*The Absolute Configuration of α-Methyladipic Acid**

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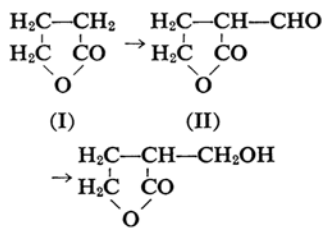
Recently, determinations of the stereostructures of terpenoids, alkaloids and antibiotics have become important. In order to obtain clear sterostructures of key-substances, absolute configurations of a few compounds containing branched alkyl groups have been determined[1]. The absolute configuration of α-methyladipic acid, obtained as an oxidation product of an alkaloid nupharidine[2], has however, never been determined. The present paper deals with the chemical determination of the absolute configuration of α-methyladipic acid by the establishment of the configurational correlation between this acid and methylsuccinic acid, the absolute configuration of which is already known[3].



(I) (II) (III)

α-Formyl-γ-butyrolactone (II) was synthesized from γ-butyrolactone (I) by the modified methods described by Korte[4] and McGraw[5]. DL-α-Hydroxymethyl-γ-butyrolactone (III) was obtained from formyl derivative II in a high

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1) Cf. K. Freudenberg, "Stereochemie", Franz Deutcke, Leipzig (1933), p. 679; W. Klyne, "Progress in Stereochemistry", Vol. I, Butterworths Scientific Publication, London (1954), p. 188.

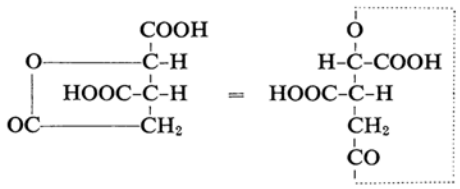
2) M. Kotake, S. Kusumoto and T. Ohara, *Ann.*, **606**, 148 (1957).

3) A. Fregda, *The Svedberg-Festschrift, Uppsala*, **1944**, 261; *Acta Chem. Scand.*, **1**, 371 (1944).

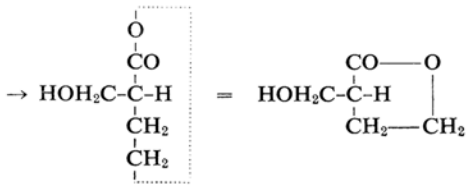
4) F. Korte and H. Machleidt, *Chem. Ber.*, **88**, 136, 1684 (1955).

5) Wm. J. McGraw, U. S. Pat. 2624723 (1953); *Chem. Abstr.*, **47**, 11232g (1953).

yield by catalytic reduction according to the method of McGraw[5]. An optical resolution of hydroxymethylbutyrolactone (III) was attempted, but no optically pure substances were obtained. Then, optically active (+)-α-hydroxymethyl-γ-butyrolactone (+III) ([α]$_D$+10.4°) was prepared from (+)-alloisocitric lactone

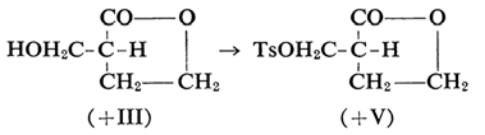


(+IV)

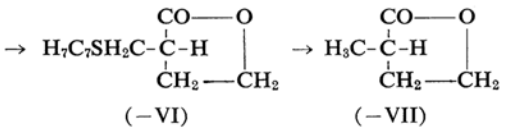


(+III)

(+IV) by the methods described earlier[6]. (−)-Benzyl thioether (−VI), which was derived from the (+)-tosylate (+V) of +III by the action of benzylmercaptan, was converted into (−)-α-methyl-γ-butyrolactone([α]$_D$ −0.2° (*c* 23,



(+III) (+V)

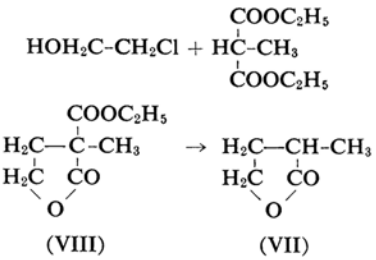


(−VI) (−VII)

