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A SIMPLE SYNTHETIC ROUTE TO A PROPOSED INTERMEDIATE IN THE BIOSYNTHESIS OF SQUALENE FROM FARNESYL PYROPHOSPHATE

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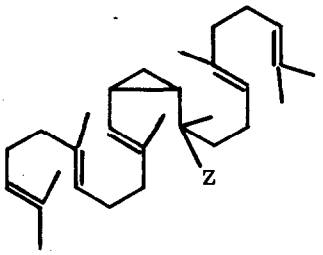
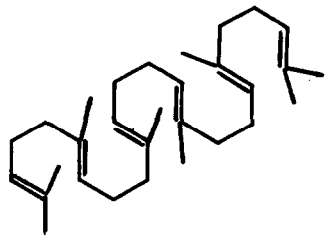
Recently a new intermediate in the biosynthesis of squalene has been obtained from farnesyl pyrophosphate as substrate in a yeast homogenate containing minimal amounts of reduced nicotinamide adenine dinucleotide (NADP-H) (1). On the basis of a number of experimental results, structure I was suggested for the new substance which was designated as "Compound X" and which was shown to be a C_{30}-pyrophosphate convertible to squalene (II) in the presence of NADP-H either by yeast homogenate or rat liver microsomes (1). This note reports a synthesis of various stereoisomers of the alcohol (III) corresponding to I and a



I, Z = pyrophosphate

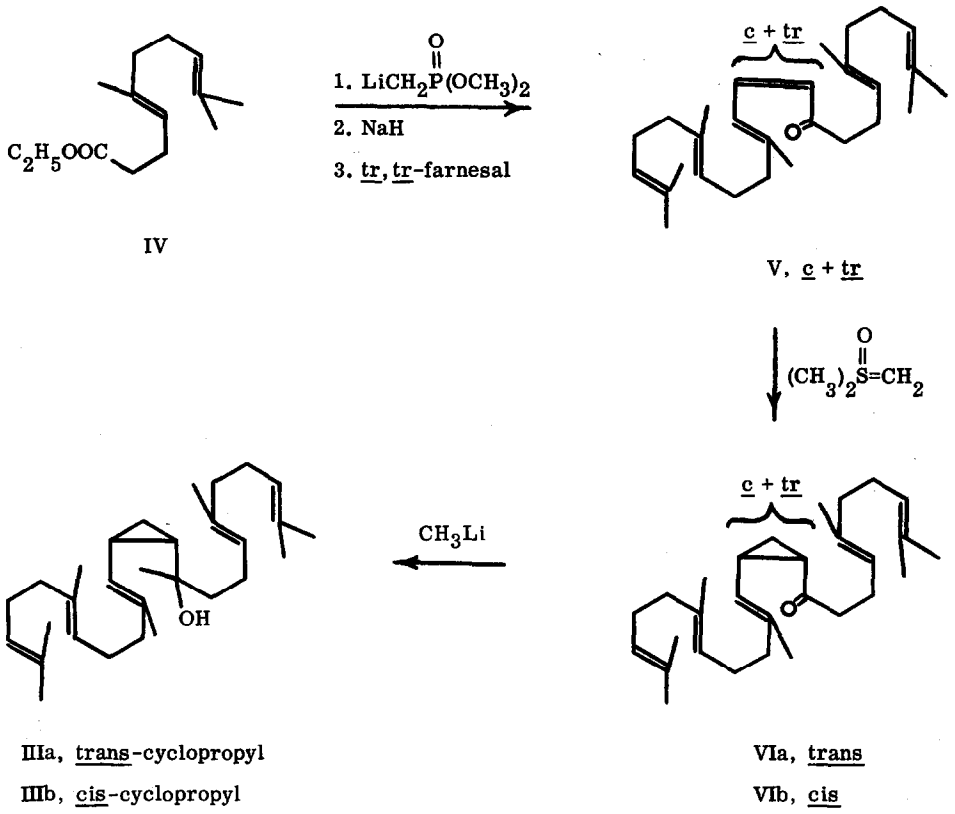
III, Z = OH



II

comparison with the alcohol obtained (1) by treatment of the intermediate "Compound X" with lithium aluminum hydride.

The synthetic approach to III is outlined in Chart 1. Ethyl geranylacetate (IV) (2) and dimethyl α-lithiomethylphosphonate (3) afforded a β-keto phosphonate which underwent smoothly the Emmons-Horner olefin synthesis (4) with trans,trans-farnesal to give a mixture of α,β-cis- and α,β-trans-enones V showing carbonyl stretching bands of approximately equal intensity at 5.92 and 6.00 μ (CCl_4 solution), molecular ion at m/e 396.3392 (calc. 396.3389) (5) and λ_{max} (hexane) at 284 nm. (ϵ = 23,200). The nmr spectrum was



IV

V, c + tr

IIIa, trans-cyclopropyl

IIIb, cis-cyclopropyl

VIa, trans

VIb, cis

Chart 1

fully in accord with the assigned structures, and vpc analysis indicated the presence of two isomers of V in the mixture in a ratio of 7 : 3. Reaction of the mixture of ketones V with dimethyloxosulfonium methylide (6) gave a mixture of the trans- and cis-substituted cyclopropyl derivatives VI in a ratio of ca. 19 : 1, respectively. The composition of this mixture was not altered by base-catalyzed equilibration experiments. However, metallation of the mixture with tritylllithium followed by protonation (H_2O) afforded a mixture of trans- and cis-VI in a ratio of 5.5 : 1. The cis and trans isomers of VI could be separated by vapor phase or thin layer chromatography; each showed a carbonyl stretching band at 5.89 μ (CCl_4) and a molecular ion at m/e 410 as expected for VI; the nmr spectra also were in accord with this structure. Methylation of the ketones VI by methyllithium in ether-tetrahydrofuran afforded the corresponding diastereomeric methyl carbinols in each case. The diastereomers IIIa from VIa were unresolved by tlc and showed R_f of 0.34 on silica gel using 2.5% ethyl acetate in benzene; the diastereomers IIIb from VIb also were unresolved by tlc and showed R_f of 0.29 in the same system. Infrared, nmr, and mass spectra were in accord with formulation

III in each case. That the alcohol obtained by reduction of "Compound X" by lithium aluminum hydride is different from the above described synthetic alcohols IIIa and IIIb was clearly shown by tlc comparison of R_f values (system as above): IIIa, 0.34; IIIb, 0.29; alcohol from "Compound X," 0.23.

Pyrophosphorylation of the alcohol from "Compound X" yields a partially synthetic "Compound X" which is convertible to squalene in the yeast + NADP-H system (7). Similar treatment of a mixture of IIIa and IIIb (both unlabelled and $^{14}CH_3$-labelled) affords relatively very unstable phosphorylated products and nothing corresponding chromatographically to "Compound X."

Thus it is concluded that the "Compound X" isolated by Rilling (1) and shown by him to be an intermediate in squalene biosynthesis does not have structure I (8).

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8. This work was supported by the National Institutes of Health and the National Science Foundation. It is taken from the Ph. D. dissertation of P. R. O. M., Harvard University, 1968.