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SYNTHETIC INVESTIGATIONS IN THE CAMPHOR SERIES. PART I A NEW SYNTHESIS OF CAMPHONONIC ACID.[1]

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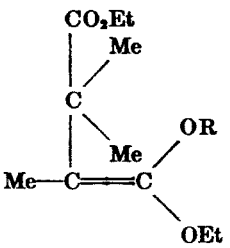
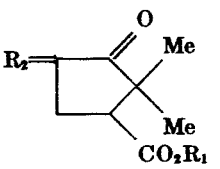
Camphononic acid (1) played a very important part in the elucidation of the constitution of the camphor molecule. Its structure was established by Lapworth and his co-workers (2) and was confirmed through synthesis by Ganguly (3). In connection with an unambiguous synthesis of *dl*-homocamphoric acid (to be described in Part II) we have developed a new synthesis of *dl*-camphononic acid.

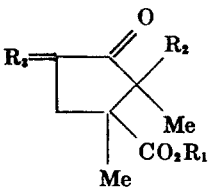
Based upon an observation of Brown and Eberly (4) that ethyl isobutyrate undergoes hydrogen exchange in presence of deutero alcohol and sodium ethoxide as well as that of Hauser and co-workers (5) that acyl groups could be introduced on the α-carbon atom after converting ethyl isobutyrate into the corresponding enolate with sodium triphenylmethyl, we attempted to synthesize homocamphoronic acid by introducing a propionic acid moiety into diethyl trimethylsuccinate. Since diethyl trimethylsuccinate is expected to give an enolate on treatment with sodium triphenylmethyl it seemed of interest to us to study the reaction of the enolate with ethyl β-chloropropionate. No condensation was observed to take place. Presumably ethyl β-chloropropionate is a stronger acid than diethyl trimethylsuccinate and decomposed the enolate of the latter. An alternative attempt for the introduction of the propionic acid moiety into diethyl trimethylsuccinate through cyanoethylation led to the isolation in poor yield of a product which seems to be an O-alkyl type of compound I (R = CH_2CH_2CN; *vide* experimental).



I



II



III

In view of the above observations we attempted to devise a new synthesis of camphononic acid by employing suitable cyclic intermediates. Our first choice was ethyl 2,2-dimethylcyclopentane-1-one-3-carboxylate II (R_1 = Et, R_2 = H_2) (6) (*cf.* Part III) in which we attempted to introduce a methyl group at C_3

[1] A preliminary communication embodying experimental results appeared in *Science and Culture (India)*, **18**, 600 (1953).

through methylation of the N-methylanilinomethylene derivative II [R_1 = Et, R_2 = CHN(Me)Ph] with sodium triphenylmethyl and methyl iodide. Persistent attempts under different conditions led uniformly to the isolation of the original compound II (R_1 = H, R_2 = H_2). An alternative attempt for the synthesis of camphononic acid from II (R_1 = H, R_2 = H_2) *via* the Favorskii rearrangement (7) failed to give any useful product.

We next attempted a synthesis of camphononic acid through the introduction of a methyl group at C_2 of the ketoester III (R_1 = Et, R_2 = H, R_3 = H_2) (8) which was converted into the N-methylanilinomethylene derivative III [R_1 = Et, R_2 = H, R_3 = CHN(Me)Ph] according to the method of Birch and Robinson (9). Methylation of III [R_1 = Et, R_2 = H, R_3 = CHN(Me) Ph] with potassium *tert*-butoxide and methyl iodide gave III [R_1 = Et, R_2 = Me, R_3 = CHN(Me)Ph] which was directly subjected to the process for the removal of the protecting N-methylanilinomethylene group. At first direct hydrolysis with 15% aqueous caustic potash (10) was attempted when an unsatisfactory yield of camphononic acid III (R_1 = H, R_2 = Me, R_3 = H_2) was obtained.

The two stage hydrolysis recommended by Birch and Robinson (9) also did not work very well. After a number of trials it was found that by prolonging the duration of alkaline hydrolysis in the Birch-Robinson procedure satisfactory results could be obtained. The product III (R_1 = H, R_2 = Me, R_3 = H_2) after purification melted at 228°, oxime, m.p. 186–187° (*vide* experimental).

