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SENEGENIC ACID, A PENTACYCLIC NOR-TRITERPENE ACID

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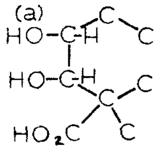
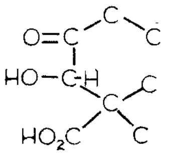
From the acid hydrolysate of the saponin from Polygala senega root, Jacobs and Isler isolated senegenin and the monoethyl ester of a dibasic acid[2]. Saponification of the latter with potassium hydroxide in amyl alcohol afforded a crude dibasic acid, m.p. 230°, to which Jacobs assigned a formula of $C_{29}H_{44}O_6$ or $C_{29}H_{46}O_6$. A reinvestigation of the saponin hydrolysate has shown that this acid, designated senegenic acid, m.p. 256-258°, $[\alpha]_D + 23°$, accompanies its monoethyl ester and senegenin in the hydrolysate mixture. This paper reports work demonstrating that senegenic acid is a pentacyclic nor-triterpenic acid of unusual structure.

Mass spectrometry[3] of the monoethyl-, ethylmethyl-, and dimethyl esters of senegenic acid indicates the correct molecular formula for the acid is $C_{29}H_{44}O_6$. It forms a diacetate, m.p. 280-81°, $[\alpha]_D$ 34°, a dimethyl ester, m.p. 198-200°, $[\alpha]_D$ 20.5°, and a dimethylester diacetate, m.p. 180-2°, $[\alpha]_D$ 31°, thus accounting for the six oxygen functions as two hydroxyl and two carboxyl groups. One inert[2] ethylenic linkage is suggested by UV absorption [λmax (EtOH) 205 mμ, (5000)]; the absence of a vinylic proton signal in the p.m.r. spectra of several derivatives indicates the double bond is tetrasubstituted. Selenium dehydrogenation studies[2,4] suggest a pentacyclic skeleton for senegenic acid. Kuhn-Roth oxidation of senegenic acid ethyl ester gives only acetic acid and no trace of higher fatty acids; thus, no alkyl side chain other than $C-CH_3$ is present.

The p.m.r. spectrum of dimethyl senegenate shows bands at τ 5.86 (lH-multiplet) and τ 6.10 (lH-doublet, J. 3.5 cps.) which shift to τ 4.5 (multiplet) and τ 4.68 (lH-doublet, J 4.2 cps.) in diacetoxydimethyl senegenate, indicating two secondary hydroxyl functions. The presence of a 1, 2-glycol function is indicated by consumption of one equivalent of periodate by either the monoethyl ester or the ethylmethyl diester. The location of a carboxyl function in the vicinity of the 1,2-glycol moiety is suggested by the behavior of dimethyl senegenate toward methanolic potassium hydroxide[5]. The formation of a monomethylester, m.p. 260-4^0, $[\alpha]_D$ 21.1^0, resistant



I



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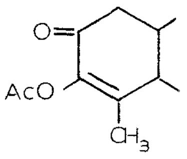

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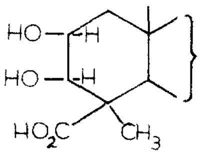


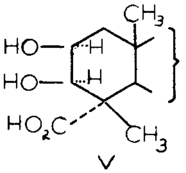
IV

to further saponification, indicates that the carbomethoxyl group undergoing saponification is located adjacent to the glycol as in I. The fact that one of the H-C-hydroxyl protons appears as a doublet in the p.m.r. spectrum is in agreement with a quaternary carbon adjacent to the carbon bearing this proton.

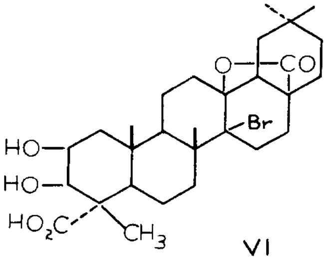
Oxidation of senegenic acid ethyl ester with Jones' reagent affords an α-ketol acid, $C_{31}H_{46}O_6$, m.p. 195-200^0, $[\alpha]_D$ 6.3^0, showing absorption in the infrared at νmax (nujol) 3448 cm.$^{-1}$ (OH) and 1709 cm.$^{-1}$, broad ($>$C=O) and a band in the p.m.r. at τ 5.32 which shifts to τ 4.36 (singlet) in the corresponding acetate, m.p. 235-238^0, $[\alpha]_D$ 30.2^0, νmax (nujol) 1757, 1232 cm.$^{-1}$ (OAc), 1724, 1701 cm.$^{-1}$. The appearance of the H-C-OAc signal as a singlet indicates that the OH function labeled "a" in I is that oxidized to a ketone as in II. Treatment of the ketol with methanolic potassium hydroxide gives rise to a diosphenol [νmax (nujol) 3413, 1724, 1672, 1645 cm.$^{-1}$, λ max (EtOH) 281 mμ; λ max (EtOH-KOH) 329 mμ],(strong ferric chloride color) which was characterized as an enol acetate (III), m.p. 194-6^0. $[\alpha]_D$ 13.2^0 [νmax (nujol) 1764, 1718, 1672, 1645 cm.$^{-1}$, λ max (EtOH) 249 mμ, (9822)]. Formation of the diosphenol by decarboxylation confirms the β-ketoacid formulation (II), while appearance of a vinylic methyl signal (τ 7.78, 3H-singlet) defines the position of the methyl group (III).

