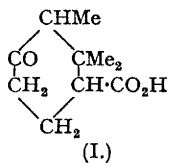
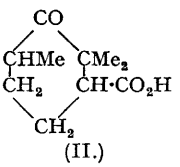
307. *Studies in the Terpenes. Part I. A Synthesis of* dl-2 : 2 : 3-*Trimethylcyclohexane*-1-*carboxylic Acid.*

By R. N. Chakravarti.

Manasse and Samuel's keto-acid, obtained by the rearrangement of camphorquinone, was previously reduced by the author to a saturated acid, $C_{10}H_{18}O_2$, the structure of which has now been finally settled by a direct synthesis. It has also been found that methyl 2-methyl*cyclo*pentan-1-ol-1-carboxylate leads to a mixture of 2 : 2 : 3-trimethyl- and 2 : 2 : 6-trimethyl-*cyclo*hexanone by pinacolic change.

In their classical researches on the action of concentrated sulphuric acid on camphorquinone, Manasse and Samuel (*Ber.*, 1897, **30**, 3157; 1902, **35**, 3831) obtained a dextrorotatory acid, $C_{10}H_{16}O_3$, which was found to have the structure (I) or (II). Of these (II) was preferred as the substance failed to given an *iso*nitroso-compound (Gibson and Simonsen, *J.*, 1925, **127**, 1295). Later researches on the action of bromine on the keto-acid, however, revealed that it should be represented as *d*-2 : 2 : 3-trimethyl*cyclo*hexan-4-one-1-carboxylic acid (I) (Bhagvat and Simonsen, *J.*, 1927, 77; cf. Bredt-Savelsberg, Zaunbrecher, and Knieke, *Ber.*, 1927, **60**, 1801).


(I.)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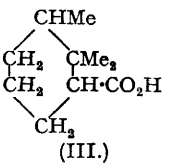

(III.)

The *dl*-modification of this acid was prepared in an analogous manner starting from *dl*-camphorquinone (Chakravarti, *J. Indian Chem. Soc.*, 1943, **20**, 301). The first clear evidence for the presence of a ketomethylene grouping in the molecule was supplied by the author (*loc. cit.*) when it was found that the corresponding ethyl ester (as I) readily reacted with ethyl oxalate in presence of sodium ethoxide, leading to the formation of an oxalyl derivative. It was also noted that the inactive keto-acid on reduction with amalgamated zinc and concentrated hydrochloric acid gave an acid, $C_{10}H_{18}O_2$ (Chakravarti, *loc. cit.*; see also *Experientia*, 1947, **3**, 27), which, on the basis of formula (I) for the keto-acid, should be represented as *dl*-2 : 2 : 3-trimethyl*cyclo*hexane-1-carboxylic acid (III). Additional support for the correctness of structure (III) for the reduced acid was afforded by the dehydrogenation of the corresponding methyl ester with selenium to give a mixture of *o*-xylene and *o*-xylene-3-carboxylic acid.

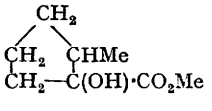
While experiments are in progress for a complete synthesis * of the keto-acid (I), it has now been possible to confirm the structure of the reduced acid as (III) by the following unambiguous synthesis.

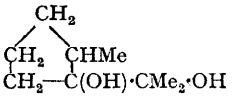
Methyl 2-*methyl*cyclo*pentan*-1-*ol*-1-*carboxylate* (IV) was allowed to react with excess of methylmagnesium iodide (cf. Meerwein and Unkel, *Annalen*, **376**, 152; Chakravarti, *J. Indian*

* A partial synthesis of the keto-acid (I) has already been described (Chakravarti, *loc. cit.*). The claim of Guha and Dasgupta (*J. Indian Inst. Sci.*, 1939, **22***A*, XX, 255) for a complete synthesis of this keto-acid cannot be justified, as the properties of the synthetic acid described by them are wholly inconsistent with those of the *dl*-modification of the acid prepared from *dl*-camphorquinone. The reason is obvious, since, owing to their wrong method of preparation, the product used by them as ethyl α-cyanoglutarate consisted almost wholly (more than 90%) of ethyl γ-cyanopentane-αγε-tricarboxylate (cf. Perkin, *J.*, 1904, **85**, 417; Ruzicka, Borges de Almeida, and Brack, *Helv. Chim. Acta*, 1934, **17**, 183).

For a conversion of santenonequinone into 2 : 3-dimethyl*cyclo*hexan-1-one-4-carboxylic acid and a complete synthesis of the latter, see Chakravarti, *J. Indian Chem. Soc.*, 1944, **21**, 319, 322.

