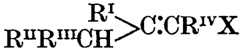
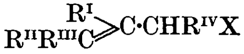
CCXIII.—*The Chemistry of the Three-carbon System. Part XVII.* cyclo*Hexylideneacetone and* cyclo*Hexylidenemethyl Ethyl Ketone.*

By ALFRED HENRY DICKINS, WILFRED EYNON HUGH, and GEORGE ARMAND ROBERT KON.

THE experiments described in the earlier papers of this series lead to the conclusion that tautomerism is to be expected in compounds of the general skeleton (I) or (II), subject to certain conditions

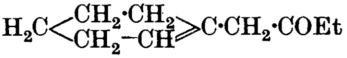
(I.)

$$\mathrm{R^{II}R^{III}CH}{>}\!\!\overset{\mathrm{R^{I}}}{}\mathrm{C{:}CR^{IV}X}$$

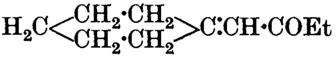

$$\mathrm{R^{II}R^{III}C}{\geqslant}\!\!\overset{\mathrm{R^{I}}}{}\mathrm{C{\cdot}CHR^{IV}X}$$
(II.)

(X = electronegative activating group; R can be H, alkyl, aryl, or acyl groups.)

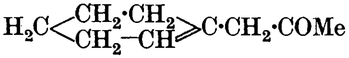
discussed there. The mobility and the point of equilibrium in any one system are the resultant of various structural factors; an estimate of the magnitude and relative importance of these factors is only possible on the strength of exact quantitative study of a variety of tautomeric systems and forms one of the principal objects of this series of researches. This task has been considerably facilitated by the elaboration of methods for the quantitative estimation of isomerides in mixtures (Linstead, J., 1927, 355; Linstead and May, *ibid.*, p. 2565), but their application is limited to cases where both individuals can be isolated in a state of purity, such as the pairs of unsaturated acids already investigated by Linstead (J., 1927, 362).

There are, however, compounds which have hitherto been isolated in one form possessing the functions of both the $\alpha\beta$- and the $\beta\gamma$-isomeride. With regard to ketones, Kon and Nutland (J., 1926, 3101) suggested that the two forms of the semicarbazone, when obtainable, are derived from the two individuals constituting the equilibrium mixture. Numerous attempts to isolate these individuals remained fruitless until the ketone (III) described by Kon (J., 1926, 1792) was synthesised. The compound obtained by the


$$\mathrm{H_2C}{<}\begin{matrix}\mathrm{CH_2{\cdot}CH_2}\\ \mathrm{CH_2{-}CH}\end{matrix}{\geqslant}\mathrm{C{\cdot}CH_2{\cdot}COEt}$$
(III.)

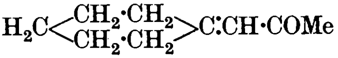

$$\mathrm{H_2C}{<}\begin{matrix}\mathrm{CH_2{\cdot}CH_2}\\ \mathrm{CH_2{\cdot}CH_2}\end{matrix}{>}\mathrm{C{:}CH{\cdot}COEt}$$
(IV.)

action of zinc ethyl iodide on *cyclo*hexylideneacetyl chloride had properties indicating the structure (IV), notably an abnormally high molecular refraction; it gave a high-melting semicarbazone, identical with that obtained by Kon and Narayanan (J., 1927, 1546), and only a small quantity of the isomeric semicarbazone, m. p. 153° (Kon, *loc. cit.*). The ketone (III) was similarly obtained from the corresponding acid and gave mainly the lower-melting semicarbazone. Under conditions avoiding the use of mineral acids and alkalis the ketones (III) and (IV) were obtained each practically free from its isomeride. The preparation of the corresponding methyl ketones (V) and (VI) was more difficult, mixtures being sometimes obtained under the most favourable conditions.



$$H_2C<\begin{matrix}CH_2\cdot CH_2\\ CH_2-CH\end{matrix}\geqslant C\cdot CH_2\cdot COMe$$

(V.)



$$H_2C<\begin{matrix}CH_2\cdot CH_2\\ CH_2\cdot CH_2\end{matrix}>C{:}CH\cdot COMe$$

(VI.)

