Tetrahedron. Vol. 26, pp. 1619 to 1629. Pergamon Press 1970. Printed in Great Britain

THE DITERPENES OF *DACRYDIUM COLENSOI* VI[1]

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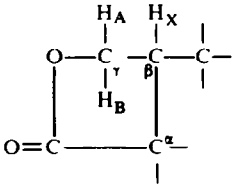
(*Received in the UK* 28 *October* 1969; *Accepted for publication* 19 *November* 1969)

Abstract—A homo-diterpene lactone isolated from *Dacrydium colensoi* has been shown to have structure **1**. The conformation of cyclopentane rings and the assignment of the configuration of the reduction products of a cyclopentanone system in A-norditerpenes by NMR is discussed.

THE neutral fraction of *Dacrydium colensoi* has proved an excellent source of diterpenes based on the oxidolabdane[2] (manoyl oxide derivatives) and pimarane[1] (sandaracopimaradiene derivatives) skeletons. We wish to report the structure of a biogenetically interesting homo-diterpene based on the oxidolabdane skeleton.

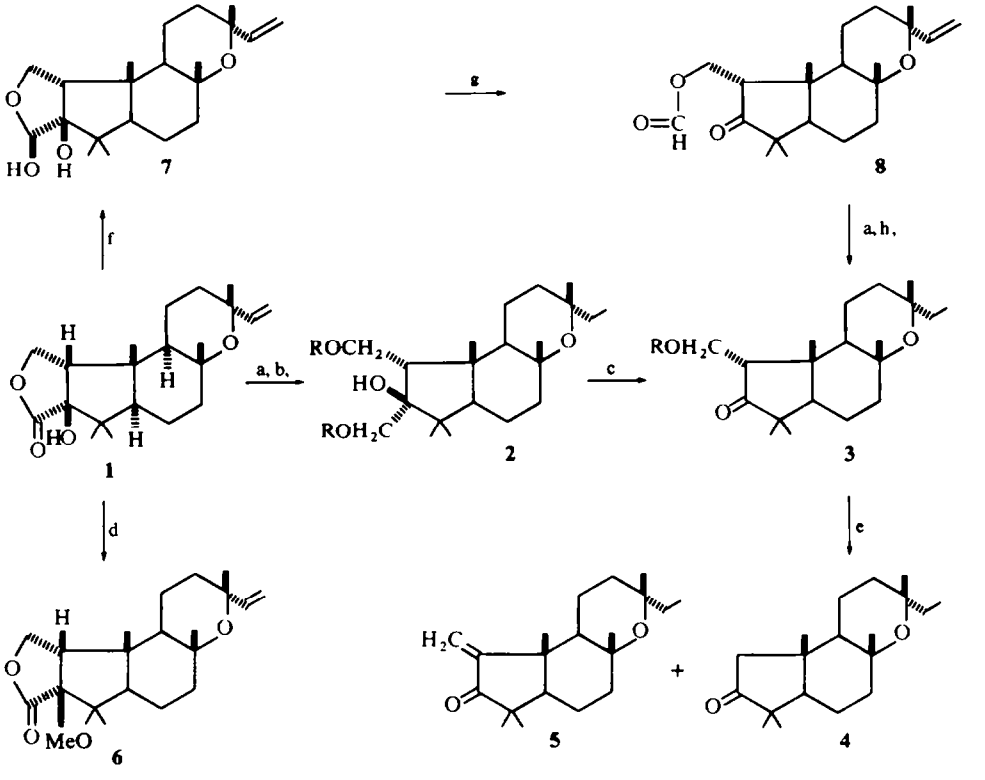
The lactone (**1**), m.p. 208–209°, and its derivatives analysed for $C_{21}H_{32}O_4$, the mol. wt. of 348 being confirmed by mass spectrometric determination. The IR spectrum showed OH absorption (3556 cm^{-1}), γ-lactone (1771 cm^{-1}), and bands characteristic of an oxide ring (1140, 1080 cm^{-1}) and a vinyl group (3085, 1645, 1410, 993, 961 cm^{-1}). The presence of a lactone grouping was confirmed by its solubility in hot alkali, a property used in the isolation of the lactone.

The NMR spectrum showed the presence of an ABX system with parameters typical of the 13α-vinyl group of the manoyl oxide series.[3] The five tertiary Me's of the oxidoditerpene skeleton which appeared at lower field than usual (1·00, 1·00, 1·10, 1·28, 1·37 δ), suggested that the lactone group was associated with ring A and excluded the possibility that the lactone was derived from the oxidation of a tertiary Me group as in rosenonolactone,[4] and other naturally occurring diterpene lactones. The two Me signals at lowest field could be assigned to the Me groups β to the ether oxygen. A two proton sextet and a one proton triplet were shown by double resonance experiments to constitute an ABX system (H_B 3·99, H_A 4·21, H_X 2·65 (J_{AB} 9·7, J_{AX} = J_{BX} = 9·5 c/s). This gave the partial structure

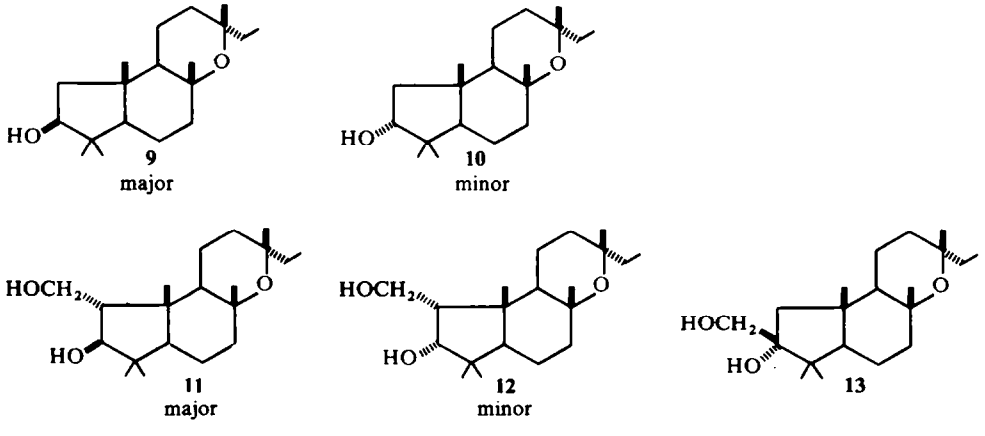


The geminal coupling of the γ methylene protons for the γ-lactone falls within the range reported by Cookson[5] for the γ methylene protons in substituted butyrolactones and is in very good agreement with J_{gem} for the 18 methylene protons of the γ-lactone in bisdehydrodihydroenmein[6] (J_{gem} = 10 c/s). The H_X proton signal was at too high a field to be a carbinol type proton but too low to be deshielded by the lactone carbonyl group alone. Further deshielding of the methine proton by Van der Waals interaction through a 1,3 diaxial or eclipsing relationship with the OH and/or ring A Me group(s)

was envisaged. The proximity of the OH to the lactone function was supported by intramolecular H-bonding in dilute solution IR studies. The OH group showed no associated carbinol proton in the NMR and was assigned as tertiary, consistent with the OH proton appearing as a singlet (3·72 δ) in DMSO.[7] Typical of tertiary OH's it could only be acetylated under acid conditions.



