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

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D-(+)-6-Methoxy-3-methylhexanoic acid * has been prepared from *L*-(+)-(methyl hydrogen β-methylglutarate) by anodic coupling with β-methoxypropionic acid. (+)-γ-Methoxy-α-methylbutyric acid was obtained by resolution of the racemic acid with cinchonidine methohydroxide.

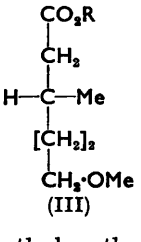
THE present work was initiated in connection with studies in the syntheses of mycolipenic (I) and mycoceranic acid (II).[1] Concurrently with other approaches we turned our attention to methyl-substituted carboxylic acids with a terminal ether grouping as possible intermediates for these syntheses, with a view to utilising one of the functional groups for elaborating, in the correct configuration, the terminal structures of the naturally occurring acids, and the other functional group for attaching the requisite long carbon chain. Some preliminary work which included the preparations of *D*-(+)-6-methoxy-3-methylhexanoic and (+)-γ-methoxy-α-methylbutyric acid is now placed on record.

$CH_3 \cdot [CH_2]_{17} \cdot CHMe \cdot CH_2 \cdot CHMe \cdot CH{:}CMe \cdot CO_2H$ (I)

$CH_3 \cdot [CH_2]_{21} \cdot CHMe \cdot CH_2 \cdot CHMe \cdot CH_2 \cdot CHMe \cdot CO_2H$ (II)

Initial attempts to resolve α-methyl-γ-phenoxybutyric acid [2] met with no success. We next converted the foregoing acid by a Bouveault–Blanc reduction of its ethyl ester into 2-methyl-4-phenoxybutan-1-ol but, after an unsuccessful attempt to resolve the corresponding hydrogen phthalate, this approach was not pursued further.

We then turned to the use of *L*-(+)-(methyl hydrogen β-methylglutarate).[3,4] Anodic coupling of the latter with β-methoxypropionic acid, readily obtainable from acrylonitrile and methanol,[5] furnished methyl *D*(+)-6-methoxy-3-methylhexanoate (III; R = Me) (the change of the prefix *L* to *D* is due to alteration of the reference group *), which on hydrolysis gave the corresponding acid (III; R = H), $[\alpha]_D$ +6·1°. However, the low yield of the mixed electrolysis, together with the numerous stages required for obtaining the optically active starting material, did not encourage further work along these lines.


(III)

Therefore, we examined the resolution of γ-methoxy-α-methylbutyric acid, easily accessible by a malonic ester synthesis from 2-methoxyethyl bromide and ethyl methylmalonate (cf. ref. 6). In attempts to crystallise the cinchonidine or cinchonine salt of the butyric acid the free bases separated from the solutions; hence we turned to the quaternary ammonium hydroxides obtainable from the natural bases as resolving agents (cf. ref. 7). Resolution of the acid was readily accomplished with cinchonidine methohydroxide, affording the (+)-enantiomer, $[\alpha]_D$ +12·2°; cinchonidine methohydroxide for which there appears to be no previous record was prepared *via* the methiodide. Resolutions with quinine and its methohydroxide [7] are also reported in the Experimental section.

EXPERIMENTAL

Optical rotations were measured in a 0·5-dm. tube, unless otherwise stated.

α-Methyl-γ-phenoxybutyric Acid.—This was prepared, as described by Bentley, Haworth, and Perkin,[2] by a malonic ester synthesis from 2-phenoxyethyl bromide and ethyl methylmalonate. The brucine salt, prepared by dissolving equimolecular amounts of the acid and alkaloid in ethanol, did not crystallise. When the strychnine salt, obtained from chloroform

