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PARTIAL HYDROLYSIS OF DIETHYL γγ-DIETHOXYCARBONYLPIMELATE: A METHOD OF PREPARING γγ-DIETHOXYCARBONYLPIMELIC ACID

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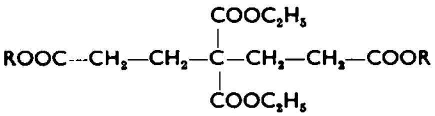
Abstract—When one mole of diethyl γγ-diethoxycarbonylpimelate was hydrolysed with exactly two moles of sodium hydroxide in absolute ethanolic solution at room temperature, γγ-diethoxycarbonylpimelic acid was produced in excellent yield. Its structure was proved beyond doubt by two independent methods.

γγ-DIETHOXYCARBONYLPIMELIC ACID (II), which was required for future synthetic work, can be prepared by partial hydrolysis of diethyl γγ-diethoxycarbonylpimelate (I). It has been shown to be a dibasic acid and its structure was proved by synthesis of dibenzyl γγ-diethoxycarbonylpimelate (III) by condensing diethyl malonate with benzyl β-bromopropionate, which was reduced catalytically with hydrogen to yield (II). The partial hydrolysis of (I) was shown to have occurred selectively, if not solely, on both unhindered ester groups at the end of the molecule, so leaving two malonic ester groups intact.*[1]

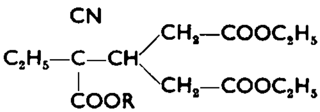
In the mean time Evstigneeva *et al.*,[2] in their brilliant synthesis of emetine, showed that when hydrolysed by one molecular equivalent of sodium hydroxide in absolute ethanol, triethyl α-cyano-α-ethyl-β-(carboxymethyl)glutarate (IV) gave preferentially he acid (V). In this case, therefore, the ester group that was hydrolysed was the hindered one and this seemed to contradict the result obtained by Sugasawa and Sakurai.[1] Thus it appeared desirable to provide additional evidence for the structure of the acid (II).

Blanc[3] cyclised 3:3-dimethylpimelic acid with loss of carbon dioxide to 4:4-dimethyl*cyclo*hexanone by treatment with acetic anhydride, and (II) on similar treatment was cyclised to 4:4-diethoxycarbonyl*cyclo*hexanone (VI), which was characterised by its semicarbazone and 2:4-dinitrophenylhydrazone. To prove the



$$ROOC{-}CH_2{-}CH_2{-}\overset{COOC_2H_5}{\underset{COOC_2H_5}{C}}{-}CH_2{-}CH_2{-}COOR$$

I: $R = -C_2H_5$
II: $R = -H$
III: $R = -CH_2-C_6H_5$



IV: $R = -C_2H_5$
V: $R = -H$

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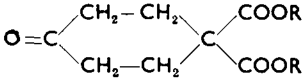
* Previously published by Sugasawa and Sakurai[1] in Japanese. The preparation of (II) is now described in English.

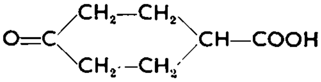
[1] S. Sugasawa and K. Sakurai, *J. Pharm. Soc. Japan*, **62**, 82 (1942).

[2] R. P. Evstigneeva, R. S. Livshits, M. S. Bainova, L. I. Zakharkin, and N. A. Preobrazhenskii, *Chem. Abst.* **42**, 5949 (1948).

[3] G. Blanc, *C. R. Acad. Sci., Paris* **144**, 143 (1906).



VI: R = —C_2H_5
VII: R = —H



VIII

structure of (VI) beyond doubt, it was hydrolysed with alkali to give 4-oxo*cyclo*hexanedicarboxylic acid (VII), which has previously been described.[4] (VII) on being heated at 160° gave 4-oxo*cyclo*hexanecarboxylic acid (VIII), previously prepared by Martin and Robinson.[5]

EXPERIMENTAL

γγ-Diethoxycarbonylpimelic acid (II). An absolute ethanolic sodium hydroxide solution containing 0·2 g (0·05 mole) of sodium hydroxide was prepared by dissolving 1·15 g (0·05 mole) of metallic sodium in 50 ml of absolute ethanol to which 0·9 ml of water had been added. Diethyl γγ-diethoxycarbonylpimelate (I) (8·7 g, 0·024 mole) was then added to this solution with shaking to give a clear solution, which was set aside at room temperature (ca. 18°) for 20 hr, when a white solid separated. Sufficient water to dissolve this solid was now added to give a clear solution, from which the ethanol was removed *in vacuo* at room temperature. The residual solution was filtered and the filtrate was acidified carefully with dilute hydrochloric acid with cooling. The whole was kept in an ice-chest, when a white crystalline substance separated, which was filtered off and washed with a little cold water. This compound, m.p. 118–121°, was purified by recrystallisation from benzene to give colourless plates (6·5–6·7 g, 90–92 per cent), m.p. 123-123·5°. (Found: C, 51·2; H, 6·6; COOH, 29·8. $C_{11}H_{18}O_4(COOH)_2$ requires C, 51·3; H, 6·6; COOH, 29·6 per cent).

