Studies in the Stereochemistry of 2-Alkyl-3-hydroxy- and 2-Alkyl-3-methoxy-butyric Acids

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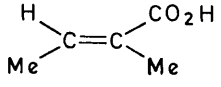
The diastereoisomeric 3-hydroxy-2-methyl- and 3-methoxy-2-methyl-butyric acids resulting on demercuriation of mercuric acetate adducts of 2-methylbut-2-enoic acids have been studied, and their i.r., n.m.r., and mass spectrometric properties compared with those of the diastereoisomeric ethyl 2-allyl-3-hydroxy- and 3-hydroxy-2-propyl-butyrates. Demercuriation of the mercuric acetate adducts of tiglic acid with sodium borohydride is found to give mixtures of the diastereoisomeric products, whereas demercuriation with hydrogen sulphide yields essentially only one of these diastereoisomers. Evidence for the configurations of these products is presented. The diastereoisomer of 3-methoxy-2-methylbutyric acid resulting on demercuriation, by means of hydrogen sulphide, of a mercuric acetate adduct of tiglic acid has been resolved *via* the quinine salt.

THE present investigation was undertaken in connection with studies of the CH(OMe)·CHMe system of the phthiocerols A (I; R = Et) and B (I; R = Me).[1] It appeared that the products obtainable *via* oxy- or methoxy-mercuriation of α-methyl-αβ-unsaturated acids could serve as suitable models for these studies, and might also provide starting points for the eventual syntheses of the naturally occurring optically active enantiomers.

$$RCH(OMe)\cdot CHMe\cdot[CH_2]_4\cdot CH(OH)\cdot CH_2CH(OH)\cdot[CH_2]_nMe$$

(I) n = 20 and 22

(II) 

(III) $MeCH(OX)\cdot CMe(HgOAc)\cdot CO_2H$

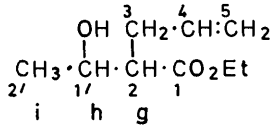
(IV) $MeCH(OX)\cdot CHMe\cdot CO_2H$

Oxymercuriation of tiglic acid (II) by reaction with aqueous mercuric acetate, followed by reduction of the product (III; X = H) with sodium borohydride in alkaline solution, gave the diastereoisomers of 3-hydroxy-2-methylbutyric acid (IV; X = H) in approximately equal quantities; the diastereoisomer with the shorter g.l.c. retention time of its methyl ester is designated *A* and the other diastereoisomer *B*. When the acetoxymercury-compound (III; X = H) was treated in aqueous sodium hydroxide with hydrogen sulphide, a product containing an overwhelming amount (*ca.* 95%) of the diastereoisomer *B* was obtained.

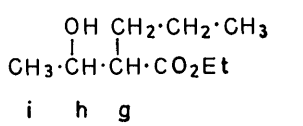
In another series of experiments tiglic acid was subjected to methoxymercuriation, using mercuric acetate in methanol. Reduction of the adduct (III; X = Me) with sodium borohydride in alkaline solution gave about equal amounts of the diastereoisomers of 3-methoxy-2-methylbutyric acid (IV; X = Me), referred to in the following as *P* and *Q* respectively, in order of increasing g.l.c. retention time of the corresponding methyl esters. When carrying out the reduction without added alkali, *P* predominated by *ca.* 4 : 1. On demercuriation of the adduct with hydrogen sulphide in aqueous alkali the product was almost entirely the diastereoisomer *P*.

Thus, while the addition of mercuric salts to simple olefins usually gives products of *trans*-addition,[2,3] the stereochemistry of the products formed by the demercuriation varied in the above experiments using different demercuriation procedures. As far as the demercuriation with sodium borohydride is concerned, it was found in certain cases[4] that the demercuriation of the adducts with sodium borodeuteride produced mixtures of diastereoisomers. There are no previous reports on the stereochemistry of the demercuriation with hydrogen sulphide in aqueous alkali. Occasional references to the demercuriation of oxymercuriation adducts of αβ-unsaturated acids and esters are found in the literature (*cf.* ref. 5), but little preparative use has been made of this reaction, and it has not been applied to adducts from which diastereoisomeric products could result.

Attention was next turned to establishing the stereochemistry of the isomers *A* and *B*. For these studies valuable information became available from a comparison of the spectroscopic properties of the isomers (in the following referred to as *C* and *D*) of ethyl 2-(1-hydroxyethyl)pent-4-enoate (V) and of 2-(1-hydroxyethyl)pentanoate (VI). The diastereoisomers of the



(V)



(VI)

ester (V), resulting on reduction of ethyl 2-allylacetoacetate with sodium borohydride, could be separated by preparative g.l.c.; *C*, obtained predominantly (6 : 5) is the isomer showing the shorter retention time. Each of these diastereoisomers on catalytic hydrogenation gave the respective diastereoisomers of the ester (VI). The following are the results of these comparative studies.

