Thio-Claisen Rearrangements of Dimethylallyl 2-Indolyl Sulphonium Salts: Possible Implications in Indole Alkaloid Biosynthesis

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Summary Dimethylallyl 2-indolyl sulphonium salts are shown to undergo thio-Claisen rearrangements readily: the possible role of this new reaction in indole alkaloid biosynthesis is described.

IN relation to our studies on the interaction of tryptophan and C_5 units, we recently described a number of thio-Claisen rearrangements of substituted allyl 2-indolyl sulphides including (Ia) → (IVa).[1] Attempts to extend the reaction to derivatives with β-alkyl substituents have been unsuccessful; (Ib) failed to rearrange in boiling toluene, and in boiling tetralin gave 3-methylindoline-2-thione and 3-methylindole, presumably by radical cleavage.

We now report that the methyl sulphonium cations derived from (Ia) and (Ib) readily rearrange at room temperature to give the *S*-alkyl derivatives (V) and (VI), respectively. This represents an hitherto unobserved type of thio-Claisen rearrangement which may have both synthetic and biosynthetic implications.

Reaction of (Ia) with methyl fluorosulphonate[2] afforded the sulphonium ion (IIa) which immediately rearranged with the subsequent loss of a proton to give the indole (V). (VI) could not be prepared by this method due to the instability of the product under the conditions of the reaction. However treatment of (IIIa) or (IIIb)† with dimethylallyl bromide in acetone or dimethylformamide over potassium carbonate afforded, as the major products‡ and in good yield, (V) and (VI), respectively. The reactions are assumed to proceed through the intermediacy of the sulphonium ions (IIa) and (IIb), since indole derivatives without a thio-substituent in the 2-position react with dimethylallyl bromide exclusively at the primary centre.[3]

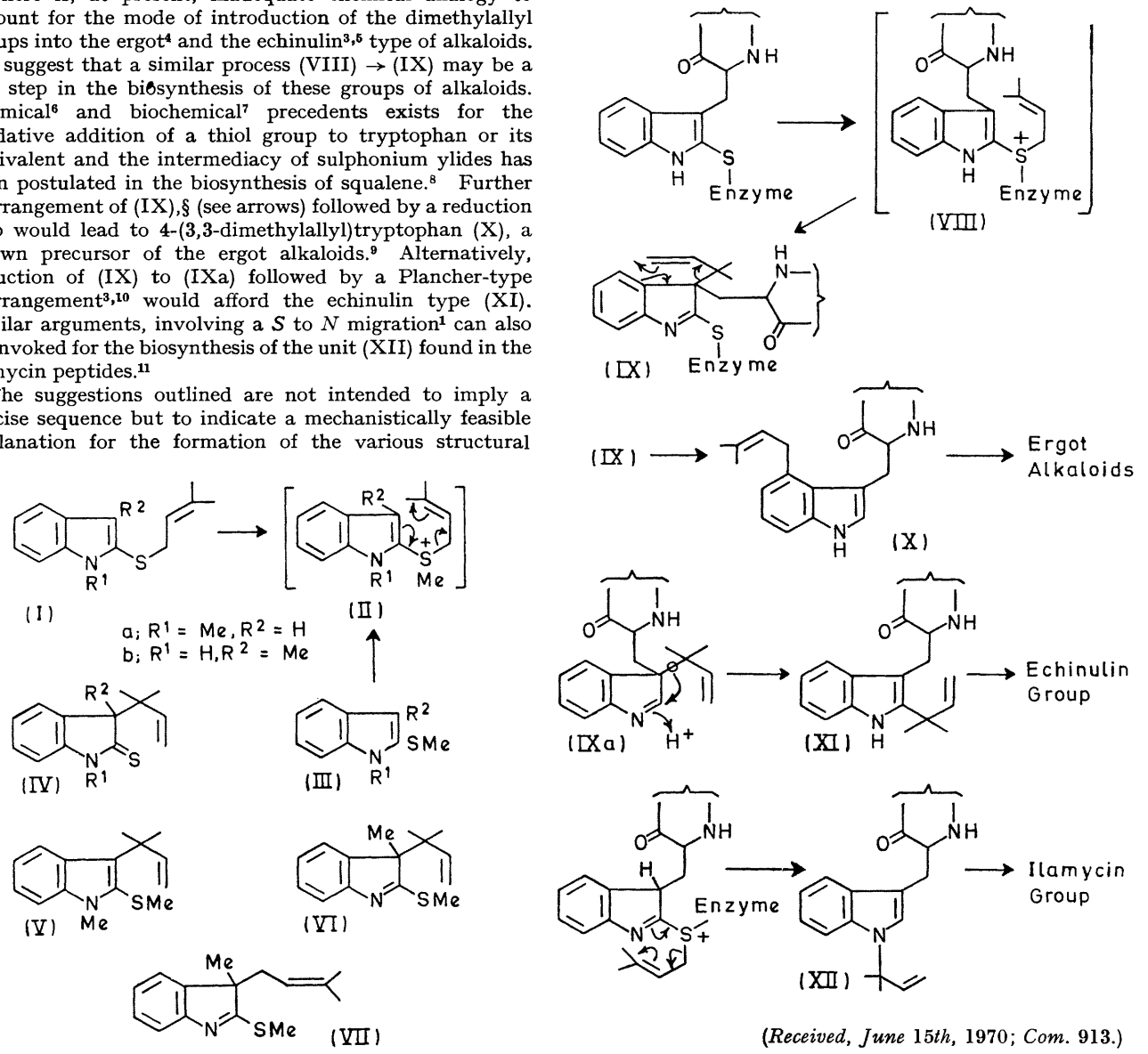
† The alkyl thio-ethers were prepared either by alkylation of the corresponding thione[1] or by reaction of the indole with methylsulphenyl chloride.[6]

