The Direct Brominative Cyclization of Methyl Farnesate

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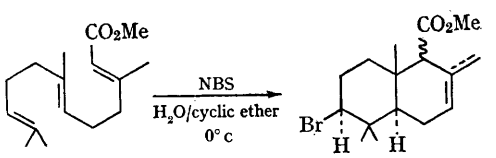
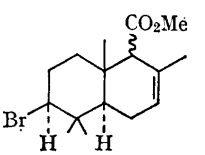
WHEN various acyclic sesqui-, and higher, terpenes are subjected to the controlled action of *N*-bromosuccinimide (NBS) in aqueous ethylene glycol methyl ether or tetrahydrofuran, *terminal* monohalogenohydrins are the major products formed in good yield.[1-3] We now report that, in the case of methyl farnesate (I) there are produced concurrently the bicyclic bromo-esters (II), arising by *direct* terminal oxidation and cyclization of the acyclic terpene, a process akin to that presumed to operate in the biogenesis of 3-hydroxylated polycyclic terpenes and steroids.[4,5]

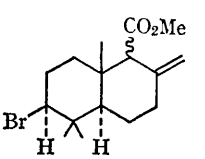


(I) (II)

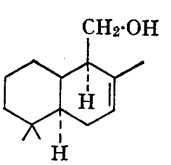
By chromatographic means (silica gel), a fraction (12—15% of total), consisting mainly of bromocyclized material,[6] was isolated as a product of the NBS reaction on ester (I). Separation into bromomonocyclic and bromobicyclic ester was achieved by selective saponification, the more hindered ester group of the bicyclic components (4—5% of the cyclized material) remaining intact. When subjected to preparative t.l.c. (silica gel/benzene–hexane), this non-saponifiable fraction was further separated into two major components in equal amount. Chemical and spectral observations permit the assignments of structures (IIIa) and (IIIb) to these compounds.[7]



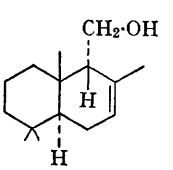
(IIIa)



(IIIb)



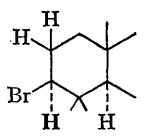
(IVa)



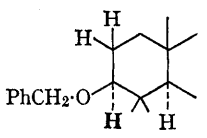
(IVb)

The general nature of these bromo-esters was revealed by lithium aluminium hydride reduction, which, in the case of (IIIa), gave rise to roughly

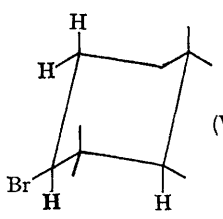
equivalent amounts of the known epimeric (±)-drimenols (IV a–b).[8] Although ester (IIIa) remained liquid, the exocyclic isomer (IIIb) was crystalline (m.p. 82·5—82·6°).[9] The n.m.r. spectrum of (IIIb) is completely consistent with the assigned structure, possessing, *inter alia*, signals (τ) at 5·2, 5·37 (=CH_2); 6·11 (quartet, > CHBr); 6·41 (–OMe); 7·34 (>CH–C=O); 8·93, 9·03 (3 C–Me) (60 Mc./sec., in CCl_4). Parallel data support structure (IIIa) for the non-crystalline isomer.



(Va)

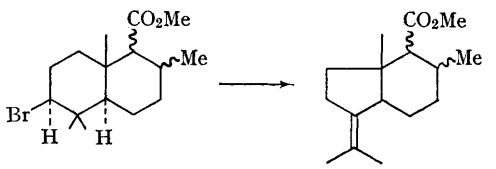


(Vb)



(Vc)

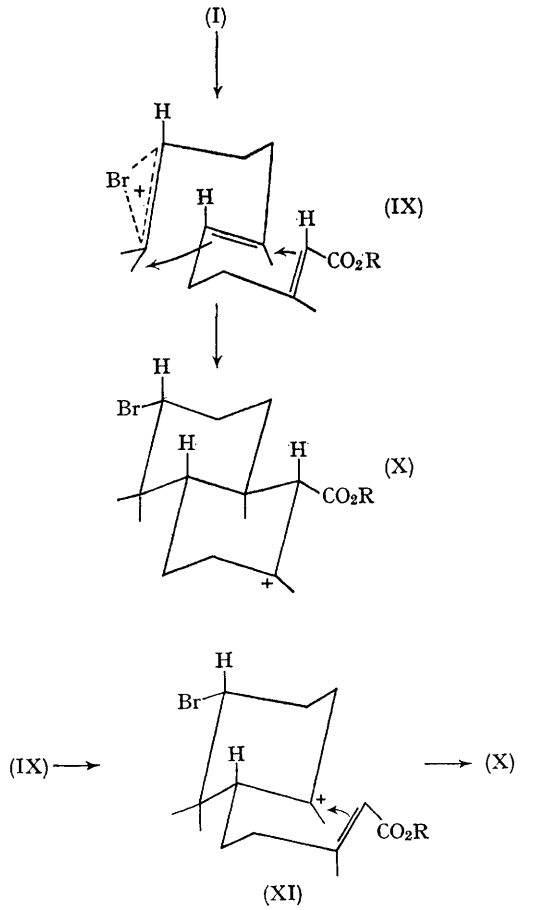
The position and stereochemistry of halogen were confirmed by means of the following observations. A 100 Mc./sec. n.m.r. spectrum displayed a clear-cut quartet for the CHBr unit (Va), with $J = 6{\cdot}0$ and 10·5 c./sec. This splitting pattern, similar to that (4·5 and 11·0 c./sec.) of the corresponding proton in (±)-β-onocerin dibenzyl ether (Vb),[3,10] signifies *axial* hydrogen interacting with two protons, one axial and one equatorial, on adjacent