Our thanks are due to Dr. P. C. Dutta for helpful suggestions.

EXPERIMENTAL[2]

Attempted condensation between diethyl trimethylsuccinate and acrylonitrile. Formation of (I, R = CH_2CH_2CN). A typical experiment is described here. Potassium (2.6 g.) was dissolved in *tert*-butyl alcohol (60 ml.) by warming and stirring. It was cooled to about 20° and diethyl trimethylsuccinate (14.5 g.) was added dropwise. This was followed by slow addition of acrylonitrile (4.3 g.) with thorough stirring of the mixture. During this addition the temperature was always maintained at 15–20° and gradually the mixture was allowed to attain room temperature (30°). After stirring for an additional five hours, it was left overnight and then just made acidic with dilute hydrochloric acid. It was diluted with a large volume of water and extracted thrice with benzene. The extract after thorough washing with water was dried and evaporated and finally the residue was distilled giving a colorless oil (7.4 g.) b.p. 130–133°/2–3 mm. and a forerun of unchanged diethyl trimethylsuccinate, b.p. 88–90°/3 mm. Redistillation of the higher-boiling product again gave low-boiling material (b.p. 106–108°/5 mm.) leaving only 3.3 g. On further distillation of 3.3 g., virtually the whole material was collected at 110°/6 mm. leaving a negligible amount of high-boiling material.

A mixture of this high-boiling fraction (1 g.) and concentrated hydrochloric acid (10 ml.) was refluxed and gave about 0.80 g. of acid, m.p. 149–150°; mixture m.p. with an authentic sample of trimethylsuccinic acid showed no depression.

In an attempt to esterify the above high-boiling fraction, it (7.4 g.) was dissolved in absolute alcohol (18 ml.) and thoroughly cooled in an ice-bath. Hydrochloric acid gas was passed for 30 minutes and then refluxed for 2 hours over a steam-bath. After working up the mixture in the usual way, it gave 7 g. of ester b.p. 85–86°/3 mm., a fraction of which after hydrolysis with hydrochloric acid gave an acid whose m.p. and mixture m.p. with an authentic specimen of trimethylsuccinic acid showed no depression.

[2] All melting points are uncorrected.

Ethyl 2,2-dimethyl-5-methylanilinomethylenecyclopentane-1-one-3-carboxylate (II, [R_1 = Et, R_2 = CHN(Me)Ph]). To a cold suspension of sodium ethoxide, prepared from sodium (3.5 g.) and absolute alcohol (8.8 ml.), in benzene (80 ml.), ethyl formate (13.5 g.) was added when a clear brown solution was obtained. After 0.5 hours, the keto ester (II; R_1 = Et, R_2 = H_2; 13 g.) in benzene (20 ml.) was added in a thin stream with continuous shaking. The mixture turned thick and reddish-brown and then the sodio salt separated out. The mixture was left overnight. Next day it was decomposed with ice-cold water and the separated benzene layer was extracted thrice with cold caustic soda solution (4%). The alkaline extract was combined with the original alkaline portion and acidified with cold dilute hydrochloric acid. The liberated reddish oil was extracted with ether which, after washing with water, was dried by distillation with benzene. The residual oil (bluish-violet color with alcoholic ferric chloride) was next treated with a solution of freshly distilled N-methylaniline (8 g.) in benzene (100 ml.). The mixture within a few minutes became turbid and warmed up. This was followed by gentle refluxing for 2 hours under a Dean and Starke water separator. After cooling, benzene was partially removed under suction and the residue, after keeping in an ice chest overnight, gave big lumps of the anilino derivative II[R_1 = Et, R_2 = CH·N(CH_3)Ph]. It was filtered, washed with a little benzene and petroleum ether (80–100°) and, after drying, weighed 8.8 g. Concentration of mother liquor gave another lot of 4.3 g. The crude derivative melts at 57–59°; on attempting purification through crystallization, the crystals disappeared and a viscous residue was obtained (9).