Ts=*p*-CH_3-C_6H_4-SO_2-

C_7H_7=C_6H_5-CH_2-

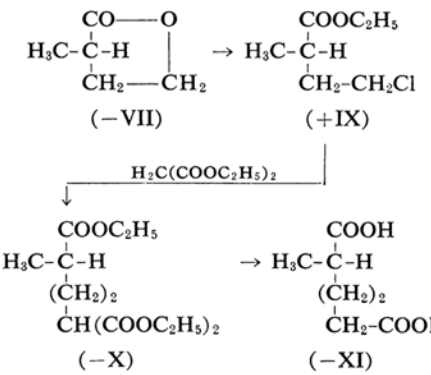
l=2 dm., absolute ethanol))(−VII) by treatment with a Raney-nickel catalyst. In another



(VIII) (VII)

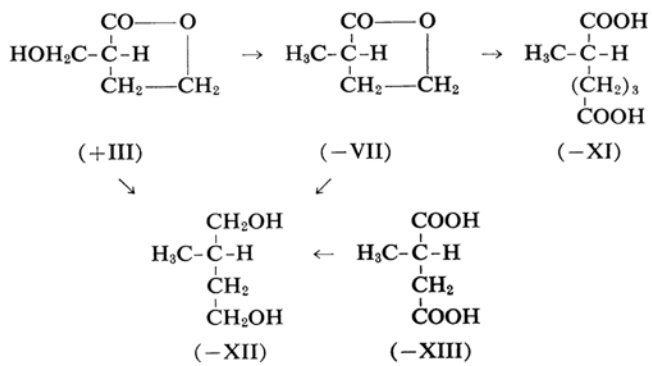
way, DL-α-methyl-γ-butyrolactone (VII) was synthesized from lactone-ester VIII, the condensation product of diethyl methylmalonate with ethylene chlorohydrin, by hydrolysis followed by decarboxylation. Its enatiomers were obtained in an almost optically pure state([α]$_D$ −21.5°, +11.9°) by methods of optical resolution.

Optically active α-methyladipic acid([α]$_D$ −1.4°)(−XV) was obtained by means of saponification and decarboxylation of triester −X, which was formed by condensation of diethyl malonate with ethyl (+)-γ-chloro-α-methylbutyrate (+IX), derived from (−)-α-methyl-γ-butyrolactone ([α]$_D$−21.5°)(−VII).



(−VII) (+IX) (−X) (−XI)

As the correlations of (+)-α-hydroxymethyl-γ-butyrolactone (+III) and (−)-2-methyl-1, 4-butanediol (−XII) with L$_a$-(−)-methylsuccinic acid (−XIII) have previously been shown by



(+III) (−VII) (−XI) (−XII) (−XIII)

6) T. Kaneko, H. Katsura, H. Asano and K. Wakabayashi, *Chem. & Ind.*, **1960**, 1187; H. Katsura, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zasshi*), **82**, 91 (1961).

us[6], it is clear that the configuration of (−)-α-methyl-γ-butyrolactone (−VII) is the same as that of L$_a$-(−)-methylsuccinic acid (−XIII) and is to be represented by L$_a$ or s.

Because the absolute value of the optical rotation of the (−)-α-methyl-γ-butyrolactone-(−VII) obtained from (+)-α-hydroxymethyl-γ-butyrolactone (+III) was small, (−)-2-methyl-1, 4-butanediol (−XII) was derived from (−)-α-methyl-γ-butyrolactone (−VII) obtained by resolution, using lithium aluminum hydride reduction to confirm the latter configuration. From the above results, it was concluded that (−)-α-methyl-γ-butyrolactone has the s-configuration, or belongs to the L$_a$-series, while (+)-α-methyl-γ-butyrolactone has the R-configuration, or belongs to the D$_a$-series, as (−)-2-methyl-1, 4-butanediol (−XII) is related to L$_a$-(−)-methylsuccinic acid (−XIII). (−)-α-Methyladipic acid had the s-configuration (L$_a$-series), as it is related to L$_a$-(−)-α-methyl-γ-butyrolactone, while (+)-α-methyladipic acid has the R-configuration (D$_a$-series).

