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THE STRUCTURE OF EUPTELEOGENIN, THE AGLYCONE OF ANTI-FUNGAL GLYCOSIDES, EUPTELEOSIDE A AND EUPTELEOSIDE B[*1]

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IN the previous paper[1] the isolation of anti-fungal glycosides, eupteleoside A and eupteleoside B[*2], from the leaves of Euptelea polyandra SIEB. et ZUCC., and some chemical properties of the aglycone eupteleogenin were recorded. It was also stated that eupteleogenin had one secondary hydroxyl, a five membered lactone, five tertiary methyl groups and one exomethylene double bond. Thus only one oxygen in the molecule still remained unclarified.

The present paper deals with the elucidation of the structure of eupteleogenin, which has now been established as 30-nor-20(29)-dehydro-11α,12α-epoxyoleanolic lactone (I).

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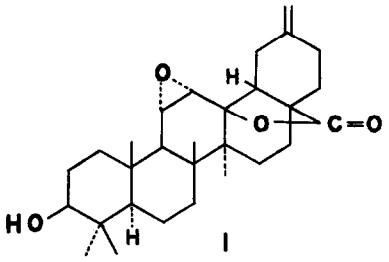
*1 This paper forms part of the series by Sueo Tatsuoka "Studies on the Useful Components in Natural Sources."

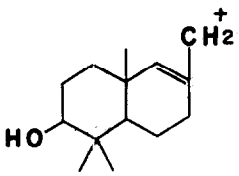
*2 Eupteloside B, $C_{48}H_{72}O_{18}.H_2O$, m.p. 266-268°, $[\alpha]_D$ +10° (pyridine), was shown to be eupteloside A monoacetate. Presented at the Annual Meeting of the Pharmacognostical Society of Japan, Tokyo, May, 1965.



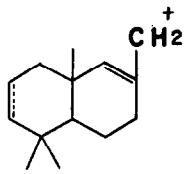
I

Mass spectrometric studies of eupteleogenin (I), eupteleogenin acetate (II) and eupteleogenone (III) provided an unequivocal proof that the aglycone is formulated $C_{29}H_{42}O_4$. Since dihydroeupteleogenin (IV) has no unsaturation in the molecule other than the lactone carbonyl, it can be concluded that eupteleogenin is pentacyclic.

Eupteleogenin (I) exhibited intense mass peaks at m/e 207 and 189, which are reasonably ascribed to the characteristic fragments common to some naturally occurring pentacyclic triterpenes.[2)]



m/e 207



m/e 189

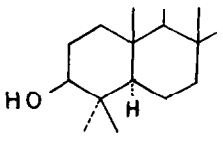
The o.r.d. curve of dihydroeupteleogenone (V), m.p. 248-251°, $[\alpha]_D^{23}$ +65°.*3 (Found: C, 76.58; H, 9.28. $C_{29}H_{42}O_4$ requires C, 76.61; H, 9.31%), shows a weak positive Cotton effect with the maximum of the first extremum at 300 mu [RD in MeOH (c=0.08), 24°: $[\alpha]_{589}$ +10°,

*3 The specific rotations are taken on chloroform solutions.

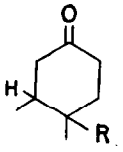
$[\alpha]_{365}$ +179°, $[\alpha]_{310}$ +379° (shoulder), $[\alpha]_{300}$ +472°, $[\alpha]_{290}$ +316°].

Eupteleogenone (III) is positive in the Zimmermann test,[3] and on sodium borohydride reduction gives eupteleogenin (I).

These data strongly suggest that eupteleogenin (I) is a 3β-hydroxy-4,4'-dimethyl-5α-triterpene having at least two additional methyls at C_8 and C_{10} (Ia).



Ia



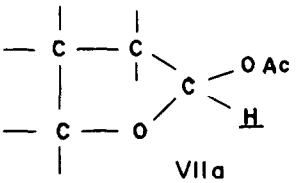
VIa

Oxidation of eupteleogenin acetate (II) with ozone gave a norketone acetate (VI), m.p. 335-337°, $[\alpha]_D^{26}$ +62°, (Found: C, 72.31; H, 8.34. $C_{30}H_{42}O_6$ requires C, 72.26; H, 8.49%). The o.r.d. curve of VI showed a negative Cotton effect, [RD in dioxane (c = 0.13), 11°: $[\alpha]_{700}$ +48°, $[\alpha]_{589}$ +61°, $[\alpha]_{356}$ +96°, $[\alpha]_{320}$ -96°, $[\alpha]_{312}$ -38°, $[\alpha]_{309}$ -59°, $[\alpha]_{300}$ +159°, $[\alpha]_{270}$ +673°, $[\alpha]_{252}$ +652°], the curve being reminiscent of the part structure VIa[4] (R = CH_3 or lactone carbonyl) in the molecule of the compound VI.