Chem. Soc., **1943**, **20**, 398) to give the *pinacol* (V). This, on distillation with an aqueous solution of oxalic acid, gave a mixture of the isomeric trimethyl*cyclo*hexanones (VI) and (VII) by pinacolic change (cf. Meerwein and Unkel, *loc. cit.*) together with a little non-ketonic product, possibly a mixture of unsaturated hydrocarbons formed by the simple process of dehydration of (V).


(IV.)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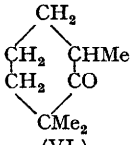
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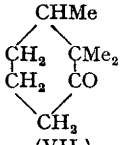
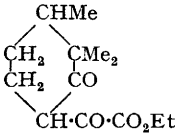
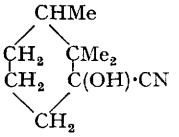

(VII.)

2 : 2 : 3-Trimethyl*cyclo*hexanone (VII) had been previously obtained together with 2 : 3 : 6-trimethyl*cyclo*hexanone by methylation of 2 : 3-dimethyl*cyclo*hexanone with sodamide and methyl iodide (Cornubert and Maurel, *Bull. Soc. chim.*, **1931**, **49**, 1520). The pure ketone (VII), however, was not obtained, but its presence in the mixture was proved by the isolation of a benzylidene derivative. The inactive modification of the other ketone, 2 : 2 : 6-trimethyl*cyclo*hexanone (VI), was isolated from oil of labdanum by Masson (*Compt. rend.*, **1912**, **154**, 518), who characterised it by the preparation of a semicarbazone, an oxime, and a monobromo-derivative.

In the present instance, the two ketones were separated from the mixture by condensation with ethyl oxalate in presence of sodium ethoxide; according to expectation, only 2 : 2 : 3-trimethyl*cyclo*hexanone (VII) furnished an *oxalyl* derivative (VIII). This oxalyl derivative was separated from the neutral matter, and from the latter a semicarbazone was prepared which on hydrolysis with dilute hydrochloric acid gave pure 2 : 2 : 6-trimethyl*cyclo*hexanone (VI). This gave an oxime, and in carbon disulphide solution reacted with bromine to give a monobromo-derivative.

The oxalyl derivative (VIII) on prolonged boiling with concentrated hydrochloric acid gave 2 : 2 : 3-*trimethyl*cyclo*hexanone* (VII) (*semicarbazone*, benzylidene derivative). (VII) combined almost quantitatively with hydrogen cyanide in presence of a trace of alkali to give a crystalline *cyanohydrin* (IX), which was smoothly dehydrated with excess of phosphorus oxychloride and pyridine to 1-*cyano*-2 : 2 : 3-*trimethyl*cyclo*hex*-6-*ene*. This, unlike similar nitriles, was unchanged by prolonged boiling with concentrated hydrochloric acid (cf. Chakravarti, *J. Indian Chem. Soc.*, **1943**, **20**, 246, 401) or with aqueous or alcoholic potassium hydroxide (cf. Cook and Linstead, *J.*, **1934**, 959; King and Robinson, *J.*, **1941**, 467), but was hydrolysed by 50% sulphuric acid to 2 : 2 : 3-*trimethyl*cyclo*hex*-6-*ene*-1-*carboxylic acid* (XI).


(VIII.)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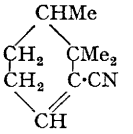
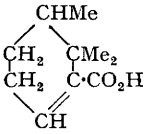

(X.)


(XI.)

Catalytic hydrogenation of the unsaturated acid (XI) in acetic acid solution in presence of Adams's catalyst gave the desired acid (III) (*p*-phenylphenacyl ester).

Experimental.

2-Methyl*cyclo*pentan-1-ol-1-carboxylic acid (as IV) was prepared by the method of Wallach (*Annalen*, **414**, 314) with some useful modifications.

The bromination of 2-methyl*cyclo*hexanone was carried out under the conditions described by Wallach. After the bromination was complete, however, the acetic acid solution was poured on crushed ice with stirring. The dibromo-ketone separated out as a viscous liquid, which soon solidified. It was filtered off at the pump and washed well with water. The crude product appeared to be rather unstable, as it darkened on keeping, and was always immediately decomposed with alkali in the following way.

