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

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(+)-γ-Ethoxy-α-methylbutyric and (+)- and (−)-6-ethoxy-3-methylhexanoic acid have been prepared.

THE work described in Part I * of this series aimed at obtaining optically active methyl-substituted carboxylic acids with a terminal ether grouping as possible intermediates for syntheses of mycolipenic and mycoceranic acid. In continuation of these studies, the preparations of the (+)-enantiomer of γ-ethoxy-α-methylbutyric (I) and the (+)- and the (—)-enantiomer of 6-ethoxy-3-methylhexanoic acid (VI) are now reported.

The starting point for both syntheses was 2-ethoxyethanol ("Ethyl cellosolve"). Condensation of its toluene-*p*-sulphonate with the sodio-derivative of ethyl malonate, followed by methylation of the resulting substituted malonic ester and the usual subsequent stages, gave γ-ethoxy-α-methylbutyric acid (I); this procedure was found superior to that of Sutton and Data [1] involving condensation of 2-ethoxyethyl bromide with ethyl methylmalonate. Resolution of the acid was accomplished with quinine, affording the (+)-enantiomer, $[\alpha]_D$ +23·6°.

(I) $EtO\cdot[CH_2]_2\cdot CHMe\cdot CO_2H$ $EtO\cdot[CH_2]_3\cdot CO\cdot CH_3$ (II)
(III) $EtO\cdot[CH_2]_3\cdot CHMe\cdot CH(CN)\cdot CO_2Et$ $EtO\cdot[CH_2]_3\cdot CHMe\cdot CH_2\cdot CN$ (IV)
(V) $EtO\cdot[CH_2]_3\cdot CMe(OH)\cdot CH_2\cdot CO_2Et$ $EtO\cdot[CH_2]_3\cdot CHMe\cdot CH_2\cdot CO_2H$ (VI)
(VII) $EtO\cdot[CH_2]_3\cdot CHMe\cdot CH_2\cdot CO\cdot CH_3$

6-Ethoxy-3-methylhexanoic acid (VI) was made *via* 5-ethoxypentan-2-one (II), obtained from the toluene-*p*-sulphonate of 2-ethoxyethanol by the acetoacetic ester method. Condensation of the ketone (II) with ethyl cyanoacetate, followed by catalytic hydrogenation of the product, gave ethyl 2-cyano-6-ethoxy-3-methylhexanoate (III) which on hydrolysis and decarboxylation of the resulting acid afforded 6-ethoxy-3-methylhexanonitrile (IV). Hydrolysis of the latter gave, however, a rather poor yield of the required acid (VI). Another route was then followed which involved a Reformatsky reaction between ethyl bromoacetate and the ketone (II) to give ethyl 6-ethoxy-3-hydroxy-3-methylhexanoate (V). Attempts to dehydrate this hydroxy-ester by refluxing it with acetic anhydride, or by treatment of the toluene-*p*-sulphonate with alkali failed, and heating it with iodine left an appreciable proportion unchanged, but dehydration was readily effected by thionyl chloride in the presence of pyridine or diethylaniline. Catalytic hydrogenation of the product, followed by hydrolysis of the saturated ester, gave 6-ethoxy-3-methylhexanoic acid (VI). Resolution with quinine gave the (+)-enantiomer, and resolution with cinchonidine the (—)-enantiomer.

As to the configurations of the resolved acids it should be noted that the lævorotatory form of 2-methyl-substituted carboxylic acids and the dextrorotatory form of 3-methyl-substituted carboxylic acids have been sterically related [2] to D-(+)-glyceric aldehyde.† Since (+)-6-methoxy-3-methylhexanoic acid has also been shown (cf. Part I) to belong to the *D*-series, it appears that the presence of a terminal ether group has no effect in this respect. This suggests that in the present case the (+)-form of γ-ethoxy-α-methylbutyric acid (I) and the (—)-form of 6-ethoxy-3-methylhexanoic acid (VI) have *L*-configuration, and the (+)-form of (VI) has *D*-configuration.

