

Electrophilic Substitution in Indoles. Part VII.¹ Cyclisation of 1- and 2-Methylindolylbutanols and their Toluene-*p*-sulphonates

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4-(1-Methylindol-3-yl)butan-1-ol cyclises to 9-methyltetrahydrocarbazole on heating with boron trifluoride-ether and the same product is also formed from alkaline or neutral solvolyses of the corresponding tosylate. The analogous 2-methylindolylbutanol and its tosylate under the same conditions affords a spirocyclic 3*H*-indole.

In earlier papers of this series,^{1,2} we have described the preparation of indolylbutanol (1a) and of its tosylate (2a), and their cyclisation to tetrahydrocarbazole (4a). In the course of these previous experiments we showed² by isotopic labelling that initial cyclisation occurred at the 3-position of the indole nucleus to give the spirocyclic 3*H*-indole salt (3a) and that this immediately rearranged to give the final product, tetrahydrocarbazole (4a). The intermediate 3*H*-indole (3a) could, however, be isolated as its free base, if solvolysis of the tosylate (2a) was carried out under alkaline, rather than acid conditions.¹

It was thus of interest to us to study the effects of methyl substituents at the 1- and at the 2-position on the course of these reactions. The 2-methylindoles (1c) and (2c) were especially interesting because a tetrahydro-

carbazole could not be formed. 2-Methylindolylbutanol (1c) was therefore synthesised from 2-methylindole by treatment of the Grignard derivative with succinic anhydride, followed by lithium aluminium hydride reduction of the intermediate keto-acid (5). 1-Methylindolylbutanol (1b) was prepared by methylation of the known keto-ester (7a) followed by diborane reduction of both the ester and the keto-function; the *N*-methylation was carried out with methyl iodide in acetone in the presence of potassium carbonate and the success of these mild conditions is due to the 3-keto-function enhancing the acidity of the indole NH group.

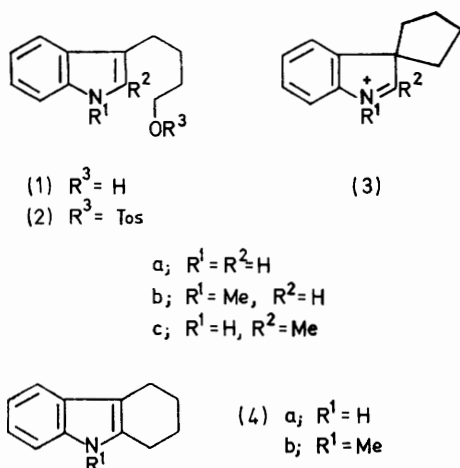
Cyclisation of the 1-methyl compound (1b) with boron trifluoride under reflux gave 9-methyltetrahydrocarbazole (4b), which was identical in all respects with a pure sample prepared by *N*-alkylation of the sodio-derivative of tetrahydrocarbazole (4a), with iodomethane in di-

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¹ Part VI, A. H. Jackson and B. Naidoo, *Tetrahedron*, 1969, **25**, 4843.

² Part IV, A. H. Jackson, B. Naidoo, and P. Smith, *Tetrahedron*, 1968, **24**, 6119; A. H. Jackson and P. Smith, *Chem. Comm.*, 1967, 260.

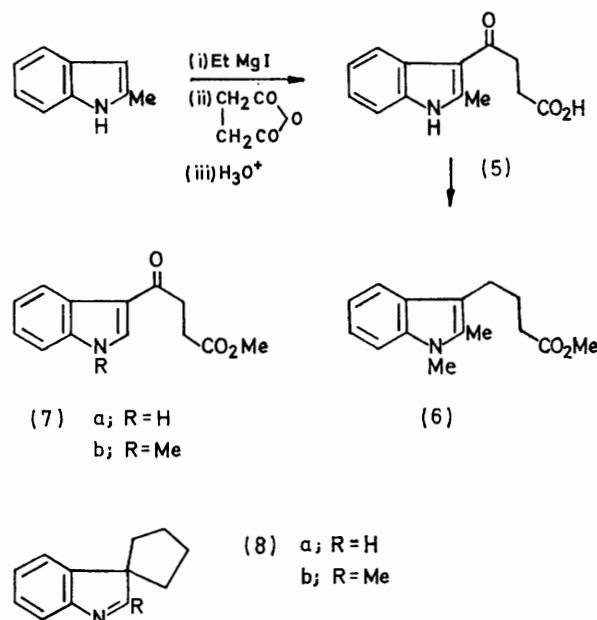
methyl sulphoxide. On the other hand, cyclisation of the 2-methyl analogue (1c) under the same conditions,



afforded the oily spirocyclic 3*H*-indole (8b). The latter was characterised spectroscopically and by elemental analyses; unlike the corresponding non-methylated spirocycle which formed a cyclic trimer, it was shown to exist in the monomeric form, the 2-methyl group presumably sterically hindering trimerisation.