High resolution i.r. spectra of dilute solutions of the

[1] D. E. Minnikin and N. Polgar, *J. Chem. Soc.* (*C*), 1966, 2107.
[2] T. G. Traylor and A. W. Baker, *J. Amer. Chem. Soc.*, 1963, **85**, 2746.
[3] S. Wolfe and P. G. C. Campbell, *Canad. J. Chem.*, 1965, **43**, 1184.
[4] D. J. Pasto and J. A. Gontarz, *J. Amer. Chem. Soc.*, 1969, **91**, 719.
[5] J. Chatt, *Chem. Rev.*, 1951, **48**, 7.

isomers in carbon tetrachloride were measured in the regions 1700—1750 and 3500—3650 cm^{-1}. Both isomers showed bands associated with an intramolecularly hydrogen-bonded β-hydroxy-ester at 3534 and 1715 cm^{-1} and bands for the free hydroxy-group and non-bonded ester carbonyl group at 3631 and 1732 cm^{-1} respectively. The ratios of extinction coefficients $\varepsilon_{3534} : \varepsilon_{3631}$ and $\varepsilon_{1715} : \varepsilon_{1732}$ for isomer *C* were 2·44 and 1·99 respectively and for isomer *D* they were 1·29 and 0·95, indicating a greater extent of intramolecular hydrogen bonding for isomer *C*.

Examination of the mass spectra of the isomers showed considerable differences. For isomer *C* peaks at *m/e* 157 and 128 arising from cleavage α to the hydroxy-group, and cleavage β to the ester group with hydrogen transfer, were of greater intensity, and the peak at *m/e* 154 ($M - H_2O$) was less prominent, than the corresponding peaks in the mass spectrum of isomer *D*. The increased ease with which β cleavage and transfer takes place and the reduced ability to lose 18 mass units by dehydration is regarded as support for the existence of a greater proportion of intramolecularly hydrogen-bonded molecules in isomer *C* than in isomer *D*.

The n.m.r. spectra of the two isomers were similar in many respects but for isomer *D* the signal corresponding to the terminal methyl group was at higher field and the signal for the hydrogen at the β-carbon atom, although the multiplicity was obscured, was discernible at lower field than the corresponding signals in the spectrum of isomer *C* (see Table 1).

TABLE 1

	τ h		*J*/Hz h.i.	*J*/Hz h.g.	τ i		*J*/Hz i.h.	τ g
(VC)	6·05	App. quintet	6	6	8·75	Doublet	6·6	
(VD)	5·96				8·80	Doublet	6·5	
(VIC)	6·10	App. quintet	6·5	6·5	8·78	Doublet	6·5	7·65
(VID)	6·02	Doublet of quartets	6·2	5·2	8·81	Doublet	6·1	7·58

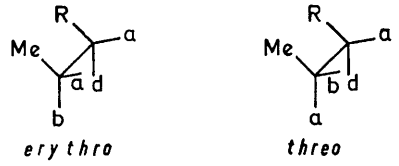
G.l.c. examination of the *C* and *D* isomers of ethyl 2-(1-hydroxyethyl)pentanoate (VI) showed that they were eluted in the same order as the unsaturated compounds but the retention times were reduced for both.

Comparison of the n.m.r. spectra showed differences corresponding to those noted for the unsaturated isomers; the signal for $HC(OH)CH_3$– appeared at lower field and the signal for $HC(OH)CH_3$– at higher field in the spectrum of isomer *D* than that of isomer *C*. In contrast to the 2-allyl compounds the multiplicity of the signal for the hydrogen attached to the β-carbon atom in each isomer was discernible. Isomer *D* showed two quartets (*J* 6·2 Hz) with a separation of 5·2 Hz and isomer *C* showed an apparent quintet with relative intensities of the components of the quintet consistent with interpretation as a superimposed pair of quartets (*J* 6·5 Hz) separated by 6·5 Hz.

The mass spectra of the two isomers were similar; differences noticed in the spectra determined at 70 e.v. were not generally maintained at lower impact energies with direct inlet at low temperature, except that the peak at *m/e* 159 (*M* — 15) was consistently more intense in the spectra of isomer *C*.

Before dealing with the configuration of the diastereoisomers, a short note on the nomenclature to be used is required.

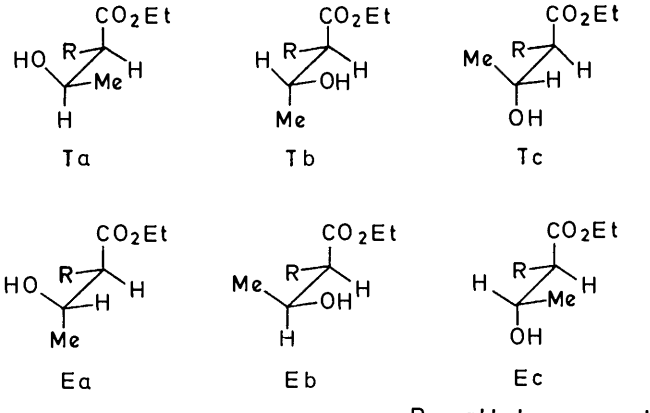
Nomenclature.—There is some divergence in literature in the way in which the *threo* and *erythro* designations are used for indicating the relative configuration of compounds containing vicinal asymmetric centres of the type Me.C(a,b).C(a,d).R (where R is Me or a similar alkyl group, *e.g.*, propyl or alkyl). In the present paper the isomer which, by rotation about the central carbon–carbon bond, can possess in one conformation two groups at one asymmetric centre eclipsed by identical or similar groups at the adjacent centre, is designated *erythro* as shown in Scheme 1. In the following discussion when referring to compounds, described elsewhere,



SCHEME 1

which have been designated according to the Fischer convention, translation into the nomenclature of Scheme 1 has been made.

