PART-III

PARTIAL SYNTHESIS OF ALL THE FOUR STEREOISOMERS OF DIMETHYL DIHYDROCEANOTHATE STARTING FROM BETULINIC ACID.

PART-III

CHAPTER-I

A Short Review on the Isolation, Structure Elucidation and Stereochemistry of Ceanothic Acid.

Section A : Isolation

Ceanothic acid was first isolated by Julian, Pikl and Dawson[1] from the root bark of *Ceanothus americanus* and has subsequently been isolated from a number of Australian plants belonging to *Rhamnaceae* species[2,3]. Ceanothic acid was characterised by Julian *et al*[1] as a hydroxy dicarboxylic acid and attributed the molecular formula $C_{29}H_{44}O_5$. It was further characterised by the preparation of a dimethyl ester and of a dimethyl ester monoacetate. In 1958, Boyer *et al*[2] isolated emmolic acid from *Emmenospermum alphitonioides* F.Muell (*Rhamnaceae*) which was subsequently shown to be identical with Ceanothic acid by Birch and co-workers[4]. de Mayo and Starratt[5] in 1962 also isolated ceanothic acid from *Ceanothus americanus*. They, however, could not isolate the acid by adopting the procedure used by Julian *et al*[1] and consequently developed a somewhat modified procedure which led to the successful isolation of pure ceanothic acid. de Mayo and Starratt[5] remarked on the variability

of the plant and subsequent workers[6] have also made similar observations. By adopting the modified procedure, de Mayo and Starratt[5] were able to isolate different proportions of the various acid constituents. Their method leading to ceanothic acid has been described here. The ground root bark of Ceanothus americanus was extracted continuously with ether in a soxhlet apparatus for 33 hours. The residue obtained by removing ether was extracted with light petroleum under reflux for 3 hours. The process was repeated four times. The residue, in ethereal solution, was extracted exhaustively with 2% potassium hydroxide solution. During the extraction a solid was separated at the interface and this was removed by filtration. Acidification of the alkaline solution and isolation with ether gave the crude acid mixture which was further defatted by extraction with light petroleum. The benzene solution of the defatted residual mixture was added to a column of silica gel. Elution with a mixture of benzene and ether (20:1) gave an acid, m.p. 350-54° (decomp.), $(\alpha)_D$ 39°. Further elution with the same solvent mixture then gave betulinic acid, m.p. 270-85°. Elution with benzene-ether (10:1) then gave a material which after several crystallisations first from a mixture of ether and benzene and then of ether and methanol gave pure ceanothic acid, m.p. 356-57° (gas evolution) (lit.[1] m.p. 354°), $(\alpha)_D$ 38°, ν_{max}^{nujol} 3480, 1720, 1641 and 883 cm^{-1}. de Mayo and Starrat[5] also showed that the molecular

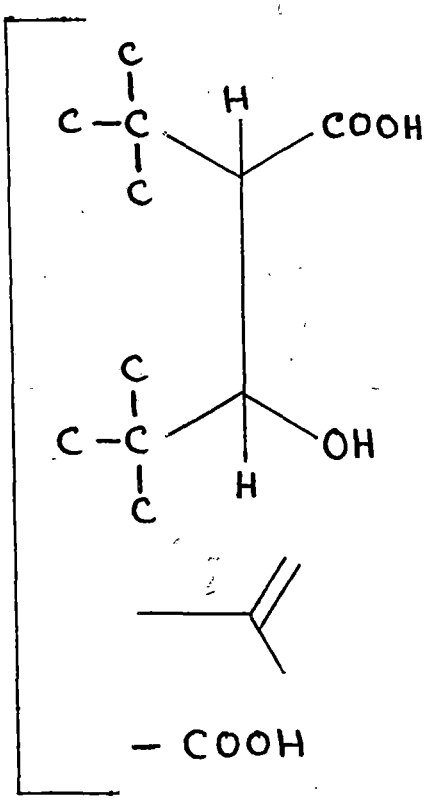
formula, $C_{29}H_{44}O_5$, suggested by Julian et al[1] for ceanothic acid was incorrect. The actual molecular formula was shown to be $C_{30}H_{46}O_5$.

Section B: Structure Elucidation of Ceanothic Acid.

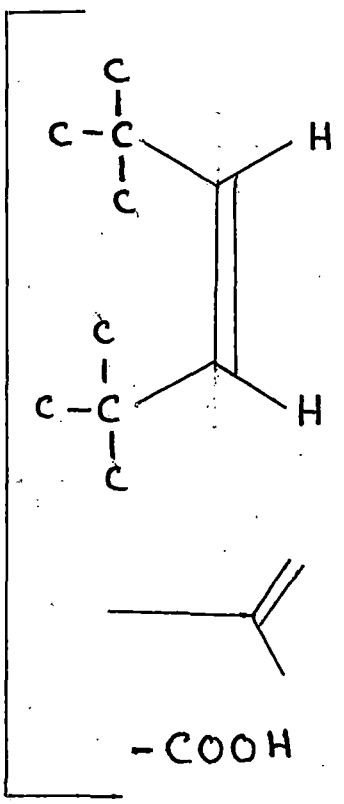
The systematic approach to the structure of ceanothic acid stems from the work of de Mayo and Starratt[5]. Their work is summarised below.

