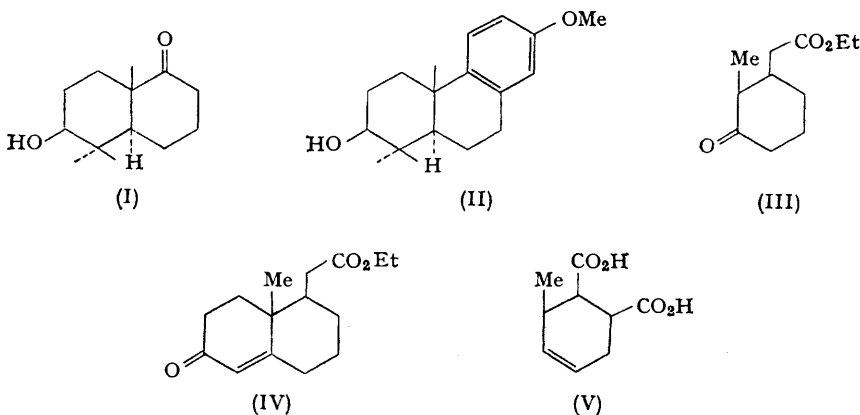


1061. Terpene Synthesis. Part IV.* The Synthesis of Oxocyclohexanecarboxylic Acids.

By F. J. McQUILLIN, W. O. ORD, and P. L. SIMPSON.

The synthesis of 4-oxocyclohexane-1,2-dicarboxylic acid derivatives of cyclohexanone from the related cyclohex-3-ene-1,2-dicarboxylic acids *via* the derived epoxide or bromo-lactone has been explored as a route to intermediates of value for terpene synthesis.

ELABORATION of the trimethyldecalone (I) or, less commonly, degradation of the aromatic ring of, *e.g.*, compound (II) have been the basis of a number of syntheses in the field of di- and higher terpenes.¹ Davis, Gupta, and Halsall² have outlined an alternative approach based on synthesis of a ketone (III) which by ring extension gave a potentially useful product (IV). We also have sought to develop intermediates of this kind starting from the readily available cyclohexenes of the type of compound (V). As a means of introduction of an oxygen function to the double bond of compound (V) we have examined the usefulness of the epoxy- and the



bromo-lactone derivatives. The epoxy-derivatives in this series do not appear to have been very fully studied.³ We first explored the chemistry of 4,5-epoxycyclohexane-1,2-dicarboxylic acid outlined in Chart 1.

Diethyl cyclohex-3-ene-1,2-dicarboxylate gave an epoxide which appeared homogeneous on careful chromatography. Hydrogenolysis either directly⁴ or by nickel treatment of the bromohydrin⁵ gave a hydroxy-ester which for the following reasons is formulated as (X). Alkaline hydrolysis of the ester (X) under mild conditions gave a hydroxy-dicarboxylic acid (XI) which by the action of acetic anhydride formed an acetoxy-anhydride (XIV), rather readily hydrolysed on standing in air to an acetoxy-dicarboxylic acid. The ester (X) after sodium ethoxide-inversion⁶ gave, on hydrolysis, a dicarboxylic acid (XII) which with acetic anhydride formed a lactone (XIII; CO₂H for CO₂Me). The hydroxyl group in structure (X)

* Part III, *J.*, 1964, 4521.

¹ Danieli, Mazur, and Sondheimer, *Tetrahedron Letters*, 1961, 310; Church, Ireland, and Marshal, *ibid.*, 1961, 34; Church and Ireland, *ibid.*, 493; Stork, Davies, and Meisels, *J. Amer. Chem. Soc.*, 1959, **81**, 5516; 1963, **85**, 3419.

² Davis, Gupta, and Halsall, *J.*, 1961, 4211.

³ (a) Gill and Munro, *J.*, 1952, 4630, (b) Gray, Heitmeier, and Kraus, *J. Amer. Chem. Soc.*, 1962, **84**, 89.

⁴ Cf. McQuillin and Ord, *J.*, 1959, 3169.

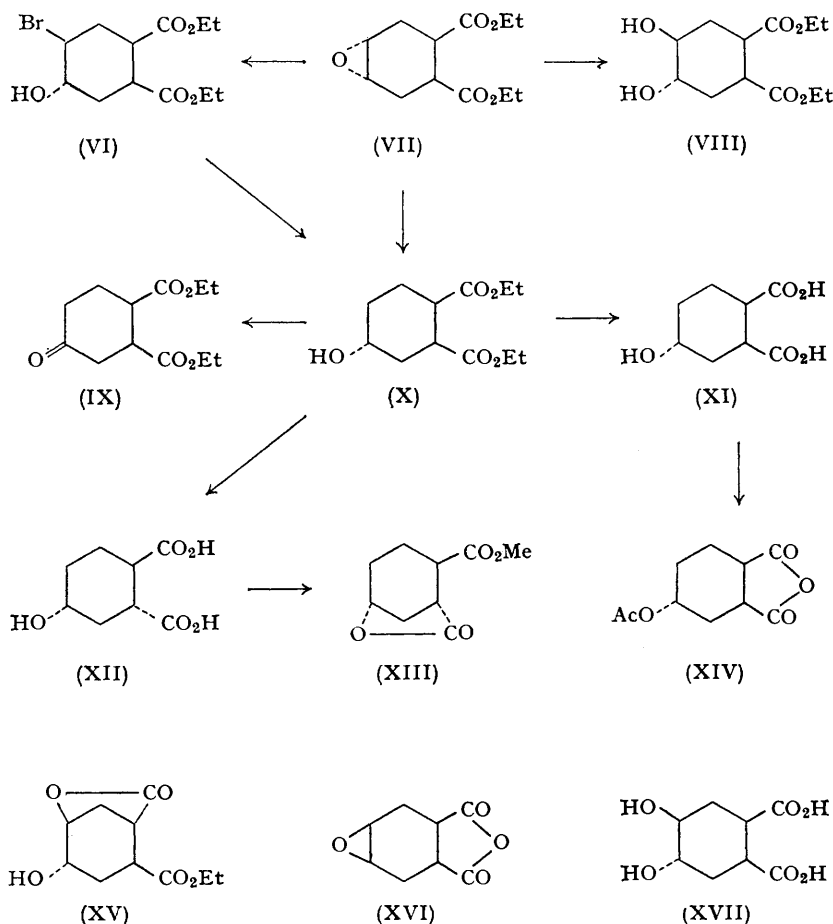
⁵ Julian, Meyer, Karpel, and Waller, *J. Amer. Chem. Soc.*, 1950, **72**, 5145.

