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ELECTROPHILIC SUBSTITUTION IN INDOLES—VI[1]

SOLVOLYSIS OF INDOLYLALKYL TOSYLATES

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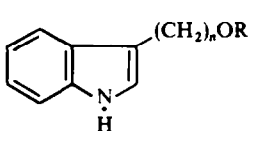
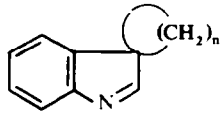
Abstract—A series of ω-(3-indolyl)-alkyl tosylates have been prepared and their solvolyses studied under a variety of conditions. The results confirm that indole can act as a powerful neighbouring group, and that the 3-position of the indole nucleus is the primary position for electrophilic attack even when this position is already substituted. The rates of the solvolyses in aqueous acetone accord with expectations based on Winstein's classical studies in the benzene series, i.e. that the degree of participation by the indole nucleus follows the order 3 ≫ 5 > 6 ≫ 4, the numbers referring to the ring size in the intermediate spirocycle.

EARLIER work [1, 2] provided evidence that electrophilic substitution at the 2-position of a 3-alkyl indole occurs by an indirect process involving prior attack at the 3-position followed by rearrangement. This was confirmed[3] by showing that the spirocyclopentanoindolenine (IIIc) is an intermediate in the acid catalysed cyclization of 4(3-indolyl)-butan-1-ol (Ic) to tetrahydrocarbazole (IVc).

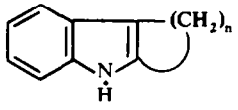


I: R = H
II: R = Tos



III

a: n = 2
b: n = 3
c: n = 4
d: n = 5



IV

It was of considerable interest to study the mechanisms of these reactions in more detail, and accordingly this paper describes an investigation of the solvolyses of the indolyl alkyl tosylates (II). The tosylates (IIa, b and d) were also included in our studies because two groups of workers[4, 5] had shown that the indole nucleus exerts a powerful neighbouring group effect in the solvolyses of derivatives of tryptophol (Ia). For example substituted tryptophols (Va–c) on treatment with phosphorus tribromide, followed by moist silver oxide are rearranged[4] into the isomers (VIa–c). The conclusion that spirocyclopropyl intermediates are involved was supported[5] by deuterium labelling experiments, and by the isolation of the unstable 3,3-spirocyclopropyl indolenine (IIIa) on solvolysis of tryptophyl tosylate (IIa) with potassium t-butoxide (in the absence of air and moisture).

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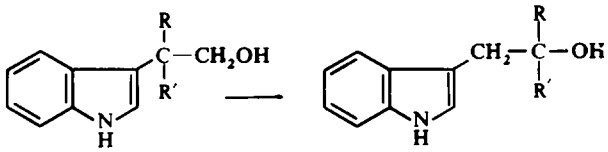


V a: R = R¹ = Me VI
b: R = H, R¹ = Me
c: R = Me, R¹ = H
d: R = R¹ = D

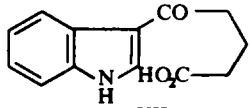
In the present investigation tryptophol (Ia) was prepared by treatment of the indole Grignard derivative with ethylene oxide, and converted into the tosylate (IIa) by treatment with *p*-toluenesulphonyl chloride in pyridine.

The indolyl propanol (Ib) was prepared by LAH reduction[6] of indolyl propionic acid, and the crystalline tosylate (IIb) obtained in the usual way.

The indolyl butanol (Ic) was synthesized by diborane reduction of indolyl butyric acid,[3] as described previously, but conversion to the tosylate (IIc) gave considerable difficulty. In preliminary experiments involving treatment of the alcohol with *p*-toluenesulphonyl chloride and pyridine the major product was a red tar, although chromatographic work-up gave a small amount of the spirocyclic indolenine (IIIc) on one occasion.

Formation of the latter implied that the desired tosylate had probably been formed but that solvolysis had occurred either during the reaction, or during work-up, due to neighbouring group participation by the indole nucleus. We, therefore, developed a method for preparing the tosylate (IIc) which involved treatment of the alcohol (Ic) with the *p*-toluenesulphonyl chloride in dry pyridine at low temperature with the rigorous exclusion of water and oxygen; the product was worked up under non-aqueous conditions (otherwise tarry material and the indolenine (IIIc) were the only products) and finally purified by chromatography on Florisil, or on thin-layer plates of silica gel. (Alumina chromatography afforded either the indolenine (IIIc) or tetrahydrocarbazole (IVc) as the only crystalline products). The indolylbutyl tosylate (IIc), prepared in this manner, was obtained as an analytically pure oil, which gave good NMR and mass spectra. However, like the alcohol (Ic), it could not be distilled without decomposition which led to tetrahydrocarbazole (IVc), and other tarry products.

The indolylpentanol (Id) was synthesized by diborane reduction of the keto-acid (VII) obtained from indole Grignard derivative and glutaric anhydride.[7] Conversion

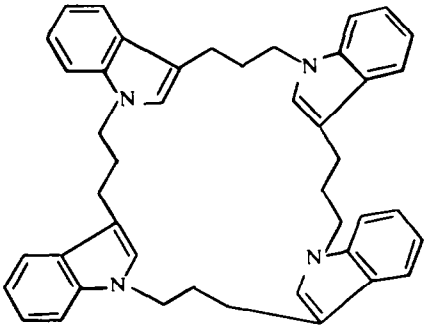


VII

to the tosylate (IId) was best effected by the same method as that used for the butyl-tosylate (IIc). The product was a low melting solid, and attempted distillation gave low yields of 3,3-spiro-cyclohexylindolenine (IIId) and cycloheptindole (IVd); at higher temperatures only the latter could be isolated.

