Naturally Occurring Compounds Related to Phenalenone. Part VII.[1] Absolute Configuration of Atrovenetin and Related Compounds †

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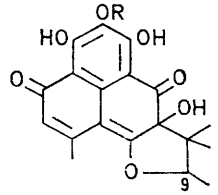
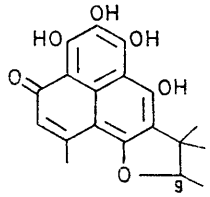
Chemical correlation of a degradation product of isoherqueinone with (−)-(*S*)-ethyl lactate has established that herqueinone and isoherqueinone have the *R*- and *S*-configuration, respectively, at the asymmetric centre in the side-chain; it follows that atrovenetin possesses the *R*-configuration.

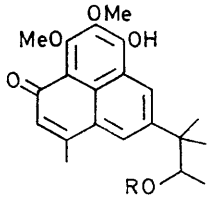
THE mould metabolites herqueinone (1a) and norherqueinone (1b) have been shown [2] to possess the same configuration at C-9 as atrovenetin (2), and to differ from isoherqueinone and isonorherqueinone respectively only in the configuration of that centre. Herqueinone and isoherqueinone may be degraded into the (−)- and (+)-enantiomers respectively of the phenalenone (3a).[2]



(1) a; R = Me
b; R = H



(2)



(3) a; R = H
b; R = $C_6H_3(NO_2)_2CO$

In the work described in this paper, these latter compounds have been correlated with (−)-(*S*)-ethyl lactate (9), thus permitting assignment of absolute configurations to all the metabolites mentioned above.

The first step in relating the configuration of the phenalenone (3a) to that of a simpler compound of known absolute configuration was the destruction of the aromatic part of the molecule by oxidation. In order to protect the aliphatic hydroxy-group, both enantiomers of the phenalenone (3a) were converted into their mono-3,5-dinitrobenzoates; that derived from the (+)-phenalenone (3a) was converted into (+)-3-(3,5-dinitrobenzoyloxy)-2,2-dimethylbutyric acid (4a), $[\alpha]_D$ +34°, by oxidation with ruthenium tetraoxide and sodium periodate.[3] In order to obtain sufficient material to permit correlation with a compound of known absolute configuration, resolution of the racemic material [obtained by treatment of the hydroxy-acid (4b) [4] with dinitrobenzoyl chloride and pyridine] was carried out.

$R^1O{\cdot}CHMe{\cdot}CMe_2{\cdot}CO_2R^2$

(4) a; $R^1 = C_6H_3(NO_2)_2CO$, R^2 = H
b; $R^1 = R^2$ = H
c; R^1 = H, R^2 = Et
d; $R^1 = C_6H_3(NO_2)_2CO$, R^2 = Et
e; R^1 = Ac, R^2 = H
f; R^1 = Ac, R^2 = Me
g; $R^1 = C_6H_3(NO_2)_2CO$, R^2 = Me

$R^1O{\cdot}CHMe{\cdot}CMe_2R^2$

(5) a; $R^1 = R^2$ = H
b; $R^1 = C_6H_3(NO_2)_2CO$, R^2 = Br
c; $R^1 = C_6H_3(NO_2)_2CO$, R^2 = CO·Cl
d; $R^1 = C_6H_3(NO_2)_2CO$, R^2 = Ac
e; $R^1 = R^2$ = Ac

$RO{\cdot}CHMe{\cdot}CMe_2{\cdot}OH$ (6) a; R = H, b; R = Ac

$[AcO{\cdot}CHMe{\cdot}CMe_2{\cdot}CO]_2O$ (7)

$AcO{\cdot}CHMe{\cdot}CMe_2{\cdot}CO_2{\cdot}CHMe{\cdot}CMe_2{\cdot}CO{\cdot}OAc$ (8)

Fractional crystallisation of the diastereoisomeric brucine salts from aqueous acetone gave a pure sample of the less soluble diastereoisomer from which, by treatment with dilute hydrochloric acid, was obtained (−)-3-(3,5-dinitrobenzoyloxy)-2,2-dimethylbutyric acid (4a), $[\alpha]_D$ −35°; by acidification of the mother liquors the dextrorotatory enantiomer of compound (4a) was obtained in a less optically pure state ($[\alpha]_D$ +28°).

The absolute configuration of 3-methylbutan-2-ol (5a) is known; [5] correlation of the 3,5-dinitrobenzoate of the alcohol (5a) with the product obtained by decarboxylation of optically active 3-(3,5-dinitrobenzoyloxy)-2,2-dimethylbutyric acid (4a) would therefore lead to assignment of absolute configurations to atrovenetin and related compounds. This possibility was investigated by applying the modified Hunsdiecker reaction [6] to the racemic form of the acid (4a) to give 2-bromo-1,2-dimethylpropyl 3,5-dinitrobenzoate (5b). Attempts to replace the bromine atom of compound (5b) with hydrogen by catalytic hydrogenolysis [7] and by reduction with triphenyltin hydride,[8] with a trace of azoisobutyronitrile [9] as initiator, were unsuccessful, however, possibly as a result of competition by reactions involving the nitro-groups.

† Preliminary account, J. S. Brooks and G. A. Morrison, *Chem. Comm.*, 1971, 1359.

[1] Part VI, D. A. Frost and G. A. Morrison, *J.C.S. Perkin I*, 1973, 2388.
[2] J. S. Brooks and G. A. Morrison, *Tetrahedron Letters*, 1970, 963; *J.C.S. Perkin I*, 1972, 421.
[3] J. A. Caputo and R. Fuchs, *Tetrahedron Letters*, 1967, 4729.
[4] M. A. Courtot, *Bull. Soc. chim. France*, 1906, **35**, 111.
[5] P. G. Stevens, *J. Amer. Chem. Soc.*, 1932, **54**, 3732.
[6] S. J. Cristol and W. C. Firth, jun., *J. Org. Chem.*, 1961, **26**, 280.
[7] R. L. Augustine, 'Catalytic Hydrogenation,' Arnold, London, 1965, p. 125.
[8] H. G. Kuivila and O. F. Beumel, jun., *J. Amer. Chem. Soc.*, 1961, **83**, 1246.
[9] H. G. Kuivila and L. W. Menapace, *J. Org. Chem.*, 1963, **28**, 2165.