When a solution of the above anilinomethylene compound (3.40 g.) dissolved in dry ether was added to a solution of sodium-triphenylmethyl from triphenylmethyl chloride (9.2 g.) and sodium amalgam (sodium 1.50 g., mercury 152 g.) a reddish-brown solution was obtained. On addition of methyl iodide (5 g.), after ten minutes and stirring no heat was developed and the reddish-brown color was not discharged within a reasonable time. After leaving overnight the mixture was decomposed with an excess of acetic acid followed by cold water. Ether-extracted material was hydrolyzed under nitrogen with a caustic potash solution (caustic potash 8 g., water 40 ml.). The hydrolyzate was repeatedly extracted with ether to remove triphenylmethane and the alkaline layer was acidified with cold hydrochloric acid (Congo Red) and extracted with ether. Removal of ether gave a grey-colored acid of m.p. 102° which was raised to 108–109° after crystallization; this acid showed no depression in m.p. when mixed with the original keto-acid II (R_1 = H, R_2 = H_2).

Ethyl 2,3-dimethylcyclopentane-1-one-3-carboxylate (III, R_1 = Et, R_2 = H, R_3 = H_2). This was prepared according to the method of Chakravarti (8) as described below. Ethyl levulinate (22.6 g.), ethyl cyanoacetate (18.0 g.), acetamide (3.60 g.), and glacial acetic acid (40 ml.) gave 21.0 g. of unsaturated cyanoester, b.p. 156–158°/3 mm.

The above unsaturated cyanoester (21.0 g.) in 95% alcohol (135 ml.), potassium cyanide (15.0 g.) in water (80 ml.), and dilute hydrochloric acid (33 ml., 20%) gave 18.5 g. of diethyl 2-methyl-1,2-dicyanobutane-1,4-dicarboxylate, b.p. 188–190°/3 mm.

The dicyano ester (41 g.) on methylation with sodium ethoxide (sodium 4.1 g. in 65 ml. of absolute alcohol) and methyl iodide (16 ml.) followed by hydrolysis with hydrochloric acid (250 ml.) for 20 hours and esterification with alcohol (125 ml.) and sulfuric acid (12.5 ml., *d.* 1.84) gave 23 g. of triethyl 3-methylpentane-2,3,5-tricarboxylate, b.p. 155–156°/6 mm. The higher-boiling fraction on further hydrolysis and esterification gave 6.8 g. more of the same ester.

The above triester (88.80 g.) was cyclized with sodium dust (8.33 g.) in dry benzene (300 ml.) and the crude ketoester, after direct hydrolysis with dilute hydrochloric acid (6%, 600 ml.) for 10 hours, was esterified with alcohol (200 ml.) and hydrochloric acid gas giving 35.60 g. of ethyl 2,3-dimethylcyclopentane-1-one-3-carboxylate, b.p. 98–99°/2.5 mm. The *semicarbazone* was crystallized from alcohol, m.p. 190–191°.

Ethyl 2,3-dimethyl-5-methylanilinomethylenecyclopentane-1-one-3-carboxylate (III, [R_1 = Et, R_2 = H, R_3 = CHN(CH_3)Ph]). A suspension of sodium ethoxide, prepared from sodium (1.5 g.) and absolute alcohol (7 ml.), in dry benzene (50 ml.), was distilled under a vacuum to remove the major portion of benzene. A further lot of benzene (10 ml.) was added and

distilled off; finally the mixture was heated to 150° under a vacuum and maintained at this temperature for ten minutes when an almost white powdered sodium ethoxide was obtained.