a: H_2/PtO_2 b: LAH/dioxan/30hr c: $Pb(OAc)_4$ or HIO_4 d: MeI/KOH
e: OH^-/HOH f: LAH/THF/5 hr g: $Pb(OAc)_4$ or CrO_3 h: H^+/HOH



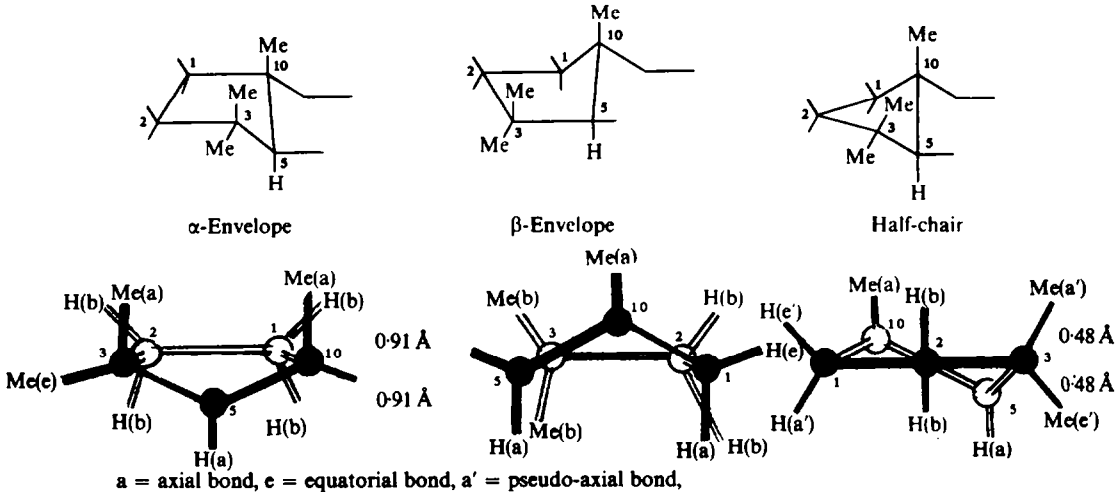
The degradative sequence which established the structure of the lactone is shown, together with additional reactions. The triol (**2**, R = H), which was further characterized as the hydroxydiacetate (**2**, R = Ac) was shown to possess a 1,2-diol system by its cleavage with $Pb(OAc)_4$ to the ketol **3** (R = H; no aldehydic proton in the NMR). The formation of a ketone, the spectral measurements for which were consistent with a cyclopentanone structure (1723 cm^{-1}; λ_{max} 301 mμ), confirmed the presence of a tertiary OH group in the lactone. The $HOCH_2CHRR'$ system appeared as a five line ABX system, approximating to an A_2X system because of the accidental chemical equivalence of the hydroxymethyl protons. In benzene an eleven line ABX pattern was observed. The hydroxymethyl protons exhibited the typical paramagnetic shift (0·44 δ) of primary carbinol protons on acetylation[8] to the acetoxy-ketone (**3**, R = Ac). The alkali induced retroaldol[9] reaction on the ketol (**3**, R = H) gave colensan-2-one (**4**) as the major product and the base catalysed β-elimination product, the methylene ketone (**5**) in minor yield. Adsorption of the ketol on basic alumina produced only the methylene ketone which showed cisoid enone spectral characteristics. The UV spectrum(λ_{max} 226 mμ; ε 5000) was in good agreement with those reported for sarkomycin[10] and 16-methylene-Δ^5-androsten-3β-ol-17-one.[11] The ratio of the carbonyl adsorption/double bond absorption in the IR spectrum showed the typical decrease associated with a cisoid chromophore and the 880 cm^{-1} absorption of an isolated exocyclic methylene system was displaced to a higher frequency.[12]

The formation of the methyl ether (**6**) with MeI/KOH confirmed the acidic nature of the hydroxyl group in the α-hydroxy lactone system. LAH reduction of the lactone in THF gave the hemiacetal (**7**) (hemiacetal proton 5·12 δ, in good agreement with the hemiacetal proton at 5·38 δ in the 5-ring hemiacetal of dihydroenmein monoacetate[6]). The *cis* nature of the 1,2-diol system in the hemiacetal was confirmed by the formation of an acetonide. The β-ketoformate (**8**), formed by $Pb(OAc)_4$ or chromic acid treatment of the hemiacetal showed the formyl proton at 8·02 δ and IR bands (1730, 1160 cm^{-1}) typical of the formate group. Acid hydrolysis of the β-ketoformate followed by hydrogenation of the vinyl group gave the ketol (**3**, R = H) previously prepared.

Stereochemistry of the lactone. By its correlation with a diterpene of known stereochemistry there remained only the stereochemistry of the lactone/ring A fusion to be established. The stability of the lactone which was shown by its recovery without rearrangement on attempted opening to the hydroxy methyl ester, even under carefully controlled conditions, indicated a *cis* fused lactone ring. Dreiding models show that a *trans* fused lactone results in intolerable bond angle deformation. The *trans* form of bicyclo [330]octane has been prepared but the enthalpy of the *trans* form exceeds that of the *cis* form by 6·0 Kcal/mole.[13] The *cis* fusion of the lactone is consistent with the failure of the lactone to dehydrate, the *anti*-periplanar prerequisite for E_2 concerted eliminations being absent.

Although the ORD of the β-ketol (**3**, R = H) was consistent with a 1α-hydroxymethyl configuration, the ORD of the corresponding acetate (**3**, R = Ac) in which no change in configuration of the 1-substituent would be expected indicated a 1β-acetoxymethyl. As ORD had proved inadequate in stereochemical assignments of the epimeric 1-methoxycarbonyl 2-keto derivatives in the ceanothic acid series, it was considered an unreliable method for the determination of the configuration of the 1-substituent.

