351. *The Synthesis of Some Cyclic Δ^{α}-Unsaturated Ketones.*

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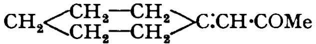
THE absence of any noticeable difference in the mobilities of *cyclo*pentylidene- and α-methyl*cyclo*pentylidene-acetone (both being greater than 3000; Kon, J., 1930, 1616; Kon and Thakur, *ibid.*, p. 2219) and the failure to synthesise α-methyl*cyclo*hexylideneacetone made it difficult to ascertain the effect of the α-methyl group in cyclic ketones of the type $(CH_2)_n > C{:}CHR$ (R = COMe). That it invariably diminishes the mobility considerably in other compounds, *e.g.*, acids, esters, and nitriles (R = CO_2H, CO_2Et, CN), has been observed before (Kon and Thakur, *loc. cit.*; Kon, Linstead, and Maclennan, J., 1932, 2454; Thakur, J., 1932, 2139, 2157). The effect of the 2-methyl group in 2-methyl*cyclo*hexylideneacetone on its mobility was also uncertain, as all attempts to prepare it gave the Δ^{β}-isomeride (Kon and Thakur, *loc. cit.*).

Although the acids, such as α-methyl*cyclo*hexylidene- and 2-methyl*cyclo*hexylideneacetic and Δ^2-octahydronaphthalene-2-α-propionic, are much less mobile than the corresponding unsubstituted acids, their acid chlorides seem to change readily into the Δ^{β}-isomerides on distillation during their preparation (compare Kon and Johnson, J., 1926, 2748; Thakur, J., 1932, 2141). The failure to obtain the Δ^{α}-ketones has been found to be partly due to this isomeric change. Using further precautions, it has now been possible to prepare α-methyl- and 2-methyl-*cyclo*hexylideneacetone and α-methyl-*trans*-decahydronaphthylidene-2-acetone from the respective Δ^{α}-acid chlorides by the Grignard or the Blaise–Maire reaction. The Δ^{α}-structure of these compounds is clear from their physical properties, low iodine addition, and their yielding the respective cyclic ketones on oxidation.

The mobilities and positions of equilibrium of α-methyl- and 2-methyl-*cyclo*hexylideneacetone have been determined under Kon and Linstead's standard conditions (J., 1929, 1269). The results are given below, those for the unsubstituted ketones being included for comparison. See also Table II (J., 1930, 2219).

Ketone (Δ^{α}-form).	% Δ^{α}- at equilibrium.	Mobility, $(k_1+k_2)\times 10^4$.
 $CH_2\!<\!\begin{smallmatrix}CH_2-CH_2\\CH_2-CH_2\end{smallmatrix}\!>\!C{:}CH\cdot COMe$	23*	700
 $CH_2\!<\!\begin{smallmatrix}CH_2-CH_2\\CH_2-CH_2\end{smallmatrix}\!>\!C{:}CMe\cdot COMe$	*ca.* 5	4—6
 $CH_2\!<\!\begin{smallmatrix}CH_2-CH_2\\CH_2-CHMe\end{smallmatrix}\!>\!C{:}CH\cdot COMe$	*ca.* 10	160
trans-β-$C_9H_{16}>C{:}CH\cdot COMe$	35†	800
trans-β-$C_9H_{16}>C{:}CMe\cdot COMe$	*ca.* 5	very low

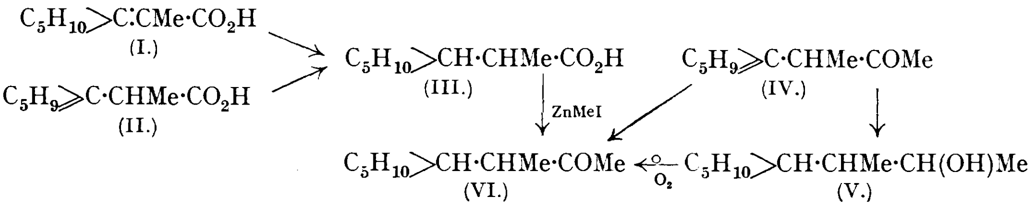
* Kon and Linstead, *loc. cit.*

† Thakur, J., 1932, 2127.

