Calciferol and its Relatives. Part XIV.[1] Total Synthesis of Des-AB-cholestane-8β,9α-diol [2] {1β-[(1*R*)-1,5-Dimethylhexyl]-7aβ-methyl-*trans*-perhydroindane-4β,5α-diol}

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In a new route to 1-substituted *trans*-3a,6,7,7a-tetrahydro-7a-methylindan-2-ones, a 1-monoester of 4-methylcyclohex-3-ene-1,*trans*-2-diol is subjected to two successive Claisen-type rearrangements to give, in a stereospecific manner, derivatives of 1-methylcyclohex-3-ene-1,*trans*-2-diacetic acid, which are then cyclised. Applied to the 1-benzoate (16) † and methyl orthodihydrocitronellate (17), the method provides a direct synthesis of the 1,5-dimethylhexylindanone (20), and thence of the title diol (22), required for use in the total synthesis of tachysterol$_3$ and precalciferol$_3$.

For work on the total synthesis of tachysterol$_3$ [3] and precalciferol$_3$ [4] we required certain des-AB-cholestane derivatives, functionalised at position 8, or 9, or both. Interconversion experiments [5] showed that they could all be obtained relatively simply from des-AB-cholest-8-ene,[6] or from the 8β,9α-diol (22) †[6] which is formed from it by *trans*-hydroxylation. These last two compounds therefore appeared as natural alternative objectives of total synthesis. Des-AB-cholest-8-ene can be prepared by the pyrolysis of the benzoate of des-AB-cholestan-8β-ol (3), an alcohol already obtained by formal total synthesis. In that synthesis, Hagemann's ester *rac*-(1) † was first converted [7] into the (+)-hydroxy-ketone (2) which, being available also from degradative work, was then used as a relay compound. By addition to its carbonyl group, the iso-octyl side-chain was built up [8] stepwise to give the 8β-ol (3) in low (*ca.* 0·001% overall) yield. By virtue of this work, all our des-AB-cholestane derivatives could, in a formal sense, be regarded as products of total synthesis. However, in the interests of a more efficient start to the synthesis of precalciferol$_3$, further work seemed warranted, and we have now devised a relatively direct and stereoselective synthesis of des-AB-cholestane-8β,9α-diol (22).

The 16-ketone (20), which contains four asymmetric centres, was a key intermediate in our plans. Its double bond provides for the future functionalisation of positions 8 and 9; its keto-group, which should be formed by the cyclisation of a derivative (19) of 1-methylcyclohex-3-ene-1,*trans*-2-diacetic acid, would allow the configuration at position 17 to be adjusted; the available evidence [9] suggested that the required 17β-configuration would be the more stable of those possible.

Our intended route to the diacetic acid (19) was the result of a decision to have the important (20*R*)- or 20β-configuration [10] pre-established in the starting materials, and to maintain it throughout the synthesis. We noted that the readily available (*R*)-dihydrocitronellic acid [*cf.* its orthoester (17)] contains configurational and structural features corresponding to those of the iso-octyl side chain, together with C-17 and C-16 of the ketone (20). In order to attach the α-carbon atom of the dihydrocitronellic acid fragment to a derivative of methylcyclohexane representing ring C and its attached methyl group, and so generate the C(13)–C(17) link, we proposed to use a variant of the Claisen rearrangement. Eschenmoser [11] showed that addition of cyclohex-2-en-1-ols to 1-dimethylamino-1-methoxyethylene, and subsequent loss of methanol, gives *NO*-acetals which rearrange by a cyclic transition state, with shift of the double bond towards the site of the hydroxy-group, and transfer of the group $CH_2{\cdot}CO{\cdot}NMe_2$ to the former terminus of the allylic system. Its mechanism makes the transfer stereospecific. We expected that this reaction could be extended to the transfer of groups of the form $CHR{\cdot}CO{\cdot}NMe_2$ capable of providing, after hydrolysis, groups $CHR{\cdot}CO_2H$. We further expected that by using at the outset a protected 4-methylcyclohex-3-ene-1,*trans*-2-diol (10), two such transfers would, with minor intermediate manipulation, be possible in succession, allowing the introduction, first of a group $CHR{\cdot}CO_2H$ ($R = C_8H_{17}$), and next of the group $CH_2{\cdot}CO_2H$, thus leading to the desired 1-methylcyclohex-3-ene-1,*trans*-2-diacetic acid derivative (19). These ideas were first tested in model experiments.

At that time, Eschenmoser's method had been used only for the transfer of the group $CH_2{\cdot}CO{\cdot}NMe_2$, although in the meantime Sucrow [12] has reported the transfer of $CHMe{\cdot}CO{\cdot}NMe_2$ groups in acyclic allylic systems. We found that the reaction of cyclohex-1-enylmethanol (4)

† Structures in this paper represent absolute configurations. Racemates are denoted by the prefix *rac*. For des-AB-cholestane derivatives steroid numbering is used.

[1] Part XIII, I. J. Bolton, R. G. Harrison, B. Lythgoe, and R. S. Manwaring, preceding paper.