The conformation of the substituted cyclopentane ring in an alicyclic system is not as well documented as that of the corresponding cyclohexane system. Conformational studies have been restricted to ring D substituted steroids, the 17 and 16 positions in the steroids being equivalent to the 1 and 2 positions respectively, in the A-norditerpenes. In diterpenes the additional effects of the 3-gemdimethyl group on the 10β-Me group, and a 1-substituent on the 11-methylene have to be considered. Brutcher and Bauer[14] have described three symmetrical, maximally puckered conformations for the rigid *trans* fused cyclopentane steroidal D ring; the α-envelope, β-envelope, and the half-chair. These conformations are considered for the 5-membered A-ring in the colensan derivatives. (Fig. 1)



a = axial bond, e = equatorial bond, a′ = pseudo-axial bond,
e′ = pseudo-equatorial bond; b = bisectional bond

FIG. 1. Conformations of Ring A in Colensan

Dreiding models show that in ring A substituted derivatives the α-envelope can be neglected as it is destabilised by the strong 10β-Me,3β-Me interaction which is minimised in the β-envelope and half chair. This interaction will offset any other energy terms stabilising the α-envelope (1αR,5αH; 1β,11αH).

Little information is available on the hydride reduction of cyclopentanones in an alicyclic system. A-norcholestan-2-one is reported as giving the 2β-alcohol in 94% and 90% yields on reduction with sodium borohydride[15] and LAH[16] respectively. Since the 2α-alcohol is more stable than the 2β-alcohol[16] these reductions must be governed by steric approach control. $NaBH_4$ reduction of 1α-bromo-A-norcholestan-2-one gave the epimeric 2β and 2α alcohols in a 3:7 ratio,[15] thus reflecting the effects of an adjacent α-substituent on α-face approach of the hydride anion and of a possible change of conformation of ring A. LAH reduction of colensan-2-one (**4**) gave the epimeric colensan-2β-ol (**9**) and colensan-2α-ol (**10**) in a 3:2 ratio, identical to that reported for the reduction of 3,3-dimethyl-A-norcholestan-2-one. In ring A cyclohexanone systems the introduction of the gem-dimethyl group increases the importance of steric approach control and increases the amount of β-alcohol formed. The reverse observation in the cyclopentanone systems can be accounted for if ring A exists in the β-envelope, as the 3α-Me has considerable α-character in this conformation and would

hinder α-face approach. Reduction of 1α-hydroxymethylcolensan-2-one (**3**, R = H) gave 1α-hydroxymethylcolensan-2β-ol (**11**) and 1α-hydroxymethylcolensan-2α-ol (**12**) in the same 3:2 ratio. This can be accounted for by a change in conformation of ring A to the half chair in **3** (R = H) and/or possible neighbouring group participation.

The configuration of the 2-OH groups in the reduction products was established from the multiplicity of the carbinol proton signal in the NMR. The Karplus equation, relating dihedral angle to coupling constant, has been used successfully to determine the stereochemistry of epimeric 16-substituted pregnenes,[17] of epimeric 16-deutero 17β and 17α-estradiols,[18] and epimeric 17-(13α)-testosterones.[19] The vicinal coupling constants ($J_{1,2}$) were calculated from dihedral angles as measured from Dreiding models for each of the three ring A conformations of the four possible 1,2-disubstituted isomers (Table 1). With the exception of the α-envelope where the 1,2 substituents

TABLE 1. NMR DATA FOR RING A 1,2 DISUBSTITUTED DERIVATIVES

H Configuration	Conformation					
	α-Envelope		β-Envelope		Half-chair	
	ϕ	J	ϕ	J	ϕ	J
1β,2α	120	2·1	96 ±4	−0·3–0·0	108 ±2	0·3–0·8
1α,2β	120	2·1	148 ±4	5·9–7·1	134 ±4	3·7–5·0
1β,2β	0	8·2	29 ±4	5·7–6·7	14 ±3	7·5–7·9
1α,2α	0	8·2	26 ±3	6·2–6·9	11 ±2	7·8–8·0

Colensan-2β-ol (**9**) $|J_{2\alpha,1\alpha} + J_{2\alpha,1\beta}| = 9{\cdot}1$ c/s
Colensan-2α-ol (**10**) $|J_{2\beta,1\beta}| = 8{\cdot}9$ c/s; $|J_{2\beta,1\alpha}| = 6{\cdot}8$ c/s
1α-Hydroxymethylcolensan-2β-ol (**11**) $J_{2\alpha,1\beta}$ = singlet, $W_{\frac{1}{2}}$ 2·0 c/s
1α-Hydroxymethylcolensan-2α-ol (**12**) $J_{2\beta,1\beta} = 7{\cdot}0$ c/s

eclipse, the values are the same as those reported by Cross for 16,17-disubstituted (C/D *trans*) steroids. As Fishman[18] has pointed out the only significant differences in the coupling constants between the three conformations are those of the two *trans* (1β,2α; 1α, 2β) couplings in the α-envelope. Comparison of the observed and calculated bandwidths $|J_{AX} + J_{BX}|$ of the 2-carbinol proton signal establishes the configuration of the OH groups in the epimeric colensan-2-ols. In each case the carbinol proton is involved in a *cis*-coupling of approximately equal magnitude. Complete analysis of the AMX system in the minor alcohol (**10**) gave $J_{2\beta,1\beta} = 8{\cdot}9$ c/s, and $J_{2\beta,1\alpha} = 6{\cdot}8$ c/s, consistent only with colensan-2α-ol. The major alcohol (**9**) gave $|J_{AX} + J_{BX}| = 9{\cdot}1$ c/s which means that the *trans* coupling ($J_{2\alpha,1\beta}$) must be very small and is consistent with colensan-2β-ol in the half chair or β-envelope conformation. These assignments of the epimeric 2-alcohols were inconsistent with the empirical rule of Bose[20] (calculation of the absolute configuration of a pair of epimeric cyclic compounds based on molecular rotation values). Other exceptions to this rule have been noted.[21]

Similarly NMR was used to establish the configuration of the reduction products (**11** and **12**) of the ketol (**3**, R = H). In the major product, (**11**) the 2-carbinol proton appeared as a singlet ($W_{\frac{1}{2}} = 2{\cdot}0$ c/s) and is consistent with a 1α-hydroxymethylcolensan-2β-ol formulation. The hydroxymethyl protons gave $|J_{AX} + J_{BX}| = 14{\cdot}5$ c/s and the 1-methine proton appeared as a quartet $|J_{AX} + J_{BX} + J_{1,2}| = 14{\cdot}4$ c/s thus confirming 1α-CH_2OH, 2β-OH orientation of the diol. Thus it followed that the minor 1,3 diol was 1α-hydroxymethylcolensan-2α-ol (**12**) which was consistent with the