Experimental

DL-α-Hydroxymethyl-γ-butyrolactone (III).—To prepare α-formyl-γ-butyrolactone (II), γ-butyrolactone (I) was condensed with ethyl formate, as described by Korte[4], except that the extraction of the reaction mixture with ethyl acetate instead of with ether was employed.

Yield, 55%; b. p., 93～100°C/3 mmHg (lit., b. p. 68°C/0.03 mmHg[4], 83～85°C/1 mmHg[5]).

This formyl derivative was reduced with a Raney-nickel catalyst to give III, following the procedures of McGraw[5]:

Yield, 76%; b. p. 105～112°C/1 mmHg. Found: C, 52.02; H, 6.98. Calcd. for $C_5H_8O_3$: C, 51.72; H, 6.94%.

Resolution of α-Hydroxymethyl-γ-butyrolactone (III).—To a solution of 18.0 g. of barium hydroxide octahydrate in 100 ml. of water, 11.6 g. of DL-α-hydroxymethyl-γ-butyrolactone (III) was added, and the solution was heated to 90°C over a 2-hr. period. After the solution had cooled, 10% sulfuric acid was added, and the precipitated barium sulfate was removed by filtration. To the filtrate, 36.0 g. of quinine was added, and the mixture was heated at 90°C to make a clear solution. After standing over night, the solution was concentrated under reduced pressure, and the residue was recrystallized from acetone-methanol six to ten times. From a purified, less soluble quinine salt, optically impure α-hydroxymethyl-γ-butyrolactone (yield 0.5 g., b. p. 105～107°C/1 mmHg, $[\alpha]_D^{14}$ −4.1° (*c* 12.2, ethanol)) was obtained, while the maximum value of its specific rotation was +10.4°.

(+)-α-Hydroxymethyl-γ-butyrolactone (+III).—It was obtained from (+)-alloisocitric lactone (+IV), as has been previously described[6].

Yield, 19%; b. p., 103～107°C/0.5～1 mmHg, $[\alpha]_D$ +10.4° (*c* 5.6, ethanol). Found: C, 51.83; H, 6.94. Calcd. for $C_5H_8C_3$: C, 51.72; H, 6.94%.

Tosylate (V) of α-Hydroxymethyl-γ-butyrolactone (III).—To an ice-cold solution of 11.9 g. of DL-α-hydroxymethyl-γ-butyrolactone (III) in 5 ml. of anhydrous pyridine, a solution of 21.5 g. *p*-toluenesulfonyl chloride in 45 ml. of anhydrous pyridine was added drop by drop during the course of 30 min., and the solution was then stirred continuously in an ice bath for another 3 hr. The reaction mixture was stirred into 3 N hydrochloric acid containing ice, and the separated crystalline substances were recrystallized from 94% ethanol.

Yield, 16 g. (60%); m. p., 86°C. Found: C, 53.26; H, 5.27; S, 11.53. Calcd. for $C_{12}H_{14}O_5S$: C, 53.32; H, 5.22; S, 11.86%.

From 7.0 g. of (+)-α-hydroxymethyl-γ-butyrolactone ($[\alpha]_D$+10.4°), (+)-tosylate (+V) was obtained in the manner described above.

Yield, 8.9 g. (54.6%); m. p., 97°C, $[\alpha]_D^{19}$ +3.0° (*c* 3.6, acetone). Found: C, 53.52; H, 5.16; S, 11.81%.

