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THE STRUCTURE, STEREOCHEMISTRY AND CONFORMATION OF ACACIC ACID*

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Recently the isolation of a new pentacyclic triterpenic acid genin, Acacic acid, has been reported from barks, pods and seeds of a number of Acacias and Albizzias[1,2]. Now on the basis of the transformations shown in Table I the structure of Acacic acid has been fixed as 3,16,21-trihydroxy-olean-12-ene-28-oic acid (I).

Earlier this structure (I) was assigned to acacic acid on the basis of its conversion to a product identified by mixed melting point with 28-nor-β-amyrin (nor-echinocystenol A)[2]. It has now been found that this identification was in fact erroneous, but that the structure of acacic acid is nevertheless correctly represented by formula I. This has been arrived at on the basis of the following evidence.

The relation of acacic acid to β-amyrin was fixed by formation of the diacetyl methyl ester of sapogenin ''B'' (VI) of Styphnodendron coriaceum[3] from acacic acid (I).

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* This paper is to be considered as Part XXVIII in our ''Saponins and Sapogenins'' series.

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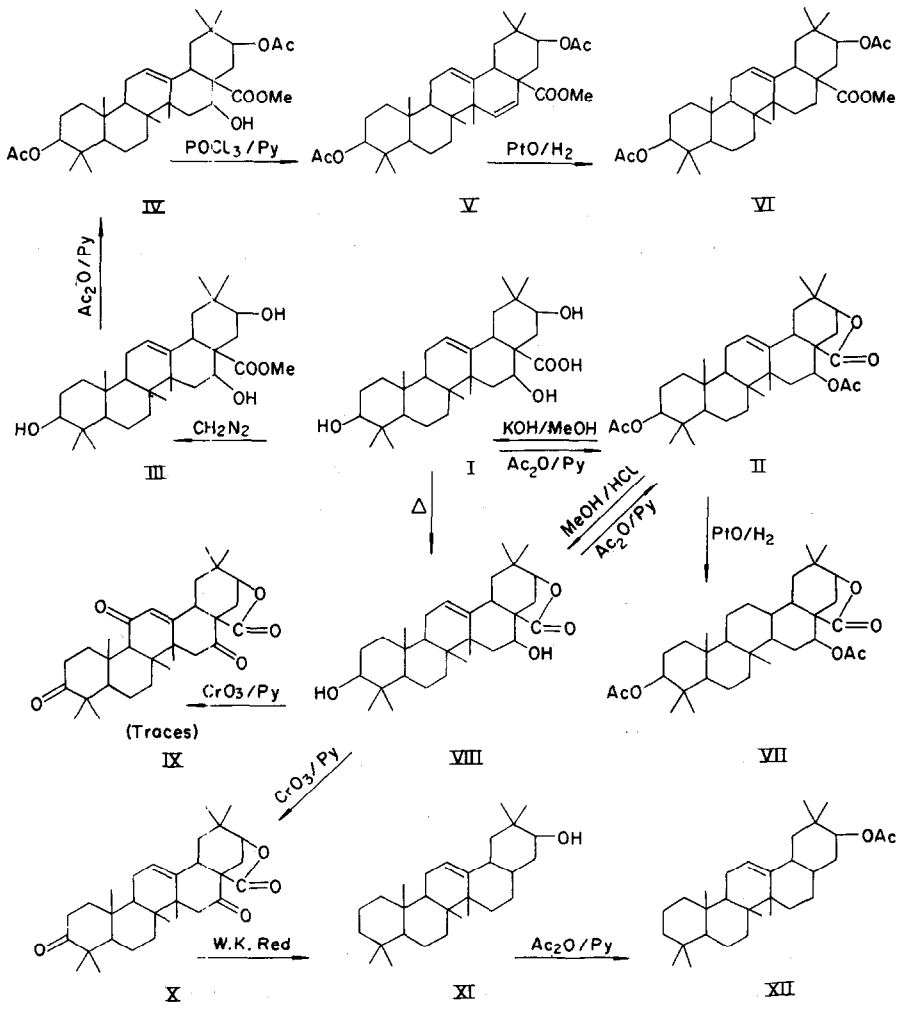
TABLE I



IV V VI

III I II

IX VIII VII

X XI XII

This conversion of I to VI conclusively establishes that one hydroxyl group is located at C-3, the second hydroxyl group at C-21 and the carboxyl group at C-28 in acacic acid (I).

