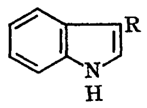
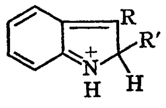
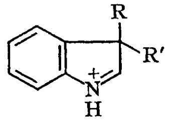
A New Theory of Electrophilic Substitution in 3-Substituted Indoles

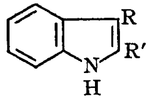
By A. H. JACKSON and P. SMITH
(The Robert Robinson Laboratories, University of Liverpool)

ELECTROPHILIC substitution in indoles[1] occurs predominantly in the 3-position, but if this is already substituted then 2,3-disubstituted indoles may be formed. Direct substitution at the 2-position is energetically unfavourable because it involves primary formation of an intermediate of general structure (II) in which the π-electron system of the benzene ring has been disturbed, whereas this is not the case for substitution at position-3 which gives an intermediate of type (III) (*cf.* also the normal mode of alkylation of enamines).


(I)

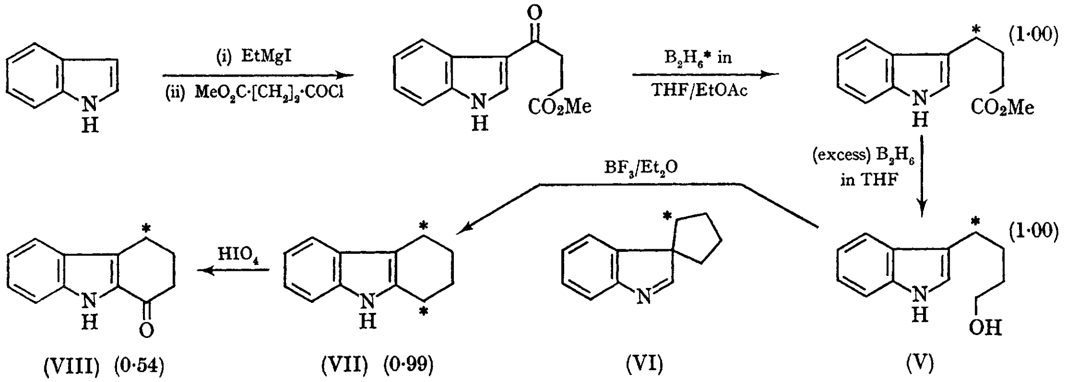

(II)


(III)

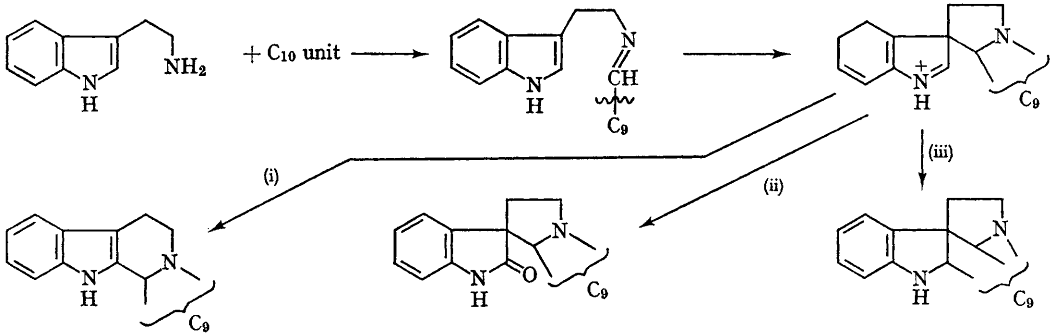

(IV)

Indolenines of type (III) (synthesised by alkylation of indole Grignard reagents) readily rearrange under acidic conditions to 2,3-disubstituted indoles, and the rates of the rearrangements, and which substituent migrates depends on their relative migratory aptitude;[3–6] moreover the rearrangement is entirely intramolecular.[5] We suggest therefore that formation of many 2,3-disubstituted indoles (IV) from 3-substituted indoles by electrophilic substitution involves the initial formation of a 3,3-disubstituted indolenine, (III) followed by rearrangement (*i.e.*, I → III → IV), *not* direct substitution at the 2-position. Other circumstantial evidence for this hypothesis has also been accumulated,[3–6] and will be described elsewhere, but we now report a direct test.

