860. *Acetals and a Ketal of Dimethyl Glucarate.*

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Condensation of dimethyl D-glucarate, as its calcium chloride complex, with benzaldehyde, acetaldehyde, or acetone has been studied. Benzaldehyde, with zinc chloride as catalyst, yields crystalline dimethyl 3,4-*O*-benzylidene-D-glucarate (27%) and the fully substituted diacetal (4%). With paraldehyde in the presence of copper sulphate, the 3,4-monoacetal is also a major product of reaction. With acetone and copper sulphate, syrupy dimethyl 3,4-*O*-isopropylidene-D-glucarate (86%) is the main compound. Structures were determined by methylation and isolation of crystalline 2,5-di-*O*-methyl-D-glucaro-1,4:6,3-dilactone, which is described for the first time. Methylation of dimethyl 2,4-*O*-methylene-D-glucarate gives unsaturated derivatives, and the 3,5-di-*O*-methyl ether is not the major product.

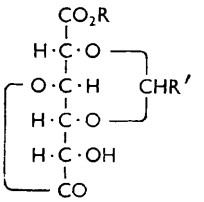
The structures of several acetals of glucarolactone have been determined by reduction to known glucitol derivatives.

Methylene derivatives of D-glucaric acid have been known for many years.[1,2] The mono-*O*-methylene-D-glucarolactone (Henneberg and Tollens [1]) was converted into its methyl and ethyl monoesters by Haworth and Jones,[3] who also prepared dimethyl mono-*O*-methylene-D-glucarate by opening the lactone ring with methanolic hydrogen chloride. These compounds were shown to have the 2,4-acetal structure by Jones and Wiggins [3a] and various derivatives have been described.[3b] A second methylene group was introduced into the dimethyl ester to give the fully substituted dimethyl 2,4:3,5-di-*O*-methylene-D-glucarate.[4-6] The only ethylidene derivative previously reported is syrupy diethyl

[1] Henneberg and Tollens, *Annalen*, 1896, **292**, 40.
[2] Bruyn and Alberda van Ekenstein, *Rec. Trav. chim.*, 1901, **20**, 331; 1902, **21**, 316.
[3] Haworth and Jones, *J.*, 1944, 65.
[3a] Jones and Wiggins, *J.*, 1944, 364.
[3b] Colón, Fernández-García, Amóros, and Blay, *J. Amer. Chem. Soc.*, 1949, **71**, 4131.
[4] Haworth, Jones, Stacey, and Wiggins, *J.*, 1944, 61.
[5] Bird, Black, Dewar, and Hare, *J.*, 1963, 1208.
[6] Mills, *Adv. Carbohydrate Chem.*, 1955, **10**, 1.

mono-*O*-ethylidene-D-glucarate,[3] prepared by condensing the calcium chloride complex of diethyl glucarate with paraldehyde in the presence of zinc chloride. A monobenzylidene derivative of glucaric acid,[7] mono-*O*-benzylidene-D-glucarolactone methyl ester,[8] and diethyl mono-*O*-benzylidene-D-glucarate [3] have been described. Treatment of the calcium chloride complex of diethyl glucarate with acetone and zinc chloride gave diethyl mono-*O*-isopropylidene-D-glucarate as a syrup.[3] With the exception of the methylene acetals, the structures of these derivatives have not been elucidated.

We have confirmed the 2,4-acetal structure (I) of mono-*O*-methylene-D-glucarolactone [1,3] by reducing its methyl and ethyl esters (II, III) [3] with potassium borohydride in aqueous solution to the known 2,4-*O*-methylene-D-glucitol; [9,10] the ethyl ester (III) was also successfully reduced with lithium aluminium hydride in tetrahydrofuran.



	R	R′
(I)	H	H
(II)	Me	H
(III)	Et	H
(IV)	Me	Ph
(V)	H	Ph
(VI)	Et	Ph

The 6,3-lactone ring-structure was proved by infrared analysis and by the slow mutarotation of compounds (II) and (III) in water, characteristic of γ-lactones. Similarly, the mono-*O*-benzylidene-D-glucarolactone methyl ester (Reeves [8]) was shown to be the 2,4-acetal (IV) by reduction with lithium aluminium hydride in tetrahydrofuran and subsequent acetylation, and isolation of crystalline 1,3,5,6-tetra-*O*-acetyl-2,4-*O*-benzylidene-D-glucitol.[11] The 2,4-acetal ring-structure (*i.e.*, β-*cis*) is predictable, and the most favourable conformationally,[6] if the generalisations formulated for the favoured structures of acetals of hexitols [12] also apply to the hexaric acids. The monobenzylidene derivative (Alberda van Ekenstein and Bruyn) [7] is almost certainly 2,4-*O*-benzylidene-D-glucaro-6,3-lactone (V), for elemental and infrared analyses indicate a lactone structure.

We were interested primarily in derivatives of glucaric acid which did not contain a lactone ring. A major disadvantage of glucaric acid as a starting material is its ready tendency to form lactones rather than esters by elimination of water from the 1,4-, 1,5-, or 6,3-positions.[13,14] However, Haworth and Jones [3] found that 2,4-*O*-methylene-D-glucaro-6,3-lactone (I) gave dimethyl 2,4-*O*-methylene-D-glucarate (XIX) on treatment with hot 4% methanolic hydrogen chloride. But when the benzylidene compound (V) was treated similarly, we failed to isolate the corresponding dimethyl ester owing to methanolysis of the benzylidene group.

We also tried unsuccessfully to prepare benzylidene derivatives of dimethyl glucarate by esterifying potassium hydrogen glucarate directly with 6% methanolic hydrogen chloride and with methanol containing sulphuric acid, followed by benzylidenation with benzaldehyde and hydrogen chloride, but in each case crystalline 2,4-*O*-benzylidene-D-glucaro-6,3-lactone 1-methyl ester (IV) was isolated.

The lactone difficulty was overcome by Haworth and Jones,[3] who used the crystalline calcium chloride complex of diethyl D-glucarate to prepare various monoacetals of diethyl glucarate as outlined above. Although this complex was first described by Heintz [15] in

[7] Alberda van Ekenstein and Bruyn, *Rec. Trav. chim.*, 1899, **18**, 305.
[8] Reeves, *J. Amer. Chem. Soc.*, 1939, **61**, 664.
[9] Bourne and Wiggins, *J.*, 1944, 517.
[10] Ness, Hann, and Hudson, *J. Amer. Chem. Soc.*, 1944, **66**, 665.
[11] Vargha, *Magyar Kém. Folyóirat*, 1934, **40**, 151.
[12] Barker and Bourne, *Adv. Carbohydrate Chem.*, 1952, **7**, 137.
[13] Smith, *J.*, 1944, 571.
[14] Smith, *J.*, 1944, 633.
[15] Heintz, *Pogg. Ann. Phys. Chem.*, 1858, **105**, 211.

