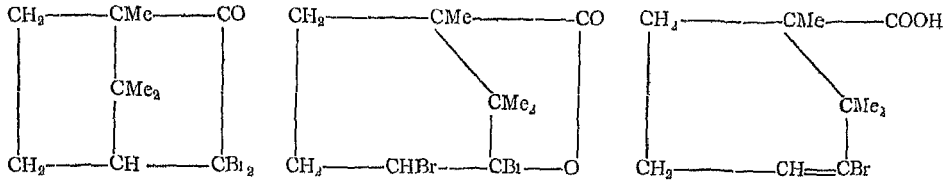
SYNTHETICAL EXPERIMENTS IN THE CAMPHANE SERIES

PART VI

SYNTHESIS OF HOMOCAMPHORONIC ACID

By P C Guha, K S Subramanian and V R Srinivasan

Homocamphoronic acid (VII) was obtained by Forster (*J C S*, 1896, **69**, 49) by the action of fuming nitric acid on dibromocamphor (A), via (dibromocampholide (B) (*J C S*, 1896, **69**, 41) and bromocamphorenic acid (C)

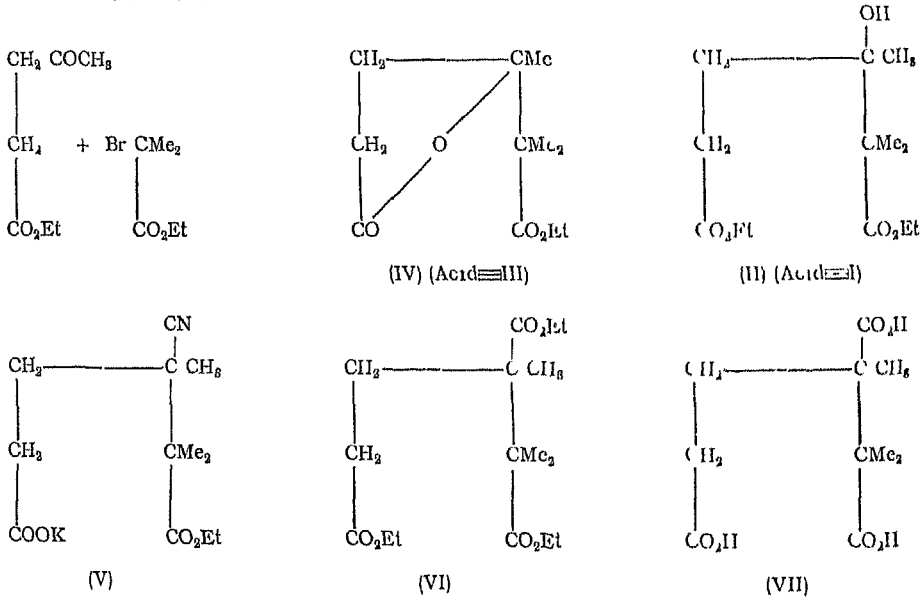


(A) (B) (C)

Kachler and Spitzer (Monatsh, 1883, **4**, 554) obtained by oxidation of dibromocamphor with dilute nitric acid what they supposed to be camphoronic acid and isocamphoronic acid Lapworth and Chapman (*J C S*, 1899, **75**, 986) indicated that isocamphoronic acid was not present, but that an acid was formed which might be easily confused with it on superficial examination The study of its properties showed that it was probably identical with the homocamphoronic acid as obtained by Forster (*loc cit*) Lapworth and Chapman (*J C S*, 1899, **75**, 995) obtained homocamphoronic acid directly in one step by the oxidation of dibromocamphor by strong nitric acid in the presence of silver nitrate In the work of the above two authors, (Forster and Lapworth, *loc cit*), it is only in the first one that some products (A, B, C, etc) formed in the intermediate stages in the final conversion of dibromocamphor into homocamphoronic acid are described Conversion of homocamphoronic acid into camphononic acid, and the formation of the latter from camphanamide (*J C S*, 1901, **79**, 1286), and from dehydrohomocamphoric acid (*J C S*, 1900, **77**, 1070), leaves no doubt as to the correctness of the structure accorded to camphononic acid. Although, the formation of homocamphoronic

acid from bromocamphoric acid, dibromocampholide, α-monobromocampholide, follows quite readily, the mechanism of formation of the above three acids from dibromocamphor is not easy to understand, as it involves the migration of the methylene carbon in position 3 to a position between 4 and 5 leading to the formation of an enlarged ring of six carbon atoms in B and C Besides, none of these acids have yet been synthesised