⁶ Huckel and Goth, *Ber.*, 1925, **58**, 447.

and hence the oxido-group in structure (VII) must evidently be located on the side of the ring opposite to the carboxylic groups. In this instance therefore the reaction of the cyclohexene with peracid appears to be directed by steric repulsion.⁷

Catalytic hydrogenolysis of the oxide (VII) was found to be very slow, but the hydroxy-ester (X) could be obtained by the use of platinum in ethyl acetate containing a little sulphuric acid.⁴ With platinum in acetic acid compound (VII) absorbed no hydrogen over several

CHART I

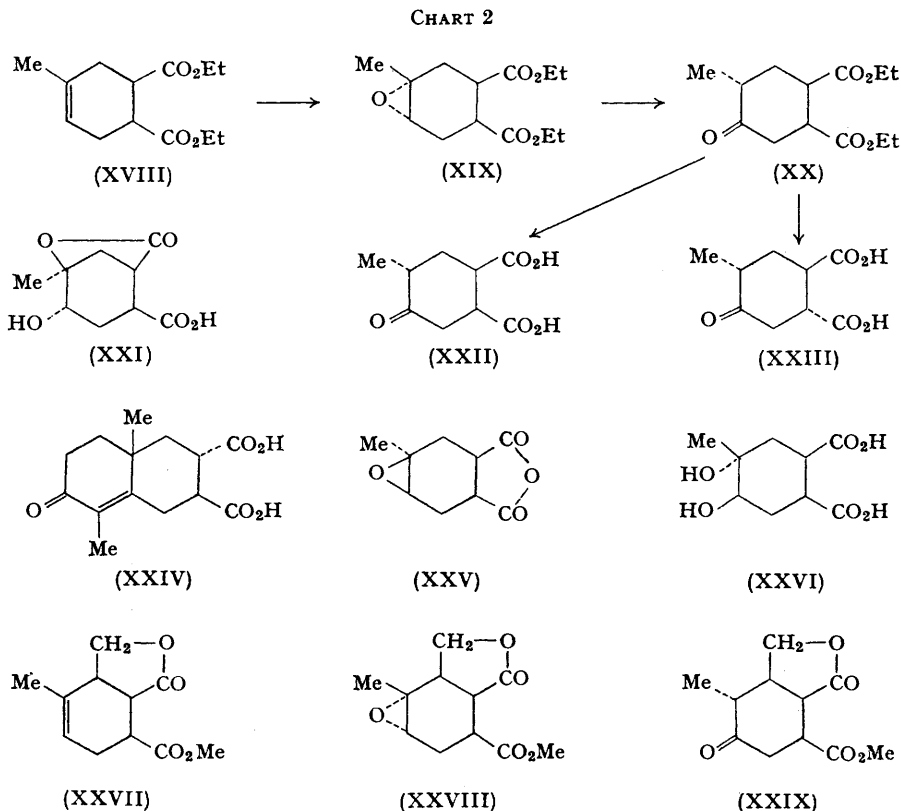


days, but the recovered material gave infrared evidence for the presence of lactonic, ester, and hydroxyl-groups. This product is evidently compound (XV). We confirmed the formation and properties of epoxytetrahydrophthalic anhydride already shown^{3b} to have the structure (XVI).

Starting from 4-methylcyclohex-4-ene-1,2-dicarboxylic acid we examined also the sequence (XVIII) \rightarrow (XX). In this case boron trifluoride treatment of the oxide, which by analogy with (VII) is formulated as (XIX), gave a ketone, (XX), in high yield. In the simpler case of the oxide (VII) attempts to rearrange it by means of boron trifluoride gave only polymeric material (cf. ref. 3a). The oxo-dicarboxylic ester (XX) could be hydrolysed to a crystalline dicarboxylic acid (XXII), or after prior inversion of the ester, to an isomeric acid (XXIII). By the Robinson annelation procedure the oxo-diester (XX) was converted

⁷ Cf. Henbest, *Proc. Chem. Soc.*, 1963, 159.

into a bicyclic ketone in acceptable yield. The annelation procedure, which uses strong base, may result in some inversion of the configuration of the ester groups. The whole reaction product was therefore subjected to vigorous hydrolysis and re-esterification to give a substance which we regard as having structure (XXIV; CO₂Me for CO₂H).



Peracid treatment of 4-methylcyclohex-4-ene-1,2-dicarboxylic acid led directly to a lactone monocarboxylic acid, most reasonably represented as (XXI). Methylcyclohexenedicarboxylic anhydride gave an oxide and the derived hydroxy-acid, (XXVI); by analogy with the evidence of Gray, Heitsmeier, and Kraus^{3b} regarding compound (VII) this oxide is represented as (XXV).

The principles established in these transformations were extended to the synthesis of a product (XXIX) which carries substituents similar to those found in a number of sesquiterpenes. Diels-Alder addition⁸ of maleic anhydride and 3-methylpenta-2,4-dienol⁹ followed by methylation of the product gave compound (XXVII) in good yield. The oxido-derivative, regarded as (XXVIII), was found to be rearranged by the action of boron trifluoride to a ketone (XXIX). The yield in this rearrangement was rather less satisfactory than in the case of (XIX) → (XX).

In parallel with this synthesis of compound (XXIX) we examined also an alternative scheme set out in Chart 3.

Bromine addition to (XXX), the adduct¹⁰ of maleic anhydride and *trans*-penta-2,4-diene, appeared likely to lead to a bromo-lactone (XXXI; R = H) in which the methyl and the

⁸ Heilbron, Jones, McCombie, and Weedon, *J.*, 1945, 84; Cymerman, Heilbron, and Jones, *ibid.*, p. 90.

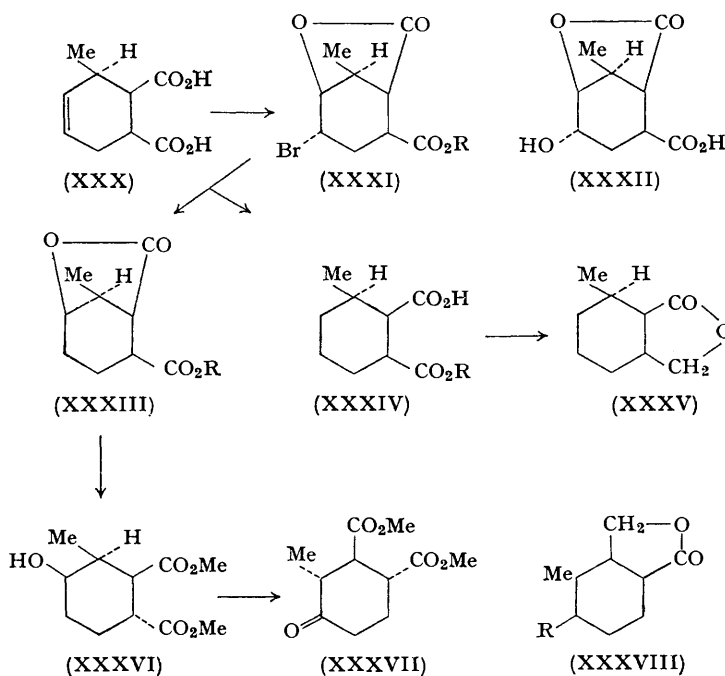
⁹ Hennion and Lieb, *J. Amer. Chem. Soc.*, 1944, 66, 1289.