1858, its preparation and characterisation apparently have not been fully reported, and we now describe the calcium chloride compounds of dimethyl, diethyl, and dipropyl glucarates. They were readily obtained in high yield by passing hydrogen chloride into a suspension of calcium glucarate in the appropriate alcohol, and their properties are given below. One molecule of calcium chloride complexes with two molecules of diester. Twin carbonyl peaks at 1760 and 1730 cm.$^{-1}$ were observed in the infrared spectra of these complexes.

Calcium chloride complexes of dialkyl D-glucarates.

			Found (%)						Required (%)				
R	Yield (%)	$[\alpha]_D$ (c 3 in H_2O)	C	H	Ca	Cl	OR	Formula of complex	C	H	Ca	Cl	OR
Me	86·3	+5·8°	32·8	4·9	6·6	11·5	20·5	$C_8H_{14}O_6,\frac{1}{2}CaCl_2$	32·7	4·8	6·8	12·2	21·1
Et	89·1	+5·3	36·3	5·7	6·25	11·0	26·7	$C_{10}H_{18}O_6,\frac{1}{2}CaCl_2$	37·3	5·6	6·2	11·0	28·0
Pr	73·5	+4·9	40·3	6·4	5·7	10·2	—	$C_{12}H_{22}O_6,\frac{1}{2}CaCl_2$	41·2	6·3	5·7	10·1	—

We have studied the condensation of the calcium chloride compound of dimethyl glucarate with benzaldehyde, acetaldehyde, or acetone. When the complex was treated with benzaldehyde and hydrogen chloride as catalyst, 2,4-*O*-benzylidene-D-glucaro-6,3-lactone 1-methyl ester (IV) was again isolated (45%), and no evidence of the dimethyl ester was obtained. The corresponding ethyl ester (VI) was similarly prepared from the diethyl glucarate–calcium chloride compound. However, with zinc chloride as catalyst, dimethyl glucarate (VII; as its calcium chloride compound) gave crystalline dimethyl 3,4-*O*-benzylidene-D-glucarate (VIII) in 27% yield, although the procedure of Haworth and Jones [3] for the diethyl ester had to be modified considerably. The structure of compound (VIII) was proved by methylation, saponification of the syrupy 2,5-dimethyl ether (IX), hydrolysis of the benzylidene residue with a cation-exchange resin, and distillation of the acid (X) to give crystalline 2,5-di-*O*-methyl-D-glucaro-1,4:6,3-dilactone (XI) in 60% yield, which was converted into the known 2,5-di-*O*-methyl-D-glucarodiamide [16] (XII).

Smith [14] found that methylation of D-glucaro-1,4:6,3-dilactone with silver oxide and methyl iodide gave chiefly the unsaturated compound, 4,5-didehydro-4-deoxy-2,5-di-*O*-methyl-Δ^4-D-glucaro-6,3-lactone 1-methyl ester (XIV), and the methylated dilactone (XI) was not isolated. In common with D-glucaro-1,4:6,3-dilactone,[14] compound (XI) shows strong carbonyl absorption at 1800 cm.$^{-1}$ in the infrared and exhibits relatively rapid mutarotation in water despite its double γ-lactone structure. Smith [14] has attributed the latter effect to strain in this *cis*-fused, bicyclic system. Unsaturated compounds were detected during the synthesis of dilactone (XI) but they were formed only in small amounts (see below).

The 3,4-monoacetal (VIII), with an *α-trans* ring, would not have been predicted as a first choice from the *gluco* configuration,[12] but the complexing of dimethyl glucarate (VII) with calcium chloride may prevent formation of the usually more favoured 2,4 (*i.e.*, β-*cis*)-monoacetal. On the other hand, it is possible that the 2,4-monoacetal was also formed with the 3,4-monoacetal, but only the latter was isolated.

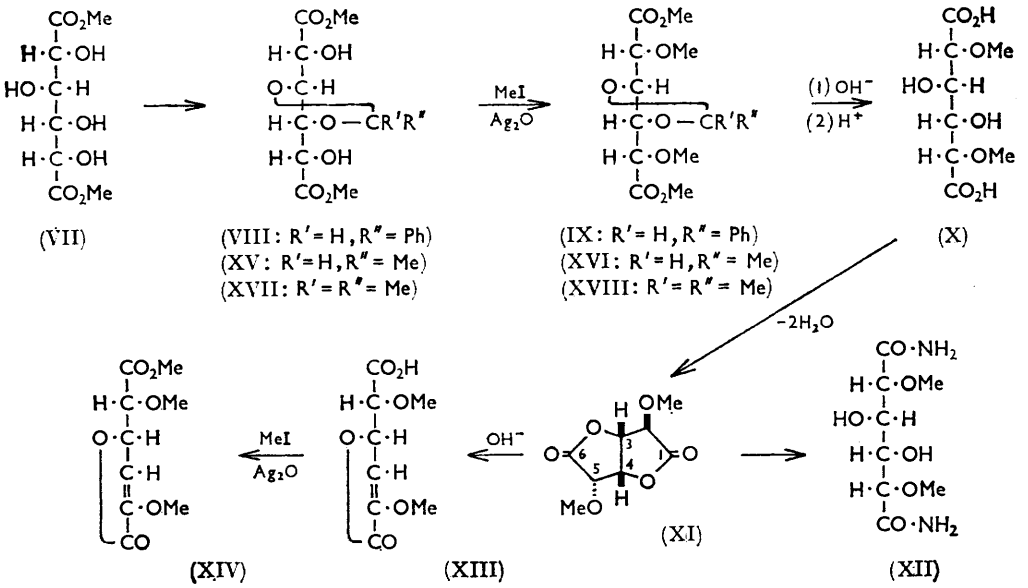
The water-insoluble fraction obtained from this reaction contained the fully substituted dimethyl 2,3,4,5-di-*O*-benzylidene-D-glucarate, which was isolated in crystalline form (4%). The structure of this compound has not been proved and is not readily predicted. A varying melting point (135—144°) indicated a mixture possibly due to stereoisomerism at the acetal carbon atom.[6]