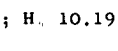
These observations led us to the assumption that eupteleogenin (I) would have either an oleanane or an ursane carbon skelton in which C_{30}- or C_{29}-methyl has been lost, provided a seven membered ring[5] is excluded.

Reduction of eupteleogenin (I) with sodium borohydride followed by acetylation with acetic anhydride and pyridine, gave the lactol diacetate (VII), m.p. 250-252°, $[\alpha]_D^{25}$ +61°, (Found: C, 73.24; H, 8.75 $C_{33}H_{48}O_6$ requires C, 73.30; H, 8.95%). The n.m.r. spectrum of VII visualized

a singlet at 6.00 p.p.m. (δ), which was reasonably attributed to the proton as formulated by the following part structure VIIa.[6] This almost certainly establishes that the lactone carbonyl in eupteleogenin (I) is present on a tertiary carbon.



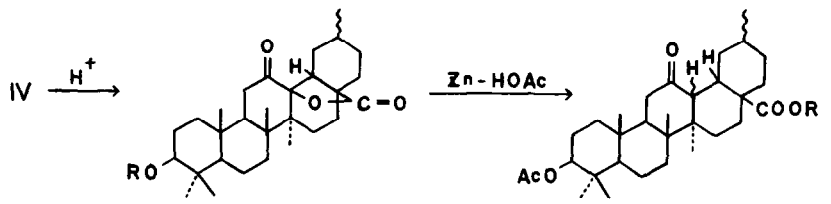
VIIa

The fourth oxygen in the aglycone was shown to be present as an epoxide by the n.m.r. signal at 3.07 p.p.m. (2H, singlet with fine splitting, ) in the compounds (I, II and III). This signal disappeared when eupteleogenin (I) was reduced with lithium alminium hydride.[7] The resulting tetrol (VIII), m.p. 214-216°, (Found: C, 74.56; H, 10.19. $C_{29}H_{48}O_4 \cdot \frac{1}{2}H_2O$ requires C, 74.83; H, 10.25%), on acetylation with hot acetic anhydride and pyridine gave the tetrol triacetate (IX), m.p. 249-250°, $[\alpha]_D^{24}$ +12°, (Found: C, 71.65; H, 9.12. $C_{35}H_{54}O_7$ requires C, 71.63; H, 9.25%), which clearly exhibited a hydroxyl band at 3500 cm^{-1} in its infrared spectrum (Nujol), and was not oxidized with chromium trioxide. This provides evidence that the hydroxyl group involved in the lactone ring is attached to a tertiary carbon atom. Further support for the above conclusion comes from the n.m.r. spectra of the compounds (I, II and III), because no signals attributable to the lactonic C<u>H</u>-O-CO proton was noticed in the spectra of these compounds.

Treatment of dihydroeupteleogenin (IV) with sulfuric acid in methanol afforded a ketolactone (X), m.p. 243-245°, $[\alpha]_D^{25}$ +4.5°, (Found: C, 76.56; H, 9.71. $C_{29}H_{44}O_4$ requires C, 76.27; H, 9.70%), IR ν_{max}^{KBr} cm^{-1}:

1710 (six-membered ring ketone), 1770 (lactone), which was acetylated to give the ketolactone acetate (XI), m.p. 258-260°, (Found: C, 74.51; H, 9.24. $C_{31}H_{46}O_5$ requires C, 74.66; H, 9.29%). The o.r.d. curve of XI shows a negative Cotton effect with the first extremum at 318 mu [RD in dioxane (c = 0.06), 25°: $[\alpha]_{589}$ +16°, $[\alpha]_{500}$ +48°, $[\alpha]_{365}$ +24°, $[\alpha]_{318}$ -138°, $[\alpha]_{270}$ +488°], which closely resembled that of 12-keto-hederageninlactone diacetate.[8], *4