The infrared spectra of ceanothic acid and of its dimethyl ester showed bands at ν_{max}^{nujol} 833 and 889 cm^{-1} respectively, which disappeared on hydrogenation to their respective saturated dihydro compounds. This indicated the presence of an exo methylene group. The NMR spectrum of the ester showed bands at τ 5.37 (2H, d, $J \sim 7.7$ c.p.s) attributed to the methylene group and at τ 8.36 (3H, S) attributed to a vinylic methyl group[7]. These observations, in the absence of any other double bond, indicated the presence of an isopropenyl group. The NMR spectrum further showed singlets (1H each) at τ 5.98 and τ 7.51 suggesting that both the hydroxyl groups and one of the carboxyl groups were attached to carbon atoms bearing only one hydrogen atom, since these signals were in appropriate positions for the respective methine hydrogens[7]. The proximity of the hydroxyl group and the secondary carboxyl group was established from a study of the "lactone",

previously obtained by Julian et al[1], by heating ceanothic acid to its melting point. This substance was shown to be an unsaturated acid by its conversion, with diazomethane, to the corresponding ester. In addition to the signals at τ 5.40 and τ 8.46 in the NMR spectrum, indicative of the continuing presence of the isopropenyl group, signals for two hydrogens producing an AB pattern (doublets at τ 4.16 and τ 4.66; $J_{AB} \sim 5.4$ c.p.s) now appeared. The formation of this pattern was suggested as due to the transformation indicated in the conversion of (1) to (2), that is, the dehydration-decarboxylation of a β-hydroxy acid.



(1)



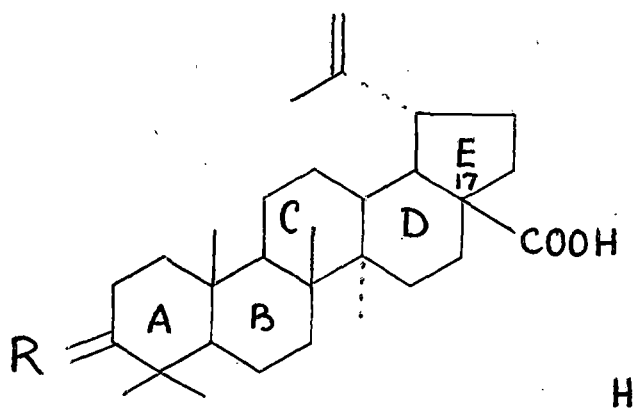
(2)

The above view was confirmed from a study of the pyrolysis of the benzoate of dimethyl ceanothate, whereby a molecule of benzoic acid was eliminated and an anhydroacid was obtained. The latter showed the ultraviolet end absorption expected for an isolated isopropenyl group and an $\alpha\beta$-unsaturated ester. Furthermore, a signal at τ 3.9 (1H, S) in the N.M.R. spectrum confirmed the presence of the expected olefinic hydrogen in addition to those of the isopropenyl group[7]. Since dihydroceanothic acid and its dimethyl ester showed no ultraviolet absorption in the region from 200 to 300 nm, they were, presumably, saturated and consequently ceanothic acid was pentacarbocyclic. Because of the presence of an isopropenyl group and its occurrence along with betulinic acid, de Mayo and Starratt[5] assumed that ceanothic acid was probably related to the lupeol-betulin-betulinic acid (3, R = H, OH) series. One of the characteristic transformations of this group of substances was the ready acid catalysed expansion of the terminal, E, ring to give derivatives of the β-amyrin series[8]. In those substances having a carboxyl function at C_{17} concomitant lactonisation occurred. Betulinic acid (3, R = H, OH) for example, was converted into (4). Ceanothic acid was similarly converted, by refluxing with formic acid for 3 hours, into a γ-lactone, ν_{max} 1696 (carboxyl) and 1762 cm^{-1} (γ-lactone) with the simultaneous disappearance of the isopropenyl

group. The resulting monocarboxylic acid lactone was further characterised as the acetate, indicating the non-participation of the hydroxyl group in the lactonisation process. One of the carboxylic acid groups remained as evidenced by the formation of a mono-methyl ester lactone. To accommodate the presence of the functions indicated in (1) in ceanothic acid, de Mayo and Starratt[5] suggested that some modification of ring A of betulinic acid was necessary. The grouping in (1) was suggestive of the occurrence of a 'biogenetic' pinacolic rearrangement at some stage in the genesis of ceanothic acid, such as may take place in the formation of gibberellic acid[9] and of the aldehyde in magnamycin[10]. Oxidation of methyl dihydroceanothate with sodium dichromate gave the corresponding Ketone diester. Alkaline hydrolysis resulted in the elimination of carbon dioxide expected of a β-ketoester and the formation of a ketonic monoester. This substance showed an unresolved band in the infrared spectrum at ν_{max} 1738 cm^{-1} for the cyclopentanone and ester, while its precursor showed bands at $\nu_{max}^{CCl_4}$ 1750 (cyclopentanone) and 1727 cm^{-1} (ester).

The above experiments led de Mayo *et al* to propose two structures (5) and (6) for the ketone, but its properties suggested that it was (6), a substance previously prepared by Ruzicka *et al*[11,12] from betulonic acid (3, R = O) by hydrogenation, nitric acid oxidation to (7), followed by pyrolysis and

esterification. Direct preparation of this substance from methyldihydrobetulonate and comparison of it, and its various derivatives showed them to be identical in every respect. Therefore, they proposed four possible structures(8), (9), (10) and (11) for ceanothic acid.



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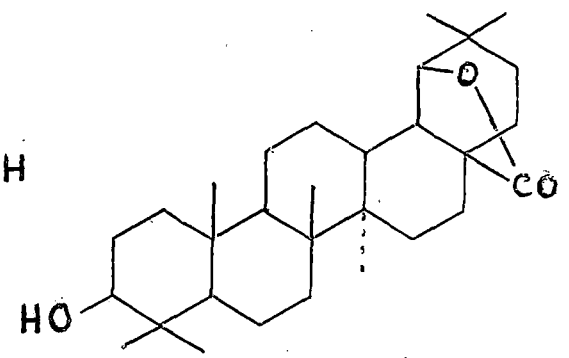

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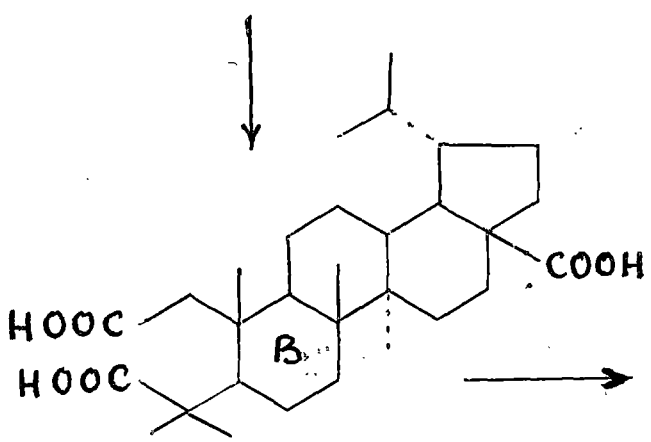