(VI) (VII)

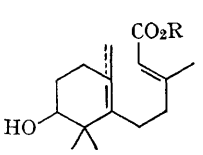
carbon. Catalytic reduction (Pt/acetic acid) of (IIIa) provided the dihydro-bromo-ester (VI), which was subjected to the action of anhydrous silver fluoroborate in benzene. On the basis of n.m.r. data, structure (VII) can be assigned to the (non-crystalline) product, an outcome quite consistent with the anticipated behaviour of halogen in the assigned position (*cf.* the corresponding ring contractions undergone by naturally occurring terpenes during dehydration of the A-ring.)[11]

Although the intimate aspects of the bromination–cyclization mechanism remain obscure, the broad outlines are somewhat clearer. That the bromobicyclic esters do not arise in a secondary process from methyl farnesate terminal bromohydrin (VIII) is suggested by the observation that no cyclized product was detectably formed when (VIII) was subjected to the approximate conditions of the original NBS reaction, including the presence of a halogen acceptor (farnesol). Also, in view of the mild conditions of pH and temperature employed in the NBS reaction, further cyclization of bromomonocyclic diene is unlikely.[12] Thus the

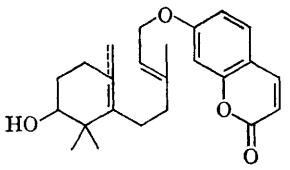


(XI)

most attractive interpretation of the cyclization course would involve (1) ring formation of an initially produced terminal bromonium ion, which



(i)



(ii)

can cyclize (IX) in an essentially synchronous process to bicyclic product (X), or (2) conversion of terminal bromonium ion into a monocyclic carbonium ion (XI), part of which does not suffer proton loss but proceeds, classically or non-classically, to observed final product (X).[13]

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[1] E. E. van Tamelen and T. J. Curphey, *Tetrahedron Letters*, 1962, 121.
[2] E. E. van Tamelen, A. Storni, E. J. Hessler, and M. Schwartz, *J. Amer. Chem. Soc.*, 1963, **85**, 3295.
[3] E. E. van Tamelen, M. Schwartz, E. J. Hessler, and A. Storni, *Chem. Comm.*, 1966, 409.
[4] (a) A. Eschenmoser, L. Ruzicka, O. Jeger, and D. Arigoni, *Helv. Chim. Acta*, 1955, **38**, 1890; (b) G. Stork and A. W. Burgstahler, *J. Amer. Chem. Soc.*, 1955, **77**, 5068; (c) L. Ruzicka, *Proc. Chem. Soc.*, 1959, 341.
[5] F. Lynen and U. Henning, *Angew. Chem.*, 1960, **72**, 820.
[6] The general nature of this fraction was ascertained by means of halogen analysis, microhydrogenation and preliminary n.m.r. analysis.
[7] On the basis of its ultraviolet spectral behaviour, a third, minor component is regarded as the isomeric $\alpha\beta$-unsaturated ester.
[8] P. A. Stadler, A. Eschenmoser, H. Schinz, and G. Stork, *Helv. Chim. Acta*, 1957, **40**, 2191.
[9] Correct elemental analysis obtained.
[10] Unpublished observations made by M. Schwartz in this laboratory.
[11] See: J. Simonsen and W. C. J. Ross, "The Terpenes," Vol. IV, University Press, Cambridge, 1956, for various examples.
[12] Monocyclic hydroxyfarnesic ester (i) is not converted to bicyclic material by phosphoric acid, nor is a monocyclic farnesiferol-type system (ii) transformed into the bicyclic farnesiferol-A series by boron trifluoride etherate (results obtained by R. M. Coates in this laboratory), both experiments being run under conditions which serve to generate bicyclic products from acyclic epoxides.
[13] Although he did not isolate and identify products, G. F. Bloomfield (*J. Chem. Soc.*, 1943, 289) suggested, on the basis of chemical analytical evidence (iodine-values and degree of hydrogen chloride evolution), that dihydromyrcene and rubber on treatment with molecular chlorine formed, to some extent, cyclized products, arising either by chlorinative cyclization or by hydrogen chloride-catalyzed cyclization of intermediate chlorine substitution products.