[2] Preliminary reports, *Chem. Comm.*, 1970, 1512, 1513.

[3] R. S. Davidson, S. M. Waddington-Feather, D. H. Williams, and B. Lythgoe, *J. Chem. Soc.* (*C*), 1967, 2534.

[4] J. Dixon, P. S. Littlewood, B. Lythgoe, and A. K. Saksena, *Chem. Comm.*, 1970, 993.

[5] P. S. Littlewood, B. Lythgoe, and A. K. Saksena, following paper.

[6] First prepared in work with D. H. Williams, Ph.D. Thesis, Leeds, 1961.

[7] H. H. Inhoffen, S. Schütz, P. Rossberg, O. Berges, K.-H. Nordsiek, H. Plenio, and E. Höroldt, *Chem. Ber.*, 1958, **91**, 2626.

[8] H. H. Inhoffen, H. Burkhardt, and G. Quinkert, *Chem. Ber.*, 1959, **92**, 1564; H. H. Inhoffen, G. Friedrich, D. Kampe, and O. Berges, *ibid.*, p. 1772.

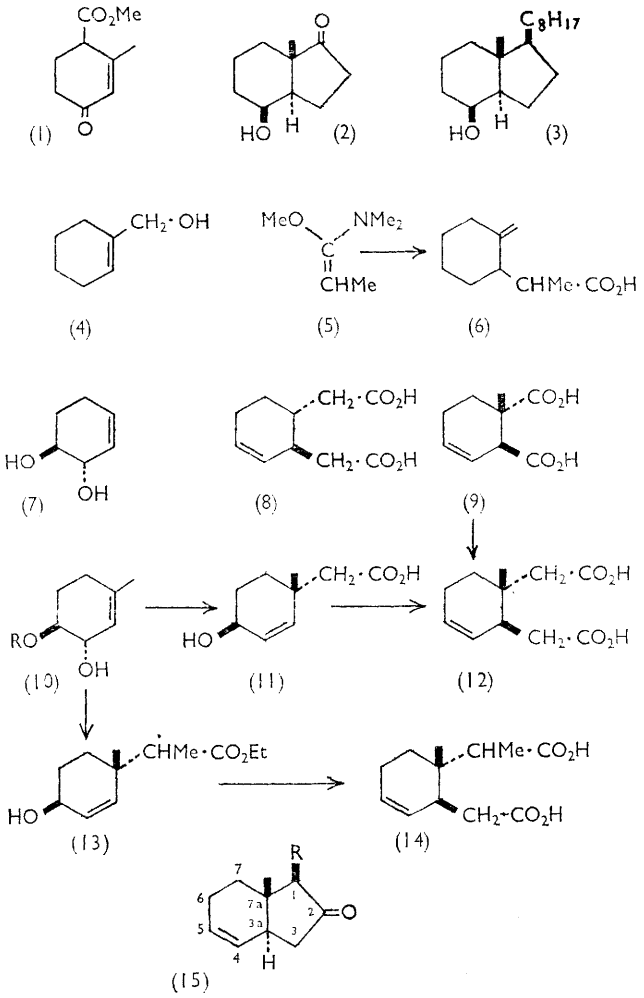
[9] *E.g.*, A. Butenandt and G. Fleischer, *Ber.*, 1937, **70**, 96.

[10] For nomenclature, see L. F. Fieser and M. Fieser, 'Steroids,' Reinhold, New York, 1959, p. 338.

[11] A. E. Wick, D. Felix, K. Steen, and A. Eschenmoser, *Helv. Chim. Acta*, 1964, **47**, 2425.

[12] W. Sucrow, *Angew. Chem.*, 1968, **80**, 626.

with 1-dimethylamino-1-methoxypropene (5) gave a dimethylamide which, after vigorous hydrolysis with alkali, provided the α-methylacetic acid derivative *rac*-(6). In spite of this encouraging initial result, we did not find this extension of Eschenmoser's method to be the most satisfactory way of achieving our purpose.



The amides which resulted from its use in our systems were highly resistant to alkaline hydrolysis, and poor yields of the required acids were sometimes obtained from them. Instead, we found it preferable to use, for the formation of derivatives of acids of the type $CHR{\cdot}CO_2H$ (where $R \neq H$), an extension of W. S. Johnson's ethyl orthoacetate method;[13] for example, the use of ethyl orthopropionate permits the Claisen transfer of the group $CHMe{\cdot}CO_2Et$. Interestingly, ethyl orthoacetate itself gave less satisfactory results in some of our systems than those obtained by using Eschenmoser's reagent (1-dimethylamino-1-methoxyethylene), and carrying out an alkaline hydrolysis of the resulting dimethylamide; and for the preparation of compounds containing the group $CH_2{\cdot}CO_2H$ we prefer this method.

