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OXIDATIVE CYCLIZATION OF FARNESYL ACETATE BY A FREE RADICAL PATH

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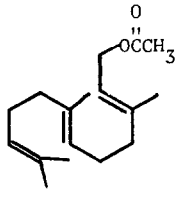
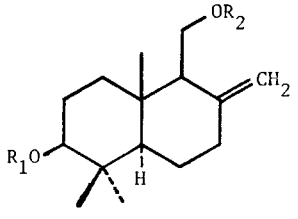
Chemical speculation on the mechanism of oxidative cyclization of squalene has led to a number of model studies. Although most attention has focussed on the cationic cyclization of polyene epoxides,[1,2] we have been concerned[3,4] with the possibility that nature might utilize a free-radical pathway. Recent studies[5,6] show that squalene epoxide is an intermediate in the oxido-cyclase reaction (probably, though not certainly, cyclizing by a carbonium ion mechanism). Although our "model" studies on free-radical pathways are thus of limited biochemical interest, they have resulted in a remarkably specific new synthetic reaction. Addition of benzoyloxy radical to the sesquiterpenoid trans, trans-farnesyl acetate (I)[7] gives the bicyclic product II(a). Benzoyloxy radicals were generated by the CuCl-catalyzed thermal decomposition[4,8] or the fluorescein-photosensitized decomposition[4] of benzoyl peroxide in acetonitrile. In both reactions, cupric benzoate was added to provide a termination mechanism.[4,8] II was isolated from the thermal reaction in 20-30% yield, from the photochemical in ca. 5% yield.[9]



I



II

(a) $R_1 = \phi C(=O)-$, $R_2 = CH_3C(=O)-$

(b) $R_1 = R_2 = CH_3C(=O)-$

(c) $R_1 = R_2 = H-$

Column chromatography gave crude II(a), from which pure II(a) was isolated by vapor phase chromatography (single symmetrical peak). In addition to recovered starting material, the other products are monocyclic compounds derived from I and some high-molecular-weight material. No evidence could be found for any bicyclic compounds other than II. Hydrolysis of

crude II(a) and preparative thin layer chromatography on silver-impregnated silica gel gave II(c). Esterification of crude II(c) gave crude II(b), purified by v.p.c. (single symmetrical peak) or preparative t.l.c. on silver-impregnated silica gel. II(a) and II(b) are colorless, viscous liquids; II(c) is a colorless crystalline solid, m.p. 111-114°.

The NMR spectrum (in $CDCl_3$) of II(a) shows, in addition to benzoate, acetate, and ring hydrogen resonances, terminal methylene resonances at 5.12 and 5.42τ (broad singlets), multiplets for C-2 hydrogen (5.2τ) and acetoxymethylene (5.82τ), and methyl singlets at 8.97, 9.01, and 9.17τ.

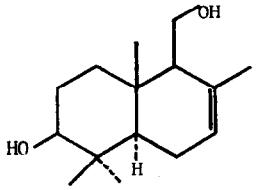
Ozonolysis of II(a) in acetic acid - ethyl acetate at -5° to -10° with H_2O_2 workup gave the expected ketone, with no terminal methylene in its NMR and methyl resonances at 8.95τ (s, 3H) and 9.12τ(s, 6H), and a parent mass spectral peak of m/e 386 (M.W. of II(a) = 384).

II(b) has terminal methylene resonances at 5.11 and 5.45τ(broad singlets), C-2 hydrogen multiplet at 5.2-5.6τ, acetoxymethylene resonances at 5.73τ(apparently two overlapping doublets with nearly identical chemical shifts, J = 6.0 and 6.5 cps), and methyl singlets at 9.12τ(6H) and 9.20τ(3H). The IR spectrum of II(b) in CS_2 shows acetate at 1740 cm^{-1} and exomethylene at 1645 and 890 cm^{-1}.

The NMR spectrum of II(c) has, besides hydroxyl and ring hydrogen resonances, terminal methylene at 5.04 and 5.33τ, C-2 hydrogen multiplet at 6.4-6.9τ, hydroxymethylene resonance at 6.21τ(apparently two overlapping doublets with nearly identical chemical shifts, J = 6.0 and 6.5 cps), and methyl singlets at 9.00, 9.22, and 9.27τ. The mass spectrum of II(c) has parent m/e fragments at P - CH_3, P - H_2O, P - $2H_2O$, among others.