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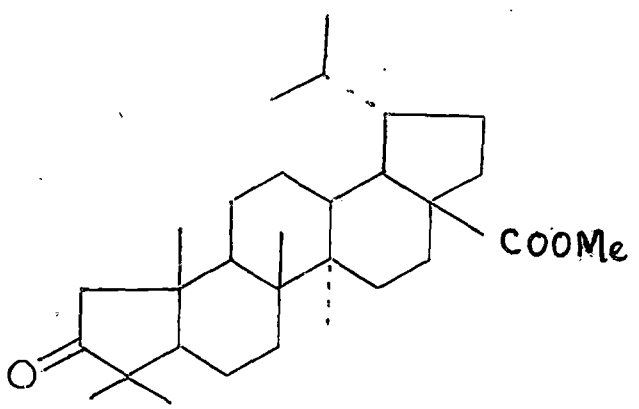

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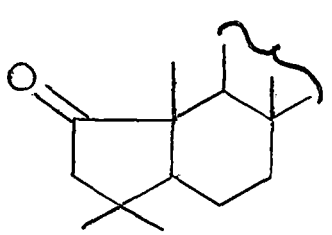

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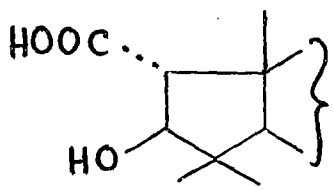

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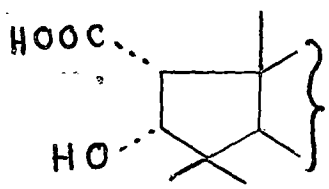

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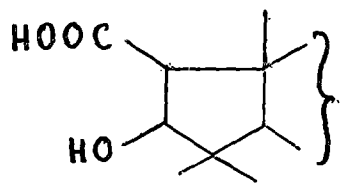

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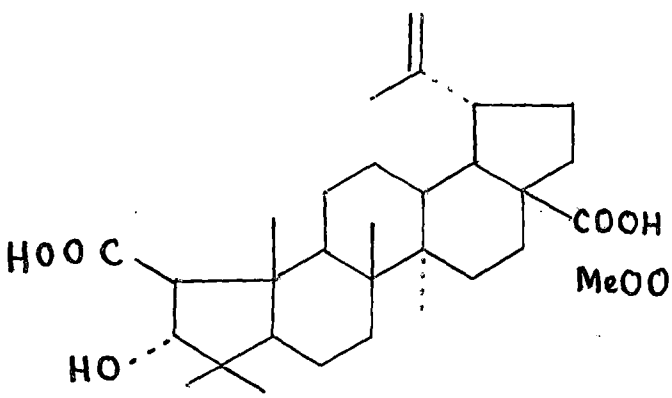

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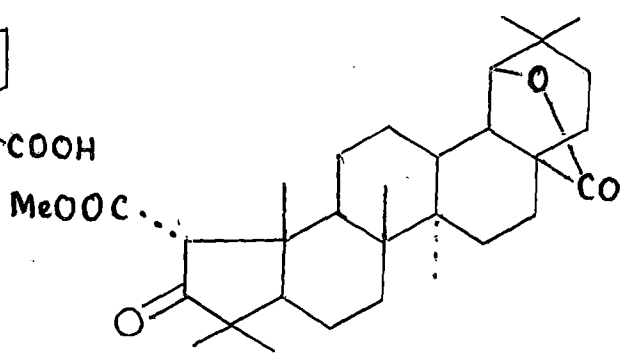


(12)

The N.M.R. spectrum of dimethyl ceanothate showed that the methine hydrogens adjacent to the carbomethoxyl and hydroxyl groups were singlets; that is, although the hydrogens were on adjacent carbon atoms, the coupling constant was close to zero. In contrast, the ketone (12), derived from methyl ceanothate lactone, on reduction with sodium borohydride gave an epimeric alcoholic lactone, methyl isoceanothate lactone. The N.M.R. spectrum of the latter showed a doublet at τ 7.0, the methine hydrogens being coupled, and a quartet at $\tau 5.9^{7}$, the hydrogen on the carbon bearing oxygen being split by the adjacent methine hydrogen and by the hydroxyl hydrogen. This suggested that in

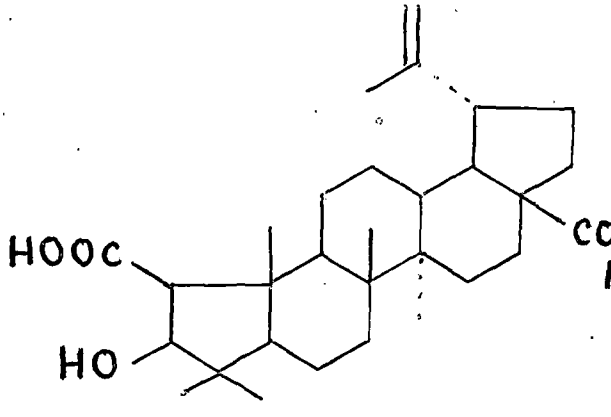
dimethyl ceanothate the hydrogen atoms were at an angle of about 90°[13,14] and, therefore, in the trans relationship.

