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STUDIES ON SESQUITERPENOIDS—IV.[1]

ABSOLUTE CONFIGURATION OF GUAIOL III.[2] ABSOLUTE CONFIGURATION OF THE SUBSTITUENT AT C-7 IN GUAIOL[3]

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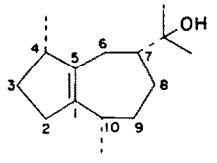
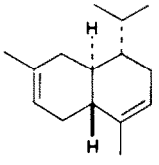
Abstract—Since S-(−)-α-isopropyl-γ-acetobutyric acid (XVII) was obtained by degradation of 10-hydroxy-2,5-dimethyl-8-isopropyl-decalone-1 (IX) derived from guaiol (I), the C-7 hydroxyisopropyl group in guaiol possesses the α-configuration and guaiol should be represented by XVIII.

IN previous papers,[2,4] it was established that the C-4 and the C-10 methyl groups in guaiol (I) possess the α-configuration, leaving the question as to whether the substituent at C-7 is α- or β-oriented.

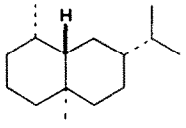
As the C-7 substituents of all hitherto known absolute configurations of sesquiterpenes and their derivatives are α-oriented (cf. II,[5] III,[6] IV[7] and V[8] in Chart 1), the configuration of the C-7 hydroxyisopropyl group in guaiol may also be regarded as α-oriented.[9]



