

651. Anodic Syntheses. Part III. Retention of Optical Activity During the Kolbe Reaction.

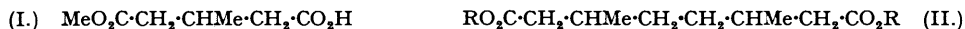
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Application of the Kolbe reaction to the enantiomorphs of a β -substituted acid has been shown to give products in which the configurations of the asymmetric centres have been retained.

Electrolysis of (+)-*L*- and (-)-*D*-methyl hydrogen β -methylglutarate (I) gives (+)- and (-)-methyl $\beta\beta'$ -dimethylsuberates (II; R = Me) respectively, no racemisation being detected. Electrolysis of (\pm)-(I) yields a mixture of *meso*- and (\pm)-diesters (II; R = Me). From these $\beta\beta'$ -dimethylsuberic acid has been obtained in all four forms, (+)-, (-)-, *meso*-, and racemic.

ATTENTION was drawn in Part II (preceding paper) to the value of the Kolbe reaction for the synthesis of branched-chain compounds. With a view to extending this method to the preparation of stereoisomers of known configuration, it was clearly desirable to determine whether anodic coupling of optically active materials could be effected without racemisation of the asymmetric centres.

Wallis and Adams (*J. Amer. Chem. Soc.*, 1933, **55**, 3838) reported a complete loss of activity during the preparation of 3 : 4-dimethylhexane from (-)- α -methylbutyric acid. Racemisation of this kind is not unexpected because the asymmetric carbon atom is directly attached to the carboxyl group eliminated in the reaction. If, for example, a free radical were involved in the process, this would mean a temporary planar distribution at the α -carbon and a loss of activity. However, it seemed likely that activity involving an asymmetric carbon further removed from the carboxyl group would be preserved during a Kolbe reaction. This has now been shown to be true by a study of the electrolysis of the readily available enantiomorphs of methyl hydrogen β -methylglutarate (I). The resolution of this half ester has recently been described in the valuable work of Ställberg-Stenhagen (*Arkiv Kemi, Min., Geol.*, 1948, **25**, A, No. 10), who has also considered the configurational relationship to glyceraldehyde.



When (+)-*L*- and (-)-*D*-(I) were electrolysed in methanol solution, (+)- and (-)-methyl $\beta\beta'$ -dimethylsuberates (II; R = Me) were obtained in 63 and 75% yields respectively and found to possess specific rotations which were numerically identical within the limits of experimental error. That partial racemisation had not occurred in both cases was established by hydrolysis of the two esters to the corresponding crystalline dicarboxylic acids (II; R = H), m. p. 83.5°, which differed only in direction of rotation; no trace of the (\pm)- or *meso*-diacid was detected in either case. On admixture of equal quantities of the (+)- and (-)-diacids, an inactive acid, m. p. 79—79.5°, was obtained. This appears to be a racemic compound, as its m. p. is depressed by admixture with either of the enantiomorphs.

It has been demonstrated previously that electrolysis of a mixture of two acids gives products by both symmetrical and unsymmetrical coupling (see Part I). Since the (\pm)-half ester (I) is an equimolar mixture of the two enantiomorphs, it was expected that on electrolysis it also would give a mixture of products. In this instance, crossed coupling would furnish the *meso*-diester (II; R = Me), whereas symmetrical couplings would give the (+)- and the (-)-diester in equal amounts, *i.e.*, the (\pm)-diester. These conclusions were confirmed by hydrolysing the diester formed in 80% yield on electrolysis of (\pm)-(I), whereupon a mixture of diacids was obtained. By fractional crystallisation of the latter, a pure stereoisomer, m. p. 105°, was isolated. Since the latter differed from the racemic diacid, prepared in the manner described above, it must possess the *meso*-configuration. The products obtained by previous workers

from the electrolysis of various other branched-chain acids and half-esters must be presumed to be mixtures of racemic and *meso*-forms.

