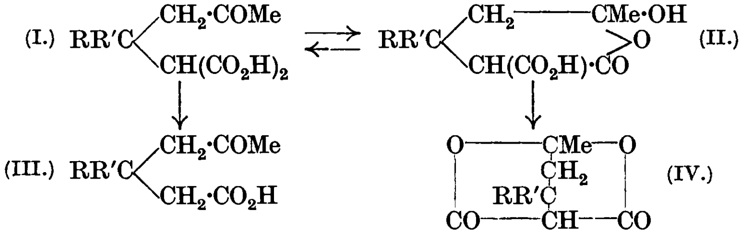
CI.—*Studies in Keto-lactol Tautomerism. Part II. Influence of the* cyclo*Hexane Ring on the Tautomeric Character of* cyclo*Hexane-*1*-acetone-*1*-malonic Acid, a Comparison with* cyclo*Pentane-*1*-acetone-*1*-malonic Acid, and Synthesis of the Corresponding δ-Keto-monobasic Acids.*

By MUHAMMAD QUDRAT-I-KHUDA.

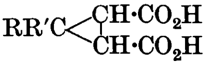
IN Part I (this vol., p. 201) it was suggested that in the liquid state α-carboxy-γ-acetyl-ββ-dimethylbutyric acid exists both in the keto-form (I) and in the carboxy-lactol form (II), which decompose at 130—140° and give the keto-monocarboxylic acid (III) and the dilactone (IV) respectively (R = R′ = Me).



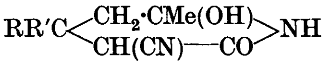
The properties of cyclo*hexane*-1-*acetone*-1-*malonic acid* (I; $RR' = C_5H_{10}>$) and cyclo*pentane*-1-*acetone*-1-*malonic acid* (I; $RR' = C_4H_8>$) and the influence of the *cyclo*hexane and *cyclo*pentane rings on their tautomerism have now been examined.

Evidence has been accumulated which shows that the forcing apart of two of the valencies of a spiran carbon atom due to its inclusion in a *cyclo*hexane ring causes the other two valencies to come closer together: *cyclo*hexane*spirocyclo*propane-1 : 2-dicarboxylic acid, therefore, is more stable than the corresponding *gem*-dimethyl compound (V; $RR' = C_5H_{10}>$ and Me_2, respectively) (Beesley, Ingold, and Thorpe, J., 1915, **107**, 1091; compare also Kon, J., 1922, **121**, 514; Ingold and Gane, J., 1928, 2268). On the other hand, the angle included by two of the valencies of a carbon atom in a *cyclo*pentane ring is almost equal to the normal tetrahedral angle, and consequently the influence exerted by this ring is comparable with that of *gem*-dimethyl groups (compare, *e.g.*, Becker and Thorpe, J., 1920, **117**, 1579; Dickens, Kon, and Thorpe, J., 1922, **121**, 1496; Lanfear and Thorpe, J., 1923, **123**, 1683; Ingold, Lanfear, and Thorpe, *ibid.*, p. 3140). The behaviour of *cyclo*hexane- and *cyclo*pentane-1-acetone-1-malonic acids supports these views: *cyclo*hexane-1-acetone-1-malonic acid, owing to the proximity of the carbonyl and the carboxyl groups (compare Ingold and Gane, *loc. cit.*), exhibits pronounced tautomeric behaviour, whereas the *cyclo*pentane analogue resembles the *gem*-dimethyl compound in its general reactions.

(V.)



$$RR'C\left<\begin{matrix}CH\cdot CO_2H\\ |\\ CH\cdot CO_2H\end{matrix}\right.$$



$$RR'C\left<\begin{matrix}CH_2\cdot CMe(OH)\\ CH(CN)\text{---}CO\end{matrix}\right>NH$$

(VI.)

The carboxy-lactol forms (II) of the two acids could not be isolated. They are δ-hydroxy-acids, and apparently it is through them, by the loss of a molecule of water, that transformation of the acids (I) into the *dilactones* (IV) takes place: the *cyclo*hexane acid undergoes the conversion when heated in an organic solvent for some time, but the *cyclo*pentane acid requires the assistance of a dehydrating agent.