¹⁰ Craig, *J. Amer. Chem. Soc.*, 1950, 72, 1687.

carboxyl groups are equatorially oriented. The adduct (XXX), by the action of *N*-bromosuccinimide and water,¹¹ gave in fact a single product which was shown to be the expected bromo-lactone (XXXI; R = H). The lactone reformed the parent olefinic acid (XXX) by zinc-acetic acid treatment, and by acid hydrolysis gave a hydroxy-lactone (XXXII) identical with the product of treating compound (XXX) with peracetic acid.

We examined the removal of bromine from the bromo-lactone by catalytic hydrogenolysis.¹² At palladised charcoal in alcohol, the compound (XXXI; R = H), or its derived methyl ester (XXXI; R = Me), was found to absorb up to 1.6 molar equivalents of hydrogen to give a product consisting of a mixture of the debrominated lactone (XXXIII; R = H or Me) and the cyclohexanedicarboxylic acid (XXXIV; R = H), or its methyl ester (XXXIV; R = Me). The lactone ester (XXXIII; R = Me) was found quite stable to hydrogenolysis and does not therefore appear to be an intermediate between the bromo-lactone (XXXI) and the dicarboxy-cyclohexane (XXXIV; R = H or Me). The bromo-lactone (XXXI; R = H) or its ester (R = Me) failed to take up hydrogen unless the solution was buffered to low acidity; an addition of at least one equivalent of potassium acetate was found effective. The bromo-lactone ester (XXXI; R = Me) was hydrogenated also in ethanol containing suspended alumina, and the bromo-lactone acid (XXXI, R = H) could be hydrogenated as its mono-sodium salt in water.

CHART 3



The monomethyl ester (XXXIV; R = Me) obtained from hydrogenolysis of the bromo-lactone ester (XXXI; R = Me), by lithium aluminium hydride reduction gave a lactone (XXXV) which by dehydrogenation with palladium on charcoal gave *m*-xylene in high yield. The eliminated carboxyl is clearly one terminus of the lactone group in compound (XXXI). The lactonic product of hydrogenation (XXXIII; R = Me) by treatment with sodium methoxide gave a hydroxy-dicarboxylic ester (XXXVI) which could be oxidised to the keto-dicarboxylic ester (XXXVII). Dehydrogenation of the latter gave *o*-cresol thus

¹¹ Guss and Rosenthal, *J. Amer. Chem. Soc.*, 1955, **77**, 2549.

¹² Cf. Fieser and Ettore, *J. Amer. Chem. Soc.*, 1953, **75**, 1700; Fieser and Huang, *ibid.*, p. 4837.

locating the position of the oxygen terminus of the lactone group in (XXXIII; R = Me) and so determining the structure of the parent bromo-lactone as (XXXI). The lactonic product of hydrogenation (XXXIII; R = H) could be converted by lithium aluminium hydride reduction into a new lactone, clearly (XXXVIII; R = OH), which was oxidised to the corresponding ketone, (XXXVIII; R = O).

The stereochemistry of the bromo-lactone (XXXI) and the derived products (XXXIII), (XXXIV), and (XXXV) is assigned on the basis of the established¹⁰ orientation of groups in the starting material (XXX). During alcoholysis with sodium methoxide, however, the lactone (XXXIII; R = Me) will be subject to equilibration at the carbomethoxy-substituted centres. The product (XXXVI) and the derived keto-ester (XXXVII) are therefore represented with the more stable configuration at centres subject to inversion.

EXPERIMENTAL

Nomenclature.—The relative orientation of substituents is referred to the plane of the cyclohexane ring, *i.e.* α , below, and β , above this plane.

4,5 β -Epoxy cyclohexane-1 β ,2 β -dicarboxylic Anhydride (XVI).— Δ^4 -Tetrahydrophthalic anhydride (15.2 g.) in chloroform (100 c.c.) kept in the refrigerator (36 hr.) with peracetic acid (1.1 equivalents) gave 4,5 β -epoxycyclohexane-1,2 β -dicarboxylic anhydride (2.4 g.), m. p. 195°, together with a quantity of recovered Δ^4 -tetrahydrophthalic anhydride. Gray, Heitmeier, and Kraus^{3b} give m. p. 193°.

4 α ,5 β -Dihydroxycyclohexane-1 β ,2 β -dicarboxylic Acid (XVII).—4,5-Epoxy cyclohexane-1,2-dicarboxylic anhydride (0.16 g.) in 0.01N-aqueous sulphuric acid (10 c.c.) gave 4 α ,5 β -dihydroxycyclohexane-1 β ,2 β -dicarboxylic acid (0.1 g.), m. p. 157—158° (gas evolved at 134—148°) (Found: C, 47.5; H, 6.3. C₈H₁₂O₆ requires C, 47.1; H, 5.9%).

Diethyl 4,5 α -Epoxy cyclohexane-1 β ,2 β -dicarboxylate (VII).—Diethyl cyclohex-4-ene-*cis*-1,2-dicarboxylate¹³ (22 g.) in chloroform (50 c.c.) kept overnight at room temperature with perbenzoic acid (1.1 eq.) in chloroform gave diethyl 4,5 α -epoxycyclohexane 1 β ,2 β -dicarboxylate (22.0 g., 94%), b. p. 117—120°/0.6 mm., n_D^{20} 1.4629 (Found: C, 59.7; H, 7.5. C₁₂H₁₈O₅ requires C, 59.4; H, 7.4%).