In order to make an assignment of configuration for the diastereoisomeric hydroxy-esters *C* and *D*, it is relevant that the allowed conformations for each isomer shown in Scheme 2 should be considered. For the *threo*-isomer, conformations Ta and Tb allow intramolecular hydrogen bonding between the ethoxycarbonyl and β-hydroxy-groups, and similarly this is allowed by the *erythro*-isomer conformations Ea and Eb. Whereas for those conformations of the *erythro*-isomer which permit hydrogen bonding any decrease in the dihedral angle



SCHEME 2

for the ethoxycarbonyl and hydroxy-groups on bonding will bring the methyl and allyl (or propyl) groups to-

wards an eclipsed position with increase of steric strain, for the *threo*-isomer such a decrease in dihedral angle will cause the methyl group at the β-position and the allyl (or propyl) group at the α-position to move towards a position where each would be eclipsed by hydrogen. The latter alternative is subject to less severe steric strain and so it may be expected that the *threo*-isomer would show a greater degree of intramolecular hydrogen bonding.

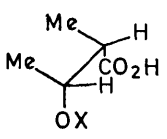
The order of elution of the isomers during g.l.c. indicates that isomer *C* is the more hydrogen bonded and is less able to bond to the chromatographic liquid phase than the more polar isomer *D*. Mass spectral measurements already described also indicate that isomer *C* is more hydrogen bonded and strong confirmation is provided by the high resolution i.r. measurements. In accordance with the above considerations of steric strain in the hydrogen bonded β-hydroxy-esters isomer *C* is assigned the *threo*-configuration for ethyl 2-(1-hydroxyethyl)pent-4-enoate (V) and for the saturated compound (VI).

Further support for this assignment is provided by the n.m.r. spectra. In previous investigations of 3-hydroxy-2-methylpentanoic acid by Snow,[6] and several long-chain 3-hydroxy-2-methyl esters by Coles and Polgar,[7] it was found that the hydrogen atoms attached to C-2 and C-3 always gave rise to signals for the *erythro*-isomer at lower field that those for the *threo*-isomer and in the compounds for which the data are recorded the signal for the 2-methyl group appears at higher field for the *erythro*-isomer. These effects are ascribed to shielding by the alkyl group at C-3, of 2-Me in the *erythro*-isomers and of 2-H in the *threo*-isomers and, by 2-Me, of 3-H in the *threo*-isomers. It would then be expected that 2-Me would shield 3-Me (where this occurs) in the *erythro*-isomers. The present compounds show chemical shift data for 1′-H, 2′-H_3 and, when clearly observable, 2-H, fully consistent with the previous findings.

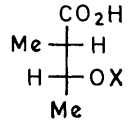
In contrast to the ethyl 2-(1-hydroxyethyl)pent-4-enoates, separation of the diastereoisomeric methyl 3-hydroxy-2-methylbutyrates (methyl esters of *A* and *B*) by preparative g.l.c. was not possible but preparative g.l.c. was employed to remove methyl tiglate from the material obtained by esterification of the product from the hydrogen sulphide demercuriation procedure. This material, containing overwhelmingly one isomer (methyl ester of *B*), was used for n.m.r. and high resolution i.r. spectroscopic examination. Comparison was made with the methylated mixture of equal quantities of the isomers *A* and *B* derived from sodium borohydride reduction of the oxymercuriation adduct. N.m.r. spectra of the corresponding acids were obtained using the crude materials since the presence of some tiglic acid in one of the materials did not obscure the relevant portions of the spectrum. It was possible to extract almost all the relevant spectroscopic data for the unseparated isomer *A* from the spectra of the mixture by inspection and the data for the isomer *A* shown in Table 2 were obtained in this manner (this Table also includes the data for the isomers *P* and *Q*, see below).

The relative spectra for the two isomeric esters are in accord with those previously described for 2-alkyl-3-hydroxy-esters. In the spectrum of the single isomer the hydrogen atoms at C-2 and C-3 give rise to signals at lower field with a markedly lower mutual coupling constant, and the hydrogens of the methyl group at C-3 appear at higher field, than corresponding signals for the alternative isomer. Similar differences are apparent in the spectra of the 3-hydroxy-2-methylbutyric acids and thus *erythro*-configuration (VII; X = H) can be assigned to the predominant isomer *B* obtained by demercuriation of the oxymercuriation adduct of tiglic acid with hydrogen sulphide. Demercuriation has occurred with retention of configuration.

