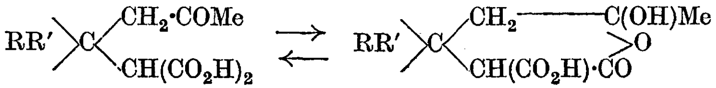
XXIX.—*Studies in Keto-lactol Tautomerism. Part IV. Chemistry of 5-Acetyl-*1 : 1 : 2-*trimethyl*cyclo*pentane-*2-*carboxylic Acid. Observations on the Constitutions of the Acid Esters of Camphoric Acid, and a Synthesis of Homoepicamphor.*

By MUHAMMAD QUDRAT-I-KHUDA.

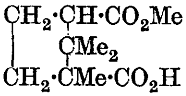
IN extending the study of ring-chain tautomerism of the keto-lactol type (I and II) to keto-monocarboxylic acids, it was suggested (J., 1929, 205) that the evidence of the existence of the hydroxy-phase of such acids would be obtained more readily by an investigation of δ-keto-monocarboxylic acids having substituents at the β- and the γ-carbon atom. The δ-keto-acids derived from the acid esters of camphoric acid fulfil this condition and their behaviour has been examined.



(I.) (II.)

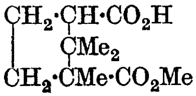
ortho-Methyl hydrogen camphorate (III) and *allo*-methyl hydrogen camphorate (IV), m. p. 77° and 86° respectively, when converted into their acid chlorides and acted on by zinc methyl iodide under parallel conditions, gave, not methyl 2-acetyl-1 : 1 : 2-trimethyl-

(III.)



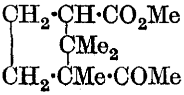
$$\begin{array}{l} CH_2\cdot CH\cdot CO_2Me \\ \quad\; CMe_2 \\ CH_2\cdot CMe\cdot CO_2H \end{array}$$

(IV.)



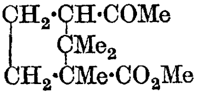
$$\begin{array}{l} CH_2\cdot CH\cdot CO_2H \\ \quad\; CMe_2 \\ CH_2\cdot CMe\cdot CO_2Me \end{array}$$

(V.)



$$\begin{array}{l} CH_2\cdot CH\cdot CO_2Me \\ \quad\; CMe_2 \\ CH_2\cdot CMe\cdot COMe \end{array}$$

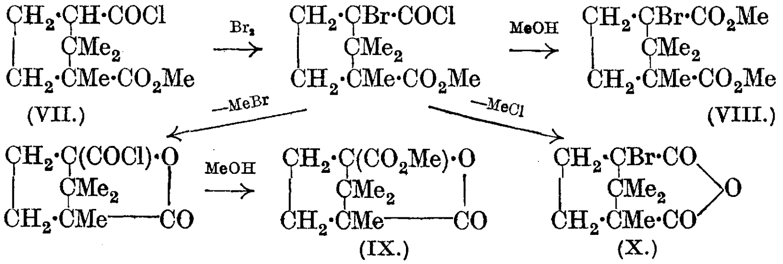
(VI.)



$$\begin{array}{l} CH_2\cdot CH\cdot COMe \\ \quad\; CMe_2 \\ CH_2\cdot CMe\cdot CO_2Me \end{array}$$

*cyclo*pentane-5-carboxylate (V, from III) and methyl 5-acetyl-1 : 1 : 2-trimethyl*cyclo*pentane-2-carboxylate (VI, from IV), but only one keto-ester; the semicarbazones obtained from specimens prepared from both sources melted, separately or mixed, at the same temperature.

The fact that only one keto-ester was obtained from the isomeric acid esters suggested that these were structurally identical and differed only in the spatial arrangement of the groups: this view was supported by the results obtained on brominating the acid chlorides produced from the two acid esters. Both chlorides absorbed bromine with almost equal ease and the products isolated after the reaction mixture had been poured into methyl alcohol were methyl camphanate (IX), ω-bromocamphoric anhydride (X), and small quantities of the *bromo-ester* (VIII) and camphanic acid. These facts, particularly the production of the bromo-ester (VIII), suggest that the *allo*- and the *ortho*-acid ester both have the carboxyl group attached to a tertiary carbon atom and that the bromination proceeds in the normal way; the intermediate product ultimately loses methyl bromide and methyl chloride, giving the ester of camphanic acid and bromo-camphoric anhydride:



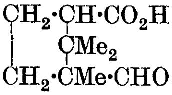
(VII.) (VIII.) (IX.) (X.)