The crude dibromo-ketone as obtained from 11·2 g. of 2-methyl*cyclo*hexanone was treated with a solution of potassium hydroxide (30 g.) in water (75 c.c.) with shaking, when it readily went into solution with evolution of much heat (some cooling under the tap is necessary as otherwise the product may darken). The solution was gently refluxed on a sand-bath for 45 minutes and then cooled and extracted twice with ether to remove some neutral matter. The alkaline solution was cooled and acidified, when the hydroxy-acid (as IV) separated as a crystalline solid (10·5 g.). The filtrate was saturated with salt and extracted with ether, when a further quantity (about 2 g.) of the acid was obtained. The total yield was directly converted into the methyl ester with methyl alcohol and sulphuric acid. *Methyl*

2-*methyl*cyclo*pentan*-1-*ol*-1-*carboxylate* (IV) was obtained as a colourless liquid (12 g.), b. p. 94°/20 mm. (Found : C, 60·4; H, 8·6. $C_8H_{14}O_3$ requires C, 60·7; H, 8·8%).

The Pinacol (V).—A solution of methyl 2-methyl*cyclo*pentan-1-ol-1-carboxylate (15·8 g.) in dry ether (25 c.c.) was added dropwise with thorough mixing to an ice-cold solution of methylmagnesium iodide prepared from methyl iodide (26 c.c.) and magnesium (9·6 g.) in ether (75 c.c.). After being kept overnight at the room temperature, the mixture was refluxed on the water-bath for 1½ hours with frequent shaking. The product was well cooled and cautiously decomposed with ice and dilute sulphuric acid. The ethereal layer was separated and the aqueous layer repeatedly extracted with more of the same solvent. The extract was washed with dilute sodium hydroxide solution to remove traces of iodine, and dried (Na_2SO_4). The oily liquid obtained after the removal of ether gave the *pinacol* (V) as a mobile liquid with a strong camphor-like odour (14 g.), b. p. 110°/19 mm. (Found : C, 68·1; H, 11·5. $C_9H_{18}O_2$ requires C, 68·3; H, 11·4%).

Action of Hot Aqueous Oxalic Acid on the Pinacol (V).—The above product (41 g.) with a 10% aqueous solution of oxalic acid (400 c.c.) was distilled slowly from a flask on a sand-bath. The level of liquid in the flask was kept constant by adding water through a tap funnel as the distillation proceeded. The heating was stopped when there were no more oily drops coming over with the distillate. The total distillate (*ca.* 500 c.c.) was extracted with ether. The ethereal extract was dried (K_2CO_3) and the solvent was evaporated. The liquid remaining, on distillation, gave a mixture (35 g.), b. p. 170—200°.

This mixture (21 g.) was mixed with ethyl oxalate (22 g.) and added dropwise during 2 hours with shaking to a solution of sodium (3·5 g.) in absolute alcohol (45 c.c.) cooled in a freezing mixture. It was then kept overnight. The product was worked up by adding ice-water and extracting the alkaline solution with ether. From the ethereal solution about 7·5 g. of the neutral unchanged matter (A) were recovered, b. p. 165—190°. The aqueous alkaline solution was acidified with ice-cold dilute sulphuric acid and the separated oil taken up in ether. The extract was washed with water, and then, after evaporation of the solvent, gave the oxalyl derivative (VIII) as an oil (18 g., containing traces of the solvent).

The neutral matter (A) obtained above, after distillation, was heated with semicarbazide acetate in aqueous alcohol. On cooling, the semicarbazone of 2 : 2 : 6-trimethyl*cyclo*hexanone separated (3·5 g.). It was obtained pure after two crystallisations from methyl alcohol, m. p. 218° (Masson, *loc. cit.*, gives 220—221°) (Found : C, 61·0; H, 9·6. Calc. for $C_{10}H_{19}ON_3$: C, 60·9; H, 9·6%). The pure semicarbazone on hydrolysis with dilute hydrochloric acid gave pure 2 : 2 : 6-trimethyl*cyclo*hexanone (VI) as a volatile liquid with a camphor-like odour, b. p. 180° (Masson, *loc. cit.*, gives b. p. 178—179°) (Found : C, 76·7; H, 11·6. Calc. for $C_9H_{16}O$: C, 77·1; H, 11·4%). It gave an oxime, m. p. 105° (Masson, *loc. cit.*, gives m. p. 106°) (Found : C, 69·6; H, 10·9. Calc. for $C_9H_{17}ON$: C, 69·6; H, 10·9%), and in carbon disulphide solution it reacted with only one mol. of bromine to give a monobromo-derivative, m. p. 41° (Masson, *loc. cit.*, gives m. p. 41°), with evolution of HBr. The monobromo-derivative is very similar to camphor in odour (Found : C, 49·1; H, 6·8; Br, 37·2. Calc. for $C_9H_{15}OBr$: C, 49·3; H, 6·8; Br, 36·5%).