The third hydroxyl group has been fixed at position 16, since Wolff-Kishner reduction of the diketo lactone (X), formed by oxidation of the dihydroxylactone (VIII), leads to a nor-compound (XI). Decarboxylation of the β-ketonic acid formed under the reaction conditions occurred during this step. Of the two possible positions which are β- to the carboxyl group (C-16 or C-22), position C-22 is eliminated because the methyl ester of acacic acid (III) fails to undergo periodic acid oxidation or to form an isopropylidene derivative. Location of the third hydroxyl group at C-16 has been further substantiated by the O.R.D. curve (Fig. 1) of the diketolactone (X) which showed a strong negative multiple cotton effect, completely resembling the O.R.D. curve of nor-echinocystenolone acetate[4].

In the earlier communication[2] acacic acid acetyl lactone (II), on treatment with methanolic hydrochloric acid, gave a product thought to be 3-acetoxy 16,21-dihydroxy-olean-12-ene-28-oic acid. This is, in fact, the dihydroxy lactone (VIII) whose elemental composition is also in agreement with the analytical results.

The compounds derived from this are therefore also erroneously identified; the acetate diketone (IV in[2]) is in fact 3,16,diketo-olean-12-ene, 28:21 olide (X), and its Wolff-Kishner reduction gives 21-hydroxy-28-nor-oleanene (XI) and not its 3-hydroxy isomer. The unsaturated ketone (IX) is a minor product present in traces in the reaction (VIII) ⟶ (X).

The easy lactonization of acacic acid between the 21-hydroxyl group and the 28-carboxyl group, even on cold acetylation, cannot be explained if the normal AB,BC trans and DE cis ring fusions with all chair conformation is applied to acacic acid. Further, the facile hydrogenation of the diacetyl lactone (II) in the presence of platinum oxide catalyst is contrary to the fact that the double bond of members of the β-amyrin group do not hydrogenate under normal conditions. This indicates that some subtle conformational differences exist in acacic acid. This result parallels the behavior of sapogenin B of Styphnodendron coriaceum[3] which also hydrogenates easily. The abnormal behavior can be explained on the basis that ring E exists in a boat form and consequently ring D in a quasi-boat form[3]. In such an arrangement the proximity of the C-21 hydroxyl and the C-28 carboxyl groups tends to make the lactonization easy, as can be seen by a study of molecular models. Such a lactonization could also occur with ring DE trans fusion but this possibility is eliminated on the basis of the O.R.D. curve of the diketolactone (X) (Fig. 1), which strongly resembles that of nor-echinocystenolone acetate[4]. The latter compound has a ring DE cis fusion and this resemblance indicates identical stereochemical arrangement around ring D in both

compounds. Thus the ring DE junction is <u>cis</u> in the case of acacic acid (I).