Diethyl 4 α ,5 β -Dihydroxycyclohexane-1 β ,2 β -dicarboxylate (VIII).—Diethyl 4,5 α -epoxycyclohexane-1 β ,2 β -dicarboxylate (2.4 g.) in acetone (30 c.c.) and water (3 c.c.) containing boron trifluoride etherate (3 drops) was kept overnight, and the solution then concentrated (*in vacuo*) to give the diester (1.8 g.), b. p. 158—163°/0.05 mm., n_D^{20} 1.4775 (Found: C, 55.5; H, 8.0. C₁₂H₂₀O₆ requires C, 55.3; H, 7.7%).

Diethyl 4 α -Hydroxycyclohexane-1 β ,2 β -dicarboxylate (X).—(i) Hydrogen bromide in acetic acid (50%, 3 c.c.) was added slowly with cooling (5—10°) to diethyl 4,5 α -epoxycyclohexane-1 β ,2 β -dicarboxylate (2 g.) in chloroform (15 c.c.) and the solution was kept for 2 hr. to give 5 β -bromo-4 α -hydroxycyclohexane-1 β ,2 β -dicarboxylate (2.7 g., 95%), b. p. 158—160°/0.4 mm., n_D^{20} 1.4965 (Found: C, 44.7; H, 6.0. C₁₂H₁₆BrO₅ requires C, 44.5; H, 5.9%). This substance (2.5 g.) in ethanol (90 c.c.) with freshly prepared Raney nickel (13 g.) was heated under reflux for 6 hr. to obtain the hydroxy-diester (1.4 g., 78%), b. p. 120°/0.55 mm., n_D^{20} 1.4663 (Found: C, 58.7; H, 8.1. C₁₂H₂₀O₅ requires C, 58.8; H, 8.2%), 3,5-dinitrobenzoate, m. p. 109° (Found: C, 51.8; H, 5.45. C₁₉H₂₂N₂O₁₀ requires C, 51.9; H, 5.05%).

(ii) Diethyl 4,5 α -epoxycyclohexane-1 β ,2 β -dicarboxylate (1.5 g.) was hydrogenated over platinum oxide (2.2 g.) in dry ethyl acetate (30 c.c.) containing sulphuric acid (1 drop). The hydrogen uptake was 200 c.c. over three days, a fresh batch of catalyst being added each day. Distillation gave some recovered oxide (0.8 g.), b. p. 90°/0.05 mm., n_D^{20} 1.4584, and the hydroxy-diester (0.3 g.), b. p. 125°/0.05 mm., n_D^{20} 1.4680 (Found: C, 58.6; H, 8.3%), which gave an infrared spectrum identical with that of the material obtained as described above.

2 β -Ethoxycarbonyl-4,5-dihydroxycyclohexane-1 β -carboxylic Acid 1 \rightarrow 5-Lactone (XV).—An attempt to hydrogenate diethyl 4,5 α -epoxycyclohexane-1 β ,2 β -dicarboxylate (0.1 g.) at platinum in acetic acid (5 c.c.) was continued for 5 days, a fresh batch of catalyst being added each day. Very little hydrogen was taken up. The recovered material consisted of the γ -lactone (0.08 g.), b. p. 130°/0.3 mm., n_D^{20} 1.4788, showing strong infrared absorption at 3540 (hydroxyl), 1784 (γ -lactone), and 1736 cm.⁻¹ (ester) (Found: C, 56.3; H, 6.9. C₁₀H₁₄O₅ requires C, 56.1; H, 6.6%).

¹³ Cope and Herrick, *Org. Synth.*, 1950, **30**, 29.

Diethyl 4-Oxocyclohexane-cis-1,2-dicarboxylate (IX).—Diethyl 4 α -hydroxycyclohexane-1 β ,2 β -dicarboxylate (0.5 g.) in acetic acid (3 c.c.) with chromium trioxide (0.2 g.) in water (3 c.c.), kept for 4 days, gave the *ketone* (0.35 g.), b. p. 95°/0.05 mm., n_D^{20} 1.4649 (Found: C, 59.4; H, 7.8. C₁₂H₁₈O₅ requires C, 59.4; H, 7.5%); *semicarbazone*, m. p. 159—160° (from methanol) (Found: C, 52.3; H, 7.0. C₁₃H₂₁O₅N₃ requires C, 52.2; H, 7.0%).

4 α -Hydroxycyclohexane-1 β ,2 β -dicarboxylic Acid (XI).—Diethyl 4 α -hydroxycyclohexane-1 β ,2 β -dicarboxylate (2.3 g.) in dioxan (20 c.c.) was kept with *N*-sodium hydroxide (30 c.c.). The hydrolysis, followed by titration, was complete after 4 hr. The solution was acidified to pH 3 and evaporated to dryness. The residue extracted with hot ethyl acetate gave an oil (2 g.) which crystallised to yield the *diacid* (1.6 g.), m. p. 183—184° (from ethyl acetate) (Found: C, 51.0; H, 6.6. C₈H₁₂O₅ requires C, 51.0; H, 6.4%).

4 α -Acetoxycyclohexane-1 β ,2 β -dicarboxylic Anhydride (XIV).—The foregoing diacid (0.3 g.) refluxed with acetic anhydride (1.5 hr.) and evaporated gave *4 α -acetoxycyclohexane-1 β ,2 β -dicarboxylic anhydride* (0.25 g.), m. p. 94° (from ethyl acetate—light petroleum) (Found: C, 56.4; H, 5.8. C₁₀H₁₂O₅ requires C, 56.5; H, 5.6%). After standing exposed to the atmosphere for several days this material was hydrolysed to form *4 α -acetoxycyclohexane-1 β ,2 β -dicarboxylic acid*, m. p. 161—162° (Found: C, 52.6; H, 5.8. C₁₀H₁₄O₆ requires C, 52.3; H, 6.1%).

4 α -Hydroxycyclohexane-1 β ,2 α -dicarboxylic Acid (XII).—(i) Diethyl 4 α -hydroxycyclohexane-1 β ,2 β -dicarboxylate (0.45 g.) was kept overnight under nitrogen in ethanolic sodium ethoxide (50%; 9 c.c.). Water (3 c.c.) was added and the solution heated (nitrogen, 4 hr.), acidified to pH 3, and evaporated. Extraction (hot ethyl acetate) gave the *1 β ,2 α -dicarboxylic acid* (0.25 g.), m. p. 194° (Found: C, 51.4; H, 6.2. C₈H₁₂O₅ requires C, 51.0; H, 6.4%).