Condensation of the calcium chloride compound of dimethyl glucarate with paraldehyde in the presence of anhydrous copper sulphate failed to give a crystalline product, but a crude dimethyl mono-*O*-ethylidene-D-glucarate was obtained as a syrup (57% calculated as monoacetal). Infrared analysis indicated contamination with a γ-lactone (C:O peak at 1790 cm.$^{-1}$), and the low methoxyl content (19·2, theory 23·5%) suggested the presence of a lactone and/or the fully substituted diacetal. When this crude material was methylated, saponified, hydrolysed, and distilled as described for the benzylidene derivative, crystalline

[16] Smith, *J.*, 1944, 584.

dilactone (XI) was recovered in 29·5% yield (from the crude methylated diester). This is one half of that obtained from dimethyl 3,4-*O*-benzylidene-2,5-di-*O*-methyl-D-glucarate (IX), from which it is deduced that about 50% of the methylated product is dimethyl 3,4-*O*-ethylidene-2,5-di-*O*-methyl-D-glucarate (XVI). Thus, the 3,4-monoacetal (XV) is a major product of this reaction.

Dimethyl glucarate (VII), as its calcium chloride complex, condenses with acetone in the presence of anhydrous copper sulphate to yield dimethyl 3,4-*O*-isopropylidene-D-glucarate (XVII) as a syrup (86%). The ketal was contaminated with a trace of γ-lactone (C:O peak at 1790 cm.$^{-1}$ in the infrared), which may be responsible for its failure to crystallise. Its structure was proved as described for the benzylidene derivative, the crystalline dilactone (XI) being recovered in 48% yield. The ester (XVII) and its 2,5-dimethyl ether (XVIII) were characterised by conversion into crystalline diamides in good yield. The 3,4-monoketal is the expected product of this reaction.[12]



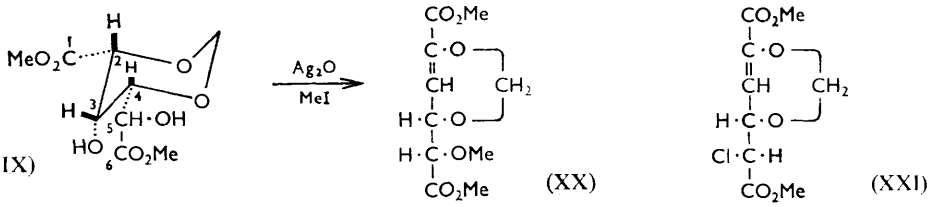
Occasionally in the course of preparation of dilactone (XI), an unsaturated isomer was also isolated from the syrupy distillate of 2,5-di-*O*-methyl-D-glucaric acid (X). It was readily separated from the dilactone by extraction with chloroform and shown to be 4,5-didehydro-4-deoxy-2,5-di-*O*-methyl-Δ^4-D-glucaro-6,3-lactone (XIII), identical to that prepared by Smith [17] by saponification of the methyl ester (XIV). Its identity was confirmed by conversion into the 1-methyl ester (XIV). Smith [18] has shown that unsaturation can be readily introduced into various glucaric acid derivatives, provided both carboxyl groups are esterified or lactonised, by treatment with alkaline reagents or by methylation with silver oxide and methyl iodide. When barium hydroxide was used to neutralise the sulphuric acid after hydrolysis of 3,4-*O*-isopropylidene-2,5-di-*O*-methyl-D-glucaric acid, the slight alkalinity (pH 10) of the filtrate was sufficient to effect the isomerism (XI) ⟶ (XIII). This conversion was prevented almost completely when barium carbonate replaced barium hydroxide (see Experimental section).

Methylation of dimethyl 2,4-*O*-methylene-D-glucarate (XIX) in dimethylformamide solution with methyl iodide and silver oxide did not give the 3,5-di-*O*-methyl ether, $C_{11}H_{18}O_8$, but an unsaturated, syrupy dimethyl ester (A) was produced, with the approximate

[17] Smith, *J.*, 1944, 510.
[18] Smith, *Adv. Carbohydrate Chem.*, 1946, **2**, 79.

formula $C_{10}H_{14}O_7$ and containing only three methoxyl groups. Unsaturation was shown by infrared analysis (peaks at 1660, 1630, 1600 cm.$^{-1}$), by selective absorption in the ultraviolet ($\lambda_{max.}$ 233 mμ; ε *ca.* 5300), and by reaction with approximately two atoms of chlorine in aqueous solution. Syrup (A), however, was impure and failed to give a crystalline amide. It contained a small amount (*ca.* 6%) of a crystalline material (B) of unknown structure and varying composition, which was separated by fractional crystallisation from water or ethanol. Its infrared spectrum was similar to that of syrup (A) except that the C:O absorption at 1725 cm.$^{-1}$ suggested a higher content of α,β-unsaturated ester. It showed strong selective absorption at $\lambda_{max.}$ 310 mμ, which indicated extended conjugation.

We suggest a partial explanation of these results by an elimination reaction. The preferred conformation of the 1,3-dioxan ring of dimethyl 2,4-*O*-methylene-D-glucarate is the chair form (XIX), and the reactivity of the axial hydroxyl group on $C_{(3)}$ should be enhanced in the absence of axial hydrogen atoms on the same side of the ring: [6]



(XIX) (XX) (XXI)

In this conformation the hydrogen atom on $C_{(2)}$ and the hydroxyl group on $C_{(3)}$ are oriented *trans*-diaxially, so that a β-elimination of water can take place in the presence of a base (silver oxide) and under the influence of the electron-withdrawing CO_2Me group at $C_{(1)}$. Thus, methylation would be expected to give the unsaturated compound (XX) with formula $C_{10}H_{14}O_7$ and having only three methoxyl groups. Methylation of the ester (XIX) in acetone solution with methyl iodide and silver oxide was claimed by Jones and Wiggins [3a] to give the saturated 3,5-di-*O*-methyl ether (27%) together with 5-*O*-methyl-2,4-*O*-methylene-D-glucaro-6,3-lactone 1-methyl ester (13%). The remaining material was not identified, and we suggest that it may have been the unsaturated compound (XX).

