Tetrahedron Vol 24, pp 6119 to 6129 Pergamon Press 1968. Printed in Great Britain

ELECTROPHILIC SUBSTITUTION IN INDOLES—IV[1]

THE CYCLIZATION OF INDOLYLBUTANOL TO TETRAHYDROCARBAZOLE*

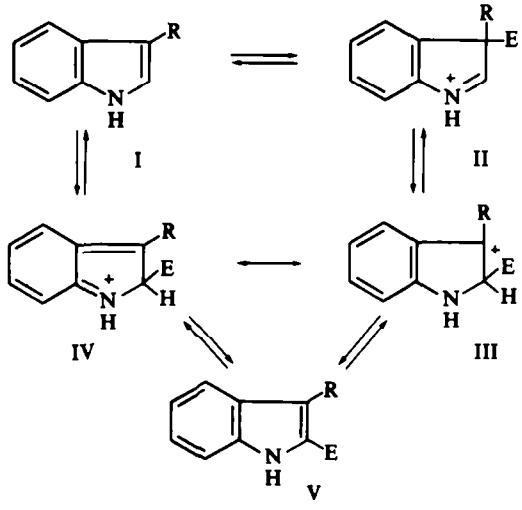
A. H. JACKSON, B. NAIDOO and P. SMITH

The Robert Robinson Laboratories, University of Liverpool

(*Received in the UK* 14 *May* 1968; *accepted for publication* 16 *May* 1968)

Abstract—The use of tritium labelling has shown that 3,3-spirocyclopentanoindolenine is an intermediate in the BF_3 catalysed cyclization of 4-(3-indolyl)butanol to tetrahydrocarbazole. This confirms our earlier suggestion that electrophilic substitution at the 2-position of a 3-substituted indole occurs by an indirect process involving prior attack at the 3-position followed by rearrangement.

AS PREVIOUSLY suggested,[1,2] electrophilic substitution at the 2-position of a 3-substituted indole (I) may occur by an indirect process involving initial attack at the 3-position followed by rearrangement to give the 2,3-disubstituted indole (V). The individual steps in this pathway (I → II → III → V) are shown in the accompanying reaction scheme, together with those of the alternative direct substitution process (I → IV → V). Whether or not π-complex formation precedes (or accompanies) formation of the π-complexes II and IV is a debatable point. Indeed, the role of π-complexes in electrophilic substitution in the benzene series is still a matter for controversy, and we do not therefore wish to discuss it in this paper as we have no evidence to bear on the question at this juncture. However it is not inconceivable that π-complexes play a more important role in the reactions of indole (and other "π-excessive" heterocyclic compounds) than they do in the reactions of benzene.



* Preliminary communication: A. H. Jackson and P. Smith, *Chem. Comm.* 260 (1967).

Energy profiles for the two alternative reaction pathways are shown in Fig. 1, and to simplify discussion, the possible intermediacy of π-complexes has been neglected. As we,[2] and others,[3] have pointed out previously, direct electrophilic substitution at the 2-position of the indole nucleus is energetically unfavourable (compared with attack at position 3) because it involves formation of an intermediate (IV) in which the

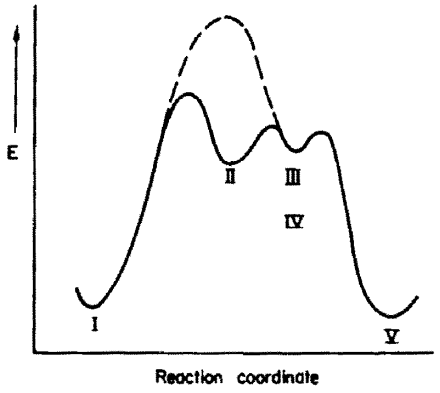


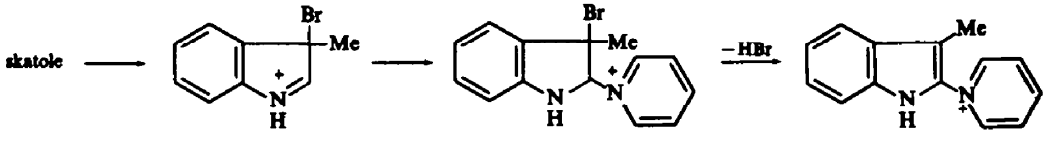
FIG. 1

π-electron system of the benzene ring has been disturbed. On the other hand substitution at the 3-position gives an intermediate indolenine (II) without involving the benzene ring, and, insofar as indole may be regarded as an enamine derived from aniline, this is also consistent with the normal mode of attack of electrophiles on enamines.[4] The energy barrier to the rearrangement II → III will presumably vary greatly with the nature of the substituents, but as we have already shown indolenines of type II (prepared by alkylation of indole Grignard derivatives) readily rearrange under acidic conditions to 2,3-disubstituted indoles.[1,5] These rearrangements are of the Wagner–Meerwein, 1,2-type, and as expected, which substituent migrates is controlled by their relative migratory aptitudes.[6] Loss of a proton in the final step (III → V) with regeneration of the fully aromatic indole nucleus would be expected to occur with great facility, and the energy barrier may be little more than an inflection in the curve. Intermediates III and IV are of course mesomeric forms of each other, and they are thus shown in the same position of the energy profile.