2-carbinol proton doublet ($J_{2\beta,1\beta} = 7$ c/s). Intramolecular H-bonding studies in dilute soln[22] confirmed the *trans* and *cis*-nature of the diols (**11** and **12**) respectively, the major diol (**11**) showing only unbonded OH absorption (3630 cm^{-1}) and the minor diol (**12**) showing bonded (3538 cm^{-1}) and unbonded (3635 cm^{-1}) OH absorption. Further, models show that 1α-hydroxymethylcolensan-2β-ol is the only one of the four 1-hydroxymethylcolensan-2-ols in which H-bonding is not possible since in nρ conformation does the O····H distance approach within 2·7 Å (see following paper).[23]

Table 2 gives the chemical shifts of the ring A Me signals and is further support for the configuration of the reduction products. Additional colensan derivatives available from earlier work were also examined. 2β-Hydroxymethylcolensan-2α-ol (**13**) was synthesized by the Wittig reaction on colensan-2-one to give 2-methylene colensan, followed by by hydroxylation with OsO_4. The additivity values for 2β-OH and 2α-OH on the 10β-Me are in good agreement with those reported[24] in the epimeric A-norcholestan-2-ols (β0·26, α0·05).

TABLE 2. CHEMICAL SHIFTS OF RING A METHYLS IN COLENSAN DERIVATIVES

	10βMe	4βMe	4αMe
Colensan	0·71	0·86	0·95
2α-OH	0·76	0·90	0·90
2α-OH, 2β-CH_2OH	0·80	0·94	1·02
2α-OH, 1α-CH_2OH	0·82	0·92	0·99
2β-OH	0·97	1·03	0·91
2β-OH, 2α-CH_2OH	0·99	1·01	0·93
2β-OH, 2α-CH_2OAc	0·99	1·03	0·96
2β-OH, 2α-CH_3	0·96	0·94	0·91
2β-OH, 1α-CH_2OH	0·97	1·05	0·89
2β-OH, 1α,2α-diCH_2OH	1·18	1·22	0·93
2β-OH, 1α,2α-diCH_2OAc	1·02	1·20	0·97

Unequivocal assignment of all the ring A Me signals is not yet possible but the greater downfield shift of the Me signals in 2β-OH derivatives is clearly evident.

Further support for the 1α-hydroxymethyl configuration in the degradation products of the lactone came from a study of long range (^4J) coupling. The 1-methylene protons of colensan-2-one (**4**) formed an AB system, the upfield spin pair (B part) being assigned to the 1α-H as the signals showed long range (4σ) coupling ($J = 1·0$ c/s) with the 10β-Me group, thus illustrating the *pseudo*axial character of the 1α-H. This long range coupling was confirmed by double resonance experiments, the 10β-Me signal (doublet, $J = 1·0$ c/s) collapsing to a singlet with corresponding increase in height on irradiation of the 1α-H signal. Similarly irradiation of the 10β-Me signal caused the 1α-H to return to a true AB system. The identity of the 10β-Me and 1α-H signals were established unambiguously by solvent shift measurements.[25] 1α-Hydroxymethylcolensan-2-one (**3**, R = H), the acetate (**3**, R = Ac), and the formate (**8**) did not show any evidence for 4σ coupling between the 1α-H and 10β-Me. The epimer (1β-hydroxymethylcolensan-2-one) in which 4σ coupling would be expected to be present could not be prepared as epimerization conditions resulted in colensan-2-one formation by the reverse aldol reaction. However in the closely related epimeric ceanothic acid

derivatives, dimethyldehydroceanothate and dimethylepidehydroceanothate, only the epi-series (the 1β-methoxycarbonyl, i.e. 1α-H) exhibited long range 4σ coupling.[26]

Having established the 1α-hydroxymethyl configuration in the ketol (3, R = H) a *cis* α-fused lactone was inferred. Application of the sector rule[27] to the lactone however was consistent only with a *cis* β-fused lactone thus inferring that epimerisation had occurred at C-1 in the subsequent degradation. This may be discounted since (i) 16-oxo steroids and A-norcholestan-2-one are enolised only with great difficulty (ii) cleavage of the triol under acid or neutral conditions gave the same ketol; (iii) a 17β-hydroxy-16-oxo steroid is the most stable of the four possible isomers and models show that there is only one additional interaction (1βe'-11αH) in the corresponding 1β-substituted 2-oxo A-norditerpenes.

A *cis* α-fused lactone is in agreement with that predicted from the rule developed by Okuda[28] from a study of the ORD of sugar-γ-lactones. He established that the orientation of the hydroxyl on the C-2 atom, i.e. the octant position of the 2-OH group, determined the sign of the Cotton effect. Application of this rule to the lactone predicted a negative Cotton effect as was observed experimentally. The lactone stereochemistry also accounts for the formation of the *cis* 1,2-diol in the lactone hemiacetal (7), the result of α-face attack on reduction of the lactone carbonyl.

EXPERIMENTAL

M.p's were determined on a Kofler hot stage and are corrected. IR spectra were recorded on a Perkin–Elmer Model 421 instrument and UV spectra were obtained on a Shimadzu RS 27 spectrophotometer. ORD are for MeOH solutions. NMR spectra, measured on a Varian-A60 or HA-100 instrument using TMS as an internal standard, are for $CDCl_3$ solns unless otherwise stated. TLC was used routinely for monitoring reactions and chromatographic separations.

Isolation of the lactone. An acetone extract of the heartwood of *Dacrydium colensoi* was taken up in ether, the acids and phenols removed by alkali extraction, and the dacrydol complex precipitated by the addition of hexane. To the ether soluble material (900 g), 10% aq methanolic NaOH (300 ml, 1:4) was added, and the mixture refluxed for 7 hr. After dilution, acidification, and ether extraction (5 × 200 ml), the acids (present in the original extract as acid esters), were removed by extraction into sat Na_2CO_3 aq leaving the lactonic material in the ethereal layer. The lactone extract (12 g) was chromatographed on florisil (200 g) from benzene. Elution with benzene gave fractions from which the lactone (2·4 g) crystallized. After recrystallization from hexane and vacuum sublimation, (165°/0·004 mm) the *lactone* (1) had m.p. 208–209°, $\nu_{max}^{CCl_4}$ 3556 (bonded-OH), 1771 (γ-lactone), 3085, 1645, 1410, 993, 916 (—CH=CH_2), 1140, 1088 cm^{-1} (C—O of oxide ring) λ_{max}^{MeOH} 217 mμ (log ε 2·7); RD (*c*, 0·089 $[\phi]_{300}$ + 580°; $[\phi]_{400}$ + 670°; $[\phi]_{300}$ + 1080°; $[\phi]_{259}$ + 1330°, (flat peak); $[\phi]_{238}$ + 250° (trough); $[\phi]_{205}$ + 13100°!, a_{205}^{238} -ve; NMR Me signals at 1·00, 1·00, 1·10, 1·28, 1·37. (100 Mc) vinyl group as an ABX system H_B 4·88, H_A 5·06, H_X 5·83 (J_{AX} 17·4, J_{AB} 1·5, J_{BX} 10·5 c/s), —CH—CH_2—O— as an ABX system H_B 3·99, H_A 4·21, H_X 2·65 (J_{AB} 9·7, J_{AX} = J_{BX} 9·5 c/s). NMR (benzene) methyl signals at 0·87, 0·87, 0·95, 1·12, 1·20, —CH—CH_2—O— as an ABX system H_A = H_B 3·43, H_X 2·35 $|J_{AX} + J_{BX}|$ 18 c/s); (DMSO) 3·72 δ (OH, 1H singlet). Found: C, 72·8; H, 9·55. $C_{21}H_{32}O_4$ requires: C, 72·4; H, 9·3%); *m/e* 348 (M^+), 333 (base peak), 303, 275, 250.