The close similarity of the above reactions to those described for medicagenic acid[5] suggests that the functional groups concerned are involved in ring A (IV) of a pentacyclic triterpene skeleton. The quaternary methyl groups at C(4) and C(10) are discernible in the p.m.r. spectra by a 3H-singlet at τ 8.65 (deshielded by the 4α-CO_2H) and at τ 8.8 (deshielded by the 2β-equatorial hydroxyl). Moreover, the p.m.r. spectra of dimethylsenegenate (τ 9.15, 9.11, 9.10) and dehydrodimethylsenegenate (vide infra) (τ 9.15, 9.09, 8.99)clearly show the presence of three other quaternary methyl groups which may be assigned to C(8) and C(20) (gem dimethyl).

The smooth hydrolysis of the 4-carbomethoxy group of dimethylsenegenate indicates the conformation of this group is α-equatorial. Dimethyl senegenate forms an acetonide, m.p. 162-4^0, $[\alpha]_D$ 40.2^0. Of the four stereochemical possibilities for the 1,2-glycol system, the 2β,3α-and 2α,3β-may, therefore, be eliminated[6]. Moreover, the 2α,3β-isomer would require a large trans diaxial coupling (J, 8-10 cps.) of the methine protons[7], whereas the observed values range from 3.5-4.2 cps. Of the two remaining possibilities, the 2α,3α-isomer may be ruled out since lactonization of the 4α-carboxyl with the 2α-hydroxyl is not observed. A 2β,3β-glycol system is therefore present. In the case of senegenic acid ethyl ester, the preferential oxidation of the axial C(2)-hydroxyl and the formation of the equatorial C(3)-monoacetate, m.p. 160-161^0, $[\alpha]_D$ 25.5^0, (τ 4.75, 1H-doublet, J 3.8 cps., H-C-OAc) confirms the presence of the 2β,3β-glycol system. Therefore, the A-ring of senegenic acid (V) is identical with that described for medicagenic acid[5] and senegenin[8].



V



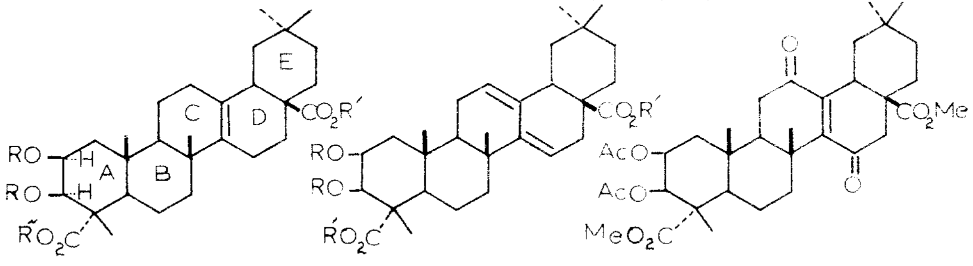
VI

The relative position of the tetrasubstituted double bond and second carboxyl group were indicated by the fact that senegenic acid readily forms a bromolactone (VI), m.p. 280-85^0, $[\alpha]_D$ 49^0, νmax (nujol) 1776 cm.$^{-1}$ (γ-lactone). Senegenic acid ethylester, on the other hand, does not form a bromolactone under similar conditions. Either a Δ^8-C(13) carboxyl or a Δ^{13}-C(17) carboxyl formulation is consistent with this behavior[9]. Since it will subsequently be demonstrated that the Δ^{13}-C(17) carboxyl system is present, the following transformations will be interpreted on the basis of a pentacyclic triterpene containing the Δ^{13}-C(17) carboxyl moiety.

