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THE SELECTIVE IN VITRO OXIDATION OF THE TERMINAL DOUBLE BONDS IN SQUALENE

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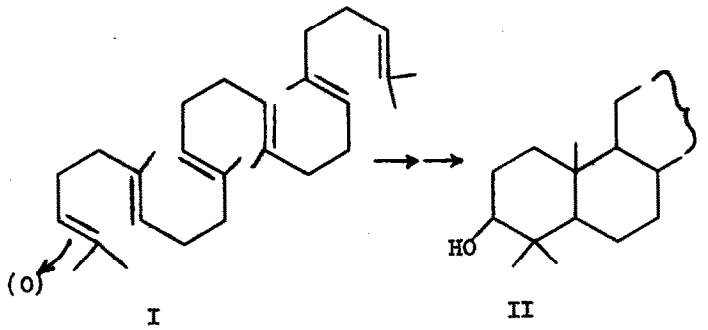
EXTENSIVE tracer experiments have demonstrated that squalene acts in vivo as a precursor of lanosterol and cholesterol (and doubtless many other steroids and triterpenoids), in a process which involves oxidation-cyclization of the polyene system, as shown (I ⟶ II).[1] The prospect of duplicating this phenomenon in the laboratory has occasioned interest in certain circles,



I II

not only because of the theoretical aspects but also because of the abundant availability of squalene. Not the least of the problems which must be faced in such an undertaking is the selective oxidation of the starting hydrocarbon at the terminus, an uncommon challenge in that all of the double

[1] For a recent review, see L. Ruzicka, Proc. Chem. Soc. 341 (1959).

bonds in the system are trisubstituted and more or less equally sterically encumbered. We report herein a solution to this problem in chemical selectivity, utilizing means which we believe to be novel and also of wider applicability.

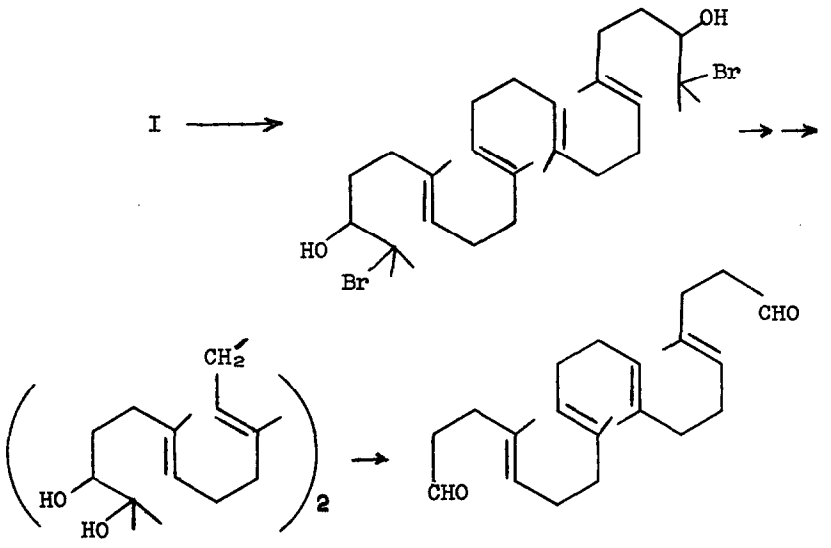
In studying such in vitro oxidations, two major variables were investigated: the nature of the oxidizing agent and the nature of the solvent.[2] The results of these experiments are summarized in Table 1. In the most successful case, conversion of squalene to a mixture of halohydrins was carried out by oxidation with N-bromosuccinimide in aqueous ethylene glycol dimethyl ether (glyme), under such conditions of temperature (23°) and concentration that the solution at the start of the reaction was saturated with squalene. Product could be separated into mono-, di- and higher bromohydrin fractions (along with unreacted squalene) by chromatography over silica gel.[3]

For further chemical work, halohydrin material was ring closed to epoxide, which was then converted to 1,2-glycol by treatment with aqueous perchloric acid in glyme. Combination of quantitative periodate oxidation and measurement of acetone formation on lead tetraacetate oxidation, demonstrated that the periodate cleavable material consisted predominantly of

[2] In regard to the latter factor, it seemed to us that the very feature which was responsible for this problem of selectivity, viz. the elongated, partially olefinic hydrocarbon system, could be turned to advantage, in that the conformation of this large hydrocarbon might be sufficiently solvent-dependent to affect markedly its chemical behavior. More precisely, in a solvent of low polarity there is no reason to suppose that squalene would not exist for the most part in an uncoiled, fully extended state, with all of the double bonds equally vulnerable to attack by an oxidizing agent. On the other hand, in a more polar medium (such as that offered by a hydroxylic solvent) it appears possible that squalene would assume a more highly coiled, compact conformation, such that the triterpenoid would be "internally solvated", and the system of hydrogen bonds in the medium would be disrupted as little as possible. Should this be the case, the internal double bonds in this coiled conformation might be sterically shielded and thus chemically less reactive, whereas the terminal olefinic links would remain exposed.

[3] Unpublished results secured by Dr. A. Storni in this Laboratory.

terminal 1,2-glycol - as high as 81% of the theoretical (i.e., all terminal glycol) amount of acetone (as dinitrophenylhydrazone) was produced from 1,2-glycol material, under conditions where the actual yield of acetone (DNP) from simple models (e.g., $C_6H_5CHOHCOH(CH_3)_2$) was 81%. Thus, the objective, a completely selective oxidation at the terminal double bonds of squalene, seemingly had been achieved.



III IV

In order to confirm the course of the oxidation reaction, a definitive degradation product of terminal 1,2-glycol was sought. After chromatography of its acetonide, the regenerated tetrol (III) fraction was cleaved with sodium metaperiodate on a preparative scale. The product was found to be the C_{24}-dialdehyde (IV), isolated and characterized as the bis-dinitrophenylhydrazone, m.p. 94-108°; $\lambda_{max}^{CHCl_3}$ 358 mμ (ε = 43,800) (Found: C, 59.98; H, 6.36; N, 15.66, 15.10, 15.57. Calc.: C, 60.15; H, 6.45; N, 15.59).

It is interesting to note that when squalene was oxidized with other

agents in dilute, usually non-aqueous solution (Table 1), very little preferential reaction at the end double bonds was observed. In each case

TABLE 1

Oxidizing agent	Solvent	Equiv. oxidant/mole squalene	Yield (%) acetone (DNP) from squalene glycol
Osmium tetroxide-pyridine	Ether	1	26, 27
Monoperphthalic acid[a]	Chloroform	2	32, 39
Potassium permanganate	Acetone-water (15:1)	10[b]	26
Iodine-silver acetate	Acetic acid	1	40
N-bromo-succinimide	Glyme-water	1	78
N-bromo-succinimide	Glyme-water	2	81

[a] In ether and dimethylformamide solutions the second order rate plots were linear up to at least four moles of peracid per mole of squalene.

[b] In experiments with less reagent, oxidation was farther from completion.

the total initial oxidation product, if not already a vicinal glycol, was converted to such material by the appropriate sequence of chemical reactions and then analyzed for acetone by the method described above. The precise relationships between solvent, oxidizing agent and conformation of squalene are under continuing investigation, as are the further transformations of tetrol (III).

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