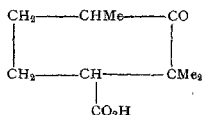


SYNTHETICAL INVESTIGATIONS IN THE CAMPHANE SERIES, PART V.

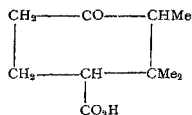
Synthesis of Manasse's ketonic acid, $C_{10}H_{16}O_3$, from camphorquinone : 2 : 2 : 3-Trimethyl-cyclohexane-4-one-carboxylic acid.

By P. C. Guha and Debabrata Das Gupta.

Menasse and Samuel (*Ber.*, 1897, **30**, 3157 ; 1902, **35**, 3831) obtained a keto acid, $C_{10}H_{16}O_3$, by the action of conc. sulphuric acid on camphorquinone, of which they made little attempt to solve the constitution. Gibson and Simonsen (*J. C. S.*, 1925, 1294) undertook investigation on the elucidation of the constitution of this acid. They ascribed the formula (I) to the keto acid, because (i) on oxidation with nitric acid it gave β -methyl-pentane- $\beta\gamma$ -tricarboxylic acid, and (ii) with amyl nitrite and hydrochloric acid it did not yield any oximino derivative, the formation of which was to be expected if the keto acid had the alternative constitution (II, cf. footnote, *loc. cit.* p. 1295).



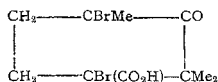
(I)



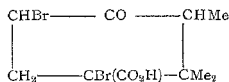
(II)

In a later paper in deciding between the two formulae (I and II) Bhagvat and Simonsen (*J. C. S.*, 1927 Jan., **131**, 77) felt that simple degradation products were unlikely to be of much assistance but considered it probable that on bromination of the keto acid a dibromo acid would result of either formula (III or IV) which on removal of two molecules of hydrogen bromide will tend to loose simultaneously

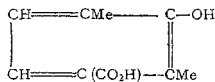
a methyl group and pass to a phenolic acid (V or VI), the identification of which would have offered little difficulty.



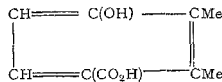
(III)



(IV)

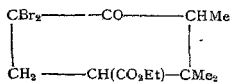


(V)

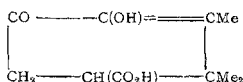


(VI)

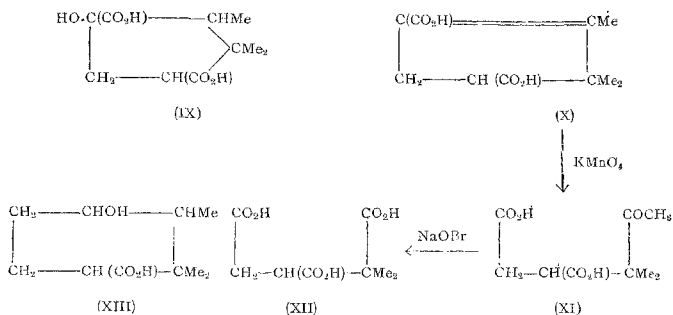
Contrary to their expectations the dibromo ester (VII) actually obtained by them was, however, different from both (III and IV) and on removal of hydrogen bromide gave a complex mixture of acids from which they isolated with considerable difficulty a hydroxy keto-acid (VIII), a dibasic hydroxy acid (IX) and two unsaturated dibasic acids (X). The hydroxy ester (VIII) on treatment with 50 % KOH, behaves in a similar manner to Wallach's hydroxy ketones (*Annalen* 1918, **414**, 296) undergoing "molecular rearrangement with addition of water" and becoming converted into a dibasic hydroxy acid identical with (IX). They, moreover, oxidised the acid (X) to γ -methylbutane- $\alpha\beta\gamma$ -tricarboxylic acid (XII) via γ -acetyl- γ -methylbutane- $\alpha\beta$ -dicarboxylic acid (XI) and arrived at the conclusion that the keto acid of Manasse and Samuel should be 2:3:3-trimethylcyclohexane-4-one-1-carboxylic acid (II). Evidences adduced by Bhagvat and Simonsen viz. conversion of (II) via (VII and VIII) to a cyclopentane derivative (IX) "involving molecular rearrangement with addition of water" for acceptance of the formula (II) for the keto acid does not appear to be conclusive.



