125. *Studies in Keto-lactol Tautomerism. Part V. The Influence of Methyl*cyclo*hexane Rings on the Tautomerism of* δ-*Ketonic Acids.*

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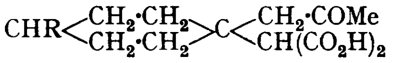
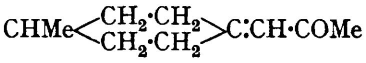
IT has been suggested (Qudrat-i-Khuda, J., 1929, 713) that the ready conversion of 1-acetonyl*cyclo*hexane-1-malonic acid (I, R = H) into the lactol (68% on melting) could be explained by the deflection of the carbon tetrahedral angle due to the *cyclo*hexane ring, in accordance with the Thorpe–Ingold theory. The difference between the *cyclo*pentane and the *gem*-dimethyl analogue of the acid (I, R = H), which should behave in the same way according to this theory, may be attributable to some additional factor. Recent results have been interpreted on the assumption of a multiplanar structure of substituted *cyclo*hexane rings (compare Qudrat-i-Khuda, *J. Indian Chem. Soc.*, **1933**, **8**, 277), and the lactol change in homologues of the acid (I, R = H) containing such rings has therefore been investigated. The results, reported below, do not however permit a definite conclusion to be drawn.

For the preparation of the acid (I, R = Me), the unsaturated ketone (II) was required. It was found, however, that a mixture of this with its Δ^{β}-isomeride could be employed and that this could be readily prepared in quantity by the method used by Jupp, Kon, and Lockton (J., 1928, 1638) for the preparation of the unsubstituted compound.

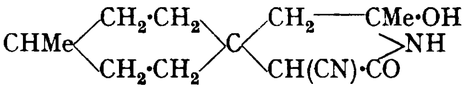
(I.) 

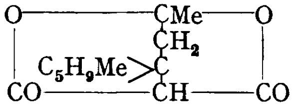
$$\mathrm{CHR}{<}\begin{matrix}\mathrm{CH_2{\cdot}CH_2}\\\mathrm{CH_2{\cdot}CH_2}\end{matrix}{>}\mathrm{C}{<}\begin{matrix}\mathrm{CH_2{\cdot}COMe}\\\mathrm{CH(CO_2H)_2}\end{matrix}$$

 (II.)

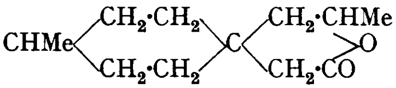
$$\mathrm{CHMe}{<}\begin{matrix}\mathrm{CH_2{\cdot}CH_2}\\\mathrm{CH_2{\cdot}CH_2}\end{matrix}{>}\mathrm{C{:}CH{\cdot}COMe}$$

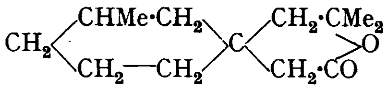
4-Methyl*cyclo*hexenylacetone was condensed with sodiocyanoacetamide to give the *imido*-compound (III), which was easily hydrolysed by concentrated hydrochloric acid to the *dilactone* (IV). This on hydrolysis with alkali gave the dibasic acid (I, R = Me), which lactonised slowly under laboratory conditions; its *silver* salt was analysed. 1-*Acetonyl*-4-*methyl*cyclo*hexane*-1-*acetic acid* was obtained in small quantity from the product of hydrolysis of the imide (III) and in some amount, together with the dilactone (IV), on decomposition of the freshly prepared dibasic acid by heat. Its *ethyl* ester, prepared by esterification of the acid and also from ethyl hydrogen 4-methyl*cyclo*hexane-1 : 1-diacetate through the acid chloride and methylzinc iodide, had the normal structure and yielded a *semicarbazone*. The acid yielded the *lactone* (V) on reduction with sodium and alcohol.

(III.) 

 (IV.)

The imido-compound (III) on hydrolysis with caustic potash yielded a mixture of 82% of the acid (I, R = Me) and 18% of the dilactone (IV). The mixture, heated above its melting point, gave 58% of the dilactone and 35·7% of 1-acetonyl-4-methyl*cyclo*hexane-1-acetic acid.

(V.) 

 (VI.)