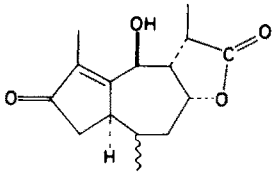
I



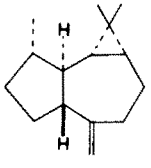
II



III



IV

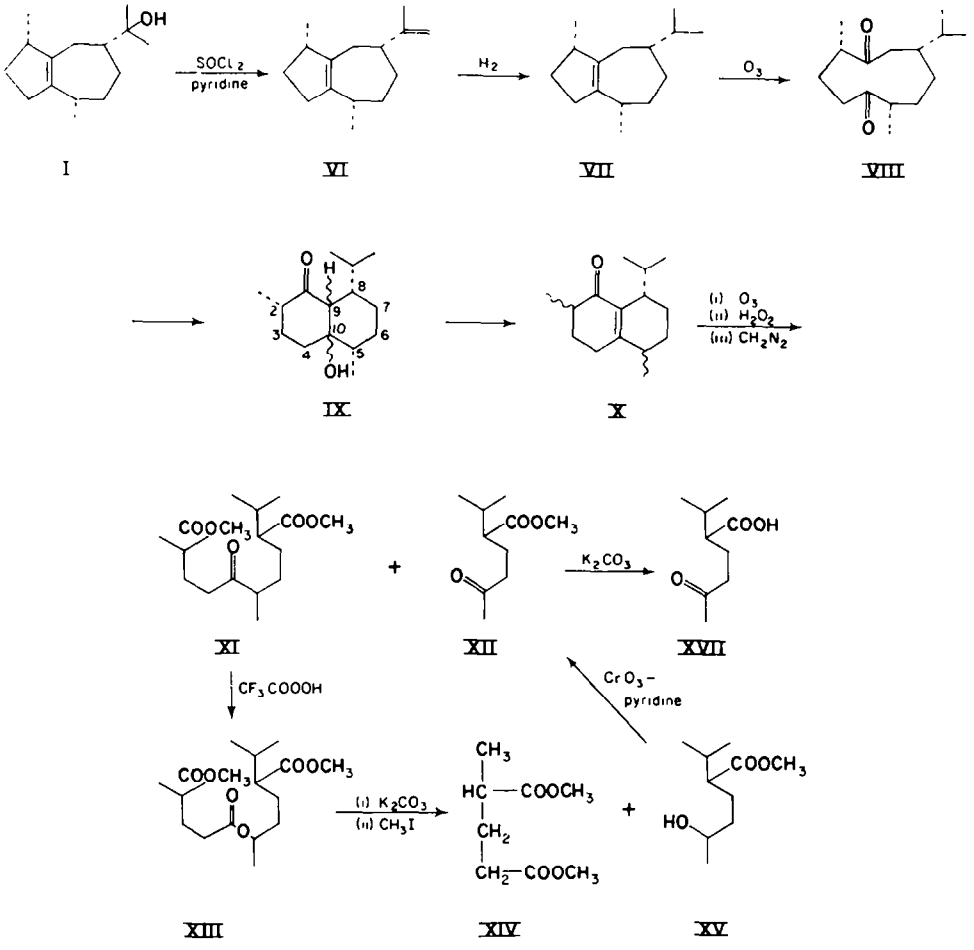


V

[1] Part III: K. Takeda, H. Minato and S. Nosaka, *Tetrahedron* **13**, 308 (1961).
[2] H. Minato, *Chem. Pharm. Bull.* (Japan) **9**, 625 (1961).
[3] A preceding communication: *Tetrahedron Letters* No. 8, 280 (1961).
[4] K. Takeda and H. Minato, *Tetrahedron Letters* No. 22, 33 (1960); *Chem. Pharm. Bull.* (Japan) **9**, 619 (1961).
[5] V. Herout and V. Sýkora, *Tetrahedron* **4**, 246 (1958).
[6] B. Riniker, J. Kalvoda, D. Arigoni, A. Fürst, O. Jeger, A. M. Gold and R. B. Woodward, *J. Amer. Chem. Soc.* **76**, 313 (1954); Ö. Kovács, V. Herout, M. Horák and F. Šorm, *Coll. Czech. Chem. Comm.* **21**, 225 (1956).
[7] D. H. R. Barton and J. E. D. Levisalles, *J. Chem. Soc.* 4518 (1958); J. A. Hamilton, A. T. McPhail and G. A. Sim, *Proc. Chem. Soc.* 278 (1960).
[8] L. Dolejš and F. Šorm, *Tetrahedron Letters* No. 17, 1 (1959). G. Büchi, S. W. Chow, T. Matsuura, T. L. Popper, H. H. Rennhard and M. Schach v. Wittenau, *Ibid.* No. 6, 14 (1959).
[9] J. B. Hendrickson, *Tetrahedron* **7**, 82 (1959).

An attempt has been made to determine the absolute configuration of the hydroxysopropyl group at C-7 in guaiol by degradation of 10-hydroxy-2,5-dimethyl-8-isopropyl-decalone-1 (IX) reported in the preceding paper.[1]

The ten-membered ring diketone (VIII) was produced via VI and VII as shown in Chart 2 and possesses a bulky isopropyl group. This fact suggests that the conformation possessing the thermodynamically more stable equatorial-like isopropyl group at C-7 is preferred in VIII.



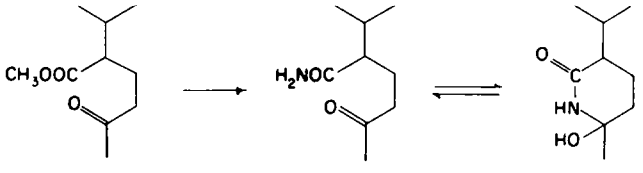
If VIII is heated at 190–200° without a solvent, or treated with acetic acid under reflux for 1 hour, or with 0·1 N solution of sodium methoxide in methanol under reflux for 1 hour, the resulting product IX, is the same in each case. It is, therefore, to be expected that the isopropyl group in IX also possesses the more stable equatorial configuration. This assumption was established by observation of the NMR spectrum of IX in chloroform. The spectrum at 56·4 Mc/sec shows a doublet signal (4·97 p.p.m. referred to chloroform) of a proton attached to a carbon atom which is α to a carbonyl group. The fact that the signal is split into a doublet with a 10·5 c.p.s. spin coupling constant indicates the existence of one proton on the adjacent carbon atom. This

interpretation of the NMR spectrum leads to the conclusion that the hydrogen atoms at C-8 and C-9 are oriented *trans*-diaxially[10] to one another and that the isopropyl group at C-8 is equatorial in IX.

