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

SYNTHETIC INVESTIGATIONS IN THE CAMPHOR SERIES. PART IV. STUDY OF INTRAMOLECULAR CYCLIZATION OF TRIETHYL 2-METHYLHEXANE-2,3,6-TRICARBOXYLATE[1]

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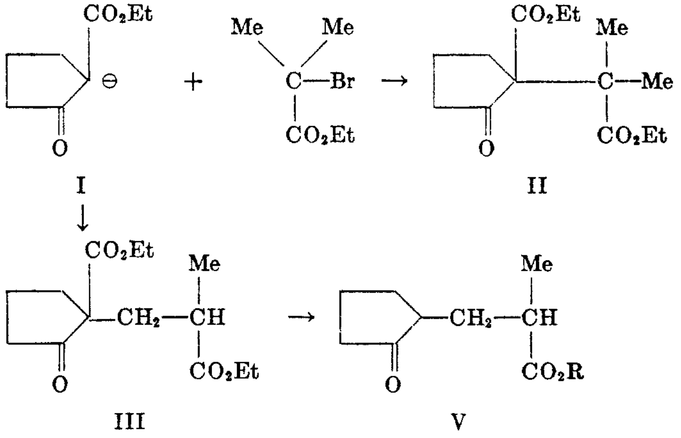
In connection with the experiments on the synthesis of camphoceenic acid (1), we had occasion to study the condensation of ethyl potassiocyclopentane-1-one-2-carboxylate with ethyl bromoisobutyrate in the presence of non-polar solvents. The product of condensation was, however, found to be not identical with II, but with III. Apparently dehydrohalogenation followed by Michael addition took place under the experimental conditions. This was readily proved by the Michael addition of methylmethacrylate to I followed by hydrolysis and esterification when the authentic ketoester V (R = Et) was obtained, the semicarbazone of which showed no m.p. depression when mixed with the corresponding derivative of the ester obtained through reaction of ethyl bromoisobutyrate with I followed by hydrolysis and esterification.



A similar observation during nucleophilic attack on ethyl isobromobutyrate has been made previously. Thus, an analogous observation was made by Bone and Perkin (2) when ethyl bromoisobutyrate was condensed with ethyl sodiocyanoacetate in a polar solvent, but when the condensation was carried out in a non-polar medium the normal condensation product resulted. These observations are in agreement with theoretical deductions (3). It is to be noted, however, that in the present case even in the absence of polar solvents the normal condensation product was not obtained. The bulkiness of the anion I perhaps hinders its approach within reaction distance of the tertiary carbon atom of the halogenated ester and, hence interfers with the SN_2 type of mechanism by causing an increase

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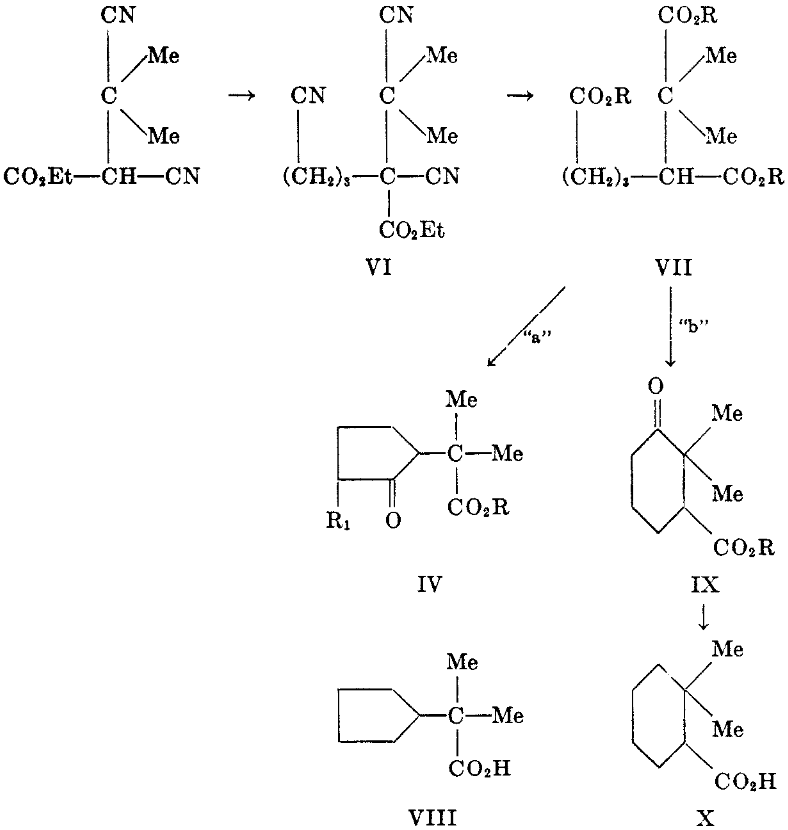
[1] A preliminary communication appeared in *Science and Culture* (*India*), **18**, 503 (1953).

