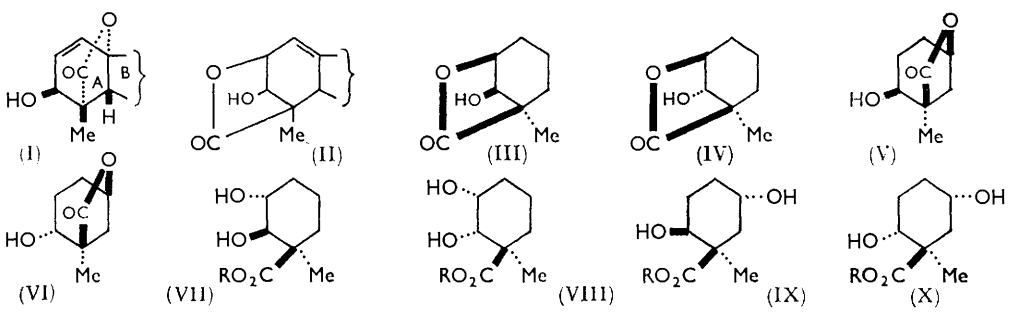
486. *Gibberellic Acid. Part XXIV.* Synthesis of Some Model Lactones.*

By J. S. Moffatt.

Some hydroxy-γ-lactones analogous to the A-ring lactone system of gibberellins have been prepared, together with some related dihydroxycyclohexanecarboxylic acids. Evidence for the geometrical configurations of the synthetic compounds is adduced. The behaviour of the models in dilute alkali is compared with that of the corresponding gibberellin derivatives.

Ring A of gibberellic acid has been shown [1] to have the absolute configuration (I).[1] When the present work began ring A was formulated [2] as (II); later work [3] led to revision to (I), and the partial structure (II) was retained for the product obtained from methyl gibberellate by alkali-induced rearrangement of ring A. In order to obtain model compounds for studies of rearrangements undergone by ring A in gibberellins [4] and of possible structure–activity relationships, the epimeric pairs of hydroxy-lactones (III), (IV) and (V), (VI) have now been prepared and evidence is here adduced for their configurations. The αβ-system [5] is used to describe geometrical configuration of the synthetic compounds, though all of them are racemic; in accordance with convention [5] the lactone bridge is written with the β-configuration. When this work was complete except for the characterisation of the 2(*ax*)-hydroxy-lactone (VI), Mori, Matsui, and Sumiki [6] reported the synthesis of lactones (III) and (IV) by a route similar to that now described. We agree with their configurational assignments to these hydroxy-lactones; we further describe the related dihydroxy-acids (VII and VIII; R = H) and also note a stereochemical rearrangement undergone by the 2(*ax*)-hydroxy-lactone (IV) under the influence of dilute alkali. The Japanese authors also prepared the 2(*eq*)-hydroxy-lactone (V) by a route somewhat similar to ours but were unable to obtain its 2(*ax*)-epimer (VI). Our preparation and comparison of the epimers make it possible to define their respective configurations.



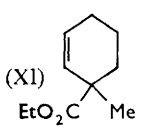
For the preparation of the hydroxy-lactones (III) and (IV) a route starting from ethyl 3-bromo-1-methyl-2-oxocyclohexanecarboxylate [7] was first investigated. This with sodium acetate gave a mixture of the epimeric 3-acetoxy-compounds which were reduced by

* Part XXIII, preceding paper.

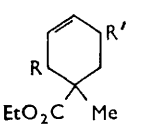
[1] Cross, Grove, McCloskey, Mulholland, and Klyne, *Chem. and Ind.*, 1959, 1345; Aldridge, Grove, Speake, Tidd, and Klyne, *J.*, 1963, 143.
[2] Cross, Grove, MacMillan, and Mulholland, *Proc. Chem. Soc.*, 1958, 221.
[3] Cross, Grove, MacMillan, Moffatt, Mulholland, Seaton, and Sheppard, *Proc. Chem. Soc.*, 1959, 302.
[4] Cross, Grove, and Morrison, *J.*, 1961, 2498.
[5] Henbest, Smith, and Thomas, *J.*, 1958, 3293.
[6] Mori, Matsui, and Sumiki, *Agric. and Biol. Chem. (Japan)*, 1961, **25**, 205.
[7] Moffatt, *J.*, 1960, 3045.

sodium borohydride to the mixed ethyl 3-acetoxy-2-hydroxy-1-methylcyclohexanecarboxylates. Fractional distillation, hydrolysis of the fractions, and fractional crystallisation gave the dihydroxy-acids (VII; R = H), m. p. 150—151°, and (VIII; R = H), m. p. 165—166°, and, in low yield, as the neutral product, a mixture of the epimeric hydroxy-lactones (III) and (IV). The configurations of these dihydroxy-acids are assigned on the following evidence: (*a*) both acids failed to lactonise; therefore the 1-carboxyl and the 3-hydroxyl group are *trans*-related; (*b*) the methyl ester of the higher-melting acid, but not of the other, yielded an isopropylidene derivative; (*c*) the acids were severally formed by *trans*- and *cis*-hydroxylation of the olefin (XI), followed by hydrolysis.

The individual hydroxy-lactones (III) and (IV) were satisfactorily obtained as follows. Sodium borohydride reduced ethyl 1-methyl-2-oxocyclohexanecarboxylate to the 2-hydroxy-compound whose methanesulphonyl derivative, on treatment with collidine, gave the olefin (XI). *cis*-Hydroxylation [8] of this with osmium tetroxide and pyridine was stereospecific; presumably the preferred conformation of (XI) is that in which the methyl group is quasiaxial because addition of the osmium complex mainly occurred on the opposite side of the ring. Thus hydrolysis of the mixture of diol esters obtained by decomposition of the adduct with hydrogen sulphide [9] afforded mainly (64%) the hydroxy-lactone (III), b. p. 118—122°/0·01 mm., together with a small quantity (2%) of the dihydroxy-acid (VIII; R = H), m. p. 165—166°. The hydroxy-lactone (III) was also obtained, in lower yield, by hydroxylation of the olefin (XI) with silver acetate and iodine in moist acetic acid,[10] followed by hydrolysis. *trans*-Hydroxylation of the olefin (XI) with performic acid,[11] followed by hydrolysis, gave predominantly (70%) the dihydroxy-acid (VII; R = H), m. p. 150—151°, together with only a small proportion (about 1%) of the hydroxy-lactone (IV), m. p. 72—74°. The latter was more conveniently prepared as follows. Oxidation of the more readily available hydroxy-lactone (III), with chromium trioxide–sulphuric acid,[12] gave the 2-oxo-lactone which showed exalted γ-lactone and oxo-group absorption frequencies (in chloroform, 1816 and 1767 cm.$^{-1}$) as would be expected [13] for such a structure. Hydrogenation of this sterically hindered ketone in the presence of platinum in acetic acid afforded predominantly, as would be expected from Barton's generalisation,[14] the 2(*ax*)-hydroxy-lactone (IV) which was also formed on reduction with sodium borohydride.