The preparation of 7-ethoxy-4-methylheptan-2-one (VII) and an attempt to resolve it

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* Part I, *J.*, 1956, 1620.

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

[1] Sutton and Data, *J. Amer. Pharm. Assoc.*, 1952, **41**, 328.

[2] Ställberg-Stenhagen and Stenhagen, *Arkiv Kemi, Mineralog. Geol.*, 1947, **24**, *B*, No. 9.

by means of (—)-menthoxycarbonylhydrazine[3] are also described in the Experimental section.

EXPERIMENTAL

Optical rotations were measured in a 0·5-dm. tube.

γ-Ethoxy-α-methylbutyric Acid (I).—Dry pyridine (474 g., 6 mol.) was added dropwise with stirring to a mixture of 2-ethoxyethanol (270 g.; 3 mol.) and toluene-*p*-sulphonyl chloride (627 g., 3·3 mol.) at 0—5° during 2 hr., and cooling and stirring were continued for a further 2 hr. After acidification with dilute hydrochloric acid, the mixture was extracted with ether, and the dried (K_2CO_3) extract evaporated, giving crude 2-ethoxyethyl toluene-*p*-sulphonate (733 g.) as an oil. The crude ester (610 g.) was condensed with the sodio-derivative of ethyl malonate (from 62 g. of sodium, 600 g. of ethyl malonate, and 1300 c.c. of ethanol), to give ethyl 2-ethoxyethylmalonate (407 g., 70%), b. p. 134—136°/13 mm. (Palomaa and Kenetti[4] give b. p. 118—119°/6 mm.; Prelog and Bozicevic[5] record b. p. 152—156°/16 mm.). This ester (464 g.) was converted into its sodio-derivative by means of sodium (51 g.) in ethanol (850 c.c.); methyl iodide (570 g.) was then added and the mixture refluxed for 10 hr. while further methyl iodide (6 × 50 g.) was introduced at intervals. The usual successive stages (hydrolysis, decarboxylation) afforded 4-ethoxy-2-methylbutyric acid (180 g.), b. p. 131—133°/14 mm., n_D^{20} 1·4261 (Found: C, 57·7; H, 9·6. Calc. for $C_7H_{14}O_3$: C, 57·5; H, 9·65%) (Sutton and Data[1] record b. p. 123—126°/10 mm.). The S-*benzylthiuronium salt* crystallised from water as white flakes, m. p. 129° (Found: C, 57·8; H, 7·5; N, 8·8. $C_{15}H_{24}O_3N_2S$ requires C, 57·7; H, 7·7; N, 9·0%).

The overall yield of the acid, calculated on the starting material, 2-ethoxyethanol, was 43%. In a comparative experiment involving a malonic ester synthesis from 2-ethoxyethyl bromide (prepared from 2-ethoxyethanol according to the directions of Harrison and Diehl[6]) and ethyl methylmalonate as described by Sutton and Data[1] the overall yield (calc. on 2-ethoxyethanol) was 23·5%.

Resolution of γ-Ethoxy-α-methylbutyric Acid.—Preliminary experiments showed that the quinine salt, prepared by dissolving quinine in an ethanolic solution of the acid and evaporating the solution, crystallised on trituration with light petroleum (b. p. 40—60°) at 0°. In attempts to recrystallise the salt from acetone the free base separated from the solution. The salt was very soluble in ethanol and methanol, and finally, the following procedure was adopted.