in the activation energy of the process with the result that even in non-polar solvents the elimination reaction predominates.

The above results naturally led us to look for some alternative route for the synthesis of suitable cyclopentane derivatives and we thought it desirable to study the Dieckmann cyclization of triethyl 2-methylhexane-2,3,6-tricarboxylate (VII, R = Et) which was synthesized by the following series of reactions.

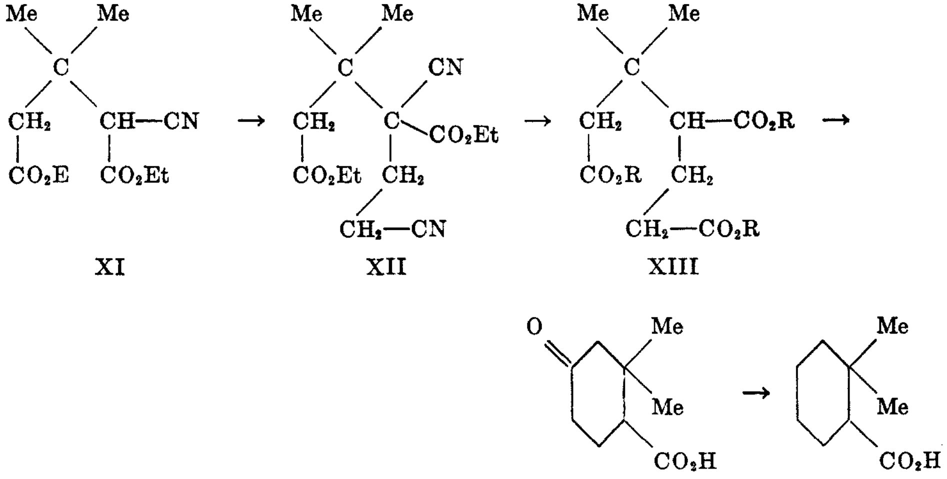
Ethyl 2-methyl-2,3-dicyanopropane-3-carboxylate, prepared according to the method of Smith and Horwitz (4), was condensed with 3-cyanopropyl bromide in the presence of alcoholic sodium ethoxide to furnish ethyl 2-methyl-2,3,6-tricyanohexane-3-carboxylate (VI) in quite good yield. Hydrolysis of VI with concentrated hydrochloric acid gave a gummy acid which, after direct esterification, was converted to triethyl 2-methylhexane-2,3,6-tricarboxylate (VII, R = Et); the acid (VII, R = H) regenerated from the ester melted at 132.5°. Cyclization of the ester (VII, R = Et) in the presence of sodium dust in boiling benzene gave a β-keto ester which, after direct hydrolysis with a mixture of glacial acetic acid and hydrochloric acid, was esterified to a colorless sweet-smelling liquid; *semicarbazone*, m.p. 153–154°. Huang-Minlon (5) reduction of this ester gave an acid with a characteristic fatty acid odor, the S-benzylthiuron-



ium salt of which was obtained in good yield and melted at 155°. Its m.p. could not be raised even after repeated crystallization from alcohol strongly suggesting the essential homogeneity of the materials in the previous steps.