(XI)



(XII)

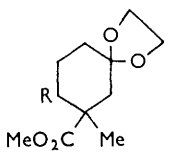
The configurations (III) and (IV) of the hydroxy-lactones, b. p. 118—122°/0·01 mm. and m. p. 72—74°, follow from their formation from the olefin (XI) by means of *cis*- and *trans*-hydroxylating reagents, respectively; they were confirmed by accurate measurement (by Dr. J. R. Bartels-Keith) of hydroxyl stretching frequencies shown by dilute (0·05 and 0·005M) solutions of the compounds in carbon tetrachloride according to the method of Cole and his co-workers.[15] The crystalline hydroxy-lactone showed bands at 3629 ± 1 cm.$^{-1}$ (*ax*-sec.-OH) and 3465 cm.$^{-1}$; the latter band was absent in the more dilute

[8] Criegee, Marchand, and Wannowius, *Annalen*, 1942, **550**, 99.
[9] Barton and Elad, *J.*, 1956, 2085.
[10] Cf. Woodward and Brutcher, *J. Amer. Chem. Soc.*, 1958, **80**, 209.
[11] Swern, "Organic Reactions," ed. Adams, Chapman and Hall, Ltd., London, 1953, vol. VII, p. 378.
[12] Curtis, Heilbron, Jones, and Woods, *J.*, 1953, 457.
[13] Burn, Moody, and Rigby, *Chem. and Ind.*, 1956, 928; Allen, Davis, Stewart, and Van Allan, *J. Org. Chem.*, 1955, **20**, 306.
[14] Barton, *J.*, 1953, 1027.
[15] Cole, Müller, Thornton, and Willix, *J.*, 1959, 1218; Cole, Jefferies, and Müller, *ibid.*, p. 1222.

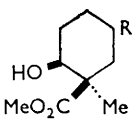
solution and is attributed to intermolecular hydrogen bonding. The oily epimer showed three bands in the more concentrated solution, at 3622 ± 1 cm.$^{-1}$ (*eq*-sec.-OH), 3591, and 3439 cm.$^{-1}$. The last band, due to intermolecular hydrogen bonding, was eliminated on dilution but the 3591 cm.$^{-1}$ band, attributed to the presence of an intramolecular bond, persisted.

The 2(*eq*)-hydroxy-lactone (III) was recovered unchanged after being treated with 0·01N-sodium hydroxide at room temperature. In the same conditions the 2(*ax*)-epimer (IV) underwent stereochemical rearrangement to give the dihydroxy-acid (VII; R = H), probably by way of an equilibrium reaction (IV) ⇌ (VII; R = H) which evidently is also acid-catalysed because the methyl ester (VII; R = Me), on treatment with a trace of sulphuric acid in acetone at room temperature, afforded a small proportion of the hydroxy-lactone (IV) in addition to starting material. The mechanism of the rearrangement is unknown; inversion of both the hydroxyl and the potential hydroxyl groups in (IV) through an epoxide seems plausible. A similar rearrangement apparently does not occur with methyl 1-carboxy-2(*ax*),3,7-trihydroxy-1-methyl-8-methylenegibb-4-ene-10-carboxylate 1 ⟶ 3-lactone, which is produced by the action of very dilute alkali on methyl gibberellate;[3] possibly this compound is stable because its lactone ring remains largely closed in the conditions used.

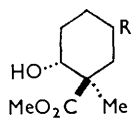
For the preparation of the epimeric hydroxy-lactones (V) and (VI) some transformations of the available[7] ethyl 5-bromo-1-methyl-2-oxocyclohex-3-enecarboxylate (XII; R = O, R′ = Br) were first investigated. With silver acetate it gave the acetoxy-olefin (XII; R = O, R′ = OAc). Reduction of this with sodium borohydride and hydrolysis of the product did not give any useful material. Hydrogenation of the olefin (XII; R = O, R′ = OAc) gave ethyl 5-acetoxy-1-methyl-2-oxocyclohexanecarboxylate which, on reduction with sodium borohydride, yielded ethyl 5-acetoxy-2-hydroxy-1-methylcyclohexanecarboxylate. Hydrolysis of this gave mainly an acidic product together with only a trace of lactone; it was concluded that in the major product the 5-hydroxyl and the carboxyl group are *trans*-related.



(XIII)



(XIV)



(XV)

(XVI)

Lukes, Poos, and Sarett[16] described the hydrogenation, in the presence of Raney nickel, of the oxo-ester (XIII; R = O) which yielded (95%) a hydroxy-ester (XIII; R = OH), m. p. 50—51°, whose configuration they did not define; we formulate this as (XIV; R = O·[CH$_2$]$_2$·O). By repetition of their experiments and chromatography of material from mother-liquors we have isolated also about 3% of the oily 2α-hydroxy-epimer. Selective hydrolysis of the crystalline and the oily epimer afforded, respectively, the crystalline hydroxy-ketone (XIV; R = O) (previously prepared by a different method[16]) and its oily epimer (XV; R = O).

Hydrogenation of the crystalline hydroxy-ketone in the presence of platinum gave the 2(*eq*)-hydroxy-lactone (V), m. p. 103—104° (42%), and the dihydroxy-ester (IX; R = Me), m. p. 106—108° (10%); hydrolysis of the latter gave the dihydroxy-acid (IX; R = H), m. p. 133—135°.

Similar reduction of the epimeric hydroxy-ketone (XV; R = O) gave about 1% of the oily 2(*ax*)-hydroxy-lactone (VI) and about 54% of the dihydroxy-ester (X; R = Me), m. p. 98—100°; hydrolysis of the latter gave the dihydroxy-acid (X; R = H), m. p. 171—172°.

[16] Lukes, Poos, and Sarett, *J. Amer. Chem. Soc.*, 1952, **74**, 1401.

Attempts to obtain larger quantities of the 2(*ax*)-hydroxy-lactone (VI) by inversion of the hydroxyl group in its epimer (V) through its toluene-*p*-sulphonate were unsuccessful (see Experimental section). Heating the toluene-*p*-sulphonyl derivative with sodium acetate in acetic acid [17] yielded, together with starting material, the olefinic lactone (XVI) which represents ring A of gibberellin A_5 and showed light absorption ($\lambda_{max.}$ 214 mμ, ε 1090) similar to that of the natural product.[18]

The 2(*ax*)-hydroxy-lactone (VI) was obtained in satisfactory yield (49%), together with its 2(*eq*)-epimer (12%), from which it was readily separated by chromatography, by Ponndorf–Meerwein reduction of 5β-hydroxy-1α-methyl-2-oxocyclohexane-1β-carboxylic acid 1 ⟶ 5-lactone that was prepared by oxidation of the hydroxy-lactone (V). Hydrogenation of the ketone gave the 2(*eq*)-hydroxy-lactone (V) in about 90% yield, and reduction with lithium hydridotri-t-butoxyaluminium [19] gave predominantly the same product.

The configurations (V) and (VI) follow from these reductions and Barton's general rule [14] that, whereas reduction of an unhindered ketone by a metal hydride gives mainly the equatorial alcohol (lithium hydridotri-t-butyoxyaluminium has been reported [20] to be highly stereospecific in this respect), Ponndorf–Meerwein reduction gives a higher proportion of the axial alcohol than do other methods. Confirmation was provided by elution of the oily hydroxylactone before the crystalline epimer and by examination (by Mr. B. K. Tidd) of the infrared absorptions. The oily hydroxy-lactone in carbon tetrachloride showed a sharp band at 3630 and a broad band at 3578 cm.$^{-1}$; the intensity of the latter relative to that of the former was diminished on progressive dilution of the solutions; therefore the broad band is due to intermolecular hydrogen bonding. On the other hand, the relative intensities of these two bands in the epimer of m. p. 103—104° did not alter on dilution, indicating the presence of an intramolecular hydrogen bond. Molecular models show that with (V) but not with (VI) there is opportunity for hydrogen bonding between the hydroxyl and the carbonyl group.

From these assignments, the configurations of the epimeric hydroxy-ketones and dihydroxy-esters follow. Since alkaline hydrolysis of the dihydroxy-esters (IX and X; R = Me) gave distinct dihydroxy-acids (IX and X; R = H), inversion of the 2-hydroxy-group could not have occurred in either acid under these conditions.