It should be noted that the acid (VII) in a Fischer projection would have the formula (VIII), *i.e.*, by the Fischer convention would be named the *threo*-form.



(VII)



(VIII)

Confirmation of the assignation is provided by comparison of high resolution i.r. measurements of dilute solutions of the isomer *B* and of the mixture in the regions 3400—3700 and 1700—1750 cm^{-1} (Table 3). The extent of intramolecular hydrogen bonding is less for the isomer *B* and this observation is in accord with its longer g.l.c. retention time. As discussed previously this behaviour is expected for the *erythro*-isomer.

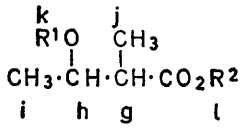
In order to establish the configuration of *P*, the methyl ester of the isomer *B* (methyl *erythro*-3-hydroxy-2-methylbutyrate) was methylated using sodium hydride and methyl iodide in dimethyl sulphoxide. Comparison of the resulting methyl *erythro*-3-methoxy-2-methylbutyrate with the methyl ester of *P*, and comparison of each material (by g.l.c.) with the methyl esters derived from the mixture *P* + *Q* showed that the methoxy-acid *P* and the hydroxy-acid *B*, had the same configuration (VII; X = Me and X = H, respectively). A similar experiment, using an approximately equimolecular mixture of the *threo*- and *erythro*-esters, produced the corresponding methoxy-esters in approximately equal amounts. The n.m.r. spectra of the acid *P* (*erythro*-3-methoxy-2-methylbutyric acid) (determined after tiglic acid had been removed by preparative g.l.c.) and its methyl ester were measured (Table 2) and by comparison with the corresponding spectra of the mixed isomers the data for the acid *Q* and its methyl ester (*threo*-isomers) were extracted. In contrast to the 3-hydroxy-compounds, 2-H gives rise to a signal at higher field for the *erythro*-isomer, the difference being accentuated in spectra measured in benzene solution, and the signals for 2- and 3-Me are at lower field in the *erythro*-isomers.

[6] G. A. Snow, *Biochem. J.*, 1964, **94**, 160.
[7] L. Coles and N. Polgar, *J. Chem. Soc.* (*C*), 1968, 1412.

3-H Remains at lower field in the *erythro*-isomers but compared with the 3-hydroxy-compounds the difference between the isomers is small and the difference in coupling constant with 2-H is less marked. For the mixture of methyl esters the signals for 3-H were superimposed in such a manner that data for the *threo*-isomer could not be obtained.

The *erthro*-isomer (VII; X = Me) has been resolved *via* its quinine salt. Prior to the resolution, tiglic acid which was present as a contaminant, was removed by treating the material with bromine in carbon tetrachloride, followed by fractional distillation of the product.

TABLE 2



	R¹	R²	Compound	Solvent	Chemical shift/τ H_g	H_h	H_i	H_j	H_k	H_l
1	Me	H	*P*	*a*	7·38	6·36	8·79	8·79	6·61	
2	Me	H	*Q*	*a*	7·34	6·41	8·83	8·85	6·63	
3	Me	H	*P*	*b*	7·61	6·52	9·02	8·86	6·95	
4	Me	H	*Q*	*b*	7·41	6·54	9·09	9·03	6·95	
5	H	H	*B*	*a*	7·43	5·85	8·78	8·79		
6	H	H	*A*	*a*	7·51	6·05	8·75	8·79		
7	H	H	*B*	*b*	7·60	5·91	8·89	8·85		
8	H	H	*A*	*b*	7·56	6·09	8·89	8·96		
9	Me	Me	*P*	*a*	7·45	6·44	8·84	8·81	6·65	6·30
10	Me	Me	*Q*	*a*	7·37		8·88	8·90	6·67	6·29
11	Me	Me	*P*	*b*	7·53	6·50	8·96	8·79	6·89	6·61
12	Me	Me	*Q*	*b*	7·39		9·04	8·99	6·89	6·59
13	H	Me	*B*	*a*	7·47	5·93	8·81	8·80		6·28
14	H	Me	*A*	*a*	7·52	6·10	8·78	8·81		6·27
15	H	Me	*B*	*b*	7·65	6·00	8·92	8·86		6·62
16	H	Me	*A*	*b*	7·60	6·05	8·91	8·98		6·60

	J/Hz H_{ig}	H_{gj}	H_{gh}	H_{hg}	H_{hi}	H_{ih}
1	7·0	7·1	5·6	5·5	6·5	6·5
2	7·0	7·0	7·0	7·0	6·3	6·2
3	7·0	6·9	5·5	5·5	6·2	6·3
4	7·0	7·0	7·0	7·0	6·2	6·2
5	7·0	7·1	4·1	4·1	6·5	6·5
6	7·0	7·0	7·0	7·0	6·5	6·7
7	7·0	7·0	4·3	4·4	6·5	6·5
8	7	7·1	7·1	7	6·5	6·3
9	7·0	7·0	6·0	6·5	6·5	6·0
10	7·0	7	7			6·1
11	7·0	7·0	6·0	6·0	6·0	5·9
12	7	7·0	7·0			6
13	7·2	7·1	4·0	4·0	6·5	6·8
14	7	7	7	7·0	6·5	6·3
15	7·0	7·1	5·0			6·4
16	7·2	7·1	7·1			6·3

[a] $CDCl_3$. [b] C_6H_6.