Attempts to cyclize the indolyl propanol (Ib) with BF_3-etherate under a variety of conditions gave only polymeric material. Treatment of the corresponding tosylate

(IIb) with potassium t-butoxide in t-butanol did not give either a spirocyclic indolenine, or cyclopentindole (IVb), and apart from tarry material the only product isolated was a crystalline polymer, tentatively formulated as the tetramer (VIII) on the basis of its UV, NMR and mass spectra. These results clearly show that direct cyclization of either the alcohol (Ib) or the tosylate (IIb) does *not* occur at the 2-position of the indole

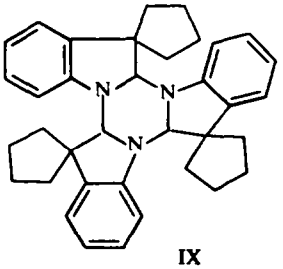


VIII

nucleus, either under acidic or basic conditions; moreover the failure to form a spirocyclobutyl indolenine is in accord with Winstein's results in the benzene series.[8,9]

Cyclization of the indolyl butanol (Ic) under acidic conditions has been described previously.[3] The oily tosylate (IIc) gave the spirocyclic indolenine (IIIc) in moderate yield on treatment with t-butoxide in t-butanol; better yields were obtained by passage through a column of basic alumina,[9] and a small amount of tetrahydrocarbazole was also formed (presumably by re-arrangement of the indolenine).

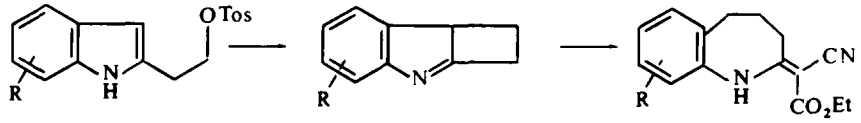
The spirocyclic indolenine (IIIc) existed almost wholly in the trimeric form (IX) in deuterochloroform solution as shown by its NMR spectrum[cf. 2,10]. It was presumably also largely in the trimeric form in the solid state since the mass spectrum (run at as low a temperature as possible) exhibited low intensity peaks due to trimer and dimer. In acidic media immediate depolymerization occurred followed by slow re-arrangement to tetrahydrocarbazole (IVc).



IX

The indolyl pentanol (Id) gave a small amount of cycloheptindole (IVd) together with tarry material, whereas its tosylate (IId) gave the expected spirocyclic indolenine. (IIId) in low yield on treatment with t-butoxide; this indolenine appeared to be largely monomeric in solution, presumably owing to the steric hindrance to trimerization afforded by the more bulky spirocyclohexyl grouping.[cf. 2]

The foregoing results clearly provide qualitative evidence for the primacy of the 3-position in electrophilic substitution reactions of indoles, even when it is already substituted. The failure of the indolylpropyl derivatives (Ib and IIb) to undergo cyclization at the 2-position is quite striking, and contrasts markedly with a recent report that (2-indolyl)2-ethyltosylates (X) in presence of strong base and ethyl-cyanoacetate undergo ring enlargement presumably via the relatively strained 2,3-cyclobutano indolenines (XI) to give the benzazepines (XII).



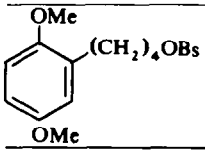
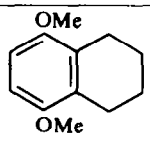
X XI XII

Quantitative evidence in support of our results is provided by the solvolytic behaviour of the indolyl alkyl tosylates (IIa–d) in aqueous acetone (Table 1) under the same conditions as those used by Julia[4] for tryptophol tosylate (IIa). The propyl-tosylate (IIb) solvolyses at approximately the same rate as ethyltosylate showing that the indole nucleus does not participate in this reaction. The pentyl tosylate (IId) solvolysis shows only slight evidence of participation by the indole nucleus, and this was confirmed by solvolysing the 1,1-dideuterio-analogue; the product was shown by NMR to be entirely the 1,1-dideuterio-alcohol. On the other hand the solvolysis of the butyl tosylate (IIc) shows a ten-fold rate enhancement, and the tryptophol tosylate (IIc) solvolyses about 1000 times as fast as ethyl tosylate. Furthermore the yields of the two products from the indolyl butyltosylate (IIc) are in accord with the partial rate factors for their formation[cf. 8] assuming that the alcohol (Ic) is formed without participation and at the same rate as indolylpropanol (Ib) is formed from its tosylate (IIb). That only alcohol is formed from tryptophol tosylate accords with the earlier findings,[4, 5] and with the known instability of spirocyclic compounds of this type to solvolytic ring opening (as well as the unlikelihood of re-arrangement or ring enlargement[cf. 5]).

The overall pattern of the results is in accord with Winstein's now classical studies[8, 9, 12] of neighbouring groups effects in simple benzenoid systems, i.e. that the degree of Ar_1- participation by the indole nucleus follows the order $3 \gg 5 > 6 \gg 4$. (the numbers referring to the ring size, n, in the intermediate spirocycle). The anchimeric assistance afforded by indole is somewhat larger than that afforded by the 2,4-dimethoxyphenyl group in Winstein's studies[8] and the activation energies are also slightly lower. The low negative entropy of activation for the solvolysis of tryptophyl tosylate is not unexpected in view of the relative regidity of the intermediate spirocyclopropyl indolenine (IIIa).