Although 2(*ax*)-hydroxygibbane 1 ⟶ 4a-lactones are epimerised to the 2(*eq*)-epimers by dilute aqueous alkali,[4] neither the 2(*eq*)-hydroxy-lactone (III) nor the 2(*ax*)-epimer (IV), whose hydroxyl group and lactone bridge have the same relative configuration as in the natural compounds, was epimerised under these conditions. A possible explanation is that the lactone ring in the synthetic, but not in the natural, compounds was readily opened in dilute aqueous alkali; the retroaldol mechanism [4] suggested by Cornforth for the epimerisation of the natural compounds requires that the lactone ring remains closed.

Experimental

M. p.s are corrected. Alumina (Spence, type H) was washed with dilute nitric acid, then repeatedly with water, and reactivated at 180°. Unless otherwise stated, infrared spectra were obtained for Nujol mulls.

2α,3α- (VIII; R = H) *and* 2β,3α-*Dihydroxy*-1α-*methylcyclohexane*-1β-*carboxylic Acid* (VII; R = H).—A mixture of ethyl 3-bromo-1-methyl-2-oxocylcohexanecarboxylate [7] (26·7 g.), fused sodium acetate (34 g.), and glacial acetic acid (128 ml.) was refluxed for 22 hr., treated with water, and extracted with ether. The extract was washed with water and then treated gradually, with stirring and cooling, with sodium hydrogen carbonate solution until it was neutral. The ethereal layer was washed with dilute aqueous sodium hydroxide and water, dried (Na_2SO_4), and evaporated. Distillation of the residue yielded a mixture of ethyl 3α- and

[17] Cf. Klyne and Ridley, *J.*, 1956, 4825.
[18] MacMillan, Seaton, and Suter, *Tetrahedron*, 1960, **11**, 60.
[19] Brown and Subba Rao, *J. Amer. Chem. Soc.*, 1958, **80**, 5377.
[20] Wheeler and Mateos, *Canad. J. Chem.*, 1958, **36**, 1431.

3β-acetoxy-1α-methyl-2-oxocyclohexane-1β-carboxylate (11·9 g., 48%), b. p. 152—159°/13 mm., n^{26} 1·4602 (Found: C, 58·9; H, 7·5; OAc, 19·0. Calc. for $C_{12}H_{18}O_5$: C, 59·5; H, 7·5; OAc, 17·8%).

This mixture (11·8 g.), in methanol (72 ml.), was cooled to 0°, treated portionwise with sodium borohydride (2 g.), stored at room temperature for 19 hr., acidified with dilute hydrochloric acid, and concentrated *in vacuo*. After the addition of water, the product was recovered in ether and then distilled to give a fore-run (0·4 g.), b. p. 120—144°/13 mm., and a mixture of stereoisomeric ethyl 3-acetoxy-2-hydroxy-1-methylcyclohexanecarboxylates (6·7 g.), b. p. 140—165°/12 mm. (Found: C, 58·4; H, 8·9. Calc. for $C_{12}H_{20}O_5$: C, 59·0; H, 8·3%). This was fractionally distilled, to give the following, arbitrary fractions: (i) (2·25 g.), b. p. 144—152°/13 mm.; (ii) (3·46 g.), b. p. 152—158°/13 mm.; and (iii) (0·88 g.), b. p. 160—170°/13 mm. Each fraction was hydrolysed with boiling, ethanolic potassium hydroxide; the crude product, obtained in each case by acidification with dilute hydrochloric acid followed by extraction with ether, was further treated as follows: (i) a solid (1·63 g.); with ether it gave a syrup (0·54 g.) and crystals (1·03 g.) which, on fractional crystallisation from ethyl acetate, yielded prisms (0·68 g.), m. p. 150—152°, and prismatic needles (0·05 g.), m. p. 160—166°; (ii) a gummy solid (2·74 g.); with ether it gave a syrup (0·34 g.) and crystals (2·32 g.) which, on fractional crystallisation from ethyl acetate yielded prisms (0·13 g.), m. p. 147—152°, and prismatic needles (1·03 g.), m. p. 164—166°; (iii) a gummy solid (0·67 g.); with ether it gave a syrup (0·14 g.) and crystals (0·45 g.) which, on repeated recrystallisation from ethyl acetate, afforded prismatic needles (0·36 g.), m. p. 165—166°. The appropriate crystalline fractions were combined and recrystallised from ethyl acetate, to give prismatic needles (1·4 g.), m. p. 165—166°, $\nu_{max.}$ 3420, 3140 (broad), and 1700 cm.$^{-1}$, of *2α,3α-dihydroxy-1α-methylcyclohexane-1β-carboxylic acid* (Found: C, 54·9; H, 8·1. $C_8H_{14}O_4$ requires C, 55·2; H, 8·1%), and prisms (0·8 g.), m. p. 150—151°, $\nu_{max.}$ 3440 and 1700 cm.$^{-1}$, of the *2β,3α-epimer* (Found: C, 55·4; H, 8·2%). The latter acid existed also in the form of prisms, m. p. 161—166°, which were usually obtained by sublimation under reduced pressure or on recrystallisation from ether; the higher-melting form reverted to the lower-melting on crystallisation from ethyl acetate or on storage. The combined ether-soluble syrups (1·02 g.) in ether (150 ml.) were washed with 2N-potassium hydrogen carbonate (6 ml.) and water. Recovery gave a neutral gum (0·18 g.) which on distillation yielded an oil (0·14 g.), b. p. 119—128° (bath)/0·1 mm., $\nu_{max.}$ (liquid film) 3500 and 1765 cm.$^{-1}$ consisting of a mixture of the epimeric 2α,3β- and 2β,3β-dihydroxy-1α-methylcyclohexane-1β-carboxylic acid 1 ⟶ 3-lactones.

Ethyl 2-Hydroxy-1-methylcyclohexanecarboxylate.—Ethyl 1-methyl-2-oxocyclohexanecarboxylate [21] (5 g.) in ethanol (25 ml.) was stirred at 0° and treated portionwise with sodium borohydride (0·52 g.). The mixture was stored at room temperature for 3 hr., cooled to 0°, decomposed with 5N-hydrochloric acid (5 ml.), and concentrated to small volume under reduced pressure. The residue was treated with water and extracted with ether. The extract was washed with sodium hydrogen carbonate solution and water, dried (Na_2SO_4), and evaporated. Distillation of the residue yielded the hydroxy-ester (4·08 g., 81%), b. p. 108—116°/13 mm., $\nu_{max.}$ (liquid film) 3530 and 1720 cm.$^{-1}$ (Found: C, 64·3; H, 10·0. Calc. for $C_{10}H_{18}O_3$: C, 64·5; H, 9·7%). With methanesulphonyl chloride (1·5 mol.) in dry pyridine for 45 hr. it yielded a *methanesulphonate* (89%), b. p. 113—118°/0·05 mm., $\nu_{max.}$ (liquid film) 1725 cm.$^{-1}$ (Found: C, 49·9; H, 8·05. $C_{11}H_{20}O_5S$ requires C, 50·0; H, 7·6%).

Ethyl 1-Methylcyclohex-2-enecarboxylate (XI).—The foregoing methanesulphonate (40 g.) was refluxed under nitrogen with collidine (purified by extraction into dilute hydrochloric acid and recovery; 390 ml.) for 7 hr. The mixture was cooled, poured into concentrated hydrochloric acid (590 ml.) and ice (550 g.), and then extracted with ether. The extract was thrice washed with 5N-hydrochloric acid, then with sodium hydrogen carbonate solution and water, dried (Na_2SO_4), and evaporated. The residue was fractionally distilled to give (i) the product (20·1 g., 78%), b. p. 75—79°/15 mm., $\nu_{max.}$ (liquid film) 1730 cm.$^{-1}$ (Found: C, 71·7; H, 9·9. Calc. for $C_{10}H_{16}O_2$: C, 71·4; H, 9·6%), and (ii) an oil (2·3 g., 5·7%), b. p. 104—112°/0·05 mm., mainly starting material. Hydrolysis of a sample of the product with ethanolic potassium hydroxide afforded 1-methylcyclohex-2-enecarboxylic acid, b. p. 60—63° (bath)/0·05 mm. (Found: C, 68·8; H, 8·8. Calc. for $C_8H_{12}O_2$: C, 68·5; H, 8·6%). Ghatak, Datta, and Ray [22] give b. p. 105—107°/3 mm.

