

Synthetic Investigations on Fused-ring Compounds. Part I. Synthesis of *cis*- β -Decalone and α -Methyl-*cis*- β -decalone

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A new method of synthesis of *cis*- β -decalone and α -methyl-*cis*- β -decalone is described starting from 2- β -cyanoethylcyclohexanone.

cis- β -Decalone¹⁻⁴ and α -methyl-*cis*- β -decalone^{5,6} have been synthesised by various workers. In the present communication, a new method has been described for the synthesis of the two compounds.*

2- β -Cyanoethylcyclohexanone⁷ (Ia) was condensed with ethyl cyanoacetate in presence of glacial acetic acid and ammonium acetate according to the method of Bhattacharyya and Chatterjee⁸ to yield ethyl 2-(β -cyanoethylcyclohexylidene)-cyanoacetate (II) which on hydrogenation in presence of 10% Pd-C afforded ethyl 2-(β -cyanoethylcyclohexyl)-cyanoacetate (IIIa). The latter was methylated according to Mukherjee⁹ to the corresponding methylated compound (IIIb). The compound (IIIa) on hydrolysis and decarboxylation, followed by esterification, afforded dimethyl cyclohexane-1-acetate-2- β -propionate (IVa). The latter on cyclisation with sodium dust in benzene and a few drops of methanol, followed by hydrolysis and decarboxylation of the resulting β -keto-ester (Va) with acid, afforded the desired β -decalone (VIa).

The compound (IIIb) on hydrolysis and decarboxylation, followed by esterification, afforded methyl α -(2- β -methoxycarbonylethylcyclohexyl)-propionate (IVb) which, when subjected to the same sequence of reactions as described above, yielded α -methyl- β -decalone (VIb).

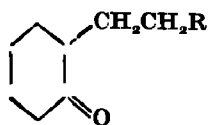
The stereochemistry of the β -decalone and α -methyl- β -decalone, thus prepared, has been established by formation of the corresponding semicarbazones^{4,6}.

The original scheme was to submit methyl cyclohexanone-2- β -propionate to the above series of reactions. The compound (Ib) with ethyl cyanoacetate and ammonium acetate yielded 2-keto-1,2,3,4,5,6,7,8-octahydroquinoline (VII) in excellent yield¹⁰

A preliminary report appeared in *Science & Culture*, 1962, 28, 81.

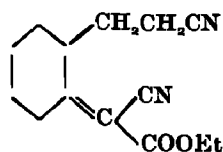
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2. Mannich *et al.*, *Ber.*, 1937, 70, 355.
3. Van Tamelen and Proost (Jr.), *J. Amer. Chem. Soc.*, 1954, 76, 3632.
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6. Banerjee *et al.*, *J. Amer. Chem. Soc.*, 1955, 77, 408.
7. Shushirina *et al.*, *Chem. Abst.*, 1956, 50, 14700i.
8. Bhattacharyya and Chatterjee, *this Journal*, 1958, 35, 19.
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10. Lions, *J. Proc. Roy. Soc., N. S. Wales*, 1938, 71, 192.

Ethyl cyanoacetate did not take part in the reaction at all, as (Ib) on heating with ammonium acetate yielded (VII) which on hydrolysis furnished (Ic).

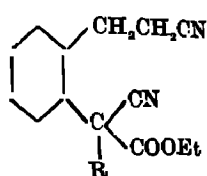


(I)

- a : R = CN
b : R = COOMe
c : R = COOH

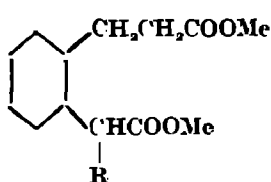


(II)



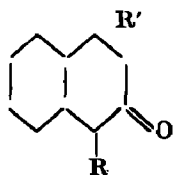
(III)

- a : R = H
b : R = Me



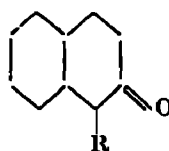
(IV)

- a : R = H.
b : R = Me.



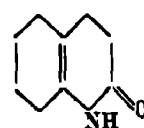
(V)

- a : R = H, R' = COOMe;
R = COOMe; R' = H.
b : R = Me, R' = COOMe.