Further work on the quantitiative aspects of the rearrangement 3,3-disubstituted indolenines to 2,3-disubstituted indoles is in progress. It is hoped that this will help to provide a more complete picture of the overall mechanisms of substitution reactions at the 2-position of a 3-substituted indole.

TABLE 1. SOLVOLYSIS OF INDOLE TOSYLATES IN ACETONE/WATER (80:20)

Compound	Temp °C	Rate (sec^{-1})	ΔH^* (kcal/mole)	ΔS^*(e–u)	Product
IIa	33·3	$1·25 \times 10^{-4}$	21·7	−3·6	Alcohol Ia
	45·5	$4·3 \times 10^{-4}$	(±0·9)	(±1·8)	
	50·5	$7·84 \times 10^{-4}$			
	56	$1·58 \times 10^{-3}$			
	69	$4·65 \times 10^{-3}$			
IIb	53·5	$8·18 \times 10^{-7}$	19·6	−24·6	Alcohol Ib
	69	$3·68 \times 10^{-6}$	(±0·9)	(±2·8)	
	84·25	$1·19 \times 10^{-5}$			
IIc	39	$5·24 \times 10^{-6}$	19·0	−21·0	Tetrahydro-
	49·8	$8·21 \times 10^{-6}$	(±0·6)	(±1·6)	carbazole IVc
	69	$4·72 \times 10^{-5}$			78%
	84·25	$1·55 \times 10^{-4}$			+ alcohol Ic
IId	53·5	$9·43 \times 10^{-7}$	20·5	−21·5	Alcohol Id +
	69	$3·18 \times 10^{-6}$	(±1·2)	(±2·5)	trace cyclo-
	84·25	$1·48 \times 10^{-5}$			heptindole
CH_3CH_2OTos[4]	40[4]	$9·0 \times 10^{-7}$			
	75° in acetic acid[8]	$6·26 \times 10^{-6}$	25·0		+ alcohol

EXPERIMENTAL

M.ps are uncorrected. UV, NMR and mass spectra were determined with Unicam SP800, Varian-A60 and HA-100, and A.E.I. M59 Spectrometers respectively.

Tryptophol (Ia)

Indole (5·5 g) in ether (10 ml) was added dropwise to a stirred soln of EtMgI (from Mg (1·2 g) and EtI (8·6 g)) in ether (15 ml). When the addition was complete the soln was boiled under reflux for 30 min and then cooled to 0°. Ethylene oxide (2·2 g) in benzene (15 ml) was then added with stirring and the mixture was kept for 3 hr at 20°. The white complex formed was decomposed by addition of 2N HCl, and the organic product extracted with ether, washed with water and dried ($MgSO_4$). Evaporation of the ether gave a brown oil which was extracted with hot hexane (to remove any unreacted indole) and the residual oil was distilled to give tryptophol (2·9 g; 40%) b.p. 150–160°/0·1 mm (m.p. 55–57°); NMR ($CDCl_3$): NH, 1·95 *b*; 7-H, 2·3 m; 4, 5, 6-H, 2·6–2·9 m; 2-H, 3·04 d (J = 2); CH_2 CH_2, 6·14 t, 7·02 t; OH, 8·15. Mass spectrum (*m/e* (%)): 161 (98), 146 (16), 144 (20), 143 (20), 131 (84), 130 (100), 129 (32), 128 (18), 118 (10), 117 (22), 115 (15), 103 (46), 102 (26), 101 (11), 91 (7), 90 (12), 89 (14), 78 (12), 77 (62). This product was identical with that prepared by Julia's method.[4]

Tryptophyl tosylate (IIa)

This tosylate was prepared by Julia's procedure[4] and had m.p. 77·5–79° (lit.[4] 79°); NMR ($CDCl_3$): NH and Ind-H, 2·2–3·0 m; Tos-H, 2·27 d, 2·72 d (J = 8); CH_2 CH_2, 5·69 t, 6·88 t; Tos-CH_3, 7·62, Mass spectrum: 315 (2), 174 (12), 173 (20), 172 (99), 155 (18), 143 (17), 130 (5), 131 (8), 109 (15), 108 (100), 107 (99), 92 (45), 91 (100), 90 (54), 89 (76), 80 (26), 79 (85), 78 (21), 77 (97).

3-(3-*Indolyl*) *propionic acid*

Indole (60 g) and freshly distilled acrylic acid (80 g) were heated at 60° for 2 hr in Ac_2O (100 ml) and AcOH (240 ml). The soln was kept for 2 days at 20° and then evaporated under reduced press. The dark viscous residue was treated with NaOH (60 g) in hot water (500 ml) and allowed to cool before filtering

off insoluble material. The clear pale yellow filtrate was acidified with SO_2, and the ppt collected and recrystallized from water to afford the colourless propionic acid (24 g, 30%) as needles, m.p. 135·5–136·5° (lit.[6] m.p. 135–136°).