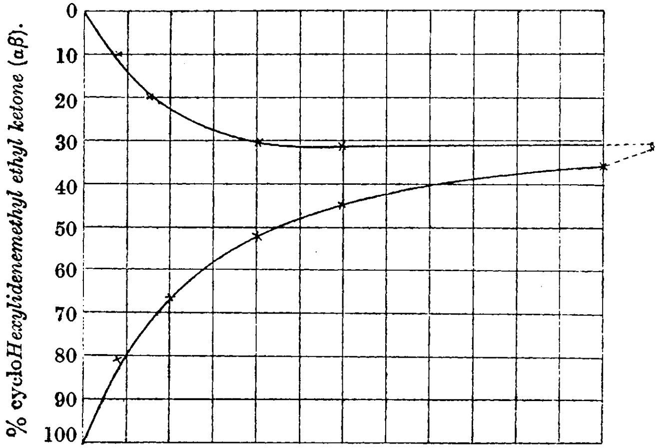
The ketone (V) is identical with that prepared by Wallach (*Annalen*, 1912, **394**, 376) and by Kon (J., 1921, **119**, 816), its semicarbazone, m. p. 145°, being identical with that obtained by previous investigators. The αβ-ketone (VI) gave a higher-melting semicarbazone identical with that isolated in minute amount by Birch, Kon, and Norris (J., 1923, **123**, 1361) and from which the new ketone could be regenerated, although a small amount of conversion into the βγ-form occurred even under very mild conditions.

The properties of the ketone (VI), like those of its higher homologue (IV), accord well with its constitution; it boils at a higher temperature than the βγ-form, has a higher density, and a much higher refractive index, the molecular refraction showing a considerable exaltation; its structure, moreover, was confirmed by oxidation with permanganate. The ketones (III) and (V) react quickly with alcoholic iodine chloride, whereas their αβ-isomerides show little reaction under the standard conditions adopted by Linstead and May (*loc. cit.*), thus allowing mixtures of isomerides to be analysed with considerable accuracy.

The equilibrium between the two pairs of ketones could therefore be studied quantitatively, different catalysts being used. In the course of this work the astonishing observation was made that although *cyclo*hexylideneacetone (and to a less extent the ketone IV) is, apparently, extremely sensitive to mineral acids *at the moment of its formation*, the pure substance is scarcely affected by them under the conditions described on p. 1635; indeed, the mobility of the substance is not of a high order, being much less than that of *iso*pulegone (Hugh, Kon, and Linstead, J., 1927, 2585). Such a discrepancy can only be attributed to an enhanced reactivity of the substance *in statu nascendi* in a manner analogous to that discussed by Goss and Ingold (J., 1925, **127**, 2776). Actually it was found that equilibration proceeded very slowly in presence of a small quantity of barium hydroxide, piperidine, or sulphuric acid. With sodium ethoxide in excess, equilibrium is completely established in 24 hours, the equilibrium mixture of (III) and (IV) containing 69% of the βγ-form; that obtained from (V) and (VI) contains

71% of the βγ-form. The crude ketones obtained by the condensation of *cyclo*hexanone with acetone and methyl ethyl ketone, respectively, should also possess this composition, as they are produced in the presence of sodium ethoxide. The numerous

FIG. 1.



