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A PROSAPOGENIN FROM POLYGALA SENEGA AND POLYGALA TENUIFOLIA

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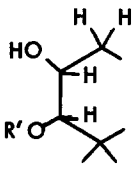
Depending upon the conditions employed, hydrolysis of the saponin (senegin) of Polygala senega gives rise to presenegenin[1,2], senegenin[3,4], senegenic acid[4,5] (polygalic acid[6]) and hydroxysenegenin[2]. A report[7] that hydrolysis of Polygala tenuifolia gives a senegenin-like sapogenin led us to examine the sapogenins of this plant. The oxidative and hydrolytic cleavage of the saponin from P. tenuifolia afforded presenegenin together with p-methoxycinnamic acid. Hydrolysis of the saponin with ethanolic hydrochloric acid gave senegenin. Thus, the P. tenuifolia saponin behaves exactly like that of P. senega in giving rearranged products under vigorous hydrolysis conditions[8].

This paper reports the isolation and structure of a new prosapogenin (I) obtained from the basic hydrolyzate of the saponin of either P. senega or P. tenuifolia. The compound (I)[9], $C_{36}H_{56}O_{12}$, mp. 249-253° dec., $[\alpha]_D$ + 49°; treatment with diazomethane yielded ester (II), $C_{38}H_{60}O_{12}$, mp. 268-271°, $[\alpha]_D$ 41.5°. Acetylation of II with acetic anhydride at room temperature (or refluxing), gave a penta-acetate (III), $C_{48}H_{70}O_{17}$, mp. 215.5-218.5°, $[\alpha]_D$ 67.7°; νmax 3540 cm.$^{-1}$ (OH). The n.m.r. spectrum of the acetate (III) shows five acetyl signals at τ = 8.04 (3H), 8.01 (6H), 7.98 (3H), 7.93 (3H); five tertiary alkyl methyl signals at τ = 9.34 (3H), 9.16 (3H), 9.09 (3H), 8.78 (3H), 8.70 (3H); a vinyl proton signal at τ = 4.45 (1H, multiplet) and two methyl ester signals at τ = 6.33 (3H), 6.40 (3H). The acetate (III) resisted further acetylation with acetic anhydride-pyridine even under refluxing conditions. Reaction of III with chromium trioxide in pyridine gave ketone (IV), $C_{48}H_{68}O_{17}$, mp. 217.5-219.5°, $[\alpha]_D$ 48°; 1720 cm.$^{-1}$ (no -OH absorption). Reduction of (IV) with sodium borohydride in ethanol followed by acetylation regenerated acetate (III). Of the twelve oxygen functions in (I), four are accounted for in two carboxyl groups and six in the six hydroxyl groups (secondary or primary). The trisubstituted double bond in (I) was characterized as follows: Oxidation of acetate (III) with m-chloroperbenzoic acid gave a ketone (V), $C_{48}H_{70}O_{18}$, mp. 280-283.5°, $[\alpha]_D$ 20°, νmax 1703 cm.$^{-1}$ (six-membered ketone), 3540 cm.$^{-1}$ (hydroxyl group), whose n.m.r. spectrum had no vinyl proton signal. Oxidation of the ketone with chromium trioxide yielded a diketone (VI), $C_{48}H_{68}O_{18}$, mp. 209-212.5°, $[\alpha]_D$ 5.5°. Treatment of ketone (V) with bromine in acetic acid gave a bromocompound (VII), $C_{48}H_{69}O_{18}$ Br, mp. 199-203°, $[\alpha]_D$ 47.5°. Debromination of (VII) with lithium chloride in dimethyl formamide afforded a debromo compound (VIII), $C_{48}H_{68}O_{18}$, mp. 190-190.5°, νmax 1665 cm.$^{-1}$, λmax 240 mμ (ϵ = 7200), τ = 4.80 (1H, vinyl proton). These spectra indicate that the debromo compound (VIII) is a trisubstituted enone. Acetylation of (I) gave an acetate (IX) as an amorphous

