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PHOTOÖXIDATION OF OLEANOLIC ACID: FORMATION OF 11α,12α-EPOXY- AND 12α-HYDROXY-OLEANOLIC LACTONES

Isao Kitagawa, Kiyoshi Kitazawa, and Itiro Yosioka
Faculty of Pharmaceutical Sciences, Osaka University
Toyonaka, Osaka, Japan

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In 1965, Corey and his co-workers reported[1] an interesting paper on the oxidative rearrangement of pentacyclic triterpenes which involved a novel skeletal rearrangement of thermodynamically more favored β-amyrin (I) towards less stable taraxerene derivative (II) by way of photochemical oxidative procedure in the acidic medium. They proposed an intermediate (III) in connection with the independent synthesis of the same product (II) starting from I by the alternate chemical oxidation. We assumed that if I carries 17-COOH function in place of 17-CH_3 as in oleanolic acid (IV), it would be appropriate to expect participation of the carboxylic function at the stage of intermediate (as in V) resulting 11α,12α-epoxy-oleanolic lactone (VI) as a final product. On the other hand, a unique nor-triterpenoid named eupteleogenin (VII)[2,3], a sapogenin of the biological active saponin, is so far the only natural occurrence possessing an 11α,12α-epoxy-13,28-lactone moiety, and as a model experiment for the biogenesis of the moiety, it seemed worthwhile to synthesize the epoxy-lactone system in one step according to the above mentioned assumption, which has now been realized although the yield of VI was rather low. It is a purpose of the present communication to describe the results obtained by photochemical oxidation of oleanolic acid.

On irradiation[4] of oleanolic acid (IV) in 95% ethanol (adjusted to PH 2.0 by HCl) for 80 hours at room temperature with slow stream of oxygen, a mixture* was obtained. After repeated silica gel column and thin layer chromatographic separations, the mixture afforded three products tentatively designated <u>0-1</u> (3%)**, <u>0-2</u> (trace), <u>0-3</u> (12.5%)** with the starting compound recovered (ca. 15%).

The major product, <u>0-3</u> (VIII), $C_{30}H_{48}O_4$(M^+: 472), mp. 274-278°; IR (KBr, cm^{-1}): 3530, 1741; NMR***(τ): seven methyls, 6.84 (1H, t-like, characteristic to $>C_{(3)}\underline{H}$-OH(eq.)), 6.20 (1H, broad

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* TLC of the total mixture disclosed the formation of small amount of oleanolic lactone (VI, without epoxy function), which was, however, not isolated in a pure state.
** Based on the pure compound obtained.
*** Measured at 100 Mc. in $CDCl_3$.

singlet, $W\frac{h}{2}$=7 cps, $>C_{(12)}\underline{H}$-OH(ax.)), was assumed to be 12α-hydroxy-oleanolic lactone (VIII) by its physical properties, and the assumption was verified by comparison of its 3β-O-acetate (IX) with the authentic specimen prepared by Barton's procedure[5)].

The very minor product, <u>O-2</u>, mp. 251-255°; IR (KBr, cm^{-1}): 3510, no carbonyl absorption band, showed a molecular ion at m/e 442. However, its structure has not yet been clarified due to the shortage of the material.

The other product, <u>O-1</u> (VI), $C_{30}H_{46}O_4$, mp. 269-271.5°, $[\alpha]_D^{23°}$ + 20.7° (c, 1.0 in $CHCl_3$); IR (KBr, cm^{-1}): 3536 (OH), 1771 (γ-lactone) 870 (a significant absorption band appeared also in VII[2)]); Mass (m/e): 470 (M^+), 189 (a most abundant peak above m/e 100); NMR (τ): seven methyls, 6.82 (1H, t-like, assigned to $>C_{(3)}\underline{H}$-OH(eq.)), 7.05* (2H, singlet, $W\frac{h}{2}$=3 cps.), seemed to have an epoxy-lactone moiety based on its IR and NMR spectra. Thus, a singlet (2H) appearing at τ 7.05 quite resembles to the corresponding signal (τ 7.08, 2H, singlet[2)], $W\frac{h}{2}$=3 cps.**) of eupteleogenin (VII)[2)] ascribable to 11β-H, 12β-H. Although the singlet due to the epoxidic protons of either VI or VII seems to be rather unusual comparing to the report by Tori et al[7)]. (e.g., the epoxide protons of methyl 11α,12α-epoxy-5β-cholanate gave an AB quartet pattern with J=4 cps.) and to J value (4.5 cps.) of the epoxide protons of II[1)], it would be approved by assuming unexpected equivalency of 11β-H and 12β-H in both VI and VII probably caused by the lactone ring***.

Finally, the structure VI for the compound <u>O-1</u> was proved by the following conversion. Thus, H_2SO_4-MeOH treatment of VI furnished a keto-lactone (X), mp. above 300°, IR (KBr, cm^{-1}): 3560, 3430 (OH), 1770, 1703 (C=O), similarly as in the case of eupteleogenin[2)], and the keto-lactone (X), $C_{30}H_{46}O_4$ was unambiguously prepared by CrO_3 oxidation of IX followed by alkaline hydrolysis and re-lactonization****.