From what has been said above, it will be clear that a direct synthesis of homocamphoronic acid is necessary to place the structure ascribed to it beyond all doubt and controversy The synthesis of homocamphoronic acid has now been achieved according to the scheme outlined below



Ethyl α-bromo*iso*butyrate reacts with ethyl lævulinate in the presence of zinc (Blaise, *Compt rend*, 1900, **130**, 1033, Harding, *J C S*, 1912, **101**, 1590) to give rise to a mixture of ethyl β-hydroxy-αaβ-trimethyladipate (II) and the ethyl ester of the lactone of β-hydroxy-αaβ-trimethyl adipic acid (IV) The ester mixture was converted into the lactonic ester (IV) via hydroxy-diacid (I) and hydroxy-diester (II) The findings of Blaise and Harding (*loc cit*) on this particular reaction being rather controversial, the reaction has

roughly studied By alkaline hydrolysis of the esters onstituent acids viz, isobutyric and lævulic acids are 'd The results (vide experimental) are contrary to the Harding (*loc cit*) and in agreement with that of Blaise The quantity of the ester thus decomposed, however, ing on the duration of heating, the strength and quantity sed The hydroxy acid is formed only under certain

ctonic ester (IV) reacts with potassium cyanide to yield which gets hydrolysed and esterified by the action of ulphuric acid to give rise to ethyl homocamphoronate homocamphoronate (VI) was hydrolysed to homocamp- VII) on treatment with hydrochloric acid It is worth- ing here that the hydroxy-diester in a pure form has l from the lactonic ester (IV) by reacting its silver salt ide

nthesis of homocamphoronic acid constitutes a new total camphor, because of the fact that the conversion of onic acid to camphononic acid and that of camphononic hor have already been achieved by previous workers

Experimental

f Ethyl Lævulinate and Ethyl α-Bromoisobutyrate of the Ethyl Ester of the Lactone of β-Hydroxy- -Trimethyladipic Acid (VI), and Diethyl-β- Hydroxy-ααβ-Trimethyl-Adipate (II)

gh the reaction between the above mentioned en tried by Blaise (*Compt rend*, 1900, **130**, 1033) and *S*, 1912, **101**, 1593), after a number of trials, the been found to be the most convenient To a mixture linate (30 g) in benzene (75 c c) and zinc (14 g) was mo-ester (10 g) After addition of a crystal of iodine, the eated on boiling water-bath till the reaction commenc- ction being extremely vigorous at the beginning, the

bromo-ester had to be added gradually with occasional cooling After all the bromo-ester had been added the mixture was heated on water-bath for 2 hours when all the zinc went into solution The gelatinous product thus obtained was poured into ice, decomposed by dilute hydrochloric acid and extracted repeatedly with benzene

The residue from the benzene extract was distilled under reduced pressure (using a column for the earlier fractions), and the following fractions collected

Fraction	Weight	B P	n_D^{30}	d_{30}^{30}	
I	3 0 grams	70–72°/15 mm	1 4262	0 8780	(d_{20}^{20})
II	5 0 „	89–90°/10 mm	1 4210	1 011	(d_{20}^{20})
III	1 0 „	135–145°/8 mm	1 4510	1 078	(d_{30}^{30})
IV	34 0 „	145–160°/8 mm	1 4530	1 080	(d_{30}^{30})
Residue	4 0 „				