3-(3-*Indolyl*)*propan*-1-*ol* (Ib)

Indolyl propionic acid (1·9 g) in THF (50 ml) was reduced with diborane generated externally from BF_3OEt_2 (4·5 g) and $NaBH_4$ (0·85 g) in diglyme (35 ml). After completion of the addition the mixture was kept at 20° for 1 hr and then evaporated to dryness. Boron complexes were decomposed by boiling the residue with MeOH (50 ml) for 30 min and the MeOH removed under reduced press. The oily residue was purified by filtration through a short (4 in) column of alumina in ether to give the colourless oily indolyl propanol (1·6 g; 91%) which solidified on standing at 0°. The *picrate* formed red needles from benzene, m.p. 100–101° (lit.[13] m.p. 101°); NMR ($CDCl_3$): NH 1·95; 7.H 2·40 m; 4, 5, 6.H 2·85 m 2H, 3·2 d (J = 2); OCH_2, 6·4 t; ind-CH_2, 7·25 t; —C—CH_2—C—, 8·15 m; OH, 7·68 s. Mass spectrum: 175 (62), 156 (15), 145 (10), 144 (20), 143 (12), 132 (13), 131 (85), 130 (100), 129 (24), 128 (20), 118 (20), 117 (23), 115 (18), 103 (28), 102 (8), 101 (6), 91 (13), 90 (10), 89 (12), 77 (36).

Attempts to cyclize this material with BF_3OEt_2 under a variety of conditions, or with polyphosphoric acid led to mixtures of polymeric indolic products; cyclopentindole was not detected spectroscopically or by TLC comparisons with authentic material prepared by the Fischer indole method.[14]

3-(3-*Indolyl*)-*propyl*-1-*toluene*-p-*sulphonate* (IIb)

Indolyl propanol (0·87 g) in dry pyridine (10 ml) cooled to −30° was stirred and *p*-toluenesulphonyl chloride (1·1 g) in pyridine (10 ml) cooled to −5° was added dropwise under N_2. The pale yellow soln was kept at −20° overnight before addition of ice-cold dil H_2SO_4 (40 ml). A red oil separated out and the aqueous layer was decanted off. After washing with water by decantation this oil slowly solidified and was filtered off and washed with n-hexane. Chromatography in benzene–ether (9:1/v:v) over alumina (25 g) then gave the required *indolyl propyl tosylate* (0·70 g, 43%) which crystallized from benzene–light petroleum (b.p. 60–80°) as chunky, white needles, m.p. 97–98°. (Found: C, 65·5; H, 5·7; N, 4·0; S, 9·7. $C_{18}H_{19}NO_3S$ requires: C, 65·5; H, 5·8; N, 4·25; S, 9·7%); λ_{max} (log ε_{max}) in EtOH: 224 (4·66), 274 (3·79), 282 (3·80), 291 (3·74); NMR ($CDCl_3$): NH 2·1; 7H 2·3 m; 4, 5, 6 H 2·8 m; 2H 3·2 d, OCH_2 6 t; ind-CH_2 7·25 t; CH_3 7·63 t; —C—CH_2—C— 8 m. Mass Spectrum, *m/e* (%): 329 (40), 175 (2), 174 (5), 173 (2), 158 (6), 157 (32), 156 (19), 144 (10), 143 (10), 131 (16), 130 (100), 129 (10), 128 (7), 117 (9), 115 (7), 103 (9), 91 (26), 77 (11), 65 (12).

Attempted cyclization of indolyl propyl tosylate (IIb)

The tosylate (0·5 g) in dry THF (35 ml) under N_2 was treated with t-BuOK (0·18 g) and the mixture boiled under reflux for 4 hr. The THF was removed by evaporation, water was added and the organic products extracted with ether. The ethereal extracts were washed with water, dried ($MgSO_4$) and evaporated to dryness. The residual yellow solid (0·3 g) was subjected to preparative thick-layer chromatography on silica gel in benzene and afforded amongst other products a crystalline *solid* (0·16 g) m.p. 180–182° from $CHCl_3$/pet. ether. The UV spectrum was indolic (λ_{max} ($CHCl_3$) 292 nm) but the absence of an NH peak in the IR spectrum, or of a shoulder[cf.15] at 290 nm in the UV spectrum confirmed, that the product was an N-substituted indole. The NMR spectrum in $CDCl_3$ (4, 5, 6, 7-H, 2·5–3·2 m; 2-H, 3·26 s; N—CH_2 CH_2 CH_2, 5·99 t, 8·70 m, 8·37 t) also clearly showed a singlet for the indole 2-proton, substitution at the 1- and 3-positions and that the structure must be symmetrical in nature (as only three sets of CH_2 resonances were observed). The mass spectrum, *m/e* (%): 628 (14), 472 (28), 471 (66), 388 (28), 332 (24), 314 (38), 188 (24), 170 (24), 158 (35), 157 (62), 156 (48), 145 (38), 144 (100), 131 (31), 130 (70), 129 (41), 115 (24), 102 (21), 97 (20), 91 (28), 71 (31). indicated the likelihood that the product was tetrameric and accordingly the product was assigned structure (VIII) although the presence of some of the analogous trimer could not be excluded.

4-(3-*Indolyl*)-*butan*-1-*ol*.

Diborane generated from $NaBH_4$ (5 g) in diglyme (100 ml) and BF_3-etherate (26 g) in diglyme (75 ml) was passed into a soln of 3-indolyl 4-oxobutyric acid (5·7 g) in dry THF (170 ml).