Note on Nomenclature.—The various stereoisomerides of fatty acids containing methyl substituents may be *represented* unambiguously by means of Fischer projections along the lines described, for example, by Hudson for the sugar group ("Advances in Carbohydrate Chemistry," Vol. 3, p. 1, New York 1948). The *naming* of such substances with precision is more difficult. In the absence of an agreed convention we give below the method which we propose to follow in the present series of papers. An asymmetric carbon atom bearing a methyl group will be said to belong to the *D*- or *L*-series according to whether the methyl group appears on the right- or the left-hand side of the main carbon chain when the Fischer projection of the molecule is written vertically with the functional group at the top. Where more than one functional group is present, the order of priority will be $-\text{CHO}$, $-\text{CO}_2\text{H}$, $-\text{CO}\cdot\text{Hal}$, $-\text{CO}_2\text{Alkyl}$, $-\text{OH}$, $-\text{Hal}$. Where two identical functional groups are present, that attached to the lowest numbered carbon atom (on the Geneva convention) will take precedence, except when the carbon atoms are designated by Greek letters, in which event the configuration of each asymmetric atom will be referred to the same group as the lettering.

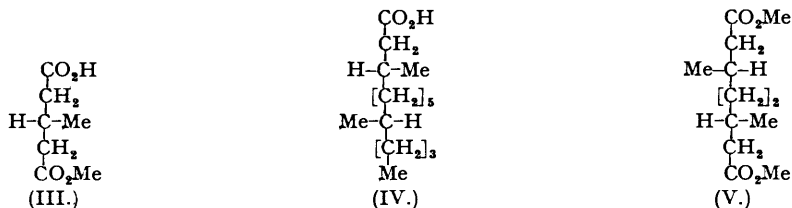
Ställberg-Stenhagen (*loc. cit.*) has related the *lævorotatory* form of methyl hydrogen β -methylglutarate to *D*-glyceraldehyde, and therefore assigned the former to the series which we call *D*. Although this relationship is perhaps not rigidly established, we propose to follow it provisionally and accordingly to represent the *lævorotatory* half-ester as (III). From similar connections with *D*-glyceraldehyde (cf. Ställberg-Stenhagen and Stenhagen, *Arkiv Kemi, Min. Geol.*, 1947, **24**, B, No. 9), the *dextrorotatory* forms of methylsuccinic acid and 2-methylbutanol are also ascribed to the *D*-series.

The following will serve as examples of the proposed nomenclature :

(i) The molecule represented by the Fischer projection (IV) is termed 3(*D*) : 9(*L*)-dimethyltridecanoic acid.

(ii) The *lævorotatory* dimethyl ester (V) formed by anodic coupling of *D*-methyl hydrogen β -methylglutarate (III) is termed methyl 2(*L*) : 5(*D*)-dimethylhexane-1 : 6-dicarboxylate, or alternatively methyl β (*L*) : β' (*L*)-dimethylsuberate.

It is regrettable that this convention leads to an apparent anomaly exemplified in (ii) above : the coupling of two optically *identical* residues yields a molecule which is so named as to imply a *difference* between the two centres. This difficulty is inherent in the use of the Fischer convention and we see no way round it. It must therefore be clearly borne in mind that the



preparation of a substance labelled *D* by coupling of an *L* intermediate does not necessarily imply an inversion : the change in prefix following solely from the conventional alteration of the reference group.

The actual direction of rotation under given experimental conditions is, of course, designated by (+) and (−) in the usual way.

[*Added*, 13.9.50.] Since these papers were submitted for publication, an admirable paper by Ställberg-Stenhagen (*Arkiv Kemi*, 1950, **2**, 95) has come to our notice which covers some of the same ground. This author describes the synthesis of optically active forms of β -methylcarboxylic acids by the electrolysis of mixtures of a fatty acid and an enantiomorphous half-ester of β -methylglutaric acid. The synthesis of the four forms of $\beta\beta'$ -dimethylsuberic acid is described, the results being in close agreement with those now given. The yields reported by the Swedish worker in these symmetrical couplings differ slightly from ours, but those which we have obtained in unsymmetrical couplings (*e.g.*, in the preparation of 3-methylundecanoic acid) are somewhat higher. In view of the similarities in methods and objectives, it seems appropriate to report that we have now effected the anodic syntheses of (+)-3-methylundecanoic acid and (+)-tuberculoostearic acid.

EXPERIMENTAL.