Electrophilic substitution reactions in indoles have been shown to take place under a variety of acidic, neutral and basic conditions.[7,8] However the majority of reactions described in the literature have been under acidic conditions, e.g. the reactions of indoles with aldehydes and ketones, and the cyclization of tryptamines with aldehydes to give tetrahydro-β-carbolines. Friedel–Crafts alkylation of indoles are little known, presumably because of the tendency towards polyalkylation, and the tendency of both starting material and product to polymerize under acidic conditions. Acylations, with or without catalysts, or through the agency of Vilsmeier reagents are, however, well-known and have proved of great utility in synthesis; polyacylation does not occur as the first acyl group introduced diminishes the reactivity of the indole nucleus to further attack. Nitration and sulphonation of the indole nucleus have been comparatively little studied to date, but halogenation reactions received a considerable amount of attention at the turn of the century. Examples of base catalysed reactions

of indoles include alkylation and acylation of indole Grignard reagents and alkali metal salts at the 1- and 3-positions, alkylations at the 3-position with alcohols at high temperatures, acylation at the 1- and 3-positions in presence of sodium acetate, and Michael-type reactions with unsaturated esters at the 1- and 3-positions. These base catalysed reactions usually only take place with N-unsubstituted indoles, and presumably involve the more reactive ambident indolyl anion, so that the activation energy is much lower than in the acid catalysed reactions (where the function of the acid is to increase the potency of the electrophile).

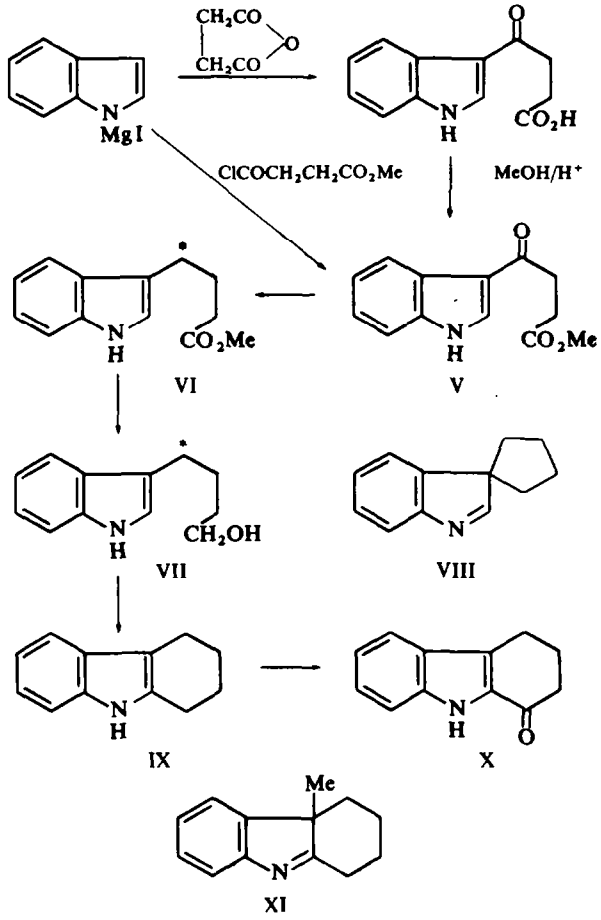
Bearing these considerations in mind it is not difficult to see why 3,3-disbustituted indolenines can only be isolated from alkylations of 3-substituted indoles under essentially alkaline conditions; in acidic media the rather more vigorous conditions generally used, or the high migratory aptitude of one of the substituents, would result in rearrangement to the 2,3-disubstituted indole. Thus the formation of such a 3,3-disubstituted indolenine (i.e. II) if it occurs in acid catalysed electrophilic substitution reactions of 3-substituted indoles can only be inferred by some indirect means, e.g. (i) by displacement of the 3-substituent already present into the 2-position and its replacement by the incoming electrophile,[cf. 5,9] or (ii) by trapping the presumed intermediate indolenine (II) by addition of an appropriate nucleophile to the 1,2-double bond. Some examples of the latter process have been discussed in our other papers,[9,10] and an interesting new example has been discovered by Noland in the reaction of indoles with quinones.[11] A related reaction presumably occurs in the treatment of skatole with N-bromsuccinimide in pyridine,[12] the initially formed indolenine undergoing addition at the 2-position, followed by elimination of hydrogen bromide as shown.