This was again suspended in dry benzene (60 ml.) and cooled in an ice-bath. A solution of ethyl formate (17 ml.) in dry benzene (10 ml.) was added with continuous swirling when a clear brown solution was obtained. A solution of the ketoester (III, [R_1 = Et, R_2 = H, R_3 = H_2]) (10 g.) in dry benzene (10 ml.) was added after ten minutes. Initially a clear solution was obtained but after some time the mixture became a slurry and was left overnight. The brown pasty mixture next was decomposed with ice-cold water and the aqueous layer was separated. The benzene portion was extracted twice with cold dilute caustic soda solution (4%) and then was combined with the original alkaline solution. After acidification with cold hydrochloric acid, the liberated oil was extracted with ether. The extract was washed with water, dried, and then the solvent was evaporated off. The residual oil (bluish-violet color with alcoholic ferric chloride) next was treated with a solution of N-methylaniline (6.5 g.) in benzene (75 ml.). The mixture warmed up and became turbid. It was gently refluxed for 1.5 hours under a Dean and Starke water separator on a steam-bath, after which the excess of benzene was distilled off under suction leaving a viscous brown oil. On keeping for several days there was no tendency for crystallization and other attempts to induce crystallization also were not successful. Distillation gave 15 g. of a pale yellow viscous oil (III, [R_1 = Et, R_2 = H, R_3 = CH·N(CH_3)Ph]), b.p. 195–196°/0.2 mm., which was used directly for the next step.

Ethyl 2,2,3-trimethylcyclopentane-1-one-3-carboxylate or ethyl camphononate (III, R_1 = Et, R_2 = Me, R_3 = H_2). (*a*) A solution of potassium *tert*-butoxide from potassium (12 g.) and sodium-dried *tert*-butyl alcohol (245 ml.) was prepared in a nitrogen atmosphere. The anilino compound (III, [R_1 = Et, R_2 = H, R_3 = CH·N(CH_3)Ph]) (15 g.) dissolved in *tert*-butyl alcohol (30 ml.) was added to the stirred solution of potassium *tert*-butoxide and immediately a deep reddish-brown solution was obtained. After 15 minutes methyl iodide (35 ml.) was added in a thin stream to the vigorously agitated solution when a considerable amount of heat was developed and the solution started refluxing. Some external cooling was necessary in order to avoid the loss of methyl iodide and within 10 minutes the whole mixture turned pale yellow due to the precipitation of potassium iodide. After 2 hours' stirring it was left overnight and again stirred for 0.5 hours after which the mixture was found to be practically neutral to litmus. An excess of *tert*-butyl alcohol was removed by distillation and the residue was cooled and decomposed with a few drops of acetic acid followed by a large volume of water. It was extracted with ether, and the extract was washed twice with water, dried, and the solvent was evaporated. The residual oil next was hydrolyzed (10) under a nitrogen atmosphere with an aqueous caustic potash solution, prepared from caustic potash (30 g.) and water (200 ml.), by refluxing for 7 hours. It was again cooled, and extracted twice with ether to remove undesirable materials. The cold aqueous alkaline solution was acidified with hydrochloric acid, saturated with salt, and then extracted with ether and dried. Removal of the ether gave a dark residue which was directly esterified by refluxing for 28 hours with a mixture of absolute alcohol (50 ml.) and sulfuric acid (4 ml., *d.* 1.84). Then it was cooled, decomposed with ice-cold water, and extracted with ether in the usual way. Distillation gave 2.5 g. of ester (III, R_1 = Et, R_2 = Me, R_3 = H_2); b.p. 96–100°/3–4 mm.; 97–99°/4 mm.; n_D^{22} 1.4512; n_D^{30} 1.4499.

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

Found: C, 66.23; H, 8.77.

The *semicarbazone* crystallized from alcohol, m.p. 183–184°. It showed a depression in m.p. on admixture with the semicarbazone of (III, R_1 = Et, R_2 = H, R_3 = H_2).

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

Found: C, 56.00; H, 8.27.

(*b*). Owing to an unsatisfactory yield the above procedure was repeated with the following modification during hydrolysis.

A solution of potassium (20 g.) in *tert*-butyl alcohol was prepared and then the anilino-

methylene derivative (III, [R_1 = Et, R_2 = H, R_3 = CH·N(CH_3)Ph]) (25 g.) was added followed by the addition of methyl iodide (50 ml.) as described before. The crude methylated compound (III, [R_1 = Et, R_2 = Me, R_3 = CH·N(CH_3)Ph]) was gently refluxed with aqueous alcoholic hydrochloric acid solution (alcohol 25 ml., hydrochloric acid 25 ml., and water 25 ml.) for one hour. It was cooled, diluted with cold water, and extracted with ether. The ether extract was washed with water, dried, and the ether was evaporated. The residual oil was hydrolyzed with caustic soda solution (4%, 300 ml.) in an oil-bath for 25 hours. It again was cooled, acidified with cold hydrochloric acid, and extracted with ether after saturation with salt. The ether extract was washed with water and the ether was evaporated. The grey colored residue was dried by repeated distillation with benzene.