Further evidence supporting this view was obtained from a study of infrared spectra. Treatment of methyl dehydroceanothate lactone (12), with sodium methoxide resulted in a rapid epimerisation of the carbomethoxyl group-which must, therefore, be in the unstable configuration - and the formation of the isomeric methyl dehydroepiceanothate lactone. Reduction of this with sodium borohydride then gave methyl epiceanothate lactone. Having prepared three of the four possible epimeric hydroxy esters, de Mayo and Starratt[5] carefully examined the carbonyl and hydroxyl regions of the infrared spectra of these substances in solution. It was found that methyl dihydroceanothate showed a normal unbonded ester and, in agreement, the hydroxyl group showed intermolecular hydrogen bonding only in the most concentrated solution. In contrast, both the epimeric methyl isoceanothate lactone and methyl epiceanothate lactone showed a bonded ester group and a bonded hydroxyl band even in dilute solution. These results supported the trans and cis configurations, respectively, allocated to dimethyl ceanothate and methyl isoceanothate lactone. They suggested that methyl epiceanothate lactone was, also, probably cis.

Considering all the above observations, de Mayo and Starratt[5] suggested that only two structures (8) and (11)

remained for ceanothic acid. From an inspection of models they suggested that the β-carbomethoxyl group was under more severe non-bonded interaction than the α-epimer. In view of the observed ready epimerisation of methyl dehydroceanothate lactone, they preferred the stereostructure (11) for ceanothic acid.

In 1961, just prior to the publication of the work of de Mayo and Starratt[5], Mechoulam[15] published a paper in which he assigned the β-configuration of the carboxyl group in ring A and a cis relationship between this carboxyl and the adjacent hydroxyl groups (13). His arguments were as follows. None of the secondary and the tertiary carbomethoxyl groups of dimethyl ceanothate underwent hydrolysis with 10% KOH solution



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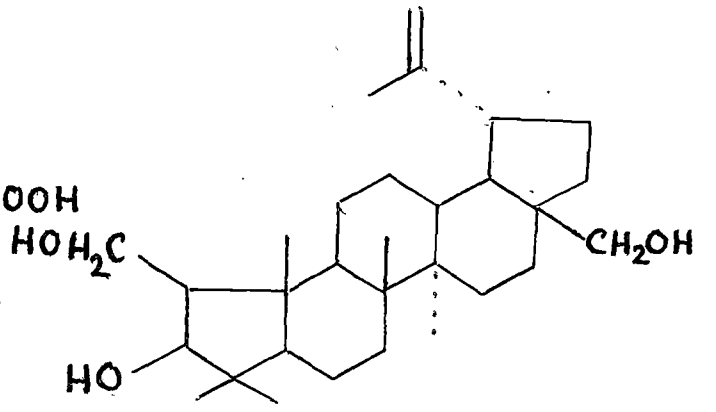


(14)

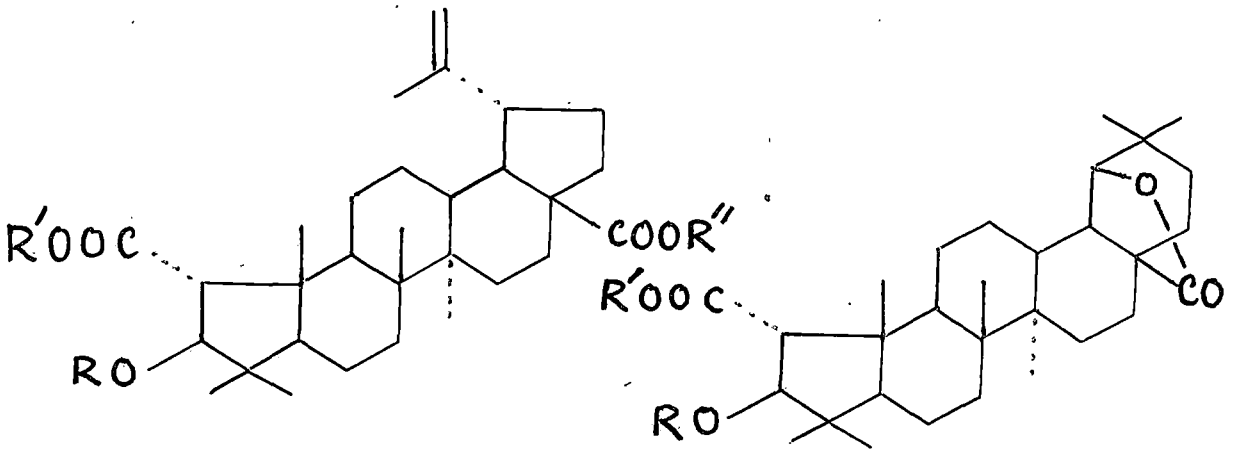
and consequently both of them were hindered. Inspection of the model showed that a 2β-, but not 2α-, carboxyl group was considerably hindered; therefore, they ascribed a β-carboxyl configuration to the natural product. Furthermore, they showed that both dimethyl ceanothate and dimethyl - 3-oxo-ceanothate on lithium aluminium hydride reduction, gave the same triol[2] (14), m.p. 226-28°, $(\alpha)_D$ 46° (EtOH). They argued that since for steric reasons the latter would be expected to give the 3β-ol by this type of reduction, the natural product thus contained β-hydroxyl grouping. The cis relationship, thus obtained, was supported by the presence of an intramolecular hydrogen bond as evidenced from the I.R. spectrum of a very dilute solution of the triol (14). Later Eade, Kornis and Simes[16,17] and Mechaulam[18] himself negated the idea of cis relationship of the carboxyl and hydroxyl group and gave further evidence in support of the structure proposed by de Mayo and Starratt[5].

Eade et al[16] using lithium fluoride optics, examined the I.R. spectrum of dimethyl ceanothate at various concentrations. From the results, they concluded that intramolecular hydrogen bonding was absent. Inspection of the model showed that intramolecular hydrogen bonding would be expected to occur only when the adjacent methoxycarbonyl and hydroxyl groups were cis[19]. Thus in dimethyl ceanothate these groups were, presumably, trans.