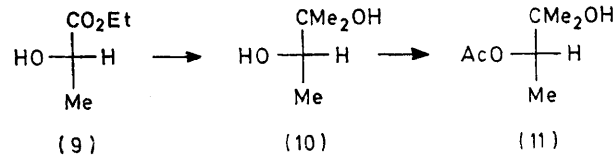
The required absolute configurations were finally determined by correlation of both enantiomers of 3-(3,5-dinitrobenzoyloxy)-2,2-dimethylbutyric acid (4a) with ethyl lactate. The first stage of this sequence, involving the transformation of the acid (4a) into the diol (6a) was attempted, in the racemic series, by treatment of the derived acid chloride (5c) with dimethylcadmium to give the methyl ketone (5d), which was then subjected to a Baeyer–Villiger reaction. The ketone (5d) was unaffected by *m*-chloroperbenzoic acid, but heating under reflux in methylene chloride with a large excess of trifluoroperacetic acid followed by oxidation of unchanged methyl ketone with alkaline sodium hypochlorite gave a very small yield of the diol (6a). The methyl ketone (5e), obtained by treatment with diazomethane and hydrogen iodide of the acid chloride derived from the acetoxy-acid (4e), was similarly resistant to Baeyer–Villiger oxidation, being recovered unchanged after treatment with *m*-chloroperbenzoic acid or trifluoroperacetic acid.

Direct replacement of the carboxy-group of the (±)-acetoxy acid (4e) with a hydroxy-group was achieved by heating the derived peroxy-acid (obtained in a yield of 78% by treatment of the corresponding acid chloride with alkaline hydrogen peroxide [10]) in olefin-free light petroleum.[11] The product was a mixture of the diol monoacetate (6b) (79%) and the acetoxy-acid (4e) (15%).

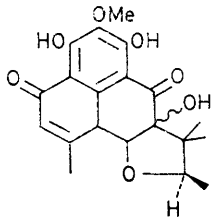
An optically active sample of 3-acetoxy-2,2-dimethylbutyric acid (4e), $[\alpha]_D$ −14°, was obtained by acetylation of (+)-3-hydroxy-2,2-dimethylbutyric acid (4b), $[\alpha]_D$ −9·1°, derived from the dinitrobenzoyloxy-acid (4a), $[\alpha]_D$ −35°, by saponification. By a similar route, (+)-3-acetoxy-2,2-dimethylbutyric acid (4e), $[\alpha]_D$ +8·7°, was obtained from the (+)-dinitrobenzoyloxy-acid (4a), $[\alpha]_D$ +28°. In the latter sequence a neutral compound, formulated as (—)-3-acetoxy-2,2-dimethylbutyric anhydride (7), $[\alpha]_D$ −16·0°, was also isolated in the acetylation step: the alternative structure (8), also consistent with the micro-analysis and spectra recorded, was eliminated by conversion of the compound, in almost quantitative yield, into methyl 3-acetoxy-2,2-dimethylbutyrate (4f) by heating under reflux in methanol–pyridine followed by treatment of the product with diazomethane.

The (+)- and (—)-enantiomers of the acetoxy-acid (4e) were converted into the enantiomers of 2-hydroxy-1,2-dimethylpropyl acetate (6b), $[\alpha]_D$ +12·2 and −13·2°, respectively, by the method already described for the racemic series. Correlation of the configurations with those of compounds of known absolute configuration was completed by treating (—)-(*S*)-ethyl lactate (9), $[\alpha]_D$ −11·4°, with methylmagnesium iodide to give (+)-2-methylbutane-2,3-diol (10), $[\alpha]_D$ +4·1° (84% yield),* acetylation of which gave (+)-2-hydroxy-1,2-dimethylpropyl acetate (6b), $[\alpha]_D$ +12·3°.

The correlation described above establishes that the laevorotatory enantiomer of compound (6b) possesses the *R*-configuration, from which the absolute configurations of all the optically active compounds described may be deduced; individual assignments are indicated in the Experimental section. In particular, the (—)- and (+)-phenalenones (3a) which are derived ultimately from herqueinone and isoherqueinone, respectively, belong to the *R*- and *S*-series, respectively. The formula of herqueinone may now be expressed as (12); isoherqueinone differs from it only in the configuration of the asymmetric centre in the side-chain. Similarly, the complete stereoformula of atrovenetin (extracted from the mycelium of *P. Atrovenetum*) may be written as (13).



(9) (10) (11)



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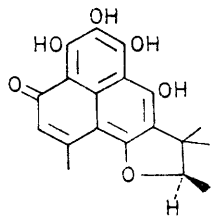

(13)

EXPERIMENTAL

M.p.s were measured on a Kofler hot-stage apparatus. I.r. spectra were recorded on a Unicam SP 1000G spectrophotometer or on a Perkin-Elmer 125 instrument. U.v. spectra were recorded on a Unicam SP 800 spectrophotometer, with 95% ethanol as solvent. N.m.r. spectra were measured on a Varian A60A instrument with deuteriochloroform as solvent unless specified otherwise. Mass spectra were recorded on an A.E.I. MS 902 spectrometer. Optical rotations were measured on a Perkin-Elmer 141 polarimeter for solutions in chloroform in a 1 dm cell unless specified otherwise. Gas chromatography was carried out using a Perkin-Elmer F11 gas chromatograph or a Varian 1527 B instrument. T.l.c. was carried out using plates coated with Merck Kieselgel G or GF_{254}. Solutions in organic solvents were dried with anhydrous sodium sulphate or magnesium sulphate.

7-Hydroxy-5-[2-(3,5-dinitrobenzoyloxy)-1,1-dimethylpropyl]-8,9-dimethoxy-3-methylphenalen-1-one (3b).—(i) (S)-*Isomer*. A solution of the (+)-(*S*)-phenalenone (3a) (210 mg), $[\alpha]_D$ +28°, and 3,5-dinitrobenzoyl chloride (170 mg) in

* Our present results are at variance with an earlier report [12] that reaction between (—)-ethyl lactate and 2 mol. equiv. of methylmagnesium iodide gives (—)-2-methylbutane-2,3-diol (6a). The b.p. reported by these earlier workers for their product was quite different from that recorded by us, and no analytical or spectrosopic data were quoted in support of their assigned structure. Our own observations accord well with a report [13] that treatment of (+)-(*R*)-methyl lactate with methylmagnesium iodide affords (—)-2-methylbutane-2,3-diol (6a).