α-Benzylthiomethyl-γ-butyrolactone (VI).—To a boiling sodium ethoxide solution (4.2 g. of metallic sodium in 100 ml. of absolute ethanol), 22.0 g. of benzylmercaptan was added drop by drop over a half-hour period, and to this mixture, a solution of DL-tosylate (V) in 250 ml. of hot absolute ethanol was added at once. Crystals of sodium *p*-toluenesulfonate began to separate immediately. After the reaction mixture had been heated and stirred for 3 hr., the crystals were removed by filtration and the filtrate was evaporated under reduced pressure. The residue obtained was dissolved in water, and after acidifying with concentrated hydrochloric acid, the solution was extracted with benzene. After the benzene layer had been dried and the solvent removed by distillation, the residue was distilled to give DL-benzylthiomethyl-γ-butyrolactone.

Yield, 12.9 g. (58%); b. p., 145～152°C/1 mmHg. Found: C, 64.95; H, 6.29. Calcd. for $C_{12}H_{14}O_2S$: C, 64.85; H, 6.35%.

From 8.9 g. of (+)-tosylate (+V), (−)-benzyl thioether (Yield, 4.4 g. (59.4%); b. p., 163°C/0.05 mmHg, $[\alpha]_D$−0.46° (*c* 8.0, benzene)) (−VI) was obtained in the manner described above.

Found: C, 65.28; H, 6.46; S, 14.21. Calcd. for $C_{12}H_{14}O_2S$: C, 64.85; H, 6.35; S, 14.42%.

α-Methyl-γ-butyrolactone (VII) from Benzyl Thioether (VI).—To a solution of 12.9 g. of benzyl thioether (VI) in 400 ml. of absolute ethanol, Raney-nickel (developed from 100 g. of alloy) was added and refluxed for 12 hr. The insoluble materials were removed by centrifugation, and the alcohol was removed carefully by rectification using a 50 cm. column. DL-α-Methyl-γ-butyrolactone (yield, 2.5 g. (55%); b. p., 92.5°C/20 mmHg) (VII) was obtained on distillation of the residual oil.

Found: C, 60.21; H, 7.96. Calcd. for $C_5H_8O_2$: C, 59.98; H, 8.05%.

From 4.4 g. of (−)-benzyl thioether (−VI), (−)-α-methyl-γ-butyrolactone (b. p., 94～95°C/20 mmHg, $[\alpha]_D^{19}$ −0.2° (*c* 23, l=2 dm., absolute ethanol)) (−VII) was obtained in the manner described above.

Found: C, 60.45; H, 8.28%.

DL-α-Methyl-γ-butyrolactone (VII) from Diethyl Methylmalonate.—To a warm sodium ethoxide

solution (50°C) (9.5 g. of sodium in 120 ml. of absolute ethanol), 140 g. of diethyl methylmalonate was added drop by drop; the solution was then heated under reflux for 30 min. To this solution, 32 g. of ethylene chlorohydrin was added drop by drop and after the solution had been refluxed for 3 hr., the ethanol was removed by distillation. The residue was dissolved in water and extracted with ether. After the solvent was removed by distillation from the extract, α-carbethoxy-α-methyl-β-butyrolactone (yield, 43.5 g. (63.3%); b. p., 130~131°C/10 mmHg) (VIII) was obtained by fractional distillation of the residue.

Found: C, 55.74; H, 7.07. Calcd. for $C_8H_{12}O_4$: C, 55.80; H, 7.03%.

A mixture of 33 g. of this ester VIII and 350 ml. of 3 N hydrochoric acid was refluxed for about 20 hr. until hydrolysis and decarboxylation were complete. The reaction mixture was evaporated under reduced pressure, and the residue was dissolved in ether. After the ether extract had been dried over anhydrous sodium sulfate and the solvent removed, DL-α-methyl-γ-butyrolactone (yield, 13.1 g. (70%); b. p., 95~98°C/21mm Hg) (VII) was obtained by distillation of the residue.

Found: C, 59.77; H, 8.29. Calcd. for $C_5H_8O_2$: C, 59.98; H, 8.05%.