The structural identity of the two acid esters is rendered very probable by the fact that, when the *ortho*-acid ester (m. p. 77°) is converted into the acid chloride by heating with thionyl chloride and then treated with water, the product obtained melts at the same temperature as *allo*-methyl hydrogen camphorate; its crystalline structure is identical with that of the latter and there is no depression of the melting point of a mixture of the two compounds.

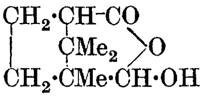
In view of these facts the work of Walker and his collaborators (Walker, J., 1893, **63**, 495; Walker and Henderson, J., 1895, **67**, 337; Walker and Cormack, J., 1900, **77**, 374), Noyes and Blanchard (*Amer. Chem. J.*, 1901, **26**, 285), and Haller and Blanc (*Compt. rend.*, 1905, **141**, 697) requires revision, which is being undertaken.

Camphoraldehydic acid (XI) (Bredt, *J. pr. Chem.*, 1917, **95**, 63), when heated with acetic anhydride, gives an acetoxy-derivative

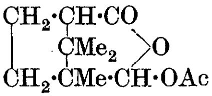
(XIII), the reaction taking place with the isomeric hydroxy-lactonic form (XII) of the aldehydic acid.



(XI.)



(XII.)

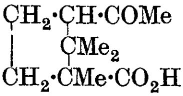


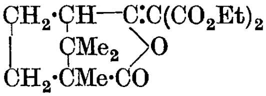
(XIII.)

The keto-acid (XIV) shows similar properties.

The ester (VI) on treatment with alcoholic potassium hydroxide gave a mixture of two solids, *viz.*, the *keto-acid* (XIV) and a *diketo-compound* (XVII), and a liquid substance, which was apparently the hydroxy-lactonic form (XVIII) of the keto-acid (XIV). The same keto-acid appears to have been obtained by Winzer (*Annalen*, 1890, **257**, 298) from the product of hydrolysis of camphorylmalonic ester (XV). On treatment with semicarbazide acetate, the acid (XIV) gave a crystalline *semicarbazone* having the properties of the normal compound (XVI), whereas the liquid acid (XVIII) gave an isomeric *substance*, of indefinite crystalline structure and very soluble in alcohol (compare the addition compound of Balbiano's acid and phenylhydrazine; Mahla and Tiemann, *Ber.*, 1895, **28**, 2151), probably to be represented by the formula (XIX) :

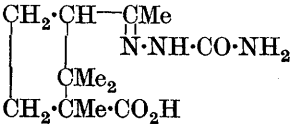
(XIV.)

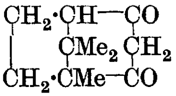




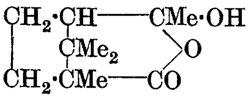
(XV.)

(XVI.)

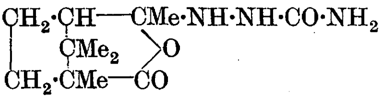




(XVII.)



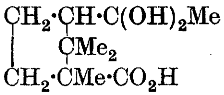
(XVIII.)

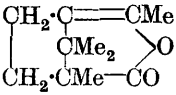


(XIX.)

When the keto-acid (XIV) or the hydroxy-lactone (XVIII) was treated with acetyl chloride, very little neutral product was obtained; the material was recovered in a *hydrated* form (XX), which was converted into the keto-acid (XIV) on drying. Both the keto-acid and the hydroxy-lactone, however, when treated with acetic anhydride, were converted into the same unsaturated *lactone* (XXI), which still exhibited optical activity although one of the two asymmetric carbon atoms had lost its asymmetry.

(XX.)

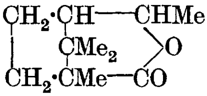




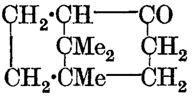
(XXI.)

The keto-acid (XIX), on reduction with sodium and alcohol, gave *methylcampholide* (XXII): the introduction of the third asymmetric carbon atom changed the direction of rotation from dextro to lævo.

(XXII.)



$$\begin{array}{l}CH_2\cdot CH\text{—}CHMe\\ |\quad\;\; CMe_2\quad >O\\ CH_2\cdot CMe\text{—}CO\end{array}$$

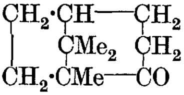


$$\begin{array}{l}CH_2\cdot CH\text{—}CO\\ |\quad\;\; CMe_2\quad CH_2\\ CH_2\cdot CMe\text{—}CH_2\end{array}$$

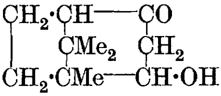
(XXIII.)