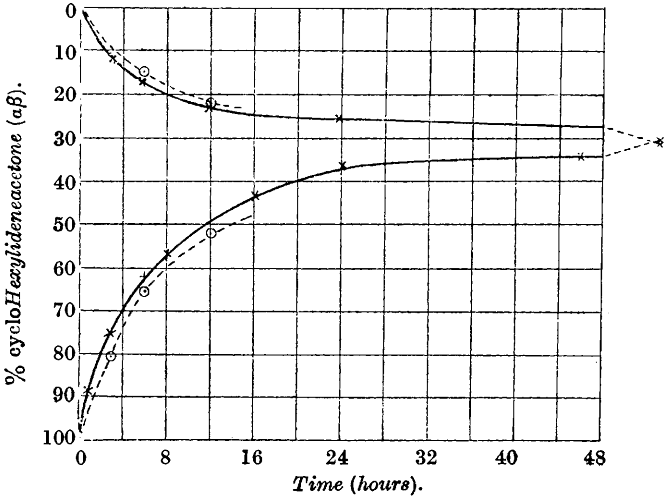


FIG. 2.

fractionations which are inevitable in these preparations, however, alter the proportion of the two isomerides; *e.g.*, a mixture of (III) and (IV) prepared as described by Kon (*loc. cit.*) contained 85% of the βγ-ketone, whereas a specimen of crude *cyclo*hexylacetone produced by the condensation of *cyclo*hexanone with ethyl sodioacetoacetate (see following paper) contained a slight excess of the αβ-ketone.

The point of equilibrium of the ketones now described is much nearer the αβ-side than that found by Linstead (*loc. cit.*) for the corresponding acids. A similar difference appears to exist between the diethylacrylic acids and the ketones derived from them (Linstead, *loc. cit.*), but further examples must be studied before any conclusion can be drawn from this observation.

The mobility of the two pairs of ketones in presence of sodium ethoxide in less than molecular quantity has been examined under comparable conditions; the results are shown in Figs. 1 and 2, from which it will be seen that the reaction appears to be a reversible unimolecular one; no attempt, however, has yet been made to follow this with great accuracy. It is hoped in the near future to develop an improved technique enabling quantitative comparisons to be made between the mobilities of different tautomeric substances under standard conditions. In the meantime, it appeared of interest to ascertain the effect of hydroxyl ions on the course of the equilibration. The addition of a slight excess of water to the mixture of the ketones and sodium ethoxide was found to have but little effect; it slightly retarded the change (Fig. 2, dotted curve).

The proof now supplied of the existence of pairs of individual substances forming an equilibrium mixture in presence of catalysts serves to emphasise the close analogy, foreshadowed in former communications, existing between substances exhibiting three-carbon tautomerism and those of the better-known keto-enol class.

EXPERIMENTAL.

cyclo*Hexylidenemethyl Ethyl Ketone* (IV).—The procedure described by Birch, Kon, and Norris (*loc. cit.*) was adopted, *cyclo*hexylideneacetyl chloride and zinc ethyl iodide being used. A fraction, b. p. 118—120°/25 mm., was obtained (yield, usually about 60%). It was treated with semicarbazide, a crude caseous semicarbazone being isolated. This, after being washed with petroleum to remove a small quantity of ester (which is always present, especially in the preparation of the βγ-ketone; compare Kon and Narayanan, J., 1927, 1546), was repeatedly crystallised from methyl alcohol, giving a less soluble portion, m. p. about 188°, and a more soluble portion from which a small amount of semicarbazone, m. p. 153°, was isolated; these were identical with the two compounds isolated by Kon and Narayanan (*loc. cit.*). When quite pure, the higher-melting compound formed fine prisms, m. p. 191°. The *ketone* regenerated from it with oxalic acid had b. p. 112°/22 mm.; $d_{4^\circ}^{18 \cdot 1^\circ}$ 0·93810, and $n_{\mathrm{D}}^{18 \cdot 1^\circ}$ 1·48945; whence $[R_L]_{\mathrm{D}} =$ 46·82 (calc., 45·84).