In view of the manner of production of IX, the C-4 and C-10 methyl groups and the C-7 hydroxyisopropyl group in guaiol are considered to have maintained these original configurations in IX. Therefore, the absolute configuration of the C-7 hydroxyisopropyl group in guaiol should be explained by assignment of the configuration of the C-8 isopropyl group in IX.

It has also been reported in the preceding paper[1] that IX may be dehydrated to an α,β-unsaturated ketone (X) by treatment with 5 per cent sodium ethoxide in ethanol under reflux for 4 hours or by pyrolysis of its acetate at 400–450°. Furthermore, treatment of IX with 1 mole sodium hydride in absolute toluene followed by mesylation with mesyl chloride and chromatography on neutral alumina gives X and two stereoisomers of IX, m.p. 112–112·5° $[\alpha]$ +24·5° and m.p. 130–131·5°, $[\alpha]_D$ −31·4°, as by-products. During the course of this reaction, it is obvious that epimerization of the quasi-equatorial isopropyl group at C-8 in X does not occur, although its racemization may occur to some extent.

Ozonolysis of this α,β-unsaturated ketone (X) in ethyl acetate followed by hydrogen peroxide oxidation in a neutral medium affords a mixture of carboxylic acids. The methyl ester obtained by the action of diazomethane was chromatographed on neutral alumina and fractionated to give the following fractions: Fraction 1, a colourless mobile oil, b.p. 70–84°/1 mm and Fraction 2, a pale yellow oil, b.p. 144–145°/1 mm. The latter, the dimethyl ester of the expected ketodibasic acid (XI), $[\alpha]_D$ −9·8°, may be rearranged by the Baeyer-Villiger reaction with trifluoroperacetic acid to the ester (XIII), b.p. 142–143°/1 mm, $[\alpha]_D$ −2·4°. As already discussed in the previous papers,[4] it is obvious that this oxidation product is XIII. Treatment of Fraction 1



XII XVI a XVI b

with Girard's reagent T gives laevorotatory methyl α-isopropyl-γ-acetobutyrate (XII), b.p. 81–82°/3 mm, $[\alpha]_D$ −9·0°. This ketoester yields a semicarbazone, m.p. 128–129·5°, $[\alpha]_D$ −1·2° and an acid amide (XVI), m.p. 147–148°, $[\alpha]_D$ +22·3° (in ethanol).

Since the acid amide (XVI) shows a positive rotatory power in spite of the fact that the ketoester (XII) shows a negative rotation, $[\alpha]_D$ −9·0°, it is unreasonable to assume that this acid amide is represented by the formula XVIa. In the infra-red spectra of XVI, the ratio of the optical density of a band at 1705 cm^{-1} (ketone) to that of a band at 1648 cm^{-1} (acid amide) is 1:1 in the crystalline state, but is 1:2·1 in dioxane solution and roughly 1:3·5 in ethanol solution. From this observation, it was shown that XVI exists as XVIa in the crystalline state and as an equilibrium[11] between XVIa and XVIb

[10] A. D. Cohen, N. Sheppard and J. J. Turner, *Proc. Chem. Soc.* 118 (1958); R. U. Lemieux, R. K. Kullnig, H. J. Bernstein and W. G. Schneider, *J. Amer. Chem. Soc.* **79**, 1005 (1957), **80**, 6098 (1958); R. U. Lemieux, R. K. Kulling and R. Y. Moir, *Ibid.* **80**, 2237 (1958).

[11] N. H. Cromwell and K. E. Cook, *J. Amer. Chem. Soc.* **80**, 4573 (1958).

in solution. Assuming that the formula XVIb shows a positive rotation, it may be explained that the acid amide (XVI) shows a positive rotatory power in ethanol solution.