(ii) This product could also be obtained as follows. Diethyl 4,5 α -epoxycyclohexane-1 β ,2 β -dicarboxylate (6 g.) in dry ether (40 c.c.) was added with stirring to sodium (1.3 g.) in liquid ammonia (100 c.c.) and after 0.5 hr. ammonium chloride (3 g.) was added and the ammonia allowed to evaporate. The residue, taken up in a little water and extracted with ether, gave the *2 β -ethoxycarbonyl-5 α -hydroxycyclohexane-1 α -carboxylic acid lactone* (2.9 g., 59%), b. p. 117—124°/1.7 mm., n_D^{20} 1.4668 (Found: C, 60.55; H, 7.3. C₁₀H₁₄O₄ requires C, 60.55; H, 7.3%). This lactone (0.6 g.) was kept overnight with potassium hydroxide (0.85 g.) in 60% aqueous ethanol (30 c.c.) and the solution was then acidified and evaporated. Extraction with acetone gave *4 α -hydroxycyclohexane-1 β ,2 α -dicarboxylic acid* (0.2 g.), as above, m. p. 195° (Found: C, 50.7; H, 6.4%).

5 α -Hydroxy-2 β -methoxycarbonylcyclohexane-1 α -carboxylic Acid Lactone (XIII).—Cyclohexan-4 α -ol-1 β ,2 α -dicarboxylic acid (0.2 g.) refluxed with acetic anhydride (15 hr.) and evaporated gave an oil which was methylated with diazomethane to give the *γ -lactone* (0.1 g.), b. p. 110—116°/1.5 mm., n_D^{20} 1.4670 (Found: C, 58.9; H, 6.9. C₉H₁₂O₄ requires C, 58.7; H, 6.5%).

4-Methylcyclohex-4-ene-cis-1,2-dicarboxylic Anhydride.—Maleic anhydride (22 g.) and isoprene (22 g.) in benzene (200 c.c.) were kept in the refrigerator overnight and for a further day at room temperature to give *4-methylcyclohex-4-ene-1,2-dicarboxylic anhydride* (32 g., 82%), m. p. 64° (from benzene—light petroleum) (lit.,¹⁴ 64°). Hydrolysis gave *4-methylcyclohex-4-ene-cis-1,2-dicarboxylic acid*, m. p. 159° (lit.,¹⁴ 148°) (Found: C, 58.4; H, 6.8. Calc. for C₉H₁₂O₄: C, 58.6; H, 6.5%).

4,5 β -Epoxy-4 α -methylcyclohexane-1 β ,2 β -dicarboxylic Anhydride (XXV).—Peracetic acid solution (1.1 eq.) with 4-methylcyclohex-4-ene-*cis*-1,2-dicarboxylic anhydride (2 g.) in chloroform (20 c.c.) were kept overnight in the refrigerator. The solution, concentrated *in vacuo* at room temperature, gave the anhydride (0.8 g.), m. p. 110—111° (from benzene) (Found: C, 59.3; H, 5.5. C₉H₁₀O₄ requires C, 59.3; H, 5.5%).

4 α ,5 β -Dihydroxy-4 β -methylcyclohexane-1 β ,2 β -dicarboxylic Acid (XXVI).—4,5-Epoxy-4 α -methylcyclohexane-1,2 β -dicarboxylic anhydride (0.1 g.) in wet benzene (10 c.c.) refluxed (2 hr.) gave the *dihydroxydicarboxylic acid* (0.11 g., 91%), m. p. 158—159° (from acetone) (Found: C, 49.45; H, 6.55. C₉H₁₄O₆ requires C, 49.4; H, 6.4%).

4 β ,5 α -Dihydroxy-4 α -methylcyclohexane-1 β ,2 β -dicarboxylic Acid 2 \rightarrow 4-Lactone (XXI).—Peracetic acid (1.1 equiv.) and 4-methylcyclohex-4-ene-1,2-dicarboxylic acid (2.85 g.) in chloroform (20 c.c.) and methanol (20 c.c.) were kept (refrigerator) overnight. Concentration (*in vacuo*) followed by addition of light petroleum gave the *γ -lactone* (1.5 g.), m. p. 180—181° (from acetone) (Found: C, 53.7; H, 6.2. C₉H₁₂O₅ requires C, 53.9; H, 6.0%).

Diethyl 4,5 α -Epoxy-4 β -methylcyclohexane-1 β ,2 β -dicarboxylate (XIX).—Diethyl 4-methyl-

¹⁴ Boeseken and Van der Gracht, *Rec. Trav. chim.*, 1937, **56**, 1203.

cyclohex-4-ene-*cis*-1,2-dicarboxylate¹⁵ (XVIII), b. p. 94—96°/0.4 mm. n_D^{20} 1.4625 was obtained from the acid in 80% yield by the method of Cope and Herrick.¹³ Perbenzoic acid in chloroform gave the *diester* (91%), b. p. 119°/0.5 mm., n_D^{20} 1.4580 (Found: C, 61.0; H, 7.95. C₁₃H₂₀O₅ requires C, 60.8; H, 7.8%).

Diethyl 5 α -Methyl-4-oxocyclohexane-1 β ,2 β -dicarboxylate (XX).—The foregoing epoxide (1 g.) in dry benzene (25 c.c.) with boron trifluoride ether complex (0.1 c.c.) was kept for 2 hr. Washed with aqueous sodium hydrogen carbonate solution the product gave the *ketone* (1 g.), b. p. 95°/0.2 mm., n_D^{20} 1.4610 (Found: C, 60.5; H, 8.1. C₁₃H₂₀O₅ requires C, 60.8; H, 7.8%), infrared absorption: 1733 (ester), and 1715 cm.⁻¹ (saturated ketone); 2,4-dinitrophenylhydrazone, m. p. 128—129° (from ethanol) (Found: C, 52.1; H, 5.8. C₁₉H₂₄N₄O₈ requires C, 52.2; H, 5.5%). From a larger-scale experiment we isolated also a small yield of what was presumably *diethyl 4 β ,5 α -dihydroxy-4 α -methylcyclohexane-1 β ,2 β -dicarboxylate*, m. p. 123—124° (from benzene—light petroleum) (Found: C, 56.9; H, 8.1. C₁₃H₂₂O₆ requires C, 56.8; H, 8.0%).

5 α -Methyl-4-oxocyclohexane-1 β ,2 β -dicarboxylic Acid (XXII).—This was obtained, m. p. 150.5—151.5° (from dry ethyl acetate—dry benzene) (Found: C, 54.2; H, 6.1. C₉H₁₂O₅ requires C, 54.0; H, 6.0%), from hydrolysis of the diethyl ester with sodium hydroxide in aqueous dioxan at the ordinary temperature.