The amount of βγ-ketone formed could be reduced by using acetic acid in place of mineral acid to liberate the ketone from the reaction product, and almost pure αβ-ketone was obtained by the following process : the acid chloride was slowly added to an excess of zinc ethyl iodide solution efficiently cooled in a bath of ice and calcium chloride, dry ether being added to prevent the solution from freezing. The product was immediately decomposed with ice, any rise of temperature being prevented, and carbon dioxide, scrubbed by passage through sodium carbonate, was bubbled through the solution until the decomposition was complete. The solution was then filtered, the sludge washed with ether, and the combined ethereal and benzene solutions were washed with water, shaken with saturated ammonium sulphate solution, dried, and distilled through an efficient column, finally under reduced pressure.

On several occasions the ketone so produced gave a low-melting semicarbazone which after several crystallisations formed long needles of constant m. p. 167°. The ketone regenerated from it appeared in every way identical with that obtained from the higher-melting form : b. p. 110—111°/18 mm., $d_{4^\circ}^{19\cdot0^\circ}$ 0·937101, $n_{\mathrm{D}}^{19\cdot0^\circ}$ 1·48859; whence $[R_L]_{\mathrm{D}} = 46\cdot82$; this gave on recombining with semicarbazide the high-melting semicarbazone. The form, m. p. 167°, may perhaps be a stereoisomeride of the latter.

Δ^1-cyclo*Hexenylmethyl Ethyl Ketone* (III).—The action of zinc ethyl iodide on Δ^1-*cyclo*hexenylacetyl chloride gave a ketonic fraction boiling some 4° lower than in the preceding case. Under ordinary conditions, this fraction gave a semicarbazone which was difficult to purify, although the form crystallising in plates, m. p. 153°, predominated and could be isolated by repeated crystallisation. It was practically the sole product when the isolation of the ketone was carried out with the aid of carbon dioxide. The *ketone* was regenerated from it more easily than in the case of the αβ-isomeride and boiled at 107°/22 mm.; it had $d_{4^\circ}^{17\cdot5^\circ}$ 0·93020 and $n_{\mathrm{D}}^{17\cdot5^\circ}$ 1·47320, whence $[R_L]_{\mathrm{D}} = 45\cdot89$ (calc., 45·84), and showed no change in optical properties after being kept in a sealed tube for 4½ months.

Equilibrium between the Ketones (III) *and* (IV).—May and Linstead's iodometric method (*loc. cit.*) was used, the conditions being the same as for pulegone and *iso*pulegone (Hugh, Kon, and Linstead, *loc. cit.*). The values obtained in 10 minutes with *M*/300-solutions in chloroform (mean of 3 concordant determinations in each case) were :

Mixture (% αβ)	0	10	25	50	75	90	100
% Addition	87·4	83·8	78·05	60·99	38·49	23·49	14·84

From the above data a reference curve was constructed similar to that used by Hugh, Kon, and Linstead (*loc. cit.*, p. 2590).

1. *With excess of sodium ethoxide.* 4 C.c. of the αβ-ketone were

kept at room temperature for 22 hours with 0·75 g. of sodium in 12·5 c.c. of alcohol; water was then added. The ketone isolated by means of ether boiled at 105—112°/18 mm. (the first two drops of distillate were rejected) and had $d_{4^\circ}^{17\cdot2^\circ}$ 0·934595 and $n_{\mathrm{D}}^{17\cdot2^\circ}$ 1·47606; the % addition of iodine (mean of three concordant determinations) was 73·85, corresponding to 31·5% of αβ-ketone. The experiment was simultaneously carried out with the pure βγ-ketone; the product had b. p. 116—124°/24 mm., $d_{4^\circ}^{18\cdot2^\circ}$ 0·931576, and $n_{\mathrm{D}}^{18\cdot1^\circ}$ 1·47613; the % addition of iodine was 74·6, corresponding to 30·5% of αβ-ketone. The point of equilibrium is therefore approximately 31% αβ : 69% βγ.

2. *With insufficient sodium ethoxide.* 2 C.c. of each ketone were pipetted into a 50 c.c. graduated flask, 20 c.c. of a 1% solution (by weight) of sodium in ethyl alcohol were added, and the mixture was made up to 50 c.c. with alcohol. After the requisite time, the ketone was isolated as above and its composition estimated iodometrically (the physical properties were also determined as a check but are not quoted):

Initial material: αβ-ketone.