(VII)



(VIII)

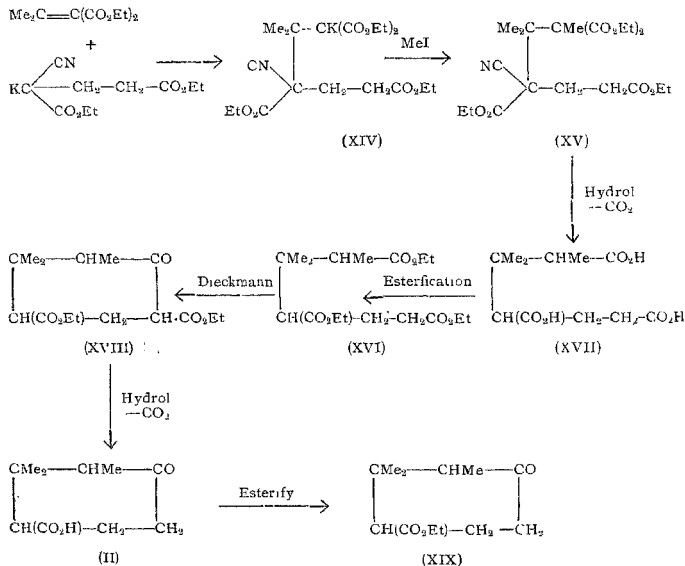


Bredt-Savelsberg, Zaunbrecher and Knieke (*Ber.*, 1927 July, 60, 1801) prepared (i) benzylidene derivative thus establishing the presence of the group $(\text{CO}\cdot\text{CH}_2)$ in the compound; and (ii) 2:2:3-trimethyl-cyclohexane-1-one-1-carboxylic acid (XIII) by some steps from the keto acid and claimed to have proved the structure to be (II).

It was therefore, considered desirable to effect a direct synthesis of the keto acid which, besides the intrinsic synthetic value, will go to establish the real structure of the acid beyond all controversy.

The desired synthesis has now been achieved as follows, with ethyl isopropylidene malonate as the starting material. The potassium derivative of ethyl α -cyanoglutarate reacts with ethyl isopropylidene malonate to yield ethyl $\gamma\gamma$ -cyano:carbethoxy- $\delta\delta$ -dimethyl- Σ -carbethoxy pimelate (XIV), which on methylation readily gives (XV). This on hydrolysis and decarboxylation gave an acid which was isolated in the shape of its ester ethyl γ -carbethoxy- $\delta\delta$ -dimethyl- Σ -methyl pimelate (XVI). The corresponding tri-acid (XVII) has been prepared from the ester on hydrolysis. The tri-ester (XVI) on treatment with sodium in dry xylene medium gave a product containing a portion soluble in dilute alkali and giving a red coloration with ferric chloride. The alkaline solution on acidification and extraction with ether yielded a pasty mass which (XVIII) could not be distilled undecomposed. The

product on hydrolysis and decarboxylation with hydrochloric acid (1 : 1) gave the acid as a pasty mass and hence was directly esterified. The ester boiled at 115–19°/7 mm., and was ethyl 2 : 2-dimethyl-3-methyl-*cyclohexane*-4-one-1-carboxylate (XIX). The ester was readily hydrolysed to 2 : 2-dimethyl-3-methyl-*cyclohexane*-4-one-1-carboxylic acid (II), m.p. 69–70°, its melting point, neutral equivalent and combustion values agreeing with those of Manasse's keto acid.



EXPERIMENTAL.

