[CONTRIBUTION FROM THE INDIAN ASSOCIATION FOR THE CULTIVATION OF SCIENCE]

SYNTHETIC INVESTIGATIONS IN THE CAMPHOR SERIES. PART III. NEW SYNTHESIS OF *dl*-HOMOAPOCAMPHORIC ACID[1]

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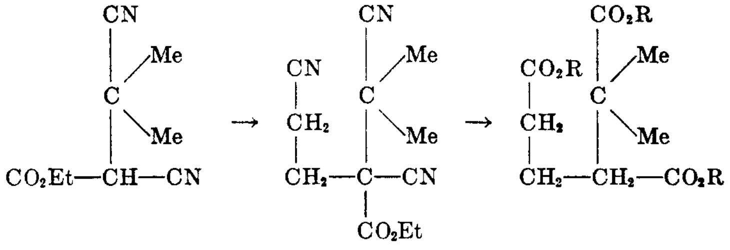
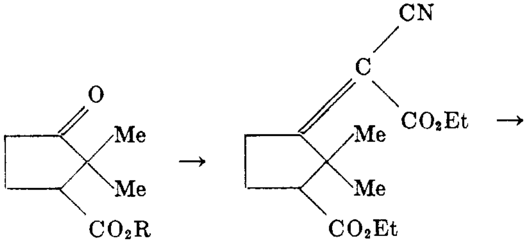
Komppa (1) synthesized homoapocamphoric acid as an intermediate in his synthesis of apocamphor on the model of Haller-Komppa (2) synthesis of camphor. In connection with experiments on an unambiguous synthesis of *dl*-homocamphoric acid (*cf.* Part II), we felt the necessity of studying a suitable method for the introduction of an acetic acid side chain into the molecule of ethyl 2,2-dimethylcyclopentane-1-one-3-carboxylate (III, R = Et) (3). Of the two methods available, namely the Reformatsky reaction with ethyl bromoacetate and a Knoevenagel reaction with ethyl cyanoacetate, we preferred the latter in the hope that catalytic reduction of the resultant cyclopentylidenecyanoacetate would lead to a *cis*-isomer (*cf.* 4, 5).

Ethyl 2,2-dimethylcyclopentane-1-one-3-carboxylate (III, R = Et) was synthesized for our purpose in the following way. Ethyl 2-methyl-2,3-dicyanopropane-3-carboxylate (6) was cyanoethylated (7) to give ethyl 2-methyl-2,3,5-tricyanopentane-3-carboxylate (I) which, after hydrolysis with concentrated hydrochloric acid, afforded 2-methylpentane-2,3,5-tricarboxylic acid (II, R = H) (3). The corresponding ethyl ester II (R = Et) after Dieckmann cyclization followed by hydrolysis with a mixture of hydrochloric acid and glacial acetic acid gave a good yield of 2,2-dimethylcyclopentane-1-one-3-carboxylic acid (III, R = H). This method of synthesis of (III, R = H) has been found to be much more satisfactory than the older method of Perkin and Thorpe (3).



I II



III IV

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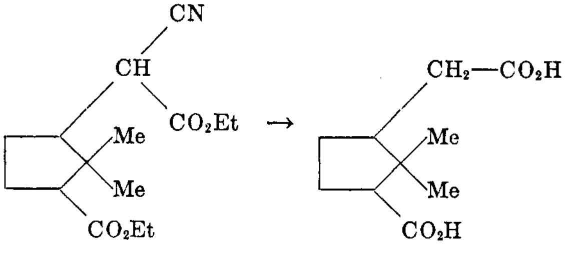
[1] A preliminary note embodying experimental results appeared in *Science and Culture (India)*, **18**, 201 (1953).



V VI

The ketoester (III, R = Et) easily underwent a Knoevenagel condensation with ethyl cyanoacetate by the procedure of Cope, *et al.* (8) as modified by Cragoe, *et al.* (9) to furnish the corresponding ethyl cyclopentylidenecyanoacetate IV ($\lambda^{\text{alc}}_{\text{max}}$ 238 mμ, log E 4.015) in fairly good yield. Catalytic reduction of the ester IV over palladized charcoal (5%) followed by hydrolysis afforded acid VI which after two crystallizations from water melted at 202–203° which could not be raised further. Komppa (1) has given m.p. 203–204° for his synthetic *dl-cis*-homoapocamphoric acid. Although direct comparison of our sample with an authentic specimen was not carried out, we have no doubt that our product is identical with Komppa's *dl-cis*-homoapocamphoric acid VI in view of our observations during the synthesis of *dl*-homocamphoric acid (*cf.* Part II).