Time (hrs.)	3	8	16	24	48
% Iodine addition	33·11	48·05	49·28	65·43	70·51
% αβ-Ketone	81	66	52·5	45	37

Initial material: βγ-ketone.

Time (hrs.)	3	6	16	24
% Iodine addition	84·3	80·42	74·5	74·02
% αβ-Ketone	10	20	30·5	31

These results are expressed graphically in Fig. 1.

3. *With sulphuric acid.* 2 C.c. of each ketone were mixed with 10 c.c. of *N*-sulphuric acid, made up to 50 c.c. with alcohol, and kept for 16 hours at room temperature. The αβ-ketone underwent about 7·5% conversion; no change could be detected in the βγ-ketone.

4. *With piperidine.* Similar experiments were performed, 10 c.c. of *M*/2-alcoholic piperidine being used in place of sulphuric acid. There was no measurable change in the βγ-ketone and the αβ-ketone underwent 8·5% conversion.

Direct Condensation of cyclo*Hexanone and Methyl Ethyl Ketone.*—A sample of the ketone prepared by Kon's method (*loc. cit.*) and having properties similar to those recorded was found to contain approximately 84·5% of the βγ-ketone.

Condensation of the βγ-Ketone with Ethyl Sodiomalonate.—This condensation was carried out exactly as described by Norris and Thorpe (J., 1921, **119**, 1199). The dihydroresorcinol ester was formed in good yield, but was only obtained as a viscous liquid giving a dark red colour with ferric chloride. It was therefore hydrolysed with barium hydroxide to cyclo*hexane*spiro-4-*methyl*-cyclo*hexane*-3 : 5-*dione*, which crystallised from dilute methyl alcohol in clusters of needles, m. p. 179° (Found : C, 74·0; H, 9·3. $C_{12}H_{18}O_2$ requires C, 74·2; H, 9·4%).

cyclo*Hexylideneacetone* (VI).—This compound was prepared from *cyclo*hexylideneacetyl chloride and zinc methyl iodide by the modified procedure given on p. 1634, otherwise equilibrium mixtures were always obtained; indeed, the preparation sometimes gave a mixture without ascertainable reason. Esters do not appear to be formed when zinc methyl iodide is employed and the ketone can be obtained sufficiently pure by repeated fractionation of the reaction product. The fraction boiling at 89°/12·5 mm. had $d_{4^\circ}^{19\cdot0^\circ}$ 0·94931 and $n_D^{19\cdot0^\circ}$ 1·49128, whence $[R_L]_D = 42\cdot16$ (calc., 41·22); this was used for the reference curve. The *semicarbazone* obtained from it was much less soluble than that of the βγ-ketone; it melted in the crude state at 169—170° and formed plates, m. p. 180°, after repeated crystallisation from methyl alcohol (Found: C, 61·8; H, 8·9. $C_{10}H_{17}ON_3$ requires C, 61·5; H, 8·8%). The *ketone* can be regenerated from it *practically* unchanged, b. p. 95°/17 mm., $d_{4^\circ}^{17\cdot3^\circ}$ 0·94673, $n_D^{17\cdot3^\circ}$ 1·48917, although the iodine absorption of the product obtained is slightly higher than that of the ketone purified by fractionation. The semicarbazone obtained on treating the regenerated product with semicarbazide had no definite crystalline form and melted much too low.

The odour of the new ketone is sharper and less pleasant than that of its isomeride. The ketone develops a colour with alcoholic ferric chloride only on standing. The structure of the ketone was confirmed by oxidation, the ketone being suspended in ice-water and a slight excess of 3% aqueous potassium permanganate slowly added with constant shaking; ether extraction of the filtered solution gave a good yield of *cyclo*hexanone, which was identified in the form of its semicarbazone, m. p. 165—166°.

