132. *Intermediates for the Synthesis of Optically Active Methyl-substituted Long-chain Acids. Part V.**

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β-Methoxy-α-methylpropionic acid (V) has been resolved, with isolation of the (+)-enantiomer which is shown to have *L*-configuration.† This enantiomer was converted into the (+)-form of the methoxy-chloride (III; X = Cl); the latter has the requisite configuration for a projected [1] synthesis of mycoceranic acid.

The present work was undertaken in connection with studies in the synthesis of mycoceranic acid. This acid has been shown [2] to have the structure (I) where *n* was stated to be probably 21; all three asymmetric centres were assigned to the *D*-series.[1] From mass-spectrometric studies Asselineau, Ryhage, and Stenhagen [3] concluded that *n* is 22. One of the routes considered earlier [1] for the synthesis of this acid involved a Grignard reaction between the *D*-form of the ketone (II) and the requisite enantiomer of the methoxy-halide (III; X = halogen), to give by further steps the methoxy-derivative (IV). The present paper records the synthesis of the (+)-enantiomer of 1-chloro-3-methoxy-2-methylpropane (III; X = Cl) which is found to be the requisite enantiomer for the above synthesis.

(I) $Me\cdot[CH_2]_n\cdot CHMe\cdot CH_2\cdot CHMe\cdot CH_2\cdot CHMe\cdot CO_2H$

(II) $Me\cdot[CH_2]_n\cdot CHMe\cdot CH_2\cdot COMe$

(III) $X\cdot CH_2\cdot CHMe\cdot CH_2\cdot OMe$ $\qquad$ $MeO\cdot CH_2\cdot CHMe\cdot CO_2H$ (V)

(IV) $Me\cdot[CH_2]_n\cdot \overset{D}{C}HMe\cdot CH_2\cdot \overset{DL}{C}HMe\cdot CH_2\cdot \overset{D}{C}HMe\cdot CH_2\cdot OMe$

The starting point was methyl α-methylacrylate which, by reaction with methanol in the presence of sodium methoxide,[4 5] followed by hydrolysis of the resulting methoxy-ester, gave β-methoxy-α-methylpropionic acid (V). Resolution of this acid was accomplished with quinine, affording the (+)-enantiomer, $[\alpha]_D$ +14·4°, whose configuration was established by the following experiments.

L-(+)-2-Methylpent-4-enoic acid [6] (VI) was converted by way of the corresponding alcohol [7] (VII; R = H) into the methoxy-derivative (VII; R = Me) which on oxidation with sodium metaperiodate and potassium permanganate (cf. Lemieux and von Rudloff [8]) afforded *D*-(−)-γ-methoxy-β-methylbutyric acid (VIII) (the change of prefix *L* to *D* is due to the conventional † alteration of the reference group).

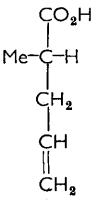
A lævorotatory specimen of γ-methoxy-β-methylbutyric acid also resulted from a partially resolved sample of the (−)-enantiomer of β-methoxy-α-methylpropionic acid (V) by reduction to the corresponding alcohol (III; X = OH) and conversion of the latter through the iodide (III; X = I) into the cyanide (III; X = CN), followed by hydrolysis (*i.e.*, by a sequence of reactions involving no change of configuration). It follows that the (−)-enantiomer of the methoxy-acid (V) has *D*-configuration; consequently, the above fully resolved (+)-form of this methoxy-acid is the *L*-isomer.

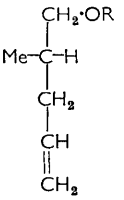
* Part IV, *J.*, preceding paper.

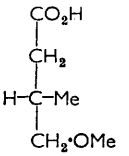
† The symbols *D* and *L* are used in the sense defined by Linstead, Lunt, and Weedon (*J.*, 1950, 3333).