(VI)

- a : R = H.
b : R = Me.



(VII)

EXPERIMENTAL*

2-β-Cyanoethylcyclohexanone (Ia).—In a three-necked flask fitted with a mechanical stirrer and a dropping funnel cyclohexanone (400 g.) was taken and cooled in freezing mixture. A solution of NaOH (2 g.) in water (16 ml) was added following the addition of methanol (5 ml). To the cooled solution acrylonitrile (43 g.) in methanol (60 ml) was added dropwise with constant stirring and the mixture was left for 16 hours. It was diluted with ice-cold water (200 ml), acidified with HCl (cold, dil.), and extracted with benzene. The extract was washed with saturated NaHCO₃ solution and then with water; on removal of the solvent an oily residue was obtained which on distillation afforded the unchanged cyclohexanone (300 g.), b.p. 154–56°. The residual liquid was distilled in vacuum to give the desired material (Ia), yield 40 g., b.p. 145–50°/14 mm. (Found: C, 71.4; H, 8.48. Calc. for C₈H₁₃ON: C, 71.5; H, 8.6%).

Ethyl (2-β-Cyanoethylcyclohexylidene)cyanoacetate (II).—To the above compound (Ia, 27 g.), ethyl cyanoacetate (45 g.), glacial acetic acid (17.5 g.) and dry benzene (125 ml) were added, following the procedure of Bhattacharyya and Chatterjee⁸ and the mixture was heated under reflux for 36 hours (Dean-Stark). When no more water separated, the

*All m.p.'s and b.p.'s are uncorrected. The UV absorption spectrum was determined in 95% ethanol by the Unicam spectrophotometer, s.p. 500.

product was poured into cold water (300 ml), the benzene layer separated, and the aqueous layer extracted with benzene. The organic layer was washed with saturated NaHCO_3 solution until alkaline, then with water and the solvent was distilled. The residual liquid distilled at $190\text{--}200^\circ/0.6\text{--}0.8\text{ mm}$ to furnish the desired material (31 g., 68%) as a viscous oil. (Found: C, 68.49; H, 7.42. $\text{C}_{14}\text{H}_{18}\text{O}_2\text{N}_2$ requires C, 68.29; H, 7.3%).

Ethyl 2- β -Cyanoethyl(cyclohexyl)-cyanoacetate (IIIa).—The unsaturated ester (II, 30 g.) was hydrogenated in presence of 10% Pd-C (250 mg.) and pure dry ethanol (25 ml). The absorption of one mole of hydrogen was completed in 9 hours. It was then filtered, most of the ethanol was removed under reduced pressure, and the liquid distilled very carefully to afford a colorless oil (26 g., 86%), b.p. $180\text{--}85^\circ/0.5\text{ mm}$. (Found: C, 67.43; H, 7.42. $\text{C}_{14}\text{H}_{20}\text{O}_2\text{N}_2$ requires C, 67.7; H, 8.06%).

Dimethyl Cyclohexane-1-acetate-2- β -propionate (IVa).—The above cyano-ester (IIIa, 25 g.) was hydrolysed and decarboxylated with HCl (conc., 350 ml) by heating under reflux for 96 hours. The reaction mixture was allowed to evaporate on a water bath when a gummy mass was obtained which was extracted with ether (400 ml). After removal of the solvent the residual acid was made free of water by distillation with dry benzene for 3-4 times (50 ml each time). The crude oil on esterification by heating with dry methanol (200 ml) and H_2SO_4 (conc., 20 ml) for 48 hours furnished the desired di-ester as a colorless oil; yield 13.5 g., b.p. $140\text{--}42^\circ/3\text{ mm}$. (Found: C, 64.18; H, 8.91. Calc. for $\text{C}_{13}\text{H}_{22}\text{O}_4$: C, 64.46; H, 9.09%).