Δ^1-cyclo*Hexenylacetone* (VI).—This ketone was prepared from *cyclo*hexenylacetyl chloride and zinc methyl iodide in the same way as the αβ-ketone. It gave a crystalline semicarbazone, m. p. 136—137° (crude), 145° (after one crystallisation from methyl alcohol), and the ketone regenerated from this had properties agreeing with those recorded by Wallach (*loc. cit.*), namely, b. p. 83°/12 mm., $d^{18\cdot6^\circ}$ 0·93751, $n_D^{18\cdot6^\circ}$ 1·47310; whence $[R_L]_D = 41\cdot33$. A homogeneous, crystalline semicarbazone was obtained from the regenerated ketone.

Equilibrium between Ketones (V) *and* (VI).—It was first necessary to ascertain whether the αβ-ketone, purified by distillation only, could be used, in view of the fact that it is partly equilibrated on regeneration from the semicarbazone. If the lower iodine absorption of this crude ketone is due to the presence of saturated impurities, this should be detected by ascertaining whether the same final equilibrium mixture is formed from the crude as from the regenerated ketone. It was found that the difference between the iodine values of the two samples diminished considerably on equilibration and it appeared best to use a carefully fractionated specimen of αβ-ketone for the reference curve and the points on the αβ-side of the curve in Fig. 2; the regenerated ketone was used for ascertaining the final equilibrium and points near it (16, 24, and 48 hours); and a regenerated sample of *cyclo*hexenylacetone was used throughout.

The reference curve was constructed as in the preceding case, the values obtained being as follows :

Mixture (% *αβ*)	0	10	25	50	75	90	100
% Addition	83·7	80·7	74·7	60·5	40·7	26·8	15·8

1. *With excess of sodium ethoxide.* The experiment was carried out as described on p. 1635, except that the reaction was allowed to proceed for 24 hours. The product from the αβ-ketone had b. p. 88—94°/19 mm., $d_{4^\circ}^{16\cdot2^\circ}$ 0·94446, and $n_{\mathrm{D}}^{16\cdot2^\circ}$ 1·47633; the % iodine addition (mean of three concordant determinations) was 73·37, corresponding to 28·5% of αβ-ketone. The product from the βγ-ketone had b. p. 90—96°/17 mm., $d_{4^\circ}^{16\cdot4^\circ}$ 0·94446, and $n_{\mathrm{D}}^{16\cdot4^\circ}$ 1·47693; the % iodine addition was 73·10, corresponding to 29·0% of αβ-ketone.

2. *With insufficient sodium ethoxide.* The method of procedure was the same as for the higher homologues (p. 1635). Results :

Initial material : *αβ*-ketone.

Time (hrs.)	1	3	6	8	16	24	46
% Iodine addition	28·0	39·2	50·9	54·8	64·6	68·0	70·2
% *αβ*-Ketone	89·0	76·8	62·5	57·5	43·0	37·5	34·0

Initial material : *βγ*-ketone.

Time (hrs.)	3	6	12	24
% Iodine addition	80·8	78·7	75·8	74·4
% *αβ*-Ketone	12·0	17·0	23·5	26·5

These results are shown graphically in Fig. 2.

3. *With sodium hydroxide.* The catalyst used was prepared by dissolving 2 g. of sodium in 200 g. of alcohol, 10 c.c. of water being then added; 20 c.c. of this solution were used as before. The results were :

Initial material.	Time (hrs.).	% Iodine addition.	% *αβ*-Ketone.
αβ-Ketone	3	35·6	80·5
,, ...	6	48·1	66·0
,, ...	12	58·2	52·5
βγ-Ketone	6	79·5	15·0
,, ...	12	76·5	22·5

These results are marked ⊙ on Fig. 2.

The authors' thanks are due to the Royal Society and the Chemical Society for grants which have partly defrayed the cost of this investigation.

Imperial College of Science and Technology,
London, S.W. 7.

[*Received, March* 15*th*, 1928.]