Our thanks are due to Dr. P. C. Dutta for his keen interest and helpful discussion.

EXPERIMENTAL[2]

Ethyl 2-methyl-2,3-dicyanopropane-3-carboxylate. The method of its preparation was essentially the same as that of Smith and Horwitz (6). The only exception was that we used "commercial pyridine" b.p. 140–160°, in place of pure pyridine and obtained equally good results. Thus 1 mole of each of the following, namely, acetone, ethyl cyanoacetate, glacial acetic acid, pyridine (80 g.) of above stated quality, potassium cyanide (70 g.), and absolute alcohol (100 ml.) gave 127.2 g. (70.6%), of the nitrile, b.p. 140–142°/4–4.5 mm; n_D^{34} 1.4339.

Ethyl 2-methyl-2,3,5-tricyanopentane-3-carboxylate (I). Following the usual technique of Bruson (7), to a solution of ethyl 2-methyl-2,3-dicyanopropane-3-carboxylate (49 g.) in dioxane (28 ml.), trimethylbenzylammonium hydroxide (Triton B, 4 ml.) was added and the mixture was cooled in an ice-bath. Freshly distilled acrylonitrile (23 ml.) was added dropwise with constant swirling and the mixture was left for 72 hours at room temperature. At the end of this period usually the mixture turned brown. It was decomposed by acidifying with acetic acid followed by an excess of cold water, when a heavy oil separated out. The aqueous portion was extracted twice with benzene and combined with the oil. The combined extract was washed with water and benzene was evaporated off. Distillation of the residual oil *in vacuo* gave 56.6 g. (89.2%) of a yellowish viscous oil, b.p. 196–198°/3–4 mm; $n_D^{31.5}$ 1.4595.

Anal. Calc'd for $C_{12}H_{15}N_3O_2$: C, 61.80; H, 6.43.

Found: C, 62.20; H, 6.50.

Triethyl 2-methylpentane-2,3,5-tricarboxylate (II, R = Et). Long hours of refluxing, usually 45–50 hours, over a free flame with 10–12 volumes of hydrochloric acid has been found to be a very convenient method of hydrolysis after a number of trial experiments

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[2] All melting points are uncorrected.

using different conditions. The nitrile I (56 g.) after 50 hours of refluxing with concentrated hydrochloric acid (560 ml.) gave stout cubes, m.p. 159–160° (II, R = H); recrystallization of a portion from water and dilute hydrochloric acid did not raise the m.p. beyond 160°; the literature gives m.p. 155–157° (3).

Anal. Calc'd for $C_9H_{14}O_6$: C, 49.54; H, 6.42.

Found: C, 51.00; H, 6.50.

The residue obtained by evaporation of the hydrolysate was directly esterified with a mixture of absolute alcohol (135 ml.) and sulfuric acid (30 ml., *d.* 1.84) by refluxing on water-bath for 35 hours. It then was cooled and poured over crushed ice and water. A dark oil immediately separated out. The aqueous portion was extracted thrice with benzene. The combined organic portion was successively washed with water, dilute sodium bicarbonate solution, and again with water. Removal of benzene left an oil which after distillation gave 35 g. (75.8%) of the ester (II, R = Et) as a colorless mobile oil, b.p. 166–170°/5–6 mm; $n_D^{33.5}$ 1.4356; $n_D^{28.5}$ 1.4382; the literature gives b.p. 195°/40 mm. (3).

About 5 g. of material was obtained as high-boiling fraction; b.p. 175–185°/5–6 mm.; $n_D^{28.5}$ 1.4408. This was combined with the small amount left in the Claisen flask and was re-hydrolyzed with hydrochloric acid giving another 6 g. of acid (II, R = H), m.p. 160°, and thus brought the yield of the ester to 87.2% over-all.

