

ISOMERISATIONS OF SUBSTITUTED β -KETO-ESTERS

Part II. Isomerisation of Ethyl 1-Ethoxycarbonyl-2-Oxocyclopentylacetate into 2, 3-Diethoxycarbonylcyclohexanone

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In an earlier paper¹ it was reported that the treatment of ethyl 1-ethoxycarbonyl-2-oxocyclopentylacetate (I) with alcohol-free sodium ethoxide in refluxing benzene led to a cyclohexane system, since the product on hydrolysis and decarboxylation yielded 3-carboxycyclohexanone (VI). The mechanism suggested is detailed below.

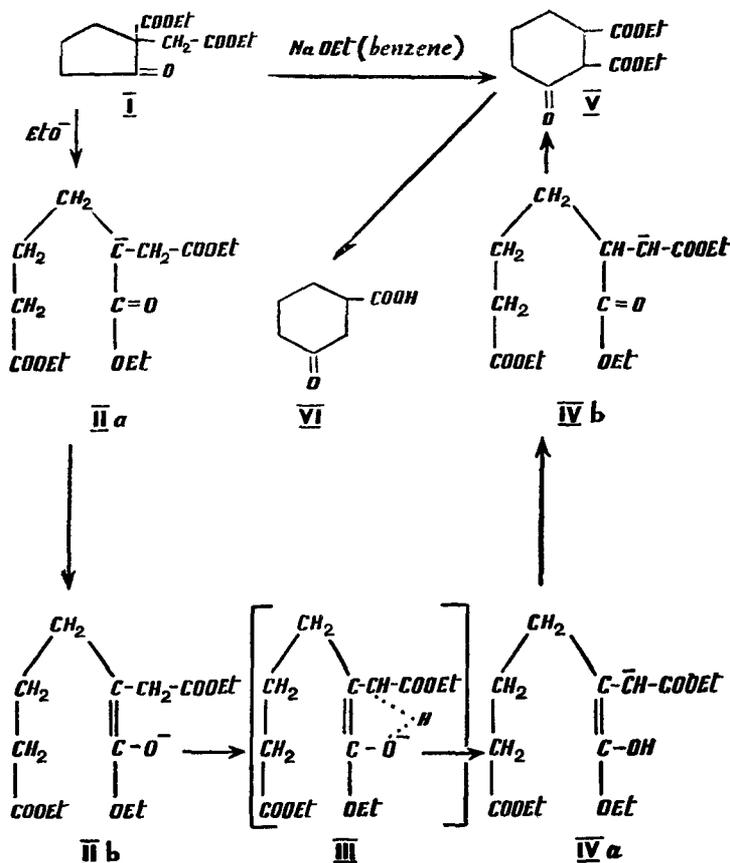


FIG. 1

* Part I. Banerjee, D. K., Dutta, J. and Bagavant, G., *Proc. Ind. Acad. Sci.*, 1957, 46 A, 80.

Fission of ethyl 1-ethoxycarbonyl-2-oxocyclopentylacetate (I) by the ethoxyl ion leads to the anion (II *a*). The negatively charged oxygen atom of the enol anion (II *b*) would attack the methylene group *a* to an ethoxycarbonyl function furnishing the carbanion (IV *a*) via the transition intermediate (III); this is similar to the first step in an aldol condensation where a base attacks a reactive methylene group to produce a carbanion. The keto form (IV *b*) of the enol carbanion (IV *a*) would then cyclise to 2, 3-diethoxycarbonylcyclohexanone (V)¹ which on hydrolysis and decarboxylation should yield 3-carboxycyclohexanone (VI).

However, according to an alternative mechanism, ethyl 1-ethoxycarbonyl-2-oxocyclopentylacetate (I) may undergo a Claisen reaction in the presence of sodium ethoxide giving a bicyclic β -diketone (VII). This diketone

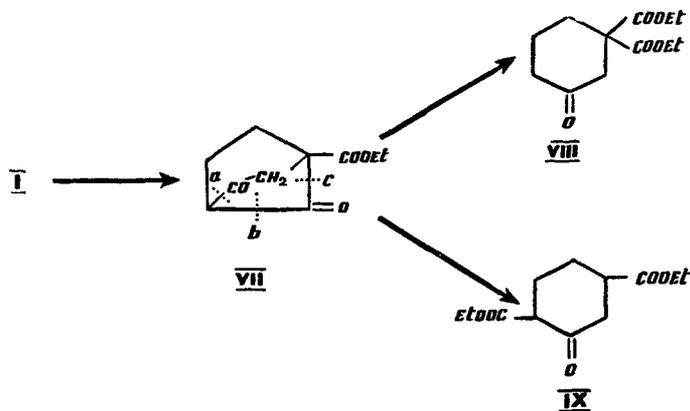


FIG. 2

may cleave in any of three ways (dotted lines) in the presence of ethoxide ion to furnish (a) the original compound (I), (b) 3, 3-diethoxycarbonylcyclohexanone (VIII), (c) 2, 5-diethoxycarbonylcyclohexanone (IX); but, only the last of these would be soluble in 5% alkali and yield 3-carboxycyclohexanone (VI) on hydrolysis and decarboxylation.