[1] Marks and Polgar, *J.*, 1955, 3851.
[2] Polgar, *J.*, 1954, 1011.
[3] Asselineau, Ryhage, and Stenhagen, *Acta Chem. Scand.*, 1957, **11**, 96.
[4] Bieber, *Compt. rend.*, 1952, **234**, 1783.
[5] Bieber, *Ann. Chim. France*, 1954, **9**, 674.
[6] Ställberg-Stenhagen, *Arkiv Kemi, Mineralog. Geol.*, 1946, **23**, *A*, No. 15.
[7] Fray and Polgar, *J.*, 1956, 2036.
[8] Lemieux and von Rudloff, *Canad. J. Chem.*, 1955, **33**, 1701, 1710.

Reduction of the *L*-(+)-enantiomer of the methoxy-acid (V) with lithium aluminium hydride gave (−)-3-methoxy-2-methylpropan-1-ol (III; X = OH) which on reaction with thionyl chloride in the presence of pyridine afforded (+)-1-chloro-3-methoxy-2-methylpropane (III; X = Cl). A Grignard reaction between this chloride and the *D*-form of the ketone (II), followed by the stages already mentioned,[1] would give the methoxy-derivative (IV) in the requisite 2(*D*) : 6(*D*)-form, the change in prefix in respect of the asymmetric centre at $C_{(2)}$ [corresponding to the active centre in the *L*-enantiomer of the methoxy-acid (V)] following from the conventional alteration of the reference group.


(VI)


(VII)


(VIII)

It is of interest that *D*-γ-methoxy-β-methylbutyric acid (VIII) is, as shown above, lævorotatory, whereas *D*-6-methoxy-3-methylhexanoic acid was dextrorotatory.[9] The sign of rotation of these methoxy-acids is in agreement with earlier findings[10] that all 3(*D*)-methylalkanoic acids $Me\cdot[CH_2]_n\cdot CHMe\cdot CH_2\cdot CO_2H$ are dextrorotatory with the exception of the first member of this series ($n = 1$).

Experimental

α refers to homogeneous liquids ($l = 1$). Ethereal solutions were dried over Na_2SO_4.

β-*Methoxy-α-methylpropionic Acid* (V).—Methyl β-methoxy-α-methylpropionate, b. p. 148—149°, was obtained in 43% yield by Bieber's procedure [5] (Bieber [5] gives the same b. p.; Glover and Jones [11] referring to Bieber's note,[4] but unaware of his later paper,[5] report yields varying from 0 to 30%). Hydrolysis of this ester according to Bieber's directions [5] gave β-methoxy-α-methylpropionic acid, b. p. 114°/24 mm., which formed a *p*-bromophenacyl ester of m. p. 63·5° (from aqueous ethanol) (Bieber [5] gives m. p. 63·5—64°; Gresham [12] records b. p. 110—112°/20 mm. for the acid).

Resolution of β-*Methoxy-α-methylpropionic Acid.*—The (±)-acid (60 g., 1 mol.) and quinine (164·6 g., 1 mol.) were dissolved in hot acetone (1·5 l.) and the mixture set aside. The quinine salt which crystallised overnight gave, after three recrystallisations from acetone, on decomposition with 2N-hydrochloric acid followed by ether-extraction and distillation, an acid with α_D^{22} +12·4°. After three further recrystallisations of the quinine salt the regained acid had α_D^{22} +14·64°; a further recrystallisation of the quinine salt gave acid with the same rotation. In further experiments six batches (in all 367 g.) of the racemic acid were resolved by this procedure. The (+)-*acid* so obtained had $\alpha_D^{17\cdot5}$ +15·02° and α_D^{19} +14·98° (for two different specimens), d_{19}^{19} 1·04, $[\alpha]_D^{19}$ +14·4° (Found: C, 50·8; H, 8·4; OMe, 25·8. $C_5H_{10}O_3$ requires C, 50·8; H, 8·4; OMe, 26·3%).