Dihydrolactone. The lactone (203 mg) in AcOEt (30 ml) was hydrogenated over Adams catalyst. One mole of H_2 was absorbed to give the *dihydrolactone* (200 mg), m.p. 211–212° (after sublimation at 165°/0·004 mm); $\nu_{max}^{CCl_4}$ 3560 (bonded OH), 1770 cm^{-1} (γ-lactone); NMR Me signals at 0·85, triplet (*J* 7·0 c/s), 1·00, 1·00, 1·07, 1·21, 1·33 δ; (Found: C, 72·0; H, 9·9. $C_{21}H_{34}O_4$ requires: C, 72·0; H, 9·8%).

Opening of the Lactone. The dihydrolactone (270 mg) in dry dioxan (50 ml) was added to dioxan containing excess LAH, and the mixture refluxed for 30 hr. Excess LAH was destroyed by the addition of AcOEt. Sat Na_2SO_4 aq (30 ml) was added and the mixture extracted with ether (3 × 30 ml). Evaporation of the solvent gave an oil (250 mg) which was purified by PLC (ether development) and gave the triol, 1α,2α-*dihydroxymethylcolensan-2β-ol* (2, R = H; 120 mg), m.p. 148–149·5° (aq acetone); $\nu_{max}^{CCl_4}$ 3640 (free OH), 3530, 3500 (bonded OH); NMR Me signals at 0·83, triplet (*J* 6·4 c/s), 0·93, 1·18, 1·22, 1·23, 1·33;

CH—CH$_2$—OH and C(OH)—CH$_2$—OH 3·63 δ (broad multiplet). (Found: C, 71·2; H, 10·9. $C_{21}H_{38}O_4$ requires: C, 71·1; H, 10·8%.)

Acetylation of the triol. The triol (214 mg) in Ac_2O-pyridine (1:1, 10 ml) was set aside overnight. Isolation with ether gave the diacetate **2** (R = Ac; 220 mg), m.p. 108·5–109·5° (aq acetone); $\nu_{max}^{CCl_4}$ 3598 (OH·····O—C=O, bonded OH), 1742 (acetate C=O), ν_{max}^{Nujol} 1247, 1234 cm^{-1} (C—O of acetate): NMR Me signals at 0·82, triplet (*J* 7·6 c/s), 0·97, 1·02, 1·20, 1·20, 1·35; CH_3COO 2·05, 2·10; CH—CH$_2$—OAc as ABX system, AB part multiplet 4·18; C(OH)—CH$_2$—OAc as collapsed AB system, singlet 4·28 δ. (Found: C, 68·7; H, 9·5. $C_{25}H_{42}O_6$ requires: C, 68·5; H, 9·65%.)

Cleavage of the triol.

(a) The triol (514 mg) in MeOH (10 ml) was added to a soln of HIO_4 (2 g) in water (10 ml) and the mixture set aside at room temp for 24 hr. Isolation with ether in neutral conditions gave a product (420 mg) which was chromatographed on silica gel from hexane. Elution with hexane–ether (1:3) gave 1α-*hydroxymethylcolensan-2-one* (**3**, R = H; 300 mg), m.p. 97–98° (aq MeOH); $\nu_{max}^{CCl_4}$ 3631 (free OH), 3558 (bonded OH), 1723 cm^{-1} (>C=O); λ_{max} 301 mμ (ε 58); RD (*c*, 0·033) $[\phi]_{500}$ +1330°; $[\phi]_{400}$ +1330°; $[\phi]_{312}$ +9100° (peak); $[\phi]_{274}$ −7620° (trough); $[\phi]_{244}$ −3650°; $[\phi]_{215}$ −3080°; $[\phi]_{204}$ −1330°; a_{274}^{312} + 168; NMR Me signals at 0·82, triplet (*J* 7·0 c/s), 0·85, 0·99, 1·06, 1·21, 1·35, CO—CH—CH$_2$—O as an ABX system, five lines, $H_A = H_B$ 3·78, H_X 2·20 ($\frac{1}{2}|J_{AX} + J_{BX}|$ 7·2 c/s). In benzene CO—CH—CH$_2$—O— as an ABX system, H_B 3·42, H_A 3·69, H_X 2·09 δ ($J_{AX} = J_{BX}$ 6·7, J_{AB} 10·8 c/s). (Found: C, 74·9; H, 10·5. $C_{20}H_{34}O_3$ requires: C, 74·5; H, 10·6%.)

(b) The triol (400 mg, 1·1 mmole) in dry benzene (40 ml) and $PbOAc_4$ (610 mg, 1·4 mmole, 1·2 mol/mol, dried over KOH), was stirred for ½ hr at room temp. The mixture was isolated with ether to give an oil (360 mg) which was adsorbed on florisil from hexane. Elution with hexane–ether (13:7) gave **3** (R = H) identical to that obtained by the periodate cleavage (m.m.p., and IR). The aq layer from the ether extraction of the LTA cleavage reaction was steam distilled into an aq, buffered, dimedone soln (20 ml). The formaldehyde dimedone derivative separated out overnight and had m.p. 192–193° (aq MeOH), undepressed on admixture with authentic formaldehyde dimedone derivative.