[10] Y. Ogata and Y. Sawaki, *Tetrahedron*, 1967, **23**, 3327; see also R. N. McDonald, R. N. Steppel, and S. E. Dorsey, *Org. Synth.*, 1970, **50**, 15.

[11] D. Lefort, C. Paquot, and J. Sorba, *Bull. Soc. chim. France*, 1959, 1385.

[12] K. Thaker and I. G. Vasi, *J. Sci. Ind. Res.*, 1961, **20B**, 66.

[13] B. W. Christensen and A. Kjaer, *Proc. Chem. Soc.*, 1962, 307.

dry benzene (8 ml) and pyridine (2 drops) was heated under reflux for 2 h. The excess of dinitrobenzoyl chloride was destroyed by addition of water to the cooled mixture, most of the benzene was evaporated off under reduced pressure, and the resulting yellow solid was dissolved in dichloromethane (100 ml). The solution was washed successively with dilute aqueous sodium carbonate, dilute hydrochloric acid, and water, then dried and evaporated *in vacuo* to give, in almost quantitative yield, the *ester* (3b), which gave yellow crystals from dichloromethane–methanol, m.p. 282—283° (Found: C, 61·05; H, 4·7; N, 5·4. $C_{28}H_{26}N_2O_{10}$ requires C, 61·1; H, 4·75; N, 5·1%), $\lambda_{max.}$ 235, 347, 414, and 436 nm (log ε 4·63, 4·28, 4·08, and 4·08); $\nu_{max.}$ (Nujol) 720, 732, 1550, 1595, 1628, 1720, and 3100 cm^{-1}; τ ([$^2H_5$]-pyridine) 0·63 (1H, t, *J* 2 Hz, ArH), 0·79 (2H, d, *J* 2 Hz, ArH), 1·40 (1H, d, *J* 2 Hz, ArH), 4·09 (1H, q, *J* 6·5 Hz, OC*H*Me), 5·65 and 5·86 (each 3H, s, OMe), 7·22 (3H, s, ArMe), 8·29 and 8·33 (each 3H, s, CMe_2), and 8·60 (3H, d, *J* 6·5 Hz, OCH*Me*) (signals given by two aromatic protons were apparently concealed by overlapping solvent absorptions).

(ii) (R)-*Isomer*. Similar treatment of the (−)-(*R*)-phenalenone (3a) (110 mg), $[\alpha]_D$ −31°, gave the *3,5-dinitrobenzoate* (3b), m.p. 282—283° (Found: C, 61·25; H, 4·85; N, 4·75%; *m/e*, 550·1586. $C_{28}H_{26}N_2O_{10}$ requires C, 61·1; H, 4·75; N, 5·1%; *M*, 550·1587), u.v. and i.r. spectra identical with those of its enantiomer.

3-(3,5-*Dinitrobenzoyloxy*)-2,2-*dimethylbutyric Acid* (4a).—(a) *Racemic material*. (±)-3-Hydroxy-2,2-dimethylbutyric acid (4b) [4] (44 g) was heated and stirred at 70° for 70 min with dry benzene (200 ml), 3,5-dinitrobenzoyl chloride (44 g), and pyridine (16 ml). Two layers separated as the mixture cooled, and on cooling to 0° the lower layer crystallised rapidly. After filtration the solution was extracted with aqueous sodium carbonate, and the crystalline material was taken up in the same solution, which contained, in addition to the required acid (4a), some 3,5-dinitrobenzoic acid. The aqueous solution was washed with benzene, and its pH was carefully adjusted to 7 by addition of dilute hydrochloric acid with stirring. The white precipitate which separated was filtered off, washed with water, and recrystallised from aqueous ethanol to give the (±)-*acid* (4a) (26·7 g) as needles, m.p. 170—171° (Found: C, 48·05; H, 4·4; N, 8·8. $C_{13}H_{14}N_2O_8$ requires C, 47·85; H, 4·35; N, 8·6%), $\lambda_{max.}$ 210 nm (log ε 4·42); $\nu_{max.}$ (Nujol) 720, 730, 1550, 1630, 1698, 1720, 2500—3200, and 3080 cm^{-1}; τ ([$^2H_6$]acetone) 0·82 (1H, t, *J* 2 Hz, ArH-4), 0·90 (2H, d, *J* 2 Hz, ArH-2 and -6), 4·50 (1H, q, *J* 6·5 Hz, OC*H*Me), 5·1br (1H, s, exchangeable with D_2O, CO_2H), 8·58 (3H, d, *J* 6·5 Hz, OCH*Me*), and 8·63 and 8·69 (each 3H, s, CMe_2).

The base-extracted benzene solution was washed successively with dilute hydrochloric acid and water, dried, and evaporated *in vacuo* to give a brown oil (14·96 g) which was homogeneous by t.l.c. and exhibited the i.r. spectrum of an anhydride; $\nu_{max.}$ (benzene) 1720 (aryl ester C=O) and 1730 and 1805 (anhydride C=O) cm^{-1}. The anhydride was hydrolysed by heating its solution in water (15 ml) and pyridine (50 ml) under reflux for 30 h. The cooled solution was extracted with dilute aqueous sodium carbonate, and from the extract was isolated, by the method described above, a pale yellow solid. An ethanolic solution of this material was decolourised (charcoal); recrystallisation from ethanol then gave more (5·1 g) of the (±)-acid, m.p. and mixed m.p. 167—169° (total yield 31·8 g, 29%).

When the dinitrobenzoylation was attempted in refluxing benzene solution for 1 h [conditions which quantitatively converted the ethyl ester (4c) into its 3,5-dinitrobenzoate (4d)], or in pyridine solution at room temperature for 5 days, the only product isolated was a non-crystalline material exhibiting i.r. absorption at 1725 and 1805 cm^{-1}, characteristic of an anhydride; in agreement with this assignment, hydrolysis with aqueous pyridine gave a small quantity of the required 3,5-dinitrobenzoyloxy-acid (4a).