TABLE 3

	ν/cm⁻¹	3631	3548	1740	1726	$\varepsilon_{3548}/\varepsilon_{3631}$	$\varepsilon_{1726}/\varepsilon_{1740}$
B	ε	9·6	14·3	111	129	1·5	1·15
Mixture	ε	10·0	16·5	116	146		
A (calc.)	ε	10·4	18·6	121	164	1·79	1·36

In further experiments angelic acid was subjected to methoxymercuriation, followed by demercuriation, with a view to obtaining *threo*-3-methoxy-2-methylbutyric acid. Methoxymercuriation of angelic acid was carried out in the manner previously described for tiglic acid. Demercuriation of the adduct with sodium borohydride in aqueous alkali gave, as with tiglic acid, approximately equal amounts of the *threo*- and *erythro*-forms.

The methoxymercuriation adducts of tiglic and angelic acids were not soluble in solvents convenient for measurements of n.m.r. spectra but they were shown to be distinct by comparison of *X*-ray powder photographs of the two adducts. Methoxymercuriation adducts of methyl angelate amd methyl tiglate (prepared by J. Proby) were soluble in chloroform, and comparison of the n.m.r. spectra showed that the adducts were different homogeneous diastereoisomers, thus confirming that the adduct formation was stereospecific.

It has been shown that sodium borohydride reduction of acetoxymercury adducts of alkenes can produce a mixture of isomers, and this may occur by way of a radical intermediate.[4] Production of the same mixture of isomeric 3-methoxy-2-methylbutyric acids from angelic and tiglic acids may be caused by equilibration of possible intermediate radical conformers in the interval

between rupture of the C–Hg bond and abstraction of hydrogen.

Demercuriation of the methoxymercuriation adduct of angelic acid with hydrogen sulphide in aqueous alkaline solution gave a small quantity of angelic acid with only *erythro*-3-methoxy-2-methylbutyric acid. This result suggests that mixtures of *cis*- and *trans*-isomers of α-methyl-substituted αβ-unsaturated acids may be used in preparative procedures to obtain stereochemically almost pure products, thus avoiding the laborious separation of the *cis*- and *trans*-isomers.

EXPERIMENTAL

Solutions in organic solvents were dried over magnesium sulphate. Analytical g.l.c. was carried out with a Perkin-Elmer F11 gas chromatograph incorporating a flame ionisation detector using a 2 m × ⅛ in o.d. steel column packed with 20% diethylene glycol succinate at the stated temperatures and nitrogen carrier gas at 15 lb in^{-2}. Optical rotations were measured with a Perkin-Elmer 141 polarimeter using 1% solutions in chloroform. High resolution i.r. spectra of solutions in carbon tetrachloride were obtained with a Perkin-Elmer 521 spectrophotometer. N.m.r. spectra were determined in deuteriochloroform unless otherwise stated, with a Perkin-Elmer R14 spectrometer at 100 MHz. Mass spectra were recorded with an A.E.I. MS9 spectrometer.

Acetoxymercury Adducts of Tiglic Acid.—Tiglic acid (2·0 g, 0·02 mol) was added in several portions to a stirred solution or suspension of mercuric acetate (6·38 g, 0·02 mol) in water or methanol (30 cm^3). Stirring was continued at room temperature for 3 days and the precipitated acetoxymercury compounds were collected. More of the adduct prepared in methanol was obtained after stirring the filtrate for a further 3 days.

3-*Hydroxy*-2-*methylbutyric Acid.*—The acetoxymercury compound prepared from tiglic acid in aqueous solution was dissolved in 2M-sodium hydroxide solution (15 cm^3) and stirred at room temperature during addition of a solution of sodium borohydride (0·3 g) in 2M-sodium hydroxide solution (10 cm^3). After acidification with dilute hydrochloric acid the aqueous solution was decanted, saturated with sodium chloride and extracted with ether (20 cm^3 × 4). The extract was washed with saturated sodium chloride solution, dried and evaporated to give 3-hydroxy-2-methylbutyric acid (1·32 g, 56% overall); n_D^{19} 1·4375; *m/e* 103 (*M* − 15, 5%), 100 (*M* − 18, 10), and 74 [Me·CH:C(OH)$_2^+$, 85].