A white complex precipitated out and the mixture was allowed to stand overnight at room temp. MeOH (100 ml) was then added to decompose the complex and the mixture refluxed for 30 min. Evaporation of the solvents gave the required alcohol as a pale-brown oil (4·8 g). It was further purified by filtration over Florisil (70 g) with benzene/ether (85:15) as eluent when the alcohol (4·5 g) (92%) was obtained as a colour-

less oil. (Found: C, 76·2; H, 7·8; N, 7·3. $C_{12}H_{15}NO$ requires: C, 76·15; H, 8·0; N, 7·4%). Attempts to distil this compound under reduced press gave tetrahydrocarbazole; NMR ($CDCl_3$): NH, 2·06; 7H 2·45 m; 4, 5, 6. H 2·85 m, 2-H, 3·15 d (J = 2); OCH_2, 6·40 t; ind.-CH_2, 7·25 t; —CH_2 —CH_2 −8·3 m; OH, 8·1; mass spectrum *m/e* (%): 189 (24), 171 (9), 150 (9), 143 (14), 130 (100), 117 (14), 103 (13), 74 (50), 59 (90).

4-(3-*Indolyl*)-*butyl*-1-p-*toluenesulphonate* (IIc)

p-Toluenesulphonyl chloride (3·0 g) in dry pyridine (10 ml) was added dropwise to a stirred soln of 4-(3-indolyl)-butan-1-ol (2·7 g) in dry pyridine (10 ml) at −30° under N_2. The orange soln was kept at −30° for 4 hr under N_2, and most of the pyridine was then extracted with dry pentane (cooled to −5°) (5 × 20 ml). The red oily product was evaporated under reduced press (0·1 mm) for several hours at 0–10° to remove residual pentane and pyridine. The product was finally purified by chromatography over Florisil (60–100 mesh) in dry ether to afford the unstable *tosylate* (1·8 g; 30%) as a light yellow oil (NMR in $CDCl_3$: Ar-H, 2·0–3·2; O—CH_2, 5·95 m; Ind.-CH_2, 7·30 t; —CH_2—CH_2—, 8·3 m; Ar-CH_3, 7·59). A small amount of tetrahydrocarbazole was also obtained in the early fractions.

For analysis the oily product was chromatographed on thick-layer plates (Kieselgel G) in ether and the tosylate recovered from the appropriate band by extraction with ether followed by evaporation to dryness. (Found: C, 66·25; H, 6·4; N, 3·7. $C_{19}H_{21}NO_3S$ requires: C, 66·5; H, 6·1; N, 4·1%). This material could not be distilled as it decomposed on warming to give mainly tetrahydrocarbazole together with some polymeric material. It also slowly decomposed on standing at room temperature for several days; λ_{max} (log ε_{max}) in EtOH: 227 (4·53); 275 (3·77); 283 (3·77); 291 (3·69), nm. Mass Spectrum *m/e* (%): 343 (84), 284 (20), 230 (16), 207 (31), 185 (25), 184 (24), 172 (100), 171 (97), 170 (90), 155 (40), 143 (100), 144 (52), 131 (40), 130 (100), 117 (32), 108 (39), 107 (71), 91 (100), 90 (32), 89 (32), 77 (49).

In preliminary experiments in which aqueous work-ups were employed only red tarry products were obtained. In another experiment in which the red oily reaction mixture was chromatographed directly on alumina (grade III) in pet. ether (60–80): benzene (90:10) a low yield (4%) of a crystalline *product* was obtained. This crystallized from acetone as needles, m.p. 145–146°, and was shown by mixed m.p. and spectral comparisons to be identical with the trimer of spirocyclopentyl indolenine (see below).

3,3-*Spirocyclopentylindolenine* (IIIc or IX)

(a) Indolyl butyl tosylate (0·90 g) in dry THF (80 ml) under N_2 was treated with t-BuOK (0·35 g) at room temp. The yellow soln turned rapidly brown on standing and after 2 hr it was filtered and the THF evaporated off. The product was partitioned between water and ether, the ether layer dried ($MgSO_4$) and the ether evaporated. The residual brown oil (0·5 g) was chromatographed over Florisil (30 g: 60/100 mesh) first in benzene, and then in benzene/ether (9:1). Tetrahydrocarbazole (40 mg) was eluted first, followed by the required *indolenine* (0·18 g; 40%) which crystallized from aqueous acetone as needles, m.p. 146–147°. (Found: C, 84·0; H, 7·8; N, 8·1. ($C_{12}H_{13}N$) requires: C, 84·2; H, 7·65; N, 8·2%); λ_{max} (log ε_{max}); in EtOH, 215 (4·13) 220 (4·18), 226 (4·12), 267 (3·96); in EtOH + 1 drop conc HCl, 227 (4·13), 276 (3·815). On standing for a few days at 20° the spectrum slowly became indolic owing to formation of tetrahydrocabazole. The NMR spectrum ($CDCl_3$): Ar-H, 2·9–3·9 m (10H), 4·1 d (1H), 4·5 m (1H); 5·12 (1H), 5·72 (1H), 5·86 (1H); 8·2 m (8H), showed that the product was largely in the trimeric form in $CDCl_3$ and at 0·1M concentration. On addition of trifluoroacetic acid to the $CDCl_3$ soln depolymerization occurred immediately, and rearrangement to tetrahydrocarbazole rapidly followed. The NMR spectrum immediately after addition of TFA showed resonances corresponding both to the indolenine salt (2-H, 2·80; Ar-H 2·55; —$(CH_2)_4$— 7·5–7·9) and to tetrahydrocarbazole (8-H, 2·3 m; 5, 6, 7-H, 2·4–2·8 m; 1-CH_2 and 4-CH_2, 6·7–7·4 m; 2,3-CH_2—CH_2—, 7·9–8·3 m). The mass spectrum (at source temp 100°) confirmed that the crystalline material was also trimeric, *m/e* (%); 513 (0·2%), 342 (1%), 171 (30), 170 (20), 144 (14), 143 (100), 142 (8), 130 (12), 129 (13), 128 (12), 117 (6), 116 (8), 115 (28), 102 (15), 89 (10), 78 (14), 77 (12), 76 (10), 75 (10), 63 (15). At source temp > 150°, only monomer was obtained.