The structure of the keto-ester obtained in this isomerisation was therefore investigated. The procedure was similar to that adopted by Sen and Bagchi in their investigation of the product of Dieckmann cyclisation of ethyl pentane-1, 2, 5-tricarboxylate with sodium in benzene.² Methylation of the β -keto-ester gave a product which on ketonic hydrolysis yielded an acid which was identified as 3-carboxy-2-methylcyclohexanone. Further, the methylated product on being fissioned with a trace of sodium ethoxide in alcohol furnished a hexane-triester with a refractive index higher than that

of the authentic sample of ethyl hexane-1, 2, 5-tricarboxylate (XIV) *vide infra*. An identical difference between the refractive indices of ethyl hexane-1, 4, 5-tricarboxylate and ethyl hexane-1, 2, 5-tricarboxylate was noted by Sen and Bagchi.²

The formation of 3-carboxy-2-methylcyclohexanone and ethyl hexane-1, 4, 5-tricarboxylate indicates the product of the isomerisation to be 2, 3-diethoxycarbonylcyclohexanone (V) and supports the mechanism earlier suggested.

An authentic sample of 3-carboxy-2-methylcyclohexanone was prepared by methylation of 2, 3-diethoxycarbonylcyclohexanone followed by hydrolysis and decarboxylation.²

5-Carboxy-2-methylcyclohexanone (XVI) and ethyl hexane-1, 2, 5-tricarboxylate (XIV), which would have resulted from the aforementioned series of reactions according to the second mechanism, were prepared as reference compounds by a different procedure from that of Bradfield *et al.*³ who had earlier prepared these compounds.

Dieckmann cyclisation of ethyl pentane-1, 2, 5-tricarboxylate (X) with alcoholic sodium ethoxide gave ethyl 3-ethoxycarbonyl-2-oxocyclopentylacetate (XI).¹ Methylation of the β -keto-ester (XI) yielded 3-ethoxycarbonyl-3-methyl-2-oxocyclopentylacetate (XII). The structure of (XII) was confirmed by its conversion into 3-methyl-2-oxocyclopentylacetic acid (XIII) which was previously prepared by Bradfield *et al.*³ Fission of the methylated β -keto-ester (XIII) with a trace of sodium ethoxide in alcohol yielded an authentic sample of ethyl hexane-1, 2, 5-tricarboxylate (XIV). The tri-ester (XIV) on Dieckmann cyclisation gave 2, 3-diethoxycarbonyl-6-methylcyclohexanone (XV) which on ketonic hydrolysis furnished 5-carboxy-2-methylcyclohexanone (XVI).

The keto-ester (XV) could also be prepared directly from 3-ethoxycarbonyl-3-methyl-2-oxocyclopentylacetate (XII) by refluxing with a molar quantity of alcoholic sodium ethoxide.

EXPERIMENTAL

Methylation of the cyclohexane β -keto-ester¹ obtained in the isomerisation of ethyl 1-ethoxycarbonyl-2-oxocyclopentylacetate with alcohol-free sodium ethoxide in benzene.—To sodium dust (1.38 g.) under benzene (100 ml.) was added the β -keto-ester (12.1 g.) at 0°. The clear solution containing a few particles of sodium was refluxed for 1.5 hours and then cooled to 0°,