In contrast the work of Mechaulam[15], Eade et al[16] reported that lithium aluminium hydride reduction of dimethyl dihydroceanothate and the corresponding ketone, dimethyl 3-oxo- dihydroceanothate gave different triols. They explained this observation on the basis of two possible factors: (I) the reducing agent could chelate with the hindering group and this might affect the stereochemical course of the reduction of the ketone, and (II) epimerisation of the methoxycarbonyl group might occur during reduction.

In 1958, Boyer et al[2] reported that dimethyl ceanothate was stable to boiling 10% ethanolic potassium hydroxide for 2 hours. But Eade et al[16] found that when refluxed for 48 hours with 20% methanolic potassium hydroxide, dimethyl ceanothate was converted into an equilibrium mixture from which the major product, mono-methyl ester (15A) could be isolated in 50% yield. Methylation of (15A) gave a dimethyl ester (15B) which was isomeric with dimethyl ceanothate. The corresponding acid (15C), isomeric with ceanothic acid, was named isoceanothic acid. Lactonisation (H_2SO_4/Acetic acid/Benzene) of compound (15D) [obtained by acetylation of (15A)] gave the lactone (16B) indicating that it was the methoxycarbonyl group which had been hydrolysed by alkali. Both lactone (17A) (normal series, prepared by lactonisation of dimethyl ceanothate) and lactone (16C) (iso-series) were converted into the corresponding oxo-esters (18A)

and (18B) respectively having different physical constants; both (18A) and (18B), however, yielded the same nor-ketone (18C).



(15A) $R = R' = H$, $R'' = CH_3$

(15B) $R = H$, $R' = R'' = CH_3$

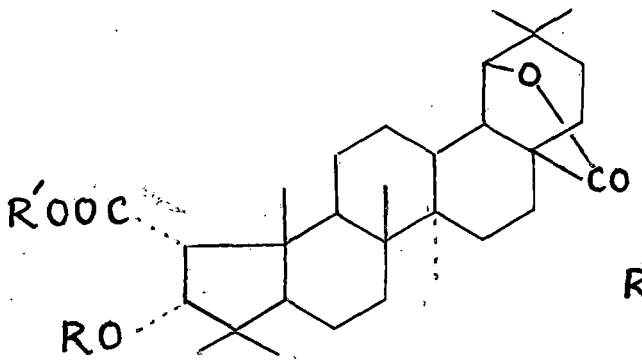
(15C) $R = R' = R'' = H$

(15D) $R = COMe$, $R' = H$, $R'' = CH_3$

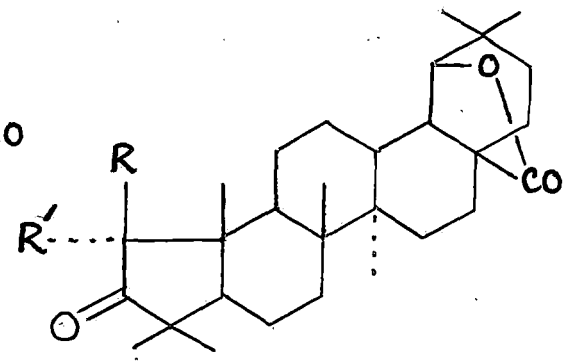
(16A) $R = R' = H$

(16B) $R = COMe$, $R' = H$

(16C) $R = H$, $R' = Me$



(17A) R = H, R′ = CH_3



(18A) R = COOMe, R′ = H

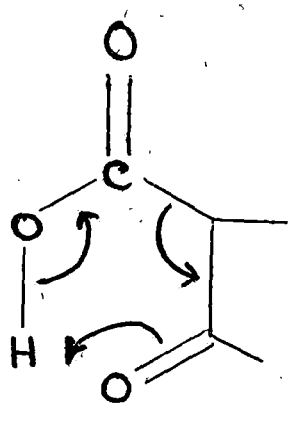
(18B) R = H, R′ = COOMe

(18C) R = R′ = H

Thus the methoxycarbonyl group in ceanothic acid and that in isoceanothic acid were epimeric. From an examination of the model, Eade et al[16] suggested that if the methoxycarbonyl group in ring A had the β-configuration it would be under considerable non-bonded interaction. Such interaction would be virtually absent if it possessed the α-configuration. Thus they concluded that the carboxyl group in ring A of ceanothic acid probably possessed the more strained β-configuration leading to the α-assignment for the hydroxyl group. The ring A substituents of isoceanothic acid were also assigned a trans relationship since the infrared spectra of the dimethyl ester (15B) showed the

absence of any intramolecular hydrogen bonding. Consequently formation of isoceanothic acid from ceanothic acid required an opening of ring A in a reverse aldol type reaction to an A-seco derivative followed by subsequent ring closure.

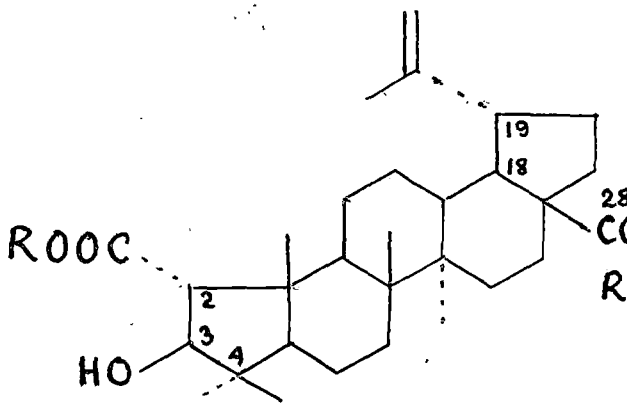
Crowley[20], in 1962, reported the natural occurrence of a 2,3 - seco triterpene and this supported the suggested biogenesis[3] of ceanothic acid by ring closure of a similar 2,3-seco derivative derived from 2-hydroxybetulinic acid; the latter has recently been isolated along with ceanothic acid from Alphitonia Whitei Braid[3]. Eade et al[16] found that the β-keto acid derived from the iso-series by oxidation of either (15A) or (16A) were quite stable and could be dried in vacuo at 100°. However, each acid underwent decarboxylation only at higher temperatures, for example, (16A) gave (18C) at 220°C. They attributed this stability as due to the difficulty in finding a cyclic planar transition state (A). In this connection, they cited the example of a stable β-keto acid, camphor-3-carboxylic acid, which, according to them was stereochemically similar.