Both these indolylbutanols (1b) and (1c) were then converted into the corresponding tosylates by the same procedure¹ as used previously for the unmethylated analogue (1a). Solvolysis of the 1-methyl derivative (2b) with potassium *t*-butoxide in *t*-butanol, or on basic alumina, afforded mainly 9-methyltetrahydrocarbazoles (4b) rather than the spirocyclic 3*H*-indole salt (3b); a small amount of alcohol (1b) was also formed. These results were not surprising as the 3*H*-indole (3b) (being of necessity a quaternary salt) would be expected to rearrange spontaneously whereas in the NH series originally studied, deprotonation occurred to give the relatively stable free base (8a). Similar solvolyses of the 2-methyl-

compared with those of the solvolyses of the non-methylated analogue in the Table. These data were obtained by titration of the toluene-*p*-sulphonic acid liberated and hence reflects the rates of the initial cyclisation reactions rather than the subsequent steps, such as rearrangement to tetrahydrocarbazoles (4). [In the solvolyses of the unsubstituted tosylate (2a) and the *N*-methyl-tosylate (2b) simultaneous formation of the corresponding alcohols also makes a small contribution to the overall rate.] The relative rates of these solvolyses follow the same order, (2c) > (2b) > (2a), as the pK_a



values of the conjugate acids³ of the corresponding simple methylated indoles (see Table), although there is no simple relationship between them.

The fact that the 2-methylindolylbutyl tosylate (2c) gave only the spirocyclic 3*H*-indole on solvolysis (rather

Solvolyses of indolylbutyl tosylates

Substrate	$t/^\circ\text{C}$	k/s^{-1}	Products	$\Delta H^\ddagger / \text{kcal mol}^{-1}$	$\Delta S^\ddagger / \text{cal mol}^{-1} \text{K}^{-1}$	$5 + \log k$ at 69°	pK_a of related alkyl-indole (ref. 3b)
(2a)	39	5.24×10^{-6}	(4a) (80%)	19.0	-21.1	0.67	3-Methylindole -4.55
	49.8	8.21×10^{-6}	(1a) (20%)				
	69	4.72×10^{-5}					
	84.2	1.55×10^{-4}					
(2b)	53.5	1.72×10^{-5}	(4b) (85%)	21.4	-14.4	0.78	1,3-Dimethylindole -3.37
	69	6.0×10^{-5}	(1b) (10%)				
	84.25	2.2×10^{-4}					
(2c)	39	1.24×10^{-5}	(8b) (100%)	20.2	-14.4	1.36	2,3-Dimethylindole -1.49
	69	2.27×10^{-4}					
	84.25	8.82×10^{-4}					

indolylbutyl tosylate either with *t*-butoxide, or by passage through a column of basic alumina, afforded exclusively the expected spirocyclic 3*H*-indole (8b).

We also studied the rates of solvolyses of these two new tosylates in aqueous acetone and the results are

than a mixture containing the corresponding alcohol), may be attributed to the much higher basicity of 2-methylindoles³ leading to a much greater degree of neighbouring group participation by the indole nucleus.

EXPERIMENTAL

U.v., n.m.r., and mass spectra were determined with Unicam SP 800, Varian A-60 and HA-100, and Varian M66 and A.E.I. MS9 spectrometers respectively.

³ (a) G. Berti, A. da Settimo, and D. Segnini, *Gazzetta*, 1961, 91, 571; (b) R. L. Hinman and J. Lang, *J. Amer. Chem. Soc.*, 1964, 86, 3796.