‡ (VII) was also isolated from the reaction of (IIIb) with dimethylallyl bromide.

The driving force of the reaction can be ascribed to the rapid irreversible deprotonation step following rearrangement.

There is, at present, inadequate chemical analogy to account for the mode of introduction of the dimethylallyl groups into the ergot[4] and the echinulin[3,5] type of alkaloids. We suggest that a similar process (VIII) → (IX) may be a key step in the biosynthesis of these groups of alkaloids. Chemical[6] and biochemical[7] precedents exists for the oxidative addition of a thiol group to tryptophan or its equivalent and the intermediacy of sulphonium ylides has been postulated in the biosynthesis of squalene.[8] Further rearrangement of (IX),§ (see arrows) followed by a reduction step would lead to 4-(3,3-dimethylallyl)tryptophan (X), a known precursor of the ergot alkaloids.[9] Alternatively, reduction of (IX) to (IXa) followed by a Plancher-type rearrangement[3,10] would afford the echinulin type (XI). Similar arguments, involving a *S* to *N* migration[1] can also be invoked for the biosynthesis of the unit (XII) found in the ilamycin peptides.[11]

The suggestions outlined are not intended to imply a precise sequence but to indicate a mechanistically feasible explanation for the formation of the various structural types of tryptophan–C_5 metabolites in the light of available biosynthetic data.[4,5]



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§ A related concerted rearrangement has been reported: J. A. Ballantine, A. Katner, and A. W. Johnson, *J. Chem. Soc.*, 1964, 3323. The same arguments can be applied to the intermediate lacking the thio-substituent but its mode of formation poses further mechanistic problems.

[1] B. W. Bycroft and W. Landon, *Chem. Comm.*, 1970, 168.
[2] M. G. Ahmed, R. W. Alder, G. H. James, M. L. Sinnott, and M. C. Whiting, *Chem. Comm.*, 1968, 1533.
[3] G. Casnati, M. Francioni, A. Guareschi, and A. Pochini, *Tetrahedron Letters*, 1969, 2485; A. H. Jackson and A. E. Smith, *Tetrahedron*, 1965, **21**, 989; B. W. Bycroft and W. Landon, unpublished results.
[4] F. Weygand and H. G. Floss, *Angew. Chem. Internat. Edn.*, 1963, **2**, 243; H. Plieninger, R. Fischer, and V. Liede, *Annalen*, 1964, **672**, 223.
[5] A. J. Birch, G. E. Blance, S. David, and H. Smith, *J. Chem. Soc.*, 1961, 3128; A. J. Birch and J. J. Wright, *Chem. Comm.*, 1969, 644.
[6] T. Wieland, K. Freter, and E. Gross, *Annalen*, 1959, **626**, 154 and references cited therein.
[7] T. Wieland, *Fortschr. Chem. org. Naturstoffe*, 1967, **25**, 214; K. A. Schellenberg, *J. Biol. Chem.*, 1967, **242**, 1815.
[8] J. E. Baldwin, R. E. Hackler, and D. P. Kelly, *Chem. Comm.*, 1968, 537; G. M. Blackburn and W. D. Ollis, *ibid.*, p. 1261.
[9] H. Plieninger and R. Fischer, *Angew. Chem. Internat. Edn.*, 1962, **1**, 399; J. E. Robbers and H. G. Floss, *Arch. Biochem. Biophys.*, 1968, **126**, 967.
[10] P. L. Julian, E. W. Meyer, and H. C. Printy, "Heterocyclic Compounds," ed. R. C. Elderfield, Wiley, New York, 1952, vol. 4, p. 80.
[11] T. Takita, H. Naganawa, K. Maeda, and H. Umezawa, *J. Antibiotics*, 1964, **17**, 264 and references cited therein.