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TRITERPENOIDS—XXVI

THE CONSTITUTION OF ENTAGENIC ACID

A. K. BARUA, P. CHAKRABARTI and B. C. DAS†
Department of Chemistry, Bose Institute, Calcutta 9, India

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Abstract—The constitution of the entagenic acid—a new triterpenoid sapogenin isolated from the seed kernels of *Entadaph aseoloides* Merrill—has been established as 3β,21α,22α-trihydroxyolean-12-ene-28-oic acid.

IN A previous communication[1] structure Ia was proposed for entagenic acid. Further experiments, which support this structure, are described in the present paper.

Methyl entagenate (Ib) on treatment with pyridine and acetic anhydride gives triacetate Ic which on oxidation with selenium dioxide in glacial acetic acid furnishes a product showing triple UV absorption maxima at 243, 251 and 258 mμ (log ϵ 4·44, 4·48 and 4·35) characteristic of $\Delta^{11:12,13:18}$-dienes of the oleanane series.[2] Lithium aluminium hydride reduction of methyl entagenate yields tetrol II.

The mass spectrum (Fig. 1) of Ib (M = 502) exhibits typical retro-Diels–Alder fragmentation[3] involving the 12:13-double bond. The peak arising out of such a fragmentation is observed at m/e 294 (ion *a*) which can then lead to the ion fragment *b* appearing at m/e 235 due to the loss of the angular carbomethoxy group at C-17. Further loss of a molecule of water from *b* gives rise to an intense peak at m/e 217 (ion *c*). The mass spectrum also exhibits a peak at m/e 207 attributed to the ion species *d*.

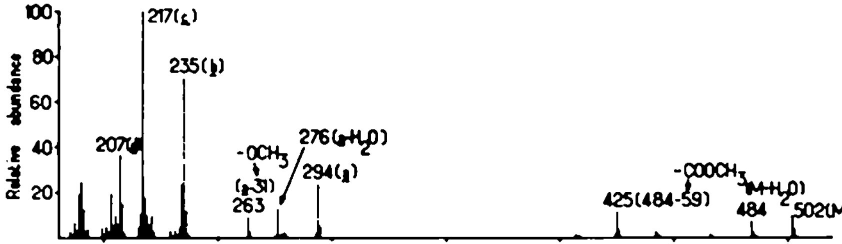

FIG. 1

The mass spectrum (Fig. 2) of acetonide IIIa[1] derived from methyl entagenate shows the expected molecular ion peak at m/e 542. Loss of a molecule of acetone from the acetonide gives rise to a peak at m/e 484 (M-58). The peak corresponding to retro-Diels–Alder fragmentation is found at m/e 334 (ion *a'*). The latter can then lose acetone (58 mass units) showing the ion fragment m/e 276 (*b'*) which again loses

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† Institut de chemie des Substances Naturelles, Gif-Sur-Yvette, Essonne, France.

[1] A. K. Barua, *Tetrahedron* **23**, 1499 (1967).

[2] L. Ruzicka, G. Muller and H. Schellenberg, *Helv. Chim. Acta* **22**, 767 (1939).

[3] H. Budzikiewicz, J. M. Wilson and C. Djerassi, *J. Am. Chem. Soc.* **85**, 3688 (1963).

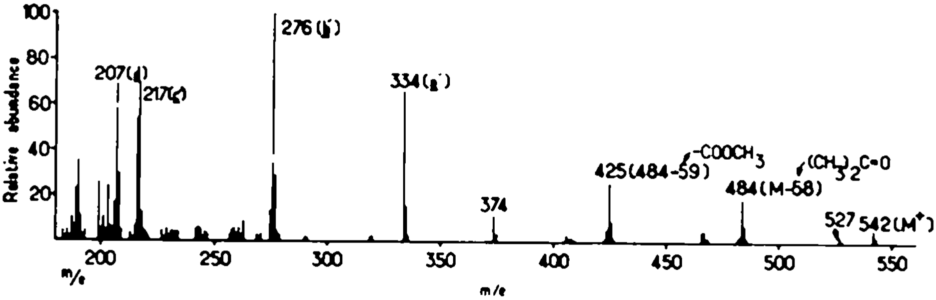
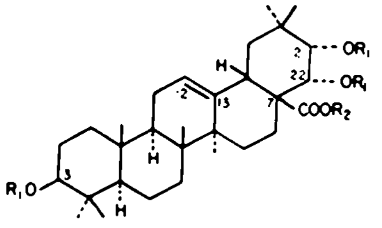
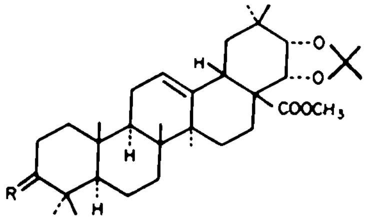


Fig. 2

the —$COOCH_3$ group to give the peak appearing at m/e 217 (c'). The peak due to ion *d* is observed at m/e 207. There is also a peak at m/e 374.