The acid is stable on being heated to 180° without decomposition and colour change, and this stability toward heat suggests that both malonic ester groups remain intact.

Dibenzyl γγ-diethoxycarbonylpimelate (III). Metallic sodium (1 g, 0·043 mole) was finely powdered in dry xylene and to this suspension was now added diethyl malonate (3·52 g, 0·022 mole). The mixture was vigorously shaken to form a white pasty mass. Benzyl β-bromopropionate (9·5 g, 0·043 mole), a colourless oil of b.p.$_6$ 133–135°, was added with shaking and the mixture was heated on a steam-bath for 6–7 hr with stirring, when a neutral solution resulted. Xylene was removed by steam-distillation and the oily residue was taken up in ether, washed, dried and evaporated. The remaining oil distilled at 155–158°/0·05–0·06 mm, as a pale-yellow viscous syrup (5·1 g, 48·1 per cent) (Found: C, 66·7; H, 6·4. $C_{27}H_{32}O_8$ requires C, 66·9; H, 6·7 per cent).

γγ-Diethoxycarbonylpimelic acid (II). The dibenzyl ester (III) (1 g) in ethanol was reduced with hydrogen activated over Adams's platinum catalyst, when about 90 ml of hydrogen, corresponding roughly to two moles, was smoothly absorbed. After being worked up as usual, a crystalline solid was obtained, which formed colourless plates, m.p. 123°, from benzene and was proved to be identical by mixed melting point with the specimen prepared by partial alkaline hydrolysis.

*Diethyl 4-oxo*cyclo*hexanedicarboxylate* (VI). γγ-Diethoxycarbonylpimelic acid

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[4] E. Hardeggar, Pl. A. Plattner and F. Blanc, *Helv. Chim. Acta* **24**, 796 (1944). M.p. 147·5–149·5° according to these authors.

[5] R. H. Martin and R. Robinson, *J. Chem. Soc.* 496 (1943).

(II) (3·5 g) was dissolved in 10 ml of acetic anhydride containing 1 ml of pyridine. The mixture was gently heated under reflux in an oil-bath for 2 hr, during which time the evolution of carbon dioxide had occurred and ceased. After removal of acetic acid and excess of actic anhydride *in vacuo*, the residue was subjected to vacuum distillation, to give a colourless oil of camphor-like fragrance (2·6 g, 93 per cent), b.p.$_6$ 141°.

The semicarbazone was obtained as colourless spheroidal crystals from ethanol, m.p. 185–186° (Found: C, 52·5; H, 7·0; N, 13·6. $C_{13}H_{21}O_5N_3$ requires C, 52·2; H, 7·1; N, 14·0 per cent).

The 2:4-dinitrophenylhydrazone was obtained as yellow needles from ethanol, m.p. 119° (Found: C, 50·9; H, 5·0; N, 13·6. $C_{18}H_{22}O_8N_4$ requires C, 51·2; H, 5·25; N, 13·3 per cent).

4-*Oxo*cyclo*hexanedicarboxylic acid* (VII). (VI) (1·5 g) was hydrolysed by being heated on a steam-bath with sodium hydroxide in aqueous ethanol. Ethanol was then removed by distillation, the residue was dissolved in water, and the solution was filtered through a wet filter-paper. The filtrate was acidified with dilute hydrochloric acid and thoroughly extracted with ether, dried and evaporated. The solid obtained was purified from acetone–benzene, to give colourless needles (1 g), m.p. 149–150° (dec.).

4-*Oxo*cyclo*hexanecarboxylic acid* (VIII). (VII) (1 g) was heated at 160° for 10 min and was then distilled. The distillate (0·65 g), b.p. 129°/2 mm, solidified on standing. This forms colourless needles, m.p. 67°, after recrystallisation from ether–light petroleum (Found: C, 59·5; H, 7·0. $C_7H_{10}O_3$ requires C, 59·1; H, 7·1 per cent).

The 2:4-dinitrophenylhydrazone was obtained as golden yellow needles from ethanol, m.p. 191–192° (dec.).

An authentic sample of 4-oxo*cyclo*hexanecarboxylic acid was prepared from ethyl *p*-hydroxybenzoate by the method of Martin and Robinson.[5] This acid melted at 67° alone or admixed with the one obtained above, and formed a yellow 2:4-dinitrophenylhydrazone having the same melting point.