Methyl 3-*Hydroxy*-2-*methylbutyrate.*—The preceding acid was esterified with diazomethane. Distillation of the product gave *methyl* 3-*hydroxy*-2-*methylbutyrate*, b.p. 178° at 743 mmHg; n_D^{20} 1·4270 (Found: C, 54·1; H, 8·9. $C_6H_{12}O_3$ requires C, 54·5; H, 9·2%) as a mixture of *threo*- and *erythro*-isomers.

G.l.c. (110°) showed the presence of two components R_t 18·4 and 19·6 min in approximately equal amounts. The material prior to distillation contained a small quantity of methyl tiglate (approx. 1%).

3-*Methoxy*-2-*methylbutyric Acid.*—An acetoxymercury adduct prepared in methanol from tiglic acid (10·0 g, 0·1 mol) was reduced with sodium borohydride in aqueous alkaline solution as described above to give, after distillation, 3-methoxy-2-methylbutyric acid (9·47 g, 72%); b.p. 102—103° at 8 mmHg; n_D^{20} 1·4270 (lit.,[8] b.p. 71—72° at 0·5 mmHg; n_D 1·4265).

G.l.c. (80°, material esterified with diazomethane) showed the presence of two components R_t 12·1 and 14·0 min in approximately equal amounts and *ca.* 1% of methyl tiglate.

In a further experiment the acetoxymercury adduct was suspended in water and reduced by sodium borohydride in the absence of sodium hydroxide. G.l.c. examination of the products showed that of the two isomeric acids, that with R_t 12·1 min (as methyl ester) predominated by *ca.* 4 : 1.

Methyl 3-*Methoxy*-2-*methylbutyrate.*—3-Methoxy-2-methylbutyric acid was esterified with diazomethane and gave on distillation methyl 3-methoxy-2-methylbutyrate; b.p. 159—160° at 744 mmHg, n_D^{20} 1·4123 (lit.,[8] 54—55° at 3 mmHg; n_D 1·4110).

erythro-3-*Hydroxy*-2-*methylbutyric Acid.*—The acetoxymercury adduct (5·3 g) prepared from tiglic acid in water was dissolved in water (20 cm^3) and 2M-sodium hydroxide solution (15 cm^3). Hydrogen sulphide was bubbled into the cooled solution until precipitation of mercuric sulphide was complete. After filtration the filtrate was acidified, saturated with sodium chloride, and extracted several times with ether. The ethereal solution was washed with saturated sodium chloride solution, dried, and a portion was evaporated to give crude *erythro*-3-hydroxy-2-methylbutyric acid (0·25 g).

Methyl erythro-3-*Hydroxy*-2-*methylbutyrate.*—The remainder of the ethereal solution was treated with ethereal diazomethane and after the decomposition of excess of reagent the solution was washed successively with 0·5M-hydrochloric acid, 0·5M-sodium hydroxide solution, and saturated sodium chloride solution, dried, and evaporated to give the crude product (0·63 g). Some of this material was subjected to preparative g.l.c. (2 m × ⅜ in o.d. copper column, packed with 15% Carbowax 6000, at 140°, nitrogen carrier gas at 145 cm^3 min^{-1}). A small amount of methyl tiglate was rejected and *methyl* erythro-3-*hydroxy*-2-*methylbutyrate* (containing *ca.* 5% of the *threo*-isomer) R_t 15·0 min was collected.

The mass spectrum showed peaks at *m/e* 117 (*M* − 15, 6%), 115 (*M* − 17, 44), 101 (*M* − 31, 20), and 88 (*M* − CH_3·CHO, 100).

G.l.c. (110°) comparison of the product with the mixture of *threo*- and *erythro*-isomers showed that it contained predominantly the more polar isomer R_t 19·6 min.

erythro-3-*Methoxy*-2-*methylbutyric Acid.*—The acetoxymercury adduct prepared in methanol from tiglic acid (40 g, 0·4 mol) was demercuriated without delay in three batches using hydrogen sulphide in aqueous alkaline solution as described above. Distillation gave the crude acid product (43·2 g, 81%).

G.l.c. (80°, methyl ester) comparison with the mixture of *threo*- and *erythro*-isomers showed the product to be mainly the isomer R_t 12·1 min contaminated with *ca.* 2% each of the other isomer and tiglic acid.

A solution of bromine in carbon tetrachloride [1 : 9 (v/v)] was added in small quantities to a solution of the crude acid (25 g) in carbon tetrachloride (150 cm^3) until no further reaction occurred. Solvent and excess of bromine were removed by distillation, and fractional distillation of the residue through a 10 cm Vigreux column gave *erythro*-3-methoxy-2-methylbutyric acid, b.p. 110—113° at 11 mmHg, containing *ca.* 2% of the *threo*-isomer.

[8] A. V. Bogatskii, N. A. Goryachuk, and G. T. Parnak, *Zhur. obshchei Khim.*, 1962, **32**, 1498 (*Chem. Abs.*, 1963, **58**, 4414).