(A)

Section C: Stereochemistry of Ceanothic Acid.

The stereochemistry of ceanothic acid was finally established by Eade et al[21,22]. These authors observed[17] that the ester group at C_2 in dimethyl ceanothate (19, R = Me) could be epimerised only with great difficulty, whereas in the corresponding ester, dimethyl ceanothate lactone (19A, R = Me), with a modified ring E area, it could be comparatively easily epimerised and was accompanied by simultaneous hydrolysis. They suggested[17] that this considerable difference in reactivity might be caused by a long range conformational transmission effect. They expected that a comparison of the coupling constants



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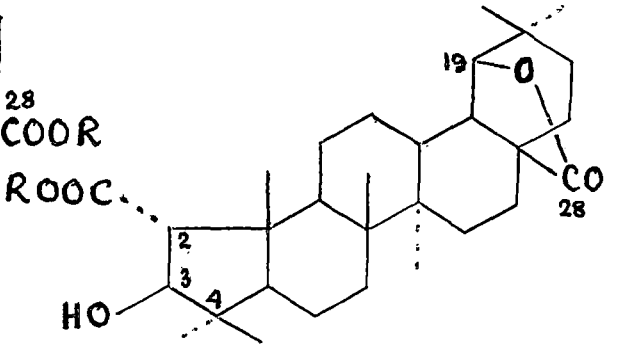


(19 A)

of the C_2 and C_3 protons of the four possible C_2- CO_2Me/C_3-OH isomers (and their acetates) in the dimethyl ceanothate series [carbon skeleton type (19)] with those of the corresponding compounds in the lactone series [carbon skeleton type (19A)] would reveal any significant differences in the shape of ring A between the relevant compounds. An explanation might also be found for the singlet for the C3 proton in the N.M.R. spectrum of dimethyl ceanothate[5] which was not in agreement with the structure then assigned to ceanothic acid even if ring A existed in the α-envelope conformation[23,24]. Further they expected that the preparation of the entire group of four isomers in each series would solve the controversy whether the "methyl epiceanothate" of de Mayo and Starratt had a cis or trans relationship of the ring A substituents[5,17].

Eade et al[21] finally proposed structure (19) for ceanothic acid in which the ring A substituents, while still having a trans relationship, possessed the configurations opposite to those originally put forward by de Mayo and Starratt[5]. Their works[22] are described below.

Preparation of the Dimethyl Ceanothate Series.

Of the four isomers in the dimethyl ceanothate series, two have been previously prepared. One was dimethyl ceanothate itself (19, R = Me) and the other was its C2 epimer (23) [methyl

-3β-hydroxy-2β-methoxycarbonyl-A(I)-Norlup-20(29)-en-28-oate] (Scheme 1) reported by Eade et al[17] who incorrectly formulated it as the trans isomer of dimethyl ceanothate epimerised at both C2 and C3 and was originally given the name dimethyl epiceanothate in accordance with the nomenclature used by de Mayo and Starratt[5]. This isomer (23) was first prepared[17] by epimerisation of the C2 methoxycarbonyl group by prolonged treatment of dimethyl ceanothate with concentrated methanolic sodium methoxide to give after separation of the mixture through the half ester of (23), followed by methylation with diazomethane to give (23). Eade et al[22] prepared this compound by the procedure[5] for the analogous compound in the lactone series. Oxidation of dimethyl ceanothate (19) with Jones' reagent gave the known methyl 2α-methoxycarbonyl-3-oxo-A(1)-Norlup-20(29)-en-28-oate (dimethyl dehydroceanothate) (20) which was rapidly epimerised by alkali to an equilibrium mixture containing 40% of the starting material and 60% of the isomer, epimeric at C2, methyl 2β-methoxycarbonyl-3-oxo-A(1)-Norlup-20(29)-en-28-oate (22) (dimethyl epidehydroceanothate). Reduction of (22) with sodium borohydride gave the cis isomer (23) as the sole product.

Reduction of (20) with sodium borohydrohydride gave a 1:1 mixture of dimethyl ceanothate (19, R = Me) and its C3 epimer (21) which were readily separated by column chromatography.

The fourth isomer, methyl 3α-hydroxy-2β-methoxycarbonyl-A(1)-Norlup-20(29)-en-28-oate (24) was prepared by long heating

of a solution of methyl 3α-hydroxy 2α-methoxycarbonyl-A(1)-norlup-20(29)-en-28-oate (21) in methanolic sodium methoxide whereupon partial epimerisation of the C2 methoxycarbonyl group occurred. After re-methylation of the total crude product, the isomer (24) could be separated from the starting material by column chromatography.