From these results it is evident that the α-methyl group considerably retards the mobility of the *cyclo*hexane and the *trans*-β-decalin compounds. In this respect, the corresponding *cyclo*pentane ketones offer a contrast, although the retarding effect has been observed in the acids, esters and nitriles of this series in common with other ring structures. The equilibrium, however, is shifted towards the Δ^{β}-side irrespective of the nature of the ring. This cannot be regarded as a general rule, considering the anomalous effect observed in the study of the unsaturated esters (Thakur, J., 1932, 2160; Kon, Linstead, and Maclennan, *loc. cit.*).

Similarly, diminution in the mobility and shifting of the equilibrium towards the Δ^{β}-side follow from the introduction of a 2-methyl group in the *cyclo*hexane ring. The order in which the mobility of the ketones (methyl substitution in the ring) seems to diminish is the same as that in the corresponding acids, *viz.* 4>3>2 (see Table I; J., 1930, 2218). From this orderly decrease it would appear that the more distant is the methyl group from the three-carbon system, the less is its effect on it. The general decrease in the mobility caused by the substitution cannot, however, be ascribed to the increased molecular weight, since the *trans*-hexahydrohydrindene compounds have been found to be much more mobile than the corresponding *cyclo*pentane compounds.

The preparation of a few reduction products, derived from the unsaturated α-methyl*cyclo*hexane compounds, was carried out by catalytic hydrogenation with no positive evidence for the " C " and " Z " forms of the six-membered ring.



Experimental.

cyclo*Hexylideneacetyl and* α-cyclo*Hexylidenepropionyl Chlorides*.—The α-*cyclo*hexylidenepropionic acid crystallised from *n*-hexane in long prismatic needles, m. p. 81—82° (Auwers and Ellinger, *Annalen*, 1912, **387**, 230, give m. p. 79°). This acid (4 g.) and thionyl chloride (4 c.c.) were left together for ½ hour at room temperature and then heated for ½ hour on the steam-bath. After removal of the thionyl chloride under diminished pressure, the acid chloride was distilled (considerable frothing). One half of the distillate was treated immediately, and the other half after being left at room temperature for 24 hours, with 25 c.c. of cold 10% aqueous sodium carbonate and after some time warmed on the steam-bath to complete the decomposition. The acid obtained in each case was freed from neutral matter in the usual way. Both acids (total, 2 g.) were oily and had the same *J* (43·9%, corresponding to 45% of Δ^{β}-acid). The preparation of the acid chloride (from 1 g. of the acid in the above manner) and its conversion into the acid were repeated. The acid had *J* = 47·5%, corresponding to 49% of Δ^{β}-acid.

*cyclo*Hexylideneacetyl chloride was similarly prepared (from 4 g. of the acid and 4 c.c. of thionyl chloride) and similarly treated. The acid (total 3·5 g.) obtained from each half of the distillate was colourless and crystalline and had *J* = 1·9%. Hence it may be concluded that there was no tautomerism of the acid chloride during the distillation.

α-*Methyl*cyclo*hexylideneacetonesemicarbazones*.—The ketone was prepared by the action of methylzinc iodide on the undistilled α-*cyclo*hexylidenepropionyl chloride (to which a drop of formic acid was added to destroy any residual thionyl chloride) by the Blaise–Maire reaction. The use of dry toluene or ether as a diluent made little difference to the yield, which varied considerably in different experiments. After the reaction product had been worked up, and the unchanged acid removed with very dilute aqueous ammonia, the solvent was distilled (the toluene under diminished pressure), and the residue treated with semicarbazide acetate. The m. p. of the resulting semicarbazone was 180—184°, 155—160°, and 160—163° in different preparations. All these, however, depressed the m. p. of the Δ^{β}-semicarbazone. On fractional crystallisation from methyl alcohol, the least soluble *semicarbazone* separated in elongated plates, m. p. 192—193° (rapid heating), 187° (slow heating); mixed m. p. with Δ^{β}-semicarbazone 145—154° (Found : C, 63·0; H, 9·1. $C_{11}H_{19}ON_3$ requires C, 63·2; H, 9·2%).

The semicarbazones of m. p. 155—160° and 160—163° gave considerable quantities of the higher-melting form (m. p. 191—192°) on crystallisation from methyl alcohol. The residue left on evaporation of the solvent from the filtrate was triturated with light petroleum and had an indefinite m. p. On repeated crystallisation a semicarbazone, m. p. 155—160°, was obtained (Found : C, 63·4; H, 9·3%). It was difficult to isolate this lower-melting form in a pure state. That it was derived from the Δ^{α}-ketone is shown from the physical properties and low iodine addition of the regenerated ketone (see below).