(+) *and* (−)-erythro-3-*Methoxy*-2-*methylbutyric Acids*.—Quinine (67·5 g, 0·178 mol) was added in several portions to a solution of *erythro*-3-methoxy-2-methylbutyric acid (31·4 g, 0·238 mol) in acetone (300 cm³). Ethanol was added to the boiling mixture until solution was complete and on cooling the quinine salt crystallised. Recrystallisation was carried out by suspending the salt in a convenient volume of boiling acetone, effecting solution with ethanol, and allowing the solution to cool undisturbed. The progress of resolution was followed by measurement of the rotation of the acid liberated from small portions of the salt; after fourteen recrystallisations the rotation reached a steady value, unchanged by three further recrystallisations. The main batch of quinine salt was suspended in ether and shaken with 4M-hydrochloric acid; the ethereal solution was washed with 2M-hydrochloric acid, water, and saturated sodium chloride solution, dried, and evaporated. Distillation gave (+)-erythro-3-*methoxy*-2-*methylbutyric acid* (6·25 g, 40%); b.p. 112° at 13 mmHg; n_D^{18} 1·4260; $[\alpha]_D^{20}$ +17·5° (Found: C, 53·6; H, 8·9. $C_6H_{12}O_3$ requires C, 53·5; H, 9·2%); *m/e* 117 (*M* − 15, 4%), 74 (McLafferty rearrangement, 9), and 59 (Me·CHOMe, 100).

Part of the mother liquor was treated to liberate an acid (7·5 g), $[\alpha]_D^{20}$ −5·7°, which was subjected to further resolution by recrystallisation of its cinchonidine salt from a mixture of acetone and ethanol. Some decomposition of the salt occurred during recrystallisations and cinchonidine was filtered from the hot solutions. After six recrystallisations the salt was treated to liberate (−)-erythro-3-*methoxy*-2-*methylbutyric acid*, $[\alpha]_D^{20}$ −13·6°.

(+)-*Methyl* erythro-3-*Methoxy*-2-*methylbutyrate*.—A solution of (+)-*erythro*-3-methoxy-2-methylbutyric acid, $[\alpha]_D^{20}$ +17·5°, was cooled during the addition of a slight excess of ethereal diazomethane and left for 15 min. Excess of diazomethane was decomposed with hydrochloric acid, the solution was washed with 2M-hydrochloric acid and water, dried, and evaporated. Distillation gave (+)-*methyl* erythro-3-*methoxy*-2-*methylbutyrate* (5·2 g, 76%) b.p. 156—158°; n_D^{20} 1·4100; $[\alpha]_D^{20}$ +9·0° (Found: C, 57·2; H, 10·0. $C_7H_{14}O_3$ requires C, 57·5; H, 9·7%); *m/e* 146 (*M*, 0·2%), 131 (*M* − 15, 5), 115 (*M* − OMe, 10), and 59 ($Me{\cdot}CHOMe^+$, 100).

Methylation of Methyl erythro-3-*Hydroxy*-2-*methylbutyrate*.—Sodium hydride (50% dispersion in oil; 0·02 g) was stirred under nitrogen with dimethyl sulphoxide (1·5 cm³) at 65° for 1 h. Methyl 3-hydroxy-2-methylbutyrate (0·013 g containing mainly the *erythro*-isomer) in DMSO (0·5 cm³) was added to the cooled solution and the mixture was stirred at 45° for 1 h. Methyl iodide (0·1 g) in DMSO (1 cm³) was added to the cooled mixture and stirring was continued overnight at room temperature. The mixture was poured into water and extracted with methylene chloride. The methylene chloride solution was washed with water, dried, and evaporated. G.l.c. (80°) examination of the product showed the presence of the methyl 3-methoxy-2-methylbutyrates, R_t 12·1 and 14·0 min, with a great preponderance of the isomer having a shorter retention time.

Methoxymercuriation and Demercuriation of Angelic Acid.—Methoxymercuriation of angelic acid (prepared from tiglic acid by the method of Buckles and Mock [9]) by treatment with mercuric acetate in methanol was carried out in the manner described for tiglic acid.

The adduct was reduced in aqueous alkali with sodium borohydride, as described, to give 3-methoxy-2-methylbutyric acid. G.l.c. examination of the corresponding methyl ester showed that *erythro*- and *threo*-isomers were present in the same proportions as those obtained by the same treatment of the tiglic acid adduct.

A further portion of the adduct was demercuriated in aqueous sodium hydroxide solution by hydrogen sulphide. G.l.c. examination of the methyl ester of the product showed the presence of one major component corresponding to methyl *erythro*-3-methoxy-2-methylbutyrate, contaminated with a small amount of methyl angelate. The major acid product was purified by preparative g.l.c. (4 m × ⅜ in o.d. copper column packed with 20% PEGS at 160°, nitrogen 120 cm³ min⁻¹), R_t 65 min, and shown by its n.m.r. spectrum to be identical with the product obtained in a similar manner from tiglic acid.

