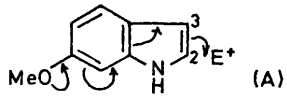
Electrophilic Substitution in 6-Methoxyindoles

By R. IYER, A. H. JACKSON,* and P. V. R. SHANNON
(*Department of Chemistry, University College, Cardiff* CF1 1XL)
and B. NAIDOO
(*Robert Robinson Laboratories, University of Liverpool*)

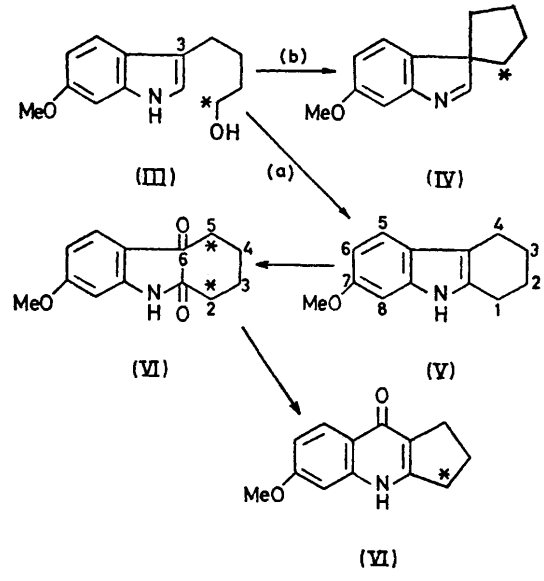
Summary Whereas indole and its simple alkyl derivatives react initially with electrophiles at the 3-position, the presence of a 6-methoxy-group activates the indole nucleus so that direct substitution at the 2-position becomes a significantly competitive process.

ELECTROPHILIC substitution in indoles normally takes place initially at the 3-position,[1] even when this position is already substituted by an alkyl group.[2] However, there is evidence[3] to suggest that a methoxy-group in the 6-position of the indole nucleus can activate the 2-position towards electrophilic attack, as shown in (A); we have now investigated the extent of this activation.

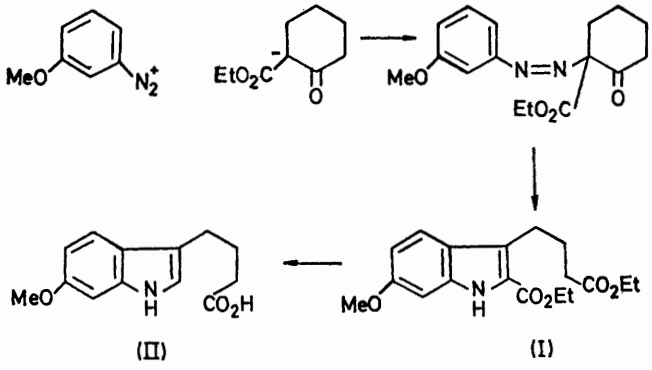


(A)

We synthesised the 6-methoxyindolylbutyric acid ester (I) which, after hydrolysis and thermal decarboxylation, gave the mono-acid (II), m.p. 136—137°. (II) was reduced to the alcohol (III), m.p. 85—86°, which was then cyclised



to (V), m.p. 147—148° (lit.[4] 146°), with BF_3–Et_2O at 80°. Oxidation of (V) with $NaIO_4$ gave, as the major product, the keto-amide (VI) which softened on heating at 160°, but then cyclodehydrated quantitatively to the crystalline 4-quinolone derivative (VII), which decomposed without melting at *ca.* 310°.



To study the mechanism of cyclisation of the alcohol (III) the analogue, fully deuteriated at the asterisked position, was prepared by $LiAlD_4$ reduction of the acid (II).

The deuteriated alcohol (III) was then cyclised under the same conditions as above, to (V). N.m.r. analysis of the relative extent of deuteriation in the methylene groups neighbouring the two carbonyl functions of the corresponding deuteriated keto-amides (VI), showed that the cyclisation of (III) to (V) had taken place both by direct 2-substitution, path (a) (*ca.* 25%) and by the indirect route path (b) (*ca.* 75%) *via* the spiroindolenine (IV). These results were concordant with related studies using tritium-labelled alcohol (III), and confirm that a 6-methoxy-group has a pronounced effect on the mechanism of electrophilic substitution reactions of indoles.

The possibility that equilibration of (V) and (IV) might have occurred, as has been shown in the β-carboline series,[5] was excluded by subjecting [1,1-$^2H_2$]-(V) to treatment with BF_3–Et_2O under the same conditions as in the cyclisation experiment. Oxidation followed by n.m.r. analysis of the resultant deuteriated keto-amide confirmed that no rearrangement of deuterium had occurred.

(*Received, 8th February* 1972; *Com.* 205.)

[1] R. J. Sundberg, "The Chemistry of Indoles," Academic Press, London, 1970, ch. 1; R. M. Acheson, "Introduction to the Chemistry of Heterocyclic Compounds," Interscience, New York, 1967, p. 131.
[2] A. H. Jackson, B. Naidoo, and P. Smith, *Tetrahedron*, 1968, **24**, 6119.
[3] J. B. Hester, *J. Org. Chem.*, 1964, **29**, 2864; A. J. Gaskell and J. A. Joule, *Tetrahedron*, 1967, **23**, 4053.
[4] J. R. Chalmers, H. T. Openshaw, and G. F. Smith, *J. Chem. Soc.*, 1957, 1115.
[5] J. Harley-Mason and W. R. Waterfield, *Tetrahedron*, 1963, **65**, 19; J. E. D. Barton and J. Harley-Mason, *Chem. Comm.*, 1965, 298; J. Harley-Mason and M. Kaplan, *ibid.*, 1967, 915.