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

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The action of methylzinc iodide on the acid chloride of *L*-(+)-(methyl hydrogen β-methylglutarate) † proceeds without racemisation of the half-ester chloride. This is proved by conversion of the resulting keto-ester, *D*-(−)-methyl 3-methyl-5-oxohexanoate (I; R = Me), into *D*-(+)-3-methylhexanoic acid.

The nature of a by-product arising on Clemmensen reduction of the keto-ester is discussed, and evidence is presented which indicates that the by-product is *D*-(+)-3 : 4-dihydro-4 : 6-dimethyl-2-pyrone (II); the latter was obtained by enol-lactonisation of the keto-acid (I; R = H).

A synthesis of *L*-(−)-3-methylhexanoic acid (V) from *L*-(+)-2-methylpent-4-enoic acid (III) *via* *L*-(−)-2-methylpentan-1-ol (IV) is also described.

Previous experiments [1] involving reaction of methylzinc iodide with the acid chloride derived from *L*-(+)-(methyl hydrogen β-methylglutarate) † gave a product for which the structure of *D*-methyl 3-methyl-5-oxohexanoate (I; R = Me) was proposed. In an attempt to convert this product, by Clemmensen reduction, into *D*-(+)-3-methylhexanoic acid, the resulting material, although giving correct analyses for the expected acid, showed a considerably higher $[\alpha]_D$ than previously recorded. A re-investigation of the keto-ester (I; R = Me) and its reduction product was, therefore, necessary.

Repetition of the earlier work [1] to obtain the keto-ester (I; R = Me) gave essentially the same result. Clemmensen reduction of the keto-ester, followed by hydrolysis of the reduced ester, gave a product with $[\alpha]_D$ +9·4°, to be compared with the value +11·05°

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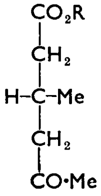
* Part II, preceding paper.

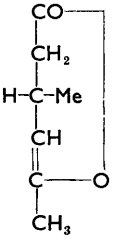
† The symbols *D* and *L* are used in the sense defined by Linstead *et al.* (*J.*, 1950, 3333).

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

found in the earlier work.[1] In further experiments, reduction of the keto-ester by the Huang-Minlon method [2] gave the deoxy-acid with $[\alpha]_D$ +2·4° in agreement with the values previously recorded [3] for 3-methylhexanoic acid. Attention was, therefore, turned to examining the product resulting from the Clemmensen reduction. Its infrared spectrum showed (in CS_2) three bands (1783, 1739, and 1712 cm.$^{-1}$) in the carbonyl region as compared with a single band (1712 cm.$^{-1}$) for the acid obtained by the Huang-Minlon method; the infrared spectrum of the latter was indistinguishable from that of *L*-(—)-3-methylhexanoic acid prepared by the procedure described later. When the product from the Clemmensen reduction was subjected to catalytic hydrogenation, a small quantity of hydrogen was taken up, and the infrared spectrum of the reduced acid showed no difference from that of *L*-(—)-3-methylhexanoic acid. These observations suggested that before the hydrogenation some of the enol lactone (II), possibly arising during the Clemmensen reduction by enol-lactonisation of the keto-acid (I; R = H), might have been present. It is known [4] that enol lactones derived from δ-keto-acids on catalytic hydrogenation readily yield the corresponding saturated deoxy-acids.

For comparison, the enol lactone (II), *D*-3 : 4-dihydro-4 : 6-dimethyl-2-pyrone, was prepared by heating the keto-acid (I; R = H) with acetic anhydride and sodium acetate (cf. ref. 5). It had $[\alpha]_D$ +49·5° and gave on catalytic hydrogenation (+)-3-methylhexanoic acid of $[\alpha]_D$ +2·5°.


(I)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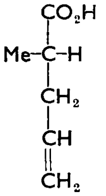
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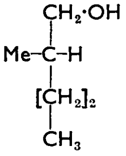
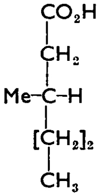

(IV)


(V)

The present results show that the reaction between methylzinc iodide and the acid chloride of optically active methyl hydrogen β-methylglutarate proceeds without racemisation of the ester chloride. Alkylzinc halides are, therefore, in this respect superior to those of alkylcadmium which latter at the requisite higher reaction temperatures have been shown [6] to effect racemisation of the optically active ester chloride owing to rearrangement involving interchange of the ester and acid chloride groups.

