TERPENE BIOSYNTHESIS

Chains, Triangles and Squares

from our Biological Chemistry Correspondent

J. W. CORNFORTH and his collaborators have managed to solve most of the secrets of farnesol pyrophosphate biosynthesis and its conversion into squalene. The source and stereochemistry of all fifty hydrogens in squalene are known, excepting only the methyl hydrogens at the ends of the chain. This last problem, more severe than the rest, requires the power to discriminate between three equivalent hydrogens bonded to the same carbon. Of late, both Cornforth and Arigoni have developed techniques for the solution of this problem, based on the chemical synthesis of CH_3-groups containing one atom each of the three hydrogen isotopes, protium, deuterium and tritium, in a defined array which can be identified by an enzymatic assay.

Cornforth has now applied this method to resolve the nature of hydrogen transfers in the isomerization of 3-methyl-3-butenyl pyrophosphate (1) into 3-methyl-2-butenyl pyrophosphate (2) (*Chem. Comm.*, **1971**, 1599). The enzyme isopentenyl pyrophosphate isomerase removes the 2-*pro*-*R*-hydrogen (H*) from (1) and a proton is supplied from the medium to the upper (*re*) side of (2) which, by suitable choice of isotopes, contains a methyl group with protium, deuterium and tritium. The stereochemical relation of incoming and outgoing hydrogens in the isomerization suggests a concerted addition-abstraction process.

The hypothesis which is currently in favour for the conversion of farnesyl pyrophosphate into squalene involves presqualene pyrophosphate (see *Nature*, **230**, 429; 1971) though in the past there has been some disagreement about its structure. This is largely resolved by Popják's revision of his structure for presqualene pyrophosphate to accord with that of Rilling in the light of new and refined data (*J. Biol. Chem.*, **246**, 6254; 1971). Most groups have their own hypothesis for its conversion into squalene: Popják's novelty is the transformation of the cyclopropylcarbinyl system (3) into a cyclobutane derivative (4) *en route* to the linear squalene chain (5).

An important feature of the natural terpenes is the regular head-to-tail linkage produced by the addition of (1) to (2). There is something peculiar about daisies (Compositae) which provide an apparently exclusive source of anomalous skeletal types including chrysanthemyl (6), artemisyl (7) and santolinyl (8) monoterpenes. The obvious genetic link plus particular chemical considerations has been an inspiration for several model studies which Poulter has now capped (*Tetrahedron Lett.*, **1972**, 69, 71) by demonstrating the production of santolina alcohol (8) from chrysanthemyl alcohol (6) with the correct stereochemical correlation. Because compounds of the artemisyl group, yomogi (9) and artemisia (7) alcohols, are formed at the same time, it seems plausible that a common precursor, also related to presqualene pyrophosphate, features in the biosynthesis of the diverse monoterpene types of the daisy family.

The chemistry of these processes hinges around a common cation, very probably of the non-classical type which is well known to interrelate cyclobutyl, cyclopropylcarbinyl and homoallyl systems, represented here as (10). The dying embers of heatedly discussed hypotheses invoking sulphonium ylides in squalene biogenesis have been stirred by Barry Trost (*Chem. Comm.*, **1971**, 1639). His group show that the formation of (7) from (6) can be reversed by solvolysis of the sulphonium salt derived from artemesia thiol ((7); O=S). Although this reaction gives largely yomogi-type product (9), small but highly significant amounts of santolina (8) and chrysanthemyl (6) compounds are produced and also the head-to-head linked monoterpene of the squalene type ((5); R=Me, *H=OMe).

Perhaps, after all, the biosynthesis of squalene does involve sulphonium ylide rearrangements which furnish a cation inside the enzymatic site that is normally reduced to squalene (5) but, in the absence of NADPH, is trapped by pyrophosphate with a different regiospecificity to yield "presqualene" pyrophosphate.

GLASS

Phase Separation

from our Materials Science Correspondent

WITH the growing application of transmission electron microscopy and small-angle X-ray scattering to the examination of glasses, it has come to be recognized that the existence of miscibility gaps in the constitutional diagrams of glasses is quite common. Glass-in-glass phase separation during cooling is now seen to be the rule rather than the exception, and this has important implications for the understanding and control of devitrification. But although much effort has gone into the investigation of phase separation in glasses, by the fore-mentioned techniques especially, scarcely anything is known of the actual form of the miscibility gaps in specific glass systems.

This lack is now beginning to be