A similar reaction occurred when dimethyl 2,4-*O*-methylene-D-glucarate (XIX) was treated with sulphuryl chloride in pyridine solution.[19] A crystalline, unsaturated dimethyl ester, containing only one chlorine atom, was isolated (38%), and its structure is believed to be dimethyl 5-chloro-2,3-didehydro-3,5-dideoxy-2,4-*O*-methylene-Δ^2-L-idarate (XXI) on the basis of a similar reaction mechanism to that outlined above. Replacement of a hydroxyl group by chlorine occurs with inversion.[20]

Experimental

Methods.—Specific rotations were measured at 20° in a 2-dm. tube. Melting points were recorded on a Kofler hot-stage. Infrared spectra of liquids were determined as films between sodium chloride plates, and those of solids as potassium chloride discs or as Florube mulls. Isopropylidene content was determined by a modification of the micro-method of Bell and Harrison.[21] The aqueous acetone distillate (*ca.* 20 ml.) was collected in water (10 ml.) at 0° as in Pregl's method,[22] and the solution was then treated with N-sodium hydroxide (5 ml.) and 0·02N-iodine (10 ml.) for 15 min. in a stoppered flask with frequent shaking to convert acetone into iodoform; after the addition of N-sulphuric acid (7 ml.), excess of iodine was titrated with 0·02N-sodium thiosulphate. Benzylidene content was determined gravimetrically with a solution of 2,4-dinitrophenylhydrazine in N-hydrochloric acid.[23]

[19] Bragg, Jones, and Turner, *Canad. J. Chem.*, 1959, **37**, 1412.
[20] Jones, Perry, and Turner, *Canad. J. Chem.*, 1960, **38**, 1122.
[21] Bell and Harrison, *J.*, 1939, 350.
[22] Pregl, "Quantitative Organic Microanalysis," J. and A. Churchill Ltd., London, 4th edn., 1945, p. 170.
[23] Angyal and Lawler, *J. Amer. Chem. Soc.*, 1944, **66**, 837.

Reduction of 2,4-O-*Methylene*-D-*glucaro*-6,3-*lactone* 1-*Methyl Ester* (II).—Compound (II), prepared as described by Haworth and Jones,[3] had m. p. 209—211°, $[\alpha]_D$ +134° ⟶ +133° (after 7 days, *c*, 0·87 in H_2O); $\nu_{max.}$ 1800 (γ-lactone C:O), 1760 cm.$^{-1}$ (ester C:O) (Found: C, 43·9; H, 4·7; OMe, 14·0. Calc. for $C_8H_{10}O_7$: C, 44·0; H, 4·6; OMe, 14·2%). Potassium borohydride (216 mg.; 4 mmoles) was added to a solution of the ester lactone (202 mg.; 0·93 mmole) in water (10 ml.) at 20°, and after 30 min. a second addition of borohydride was made. After 22 hr. at 20°, the solution was passed through an Amberlite resin IR-120-H column, the eluate concentrated, and the residue dissolved in methanol (50 ml.) and the solvent distilled to remove volatile methyl borate. This treatment with methanol was repeated three times, after which an aqueous solution of the product was passed through an Amberlite resin IRA-401-OH column to remove unreduced acidic material. The eluate was concentrated, and crystalline 2,4-*O*-methylene-D-glucitol (125 mg.; 70%) recrystallised from ethanol to give small needles, m. p. 163—164°, $[\alpha]_D$ −8·5° (*c* 4·46 in H_2O) (lit.,[9] m. p. 162°, $[\alpha]_D$ −9·1°) (Found: C, 43·3; H, 7·2. Calc. for $C_7H_{14}O_6$: C, 43·3; H, 7·3%). Acetylation with acetic anhydride and pyridine[10] yielded 1,3,5,6-tetra-*O*-acetyl-2,4-*O*-methylene-D-glucitol (60%), m. p. 151°, $[\alpha]_D$ −1·1° (*c* 7·1 in $CHCl_3$) (lit.,[10] m. p. 150—151°, $[\alpha]_D$ −1·5°) (Found: C, 49·6; H, 6·3. Calc. for $C_{15}H_{22}O_{10}$: C, 49·7; H, 6·1%).

Reduction of 2,4-O-*Methylene*-D-*glucaro*-6,3-*lactone* 1-*Ethyl Ester* (III).—(*a*) *With potassium borohydride.* The ester lactone (III), prepared as described by Haworth and Jones,[3] had m. p. 195—196°, $[\alpha]_D$ +143° ⟶ 137° (after 12 days, *c* 1 in H_2O); $\nu_{max.}$ 1790 (γ-lactone C:O), 1740 cm.$^{-1}$ (ester C:O) (Found: C, 46·8; H, 5·3; OEt, 18·8. Calc. for $C_9H_{12}O_7$: C, 46·55; H, 5·2; OEt, 19·4%). Compound (III) (101 mg.) was reduced with potassium borohydride in aqueous solution as described for the methyl ester (II) to yield pure 2,4-*O*-methylene-D-glucitol (29 mg.; 34%), m. p. 163—164°, $[\alpha]_D$ −8·2° (*c* 2 in H_2O), having an infrared spectrum identical with that of the compound characterised above.

(*b*) *With lithium aluminium hydride.* A solution of the lactone ethyl ester (232 mg.; 1 mmole) in dry tetrahydrofuran (25 ml.) was added dropwise with stirring to a slurry of lithium aluminium hydride (190 mg.; 5 mmoles) in tetrahydrofuran (5 ml.), and the mixture refluxed with stirring for 2 hr. in an anhydrous atmosphere. After the addition of ethanol (5 ml.), the mixture was poured into water (100 ml.), and filtered; the filtrate was deionised by passage through columns of Amberlite resins IR-120-H and IRA-401-OH. The final eluate was concentrated, and the solid (113 mg.) recrystallised from ethanol to give 2,4-*O*-methylene-D-glucitol (49 mg.; 25%), m. p. 162°, $[\alpha]_D$ −8·7° (*c* 1·86 in H_2O).

Reduction of 2,4-O-*Benzylidene*-D-*glucaro*-6,3-*lactone* 1-*Methyl Ester* (IV).—This compound, first described by Reeves,[8] was prepared from potassium hydrogen glucarate as detailed later. The lactone methyl ester (297 mg.; 1·01 mmole) was reduced with lithium aluminium hydride as described in (*b*) above, and excess reagent destroyed with ethanol. The reaction mixture was poured into water (100 ml.), neutralised (phenolphthalein) with 2N-acetic acid, and concentrated, the residue was dried by repeated distillation of ethanol and benzene. The white solid was acetylated with dry pyridine (10 ml.) and acetic anhydride (5 ml.), and after 24 hr. at 20° the mixture was poured into a mixture of water (50 ml.) and chloroform (50 ml.) and filtered. The chloroform layer was washed with water, dried (Na_2SO_4), and concentrated; the syrupy residue (542 mg.) was crystallised from ethanol–water (1 : 1) to yield 1,3,5,6-tetra-*O*-acetyl-2,4-*O*-benzylidene-D-glucitol as long needles (214 mg.; 48·4%), m. p. 83°, $[\alpha]_D$ −6·5° (*c* 4·71 in $CHCl_3$) (lit.,[11] m. p. 87—88°, $[\alpha]_D$ −6·7°) (Found: C, 56·8; H, 5·9; PhCH:, 21·9. Calc. for $C_{21}H_{26}O_{10}$: C, 57·5; H, 6·0; PhCH:, 20·55%).