Methyl 4-(2-methylindol-3-yl)-4-oxobutyrate.—Ethyl iodide (16 g) was added dropwise to a magnesium turnings (2.5 g) in anisole (25 ml) heated to 60°. When all the magnesium had dissolved the solution was cooled and 2-methylindole (12.5 g) in anisole (25 ml) added dropwise, and the temperature raised to 70° for 30 min to complete reaction. After cooling again succinic anhydride (50 ml) was added rapidly with vigorous stirring; the mixture became hot and a red complex formed. After heating for 1 h at 100° the mixture was cooled and poured into glacial acetic acid (15 ml) in water (75 ml). The precipitated keto-acid was filtered off, washed with water, and dissolved in aqueous 10% sodium hydroxide. After reprecipitation with sulphur dioxide and crystallisation from ethanol the keto-acid (11 g, 90%) formed needles, m.p. 223—224°, τ (NaOD) 7.29 (Me), 4.95 (s, $\text{CH}_2\text{CH}_2\text{CO}_2\text{H}$), and 2.8—2.3 (3H, m) and 2.1—1.8 (1H, m) (Ind-H).

The keto-acid (2.7 g) was then dissolved in methanol (150 ml) containing concentrated sulphuric acid (4.5 ml). After standing overnight, it was poured into methylene chloride and added to a saturated solution of sodium acetate. Evaporation of the methylene chloride layer gave a pink solid. This was treated with charcoal and recrystallised from chloroform-benzene to give the required *keto-ester* (2.5 g, 90%) as shiny, white platelets, m.p. 146—147° (Found: C, 68.4; H, 6.3; N, 5.6. $\text{C}_{14}\text{H}_{15}\text{NO}_3$ requires C, 68.55; H, 6.2; N, 5.7%), τ (CDCl_3) 7.37 (Ind-Me), 7.16 (t, COCH_2CH_2), 6.68 (t, COCH_2CH_2), 6.28 (CO_2Me), 2.9—2.6 (3H, m, Ind-H), ca. 2.7 (NH), and 2.1—1.8 (1H, m, Ind-H), *m/e* 245 (31%; M^+), 214 (15; $M - \text{Me}^+$), 186 (6), 158 (100; $M - \text{CH}_2\text{CH}_2\text{CO}_2\text{Me}^+$), and 130 (13), λ_{max} (95% EtOH) 223 (log ϵ 4.14), 244 (4.17), 268 (4.10), and 299 (4.06) nm.

Methyl 4-(1-methylindol-3-yl)-4-oxobutyrate.—Methyl 4-indol-3-yl-4-oxo-butyrate was methylated by treatment with excess of methyl iodide in boiling acetone over anhydrous potassium carbonate for 2 h. After filtration and evaporation to dryness, the residue was crystallised from benzene and gave the desired *N-methyl-ester* (80%) as long needles, m.p. 115—116° (Found: C, 68.7; H, 6.3; N, 5.9%), τ (CDCl_3) 7.2 (m, COCH_2CH_2), 6.8 (m, COCH_2CH_2), 6.35 (NMe), 6.28 (CO_2Me) 3.26 (Ind-2-H), 3.0—2.7 (3H, m, Ind-H), and ca. 2.5 (1H, m, Ind-H) *m/e* 246 (93%), 245 (100), 231 (19), 215 (33), 214 (98), 186 (33), 160 (20), 159 (97), 158 (97), 157 (20), 144 (60), 131 (37), 130 (93), 129 (30), 128 (26), 115 (29), 107 (50), 103 (88), 102 (40), and 89 (30), λ_{max} (95% EtOH) 215 (log ϵ 3.89), 250 (3.83), 275 (3.81), and 290sh (3.80) nm.

4-(2-Methylindol-3-yl)butan-1-ol.—Diborane, generated from sodium borohydride (2.7 g) and boron trifluoride-ether (14 g) in diglyme (100 ml), was passed through a solution of the 2-methylindole keto-ester (3.5 g) in tetrahydrofuran (100 ml). The reaction was exothermic and after 30 min a white precipitate appeared. The mixture was left overnight; methanol (100 ml) was then added and the mixture refluxed for 1 h. Evaporation of the solvents gave the required *alcohol* (3.0 g, 95%) as a gum. This was sublimed at 115° and 0.1 mmHg to give an oil which solidified on standing, m.p. 70—71° (Found: C, 76.1; H, 8.1; N, 7.5. $\text{C}_{13}\text{H}_{17}\text{NO}$ requires C, 76.15; H, 8.0; N, 7.4%), τ (CDCl_3) 8.4 (4H, m, Ind- $\text{CH}_2[\text{CH}_2]_2$), 7.9 (OH), 7.70 (Ind-2-Me), 7.3 (m, Ind- CH_2), 6.4 (m, CH_2OH), and 3.1—2.2 (m, Ind-H and NH), *m/e* 203 (28%; M^+), 185 (8), 170 (20), 144 (100), 132 (16), 131 (19), and 130 (20).