Now the cyclization of the ester (VII, R = Et) may proceed along either of the two routes "a" or "b" giving ultimately 2-methyl-2-cyclopentylpropanoic acid (VIII) or 2,2-dimethylcyclohexanecarboxylic acid (X) as indicated in the reaction scheme. The course of cyclization was proved beyond doubt by comparison with authentic specimens of acids VIII and X which were synthesized by unambiguous methods.

2-Methyl-2-cyclopentylpropanoic acid (VIII) was prepared according to the method recommended by Hintikka (6) (*vide* experimental) and the acid so obtained had an almost identical boiling point and refractive index with the acid obtained through cyclization of VII (R = Et) followed by hydrolysis and Huang-Minlon reduction. Moreover the S-benzylthiuronium derivatives, m.p. 155°, showed no depression in m.p. on admixture, thus proving their identity.



XI XII XIII

XIV X

Synthesis of 2,2-dimethylcyclohexane-1-carboxylic acid was accomplished with the help of the sequence of reactions mentioned above.

Diethyl 2,2-dimethyl-3-cyanopropane-1,3-dicarboxylate (XI), prepared according to the method of Perkin and Thorpe (7), was cyanoethylated (8) in dioxane medium at room temperature in the presence of benzyltrimethylammonium hydroxide (Triton B) to give the dicyano ester (XII). In the course of the hydrolysis of XII with concentrated hydrochloric acid it was found that there was always some unhydrolyzed or partially hydrolyzed material. But use of 48% hydrobromic acid was an excellent procedure as it readily gave substantially pure acid (XIII, R = H) which usually crystallized out of the cold hydrolysate. Dieckmann cyclization of the ester (XIII, R = Et) gave a β-keto-ester which was directly hydrolyzed to XIV which was obtained as a waxy solid after evaporative distillation. It was highly hygroscopic and several attempts to induce crystallization were not successful. Huang-Minlon reduction of XIV gave 2,2-dimethylcyclohexane-1-carboxylic acid (X) as a colorless liquid whose S-benzylthiuronium derivative melted at 158.5° and showed a m.p. depression when mixed with the corresponding derivative from VIII obtained through cyclization of (VII, R = Et).

Thus there is no doubt that the Dieckmann cyclization of triethyl-2-methylhexane-2,3,6-tricarboxylate (VII, R = Et) proceed along the route "a"; also the homogeneity of the S-benzylthiuronium derivative of the acid VIII obtained from the cyclization product of (VII, R = Et) is strongly suggestive of the fact that (IV, R = Et, R_1 = CO_2Et) is the sole product of the Dieckmann cyclization.

In this connection, reference should be made to the work of Brown (9).

EXPERIMENTAL[2]

Ethyl 2-methyl-3-(2'-ketocyclopentyl)propanoate (V). (*a*). *Through condensation of ethyl bromoisobutyrate with ethyl cyclopentane-1-one-2-carboxylate.* To a suspension of potassium dust (4 g.) in dry xylene (150 ml.) the ketoester (15.6 g.) was added dropwise with slight cooling. When the vigor of the reaction completely subsided, ethyl bromoisobutyrate (21.5 g.) was added. Refluxing was started after 0.5 hour and was continued for 22 hours in an oil-bath. The mixture was found to be slightly alkaline; it was decomposed with cold water and extracted with ether. The extract was repeatedly washed with water and dried over sodium sulphate. The solvent was removed and the residual oil was distilled, b.p. 140–146°/2–3 mm.; n_D^{33} 1.4552; *semicarbazone*, m.p. 146–147°. Yield 4.5 g. A large amount of high-boiling material also was formed. When xylene was replaced by toluene essentially similar results were obtained.

Anal. Calc'd for $C_{14}H_{22}O_5$: C, 62.22; H, 8.15.

Found: C, 61.98; H, 7.88.