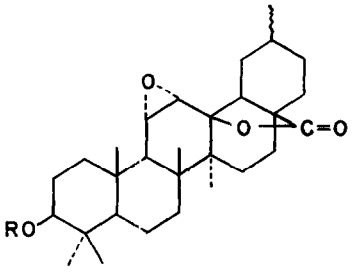
When compound XI was heated with zinc dust in acetic acid, somewhat surprisingly was obtained a ketocarboxylic acid (XII), m.p. 185-186°, $[\alpha]_D^{25}$ -9.6°, IR ν_{max}^{KBr} cm^{-1}: 1695 (carboxyl), 1710 (ring ketone), 1735 (acetyl), (Found: C, 74.17; H, 9.85. $C_{31}H_{48}O_5$ requires C, 74.36; H, 9.66%), the latter was treated with diazomethane to give the methyl-ester (XIII), m.p. 114-116° (202-204°, after drying), $[\alpha]_D^{25}$ -7.6°, (Found: C, 74.58; H, 9.70. $C_{32}H_{50}O_5$ requires C, 74.66; H, 9.79%). These reactions are now summarized in the following scheme.



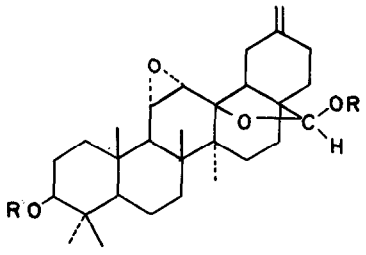
X R = H
XI R = Ac

XII R = H
XIII R = CH_3

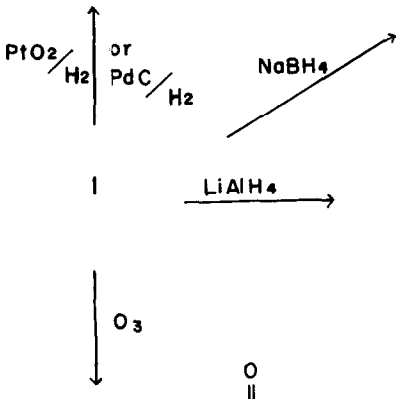
*4 12-Ketohederageninlactone diacetate showed RD in dioxane (c = 0.16), 24°: $[\alpha]_{589}$ +14°, $[\alpha]_{500}$ +20°, $[\alpha]_{365}$ +12°, $[\alpha]_{320}$ -105°, $[\alpha]_{270}$ +300°.

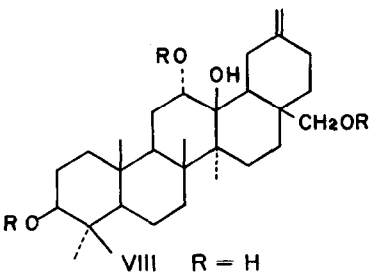


IV R=H

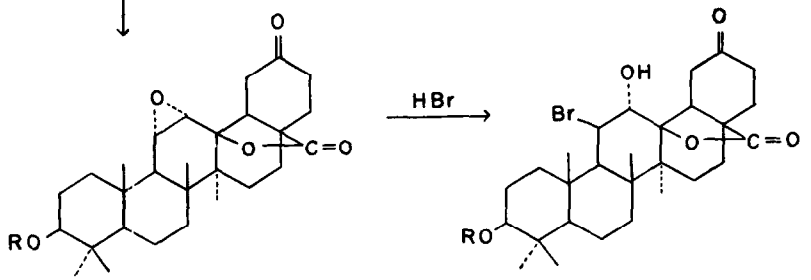


VII R=Ac





VIII R = H
IX R = Ac



VI R = Ac

XIV R = Ac

Confirmation of the structure I was obtained at this stage from the methyl signals of the n.m.r. spectra of norketone acetate (VI) and the bromohydrin acetate (XIV), the latter being prepared by the treatment of VI with hydrogen bromide in methylenechloride.

The methyl signals of VI appeared at 0.88(6 H), 1.08(6 H) and 1.19 (3 H), while XIV revealed the signals at 0.92(6 H), 1.39(3 H), 1.46(3 H) and 1.48(3 H).

In the light of the fact that a 1,3-diaxial interaction[9] between methyl group and bromine and/or hydroxyl usually causes a marked downfield shift of the methyl signal and that the epoxide opens to give rise to trans-diaxial substituents, one could reasonably conclude that the epoxide in the molecule of the norketone acetate (VI) was located in the 11,12-positions.

That the epoxide is α-oriented is concluded from the fact that the tetrol (VIII) gave the triacetate (IX), because the corresponding 11β,12β-epoxide should give the 11β-hydroxy compound which would not be acetylated by the usual acetylation conditions as evidenced in the steroid chemistry.

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