5 α -Methyl-4-oxocyclohexane-1 β ,2 β -dicarboxylic Acid (XXIII).—The above *cis*-diester (XX) (0.4 g.) kept in ethanolic sodium ethoxide (10%, 10 c.c.), before hydrolysis gave the *trans*-*diacid* (0.2 g.), m. p. 169—170° (Found: C, 54.0; H, 6.0%).

3 β -Hydroxymethyl-4-methylcyclohex-4-ene-1 β ,2 β -dicarboxylic Acid γ -Lactone.—3-Methylpenta-1,4-dien-3-ol⁹ (6 g.) in 1% aqueous sulphuric acid (20 c.c.) with a little hydroquinone was shaken for 4 hr. in nitrogen. The resulting 3-methylpenta-2,4-dien-1-ol was taken into ether by continuous extraction. The ethereal solution was dried (K₂CO₃) and concentrated by distillation through a short column, and to the residue maleic anhydride (6 g.) in dry benzene (30 c.c.) was added with cooling. After 1 hr. the γ -lactone (5 g., 41%) was obtained, m. p. 180—181° (from ethyl acetate—ethanol) (Found: C, 60.9; H, 6.2. C₁₀H₁₂O₄ requires C, 61.2; H, 6.1%). Diazomethane gave the γ -lactone *methyl ester* (XXVII), m. p. 92° (from benzene—light petroleum) (Found: C, 62.8; H, 6.8. C₁₁H₁₄O₄ requires C, 62.8; H, 6.6%).

3,4 α -Epoxy-2 β -hydroxymethyl-6 β -methoxycarbonyl-3 β -methylcyclohexane-1 β -carboxylic Acid γ -Lactone (XXVIII).—Perbenzoic acid (1.1 equivalents) in chloroform was added slowly with cooling and stirring to a solution of the foregoing γ -lactone methyl ester (6 g.) in chloroform, and the mixture was kept overnight in the refrigerator. The solution, washed with aqueous sodium carbonate and water and then dried, gave the γ -lactone (5.5 g., 85%), m. p. 135.5° (from ethanol—benzene) (Found: C, 58.2; H, 6.6. C₁₁H₁₄O₅ requires C, 58.3; H, 6.2%).

2 β -Hydroxymethyl-6 β -methoxycarbonyl-3 α -methyl-4-oxocyclohexane-1 β -carboxylic Acid γ -Lactone (XXIX).—3,4 β -Epoxy-2 β -hydroxymethyl-6 β -methoxycarbonyl-3 α -methylcyclohexane-1 β -carboxylic acid γ -lactone (0.5 g.) in dry benzene (25 c.c.) was heated gently under reflux for 2 hr. with boron trifluoride etherate (0.25 c.c.). The solution, washed with dilute aqueous sodium hydrogen carbonate and water, and then dried, gave the γ -lactone (0.2 g., 40%), m. p. 141° (from ethyl acetate) (Found: C, 58.4; H, 6.3. C₁₁H₁₄O₅ requires C, 58.3; H, 6.2%). 2,4-dinitrophenylhydrazone, m. p. 224° (from ethyl acetate) (Found: C, 50.0; H, 4.7. C₁₇H₁₈N₄O₈ requires C, 50.3; H, 4.5%).

5 α -Bromo-4 β -hydroxy-3 β -methylcyclohexane-1 β ,2 β -dicarboxylic Acid 2 \rightarrow 4-Lactone (XXXI; R = H).—*N*-Bromosuccinimide (60 g.) was added with vigorous stirring to 3 β -methylcyclohex-4-ene-1 β ,2 β -dicarboxylic acid¹⁰ (50 g.) dissolved in water (250 c.c.) at 50°. After 3 hr. the product was filtered and washed with warm water to give the γ -lactone (48.6 g., 65%), m. p. 222°, which was recrystallised from ethyl acetate, infrared absorption: 1779 (γ -lactone) and 1705 cm.⁻¹ (carboxylic acid) (Found: C, 41.0; H, 4.5. C₉H₁₁BrO₄ requires C, 41.0; H, 4.3%).

4 β ,5 α -Dihydroxy-3 β -methylcyclohexane-1 β ,2 β -dicarboxylic Acid 2 \rightarrow 4-Lactone (XXXII).—(i) The foregoing γ -lactone (XXXI) (0.5 g.) was dissolved in sulphuric acid solution (10%) by heating. The solution was then adjusted to pH 4 with sodium hydroxide solution and the liquid evaporated. The residue extracted with ethyl acetate (2 \times 50 c.c. portions) gave the γ -lactone (0.32 g., 75%), m. p. 190° from ethyl acetate, infrared absorption: 3410 (hydroxyl), 1764 (γ -lactone) and 1724 cm.⁻¹ (carboxylic acid) (Found: C, 53.5; H, 6.2. C₉H₁₂O₅ requires C, 53.9; H, 6.0%).

(ii) Peracetic acid¹⁶ solution was added to 3 β -methylcyclohex-4-ene-1 β ,2 β -dicarboxylic acid

¹⁵ Bailey, Rosenberg, and Young, *J. Amer. Chem. Soc.*, 1954, **76**, 2251.

¹⁶ Hopff and Hoffman, *Helv. Chim. Acta*, 1957, **40**, 1585.

(5 g.) in chloroform (10 c.c.) and methanol (10 c.c.) and the mixture kept 2 days at 0°. Cautious removal of solvent left a residue which crystallised to give the γ -lactone (3.1 g., 70%), m. p. and mixed m. p. 190°, with the substance obtained as described in (i) above.

Debromination of the γ -Lactone (XXXI; R = H).—(a) *Zinc dust reduction.* The lactone (0.5 g.) in acetic acid (25 c.c.) with zinc powder (1 g.) was heated (5 hr.). The zinc was filtered and the filtrate evaporated. The residue extracted with ethyl acetate gave 3 β -methylcyclohex-4-ene-1 β ,2 β -dicarboxylic acid (0.3 g., 75%), m. p. and mixed m. p. 153° with an authentic sample.

(b) *Raney nickel treatment.* The lactone (0.5 g.) was titrated with sodium hydroxide solution to form the monosodium salt. Freshly prepared Raney nickel (5 g.) and ethanol (50 c.c.) was added and the mixture was refluxed (6 hr.). The nickel was filtered, the filtrate evaporated, and the product, released by acidification, was extracted (ethyl acetate) to give a solid, m. p. 145° (from ethyl acetate) (0.05 g., *i.e.* 15%). The remaining material was retained on the nickel.

(c) *Hydrogenation.* (i) The lactone (0.5 g.) with palladium-charcoal catalyst (0.2 g.) in ethanol or in acetic acid (25 c.c.) with potassium acetate (1.2 g.) took up no hydrogen in 12 hr.