2,4-O-*Benzylidene*-D-*glucaro*-6,3-*lactone* (V).—The preparation of this derivative[7] has been improved. Potassium hydrogen glucarate (10 g.) was treated with concentrated hydrochloric acid (20 ml.) and benzaldehyde (20 ml.) at 20° for 16 hr., and the solid mixture washed with water, ethanol, and ether. The lactone (9·635 g.; 85·4%) recrystallised from ethanol (1 l.) as small needles, m. p. 221° (decomp.); $[\alpha]_D$ +100° (*c* 0·46 in MeOH), +174° (*c* 1 in pyridine); $\nu_{max.}$ 1790, 1760 cm.$^{-1}$ (Found: C, 55·6; H, 4·5. Calc. for $C_{13}H_{12}O_7$: C, 55·7; H, 4·3%).

Esterification of Potassium Hydrogen Glucarate and Condensation with Benzaldehyde.—The potassium salt (10 g.) was refluxed with stirring with 6% (w/w) methanolic hydrogen chloride (100 ml.) for 4 days, potassium chloride filtered, and the filtrate concentrated to a thin syrup (13·5 g.), which still contained some methanol, potassium chloride, and hydrogen chloride. Dry hydrogen chloride was passed through a suspension of this syrup (2·21 g.) in benzaldehyde (10 ml.) for 1 hr., and the solid washed with light petroleum, water, ethanol, and ether to yield

2,4-*O*-benzylidene-D-glucaro-6,3-lactone 1-methyl ester (IV) (1·667 g.; 85·9%), which recrystallised from ethanol (300 ml.) as long needles (1·404 g.), m. p. 229—231°, $[\alpha]_D$ +146° (*c* 0·5 in pyridine) (lit.,[8] m. p. 237—238°, $[\alpha]_D$ +147°); $\nu_{max.}$ 1780 (γ-lactone C:O), 1750 cm.$^{-1}$ (ester C:O) (Found: C, 57·4; H, 5·0; OMe, 10·5. Calc. for $C_{14}H_{14}O_7$: C, 57·2; H, 4·8; OMe, 10·5%). The same compound was obtained when the methanolic hydrogen chloride was replaced by methanol (50 ml.) containing sulphuric acid (1·8 ml.) in the esterification.

Calcium D-*Glucarate*.—Potassium hydrogen glucarate (10 g.; 40·3 mmoles) in water (500 ml.) was heated at 100° for 3 hr. with a solution of calcium acetate monohydrate (7·4 g.; 42 mmoles) in water (100 ml.), and the mixture stirred at 20° for 17 hr. The precipitated calcium glucarate (7·76 g.; 77·6%) was washed with water, ethanol, and ether, and dried at 120° for 22 hr. (Found: Ca, 15·0. Calc. for $C_6H_8CaO_8$: Ca, 16·1%).

Calcium Chloride Complexes of Dialkyl D-*Glucarates* (with Mr. JOHN W. CAMPBELL).—Dry hydrogen chloride was passed through a suspension of calcium glucarate (20·2 g.) in methanol (130 ml.) for 5 hr. The calcium salt dissolved and the complex separated after 3 hr. After 17 hr. at 0°, the crystalline compound was washed with ether and isolated as a white powder (20·6 g.; 86%). The complex of the diethyl ester was prepared similarly from ethanol; it could be recrystallised [15] by concentrating a 25% (w/w) aqueous solution in a desiccator over sulphuric acid to about half volume. With anhydrous propan-1-ol, the calcium glucarate failed to dissolve completely before the complex began to precipitate and reaction was incomplete; the addition of 5% (v/v) of water to the alcohol overcame this difficulty, and the calcium chloride compound did not contain water. The properties of these complexes are tabulated in the text. The di-isopropyl and dibutyl ester compounds were also prepared but they were not isolated in pure form.

Condensation of Dimethyl D-*Glucarate–Calcium Chloride Complex with Benzaldehyde in the Presence of Hydrogen Chloride*.—Hydrogen chloride was passed through a suspension of the complex (5·1 g.) in benzaldehyde (50 ml.) for 5 hr. The solution was poured into light petroleum (b. p. 40—60°), and the syrupy precipitate washed with water, ethanol, and ether to give 2,4-*O*-benzylidene-D-glucaro-6,3-lactone 1-methyl ester (IV) (2·29 g.; 44·9%), m. p. 233—234°, $[\alpha]_D$ +147° (*c* 0·5 in pyridine), identical with that described above. The water washings were extracted with chloroform and the chloroform extracts concentrated, but no benzylidene derivative of dimethyl glucarate was recovered.

2,4-O-*Benzylidene*-D-*glucaro*-6,3-*lactone* 1-*Ethyl Ester* (VI).—This compound was prepared from the calcium chloride complex of diethyl glucarate in the manner described above for the methyl ester. The *lactone ethyl ester* was obtained as needles (18·5%), m. p. 235°, $[\alpha]_D$ +147° (*c* 1·1 in pyridine); $\nu_{max.}$ 1780 (γ-lactone C:O), 1750 cm.$^{-1}$ (ester C:O) (Found: C, 58·3; H, 5·4; OEt, 14·7. $C_{15}H_{16}O_7$ requires C, 58·4; H, 5·2; OEt, 14·6%).