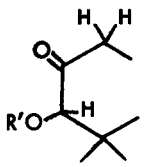
solid. Methylation of (IX) with diazomethane afforded the acetate (III). Oxidation of (IX) with hydrogen peroxide in acetic acid gave, after methylation with diazomethane, an amorphous lactonic ester, ν max 1775 cm.$^{-1}$ (γ-lactone). Oxidation of the latter with chromium trioxide in pyridine gave a keto lactone (X), $C_{47}H_{68}O_{18}$, mp. 255-256°, $[\alpha]_D$ 3°, ν max 1775 cm.$^{-1}$ The n.m.r. spectrum of the lactone was similar to that of the diketone (VI) except for signals of methyl ester groups.

The molecular formula of (I) coupled with the many oxygen functions suggested that (I) is an aglycone of glucose and a triterpenoid such as presenegenin. The dimethyl ester (II) which showed a negative Fehling's test was hydrolyzed with hydrochloric acid in dioxane to give a substance which showed a positive Fehling's test. The sugar moiety was identified as glucose by paper-chromatography. Hydrolysis of ester (II) with hydrochloric acid in aqueous alcohol gave senegenin dimethylester, identified by t.l.c. and infrared spectrum. Apparently under the acidic hydrolysis conditions the presenegenin moiety in I rearranges to senegenin[8].

The location of the glucose residue on the presenegenin moiety was determined as follows: The n.m.r. spectrum of the acetate (III) has a doublet centered at τ =5.50 (1H, J = 8 c.p.s.) due to R-O-C(H)-H and a multiplet at τ = 5.00 (HO-C(H)-H). In the spectrum of the ketone (IV), however, this doublet signal appears as a singlet at τ 5.21 while the multiplet signal at τ = 5.00 has disappeared. This behavior suggests that the acetate (III) has partial structure (A) and is oxidized to the ketone (B). Similar changes

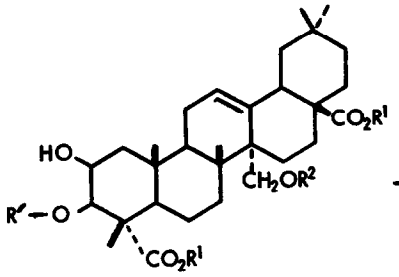


A

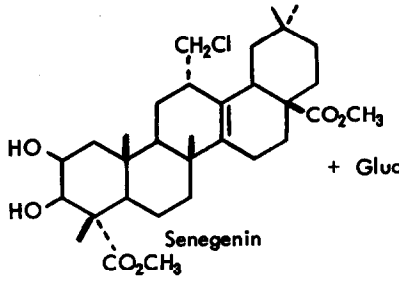


B

were also observed in the n.m.r. spectra of derivatives obtained as follow. Reduction of the acetate (III) with lithium aluminum hydride in tetrahydrofurane gave an amorphous solid (XI) which showed no carbonyl absorption in the infrared spectrum. Acetylation of (XI) afforded a heptaacetate (XII), $C_{50}H_{74}O_{17}$, mp. 171-172°, $[\alpha]_D$ 60.8°; ν max 3650 cm.$^{-1}$ (OH); τ 7.90 (3H), 7.89 (3H) 7.91 (3H) 7.92 (3H), 7.93 (3H), 7.94 (6H). Oxidation of XII with chromium trioxide gave a ketone (XIII), mp. 182-183°, $[\alpha]_D$ 55.6°. The spectrum of the acetate (XII) had a doublet at τ 5.35 (1H, J = 8 c.p.s.) while the ketone (XIII) had a singlet at τ 5.50 (1H). These findings and the fact that the aglycone dimethylester (II) on hydrolysis with ethanolic hydrochloric acid afforded senegenin dimethylester, suggest that partial structure (A) corresponds to ring A of the sapogenin. The substituent R' in the partial structure (A) was shown to be glucose by the following reactions. Presenegenin or senegenic acid, on reaction with acetic anhydride-pyridine gives the corresponding acetate. But the C(2) hydroxyl group in the ester (II) was not acetylated under similar conditions. These facts can be explained by the presence of the bulky glucose group at C(3). Attack of a reagent on the 2β-hydroxyl group is shielded by the 3β-glucose residue. This is supported by the fact that