1α-*Acetoxymethylcolensan-2-one* (**3**, R = Ac). Compound **3** (R = H; 197 mg) was acetylated with Ac_2O-pyridine (1:1, 10 ml) and gave 1α-*acetoxymethylcolensan-2-one* (**3**, R = Ac; 210 mg), m.p. 63–64° (aq acetone); ν_{max}^{Nujol} 1760 (broad, >C=O of acetate and ketone), 1240 cm^{-1} (C—O of acetate); λ_{max} 304 mμ (ε 44); RD (*c*, 0·050), $[\phi]_{500}$ +1450°; $[\phi]_{400}$ +1610°; $[\phi]_{316}$ +13100° (peak); $[\phi]_{311}$ +1175° (shoulder); $[\phi]_{273}$ −11200° (trough); $[\phi]_{250}$ −6280°; $[\phi]_{222}$ −4580°; $[\phi]_{204}$ −4710°; a_{273}^{316} +243; NMR Me signals at 0·83, triplet (*J* 7·0 c/s), 0·84, 0·99, 1·05, 1·21, 1·35; CH_3COO 2·04; CO—CH—CH$_2$—OAc as ABX system, five lines, $H_A = H_B$ 4·22, H_X 2·33 δ ($\frac{1}{2}|J_{AX} + J_{BX}|$ 7·0 c/s). (Found: C, 72·3; H, 10·2. $C_{22}H_{36}O_4$ requires: C, 72·5; H, 10·0%.)

Retroaldol reaction. Compound **3** (R = H; 112 mg) in MeOH (10 ml, purified to eliminate aldehydes and ketones) was added to KOH (1 g) in water (2 ml). The mixture was heated on a water bath for 10 min and left to stand overnight at room temp. Dilution with water and isolation with ether (2 × 30 ml) gave an oily solid which was chromatographed on neutral alumina from hexane. Elution with hexane–ether (19:1) gave a solid which was purified by PLC (hexane–ether (4:1) development). The lower portion of the major band gave **4** (60 mg), identical in all respects with the dihydro derivative of the naturally occurring colensen-2-one (m.m.p., IR, NMR), $[\alpha]_D^{20}$ +162° (*c*, 0·47); NMR (100 Mc) Me signals at 0·79, doublet (*J* 1·0 c/s), 0·85, triplet (*J* 7·0 c/s), 0·95, 1·01, 1·20, 1·31; CO—CH$_2$— as AB system, H_B 1·96, H_A 2·17 (J_{AB} 15·5 c/s, H_B as doublet, 4 σ coupling, *J* 1·0 c/s); NMR (100 Mc) (CCl_4) 0·77, doublet (*J* 1 c/s), 0·82, triplet (*J* 7·0 c/s), 0·90, 0·96, 1·15, 1·26; CO—CH$_2$ as AB system, H_B 1·84, H_A 2·04 (J_{AB} 15·0 c/s); NMR (100 Mc) (benzene) 0·51, doublet (*J* 1·0 c/s), 0·87, 0·90, 0·96, triplet (*J* 7·0 c/s), 1·11, 1·11; CO—CH$_2$ as AB system, H_B 1·57, H_A 1·96 (J_{AB} 15·0 c/s); NMR (100 Mc) (pyridine) 0·70, broad, 0·91, triplet (*J* 7·0 c/s), 0·94, 1·01, 1·17, 1·25; CO—CH$_2$ as AB system, H_B 1·93, H_A 2·10 δ (J_{AB} 15·0 c/s). The aq layer from the above retroaldol reaction gave, on steam distillation into a dimedone soln, the formaldehyde dimedone derivative, m.p. 191–192°.

1α-*Hydroxymethylcolensan-2-one* (**3**, R = H) *on basic alumina.* The β-ketol (150 mg) was adsorbed on basic alumina (Woelm, grade 1) from hexane for 2 days. Elution with hexane-ether (4:1) gave the methylene-ketone, 1-*methylene-colensan-2-one* (**5**; 50 mg), m.p. 127–129° (aq MeOH); ν_{max}^{Nujol} 1720 (>C=O), 1645, 950 cm^{-1} (cisoid enone); λ_{max} 226 mμ (log ε 3·7); NMR 0·87, triplet (*J* 7·0 c/s), 0·97, 1·03, 1·03, 1·23, 1·37; >C=CH$_2$ 5·23, 5·65 δ. (Found: C, 78·6; H, 10·6. $C_{20}H_{32}O_2$ requires: C, 78·9: H, 10·6%.) The minor product from the retroaldol reaction on the β-ketol proved identical in all respects with the above methylene-ketone (m.mp., IR).

Acetylation of the lactone. The lactone (117 mg) in isopropenyl acetate (20 ml) and *p*-toluenesulphonic acid (90 mg) was allowed to stand at room temp for 20 hr. Solid $NaHCO_3$ was added and the product isolated with ether to give the *lactone acetate*, (125 mg), m.p. 167–168° (from hexane and vacuum sublimation); ν_{max}^{Nujol} 1780 (γ-lactone), 1737, 1240 cm^{-1} (acetate); NMR Me signals at 0·98, 1·07, 1·12, 1·28, 1·33; CH_3COO 2·13; $CH{-}CH_2{-}O$ as an ABX system, H_B 4·01, H_A 4·40, H_X 2·98 δ (J_{AB} 9·8, J_{AX} 10·0, J_{BX} 7·1 c/s). (Found: C, 70·6; H, 8·9. $C_{23}H_{34}O_5$ requires: C, 70·7; H, 8·8%.)

Dihydrolactone methyl ether (**6**). KOH (170 mg) and MeI (5 ml) were added to the dihydrolactone (353 mg) in acetone (7·5 ml), and the mixture refluxed for 6 hr. Dilution with water and ether extraction (3 × 30 ml) gave the *dihydrolactone methyl ether* (**6**; 350 mg), m.p. 110–111° (aq MeOH and vacuum sublimation at 105°/0·005 mm); $\nu_{max}^{CCl_4}$ 1780 (γ-lactone), 1394, 1385, 1372, 1369 cm^{-1} ($-CH_3$); NMR (100 Mc) Me signals at 0·83, triplet (*J* 7·0 c/s), 0·99, 0·99, 1·01, 1·19, 1·31; $-CH{-}CH_2{-}O-$ as an ABX system, H_B 4·03, H_A 4·23, H_X 2·88 (J_{AB} 9·9, J_{AX} 10·4, J_{BX} 8·8 c/s); $-OCH_3$ 3·24 δ. (Found: C, 72·3; H, 10·2; OMe 7·95. $C_{22}H_{36}O_4$ requires: C, 72·5; H, 10·0; OMe (1) 8·5%.)