Ethyl 2-(1-*Hydroxyethyl*)*pent*-4-*enoate*.—A solution of sodium borohydride (1·50 g, 0·039 mol) in ethanol (40 cm³) was added during 1 h to a cooled, stirred solution of ethyl α-allylacetoacetate (obtained from ethyl acetoacetate and allyl chloride by a standard procedure) (17·0 g, 0·1 mol) in ethanol (60 cm³). Stirring was continued at room temperature for 2 h then dilute hydrochloric acid was added to decompose excess of sodium borohydride. Most of the solvent was evaporated, the residue was suspended in water, and extracted with ether. The ethereal solution was washed successively with 5% sodium carbonate solution, water, and saturated sodium chloride solution, dried, and evaporated. Distillation of the residue gave *ethyl* 2-(1-*hydroxyethyl*)*pent*-4-*enoate* (15·6 g, 92%) b.p. 97—98° at 8 mmHg; n_D^{20} 1·4475 (Found: C, 62·7; H, 9·4. $C_9H_{16}O_3$ requires C, 62·8; H, 9·4%).

Ethyl threo- *and* erythro-2-(1-*Hydroxyethyl*)*pent*-4-*enoates*.—The ester (V) was subjected to preparative g.l.c. (4 m × ⅜ in o.d. copper column packed with 15% PEGS at 130°, nitrogen flow 150 cm³ min⁻¹). Injections of samples (0·05 cm³) were made and the threo- R_t 62 min, and erythro-*isomers*, R_t 79 min, were collected. High-resolution i.r. data are in Table 4, the n.m.r. data for the *threo*-isomer are in Table 5, and mass spectral data are in Table 6. The

TABLE 4

	ν/cm⁻¹	3631	3534	1732	1715
threo-Isomer(0·0078M)	ε	7·5	18·3	97	193
erythro-Isomer(0·0084M)	ε	11·1	14·3	148	140

TABLE 5

τ		*J*/Hz		
4·20	Multiplet		$CH_2{:}CH{\cdot}CH_2{\cdot}$	1H
4·91	Doublet	18	$CH_2{\cdot}CH{\cdot}CHH$ *trans*	2H
4·95	Doublet	10	$CH_2{\cdot}CH{:}CHH$ *cis*	
5·80	Quartet	7	$\cdot CO_2CH_2CH_3$	3H
6·05	App. quintet	6	$CH_3{\cdot}CHOH{\cdot}$	
7·57	Multiplet		$CH_2{:}CH{\cdot}CH_2{\cdot}$	2H
8·72	Triplet	7	$\cdot CO_2{\cdot}CH_2{\cdot}CH_3$	6H
8·75	Doublet	6·6	$CH_3{\cdot}CHOH{\cdot}$	

TABLE 6

Relative abundance (%)

m/e	*threo*-Isomer	*erythro*-Isomer
157(*M* − 15)	15	4
154(*M* − 18)	26	37
130(*M* − 42)	55	22
128(*M* − CH_3CHO)	100	57
100(*M* − 44 − 28)	89	58
81(*M* − 18 − 73)	96	100

[9] R. E. Buckles and G. V. Mock, *J. Org. Chem.*, 1950, **15**, 680.

TABLE 7

	τ		J/Hz		
	5·82	Quartet	7	$CO_2{\cdot}CH_2{\cdot}CH_3$	3H
erythro	6·02	Doublet of quartets	6·2, 5·2	$CH_3{\cdot}CHOH{\cdot}$	
threo	6·10	Apparent quintet	6·5	$CH_3{\cdot}CHOH{\cdot}$	
erythro	7·58	Multiplet		·CHPr	1H
threo	7·65	Multiplet		·CHPr	1H
	8·72	Triplet	7·5	$\cdot CO_2{\cdot}CH_2{\cdot}CH_3$	
threo	8·78	Doublet	6·5	$CH_3{\cdot}CHOH{\cdot}$	
erythro	8·81	Doublet	6·1	$CH_3{\cdot}CHOH{\cdot}$	
	9·08	Triplet	7	$\cdot CH_2{\cdot}CH_2{\cdot}CH_3$	3H

n.m.r. spectrum of the *eyrthro*-isomer is similar in most respects except that the terminal methyl doublet is at τ 8·80 and the $CH_3{\cdot}CHOH{\cdot}$ multiplet is at τ 5·96, the multiplicity being obscured by a quartet at τ 5·83.

Ethyl threo- *and* erythro-2-(1-*Hydroxyethyl*)*pentanoates*.—The *threo*- and *erythro*-isomers (V) were separately hydrogenated in cyclohexane over 5% palladium–charcoal for 1 day. The catalyst was removed by filtration, and evaporation of the solvent gave *ethyl* threo-2-(1-*hydroxyethyl*)-*pentanoate* and the erythro-isomer. N.m.r. data are in Table 7 and mass spectral data are in Table 8.

TABLE 8

m/e	*threo-*	*erythro*
159(*M* − 15)	14%	3%
156(*M* − 18)	7%	2%
130(*M* − $CH_3{\cdot}CHO$)	80%	56%
131(*M* − 44 − 29)	100%	100%

[2/996 *Received, 4th May,* 1972]