[Jour. Indian Chem. Soc., Vol. 42, No. 7, 1965]

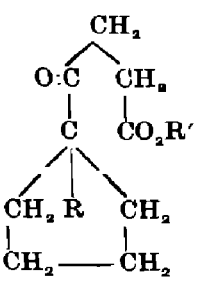
Cyclic Compounds. Part I. Experiments on the Synthesis of Cyclopentane Derivatives Related to Wieland's Tricarboxylic Acid

P. C. Bhattacharyya

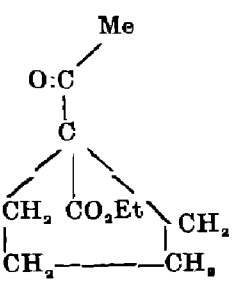
β-Carboxypropionylcyclopentane (I: R=R′=H) has been synthesised by an extension of the Perkin ring-closure[1], applied to ethyl β-oxo-adipate[2] and 1,4-di-iodobutane and the constitution elucidated. A useful variation of the reaction, applied to ethyl 7-methyl-3-oxo-octanoate[3a,3b] (V) and 1,4-di-iodobutane, provides a new route to the synthesis of 5-methylhexanoylcyclopentane (III: R=H).

A synthesis of 2-methyl-1-(β-carboxypropionyl) cyclopentane-2,3-dicarboxylic acid (VII: R=R$_1$=R$_2$=R$_3$=H) is also described analogously.

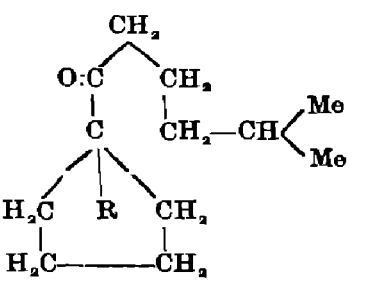
Alkylation of ethyl β-oxo-adipate with 1,4-di-iodobutane involves two steps, the last of which occurs intramolecularly to afford ethyl 1-(β-ethoxycarbonylpropionyl)-cyclopentane-1-carboxylate (I: R=CO_2Et; R′=Et) in good yield. The latter on hydrolysis with acetic acid and hydrochloric acid depsosits crystalline β-carboxypropionylcyclopentane (I:R=R′=H).



(I)



(II)

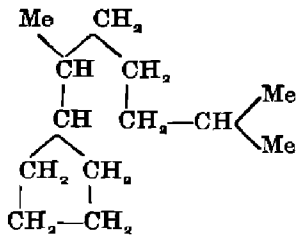


(III)

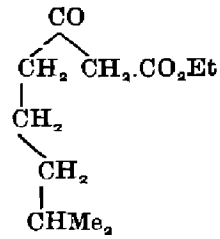
The same ketonic acid was also obtained from ethyl 1-acetylcyclopentane-1-carboxylate[4] (II) by bromination, malonic ester condensation, and hydrolysis, thus affording a direct proof as to its constitution.

Ethyl 7-methyl-3-oxo-octanoate (V) and 1,4-di-iodobutane afforded ethyl 1-(5′-methylhexanoyl)cyclopentane-1-carboxylate (III: R=CO_2Et) from which 5-methylhexanoylcyclopentane (III: R=H) was obtained by hydrolysis.

1. Perkin, *J. Chem. Soc.*, 1929, 1347.
2. Bardhan, *ibid.*, 1936, 1848.
3. (*a*) Bardhan *et al.*, *ibid.*, 1963, 2407.
   (*b*) Wellingford *et al.*, *J. Amer. Chem. Soc.*, 1941, **63**, 2252.
4. Goldsworthy, *J. Chem. Soc.*, 1934, 377.



(IV)

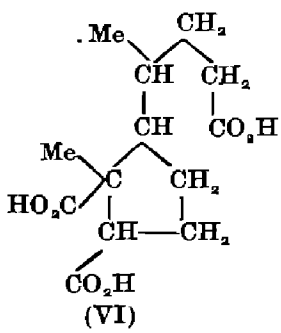


(V)

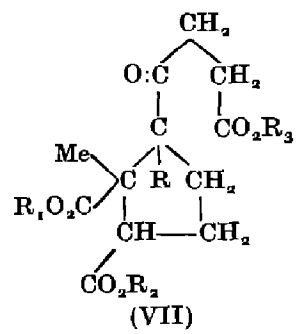
The latter (III: R=H) on the Grignard reaction with methylmagnesium iodide, followed by dehydration[5] with $POCl_3$ and pyridine and catalytic hydrogenation, formed chiefly 2-cyclopentyl-6-methylheptane (IV). The iso-octyl residue so created is expected to produce the valeric acid side chain on oxidation[6].

