

STUDIES ON THE DIECKMANN CYCLIZATION OF SOME TETRA ESTERS

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Received September 16, 1953

3-Carboxy-2-methylcyclopentanone-2- β -propionic acid was required by us in connection with a projected scheme for the synthesis of steroids. Since this compound was the starting point for a series of subsequent operations it was desirable to find out a convenient way of obtaining it in large quantities from readily available materials.

With this object in view it was decided to study the Dieckmann cyclization of 1,3,4,6-tetracarboethoxy-3-methylhexane (III, R = C₂H₅), which was readily available from levulinic acid. This tetraester could theoretically cyclize in either of the two ways, A or B to give after hydrolysis the desired ketodiacid (IVa, R = H) or the isomeric compound (IV, R = H). We were somewhat encouraged from the observations of Banerjee and Shafer (1), who found that the cyclization of the homologous tetraester, 1,4,5,7-tetracarboethoxy-4-methylheptane with one molar equivalent of sodium hydride, followed by hydrolysis and esterification gave the cyclopentanone derivative (VIII), closely related to the compound we had desired to obtain. Contrary to this expectation however the ring closure in the present case went the other way, route B, to yield after hydrolysis, 3-methyl-3-carboxy-cyclopentanone-2- β -propionic acid (IV, R = H).

The tetraester (III, R = C₂H₅) required for this work was readily obtained by the addition of acrylonitrile to ethyl 3-methyl-3,4-dicyanobutane-1,4-dicarboxylate [I, Banerjee (2)] followed by hydrolysis of the resulting adduct (II) with concentrated hydrochloric acid and subsequent esterification of the tetraacid with an alcohol-sulfuric acid mixture. The tetra basic acid (III, R = H) could be readily obtained as a crystalline solid, m.p. 169–170° and the overall yield of the corresponding tetraester (III, R = C₂H₅) from the dicyano compound (I) was about 70%. The Dieckmann cyclization of the tetraester (III, R = C₂H₅) in presence of sodium dust in benzene very smoothly gave a β -keto ester which on hydrolysis and decarboxylation gave a solid keto acid, m.p. 84–85°. This ketoacid was quite homogeneous indicating that cyclization had proceeded only in one direction. This was confirmed by preparing solid derivatives of the ketoacid as well as of the corresponding ester. In order to decide between the two alternative structures (IV and IVa) theoretically possible for this ketoacid depending on the course of the Dieckmann cyclization the following experiments were performed.

Clemmensen reduction of the above keto acid or its ester afforded a gummy desoxy acid which was esterified as such. The corresponding diethyl ester V or Va, R = C₂H₅) very smoothly underwent a Dieckmann cyclization to a β -keto ester which on hydrolysis gave a ketone with a strong camphoraceous odor. This ketone, which very readily formed a semicarbazone, m.p. 265–266° and a