(ii) The lactone (0.5 g.) was titrated with sodium hydroxide solution (5%), using phenolphthalein, to form the monosodium salt and then hydrogenated in ethanol (20 c.c.) with palladium-charcoal (0.5 g.). After the uptake of 1 mole of hydrogen (46 c.c.), the material still contained bromine; after the reaction had been allowed to go to completion, 74 c.c. (1.6 mole) hydrogen had been adsorbed. The product, extracted (ethyl acetate) after evaporation, formed the solid, m. p. 142° (0.29 g., 85%), as was obtained from Raney nickel reduction.

(iii) Hydrogenated in ethanol (40 c.c.) with potassium acetate (0.25 g.) and catalyst (0.2 g.), the lactone adsorbed 92 c.c. (1.65 moles) of hydrogen. The product (0.32 g., 87%) formed a solid, m. p. 142°, from ethyl acetate.

(iv) The lactone (0.057 g.), hydrogenated in dioxan (8 c.c.) with palladium on charcoal (0.025 g.) in the presence of potassium acetate (0.025 g.) absorbed 8.9 c.c. (1.7 moles) of hydrogen to give the same product (0.027 g., 69%), m. p. 142° as above.

The material, m. p. 142°, from these experiments was separated to give 3 β -methylcyclohexane-1 β ,2 β -dicarboxylic acid,¹⁰ m. p. 169°, and 4 β -hydroxy-3 β -methylcyclohexane-1 β ,2 β -dicarboxylic acid 2 \rightarrow 4-lactone as plates, m. p. 160–161° (from ethyl acetate), infrared absorption 3185 (hydrogen bonded carboxylic acid), 1751 (γ -lactone), and 1718 cm.⁻¹ (carboxylic acid) (Found: C, 58.6; H, 6.6. C₉H₁₂O₄ requires C, 58.7; H, 6.5%).

Debromination of Lactone (XXXI; R = Me).—5 α -Bromo-4 β -hydroxy-3 β -methylcyclohexane-1 β ,2 β -dicarboxylic acid (1 g.) in methanol (35 c.c.) with a small excess of diazomethane, gave the 2 \rightarrow 4-lactone methyl ester (0.95 g., 92%), as plates, m. p. 72° (from ether-light petroleum), infrared absorption 1779 (γ -lactone) and 1733 cm.⁻¹ (ester) (Found: C, 43.3; H, 4.7%).

(i) This lactone (0.63 g.) with palladised charcoal (0.2 g.) and potassium acetate (0.25 g.) in ethanol (30 c.c.) and water (10 c.c.) absorbed 89 c.c. (1.6 moles) of hydrogen to give a product which was separated into acidic and neutral fractions. The latter formed needles, m. p. 71° (from ethyl acetate-light petroleum), of 4 β -hydroxy-1 β -methoxycarbonyl-3 β -methylcyclohexane-2 β -carboxylic acid lactone (0.20 g., 45%), infrared absorption: 1773 (γ -lactone) and 1727 cm.⁻¹ (ester) (Found: C, 60.4; H, 7.5. C₁₀H₁₄O₄ requires C, 60.6; H, 7.2%). The acid product gave 1 β -methoxycarbonyl-3 β -methylcyclohexane-2 β -carboxylic acid (0.22 g., 49%), as plates, m. p. 101° (from ethyl acetate), infrared absorption: 1735 (ester), and 1704 cm.⁻¹ (carboxylic acid) (Found: C, 59.9; H, 7.9. C₁₀H₁₆O₄ requires C, 60.0; H, 8.0%).

(ii) 5 α -Bromo-4 β -hydroxy-1 β -methoxycarbonyl-3 β -methylcyclohexane-2 β -carboxylic acid lactone (9.6 g.) was heated in ethanol (500 c.c.) with freshly prepared Raney nickel (approx. 40 g.) for 5 hr. The neutral product (3.5 g., 50%) was 4 β -hydroxy-1 β -methoxycarbonyl-3 β -methylcyclohexane-2 β -carboxylic acid lactone, m. p. 71°, as in (i) above. The acidic product amounted to only 0.5 g. (7%) of 1 β -methoxycarbonyl-3 β -methylcyclohexane-2 β -carboxylic acid, m. p. 101°, as in (i) above. The remainder of the material, presumably acidic, remained on the nickel.

4 β -Hydroxy-1 β -methoxycarbonyl-3 β -methylcyclohexane-2 β -carboxylic acid lactone was hydrolysed to give 4 β -hydroxy-3 β -methylcyclohexane-1 β ,2 β -dicarboxylic acid 2 \rightarrow 4-lactone, m. p. 160°, identical with that of a previous sample.

Dimethyl 5 α -Bromo-4 β -hydroxy-3 β -methylcyclohexane-1,2-dicarboxylate.—3 β -Methylcyclohex-4-ene-1 β ,2 β -dicarboxylic acid (5 g.) in ethanol (100 c.c.) esterified with diazomethane, gave dimethyl 3 β -methylcyclohex-4-ene-1 β ,2 β -dicarboxylate (94.2 g., 82%), b. p. 88°/0.5 mm.,

n_D^{20} 1.4695, Sopov¹⁷ gives b. p. 144°/20 mm., n_D 1.4706. *N*-Bromosuccinimide (4 g.) in dioxan (20 c.c.) and water (20 c.c.) was added with stirring to dimethyl 3 β -methylcyclohex-4-ene-1 β ,2 β -dicarboxylate (4 g.) in dioxan (30 c.c.) at 50°. After 2 hr., excess of hypobromite was destroyed by sulphur dioxide and the mixture was diluted and extracted with chloroform. Distillation gave (i) material b. p. 145°/0.1 mm., which gave 5 α -bromo-4 β -hydroxy-1 β -methoxycarbonyl-3 β -methylcyclohexane-2 β -carboxylic acid lactone (0.5 g., 10%), m. p. 70°, (ii) an intermediate fraction, and (iii) 1.1 g. (20%) of the *dimethyl ester*, b. p. 160°/0.1 mm., forming plates, m. p. 95° (from ethyl acetate—light petroleum), infrared absorption: 3509 (hydroxyl) and 1724, 1712 cm.⁻¹ (dicarboxylic ester) (Found: C, 43.0; H, 5.5. C₁₁H₁₇BrO₅ requires C, 42.7; H, 5.5%).