In the course of this work *L*-(—)-3-methylhexanoic acid (V) was prepared from *L*-(+)-2-methylpent-4-enoic acid [7] (III). Catalytic hydrogenation gave *L*-(+)-2-methylpentanoic acid which was reduced by means of lithium aluminium hydride to furnish *L*-(—)-2-methylpentan-1-ol (IV). The latter *via* the corresponding iodide and cyanide gave the acid (V) having $[\alpha]_D$ —2·5°.

EXPERIMENTAL

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

D-(—)-*Methyl* 3-*Methyl*-5-*oxohexanoate* (I; R = Me).—Reaction of methylzinc iodide with the acid chloride of *L*-(+)-(methyl hydrogen β-methylglutarate) according to the procedure

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[2] Huang-Minlon, *J. Amer. Chem. Soc.*, 1946, **68**, 2487.

[3] Levene and Marker, *J. Biol. Chem.*, 1931, **91**, 77; Cason and Coad, *J. Amer. Chem. Soc.*, 1950, **72**, 4695; Ställberg-Stenhagen, *Arkiv Kemi*, 1951, **2**, No. 2, and ref. 6.

[4] Jacobs and Scott, *J. Biol. Chem.*, 1930, **87**, 601; 1931, **93**, 139.

[5] Woodward, Sondheimer, Taub, Heusler, and McLamore, *J. Amer. Chem. Soc.*, 1952, **74**, 4223.

[6] Ställberg-Stenhagen, *Arkiv Kemi, Min., Geol.*, 1948, **26**, *A*, No. 12; Chase and Hey, *J.*, 1952, 553.

[7] Ställberg-Stenhagen, *Arkiv Kemi, Min., Geol.*, 1946, **23**, *A*, No. 15.

earlier described [1] gave the keto-ester, b. p. 101°/15 mm., $[\alpha]_D^{16}$ −1·02° (homog.), n_D^{15} 1·4302. Marks and Polgar [1] record b. p. 99°/13 mm., $[\alpha]_D^{16}$ −1·1° (in Et_2O), n_D^{17} 1·4290.

Clemmensen Reduction.—The above keto-ester gave on Clemmensen reduction, followed by hydrolysis with aqueous potassium hydroxide and acidification of the product as described earlier,[1] an oil, $[\alpha]_D^{15}$ +9·4° (*c*, 4·62 in C_6H_6) (Found : C, 65·4; H, 10·8%). When this product (0·3 g.) was shaken in ethanol (12 c.c.) containing a drop of glacial acetic acid and platinic oxide (40 mg.) in hydrogen a small quantity of hydrogen was taken up. Removal of the catalyst and solvent gave 3-methylhexanoic acid, n_D^{21} 1·4214 (Found : C, 64·8; H, 10·4. Calc. for $C_7H_{14}O_2$: C, 64·6; H, 10·8%). The infrared spectrum was indistinguishable from that of the authentic specimen described below.

Huang-Minlon Reduction.—The keto-ester (1·9 g.) was refluxed with triethylene glycol (17 c.c.), 78% aqueous hydrazine hydrate (5·5 c.c.), and potassium hydroxide (1·9 g.) for 2 hr. Water was then boiled off until the temperature of the mixture reached 180° (1½ hr.) and refluxing continued for a further 2 hr. The mixture was acidified with dilute hydrochloric acid, then extracted with ether, and the residue after evaporation refluxed with 10% aqueous potassium hydroxide for 3 hr. Acidification, extraction with ether, and distillation of the extract gave *D*-(+)-3-methylhexanoic acid (1 g.), b. p. 130° (bath) /20 mm., $[\alpha]_D^{19}$ +2·4°(*c* 9·75 in C_6H_6) (Found : C, 64·7; H, 10·6%).