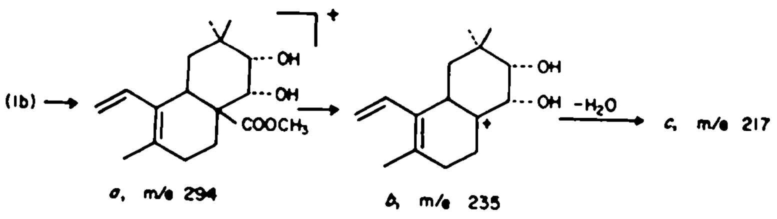
Acetonide IIIa on oxidation with CrO_3-pyridine complex furnishes ketone IIIb. Its mass spectrum (M = 540) shows fragmentation process similar to that of IIIa, the peaks being observed at m/e 334, 276, 217, 205 and 372. The peaks at m/e 374 and 372 in the mass spectra of IIIa and IIIb respectively most probably originate by loss of some part of the molecule around ring E. Reduction of this ketone with sodium borohydride regenerates acetonide IIIa. This observation together with the molecular rotation difference[4] ($[M]_{IIIb} - [M]_{IIIa} = +54°$) indicates the β-orientation of the C-3 hydroxyl group in entagenic acid.





(Ia) $R_1 = R_2 = H$
(Ib) $R_1 = H, R_2 = CH_3$
(Ic) $R_1 = COCH_3, R_2 = CH_3$
(Id) $R_1 = H, R_2 = CH_2CH_3$

(IIIa) R = $<^{H}_{OH}$
(IIIb) R = O



Machaerinic acid (IV) on refluxing with sulphuric acid in dioxane-water formed a 28 → 21 lactone.[5] It was not isolated in a pure state but characterized by its IR

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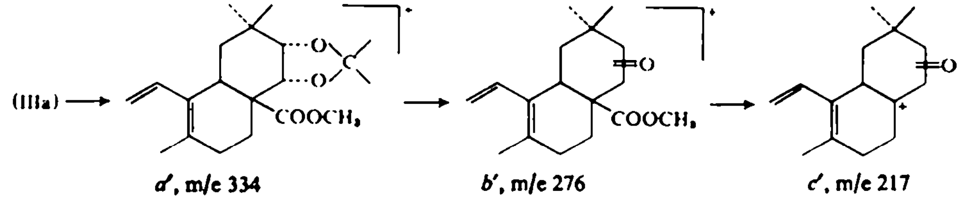
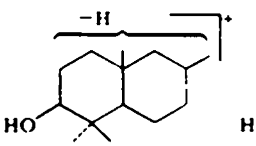
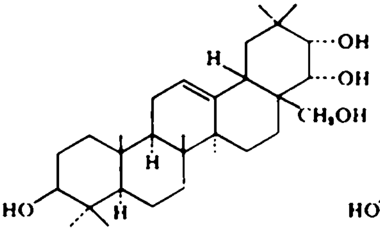
[4] D. H. R. Barton and E. R. H. Jones, *J. Chem. Soc.* 659 (1944).
[5] C. Djerassi and J. S. Mills, *J. Amer. Chem. Soc.* **80**, 1236 (1958).

spectrum which showed a γ-lactone band. A similar lactone and ethyl machaerinate were isolated by us in pure state by refluxing machaerinic acid with alcoholic hydrochloric acid followed by chromatography over acid-washed alumina.[6] Entagenic acid forms small amount of ethyl ester Id but no lactone under the similar condition thus suggesting the α-orientation of the C-21 hydroxyl group.

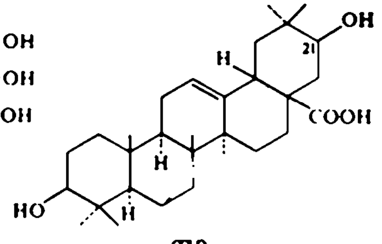




d, m/e 207



(II)



(IV)

Methyl entagenate consumes 1 mole of lead tetraacetate at a faster rate than barringtogenol C[7] which contains a *trans* α-glycol system in ring E. This fact along with acetonide IIIa formation proves the α-glycol system in entagenic acid to be *cis* (α).

The structure and stereochemistry of entagenic acid is thus established as 3β,21α,22α-trihydroxyolean-12-ene-28-oic acid (Ia).

EXPERIMENTAL

M.ps (uncorrected and recorded in a bisulphate bath). Pet. ether (b.p. 60–80°). Brockmann's alumina (S. Merck) was used for chromatography and acid-washed alumina refers to Brockmann's alumina deactivated with 5%of 10%AcOH. Optical rotations (in chf soln. unless otherwise specified). Mass spectra (an A.E.I. MS 9 mass spectrometer operating at 70 ev).