The *methyl ester* (4g), prepared by treatment with ethereal diazomethane, crystallised from ethanol as needles, m.p. 89—90° (Found: C, 49·4; H, 4·7; N, 8·0. $C_{14}H_{16}N_2O_8$ requires C, 49·4; H, 4·75; N, 8·25%), $\lambda_{max.}$ 210 nm (log ε 4·39); $\nu_{max.}$ (Nujol) 1720br cm^{-1}; τ 0·77 (1H, t, *J* 2 Hz, ArH-4), 0·88 (2H, d, *J* 2 Hz, ArH-2 and -6), 4·52 (1H, q, *J* 6·5 Hz, OC*H*Me), 6·29 (3H, s, OMe), 8·60 (3H, d, *J* 6·5 Hz, OCH*Me*), and 8·65 and 8·70 (each 3H, s, CMe_2).

(b) (+)-(S)- *and* (−)-(R)-*Enantiomers by resolution of racemic material*. A solution of brucine (62·2 g) in acetone (270 ml) and water (30 ml) was added to a hot, stirred solution of the (±)-3,5-dinitrobenzoyloxy-acid (4a) (51·4 g) in a solvent mixture (300 ml) of the same composition. The solution became deep red and crystals began to form immediately. The solution was left overnight at 0°, and the crystals were filtered off and dried to give a mixture of the diastereoisomeric brucine salts (72·6 g) as red needles, $[\alpha]_D$ −70·5° (*c* 1·75 in pyridine). Three recrystallisations from acetone–water (9 : 1; 1500 ml reduced to 1000 ml by distillation under reduced pressure after complete dissolution) gave the *brucine salt* of the (−)-(R)-*acid* (26·6 g) as deep red needles, m.p. 208—209°, $[\alpha]_D$ −82° (*c* 1·29 in pyridine) (Found: C, 60·3; H, 5·7; N, 7·6. $C_{36}H_{40}N_4O_{12}$ requires C, 60·0; H, 5·6; N, 7·75%), $\lambda_{max.}$ 214 and 301 nm (log ε 4·5 and 3·92); $\nu_{max.}$ (Nujol) 720, 730, 1640, and 1715 cm^{-1}.

The mother liquor (600 ml) from the initial crystallisation was evaporated under reduced pressure to *ca.* 300 ml, and was kept overnight at 0° to give the brucine salt of the (+)-(*S*)-acid (33·8 g) as red needles, $[\alpha]_D$ −55° (*c* 2·30 in pyridine).

The brucine salt of $[\alpha]_D$ −82° (26·5 g) was suspended in acetone (100 ml) and stirred while dilute hydrochloric acid (50 ml) was added. The deep red colour of the suspension was discharged immediately and a homogeneous solution was obtained. Addition of more dilute hydrochloric acid (150 ml), with stirring for a further 15 min gave a precipitate which was filtered off, washed successively with dilute hydrochloric acid and water, and recrystallised from aqueous ethanol to give the (−)-(R)-*acid* (4a) (10·68 g, 89%; 41% overall) as needles, m.p. 195—197°, $[\alpha]_D$ −35° (*c* 4·2 in acetone) (Found: C, 48·15; H, 4·45; N, 8·75. $C_{13}H_{14}N_2O_8$ requires C, 47·85; H, 4·35; N, 8·6%), $\lambda_{max.}$ 210 nm (log ε 4·42); $\nu_{max.}$ (Nujol) 725, 735, 1550, 1630, 1700, and 1720 cm^{-1}, n.m.r. and u.v. spectra identical with those of the racemic acid [i.r. spectra (Nujol mulls) differed considerably in the 700—1200 cm^{-1} region].

In the same way, the brucine salt of $[\alpha]_D$ −55° (33·8 g) was suspended in acetone (100 ml) and stirred with dilute hydrochloric acid (200 ml) to give, after work-up as described above and recrystallisation from aqueous ethanol, the (+)-(S)-*acid* (4a) (13·59 g, 88%; 53% overall) as needles, m.p. 189—194°, $[\alpha]_D$ +28° (*c* 3·78 in acetone) (Found: C, 47·95; H, 4·35; N, 8·55. $C_{13}H_{14}N_2O_8$ requires C, 47·85; H, 4·35; N, 8·6%), i.r. and u.v. spectra identical with those of the (−)-(*R*)-acid.

(c) (+)-(S)-*Enantiomer by oxidation of the* 3,5-*dinitrobenzoate of the* (+)-(S)-*phenalenone* (3a). To a suspension of the 3,5-dinitrobenzoate (3b) (420 mg) in a mixture of carbon tetrachloride (15 ml), sodium periodate (4 g), and water (25 ml) a crystal of ruthenium dioxide (*ca.* 40 mg) was added and the mixture was stirred vigorously at 60°. After 3 days all the organic material had dissolved, and after 7 days the cooled mixture was poured into water and extracted with ether. The extract was washed successively with sodium hydrogen sulphite solution and water, then dried and evaporated under reduced pressure to give a semicrystalline residue (273 mg) from which the (+)-(S)-acid (4a) (35 mg, 14%) was obtained as a solid by preparative t.l.c. on Kieselgel GF_{254} (5% methanol–chloroform as eluant). Two recrystallisations from aqueous ethanol gave needles (26 mg), m.p. 192—194°, $[\alpha]_D$ +34° (*c* 1·10 in acetone), i.r. (KCl), u.v., and n.m.r. spectra identical with those of the (+)-(S)-acid (4a), $[\alpha]_D$ +28°, obtained by resolution of racemic material.