Optical Resolution of DL-α-Methyl-γ-butyrolactone (VII).—To a solution of 15 g. of barium hydroxide octahydrate in 100 ml. of water, 8.4 g. of DL-α-methyl-γ-butyrolactone was added. After the solution had been heated at 90°C for 2 hr., it was neutralized by the addition of 10% sulfuric acid; the barium sulfate precipitated was removed by filtration. To this filtrate, 35 g. of quinine was added; it was then heated at 90°C until dissolution was complete. After standing overnight, the reaction mixture was evaporated under reduced pressure, and the residue was dissolved in 85 ml. of acetone. After the solution had stood overnight in a refrigerator, the less soluble quinine salt precipitated was collected and recrystallized 3 times from acetone-methanol (9 : 1). (−)-α-Methyl-γ-butyrolactone (yield, 1.5 g.; b. p., 92.5°C/20 mmHg, $[\alpha]_D^{15}$ −21.5°C (*c* 5.5, absolute ethanol)) was obtained from this purified, less soluble quinine salt by the usual manner.

Found: C, 59.69; H, 7.98. Calcd. for $C_5H_8O_2$: C, 59.98; H, 8.05%.

From the mother liquor, after removing less soluble salt, (+)-α-methyl-γ-butyrolactone (yield, 1.2 g.; b. p., 93~95°C/22 mmHg, $[\alpha]_D^{15}$ +11.9° (*c* 6.9, absolute ethanol)) was obtained.

Ethyl γ-Chloro-α-methylbutyrate (IX).—A solution of 20 g. of DL-α-methyl-γ-butyrolactone (VII) in 150 ml. of absolute ethanol was saturated with dry hydrogen chloride under cooling with ice-water. After standing for 48 hr., the reaction mixture was poured into ice-water to give an oily layer, which was separated. The aqueous layer was extracted with chloroform. The oily layer and the chloroform extract were then combined, washed with water and aqueous sodium hydrogen carbonate solution, and dried over anhydrous sodium sulfate. After the solvent was removed, ethyl DL-γ-chloro-α-methylbutyrate (yield, 29.5 g. (90%); b. p., 92~95°C/25 mmHg) was obtained by means of fractional distillation of the residual oil under reduced pressure.

Found: C, 50.93; H, 7.82. Calcd. for $C_7H_{13}O_2Cl$: C, 51.06; H, 7.96%.

From 1.5 g. of (−)-α-methyl-γbutyrolactone ($[\alpha]_D$ −21.5°), ethyl (+)-γ-chloro-α-methylbutyrate (yield, 1.9 g. (77%); b. p., 90.7°C/23 mmHg, $[\alpha]_D^{15}$ +26.7° (*c* 14.9, absolute ethanol)) was obtained in the manner described above.

Found: C, 50.98; H, 7.80%.

Diethyl α-Methyl-α'-carbethoxyadipate (X).—Seventy three milliliters of absolute ethanol, 1.8 g. of sodium and 3.1 g. of sodium iodide were dissolved. Into this solution, 21.0 g. ethyl malonate was stirred at 80°C, and the mixture was refluxed for 30 min. To the reaction mixture 11.0 g. of ethyl DL-γ-chloro-α-methylbutyrate was added over a 1 hr. period, and the solution was refluxed for 20 hr. After reaction had ceased, the solvent was removed by distillation in vacuo, and the residue was acidified by the addition of 5 ml. of glacial acetic acid. After water was added to the mixture, the solution was extracted with benzene; the extract was washed with water and aqueous sodium hydrogen carbonate solution, and then dried with anhydrous magnesium sulfate. After the solvent was removed, diethyl DL-α-methyl-α'-carbethoxyadipate (yield, 11.3 g. (60%); b. p. 111~114°C/1 mmHg) (X) was obtained on distillation of the oily residue.

Found: C, 58.32; H, 8.44. Calcd. for $C_{14}H_{24}O_6$: C, 58.31; H, 8.39%.