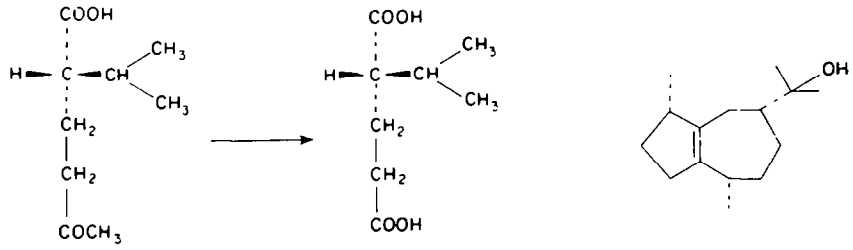
On the other hand, XIII is saponified by potassium carbonate in methanol, and its potassium salt refluxed with methyl iodide in absolute methanol gives a mixture of methyl esters. Chromatography of this mixture on neutral alumina affords methyl α-methylglutarate (XIV) as well as methyl α-isopropyl-δ-hydroxy-caproate (XV), b.p.

TABLE 1. COMPARISON OF $[\alpha]_D$ OF XVII

	Acid		Ester	
	$[\alpha]_D$	semicarbazone m.p.	$[\alpha]_D$	$[\alpha]_D$ of semicarbazone
XVII	−5·0° (in dioxane)	140–142°	−9·0° (in dioxane)	−1·2° (in dioxane)
Wallach's XVII	−6·18° (without solvent)	138–140°	−5·58°*	—

* Ethylester J. L. Simonsen, *J. Chem. Soc.* **119**, 1646, 1653 (1921).

110–111°/5 mm, $[\alpha]_D$ +1·3°, which is oxidized to XII with chromium trioxide-pyridine. Saponification of XII with potassium carbonate in methanol yields laevorotatory α-isopropyl-γ-acetobutyric acid (XVII), b.p. 147–150°/2 mm (bath temp), $[\alpha]_D$ −5·0° (semicarbazone, m.p. 140–142°). Wallach[12,13] obtained laevorotatory α-isopropylglutaric acid, m.p. 92–93°, $[\alpha]_D$ −15·82°, by oxidation of laevorotatory α-isopropyl-γ-acetobutyric acid, b.p. 175–180°/19 mm, $[\alpha]_D$ −6·18°, which was derived from dextrorotatory fenchone, with sodium hypobromite (see Table 1 and Chart 4).



XVII S-(−)-α-isopropyl-glutaric acid XVIII

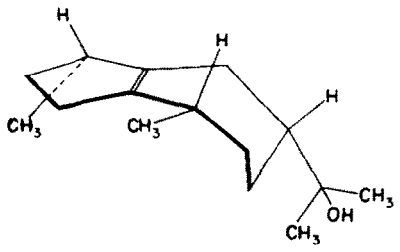
Since Fredga[14] established that laevorotatory α-isopropyl-glutaric acid has the S† (or D)-configuration, XVII should belong to the S-series. Further, as the C-8 isopropyl group in 10-hydroxy-2,5-dimethyl-8-isopropyl-decalone-1 (IX) possesses the α-configuration, guaiol should be represented by XVIII.

It follows, therefore, that guaiol possesses the structure XVIIIa or XVIIIb. All of

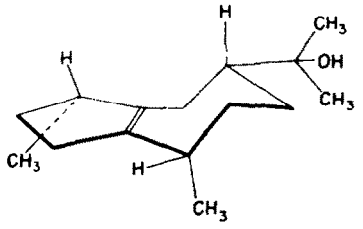
† The configurational symbol S is based on the nomenclature sequence rule (R. S. Cahn, C. K. Ingold and V. Prelog, *Experientia* **12**, 81 (1956)).

[12] O. Wallach, *Liebigs Ann.* **369**, 63 (1909); **379**, 182 (1911).
[13] K. Freudenberg and W. Lwowski, *Liebigs Ann.* **587**, 213 (1954).
[14] A. Fredga, *Acta. Chem. Scand.* **1**, 371 (1947).

the substituents in the boat form (XVIIIa) possess the more stable equatorial-like configuration, whereas the C-10 methyl group in the chair form (XVIIIb) possesses the axial-like configuration. This fact suggests that the boat form (XVIIIa) is preferred in guaiol (see Chart 5). Moreover, since Pauncz and Ginsburg[15] stated that the boat form



XVIII a



XVIII b

is more stable by a value of 0·67 kcal/mole than the chair form in cycloheptene, guaiol may be represented by the structure XVIIIa.