Ethyl 3-(3,5-*Dinitrobenzoyloxy*)-2,2-*dimethylbutyrate* (4d).—Ethyl 3-hydroxy-2,2-dimethylbutyrate (4c) (150 mg) in dry benzene (2 ml) was heated under reflux with 3,5-dinitrobenzoyl chloride (150 mg) and pyridine (1 ml) for 1 h, then the cooled mixture was poured into water and extracted with ether. The extract was washed successively with dilute aqueous sodium carbonate, dilute hydrochloric acid, and water, then dried and evaporated *in vacuo* to give a red gum which slowly crystallised. Preparative t.l.c. [20 × 20 cm plate; 0·5 mm coating of Kieselgel GF_{254}; ether–benzene (5 : 95)] gave, almost quantitatively, the *diester* (4d), which crystallised from ether–light petroleum (b.p. 40—60°) as needles, m.p. 50—52° (Found: C, 51·0; H, 5·1; N, 7·85. $C_{15}H_{18}N_2O_8$ requires C, 50·85; H, 5·1; N, 7·9%), $\lambda_{max.}$ 210 nm (log ε 4·40); $\nu_{max.}$ (Nujol) 1720 cm^{-1}; τ 0·57 (1H, t, *J* 2 Hz, ArH), 0·67 (2H, d, *J* 2 Hz, ArH), 4·39 (1H, q, *J* 6·5 Hz, OC*H*Me), 5·76 (2H, q, *J* 7 Hz, $CO_2{\cdot}CH_2Me$), 8·59 (3H, d, *J* 6·5 Hz, OCH*Me*), 8·62 and 8·69 (each 3H, s, CMe_2), and 8·73 (3H, t, *J* 7 Hz, $CO_2{\cdot}CH_2Me$).

2-*Bromo*-1,2-*dimethylpropyl* 3,5-*Dinitrobenzoate* (5b).—A suspension of the acid (4a) (2 g) and red mercuric oxide (665 mg) in carbon tetrachloride (12 ml) was stirred and heated under reflux while a solution of bromine (1 g) in carbon tetrachloride (8 ml) was added dropwise during 15 min. The mixture was stirred and heated under reflux for a further 75 min, after which all the organic material had dissolved. Inorganic material was filtered off and washed with chloroform, and the combined filtrate and washings were shaken successively with aqueous sodium hydrogen sulphite, dilute aqueous sodium carbonate, and water, then dried and evaporated *in vacuo*. The solid residue was recrystallised twice from ether–light petroleum (b.p. 40—60°) to give the *bromo-ester* (5b) (1·8 g, 85%), m.p. 118—119° (Found: C, 40·25; H, 3·7; Br, 21·9; N, 7·65. $C_{12}H_{13}BrN_2O_5$ requires C, 39·9; H, 3·6; Br, 22·1; N, 7·75%), $\lambda_{max.}$ 212 nm (log ε 4·16); $\nu_{max.}$ (Nujol) 1715 cm^{-1}; τ 0·60 (3H, m, ArH), 4·60 (1H, q, *J* 6·5 Hz, OC*H*Me), 8·10 (6H, s, CMe_2), and 8·43 (3H, d, *J* 6·5 Hz, OCH*Me*).

3-(3,5-*Dinitrobenzoyloxy*)-2,2-*dimethylbutyryl Chloride* (5c).—The acid (4b) (200 mg) was treated with thionyl chloride (200 mg) and dimethylformamide (1 drop) at 70° for 1 h. The excess of thionyl chloride was distilled off *in vacuo* and the resulting solid was recrystallised from carbon tetrachloride to give, in almost quantitative yield, the *acid chloride* (5c) as needles, m.p. 98—99° (Found: C, 45·6; H, 3·75; Cl, 10·4; N, 8·0. $C_{13}H_{13}ClN_2O_7$ requires C, 45·3; H, 3·75; Cl, 10·3; N, 8·1%); $\nu_{max.}$ (Nujol) 1718, 1770, and 1798 cm^{-1}; τ 0·56 (1H, t, *J* 2 Hz, ArH), 0·71 (2H, d, *J* 2 Hz, ArH), 4·27 (1H, q, *J* 6·5 Hz, OC*H*Me), 8·45 and 8·50 (each 3H, s, CMe_2), and 8·50 (3H, d, *J* 6·5 Hz, OCH*Me*).

1,2,2-*Trimethyl*-3-*oxobutyl* 3,5-*Dinitrobenzoate* (5d).—A solution of the acid chloride (5c), prepared from the corresponding acid (4b) (990 mg), in dry benzene (10 ml) was added dropwise to a stirred suspension of dimethylcadmium [14] (large excess) in refluxing benzene (15 ml). The mixture was heated under reflux for a further 1·5 h, then cooled, and stirred during the addition of dilute sulphuric acid (35 ml). The organic layer was washed successively with dilute aqueous sodium carbonate and water, dried, and evaporated under reduced pressure. The resulting yellow gum (750 mg) was chromatographed on a column of Kieselgel H (90 g) and Hyflo Supercel (9 g) [benzene–chloroform (1 : 1) as eluant] to give the *keto-ester* (5d) (218 mg, 22%), which crystallised from ether–light petroleum (b.p. 40—60°) as almost colourless crystals, m.p. 75—77° (Found: C, 51·6; H, 4·9; N, 8·8. $C_{14}H_{16}N_2O_7$ requires C, 51·85; H, 4·95; N, 8·65%), $\lambda_{max.}$ 211 nm (log ε 4·12); $\nu_{max.}$ (Nujol) 1704 and 1718 cm^{-1}; τ 0·80 (1H, t, *J* 2 Hz, ArH), 0·92 (2H, d, *J* 2 Hz, ArH), 4·40 (1H, q, *J* 6·5 Hz, OC*H*Me), 7·80 (3H, s, COMe), 8·63 (3H, d, *J* 6·5 Hz, OCH*Me*), and 8·69 and 8·73 (each 3H, s, CMe_2).

