3); $\lambda_{max.}$ (EtOH) 241 and 299 nm (log ε 3.81 and 3.27). *Compound* (14) had m.p. 115—116 °C (from n-hexane) (Found: C, 60.9; H, 5.95; N, 27.0. $C_{13}H_{15}N_5O$ requires C, 60.7; H, 5.9; N, 27.2%); $\nu_{max.}$ ($CHCl_3$) 3 430 (NH), 2 110 (N_3), and 1 660 cm^{-1} (C=O); δ (60 MHz; $CDCl_3$) 9.0 (1 H, br, NH), 6.95—7.7 (4 H, m, arom.), 5.80 (1 H, br, NH), 4.48 (2 H, s, CH_2N_3), 3.48 (2 H, t, *J* 6 Hz, CH_2CH_2NH), 2.95 (2 H, t, *J* 6 Hz, CH_2CH_2NH), and 1.90 (3 H, s, $COCH_3$); $\lambda_{max.}$ (EtOH) 223, 278, 284, and 292 nm (log ε 4.40, 3.81, 3.86, and 3.75).

3a-*Azido*-1-*acetyl*-1,2,3,3a,8,8a-*hexahydropyrrolo*[2,3-b]-*indole* (13).—Similar treatment of (10) (300 mg) with iodine azide [prepared from iodine chloride (270 mg) and sodium azide (385 mg) in dry acetonitrile] as for the preparation of (12) gave a crude mixture of at least three products. Separation by chromatography on silica gel with ethyl acetate gave (13) (71 mg, 20%), starting material (50 mg), an unstable oily product, and an unidentified polar substance (52 mg). *Compound* (13) had m.p. 136—137 °C (from ether) (Found: C, 59.0; H, 5.3; N, 28.5. $C_{12}H_{13}N_5O$ requires C, 59.25; H, 5.4; N, 28.8%); $\nu_{max.}$ (KCl) 3 260 (NH), 2 090 (N_3), and 1 630 cm^{-1} (C=O); δ (90 MHz; $CDCl_3$) 6.5—7.3 (4 H, m, arom.), 5.42 (1 H, s, 8a-H), 5.36 (1 H, br s, NH), 3.1—3.9 (2 H, m, NCH_2CH_2), 2.1—2.6 (2 H, m, NCH_2CH_2), and 2.02 (3 H, s, $COCH_3$); $\lambda_{max.}$ (EtOH) 241 and 302 nm (log ε 3.08 and 3.20); *m/e* 243 (M^+).

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