Lactone hemiacetal (**7**). The lactone **1** (1·0 g) in dry THF (100 ml) was refluxed with excess LAH for 3 hr. The excess hydride was destroyed by the addition of AcOEt. Solid anhyd Na_2SO_4 was added, the reaction mixture diluted with water, and ether extracted (3 × 100 ml) to give a product which was chromatographed on florisil from benzene. Elution with hexane–ether (1:1) gave the *lactone hemiacetal* (**7**; 950 mg), m.p. 159–161° (aq MeOH); $\nu_{max}^{CCl_4}$ 3625 (free OH), 3560 cm^{-1} (bonded OH); NMR Me signals at 0·98, 0·98, 1·08, 1·25, 1·31; $O{-}CH_2{-}CH-$, AB part of ABX system, 3·85, multiplet; $O{-}CH(OH)$ 5·12 δ, singlet. (Found: C, 72·25; H, 9·9. $C_{21}H_{34}O_4$ requires: C, 72·0; H, 9·8%.)

Lactone hemiacetal acetonide. The hemiacetal (**7**; 43 mg) in acetone (12 ml) containing 20% $HClO_4$ (5 drops) was set aside for 24 hr. Neutralization of the acid with solid $NaHCO_3$, and removal of the solvent gave the *lactone hemiacetal acetonide* (40 mg), m.p. 103–104° (aq MeOH and vacuum sublimation at 95°/0·005 mm); ν_{max}^{Nujol} 1253 cm^{-1} (acetonide); NMR Me signals at 0·97, 1·02, 1·03, 1·27, 1·32, 1·37, 1·52; $>CH{-}CH_2{-}O-$ as ABX system, H_{AB} 3·83, H_X 2·29 ($|J_{AX} + J_{BX}|$ 17·5 c/s); $O{-}CH{-}O-$ 5·55 δ singlet. (Found: C, 73·9; H, 10·0. $C_{24}H_{38}O_4$ requires: C, 73·8; H, 9·7%.)

Oxidative cleavage of the lactone hemiacetal (**7**)

(a) The hemiacetal (440 mg) in acetone (50 ml) was oxidized with Jones reagent (0·4 ml) at 0°. The mixture was poured into a 5% K_2CO_3 aq and ether extracted to give an oily product (420 mg) which was chromatographed on florisil (30 g) from hexane. Elution with hexane–ether (3:1) gave the β-ketoformate, 1α-*hydroxymethylcolensen-2-one monoformate* (**8**; 380 mg), b.p. 100°/0·005 mm; ν_{max}^{film} 1730 (>C=O and H—C=O), 1160 cm^{-1} (C—O of formate). (Found: C, 72·4; H, 9·6. $C_{21}H_{32}O_4$ requires: C, 72·4; H, 9·3%.) Purification was attempted by PLC but hydrolysis of the formate group occurred. This was minimised by purification on florisil. Further elution of the column with hexane–ether (1:1) gave the lactone (**1**; 35 mg; m.m.p., IR).

(b) The lactone hemiacetal (100 mg) in dry benzene (30 ml) and acetic acid free $Pb(OAc)_4$ (165 mg, 1·3 mol/mol) was stirred for 5 hr. at room temp. The product (80 mg) was identical to the β-ketoformate from the chromic acid oxidation of the lactone hemiacetal.

Hydrogenation of the β-ketoformate (**8**). The β-ketoformate (100 mg) in AcOEt (30 ml) was hydrogenated over Adams catalyst (1 mol of H_2 absorbed) to give 1α-*hydroxymethylcolensan-2-one monoformate* b.p. 100°/0·005 mm; ν_{max}^{film} 1730 (>C=O and H—C=O), 1160 cm^{-1} (C—O of formate); λ_{max} 303 mμ (ε 59); NMR Me signals at 0·84, triplet (*J* 7·2 c/s), 0·85, 1·00, 1·07, 1·22, 1·35; $CO{-}CH{-}CH_2{-}O-$ as ABX system, five lines, $H_A = H_B$ 4·32, H_X 2·37 ($\frac{1}{2}|J_{AX} + J_{BX}|$ 7·2 c/s); $O{-}CHO$ 8·02, singlet. (Found: C, 71·9; H, 10·0. $C_{21}H_{34}O_4$ requires: C, 72·0; H, 9·8%.)

Hydrolysis of the β-ketoformate (**8**). The β-ketoformate (250 mg) was adsorbed on a column of acid alumina (Merck, grade 1) from hexane. Immediate elution with hexane–ether (17:3) gave a compound which was not characterized but had bands in the IR similar to **5**. Further elution with ether–MeOH (49:1) gave 1α-*hydroxymethylcolensen-2-one* (150 mg), m.p. 86–88° (aq MeOH and fusion at 120°/0·005 mm); $\nu_{max}^{CCl_4}$ 3633 (free OH), 3557 (bonded OH), 1724 cm^{-1} (>C=O); (Found: C, 74·6; H, 10·3. $C_{20}H_{32}O_3$ requires: C, 75·0; H, 10·1%, analytical sample fused at 120°/0·005 mm.) Hydrogenation of 1α-hydroxymethylcolensen-2-one (112 mg) in AcOEt (30 ml) over Adams catalyst (1 mol of H_2 absorbed) gave **3** (R = H; 100 mg), identical in all respects with the β-ketol obtained from the cleavage of **2** (R = H).

LAH reduction of colensan-2-one (**4**). Compound **4**, (985 mg) in dry ether (50 ml) was refluxed with excess LAH for 4 hr. The usual acidic workup (dil H_2SO_4) gave a product which was chromatographed on silica gel (50 g) from hexane. Elution with hexane–ether (19:1) gave unchanged colensan-2-one (60 mg). Further

elution with hexane–ether (17:3) gave *colensan-2β-ol* (**9**; 380 mg), m.p. 96·5–97·5° (aq MeOH and vacuum sublimation at 85°/0·005 mm); $\nu_{max}^{CCl_4}$ 3631 cm^{-1} (free OH); $[\alpha]_D^{20}$ +23° (*c*, 0·50); NMR (100 Mc) Me signals at 0·84, triplet (*J* 7·5 c/s), 0·91, 0·97, 1·03, 1·19, 1·27; >CH(OH) as X part of ABX system, 4·02 δ, multiplet, ($|J_{AX} + J_{BX}|$ 9·1 c/s). (Found: C, 77·7; H, 11·8. $C_{19}H_{34}O_2$ requires: C, 77·5; H, 11·6%.) Further elution of the column with hexane–ether (17:3) gave a mixture of colensan-2β-ol and colensan-2α-ol, richer in the latter. PLC of this fraction (hexane–ether (2:3) development) gave *colensan-2α-ol* (**10**; 250 mg), m.p. 116–117° (aq MeOH and vacuum sublimation at 90°/0·003 mm); $\nu_{max}^{CCl_4}$ 3622, 3625 cm^{-1} (free OH); $[\alpha]_D^{20}$ −5·1° (*c*, 0·49); NMR (100 Mc) Me signals at 0·76, 0·83, triplet (*J* 7·0 c/s), 0·90, 0·90, 1·17, 1·25; —CH(OH)—CH_2— as AMX system, H_M 2·12. H_X 4·09 δ (J_{AM} 11·4, J_{AX} 8·9, J_{MX} 6·8 c/s). (Found: C, 77·3; H, 11·45. $C_{19}H_{34}O_2$ requires: C, 77·5; H, 11·6%.)