The above condensation product (2 g.) was hydrolyzed with a mixture of glacial acetic acid (20 ml.), hydrochloric acid (15 ml.), and water (5 ml.) by refluxing at 160–170° for 6 hours. The excess acids were removed under suction and the residue was esterified with a mixture of alcohol (5 ml.) and sulfuric acid (0.5 ml., *d.* 1.84) by refluxing for 11 hours. After working up in the usual way, distillation gave a colorless ester, b.p. 93–95°/1 mm.; n_D^{21} 1.4428; yield 0.6 g.; the *semicarbazone* crystallized from alcohol, m.p. 168–169°.

(*b*). *Through addition of methyl methacrylate to ethyl cyclopentan-1-one-2-carboxylate.* To a solution of sodium ethoxide, prepared from sodium (0.27 g., 0.012 g.-atom) and alcohol (5 ml.), the keto ester (15.6 g., 0.1 mole) was added with swirling. The mixture was thoroughly cooled and the acrylate (12.5 g., 0.11 mole) was dissolved in a mixture of ether (5 ml.) and alcohol (5 ml.) was added in a thin stream and left overnight. The next day the reaction was completed by refluxing for 2 hours on steam-bath. It was cooled, and decomposed with acetic acid (3 ml.) followed by large volume of water. Then it was worked up with benzene in the usual manner and distillation gave 18 g. of ester, b.p. 135–137°/1.5 mm.; n_D^{22} 1.4530.

Anal. Calc'd for $C_{13}H_{20}O_5$: C, 60.94; H, 7.81.

Found: C, 61.01; H, 7.67.

The keto ester (5 g.) then was hydrolyzed with a mixture of glacial acetic acid (48 ml.), hydrochloric acid (36 ml.), and water (6 ml.) by refluxing at 160–170° for 6 hours. Removal of the acids was followed by esterification of the residue with a mixture of alcohol (12 ml.) and sulfuric acid (1 ml., *d.* 1.84) by refluxing for 14 hours. Then it was worked up in the

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[2] All melting points are uncorrected.

usual way and distillation gave 2.8 g. of the keto ester (V, R = Et), b.p. 114–115°/4 mm.; $n_D^{23.5}$ 1.4463.

Anal. Calc'd for $C_{11}H_{18}O_3$: C, 66.67; H, 9.09.
Found: C, 66.38; H, 9.01.

The *semicarbazone* was crystallized from alcohol, m.p. 170–171°; a mixture m.p. with the corresponding product obtained as described under (*a*) showed no depression.

Anal. Calc'd for $C_{12}H_{21}N_3O_3$: C, 56.47; H, 8.23.
Found: C, 56.90; H, 8.28.

Ethyl 2-methyl-2,3,6-tricyanohexane-3-carboxylate (VI). To a cold solution of sodium ethoxide, prepared from sodium (6.3 g.) and alcohol (100 ml.), ethyl 2-methyl-2,3-dicyanopropane-3-carboxylate (49 g.) dissolved in little alcohol was added dropwise. After some time 3-cyanopropyl bromide (40 g.) was added with swirling and without allowing any undue rise in temperature. After half an hour, the mixture was refluxed on a steam-bath until it was found to be neutral to litmus. The excess of alcohol was distilled off from a water-bath and the residue was cooled and diluted with an excess of water. The liberated oil was separated and the aqueous portion was extracted thrice with benzene. The combined organic portions were washed several times with water, dried, benzene was removed, and the residual oil was distilled giving a highly viscous oil, b.p. 205–207°/3 mm.; n_D^{22} 1.4638; yield 50 g. (74.07%).

Anal. Calc'd for $C_{13}H_{17}N_3O_2$: C, 63.15; H, 6.88.
Found: C, 63.51; H, 7.10.