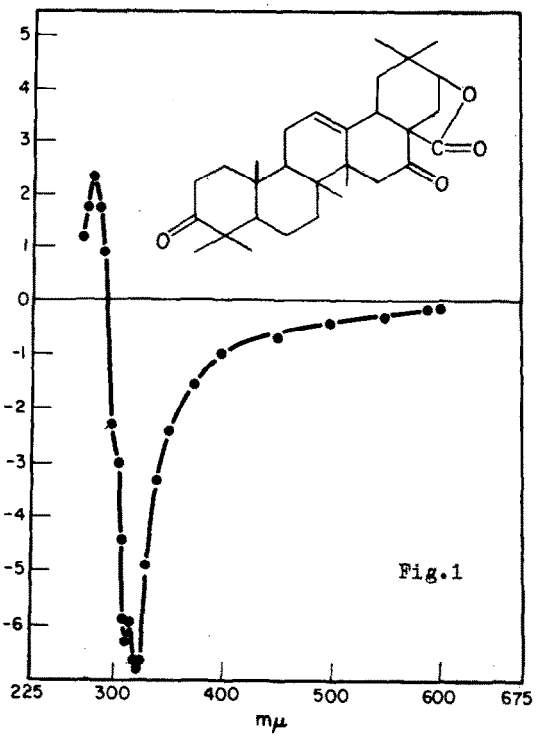


Fig.1

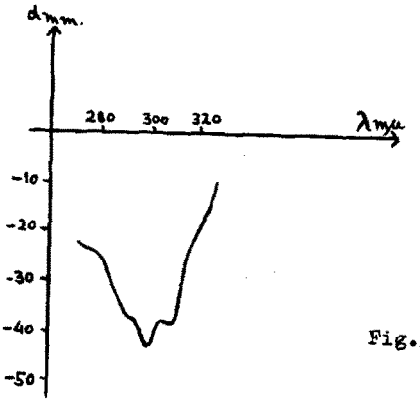


Fig.2

The stereochemistry of acacic acid has been deduced from O.R.D., circular dichroism (Fig. 2) and N.M.R. studies. Comparison of the N.M.R. spectra of various derivatives permits an unambiguous assignment of the three protons of type HC-O in acacic acid diacetyl lactone. For instance the N.M.R. spectrum of diacetylactone (II) (Fig. III) showed signals corresponding to a lactonic proton at 4.22 ppm., J = 4 cps., as a doublet. This is quite in agreement with the structure formulated where the lactone bridge is necessarily β. The dihedral angle between the hydrogen at C-21 and one of the hydrogens at C-22 is about 90° and therefore gives a doublet rather than the triplet normally obtained through splitting by two vicinal hydrogens. This is because one of the coupling constants in the ABX system becomes negligible. The acetoxyl proton on C-3 appears in the form of a pair of doublets centered at 4.5 ppm. (J_1 = 9 cps. and J_2 = 2 cps.), as expected for an axial proton. The 3-hydroxyl group of acacic acid is therefore β-oriented. The other acetoxyl proton on C-16 appears also in the form of a pair of doublets centered at 5.0 ppm (J_1 = 12 cps.; J_2 = 5 cps.), which indicates an equatorial conformation for the 16-hydroxyl group. In the preferred ring conformation (see below), this is the 16β-configuration. As the assignments made by Djerassi *et al*[4] are accepted for nor-echino-

cystenolone, therefore, acacic acid has an 18β-H configuration. This indicates that all three hydroxyl groups in acacic acid are β-oriented and it has an 18β-H configuration.

While acacic acid (I) itself could possibly exist in the normal all chair conformation, this is impossible for the 28:21-lactone of this series. Consideration of models shows that such a lactone can easily be formed, provided ring E is constrained in a boat form. Ring D can then adopt several conformations, one of which, a twist form, appears to minimize effectively all interactions. In this conformation the 16β-bond is quasi-equatorial, and the geometrical relationship between 16α-H and the 15-CH_2 group is such that the observed coupling constants are explained.

The possibility of a trans DE fusion is eliminated by the CD and O.R.D. curves as indicated above, except in the improbable event of an erroneous assignment of configuration to nor-echinocystenolone[4]. This would not change the conclusions regarding the stereochemistry of acacic acid, except as regards configuration at C-18.