LAH reduction of the β-ketol (**3**, R = H). The β-ketol (125 mg) in dry ether (30 ml) was refluxed with excess LAH for 6 hr. After the addition of AcOEt and sat Na_2SO_4 aq, the usual workup gave a crystalline product (100 mg) which was purified by PLC (ether development). The band of higher R_f gave the *cis*-1,3-diol, *1α-hydroxymethylcolensan-2α-ol* (**12**; 38 mg), m.p. 174–176° (aq MeOH and vacuum sublimation at 145°/0·002 mm); $\nu_{max}^{CCl_4}$ (0·005M) 3635 (free OH), 3558 cm^{-1} (bonded OH); NMR (100 Mc) Me signals at 0·82, 0·83, triplet (*J* 7·0 c/s), 0·92, 0·99, 1·20, 1·30; —CH—CH_2—OH 3·77, multiplet; >CH(OH) 4·38 δ doublet (*J* 7 c/s). (Found: C, 74·1; H, 11·25. $C_{20}H_{36}O_3$ requires: C, 74·0; H, 11·2%.) The band of lower R_f from the chromatoplate gave the *trans*-1,3-diol, *1α-hydroxymethylcolensan-2β-ol* (**11**; 55 mg), m.p. 179–180° (aq MeOH and vacuum sublimation at 145°/0·002 mm); $\nu_{max}^{CCl_4}$ (0·01M) 3630 cm^{-1} (free OH); NMR (100 Mc) ($CDCl_3$ + D_2O) Me signals at 0·81, triplet (*J* 7·5 c/s), 0·89, 0·97, 1·05, 1·18, 1·28; >CH—CH_2—OH as AB part of an ABX system, H_B 3·40, H_A 3·80 (J_{AB} 9·9, J_{AX} 4·3, J_{BX} 10·2 c/s); >CH(OH) 4·06, singlet ($W_{\frac{1}{2}}$ 2·0 c/s); NMR (100 Mc) (pyridine + D_2O) Me signals at 0·88, triplet (*J* 7·0 c/s), 1·13, 1·17, 1·17, 1·23, 1·32; —CH—CH_2—OH as ABX system H_B 3·68, H_A 4·03, H_X 2·22 (J_{AB} 10·5, J_{AX} 4·7, J_{BX} 10·4, $J_{1\beta,2\beta}$ 0 c/s); >CH—CH(OH) 4·56 δ, singlet ($W_{\frac{1}{2}}$ 2·0 c/s). (Found: C, 74·25; H, 11·3. $C_{20}H_{36}O_3$ requires: C, 74·0; H, 11·2%.)

2β-Hydroxymethylcolensan-2α-ol (**13**). Triphenylmethyl phosphonium bromide (4·5 g, 12·5 mmoles; from triphenylphosphine and MeBr) in dry ether (60 ml) was treated with a soln of t-BuOK in t-BuOH (13 ml, 1·0 N) to form the corresponding methylene triphenylphosphorane. To allow complete formation of the free phosphorane, the soln was stirred for 1 hr under N_2. Colensan-2-one (**4**; 850 mg; 2·91 mmoles) in hexane (30 ml) was added to the yellow phosphorane soln and stirred for 24 hr at room temp under N_2, and then refluxed for 3 hr. A further quantity of the phosphorane was generated *in situ* by adding triphenylmethylphosphonium bromide (2·7 g, 7·5 mmoles) and t-BuOK in t-BuOH (8 ml, 1·0 N), and the reaction continued at room temp for a further 20 hr. The reaction mixture was diluted with water and extracted with hexane. Removal of the solvent gave a solid which was chromatographed on alumina from hexane. Elution with hexane–ether (49:1) gave *2-methylene-colensan* (270 mg), m.p. 66·5–67·5° (aq MeOH); ν_{max}^{Nujol} 3068, 1646, 881 cm^{-1} (>C=CH_2); NMR (100 Mc) (CCl_4) Me signals at 0·69, 0·80, triplet (*J* 7·0 c/s); 0·90, 0·99, 1·12, 1·19; >C=CH_2 4·75, 4·82 δ. (Found: C, 82·35, H, 11·7. $C_{20}H_{34}O$ requires: C, 82·7; H, 11·8%.) Further elution of the column with hexane–ether (9:1) gave unchanged **4** (546 mg), identified by m.m.p. and IR. OsO_4 (0·3 g) was added to 2-methylene-colensan (262 mg) in dry pyridine (15 ml) and the soln stirred for 24 hr at room temp. The osmate ester was cleaved by saturating the soln with H_2S. The black ppt was filtered off and washed well with several portions of $CHCl_3$. The filtrate, on evaporation, gave a brown oil which was filtered down alumina with wet ether. The oil in dry THF (30 ml) was refluxed with excess LAH for 3 hr to complete cleavage of the osmate ester. Workup in the usual manner gave a product which was purified by PLC (hexane–ether (1:4) development) to give *2β-hydroxymethylcolensan-2α-ol* (**13**; 160 mg), m.p. 50–52° (aq MeOH, depressed on admixture with 2α-hydroxymethyl-colensan-2β-ol lit.[3] m.p. 74–75°); $\nu_{max}^{CCl_4}$ 3644 (free OH), 3578 cm^{-1} (bonded OH); NMR (100 Mc) Me signals at 0·80, 0·83, triplet (*J* 7·0 c/s), 0·94, 1·02, 1·17, 1·24; —CH_2OH as AB system, H_B 3·50, H_A 3·71 δ (J_{AB} 11·0 c/s). (Found: C, 73·8; H, 11·3. $C_{20}H_{36}O_3$ requires: C, 74·0; H, 11·2%; analytical sample fused at 120°/0·035 mm.)

Cleavage of the diol (**13**). The diol (25 mg) in MeOH (5 ml) was added to HIO_4 (100 mg) in water (1 ml) and the soln left at room temp overnight. Dilution and ether extraction gave **4** m.p. 106–107° (aq MeOH; lit.[3] 105–106°) identified by m.m.p. and IR.

Acknowledgements—We gratefully acknowledge aid from the Research Committee of the N.Z. University Grants Committee, including a Research Fellowship (to M.J.A.M.) ORD were kindly measured by Professor W. Klyne.

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