4-(1-Methylindol-3-yl)butan-1-ol.—Methyl 4-(1-methyl-3-indolyl)-4-oxobutyrate (8 g) was reduced with excess of

diborane in the same manner as its analogue in the preceding experiment. The crude product was chromatographed over Florisil and obtained as a viscous oil (6.4 g, 95%) which could not be distilled owing to decomposition on heating (see below) (Found: C, 76.9; H, 8.3; N, 7.1%), τ (CDCl_3) 8.35 (m, Ind- $\text{CH}_2[\text{CH}_2]_2$), 7.3 (m, Ind- CH_2), 6.34 (NMe), 6.2 (m, CH_2OH), 3.25 (Ind-2-H), 3.1—2.8 (3H, m, Ind-H), and 2.6—2.4 (1H, m, Ind-H), *m/e* 203 (23%; M^+), 162 (7), 145 (13), 144 (100), 115 (6), 103 (6), and 102 (6).

4-(2-Methylindol-3-yl)butyl Toluene-p-sulphonate.—Toluene-*p*-sulphonyl chloride (1.5 g) in dry pyridine (5 ml) was added dropwise to a stirred solution of 4-(2-methylindol-3-yl)butan-1-ol (1.45 g) in dry pyridine (5 ml) at -30° under nitrogen. The solution was kept under these conditions for 4 h and then most of the pyridine extracted with dry pentane (cooled to -5°) (5×10 ml). The red oily product was evaporated under reduced pressure for several hours at 0—10° to remove residual pentane and pyridine, and finally purified by chromatography over Florisil in ether to afford the *tosylate* (1.45 g, 45%) as a light buff oil, which decomposed on warming (Found: C, 67.4; H, 6.6; N, 3.8. $\text{C}_{20}\text{H}_{23}\text{NO}_3\text{S}$ requires C, 67.2; H, 6.4; N, 3.9%), τ (CDCl_3) ca. 8.35 (4H, m, Ind- $\text{CH}_2[\text{CH}_2]_2$), 7.78 (Ind-Me), 7.60 (Ts-Me), 7.35 (Ind- CH_2), 5.98 (m, CH_2OTs), 3.1—2.6 (3H, m, Ind-H), 2.85 (d, Ts-H), 2.4—2.1 (1H, m, Ind-H), and 2.35 (d, Ts-H), *m/e* 357 (2%; M^+), 324 (3), 185 (60), 184 (44), 170 (50), 157 (23), 156 (16), 144 (23), 130 (16), 129 (16), 115 (38), 91 (35), 78 (100), and 77 (44), λ_{max} (95% EtOH), 231 (log ϵ 4.88), 275 (3.91), 285 (3.80), and 292 (3.61) nm.

4-(1-Methylindol-3-yl)butyl Toluene-p-sulphonate.—4-(1-Methylindol-3-yl)butan-1-ol was converted into its *tosylate* by a similar procedure to that described for the foregoing compound. The *tosylate* (48%) was obtained as a viscous oil, which decomposed on warming (see below) (Found: C, 67.35; H, 6.2; N, 3.9%), τ (CDCl_3) 8.3 (4H, m, Ind- $\text{CH}_2[\text{CH}_2]_2$), 7.59 (Ts-Me), 7.3 (m, Ind- CH_2), 6.95 (m, CH_2OTs), 6.33 (NMe), 3.25 (Ind-2-H), 3.0—2.4 (m, Ind-H), and 2.75 and 2.2 (2 \times d, Ts-H), *m/e* 357 (2%; M^+), 185 (21), 184 (97), 183 (54), 167 (14), 166 (19), 157 (24), 156 (100), 155 (23), 143 (21), 141 (14), 130 (21), 115 (24), and 91 (25), λ_{max} (95% EtOH) 230 (log ϵ 4.84) and 285 (4.21) nm.

