

The Synthesis of Squalene involving Sulphonium Ylid Intermediates

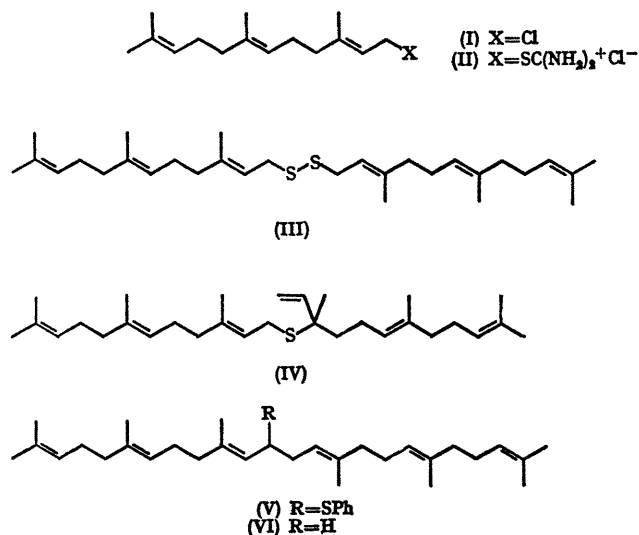
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OUR interest in the sigmatropic rearrangement of allylic sulphonium ylids was initiated by the possibility that such intermediates could be involved in the biosynthesis of squalene.¹ Three processes have been envisaged for the creation of the inter-farnesyl bond in squalene biosynthesis: (i) a five-centre, intramolecular rearrangement² of an ylid derived from a farnesyl-nerolidyl sulphonium cation, (ii) a Stevens (three-centre) intramolecular rearrangement³ of an ylid derived from a difarnesyl sulphonium cation, and (iii) bimolecular alkylation by farnesyl pyrophosphate of an ylid⁴ derived from a sulphonium cation containing one farnesyl residue. A chemical synthesis of squalene has now been achieved which demonstrates the chemical feasibility of process (i) as a possible model for one step in the biosynthesis of squalene.

Farnesyl chloride⁵ (I) and thiourea gave the crystalline thiouronium chloride† (II) [n.m.r. [D₂O, (CD₃)₂CO], τ 4.77 (m, 3H, vinyl-H), 6.01 (d, $J = 8.0$ Hz, 2H, S-CH₂), 7.9 (m, 8H, vinyl-CH₂), 8.2 (s, 3H, vinyl-CH₃), and 8.37 (s, 9H, vinyl-CH₃)] free from the nerolidyl isomer. Alkaline hydrolysis and aerobic oxidation yielded the unstable difarnesyl disulphide (III) which, without purification, was converted by triphenylphosphine⁶ into farnesyl nerolidyl sulphide (IV) [ν_{\max} 910 cm.⁻¹; n.m.r. (CDCl₃), τ 3.9—5.2 (m, 8H, vinyl-H); 7.02 (d, J 8.0 Hz, 2H, S-CH₂), 8.0 (m, 16H, CH₂), 8.4 (m, 21H, vinyl-CH₃), and 8.65 (s, 3H, CH₃)]. Treatment of farnesyl nerolidyl sulphide (IV) with benzyne (from *o*-fluorophenylmagnesium bromide) gave one major product in high yield identified as 12-phenylthiosqualene (V) [n.m.r. (CCl₄), τ 2.8 (m, 5H, C₆H₅), 4.9 (m, 6H, vinyl-H), 6.25 (t, J 10 Hz, 1H, PhS-CH), 8.0 (m, 18H, vinyl-CH₂), and 8.4 (m, 24H, vinyl-CH₃); M , 518.3931]. Lithium-liquid ammonia reduction

of 12-phenylthiosqualene (V) gave squalene (VI) which was purified by chromatography and clathrate formation with thiourea.⁷ This synthetic squalene [n.m.r. (CDCl₃), τ 4.85 (m, 6H, vinyl-H), 7.96 (m, 20H, vinyl-CH₂), 8.4 (m, 24H, vinyl-CH₃); M , 410] was identical (i.r., n.m.r., and mass spectra) with natural squalene.



Attempts to convert the sulphide (IV) into the corresponding methylsulphonium cation with trimethyloxonium tetrafluoroborate^{2b} were unsuccessful and gave a mixture of products.

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† All new compounds have been fully characterised by analysis and by their i.r., n.m.r., and mass spectra.

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⁵ Modification of the method due to M. O. Forster and D. Cardwell, *J. Chem. Soc.*, 1913, **103**, 1308.

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⁷ D. W. Dicker and M. C. Whiting, *J. Chem. Soc.*, 1958, 1994.