Treatment of the bromolactone (VI) with pyridine at 125^0 afforded a crystalline dehydroacid (VIIIc), $C_{29}H_{42}O_6$, m.p. 228-30^0, $[\alpha]_D$ 59^0; λmax (EtOH) 237 mμ (12,460), 246 mμ (14,922) and 254 mμ (11,500); p.m.r., 2 vinylic protons at τ 4.54. Moreover, oxidation of either dimethylsenegenate (VIIb) or diacetoxydimethylsenegenate (VIIa) with perbenzoic acid followed by chromatography over neutral alumina gives amorphous dehydroderivatives[10], VIIIb and VIIIa, respectively [λmax (EtOH) 238 mμ (8810), 246 mμ (10,468) and 255 mμ (7212)] which on hydrolysis (amylalcoholic KOH) afford dehydrosenegenic acid (VIIIc).

Reduction of the dehydroacid (VIIIc) in the presence of PtO_2/EtOH afforded senegenic acid (VIIc) in quantitative yield - a reaction readily interpretable on the basis of 1,4-addition of hydrogen to the α-face of a $\Delta^{12,14}$ diene, but not applicable in the case of a $\Delta^{7,9(11)}$ diene exhibiting the same type of absorption maxima[11].

Oxidation of VIIa with chromium trioxide in acetic acid gave a pale yellow amorphous enedione (IX), λmax (EtOH) 270 mμ (5623), which undergoes reduction to give the corresponding saturated diketone [λmax (EtOH) 284 mμ (40)].

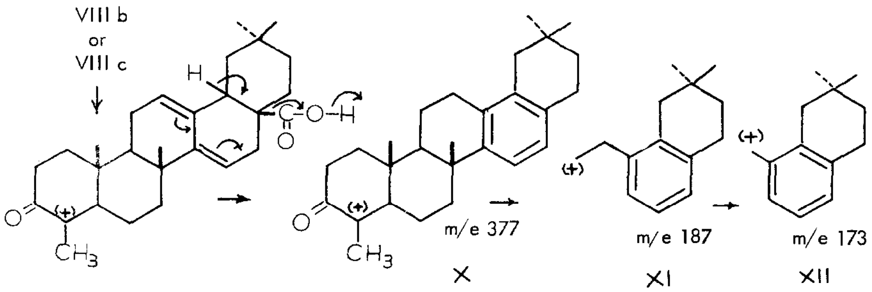


VIIa, R = Ac, R' = R'' = Me
VIIb, R = H, R' = R'' = Me
VIIc, R = R' = R'' = H
VIId, R = R'' = H, R' = Et

VIIIa, R = Ac, R' = Me
VIIIb, R = H, R' = Me
VIIIc, R = R' = H

IX

Mass spectra[3] of dehydrosenegenic acid (VIIIc) and its dimethylester (VIIIb) showed significant peaks at m/e 486 (M^+), 377 (M-109), 187 and m/e 514 (M^+), 377 (M-109), 187, respectively, and a strong base peak at m/e 173 in both compounds. The base peak (XII) can arise from a species such as (XI) as indicated below. A similar pronounced base peak with two more mass units (m/e 175) is also discernible in the spectrum of senegenic acid ethylester [m/e 516 (M^+), 442 (M-74), 427]. These species can be derived by known processes from the D-E ring system of a $\Delta^{12,14}$ diene or a Δ^{13} system, but not from a Δ^{8} or derived $\Delta^{7,9}$ diene.



The above evidence leads to structure VIIc and VIId for senegenic acid and senegenic acid ethylester respectively[12]. Undoubtedly these compounds are artifacts which arise during the vigorous acid hydrolysis of the parent saponin. The nor-structure probably arises from a Δ^{12}-precursor by migration of the double bond to Δ^{13} and concomitant elimination of a carbon, in a suitable oxidation state, at C(14).

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3. We are grateful to Professor K. Biemann and Dr. B. Das, Massachusetts Institute of Technology, Cambridge, for the mass spectral determinations.
4. Jacobs[2] reported the isolation of 1,8-dimethylpicene and a chrysene homolog similar to that obtained from the triterpene acid, hederagenin.
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9. A structure with a C-17 carboxyl and a $\Delta^{13(18)}$ double bond may be ruled out

since senegenic acid is unaffected by heating above its melting point. Likewise, a structure with a C(13)-carboxyl and $\Delta^{8(14)}$ double bond need not be considered. A Δ^{8} - 13β-carboxyl-14αH system will explain bromolactone and diene formation, but does not fit the mass spectra data.

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12. After we had derived structure VIIc for senegenic acid and while our manuscript was in preparation we were informed by Dr. P. de Mayo that they have also come to the same conclusions regarding the structure of senegenic acid (polygalic acid). We thank Dr. de Mayo for a copy of his manuscript prior to publication.