Tetrahedron Letters No.39, pp. 4717-4719, 1966. Pergamon Press Ltd.
Printed in Great Britain.

A NOVEL OXIDATIVE TERPENE CYCLIZATION

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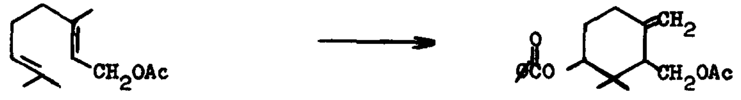
(Received 11 July 1966)

The biological oxidocyclization of squalene to polycyclic triterpenes, including steroid precursors, has stimulated a number of groups to investigate models for cationic cyclization of polyenes. As we have pointed out elsewhere,[1] many of the mechanistic requirements of squalene cyclization are better met by a free radical process. We have found that squalene reacts selectively at the terminal double bonds with some free radicals, although in our previous studies appreciable cyclization did not occur.[1] We now wish to report a free radical oxidative cyclization reaction which provides a good model for squalene cyclization.



I

II

Treatment of geranyl acetate (I) with benzoyl peroxide, cuprous chloride, and cupric benzoate in benzene or acetonitrile solution[2] at 70°C. affords a 55-60% yield of the oxidatively cyclized product II. The compound was isolated by chromatography and shows a single spot on thin layer chromatography (two systems) and a single peak in the v.p.c. (retention time 21.5 min. at 220°C. and 15 lbs. on a 5 foot SF-96 column). The mass spectrum shows a parent at m/e 316, and reasonable fragments at m/e 257, 256, 194, 152, and 134 (100% peak). The n.m.r. spectrum has two sharp three-proton singlets at 1.01 and 1.09 δ ($C-(CH_3)_2$), an eight-proton multiplet from 1.5 - 2.5 δ containing a sharp acetate singlet at 1.97 δ, a five-proton multiplet from 4.2 - 5.0 δ (CH-O and $C=CH_2$) and benzoate signals at 7.4 and 8.0 δ. The infrared spectrum was as expected, including a moderate band at 900 $cm.^{-1}$ ($C=CH_2$). The compound has 1.0 ± 0.1 double bond (bromate-bromide titration) and absorbs 0.96 moles of H_2 (Pt in ethyl acetate) to afford a saturated compound with the expected n.m.r. spectrum, including a one-proton apparent triplet (J = 4 c.p.s.) at 4.82 δ (CH-O Benzoate) and a new doublet methyl in the 1.0 δ region. Ozonolysis of II affords formaldehyde, isolated as the dimedon derivative (15%) and analyzed by the colorimetric Schiff procedure[3] (60%).

II is also obtained in 37% yield as the only monomeric adduct by photolysis of benzoyl peroxide (benzophenone- or anthracene-sensitized)[4] with geranyl acetate in benzene in the presence of cupric benzoate; in the absence of cupric benzoate, photolysis produces 5-10% of II along with saturated cyclized products. Thus, in both of these reactions benzoyloxy radical adds to the more reactive double bond, the product radical cyclizes,[5] and termination then occurs by oxidation (cupric benzoate) or hydrogen transfer. The course of these reactions is not unexpected based on previous studies.[1,2] However, the high yield and specificity of this oxidocyclization provide both an interesting biochemical model and a reaction of potential synthetic utility.

References

1. R. Breslow, E. Barrett, and E. Mohacsi, Tetrahedron Letters, No. 25, 1207 (1963).
2. J. K. Kochi, J. Am. Chem. Soc., **84**, 1572 (1962) and other papers.
3. J. F. Walker, "Formaldehyde", Reinhold Publishing Corporation, New York, 1953, p. 366-368.
4. M. J. Gibian, and C. Walling, J. Am. Chem. Soc., **87**, 3361 (1965).

5. In the experiments with cupric benzoate present it is formally possible that oxidation precedes cyclization, which would then involve a carbonium ion. This is much less likely than the sequence we suggest.