2-Methyl-3H-indole-3-spirocyclopentane.—A slight excess of potassium *t*-butoxide (0.25 g) was added to a solution of 2-methylindol-3-ylbutyl *tosylate* (0.6 g) in tetrahydrofuran. After stirring for 2 h the solid was filtered off and the tetrahydrofuran evaporated. Water was added and was followed by ether extraction (2×100 ml); after drying (MgSO_4) the ether was evaporated and a brown oil (0.34 g) was left. Chromatography over Florisil in ether gave the desired spiro-compound (0.16 g, 55%) as an oil which readily formed a yellow picrate, m.p. 189—191° (lit.,⁴ 188—192°) (Found: C, 55.3; H, 4.45; N, 13.5. Calc. for $\text{C}_{13}\text{H}_{15}\text{N}$, $\text{C}_6\text{H}_3\text{N}_3\text{O}_7$: C, 55.1; H, 4.4; N, 13.5%), τ (of free base) (pyridine) 8.4—8.0 (8H, m, $4 \times \text{CH}_2$) and 7.8 (Ind-2-Me), λ_{max} (of free base) (95% EtOH) 236 (log ϵ 3.51) and 258 (3.80) nm, *m/e* (of free base), 185 (40%; M^+), 170 (34), 157 (17), 156 (13), 144 (13), 143 (17), 128 (14), 129 (15), 130 (9), 115 (25), 102 (9), 91 (19), 78 (100), 79 (15), and 77 (35).

9-Methyl-1,2,3,4-tetrahydrocarbazole.—(a) *N*-Methylindol-3-ylbutanol (1b) (1 g) was dissolved in boron trifluoride-ether and heated under reflux for 1 h. The mixture was then poured into water and extracted with ether (2×100

⁴ B. Witkop and J. B. Patrick, *J. Amer. Chem. Soc.*, 1951, **73**, 1558.

ml). After washing with water and drying (MgSO_4) the ether layer was evaporated under reduced pressure to give a brown oil (0.8 g) which after chromatography in benzene over alumina (grade II; 30 g) afforded 9-methyltetrahydrocarbazole (0.34 g; 40%), m.p. 49–50° (lit.,⁵ 50°).

(b) The foregoing product was identical in all respects with another sample prepared as follows. To a solution of sodium hydride (0.8 g) in dimethyl sulphoxide (DMSO) (60 ml) at 60 °C and under nitrogen was added a solution of tetrahydrocarbazole (5.1 g) in DMSO and the mixture was heated to 70° for 40 min. After cooling methyl iodide (6 g) was added and the mixture was stirred at 40° for 1 h. The reaction was completed by heating at 80° for 30 min; excess of DMSO was then distilled off under reduced pressure and the residue was taken up in ether. After repeatedly washing with water and drying (MgSO_4) the ether layer was evaporated to leave a brown oil (7 g). Chromatography over alumina (grade II; 250 g) and benzene as eluant gave pure 9-methyltetrahydrocarbazole (3.1 g, 74%) as an oil which solidified on standing, m.p. 49°, τ (CDCl_3) 8.26–8.05 (4H, m, 2- and 3- H_2), 7.85 (4H, m, 1- and 4- H_2), 6.58 (NMe), and 3.0–2.5 (m, ArH), m/e 185 (100%; M^+), 184 (33), 167 (10), 158 (15), 157 (100), and 115 (10).

(c) Chromatography of *N*-methylindol-3-ylbutyl tosylate (2b) (0.7 g) on basic alumina (35 g) also gave 9-methyltetrahydrocarbazole (0.15 g, 50%) on elution with benzene.

⁵ T. S. Stevens and S. H. Tucker, *J. Chem. Soc.*, 1923, 2140.

Solvolyses of Indolylbutyl Tosylates.—The solvolyses were carried out in acetone–water (80 : 20 v/v), the acetone being purified by passage through an alumina column followed by distillation. The oily tosylates were purified immediately before use by thick layer chromatography on silica gel. Each tosylate (0.01 mol) was dissolved in acetone (80 ml) and water (20 ml) measured at 0°, and portions (10 ml) of the solution (measured at 0°) were then transferred into test tubes cooled in ice and immediately sealed before placing in a thermostat at the appropriate temperature. The tubes were removed at intervals and titrated with 0.05N-NaOH using Bromothymol Blue as indicator, zero time being counted as 2 min after immersion. Both solvolyses showed good first-order kinetics and the results are shown in the Table. Product analyses were carried out by preparative thick layer chromatography on silica gel on samples (0.01 mol) after solvolyses at 80° over ten half-lives. The (2-methylindol-3-yl)butyl tosylate (2c) gave almost exclusively the spiro-compound (8b), whilst the *N*-methyl analogue (2b) gave 9-methyltetrahydrocarbazole (ca. 85%) and the *N*-methylindol-3-ylbutanol (1b) (10%).

The spiro-compound (8b) was also the main product (t.l.c.) resulting from the thermal decomposition of the (2-methylindol-3-yl)butyl alcohol (1c) and its tosylate (2c), and similarly 9-methyltetrahydrocarbazole was found to be the major product arising from heating the *N*-methyl compound (1b) or its tosylate (2b).

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