In the present paper we wish to discuss an investigation involving the first of the two approaches outlined above. A cyclization of the indolylbutanol (VII) under Friedel Crafts conditions was chosen because this might be expected to occur fairly cleanly without the complication of polyalkylation, and moremóver the product, being a 2,3-disubstituted indole, would be fairly resistant to polymerization. This approach was also attractive because of the parallel with the cyclization of alkylidene tryptamines to tetrahydro-β-carbolines which occurs under mildly acidic conditions, and is also presumably involved in the biosynthesis of a large number of indole alkaloids.[cf. 2]

The required indolylbutanol (VII) was prepared from indole as shown below via the keto-ester (V); in the acylation of the indole Grignard derivative the 1,3-diacyl derivative was also formed. Reduction of the keto-ester with tritiated diborane (generated externally from sodium borotritiide) in tetrahydrofuran-ethyl acetate then gave the indolylbutyrate (VI). (The ethyl acetate served to inhibit the slow reduction of the ester group which would otherwise have occurred.[13]) Further reduction of the ester (VI), in a separate step, with an excess of inactive diborane in tetrahydrofuran alone then gave the desired indolylbutanol (VII) specifically labelled with tritium

in the methylene group neighbouring the indole nucleus. On brief heating with boron trifluoride etherate the indolylbutanol then afforded tetrahydrocarbazole (IX) in good yield, and all that remained was to establish the distribution of the tritium label. Direct cyclization at the α-position of the indole nucleus would have given tetrahydrocarbazole labelled exclusively in the 4-position, whereas the indirect process involving initial substitution at the β-position to give the *symmetrical* spirocyclic indolenine (VIII) followed by rearrangement would afford tetrahydrocarbazole with the tritium label distributed *equally* between the 1- and 4-positions.



Several approaches to the possibility of oxidizing the 1-methylene group of tetrahydrocarbazole were investigated in preliminary experiments, e.g. via the 11-hydroperoxide, or by conversion to the 11-methylcarbazolenine (XI) followed by autoxidation or oximination, but these unfortunately met with little success. Another possibility considered, but not investigated, was base catalysed exchange of the hydrogens at the 1-position of the 11-methylcarbazolenine (XI), as other work in progress at this time had confirmed that these were acidic towards Grignard reagents.[10] However at this point in our work Dolby and Booth reported[16] that periodic acid oxidation of tetrahydrocarbazole gave the 1-oxo derivative (X) in good yield and we therefore immediately applied this reaction to our radioactive tetrahydrocarbazole. The activity

of the 1-oxotetrahydrocarbazole obtained was about 53–55% of that of the indolylbutanol (VII) and the indolyl butyrate (VI) thus providing very good evidence for the intermediacy of the spirocyclic indolenine (VIII) in the cyclization.

The results of three separate cyclization experiments are recorded in the Experimental, and it is interesting to note that the activity of the 1-oxotetrahydrocarbazole was consistently slightly greater than 50% of that of its precursors. Three reasons for the slight deviation from the nominal 50% may be advanced, (i) that there is a slight secondary isotope effect in the rearrangement of the intermediate spirocyclic indolenine (VIII), (ii) that a small amount of tritium had been incorporated into the benzene ring during diborane reduction of the keto-ester (V), and (iii) that a small percentage of the indolylbutanol had cyclized by direct substitution at the 2-position of the indole nucleus. The third possibility seems unlikely in view of the evidence accumulating from all our other work, although it cannot be entirely excluded (see below) but the first possibility seems very likely in the light of the well known high primary isotope effect observed with tritium. Evidence for a small amount of exchange of the aromatic hydrogens for tritium during the diborane reduction was provided by the reduction of inactive 1-oxotetrahydrocarbazole (X) with tritiated diborane, followed by periodic acid oxidation; the recovered 1-oxotetrahydrocarbazole (X) contained about 1% of the activity in the starting material.

A number of other possible interpretations of our results have geen considered, but all have been rejected for the reasons outlined below.

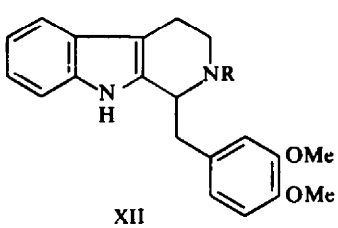
(i) Exchange of tritium at the 4-position of tetrahydrocarbazole might have occurred, either under the acidic conditions of the cyclization reaction, or of the periodic acid oxidation. This seems very unlikely not only on the basis of the known chemistry of indole, but also because of the consistency of the results which were not dependent on the precise time of reaction etc. Moreover subjection of active 1-oxotetrahydrocarbazole (X) to a further period of contact with periodic acid did not diminish its specific activity.

(ii) Another possibility is that under the conditions of the cyclization reaction tetrahydrocarbazole (formed either directly or indirectly) might equilibrate with the spirocyclic indolenine (VIII). However, treatment of 1-^{3}H-tetrahydrocarbazole with boron trifluoride etherate under the same conditions as those used in the cyclization experiments, followed by oxidation afforded 1-oxotetrahydrocarbazole of negligible activity, thus showing that no such equilibration had occurred.

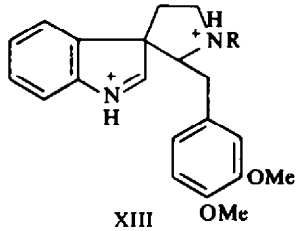
(iii) The spirocyclic indolenine might be formed initially, but could then rearrange by ring-opening followed by the admittedly less favourable direct cyclization at the 2-position. In terms of the scheme set out at the beginning of this paper this would be equivalent to equilibration between I and II accompanied by a slow, energetically unfavourable, formation of IV and its virtually irreversible conversion to the 2,3-disubstituted indole (V). This objection also seems untenable, especially in our cyclization reaction, because it implies the formation of a free carbonium ion in the ring-opening of the spirocyclic indolenine, and our previous experiments on the rearrangement of 3,3-disubstituted indolenines have demonstrated[1] that the process is strictly intramolecular, e.g. no cross-over occurs in the simultaneous rearrangement of 3,3-dimethyl- and 3,3-diethyl-indolenines in the same reaction medium.