The mother liquor obtained above in the preparation of the semicarbazone gave 3·5 g. of a volatile liquid with a terpene-like smell. This appeared to be a mixture of unsaturated hydrocarbons, but was not further investigated.

Hydrolysis of the Oxalyl Derivative (VIII).—The crude oxalyl derivative obtained above was directly hydrolysed by refluxing it with 20% hydrochloric acid for 48 hours The liquid was then distilled till the distillate was free from oily drops. The distillate was extracted with ether and the extract dried (K_2CO_3) and fractionated. 2 : 2 : 3-*Trimethyl*cyclo*hexanone* (VII) was obtained as a colourless liquid with camphoraceous odour (9 g.), b. p. 191° (Found : C, 76·8; H, 11·5. $C_9H_{16}O$ requires C, 77·1; H, 11·4%). With semicarbazide acetate in aqueous alcohol it readily gave a *semicarbazone* crystallising in plates from methyl alcohol, m. p. 214° (mixed m. p. with the semicarbazone of 2 : 2 : 6-trimethyl*cyclo*hexanone, 180—185°) (Found : C, 60·9; H, 9·6. $C_{10}H_{19}ON_3$ requires C, 60·9; H, 9·6%). The benzylidene derivative separated from methanol in light yellow needles, m. p. 85° (Found : C, 84·0; H, 8·6. Calc. for $C_{16}H_{20}O$: C, 84·2; H, 8·7%).

1-*Cyano*-2 : 2 : 3-*trimethyl*cyclo*hex*-6-*ene* (X).—2 : 2 : 3-Trimethyl*cyclo*hexanone (6 g.) was allowed to react with excess of hydrogen cyanide at a low temperature in presence of a drop of potassium cyanide solution. After 10 hours the cyanohydrin was stabilised with a drop of sulphuric acid and the excess of hydrogen cyanide sucked off at the pump, when the product solidified. A small portion of this substance after drying on a porous plate was crystallised from light petroleum, when the pure cyanohydrin (IX) was obtained in colourless needles, m. p. 111°.

The crude cyanohydrin was refluxed for an hour in an oil-bath with excess of phosphorus oxychloride (18 c.c.) and dry pyridine (60 c.c.). It was then cooled and carefully decomposed with ice–water and acidified with hydrochloric acid. By repeated extraction with ether, 1-*cyano*-2 : 2 : 3-*trimethyl*cyclo*hex*-6-*ene* (X) was isolated as a colourless liquid (6 g.) with an odour similar to that of phenyl cyanide, b. p. 119°/30 mm. (Found : C, 80·2; H, 9·8. $C_{10}H_{15}N$ requires C, 80·5; H, 10·0%).

2 : 2 : 3-*Trimethyl*cyclo*hex*-6-*ene*-1-*carboxylic Acid* (XI).—The unsaturated nitrile obtained above appeared to be particularly resistant to boiling concentrated hydrochloric acid or aqueous or alcoholic potassium hydroxide. It was hydrolysed by gently heating it on a sand-bath for 48 hours with 50% sulphuric acid. In this way a yield of 73% of the unsaturated acid (XI) was obtained. A little neutral matter was also recovered. 2 : 2 : 3-*Trimethyl*cyclo*hex*-6-*ene*-1-*carboxylic acid* (XI) crystallised from methyl alcohol in colourless plates, m. p. 135° (Found : C, 71·1; H, 9·4. $C_{10}H_{16}O_2$ requires C, 71·4; H, 9·5%).

2 : 2 : 3-*Trimethyl*cyclo*hexane*-1-*carboxylic Acid* (III).—The unsaturated acid obtained above was hydrogenated in acetic acid solution in presence of Adams's catalyst. The product had b. p. 110°/3 mm. On being kept in the ice-chest it solidified completely. 2 : 2 : 3-Trimethyl*cyclo*hexane-1-carboxylic acid (III) crystallised from methanol, at a low temperature, in shining plates, m. p. 58°, undepressed in admixture with the reduced acid (III) as obtained previously (Found : C, 70·5; H, 10·6. Calc. for $C_{10}H_{18}O_2$: C, 70·6; H, 10·6%).

The *p*-phenylphenacyl ester of the synthetic acid had m. p. 114°, undepressed in admixture with the *p*-phenylphenacyl ester of the reduced acid (III) (Found: C, 79·1; H, 7·6. Calc. for $C_{24}H_{28}O_3$: C, 79·1; H, 7·7%).

My best thanks are due to Prof. J. C. Bardhan for encouragement and to Mr. J. Chakraverti for facilities.

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[*Received, January 23rd,* 1947.]