SeO_2 *oxidation of acetyl methyl entagenate.* Methyl entagenate (500 mg) was heated with Ac_2O (5 ml) and pyridine (5 ml) on a steam-bath for 3 hr. The product was poured onto crushed ice and then worked up in the usual way. The crude product was dissolved in benzene (8 ml) and adsorbed on a column of acid-washed alumina (10 g). Elution with pet. ether (2l) furnished a colourless glassy material. Repeated attempts to crystallize this material were not successful. It was found to be homogeneous in TLC. Its IR spectrum did not show any band for free hydroxyl group. It was directly used for oxidation with SeO_2.

The above glassy material was dried *in vacuo* and then dissolved in glacial AcOH (5 ml) and the soln was refluxed with freshly prepared SeO_2 (500 mg) for 5 hr. The soln was filtered hot and the filtrate was diluted with water and then worked up in the usual way. The crude product was dissolved in benzene (10 ml) and then adsorbed on a column of acid-washed alumina (15 g). Elution with pet. ether furnished small amount of coloured glassy material. Further elution with pet. ether–benzene mixture (1:2, 2l) furnished a colourless glassy material which was crystallized from aqueous MeOH (charcoal), m.p. 226–230°, $[\alpha]_D^{27°}$ −139°. UV(EtOH) 243, 251, and 258 mμ (log ε 4·44, 4·48 and 4·35). Mass spectrum: M = 542. (Found: C, 73·0; H, 9·3. $C_{33}H_{50}O_6$ requires: C, 73·1; H, 9·2%.) It is evident that in the formation of the above diene from Ic, two acetyl groups were eliminated.

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[6] A. K. Barua, A. Ray and S. Ray, unpublished data.

[7] A. K. Barua and P. Chakrabarti, *Tetrahedron*, 21, 381 (1965).

LAH *reduction of* Ib *to tetrol* II. A slurry of LAH (2 g) in dry ether (200 ml) was refluxed with a soln of methyl entagenate (500 mg) in dry ether (40 ml) for 8 hr and then worked up in the usual way. The reaction product was crystallized from chf, m.p. 254–256°. (Found: C, 76·0; H, 10·45. $C_{30}H_{50}O_4$ requires C, 75·9; H, 10·5%.)

Oxidation of acetonide IIIa *to* IIIb. A cold soln of IIIa (300 mg) in pyridine (5 ml) was added to a slurry of CrO_3-pyridine complex (from 300 mg of CrO_3 and 5 ml of pyridine) at 0° and left overnight at room temp. It was worked up in the usual way. The crude material was dissolved in benzene and then chromatographed over acid-washed alumina (6 g). Elution with pet. ether–benzene (3:1, 1·5l) furnished a colourless glassy material which was crystallized from MeOH, m.p. 162–165°, $[\alpha]_D^{28°}$ +76°. (Found: C, 75·7; H, 9·4. $C_{34}H_{52}O_5$ requires C, 75·6; H, 9·6%.)

A soln of IIIb (120 mg) in MeOH (15 ml) was treated with KBH_4 (500 mg) and left overnight at room temp and then worked up in the usual way. Benzene soln of the product was filtered through a column of acid-washed alumina and then crystallized from MeOH as needles, m.p. 207–208°, alone or when admixed with IIIa, m.p. 207–208°.

Lead tetra-acetate oxidation of methyl entagenate Ib. A soln of Ib (0·001 mole) in glacial AcOH was mixed with 15–16 times the molar excess of lead tetra-acetate and the volume made up to 25 ml with glacial AcOH. An aliquot sample (5 ml) was taken out at definite intervals and added to the aq soln (10 ml) of NaI (200 mg) and AcONa (2 g). The liberated I_2 was titrated with 0·02N $Na_2S_2O_3$. All oxidations were carried out at room temp and blank experiments were performed side by side. Consumption of 1 mole of lead tetra-acetate was complete within 40 min. There was no further uptake after this time.

Attempt to prepare lactone on entagenic acid Ia. Compound Ia (200 mg) in abs EtOH (30 ml) was refluxed with conc. HCl (6 ml) for 6 hr and then extracted with ether after diluting the reaction mixture with water. The ethereal extract was separated into acid and neutral part by washing with 5% NaOH aq. The acid part was crystallized from EtOH, m.p. 310–315° (dec.), $[\alpha]_D^{28°}$ +35° (EtOH). It did not depress the m.p. of Ia. The neutral part was crystallized from chf–pet. ether, m.p. 237–239°, alone or when admixed with ethyl entagenate (Id).

Ethyl entagenate Id. An ethereal soln. of Ia was treated with ethereal diazoethane and then worked up in the usual way. The crude material in benzene (7 ml) was chromatographed over Brockmann's alumina (5 g). Elution with benzene–chf (3:1) furnished a crystalline residue, which was crystallized from chf–pet. ether, m.p. 237–239°, $[\alpha]_D^{30°}$ +37°. (Found: C, 74·6; H, 10·0. $C_{32}H_{52}O_5$ requires C, 74·4; H, 10·1%.)

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