3-Methyl*cyclo*hexenylacetone condensed fairly well with cyanoacetamide in presence of sodium ethoxide. The *imido*-compound (III, with Me in position 3 instead of 4) behaved similarly to other imido-compounds. 1-Acetonyl-3-methyl*cyclo*hexane-1-malonic acid could be obtained only in an impure condition by hydrolysis of the corresponding *dilactone* (as IV), because it underwent extensive lactonisation on standing. The freshly prepared acid, when heated above its melting point, decomposed with the production of a mixture of 67% of the dilactone and 25% of 1-*acetonyl*-3-*methyl*cyclo*hexane*-1-*acetic acid*. The *ethyl* ester of the latter acid was prepared as before, and on hydrolysis yielded the acid in a fairly pure condition. The ester reacted with methylmagnesium iodide to give the *lactone* (VI), with sodium ethoxide it gave 3-methyl*cyclo*hexane*spirocyclo*hexane-3′ : 5′-dione, and on reduction it yielded the *lactone* (as V).

Much difficulty was experienced in preparing the corresponding unsaturated ketone from 2-methyl*cyclo*hexanone and the work is not yet complete.

EXPERIMENTAL.

4-*Methyl*cyclo*hexenylacetone.*—Acetoacetic ester (72 g.) was poured into a cold solution of sodium (11·5 g.) in absolute alcohol (160 c.c.), 4-methyl*cyclo*hexanone (56 g.) added, and the mixture heated on a water-bath for 26 hours, and again for 8 hours after addition of water (60 c.c.). Alcohol was then distilled off from a water-bath, and the remaining oil refluxed with concentrated hydrochloric acid (100 c.c.) for 1½ hours. The ketone, extracted from the cooled diluted product with ether, washed with sodium bicarbonate solution, and dried over calcium chloride, had b. p. 121—122°/40 mm. (yield, 60—70%) and gave a semicarbazone, m. p. 126° (Kon and Thakur, J., 1930, 2229). Iodometric estimation (Linstead and May, J., 1927, 2565) showed that it consisted of 30·3% of the Δ^{α}- and 69·7% of the Δ^{β}-isomeride.

4-*Methyl*cyclo*hexane*-1 : 4-spiro-2′-*hydroxy*-6′-*keto*-5′-*cyano*-2′-*methylpiperidine* (III).—A hot saturated alcoholic solution of cyanoacetamide (8·4 g.) was added to a solution of sodium (2·3 g.) in absolute alcohol (30 c.c.) and heated with the preceding ketone (15 g.) on a water-bath for 4—5 hours, the odour of ammonia then being perceptible. The alcohol was distilled off and the residue was cooled, dissolved in water, and extracted with ether to remove neutral products. Acidification of the aqueous solution with dilute hydrochloric acid gave the *imide* (III) (11·5 g.), which was crystallised from dilute methyl alcohol; it did not melt below 300° (Found : C, 66·5; H, 8·8. $C_{13}H_{20}O_2N_2$ requires C, 66·1; H, 8·5%).

Hydrolysis. The imido-compound (III) (10 g.) was heated with concentrated hydrochloric acid (100 c.c.) on a water-bath for 4 hours. The crystalline *dilactone* (IV) that separated on cooling was washed with water and recrystallised from dilute alcohol; m. p. 172° (Found : C, 65·2; H, 7·6. $C_{13}H_{18}O_4$ requires C, 65·5; H, 7·5%).

The dilactone (5 g.) was heated with 10% aqueous sodium hydroxide (50 c.c.) on a water-bath for 1½ hours, and the clear solution acidified at 0° with hydrochloric acid. The dibasic acid (I, R = Me), obtained as an oil, was isolated by means of ether and kept in a vacuum desiccator; after 3 weeks it had almost completely changed into the dilactone. The *silver* salt, obtained from the freshly prepared acid through the ammonium salt, was only slightly soluble in water (Found : Ag, 45·8. $C_{13}H_{18}O_5Ag_2$ requires Ag, 45·9%).

1-*Acetonyl*-4-*methyl*cyclo*hexane*-1-*acetic Acid.*—(1) The freshly prepared dibasic acid (I, R = Me) (5 g.) was heated at 170° for an hour and the residue was cooled, treated with cold dilute sodium bicarbonate solution, and shaken with ether (which extracted 3 g. of the dilactone, m. p. 172°). The aqueous solution on acidification deposited 1·8 g. of the monobasic acid as a thick syrup (Found for the *silver* salt : Ag, 33·5. $C_{12}H_{19}O_3Ag$ requires Ag, 33·8%), which gave a *semicarbazone* crystallising from alcohol in needles, m. p. 195° (decomp.) (Found : C, 58·5; H, 8·6. $C_{13}H_{23}O_3N_3$ requires C, 58·0; H, 8·5%).