The best method for the preparation of *cyclo*hexane- and *cyclo*pentane-1-acetone-1-malonic acids is the alkaline hydrolysis of the condensation products of *cyclo*hexenylacetone and *cyclo*pentenylacetone, respectively, with sodiocyanoacetamide in hot alcoholic solution (the condensation could not be effected with a small quantity of sodium ethoxide as in the case of mesityl oxide; this vol., p. 205): the cyclo*hexane*- and cyclo*pentane*-spiro-3-*hydroxy*-6-*cyano*-3-*methyl*-5-*piperidones* (VI; $RR' = C_5H_{10}>$ and $C_4H_8>$

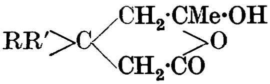
respectively) obtained, on hydrolysis with concentrated aqueous potash, yield the desired acids as the sole products.

When treated with alcoholic hydrogen chloride, *cyclo*pentane-1-acetone-1-malonic acid gives the normal *keto-ester* (formula as I), but the *cyclo*hexane acid gives a mixture of its *keto-ester* with a substance, probably the dilactone, which is very difficult to purify: the pure keto-ester, however, can be obtained from the silver salt. The keto-esters have the normal configuration, since they give characteristic *semicarbazones*.

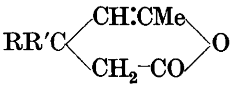
Like the *gem*-dimethyl acid, *cyclo*hexane- and *cyclo*pentane-1-acetone-1-malonic acids in the liquid state exist each as an equilibrium mixture of the keto and the lactol form (I $\rightleftharpoons$ II). The composition of the equilibrium mixture is deduced from the quantities of the decomposition products of the two forms, namely, the keto-monobasic acid (III) from the keto-form and the dilactone (IV) from the lactol form: the *cyclo*hexane acid yields 68—70%, and the *cyclo*pentane acid 47—48%, of dilactone; the rest of the acid decomposes into and is isolated as keto-monobasic acid. The constitutions of the two keto-monobasic acids have been established by the syntheses of their *methyl* esters from the acid chlorides of the corresponding diacetic acids and zinc methyl iodide.

The keto-monobasic acids were examined for evidence of their existence in the lactol form (VII). It was expected that from *cyclo*hexane-1-acetone-1-acetic acid, at least, it might be possible to get an ethoxy-lactone (VII with OEt in place of OH). The reaction with alcoholic hydrogen chloride, however, proceeded in a different direction, giving mainly Norris and Thorpe's *cyclo*hexane-*spirocyclo*hexane-3:5-dione (J., 1921, **119**, 1205) and a small quantity of the keto-ester. Esterification of *cyclo*pentane-1-acetone-1-acetic acid gave, as in the case of the *gem*-dimethyl analogue, mainly the keto-ester.

(VII.)



$$\mathrm{RR'{>}C}\begin{matrix}\mathrm{CH_2{\cdot}CMe{\cdot}OH} \\ \mathrm{CH_2{\cdot}CO}\end{matrix}\mathrm{{>}O}$$



$$\mathrm{RR'C}\begin{matrix}\mathrm{CH{:}CMe} \\ \mathrm{CH_2{-}CO}\end{matrix}\mathrm{{>}O}$$

(VIII.)

Methyl *cyclo*hexane- and *cyclo*pentane-1-acetone-1-acetate, when heated with alcoholic sodium ethoxide solution, are converted into *cyclo*hexane- and *cyclo*pentane-*spirocyclo*hexane-3:5-dione (Norris and Thorpe, *loc. cit.*), respectively. The keto-acids of the general formula (III), when treated with acetyl chloride, react, however, in their lactol form (VII) with the production of unsaturated lactones (VIII) by loss of a molecule of water: the *cyclo*hexane acid undergoes the change at the ordinary temperature, but the *cyclo*pentane analogue requires heating on a steam-bath.

The effect of bulky substituents on the tautomerism of such δ-ketonic acids will be discussed in a future communication.

EXPERIMENTAL.