EXPERIMENTAL

The Rudolph Photoelectic Polarimeter Model 200 was used for all determination of optical rotations. All m.p. were measured by use of Kofler block ("Monoscope" Hans Bock Co. Ltd., Frankfurt am Main, Germany) and corrected.

NMR spectra of 10-*Hydroxy*-2,5-*dimethyl*-8-*isopropyl*-*decalone*-1 (IX). The spectra were measured at room temp with a Varian High Resolution NMR Spectrometer Model V 4300B and a Varian HR-60 High Resolution NMR Spectrometer System on solution (0·9 molar or less, 0·3 ml) of IX in chloroform.

The spectrum at 40 Mc/sec shows a doublet signal at 4·92 p.p.m. referred to chloroform (spin coupling constant = 10·0 c.p.s.). The spectrum at 56·4 Mc/sec shows a doublet signal at 4·97 p.p.m. referred to chloroform (spin coupling constant = 10·5 c.p.s.).

2,5-*Dimethyl*-8-*isopropyl*-Δ^{9-10}-*decalone*-1 (X). A mixture of IX (3·0 g) in absolute toluene (60 ml) and sodium hydride (30·2 mg, 1.0 equiv) in absolute toluene (20 ml) was refluxed with stirring for 4 hr, during which time an amorphous sodium-salt of IX separated from the solution. To this mixture was added dropwise a solution of mesyl chloride (1·52 g, 1·05 equiv) in absolute toluene (30 ml) with stirring under reflux for 3·5 hr. Water (15 ml) was added to this solution, and then the mixture was stirred for 1 hr at room temp and extracted with ether. The ether extract was washed with saturated potassium bicarbonate solution, dried (Na_2SO_4) and evaporated *in vacuo* giving a brown oil (3·0 g), which was chromatographed on neutral alumina (90 g; "Woelm", Activity Grade III). Elution with pet ether afforded a colourless oil (X; 1·79 g, 64·7%), b.p. 111°/1 mm, $[\alpha]_D^{20}$ −10·4° ±2° (*c* 0·981, dioxane), λ_{max}^{alc} 247 mμ (ε 11800), ν_{max}^{film} 1665 and 1622 cm^{-1}. (Found: C, 81·46; H, 11·01. $C_{15}H_{24}O$ requires: C, 81·76; H, 10·98%).

Further elution with pet ether-benzene (4:1 and 2:1) afforded a stereoisomer of IX, colourless needles (28 mg), m.p. 112–112·5° (from pet ether), $[\alpha]_D^{28}$ +24·5° ± 2° (*c* 1·224, dioxane), ν_{max}^{Nujol} 3571 and 1694 cm^{-1}. (Found: C, 75·61; H, 10·93. $C_{15}H_{26}O_2$ requires: C, 75·58; H, 11·00%).

Further elution with pet ether–benzene (1:1) and benzene afforded another stereoisomer of IX, colourless needles (120 mg), m.p. 130-131·5° (from pet ether), $[\alpha]_D^{23}$ −31·4° ± 2° (*c* 0·992, ethanol), ν_{max}^{Nujol} 3560 and 1706 cm^{-1}. (Found: C, 75·68; H, 10·91. $C_{15}H_{26}O_2$ requires: C, 75·58; H, 11·00%).

Further elution with benzene and benzene–chloroform (9:1) afforded the recovered IX (353 mg), m.p. 146–147°.