Quinine (42·2 g.) was added gradually to a solution of the acid (19 g.) in ethyl acetate (100 c.c.), kept at about 40°. The solution was filtered, light petroleum (b. p. 40—60°, 45 c.c.) added to the filtrate, and the mixture left to crystallise. Several batches (in all 150 g.) of the racemic acid were converted into the quinine salt in the same way. The salt was recrystallised by dissolving it in ethyl acetate and adding light petroleum (b. p. 40—60°) until a slight turbidity resulted; the solution was then left to crystallise for at least 24 hr. After five recrystallisations the quinine salt had $[\alpha]_D^{14}$ $-114·2°$ (*c* 1·02 in EtOH), and gave on decomposition with dilute hydrochloric acid the acid with $[\alpha]_D^{13}$ $+13·7°$ (*c* 6·0 in $COMe_2$), $[\alpha]_D^{17}$ $+18·14°$ (homog.). Four further recrystallisations gave quinine salt having $[\alpha]_D^{16}$ $-111·3°$ (*c* 1·08 in EtOH); the regained acid had $[\alpha]_D^{15}$ $+18·6°$ (*c* 3·94 in $COMe_2$), $[\alpha]_D^{26}$ $+21·96°$, $[\alpha]_D^{22}$ $+22·07°$ (homog.). After six further recrystallisations of the quinine salt (when almost optically pure, the salt crystallised as long white feathery needles) the regained acid had $[\alpha]_D^{24}$ $+23·60°$ (homog.) which did not increase upon further recrystallisation of the quinine salt.

The mother-liquors from the first crystallisation of the quinine salt yielded acid having $[\alpha]_D^{16}$ $-6·6°$ (*c* 11·2 in $COMe_2$). The cinchonidine salt of this acid, prepared in ethyl acetate, crystallised when the solution was kept at 0° for several days. Decomposition of the salt gave the partially resolved (−)-acid with $[\alpha]_D^{20}$ $-10·5°$ (*c* 7·4 in $COMe_2$).

In an exploratory experiment with (+)-1-phenylethylamine, obtained by the method of Helferich and Portz,[7] the γ-ethoxy-α-methylbutyrate, prepared in methanol, gave after two recrystallisations from light petroleum (b. p. 40—60°), partially resolved (+)-acid with $[\alpha]_D^{15}$ $+5·4°$ (*c* 7·0 in $COMe_2$).

[3] Woodward, Kohman, and Harris, *J. Amer. Chem. Soc.*, 1941, **63**, 120.

[4] Palomaa and Kenetti, *Ber.*, 1931, **64**, 797.

[5] Prelog and Bozicevic, *Ber.*, 1939, **72**, 1103.

[6] Harrison and Diehl, *Org. Synth.*, Coll. Vol. III, 1955, p. 370.

[7] Helferich and Portz, *Chem. Ber.*, 1953, **86**, 1034.

5-*Ethoxypentan*-2-*one* (II).—This was prepared according to the directions given by Tracy and Elderfield,[8] except that 2-ethoxyethyl iodide (obtained from the toluene-*p*-sulphonate by refluxing with anhydrous sodium iodide in 95% ethanol) was used for the condensation with ethyl acetoacetate. The ketone (63% yield) was an oil, b. p. 168—172° (Tracy and Elderfield [8] give b. p. 169—172°).

Ethyl 2-*Cyano*-6-*ethoxy*-3-*methylhex*-2-*enoate*.—The procedure of Cope *et al.*[9] was followed. 5-Ethoxypentan-2-one (65 g., 0·5 mol.), ethyl cyanoacetate (56·5 g., 0·5 mol.), glacial acetic acid (24 g., 0·2 mol.), ammonium acetate (7·7 g., 0·1 mol.), and benzene (100 c.c.) were refluxed in a flask fitted with a Dean–Stark water-separator for 20 hr. The benzene solution was then washed with water, the washings were re-extracted with benzene, and the combined benzene extracts distilled, to give *ethyl* 2-*cyano*-6-*ethoxy*-3-*methylhex*-2-*enoate* (86 g., 76%), b. p. 150—152°/10 mm., n_D^{20} 1·4682 (Found: C, 63·9; H, 8·3; N, 6·4. $C_{12}H_{19}O_3N$ requires C, 64·0; H, 8·4; N, 6·2%).