However, although the experiments described above showed that tetrahydrocarbazole (IX) does not equilibrate with the spirocyclic indolenine under mildly acidic

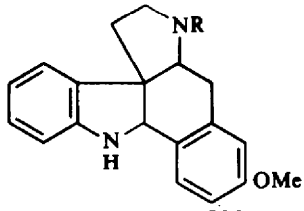
conditions, the possibility that such an equilibration occurs in strongly acidic media was investigated because Harley-Mason and Waterfield[17] have shown that the tetrahydrocarboline (XII) rearranges in boiling concentrated hydrochloric acid to the spirocyclic indoline (XIV), presumably via the spirocyclic indolenine (XIII). Harley-Mason has also described further examples of this type of reaction more recently.[18] 1-^{3}H-Tetrahydrocarbazole was therefore heated under reflux in boiling concentrated hydrochloric acid and its activity redetermined. After 45 min the tritium content had decreased to 42%, and after 2 hr to 21% of that in the starting material; periodic acid oxidation of the recovered tetrahydrocarbazole gave 1-oxotetrahydrocarbazole with activities 2·9% and 2·8% respectively. The latter result showed that little rearrangement



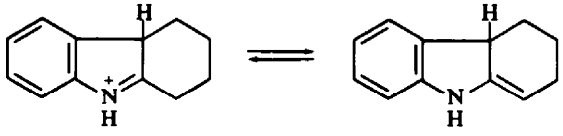
XII



XIII

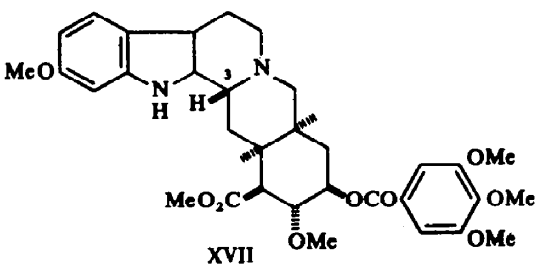


XIV

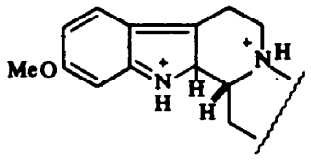


XV XVI

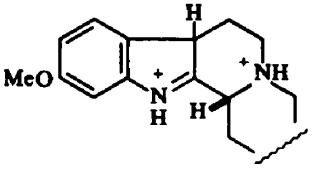
had occurred for part of the residual activity in the 1-oxotetrahydrocarbazole can be attributed to tritiation of the aromatic nucleus during the diborane reduction. The loss of tritium from the 1-position of the tetrahydrocarbazole under these strongly acidic conditions may be accounted for by equilibration of the conjugate acid (XV) with the tetrahydrocarbazolenine (XVI), although very little of the latter can be present for the UV spectrum of tetrahydrocarbazole in concentrated hydrochloric acid, and the NMR spectrum in trifluoroacetic acid are entirely consistent with the indolium salt structure (XV). The results obtained in the detritiation experiments were confirmed by heating tetrahydrocarbazole in deuterated hydrochloric acid for 30 min; the NMR spectrum of the recovered tetrahydrocarbazole showed that the intensities of both the aromatic and the 1-methylene proton resonances were considerably diminished as a result of deuterium exchange, and the mass spectra showed that up to six deuterium atoms had been incorporated.



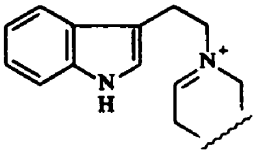
XVII



XVIII



XX



XIX

These experiments clearly indicated that equilibration of tetrahydrocarbazole with the spirocyclic indolenine (VIII) in strong acid is much less pronounced than the similar reaction in the tetrahydro-β-carboline series. On the other hand it could be argued that formation of the presumed spirocyclic intermediate (XIII) in Harley-Mason and Waterfield's example[17] is effected by initial protonation at the α- (rather than the β-) position followed by rearrangement. This possibility is supported by Gaskell and Joule's recent finding[19] that the epimerisation at C_3- in reserpine (XVII) can be accomplished without exchange of the 3-hydrogen, e.g. in boiling acetic acid the 3-deuterio analogue epimerises but does not exchange. At higher temperatures exchange also occurs presumably by a rather similar mechanism to that which we have suggested for the exchange at the 1-position in tetrahydrocarbazole, although participation by N-*b* cannot be excluded. The mechanism of epimerisation cannot however involve formation of a double bond at C_2-C_3 or at C_3-N*b* as this would exchange the C_3-H and Gaskell and Joule conclude that protonation occurs at the α-position of the indole nucleus followed by ring opening as shown in the accompanying scheme; ring closure then leads to the observed epimerization with retention of the C_3—H as cyclization of the Schiff's base (XIX) can occur either from below or from above the plane of the indole nucleus. The 11-methoxy group in reserpine probably assists in the epimerization because deserpidine (the 11-desmethoxy analogue of reserpine) epimerizes more slowly at a higher temperature and exchange occurs simultaneously. Acceptance of Gaskell and Joule's mechanism is, however, at variance with our results in the tetrahydrocarbazole cyclization for it involves direct electrophilic attack (i.e. protonation) at the α-position of the indole nucleus. On the other hand it may be that when the favoured attack (i.e. protonation at the indole β-position to give XX) does not lead to any further product then the energetically unfavourable pathway[ref. 3] (i.e. protonation at the indole α-position to give XVIII) becomes more important as it leads to XIX. Another possible explanation, which we are inclined to favour, is that protonation occurs at the β-position first (to give XX) and this is followed by hydride rearrangement to the α-position (to give XVIII); we have suggested a