Ozonolysis of X *and hydrogen peroxide oxidation of the ozonide.* A solution of X (5·0 g) in ethyl acetate (70 ml) was treated at −75° with ozone stream (3·2% O_3). After 3·0 equiv of ozone was passed through the solution, it was allowed to stand at −75° for 30 min. The solvent was removed under high

[15] R. Pauncz and D. Ginsburg, *Tetrahedron* **9**, 40 (1960).

vaccum at room temp leaving a yellow oil. A mixture of this residue and 27% hydrogen peroxide (100 ml) was stirred at room temp for 4 hr, during which time potassium bicarbonate solution was occasionally added to this mixture in order to neutralize the acid produced. This reaction mixture was extracted with ether, and the aqueous layer was made negative to colour-test with zinc iodide–starch paper by addition of sodium bisulphite solution in an ice bath, acidified to Congo red with 2N H_2SO_4 and extracted with ether. The ether extract was washed with water, dried (Na_2SO_4) and evaporated *in vacuo* giving a colourless oil (3·14 g). Application of diazomethane to this oil afforded its methyl ester (3·4 g), which was dissolved in pet ether (300 ml) and filtered through a column of neutral alumina (100 g; "Woelm", Activity Grade III) giving a colourless oil (2·36 g) (from fractions of pet ether, pet ether–benzene (9:1, 4:1 and 1:1), benzene and benzene–chloroform (9:1 and 4:1)). This oil was distilled to furnish the following two fractions: Fraction 1, a colourless mobile oil (725 mg), b.p. 70–84°/1 mm and Fraction 2, a pale yellow oil (1·56 g), b.p. 138–148°/1 mm. Fraction 1 was redistilled at 83–86°/3 mm giving a colourless oil (570 mg), which was treated with Girard's reagent T to afford methyl α-isopropyl-γ-acetobutyrate (XII; 175 mg), b.p. 81–82°/3 mm, $[\alpha]_D^{16}$ −9·0° ± 2° (*c* 1·994, dioxane), ν_{max}^{film} 1733 and 1721 cm^{-1}. (Found: C, 64·16; H, 9·87. $C_{10}H_{18}O_3$ requires: C, 64·49; H, 9·74%). *Semicarbazone:* colourless needles, m.p. 128–129·5° (from n-propylalcohol-ligroin), $[\alpha]_D^{16}$ −1·2° ± 2° (*c* 1·049, dioxane). (Found: C, 54·59; H, 8·82; N, 16·98. $C_{11}H_{21}O_3N_3$ requires: C, 54·30; H, 8·70; N, 17·27%). Acid amide (XVI): colourless needles, m.p. 147–148° (from n-propylalcohol–ligroin), $[\alpha]_D^{26}$ +22·3° ± 2° (*c* 1·050, ethanol), ν_{max}^{Nujol} 3380, 3180, 1705, 1648 and 1540 cm^{-1}; $\nu_{max}^{ethanol}$ 1706 and 1674 cm^{-1}; $\nu_{max}^{dioxane}$ 3496, 3340, 1724, 1689 and 1619 cm^{-1}. (Found: C, 62·86; H, 10·03; N, 7·90. $C_9H_{17}O_2N$ requires: C, 63·13; H, 10·00; N, 8·18%).

Fraction 2 was redistilled at 144–145°/1 mm giving a pale yellow oil (XI; 1·35 g), $[\alpha]_D^{16}$ −9·8° ± 2° (*c* 1·132,di oxane), ν_{max}^{film} 1738 and 1713 cm^{-1}. (Found: C, 64·90; H, 9·47. $C_{17}H_{30}O_5$ requires: C, 64·94; H, 9·62%).

Oxidation of XI *with trifluoroperacetic acid.* A solution of trifluoroperacetic acid was prepared by dropwise addition of a solution of trifluoroacetic anhydride (3·45 g, 4 equiv) in methylene chloride (4 ml) to a suspension of 80% hydrogen peroxide (610 mg, 3·5 equiv) in methylene chloride (2 ml) with stirring in an ice bath. This solution was added dropwise to a stirred suspension of dry, finely ground disodium phosphate (6·0 g) in a solution of XI (1·29 g) in methylene chloride (15 ml) over a 30 min period and until the exothermic reaction ceased. The mixture was then stirred for 1 hr, allowed to stand for 45 hr at room temp, and refluxed for an additional 3·5 hr. The insoluble salts were collected and washed with methylene chloride. The combined filtrate was washed with sodium bisulphite solution, water, potassium bicarbonate solution and water, dried (Na_2SO_4) and evaporated *in vacuo* giving a pale yellow oil (1·4 g). The residue was distilled at 142–143°/1 mm giving a colourless oil (XIII; 1·2 g), $[\alpha]_D^{23}$ −2·4° ± 2° (*c* 0·958, dioxane), ν_{max}^{film} 1740 cm^{-1}. (Found: C, 62·25; H, 9·31. $C_{17}H_{30}O_5$ requires: C, 61·79; H, 9·15%).