The keto-ester (VI), when heated with alcoholic sodium ethoxide, was converted into the diketo-compound (XVII), which, as already mentioned, was also obtained in small quantity by hydrolysis of the ester. The reduction of the diketo-compound by Clemmensen's method gave a waxy mass, with a strong camphoraceous odour, consisting of a ketone and a second substance. The ketone, produced in very small quantity, forms a *semicarbazone*, m. p. 220°, isomeric with the semicarbazone of homocamphor (XXIV), m. p. 250° (Lapworth and Royle, J., 1920, **117**, 743), and is provisionally regarded as homoepicamphor (XXIII). The second substance is probably the keto-alcohol (XXV); it could not be obtained sufficiently pure for analysis.

(XXIV.)



$$\begin{array}{l}CH_2\cdot CH\text{—}CH_2\\ |\quad\;\; CMe_2\quad CH_2\\ CH_2\cdot CMe\text{—}CO\end{array}$$



$$\begin{array}{l}CH_2\cdot CH\text{—}CO\\ |\quad\;\; CMe_2\quad CH_2\\ CH_2\cdot CMe\text{—}CH\cdot OH\end{array}$$

(XXV.)

Experiments are now in progress on the action of potassium cyanide on the lactone (XXII); it is also hoped to prepare the ketone (XXIII) and the keto-alcohol (XXV) in quantity in order to settle their constitutions.

EXPERIMENTAL.

ortho-Methyl hydrogen camphorate was prepared by Walker's method (*loc. cit.*). After crystallising twice from light petroleum (b. p. 40—60°), it melted at 77° and had $[\alpha]_D^{17.5^\circ} + 53.94^\circ$ in 2·95% alcoholic solution.

allo-Methyl hydrogen camphorate was obtained by Walker's method (*loc. cit.*) by the partial hydrolysis of methyl camphorate, prepared by a method based on the one used by Frankland and Aston (J., 1901, **79**, 517) for the esterification of tartaric acid and also by the method recommended by Haller and Blanc (*loc. cit.*). After crystallising twice from petroleum (b. p. 60—80°), the *allo*-ester melted at 86° and had $[\alpha]_D^{19^\circ} + 45.1^\circ$ in 4·3% alcoholic solution.

Bromination of the Chloride of the allo-*Ester.*—The acid ester (42 g.) was mixed with phosphorus pentachloride (41 g.). When the vigour of the reaction had abated, the mixture was heated at 75—80° for an hour, 12 c.c. of dry bromine were gradually added, and the heating was continued for 4—5 hours. The excess of bromine was then evaporated and the reaction mixture was poured into methyl alcohol (150 c.c.) and heated on the steam-bath for some time. After most of the alcohol had evaporated, the residue was poured into water and shaken with ether. The extract was washed with sodium carbonate solution and dried, and the solvent removed. The residue, consisting of crystalline material mixed with a little oil (A), was triturated with petroleum. The solid then remaining was partly soluble in hot petroleum (b. p. 60—80°); on cooling, the solution deposited methyl camphanate, m. p. 110° after recrystallisation (Found: C, 62·1; H, 7·5. Calc. for $C_{11}H_{16}O_4$: C, 62·3; H, 7·5%), hydrolysis of which gave camphanic acid, m. p. 201° (compare Bredt, *Annalen*, 1913, **395**, 39). The portion of the solid insoluble in hot petroleum crystallised well from chloroform, melted at 215° (Found: Br, 30·8. Calc. for $C_{10}H_{13}O_3Br$: Br, 30·7%), and had all the properties of Wreden's bromocamphoric anhydride (*Annalen*, 1872, **163**, 332).

The oil (A) was recovered from the petroleum solution and distilled in a vacuum: a little methyl camphorate came over and then *methyl bromocamphorate* distilled at 162—164°/12 mm. with slight decomposition. The yield was very small and the bromo-ester was not pure (Found: Br, 25·0. $C_{12}H_{19}O_4Br$ requires Br, 26·0%).

The above sodium carbonate extract on acidification gave an oil which, when hydrolysed with caustic soda, yielded camphoric acid and a small quantity of camphanic acid.

The products obtained in a similar way from *ortho*-methyl hydrogen camphorate were essentially of the same nature as the above.