The use of a protected cyclohex-3-ene-1,*trans*-2-diol was first tested with the parent compound *rac*-(7).[14] From a mixture of its 1-benzoate and the 2-isomer we obtained, as described in the Experimental section, cyclohex-3-ene-1,*trans*-2-diacetic acid *rac*-(8), which was identified by hydrogenation to the known[15] saturated acid. The work described in Part XIII [1] was then put in hand; it provided the racemic 1-mesitoate *rac*-(10; $R = C_6H_2Me_3{\cdot}CO$) as the first homogeneous 1-monoester of 4-methylcyclohex-3-ene-1,*trans*-2-diol, and it was with this and its optically active counterpart that our preliminary experiments [2] were carried out.

Reaction of the racemic 1-mesitoate with 1-dimethylamino-1-methoxyethylene, followed by vigorous alkaline hydrolysis, gave the racemic hydroxy-acid *rac*-(11). Its methyl ester, subjected to the same two reactions, gave 1-methylcyclohex-3-ene-1,*trans*-2-diacetic acid *rac*-(12). For identification purposes this acid was also prepared from 1-methylcyclohex-3-ene-1,*trans*-2-dicarboxylic acid [1] *rac*-(9). The acid *rac*-(9) was reduced to the bis-primary diol with lithium aluminium hydride, and then bis-homologated by way of the ditosylate and dinitrile. The double bond in compounds of the type (15) occupies an energy-rich position, and it was thought that this might result in poor yields when they are formed by cyclisation. However, cyclisation of the dimethyl ester of the acid *rac*-(12) in dimethyl sulphoxide with sodium hydride gave a β-keto-ester which, after hydrolysis and decarboxylation with toluene-*p*-sulphonic acid in hot acetic acid, gave the ketone *rac*-(15; R = H) in good yield. It was identified by hydrogenation to *trans*-perhydro-3a-methylindan-2-one.[16]

The application of the reaction sequence to the preparation of a representative 1-alkyl derivative, *viz.*, *rac*-(15; R = Me), was then tested. Our preliminary report [2] described a preparation of this compound from a mixture of the 1-acetate and the 2-acetate of the diol *rac*-(10; R = H). It is, however, more convenient to start from an isolated 1-monoester; and since the use of the 1-mesitoate necessitates drastic conditions at the first hydrolysis stage, we recommend the use of the 1-benzoate *rac*-(10; R = Bz), which is now [1] available. Reaction of this ester with ethyl orthopropionate gave a product which, after mild treatment with ethanolic potassium hydroxide, gave the hydroxy-ester *rac*-(13); its ester group is somewhat resistant to hydrolysis. Reaction with 1-dimethylamino-1-methoxyethylene, followed by vigorous alkaline hydrolysis, gave the dibasic acid *rac*-(14). Cyclisation of the dimethyl esters as already described gave initially a mixture of two ketonic compounds in the ratio *ca.* 1 : 1 (g.l.c.). Further heating with toluene-*p*-sulphonic acid in acetic acid converted most of one of the components into the other

[13] W. S. Johnson, L. Werthemann, W. R. Bartlett, T. J. Brocksom, T. Li, D. J. Faulkner, and M. R. Petersen, *J. Amer. Chem. Soc.*, 1970, **92**, 741.

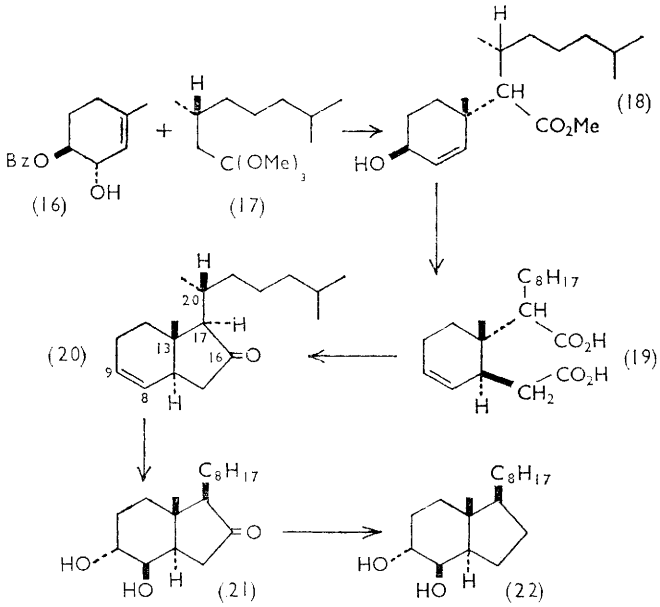
[14] T. Posternak and H. Friedli, *Helv. Chim. Acta*, 1953, **36**, 251.

[15] M. E. Ali and L. N. Owen, *J. Chem. Soc.*, 1958, 2111.

[16] D. C. Hibbitt and R. P. Linstead, *J. Chem. Soc.*, 1936, 470; R. L. Kronenthal and E. I. Becker, *J. Amer. Chem. Soc.*, 1957, **79**, 1095.

component, giving a mixture (*ca.* 7 : 1 by g.l.c.) from which the major component was isolated as the crystalline semicarbazone. From this evidence the major component is regarded as the 1β-isomer *rac*-(15; R = Me), and the minor component as the 1α-isomer.

