Correlation of α-Asymmetric Carbon Atom of α-Methylglutaric Acid to Methyladipic Acid: a Correction

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(Received January 11, 1968)

Previously, Kaneko *et al.* reported that (−)-α-methyladipic acid is considered to have the S-configuration on the basis of its synthesis from (−)-α-methyl-γ-butyrolactone, which configuration was correlated with S(−)-methylsuccinic acid.[1] Recently, however, Turner *et al.* showed that (−)-α-methyladipic acid must have the R-configuration because R(−)-α-methylglutaric acid, R(+)-β-methyladipic acid and (−)-α-methyladipic acid were isolated from the oxidation products of cytochalasin A and B, metabolites of *Helminthosporium dematioideum*.[2]

In order to confirm the configuration by an unequivocal process, the stereochemical relation between methyladipic acid and α-methylglutaric acid, absolute configuration of which was already known,[3] was established directly by the Arndt-Eistert synthesis of optically active α- and β-methyladipic acid from the ester chloride of α-methylglutaric acid. Treatment of S(+)-α-methylglutaric anhydride with methanol and then with thionyl chloride afforded the methyl ester chloride, which gave diazoketones with the treatment of ethereal diazomethane. The diazoketones were rearranged with silver benzoate as a catalyst in methanol to give a mixture of α- and β-methyladipic ester, which were separated into (+)-α- and S(−)-β-methyladipic ester[4] by vapor phase chromatography.

It is evident, therefore, (−)-α-methyladipic acid should have R-configuration as pointed out by Turner *et al.* The incorrect assignment presented in our previous paper was probably due to the very small optical rotation of α-methyladipic acid, decreased by the racemization occurred at the condensation of optical active ethyl γ-chloro-α-methylbutyrate with diethyl malonate.

Experimental

S(+)-α-Methylglutaric Acid. This compound was obtained by the resolution with the aid of strychnine,[5] mp 81°C; $[\alpha]_D^{15}$ +22.3° (*c*, 5.38 in abs EtOH).

S(+)-α-Methylglutaric Anhydride. (+)-α-Methylglutaric acid (4.3 g) afforded 3.4 g of the anhydride (93%), bp 112—114°C/2 mmHg, mp 56°C.[5]

Methyl Hydrogen α-Methylglutarate. To the above anhydride (3.4 g) was added methanol (0.9 g). The solution was heated on the water bath for 30 min and then distilled at 93—103°C/1 mmHg to give 4.1 g of the half ester (94%).

Methyl Ester Chloride of α-Methylglutaric Acid. A mixture of above half ester (4.1 g) and thionyl chloride (12 m*l*) was warmed at 50°C for 30 min and then distilled at 110—114°C/20 mmHg to give 3.6 g of the ester chloride (79%).

Dimethyl Methyladipate. The ester chloride (3.6 g) was converted into the diazoketone by means of diazomethane in ether solution. After standing for 3 hr, excess diazomethane and ether was removed. The residue was dissolved in absolute methanol (30 m*l*) and a mixture of silver benzoate (0.5 g) and trimethylamine (4.5 m*l*) was added to the solution with stirring. After a gentle evolution of gas a vigorous reaction occurred. The mixture was heated under reflux for 30 min. The catalyst was then filtered off, and the filtrate was evaporated. After the residue was dissolved in ether, the solution was washed with sodium carbonate solution and dried. The solvent was removed and the residual oil was distilled at 65—73°C/0.1 mmHg; yield, 2.95 g (79% from the ester chloride).

Separation of α- and β-Methyladipic Ester. The mixture of above ester was separated into dimethyl α- and β-methyladipate by vapor phase chromatography in a Varian Aerograph Model A-700 using a column (3/8 inch × 20 ft aluminum column) packed with 20% carbowax 20 M on chromosorb W with a helium as carrier gas at 200°C.

First fraction gave dimethyl (+)-α-methyladipate which was identical with authentic specimen in IR spectra; $[\alpha]_D^{23}$ +13.5° (*c*, 1.48 in EtOH), NMR; 1.12 ppm (doublet J=7 cps). From which (+)-α-methyladipic acid was obtained by acid hydrolysis and recrystallised from benzene, mp 81—83°C; $[\alpha]_D^{23}$ +13.8° (*c*, 1.91 in EtOH).

Found: C, 52.62; H, 7.57%. Calcd for $C_7H_{12}O_4$: C, 52.49; H, 7.55%.

Second fraction gave dimethyl (−)-β-methyladipate which was identical with authentic specimen in IR spectra; $[\alpha]_D^{23}$ −2.5° (*c*, 1.18 in EtOH), NMR; 0.95 ppm (doublet J=6 cps). From which (−)-β-methyladipic acid was obtained by acid hydrolysis and recrystallised from benzene, mp 86—87°C; $[\alpha]_D^{23}$ −3.4° (*c*, 2.75 in EtOH).

Found: C, 52.60; H, 7.51%.

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