Conversion of ortho- *into* allo-*Methyl Hydrogen Camphorate*.—The *ortho*-ester (7 g.) was treated with thionyl chloride (4 c.c.) at 70—75° for an hour, the excess of thionyl chloride then removed under reduced pressure, and the residue diluted with dry benzene (50 c.c.) and decomposed with water. The acid was extracted with dilute sodium carbonate solution, precipitated by acidification with hydrochloric acid, and extracted with ether. After drying and removal of the ether, the oily residue obtained partly solidified on cooling. The solid was separated from the oily impurities by trituration with petroleum and crystallised from the same solvent; it then melted at 86° (Found: C, 61·5; H, 8·6. Calc. for $C_{11}H_{18}O_4$: C, 61·7; H, 8·4%).

The *allo*-ester, when similarly treated, was recovered unchanged.

Methyl 5-*Acetyl*-1 : 1 : 2-*trimethyl*cyclo*pentane*-2-*carboxylate* (VI).—*ortho*-Methyl hydrogen camphorate was mixed with thionyl chloride (15 c.c.) and the acid chloride obtained after the removal of the excess of thionyl chloride as stated above was cooled, diluted with an equal volume of dry benzene, and added to a cold solution of zinc methyl iodide prepared from methyl iodide (35 c.c.), ethyl acetate (18 c.c.), and zinc-copper couple (35 g.) in benzene solution in the usual way. The *keto-ester* was isolated by treatment of the solution with water and dilute sulphuric acid and subsequent removal of the solvent and treated with a slight excess of semicarbazide acetate in aqueous-alcoholic solution. The *semicarbazone*, after crystallising several times from alcohol, melted at 198° (Found : C, 58·0; H, 8·8. $C_{13}H_{23}O_3N_3$ requires C, 58·0; H, 8·6%). When it (36 g.) was heated with 50 c.c. of concentrated hydrochloric acid and 150 c.c. of water on the steam-bath for 2½ hours, the ester separated as an oil. After cooling, this was taken up in ether, washed with dilute caustic soda solution, dried, and distilled in a vacuum, the keto-ester being obtained as a mobile colourless liquid with a characteristic odour, b. p. 135°/11 mm., $d_4^{14\cdot7^\circ}$ 1·04555, $n_D^{14\cdot7^\circ}$ 1·4733 (whence $[R_L]_D = 56\cdot91$. Calc., 57·08), $[\alpha]_D^{15^\circ} + 21\cdot3^\circ$ in 2·2% alcoholic solution (Found : 67·9; H, 9·6. $C_{12}H_{20}O_3$ requires C, 67·9; H, 9·4%).

The same semicarbazone was obtained from the keto-ester produced from *allo*-methyl hydrogen camphorate by a similar series of reactions.

Hydrolysis of the Keto-ester (VI). *Preparation of the Keto-acid* (XIV) *and the Hydroxy-lactone* (XVIII).—The keto-ester (14 g., purified through the semicarbazone) was heated with aqueous-alcoholic potassium hydroxide (16 g.) on the steam-bath for 18—20 hours, the alcohol evaporated, the residue diluted with water and extracted with ether to remove any unchanged ester, and the alkaline solution acidified with hydrochloric acid. After a day or two, the oil that had separated partly solidified. The solid was drained on porous plate and crystallised from petroleum (b. p. 60—80°). Feathery needles of the diketo-compound (XVII) described below separated first, and then the keto-acid (XIV) in well-formed rhombic plates, m. p. 96° after two recrystallisations (Found : C, 66·7; H, 9·3; *M*, by titration, 197. $C_{11}H_{18}O_3$ requires C, 66·7; H, 9·1%; *M*, 198).

5-*Acetyl*-1 : 1 : 2-*trimethyl*cyclo*pentane*-2-*carboxylic acid* is very soluble in the ordinary organic solvents except light petroleum. It has $[\alpha]_D^{22\cdot5^\circ} + 99\cdot1^\circ$ in about 2·3% solution in chloroform. The *semicarbazone* (XVI), crystallised from methyl alcohol, melts at 225° (Found : C, 56·8; H, 8·5. $C_{12}H_{21}O_3N_3$ requires C, 56·5; H, 8·2%).

The oil absorbed in the porous plate (above) was extracted with ether, dried, and distilled in a vacuum; the somewhat viscous mass obtained, b. p. 186—187°/14 mm., showed no tendency to solidify (Found: C, 66·8; H, 9·1%). The oil was slowly attacked by dilute sodium bicarbonate solution. After treatment with semicarbazide acetate in dilute methyl alcohol, it gave on dilution a gummy mass which gradually solidified: by slow evaporation of a solution of the solid in hot dilute methyl alcohol, a *substance* of indefinite crystalline structure was obtained. This was dried in the air, washed with benzene to remove a small quantity of colouring matter, and dried over sulphuric acid in a vacuum desiccator; it then melted at 172° and decomposed at a higher temperature. The substance (? XIX) is isomeric with the semicarbazone (XVI) (Found: C, 56·8; H, 8·3%). It dissolves slowly in dilute sodium hydroxide solution and is recovered on acidification.