Ethyl 2,2-dimethylcyclopentane-1-one-3-carboxylate (III, *R = Et*). The ester (II, R = Et, 55 g.) was refluxed with sodium dust (6.3 g.) in dry benzene (200 ml.) under nitrogen atmosphere. It was observed that the reaction could not be initiated, even after prolonged heating, unless a few drops of alcohol were added. Addition of alcohol started a vigorous reaction and the sodium completely dissolved within 3 hours. The mixture was cooled under a nitrogen atmosphere and decomposed by acidifying with acetic acid followed by cold dilute hydrochloric acid and water. The benzene layer was separated and the aqueous portion was extracted thrice with benzene and the combined extract was washed with water and benzene removed leaving a deep brown oil (violet color with alcoholic ferric chloride). It was directly hydrolyzed with a mixture of glacial acetic acid (400 ml.), concentrated hydrochloric acid (300 ml.), and water (100 ml.) by refluxing in an oil-bath for 9 hours. On removal of the excess acids under water suction, a dark grey colored solid was obtained. A small portion was crystallized from dilute hydrochloric acid, m.p. 108–109°, the literature gives m.p. 109–110° (3). The crude acid was directly esterified with absolute alcohol (90 ml.) and sulfuric acid (10 ml., *d.* 1.84) by refluxing on a steam-bath for 25 hours. The mixture was cooled and poured into crushed ice and water when an oil was liberated immediately; it was worked up with ether in the usual way and after distillation *in vacuo* gave 23 g. (76.1% over-all from the ester II, R = Et); b.p. 96–98°/3 mm; $n_D^{34.5}$ 1.4413; the literature (3) gives b.p. 170–172°/100 mm.

The *semicarbazone* was crystallized from alcohol, m.p. 189–190° d.

Anal. Calc'd for $C_{11}H_{19}N_3O_3$: C, 54.77; H, 7.88.

Found: C, 54.79; H, 7.51.

Ethyl 2,2-dimethyl-3-carbethoxycyclopentylidenecyanoacetate (IV). A mixture of the keto ester (III, R = Et, 9.1 g.), ethyl cyanoacetate (7.0 g.), glacial acetic acid (3.0 g.), ammonium acetate (0.4 g.), and dry benzene (10.0 ml.) was gently refluxed with a water separator until the separation of water was complete. Then another lot of ammonium acetate (0.4 g.) was added and the refluxing was continued; the process was repeated until the quantity of ammonium acetate amounted to 1.6 g. The mixture was cooled and the benzene layer was washed thoroughly with water and the benzene was removed. Distillation of the residual oil gave a slightly viscous oil, b.p. 172–173°/3.5 mm; n_D^{22} 1.4752; yield 8.8 g. (66%).

Ultraviolet absorption: λ_{max}^{alc} 238 mμ, log E 4.015.

Anal. Calc'd for $C_{15}H_{21}NO_4$: C, 64.50; H, 7.52.

Found: C, 64.00; H, 7.22.

Ethyl 2,2-dimethyl-3-carbethoxycyclopentylcyanoacetate (V). A solution of the unsaturated ester IV (5.4 g.) in alcohol (10 ml.) was added to a pre-reduced suspension of palladized charcoal (5%, 1.0 g.) in alcohol (40 ml.) in an atmosphere of hydrogen. Since the uptake of hydrogen was very slow, 3 ml. of glacial acetic acid followed by another lot of palladized charcoal (5%, 0.2 g.) was added after which rapid reduction took place. The total absorption was 687 ml. of hydrogen at room temperature (34°). Then it was filtered and the alcohol was removed from the filtrate. The residual oil was taken up in ether and washed with water. The ether extract was dried over sodium sulfate, and the ether was evaporated. Distillation of the residual oil gave a colorless oil, b.p. 164–165°/2 mm; $n_D^{33.5}$ 1.4608; yield 5.05 g. (92.8%).

Anal. Calc'd for $C_{15}H_{23}NO_4$: C, 64.05; H, 8.18.

Found: C, 63.64; H, 8.52.

dl-Homoapocamphoric acid (VI). A mixture of the ester V (4.4 g.) and hydrochloric acid (50 ml.) was refluxed in an oil-bath for 30 hours. The crude acid was collected by filtration and recrystallized from water, m.p. 202–203°, yield 2.4 g. From the mother liquor another 0.6 g. of acid was obtained. The literature (1) gives m.p. 203–204° for *dl-cis*-homoapocamphoric prepared from apocamphoric anhydride.

Anal. Calc'd for $C_{10}H_{16}O_4$: C, 60.00; H, 8.00.

Found: C, 60.00; H, 8.01.

SUMMARY

Condensation of ethyl 2,2-dimethylcyclopentane-1-one-3-carboxylate with ethyl cyanoacetate followed by catalytic reduction and hydrolysis gave *dl-cis*-homoapocamphoric acid.

JADAVPUR, CALCUTTA—32.

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