1,1,2-*Trimethyl*-3-*oxobutyl Acetate* (5e).—3-Acetoxy-2,2-dimethylbutyric acid [4] (4e) (1 g) was treated with thionyl chloride (860 mg) at 70° for 1 h. The excess of thionyl chloride was evaporated off under reduced pressure and the residual acid chloride [15] [$\nu_{max.}$ (liquid) 1740, 1770, and 1795 cm^{-1}] was dissolved in benzene (10 ml) and added, during 5 min, to a stirred ethereal solution of diazomethane (5 equiv.; 59 ml) at 0°. The mixture was stirred at room temperature for a further 2 h, then evaporated under reduced pressure to give the derived diazo-ketone [$\nu_{max.}$ ($CHCl_3$) 1730br and 2140 cm^{-1}], which was taken up in chloroform (10 ml) and shaken with aqueous hydroiodic acid (55%; 1·2 equiv.). More chloroform was added and the solution was washed successively with aqueous sodium thiosulphate, saturated aqueous sodium hydrogen carbonate, and water, then dried and evaporated *in vacuo*. The residual liquid was chromatographed on a column of Kieselgel H (45 g) and Hyflo Supercel (5 g) (chloroform as eluant). The fraction of highest R_F value gave, after short-path distillation at 105° (10 mmHg), a liquid (300 mg), which was shown by g.l.c. to be almost homogeneous. Preparative g.l.c. of a portion gave the *keto-acetate* (5e) (Found: C, 62·55; H, 9·0. $C_9H_{16}O_3$ requires C, 62·75; H, 9·35%), $\nu_{max.}$ (liquid) 1705 and 1730 cm^{-1}; τ 4·70 (1H, q, *J* 6·5 Hz, OC*H*Me), 7·81 (3H, s, COMe), 7·94 (3H, s, OAc), 8·82 (3H, d, *J* 6·5 Hz, OCH*Me*), and 8·84 (6H, s, CMe_2).

3-*Hydroxy*-2,2-*dimethylbutyric Acid* (4b).—(a) *Racemic material*.[4] This had m.p. 31—34° (lit.,[4] 31°), $\nu_{max.}$ (liquid) 1700 and 2500—3500 cm^{-1}; τ 3·14br (2H, s, exchangeable with D_2O, OH, CO_2H), 5·99br (1H, sharpened to q on addition of D_2O, *J* 6·5 Hz, MeC*H*OH), 8·76 and 8·78 (each 3H, s, CMe_2), and 8·79 (3H, d, *J* 6·5 Hz, *Me*CHOH).

(b) (−)-(R)-*Enantiomer*. Aqueous potassium hydroxide (2·22N; 53 ml) was added to a stirred suspension of the (−)-acid (4a) (10·5 g), $[\alpha]_D$ −35°, in 95% ethanol (53 ml) to give a deep red solution, the colour of which slowly

[14] J. Cason, *J. Amer. Chem. Soc.*, 1946, **68**, 2078.
[15] R. Anshütz and G. Quitmann, *Annalen*, 1928, **462**, 97.

faded. The mixture was stirred for 2 h, and the precipitate of potassium 3,5-dinitrobenzoate was filtered off and washed with 95% ethanol. The combined filtrate and washings were acidified with dilute hydrochloric acid and extracted with ethyl acetate. The extract was washed once with brine. T.l.c. indicated that in addition to the desired product the solution contained some 3,5-dinitrobenzoic acid. The latter was removed by hydrogenation of the nitro-groups over 10% palladised charcoal (500 mg), followed by removal of the catalyst by filtration and successive washing of the filtrate with dilute hydrochloric acid and brine. The ethyl acetate solution thus obtained was dried and evaporated *in vacuo* to give a yellow liquid from which, by short-path distillation at 130° (1 mmHg), was obtained the (−)-(R)-*acid* (4b) (1·61 g, 38%) as a liquid which slowly crystallised. One recrystallisation from light petroleum (b.p. 40—60°) gave material, m.p. 42—44°, $[\alpha]_D$ −9·1° (*c* 2·38) (Found: C, 54·55; H, 9·15. $C_6H_{12}O_3$ requires C, 54·55; H, 9·15%), i.r. and n.m.r. spectra identical with those of the (±)-hydroxy-acid.

(c) (+)-(S)-*Enantiomer*. A suspension of the (+)-(*S*)-acid (4a) (13·4 g), $[\alpha]_D$ +28°, in 95% ethanol (65 ml) was stirred with aqueous potassium hydroxide (2·28N; 65 ml) for 1 h. The yellow liquid obtained by work-up as described in (b) was distilled under reduced pressure to give the (+)-(S)-*acid* (4b) (1·8 g, 33%) as a liquid, b.p. 96—100° (0·3 mmHg), which slowly crystallised. Two recrystallisations from light petroleum (b.p. 40—60°) gave crystals, m.p. 36—43°, $[\alpha]_D$ +8·0° (*c* 19·6), n.m.r. spectrum and t.l.c. behaviour identical with those of the (−)-(*R*)-enantiomer.

3-*Acetoxy*-2,2-*dimethylbutyric Acid* (4e).—(a) *Racemic material*.[4] This had m.p. 54—56° (lit.,[4] 58°), $\nu_{max.}$ (Nujol) 1685, 1725, and 2500—3500 cm^{-1}; τ 0·52 (1H, s, exchangeable with D_2O, CO_2H), 4·71 (1H, q, *J* 6·5 Hz, OC*H*Me), 7·92 (3H, s, OAc), 8·73 and 8·76 (each 3H, s, CMe_2), and 8·75 (3H, d, *J* 6·5 Hz, OCH*Me*).

(b) (−)-(R)-*Enantiomer*. The (−)-(*R*)-acid (4b) (1·5 g), $[\alpha]_D$ −9·1°, was acetylated with acetic anhydride (1·75 ml) and pyridine (3·5 ml) at room temperature for 9 h. The excess of acetic anhydride was destroyed with ethanol, and the mixture was diluted with chloroform and extracted with dilute aqueous sodium carbonate. The extract was washed with chloroform, then acidified with dilute hydrochloric acid, and extracted with chloroform. The chloroform extract was washed with water, dried, and evaporated *in vacuo* to give a liquid which, by short-path distillation at 140° (15 mmHg), afforded the (−)-(R)-*acid* (4e) (1·68 g, 85%) as an oil which slowly formed crystals, m.p. 65—67°. Two recrystallisations from light petroleum (b.p. 60—80°) gave material, m.p. 66—67°, $[\alpha]_D$ −14·0° (*c* 2·70) (Found: C, 55·5; H, 7·95. $C_8H_{14}O_4$ requires C, 55·15; H, 8·1%), $\nu_{max.}$ (Nujol) 1685, 1715, and 2500—3300 cm^{-1}, n.m.r. spectrum and t.l.c. behaviour identical with those of the (±)-acetoxy-acid. The i.r. spectra of the two materials (Nujol mulls) showed significant differences in the 800—1500 cm^{-1} range.