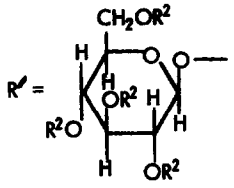
HCl



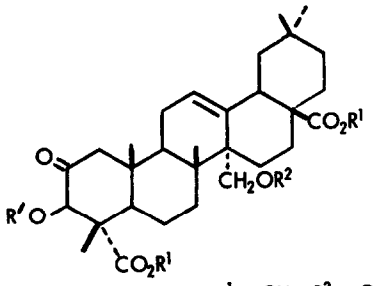
+ Glucose

Senegenin

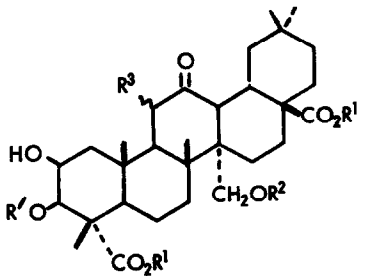
CrO_3-Pyr.



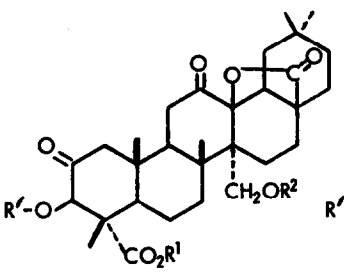
I, $R^1 = R^2 = H$
II, $R^1 = CH_3$; $R^2 = H$
III, $R^1 = CH_3$; $R^2 = Ac$
IX, $R^1 = H$, $R^2 = Ac$



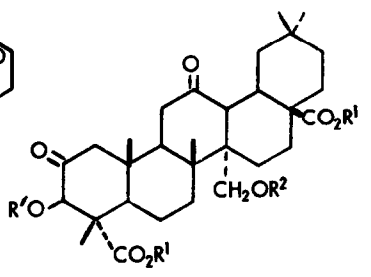
IV, $R^1 = CH_3$; $R^2 = OAc$



V, $R^1 = CH_3$; $R^2 = Ac$; $R^3 = H$
VII, $R^1 = CH_3$; $R^2 = Ac$; $R^3 = Br$

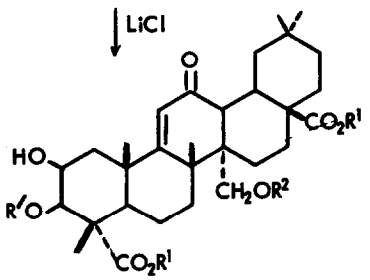


X, $R^1 = CH_3$; $R^2 = Ac$

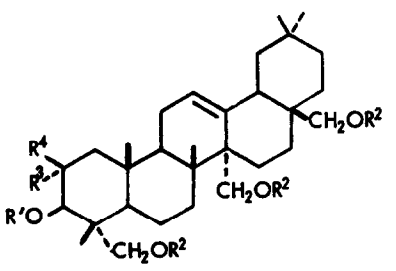


VI, $R^1 = CH_3$; $R^2 = Ac$

LiCl



VIII, $R^1 = CH_3$; $R^2 = Ac$



XI, $R^2 = H$; $R^4 = OH$; $R^5 = H$
XII, $R^2 = Ac$; $R^4 = OH$; $R^5 = H$
XIII, $R^2 = Ac$; R^4, $R^5 = O$

reduction of the ketone (IV) with sodium borohydride gave, after acetylation only a 2β-hydroxyl compound (III). The n.m.r. spectrum of the acetate (III) shows a doublet signal at $\tau = 4.78$ (1H, $J = 9$ c.p.s.) indicative of β-orientation for the glucosidic linkage.[10,11]

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