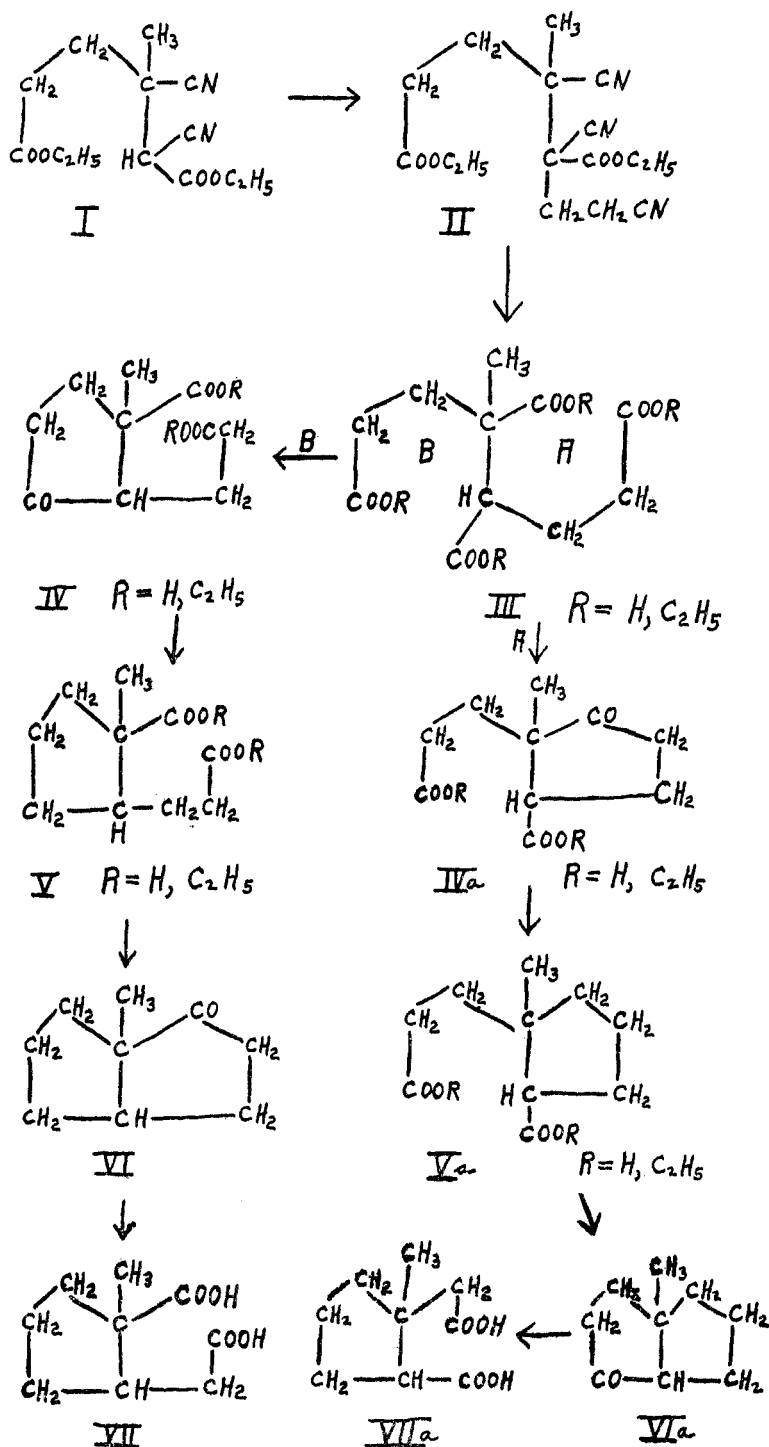


Fig. 1

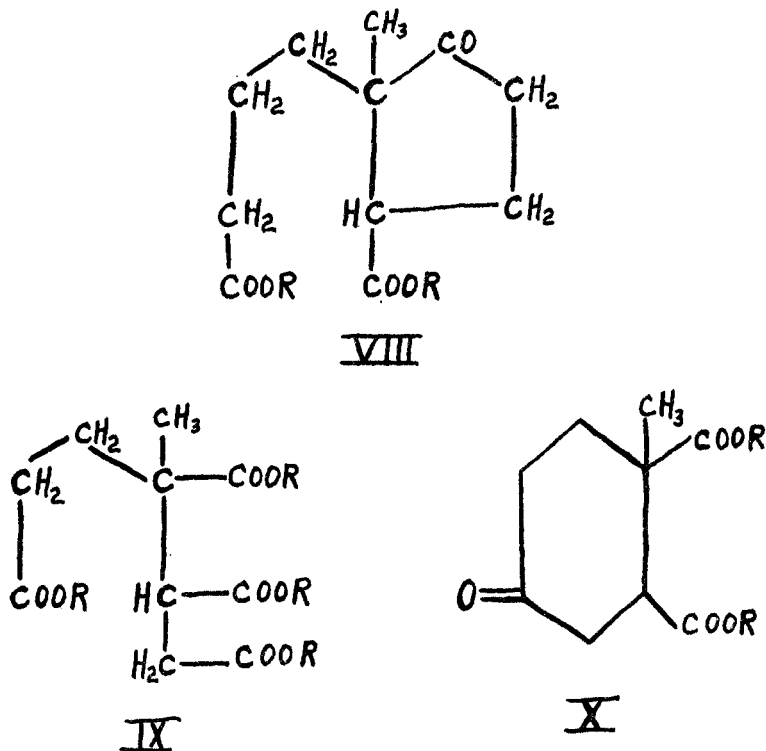


FIG. 2

2,4-dinitrophenylhydrazone, m.p. 232–233°, could be either the 1-keto compound (VI) or the isomeric 4-ketone (VIa). On oxidation with concentrated nitric acid the ketone readily furnished a dicarboxylic acid, which after two crystallizations from water had m.p. 107°. The mixture melting point with an authentic specimen of *cis*-1-methylcyclopentane-1-carboxy-2-acetic acid, m.p. 110° was 109°. The identity of the acid obtained on oxidation with the above *cis* acid at once confirms the structure and stereochemistry of the ketone obtained above as VI, since of the two possible ketones (VI and VIa), only the former on oxidation could give the above dicarboxylic acid (VII). The confirmation of the structure of this ketone as VI also settles the structure of the keto diacid obtained from the tetraester (III, R = C₂H₅) as represented by (IV, R = H).