(2) The anhydride (52 g.) obtained from 4-methyl*cyclo*hexane-1 : 1-diacetic acid (70 g.) (Wood and Thorpe, J., 1913, **103**, 1583), when boiled with ethyl alcohol (45 c.c.), yielded ethyl hydrogen 4-methyl*cyclo*hexane-1 : 1-diacetate (68 g.) as a thick syrup (Found for the insoluble *silver* salt : Ag, 31·1. $C_{13}H_{21}O_4Ag$ requires Ag, 31·0%). This acid ester (20 g.) was treated with thionyl chloride (25 c.c.), the excess of the latter removed under reduced pressure, and the acid chloride added to a solution of methylzinc iodide prepared from 43 g. of zinc–copper couple, 11 c.c. of dry ethyl acetate, 25 c.c. of dry methyl iodide, and 50 c.c. of sodium-dried benzene. The keto-ester was obtained as a mobile liquid, b. p. 163—165°/31 mm., the *semicarbazone* of which had m. p. 140° after crystallisation from dilute ethyl alcohol (Found : C, 60·8; H, 9·2. $C_{15}H_{27}O_3N_3$ requires C, 60·6; H, 9·1%). *Ethyl* 1-*acetonyl*-4-*methyl*cyclo*hexane*-1-*acetate* regenerated from the semicarbazone had b. p. 133°/3 mm., $d_{4^\circ}^{30^\circ}$ 0·99033, $n_{\mathrm{D}}^{30^\circ}$ 1·45781, $[R_L]_{\mathrm{D}}$ 66·1 (calc., 66·3) (Found : C, 70·2; H, 9·9. $C_{14}H_{24}O_3$ requires C, 70·0; H, 10·0%) and on hydrolysis (20 g.) with caustic potash (9 g.) in water (9 c.c.) and rectified spirit (70 c.c.) gave, after 3 hours' heating, a liquid (14 g.), the semicarbazone of which, m. p. 195°, was identical with that described under (I). The *acid* regenerated from the semicarbazone was a thick syrup, b. p. 183°/6 mm. (Found : C, 68·2; H, 9·4. $C_{12}H_{20}O_3$ requires C, 67·9; H, 9·4%). The *methyl* ester, b. p. 120°/2 mm., was prepared from the acid and methyl-alcoholic hydrogen chloride at − 6° and then on a steam-bath (Found : C, 69·1; H, 9·7. $C_{13}H_{22}O_3$ requires C, 69·0; H, 9·7%); it gave a *semicarbazone* which crystallised from dilute alcohol in short needles, m. p. 155° (Found : C, 59·6; H, 9·0. $C_{14}H_{25}O_3N_3$ requires C, 57·3; H, 8·8%).

Reduction. To a mixture of absolute alcohol (25 c.c.) and 1-acetonyl-4-methyl*cyclo*hexane-1-acetic acid (10 g.) heated at 110° under reflux, sodium (9 g.) was gradually added, followed by alcohol (3 × 25 c.c.) at 15-minute intervals. The alcohol was removed in steam, the hot alkaline solution acidified with hydrochloric acid, and the oily product extracted with ether, washed with sodium bicarbonate solution, dried, and distilled, yielding the *lactone* (V) as a mobile liquid, b. p. 142°/3 mm., $d_{4^\circ}^{30\cdot7^\circ}$ 1·00126, $n_{\mathrm{D}}^{30\cdot7^\circ}$ 1·47165, $[R_L]_{\mathrm{D}}$ 54·78 (calc., 54·87) (Found: C, 74·0; H, 9·7. $C_{12}H_{20}O_2$ requires C, 73·45; H, 10·2%).

3-*Methyl*cyclo*hexenylacetone.*—Prepared from 3-methyl*cyclo*hexanone (56 g.) and acetoacetic ester (72 g.) by the method described for the 4-methyl compound, the ketone, b. p. 93—

94°/12 mm., consisting of 31% of the Δ^{α}- and 69% of the Δ^{β}-isomeride, was obtained in 50—55% yield; it gave a semicarbazone, m. p. 188—189° (Kon and Thakur, *loc. cit.*).

The Imido-compound (as III).—Condensation of 3-methyl*cyclo*hexenylacetone (7·5 g. and cyanoacetamide (4·2 g.) yielded the *imido*-compound in 58% yield; m. p. above 300° after crystallisation from dilute methyl alcohol (Found: C, 65·5; H, 8·4%).