(c) (+)-(S)-*Enantiomer*. The (+)-(*S*)-acid (4b) (1·8 g), $[\alpha]_D$ + 8·0°, was acetylated with acetic anhydride (2·8 ml) and pyridine (5 ml) at room temperature for 18 h. The mixture was worked up as in (b) to give an oil which afforded, by short-path distillation at 140° (16 mmHg), the (+)-(S)-*acid* (4e) (1·92 g, 81%) as an oil, $[\alpha]_D$ +8·7° (*c* 7·6), which did not crystallise. The material was shown to be homogeneous by t.l.c. and by g.l.c. of the derived methyl ester, prepared by the action of diazomethane. Its n.m.r. spectrum was identical with those of the (±)- and (−)-(*R*)-isomers.

The base-extracted chloroform solution was washed successively with dilute hydrochloric acid and water, dried, and evaporated *in vacuo* to leave a liquid, short-path distillation of which at 140° (0·05 mmHg) gave (−)-(S)-3-*acetoxy*-2,2-*dimethylbutyric anhydride* (7) (165 mg, 7%) as a liquid, $[\alpha]_D$ −16° (*c* 4·12) (Found: C, 58·25; H, 7·95. $C_{16}H_{26}O_7$ requires C, 58·15; H, 7·95%), $\nu_{max.}$ (liquid) 1730br and 1805 cm^{-1}, τ 4·76 (2H, q, *J* 6·5 Hz, 2 × OC*H*Me), 7·94 (6H, s, 2 × OAc), 8·71 and 8·74 (each 6H, s, CMe_2), and 8·76 (6H, d, *J* 6·5 Hz, 2 × OCH*Me*).

Methanolysis of (−)-(S)-3-*Acetoxy*-2,2-*dimethylbutyric Anhydride* (7).—A solution of the anhydride (7) (50 mg), $[\alpha]_D$ −16°, in methanol (2 ml) and pyridine (1 ml), was heated under reflux for 18 h, cooled, poured into dilute hydrochloric acid, and extracted with chloroform. The extract was washed successively with dilute hydrochloric acid and water, dried, and evaporated *in vacuo*. The residual liquid was treated with an excess of ethereal diazomethane to give, after short-path distillation at 80° (16 mmHg), *methyl* (+)-(S)-3-*acetoxy*-2,2-*dimethylbutyrate* (4f) in almost quantitative yield (Found: C, 57·1; H, 8·5. $C_9H_{16}O_4$ requires C, 57·45; H, 8·55%), $\nu_{max.}$ (liquid) 1735 cm^{-1}; τ 4·71 (1H, q, *J* 6·5 Hz, OC*H*Me), 6·25 (3H, s, OMe), 7·94 (3H, s, OAc), 8·77 and 8·80 (each 3H, s, CMe_2), and 8·80 (3H, d, *J* 6·5 Hz, OCH*Me*).

2-*Methylbutane*-2,3-*diol* (6a).—(a) (+)-(S)-*Enantiomer*. A solution of (−)-(*S*)-ethyl lactate (9) (17·9 g), $[\alpha]_D$ −11·4°, in dry ether (50 ml) was added dropwise during 30 min to a stirred solution of methylmagnesium iodide [from magnesium (12 g)] in ether (190 ml), which was cooled in ice–salt. The mixture was heated under reflux for 2·5 h, then cooled to room temperature and stirred while saturated ammonium chloride (80 ml) was added dropwise. The mixture was left for 1 h, and the ether layer was then decanted from the precipitated salts, which were washed with ether. Evaporation of the combined ethereal solutions gave only a small amount of material, shown by t.l.c. to be a mixture of the required diol and unchanged starting material. Saturated ammonium chloride (60 ml) was added to the precipitated salts to give a thick slurry to which was added sufficient 6N-hydrochloric acid to give a clear solution (pH *ca.* 2). Aqueous sodium hydroxide (2N) was then added slowly, with stirring, until a slight precipitation was observed (at pH *ca.* 9); the solution was then saturated with brine and continuously extracted with ether for 2 days. The residue obtained by removal of solvent *in vacuo* was combined with the small quantity of material previously isolated, and moisture was removed by azeotropic distillation with benzene. The residue was distilled under reduced pressure to give (+)-(*S*)-2-methylbutane-2,3-diol (6a) (13·3 g, 84%) as a liquid, b.p. 85° (19 mmHg), $[\alpha]_D$ +4·1° (neat; *l* 0·15), n_D^{25} 1·4360 {lit.,[13] b.p. 74° (10·5 mmHg), $[\alpha]_D$ +4·6°, n_D^{25} 1·4363}, $\nu_{max.}$ (liquid) 3400 cm^{-1}; τ 6·34 (1H, q, *J* 6·5 Hz, OC*H*Me), 7·02 (2H, s, exchangeable with D_2O, OH), 8·77 and 8·82 (each 3H, s, CMe_2), and 8·83 (3H, d, *J* 6·5 Hz, OCH*Me*).*

Treatment with an excess of 3,5-dinitrobenzoyl chloride in pyridine at room temperature for 15 min gave the 3-(3,5-*dinitrobenzoate*), which crystallised from ethyl acetate–

* The compound obtained by us differs from the material, $[\alpha]_D$ − 6·965° (neat), b.p. 176—178° (20 mmHg), otherwise uncharacterised, previously reported [12] to arise by reaction between (−)-ethyl lactate and methylmagnesium iodide.

light petroleum (b.p. 60—80°); m.p. 101—102° (Found: C, 48·3; H, 4·75; N, 9·25. $C_{12}H_{14}N_2O_7$ requires C, 48·35; H, 4·75; N, 9·4%), $\nu_{max.}$ (Nujol) 720, 730, 1535, 1630, 1713, and 3460 cm^{-1}; τ 0·77 (1H, t, J 2 Hz, ArH), 0·84 (2H, d, J 2 Hz, ArH), 4·79 (1H, q, J 6·5 Hz, OC*H*Me), 8·04br (1H, s, exchangeable with D_2O, OH), 8·57 (3H, d, J 6·5 Hz, OCH*Me*), and 8·63 (6H, s, CMe_2).