The condensation of cyanoacetamide with *cyclo*hexenylacetone or *cyclo*pentenylacetone was effected by heating the suspension of the sodio-derivative, obtained by adding cyanoacetamide (1 mol.) in 1000 c.c. of hot absolute alcohol to a solution of sodium (1 atom) in 350 c.c. of hot absolute alcohol, with the unsaturated ketone (1 mol.) on the steam-bath for 6 hours, the sodiocyanoacetamide dissolving and the sodio-derivative of the condensation product separating. The alcohol is then distilled off, the residue dissolved in water, any unchanged ketone extracted with ether, and the solution acidified with cold hydrochloric acid : the condensation product crystallises. A few grams more are obtained when the mother-liquor is made just alkaline with sodium carbonate solution and concentrated on the steam-bath.

cyclo*Hexane Series.*

cyclo*Hexane*spirocyclo-3-*hydroxy*-6-*cyano*-3-*methyl*-5-*piperidone* (VI; $RR' = C_5H_{10}>$).—When *cyclo*hexenylacetone (b. p. 90°/15 mm., $d_{4^\circ}^{16\cdot2^\circ}$ 0·9404, $n_D^{16\cdot2^\circ}$ 1·47751; prepared by Wallach's method, *Annalen*, 1912, **394**, 376, and purified by two distillations) (27·6 g.) is condensed with cyanoacetamide (16·8 g.) and sodium (4·6 g.) as described above, cyclo*hexane*spirocyclo-3-*hydroxy*-6-*cyano*-3-*methyl*-5-*piperidone* is obtained (35 g.). It crystallises well from methyl alcohol and melts with charring at 258° (Found : C, 65·4; H, 8·5; N, 12·7. $C_{12}H_{18}O_2N_2$ requires C, 64·9; H, 8·1; N, 12·6%). It is unaffected by hot dilute caustic soda solution, is appreciably soluble in caustic alkalis and in dilute acids, and dissolves in hot alcohol or acetic acid, but is insoluble in ether, benzene, or chloroform.

cyclo*Hexane*-1-*acetone*-1-*malonic Acid* (I).—The preceding *spiro*-compound (25 g.) is heated with potassium hydroxide (25 g.) in 100 c.c. of water for 28 hours and the solution is cooled, diluted, extracted with ether to remove any neutral product, and acidified in the cold. The oil obtained, after being dried in ether and recovered, slowly solidifies in a vacuum desiccator (yield, 25 g.). After being triturated with cold benzene and dried in a vacuum desiccator for several days, the *acid* melts at 116° and decomposes at about 118° (Found : C, 59·2; H, 7·6; *M*, by titration, 242. $C_{12}H_{18}O_5$ requires C, 59·5; H, 7·4%; *M*, 242). When crystallised from hot benzene or chloroform, or precipitated from cold ethyl acetate solution by petrol, it invariably contains a gummy impurity. The acid is almost insoluble in cold benzene, but after it has been heated with an excess of this solvent (or high-boiling organic solvents) on the steam-bath for 45 minutes, the dilactone described below is the only product that can be isolated on evaporation of the solvent. The acid, on treatment with semicarbazide acetate in aqueous methyl-alcoholic solution, gives a semicarbazone mixed with some of the dilactone. The *semicarbazone*, after treatment with cold benzene and repeated crystallisation from methyl alcohol, has m. p. 183° (decomp.) (Found: C, 52·1; H, 7·4. $C_{13}H_{21}O_5N_3$ requires C, 52·2; H, 7·0%).

The ethyl ester. The dry silver salt (15 g.) is heated under reflux over-night with ethyl iodide (10 c.c. in 60 c.c. of alcohol); the filtered solution is then concentrated under reduced pressure. The *ester*, isolated in the usual way, is a colourless liquid, b. p. 192°/14 mm., $d_{4°}^{18·5°}$ 1·0681, $n_D^{18·5°}$ 1·46984, whence $[R_L]_D = 77·3$ (calc. for the normal ester, 77·2) (Found: C, 64·6; H, 9·0. $C_{16}H_{26}O_5$ requires C, 64·4; H, 8·7%). It gives a *semicarbazone*, m. p. 104° after crystallising from ethyl acetate–light petroleum (Found: C, 57·3; H, 8·3. $C_{17}H_{29}O_5N_3$ requires C, 57·4; H, 8·2%). When the acid is esterified with alcohol and a mineral acid, an ester is obtained which gives the same semicarbazone as the above and thus appears to be the same normal ester, but its physical properties indicate that it is not quite pure.

