The Stereochemistry of Ceanothic Acid

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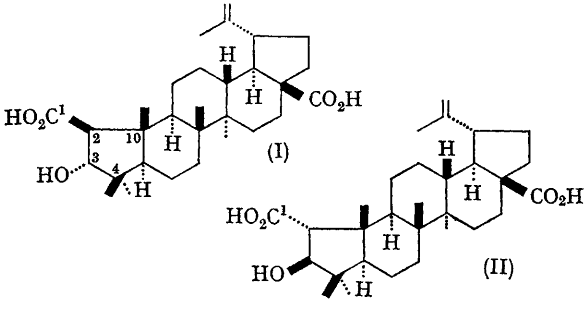
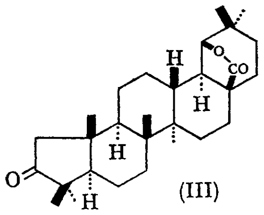
THE stereochemistry[1] assigned to ceanothic acid (I) is not consistent with the singlet reported[1] for the 3-carbinol proton§ even if ring A exists in the α-envelope conformation.[3,4] Dreiding models show that this conformation is destabilised by the strong 10β-Me–4β-Me interaction and work by Fishman[5] on the analogous 16,17-disubstituted steroids, which lack the Me–Me interaction, suggests the α-envelope need not be considered.

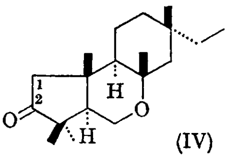


(I)

(II)



(III)



(IV)

After re-examination of the n.m.r. spectra of ceanothic acid and its derivatives, we now report the stereochemistry of ceanothic acid as (II). In the nor-ketone (III) of the lactone series, the upfield spin-pair (2α-H) of the 2-methylene AB system appeared as broadened signals ($\nu/2 = 2{\cdot}4$ c./sec.) due to long-range coupling (4σ) with the 10β-Me. Similar long-range coupling between the 1α-H and the 10β-Me (J 1·0 c./sec.) has been observed[6] in the norditerpene colensan-2-one (IV) and the assignments confirmed by solvent-shift studies.[7] In both instances double irradiation confirmed these splittings. These couplings illustrate the *pseudo*-axial character of the 2α- and 1α-hydrogens and thus eliminate the α-envelope but are consistent with the half-chair or β-envelope conformation for ring A in which the 2α- (or 1α-) hydrogen and the 10β-Me show some degree of coplanarity. Similar 4σ coupling (J 0·5 c./sec.)

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§ For numbering, see ref. **2**.

TABLE

*N.m.r. data for the ring-*A *isomers (lactone series)*

H Configuration	$J_{calc.}$			$J_{obs.}$	
	α-Envelope	Half-chair	β-Envelope	R = H	R = Ac
2β,3α (VII)	1·8—2·9	0·3—0·8	−0·3—0·0	1·0	0
2α,3β (VIII)	1·8—2·9	3·5—5·0	5·9—7·1	9·0	9·5
2α,3α (IX)	8·2	7·8—8·0	6·2—6·9	7·4	7·6
2β,3β (X)	8·2	7·5—7·9	5·7—6·7	7·0	7·7

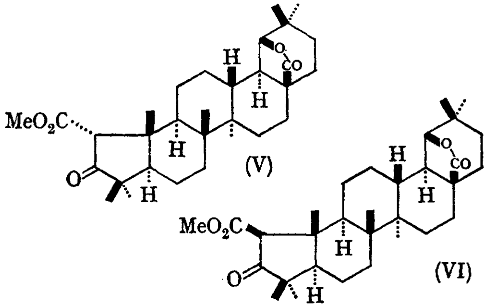
in a cyclopentane system has been reported between the 17α-H and the 18β-Me in a steroid derivative.[7]

In the normal and epi-series of dimethyl dehydroceanothate and methyl dehydroceanothate lactone respectively, the signal due to the hydrogen at C-2 was examined for similar long-range coupling with the 10β-Me group. In the normal series the hydrogen at C-2 appeared as a sharp singlet ($\nu/2$ = 1·5 c./sec.) but in the epi-series it appeared as a broadened singlet ($\nu/2$ = 2·5 c./sec.). This broadening was confirmed by double resonance ($\nu/2$ = 1·6 c./sec.) and is consistent with the 2β-orientation of the methoxycarbonyl group in the epi-series and the 2α-orientation in the normal series, and hence 2α in ceanothic acid. The strong positive circular dichroism of the three ketones of the lactone series, (III), (V), and (VI) ($\Delta\epsilon_{309}$ + 5·56, $\Delta\epsilon_{312}$ + 4·70, and $\Delta\epsilon_{301}$ + 5·16 respectively) support a conformation close to a half chair for the three ketones. This is due to the first-order asymmetry (*i.e.*, two skewed ring atoms). Slight deviations in conformation which must operate, *e.g.* (VI), are unable to be defined accurately as lack of knowledge of the respective contributions to the asymmetry of the 3-keto-group precludes accurate quantitative treatment.

The vicinal coupling constants ($J_{2,3}$) of the four possible 2,3-disubstituted isomers (VII—X) (and their corresponding acetates) have been compared (Table) with those calculated for the three possible ring-A conformations from the dihedral angles as measured from models. With the exception of the α-envelope where the 2,3-substituents eclipse, the values are the same as those reported by Cross[4] for 16,17-disubstituted steroid derivatives. As Fishman[5] has pointed out the only significant differences between the three conformations are those for the two *trans*-couplings in the α-envelope. The observed couplings are consistent with the stereochemistry assigned, but not consistent with the invert assignments as required by de Mayo's stereochemistry for ceanothic acid.

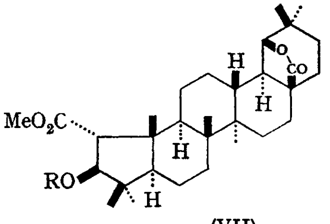
The alcohols with a normal ring E corresponding to the lactones (VII) and (X) have identical values to those of the lactone series.

As 16-oxo-steroids[9] and A-norcholestan-2-one[10] are enolised only with difficulty, the ease of epimerization of dimethyl dehydroceanothate and the corresponding lactone can be attributed to the methoxycarbonyl group at C-2. The epimerisation of a 2α-substituent to the pseudo-equatorial orientation is to be expected (although in all cases

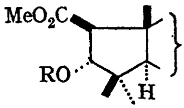


(V)

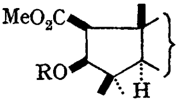
(VI)



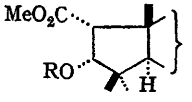
(VII)



(VIII)



(IX)



(X)

equilibrium mixtures of the two epimers were obtained) and models show that the 2β-substituent bisects the 11-methylene; it is also consistent with the preferred 17β-orientation in steroid derivatives.

(*Received, June 19th*, 1967; *Com.* 613.)

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The purity of all compounds (which gave satisfactory elemental analyses) was established by t.l.c.