Triethyl 2-methylhexane-2,3,6-tricarboxylate (VII, *R* = *Et*). The above nitrile (48 g.) was refluxed with concentrated hydrochloric acid (700 ml.) over a free flame. The mixture was cooled and evaporated to dryness over a steam-bath and the crude residue was esterified by refluxing with ethanol (150 ml.) and sulfuric acid (18 ml., *d.* 1.84). After 25 hours the mixture was cooled, poured into crushed ice and water, and worked up in the usual manner. Distillation gave (VII, R = Et) as a colorless oil. Yield, 28.5 g. (46.7% based on VI), b.p. 144–146°/2 mm.; n_D^{24} 1.4390.

Anal. Calc'd for $C_{16}H_{28}O_6$: C, 60.75; H, 8.86.
Found: C, 61.10; H, 8.39.

The acid (VII, R = H) was regenerated by hydrolysis of the ester (VII, R = Et) with hydrochloric acid and was crystallized from water containing a few drops of hydrochloric acid, m.p. 132.5°.

Anal. Calc'd for $C_{10}H_{16}O_6$: C, 51.72; H, 6.89.
Found: C, 52.00; H, 7.06.

Dieckmann cyclization of the ester (VII, R = Et). *Formation of ethyl 2-methyl-2-(2′-ketocyclopentyl)propanoate* (IV, R = Et, R_1 = H). To a suspension of sodium dust (1.7 g.) in dry benzene (75 ml.), the ester (15.5 g.) was added in an atmosphere of nitrogen. A brisk reaction took place and the sodium dissolved within 3.5 hours. The red solution was cooled, and decomposed with acetic acid (5 ml.) then with cold water and dilute hydrochloric acid. The mixture was thoroughly shaken and benzene layer was separated. The aqueous portion was extracted twice with benzene and the combined benzene portions were washed once with water. After removing benzene by distillation, the crude product (which gives a bluish-violet color with alcoholic ferric chloride) was directly hydrolyzed with a mixture of hydrochloric acid (96 ml.), glacial acetic acid (128 ml.), and water (32 ml.) by refluxing at 160–170° for 14 hours. The excess of acids was removed under a water suction and the grey residual oil was esterified directly with alcohol (25 ml.) and sulfuric acid (2 ml., *d.* 1.84). After 16 hours of refluxing, the mixture was cooled, and poured into crushed ice and water. The oily layer was separated and the aqueous layer was extracted thrice with ether. The combined organic portion was washed with water, dilute sodium bicarbonate solution, and water and dried over sodium sulfate. The residual oil after evaporation of the ether was distilled under a vacuum giving a colorless, mobile oil with sweet odor, b.p. 104–106°/3–4 mm.; $n_D^{24.5}$ 1.4488; yield, 5 g. (51.5% over-all).

Anal. Calc'd for $C_{11}H_{18}O_3$: C, 66.70; H, 9.09.
Found: C, 66.68; H, 8.60.

2-Methyl-2-cyclopentylpropanoic acid (VIII). (*a*). *From* (IV, *R* = *Et*, *R_1* = *H*). The keto ester (1.5 g.) was dissolved in diethylene glycol (17.5 ml.) containing caustic potash (2.25 g.) and hydrazine hydrate (3 ml., 50% w/w) and the mixture was heated gradually in an oil-bath up to 190°. There was a vigorous evolution of nitrogen. After maintaining the mixture at this temperature for two hours, the excess of water was distilled off and it was refluxed again for additional two hours. Then it was cooled, diluted with water, and acidified with hydrochloric acid. The well cooled mixture was extracted four times with ether, dried over sodium sulfate, and distilled after evaporation of the ether; b.p. 120–125°/3–4 mm.; $n_D^{21.5}$ 1.4611. Yield, 0.6 g. (40.4%). On keeping for long periods there was no tendency for crystallization.

It gave a characteristic *S-benzylthiuronium* salt (light shining flakes from alcohol) m.p. 155°.

Anal. Calc'd for $C_{17}H_{26}N_2O_2S$: C, 63.35; H, 8.07.
Found: C, 63.04; H, 7.55.