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

[1] Polgar, *J.*, 1954, 1008, 1011; Marks and Polgar, *J.*, 1955, 3851.
[2] Bentley, Haworth, and Perkin, *J.*, 1896, **69**, 171.
[3] Ställberg-Stenhagen, *Arkiv Kemi, Mineralog. Geol.*, 1947, **25**, *A*, No. 10.
[4] Linstead, Lunt, and Weedon, *J.*, 1950, 3333.
[5] MacGregor and Pugh, *J.*, 1945, 535.
[6] Prelog and Zalan, *Helv. Chim. Acta*, 1944, **27**, 531.
[7] Major and Finkelstein, *J. Amer. Chem. Soc.*, 1941, **63**, 1368.

solution, was dissolved in hot methanol and the solution cooled, crystals were deposited which were mainly strychnine. The cinchonidine salt also gave the free base on attempted crystallisation from aqueous methanol or acetone.

2-Methyl-4-phenoxybutan-1-ol.—Ethyl α-methyl-γ-phenoxybutyrate (22·2 g.; obtained from the foregoing acid by means of ethanolic sulphuric acid) was reduced with sodium (12 g.) and butanol (200 g.) (cf. ref. 8). *2-Methyl-4-phenoxybutan-1-ol*, b. p. 160°/18 mm., was obtained as a viscous oil (9·7 g.) (Found: C, 73·1; H, 8·9. $C_{11}H_{16}O_2$ requires C, 73·3; H, 8·9%). The *α-naphthylurethane* crystallised from light petroleum (b. p. 100—120°) as white plates, m. p. 81° (Found: C, 75·8; H, 6·3; N, 4·1. $C_{22}H_{23}O_3N$ requires C, 75·6; H, 6·6; N, 4·0%). The *hydrogen phthalate* had m. p. 55—57° (Found: C, 69·3; H, 6·3. $C_{19}H_{20}O_5$ requires C, 69·5; H, 6·1%); an attempt to resolve it with brucine failed.

β-*Methoxypropionic Acid.*—MacGregor and Pugh's procedure [5] was followed. Acrylonitrile (106 g., 1 mol.), methanol (64 g., 1 mol.), and 2% aqueous sodium hydroxide were shaken until no more heat was evolved (20 min.). The upper layer was then separated, neutralised with glacial acetic acid, dried (Na_2SO_4), and distilled. The resulting β-methoxypropionitrile (103 g., 60%), b. p. 164°, when heated under reflux with concentrated hydrochloric acid afforded β-methoxypropionic acid, b. p. 113—114°/17 mm. (Jones and Power [9] give b. p. 126°/30 mm.).

D-(+)-6-*Methoxy*-3-*methylhexanoic Acid* (III; R = H).—*L*-(+)-(Methyl hydrogen β-methylglutarate), $\alpha_D^{17\cdot5}$ +0·32° (homogenous), was obtained by Ställberg-Stenhagen's procedure [3] with the modifications suggested by Linstead, Lunt, and Weedon.[4] The half-ester (8 g., 1 mol.) and β-methoxypropionic acid (10·4 g., 2 mol.) were added to a solution of methoxide [from sodium (0·5 g.) and methanol (250 c.c.)], and the mixture electrolysed in a cell containing two parallel platinum plate cathodes (2 × 3 cm.) set 1 cm. apart with a single platinum plate anode placed between (the apparatus was kindly lent by Dr. A. S. Bailey). The cell was cooled by immersion in an ice-bath and a current of about 2·3 amps. was passed until the solution became alkaline (1·5 hr.). It was then neutralised with glacial acetic acid and evaporated. Ether (50 c.c.) and 5% aqueous sodium carbonate (50 c.c.) were added to the residue, and, after the mixture had been shaken, the ethereal layer was separated, dried ($MgSO_4$), and distilled. Five runs on the above scale were worked up together, and the fraction, b. p. 99—101°/14 mm. (7·2 g., 16%), was hydrolysed by refluxing it with a solution of potassium hydroxide (4 g.) in water (20 c.c.) and ethanol (20 c.c.) for 3 hr. The solution was concentrated and extracted with ether to remove non-acidic material. Acidification of the aqueous phase, followed by extraction with ether and distillation, gave, after rejection of a small fore-run, D-(+)-6-*methoxy*-3-*methylhexanoic acid*, b. p. 149—151°/12 mm., n_D^{18} 1·4382, $[\alpha]_D^{18}$ +6·14° (*c*, 5·1 in ether; *l*, 1) (Found: C, 59·7; H, 10·2. $C_8H_{16}O_3$ requires C, 60·0; H, 10·0%). The S-*benzylthiuronium* salt had m. p. 136·5° (from ethanol) (Found: C, 58·9; H, 8·2; N, 8·4. $C_{16}H_{26}O_3N_2S$ requires C, 58·9; H, 8·0; N, 8·6%).