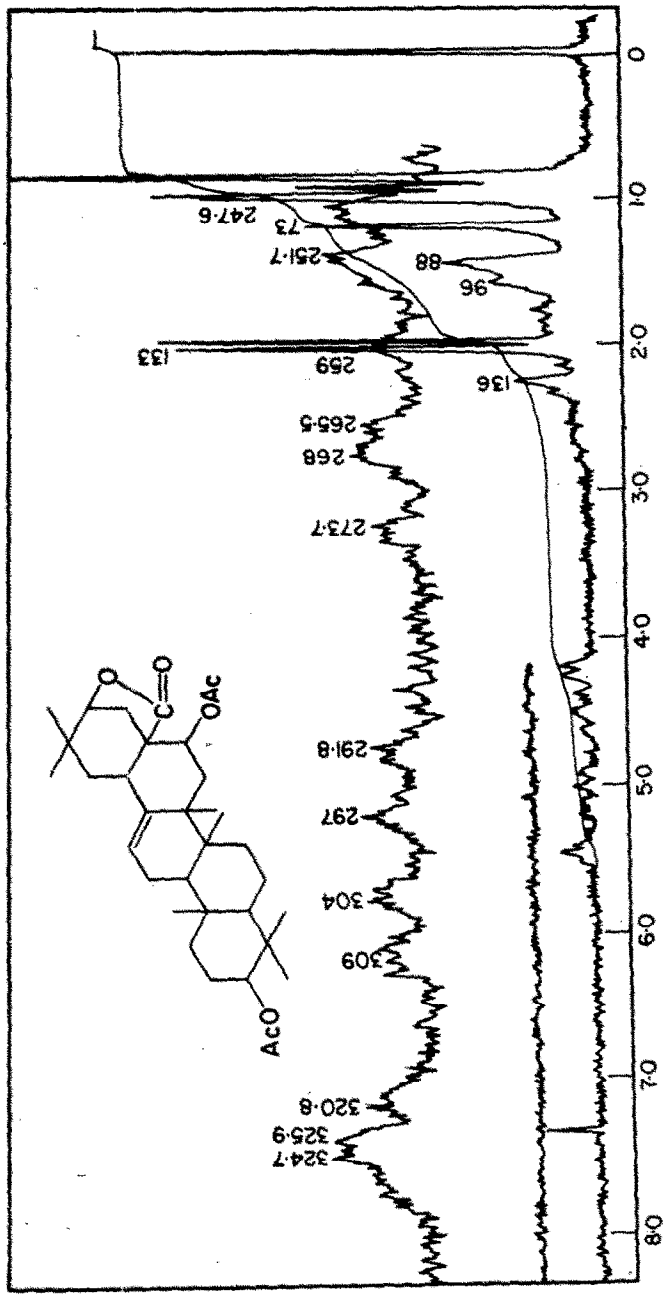
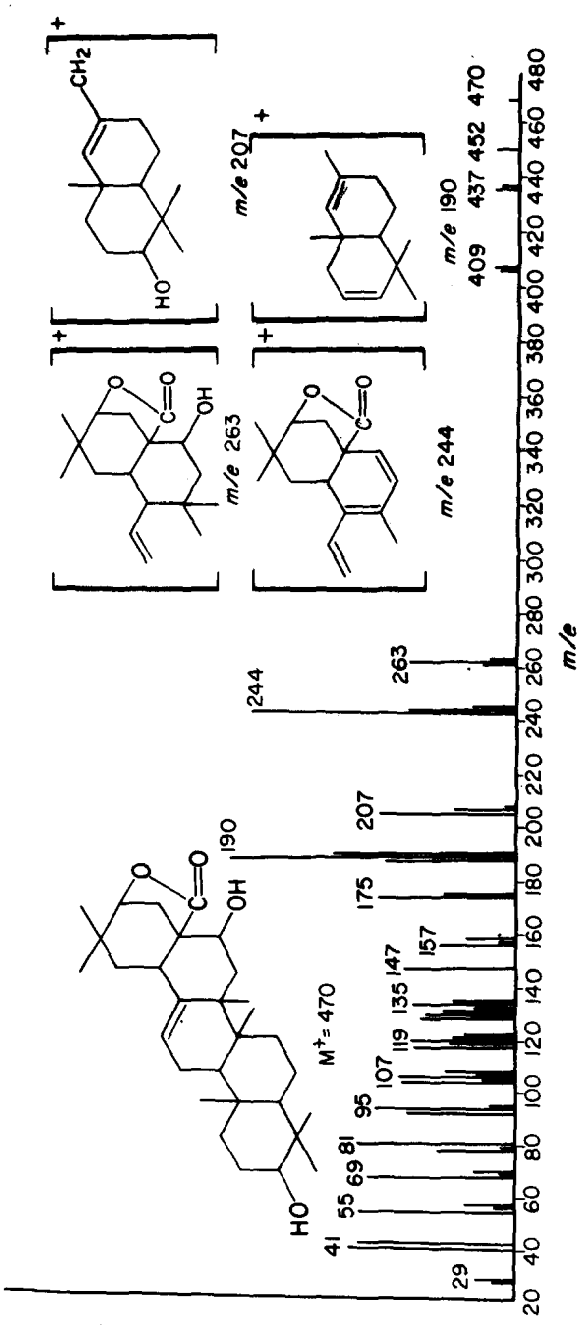
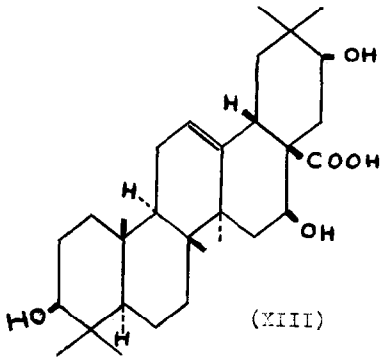

0
1·0
2·0
3·0
4·0
5·0
6·0
7·0
8·0
δ, ppm
247·6
73
251·7
88
96
133
259
136
265·5
268
273·7
291·8
297
304
309
320·8
325·9
324·7
OAc
AcO

FIG III


m/e 263
m/e 244
m/e 207
m/e 190
M+= 470
m/e
20 40 60 80 100 120 140 160 180 200 220 240 260 280 300 320 340 360 380 400 420 440 460 480
29 41 55 69 81 95 107 119 135 147 157 175 190 207 244 263 409 437 452 470

The mass spectrum of the dihydroxy lactone (VIII) (Fig. IV) shows peaks entirely compatible with the assigned structure.

Therefore, Acacic acid is 3β, 16β, 21β-trihydroxy olean-12-ene-18β-28-oic acid with rings E and D in boat and quasi-boat forms respectively and with a D-E cis fusion (XIII).



(XIII)

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