Ethyl isopropylidene malonate was prepared according to the method of Cope and Hancock (*J. Amer. Chem. Soc.*, 1938, **60**, 2644). Ethyl-*a*-cyanoglutarate was prepared according to the method of Barthe (*C.r.*, 1894, **118**, 1268) with the following modification: Potassium (39 g.) was added to calcium dried absolute alcohol (500 c.c.). To the

cold solution of this, ethyl cyanacetate (113 g.) was added slowly. The potassium derivative separated instantaneously. Ethyl β -bromopropionate (b.p. 61-65°/15 mm.) (182 g.) was then very slowly added to the ice-cold solution of the potassium derivative. This was left over-night and then heated on the water-bath until neutral to litmus. The potassium iodide formed was filtered off and the excess of alcohol removed by distillation. The residue was poured into water, acidified with dilute hydrochloric acid, extracted with ether, dried over anhydrous magnesium sulphate and ether distilled off. From the residual liquid the unreacted substance was distilled off at 100°/3 mm., during about 4-5 hours. The temperature was not raised further as the yield of ethyl α -cyano-glutarate suffers on distillation (Barthe, *loc. cit.*). The contents in the flask at this stage weighed, 154 g.

*Condensation of ethyl- α -cyanoglutarate with ethyl isopropylidene malonate and isolation of ethyl $\gamma\gamma$ -cyano:carbethoxy- $\delta\delta$ -dimethyl- $\Sigma\Sigma$ -methyl:-carbethoxy-pimelate (XV).—*Ethyl- α -cyanoglutarate (154 g.) was added slowly to potassium (28.2 g.) dissolved in calcium dried absolute alcohol (350 c.c.) and kept at room temperature for 12 hours. Isopropylidene malonic ester (145 g.) was then added. The product was kept at room temperature for 24 hours and heated for 17 hours on the water-bath. Methyl iodide (115 g.) was added slowly to the ice-cold solution. After the addition of methyl iodide was complete the reaction mixture was allowed to stand at ordinary temperature for 24 hours and then heated on the water-bath until neutral to litmus. After removal of potassium iodide by filtration most of the alcohol was removed by distillation and the product poured into water, acidified with dilute hydrochloric acid and extracted with ether, dried over anhydrous magnesium sulphate and the ether removed. The residue on distilling gave two fractions: (i) 122-135°/10 mm. (30 g.) and (ii) 145-200°/10 mm. (140 g.). The higher boiling fraction on repeated distillation boiled at 160-190°/10 mm.; yield 124 g. (Found: N, 3.12. $C_{21}H_{33}O_8N$ requires N, 3.27 per cent.).

*Hydrolysis and decarboxylation of the compound (XV): Isolation of the tri-ester (XVI).—*The ester (124 g.) was hydrolysed

with hydrochloric acid (2 : 1 ; 500 c.c.) by heating on a sand bath for 8-9 hours when the product became clear and homogeneous. The whole was then evaporated to dryness. The separated ammonium chloride was removed by filtration, the filtrate extracted with ether and the extract dried over magnesium sulphate. The residue (64 g.) after removal of ether gave viscous mass on keeping under suction in a vacuum desiccator, and could not be distilled undecomposed. Hence the acid (64 g.) was dissolved in absolute alcohol (500 c.c.) and dry hydrochloric acid gas was passed into the ice-cold solution until it was saturated. It was then left over-night and heated for 2 hours under reflux and then cooled. The excess of alcohol was then distilled off, the residue poured into water and extracted with ether. The ethereal solution was washed 4-5 times with dilute sodium bicarbonate solution and then with water, and was dried with anhydrous sodium sulphate. After removal of ether, the residue was distilled. The ester boiled at 118-122°/14 mm. (53 g.) (Found: C, 61.23; H, 9.66. $C_{17}H_{30}O_6$ requires C, 61.81; H, 9.09 per cent.).

Hydrolysis of the tri-ester (XVI).—The ester (6 g.) was heated with 15% alcoholic KOH (25 c.c.) for 8 hours on the water-bath and then cooled. Excess of alcohol was distilled off under suction. The residue was dissolved in water and acidified and was then extracted with ether. The ethereal solution was then washed repeatedly with sodium bicarbonate solution. The bicarbonate solution after acidification was extracted with ether, dried over anhydrous magnesium sulphate and the ether removed. The residue from ether gave a semi-solid substance on keeping under suction in a vacuum desiccator for about a week. This gave a solid on keeping over a porous plate over conc. sulphuric acid under suction in a vacuum desiccator. The solid on careful recrystallisation from a small quantity of ether gave an acid, m.p. 61-62° (Found: Eq. Wt., 80.17. $C_{11}H_{18}O_6$ requires 82).