(b) The indolyl butyl tosylate (3·0 g) was chromatographed in benzene/light petroleum over basic alumina[9] (prepared from alumina (200 g), KOH (20 g) and water 15 ml). Elution with benzene/light petroleum (1:1) afforded the indolenine trimer (1·4 g; 93%) which crystallized from aqueous acetone as chunky crystals, m.p. 148–149°, identical with the material prepared as in method (a).

5-*Oxo*-5(3 *indolyl*)*pentanoic acid*

Ethyl iodide (32 g) was added portionwise to Mg (5·0 g) in dry anisole (50 ml) and when addition was complete the mixture was heated at 70° for 30 min. It was then cooled to 0° and indole (23 g) in anisole

(50 ml) added dropwise with vigorous stirring. After heating to 70° for 30 min the soln was treated rapidly with a hot soln of glutaric anhydride (22·8 g) in anisole (100 ml) and stirred vigorously. The soln became bright red and then quickly became a thick paste which was stirred on the hot water bath at 100° to complete the reaction. The complex was decomposed with AcOH (30 ml) in water (150 ml) and the pink ppt filtered off. After washing repeatedly with water the latter was taken up in dil NaOH aq and re-precipitated with SO_2. The cream ppt was collected at the pump and crystallization from aqueous EtOH afforded the keto-acid (23 g; 50%) needles, m.p. 233–236° (lit.[7] m.p. 232°); NMR (NaOD/D_2O): 2-H, 1·64; 4-H, 1·9 m; 7-H, 2·4 m; 5, 6-H, 2·85 m; CH_2CO_2H, 7·2 m; —$COCH_2$, 7·72 t; —CH_2— 8·0 m.

Methyl 5-oxo-5(3-indolyl) pentanoate

The foregoing keto-acid (12 g) was dissolved in MeOH (450 ml) and conc H_2SO_4 (12·5 ml) and kept overnight at 20°. The *keto-ester* (10·6 g; 83%) crystallized out, and was recrystallized from MeOH (charcoal) to give needles, m.p. 173–174°; NMR (TFA): 2-H, 1·26 d (J = 4); 4-H, 1·7 m; 4, 5, 6-H, 2·8–3·0 m; $COCH_2$ $CH_2CH_2CO_2CH_3$, 7·2 t, 7·6 q, 6·65 t, 6·07; λ_{max} (log ε_{max}) in EtOH: 243 (4·08), 264 (4·09), 294 (4·16) nm. (Found: C, 68·7; H, 6·1; N, 5·7. $C_{14}H_{15}NO_3$ requires: C, 68·55; H, 6·2; N, 5·7%); Mass Spectrum; *m/e* (%): 245 (21), 214 (8), 186 (3), 172 (5), 159 (13), 145 (11), 144 (100), 130 (3), 116 (10), 117 (5), 89 (10).

5(3-*Indolyl*) *pentan*-1-*ol* (Id)

Diborane generated externally from $NaBH_4$ (2·7 g) in diglyme (80 ml) and BF_3OEt_2 (13·4 g) in diglyme (50 ml) was passed slowly (1 hr) into a soln of the oxo-acid (2·8 g) in dry THF (200 ml). After standing overnight the white complex which had formed was decomposed by addition of MeOH (70 ml) and boiling under reflux for 30 min. Upon evaporation of the solvents the *pentanol* (2·4 g; 96%) was obtained as a pale green oil (one spot on TLC), and this was purified for analysis by passage through an alumina column in ether to give a colourless oil. (Found: C, 76·9; H, 8·6; N, 6·6. $C_{13}H_{17}NO$ requires: C, 76·8; H, 8·4; N, 6·9%). This product was thermally unstable and attempted distillation gave low yields of cycloheptindole, spirocyclohexyl indolenine as well as polymeric products; NMR ($CDCl_3$): NH, 2·1 t; 7-H, 2·5 m; 4, 5, 6-H, 2·6–3·1 m; 2-H, 3·13 d (J = 1·5); OCH_2—, 6·42 t; Ind-CH_2—, 7·3 b t; —$CH_2CH_2CH_2$ 8·0–8·6 m; OH, 7·9; mass spectrum, *m/e* (%): 203 (28), 160 (47), 144 (15), 131 (25), 130 (100), 118 (23), 117 (23), 104 (12), 91 (17), 77 (17), 76 (15).

2,3-*Cycloheptindole*

The indolyl pentanol (200 mg) in BF_3OEt_2 (15 ml) was heated under reflux for 2 hr and the product poured into dil $NaHCO_3$ aq. Extraction with ether gave a brown oily product (170 mg) which was subjected to preparative thick layer chromatography on silica gel in benzene; one of the four bands (R_f, 0·8) afforded cycloheptindole (8 mg), which formed needles m.p. 143–144°. (lit.[16] m.p. 145°). This product was identical with an authentic sample prepared by Fischer indolization of cycloheptanonephenylhydrazone.[16]

Cycloheptindole was also obtained in low yield from polyphosphoric acid cyclization of the indolylpentanol; NMR ($CDCl_3$): NH and 7-H, 2·4–2·7 m; 4, 5, 6-H, 2·8–3·0 m; $(CN_2)_5$ 7·25 m (4H), 8·2 m (6H).