[21] Bachmann and Raunio, *J. Amer. Chem. Soc.*, 1950, **72**, 2530.
[22] Ghatak, Datta, and Ray, *J. Amer. Chem. Soc.*, 1960, **82**, 1728.

2β,3β-*Dihydroxy*-1α-*methylcyclohexane*-1β-*carboxylic Acid* 1 ⟶ 3-*Lactone* (III).—(*a*) Ethyl 1-methylcyclohex-2-enecarboxylate (2 g.) in dry benzene (19 ml.) was treated with osmium tetroxide (3 g.), followed by dry pyridine (2·3 g.), and set aside for 5 days. The complex (5·29 g.) which had separated was collected, washed with ether, suspended in purified dioxan (50 ml.), cooled to 0°, saturated with hydrogen sulphide, and stored for 19 hr. The mixture was filtered and the residue washed with ether. The filtrates were evaporated at 40° *in vacuo*. Distillation of the residue gave an oil (1·71 g.), b. p. 92—98° (bath)/0·01 mm. This was refluxed with 9·4N-potassium hydroxide (1·4 ml.) in methanol (12 ml.) for 3 hr. The solution was concentrated at 20—25° *in vacuo* to small volume. The residue was dissolved in water (8 ml.) and extracted with ether. The aqueous layer was separated, acidified to pH 2 with 10N-hydrochloric acid, and extracted with ether. Evaporation of the extract gave an oil (1·31 g.). This was redissolved in ether (10 ml.), cooled at 0°, and stirred with 2N-potassium hydrogen carbonate (3 ml.) for 20 min. The layers were separated and the aqueous layer further extracted with ether (4 × 50 ml.). These extracts were washed with water (3 ml.) and dried (Na_2SO_4). The aqueous washing was combined with the potassium hydrogen carbonate layer, acidified to pH 2 with 5N-hydrochloric acid, and extracted with ether (4 × 50 ml.). The last extracts were dried (Na_2SO_4); recovery from the first, neutral extract yielded an oil (1·09 g., 59%), b. p. 118—122° (bath)/0·01 mm., $\nu_{max.}$ (liquid film) 3550 and 1775 cm.$^{-1}$, or (in CS_2) 3590, 3490 (broad), and 1784 cm.$^{-1}$, which on long storage afforded crystals of the hydroxy-lactone (III) (Found: C, 61·2; H, 8·0. Calc. for $C_8H_{12}O_3$: C, 61·5; H, 7·75%). This yielded a p-*nitrobenzoate*, prismatic needles [from benzene–light petroleum (b. p. 60—80°)], m. p. 141° (Found: C, 59·4; H, 5·2. $C_{15}H_{15}NO_6$ requires C, 59·0; H, 4·95%), and a 3,5-*dinitrobenzoate*, prisms (from ethyl acetate), m. p. 239—241° (Found: C, 51·4; H, 4·3; N, 8·1. $C_{15}H_{14}N_2O_8$ requires C, 51·4; H, 4·0; N, 8·0%). Evaporation of the acidic, ethereal solution gave a gum (149 mg.) which, on treatment with ether, formed prisms (43 mg.), m. p. 164—166°, of 2α,3α-dihydroxy-1α-methylcyclohexane-1β-carboxylic acid (VIII; R = H), identified by mixed m. p. and infrared spectrum. The ethereal mother-liquor of this yielded a further quantity (98 mg., total yield 64%) of the hydroxy-lactone (III), identified by its infrared spectrum.

(*b*) A stirred mixture of the olefin (5 g.) and silver acetate (12·5 g.) in glacial acetic acid (100 ml.) was treated with water (0·85 ml.) and then portionwise, during 25 min., with powdered iodine (7·55 g.). It was stirred for 30 min. longer and then heated, under reflux on a water-bath, for 2¼ hr. The mixture was cooled, diluted with ether (100 ml.), and filtered. The residue was washed with ether (100 ml.); the combined filtrates were evaporated *in vacuo*, finally at 40—50°. The residue was extracted with ether; the extract was washed with sodium hydrogen carbonate solution and evaporated. This residue (8·7 g.) was refluxed with 10N-potassium hydroxide (11·9 ml.) and methanol (50 ml.) for 2½ hr. The solution was evaporated *in vacuo*. The residue was acidified with 5N-hydrochloric acid and extracted with ether. This extract was successively washed with 10% sodium metabisulphite solution, water, 2N-potassium hydrogen carbonate, and water, dried (Na_2SO_4), evaporated, and distilled, affording 2β,3β-dihydroxy-1α-methylcyclohexane-1β-carboxylic acid 1 ⟶ 3-lactone (720 mg., 16%), b. p. 100—107° (bath)/0·05 mm., identical (infrared spectrum) with material prepared as described above. The acidic products of the reaction consisted of an intractable brown gum (2·7 g.).

Action of Performic Acid on Ethyl 1-*Methylcyclohex*-2-*enecarboxylate*.—A solution of the olefin (10 g.) in 90% formic acid (40 ml.) was treated dropwise, at 0°, during 15 min. with 31·8% w/v hydrogen peroxide solution (6·7 ml.). The mixture became homogeneous on being shaken at room temperature, with occasional cooling, for 1 hr. It was set aside for 70 hr. and then heated under reflux at 40—45° for 8 hr. Formic acid was removed by distillation under reduced pressure at 40°. The residue was extracted with ether; the extract was washed with sodium hydrogen carbonate solution and dried (Na_2SO_4). Recovery gave an oil (12·2 g.) which was refluxed with 9·4N-potassium hydroxide (20 ml.) and methanol (78 ml.) for 3 hr. The solution was evaporated *in vacuo*; the residue was dissolved in water (30 ml.) and extracted with ether. The aqueous layer was acidified with 5N-hydrochloric acid (37 ml.) and extracted with ether (3 × 550 ml.). The extract was dried (Na_2SO_4), concentrated to 130 ml., and then stored overnight at 5°. The crystals which had separated (6·73 g.; prisms, m. p. 161—164°) were collected and washed with a small quantity of ether; they consisted of the higher-melting form of 2β,3α-dihydroxy-1α-methylcyclohexane-1β-carboxylic acid (VII; R = H), identified by mixed m. p. and infrared spectrum. The ethereal mother-liquor was stirred at 0° with 2N-potassium hydrogen carbonate (30 ml.) for 30 min. The aqueous layer was extracted

with ether (3 × 100 ml.), acidified with 5N-hydrochloric acid, and re-extracted with ether. Recovery of the acidic material gave a syrup (1·4 g.) which, with ethyl acetate, afforded prisms, m. p. 149—150°, of the lower-melting form (0·53 g., total yield 70%) of the above acid. Recovery of the neutral material yielded an oil (251 mg.) which, in benzene, was chromatographed on a column of alumina (7·5 g.). Elution with benzene–ether (7 : 3) gave an oil (169 mg.), b. p. 102—106° (bath)/0·05 mm., which with ether–light petroleum (b. p. 40—60°) yielded plates (117 mg., 1·3%), m. p. 54—62°, of slightly impure 2α,3β-dihydroxy-1α-methylcyclohexane-1β-carboxylic acid 1 ⟶ 3-lactone (IV), identified (mixed m. p.; infrared spectra) by comparison with a pure specimen prepared as described below.