Dimethyl 3,4-O-*Benzylidene*-D-*glucarate* (VIII).—Dimethyl glucarate–calcium chloride complex (5·17 g.), powdered fused zinc chloride (2·5 g.), and benzaldehyde (40 ml.) were shaken at 20° for 3 days, and the clear solution poured into light petroleum (b. p. 40—60°). The precipitated syrup was washed with light petroleum, extracted with water (3 × 400 ml.), and the aqueous solution extracted with chloroform (4 × 200 ml.). The dried (Na_2SO_4) chloroform extracts were concentrated, and the semi-solid residue (4·43 g.) crystallised from a 1 : 1 : 1-mixture (21 ml.) of methanol, light petroleum, and ether to yield pure *dimethyl* 3,4-*O*-*benzylidene*-D-*glucarate* (1·53 g.; 26·6%) as plates, m. p. 119·5—120·5°, $[\alpha]_D$ +36° (*c* 1 in $CHCl_3$) (Found: C, 55·7; H, 5·6; OMe, 18·7. $C_{15}H_{18}O_8$ requires C, 55·2; H, 5·6; OMe, 19·0%).

Dimethyl 2,3,4,5-*Di*-O-*benzylidene*-D-*glucarate*.—The water-insoluble fraction of the above syrup, obtained on pouring the reaction solution into light petroleum, was dissolved in hot ethanol (20 ml.), and the solution cooled to give a gel which was broken up, washed with ether, and recrystallised from ethanol to give *dimethyl* 2,3,4,5-*di*-O-*benzylidene*-D-*glucarate* (270 mg.; 3·7%), m. p. 135—144°, $[\alpha]_D$ +22° (*c* 2 in Me_2CO) (no OH absorption in the infrared) (Found: C, 63·65; H, 5·3; OMe, 14·4. $C_{22}H_{22}O_8$ requires 63·75; H, 5·35; OMe, 15·0%).

Dimethyl 3,4-O-*Benzylidene*-2,5-*di*-O-*methyl*-D-*glucarate* (IX).—Dimethyl 3,4-*O*-benzylidene-D-glucarate (13·88 g.) was methylated three times with methyl iodide (84 ml.) and silver oxide (49 g.) in the usual way, and the product distilled to yield the 2,5-*di*-O-*methyl ether* (13·82 g.; 91·6%), b. p. 174—178°/0·01 mm., n_D^{18} 1·5008, $[\alpha]_D$ +45·9° (*c* 2·2 in $CHCl_3$) (no OH absorption in the infrared) (Found: C, 57·75; H, 6·4; OMe, 34·6. $C_{17}H_{22}O_8$ requires C, 57·6; H, 6·3; OMe, 35·0%).

2,5-*Di*-O-*methyl*-D-*glucaro*-1,4:6,3-*dilactone* (XI).—The above ester (IX) (2·285 g.; 6·45

mmoles) in ethanol (150 ml.) was heated at 60° for 3 hr. with a solution of barium hydroxide octahydrate (2·2 g.; 6·97 mmoles) in water (450 ml.). The solution was stirred with Amberlite resin IR-120 (H^+ form) for 30 min. at 20° to remove Ba^{2+} and to hydrolyse the benzylidene residue, the filtrate concentrated, and the residue distilled (b. p. 153—158°/0·01 mm.) to give a pale yellow syrup (953 mg.), showing $\nu_{max.}$ at 1800 and 1660 $cm.^{-1}$, the latter absorption indicating some unsaturation. The syrup (532 mg.) crystallised on trituration with dry ether (4 ml.), yielding 2,5-*di*-O-*methyl*-D-*glucaro*-1,4:6,3-*dilactone* (428 mg.; 59·6%), m. p. 50·5—51°; $\nu_{max.}$ 2850 (OMe), 1800 $cm.^{-1}$ (double γ-lactone C:O) (no OH and C:C absorption) (Found: C, 47·4; H, 4·8; OMe, 30·3%; Equiv., 101·0. $C_8H_{10}O_6$ requires C, 47·5; H, 5·0; OMe, 30·7%; Equiv., 101·1). The dilactone showed $[\alpha]_D$ (*c* 0·68 in H_2O): +179° (5 min.), +159 (30 min.), +136 (1 hr.), +97 (2·5 hr.), +68 (5·5 hr.), +62 (22 hr.), +59 (3 days), +54 (6 days).

Treatment of the dilactone (111 mg.) with liquid ammonia [24] at 20° for 48 hr., and recrystallisation of the solid from methanol (3 ml.) yielded 2,5-di-*O*-methyl-D-glucarodiamide (60 mg.; 46·5%), m. p. 171°, $[\alpha]_D$ +15° (*c* 2 in H_2O) (lit.,[16] m. p. 175°, $[\alpha]_D$ +17° in H_2O) (Found: C, 41·0; H, 6·7; N, 11·7; OMe, 26·6. Calc. for $C_8H_{16}N_2O_6$: C, 40·7; H, 6·8; N, 11·9; OMe, 26·3%). The diamide gave a negative Weerman test [16] for α-hydroxy-amides, thus confirming that the methoxyl groups are located on $C_{(2)}$ and $C_{(5)}$.

Condensation of Dimethyl D-*Glucarate–Calcium Chloride Complex with Paraldehyde in the presence of Copper Sulphate.*—The complex (5·065 g.) and anhydrous copper sulphate (5 g.) were shaken with paraldehyde (50 ml.) for 3 days at 20°, the residue filtered and washed with paraldehyde, and the filtrate and washings concentrated. The concentrate was extracted with chloroform (150 ml.), the filtered extract concentrated, and the green syrup (3·7 g.) distilled to give crude syrupy dimethyl mono-*O*-ethylidene-D-glucarate (2·606 g.; 57·2%), b. p. 155—160°/0·01 mm., n_D^{21} 1·4711, $[\alpha]_D$ +27·3° (*c* 0·66 in $CHCl_3$). $\nu_{max.}$ 1790 (γ-lactone C:O, weak), 1750 $cm.^{-1}$ (ester C:O, strong) (Found: C, 46·5; H, 6·4; OMe, 19·2. $C_{10}H_{16}O_8$ requires C, 45·45; H, 6·1; OMe, 23·5%).

*Methylation of Impure Dimethyl Mono-*O*-ethylidene-*D*-glucarate and Isolation of* 2,5-*Di*-O-*methyl*-D-*glucaro*-1,4:6,3-*dilactone* (XI).—The above crude ester (2·3 g.) was methylated three times with methyl iodide (15 ml.) and silver oxide (10 g.) and the product distilled to yield crude dimethyl mono-*O*-ethylidene-di-*O*-methyl-D-glucarate (1·86 g.; 73%), b. p. 124—128°/0·01 mm.; $\nu_{max.}$ 2850 (OMe), 1760 $cm.^{-1}$ (ester C:O) (OH, γ-lactone C:O, and C:C absorptions absent) (Found: C, 49·85; H, 6·7; OMe, 33·1. $C_{12}H_{20}O_8$ requires C, 49·3; H, 6·9; OMe, 42·45%).