similar mechanism for the slow rate of exchange of deuterium at the α-position of indole under strongly acidic conditions. On the basis of our mechanism cyclization of the Schiff's base (XIX) would take place first at the 3-position and a rearrangement would regenerate the β-carboline (XVII).

In conclusion, therefore, the results described in this paper clearly support our contention that electrophilic alkylation of 3-substituted indoles at the 2-position is largely (if not completely) an indirect process, i.e. I → II → III → V. The indolenine (II) may be regarded as the product of kinetic control, whereas the thermodynamically controlled product is the 2,3-disubstituted indole (V). Only under the less vigorous conditions of base catalysed alkylations (e.g. of indole Grignard derivatives) in which the indole is activated towards electrophilic attack, is it possible to isolate the kinetically controlled product (II). Further work on the kinetics of the reactions we have discussed, and of related reactions, is in progress and will be described in a later paper. Meanwhile it is interesting to note that isopropylation of methylpyrrole-2-carboxylate in presence of aluminium chloride gives a mixture of the 4- and 5-isopropyl and the 4,5-diisopropyl derivatives,[20] and evidence has been presented that initial attack at the kinetically favoured 4-position is followed by rearrangement to the 5-position;[20] the 4,5-diisopropylpyrrole arises by further alkylation at the highly reactive 4-position of the 5-isopropyl derivative.

EXPERIMENTAL

M.pt are uncorrected. UV, NMR and mass spectra were determined with Unicam SP 800, Varian A-60 and HA-100, and A.E.I. MS9 spectrometers respectively.

Radioactive assays. Activities were measured by scintillation counting in toluene soln with a Packard "Tri-Carb" Scintillation Counter. Efficiencies (~20% for ^3H) were determined by internal standardization. Each sample was recrystallized first to constant m.p. and then to constant activity (±2%).

Methyl 4-(3-indolyl)4-oxobutyrate

(a) Excess EtBr (7·0 g) was added to Mg turnings (1·2 g) in dry ether (50 ml) and warmed gently until reaction started. When all the Mg had dissolved dry benzene (50 ml) was added and the ether and excess EtBr were distilled out. Indole (5·8 g) in benzene (20 ml) was then added slowly and the soln heated under reflux for 30 min. β-Methoxycarbonylpropionyl chloride (8·5 g) in ether (15 ml) was next added dropwise, with stirring, to the cooled soln, and the mixture poured into 2N HCl (50 ml). The ether layer was separated, the aqueous layer re-extracted with ether (2 × 40 ml) and the combined extracts dried ($MgSO_4$) and evaporated to dryness. The residual oil was chromatographed on alumina (Brockmann Grade I) in benzene.

The first fraction, eluted with benzene, gave *1,3-di-(2-methoxycarbonylpropionyl) indole* (2·0 g; 12%) which crystallized from benzene as needles, m.p. 153°. (Found: C, 62·9; H, 5·6; N, 4·1. $C_{18}H_{19}NO_6$ requires: C, 62·6; H, 5·6; N, 4·1%). NMR ($CDCl_3$); Indole 4·7-H ~1·6 *m*; 5,6-H ~2·7 *m*; 2-H 1·89; OCH_3 6·28, 6·30; $—CH_2CH_2—$ 6·6–6·9 *m* 7·0–7·4 *m*, Mass spectrum: *m/e* (%); 345 (15) M^+, 314(4) $(M\text{-}OMe)^+$, 254 (6), 231 (28), 200 (13), 144 (100), 117 (8), 116 (20), 115 (85), 89 (43), 88 (6), 87 (15), m*: 154·7 (345 → 231); 43·6 (144 → 116); 68·3 (116 → 89).

The second fraction eluted with ether/EtOAc afforded the desired *methyl indolyl oxobutyrate* (3·5 g; 31%) which crystallized from alcohol as needles, m.p. 110–111°. (Found: C, 67·8; H, 5·6; N, 6·3. $C_{13}H_{13}NO_3$ requires: C, 67·5; H, 5·7; N, 6·1%). NMR ($CDCl_3$); NH, 0·1; 7-H, ~1·6 *m*; 2-H, 2·28 *d*; 4,5,6-H, 2·6–2·9 *m*; CH_2-CH_2, ~6·9 *m*, ~7·25 *m*; OCH_3, 6·35 τ. Mass spectrum: *m/e* (%); 231 (60) M^+, 200 (25) $(M\text{-}OMe)^+$, 172 (5) $(M\text{-}CO_2Me)^+$ 145 (28), 144 (100) $(M\text{-}CH_2CH_2CO_2Me)^+$, 143 (12), 117 (7), 116 (29), 115 (10), 100 (4), 90 (5), 89 (30), 72 (13). m*: 148 (200 → 172); 93·5 (144 → 116); 89·7 (231 → 144); 68·3 (116 → 89).