Cyclisation of the ester (XVI).—The ester (XVI, 40 g.) was added slowly to dry xylene (150 c.c.) containing molecular sodium (4.1 g.) and kept at room temperature for 24 hours, and then heated on an oil-bath at 120-130°. After about half an hour the reaction set in

and was complete after 4 hours. The flask containing the reaction mixture was cooled with a mixture of ice and common salt, and ice and dilute hydrochloric acid was added to decompose the sodium derivative formed. The xylene layer was then separated and was washed with ice-cold 2% sodium hydroxide solution 10-12 times, and then acidified, extracted with ether, dried with anhydrous magnesium sulphate and the ether removed. The residue on keeping under suction gave a pasty mass (18 g.) which could not be distilled. It gave a reddish coloration with alcoholic ferric chloride.

Hydrolysis and decarboxylation of the cyclicised product (XVIII).—The ester (XVIII) (18 g.) was heated with hydrochloric acid (1:1; 250 c.c.) on a sand-bath for 72 hours. A portion of the ester (8 g.) still remained insoluble. The clear acid solution evaporated as far as possible on the water-bath, extracted with ether and the ethereal solution repeatedly extracted with dilute sodium bicarbonate solution. The bicarbonate solution was acidified and extracted with ether. The ethereal solution was dried with anhydrous magnesium sulphate and the ether distilled off. The residue was a pasty mass and did not show any tendency for solidification even in a desiccator.

Esterification of the above acid to (XIX).—The pasty acid described above was dissolved in absolute alcohol (50 c.c.) and dry hydrochloric acid gas was passed into the solution under ice cooling until it was saturated. This was left over-night and then heated for 2 hours under reflux. It was cooled and then poured into water and extracted with ether. The ethereal solution was washed repeatedly with dilute bicarbonate solution and then dried with anhydrous sodium sulphate. After removal of ether, the product was distilled, the first fraction coming over at 115-119°/7 mm. was collected; yield, 1.5 g. (Found: C, 67.41; H, 9.79. $C_{12}H_{20}O_3$ requires C, 67.93; H, 9.43 per cent.). The second fraction contained higher boiling substances (0.5 g.) having no constant boiling point and the rest decomposed.

The insoluble portion of the hydrolysed product.—The insoluble portion (8 g.) was dissolved in dilute sodium bicarbonate

solution, acidified and extracted with ether. The ethereal solution dried and evaporated. The residue esterified with absolute ethyl alcohol and dry hydrochloric acid gas, and then poured into water. It was then extracted with ether. The ethereal solution was washed with dilute sodium bicarbonate solution and dried with anhydrous sodium sulphate. After removing ether, the residue distilled at a wide range of temperature viz., between 170-200°/7 mm. (1 g.) the rest decomposed. This was not further studied.

Hydrolysis of the ester (XIX) : Isolation of 2 : 2 : 3-trimethyl-cyclohexane-4-one-1-carboxylic acid (II).—The above ester (0.84 g.) was treated with 5% alcoholic KOH (5 c.c.) and kept for 2 days at room temperature and then heated on the water-bath for half an hour. It was evaporated to dryness and dissolved in a small quantity of water, acidified and extracted with ether. The ethereal solution was dried over anhydrous magnesium sulphate and the ether removed. The residue was a viscous mass, which on keeping under suction in a vacuum desiccator in a refrigerator for about 3 weeks deposited a small quantity of a crystalline product, m.p. 69-70° (Found : C, 60.22; H, 8.57. $C_{16}H_{18}O_3 + H_2O$ requires C, 59.41; H, 8.91 per cent. Eq. Wt. of the viscous mass 194.1. $C_{16}H_{18}O_4 + H_2O$ requires 202).

*Department of Pure and Applied Chemistry,
Indian Institute of Science,
Bangalore.*