Subsequent to the completion of this work we became aware that the keto diester (IVa, R = C₂H₅) had been prepared by an unambiguous method from ethyl 2-methylcyclopentanone-3-carboxylate (3). The semicarbazone of this ketodiester had m.p. 140–141° which is quite different from the semicarbazone, m.p. 110–112°, obtained by us in the present work. This offers further confirmatory evidence of the structure of the Dieckmann cyclization product as IV.

The cyclization of 1,3,4,5-tetracarboxy-3-methylpentane (IX, R = C₂H₅) was also investigated and after hydrolysis, the ketoacid (X, R = H) having a

six-membered ring was obtained. This keto acid could not be obtained in crystalline form and hence it was converted to its diethyl ester (X, R = C₂H₅) and characterized as the semicarbazone, m.p. 140–141°. The structure (X, R = H) was deduced by reduction to *trans*-1-methylcyclohexane-1,2-dicarboxylic acid which was identified by a mixture melting point determination with an authentic specimen obtained according to Mukharji (4). It is interesting to note that in the case of this particular tetraester also, which could cyclize either way to give a six membered or a five membered ring compound, only the former was formed preferentially.

EXPERIMENTAL

Ethyl 3-methylhexane-3,4,6-tricyano-1,4-dicarboxylate (II). Ethyl 3-methyl-3,4-dicyano-butane-1,4-dicarboxylate (29.5 g.), prepared according to Banerjee (2) was dissolved in peroxide-free dioxane (11 ml.) and freshly distilled acrylonitrile (6.5 g.) was added, followed by 40% Triton B (1 ml.). The reaction mixture was usually left at room temperature for one week and then was poured into acidulated water. The precipitated heavy oil was extracted with ether, washed successively with water, dilute sodium bicarbonate solution, and water, and finally dried over sodium sulfate. On removal of ether, a thick liquid was obtained which boiled during a flash distillation at 215–216°/1.5 mm.; yield, 25 g.

Anal. Calc'd for C₁₆H₂₁N₃O₄: C, 60.18; H, 6.58.

Found: C, 59.73; H, 6.89.

1,3,4,6-Tetracarboethoxy-3-methylhexane (III, R = H). The above tricyano compound (32 g.) was refluxed for 100–120 hours with 20% hydrochloric acid (250 ml.). The liquid was then completely evaporated to dryness on a steam-bath. The residual dirty white solid was triturated with water (15 ml.) and the insoluble residue was filtered and dried. Yield, 23–25 g. (crude). After crystallization from dilute acetic acid this tetraacid (III, R = H) had m.p. 169–170°.

Anal. Calc'd for C₁₁H₁₆O₈: C, 47.82; H 5.79.

Found: C, 47.79; H, 5.91.

The dry acid (16 g.) was esterified in the usual way with a mixture of alcohol and concentrated sulfuric acid to yield the tetraethyl ester (III, R = C₂H₅), b.p. 178–179°/1.5 mm.; yield 14.5 g.

Anal. Calc'd for C₁₉H₃₂O₈: C, 58.76; H, 8.2.

Found: C, 58.79; H, 8.16.

Dieckmann cyclization of 1,3,4,6-tetracarboethoxy-3-methylhexane (III, R = C₂H₅); *Formation of 3-methyl-3-carboxycyclopentanone-2-β-propionic acid* (VI, R = H). The tetraester (74 g.) was dissolved in anhydrous benzene (50 ml.) and added to sodium dust, prepared from metallic sodium (5 g.) under benzene (150 ml.). To this mixture was then added a few drops of alcohol, and the flask was evacuated and refilled with nitrogen. The reaction mixture was heated on a steam-bath; a vigorous reaction started very soon and a red solution was obtained. After one hour of heating at the reflux temperature the sodium particles had completely disappeared. The mixture then was cooled in a nitrogen atmosphere and was extracted thoroughly with water. The benzene layer gave 14 g. of the unconverted tetra ester.

The aqueous layer was carefully acidified with dilute acetic acid and then was extracted with benzene several times. The benzene extract was washed with 10% sodium carbonate solution, then with water, and finally was dried over sodium sulfate. The residual oil left after removal of the benzene gave an instantaneous violet-red coloration with an alcoholic ferric chloride solution. This β-ketoester could not be easily distilled without some decomposition, but on a small scale distillation it was possible to obtain an analytically pure sample, b.p. 156–157°/1.5 mm.