(*b*). *According to the method of Hintikka.* Cyclopentanone (12.6 g.), ethyl bromoisobutyrate (36.6 g.), zinc wool (19.5 g.), and dry benzene (180 ml.) gave 18.5 g. of the hydroxy ester, b.p. 98–99°/3 mm.; n_D^{30} 1.4652.

Dehydration of this ester (18.5 g.) with phosphorus pentoxide (21 g.) in dry benzene (100 ml.) gave 10 g. of unsaturated ester, b.p. 75–77°/3 mm.; n_D^{30} 1.4497.

Catalytic reduction of the unsaturated ester (6.10 g.) with palladized charcoal (1 g., 5%) in absolute alcohol (45 ml.) at room temperature (24°) gave the corresponding saturated ester, b.p. 209°; yield 5.0 g.

The above ethyl ester (3.5 g.) was hydrolyzed with a solution of caustic potash (2 g.) in aqueous alcohol (1:1, 20 ml.) by refluxing for 30 hours in an oil-bath. The alkaline solution was concentrated on a steam-bath, cooled, and acidified with hydrochloric acid with cooling. After saturation with sodium chloride it was extracted several times with ether, and dried over sodium sulphate. Evaporation of ether left an oil which distilled at 113–114°/2.5 mm.; $n_D^{20.5}$ 1.4610; yield, 2.4 g. (81.75%).

Anal. Calc'd for $C_9H_{16}O_2$: C, 69.23; H, 10.25.
Found: C, 68.90; H, 10.2.

The acid gave an *S-benzylthiuronium* derivative m.p. 155° (crystallized in flakes from alcohol) and there was no depression in m.p. when this was mixed with the corresponding derivative described under (*a*).

Diethyl 2,2-dimethyl-3,5-dicyanopentane-1,3-dicarboxylate (XII). Diethyl 2,2-dimethyl-3-cyanopropane-1,3-dicarboxylate (XI) (7) (10 g.) was dissolved in dioxane (8 ml.) to which a solution of benzyltrimethylammonium hydroxide (Triton B, 1.5 ml.) then was added. The mixture was slightly cooled and freshly distilled acrylonitrile (5 ml.) was added dropwise. The dark brown mixture was kept for 72 hours at room temperature, then decomposed with a few drops of acetic acid followed by an excess of water. The liberated heavy oil was removed and aqueous portion was extracted once with benzene which was combined with the oil. This extract was washed with water and the benzene was evaporated off leaving a thick oil which, after vacuum distillation, gave 13.3 g. (71.6%) of XII, b.p. 198–200°/2 mm.; n_D^{32} 1.4606.

Anal. Calc'd for $C_{15}H_{22}N_2O_4$: C, 61.22; H, 7.50.
Found: C, 60.84; H, 8.00.

Triethyl 2,2-dimethylpentane-1,3,5-tricarboxylate (XIII, R = Et). The above nitrile (34 g.) was refluxed with concentrated hydrochloric acid (350 ml.) over a free flame for 44 hours. The hydrolyzate was evaporated on a steam-bath and the residue was esterified with absolute ethanol (110 ml.) and sulfuric acid (12 ml., *d.* 1.84). After 30 hours of refluxing, it was cooled, decomposed, and worked up in the usual manner as described earlier. After distillation 27.05 g. of a substance was obtained whose varying b.p. indicated (also shown by varying refractive indices of different cuts) incomplete hydrolysis. Therefore the whole lot was again refluxed with sulfuric acid (65%, 100 ml.) over a small flame. There was some initial charring and frothing. After one hour it was warmed on a water-bath for another 15 hours and then refluxed over a free flame for two hours more. The dark black solution was cooled, and filtered through sintered glass, and the filtrate was saturated with ammonium sulfate and extracted seven times with ether. The extract was dried over sodium sulfate, ether was removed and the crude material was further dried by azeotropic distillation with benzene. The brown residue then was esterified with absolute alcohol (100 ml.) and sulfuric acid (10 ml., *d.* 1.84). After 30 hours of refluxing, the mixture was cooled, decomposed, and worked up in the usual way. Two fractions were isolated by distillation; (a) 11 g., b.p. 178–180°/5 mm.; $n_D^{31.5}$ 1.4455; almost odorless.