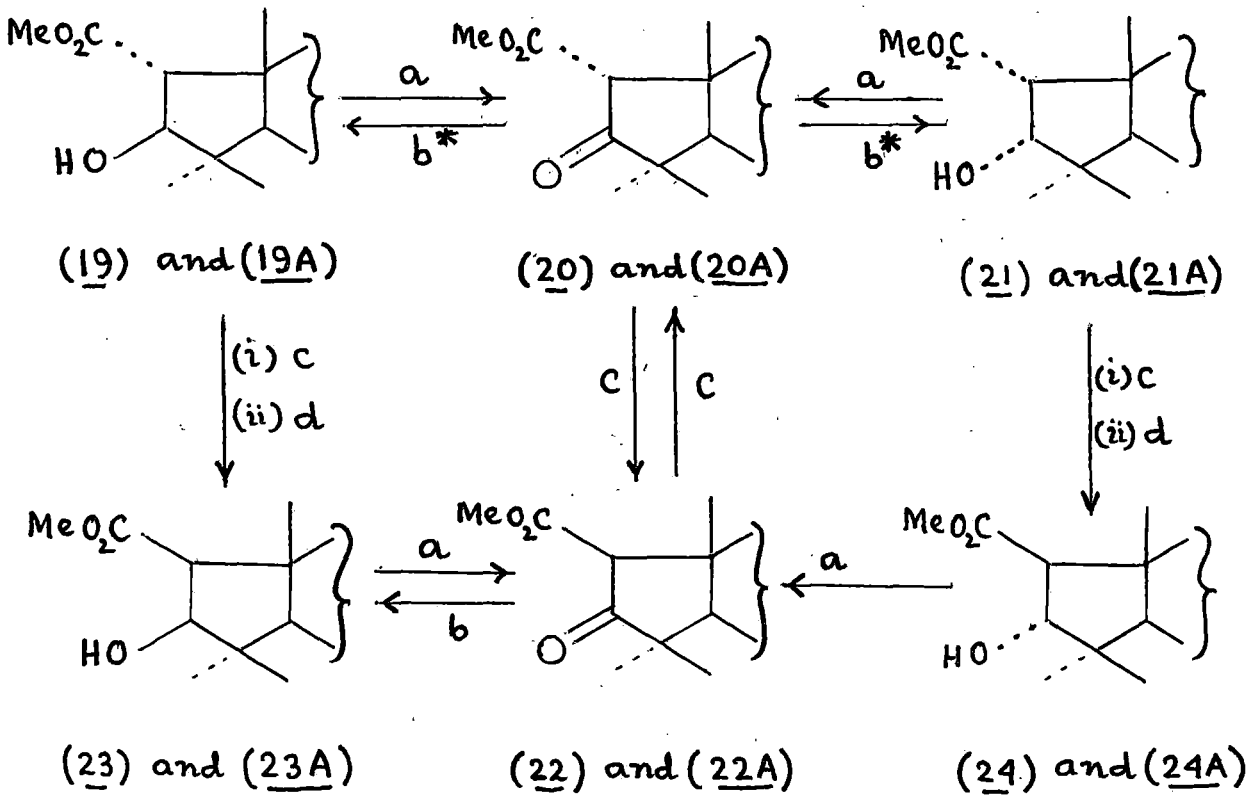
The identity of each of the above alcohols was established by oxidation (Jones' reagent) to the corresponding ketones. Eade et al[22] also converted each alcohol into its corresponding acetate.

Preparation of the Lactone Series.

Three of the four isomers in this series were previously reported[5,17]. Methyl ceanothate lactone (19A, R = Me) was prepared from ceanothic acid by formic acid catalysed lactonisation followed by hydrolysis and methylation[5] and also by lactonisation of dimethyl ceanothate in acetic acid and sulphuric acid followed by deacetylation[17]. The compounds (21A) and (23A) were prepared by borohydride reduction of the corresponding ketones (20A) and (22A). Eade et al[22] prepared the fourth and previously unknown isomer (24A) by isomerisation of (21A) with sodium methoxide in methanol, followed by remethylation with diazomethane. Each of the above alcohols was converted to the corresponding ketone and acetate.

A summary of the preparation of the four isomers by Eade et al[22] in the two series is shown in Scheme-1. The

Scheme-1 (Preparation of Isomers).



a. Jones' Reagent, b. Sodium borohydride

c. Sodium methoxide, d. Diazomethane.

* (20) $\xrightarrow{b}$ (19) + (21), but (20A) $\xrightarrow{b}$ (21A) Only.

epimerisation of both ketones in each series were reversible equilibria. Eade et al[22] also showed that the equilibrium mixture contained 60% of (22) or (22A) and 40% of (20) or (20A).

N.M.R. Results.

Eade et al[22] measured the coupling constants between the protons on C-2 and C-3 for each isomer and its acetate belonging to both the series. They also calculated the vicinal coupling constants ($J_{2,3}$) of the four isomers for the three possible ring A conformations from the dihedral angle measured from Drieding models. These were shown in Table-1. Of these three possible conformations, they argued that the α-envelope seemed least

Table-1

Coupling Constants of C-2 and C-3 Protons.

	Configuration of ring A substituents.			
	2α,3β;	2β,3β;	2α, 3α;	2β, 3α
Observed $J_{2,3}$ (H_z)				
Dimethyl Ceanothate Series:				
C3-OH	1.0	7.3	7.0	9.0
C3-OAc	0.2	7.6	7.6	9.5
Lactone Series:				
C3-OH	1.0	7.4	7.0	9.0
C3-OAc	0	7.6	7.7	9.5

Contd..

Table-1 (Contd.)

	Configuration of ring A substituents.			
	2α, 3β ;	2β, 3β ;	2α, 3α ;	2β, 3α
Calculated $J_{2,3}(H_z)$				
α-Envelope	1.8-2.9	8.2	8.2	1.8-2.9
β-Envelope	-0.3-0.0	6.2-6.9	5.7-6.7	5.9-7.1
Half Chair	0.3-0.8	7.2-8.0	7.5-7.9	3.5-5.0

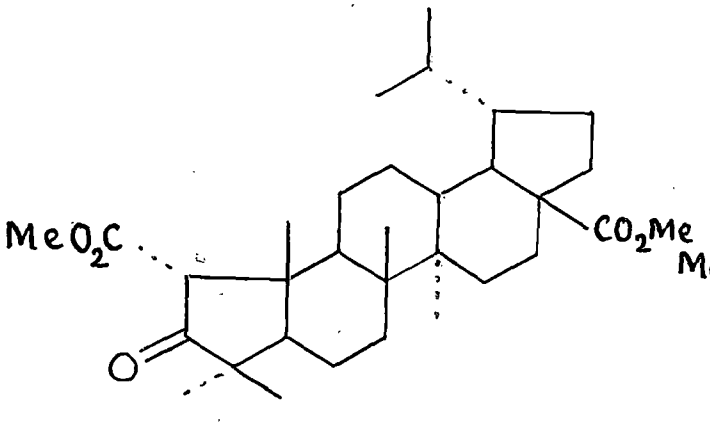
likely since examination of the models showed strong 10β-methyl/4β-methyl interaction which would be expected to destabilise this conformation. In addition, the investigation by Fishman[25] on analogous 16,17-disubstituted steroids lacking these methyl/methyl interactions suggested that the α-envelope need not be considered. The only significant difference between the three conformations were the two trans couplings in the α-envelopes[25] and hence these results, although excluding the α-envelope, did not distinguish between the other two conformations. Eade et al[22] pointed out that the observed couplings were clearly consistent with the proposed formula for ceanothic acid (19, R = Me) but

obviously did not conform with the original stereochemistry suggested by de Mayo and Starratt[5].