Fraction (I) appears to consist mainly of ethyl *iso*butyrate since it gives a saponification equivalent of 115 *Iso*butyric ester requires equivalent, 116 0

Fraction (II) (B P. 96°/15 mm , n_D^{15} 1 4231 ; d_{20}^{20} 1 0156, Kenner and Tollen) appears to consist of unreacted ethyl lævulinate (Found Equiv 147 4 , Ethyl lævulinate requires 141 0) Free lævulinic acid prepared from the ester boiled at 135–140°/10 mm , semicarbazone, m p 187°

Fraction (III) and (IV) consisting of the main bulk of the distillate, is the required condensation product It was a mixture of the hydroxy adipic ester (II) and the mono ester of the corresponding γ-lactone (IV) , yield 70–80% Three samples of the fraction (IV), from three different preparations gave the following constants

Sample	n_D^{30}	d_{30}^{30}	Sapn Equiv
A	1 4530	1·0800	114 8
B	1 4542	1 0804	111 7
C	1 4522	1·0796	116 3

The *hydroxy ester* ($C_{13}H_{24}O_5$) requires Equiv 130 0, the lactonic ester ($C_{11}H_{18}O_4$) requires Equiv 107 0, the unsaturated ester ($C_{13}H_{22}O_4$) requires Equiv 121 0 Fraction (iv) gave the following values for carbon and hydrogen C, 60 3, H, 8 5 per cent (Harding, Found C, 60 3, 60 6, H, 8 5, 8 5 Blaise, Found C, 59 96, H, 8 17 per cent) The hydroxy ester ($C_{13}H_{24}O_5$) requires C, 60 0, H, 9 2 per cent The lactonic ester ($C_{11}H_{18}O_4$) requires C, 61 7, H, 8 5 per cent

Hydrolysis of the Fraction (IV) by Alcoholic Potash

There seems to be some controversy about the behaviour of this ester mixture on hydrolysis with potash According to Blaise (*loc cit*) the esters are decomposed to their original constituents Harding (*loc cit*) suggests that this result is erroneous, the hydroxy acid being formed instead He, however, obtained the original constituents as mentioned by Blaise only by distillation with 20% sulphuric acid in a current of steam This reaction has now been studied in this laboratory with the following results.

A (i) The ester (5 g) was boiled for 2 hours with alcoholic potash (40 c c, 10 %) The golden yellow solution was poured into cold water (100 c c), the alcohol removed, the aqueous solution cooled in ice and made just acid to methyl red with dilute hydrochloric acid and immediately extracted with ether The residue from the ether extract was distilled and collected in two fractions

Fr (i) 4 0 g, B P upto 80°/30 mm, n_D^{23} 1 3938, d_{20}^{20} 0 2546

Fr (ii) 2 0 g, B P 170–180°/2–3 mm, n_D^{23} 1 4432

Fraction (i) from its odour, solubility in water and boiling point (150–152°), seems to consist mainly of *iso*butyric acid It had equivalent 92 5, *iso*butyric acid requires 88 0. The m p 129° of the amide and m p 105° of the anilide are in agreement with the melting points of the amide and the anilide of *iso*butyric acid

Fraction (ii) was a yellow viscous oil with no tendency to crystallise It corresponded to the β-hydroxy-ααβ-trimethyladipic acid (I) of Harding. On titration against sodium hydroxide with

phenolphthalein as indicator, it gave an equivalent 125 7 Hydroxy-dibasic acid $C_9H_{16}O_5$ requires 102 0, mono-basic lactonic acid $C_9H_{14}O_4$ requires 186 0 On hydrolysis for 2 hours with excess of boiling alcoholic potash and titration of the excess, the equivalent was found to be 98 2 Hydroxy acid requires 102 0, lactonic acid requires 93 0 Hence fraction (ii) is mainly the hydroxy acid contaminated with small quantities of the lactone