2 β -Hydroxymethyl-6 β -methylcyclohexane-1 β -carboxylic Acid and its Lactone (XXXV).—A solution of lithium aluminium hydride (1 mol.) in dry tetrahydrofuran (25 c.c.), was added with cooling to 2 β -methoxycarbonyl-6 β -methylcyclohexane-1 β -carboxylic acid (1 g.) in dry tetrahydrofuran (10 c.c.) and kept overnight. The product gave 2 β -hydroxymethyl-6 β -methylcyclohexane-1 β -carboxylic acid (0.6 g., 70%), m. p. 108—109° (from ether—ethyl acetate), infrared absorption: 3394 (strong hydroxyl) and 1688 cm.⁻¹ (carboxylic acid) (Found: C, 63.0; H, 9.4. C₈H₁₆O₃ requires C, 62.8; H, 9.3%). This material was refluxed with acetic anhydride (5 c.c.) for 1 hr. and distilled giving the γ -lactone (0.3 g., 70%), b. p. 135°/20 mm., n_D^{20} 1.4730, strong infrared absorption 1768 cm.⁻¹ (lactone) (Found: C, 69.8; H, 9.2. C₉H₁₄O₂ requires C, 70.0; H, 9.0%).

This substance (2 g.) was dehydrogenated by heating with palladium on charcoal catalyst (1 g.) at 280° for 8 hr. to give *m*-xylene (0.6 g., 45%), b. p. 138°, n_D^{20} 1.4925, identified by its infrared spectrum and by oxidation to isophthalic acid, m. p. 348°.

Dimethyl 3 α -Methyl-4-oxocyclohexane-1 α ,2 β -dicarboxylate (XXXVII).—3 β -Hydroxy-6 β -methoxycarbonyl-2 β -methylcyclohexane-1 β -carboxylic acid lactone (2 g.) with sodium (0.05 g.) in dry methanol (120 c.c.) was refluxed (4 hr.) and the solution was then brought to pH 7 with hydrochloric acid (10%). The residue, after evaporation, was extracted with ether and the extracted material in acetic acid (10 c.c.) was treated with chromium trioxide (0.7 g.) in water (2 c.c.). The *ketone* (1.3 g., 60%), was obtained, b. p. 115°/0.1 mm., n_D^{20} 1.4710, strong infrared absorption: 1733 cm.⁻¹ (ester and ketone) (Found: C, 58.5; H, 7.0. C₁₁H₁₆O₅ requires C, 58.1; H, 7.0%); 2,4-dinitrophenylhydrazones, yellow-orange needles, m. p. 153° (from ethanol) (Found: C, 49.6; H, 5.2. C₁₇H₂₀O₈N₄ requires C, 50.0; H, 4.9%).

Dehydrogenation of Dimethyl 3 α -Methyl-4-oxocyclohexane-1 α ,2 β -dicarboxylate.—The diester (1.0 g) was heated with palladium—charcoal (1.0 g.) at 280° for 6 hr. Distillation gave *o*-cresol (0.5 g., 65%), b. p. 200—203°, n_D^{20} 1.5420, identified by its infrared spectrum, and by formation of the 3,5-dinitrobenzoate, m. p. and mixed m. p. 137—138°.

The γ -Lactone (XXXVIII; R = OH) of 4 β -Hydroxy-2 β -hydroxymethyl-3 β -methylcyclohexane-1 β -carboxylic Acid.—Lithium aluminium hydride (1 molar equiv.) was added to 4 β -hydroxy-3 β -methylcyclohexane-1 β ,2 β -dicarboxylic acid 2 \rightarrow 4-lactone (1 g.) in dry tetrahydrofuran (30 c.c.) and kept overnight. Water (10 c.c.) was cautiously added and the solution brought to pH 2. Extraction with chloroform gave the γ -lactone (0.6 g., 65%), b. p. 140°/0.3 mm., n_D^{20} 1.4970, infrared absorption: 3502 (hydroxyl) and 1776 cm.⁻¹ (γ -lactone) (Found: C, 63.5; H, 8.7. C₉H₁₄O₃ requires C, 63.6; H, 8.3%).

2 β -Hydroxymethyl-3 β -methyl-4-oxocyclohexane-1 β -carboxylic Acid Lactone (XXXVIII; R = O).—The foregoing lactone (0.3 g.) in acetic acid (5 c.c.) and chromium trioxide (0.15 g.) in water (1 c.c.) were kept overnight to give the *oxo-lactone* (0.17 g., 60%), b. p. 130—135°/0.2 mm., n_D^{20} 1.4940, strong infrared absorption at 1783 (lactone) and 1721 cm.⁻¹ (ketone) (Found: C, 64.5; H, 7.6. C₉H₁₂O₃ requires C, 64.3; H, 7.2%).

$\Delta^{4a,5}$ -Octahydro-5,8a-dimethyl-6-oxonaphthalene-2,3-dicarboxylic Acid (XXIV).—Diethyl 5-methyl-4-oxocyclohexane-1,2-dicarboxylate (4.5 g.) in dry benzene (20 c.c.) was added to the methiodide prepared from 1-diethylaminopentan-3-one (2.8 g.) and methyl iodide (2.5 g.) followed by a solution of sodium (0.55 g.) in methanol (20 c.c.). The reaction product isolated after 60 hr. gave a substance (3.1), b. p. 180—210°/0.2 mm., which by alkaline hydrolysis gave an acid (2.8 g.) which partly crystallised. The crystalline product (0.9 g.) formed the *diacid*, m. p. 231—233° (from acetone—light petroleum) (Found: C, 63.0; H, 6.7. C₁₄H₁₈O₅ requires C, 63.2; H, 6.7%). The non-crystalline product, methylated with diazomethane, gave the *dimethyl ester* (0.9 g.), b. p. 172°/0.1 mm., n_D^{20} 1.5090 (Found: C, 65.2; H, 7.6. C₁₆H₂₂O₅ requires C, 65.3; H, 7.5%). The latter product on hydrogenation at palladised charcoal in ethanol

¹⁷ Sopov, *Zhur. obshchei Khim.*, 1956, **28**, 1602.

[1964]

Denton, McQuillin, and Simpson.

5535

absorbed 1 molar equivalent of hydrogen rather slowly to give crystalline *dimethyl 5,8a-dimethyl-6-oxodecalin-2,3-dicarboxylate*, m. p. 163°, in high yield (Found: C, 64.3; H, 8.3. $C_{16}H_{24}O_5$ requires C, 64.7; H, 8.1%).

We thank the D.S.I.R. for Studentships to W. O. O. and P. L. S.

DEPARTMENT OF ORGANIC CHEMISTRY,
UNIVERSITY OF NEWCASTLE UPON TYNE.

[Received, June 17th, 1964.]