Anal. Calc'd for $C_{16}H_{28}O_6$: C, 60.75; H, 8.86.
Found: C, 60.37; H, 9.04.

(b) 9.2 g.; b.p. 198–203°/5 mm.; $n_D^{31.5}$ 1.4530; more viscous than (a).

Fraction (b) was further hydrolyzed with 48% hydrobromic acid (50 g.) over a free flame for 46 hours. Then it was evaporated on a steam-bath and stout cubes of the acid were obtained on cooling. These were dissolved in the minimum quantity of water and were boiled with Norit for 0.5 hour and filtered. After concentration of the filtrate, 8.5 g. of the acid, 2,2-dimethylpentane-1,3,5-tricarboxylic acid (XIII, R = H); m.p. 137.5° was obtained.

Anal. Calc'd for $C_{10}H_{16}O_6$: C, 51.72; H, 6.89.
Found: C, 51.45; H, 6.72.

3,3-Dimethylcyclohexan-1-one-4-carboxylic acid (XIV). To a suspension of sodium dust (1 g.) in dry benzene (45 ml.) the ester (XIII, R = Et) (10 g.) was added, followed by a few drops of ethanol. (The entire system was in an atmosphere of nitrogen.) After a few minutes of heating sodium began to dissolve and the solution turned reddish. When dissolution was complete, the whole was cooled and acidified with acetic acid followed by cold water and little dilute hydrochloric acid. The mixture was thoroughly shaken, the benzene layer was separated, and the aqueous portion was extracted with benzene. The combined benzene extract was washed with water, and benzene was removed by distillation. The residue, which gave a bluish-violet color with alcoholic ferric chloride, was hydrolyzed with glacial acetic acid (72 ml.), hydrochloric acid (54 ml.), and water (18 ml.). After 14 hours, the refluxing was stopped, and the acids were removed under a water suction. From the residue 3.65 g. (70%) of the cyclohexane acid (XIV) was obtained by evaporative distillation at 160–170° (bath temperature)/0.4 mm. The oily acid on keeping gradually solidified to a waxy solid. The acid XIV was found to be highly hygroscopic and slight exposure to atmosphere made it pasty.

The *semicarbazone* crystallized from alcohol, m.p. 214–215° d.

Anal. Calc'd for $C_{10}H_{17}N_3O_3$: C, 52.86; H, 7.50.
Found: C, 53.14; H, 7.58.

2,2-Dimethylcyclohexane-1-carboxylic acid (X). The keto acid (2.4 g.) was treated with a solution of caustic potash (3.8 g.) in diethylene glycol (46 ml.) and hydrazine hydrate (4.6 ml., 50%) was added to the mixture. After 1.5 hours of reflux in an oil-bath at 135–140°, water was distilled off by raising the temperature up to 195°. It was heated again at 195° for 4 hours, cooled, diluted with water (50 ml.), acidified with hydrochloric acid (6 *N*), and extracted with ether. The extract after drying and evaporation gave a residue which distilled at 103–105°/3–4 mm.; n_D^{21} 1.4621; yield, 1.85 g. (84.1%).

Anal. Calc'd for $C_9H_{16}O_2$: C, 69.23; H, 10.25.
Found: C, 68.84; H, 10.11.

The *S-benzylthiuronium* derivative melted at 158.5° and showed a m.p. depression when mixed with the corresponding derivative of the acid obtained by cyclization of the ester (VII, R = Et).

Anal. Calc'd for $C_{17}H_{26}N_2O_2S$: C, 63.35; H, 8.07.
Found: C, 63.20; H, 7.68.

SUMMARY

Dieckmann cyclization of triethyl 2-methylhexane-2,3,6-tricarboxylate has been shown to give ethyl 2-methyl-2-(2′-keto-3′-carboethoxycyclopentyl)propanoate.

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