Chemical Communications

NUMBER 10/1968 22 MAY

The Rearrangement of Vinylsulphonium Ylids. An Alternative Mechanism for Squalene Synthetase

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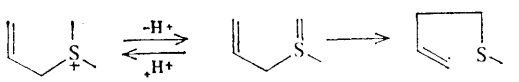
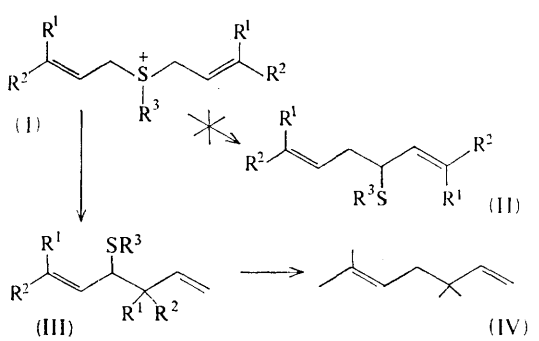
ONE of the postulated mechanisms for the enzyme squalene synthetase involves a Stevens rearrangement of an enzymically bound sulphonium salt (I) to the thiosubstituted squalene (II).[1,2] We have tested the chemical validity of this step and in view of a recent communication[3] report some of our results. The dimethylallyl sulphonium salt (I; $R^1 = R^2 = Me$, $R^3 = Et$) obtained quantitatively from the sulphide with triethyloxonium fluoroborate[4] reacts smoothly, at room temperature, with a variety of bases (aqueous sodium hydroxide, methanolic sodium methoxide, and potassium t-butoxide in benzene) to produce (95% yield) the rearranged sulphide (III; $R^1 = R^2 = Me$, $R^3 = Et$).† The structure of this compound was established by n.m.r. and confirmed by mild reduction (lithium in ammonia) to the known diene (IV)[5] (identical in spectral and g.l.c. properties). Similar conversions were obtained in high yield under mild conditions with the sulphonium salts (I; $R^1 = H$, $R^2 = Ph$, $R^3 = Et$), (I; $R^1 = R^2 = H$, $R^3 = Et$), and the salt from benzyldimethylallyl sulphide. These results justify our belief[6] that there exists a ready six-electron reorganization of these ylides, which may be expressed by Scheme 1. The driving force of this

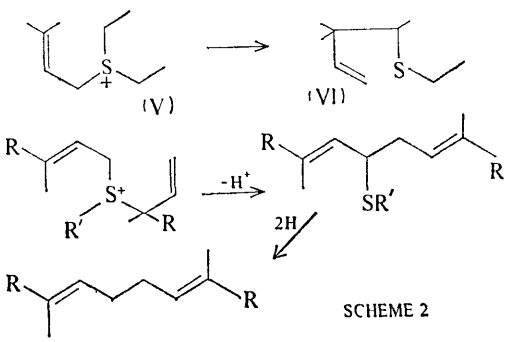


SCHEME 1

rearrangement is derived from the change in formal valence of sulphur from four to two. The rearrangement also proceeds readily when only one of the substituting functions is an allyl residue. Thus the salt (V) was rearranged in high yield to the sulphide (VI), although in this case the choice of base must be restricted to a non-nucleophilic species, *e.g.* potassium t-butoxide, since a competing displacement reaction is noted with sodium methoxide. With regard to the fine details of the mechanism our results show that in the presence of *O*-deuteriated methanol the salt (I; $R^1 = R^2 = Me$, $R^3 = Et$) reacts with exchange of 80% of the allylic methylene hydrogens, there being no exchange in the ethyl group. These results suggest



† All new compounds mentioned here have satisfactory elemental analyses and spectroscopic properties.



SCHEME 2

the mechanistic Scheme 1, in which, with methanol, the reprotonation reaction of the ylid with solvent is faster than the rearrangement step. From this work we conclude: (i) this procedure constitutes an experimentally simple and effective way of linking allylic residues in the head-to-tail sense under mild conditions and in high yield; (ii) if the mechanism of the enzyme squalene synthetase involves a sulphonium salt which bridges two farnesyl residues then the Scheme 2 is chemically valid and in agreement with our *in vitro* results.

(*Received, February 19th*, 1968; *Com.* 198.)

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[4] H. Meerwein, G. Hinz, P. Hofmann, E. Kroning, and E. Pfeil, *J. prakt. Chem.*, 1937, **147**, 257.
[5] H. Kwart and R. K. Miller, *J. Amer. Chem. Soc.*, 1954, **76**, 5403.
[6] See following Communication.