[Contribution from the Chemical Laboratories of the Johns Hopkins University]

A DIRECT SYNTHESIS OF γ,γ-DIMETHYLPIMELIC ACID

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The literature contains two descriptions of the synthesis of γ,γ-dimethylpimelic acid, both utilizing essentially the same procedure. In the first of these (1), β,β-dimethylglutarimide was reduced by means of sodium and alcohol to form 4,4-dimethylpiperidine. The latter, on treatment with benzyl chloride and phosphorus pentachloride presumably yielded 3,3-dimethyl-1,5-dichloropentane. The dichloropentane was then converted to the dinitrile, hydrolysis of which furnished the alleged γ,γ-dimethylpimelic acid.

The second synthesis (2) utilized the oxidation of dimethyldihydroresorcinol (3) to prepare β,β-dimethylglutaric acid. This was then reduced catalytically under high pressure to the corresponding diol, and the diol was converted to the dichloropentane. The remaining steps duplicated those described above. It is noteworthy, however, that there are several inconsistencies in these two syntheses. Thus, Komppa (3) described his dichloropentane as a liquid of boiling point 108° at 80 mm.,[2] and his pentanedinitrile as a solid of melting point 123°. These compounds, however, are respectively described by Miller and Adams (2) as liquids of boiling points 135° at 80 mm., and 155–157° at 7 mm. A direct comparison at the pimelic acid stage is not possible since Miller and Adams prepared the ethyl ester directly from the dinitrile. Komppa reported his acid to melt at 83°, but did not prepare the ester.

Our synthesis, which was used to prepare the dimethylpimelic acid in quantity, begins with Guareschi's imide[2a] (4, 5) which was hydrolyzed to β,β-dimethylglutaric acid. The glutaric acid was reduced, either directly or as its ester, to the diol with lithium aluminum hydride (6). Since our diol had a boiling point 40° below the reported value (2), it was necessary to prove its structure. This was done by oxidation with a chromic acid mixture, forming the original β,β-dimethylglutaric acid in high yield. On preparation of 3,3-dimethyl-1,5-dichloropentane we obtained a liquid whose boiling point agreed with that reported by Miller and Adams (2) as opposed to that given by Komppa (1). However, the properties of our γ,γ-dimethylpimelonitrile, prepared either from the dichloro- or dibromopentane, did not agree with those reported by either of the two other groups. Further, hydrolysis of our dinitrile yielded γ,γ-dimethylpimelic acid, a solid melting 13° above the value given by Komppa (1), and forming a liquid ethyl ester that distilled 20° above the value given by Miller and Adams (2).

To establish the structure of our product, the diethyl ester was submitted to a Dieckmann condensation (7), forming the strongly enolic ethyl 4,4-dimethyl-

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[2] Corrected to 80 mm. by means of a nomographic chart for comparison with the data of Miller and Adams.

[2a] β,β-dimethyl-α,γ-dicyanoglutarimide.

2-cyclohexanonecarboxylate, from which, *via* acid hydrolysis and decarboxylation the known 4,4-dimethylcyclohexanone was formed (8). It is of interest that Miller and Adams report their ester to be transformed into the same dimethylcyclohexanone, although they state that the over-all yield was not satisfactory. While we can offer no explanation for the differences in the results obtained by the three laboratories we feel that the synthesis we have described is free from ambiguity.

EXPERIMENTAL

β,β-Dimethylglutaric acid. The crude salt of Guareschi's imide was hydrolyzed according to the known procedure (9), with the modification that a diluted sulfuric acid was first used, followed by more concentrated. One mole of salt was cautiously heated with a solution of 255 ml. of concentrated sulfuric acid containing 90 ml. of water. After two hours, 90 ml. of water was added, and refluxing was continued for 14 hours. After cooling 200 ml. of concentrated sulfuric acid was added, and the mixture was refluxed for one-half hour. The solution was again cooled, diluted with 150 ml. of water, and refluxed until no more carbon dioxide was evolved (about three hours). After addition of ammonium sulfate, the acid was isolated by extraction with ether, decolorized with Norit, and recrystallized from water. The product, obtained in 70% yield, had m.p. 97–100°.

Diethyl β,β-dimethylglutarate. The acid (one mole), was refluxed for two hours with thionyl chloride (68% excess). After removal of excess thionyl chloride, absolute ethanol (109% excess) was added slowly. The mixture was refluxed for three hours, allowed to stand overnight, and the product collected. The yield was 98% of ester, b.p. 90–91° at 3 mm.

3,3-Dimethyl-1,5-pentanediol. To a solution of 24 g. (0.635 mole) of lithium aluminum hydride in 860 ml. of absolute ether was added dropwise and with rapid stirring a solution of 124 g. (0.575 mole) of diethyl β,β-dimethylglutarate in 250 ml. of absolute ether. The mixture refluxed gently during the addition; it was then refluxed for two additional hours, allowed to stand overnight, and refluxed for four hours more. The mixture was then cooled, and 25 ml. of water was added cautiously to decompose excess lithium aluminum hydride, and 500 ml. of 15% sulfuric acid was added to decompose the resulting salt. The solution was then extracted for eight days in a continuous ether liquid-liquid extractor. The extract was washed with concentrated sodium bicarbonate solution, and water, and then evaporated. The diol was obtained as a hygroscopic oil in 89% yield, b.p. 95° at 1.0 mm. The *di-p-nitrobenzoate* was prepared and had m.p. 99–99.5°.