These model reactions adumbrate a general stereospecific route to tetrahydroindan-2-ones. Obvious modifications should permit the preparation, for example, of *trans*- or *cis*-3a,4,5,7a-tetrahydro-3a-methylindan-2-ones with substituents at position 1, and (from 3-methylcyclohex-3-ene-1,2-diols), *trans*- or *cis*-3a,6,7,7a-tetrahydro-3a-methylindan-2-ones. Indeed, by the use of other cycloalk-3-ene-1,2-diols, the route could well be adapted to a general synthesis of compounds containing two vicinally fused rings.



For the synthesis of the ketone (20), the optically active benzoate (16) [1] was used as a starting material. To prepare the second component, citronellonitrile M [17] was hydrogenated to give the dihydro-compound, which was converted by way of its imino-ether into the methyl orthoester (17). Reaction of the two starting materials gave, after mild alkaline hydrolysis, the hydroxy-esters (18). Treatment with 1-dimethylamino-1-methoxyethylene, followed by vigorous alkaline hydrolysis, gave the dibasic acids (19). Cyclisation of the dimethyl esters afforded a mixture (*ca.* 6 : 1 by g.l.c.) of two ketones, which were separated by chromatography. The major component (20) crystallised, and was also characterised as the semicarbazone. By treatment of the minor component (the 17α-epimer) with toluene-*p*-sulphonic acid in acetic acid, more of the 17β-epimer was obtained, so that over 90% of the product of cyclisation was obtained as the desired ketone (20). This ketone was so obtained from the starting benzoate (16) in three synthetic steps in a yield of *ca.* 30%, with the absolute configurations at positions 13, 14, and 20 predetermined by those of the starting materials, and with that at position 17 established with a high degree of selectivity.

Huang-Minlon reduction of the ketone (20) proved unsatisfactory, so instead it was converted, by way of the crystalline 8α,9α-epoxide, into the 8β,9α-diol (21). The corresponding diacetate reacted with ethanedithiol in the presence of boron trifluoride–ether complex to give the corresponding ethylene thioacetal. Desulphurisation with Raney nickel, followed by deacetylation, gave the crystalline *trans*-diol (22), identical with material obtained by *trans*-hydroxylation [5] from des-AB-cholest-8-ene. The yield of the synthetic 8β,9α-diol (22) was *ca.* 18% overall from the yield-limiting starting material (16).

The transformation of the diol (22) into intermediates for the synthesis of tachysterol$_3$ and precalciferol$_3$ is described in a later paper.[5]

EXPERIMENTAL

Unless otherwise specified, light petroleum means the fraction b.p. 40—60°. N.m.r. data relate to solutions in deuteriochloroform.

Reaction of 1-*Dimethylamino*-1-*methoxyethylene* (5) *with Cyclohex*-1-*enylmethanol* (4).—The hydroxymethyl compound (1 g.) and 1-dimethylamino-1-methoxyethylene [11] (1·5 g.) were heated together under reflux in dry xylene (10 c.c.) for 16 hr., with continuous removal of methanol. Distillation at 90—95°/1·5 mm. gave the dimethylamide of the acid (6) (1·45 g.), $\nu_{max.}$ (film) 1735s, 1650m, and 900m cm.$^{-1}$; it was homogeneous on g.l.c. Hydrolysis in ethanol (5 c.c.) and water (15 c.c.) with sodium hydroxide (4 g.) under reflux for 16 hr., and isolation with ether, gave 2-(2-*methylenecyclohexyl*)*propionic acid rac*-(6) (1·2 g.), b.p. 113—115°/0·8 mm., τ 5·33 (=CH_2) and 8·80 (d, *J* 7 Hz, CH*Me*) (Found: C, 71·7; H, 9·35. $C_{10}H_{16}O_2$ requires C, 71·4; H, 9·6%). The p-*bromophenacyl ester* formed needles, m.p. 70—71° (from ethanol) (Found: C, 59·05; H, 5·8. $C_{18}H_{21}BrO_3$ requires C, 59·2; H, 5·75%).

Cyclohex-3-*ene*-1,trans-2-*diacetic Acid* rac-(8).—The *trans*-diol *rac*-(7) (3·0 g.) and benzoyl chloride (3·7 g.) were stirred together at 0° in pyridine (30 c.c.) for 1 hr., and then at 20° for 16 hr. The product, isolated in the usual way, was chromatographed on silica gel (400 g.), from which benzene eluted a fraction (1·05 g.) which crystallised from ether–light petroleum giving the *dibenzoate* of the diol *rac*-(7) (0·98 g.), m.p. 76·5—77°, $\nu_{max.}$ 1720 cm.$^{-1}$ (Found: C, 74·55; H, 5·55. $C_{20}H_{18}O_4$ requires C, 74·5; H, 5·6%). Elution with 5% ether–benzene gave a fraction (3·9 g.) which crystallised from ether–light petroleum to give the 2-*monobenzoate* (3·2 g.) of the diol *rac*-(7), m.p. 84—85°, $\nu_{max.}$ (Nujol) 3530, 1720, and 715 cm.$^{-1}$ (Found: C, 71·3; H, 6·3. $C_{13}H_{14}O_3$ requires C, 71·5; H, 6·5%). The oily keto-benzoate obtained from it by oxidation with chromic oxide and sulphuric acid in acetone had $\nu_{max.}$ (film) 1720 cm.$^{-1}$. The mother liquor material (690 mg.) from the monobenzoate fraction contained (n.m.r.) some of the 2-monobenzoate, and also much of the 1-monobenzoate, which, unlike its isomer, had τ 4·90 (m, >C*H*·OBz). A portion (500 mg.) of the mixture and 1-dimethylamino-1-methoxyethylene (600 mg.) were heated together under