Hydrolysis. (1) The imido-compound (10 g.), heated with concentrated hydrochloric acid (100 c.c.) on the water-bath for 4 hours, gave the *dilactone* (as IV), m. p. 144° after crystallisation from dilute ethyl alcohol (Found: C, 65·4; H, 7·5%). The acid mother-liquor gave an oily product, which was completely soluble in sodium carbonate solution and formed a semicarbazone, m. p. 212°, identical with that of 1-acetonyl-3-methyl*cyclo*hexane-1-acetic acid (below).

(2) The imido-compound (10 g.) was heated with caustic potash (10 g.) in water (50 c.c.) on a sand-bath for 30 hours. The product was a mixture of the dilactone (as IV) and 1-acetonyl-3-methyl*cyclo*hexane-1-malonic acid; after it had been kept for a fortnight in a vacuum desiccator, it contained 80% of the dilactone. The *silver* salt of the acid was a white amorphous mass (Found: Ag, 45·9%).

The dilactone (4 g.) was hydrolysed with 10% caustic potash solution (40 c.c.) and the dibasic acid produced was extracted with ether (yield 3·5 g.). The freshly prepared acid (5·94 g.) was heated at 160—164° till the evolution of carbon dioxide ceased; the cooled mass was extracted with sodium carbonate solution, 4·02 g. of the dilactone and 1·5 g. of 1-acetonyl-3-methyl*cyclo*hexane-1-acetic acid being obtained. The semicarbazone, m. p. 212°, of this acid was identical with that of the synthetic acid (below).

*1-Acetonyl-3-methyl*cyclo*hexane-1-acetic Acid.*—3-Methyl*cyclo*hexane-1 : 1-diacetic anhydride (64 g.) was heated with absolute alcohol (40 c.c.) on a water-bath for 6 hours. The acid ester obtained was a thick syrup (70 g.); it formed an amorphous *silver* salt insoluble in water (Found: Ag, 30·8%). The ester (20 g.) was converted by thionyl chloride into the acid chloride, which was treated with methylzinc iodide. The *ethyl 1-acetonyl-3-methyl*cyclo*hexane-1-acetate* (17 g.) obtained had b. p. 175—178°/35 mm. and gave a *semicarbazone*, m. p. 105° (decomp.) after crystallisation from benzene–petroleum (Found: C, 60·1; H, 9·5%). The keto-ester regenerated from the semicarbazone had b. p. 129°/5 mm., $d_{4°}^{30·6°}$ 0·986547, $n_D^{30·6°}$ 1·45710, $[R_L]_D$ 66·27 (Found: C, 70·0; H, 9·4%). By internal Dieckmann condensation in presence of sodium ethoxide it yielded 3-methyl*cyclo*hexane*spirocyclo*hexane-3′ : 5′-dione, m. p. 137° after crystallisation from benzene–light petroleum (Kon and Thakur, *loc. cit.*).

Hydrolysis of the keto-ester (20 g.) with potassium hydroxide (10 g.) in alcoholic solution gave the acid as a thick syrup (15 g.), the *semicarbazone* of which crystallised in needles, m. p. 212° (Found: C, 58·0; H, 8·7%). The keto-acid regenerated from the semicarbazone had b. p. 161°/2 mm. (Found: C, 67·5; H, 9·6%). The *methyl* ester, prepared with methyl-alcoholic hydrogen chloride, had b. p. 135—136°/13 mm. (Found: C, 68·8; H, 9·7%) and formed a *semicarbazone*, m. p. 162° (decomp.) after crystallisation from dilute methyl alcohol (Found: C, 59·4; H, 8·9%).

The Grignard reagent prepared from magnesium (2 g.), methyl iodide (7 c.c.), and ether (25 c.c.) was added slowly to ethyl 1-acetonyl-3-methyl*cyclo*hexane-1-acetate (8 g.) in ether (50 c.c.) cooled in a freezing mixture. After being left at the ordinary temperature for 15 minutes, the product was decomposed with ice and dilute sulphuric acid and the oil that separated was extracted with ether, washed, and distilled under reduced pressure, yielding the *lactone* (VI), b. p. 159°/10 mm., $d_{4°}^{30·5°}$ 1·00072, $n_D^{30·5°}$ 1·46566, $[R_L]_D$ 58·1 (calc., 59·5) (Found: C, 73·9; H, 10·4. $C_{13}H_{22}O_2$ requires C, 74·2; H, 10·4%).

Reduction of the keto-acid (10 g.) with sodium and alcohol under the conditions employed in the previous case produced the *lactone* (as V) (1·5 g.), b. p. 187°/4 mm., $d_{4°}^{29·8°}$ 1·01913, $n_D^{29·8°}$ 1·47796, $[R_L]_D$ 54·4 (Found: C, 73·1; H, 9·6%).

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