3β-Hydroxy-1α-methyl-2-oxocyclohexane-1β-carboxylic Acid 1 ⟶ *3-Lactone.*—2β,3β-Dihydroxy-1α-methylcyclohexane-1β-carboxylic acid 1 ⟶ 3-lactone (557 mg.) in purified acetone (5·8 ml.) was cooled to 0° and treated dropwise with chromium trioxide–sulphuric acid solution [12] (8N with respect to oxygen; 0·96 ml.). The mixture was stored at 0° for 1 hr. and then at room temperature for 15 hr. It was treated with methanol (0·2 ml.), concentrated *in vacuo*, treated with water, and extracted with ether. Recovery and fractional distillation of the product gave: (i) a crystalline sublimate (122 mg.), at 60—64° (bath)/0·05 mm., which formed needles (from ether–light petroleum, b. p. 40—60°), m. p. 89—94°, $\nu_{max.}$ 1790 and 1760 cm.$^{-1}$, of the *keto-lactone* (Found: C, 62·0; H, 6·6. $C_8H_{10}O_3$ requires C, 62·3; H, 6·5%); and (ii) starting material (325 mg.), b. p. 118—124° (bath)/0·05 mm., identified by its infrared spectrum.

2α,3β-Dihydroxy-1α-methylcyclohexane-1β-carboxylic Acid 1 ⟶ *3-Lactone* (IV).—The foregoing keto-lactone (100 mg.) in glacial acetic acid (3 ml.) was hydrogenated at room temperature in the presence of Adams platinum oxide (50 mg.) until uptake of hydrogen ceased (2 hr.). Distillation yielded an oil (87 mg.), b. p. 96—104° (bath)/0·01 mm., which crystallised. It was chromatographed in benzene on alumina (3 g.). Elution with benzene–ether (9 : 1) afforded crystals (77 mg.) which formed plates [from ether–light petroleum (b. p. 40—60°)], m. p. 72—74°. $\nu_{max.}$ (in CS_2) 3610, 3460, and 1789 cm.$^{-1}$ of the 2(*ax*)-hydroxy-lactone (Found: C, 61·7; H, 7·7. Calc. for $C_8H_{12}O_3$: C, 61·5; H, 7·75%); this gave a 3,5-*dinitrobenzoate*, prisms (from methanol), m. p. 157—159° (Found: C, 51·6; H, 4·25. $C_{15}H_{14}N_2O_8$ requires C, 51·4; H, 4·0%). Further elution with benzene–ether (7 : 3) gave an oil (3 mg.) which partly crystallised; its infrared spectrum indicated that it was a mixture of 2α- and 2β-hydroxy-lactones.

Reduction of the keto-lactone (50 mg.) with sodium borohydride in methanol yielded an oil (43 mg.) which partly crystallised and evidently consisted mainly of the 2α-hydroxy-lactone because it gave a 3,5-dinitrobenzoate (40 mg.; m. p. 155—156°) identical with that described above.

2β,3β-Dihydroxy-1α-methylcyclohexane-1β-carboxylic acid 1 ⟶ 3-lactone (III) (53 mg.) in 0·0115N-sodium hydroxide (50 ml.) was stored at room temperature for 4 hr., then acidified with N-hydrochloric acid (0·90 ml.), treated with sodium chloride (8·5 g.), and extracted with ether (5 × 100 ml.). Recovery gave starting material (52 mg., 98%), b. p. 96—101° (bath)/0·01 mm., identified by infrared spectrum and conversion into its 3,5-dinitrobenzoate (79%), m. p. 240—242°.

Action of Dilute Alkali on 2α,3β-Dihydroxy-1α-methylcyclohexane-1β-carboxylic Acid 1 ⟶ *3-Lactone* (IV).—A solution of the hydroxy-lactone (20 mg.) in 0·0115N-sodium hydroxide (25 ml.) was stored at room temperature for 4½ hr. It was acidified with N-hydrochloric acid (0·45 ml.), treated with sodium chloride (4·5 g.), and extracted with ether (3 × 100 ml.). Evaporation of the extract and fractional distillation of the residue yielded (i) an oil (2·1 mg.), b. p. 90—96° (bath)/0·01 mm., which crystallised and was identified (infrared spectrum) as starting material, and (ii) a crystalline sublimate (13·6 mg.; m. p. 161—164°) at 138—146° (bath)/0·01 mm. which formed prisms (from ether), m. p. 162—166°, of the higher-melting form of 2β,3α-dihydroxy-1α-methylcyclohexane-1β-carboxylic acid (VII; R = H), identified by mixed m. p. and its infrared spectrum.

Repetition of the experiment with a reaction time of 32 min. gave starting material (6·4 mg.) and the dihydroxy-acid (9·8 mg.).

Methyl 2α,3α-Isopropylidenedioxy-1α-methylcyclohexane-1β-carboxylate.—The *methyl ester* prepared from the corresponding acid with ethereal diazomethane, consisted of an oil, b. p. 95—102° (bath)/0·01 mm., $\nu_{max.}$ (liquid film) 3500 and 1735 cm.$^{-1}$, which solidified to form prisms, m. p. 56—58° (Found: C, 57·5; H, 8·5. $C_9H_{16}O_4$ requires C, 57·4; H, 8·6%). It (134 mg.) was dissolved in acetone (30 ml.) containing sulphuric acid (0·3% w/v), and the

solution was set aside for 68 hr. The resulting faintly yellow solution was shaken with anhydrous sodium carbonate (0·3 g.) for 2 hr. The mixture was filtered. Evaporation and distillation yielded the *isopropylidene derivative* (124 mg.), b. p. 52—56° (bath)/0·01 mm., $\nu_{max.}$ (liquid film) no OH absorption, 1735 cm.$^{-1}$ (Found: C, 62·9; H, 8·8. $C_{12}H_{20}O_4$ requires C, 63·1; H, 8·8%).

Action of Acid on Methyl 2β,3α-*Dihydroxy*-1α-*methylcyclohexane*-1β-*carboxylate* (VII; R = Me).—The *methyl ester*, prepared from the corresponding acid with ethereal diazomethane, consisted of an oil, b. p. 76—81° (bath)/0·01 mm., $\nu_{max.}$ (liquid film) 3500 and 1735 cm.$^{-1}$ (Found: C, 57·4; H, 8·7. $C_9H_{16}O_4$ requires C, 57·4; H, 8·5%). It (90 mg.) was dissolved in acetone (20 ml.) and sulphuric acid (0·3% w/v). The solution was set aside for 67 hr. and then treated as in the foregoing experiment. Fractional distillation of the product yielded (i) an oil (20 mg.) b. p. 136—142° (bath)/13 mm., identified (infrared spectrum) as starting material, (ii) an oil (41 mg.), b. p. 144—148° (bath)/13 mm., identified (infrared spectrum) as starting material containing a small proportion of a γ-lactone (weak band at 1770 cm.$^{-1}$), and (iii) an oil (11 mg.), b. p. 98—102° (bath)/0·05 mm., identified (infrared spectrum) as 2α,3β-dihydroxy-1α-methylcyclohexane-1β-carboxylic acid 1 ⟶ 3-lactone (IV).

Ethyl 5-*Acetoxy*-1-*methyl*-2-*oxocyclohex*-3-*enecarboxylate* (XII; R = O, R′ = OAc).—Ethyl 5-bromo-1-methyl-2-oxocyclohex-3-enecarboxylate [7] (0·5 g.) in glacial acetic acid (2·5 ml.) was heated with anhydrous silver acetate (0·84 g.) under reflux at 125—135° (oil-bath) for 4 hr. The mixture was cooled and filtered; the residue was washed with acetic acid. The filtrate was evaporated *in vacuo*. The residue, in ether, was washed with dilute sodium hydrogen carbonate solution and recovered. Distillation gave the *product* (248 mg.), b. p. 76—83° (bath)/0·01 mm., $\lambda_{max.}$ (in ethanol) 221 mμ (ε 11,000) (Found: C, 59·2; H, 6·6; OAc, 16·6. $C_{12}H_{16}O_5$ requires C, 60·0; H, 6·7; OAc, 17·9%).