[17] C. Herschmann, *Helv. Chim. Acta*, 1949, **32**, 2537.

reflux in xylene (10 c.c.) for 16 hr. Solvents were then removed under reduced pressure, and the residue was chromatographed on silica gel (40 g.); elution with 1% ether–benzene gave an oily benzoyloxy-amide (315 mg.), $\nu_{max.}$ (film) 1720, 1655, and 710 cm.$^{-1}$. It was stirred at 20° for 16 hr. with ethanol (1 c.c.) and aqueous 2N-sodium hydroxide (10 c.c.); isolation with ether then gave a hydroxy-amide as an oil (175 mg.), $\nu_{max.}$ (film) 3500 and 1650 cm.$^{-1}$. Reaction as before with 1-dimethylamino-1-methoxyethylene gave an oily diamide (188 mg.), $\nu_{max.}$ (film) 1655 cm.$^{-1}$. Hydrolysis with aqueous ethanolic potassium hydroxide in the usual way gave *cyclohex*-3-*ene*-1,trans-2-*diacetic acid* (140 mg.), which separated from ether–light petroleum as crystals, m.p. 120—121° (Found: C, 60·8; H, 7·15. $C_{10}H_{14}O_4$ requires C, 60·6; H, 7·1%).

Hydrogenation with 5% palladised charcoal gave cyclohexane-1,*trans*-2-diacetic acid, m.p. 166—167° (from acetone–water) (lit.,[15] 167°).

1-*Methylcyclohex*-3-*ene*-1,trans-2-*diacetic Acid* rac-(12).—(*a*) The 1-mesitoate *rac*-(10; R = CO·$C_6H_2Me_3$) (0·65 g.) and 1-dimethylamino-1-methoxyethylene (0·75 g.) were heated together under reflux in dry xylene (12 c.c.) under nitrogen for 16 hr. Removal of the solvents gave an oil which was heated under reflux in ethylene glycol (15 c.c.) and water (6 c.c.) with potassium hydroxide (6 g.) for 48 hr. After dilution with water the solution was freed from neutral material by extraction with ether; acidification and extraction with benzene then removed mesitoic acid. Continuous extraction with ether gave the crude hydroxy-acid *rac*-(11), which was converted into the *methyl ester* with diazomethane, and purified by preparative t.l.c. (Kieselgel G; 20% ethyl acetate–benzene); this gave an oily product (0·26 g.) (96% pure by g.l.c.), $\nu_{max.}$ (film) 3500 and 1730 cm.$^{-1}$, τ 4·38 (–C*H*=C*H*–), 6·37 (OMe), and 8·87 (CMe) (Found: M^+, 184·1091. $C_{10}H_{16}O_3$ requires M, 184·1099). The *hydroxy-acid rac*-(11) formed crystals (from ether–light petroleum), m.p. 91—92° (Found: C, 63·75; H, 8·0. $C_9H_{14}O_3$ requires C, 63·5; H, 8·3%).

The foregoing methyl ester (200 mg.) was treated as before with 1-dimethylamino-1-methoxyethylene to give a crude dimethylamide (220 mg.). This was heated under reflux with potassium hydroxide (2·5 g.) in ethanol (2 c.c.) and water (5 c.c.) for 20 hr. The acidic product, isolated in the usual way, crystallised from ether–light petroleum as needles (164 mg.), m.p. 169—171°, of 1-methylcyclohex-3-ene-1,*trans*-2-diacetic acid, identical with material prepared as described in (*b*).

(*b*) *From* 1-*methylcyclohex*-3-*ene*-1,trans-2-*dicarboxylic acid*. The acid *rac*-(9) (1 g.) in ether (50 c.c.) was added slowly to lithium aluminium hydride (350 mg.) in ether (50 c.c.) at 20° with stirring, which was continued for 16 hr.; the excess of hydride was then decomposed with ethyl acetate, and the product was isolated in the usual way. It formed an oil (788 mg.), $\nu_{max.}$ 3400s and 1655w cm.$^{-1}$, which was converted into the oily di(toluene-*p*-sulphonate) (2·22 g.) in the usual way. This compound was stirred with sodium cyanide (1·0 g.) in dimethyl sulphoxide (25 c.c.) at 90° for 20 hr. The solution was diluted with water and extracted with ether; the washed (brine) and dried extract was evaporated to give an oily dinitrile (605 mg.), $\nu_{max.}$ 2265 cm.$^{-1}$, τ 4·25 (–C*H*=C*H*–) and 8·92 (CMe). The dinitrile was heated under reflux for 40 hr. with potassium hydroxide (2·5 g.) in ethylene glycol (9 c.c.) and water (1 c.c.). The acidic product, isolated in the usual way, crystallised from ether–light petroleum to give 1-*methylcyclohex*-3-*ene*-1,trans-2-*diacetic acid* *rac*-(12) (595 mg.), m.p. 171—172° (Found: C, 62·5; H, 7·6. $C_{11}H_{16}O_4$ requires C, 62·25; H, 7·6%).