D-(+)-3 : 4-*Dihydro*-4 : 6-*dimethyl*-2-*pyrone* (II).—*D*-3-Methyl-5-oxohexanoic acid (1·5 g.; obtained from the methyl ester by alkaline hydrolysis) was refluxed with acetic anhydride (5 g.) and sodium acetate (4 g.) for 6 hr. Most of the acetic anhydride was then removed and the mixture poured into water. The ethereal extract of the product, after being washed with aqueous sodium carbonate (10%) and water, yielded on distillation D-(+)-3 : 4-*dihydro*-4 : 6-*dimethyl*-2-*pyrone*, b. p. 105° (bath)/20 mm., $[\alpha]_D^{19}$ +49·5° (*c* 3·60 in C_6H_6), n_D^{20} 1·4489 (Found : C, 66·2; H, 7·9. $C_7H_{10}O_2$ requires C, 66·7; H, 7·9%). Catalytic hydrogenation of this enol lactone (0·28 g.) in ethanol (12 c.c.) over platinic oxide (55 mg.), and isolation of the resulting acid in the usual way, gave *D*-(+)-3-methylhexanoic acid, $[\alpha]_D^{18}$ +2·5° (*c* 8·82 in C_6H_6) (Found : C, 64·6; H, 10·8%).

L-(+)-2-*Methylpentanoic Acid.*—*L*-(+)-2-Methylpent-4-enoic acid, obtained according to the directions of Ställberg-Stenhagen,[7] was hydrogenated in ethanol at 5 atm./room temperature in the presence of 5% palladised charcoal, to give *L*-(+)-2-methylpentanoic acid, $[\alpha]_D^{14}$ +18·08° (homog.). Ställberg-Stenhagen [7] gives $[\alpha]_D^{16}$ +18·3°.

L-(−)-2-*Methylpentan*-1-*ol* (IV).—The above acid (5·5 g.) in ether (25 c.c.) was added to a stirred solution of lithium aluminium hydride (1·9 g.) in ether (90 c.c.) during 1·5 hr. at such a rate that the solvent refluxed gently. After a further 0·5 hr., ethyl acetate (10 c.c.) was added, followed by 2N-sulphuric acid. The aqueous phase was extracted with ether, and the combined ethereal extracts were washed with 10% aqueous potassium hydroxide, then with water, and dried (Na_2SO_4). Distillation gave L-(−)-2-*methylpentan*-1-*ol*, b. p. 103°/110 mm., $\alpha_D^{11\cdot5}$ −8·36° (homog.), n_D^{14} 1·4182 (Found : C, 70·4; H, 13·5. $C_6H_{14}O$ requires C, 70·5; H, 13·8%).

L-(−)-3-*Methylhexanoic Acid* (V).—Dry pyridine (4·6 g.) was gradually added with stirring to an ice-cold mixture of *L*-(−)-2-methylpentan-1-ol (2·9 g.) and toluene-*p*-sulphonyl chloride (5·4 g.), and stirring and cooling were continued for 1 hr. The product was acidified with dilute hydrochloric acid, then extracted with ether, and the dried (Na_2SO_4) extract evaporated. The resulting crude toluene-*p*-sulphonate was refluxed with a solution of anhydrous sodium iodide (10 g.) in dry acetone (100 c.c.) for 9 hr. The iodide, isolated in the known manner, was gradually added in ethanol (30 c.c.) to a hot solution of potassium cyanide (3·2 g.) in water (10 c.c.), and the mixture refluxed for 8 hr. The resulting crude cyanide was refluxed with a mixture of concentrated sulphuric acid, acetic acid, and water (10 c.c. each) for 8 hr. The product was poured into water and extracted with ether from which the acidic fraction was removed with 5% aqueous potassium hydroxide. Acidification of the alkaline extract and ether-extraction, followed by distillation, gave *L*-(−)-3-methylhexanoic acid, b. p. 125° (bath)/20 mm., $[\alpha]_D^{16}$ −2·5° (*c* 4·31 in C_6H_6), n_D^{21} 1·4212 (Found : C, 65·0; H, 10·8. Calc. for $C_7H_{14}O_2$: C, 64·6; H, 10·8%).

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