Ethyl 2-*Cyano*-6-*ethoxy*-3-*methylhexanoate* (III).—The preceding unsaturated ester (37 g.) in ethanol (60 c.c.) was shaken with 10% palladised charcoal under hydrogen at 5 atm. until absorption ceased (24 hr.). After filtration, the solution was distilled, to give *ethyl* 2-*cyano*-6-*ethoxy*-3-*methylhexanoate*, b. p. 154—155°/10 mm., n_D^{20} 1·4399 (Found: C, 63·2; H, 9·0. $C_{12}H_{21}O_3N$ requires C, 63·4; H, 9·3%).

6-*Ethoxy*-3-*methylhexanonitrile* (IV).—The above saturated cyano-ester (72 g.) was stirred with 5% aqueous sodium hydroxide (600 c.c.) at the room temperature for 2 hr. The solution was acidified (hydrochloric acid) and the cyano-acid isolated by ether-extraction. Decarboxylation by copper powder at 160° for 6 hr., then shortly at 180°, gave the *nitrile* (35 g., crude), b. p. 101—102°/10 mm., n_D^{20} 1·4296 (Found: C, 69·4; H, 11·1. $C_9H_{17}ON$ requires C, 69·7; H, 11·0%).

Ethyl 6-*Ethoxy*-3-*hydroxy*-3-*methylhexanoate* (V).—A solution of ethyl bromoacetate (70 g.) in 1 : 1 benzene–ether (100 c.c.) was added with stirring to a refluxing mixture of granulated zinc (46 g.), 5-ethoxypentan-2-one (100 g.), and 1 : 1 benzene–ether (150 c.c.) during 45 min., and then a further quantity of zinc (41 g.); another portion (70 g.) of ethyl bromoacetate in 1 : 1 benzene–ether (100 c.c.) was introduced during 45 min., and refluxing continued for a further 1·5 hr. Next day the mixture was poured into 10% aqueous sulphuric acid, and the benzene–ether layer washed with aqueous ammonia and water. Distillation of the dried (Na_2SO_4) extract gave the *hydroxy-ester* (75 g.), b. p. 139—142°/16 mm., n_D^{20} 1·4378 (Found: C, 60·2; H, 10·0. $C_{11}H_{22}O_4$ requires C, 60·5; H, 10·1%).

Dehydration of Ethyl 6-*Ethoxy*-3-*hydroxy*-3-*methylhexanoate*.—Thionyl chloride (15 g.) was added during 0·5 hr. to the above hydroxy-ester (19 g.) in dry benzene (19 g.) and pyridine (15·5 g.) while the mixture was cooled and stirred. Next day the mixture was poured into ice-water, and the product isolated by extraction with benzene. Distillation gave the unsaturated *ester* (15 g., 85%), b. p. 114—117°/10 mm., n_D^{20} 1·4469 (Found: C, 65·7; H, 9·9. $C_{11}H_{20}O_3$ requires C, 66·0; H, 10·0%). Light absorption: maxima at 2140 and 2200 Å (ε 7750 and 7000, respectively). Slightly smaller yields resulted when diethylaniline replaced pyridine.

6-*Ethoxy*-3-*methylhexanoic Acid* (VI).—(i) *From* 6-*ethoxy*-3-*methylhexanonitrile*. The nitrile (5 g.), glacial acetic acid (40 c.c.), concentrated sulphuric acid (20 c.c.), and water (16 c.c.) were refluxed for 12 hr. The product was isolated by dilution with water and ether-extraction. Distillation gave 6-*ethoxy*-3-*methylhexanoic acid* (1·2 g., 21%), b. p. 142—144°/10 mm., n_D^{20} 1·4380 (Found: C, 61·8; H, 10·1. $C_9H_{18}O_3$ requires C, 62·1; H, 10·3%).