Hydrogenation gave 1-methylcyclohexane-1,*trans*-2-diacetic acid, m.p. and mixed m.p. 198—199·5° (lit.,[18] 198—199°).

trans-3a,4,5,7a-*Tetrahydro*-3a-*methylindan*-2-*one* rac-(15; R = H).—The acid *rac*-(12) (425 mg.) was converted (diazomethane) into its dimethyl ester, which was stirred under dry nitrogen at 95° for 2 hr. with sodium hydride (100 mg.) in dry dimethyl sulphoxide. Water was then added to the cooled solution, and the oily β-keto-ester (305 mg.) was isolated with ether; it had $\nu_{max.}$ (film) 1756s and 1728s cm.$^{-1}$. It was heated under reflux for 1 hr. with toluene-*p*-sulphonic acid (1 g.) in acetic acid (10 c.c.) and water (1 c.c.); the solvent was then removed under reduced pressure, and the neutral product was isolated with ether. The crude oily ketone *rac*-(15; R = H) (185 mg.) had $\nu_{max.}$ 1743 cm.$^{-1}$. A portion (100 mg.) was converted into the 2,4-*dinitrophenylhydrazone* (167 mg.), which formed needles (from ethanol), m.p. 156—157° (Found: C, 57·95; H, 5·55; N, 16·95. $C_{16}H_{18}N_4O_4$ requires C, 58·2; H, 5·5; N, 17·0%).

Hydrogenation of the ketone *rac*-(15; R = H) gave 3a-methyl-*trans*-perhydroindan-2-one, characterised as the 2,4-*dinitrophenylhydrazone*, m.p. 140—142° (Found: C, 57·6; H, 5·85; N, 16·8. $C_{16}H_{20}N_4O_4$ required C, 57·8; H, 6·1; N, 16·9%), identified by comparison with a specimen prepared from *trans*-3a,4,7,7a-tetrahydro-3a-methylindan-2-one by hydrogenation and reaction with 2,4-dinitrophenylhydrazine.

trans-3a,6,7,7a-*Tetrahydro*-1,7a-*dimethylindan*-2-*one* rac-(15; R = Me).—The benzoate *rac*-(10; R = Bz) (1·95 g.) and ethyl orthopropionate (5 g.) were refluxed in dry xylene (30 c.c.) with propionic acid (10 mg.) for 20 hr. Removal of the solvent and excess of reagent under reduced pressure gave an oil, which was kept for 20 hr. at 20° with ethanol (20 c.c.) and aqueous 2N-sodium hydroxide (30 c.c.). Dilution with water and extraction with ether gave the hydroxy-esters *rac*-(13) (1·65 g.) as an oil, $\nu_{max.}$ 3470s, 1724s, and 1065s cm.$^{-1}$, τ 8·93 (s, >CMe) (Found: M^+, 212·1407. Calc. for $C_{12}H_{22}O_3$: M, 212·1412). G.l.c. showed the presence of two closely related compounds (*ca.* 4 : 1).

The hydroxy-esters (1·6 g.) and 1-dimethylamino-1-methoxyethylene (2·4 g.) were heated together under reflux under dry nitrogen in xylene (30 c.c.) for 20 hr.; solvent and excess of reagent were then removed under reduced pressure. The product was heated under reflux for 20 hr. with potassium hydroxide (15 g.) in ethanol (10 c.c.) and water (15 c.c.); the acidic product was then isolated in the usual way. The dimethyl esters, prepared with diazomethane, were chromatographed on neutral alumina (grade III), from which benzene eluted an oil (1·63 g.), $\nu_{max.}$ 1740 and 1170 cm.$^{-1}$, containing two closely related products (*ca.* 73 : 27 by g.l.c.) (Found: M^+, 254·1523. Calc. for $C_{14}H_{22}O_4$: M, 254·1518), τ 6·33 and 6·35 (OMe), 8·9 (d, J 7 Hz, >CH*Me*), and 9·16 (s, >CMe).

