Jingullic Acid, a Triterpene of the Lupane Series Containing a C-28 → 19-Lactone Group

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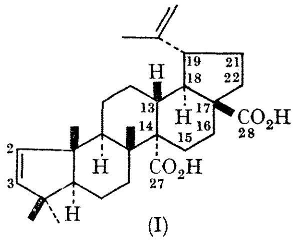
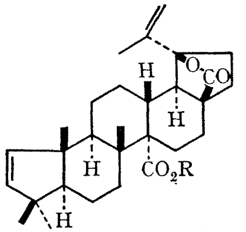
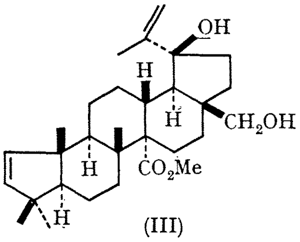
TRITERPENES from the *Rhamnaceae* include lupane derivatives showing considerable variation in their oxidation pattern. There are the unusual structural features associated with those members where ring A is five-membered,[1–4] the comparatively rare oxygenation of the C-27 methyl group in, *e.g.*, ceanothenic acid (I)[3] and emmolactone[4], and emmolactone is also oxygenated at C-18 and C-22 and contains a C-16,17 double bond. We report the occurrence of a new acid (IIa) in the bark of *Emmenospermum alphitonioides* F. Muell, which has an oxygen function at C-19 in the form of a C-28 → 19-lactone. With the recent revision of the structures of stellatogenin and thurberogenin,[5] this acid is the only naturally occurring triterpene with this structural feature. The new acid, which we name jingullic acid after the Aboriginal name "jingull" for the tree *E. alphitonioides*, has been obtained only in the form of its methyl ester (IIb), m.p. 179—181°, $[\alpha]_D$ (chloroform) + 129°, obtained by methylation (diazomethane) of the mixture of triterpenoid acids extracted from the bark. Methyl jingullate was obtained in good yield from only one specimen of bark (70 mg./kg.), all other specimens giving yields of 2 mg./kg. or less.



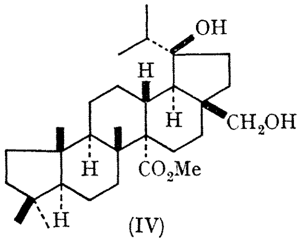
(I)



(II) a; R=H
b; R=Me



(III)



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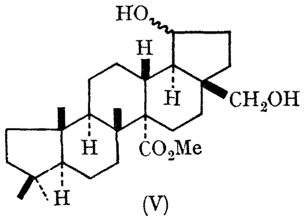
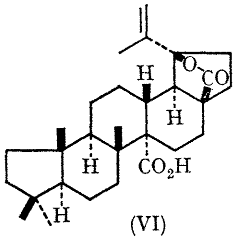
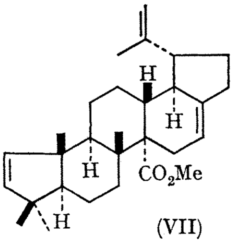


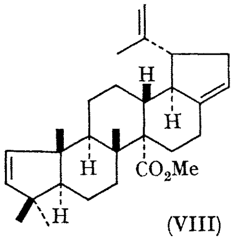
(V)



(VI)



(VII)



(VIII)

Methyl jingullate has the formula $C_{30}H_{42}O_4$ (mass spectrum and elemental analyses). Its i.r. spectrum showed absorption at 3070, 3020, 1650, 895, and 755 cm.$^{-1}$ (Nujol) (*gem*-disubstituted double bond and a *cis*-disubstituted double bond) and strong absorption at 1760 and 1721 cm.$^{-1}$ (carbon tetrachloride) (γ-lactone and a methoxycarbonyl group, respectively). In its n.m.r. spectrum, a pair of doublets (J 5·6 c./sec.) at δ 5·88 and δ 5·42 indicated a *cis*-disubstituted double bond flanked by quaternary carbon atoms and located in a five-membered ring. The n.m.r. also showed the presence of the isopropenyl group [δ 4·64 (m, 1H), δ 4·53 (m, 1H) and δ 1·62 (s, 3H)], the methoxycarbonyl group, and four tertiary methyl groups. The absence of any additional absorption near δ 4·0 indicated that the γ-lactone terminated at a tertiary centre.