The narrow melting range of II(c) and the fact that four derivatives of II have only three sharp methyl resonances in the 9.0τ region argue strongly that II is a single diastereomer. The chemical shift and broadness of the C-2 hydrogen resonance suggest that the C-2 hydrogen resonance suggest that the C-2 hydrogen is axial.[10] The chemical shifts of the methyls correlate very well with those in models with the proposed stereochemistry.[11] The positions of the terminal methylene resonances in II(c) are as expected for equatorial hydroxymethylene.[12]

To confirm the assigned stereochemistry, II was converted to the known III.[13] Isomerization of the diacetate II(b) was effected by 0.7 M $HClO_4$ in 3% aqueous ethyl acetate (2 hours at r.t.). Treatment with lithium aluminum hydride in tetrahydrofuran gave isomerized diol, m.p. 105-114°.



III

The NMR spectrum of isomerized diol had no exo-methylene resonance, a new olefinic multiplet at 4.45τ (1H), a new, slightly split methyl singlet at 8.20τ, and sharp methyl singlets at 9.02τ (3H) and 9.15τ (6H). Its infrared spectrum in KBr was exactly identical, band for band in position and relative intensities, with that of authentic III.[14]

II is formed by addition of benzoyloxy radical to farnesyl acetate and free radical closure of both rings, followed by oxidation of the radical by cupric benzoate with concerted proton transfer. Several arguments exclude the possibility that this is instead a carbonium ion process in which the radical is oxidized before cyclization. Thus, van Tamelen and co-workers have obtained only endocyclic olefin from the carbonium ion cyclization of trans, trans-farnesyl acetate terminal epoxide with BF_3· etherate in benzene.[13] We find that II(b) is not isomerized from exo- to endocyclic under even more stringent conditions. Also, the addition of benzoyloxy radical to the analogous monoterpene geranyl acetate with cupric benzoate present gives both cyclic and acyclic terminal methylene products, the relative yield of acyclic product increasing with increasing cupric benzoate concentration. This shows that oxidation of the radical competes with cyclization in our system.

Addition of benzoyloxy radical to trans, trans-farnesyl acetate in a chair-chair conformation with concerted closure of both rings would give the stereochemistry of II, although a concerted process is not required.[15] However, by whatever detailed mechanism this reaction is both structurally and stereochemically selective. In one step an acyclic sesquiterpene is converted to the oxidocyclized II in which four asymmetric centers have been established in specific relative configurations. Furthermore, both this stereochemistry and the new oxygen and exocyclic methylene groups reflect the natural functionality of α-onocerin, a product of enzymatic oxidocyclization of squalene. Considering the complexity of the changes effected in one step, this is a new synthetic reaction of considerable potential.[16]

References

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5. E.J. Corey, W.E. Russey, and P.R. Ortiz de Montellano, J. Am. Chem. Soc., 88, 4750 (1966).

6. E.E. van Tamelen, J.D. Willett, R.B. Clayton, and K.E. Lord, J. Am. Chem. Soc., 88, 4752 (1966).

7. Purified by preparative vapor phase chromatography.

8. J. Kochi, Rec. Chem. Prog., 27, 207 (1966).

9. Isolated yields, based on farnesyl acetate consumed.

10. In α-onocerin, the corresponding hydrogen (axial) has its resonance at 6.3-6.9τ; c.f. R.U. Lemieux, R.K. Kullnig, H.J. Bernstein, and W.G. Schneider, J. Am. Chem. Soc., 80, 6098 (1958).

11. α-Onocerin dibenzoate has methyl resonances at 9.00, 9.03, and 9.27τ. If the angular methyl chemical shift (9.27τ) is corrected for the acetate in II(a) (downfield shift of 5 cps), it becomes 9.19τ, and the resonances in II(a) compare very well. II(c) compares equally well with α-onocerin (with similar correction of the angular methyl chemical shift).

12. As in the diol of the previously reported[4] geranyl acetate cyclization product (5.05 and 5.25τ).

13. E.E. van Tamelen, A. Storni, E.J. Hessler, and M. Schwartz, J. Am. Chem. Soc., 85, 3295 (1963).

14. Kindly supplied by Professor E.E. van Tamelen.

15. The reaction of benzoyloxy radical with cis,trans-farnesyl acetate under similar conditions does not give II. Monocyclic exo-methylene product is also formed in the trans, trans-farnesyl acetate reaction.

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