(ii) *From the dehydrated Reformatsky ester*. The unsaturated ester was refluxed in ethanolic solution with Raney nickel for 2 hr. in order to remove any catalyst poisons. The filtered solution was then hydrogenated over Raney nickel at 75 atm./100° (6 hr.), then distilled, and the product again hydrogenated in ethanol over Raney nickel at 100 atm./100° (5 hr.). On distillation *ethyl* 6-*ethoxy*-3-*methylhexanoate*, b. p. 101°/9 mm., n_D^{20} 1·4274, was obtained (Found: C, 65·2; H, 10·8. $C_{11}H_{22}O_3$ requires C, 65·3; H, 10·9%). This on hydrolysis by refluxing it with 10% aqueous-ethanolic (1 : 2) potassium hydroxide, followed by acidification of the mixture gave the required acid, b. p. 145—146°/9 mm. The S-*benzylthiuronium salt* had m. p. 133·5° after crystallisation from aqueous ethanol (1 : 1) and water (Found: C, 60·0; H, 8·2; N, 8·1. $C_{17}H_{28}O_3N_2S$ requires C, 60·0; H, 8·3; N, 8·2%).

Resolution of 6-*Ethoxy*-3-*methylhexanoic Acid*.—Quinine (49·5 g.) was added gradually to a solution of the (±)-acid (26 g.) in aqueous ethanol (1 : 1; 100 c.c.); the solution was then

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[8] Tracy and Elderfield, *J. Org. Chem.*, 1941, **6**, 63.

[9] Cope, Hofmann, Wyckoff, and Hardenbergh, *J. Amer. Chem. Soc.*, 1941, **63**, 3452.

filtered, and water (*ca.* 40 c.c.) added to the filtrate. The quinine salt which separated was recrystallised eight times from aqueous acetone (2 : 1), then decomposed with hydrochloric acid to yield acid having $[\alpha]_D^{19}$ $+6{\cdot}22°$ (homog.).

The mother-liquors from the first crystallisation of the quinine salt gave acid having $[\alpha]_D^{19}$ $-1{\cdot}5°$ (homog.). This acid (16 g.) and cinchonidine (27 g.) were dissolved in warm aqueous ethanol (1 : 1), then kept at $-10°$ for 48 hr. The salt which crystallised in clusters of long white needles was recrystallised eight times from aqueous ethanol (4 : 3); the solutions were kept at 0° for about 4 days during each crystallisation. Decomposition with 2N-hydrochloric acid gave the (−)-acid with $[\alpha]_D^{19}$ $-6{\cdot}02°$ (homog.).

7-*Ethoxy*-4-*methylheptan*-2-*one* (VII).—6-Ethoxy-3-methylhexanoic acid (5 g.) was converted by means of thionyl chloride into its acid chloride, and the latter caused to react, according to Blaise's procedure,[10] with a solution of methylzinc iodide (from 21 g. of methyl iodide, 20 c.c. of toluene, 4 g. of ethyl acetate, and 18 g. of zinc–copper couple). The mixture was worked up as described earlier for analogous cases.[11] Distillation gave the *ketone* (2·8 g.), b. p. 92—94°/9 mm. (Found: C, 69·4; H, 11·3. $C_{10}H_{20}O_2$ requires C, 69·8; H, 11·6%).

In a resolution experiment, the ketone (2·1 g.) and (−)-menthyloxycarbonylhydrazine (2·6 g.; prepared according to the directions of Woodward *et al.*[3]) were refluxed overnight with sodium acetate (0·06 g.), acetic acid (0·03 g.), and ethanol (3 c.c.). The resulting solid crystallised from acetone as fine needles. Heating with 7% aqueous sulphuric acid (40 c.c.) for 0·5 hr., followed by distillation in steam and ether-extraction of the distillate, gave ketone (0·26 g.) with $[\alpha]_D^{15}$ $-1{\cdot}2°$ (*c* 28·5 in EtOH).

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[*Received, February 6th,* 1957.]

[10] Blaise, *Bull. Soc. chim. France*, 1911, **9**, pp. i—xxvi.

[11] Marks and Polgar, *J.*, 1955, 3851.