The aqueous solution after ether extraction, was evaporated on the water-bath and the residue again extracted with ether The acid (3 g) obtained after removal of ether had b p 135-140°/10 mm It gave a semicarbazone, m p. 187°, showing that it was pure lævulinic acid

B If, however, the ester mixture (10 g) is boiled for 30 minutes with just the necessary quantity of alcoholic potash (75 c c, 8 0%) and the mixture worked up, about 50% of the product is obtained as hydroxy acid

Following the method of Harding, ethyl β-hydroxy-ααβ-trimethyl adipate (II) was prepared from the ester mixture by hydrolysis with alcoholic potassium hydroxide and subsequent esterification of the hydroxy acid formed, B P 165–66°/2 mm, n_D^{30} 1 4530, d_{30}^{30}, 1 080

Action of Hydrobromic Acid on Ethyl β-Hydroxy-ααβ-Trimethyl Adipate (II) Formation of the Lactone of β-Hydroxy-ααβ-Trimethyl Adipic Acid (III)

The lactonic acid (III) was prepared according to the method of Harding with the following modification The hydroxy ester (II) was warmed on the water-bath for 4–6 hours with hydrobromic acid obtained by saturating water at 0°C with hydrogen bromide, it was then poured into water, extracted with ether and the residue from the ether extract after being dried on porous plate, was recrystallised from ether in colorless prisms, m.p 108-109° (Found C, 57 6, H, 7 5 $C_6H_{14}O_4$ requires C, 58 0, II, 7 5 per cent.)

The lead salt—The acid was neutralised with N/2 sodium hydroxide against phenolphthalein To this solution was added a solution of neutral lead acetate (20 c c , 10%) After a few minutes the lead salt crystallises out, m p 165–176° (decomp) (Found Pb, 34 2 , $(C_9H_{15}O_4)_2Pb$ requires Pb, 35.9)

The copper salt—To a solution of the mono-sodium salt of the acid in water, excess of copper sulphate solution was added when the copper salt separated as a bluish-green crystalline powder Hence the mono-copper salt is almost insoluble in water (Found Cu, 13 4 $(C_9H_{15}O_4)_2Cu$ requires Cu, 14 7 per cent) The salt does not melt but decomposes slowly above 200°

The sodium salt—The mono-sodium salt of the acid was prepared by titrating the free acid with sodium hydroxide to neutrality using phenolphthalein as indicator, then concentrating the aqueous solution and final evaporation to dryness over sulphuric acid The salt thus prepared was a white crystalline powder, hygroscopic in the air, m.p 185° (decomp).

The silver salt separates in crystals after a time by the action of silver nitrate on an aqueous solution of the sodium salt

Decarboxylation of the Lactonic Acid (III)

The pure lactonic acid (20 g) was heated on a wire-gauze over a free flame in a flask fitted with an air condenser Within a few minutes there commenced the evolution of carbon dioxide which came to an end in about an hour After two more hours' heating, the reaction mixture was poured into ice-water, treated with excess of sodium carbonate solution and the (neutral) insoluble oil was extracted with ether (A) The solution was then acidified and the oily acid extracted with ether (B).

2 3-Dimethyl hexanolide (3 6) prepared from the neutral oil (A) according to Blaise had equivalent 142 $C_8H_{14}O_2$ requires 142

Acid (B) was pure dimethyl hexenonic acid (Blaise) It boiled at 229–230°/684 mm and had equivalent 140 $C_8H_{14}O_2$ requires 142

Ethyl Ester of the Lactone of β-Hydroxy-aaβ-Trimethyl Adipic Acid (IV)

This ester was prepared according to the method of Harding, by gently heating on the water-bath equi-molecular amounts of impure diethyl-β-hydroxy-aaβ-trimethyl adipate and phosphorus pentabromide The resulting product was cooled, poured into ethyl alcohol, allowed to remain for some time, and the alcoholic solution poured into water The oil which separated was extracted with ether, the ether evaporated, and the residue without any further purification, boiled for four hours with twice its volume of diethylaniline The resulting solution was then poured into dilute hydrochloric acid and the lactone ester extracted by means of ether and distilled The ester is a colorless oil boiling at 165–168°/18 mm , n_D^{30}, 1 4529 , d_{30}^{30}, 1 079 (Found C, 61 6 , H, 8 2 $C_{11}H_{11}O_4$ requires C, 61 7 , H, 8 4 per cent).