Anal. Calc'd for C₁₇H₂₆O₇: C, 59.6; H, 7.60.

Found C, 59.81; H, 7.94.

The crude β -ketoester obtained above was hydrolyzed for 60 hours with a mixture of acetic acid (250 ml.), concentrated hydrochloric acid (100 ml.), and water (75 ml.) in an atmosphere of nitrogen. The solution was then concentrated under reduced pressure to a very small volume, almost to dryness. The residual dirty brown gum solidified after about a week in an ice-chest. It was crystallized from the minimum amount of water containing a few drops of hydrochloric acid, yield 37 g. The pure crystallized ketoacid had m.p. 84.5°.

Anal. Calc'd for $C_{16}H_{14}O_5$: C, 56.08; H, 6.54.

Found: C, 56.38; H, 6.83.

The 2,4-dinitrophenylhydrazone prepared in the usual manner had m.p. 118–119°.

Anal. Calc'd for $C_{18}H_{18}N_4O_8$: C, 48.73; H, 4.57.

Found: C, 48.31; H, 4.77.

The diethyl ester was prepared in the usual way by refluxing the above acid (35 g.) with a mixture of absolute alcohol (200 ml.) and concentrated sulfuric acid (15 ml.). The ester was isolated in the usual way and purified by distillation, b.p. 132–133°/1.5 mm.

Anal. Calc'd for $C_{14}H_{22}O_5$: C, 62.22; H, 8.14.

Found: C, 62.22; H, 8.53.

The semicarbazone of the above ester was prepared in the usual manner and after crystallization from dilute alcohol had m.p. 110–112°.

Anal. Calc'd for $C_{15}H_{25}N_3O_5$: N, 12.84. Found N, 12.90.

Clemmensen reduction of the above keto acid. The above ketodiacid (17 g.) was reduced by refluxing for 50 hours with zinc amalgam (55 g.), concentrated hydrochloric acid (75 ml.), and water (45 ml.). After every eight hours 3 ml. of concentrated hydrochloric acid was added and the refluxing was continued. Afterwards, the mixture was cooled and thoroughly extracted with ether. The ether extract was washed with water, dried, and the solvent removed. The residual gummy acid was well dried and as such esterified with an alcohol and sulfuric acid mixture. The ester isolated in the usual way and purified by distillation had b.p. 172–173°/7 mm. Yield 12 g.

Anal. Calc'd for $C_{14}H_{24}O_4$: C, 65.63; H, 9.38.

Found: C, 65.69; H, 9.41.

Dieckmann cyclization of the above ester. The above ester (5.5 g.), dissolved in dry benzene (10 ml.), was added to pulverised sodium (0.6 g.) under dry benzene (30 ml.) and the mixture was heated on a steam-bath under nitrogen. After about 30 minutes a vigorous reaction started and soon a solid cake was formed. The reaction mixture was then cooled and the solid cake very carefully was dissolved in water. The aqueous extract was then separated and acidified with ice cooling. The precipitated oil was extracted with ether; the ether extract was then washed with 10% sodium carbonate solution, and water, and then dried over sodium sulfate. The oil remaining after the removal of ether gave a positive ferric chloride coloration. A small portion was distilled, b.p. 135–136°/10 mm.

Anal. Calc'd for $C_{12}H_{13}O_3$: C, 68.58; H, 8.57.

Found: C, 68.69; H, 8.71.

The crude β -ketoester obtained above then was hydrolyzed with 10% hydrochloric acid solution in an atmosphere of nitrogen. The insoluble oil was extracted with benzene, and the benzene extract was washed with water, dried over sodium sulfate, and the solvent removed. The residual oil which had a strong camphoraceous odor was purified by distillation, b.p. 114–115°/10 mm., yield 1.5 g.

Anal. Calc'd for $C_6H_{14}O$: C, 78.26; H, 10.14.

Found: C, 78.61; H, 9.99.

The semicarbazone, which formed very readily, was crystallized from water containing drops of acetic acid, m.p. 265–266°.

Anal. Calc'd for $C_{10}H_{17}N_3O$: N, 21.54. Found: N, 21.71.

The 2,4-dinitrophenylhydrazone had m.p. 232–233°.

Anal. Calc'd for $C_{15}H_{15}N_4O_4$: N, 17.60. Found: N, 17.81.