Verious attempts[7a-7b] were made earlier to complete the synthesis of the tricarboxylic acid (VI). The stereochemical disposition of each of the asymmetric centres in the tricarboxylic acid (VI) is always a hindrance towards the total synthesis.

A synthesis of 2-methyl-1-(β-carboxypropionyl)cyclopentane-2,3-dicarboxylic acid (VII: $R=R_1=R_2=R_3=H$) is further presented.

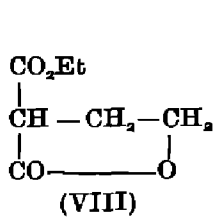


(VI)

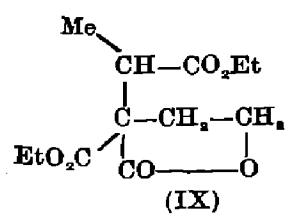


(VII)

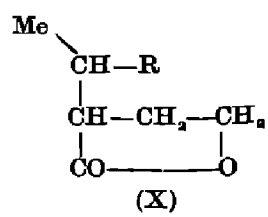
α-Ethoxycarbonyl-γ-butyrolactone[8] (VIII) on alkylation with ethyl α-bromopropionate afforded chiefly α-ethoxycarbonyl- α-(1-ethoxycarbonyl)ethyl-γ-butyrolactone (IX) in good yield. The acid hydrolysis of (IX) afforded α-1-carboxyethyl-γ-butyrolactone (X: $R=CO_2H$). The resulting acid chloride (X: R=COCl) was brominated and then treated with PBr_5 and EtOH. The resulting worked-up dibromo compound furnished crystalline oxo-acid (VII: $R=R_1=R_2=R_3=H$) with ethyl β-oxo-adipate through acid hydrolysis.



(VIII)



(IX)



(X)

5. Bardhan *et al.*, *J. Chem. Soc.*, 1963, 62.
6. Windaus *et al.*, *Ber.*, 1919, **52**, 1915.
7. (*a*) Bardhan *et al.*, *Science & Culture*, 1927, **2**, 656.
   (*b*) Dutta *et al.*, this *Journal*, 1954, **31**, 881 and references cited therein.
8. Cf. *Ber.*, 1901, **34**, 1971.

The quantity of the oxo-acid (VII: $R=R_1=R_2=R_3=H$) was too small for further study.

EXPERIMENTAL

β-Carboxypropionylcyclopentane (I: R=R′=H).—Ethyl β-oxo-adipate (21.6 g.) and 1,4-di-iodobutane (15.5 g.) were heated with sodium (2.3 g.) in ethanol (32 ml) under pressure on a steam bath for 8 hr. The solvent was removed on a water bath; the residue was cooled and extracted with ether. The ethereal solution was once washed with water, dried ($CaCl_2$), and evaporated. The residue was distilled to provide ethyl 1-(β ethoxycarbonylpropionyl)cyclopentane-1-carboxylate (I: $R=CO_2Et$; R′=Et) (10 g.), b.p. 150-52°/4mm. (Found: C, 62.14; H, 8.15. $C_{14}H_{22}O_5$ requires C, 62.20; H, 8.14%).

The preceding oxo-ester (10 g.), HCl (conc., 20 ml), and glacial acetic acid (40 ml) were heated on a sand bath for 20 hr. The solvent was removed and the residue evaporated almost to dryness. Crystals separated on cooling. The oxo-acid (I: R=R′=H), purified through the ethyl ester, formed needles from petroleum (60-80°), m.p. 71°. (Found: C, 63.40; H, 8.30. $C_9H_{14}O_5$ requires C, 63.50; H, 8.23%).

Ethyl 1-acetylcylopentane-1-carboxylate (II) (14 g.) in ether (14 ml) was treated with bromine (4 ml) in the cold and allowed to stand overnight at the room temperature. HBr was removed, solvent evaporated, and the residue dried. Ethyl malonate (14 ml) and the crude bromo compound (14 g.) were heated with finely divided sodium (1.8 g.), suspended in dry benzene (40 ml), on a steam bath for 6 hr. The product was diluted with water and extracted with ether. The ethereal solution was once washed with water, dried ($CaCl_2$), and the solvent removed. The residue (10.8 g.) had b.p. 160-62°/4 mm. The oxo-acid (I: R=R′=H) was isolated from the preceding compound by hydrolysis. It had m.p. and mixed m.p. 71°.

Ethyl 1-(5′-Methylhexanoyl)cyclopentane-1-carboxylate (III: $R=CO_2Et$).—Ethyl 7-methyl-3-oxo-octanoate (20 g.) and 1,4-di-iodobutane (15.5 g.) were heated with sodium (2.3 g.) in ethanol (32 ml) under pressure on a steam bath for 8 hr. On removing the solvent, the residue was cooled and extracted with ether. On removing the ether, the residue was distilled to provide the oxo-ester (III: $R=CO_2Et$) (11 g.), b.p. 133-35°/4 mm. (Found: C, 70.80; H, 10.30. $C_{15}H_{26}O_3$ requires C, 70.86; H, 10.20%).