Formation of the Hydroxy Diester (II) from the Lactonic Ester (IV)

Sodium hydroxide (2 5 g), in water (1000 c c) was gradually added to the *lactonic ester* (15 g), left for 10 minutes with shaking, the undissolved ester being extracted by ether The aqueous solution was then treated with excess of silver nitrate solution, filtered and the colorless silver salt was washed with water and dried in vacuo over calcium chloride The salt decomposes with blackening at about 110°

The silver salt (18 g) was finely powdered and mixed with 50 c c of dry ether , boiled under reflux with ethyl iodide in excess (15 g) for 8 hours Then poured the reaction product into water, extracted with ether and washed several times with water The silver iodide was washed with some more ether and the combined ether extracts upon distillation at reduced pressure gave the following fractions

Fr i B P. 160–65°/12 mm (0 5 g)

Fr ii B P 165–66°/12 mm (10·0 g), n_D^{30} 1 4529 , d_{30}^{30} 1 079

The boiling point, refractive index and density of fraction (ii) indicated

ıtıcal with ethyl α α β-trımethyl-β-hydroxy adıpate
ıusly

ssıum Cyanıde on the Lactonıc Ester (IV) followed
ıon of Alcohol and Sulphurıc Acıd Accoı dıng
Method of Ruzıcka Formatıon of Ethyl
Homocamphoronate (IV)

and dıy lactonıc ester (22 g) was heated with finely
sıum cyanıde (10 g) at 220–25° for 8–12 hours ın a flask
ı condensei and soda-lıme guard tube For the com-
hc ı eactıon ıt took 15–20 mınutes, after the bath had
ıperature of 220° At this stage, the temperature had to
ly controlled, as otherwise the reactıon became very
t out of control Afteı about 12 hours, the reactıon was
a hard dark-brown solıd was obtaıned To this was
e of concentıated sulphurıc acıd (20 c c) and alcohol
e mıxtuıe heated for 15 days ın an oıl-bath at 120°,
s then pouıed ınto water (500 c.c), cooled and extı act-
The ethei extract was dried over anhydıous mag-
te and dıstılled under reduced pressure after the
ɔı The followıng fractıons weıe obtaıned

Fı ı 85–100°/5 mm

Fı ıı 120–150°/5 mm

Fı ıı 150–160°/5 mm (1 5 g)

was refıactıonated and the portıon comıng over at
was collected and found to be the pure ıequıred ester
I 3, H, 8 4 $C_{16}H_{28}O_6$ requıres C, 60 8, H, 8 9 per

of the Esteı (VI) to Homocamphoıonıc Acıd (VII)

ter (0 5 g) was refluxed with hydıochlorıc acıd (25 c c ,
hours when the contents of the flask became peıfectly
mogeneous The acıd solutıon upon evaporatıon to
a lıght brown solıd crystallısıng ın beautıful prısms fıom
ıcetone and ethyl acetate, m p 184°, the mıxed meltıng

point of this acid and a specimen of homocamphoronic acid obtained by oxidising α-dibromo-camphor with nitric acid in the presence of silver nitrate, according to the method of Lapworth and Chapman (*loc. cit*) remained undepressed (Found Equiv 76, $C_{10}H_{16}O_6$ requires 77)

Though it was intended to prepare *d*- and *l*- camponomic acids and from the *d*- and *l*- forms of homocamphoronic acid starting from racemic camphononic acid obtained from our racemic homocamphoronic acid, this could not be done now for want of necessary starting materials and reagents

Organic Chemistry Laboratory,
Department of Pure and Applied Chemistry,
Indian Institute of Science,
Bangalore

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