Reduction of methyl jingullate with lithium aluminium hydride gave the diol (III), $C_{30}H_{46}O_4$. The absorption of the protons of the *cis*-disubstituted double bond was practically unaltered at δ 5·91 and 5·40 but the absorption due to the olefinic protons of the isopropenyl group had shifted to δ 5·05 and δ 4·88, while that of the isopropenyl methyl group had shifted to δ 1·82. Catalytic hydrogenation of this diol gave the tetrahydro-diol (IV).

In view of the co-occurrence of ceanothenic acid and jingullic acid, plus the fact that all the structural features of jingullic acid elucidated above except the γ-lactone group are common to both, it appeared probable that jingullic acid was related to ceanothenic acid simply by lactonisation of one of the latter's two carboxyl groups. Since it is known that the C-27 methoxycarbonyl group in methyl esters of ceanothenic acid and melaleucic acid[4] is not reduced by lithium aluminium hydride, the methoxycarbonyl group in methyl jingullate can be assigned as C-27 and consequently the C-28 carboxyl group is the one involved in lactone formation. Two tertiary lactones are possible involving this carboxyl group, the C-28 → 19-lactone and the C-28 → 13-lactone, the C-28 → 19-lactone being favoured because of the relatively large shifts (0·2 p.p.m. and 0·41, 0·35 p.p.m., respectively) in the n.m.r. absorption of the methyl and methylene protons of the isopropenyl group on reduction of the lactone (IIb) to the diol (III).

A correlation between jingullic acid and ceanothenic acid was effected through the tetrahydrodiol (IV) which was synthesised from ceanothenic acid in the first instance by a low yielding, ten-step procedure *via* the trisnor-intermediate (V). With the elucidation of the course of mercuric acetate oxidation of betulic acid and similar compounds[6] a much simpler route was available. Thus oxidation of dihydroceanothenic acid gave the γ-lactone (VI)[6] which was methylated (diazomethane), reduced with lithium aluminium hydride, and finally catalytically hydrogenated to give the tetrahydro-diol (IV) identical with that prepared from methyl jingullate. Attempts to prepare jingullic acid directly by oxidation (mercuric acetate) of ceanothenic acid itself were unsuccessful.

This partial synthesis resolved all features of the structure of jingullic acid except for the location of the *cis*-disubstituted double bond which on n.m.r. evidence could be sited either in ring A as in ceanothenic acid or in ring E (C-21,22). The location of the double bond in ring A is strongly favoured on biogenetic grounds, and the possibility of its location in ring E can be excluded from the following n.m.r. evidence. Thus in dimethyl ceanothenate, emmolactone, acetylemmolactone, the deoxyemmolactones (VII) and (VIII),[7] the ring-A vinyl protons absorb as a pair of doublets (*J* 5·7—6·0 c./sec.) at δ 5·37—5·47 and 5·88—5·97. The absorption of the protons of the *cis*-disubstituted double bond, not only in methyl jingullate (IIb), but also in the derived diol (III) fall within this narrow range. If the double bond were in fact in ring E the proximity of the lactone group should have an observable effect on the n.m.r. absorption of these protons but, and more importantly, the reduction of the lactone group to the corresponding diol would confidently be expected to change the electronic environment sufficiently to produce a marked change in their absorption. Consequently the preferred location for the double bond is that in ring A, thus leading to (IIa) as the structure for jingullic acid.

N.m.r. spectra were determined in deuteriochloroform.

(*Received, March 7th,* 1969; *Com.* 322.)

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