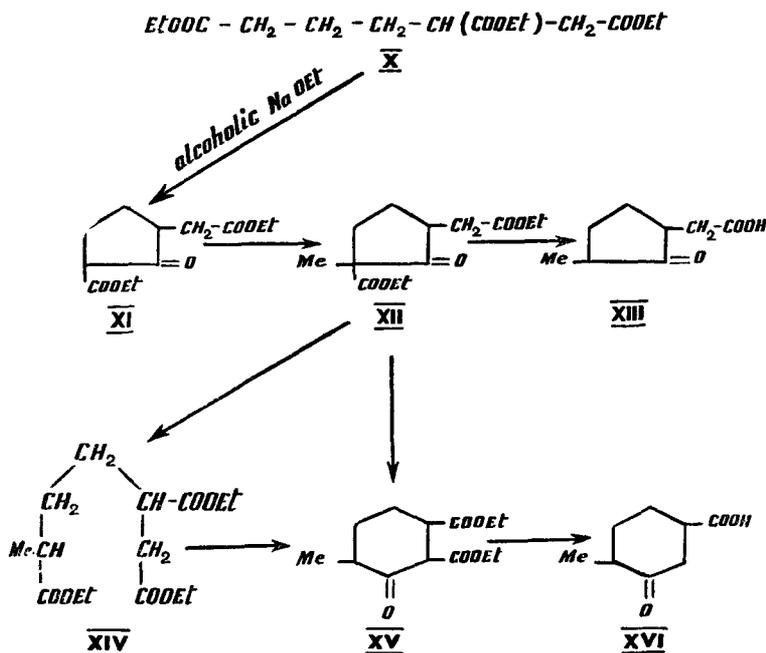


FIG. 3

and methyl iodide (8 ml.) was added to it. After standing the contents for 0.5 hour at room temperature, it was gently refluxed for 8 hours. The cooled contents were poured into water (150 ml.), the benzene layer was separated and the aqueous layer was extracted with benzene. The combined benzene extract, which showed no colour with alcoholic ferric chloride, was washed with brine. After removal of the benzene, the methylated product was distilled, b.p. 129–31°/0.7 mm., yield 10.60 g. (Found: C, 61.0; H, 7.8. Calc. for $C_{13}H_{20}O_5$: C, 60.95; H, 7.9%).

Ketonic hydrolysis of the methylated product.—A mixture of the aforementioned methylated β -keto-ester (2 g.) and 6 N-hydrochloric acid (40 ml.) was refluxed for 20 hours. On complete removal of the lower boiling products, a solid with adhering gum (1.2 g.) was obtained. After pressing on a porous plate the acid melted at 86–93°. It was crystallised from ether-light petroleum (40–60°), m.p. 93–97°; mixed melting point with an authentic sample of 3-carboxy-2-methylcyclohexanone, kindly furnished by Prof. Bagchi, was 93–96°.

The 2, 4-dinitrophenylhydrazone prepared by the perchloric acid method after crystallisation from dilute acetic acid melted at 207–08°; the melting point was not depressed on admixture with an authentic sample of the 2, 4-dinitrophenylhydrazone of 3-carboxy-2-methylcyclohexanone, while it was

depressed to 182–90° on mixing with the 2, 4-dinitrophenylhydrazone of 5-carboxy-2-methylcyclohexanone.

The semicarbazone, prepared by the sodium acetate method, was crystallised from alcohol, m.p. 203–04° (lit.³ 204°). The mixed melting point with an authentic sample of the semicarbazone of 3-carboxy-2-methylcyclohexanone was not depressed, while the melting point was depressed to 173–79° on admixture with an authentic sample of the semicarbazone of 5-carboxy-2-methyl-cyclohexanone.

Fission of the methylated product.—The aforementioned methylated β -keto-ester (8.4 g.) was added at 0° to a solution of sodium ethoxide, prepared from sodium (71 mg.) and ethanol (1.1 ml.). The mixture was heated for 4 hours on a water-bath, and the cooled product was acidified at 0° with hydrochloric acid (0.5 ml.) in water (10 ml.). Ether (100 ml.) was added to it and shaken, and the separated ethereal layer was washed with sodium bicarbonate solution and brine. After drying (CaCl_2) and removal of the ether, the triester was collected at 165–68°/2 mm., n_D^{27} 1.4373 (Found: C, 59.2; H, 8.4. Calc. for $\text{C}_{15}\text{H}_{26}\text{O}_6$: C, 59.6; H, 8.7%).

Authentic sample of 3-carboxy-2-methylcyclohexanone.—This was prepared by a modified procedure of Sen and Bagchi.²

Sodium dust (2 g.) in benzene (100 ml.) and ethyl pentane-1, 2, 5-tricarboxylate (X) (14.4 g.) were refluxed for 3.5 hours on a water-bath under anhydrous conditions. The reaction product was cooled to 0° and methyl iodide (40 g.) was added slowly with swirling. After 0.5 hour at 0° it was refluxed gently for 8 hours. The supernatant liquid was neutral to litmus and showed no colour with alcoholic ferric chloride. Water (60 ml.) was added to the reaction mixture, and the benzene layer was separated and washed with brine (30 ml.). The benzene was removed and 2, 3-diethoxycarbonyl-2-methylcyclohexanone was distilled at 132–34°/0.8 mm., yield 9.4 g. (Found: C, 61.1; H, 7.8. Calc. for $\text{C}_{13}\text{H}_{20}\text{O}_5$: C, 60.95; H, 7.9%).