(b) EtI (32 g) was added dropwise to Mg turnings (5·0 g) in anisole (50 ml) heated to 60°. When all the Mg had dissolved the soln was cooled and indole (23 g) in anisole (50 ml) added dropwise and the temp raised to 70° for 30 min to complete reaction. After cooling again succinic anhydride (20 g) in anisole

(100 ml) was added rapidly with vigorous stirring. The mixture became hot and a bright red complex was formed. After heating for 1 hr on a boiling water-bath the mixture was cooled and poured into glacial AcOH (30 ml) in water (150 ml). The keto-acid, which precipitated, was filtered off, washed with water, and dissolved in 10% NaOH aq. The acid was reprecipitated with SO_2, filtered off, washed in water, dried, and crystallized from EtOH. The keto-acid (20·5 g; 51%) formed micro-needles m.p. 239–240° (lit.[21] m.p. 240–241°) and was converted into the methyl ester by dissolving in MeOH containing 3% conc. H_2SO_4 (v/v). After allowing the soln to stand overnight at 20° it was poured into AcONa, and the ester extracted into CH_2Cl_2 (2 × 300 ml). The extracts were washed with water, dried ($MgSO_4$) and evaporated to dryness. The residue crystallized from benzene to give the methyl indolyloxobutyrate (18·2 g; 83%) as needles m.p. 116–118°.

Ethyl 4-(3-*indolyl*)4-*oxobutyrate* was prepared in a similar fashion from indole Grignard derivative and 3-ethoxycarbonyl propionyl chloride. It formed needles, m.p. 131–132° from EtOH. (Found: C, 68·3; H, 6·1; N, 5·7. $C_{14}H_{15}NO_3$ requires: C, 68·55; H, 6·16; N, 5·7%); NMR ($CDCl_3$); NH, ~0·5; 4-H, ~1·6 *m*; 2-H, 2·26 *d*; 5,6,7-H, 2·6–2·8 *m*; —CH_2—CH_2—, 6·87 *t*; 7·22 *t*; CH_3—CH_2—O—, 8·76 *t*; 6·84 *q* τ.

Methyl 4-(3-*indolyl*) *butyrate*

(a) Diborane, generated from $NaBH_4$ (0·68 g) in diglyme (14·0 ml) and BF_3-etherate (3·9 ml) was passed into a soln of 3-(2-methoxycarbonylpropionyl) indole (0·69 g) in dry THF (15 ml) and dry EtOAc (15 ml). After 10 min the solvents were evaporated under reduced press at 35°, MeOH (15 ml) was added, and the mixture heated under reflux for 15 min. The MeOH was evaporated to dryness and the residual oil (0·7 g) crystallized from MeOH to give methyl 4-indolylbutyrate (0·33 g; 51%) as needles m.p. 71–72° (lit.[22] 72–73°).

(b) 4-^{3}H Methyl 4-(3-indolyl)butyrate was prepared in the same manner as the unlabelled material by the "sandwich" technique i.e. the diborane generator was charged first with a quarter of the inactive borohydride, then with the tritiated borohydride (0·010 g; 50 μC/mmole), and finally with the remainder of the inactive borohydride.

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

(a) Diborane, generated from $NaBH_4$ (2·5 g) in diglyme (10 ml) and BF_3-etherate (15 ml) was passed into methyl 4-(3-indolyl)butyrate (0·27 g) in dry THF (25 ml). The mixture was kept for 1 hr at 20° and then evaporated to dryness. Excess diborane and borane complexes were destroyed by heating the residue with MeOH (15 ml) under reflux for 15 min. The soln was then re-evaporated to dryness and gave the desired indolylbutanol (0·23 g; 90%) as a viscous oil; NMR ($CDCl_3$): Ind-7-H, ~2·4 *m*; 4,5,6-H, ~2·8 *m*; 2-H, 3·15 *d*; NH, 1·8; Ind—CH_2—7·30 *t*; —CH_2—O, 6·43 *t*; —CH_2—CH_2— ~8·35 *m*.

Attempts to distil this product at 120° under reduced press (0·01 mm) led to decomposition and formation of some tetrahydrocarbazole.

(b) The 4-^{3}H 4-(3-Indolyl)butanol was prepared in the same manner from the labelled indolyl butyrate.

(c) 4-(3-Indolyl)4-oxobutanoic acid (2·2 g) in THF (90 ml) was reduced with diborane generated from $NaBH_4$ (0·85 g) in diglyme (22 ml) BF_3 (4·5 ml) in diglyme (15 ml). The soln was left to stand overnight, then evaporated to dryness and the residual oily complex decomposed by heating under reflux with MeOH (50 ml) for 30 min. The solvent was removed *in vacuo* to leave the oily 4-(3-indolyl)butanol (1·6 g), which was identical spectroscopically and by TLC with the product obtained in (a) above.