α-*Methyl*cyclo*hexylideneacetone*.—(i) *From the semicarbazone, m. p.* 191—192°. The regeneration by Kon's method was extremely slow (J., 1930, 1616), although an excess of *N*/2-sulphuric acid and ether were used. The ketone was therefore regenerated with oxalic acid by steam distillation. It had b. p. 97—98°/14 mm., $d_{4^\circ}^{20^\circ}$ 0·9410, $n_D^{20^\circ}$ 1·4877, $[R_L]_D$ 46·56 (calc., 45·82), *J* 4·4% (5 mins.) and 5·9% (10 mins.). On oxidation in aqueous sodium hydrogen carbonate suspension with cold 3% aqueous permanganate, it gave *cyclo*hexanone (characteristic odour; semicarbazone, m. p. and mixed m. p. 164—166°).

A small quantity of the ketone on catalytic reduction with Adams's catalyst (see below) gave a semicarbazone which separated from petroleum–acetone in glistening crystals, m. p. 112—125° (see below).

A small quantity of the Δ^{α}-ketone was treated with semicarbazide acetate and left for a few days. The resulting crystalline semicarbazone melted at 155—170° in the crude state, the existence of the two isomeric forms thus being shown.

(ii) *From the semicarbazone, m. p.* 155—160°. The semicarbazone (3·4 g.) was steam-distilled with oxalic acid. The ketone had b. p. 100—101°/16—17 mm., $d_{4^{\circ}}^{19\cdot7^{\circ}}$ 0·9412, $n_{D}^{19\cdot7^{\circ}}$ 1·4857, $[R_L]_D$ 46·38 (calc., 45·82), *J* 12·9% (5 mins.) and 14·8 (10 mins.). The value of *J* corresponds to the presence of about 7·5% of the Δ^{β}-ketone. The physical properties clearly indicate the presence of a lower-melting Δ^{α}-semicarbazone.

The regenerated ketone was reconverted into the semicarbazone. The first crop consisted of plates, m. p. 176—188° in the crude state. On recrystallisation from methyl alcohol, the semicarbazone, m. p. 191—192° (rapid heating), was obtained. The lower-melting semicarbazone (m. p. 155—165°; m. p. 153—155°) was obtained from subsequent crops.

α-*Methyl*cyclo*hexenylacetone*.—The regenerated ketone had b. p. 93—94°/14 mm., $d_{4^{\circ}}^{20^{\circ}}$ 0·9287, $n_{D}^{20^{\circ}}$ 1·4701, $[R_L]_D$ 45·71 (calc., 45·82), *J* 89·1% (5 mins.) and 98% (10 mins.) (Kon, J., 1926, 1796, gives $d_{4^{\circ}}^{19\cdot9^{\circ}}$ 0·92766, $n_{D}^{19\cdot9^{\circ}}$ 1·47153, $[R_L]_D$ 45·88).

Reference curve.

Mixture (% Δ^{α}-ketone).........	100	90	75	50	25	10	0
J % (5 mins.)	4·4	15·9	33·3	60·3	79·1	85·4	89·1

Equilibration. The following experiments were carried out with α-methyl*cyclo*hexylideneacetone under Kon and Linstead's standard conditions (*loc. cit.*) :—

Expt.	Time.	*J.*	% Δ^{α}-Ketone.
1	10 mins.	3·7	100
2	30 ,,	6·5	98
3	18 hours	71·5	35
4	63 ,,	85·3	10

In (3), the Δ^{α}-ketone used had $J = 6{\cdot}2\%$ (*i.e.*, about 98·5% of the Δ^{α}-form). In (4), the ketone recovered from (1) and (2) was used.

The semicarbazone, prepared from the fully equilibrated Δ^{α}-ketone, crystallised from alcohol in clusters of small prismatic needles, m. p. 170°. It did not depress the m. p. of the Δ^{β}-semicarbazone, whereas the mixed m. p. with Δ^{α}-semicarbazone (of m. p. 191—193°) was 148—152°.

α-cyclo*Hexylpropionic Acid* (III).—α-*cyclo*Hexylidenepropionic acid (I) was catalytically reduced in rectified spirit solution, 0·2 g. of the platinum catalyst (Adams, " Organic Syntheses," VIII, 92) being used. After removal of the catalyst, the solvent was distilled completely under reduced pressure. The resulting *acid*, which did not reduce permanganate solution, was purified by treatment with aqueous sodium hydrogen carbonate, though this was hardly necessary; it then separated from *n*-hexane at 0° in colourless granular crystals, m. p. 62°; mixed m. p. with α-*cyclo*hexylidenepropionic acid (m. p. 81—82°) 40—45° (Found : C, 69·1; H, 10·2; equiv., 155·9. $C_9H_{16}O_2$ requires C, 69·2; H, 10·3%; equiv., 156·1).