The mother-liquors from the first crystallisation of the quinine salt yielded acid having α_D^{21} −8·14°.

In other experiments the partially resolved (+)-acid was obtained by resolution with cinchonidine. After eight recrystallisations of the cinchonidine salt from acetone the regained acid had α_D^{24} +13·08°; the mother-liquors of the first crystallisation of the cinchonidine salt (from acetone) gave acid having α_D^{20} −4·74°.

3-*Methoxy-2-methylpropan-1-ol* (III; X = OH).—The above fully resolved (+)-acid (19 g.) in ether (100 c.c.) was added to a stirred mixture of lithium aluminium hydride (9·2 g.) and ether (150 c.c.) during 2 hr., at such a rate that the ether boiled gently. After a further 0·5 hr.

[9] Brettle and Polgar, *J.*, 1956, 1620.
[10] Mills and Klyne, in "Progress in Stereochemistry," Butterworths, London, 1954, Vol. I, p. 205.
[11] Glover and Jones, *J.*, 1958, 3021.
[12] Gresham, U.S.P. 2,504,080 (see *Chem. Abs.*, 1950, **44**, 6878).

the excess of lithium aluminium hydride was decomposed in the usual manner; concentrated hydrochloric acid (90 c.c.) was then added, and stirring continued for another 0·5 hr. The ethereal layer was separated, and the aqueous phase extracted with ether (continuous extractor). The combined ethereal solutions were shaken with potassium carbonate, dried, and distilled, affording (−)-*3-methoxy-2-methylpropan-1-ol* (12·65 g.), b. p. 154—156°, n_D^{21} 1·4160, α_D^{23} −2·26°, d_{23}^{23} 0·915, $[\alpha]_D^{23}$ −2·47°. Elderfield, Pitt, and Wempen [13] record b. p. 154—155°, n_D^{27} 1·4140, d^{27} 0·916, for the racemic alcohol.

The partially resolved (−)-enantiomer of β-methoxy-α-methylpropionic acid (24·7 g.) having α_D^{21} −8·14° (see above) gave by the foregoing procedure partially active alcohol (16·63 g.) with α_D^{23} +1·14°.

The (±)-acid gave, by the same procedure, (±)-3-methoxy-2-methylpropan-1-ol, b. p. 154—156°, yielding a 3 : 5-dinitrobenzoate as needles of m. p. 63·5° (from aqueous ethanol or light petroleum, b. p. 60—80°) (Found: OMe, 10·3; N, 9·5. Calc. for $C_{12}H_{14}O_7N_2$: OMe, 10·4; N, 9·4%). Elderfield *et al.*[13] record m. p. 63—64°.

(+)-*1-Chloro-3-methoxy-2-methylpropane* (III; X = Cl).—This was obtained from (−)-3-methoxy-2-methylpropan-1-ol by means of thionyl chloride in the presence of pyridine according to the directions given by Elderfield *et al.*[13] for the racemic chloride. The (+)-*chloride* had b. p. 125°, α_D^{24} +12·68°, d_{20}^{24} 0·963, $[\alpha]_D^{24}$ +13·2°. Elderfield *et al.*[13] record b. p. 124—124·5°, d_4^{27} 0·966, for the racemic chloride.

5-Methoxy-4-methylpent-1-ene.—2-Methylpent-4-en-1-ol [7·2 g.; obtained from (±)-2-methylpent-4-enoic acid by the procedure described [7] for the preparation of the (−)-enantiomer] was refluxed with methyl iodide (30·5 g.) and silver oxide (25 g.; prepared according to the directions of Helferich and Klein; [14] added in 5 g. portions) for 7 hr. The mixture was filtered, and the silver salts were washed with ether; the filtrate and washings were then evaporated. After two further methylations by the same procedure, the product was distilled, affording *5-methoxy-4-methylpent-1-ene* (1·65 g.), b. p. 109° (Found: C, 73·7; H, 12·4. $C_7H_{14}O$ requires C, 73·7; H, 12·3%).