The impure methylated diester (1·774 g.) in ethanol (5 ml.) was saponified by heating with 0·2N-sodium hydroxide (20 ml.) at 50° for 1 hr., and the solution was neutralised (phenolphthalein) with 0·2N-sulphuric acid and concentrated. The dry residue was extracted with boiling chloroform and the filtered extracts concentrated to a syrup (1·541 g.). This material (959 mg.) was heated with N-sulphuric acid (40 ml.) at 100° for 4 hr. to hydrolyse the ethylidene residue, the cold solution neutralised (phenolphthalein) with N-sodium hydroxide and concentrated, and the dry residue again extracted with boiling chloroform. The filtered extracts were concentrated, the syrup dissolved in water (20 ml.), and Na^+ removed with Amberlite resin IR-120 (H^+ form), the solution concentrated, and the acid–lactone mixture (551 mg.) distilled (b. p. 140—160°/0·002 mm.) to give a syrup (285 mg.; 37·3% from the methylated diester), which was chiefly 2,5-di-*O*-methyl-D-glucaro-1,4:6,3-dilactone; $\nu_{max.}$ at 2850 and 1800 $cm.^{-1}$, with small bands at 3700—3100 (carboxylic acid OH) and 1660 $cm.^{-1}$ (C:C). Crystallisation from dry ether yielded the pure dilactone (226 mg.; 29·5%), m. p. 48·5—49°, identical with that described above from the benzylidene compound (IX).

Dimethyl 3,4-O-*Isopropylidene*-D-*glucarate* (XVII).—Dimethyl glucarate–calcium chloride complex (20 g.) and anhydrous copper sulphate (85 g.) were shaken with dry acetone (1·8 l.) for 7 days, the mixture filtered, the solids washed with acetone, and the filtrate and washings concentrated. The syrupy residue was purified by extraction with chloroform, the filtered extracts concentrated, the concentrate re-extracted with dry ether, and the resulting ether extract evaporated and dried. *Dimethyl* 3,4-O-*isopropylidene*-D-*glucarate* was recovered as a viscous syrup (16·27 g.; 85·8%) n_D^{20} 1·468, $[\alpha]_D$ +18·8° (*c* 1·05 in $CHCl_3$); $\nu_{max.}$ 1790 (trace, γ-lactone C:O), 1750 $cm.^{-1}$ (ester C:O) (Found: C, 46·7; H, 6·7; OMe, 21·2; Me_2CO, 20·6. $C_{11}H_{18}O_8$ requires C, 47·5; H, 6·5; OMe, 22·3; Me_2CO, 20·9%). High-vacuum distillation of this ester is not recommended, for it increases the amount of lactone impurity. Introduction of water at any stage in the working up of this ester also leads to lactone formation.

[24] Mitchell, *Canad. J. Chem.*, 1963, **41**, 214.

3,4-O-*Isopropylidene*-D-*glucarodiamide*.—A solution of the preceding ester (193 mg.) in dry methanol (50 ml.) was saturated with dry ammonia at 0° and kept at 0° for 7 days. The syrup obtained on concentration crystallised from acetone (5 ml.) as long needles (114 mg.; 54%) containing one molecule of acetone of crystallisation. Solvent was lost on heating at 100°/0·1 mm./24 hr. over phosphoric oxide to give the *diamide* as a white powder, m. p. 186·5—187°, $[\alpha]_D$ +28·0° (*c* 2 in H_2O) (Found: C, 43·9; H, 6·8; N, 11·45. $C_9H_{16}N_2O_6$ requires C, 43·5; H, 6·5; N, 11·3%).

Dimethyl 3,4-O-*Isopropylidene*-2,5-*di*-O-*methyl*-D-*glucarate* (XVIII).—The above ester (XVII) (15·66 g.) was methylated three times with methyl iodide (100 ml.) and silver oxide (60 g.) in the usual way, and the product distilled to yield the 2,5-*di*-O-*methyl ester* (15·17 g.; 88%), b. p. 105—110°/0·01 mm., n_D^{21} 1·449, $[\alpha]_D$ +20° (*c* 1 in $CHCl_3$); $\nu_{max.}$ 2850 (OMe) and 1750 cm.$^{-1}$ (ester C:O). (There was a trace of a lactone band at 1790 cm.$^{-1}$, but OH and C:C absorptions were absent) (Found: C, 51·7; H, 7·4; OMe, 37·4; Me_2CO, 20·4. $C_{13}H_{22}O_8$ requires C, 51·0; H, 7·2; OMe, 40·5; Me_2CO, 19·0%). Treatment of the ester (620 mg.) with methanolic ammonia at 0° and recrystallisation of the solid from ethanol (10 ml.) produced 3,4-O-*isopropylidene*-2,5-*di*-O-*methyl*-D-*glucarodiamide* (350 mg.; 62·5%), m. p. 207·5—208°, $[\alpha]_D$ +24° (*c* 2·17 in H_2O) (Found: C, 48·35; H, 7·55; N, 10·1; OMe, 21·9. $C_{11}H_{20}N_2O_6$ requires C, 47·8; H, 7·3; N, 10·1; OMe, 22·5%).