Ethyl α -(2- β -Cyanoethylcyclohexyl)- α -cyanopropionate (IIIb).—Methylation of the cyano-ester (IIIa, 24 g.) in absolute ethanol (20 ml) was carried out according to Mukherjee⁹ with sodium (1.8 g.) in dry ethanol (50 ml) and methyl iodide (30 ml) by heating on a water bath for 4 hours. The reaction mixture was decomposed by pouring into iced water (250 ml) containing a few mls. of acetic acid. The precipitated oil was taken up in a mixture of ether and benzene, washed with 10% ice-cold NaOH solution, and then with water. After removal of the dry solvent the residue was distilled to yield a viscous material (21 g.), b.p. $165\text{--}70^\circ/0.4\text{ mm}$. (Found: C, 68.47; H, 8.23. $\text{C}_{15}\text{H}_{22}\text{O}_2\text{N}_2$ requires C, 68.7; H, 8.4%).

Methyl α -(2- β -Methoxycarbonylethylcyclohexyl)-propionate (IVb).—The compound (IIIb, 20 g.) was hydrolysed and decarboxylated with refluxing HCl (conc., 300 ml) for 96 hours and was worked up by the method described before. The crude acid was esterified with dry methanol (175 ml) and H_2SO_4 (conc., 17.5 ml) by heating under reflux for 48 hours. The di-ester was worked up in the usual way and was finally distilled to yield 11 g. of the product, b.p. $150\text{--}54^\circ/4\text{--}5\text{ mm}$, as a colorless mobile oil. (Found: C, 65.42; H, 9.15. $\text{C}_{14}\text{H}_{24}\text{O}_4$ requires C, 65.6; H, 9.37%).

3-Methoxycarbonyldecal-2-one (Va).—Cyclisation of the di-ester (IVa, 12 g.) was carried out with sodium dust (2.3 g.) in dry thiophen-free benzene (120 ml) and absolute methanol (a few drops) in an atmosphere of nitrogen by heating under reflux for 7-8 hours. It was then left for 15 hours in room temperature. The reaction mixture was cooled and poured into iced HCl (dil.). The benzene layer was separated and the aqueous layer was extracted twice with ether. The combined extract was washed free of acid with water and dried over anhydrous Na_2SO_4 . After removal of the solvent the residue was distilled to furnish the desired product (7.5 g.), b.p. $126\text{--}29^\circ/3\text{ mm}$

which gave an intense violet colour with ethanolic FeCl_3 . (Found: C, 68.38; H, 8.31. $\text{C}_{12}\text{H}_{18}\text{O}_3$ requires C, 68.57; H, 8.57%).

cis- β -Decalone (VIa).—A mixture of the β -keto-ester (Va, 7 g.), glacial acetic acid (30 ml), and 20% HCl (18 ml) was refluxed for 12 hours under nitrogen. The reaction mixture was cooled, diluted with water (200 ml) and extracted with ether. The ethereal layer was washed successively with a saturated solution of NaHCO_3 , saturated NaCl solution, and a small quantity of water. After evaporation of the solvent, the residue was distilled to furnish an oil, yield (3 g.), b.p. 114–18°/15 mm. (Found: C, 78.85; H, 10.41. Calc. for $\text{C}_{11}\text{H}_{18}\text{O}$: C, 78.94; H, 10.5%). The crude semicarbazone (200 mg.) melted at 265–70°, which after seven recrystallisations from methanol recorded m.p. 177.5–78°. The m.p. showed no depression on admixture with an authentic sample⁴. (Found: C, 63.08; H, 9.11. Calc. for $\text{C}_{11}\text{H}_{19}\text{N}_3\text{O}$: C, 63.2; H, 9.09%).

1-Methyl-3-methoxycarbonyldecal-2-one (Vb).—The cyclisation of the di-ester (IVb, 10 g.) in dry thiophen-free benzene (50 ml) was carried out with sodium dust (1.67 g.) as before. The brown-red reaction mixture was worked up to afford the β -keto-ester (5.5 g.), b.p. 141–45°/3–4 mm. It developed a deep violet colour with ethanolic FeCl_3 . (Found: C, 69.43; H, 8.68. $\text{C}_{13}\text{H}_{20}\text{O}_3$ requires C, 69.64; H, 8.9%).