Resolution of Methyl Hydrogen β -Methylglutarate.—As our method differs in some respects from that of Ställberg-Stenhagen (*Arkiv Kemi, Min., Geol.*, 1948, **25**, A, No. 10) the details are given below.

(+)-*L*-Methyl Hydrogen β -Methylglutarate.—Cinchonidine (58.4 g.; 0.2 mol.) was added gradually to a warm solution of the (\pm)-half ester (for preparation see Part II) (31.8 g., 0.2 mol.) in water (320 c.c.) and methanol (45 c.c.). After the addition was complete, the solution was kept at 80° for a further 5 minutes and then filtered. On cooling of the filtrate, the cinchonidine salt of (+)-*L*-methyl hydrogen β -methylglutarate separated, and after recrystallisation once from 4% methanol (*ca.* 280 c.c.) and once from water (200 c.c.), was obtained as long needles (27.6 g.), m. p. *ca.* 89°, $[\alpha]_D^{21.8} - 88.6^\circ$ ($l = 1$; $c = 5\%$ in methanol). The specific rotation remained constant, within the limits of experimental error, on further recrystallisation.

The cinchonidine salt (27.6 g.) was dissolved in warm water (*ca.* 160 c.c.) and, after the solution had been cooled rapidly, the equivalent amount of 2*N*-hydrochloric acid was added. The regenerated half ester was isolated by ether extraction and the ethereal solution was washed with a small volume of water, dried, and evaporated. Distillation of the residue gave (+)-*L*-methyl hydrogen β -methylglutarate (7.0 g., 44%), b. p. 103–104.5°/0.4 mm., $n_D^{20} 1.4380$, $\alpha_D^{17.7} + 0.65^\circ$ (homogeneous; $l = 1$) (*idem, ibid.*, gives $n_D^{20} 1.4389$, $\alpha_D^{20} + 0.64^\circ$).

(-)-*D*-Methyl Hydrogen β -Methylglutarate.—Quinine (40 g., 0.125 mol.) was added gradually to a warm solution of the (\pm)-half ester (20 g., 0.125 mol.) in water (200 c.c.) and methanol (30 c.c.). The resulting solution was filtered and kept at 0° for 2–3 days during which the quinine salt separated. The salt was recrystallised once from 5% methanol (160 c.c.) and then once from water (140 c.c.), giving long needles (28.3 g.), m. p. 79.5–80°, $[\alpha]_D^{18} - 128.3^\circ$ ($l = 1$; $c = 2\%$ in methanol). The m. p. and specific rotation were unaltered by further recrystallisation.

Regeneration of the half-ester in the manner described above for the cinchonidine salt gave (-)-*D*-methyl hydrogen β -methylglutarate (3.75 g., 37.5%), b. p. 94°/0.07 mm., $n_D^{20} 1.4385$, $\alpha_D^{18.8} - 0.63^\circ$ (homogeneous; $l = 1$) (*idem, ibid.*, gives $n_D^{20} 1.4387$, $\alpha_D^{20} - 0.64^\circ$).

Methyl $\beta\beta'$ -Dimethylsuberate (II; R = Me).—Methyl hydrogen β -methylglutarate (35 g., 0.22 mol.) was added to a solution of sodium (0.57 g., 0.025 mol.) in methanol (90 c.c.) and water (10 c.c.). The resulting solution was cooled in an ice-bath and electrolysed using a platinum plate as cathode, a spiral of platinum wire (3.52 sq. cm. surface area) as anode, and a current of 2.0 amps. When the electrolyte became slightly alkaline (210 minutes), the electrolysis was interrupted and concentrated sulphuric acid (1.22 g.) added to the cell contents which were then filtered and evaporated under reduced pressure until most of the solvent had been removed. Ether was added to the residue, and the ethereal solution was washed with sodium hydrogen carbonate solution, then with water, dried, and evaporated. Distillation of the residue gave methyl $\beta\beta'$ -dimethylsuberate (18.4 g., 80%), b. p. 101.5–102.5°/0.6 mm., $n_D^{18.5} 1.4376$ (Hunsdiecker, *Ber.*, 1942, 75, 1197, gives b. p. 115°/1.5 mm.) (Found: C, 62.8; H, 9.7. Calc. for $C_{12}H_{22}O_4$: C, 62.6; H, 9.65%).