To shed further light on the participation of the other oxygen function at C_{17}, an analogous study on erythrodiol having a carbinol function at C_{17} (I, R=CH_2OH) is in progress in our laboratory.

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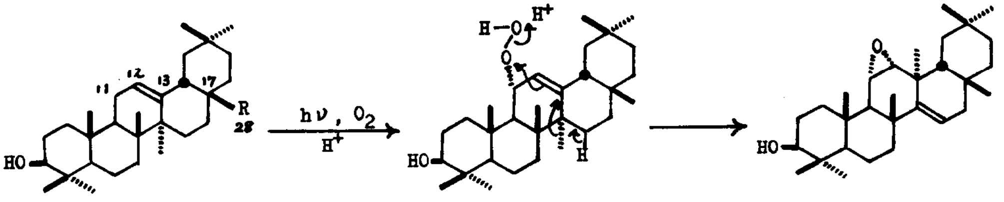
* The epoxidic protons are known to appear in the range τ 6.5-7.2[6)].

** Dr. T.Murata of Res. Lab. of Takeda Chemical Industries very kindly allowed us to compare our spectra with his spectra of eupteleogenin derivatives[2)], to whom we wish to express our sincere thanks.

*** The signal due to 12β-H of II appeared at higher chemical shift (τ 7.21) than 11β-H (τ 6.88)[1)], while 12β-H of VI or VII seems to be deshielded by the oxygen function nearby which may result the equivalency of 12β-H and 11β-H.

**** $LiAlH_4$ reduction of X yielded two tetrahydroxy derivatives, i.e., 3β,<u>12β</u>,13β,28-tetrahydroxy- and 3β,<u>12α</u>,13β,28-tetrahydroxy-oleananes (XI,XII). An attempt (in a TLC scale) was made to prepare XII from VI by the epoxide ring opening with $LiAlH_4$ as reported in the case of eupteleogenin (VII)[2)], however the product was found non-identical with either XI or XII. Although we have no definite evidence at this stage of discussion, we assume that the epoxide ring of VI could be cleaved by $LiAlH_4$ leaving a hydroxyl function at 11α as in the case of II[1)] rather than 12α as assumed in the paper of VII[2)].

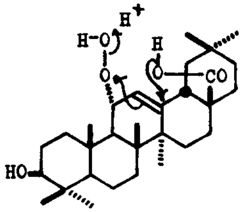


I R=CH_3 β-amyrin

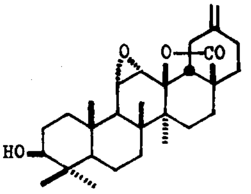
IV R=COOH oleanolic acid

III

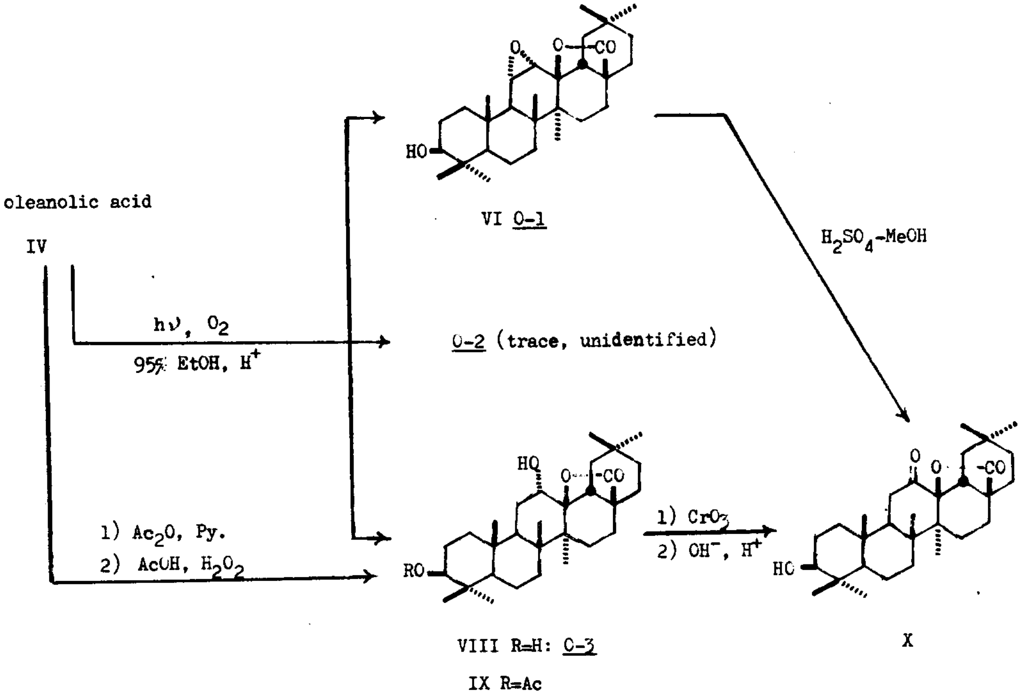
II



V



VII eupteleogenin



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4) As the light source, a 100W high-pressure mercury lamp (Osawa Denki Co., Tokyo) was used. The similar result was obtained on using a 30W low pressure mercury lamp (Type PIL 30, Eiko-sha, Osaka).

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