α -Methyl-*cis*- β -decalone (VIb).—The ester (Vb, 5 g.) was refluxed with a mixture of glacial acetic acid (35 ml) and 20% HCl (20 ml) in an atmosphere of nitrogen for 12 hours. The reaction mixture was worked up as described before and yielded the desired ketone (3 g.), b.p. 120–24°/12 mm. (Found: C, 79.32; H, 10.64. Calc. for $\text{C}_{11}\text{H}_{18}\text{O}$: C, 79.5; H, 10.84%). The crude semicarbazone, m.p. 190–91° after four recrystallisation from ethanol recorded m.p. 192°. (Found: N, 19.1. Calc. for $\text{C}_{12}\text{H}_{21}\text{O}_3\text{N}_3$: N, 18.8%). Robinson *et al.*⁵ reported m.p. 192.5°.

Methyl Cyclohexanone-2- β -propionate (Ib).—Methyl β -(1-ethoxycarbonyl-2-ketocyclohexyl)-propionate (46 g., 92%), b.p. 145°–50°/2 mm, was prepared from ethyl cyclohexanone carboxylate (34 g.), methyl acrylate (17 g.), sodium (0.1 g.), and dry ethanol (20 ml) following the procedure of Banerjee and Bhattacharyya¹¹. It was hydrolysed and decarboxylated by heating under reflux for 16 hours with HCl (conc., 150 ml) and water (150 ml). The hydrolysed product was evaporated on a water bath to a gummy residue which was extracted with ether (300 ml). On removal of the solvent the acid was dried by distillation with dry benzene (50 ml, 3–4 times) when a solid resulted. After recrystallisation from a mixture of ether-petroleum ether (40–60°) it melted at 62–63°. Lions¹⁰ reported m.p. 62°. The crude solid was esterified with dry methanol (100 ml) and H_2SO_4 (conc., 7.5 ml) by heating under reflux for 30 hours and was worked up in the usual way. After removal of the solvent, (Ib) was obtained (23 g., 90%), b.p. 110–15°/3 mm.

2-Keto-1,2,3,4,5,6,7,8-octahydroquinoline (VII).—Cyclohexanone-2- β -propionate (Ib, 18.4 g.) was treated with ethyl cyanoacetate (11.5 ml), glacial acetic acid (10 ml), dry benzene (50 ml), and ammonium acetate (3.5 g.) according to Bhattacharyya and Chatterjee⁸ using a Dean-Stark constant water separator. The reaction mixture was refluxed for 10

hours when 2.5 ml of water separated. This was worked up in the usual way. The high-boiling fraction could not be distilled due to formation of a solid during distillation and so the material after removal of the lower-boiling fraction was crystallised from benzene; yield 8 g., m.p. 141-42° (white needles), λ_{max} 255 m μ (log ϵ , 3.684). (Found: C, 71.03; H, 8.39. $\text{C}_{13}\text{H}_{21}\text{O}_4\text{N}$ requires C, 64.51; H, 7.55. Calc. for $\text{C}_9\text{H}_{13}\text{ON}$: C 71.48; H, 8.66%).

The same experiment was repeated with cyclohexanone 2- β -propionate (4 g.), ammonium acetate (2.3 g.), glacial acetic acid (4 ml), and dry benzene (25 ml). The mixture was refluxed for 2 hrs. as described before and worked up in the usual way, giving 3.2 g. (70%) of a needle-shaped solid, m.p. 140-42° (crude) which on recrystallisation from benzene melted at 143°. The m.p. remained undepressed on admixture with the previous solid.

Cyclohexanone-propionic Acid(Ic).—The compound (VII, 3.1 g.) was hydrolysed with HCl (conc., 15 ml) for 15 hrs. The reaction mixture was extracted with ether and the solvent removed. The residue was evaporatively distilled at 110°/0.4 mm to give a solid (2.8 g. 80%). The m.p. of the crude product was 54°. It was then recrystallised from a mixture of ether-pet. ether (40-60°) and after few crystallisations the m.p. was 62-63°. The mixed m.p. remained undepressed on admixture with an authentic sample obtained by hydrolysis of (Ib).

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