1,2,3,4-*Tetrahydrocarbazole*

(a) The foregoing indolylbutanol (0·42 g) was heated under reflux with BF_3-etherate (20 ml) for 1 hr, and the product poured into water. The mixture was extracted with ether (3 × 50 ml), the extracts washed with water, dried ($MgSO_4$), and evaporated to dryness. The residual yellow solid crystallized from aqueous alcohol to give tetrahydrocarbazole (0·28 g; 70%) as plates, m.p. 118·5–119·5°; NMR ($CDCl_3$): NH, ~2·6; 7-H ~2·6 *m*; 4,5,6-H, 2·8–3·0 *m*; 1,4-CH_2, 7·25–7·45; 2,3-CH_2, 8·05–8·2 *m*; (TFA): Ar-H, 2·34, 11-H, 2·85 *m*; 1-CH_2, 6·5–7·0 *m*; 4-CH_2, 6·8–7·0 *m* and 7·2–7·5 *m*; 2,3-CH_2, 7·8–8·4 *m* τ; mass spectrum, *m/e* (%): 171 (58) M^+, 170 (22), 168 (8), 167 (6), 154 (4), 144 (13), 143 (100), 142 (4), 130 (4), 128 (5), 166 (3), 115 (10), 102 (4), 85·5 (5) M^{2+}, 83·5 (5), 77 (6). m*: 166 (170 → 168); 141 (143 → 142); 119·5 (171 → 143); 114·8 (143 → 128).

(b) Cyclization of the tritiated indolyl butanol was effected in the same manner on a 0·25 g scale. In some experiments it was found more convenient to dilute the crude product with inactive material (1–2 g) and obtain tetrahydrocarbazole of lower activity which was still perfectly satisfactory for oxidation to the 1-oxo derivative to determine the distribution of the tritium label.

1-Oxo-1,2,3,4-tetrahydrocarbazole[cf. 16]

(i) 1,2,3,4-Tetrahydrocarbazole (2·1 g) in MeOH (50 ml) was added dropwise to a stirred soln of periodic acid (6·0 g) in water (10 ml) and MeOH (25 ml). After keeping for 30 min at 20° the soln was diluted with water, and extracted with ether (2 × 100 ml). The ether extracts were washed with $Na_2S_2O_3$ aq, then with water, dried ($MgSO_4$) and evaporated to dryness. The residue crystallized from aqueous acetone to afford the 1-oxotetrahydrocarbazole (1·3 g; 60%) as pale cream needles, m.p. 169–170°; NMR ($CDCl_3$): NH ~0·5; Ar-H, 2·35–3·0 *m*; 4-CH_2, 7·05 *t*; 2-CH_2, 7·34 *t*; 3-CH_2 ~7·78 *m* τ.

(ii) Tritiated tetrahydrocarbazole, prepared by cyclization of the tritiated indolyl butanol, was oxidized in the same manner and the 1-oxo derivative prepared was crystallized to constant m.p. and constant activity (see Table below).

This active 1-oxotetrahydrocarbazole (20 ml) was treated in the same manner with a further quantity of periodic acid (1·5 g) in aqueous MeOH for 3½ hr. After work-up the recovered 1-oxotetrahydrocarbazole (12 mg) had m.p. 171–172°, and showed no diminution in activity.

TABLE 1. RESULTS OF RADIOACTIVE TRACER EXPERIMENTS ON THE CYCLIZATION OF 4-(3-INDOLYL)BUTANOL TO TETRAHYDROCARBAZOLE

	Molar activity (millicuries/mole)		
	(a)	(b)	(c)
1. Methyl 4-(3-indolyl)butyrate	1·04	60·0	52·4
2. 1,2,3,4-Tetrahydrocarbazole (undiluted)	1·01	—	—
3. 1,2,3,4-Tetrahydrocarbazole (diluted)	0·0430	0·252	0·173
4. 1-oxo-1,2,3,4-tetrahydrocarbazole	0·0241	0·130	0·0935
Ratio $\frac{\text{activity in 1-oxu-THC}}{\text{activity in THC}} \times 100$	56%	52%	54%

1-^{3}H-1,2,3,4-Tetrahydrocarbazole

(a) *Preparation.* Inactive 1-oxotetrahydrocarbazole (0·6 g) in THF (30 ml) was reduced with diborane generated from $NaBH_4$ (1·2 g) and tritiated $NaBH_4$ (0·004 g) in diglyme and BF_3-etherate (6 g) in diglyme (30 ml) using the "sandwich" technique described above.

The soln was kept for 2 hr at 20°, evaporated to dryness and the residual complex decomposed by heating for 15 min with MeOH (15 ml). After removal of the methanol *in vacuo* the 1-^{3}H-tetrahydrocarbazole remaining was recrystallized from EtOH and gave plates (0·35 g; 60%) m.p. 115–116°. After reoxidation to 1-oxotetrahydrocarbazole less than 1% of the activity remained showing that the label was almost entirely in the 1-position.

(b) *Treatment with borontrifluoride etherate.* The foregoing 1-^{3}H-tetrahydrocarbazole (0·35 g) was heated in soln with BF_3-etherate (10 ml) under reflux for 1 hr. The product was poured into water, ether extracted and the ether extracts dried ($MgSO_4$) and evaporated to dryness. The residue crystallized from EtOH and gave plates m.p. 115–116° whose activity was the same as the starting material. This product was then oxidized to 1-oxotetrahydrocarbazole, as described above; the latter proved to contain only 3% of the activity of the starting material showing that the tritium label in the tetrahydrocarbazole had largely remained in the 1-position.