Behaviour of cyclo*Hexane*-1-*acetone*-1-*malonic Acid on Heating. Formation of the Dilactone* (IV) *and* cyclo*Hexane*-1-*acetone*-1-*acetic Acid* (III).—The acid (5 g.) is heated for 5—6 hours at 130—140°, the melt cooled and dissolved in benzene, and the benzene solution extracted with dilute aqueous sodium carbonate, dried, and evaporated. The *dilactone* thus obtained (3·13 g., representing 68% of the keto-dibasic acid) has m. p. 141° after crystallising from methyl alcohol (Found: C, 64·1; H, 7·5. $C_{12}H_{16}O_4$ requires C, 64·2; H, 7·2%). It is the sole product obtained when the *cyclo*hexane acid is treated with concentrated hydrochloric acid or a dehydrating agent, and gives this acid on being hydrolysed with hot dilute caustic alkali solution. It is very soluble in benzene, chloroform, and ethyl acetate, but sparingly soluble in ether and cold alcohol.

The sodium carbonate extract on acidification gives an oil (1·3 g.) which gradually crystallises. After recrystallisation from petroleum (b. p. 60—80°), it melts at 73°, alone or mixed with the cyclo*hexane*-1-*acetone*-1-*acetic acid* (III) described below (Found: C, 66·3; H, 9·3. $C_{11}H_{18}O_3$ requires C, 66·6; H, 9·1%).

Several experiments on heating were carried out with different quantities of the acid. The percentage of the dibasic acid converted into the dilactone was always 68—70% and the other product was the keto-monobasic acid (III).

Synthesis of Methyl cyclo*Hexane*-1-*acetone*-1-*acetate*.—*cyclo*Hexane-

1 : 1-diacetic anhydride [readily prepared by heating the acid (Kon and Thorpe, J., 1919, **115**, 693; compare also Thole and Thorpe, J., 1911, **99**, 445) with acetic anhydride] (91 g.) is heated with methyl alcohol (40 c.c.) for 4 hours on the steam-bath and the alcohol is then removed by evaporation. The acid ester obtained is purified through the sodium salt, but cannot be made to solidify (Found for the *silver* salt: Ag, 33·8. $C_{11}H_{17}O_4Ag$ requires Ag, 33·6%). The acid ester (30 g.) is heated with thionyl chloride (15 c.c.) on the steam-bath, the excess of thionyl chloride removed under diminished pressure, and the acid chloride added to a cold benzene solution of zinc methyl iodide (compare this vol., p. 207). The keto-ester obtained is converted into the *semicarbazone*, m. p. 137° after crystallising from methyl alcohol (Found: C, 57·7; H, 9·0. $C_{13}H_{23}O_3N_3$ requires C, 57·9; H, 8·5%). *Methyl* cyclo*hexane*-1-*acetone*-1-*acetate*, regenerated from this, has b. p. 152°/18 mm., $d_4^{20\cdot4^\circ}$ 1·0363, $n_D^{20\cdot4^\circ}$ 1·46748, whence $[R_L]_D = 56{\cdot}81$ (calc. for the normal ester, 57·08) (Found: C, 67·5; H, 9·8. $C_{12}H_{20}O_3$ requires C, 67·8; H, 9·5%). On being heated with the required amount of alcoholic sodium ethoxide it is converted completely into *cyclo*hexane*spirocyclo*hexane-3 : 5-dione, which crystallises from benzene in needles, m. p. 169—170° (Norris and Thorpe, *loc. cit.*).

cyclo*Hexane*-1-*acetone*-1-*acetic Acid*.—The keto-ester just described (30 g.) is heated with potassium hydroxide (20 g.) in 20 c.c. of water and 100 c.c. of methyl alcohol on the steam-bath for 12 hours, the alcohol removed under diminished pressure, and the residue diluted with water, extracted with ether, and acidified with hydrochloric acid. The oil obtained, isolated by means of ether, slowly solidifies, and contains *cyclo*hexane-1-acetone-1-acetic acid and a small amount of *cyclo*hexane-1 : 1-diacetic acid. Separation is effected by hot petroleum (b. p. 60—80°), in which the former alone is soluble. On removal of the solvent the keto-acid is obtained pure, m. p. 73°. Norris gives m. p. 67° (J., 1926, 248) (Found: C, 66·3; H, 9·4%; *M*, by titration, 194). The *semicarbazone*, crystallised from methyl alcohol, melts at 185° (Found: C, 56·6; H, 8·6. $C_{12}H_{21}O_3N_3$ requires C, 56·5; H, 8·2%).