Nitric acid oxidation of the above ketone. The above ketone (0.5 g.) and concentrated nitric acid, *sp. gr.* 1.4 (7.5 ml.), were gradually warmed on a steam-bath until brown fumes

evolved. Before the reaction became too vigorous, the flask was removed from the steam-bath. When the vigor of the reaction had somewhat abated, it was heated on a steam-bath for three hours more. The residual liquid was then evaporated to dryness. The crude acid had m.p. 99–101°, yield 0.3 g. Two crystallizations from water containing traces of hydrochloric acid raised the melting point to 107°. The mixture melting point with an authentic sample of *cis*-1-methylcyclopentane-1-carboxy-2-acetic acid (m.p. 111°) was 109°.

Anal. Calc'd for $C_9H_{14}O_4$: C, 58.06; H, 7.52; Neut equiv., 93.

Found: C, 58.12; H, 7.49; Neut. equiv., 90, 93.

1,3,4,5-Tetracarboethoxy-3-methylpentane (IX, R = C_2H_5). To the sodio salt prepared from sodium (3.9 g.) and absolute alcohol (55 ml.) and the dicyano ester (I, 30.5 g.) there was added with stirring and ice-cooling, ethyl bromoacetate (11 g.). The reaction mixture was left overnight and then refluxed on a steam-bath for 12 hours. The mixture was worked up in the usual way and the condensation product was purified by distillation, b.p. 170°/1 mm., yield 31 g.

Anal. Calc'd for $C_{17}H_{24}N_2O_8$: C, 57.95; H, 6.82.

Found: C, 57.94; H, 6.99.

The above condensation product (24 g.) was hydrolyzed by prolonged refluxing (75 hours) with concentrated hydrochloric acid (160 ml.) and water (80 ml.). The solution then was completely evaporated to dryness, but the acid could not be obtained in crystalline form. It then was esterified directly in the usual way and purified by distillation, b.p. 156–157°/1 mm., yield 20 g.

Anal. Calc'd for $C_{13}H_{20}O_8$: C, 57.75; H, 8.02.

Found: C, 57.70; H, 7.89.

Dieckmann cyclization of the above tetraester. The above tetra ester (37 g.) in benzene (50 ml.) was added to sodium dust (2.3 g.) under benzene (50 ml.) and the mixture was heated on a steam-bath under nitrogen until all the sodium particles had disappeared. On cooling the red solution was thoroughly extracted with water, the aqueous extract carefully was acidified, and the oil was isolated in the usual way. It gave a positive ferric test. A small portion was distilled, b.p. 143–145°/1 mm.

Anal. Calc'd for $C_{16}H_{24}O_7$: C, 58.53; H, 7.62.

Found: C, 57.97; H, 7.44.

The β -keto ester was hydrolyzed with a mixture of acetic acid (100 ml.), concentrated hydrochloric acid (40 ml.), and water (30 ml.) for 60 hours. On removal of solvents under reduced pressure a gum was obtained which could not be crystallized. It was then esterified and the ester was purified by distillation, b.p. 127–128°/1 mm., yield 15.5 g.

Anal. Calc'd for $C_{13}H_{20}O_5$: C, 60.94; H, 7.80.

Found: C, 60.64; H, 7.931.

The *semicarbazone* of the ester prepared in the usual way was crystallized from dilute alcohol, m.p. 140–141°.

Anal. Calc'd for $C_{14}H_{23}N_3O_5$: N, 13.4. Found: N, 13.62.

Clemmensen reduction of the above ketodiester: Formation of trans-1-methylcyclohexane-1,2-dicarboxylic acid. The above keto ester (2 g.) was reduced with zinc amalgam (25 g.), concentrated hydrochloric acid (55 ml.), and water (20 ml.). The acid was isolated by ether extraction and the crude acid was purified by crystallization from water containing several drops of hydrochloric acid, m.p. 211°. A mixture melting point with an authentic specimen (4) of *trans*-1-methylcyclohexane-1,2-dicarboxylic acid, m.p. 213°, was 212°.

Acknowledgments. The work was carried out during the tenure of a National Institute of Sciences' Senior Research Fellowship (1949–1950) to one of us (P.C.M.).

One of the authors (C.R.R.) acknowledges the gift of an authentic sample of *cis*-1-methylcyclopentane-1-carboxy-2-acetic acid from Prof. D. K. Banerjee of the College of Engineering & Technology, Jadavpur, Calcutta 32, India.

SUMMARY

The Dieckmann cyclization of 1,3,4,6-tetracarbethoxy-3-methylhexane gave after hydrolysis of the intermediate β -keto ester, 3-methyl-3-carboxy-cyclopentanone-2- β -propionic acid. The analogous 1,3,4,5-tetracarbethoxy-3-methylpentane, which could theoretically cyclize to give either a cyclopentanone or a cyclohexanone derivative, gave exclusively the latter one.

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