5(3-*Indolyl*) *pentyl*-1-*toluene*-p-*sulphonate* (IId)

The pentanol was converted into the tosylate by the same procedure as for the butyl tosylate (IIc). The *product* (50% yield) was a pale cream oil which solidified slowly on standing to a low m.p. solid (45–47°). (Found: C, 67·4; H, 6.6; N, 3·8; S, 9·0. $C_{20}H_{23}NO_3S$ requires: C, 67·2; H, 6·5; N, 3·9; S, 9·0%); NMR ($CDCl_3$): NH, 2·1 b; Ind.-H, 2·5–3·1 m; Ind-2-H, 3·14 d (J = 1·5); Tos-H, 2·28 d, 2·74 (J = 8); Tos-CH_3, 7·64; CH_2O, 6·04 t; Ind-CH_2, 7·85 t; —$CH_2CH_2CH_2$—, 8·2–8·7 m; mass spectrum; *m/e* (%): 357 (21), 185 (30), 184 (19), 172 (6), 171 (7), 170 (6), 155 (9), 156 (25), 144 (13), 143 (24), 131 (21), 130 (100), 117 (21), 92 (29); λ_{max} (log ε_{max}) in EtOH: 225 (4·55), 274 (3·77), 283 (3·78), 291 (3·72) nm.

Attempts to sublime this tosylate at 100–120°/0·1 mm afforded a mixture of cycloheptindole and spirocyclohexylindolenine. At higher temperatures only the indole was formed.

3,3-*Spirocyclohexylindolenine*

(a) The foregoing pentyl tosylate (350 mg) in dry THF (120 ml) was treated, under N_2 with solid t-BuOK (0·2 g). The soln rapidly turned yellow and after warming for 20 min the solvent was partially evaporated. The reaction mixture was then partitioned between water and $CHCl_3$, and the dried ($MgSO_4$) extracts evaporated to dryness. The red oily product (200 mg) was chromatographed on silica gel in benzene and gave the *spirocyclic indolenine* (52 mg; 30%) which partially crystallized on standing; and was recrystallized

from benzene to give plates m.p. 92–94°. (Found: N, 7·5. $C_{13}H_{15}N$ requires: N, 7·6%); NMR ($CDCl_3$): Ar-H, 2·4 m (1H), 2·6–3·0 m (4H); —$(CH_2)_5$— 8·0–8·5 m (10H). The absence of singlet resonances in the 5–6 region showed that this compound was monomeric in $CDCl_3$ and this was confirmed by the mass spectrum, *m/e* (%) 185 (100), 184 (55), 170 (14), 157 (29), 156 (71), 144 (27), 143 (27), 131 (26), 130 (40), 129 (25), 128 (16), 117 (12), 116 (6), 115 (24), 103 (8), 102 (16), 91 (14), 89 (10), 77 (17), 76 (10), 75 (9), 63 (12). λ_{max} (log ε_{max}) in EtOH: 225 nm. (3·72); 248 nm. (3·45), in EtOH + 2 drops of conc HCl 233 (3·6), 285 nm. (3·26).

(b) The pentyl tosylate (1·86 g) was chromatographed on basic alumina (65 g prepared as above) in light petroleum. Cycloheptindole (28 mg) was obtained in the light petroleum eluates and on changing to light petrol/benzene mixtures unchanged tosylate (1·1 g) was eluted. Traces of the cyclohexyl indolenine were next obtained (as shown by TLC) and finally on elution with benzene a small amount of the indolylpentanol (42 mg) was isolated.

Methyl 5-(3-indolyl) pentanoate

The indolyl oxopentanoate (6·0 g) in dry THF (250 ml), and dry EtOAc (250 ml) was reduced by diborane externally generated from $NaBH_4$ (5·64 g) in diglyme (110 ml) and BF_3OEt_2 (30 ml) in diglyme (40 ml). The boron complexes were decomposed by addition of MeOH (150 ml) and heating under reflux for 30 min. After removal of the solvents the *methyl indolylpentanoate* (5·6 g; 98%) was obtained, and crystallized from light petroleum to give flake m.p. 52–53°. (Found: C, 72·6; H, 7·7; N, 6·25. $C_{14}H_{17}NO_2$ requires: C, 72·7; H, 7·4; N, 6·1%); NMR ($CDCl_3$): NH, 2·1 b; 7-H, 2·4 m; 4, 5, 6-H, 2·6–3·0 m; 2-H, 3·10 d (J = 2·5); OMe, 6·37; Ind-CH_2, 7·64 t; CH_2CO—, 7·24 t; —(CH_2)—, 8·0–8·4 m; mass spectrum, *m/e* (%): 231 (31), 200 (7), 156 (5), 144 (5), 143 (5), 131 (13), 130 (100), 117 (4), 103 (4), 77 (6); λ_{max} (log ε_{max}) in EtOH: 226 (4·36), 276 (3·88), 282 (3·89), 291 (3·80) nm.