Sodium hydride (300 mg.) in dry dimethyl sulphoxide (15 c.c.) was added during 30 min. to a stirred solution of the foregoing esters (1·6 g.) in dimethyl sulphoxide (15 c.c.) at 90° under dry nitrogen. After 2 hr. at 90° the solution was cooled (0°) and diluted with water, and the product was isolated with ether. It was heated under reflux (nitrogen)

[18] A. S. Dreiding and A. J. Tomasewski, *J. Org. Chem.*, 1954, **19**, 241.

with acetic acid (25 c.c.), water (5 c.c.), and toluene-*p*-sulphonic acid (2·5 g.). Hydrolysis and decarboxylation were complete after 2 hr., and examination of a sample by g.l.c. (5% Carbowax at 90°) showed the presence of two components in the ratio 50 : 50 (retention times 15·5 and 14·5 min.). After 4 hr. the corresponding ratio was 75 : 25, and after 12 hr. and 20 hr., 88 : 12. After 20 hr. the solution was cooled and diluted with water, and the product, isolated with ether, and dissolved in pentane, was passed through a column of neutral alumina (grade III; 30 g.). Evaporation gave the mixed epimeric ketones as an oil (712 mg.), $\nu_{max.}$ 1730 cm.$^{-1}$, τ 4·31 (–C*H*=C*H*–), 8·8 (d, *J* 7 Hz, >CH*Me*), and 9·16 (s, >CMe). The isomer ratio (g.l.c.) was *ca.* 7 : 1. The *semicarbazone* of the major isomer *rac*-(15; R = Me) was prepared from the mixture (40 mg.); it formed crystals (41 mg.) (from aqueous ethanol), m.p. 192—193° (Found: C, 65·25; H, 8·6; N, 18·6. $C_{12}H_{19}N_3O$ requires C, 65·1; H, 8·65; N, 19·0%).

Methyl Orthodihydrocitronellate (17).—Citronellonitrile M (24·7 g.) was hydrogenated in ethanol (500 c.c.) with 5% palladised charcoal (2·12 g.) to give the *dihydro-compound* (23·2 g.), b.p. 120—122°/35 mm., $[\alpha]_D^{23}$ –4·6° (neat), $\nu_{max.}$ (film) 2285 cm.$^{-1}$ (Found: C, 78·4; H, 12·35; N, 9·55. $C_{10}H_{19}N$ requires C, 78·4; H, 12·5; N, 9·1%). It was homogeneous on g.l.c.

A solution of the dihydro-nitrile (10 g.) in dry ether (25 c.c.) containing methanol (2·3 g.) was saturated with dry hydrogen chloride at 0°. The mixture was kept at 0° for 6 days and then cooled to –40°. The crystalline imino-ether hydrochloride (14·1 g.) was collected, washed with cold ether, and dried (KOH) at 0·5 mm. The hydrochloride (15·8 g.) was stirred with pentane (115 c.c.) and methanol (6·8 g.) at 20° for 48 hr. Precipitated ammonium chloride was filtered off, and the filtrate was cooled to 0°; some crystalline amide separated and was removed. Evaporation of the solvent gave the crude orthoester (9·7 g.), suitable for use in the next step. The pure *ortho-ester*, obtained by distillation at 65°/0·02 mm., had τ 6·8 (OMe) (Found: C, 67·6; H, 11·9. $C_{13}H_{28}O_3$ requires C, 67·2; H, 12·15%).

1β-[(1R)-1,5-*Dimethylhexyl*]-3aα,6,7,7aβ-*tetrahydro*-7aβ-*methylindan*-2-*one* (20).—The benzoate (10; R = Bz) (1·84 g.) and the foregoing orthoester (5·4 g.) were heated together under reflux (N_2) in dry xylene (30 c.c.) containing propionic acid (10 mg.) for 20 hr. The solvent was removed under reduced pressure, and the residue was kept at 20° for 16 hr. with ethanol (20 c.c.) and aqueous 2N-sodium hydroxide (20 c.c.); the solution was then diluted with water, and the neutral product was isolated with ether. It was chromatographed on basic alumina (grade III; 60 g.); impurities of low polarity were removed with benzene, and elution with 10% ether–benzene then gave the hydroxy-esters (18) as an oil (1·82 g.), unresolved by t.l.c., $\nu_{max.}$ 3380 and 1730 cm.$^{-1}$, τ 6·37 (OMe) and 9·19 (>CMe) (Found: M^+, 296·2342. Calc. for $C_{18}H_{32}O_3$: *M*, 296·2351).

The hydroxy-esters (18) (1·71 g.) were treated with 1-dimethylamino-1-methoxyethylene as described for the analogue *rac*-(13); the product was hydrolysed under reflux with potassium hydroxide (12 g.) in ethylene glycol (25 c.c.), and water (10 c.c.) for 36 hr. The acidic product of the hydrolysis, isolated in the usual way, was treated with an excess of diazomethane to give the dimethyl esters of the acids (19) which, after chromatography on basic alumina (grade III; 60 g.) with benzene as eluant, formed an oil (1·23 g.), $\nu_{max.}$ 1730 and 1163 cm.$^{-1}$, τ 6·29 and 6·34 (OMe) (Found: M^+, 352·2629. Calc. for $C_{21}H_{36}O_4$: *M*, 352·2613); g.l.c. (5% Carbowax at 179°) showed the presence of two components, retention times 15 min. (major component, 80%) and 14·2 min. (20%).