Resolution of γ-Methoxy-α-methylbutyric Acid.—An aqueous solution of cinchonidine methohydroxide was prepared by the following alternative procedures. (i) Methyl iodide (23·6 g., 1 mol.) was added to cinchonidine (49 g., 1 mol.) and ethanol (50 c.c.), and the mixture set aside overnight; crystallisation from hot water gave pale yellow needles of cinchonidine methiodide (55·8 g.). This was shaken with freshly precipitated silver oxide (from 70 g. of silver nitrate) and water (150 c.c.) at 0° for 15 min., then at room temperature for a further 3 hr. The aqueous solution was then decanted and filtered, and the filtrate centrifuged to remove colloidal silver oxide.

(ii) Cinchonidine methiodide (30 g.; prepared as above) was shaken with freshly precipitated silver chloride (from 10 g. of silver nitrate) and water (175 c.c.) for 2 hr.; the mixture was then heated and filtered while hot. Saturation of the cold filtrate with sodium chloride precipitated crude cinchonidine methochloride which was reprecipitated from filtered solution in dry ethanol by the addition of ether. After repetition of this purification process, the resulting methochloride was shaken with silver oxide (from 12 g. of silver nitrate) and water (20 c.c.) as above; the mixture was then filtered and the filtrate set aside overnight. A further filtration through Whatman No. 2 paper gave a clear solution of the methohydroxide.

The resulting solutions of cinchonidine methohydroxide were standardised by titration with 0·088N-sulphuric acid, phenolphthalein being used as indicator.

(±)-γ-Methoxy-α-methylbutyric acid (6·45 g., 1 mol.; obtained by Prelog and Zalan's method [6] from 2-methoxyethyl bromide [10] and ethyl methylmalonate) was added to aqueous

[8] Blatt, *Org. Synth.*, Coll. Vol. II, 1943, p. 468.
[9] Jones and Power, *J. Amer. Chem. Soc.*, 1924, **46**, 2530.
[10] Palomaa and Kenetti, *Ber.*, 1931, **64**, 797.

cinchonidine methohydroxide (0·32N; 153 c.c., 1 mol.), the solution filtered and then evaporated, and the residual salt dried *in vacuo* (P_2O_5). After four crystallisations from dioxan the cinchonidine methosalt (3·5 g.) was obtained as white needles, $[\alpha]_D^{16\cdot5}$ −100° (*c*, 3·06 in EtOH); the rotatory power was unaltered on further recrystallisation. The salt was decomposed with 2N-hydrochloric acid and the liberated acid isolated by extraction with ether. On removal of the solvent the (+)-*acid* (0·8 g.) was obtained with $[\alpha]_D^{16\cdot5}$ +12·2° (*c*, 15·28 in Et_2O).

Concentration of the mother-liquors from the above crystallisations, followed by the addition of dry ether, gave a further fraction of the cinchonidine methosalt which on decomposition as before afforded the partially resolved (−)-enantiomer (0·9 g.), $[\alpha]_D^{16\cdot5}$ −6·9° (*c*, 17·30 in Et_2O).

In small-scale experiments the partially resolved (+)-enantiomer was obtained by resolution with quinine or quinine methohydroxide.[7] The quinine salt, prepared in acetone solution, crystallised from acetone–light petroleum (b. p. 40—60°), and the quinine methosalt (obtained as described above for the cinchonidine methosalt) from alcohol–ether.

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