Action of Acetyl Chloride on cyclo*Hexane*-1-*acetone*-1-*acetic Acid*.—A mixture of the acid (5 g.) and an excess of acetyl chloride (8 c.c.) is kept at the ordinary temperature for 12 hours, hydrogen chloride being given off, and is then treated with water and extracted with ether. The extract is washed with sodium carbonate solution and with water, dried, and distilled. The neutral, mobile, colourless liquid obtained has b. p. 144°/17 mm., $d_4^{19\cdot9^\circ}$ 1·0533, $n_D^{19\cdot9^\circ}$ 1·4952, whence $[R_L]_D = 49{\cdot}85$ (calc., 49·79) (Found: C, 72·7; H, 8·9.

$C_{11}H_{16}O_2$ requires C, 73·3; H, 8·8%). The unsaturated *lactone* (VIII) is hydrolysed by alcoholic potash, giving the keto-monocarboxylic acid, m. p. 73°.

cyclo*Pentane Series.*

The compounds of this series (RR′ = $C_4H_8>$ in the formulæ) are prepared in substantially the same way as the corresponding compounds of the *cyclo*hexane series.

cyclo*Pentane*spirocyclo-3-*hydroxy*-6-*cyano*-3-*methyl*-5-*piperidone* (VI) (18 g.), prepared from *cyclo*pentenylacetone (26 c.c.), cyanoacetamide (16·8 g.), and sodium (4·6 g.), crystallises best from dilute acetic acid and melts at 282° (Found: C, 63·3; H, 8·1. $C_{11}H_{16}O_2N_2$ requires C, 63·4; H, 7·7%). It resembles the *cyclo*hexane analogue in solubility.

cyclo*Pentane*-1-*acetone*-1-*malonic acid* (I) separates from hot chloroform–petroleum in characteristic, half-pyramid-shaped crystals, m. p. 106°, decomp. near 130° (Found: C, 57·8; H, 7·4; *M*, by titration, 228. $C_{11}H_{16}O_5$ requires C, 57·9; H, 7·0%; *M*, 228). It is practically unaffected by ordinary hot solvents, but is transformed into the dilactone (IV) by concentrated hydrochloric acid or any dehydrating agent. The *semicarbazone*, after crystallising from methyl alcohol, melts at 177° (Found: C, 50·6; H, 6·8. $C_{12}H_{19}O_5N_3$ requires C, 50·5; H, 6·7%). When esterified with alcohol and hydrogen chloride, the acid gives what appears to be the normal *ethyl* ester, b. p. 179°/13 mm., $d_{4^\circ}^{18^\circ}$ 1·0767, $n_D^{18^\circ}$ 1·4632, whence $[R_L]_D$ = 72·68 (calc. for the normal ester, 72·78) (Found: C, 63·2; H, 8·7. $C_{15}H_{24}O_5$ requires C, 63·3; H, 8·4%). The ester yields readily a *semicarbazone* which melts at 109° after crystallising from ethyl acetate and light petroleum (Found: C, 56·6; H, 8·3. $C_{16}H_{27}O_5N_3$ requires C, 56·3; H, 7·9%).

Behaviour of cyclo*Pentane*-1-*acetone*-1-*malonic Acid on Heating*.—When the acid (5 g.) is heated at 140—150° for 5 hours, and the product separated into neutral and acidic portions, 2·1 g. of the *dilactone* (IV), representing about 47% of the total dibasic acid, is obtained. After crystallising from methyl alcohol, it melts at 139° (Found: C, 62·7; H, 6·5. $C_{11}H_{14}O_4$ requires C, 62·8; H, 6·6%). The same dilactone is obtained from the piperidone compound (VI) by hydrolysis with concentrated hydrochloric acid.