The ester mixture (1·23 g.) was cyclised with sodium hydride in dimethyl sulphoxide as described for the dimethyl esters of the acids *rac*-(14); the product (1·12 g.) was similarly hydrolysed and decarboxylated (reaction time 16 hr.). T.l.c. of the product (Kieselgel G; 25% benzene–light petroleum) showed two spots, not quite completely separated. Column chromatography on Kieselgel G (30 g.) with the same solvent system gave the major product (450 mg.) as an oil which crystallised completely at –20°. Further elution gave an oil (195 mg.) consisting of the minor component, contaminated with some of the major component. The oil was heated with toluene-*p*-sulphonic acid in acetic acid and water as in the hydrolysis–decarboxylation reaction; isolation and chromatography of the product gave the major crystalline component (131 mg.) and an oil (43 mg.), retreatment of which gave a further 23 mg. of the major ketone (20) (total yield 604 mg.), suitable for use in the next step. Crystallisation of a sample (410 mg.) of this material from methanol at –20° gave flakes (320 mg.) of the *ketone* (20), m.p. 23—24°, $[\alpha]_D^{21}$ –93° ($CHCl_3$), $\nu_{max.}$ 1730s, 1645w, and 684s cm.$^{-1}$, τ 4·35 (–C*H*=C*H*–) (Found: C, 82·15; H, 11·2. $C_{18}H_{30}O$ requires C, 82·4; H, 11·5%).

The *semicarbazone* formed crystals (from ethanol), m.p. 188—190°, $[\alpha]_D^{23}$ +14·1° ($CHCl_3$) (Found: C, 71·7; H, 10·45; N, 12·9. $C_{19}H_{33}N_3O$ requires C, 71·4; H, 10·4; N, 13·15%).

The Dihydroxy-ketone (21).—The ketone (20) (104 mg. of material prior to recrystallisation) and *m*-chloroperbenzoic acid (100 mg.) were kept together in methylene dichloride (2 c.c.) at 20° for 3 hr. Ether (25 c.c.) was then added; the solution was washed successively with aqueous sodium sulphite, aqueous sodium carbonate, and water, and then dried and evaporated to give a crystalline product (100 mg.), m.p. 80·5—83°. Crystallisation from pentane gave the 8α,9α-*epoxide* as needles (88 mg.), m.p. 81—83°, $[\alpha]_D^{22}$ –131° ($CHCl_3$), $\nu_{max.}$ (Nujol) 1720 cm.$^{-1}$ (Found: C, 77·7; H, 10·7. $C_{18}H_{30}O_2$ requires C, 77·65; H, 10·9%).

The crude epoxide (82·2 mg.) and 2N-sulphuric acid (0·2 c.c.) were kept together in acetone (11 c.c.) at 20° for 48 hr. Solid potassium carbonate was added, and the mixture was filtered; evaporation of the filtrate gave a colourless oil (90 mg.). Crystallisation from ether–pentane gave the *dihydroxy-ketone* (21) as needles (72 mg.), m.p. 113—114°, $[\alpha]_D^{22}$ –122° ($CHCl_3$), $\nu_{max.}$ ($CHCl_3$) 3380 and 1720 cm.$^{-1}$ (Found: C, 72·8; H, 10·6. $C_{18}H_{32}O_3$ requires C, 72·9; H, 10·9%).

Des-AB-*cholestane*-8β,9α-*diol* (22).—The crude compound (21) (90 mg.) was heated with pyridine and acetic anhydride for 20 hr. at 60°; the resulting oily diacetate (105 mg.) had $\nu_{max.}$ 1728, 1245, and 1225 cm.$^{-1}$. The diacetate (123 mg.), ethanedithiol (200 mg.), and boron trifluoride–ether complex (100 mg.) were stirred together in anhydrous acetic acid (1·5 c.c.) at 20° for 20 hr. The mixture was diluted with ether, and washed with cold 4N-sodium hydroxide, then with 2N-hydrochloric acid, and with water, and then dried and evaporated to give an oil (182 mg.). Its solution in ethanol (9 c.c.) was heated under reflux (N_2) for 12 hr. with freshly prepared W7 Raney nickel (2 g.). The nickel was filtered off, and washed with hot ethanol, and the filtrate and washings were evaporated under reduced

pressure to give an oil. The oil was kept at 20° for 2 hr. with ethanol (4 c.c.) and 2N-sodium hydroxide (4 c.c.); the neutral product of the hydrolysis was then isolated with ether; it formed a crude solid (92·8 mg.). Recrystallisation from ether–light petroleum gave the *trans*-diol (22) as needles (50·2 mg.), m.p. 143—144°; preparative t.l.c. of the mother liquor material (Kieselgel G; ethyl acetate), and recrystallisation of the product as before, gave a further crop (13·2 mg.) (total yield 63·4 mg.), m.p. 143—144°, $[\alpha]_D^{22}$ +49° ($CHCl_3$) (Found: C, 76·4; H, 11·95. Calc. for $C_{18}H_{34}O_2$: C, 76·5; H, 12·1%). Its i.r. (Nujol) and n.m.r. spectra were identical with those of material prepared from duoannelic acid,[5] and the two materials showed no mixed m.p. depression.

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