Anal. Calc'd for $C_{21}H_{22}N_2O_8$: C, 58.60; H, 5.15.
Found: C, 58.79; H, 5.25.

3,3-Dimethyl-1,5-dichloropentane. This was prepared in 90% yield by the action of thionyl chloride on 3,3-dimethyl-1,5-pentanediol, according to the directions of Miller and Adams (2). It had b.p. 135° at 80 mm., and n_D^{15} 1.4656.

3,3-Dimethyl-1,5-dibromopentane. This was prepared from the glycol in 80% yield by the procedure of Kamm and Marvel (10) using aqueous hydrobromic acid and sulfuric acid. Some charring occurred during the reaction, but attempts to eliminate this decreased the yield materially. The product had b.p. 99–105° at 5 mm., and n_D^{27} 1.4537.

Anal. Calc'd for $C_7H_{14}Br_2$: Br, 61.89. Found: Br, 62.78.

γ,γ-Dimethylpimelonitrile. Refluxing 3,3-dimethyl-1,5-dichloropentane in aqueous ethanol containing sodium cyanide for 96 hours according to the procedure of Miller and Adams (2) there resulted an 18% yield of nitrile, b.p. 165° at 7 mm., n_D^{20} 1.4570. The same product was obtained in 69% yield from the dibromopentane by the following method. A mixture of 38.9 g. of sodium cyanide (0.8 mole) and 40 ml. of water were heated until the cyanide was almost all dissolved. To this was added dropwise a solution of 6.10 g. of the dibromide (0.24 mole) in 132 ml. of ethanol. The reaction mixture was refluxed for 38 hours, and then most of the water and alcohol was distilled under aspirator pressure. The residual oil was isolated and distilled.

Anal.[3] Calc'd for $C_9H_{14}N_2$: C, 71.95; H, 9.39.
Found: C, 71.70; H, 9.31.

γ,γ-Dimethylpimelic acid. This was prepared in 89% yield by direct hydrolysis (1) of the nitrile using concentrated hydrochloric acid. Recrystallization from ether-petroleum ether formed tiny white crystals, m.p. 95–96°.

Anal.[3] Calc'd for $C_9H_{16}O_4$: C, 57.44; H, 9.57; Neut. equiv., 94.10.
Found: C, 57.71; H, 9.40; Neut. equiv., 94.20.

γ,γ-Dimethylpimelyl chloride. This was prepared by refluxing the acid with excess thionyl chloride for two hours. It was necessary to distil it through a modified Claisen flask specially constructed with a very short distillation path, otherwise much decomposition occurred. The product had b.p. 117.5–119° at 1.0 mm., and n_D^{25} 1.4752.

Anal. Calc'd for $C_9H_{14}Cl_2O_2$: Cl, 31.74. Found: Cl, 31.11.

Diethyl γ,γ-dimethylpimelate. This was prepared in 92% yield from the acid chloride and had b.p. 155° at 7 mm., and n_D^{20} 1.4399.

Anal.[4] Calc'd for $C_{13}H_{24}O_4$: OC_2H_5, 36.89. Found: OC_2H_5, 37.21.

Ethyl 4,4-dimethyl-2-cyclohexanonecarboxylate. Diethyl γ,γ-dimethylpimelate (12 g.), and several drops of absolute alcohol were heated with 2.3 g. of sodium wire. At 90° (bath temperature) vigorous reaction commenced, and the temperature of the flask was raised to and maintained at 120° for 45 minutes. After cooling, the solid sodium enolate (7) was ground under ether in a mortar, filtered, and then acidified to give the pure oil in 43% yield, b.p. 75° at 1.0 mm., n_D^{25} 1.4761.

Anal.[4] Calc'd for $C_{11}H_{18}O_3$: OC_2H_5, 22.72. Found. OC_2H_5, 22.88.

4,4-Dimethylcyclohexanone. This was isolated as the hydrolysis product of the cyclohexanonecarboxylic ester using 50% hydrochloric acid for 12 hours. It had m.p. 38–41° (8), and formed the known semicarbazone, m.p. 203–204° on rapid heating (8).

Anal.[3] of semicarbazone. Calc'd for $C_9H_{17}N_3O$: C, 58.98; H, 9.35.
Found: C, 58.95; H, 9.16.

SUMMARY

A direct synthesis of γ,γ-dimethylpimelic acid has been described which starts with β,β-dimethylglutaric acid. Differences between the properties of our compounds and those of two other laboratories have been pointed out.

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[4] We wish to thank Dr. and Mrs. George Kleinspehn for this analysis.