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POLYGALIC ACID*

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A study of the saponin of Polygala senega has resulted in the isolation of two crystalline sapogenins (1). The structure of one of these, senegenin, has recently been shown to be I (2).

The second triterpenoid, polygalic acid monoethyl ester,** was shown to be a monoethyl ester of a dibasic, dihydroxy, C_{29} acid, $C_{31}H_{50}O_6$ or $C_{31}H_{48}O_6$, m.p. 215-218°, $[\alpha]_D^{23}$ + 24.5° (EtOH). A weak colour with tetranitromethane was obtained, suggesting the presence of a double bond, and a diacetyl derivative was prepared.

The n.m.r. spectrum of the methyl ethyl ester of polygalic acid showed a singlet at τ = 6.37 (3H) in agreement with the presence of one carbomethoxy group, as well as broad absorption at $\tau \sim 6.0$ (4H) for the methine protons of two secondary hydroxyl groups and the methylene of an ethoxyl group. The monoacetate showed absorption at τ = 4.83 (1H, doublet), and a band at $\tau \sim 6.0$ (3H, multiplet). The diacetate had bands at τ = 4.64 (1H, multiplet) and τ = 4.80 (1H, doublet) while a quartet (2H) due to the

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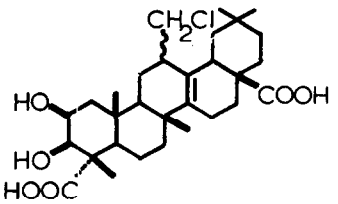
* Terpenoids, Part VI.

** The compound was named polygalic acid ethyl ester by M. Shamma and W.E. Irwin (3). These authors further confirmed the general nature of the functional groups.

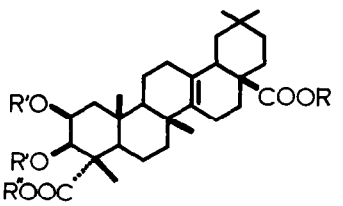
carboethoxy methylene group remained at τ = 6.01. This behavior, analogous, where relevant, to that observed for senegenin, indicated the stepwise acetylation of two secondary hydroxyl groups. These observations, coupled with the lead tetraacetate titration data (3), strongly suggested that ring A of polygalic acid ethyl ester was the same as that of senegenin.

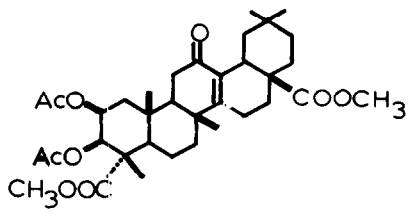
The ultraviolet absorption (λ_{max}^{EtOH} 200 mμ, ε 7300) confirmed the presence of a double bond, but the n.m.r. spectra, of the derivatives mentioned, indicated the absence both of any vinyl proton and of a methyl group on a double bond.

Accepting the C_{29} formulation, the presence of a tetrasubstituted double bond and a probable β-amyrin carbon skeleton, leads to a restricted number of possible formulae. Of these structures IIa, because of its relationship to senegenin, (I) (the ethoxyl group being as yet unplaced) appeared to be the most attractive.



I





III

IIa : R=R'=R''=H
IIb : R=R''=H, R'=Ac
IIc : R=C_2H_5, R'=R''=H
IId : R=R''=CH_3, R'=Ac

The crude acetylated sapogenin mixture was dissolved in ether and extracted with sodium bicarbonate (5%) thus removing the senegenin, and leaving polygalic acid ethyl ester monoacetate in the ether layer (4). Hydrolysis with 5% potassium hydroxide at room temperature followed by several recrystallisations from 95% ethanol gave "polygalic acid ethyl ester", m.p. 215-218° (Kofler block), $[\alpha]_D^{23}$ + 25° (EtOH), ν_{max} 1718, 1704 cm^{-1} (Nujol), (Found: OEt, 9.16%). This was, however, found to be a mixture (thin layer chromatography of the methyl ethyl ester) containing about 5-8% of an impurity that could not be removed by repeated crystallisation from acetone or alcohol.* In order to obtain pure starting material, the non-crystalline methyl ethyl ester was separated by thin-layer chromatography on silica gel.

Hydrolysis of the methyl ethyl ester with 5% potassium hydroxide in refluxing n-amyl alcohol (4 hours) followed by sodium bicarbonate (5%) extraction gave, after crystallisation from ethanol, pure polygalic acid (IIa) (25% yield), $C_{29}H_{44}O_6$, EtOH m.p. 299-301° (evacuated capillary), $[\alpha]_D^{23}$ + 18° (EtOH), λ_{max}^{EtOH} 200 (ε 8100), (Found: C, 69.68; H, 8.91). Acetylation (pyridine-acetic anhydride) gave the crystalline diacetate (IIb), $C_{33}H_{48}O_8$, m.p. 276-278° (evacuated capillary), $[\alpha]_D^{23}$ + 23° (MeOH), (Found: C, 69.19; H, 8.04). Methylation (diazomethane) and oxidation of IId with chromium trioxide in acetic acid at room temperature (5) (one hour) gave an unsaturated ketone (III) (25% yield), $C_{35}H_{50}O_9$, m.p. 245-247° (evacuated capillary), $[\alpha]_D^{23}$ + 46° ($CHCl_3$), λ_{max}^{EtOH} 253 mμ (ε 9400), ν_{max} 1613, 1661, 1745 cm^{-1} ($CHCl_3$), (Found: C, 68.15; H, 7.89). This compound proved to be identical in every respect with the unsaturated

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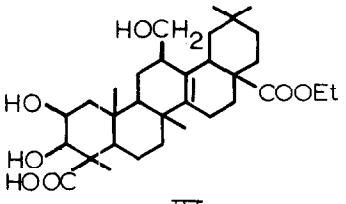
* The impurity was isolated by thin-layer chromatography and was found to contain chlorine (positive Beilstein test). Further, analysis of polygalic acid ethyl ester (mixture) gave 0.42% chlorine. Considering the insolubility of the impurity in bicarbonate and its chlorine content, it is probably senegenin ethyl ester.

ketone dimethyl ester diacetate obtained from senegenin (2).

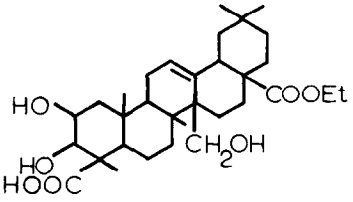
The carboethoxy group in the monoethyl ester must be placed at C_{17} as in IIc on the basis of lead tetraacetate titration (3), and its resistance to hydrolysis.

Polygalic acid was also found to be present, in very small amount, in the mother liquors of senegenin (4).

Polygalic acid ethyl ester must be an artifact that is produced, together with senegenin, during the hydrochloric acid hydrolysis of the saponin (4). It could arise by a reverse Prins on "hydroxy senegenin" (IV) (followed by double bond migration) or on the unrearranged β-amyrin derivative (V). This, or the equivalent on a different oxidation level, may, however, be an over-simplification since the esterification of the C_{17} carboxyl remains to be explained.



IV



V

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