The ketone (III: R=H), obtained from the preceding oxo-ester (III: $R=CO_2Et$) by hydrolysis, had b.p. 80-82°/4 mm. (Found: C, 79.00; H, 12.10. $C_{12}H_{22}O$ requires C, 79.10; H, 12.09%). The *semicarbazone* formed prisms, m.p. 120°, from EtOH. (Found: C, 65.18; H, 10.50. $C_{13}H_{25}ON_3$ requires C, 65.20; H, 10.40%).

2-Cyclopentyl-6-methylheptane (IV).—To the Grignard reagent, prepared from magnesium (2 g.) and methyl iodide (6 ml) in ether (30 ml.), a solution of the preceding ketone (III: R=H) (9 g.) in ether (15 ml) was added with stirring. The mixture was gently refluxed for 1 hr. and then cooled and decomposed with H_2SO_4 (cold, dil.). The ethereal layer was separated, washed with water, dried (Na_2SO_4), and evaporated. The residue had b.p. 110-12°/15 mm. This alcohol on heating with $POCl_3$ and pyridine, followed by catalytic hydrogenation, afforded 2-cyclopentyl-6-methylheptane (IV), b.p. 82°/4 mm. (Found: C, 85.60; H, 14.30. $C_{13}H_{26}$ requires C, 85.72; H, 14.28%).

α-Ethoxycarbonyl-α-(1-ethoxycarbonyl)ethyl-γ-butyrolactone(IX).— α-Ethoxycarbonyl-γ-butyrolactone (VIII) (39.5 g.) and ethyl α-bromopropionate (45 g.) were heated with sodium (5.7 g.) in ethanol (120 ml) for 6 hr. The ethanol was removed on a water bath; the residue was cooled and extracted with ether. The solvent was removed and the residue distilled. The γ-butyrolactone (IX) (43.2 g.) had b.p. 160°/4mm. (Found: C, 55.7; H, 7.0. $C_{12}H_{18}O_6$ requires C, 55.8; H, 6.9%).

α-1-Carboxyethyl-γ-butyrolactone (X: R=CO_2H).—The preceding lactonic ester (IX) (43.2g.) was heated with HCl (conc., 200 ml) on a sand bath for 10 hr. HCl was removed on a water bath and the residue distilled. α-1-Carboxyethyl-γ-butyrolactone (X: R=CO_2H) (23.2 g.) had b.p. 180-82°/4 mm. (Found: C, 53.00; H. 6.40. $C_7H_{10}O_4$ requires C, 53.16; H, 6.32%). The resulting *acid chloride* had b.p. 182-85°/4mm. (Found: C, 47.56; H, 5.11. $C_7H_9O_3Cl$ requires C, 47.59; H, 5.09%).

2-Methyl-1-(β carboxypropionyl)cyclopentane-2,3-dicarboxylic Acid (VII: R = R_1 = R_2=R_3=H).—The preceding acid chloride (30 g.) was treated slowly with bromine (12ml) for 4-5 hr. at 70°. The residue was cooled, treated with ethanol (60 ml), and left overnight. It was then diluted with water and extracted with ether. The ether extract was washed with a solution of sodium bicarbonate and water and dried ($CaCl_2$). The bromo compound (27.2 g.) had b.p. 136-40°/40mm. The bromo compound (26 g.) was added to the pentabromide, prepared from PBr_3 (10 ml) and bromine (6 ml), with occasional shaking till it went completely into solution. The mixture was gently refluxed for 1 hr. at 60°, cooled, and treated with ethanol (60 ml), and worked up as usual.

Ethyl β-oxo-adipate (14 g.) and the preceding dibromo compound (12 g.) were heated with sodium (1.15 g.) in ethanol (22 ml) under pressure on a steam bath for 8 hr. Ethanol was removed and the residue extracted with ether. The ethereal layer was once washed with water, dried ($CaCl_2$), and the solvent removed. The crude residue so obtained (12 g.) was hydrolysed directly with its two volumes of HCl (conc.) and four volumes of glacial acetic acid. HCl was removed and the residue evaporated almost to dryness. The product separating as an oil solidified on storage over a porous tile. The oxo-acid (VII: R_1=R_2=R_3 =H) formed shining needles from ethyl acetate and petroleum (60-80°), m.p. 183°. (Found: C, 52.8; H, 5.9. $C_{12}H_{16}O_7$ requires C, 52.9; H, 5.8%).

The author is indebted to late Dr. J. C. Bardhan for his advice and encouragement during the course of the investigation.

Chemistry Department,
Vidyasagar College
Calcutta.

Received January 21, 1965.