meso- $\beta\beta'$ -Dimethylsuberic Acid.—A mixture of the preceding ester (34.7 g.), sodium hydroxide (28 g.), and water (90 c.c.) was heated under reflux with vigorous stirring until a homogeneous solution was obtained. The aqueous solution was acidified with concentrated hydrochloric acid and the precipitated mixture of stereoisomeric acids, m. p. 90–92°, was separated (28 g., 91%). By fractional crystallisation of the mixture from 25% methanol, meso- $\beta\beta'$ -dimethylsuberic acid (5.6 g.) was isolated as needles, m. p. 105° (Found: C, 59.4; H, 9.0. $C_{10}H_{18}O_4$ requires C, 59.4; H, 8.95%).

Methyl (+)- $\beta(D)$: $\beta'(D)$ -Dimethylsuberate.—Electrolysis of (+) *L*-methyl hydrogen β -methylglutarate (5.04 g., 0.032 mol.) in 90% methanol (18 c.c.), to which sodium (0.08 g., 0.0035 mol.) had been added, by the method described above for the racemic compound gave methyl (+)- $\beta(D)$: $\beta'(D)$ -dimethylsuberate (2.05 g., 63%), b. p. 93–94°/0.03 mm., $n_D^{19} 1.4370$, $\alpha_D^{17.9} + 9.98^\circ$ (homogeneous; $l = 1$) (Found: C, 62.3; H, 9.7. $C_{12}H_{22}O_4$ requires C, 62.6; H, 9.65%).

(+)- $\beta(D)$: $\beta'(D)$ -Dimethylsuberic Acid.—Hydrolysis of the preceding ester (1.9 g.) with 20% aqueous sodium hydroxide (15 c.c.) in the usual way gave, on acidification, (+)- $\beta(D)$: $\beta'(D)$ -dimethylsuberic acid, which after one crystallisation from water was obtained as needles (1.0 g., 60%), m. p. 83.5°, $[\alpha]_D^{19.4} + 13.1$ (dioxan; $l = 1$; $c = 5\%$) (Found: C, 59.1; H, 8.8. $C_{10}H_{18}O_4$ requires C, 59.4; H, 8.95%).

Methyl (-)- $\beta(L)$: $\beta'(L)$ -Dimethylsuberate.—A solution of (-)-*D*-methyl hydrogen β -methylglutarate (6.84 g., 0.043 mol.) in technical absolute methanol (35 c.c.) containing sodium methoxide (from sodium, 0.02 g., 0.00087 mol.) was cooled and electrolysed for 70 minutes with a current of 1.4 amps. The electrodes consisted of two square platinum plates (2.5 cm. \times 2.5 cm.) placed *ca.* 1.5 mm. apart. Isolation of the product in the usual way gave methyl (-)- $\beta(L)$: $\beta'(L)$ -dimethylsuberate (3.5 g., 75%), b. p. 140°/12 mm., $n_D^{22.5} 1.4360$, $\alpha_D^{19.4} - 9.94^\circ$ (homogeneous; $l = 1$) (Found: C, 62.6; H, 9.55. $C_{12}H_{22}O_4$ requires C, 62.6; H, 9.65%).

(-)- $\beta(L)$: $\beta'(L)$ -Dimethylsuberic Acid.—Hydrolysis of the preceding ester (2.0 g.) in the usual manner gave (-)- $\beta(L)$: $\beta'(L)$ -dimethylsuberic acid, which crystallised from water in needles (1.25 g.), m. p. 83.5–83.7°, $[\alpha]_D^{19.6} - 13.2^\circ$ ($l = 1$; $c = 5\%$ in dioxan) (Found: C, 59.7; H, 9.0. $C_{10}H_{18}O_4$ requires C, 59.4; H, 8.95%).

Racemic $\beta\beta'$ -Dimethylsuberic Acid.—On admixture of equal amounts of the two enantiomorphs described above and crystallisation of the mixture from water, the racemic diacid was obtained as needles, m. p. 79–79.5° depressed on admixture with small amounts of either of the two optically active components.

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