2, 3-Diethoxycarbonyl-2-methylcyclohexanone (5.1 g.) and 10%-aqueous potassium hydroxide (36 ml.) were refluxed for 8.5 hours in an oil-bath (120–27°). The aqueous solution, after extraction with ether, was run into ice-cold hydrochloric acid. The acid solution was extracted with ether. On removal of the solvent, the gummy residue weighed 2.3 g. A part of it was converted into the semicarbazone by the sodium acetate method. After repeated crystallisation from alcohol it melted at 202–04° (lit.² 204°). The 2, 4-dinitrophenylhydrazone prepared by the perchloric acid method after crystallisation from alcohol melted at 208–09° (lit.² 209°).

Ethyl 3-ethoxycarbonyl-2-oxocyclopentylacetate (XI).—An ethanolic solution of sodium ethoxide, from sodium (1.2 g.) and ethanol (19.1 ml.), and ethyl pentane-1, 2, 5-tricarboxylate (X) (14.4 g.) were refluxed for 8 hours on a sand-bath. The product was cooled and decomposed at 0° with dilute hydrochloric acid. The mixture was repeatedly extracted with benzene and the combined benzene phase was washed with dilute sodium bicarbonate solution (0°) and brine. The solvent was removed completely and the residue taken up in ether (500 ml.). The ethereal solution was extracted twenty times at 0–5° using 25 ml. lot of 5%-ice-cold sodium hydroxide solution. Each alkali wash was scrubbed with 100 ml. of ether and then run into ice-cold dilute hydrochloric acid. The turbid acid solution was extracted repeatedly with ether. The ethereal extract was washed with dilute ice-cold sodium bicarbonate solution, dried (Na₂SO₄), and the ether was distilled off. The residue, which gives an intense purple colour with alcoholic ferric chloride, on distillation yielded ethyl 3-ethoxycarbonyl-2-oxocyclopentylacetate (XI), b.p. 125–29°/0.8 mm., yield 6.9 g. (Found: C, 59.9; H, 7.9. Calc. for C₁₂H₁₈O₅: C, 59.5; H, 7.5%).

Ethyl 3-ethoxycarbonyl-3-methyl-2-oxocyclopentylacetate (XII).—Ethyl-3-ethoxycarbonyl-2-oxocyclopentylacetate (XI) (34.6 g.) was methylated as described before with sodium dust (3.63 g.), benzene (120 ml.) and methyl iodide (71 g.). *Ethyl 3-ethoxycarbonyl-3-methyl-2-oxocyclopentylacetate (XII)* boiled at 139–43°/2 mm., yield 35.6 g. (Found: C, 60.6; H, 8.0. C₁₃H₂₀O₅ requires C, 60.95; H, 7.9%).

3-Methyl-2-oxocyclopentylacetic acid (XIII).—Ethyl 3-ethoxycarbonyl-3-methyl-2-oxocyclopentylacetate (XII) (5.1 g.) and 10%-aqueous potassium hydroxide (36 ml.) were refluxed for 9 hours. The reaction mixture was scrubbed with ether and then acidified with hydrochloric acid. The clear acid solution was concentrated to 25 ml. It was extracted with ether, and the solvent was removed when 3-methyl-2-oxocyclopentylacetic acid (XIII) (3.2 g.) was left as a viscous liquid. The semicarbazone of the keto-acid (XIII), prepared by the sodium acetate method, after crystallisation from alcohol, melted at 175–76° (lit.³ 175–76°).

The 2, 4-dinitrophenylhydrazone, prepared by the perchloric acid method,⁴ after crystallisation from alcohol, melted at 178–80° d. (Found: N, 17.0. C₁₄H₁₆O₆N₄ requires N, 16.7%).

Ethyl hexane-1, 2, 5-tricarboxylate (XIV).—Ethyl 3-ethoxycarbonyl-3-methylcyclopentylacetate (XII) (17.0 g.) was fissioned, as described before, with sodium ethoxide, from sodium (0.16 g.) and alcohol (3.8 ml.), to give ethyl hexane-1, 2, 5-tricarboxylate (XIV), b.p. 155–58°/1 mm., yield 18.2 g.,

n_D^{27} 1.4362 (Found: C, 60.0; H, 8.6. Calc. for $C_{15}H_{26}O_6$: C, 59.6; H, 8.7%).