Another lot of the anilinomethylene derivative (III, [R_1 = Et, R_2 = H, R_3 = CH·N(CH_3)Ph]) (25 g.) was similarly treated and the crude acid (III, R_1 = H, R_2 = Me, R_3 = H_2) thus obtained was combined with the previous lot and esterified with alcohol (200 ml.) and sulfuric acid (11 ml., *d.* 1.84) by refluxing for 25 hours. After working up in the usual way, distillation gave 15.0 g. of ethyl camphonoate (III, R_1 = Et, R_2 = Me, R_3 = H_2), b.p. 97–99°/4 mm. The high-boiling residue left in the flask after distillation was rehydrolyzed with dilute caustic soda solution (4%, 200 ml.) and then esterified giving another lot of 2.8 g. of (III, R_1 = Et, R_2 = Me, R_3 = H_2) thus bringing the yield of ester to 54.3% based on (II, [R_1 = Et, R_2 = H, R_3 = CH·N(CH_3)Ph]).

The camphononic acid (III, R_1 = H, R_2 = Me, R_3 = H_2) obtained either from the ethyl ester by hydrolysis or by sublimation of the crude acid was twice crystallized from acidulated water; it melted at 228°.

Anal. Calc'd for $C_9H_{14}O_3$: C, 63.53; H, 8.23.
Found: C, 63.70; H, 8.23.

It gave an *oxime*, m.p. 187°. Ganguly (3) recorded m.p. 230–231° for the *dl*-acid and for the corresponding oxime, m.p. 189–190°. The *d*-acid of Lapworth and Lenton (2) melted at 228° and the oxime at 186–187°.

SUMMARY

Methylation of ethyl 2,3-dimethyl-5-N-methylanilinomethylenecyclopentane-1-one-3-carboxylate with potassium *tert*-butoxide and methyl iodide followed by a two step hydrolysis with acid and alkali gave *dl*-camphononic acid.

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REFERENCES

(1) WALKER AND HENDERSON, *J. Chem. Soc.*, **69**, 748 (1896).
(2) LAPWORTH AND CHAPMAN, *J. Chem. Soc.*, **75**, 986 (1899); *J. Chem. Soc.*, **77**, 446 (1900); LAPWORTH, *J. Chem. Soc.*, **77**, 1053 (1900); LAPWORTH AND LENTON, *J. Chem. Soc.*, **79**, 1286 (1901).
(3) GANGULY, *J. Indian Chem. Soc.*, **20**, 101 (1943).
(4) BROWN AND EBERLY, *J. Am. Chem. Soc.*, **62**, 113 (1940).
(5) HUDSON, DICK, AND HAUSER, *J. Am. Chem. Soc.*, **60**, 1960 (1938); HAUSER AND RENFROW, *J. Am. Chem. Soc.*, **59**, 1823 (1937).
(6) PERKINS AND THORPE, *J. Chem. Soc.*, **85**, 128 (1904); *J. Chem. Soc.*, **89**, 795 (1906).
(7) PLATTNER, HEUSSER, AND BOYCE, *Helv. Chim. Acta*, **31**, 603 (1948).
(8) SEN GUPTA, *J. Indian Chem. Soc.*, **10**, 343 (1933); CHAKRAFARTI, *J. Indian Chem. Soc.*, **20**, 243 (1943).
(9) BIRCH AND ROBINSON, *J. Chem. Soc.*, 501 (1944).
(10) WOODWARD, SONDHEIMER, TAUB, HEUSLER, AND MCLAMORE, *J. Am. Chem. Soc.*, **74**, 4223 (1952).