Saponification of XIII. A mixture of XIII (1·2 g) in methanol (40 ml) and potassium carbonate (1·5 g) in water (8 ml) was refluxed for 2 hr on a steam bath and then evaporated *in vacuo* to dryness. The residue was dissolved in absolute methanol (30 ml) and an excess of potassium carbonate was filtered off. Methyl iodide (7·74 g) was added to the filtrate and refluxed for 5 hr. The residue obtained upon removal of the solvent was dissolved in a small amount of water and extracted with ether. The ether extract was washed with potassium bicarbonate solution and water, dried (Na_2SO_4) and evaporated giving a mobile oil (1·02 g). This oil was dissolved in pet ether (100 ml) and chromatographed on neutral alumina (30 g; "Woelm" Activity Grade III). Elution with pet ether and pet ether–ether (95:5) afforded methyl α-methyl glutarate (XIV; 299 mg), b.p. 92–102°/2·5 mm (bath temp), which was saponified with potassium carbonate giving α-methylglutaric acid, m.p. 80–82° (from benzene), $[\alpha]_D^{22}$ +0·8° ± 2° (*c* 1·019, dioxane). (Found: C, 49·52; H, 6·76. $C_6H_{10}O_4$ requires: C, 49·31; H, 6·90%).

Further elution with pet ether–ether (4:1 and 1:1) and ether afforded methyl α-isopropyl-δ-hydroxy-caproate (XV) as a colourless oil (436 mg), b.p. 110–111°/5 mm, $[\alpha]_D^{14}$ +1·3° ± 2° (*c* 0·301, dioxane), ν_{max}^{film} 3421, 1733, 1190, 1160 and 1019 cm^{-1}. (Found: C, 63·60; H, 10·83. $C_{10}H_{20}O_3$ requires: C, 63·79; H, 10·71%).

Oxidation of methyl α-isopropyl-δ-hydroxy-caproate (XV). To the chromium trioxide–pyridine complex from chromium trioxide (606 mg) and pyridine (6 ml) was added a solution of XV (303 mg) in pyridine (16 ml) at 8–10°. The mixture was left in an ice bath for 1 hr and allowed to stand overnight at room temp. Then the mixture was diluted with ice water and extracted with ether. The

ether extract was washed with 2N H_2SO_4, water, 2N Na_2CO_3 and water, dried (Na_2SO_4) and evaporated giving a colourless oil (267 mg). The residue was treated with Girard's reagent T to afford methyl α-isopropyl-γ-acetobutyrate (XII) as a colourless oil (233 mg), b.p. 75–76°/2 mm, $[\alpha]_D^{22}$ −3·1° ± 2° (*c* 1·239, dioxane). *Semicarbazone:* colourless needles, m.p. 128·5–129·5°, undepressed on admixture with the above-mentioned sample of XII.

α-*Isopropyl-γ-acetobutyric acid* (XVII). XII was saponified with potassium carbonate giving α-isopropyl-γ-acetobutryic acid (XVII), a colourless oil, b.p. 147–150°/2 mm (bath temp), $[\alpha]_D^{21}$ −5·0° ± 1° (*c* 3·023, dioxane). *Semicarbazone:* colourless needles, m.p. 140–142°. (Found: C, 52·38; H, 8·51; N, 18·08. $C_{10}H_{19}O_3N_3$ requires: C, 52·38: H, 8·35: N, 18·33%).

Acknowledgements—The author is indebted to Associate Prof. Y. Sasaki of the University of Osaka and Mr. M. Tori for the determination and interpretation of the NMR spectra.