From 1.9 g. of ethyl (+)-γ-chloro-α-methylbutyrate ($[\alpha]_D$ +26.7°C), diethyl (−)-α-methyl-α'-carbethoxyadipate (yield, 2.0 g. (60.6%); b. p., 115~116°C/1 mmHg, $[\alpha]_D^{15}$ −0.64° (*c* 11, ethanol)) was obtained in the manner described above.

Found: C, 58.37; H, 8.25%.

α-Methyladipic Acid (XI).—A mixture of 38.7 g. of ethyl DL-α-methyl-α'-carbethoxyadipate (X) and 400 ml. of 3 N hydrochloric acid was refluxed for 18 hr. After hydrolysis and decarboxylation were ended, the reaction mixture was treated with active charcoal and condensed under reduced pressure. On distillation of the residue in vacuo, a fraction, b. p., 150~155°C/1 mmHg, was obtained, which formed waxy crystals immediately. It was recrystallized from benzene, m. p., 59~60°C. This sample showed no depression of melting point on admixture with an authentic sample and its infrared spectra were identical with that of the authentic sample.

From 1.9 g. of diethyl (−)-α-methyl-α'-carbethoxyadipate ($[\alpha]_D$ −0.64°), (−)-α-methyladipic acid (m. p. 53~54°C, $[\alpha]_D$ −1.4° (*c* 4, ethanol)) was obtained in the manner described above.

Found: C, 52.07; H, 7.51. Calcd. for $C_7H_{12}O_4$: C, 52.49; H, 7.55%.

2-Methyl-1, 4-butanediol (XII) from α-Methyl-γ-butyrolactone (VII) via its Acetate.—DL-2-Methyl-1, 4-diacetoxybutane (b. p. 115~117°C/16 mmHg) was obtained from 5 g. of DL-α-methyl-γ-butyrolactone (VII) by lithium aluminum hydride reduction, followed by acetylation with acetic anhydride.

Yield, 3.0 g. (32%). Found: C, 57.22; H, 8.53. Calcd. for $C_9H_{16}O_4$: C, 57.43; H, 8.57%.

The diacetate (2.2 g.) was hydrolyzed with barium hydroxide to give 2-methyl-1, 4-butanediol (b. p., 112°C/6 mmHg). Yield, 0.8 g. (77%).

From 2.2 g. of (+)-α-methyl-γ-butyrolactone ($[\alpha]_D$ +11.9°), (+)-2-methyl-1, 4-diacetoxybutane (yield, 1.0 g.; b. p., 118°C/15 mmHg, $[\alpha]_D^{15}$ +0.41°(*c* 21, acetone)) was obtained.

Found: C, 57.21; H, 8.69. Calcd. for $C_9H_{16}O_4$: C, 57.43; H, 8.57%.

The above (+)-diacetate gave (+)-2-methyl-1, 4-butanediol ($[\alpha]_D^{17}$ +2.3°(*c* 4.2, acetone)) in the manner described above.

(−)-2-Methyl-1, 4-butanediol (−XII) from (−)-α-Methyl-γ-butyrolactone (−VII) by Means of Ether Extraction.—To a suspended mixture of 0.5 g. of lithium aluminum hydride in 25 ml. of absolute ether, a solution of 1.2 g. of (−)-α-methyl-γ-butyrolactone ($[\alpha]_D$−7.5°) in 15 ml. of absolute ether was added and refluxed for 3 hr. The reaction mixture was decomposed by the addition of water, acidified with 10% sulfuric acid, and extracted repeatedly with ether. The extract was washed with an aqueous sodium hydrogen carbonate solution and dried over anhydrous magnesium sulfate. After the solvent had been removed, the residual oil was distilled under reduced pressure.

Yield, 0.5 g.; b. p., 110~112°C/6 mmHg, $[\alpha]_D^{14}$ −2.1°(*c* 10, acetone). Diphenylurethane, m. p., 123°C. Found: C, 66.55; H, 6.47; N, 8.20. Calcd. for $C_{19}H_{22}O_4N_2$: C, 66.65; H, 6.48; N, 8.18%.

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