Saponification and Hydrolysis of Dimethyl 3,4-O-*Isopropylidene*-2,5-*di*-O-*methyl*-D-*glucarate*. —(*a*) *Isolation of* 4,5-*didehydro*-4-*deoxy*-2,5-*di*-O-*methyl*-Δ^4-D-*glucaro*-6,3-*lactone* (XIII). The methylated ester (3·21 g.) in ethanol (30 ml.) was saponified by heating at 50° for 1·5 hr. with 0·02N-sodium hydroxide (1300 ml.), 0·02N-sulphuric acid (1300 ml.) added, and the solution concentrated. The dry residue was extracted with boiling chloroform, the filtered extracts concentrated, and the syrupy acid (2·577 g.) hydrolysed with N-sulphuric acid (75 ml.) at 100° for 2 hr. The cold solution was neutralised (phenolphthalein) with 0·3N-barium hydroxide, barium sulphate separated, and the filtrate concentrated at 40° to 50 ml. After removal of Ba^{2+} with Amberlite resin IR-120 (H^+ form), the solution was concentrated and the residue (1·885 g.) distilled (b. p. 140—160°/0·005 mm.) to give a syrup (933 mg.; 44% as $C_8H_{10}O_6$), which was a mixture of dilactone (XI) and its unsaturated isomer (XIII). Extraction with hot chloroform (10 ml.) left a residue of 4,5-didehydro-4-deoxy-2,5-di-*O*-methyl-Δ^4-D-glucaro-6,3-lactone (354 mg.; 16·7%), m. p. 168—169°, $[\alpha]_D$ +73·1° (*c* 0·81 in H_2O) (lit.,[17] m. p. 168°, $[\alpha]_D$ +73·5°); $\nu_{max.}$ 3600—2500 (carboxylic acid OH), 2850 (OMe), 1780 (γ-lactone C:O), 1720 (carboxylic acid C:O), 1660 cm.$^{-1}$ (C:C) (Found: C, 47·3; H, 5·0; OMe, 30·6. Calc. for $C_8H_{10}O_6$: C, 47·5; H, 5·0; OMe, 30·7%). Treatment of this compound (162 mg.) in methanol (0·1 ml.) with methyl iodide (5 ml.) and silver oxide (0·5 g.) and recrystallisation from ethanol–ether gave the 1-methyl ester (59 mg.; 34%), m. p. 87·5—88°, $[\alpha]_D$ +97° (*c* 1·94 in H_2O) (lit.,[17] m. p. 89°, $[\alpha]_D$ +98°).

The chloroform extract was concentrated and the residue crystallised from dry ether to yield pure dilactone (XI) (191 mg.; 9%), m. p. 48—49°.

(*b*) *Isolation of* 2,5-*di*-O-*methyl*-D-*glucaro*-1,4:6,3-*dilactone* (XI). The methylated ester (XVIII) (1·686 g.) was saponified and hydrolysed as described in (*a*). The hydrolysate was neutralised with barium carbonate, the filtrate freed from Ba^{2+} and concentrated, and the residue (902 mg.) distilled to yield a syrup (603 mg.; 54·1%), which was chiefly dilactone (XI) contaminated with a small amount of the unsaturated isomer (XIII). Trituration with dry ether furnished the crystalline dilactone (534 mg.; 48%), m. p. 48·5—49°, which was converted into 2,5-di-*O*-methyl-D-glucarodiamide [16] as described above.

Methylation of Dimethyl 2,4-O-*Methylene*-D-*glucarate*.—The diester [3] (8·06 g.) in pure dimethylformamide (30 ml.) was treated with methyl iodide (12 ml.) and silver oxide (20 g.), the latter being added at hourly intervals over 5 hr. at 20°. After 16 hr. shaking at 20°, the mixture was centrifuged and the residue washed with dimethylformamide (30 ml.) and chloroform (3 × 30 ml.). After separation of a small amount (0·21 g.) of crystals (m. p. 318—319°; $[\alpha]_D$ 0·0° in pyridine), the supernatant liquid and washings were washed with 1% potassium cyanide solution (60 ml.) and then with water, dried (Na_2SO_4), and concentrated. The dark brown syrup (6·92 g.) was methylated again with methyl iodide (15 ml.) and silver oxide (15 g.) at 45° in the usual manner, and the product (6·26 g.) distilled to yield a yellow syrup (A) (4·40 g.; 55·5% as $C_{10}H_{14}O_7$), b. p. 116—122°/0·04 mm., n_D^{27} 1·4852, $[\alpha]_D$ −40·5° (*c* 2·4 in $CHCl_3$), −15° (*c* 0·66 in H_2O) changing to −29° on addition of two drops of 45% sodium hydroxide; $\nu_{max.}$ 2850 (OMe), 1740 (ester C:O), 1660, 1630, 1600 cm.$^{-1}$ (C:C) (no OH absorption); $\lambda_{max.}$ 233 mμ

(ε 5300, *c* 0·01 in H_2O). Syrup (A) consumed 2·25 atoms of chlorine in 1 hr. at 20° in the presence of excess of 0·02N-chlorine water (for conditions see ref. 17) (Found: C, 49·1; H, 6·0; OMe, 38·6. Dimethyl 2,3-didehydro-3-deoxy-5-*O*-methyl-2,4-*O*-methylene-Δ^2-D-glucarate (XX) $C_{10}H_{14}O_7$, requires C, 48·8; H, 5·7; OMe, 37·8%). Amide formation with methanolic ammonia at 0° or with liquid ammonia at 20° failed to give a crystalline compound.

Isolation of Crystalline Product (B).—The preceding syrup (A) (783 mg.) was taken up in water (100 ml.) at 70°, the solution kept at 0° for 24 hr., and product (B) isolated as needles (46 mg.), m. p. 94—96°, $[\alpha]_D$ −4° (*c* 1 in $CHCl_3$); $\nu_{max.}$ 2850 (OMe), 1720 (unsat. ester C:O), 1630 and 1600 cm.$^{-1}$ (C:C) (no OH absorption); $\lambda_{max.}$ 310 mμ (ε *ca.* 13,000 based on formula $C_{10}H_{14}O_7$; *c* 0·003 in EtOH). Composition varied in different preparations, but one analysis gave: C, 52·5; H, 5·9; OMe, 42·4%.

Reaction of Dimethyl 2,4-O-*Methylene*-D-*glucarate with Sulphuryl Chloride in Pyridine Solution.*[19]—Redistilled sulphuryl chloride (3·5 ml.) was added to a mixture of dry pyridine (15 ml.) and ethanol-free chloroform (50 ml.) at 5°, followed by dimethyl 2,4-*O*-methylene-D-glucarate [3] (2 g.) with vigorous stirring, and the mixture stirred at 5° for 2 hr. and at 20° for 2 hr. and then poured into ice–water. The solution was filtered, the chloroform layer washed with water and dried (Na_2SO_4), and the solvent removed to yield a solid residue (1·54 g.), which recrystallised from ethanol (25 ml.) as irregular plates of an unsaturated, monochlorodeoxy dimethyl ester (758 mg.; 37·8%), m. p. 135—136°, $[\alpha]_D$ +9° (*c* 1 in $CHCl_3$); $\nu_{max.}$ 1760 and 1735 (C:O), 1650 cm.$^{-1}$ (C:C) (no OH absorption) (Found: C, 43·4; H, 4·4; Cl, 14·0; OMe, 24·6. Dimethyl 5-chloro-2,3-didehydro-3,5-dideoxy-2,4-*O*-methylene-Δ^2-L-idarate (XXI), $C_9H_{11}ClO_6$, requires C, 43·1; H, 4·4; Cl, 14·2; OMe, 24·8%).

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