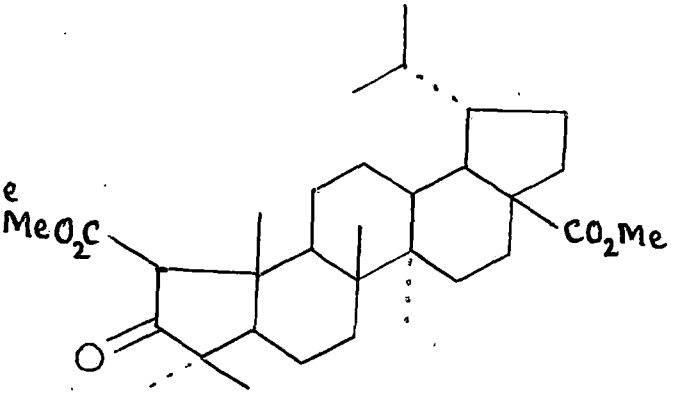
Table-1 shows that there are no significant differences between the coupling constants of the C-2 and C-3 protons among the members of the dimethyl ceanothate series compared to those among the analogous compounds in the lactone series and hence the investigation[22] did not yield any conclusive evidence which had been proposed[17] to explain the differences in reactivity in the ring A moiety between the two series. The coupling constants in Table-I, together with the interconversions summarised in Scheme-I, established unequivocally that in the epiceanothate series the ring A substituents were cis to one another, each having the β-configuration.

In addition to the evidence presented above in relation to the vicinal coupling between the protons on C-2 and C-3, the long range (4σ) coupling[26] between the 10 β-methyl group and the C-2 proton furnished further support for their assignment[22]. This coupling was studied using the following three pairs of isomers: (i) methyl dehydroceanothate lactone (20A) and its 2β-epimer (22A); (ii) dimethyl dehydroceanothate (20) and its 2β-epimer (22); (iii) dimethyl dihydrodehydroceanothate [methyl-2α-methoxycarbonyl-3-Oxo-A(1)-norlupan-28-oate] (25) and its 2β-epimer (26). The last pair of isomers were prepared by Eade et al[22] from dimethyl dihydroceanothate by

methods identical with those used to prepare (20) and (22) from dimethyl ceanothate. In each of these six compounds the C-2 proton appeared as a singlet at approximately δ 3.0; however, this signal for each of the 2β-methoxycarbonyl (epi) derivatives was broad ($W_{\frac{1}{2}}$ 2.5 H_z) compared to that in each of the 2α-methoxycarbonyl compounds ($W_{\frac{1}{2}}$ 1.5 H_z). This broadening was confirmed by spin-spin decoupling. Decoupling of the C-2 proton signal (at δ 3.08) of dimethyl epidehydroceanothate (22) increased the intensity of the C-10 methyl signal (at δ 1.06) markedly, while irradiation of this methyl frequency resulted in a sharpening of the C-2 proton signal ($W_{\frac{1}{2}}$ became 1.6 H_z). Similar sharpening of the C-2 proton signal (from $W_{\frac{1}{2}}$ 2.5 H_z to $W_{\frac{1}{2}}$ 1.6 H_z) was also observed when the relevant methyl signals in both (22A) and (26) were irradiated. The observed couplings demonstrated the pseudo-axial character of the 2α-hydrogens in (22), (22A) and (26) and supported the half-chair or β-envelope conformation of ring A for these derivatives when the 2α-proton and 10β-methyl showed some degree of co-planarity.



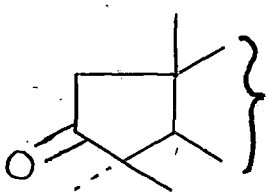
(25)



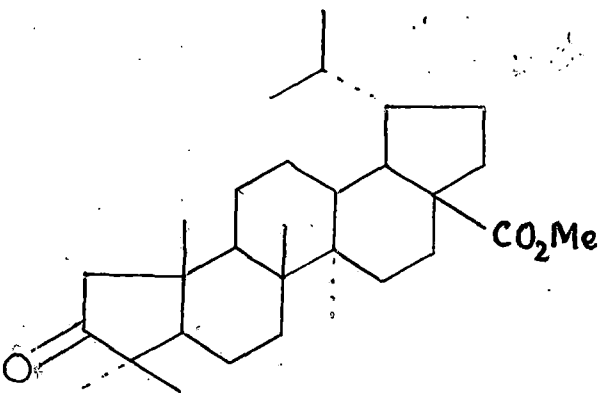
(26)

Circular Dichroism Results.

Eade et al[22] studied the circular dichroism of the two epimeric ketones (20) and (22) together with that of the corresponding nor ketone methyldecarboxydehydroceanothate [methyl-3-Oxo-A(1)-norlup-20(29)-en-28-oate] (27) and also of the corresponding sets of the three ketones in the lactone series (20A), (22A) and (27A) and in the dimethyl dihydroceanothate series (25), (26) and (28).



(27) and (27A)



(28)

Unfortunately the changes in circular dichroism between members of each set did not yield any information about the configuration of the C-2 methoxycarbonyl group. The differences between the epimeric members of each set were quite small. Work on the circular dichroism of A-nor-steroid derivatives[27] showed that changes in configuration of substituent methyl groups in the cyclopentanone ring did not yield diagnostic changes in the circular dichroism of these compounds. The investigations of Eade et al[22] thus gave further support to this interpretation with respect to cyclopentanone structure.