(c) *Treatment with concentrated hydrochloric acid.* The tritiated tetrahydrocarbazole (3·5 g) in conc HCl (140 ml) was heated (under N_2) under reflux for 45 min. The acid was then evaporated to dryness and the residue crystallized from EtOH to give tetrahydrocarbazole (3·0 g) m.p. 118–119°, which was then re-crystallized to constant activity. Finally it was oxidized to 1-oxotetrahydrocarbazole as described above and the product again re-crystallized to constant activity.

The experiment was repeated under the same conditions, but lengthening the period of heating with HCl to 2 hr, and the activities of the recovered tetrahydrocarbazole and the 1-oxo derivative determined (see theoretical section).

1-^{2}H-1,2,3,4-Tetrahydrocarbazole

1,2,3,4-Tetrahydrocarbazole (100 mg) was heated in a sealed tube with conc DCl in D_2O (2·5 ml) at 100°

for 30 min and left to cool overnight. The mixture was then poured into water, extracted with $CHCl_3$, and the extract washed with water and dried ($MgSO_4$). The partially deuterated tetrahydrocarbazole (80 mg) crystallized from alcohol, as plates, m.p. 115–116°. The integral of the 1,4-methylene proton resonances at 7·35 τ corresponded to 74% of that of the 2,3-methylene proton resonances at 8·15 τ in $CDCl_3$. The aromatic proton resonances were also considerably diminished in intensity owing to exchange for deuterium.

The mass spectrum showed that a mixture of deuterated species had been formed with incorporation of 0–6 deuterium atoms (5 being the most abundant). *m/e* (%): 177 (37), 176 (59), 175 (39), 174 (15), 173 (12), 172 (12), 171 (9), 170 (4), 150 (10), 149 (67), 148 (100), 147 (67), 146 (10), 136 (5), 135 (7), 134 (9), 133 (10), 132 (10), 131 (8), 130 (7), 121 (10), 120 (15), 119 (17), 118 (60), 117 (7), 106 (8), 105 (12).

Acknowledgements—We thank the Science Research Council and Eli Lilly & Co. for maintenance grants to P.S. and B.N. respectively, during the tenure of which this work was carried out.

REFERENCES

[1] Part III, A. H. Jackson and P. Smith, *Tetrahedron* **24**, 2227 (1968).
[2] A. H. Jackson and A. E. Smith, *Ibid.* **24**, 403 (1968).
[3] B. Robinson and G. F. Smith, *J. Chem. Soc.* 4574 (1960).
[4] J. Szmuskowicz, *Advances in Organic Chemistry* (Edited by R. A. Raphael, E. C. Taylor and H. Wynberg), Vol. IV. Interscience, New York (1964).
[5] A. H. Jackson and A. E. Smith, *Tetrahedron* **21**, 989 (1965).
[6] cf. E. S. Gould, *Mechanism and Structure in Organic Chemistry* pp. 607–610. Holt, Rinehart and Winston, New York (1959).
[7] W. C. Sumpter and F. M. Miller, *Chemistry of Heterocyclic Compounds* Vol. 8. Interscience, New York (1954).
[8] R. M. Acheson, *Introduction to the Chemistry of Heterocyclic Compounds*. Interscience, New York (1967).
[9] A. H. Jackson and K. M. Biswas, *Tetrahedron*, in press.
[10] A. H. Jackson and P. Smith, *J. Chem. Soc.* (C), 1667 (1968).
[11] W. E. Noland and F. J. Baude, *J. Org. Chem.* **31**, 3321 (1966).
[12] T. Kobayashi and N. Inokuchi, *Tetrahedron* **20**, 2055 (1964).
[13] cf. A. H. Jackson, G. W. Kenner and G. S. Sach, *J. Chem. Soc.* (C), 2045 (1967).
[14] cf. W. I. Taylor, *Proc. Chem. Soc.* 247 (1962).
[15] cf. B. Witkop and J. B. Patrick, *J. Am. Chem. Soc.* **73**, 1558 (1951).
[16] L. J. Dolby and D. I. Booth, *Ibid.*, **88**, 1049 (1966).
[17] J. Harley-Mason and W. R. Waterfield, *Tetrahedron* **19**, 65 (1963).
[18] J. E. D. Barton and J. Harley-Mason, *Chem. Comm.* 248 (1965); J. Harley-Mason and M. Kaplan, *Ibid.*, 915 (1967).
[19] A. J. Gaskell and J. A. Joule, *Tetrahedron* **23**, 4053 (1967).
[20] H. J. Anderson and L. C. Hopkins, *Canad. J. Chem.* **42**, 1279 (1964).
[21] A. N. Kost, V. N. Mitropolskaya, S. L. Portnova, and V. A. Krasnova, *Zh. Obshch. Khim.* **34**, 2989 (1964).
[22] R. W. Jackson and R. H. Manske, *J. Am. Chem. Soc.* **52**, 5029 (1930).