(b) *Racemic material.* A solution of the (±)-3,5-dinitrobenzoyloxy-ketone (5d) (260 mg) in methylene chloride (15 ml) was heated under reflux while a large excess of trifluoroperacetic acid [prepared [16] from trifluoroacetic anhydride (8·7 g)] was added during 4 h. Heating was continued for a further 1 h, then the cooled mixture was diluted with methylene chloride and made alkaline with dilute aqueous sodium carbonate. From the organic layer was obtained a pale yellow gum, the i.r. spectrum of which showed the presence of starting material. Hydrolysis of esters and removal of starting material was accomplished by stirring the crude product with aqueous sodium hydroxide (2N; 20 ml) and aqueous sodium hypochlorite (55%; 15 ml) for 4 h. The excess of sodium hypochlorite was destroyed with sodium disulphite. The mixture was left overnight at room temperature then continuously extracted with ether for 12 h. The extract was dried and evaporated *in vacuo* to leave a small quantity of liquid which was distilled (short-path) at 90° (5 mmHg) to give (±)-2-methylbutane-2,3-diol, i.r. and n.m.r. spectra identical with those of the (+)-enantiomer.

2-*Hydroxy*-1,2-*dimethylpropyl Acetate* (6b).—(a) *Racemic material.* (±)-3-Acetoxy-2,2-dimethylbutyric acid (4e) (750 mg) was converted into the acid chloride as in the preparation of the keto-acetate (5e). An ice-cold mixture of magnesium sulphate (42 mg), potassium hydroxide (726 mg), water (5·1 ml), hydrogen peroxide (95%; 465 mg), and methanol (6·48 ml) was added, and the mixture was stirred at 20° for 10 min, then immediately poured into dilute sulphuric acid, and extracted with chloroform. The extract was washed successively with dilute sulphuric acid and water, then dried. Iodimetric titration of the solution indicated 78% conversion of the acid (4e) into the corresponding peroxy-acid.

A portion of the chloroform solution (containing 387 mg of peroxy-acid, by iodimetric titration) was evaporated *in vacuo* at 30°, and, to ensure that no chloroform remained, a small amount of olefin-free light petroleum (b.p. 60—80°) was added, and the solution was again evaporated *in vacuo*. The residue was taken up in light petroleum (b.p. 60—80°) (3·38 ml) and the solution was kept at 85° for 2·5 h. After addition of a crystal of ferrous sulphate heptahydrate the mixture was maintained at 85° for a further 30 min; a test then revealed that no peroxy-acid remained. A small sample of the mixture was treated with an excess of ethereal diazomethane and examined by g.l.c., which indicated that a mixture of two compounds had been formed. The minor component, which had a retention time identical with that of methyl 3-acetoxy-2,2-dimethylbutyrate, comprised 15% of the mixture. The main bulk of the mixture was diluted with chloroform, washed successively with dilute aqueous sodium carbonate and water, dried, and evaporated *in vacuo* to give, after short-path distillation at 100° (14 mmHg), (±)-2-hydroxy-1,2-dimethylpropyl acetate [17] (233 mg; 78% from peroxy-acid) as a liquid (Found: C, 57·05; H, 9·85. Calc. for $C_7H_{14}O_3$: C, 57·5; H, 9·65%), $\nu_{max.}$ (liquid) 1715 and 3440 cm^{-1}; τ 5·22 (1H, q, J 6·5 Hz, OC*H*Me), 7·83 (1H, s, exchangeable with D_2O, OH), 7·93 (3H, s, OAc), 8·79 (3H, d, J 6·5 Hz, OCH*Me*), and 8·80 (6H, s, CMe_2).

(b) (−)-(R)-*Enantiomer.* The (−)-(*R*)-acid (4e) (700 mg), $[\alpha]_D$ −14·0°, was converted into the peroxy-acid (58% conversion by iodimetric assay) as described in (a). A solution of the peroxy-acid in olefin-free light petroleum (b.p. 60—80°) (4·6 ml) was heated at 85° and the product worked up as described in (a) to give, after short-path distillation at 95° (14 mmHg), the (−)-(R)-*ester* (6b) (268 mg, 80% from peroxy-acid, 46% overall), $[\alpha]_D$ −13·2° (*c* 4·47), n_D^{23} 1·4233, i.r. and n.m.r. spectra, and g.l.c. retention time identical with those of the racemic material.

(c) (+)-(S)-*Enantiomer.* (i) *From* (+)-(S)-3-*acetoxy*-2,2-*dimethylbutyric acid* (4e). The (+)-(*S*)-acid (4e) (1·9 g), $[\alpha]_D$ +8·7°, was converted into the peroxy-acid (89% conversion by iodimetric assay), which was heated at 85° in olefin-free light petroleum (b.p. 60—80°) for 2·5 h, after which no peroxy-acid remained. Work-up as in (a) gave, after short-path distillation at 95° (14 mmHg), the (+)-(*S*)-ester (6b) (1·26 g, 89% from peroxy-acid, 79% overall), $[\alpha]_D$ +12·2° (*c* 12·9), n_D^{21} 1·4243, i.r. and n.m.r. spectra and g.l.c. retention time identical with those of the optically inactive and (−)-isomers.

(ii) *From* (+)-(S)-2-*methylbutane*-2,3-*diol.* The diol (10) (6·7 g), $[\alpha]_D$ +4·1°, obtained by the action of methylmagnesium iodide on (−)-(*S*)-ethyl lactate, was acetylated overnight at room temperature with acetic anhydride (10 g) and pyridine (20 ml) to give the (+)-(*S*)-ester, which was distilled at 81° (16 mmHg) to give a liquid (8·29 g, 88%), $[\alpha]_D$ +12·3° (*c* 14·0) and +9·86° (neat; *l* 0·15), n_D^{23} 1·4228, i.r. and n.m.r. spectra and g.l.c. retention time identical with those of the material described in (c) (i).

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