Ethyl 5-*Acetoxy*-1-*methyl*-2-*oxocyclohexanecarboxylate*.—The foregoing acetoxy-olefin (385 mg.) in ethanol (7 ml.) was hydrogenated in the presence of 20% palladium–charcoal (130 mg.) for 2 hr. (uptake of hydrogen ceased after 1 hr.). The *product* consisted of an oil (330 mg.), b. p. 75—78° (bath)/0·01 mm. (Found: C, 59·85; H, 7·4; OAc, 16·1. $C_{12}H_{18}O_5$ requires C, 59·5; H, 7·5; OAc, 17·7%).

Ethyl 5-*Acetoxy*-2-*hydroxy*-1-*methylcyclohexanecarboxylate*.—The foregoing acetoxy-ketone (166 mg.) in ethanol (1 ml.) was treated at 0° with sodium borohydride (15 mg.). After being stored at room temperature for 2 hr., the mixture was acidified with 2N-hydrochloric acid (0·7 ml.). It was evaporated *in vacuo*, treated with water, and extracted with ether. Recovery and distillation yielded the *product* (104 mg.), b. p. 69—74° (bath)/0·01 mm., $\nu_{max.}$ (liquid film) 3520 and 1740 cm.$^{-1}$ (Found: C, 58·95; H, 8·4. $C_{12}H_{20}O_5$ requires C, 59·0; H, 8·3%).

Hydrolysis of this (83 mg.) with boiling methanolic potassium hydroxide afforded a viscous gum (36 mg.), b. p. 170—180° (bath)/0·05 mm. Dissolution of this in ether, extraction with 2N-potassium hydrogen carbonate at 0°, and recovery from the ethereal solution afforded only a trace (<1 mg.) of a neutral oil which showed absorption at 1770 cm.$^{-1}$. The acidic product, a viscous gum (33 mg.), was not further examined.

Methyl 2β-*Hydroxy*-1α-*methyl*-5-*oxocyclohexane*-1β-*carboxylate* (XIV; R = O).—Hydrogenation of methyl 5,5-ethylenedioxy-1-methyl-2-oxocyclohexanecarboxylate (10 g.; m. p. 50—51°; Lukes *et al.*[16] give m. p. 50—51°; Mori *et al.*[6] describe the same compound as an oil) in the presence of Raney nickel at room temperature and ordinary pressure, in essentially the way described by Lukes *et al.*,[16] gave a crude product which with ether–light petroleum (b. p. 60—80°) yielded (i) prisms (8·7 g.), m. p. 58—60°, of methyl 5,5-ethylenedioxy-2β-hydroxy-1α-methylcyclohexane-1β-carboxylate (XIV; R = O·$[CH_2]_2$·O), (ii) a second crop (0·73 g.; m. p. 51—57°) of slightly impure material, and (iii) an oil (0·54 g.), $\nu_{max.}$ (liquid film) 3450 and 1725 cm.$^{-1}$, which consisted mainly of 5,5-ethylenedioxy-2α-hydroxy-1α-methylcyclohexane-1β-carboxylate (XV; R = O·$[CH_2]_2$·O).

A solution of the crystalline epimer (2·72 g.) in methanol (22 ml.) was treated with 1·05N-hydrochloric acid (22 ml.) and then set aside for 48 hr. It was concentrated to a small volume at 25—30° (bath) *in vacuo*, treated with sodium hydrogen carbonate (1·95 g.), and then extracted with ether. Evaporation of the dried (Na_2SO_4) extract and crystallisation of the residue from ether–light petroleum (b. p. 60—80°) afforded methyl 2β-hydroxy-1α-methyl-5-oxocyclohexane-1β-carboxylate (XIV; R = O), prismatic needles (1·764 g., 80%), m. p. 60—61°, $\nu_{max.}$ 3385, 1725, and 1700 cm.$^{-1}$ (Found: C, 58·1; H, 7·8. Calc. for $C_9H_{14}O_4$: C, 58·05; H, 7·6%). It gave an *acetate*, prisms [from ether–light petroleum (b. p. 40—60°)], m. p. 80—81° (Found:

C, 57·65; H, 7·2. $C_{11}H_{16}O_5$ requires C, 57·9; H, 7·1%), a *toluene*-p-*sulphonate*, prismatic needles [from ether–light petroleum (b. p. 40—60°)], m. p. 131° (Found: C, 56·4; H, 6·1. $C_{16}H_{20}O_6S$ requires C, 56·5; H, 5·9%), and a 2,4-*dinitrophenylhydrazone*, crimson prisms (from methanol), m. p. 164—166° (Found: C, 48·7; H, 5·0; N, 15·8. $C_{15}H_{18}N_4O_7$ requires C, 49·2; H, 4·95; N, 15·3%).

Methyl 2α-*Hydroxy*-1α-*methyl*-5-*oxocyclohexane*-1β-*carboxylate* (XV; R = O).—The crude, oily 5,5-ethylenedioxy-derivative mentioned above (1·42 g.; derived from 3 hydrogenation experiments) was purified by chromatography, in benzene, on alumina (45 g.). Washing the column with benzene–ether (9 : 1) eluted first the 2α-hydroxy-epimer, an oil (1·05 g.), b. p. 96—99° (bath)/0·05 mm., $\nu_{max.}$ (liquid film) 3500 and 1725 cm.$^{-1}$. Continued washing of the column with the same solvent mixture and with benzene–methanol (20 : 1) gave oils (total 0·15 g.) which partly crystallised on being seeded with the 2β-hydroxy-epimer.

The 2α-hydroxy-epimer was selectively hydrolysed with dilute hydrochloric acid in the way described above for the 2β-hydroxy-epimer. The *product* (94%) consisted of an oil, b. p. 96—102° (bath)/0·1 mm., $\nu_{max.}$ (liquid film) 3330 and 1725 cm.$^{-1}$ (Found: C, 57·3; H, 7·65. $C_9H_{14}O_4$ requires C, 58·0; H, 7·6%).