2, 3-Diethoxycarbonyl-6-methylcyclohexanone (XV).—To powdered sodium (1.2 g.) suspended under dry benzene (100 ml.) was added ethyl hexane, 1, 2, 5-tricarboxylate (XIV) (12.1 g.). After refluxing the mixture for 3.5 hours under anhydrous conditions, the product was decomposed at 0° with dilute hydrochloric acid. The benzene phase was washed with sodium bicarbonate solution and brine, and the solvent removed. The residue (9.8 g.) was distilled to yield 2, 3-diethoxycarbonyl-6-methylcyclohexanone (XV) (8.2 g.), b.p. $130-33^\circ/0.8$ mm., n_D^{27} 1.4562 (Found: C, 60.9; H, 7.9. Calc. for $C_{13}H_{20}O_5$: C, 60.95; H, 7.9%).

5-Carboxy-2-methylcyclohexanone (XVI).—2, 3-Diethoxycarbonyl-6-methylcyclohexanone (XV) (5.1 g.) and 6 N-hydrochloric acid (30 ml.) were refluxed for 22 hours and on working up in the usual way the keto-acid (XVI) (3.1 g.) was obtained. The semicarbazone, obtained by the sodium acetate method, after crystallisation from alcohol, melted at $193-95^\circ$ (lit.³ $195-97^\circ$).

The 2, 4-dinitrophenylhydrazone, prepared by the perchloric acid method,⁴ after crystallisation from rectified spirit, melted at 207° (Found: N, 16.9. $C_{14}H_{16}O_6N_4$ requires N, 16.7%).

Isomerisation of ethyl 3-ethoxycarbonyl-3-methyl-2-oxocyclopentylacetate (XII) into 2, 3-diethoxycarbonyl-6-methylcyclohexanone (XV) with alcoholic sodium ethoxide.—Alcoholic sodium ethoxide, from sodium (0.84 g.) and ethanol (15 ml.), and ethyl 3-ethoxycarbonyl-3-methyl-2-oxocyclopentylacetate (XII) (8.5 g.) were refluxed for 8 hours on a sand-bath. The pale red product was decomposed with hydrochloric acid (4 ml.) and water (30 ml.) at 0° . The material was extracted with benzene, and the benzene solution washed with ice-cold sodium bicarbonate solution and brine. The product gave an intense red colour with alcoholic ferric chloride. The benzene was completely removed, and the residue was taken in ether and thoroughly extracted with 5%-sodium hydroxide solution at $0-5^\circ$. The alkali extract after being washed with ether was acidified and the turbid acid solution extracted with ether. The ethereal phase was washed with ice-cold sodium bicarbonate solution and brine and dried (Na_2SO_4). After removal of the solvent, the β -keto-ester was distilled at $133-35^\circ/0.8$ mm., yield 2.8 g., n_D^{27} 1.4560 (Found: C, 60.5; H, 8.05. Calc. for $C_{13}H_{20}O_5$: C, 60.95; H, 7.9%).

The above ester on hydrolysis and decarboxylation by refluxing with 6 N-hydrochloric acid yielded a keto-acid. The 2, 4-dinitrophenylhydrazone melted at $206-07^\circ$ and the mixed melting point with an authentic sample of the 2, 4-dinitrophenylhydrazone of 5-carboxy-2-methylcyclohexanone (*vide*

supra) was not depressed (206–07°). The semicarbazone of the keto-acid had melting point (192–95°), and mixed melting point (192–95°) with the authentic sample of the semicarbazone of 5-carboxy-2-methylcyclohexanone.

SUMMARY

A mechanism for the isomerisation of ethyl 1-ethoxycarbonyl-2-oxocyclopentylacetate (I) into a cyclohexane β -keto-ester as proceeding through an intermediate bicyclic β -diketone (VII) has been considered as an alternative mechanism to one earlier suggested.¹ The determination of the structure of the isomerised β -keto-ester as 2, 3-diethoxycarbonylcyclohexanone (V) has provided support for the earlier mechanism.

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REFERENCES

1. Banerjee, D. K., Dutta, J. and Bagavant, G. *Proc. Ind. Acad. Sci.*, 1957, **46 A**, 80.
2. Sen, K. and Bagchi, P. *Science and Culture*, 1953, **19**, 312; *J. Org. Chem.*, 1958, **23**, 1125.
3. Bradfield, A. E., Francis, E. M., Penfold, A. R. and Simonsen, J. L. *J. Chem. Soc.*, 1936, 1622.
4. Neuberg, C., Grauer, A. and Pisha, B. V. *Anal. Chim. Acta.*, 1952, **7**, 238.