The indolylbutanol (V) was prepared from indole by the sequence indicated in Scheme 1 and cyclised by brief heating with boron trifluoride etherate to give tetrahydrocarbazole (VII) (60% yield). Tritium was incorporated as shown by use of diborane generated from sodium borotritiide in the second step; reduction of the ester carbonyl group in this step was inhibited[7] by the addition of ethyl acetate to the normal solvent, tetrahydrofuran.



SCHEME 1. (Relative tritium activities are shown in brackets)



SCHEME 2

Oxidation of the tetrahydrocarbazole with periodic acid[8] then gave 1-oxotetrahydrocarbazole (VIII), which contained only half the radioactivity of the preceding compounds.[9] This result is clearly consistent with the assumption that cyclisation of the indolylbutanol (V) occurs by initial formation of a *symmetrical* spirocyclic indolenine (VI) which then rearranges to the tetrahydrocarbazole (VII).

This experiment therefore provides very good evidence for our hypothesis, and further work is in progress to test its generality. It is also of considerable interest in relation to indole alkaloid biosynthesis, for this result, and other evidence,[3–6] affords good support for the suggestion that the initial condensation product of tryptamine with a C_{10}-unit (derived from mevalonate[10]), or with an aldehyde, is a 3,3-spirocyclic indolenine (Scheme 2). This common type of intermediate could then give rise to three different series of alkaloids, (i) α-indole alkaloids (*e.g.*, yohimbine and other β-carbolines), by rearrangement, (ii) oxindole alkaloids by hydration and oxidation, or (iii) β-indole alkaloids (*e.g.*, those of the Strychnos and Aspidosperma series) by addition, at the 2-position of the indole nucleus, of a suitably situated nucleophilic centre[11] in the aliphatic C_{10}-moiety.

(*Received, February 6th,* 1967; *Com.* 114.)

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[1] See for example, R. M. Acheson "Introduction to the Chemistry of Heterocyclic Compounds", Interscience, London 1960.

[2] This point has also been recognised by B. Robinson and G. F. Smith, *J. Chem. Soc.*, 1960, 4574.

[3] A. H. Jackson and A. E. Smith, *Tetrahedron*, 1965, **21**, 989.

[4] A. E. Smith, Ph.D. Thesis, Liverpool, 1963.

[5] P. Smith, Ph.D. Thesis, Liverpool, 1966.

[6] Mr. Biswas, in these laboratories, has recently shown that indolenines of type (III) formed in the diborane reduction of 3-formylindoles are "trapped" by reduction with excess of diborane to the corresponding indolines.

[7] This procedure was devised originally for protection of side-chain esters, in the diborane reduction of pyrroketones, *cf.* A. H. Jackson, G. W. Kenner, and G. S. Sach, *J. Chem. Soc.* (*C*), 1967, in the press.

[8] L. J. Dolby and D. Booth, *J. Amer. Chem. Soc.*, 1966, **88**, 1049.

[9] The same result was obtained from four separate runs, and Mr. B. Naidoo has shown that neither (VII) nor (VIII) undergoes tritium exchange under the conditions of the reactions.

[10] *Cf. e.g.*, A. R. Battersby, R. T. Brown, R. S. Kapil, A. O. Plunkett, and J. B. Taylor, *Chem. Comm.*, **1966**, 46, and refs. therein.

[11] *Cf.* E. E. Van Tamelen, L. J. Dolby and R. G. Lawton, *Tetrahedron Letters*, 1960, No. 19, p. 30. Analogous model reactions of vinyl ketones with indoles have been investigated by Sir Robert Robinson and co-workers (D. A. Cockerill, R. Robinson, and J. E. Saxton, *J. Chem. Soc.*, 1955, **4369** and earlier Papers; see also ref. 2).