Hydrogenation of Methyl 2β-*Hydroxy*-1α-*methyl*-5-*oxocyclohexane*-1β-*carboxylate* (XIV; R = O).—The hydroxy-ketone (3 g.) in glacial acetic acid (30 ml.) was hydrogenated at room temperature in the presence of a rather old, commercial sample of Adams platinum oxide (0·75 g.) for 18 hr. Dilution with ether, filtration, and fractional distillation of the filtrate under reduced pressure afforded an oil (2·26 g.), b. p. 95—128° (bath)/0·01 mm., which partly crystallised. It was dissolved in benzene–ether (1 : 1; 220 ml.) and chromatographed on a column of alumina (68 g.), the method of fractional elution being used,[23] to give the following fractions: (i) eluted by benzene–ether (3 : 7 and 1 : 9), an oil (0·65 g.), whose infrared spectrum resembled that of the starting material; (ii) eluted by ether (6 portions), ether–chloroform (9 : 1, 7 : 3, 1 : 1, 3 : 7, 1 : 9), and chloroform, prismatic needles (1·25 g.; m. p. 93—104°); and (iii) eluted by chloroform (2 portions) and chloroform–methanol (20 : 1), prismatic needles (0·35 g.; m. p. 104—108°). Recrystallisation of fraction (ii) from ether–light petroleum (b. p. 40—60°) yielded leaflets (1·05 g., 42%), m. p. 103—104°, $\nu_{max.}$ (in $CHCl_3$) 3564, 3467, and 1753 cm.$^{-1}$, of 2β,5β-dihydroxy-1α-methylcyclohexane-1β-carboxylic acid 1 ⟶ 5-lactone (V) (Found: C, 61·8; H, 7·7. Calc. for $C_8H_{12}O_3$: C, 61·5; H, 7·75%). It gave an *acetyl derivative*, prisms [from ether–light petroleum (b. p. 40—60°)], m. p. 77—78° (Found: C, 60·9; H, 7·3. $C_{10}H_{14}O_4$ requires C, 60·6; H, 7·1), and a 3,5-*dinitrobenzoate*, yellow prisms (from ethyl acetate), m. p. 195° (Found: C, 51·4; H, 4·3; N, 7·7. $C_{15}H_{14}N_2O_8$ requires C, 51·4; H, 4·0; N, 8·0%). Recrystallisation of fraction (iii) from ether–light petroleum (b. p. 60—80°) afforded prismatic needles (0·31 g., 10%), m. p. 106—108°, $\nu_{max.}$ 3240, 3110, and 1725 cm.$^{-1}$, of *methyl* 2β,5α-*dihydroxy*-1α-*methylcyclohexane*-1β-*carboxylate* (IX; R = Me) (Found: C, 57·9; H, 8·5. $C_9H_{16}O_4$ requires C, 57·4; H, 8·6%). Hydrolysis of the ester by boiling methanolic potassium hydroxide for 12 min. yielded 2β,5α-*dihydroxy*-1α-*methylcyclohexane*-1β-*carboxylic acid* (IX; R = H), rhombs (from ether), m. p. 133—135° (Found: C, 55·4; H, 8·2. $C_8H_{14}O_4$ requires C, 55·2; H, 8·1%).

Similar results were obtained in three other experiments in which samples from the same batch of catalyst were used; in two later experiments, somewhat different results were obtained with a fresh batch of commercial platinum oxide (which appeared to be much more active) as follows. On hydrogenation of the hydroxy-ketone (3 g.) in glacial acetic acid (30 ml.) in the presence of fresh catalyst (0·75 g.) uptake of hydrogen reached a maximum after only 2 hr.; hydrogenation was continued for 1½ hr. longer. Isolation of the product yielded an oil [2·28 g.; b. p. 85—135° (bath)/0·05 mm.] which was chromatographed on a column of alumina as described above. It was separated into (i) an oil (1·1 g.), (ii) the crystalline hydroxy-lactone (360 mg., 14%; m. p. 103—104°), and (iii) the crystalline dihydroxy-ester (451 mg., 15%; m. p. 106—108°). Purification of fraction (i) by renewed chromatography and fractional distillation gave a mobile oil (0·52 g.), b. p. 99—101°/13 mm., which is probably a hydrogenolysis product, methyl 2- or 5-hydroxy-1-methylcyclohexanecarboxylate (Found: C, 62·4; H, 9·3. Calc. for $C_9H_{16}O_3$: C, 62·8; H, 9·4%); its infrared spectrum resembled that of ethyl 2-hydroxy-1-methylcyclohexanecarboxylate.

Hydrogenation of Methyl 2α-*Hydroxy*-1α-*methyl*-5-*oxocyclohexane*-1β-*carboxylate* (XV; R = O).—The hydroxy-ketone (710 mg.) in glacial acetic acid (7 ml.) was hydrogenated in the

[23] Reichstein and Shoppee, *Discuss. Faraday Soc.*, 1949, **7**, 305.

presence of Adams platinum oxide (from the batch of old catalyst mentioned above; 175 mg.) until uptake ceased (about 3 hr.) and then for 2 hr. longer. Isolation of the product gave a viscous oil [584 mg.; b. p. 118—155° (bath)/0·1 mm.] which partly crystallised; it was chromatographed in benzene–ether (1 : 1) (60 ml.) on alumina (18 g.) to give the following fractions: (i) eluted by benzene–ether, an oil (172 mg.) which showed absorption at 3450, 1765, and 1730 cm.$^{-1}$; and (ii) eluted by ether, ether–chloroform and chloroform, crystals (382 mg., 54%), m. p. 94—98°. Hydrolysis of fraction (i) with boiling methanolic potassium hydroxide for 12 min., followed by acidification and recovery in ether, afforded a gum (143 mg.) which, in ether (40 ml.), was extracted at 0° with 2N-potassium hydrogen carbonate (2 ml.). Recovery of the neutral fraction yielded an oil (10 mg.) which, in ether, was chromatographed on alumina (0·5 g.). Elution with ether gave an oil (8 mg.), b. p. 84—88° (bath)/0·05 mm., which consisted of 2α,5β-dihydroxy-1α-methyl-1β-carboxylic acid 1 ⟶ 5-lactone (VI), identified by comparison (infrared spectrum) with a specimen prepared as described below. Recrystallisation of fraction (ii) from ether–light petroleum (b. p. 40—60°) afforded prismatic needles (320 mg.), m. p. 98—100°, $\nu_{max.}$ 3300, 3200, and 1725 cm.$^{-1}$, of *methyl 2α,5α-dihydroxy-1α-methylcyclohexane-1β-carboxylate* (X; R = Me) (Found: C, 57·6; H, 8·7. $C_9H_{16}O_4$ requires C, 57·4; H, 8·6%); hydrolysis by boiling methanolic potassium hydroxide for 15 min. of this yielded prisms (from ether), m. p. 171—172°, of *2α,5α-dihydroxy-1α-methylcyclohexane-1β-carboxylic acid* (X; R = H) (Found: C, 55·2; H, 8·2. $C_8H_{14}O_4$ requires C, 55·2; H, 8·1%).

*Attempted Replacement of the Toluene-*p*-sulphonyloxy-group in 5β-Hydroxy-1α-methyl-2β-toluene-*p*-sulphonyloxycyclohexane-1β-carboxylic Acid 1 ⟶ 5-Lactone.*—(*a*) *By means of dimethylformamide.*[24] Heating the toluene-*p*-sulphonyl derivative (100 mg.) in dimethylformamide (4 ml.) at 78° for 68 hr. and recovery gave back the starting material quantitatively.

(*b*) *By means of sodium acetate in acetic acid.* The toluene-*p*-sulphonyl derivative (336 mg.), anhydrous sodium acetate (445 mg.), and 19 : 1 glacial acetic acid–acetic anhydride (7 ml.) were boiled under reflux for 48 hr. After removal of solvents by evaporation at 25—30°/0·01 mm. the residue was treated with water (5 ml.) and extracted with 1 : 1 benzene–ether (70 ml.). The extract was washed with 2N-potasiusm hydrogen carbonate and then evaporated. The residue (193 mg.), in benzene (20 ml.), was chromatographed on alumina (6 g.). Washing the column with benzene and then with benzene–methanol (20 : 1) eluted (i) an oil (58 mg.) and (ii) needles (110 mg.; m. p. 152—156°) of starting material. Distillation of fraction (i) afforded *5β-hydroxy-1α-methylcyclohex-2-ene-1β-carboxylic acid 1 ⟶ 5-lactone* (XVI) (53 mg.), b. p. 101—106° (bath)/13 mm., $\nu_{max.}$ (liquid film) 1775 cm.$^{-1}$, $\lambda_{max.}$ (in EtOH) 214 mμ (ε 1090) (Found: C, 69·2; H, 7·6. $C_8H_{10}O_2$ requires C, 69·5; H, 7·3%).