D-(−)-*γ-Methoxy-β-methylbutyric Acid* (VIII).—(i) *L*-(−)-2-Methylpent-4-en-1-ol (VII; R = H) [12·6 g.; obtained from *L*-(+)-2-methylpent-4-enoic acid [6] by the procedure described earlier [7]] was converted into the methoxy-derivative (VII; R = Me) according to the directions given above for the racemic product, except that the methylation procedure was repeated three times, and the silver salts were exhaustively extracted with boiling chloroform. Distillation of the product gave a fraction (7·9 g.), b. p. 90—115°, which on redistillation yielded the methoxy-derivative (4·35 g.), b. p. 108—112°. 0·64 g. of this product was oxidised with sodium meta-periodate (1·58 g.) and potassium permanganate (212 mg.) in aqueous sodium carbonate by the procedure of Lemieux and von Rudloff.[8] The mixture was kept at room temperature for 21 hr. with occasional shaking, then acidified with 2N-sulphuric acid and extracted with ether (continuous extractor). Six further batches (in all 4·1 g.) were oxidised by this procedure. The combined ethereal extracts gave on distillation D-(−)-*γ-methoxy-β-methylbutyric acid* (1·37 g.), b. p. 124—128°/20 mm., n_D^{18} 1·4258, $[\alpha]_D^{22}$ −8·7° (*c* 17·8 in Et_2O, *l* 0·5) (Found: C, 54·1; H, 9·4. $C_6H_{12}O_3$ requires C, 54·5; H, 9·1%). Wagner [15] gives b. p. 123—125°/20 mm., n_D^{20} 1·4235, for the racemic acid. The S-*benzylthiuronium salt* had m. p. 141·5° after crystallisation from water (Found: S, 10·8; N, 9·8. $C_{14}H_{22}O_3N_2S$ requires S, 10·7; N, 9·4%).

(ii) A partially active sample of *D*-(−)-γ-methoxy-β-methylbutyric acid was obtained from partially resolved (+)-3-methoxy-2-methylpropan-1-ol (see above), α_D^{23} 1·14°, by the following procedure.

Dry pyridine (24·9 g., 2·1 mol.) was gradually added with stirring to an ice-cold mixture of the (+)-alcohol (15·6 g., 1 mol.) and toluene-*p*-sulphonyl chloride (30 g., 1·05 mol.) during about 2 hr. The product was acidified with dilute hydrochloric acid, then extracted with ether, and the dried (K_2CO_3) extract was evaporated. The resulting crude toluene-*p*-sulphonate was refluxed with a solution of anhydrous sodium iodide (41 g.) in dry acetone (450 c.c.), with stirring, for 7 hr. The iodide, isolated in the known manner, was added during 15 min. in ethanol (150 c.c.) to a hot solution of potassium cyanide (11·85 g.) in water (40 c.c.), and the solution heated under reflux for 16½ hr. The resulting crude cyanide, isolated by ether-extraction, was refluxed with a mixture of concentrated sulphuric acid (40 c.c.), acetic acid (40 c.c.),

[13] Elderfield, Pitt, and Wempen, *J. Amer. Chem. Soc.*, 1950, **72**, 1334.
[14] Helferich and Klein, *Annalen*, 1926, **450**, 219.
[15] Wagner, *J. Amer. Chem. Soc.*, 1949, **71**, 3214.

and water (80 c.c.) for 8 hr. The product was poured into water and extracted with ether from which the acidic fraction was removed with aqueous sodium hydrogen carbonate. Acidification of the alkaline extract and ether-extraction, followed by distillation, gave (−)-acid (3·85 g.), b. p. 127°/25 mm., n_D^{16} 1·4270, $[\alpha]_D^{23}$ −5·7° (*c* 15 in Et_2O; *l* 0·5) (Found: C, 54·5; H, 9·2%).

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