Behaviour of the Keto-acid (XIV) *and the Hydroxy-lactone* (XVIII) *towards Acetyl Chloride.*—Either of the acids (3 g.) was heated with excess of acetyl chloride (8 c.c.) on the steam-bath for a few hours, the acetyl chloride then evaporated, and the residue treated with water; the oil produced was dissolved in ether and shaken with dilute sodium carbonate solution. The neutral product gave only a trace of the unsaturated lactone described below. The alkaline extract on acidification gave an *acid,* which crystallised from hot water in shimmering plates, m. p. 73°; after being dried in the air for a day, it was analysed (Found: C, 60·9; H, 9·5; *M*, by titration, 215·5. $C_{11}H_{20}O_4$ requires C, 61·1; H, 9·3%; *M*, 216). The acid is the hydrated form (XX) of the keto-acid (XIV) and is converted into this acid on being dried in a desiccator.

Action of Acetic Anhydride on the Keto-acid (XIV) *and the Hydroxy-lactone* (XVIII).—Either compound (5 g.) was refluxed with acetic anhydride (5 c.c.) for 2 hours, and the product distilled; the unsaturated *lactone* (XXI) passed over at 136°/22 mm. and solidified in the receiver. The lactone, m. p. 62°, $[\alpha]_D^{27.5°}$ + 77·7° in a 3·3% solution in chloroform (Found: C, 73·1; H, 8·9. $C_{11}H_{16}O_2$ requires C, 73·3; H, 8·8%), is extremely soluble in almost all organic solvents. It absorbs bromine very readily in chloroform solution.

Methylcampholide (XXII).—To a boiling solution of the keto-acid (XIV) (4·5 g.) in absolute alcohol (20 c.c.), sodium (5 g.) was added, followed by 75 c.c. of alcohol in three instalments during 2 hours' additional heating. The alcohol was evaporated on the steam-bath, and the residue diluted with water and acidified with concentrated hydrochloric acid. The oil obtained crystallised after the usual treatment with ether and dilute sodium carbonate solution. *Methylcampholide,* recrystallised from petroleum (b. p. 60—80°), melted at 100—101° (Found: C, 72·3; H, 9·9. $C_{11}H_{18}O_2$ requires C, 72·5; H, 9·8%) and had $[\alpha]_D^{17^\circ}$ − 44·8° in about 2·02% solution in chloroform.

1 : 8 : 8-*Trimethyl*bicyclo[1 : 2 : 3]*octane*-2 : 4-*dione* (XVII).—The keto-ester (VI) (21 g.) was heated with alcoholic sodium ethoxide (sodium, 2·5 g.; alcohol, 55 c.c.) for 48 hours, the alcohol evaporated, and the residue diluted, extracted with ether, and acidified with concentrated hydrochloric acid. The oil obtained, which solidified, was dried and crystallised from petroleum, separating in slender short needles, m. p. 220° to a red liquid (Found: C, 73·2; H, 9·1. $C_{11}H_{16}O_2$ requires C, 73·3; H, 8·8%). The *diketo*-compound was optically inactive, dissolved in dilute alkali solutions, gave a brown coloration with alcoholic ferric chloride, and absorbed bromine in chloroform with evolution of hydrogen bromide.

Homoepicamphor (XXIII) *and the Keto-alcohol* (XXV).—The compound (XVII) (5 g.) was heated under reflux with amalgamated zinc (25 g.), concentrated hydrochloric acid (100 c.c.), and water (50 c.c.); the reduction product partly distilled into the condenser. After cooling, the product was extracted with ether, the unchanged diketo-compound removed by dilute alkali solution, the ethereal solution dried, and the solvent removed. The residue was treated with semicarbazide acetate in methyl-alcoholic solution, and the mixture diluted with water and shaken with light petroleum. The residual *semicarbazone*, after crystallising from dilute methyl alcohol, melted at 220° (Found: C, 64·5; H, 9·8. $C_{12}H_{21}ON_3$ requires C, 64·5; H, 9·4%). The quantity of it was very small and the ketone could not be regenerated. The petroleum solution gave a small quantity of a semi-solid substance which was probably the keto-alcohol (XXV).

The author wishes to express his grateful thanks to Professor J. F. Thorpe, C.B.E., F.R.S., for his interest in this work and for his many valuable suggestions, and to the Government of Bengal, India, for a foreign scholarship and a grant towards the purchase of chemicals.

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