5β-Hydroxy-1α-methyl-2-oxocyclohexane-1β-carboxylic Acid 1 ⟶ 5-Lactone.—A solution of 2β,5β-dihydroxy-1α-methylcyclohexane-1β-carboxylic acid 1 ⟶ 5-lactone (600 mg.) in purified acetone (6 ml.) was cooled to 0° and treated dropwise, with shaking, with chromium trioxide–sulphuric acid solution [12] (8N with respect to oxygen; 1·01 ml.). The mixture was kept at 0° for 30 min. and then at room temperature for 3 hr. It was cooled to 0°, treated with methanol (0·15 ml.), and evaporated at 20° *in vacuo*. The residue was treated with water and extracted with ether. Recovery from the dried (Na_2SO_4) extract afforded a solid which sublimed at 80—85° (bath)/0·01 mm. as prisms (561 mg., 95%), m. p. 88—90°, which, on recrystallisation from ether–light petroleum (b. p. 40—60°), formed prismatic needles, m. p. 91°, $\nu_{max.}$ 1765 and 1720 cm.$^{-1}$, of the *oxo-lactone* (Found: C, 62·7; H, 6·5. $C_8H_{10}O_3$ requires C, 62·3; H, 6·5%).

Reduction of 5β-Hydroxy-1α-methyl-2-oxocyclohexane-1β-carboxylic Acid 1 ⟶ 5-Lactone.—(*a*) *Catalytic reduction.* The oxo-lactone (100 mg.) in glacial acetic acid (3 ml.) was hydrogenated in the presence of Adams platinum oxide (50 mg.) for 1½ hr. (uptake of hydrogen ceased after 50 min.). Isolation by distillation followed by sublimation at 85—98° (bath)/0·05 mm. afforded crystals (95 mg.) which, with ether–light petroleum (b. p. 40—60°), were separated into (i) leaflets (68 mg.), m. p. 102—104°, (ii) leaflets (18 mg.), m. p. 101—103°, and (iii) sticky crystals (8 mg.), m. p. 37—68°. Fractions (i) and (ii) (yield 90%) consisted of 2β,5β-dihydroxy-1α-methylcyclohexane-1β-carboxylic acid 1 ⟶ 5-lactone (V), identified by mixed m. p. and infrared spectra.

(*b*) *Reduction with lithium hydridotri-t-butoxyaluminium.* A solution of the oxo-lactone (154 mg.) in purified tetrahydrofuran (4 ml.) was treated dropwise, at 0° during 8 min. with shaking, with a solution of the metal hydride [19] (1 g.) in tetrahydrofuran (10 ml.). The mixture

[24] Chang and Blickenstaff, *J. Amer. Chem. Soc.*, 1958, **80**, 2906.

was kept at 0° for 15 min. longer, treated dropwise with 1 : 1 acetic acid–water (1·5 ml.) and then concentrated to small bulk *in vacuo*. The residue was treated with water; the product was recovered in ether. Sublimation at 78—96° (bath)/0·05 mm. gave crystalline material (104 mg.) which, on recrystallisation from ether–light petroleum (b. p. 40—60°), yielded leaflets (86 mg.), m. p. 101—104°, of the 2β-hydroxy-lactone (V) and (from the mother-liquor) sticky crystals (4 mg.).

(*c*) *Reduction with aluminium isopropoxide.* A solution of the oxo-lactone (385 mg.) and aluminium isopropoxide (freshly distilled; 2·2 g.) in dry toluene (5 ml.) was boiled under reflux (oil-bath 120—135°) for 30 min., then slowly distilled during 15 min. longer (oil-bath 150—153°) in such a way that about 0·5 ml. of distillate was collected. The mixture was cooled, treated with 2N-hydrochloric acid (17 ml.), and extracted with ether (3 × 120 ml.). The extract was washed with water (5 ml.), dried (Na_2SO_4), and fractionally distilled under reduced pressure, to give an oil (360 mg.), b. p. 94—99° (bath)/0·01 mm. This was chromatographed in benzene (40 ml.) on alumina (12 g.). Washing the column successively with benzene (6 portions), benzene–methanol (200 : 1; 6 portions), and benzene–methanol (100 : 1; 5 portions) afforded the following fractions: (i) an oil (28 mg.) which showed no OH absorption but bands at 1770 and 1730—1720 cm.$^{-1}$; (ii) an oil (198 mg.), $\nu_{max.}$ (liquid film) 3450 and 1760 cm.$^{-1}$; (iii) crystals (52 mg.), m. p. 94—101°; and (iv) crystalline material [53 mg.; m. p. 98—101°, strongly depressed on admixture with material from fraction (iii)]. Distillation of fraction (ii) yielded 2α,5β-*dihydroxy*-1α-*methylcyclohexane*-1β-*carboxylic acid* 1 ⟶ 5-*lactone* (VI) (192 mg., 49%), b. p. 76—81° (bath)/0·05 mm. (Found: C, 61·4; H, 8·0. $C_8H_{12}O_3$ requires C, 61·5; H, 7·75%); it gave a 3,5-*dinitrobenzoate*, yellow prisms (from ethyl acetate), m. p. 192—193° (strongly depressed on admixture with the derivative of the 2β-hydroxy-lactone) (Found: C, 51·35; H, 4·6; N, 8·3. $C_{15}H_{14}N_2O_8$ requires C, 51·4; H, 4·0; N, 8·0%). Fraction (iii), on recrystallisation from ether–light petroleum (b. p. 40—60°), yielded leaflets (45 mg., 12%), m. p. 102—104°, of the 2β-hydroxy-lactone (V), identified by mixed m. p. and infrared spectrum. Fraction (iv), on recrystallisation from ether–light petroleum (b. p. 40—60°), gave needles (35 mg., 7%), m. p. 101°, $\nu_{max.}$ 3300—3100 (broad) and 1728 cm.$^{-1}$, of *isopropyl* 2ξ,5β-*dihydroxy*-1α-*methylcyclohexane*-1β-*carboxylate* (Found: C, 61·5; H, 9·3. $C_{11}H_{20}O_4$ requires C, 61·1; H, 9·3%).

Action of Dilute Alkali on 1 ⟶ 5-*Lactones.*—(*a*) 2β,5β-*Dihydroxy*-1α-*methylcyclohexane*-1β-*carboxylic acid* 1 ⟶ 5-*lactone* (V). A solution of the hydroxy-lactone (30 mg.) in 0·0102N-sodium hydroxide (40 ml.) was stored at room temperature for 4¼ hr. It was acidified with N-hydrochloric acid (0·6 ml.), treated with sodium chloride (7·2 g.), extracted with ether (3 × 150 ml.), and then continuously extracted with ether for 48 hr. Recovery from the extracts and sublimation at 78—120° (bath)/0·1 mm. yielded crystals (28 mg.) which on recrystallisation from ether–light petroleum (b. p. 40—60°) formed leaflets (23 mg., 77%), m. p. 102—104°, of starting material. The mother-liquor afforded a sticky solid (4 mg.) whose infrared spectrum indicated that it contained about 40% of a carboxylic acid.

(*b*) 2α,5β-*Dihydroxy*-1α-*methylcyclohexane*-1β-*carboxylic acid* 1 ⟶ 5-*lactone* (VI). A solution of the hydroxy-lactone (30 mg.) in 0·105N-sodium hydroxide (40 ml.) was stored at room temperature for 4½ hr. Treatment, as described above for the 2β-epimer, gave an oil (27 mg.), b. p. 128—142° (bath)/0·3 mm., whose infrared spectrum was identical with that of starting material. Chromatography of this on alumina, under conditions which readily effected the separation of the 2α- and the 2β-epimer, failed to detect the presence of any appreciable quantity of the latter.

In another experiment in which the hydroxy-lactone (15·1 mg.) in 0·0105N-sodium hydroxide (18·5 ml.; 2 equiv.) was stored at room temperature (24·5—25°), and aliquot portions (2·0 ml.) of the solution were removed at intervals and titrated with 0·01N-hydrochloric acid, the lactone consumed 0·5 equivalent of alkali in about 15 min.

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