1,1-*Di*-^{2}H-5-(3-*indolyl*) *pentan*-1-*ol*

The foregoing ester (1·5 g) in dry THF (80 ml) was added to a stirred suspension of LAD (0·32 g) in THF (30 ml) under dry N_2. The mixture was stirred at 20° for 4 hr and the complex destroyed with saturated Rochelle salt. Extraction with $CHCl_3$ etc gave a pale yellow oil, which was shown to be the required alcohol by NMR and mass spectrum e.g. the NMR spectrum was identical with that of the undeuterated alcohol except that the triplet at 6·42 was less than 10% of the intensity showing that deuteration was over 90% complete; Mass spectrum: *m/e* (%): 205 (31), 149 (25), 144 (5), 143 (5), 131 (25), 130 (100), 117 (3), 103 (5), 77 (7).

The corresponding tosylate was also prepared (70% yield) in the same manner as its undeuterated analogue and crystallized as plates m.p. 47–48° from benzene/light petroleum. The NMR spectrum showed no signal at 6·0 as would have been expected for the undeuterated compound (see above), and thus some further fractionation in favour of deuterated material must have occurred during the preparation or crystallization. This was confirmed by the mass spectrum, *m/e* (%): 359 (2), 223 (21), 188 (6), 187 (5), 186 (3), 158 (3), 156 (3), 144 (6), 143 (5), 131 (29), 130 (100), 117 (6), 115 (6), 103 (8), 102 (5), 77 (12), 91 (5).

Tosylate solvolyses

The solvolyses were carried out in acetone/water (80/20: v/v), the acetone being purified by means of its NaI complex or by passage through an alumina column followed by distillation. The solid tosylates were purified by recrystallization to constant m.p. and the liquid tosylates by thick layer chromatography on silica gel.

Each tosylate (~0·01M) was dissolved in acetone (80 ml) and water (20 ml) measured at 0°. 10 ml portions 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 temp. The tubes were removed at intervals and titrated with 0·05M NaOH using bromothymol blue as indicator, zero time being counted as 2 min after immersion.

All the solvolyses showed good first order kinetics, and the results are shown in Table 1. Product analyses were carried out by column chromatography on silica gel or by preparative thick layer chromatography on silica gel or by preparative thick layer chromatography of 0·01M samples after solvolyses at 80° over twelve half-lives. GLC (on 5% silicone oil) was also used in the case of the indolylproply tosylate.

(a) Tryptophol tosylate (IIa) and indolyl propyltosylate (IIb) both gave the corresponding alcohols in 90–95% yields together with a small amount of tarry by-product R_f 0·0 on TLC.

(b) Indolylbutyltosylate (IIc) was solvolysed in deoxygenated solvents and after evaporation of the acetone the organic material was extracted into ether. The ether was washed with $NaHCO_3$ aq, water, and

dried ($MgSO_4$) before evaporation to dryness under reduced press. The residual solid (which consisted largely of tetrahydrocarbazole together with a small amount of alcohol, as shown by TLC) was chromatographed over silica gel and gave tetrahydrocarbazole (78%) as plates, m.p. 115–117° from aqueous EtOH.

The yield of alcohol (Ic) was about 10% but it was difficult to measure accurately owing to its oily nature and relative instability; the only other product (apart from the tetrahydrocarbazole) ran at the base line on TLC and was presumably polymeric in nature.

(c) Solvolysis of the indolylpentyltosylate (IId) gave over 90% yield of the alcohol, although traces of cycloheptindole were detected on TLC.

The 1,1-dideutero-5(3-indolyl) pentyl-1-p-toluene sulphonate was also solvolysed in the same manner and gave the 1,1-dideuteropentyl alcohol in 90% yield. The NMR spectrum of the latter was devoid of a signal due to $—CH_2$ (OH) at τ 6·4 thus showing that it had been formed by direct solvolysis without participation by the indole nucleus.

Dissection of solvolysis rate (k) *for the indoyl butyl tosylate* (IIc)

The overall solvolysis rate (k) was dissected into two parts, (k_s for solvolysis of the tosylate without participation) and K_Δ (for solvolysis involving participation), following Winstein's example in the benzene series.[8] Since $K = K_s + K_\Delta$ then the percentage yield of tetrahydrocarbazole expected would be $(K/K_s + K_\Delta) \times 100\%$. Assuming that there is virtually no participation by the indole nucleus in the solvolysis of the indolylpropyl tosylate (since it solvolyses at a very similar rate to ethyltosylate) then its rate of solvolysis can be substituted for K_s in the above relationship. Thus at 84·25° for example $K_s = 1{\cdot}20 \times 10^{-5}$ moles/litre/sec. and K (the rate of solvolysis of indolylbutyltosylate) $= 1{\cdot}55 \times 10^{-4}$ moles/litre/sec and hence $K = 1{\cdot}43 \times 10^{-4}$ moles/litre/sec. Therefore the yield of spirocyclic indolenine (and hence of its rearrangement product tetrahydrocarbazole) predicted on this bases $= (1{\cdot}43/1{\cdot}55) \times 100\% = 81\%$. This value agrees very well with the experimental value 78% recorded above.

To check that the spirocyclopentyl indolenine (IIIc or IX) was not undergoing ring cleavage with regeneration of the indolylbutanol it was heated with *p*-toluenesulphonic acid (1 equiv) in 80% acetone–water at 75° for 5 days. On work up as above tetrahydrocarbazole (93%) mp. 116–117° (from aqueous ethanol) was obtained and TLC confirmed that none of the alcohol had been formed.

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