The acid product is cyclo*pentane*-1-*acetone*-1-*acetic acid* (III) (2·05 g.); after crystallising from light petroleum, it melts at 53° (Found: C, 65·0; H, 8·9. $C_{10}H_{16}O_3$ requires C, 65·2; H, 8·7%) and is identical with the synthetic acid described below.

Synthesis of Methyl cyclo*Pentane*-1-*acetone*-1-*acetate*.—The anhydride (98 g.) of *cyclo*pentane-1 : 1-diacetic acid (Kon and Thorpe, *loc. cit.*, p. 700) is boiled with methyl alcohol (47 c.c.) for 3 hours, the oily methyl hydrogen *cyclo*pentane-1 : 1-diacetate produced (Found for the *silver* salt : Ag, 35·8. $C_{10}H_{15}O_4Ag$ requires Ag, 35·4%) is treated with a slight excess of thionyl chloride, and the crude acid chloride with zinc methyl iodide : from 60 g. of the acid ester, 44 g. of *methyl* cyclo*pentane*-1-*acetone*-1-*acetate* were obtained. The *semicarbazone*, after crystallising from methyl alcohol, melts at 119° (Found : C, 56·5 ; H, 8·5. $C_{12}H_{21}O_3N_3$ requires C, 56·5 ; H, 8·2%). The ester regenerated from it has b. p. 130°/12 mm., $d_4^{17.7°}$ 1·0386, $n_D^{17.7°}$ 1·46021, whence $[R_L]_D = 52{\cdot}24$ (calc., 52·46) (Found : C, 66·5 ; H, 9·2. $C_{11}H_{18}O_3$ requires C, 66·6 ; H, 9·1%). The ester (7 g.), on being heated with sodium (0·9 g.) in 30 c.c. of alcohol for several hours on the steam-bath, is completely converted into *cyclo*pentane*spirocyclo*hexane-3 : 5-dione, m. p. 136° (Norris and Thorpe, *loc. cit.*, p. 1207). This is the best method of preparing the dione in quantity, and the reduction of this substance to the corresponding hydrocarbon is under investigation in order to compare this product with that obtained by a different series of reactions.

cyclo*Pentane*-1-*acetone*-1-*acetic Acid* (III).—The methyl ester (31 g.) is hydrolysed with potassium hydroxide (30 g.) in aqueous-alcoholic solution. The *acid* produced contains some *cyclo*pentane-1 : 1-diacetic acid and is purified in the same way as its *cyclo*hexane analogue; after crystallising from light petroleum, it melts at 53° (Found : C, 65·0 ; H, 8·8 ; *M*, by titration, 179. $C_{10}H_{16}O_3$ requires C, 65·2 ; H, 8·7% ; *M*, 184). It is very soluble in most of the ordinary organic solvents, but insoluble in water. The *semicarbazone*, after crystallising from methyl alcohol, melts at 191° (Found : C, 54·7 ; H, 8·4. $C_{11}H_{19}O_3N_3$ requires C, 54·7 ; H, 7·9%). The acid, on esterification with methyl alcohol and hydrogen chloride, gives the above methyl ester, identified through the semicarbazone, m. p. 119°.

Action of Acetyl Chloride on cyclo*Pentane*-1-*acetone*-1-*acetic Acid*.—When a mixture of the acid (6 g.) and acetyl chloride (10 c.c.) is heated on the steam-bath, a vigorous reaction sets in and hydrogen chloride is given off. Heating is continued for about an hour and the unsaturated *lactone* (VIII) is then isolated in the same way as the *cyclo*hexane analogue. It is a mobile liquid with a characteristic odour. It has b. p. 124°/14 mm., $d_{4°}^{18.9°}$ 1·0573, $n_D^{18.9°}$ 1·49043, whence $[R_L]_D = 45{\cdot}42$ (calc., 45·17) (Found : C, 71·9 ; H, 8·5. $C_{10}H_{14}O_2$ requires C, 72·2 ; H, 8·4%). When hydrolysed with alcoholic potash, it gives the keto-acid, m. p. 53°.

In conclusion, I wish to record my grateful thanks to Professor J. F. Thorpe, C.B.E., F.R.S., for his kind interest in this investigation, and to the Government of Bengal, India, for a foreign scholarship and a grant that has partly defrayed the cost.

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