The hydrogenation of α-*cyclo*hexenylpropionic acid, carried out under exactly similar conditions, was not complete even after prolonged treatment, since the product decolorised permanganate solution readily. After the unsaturated acid had been oxidised with permanganate, α-*cyclo*hexylpropionic acid was obtained from the alkaline solution and purified by steam distillation; m. p. 62°.

The acid chloride was a mobile liquid, b. p. 91—94°/12 mm. The *amide* formed clusters of flat silky needles, m. p. 156—157°, sparingly soluble in hot water (Found : C, 69·4; H, 10·9. $C_9H_{17}ON$ requires C, 69·6; H, 11·0%); the *anilide* had m. p. 135—136° (Found : C, 77·8; H, 9·1. $C_{15}H_{21}ON$ requires C, 77·9; H, 9·2%); and the p-*toluidide*, m. p. 155—156° (Found : C, 78·3; H, 9·3. $C_{16}H_{23}ON$ requires C, 78·3; H, 9·45%). These three solids were crystallised from dilute methyl alcohol, benzene–petroleum, or benzene.

α-*Methyl*-α-cyclo*hexylacetone* (VI).—(1) *Catalytic reduction of* α-*methyl*cyclo*hexenylacetone*. The ketone (IV) (3 g.) was hydrogenated in rectified spirit for a long time, as described in the case of the Δ^{α}-acid (I). After removal of most of the solvent, the residue gave a crystalline semicarbazone: first crop, m. p. 84—106°; second crop, obtained on dilution with water, m. p. 118—125°. The substance not yielding a semicarbazone and having a strong alcoholic odour was removed by extraction and steam distillation from the semicarbazide acetate mixture.

*γ-*cyclo*Hexyl-*sec.*-butyl alcohol* (V) (1·3 g.) had b. p. 109—110°/15 mm., $d_{4^{\circ}}^{20^{\circ}}$ 0·9215, $n_D^{20^{\circ}}$ 1·4715, $[R_L]_D$ 47·4 (calc., 47·55) (Found : C, 76·4; H, 12·6. $C_{10}H_{20}O$ requires C, 76·7; H, 12·9%). It was a colourless, not very mobile liquid with a sweet odour not unlike that of *trans*-β-decalol.

(2) *Oxidation of γ-*cyclo*hexyl-*sec.*-butyl alcohol* (V). The alcohol was oxidised with Beckmann's chromic acid mixture. The resulting ketone, isolated by steam distillation, gave a crystalline semicarbazone : first crop (1·15 g.), m. p. 88—106°; second crop, m. p. 83—106°, clearing at 130°.

(3) *From α-*cyclo*hexylpropionyl chloride and methyl zinc iodide by the Blaise–Maire reaction.* As in previous cases, the ketonic product gave a crystalline semicarbazone having an indefinite melting point; first crop, m. p. 90—110°. On repeated crystallisations, a small quantity of a semicarbazone, m. p. 153—157°, was obtained in addition to the one described below (m. p. 130—131°) (Found : C, 62·6; H, 10·1. $C_{11}H_{21}ON_3$ requires C, 62·5; H, 10·0%).

After crystallisation from acetone–petroleum, a *semicarbazone*, m. p. 127—128°, 130—131° after recrystallisation, was isolated from each of the crops mentioned above (Found : C, 62·5; H, 9·9%).

*α-Methyl-α-*cyclo*hexylacetone* (VI) regenerated from the semicarbazone of m. p. 125—127° had b. p. 89—90°/13 mm., $d_{4^{\circ}}^{19\cdot7^{\circ}}$ 0·9130, $n_D^{19\cdot7^{\circ}}$ 1·4582, $[R_L]_D$ 46·08 (calc., 46·22). It was reconverted into the semicarbazone. The first crop was removed after 3 hours (plates, m. p. 110—120° after sintering from 80°); the second crop had m. p. 113—118°; the third crop, collected after many days, melted at about 148°. After crystallisation from acetone–petroleum the last crop melted at 155—156°, mixed m. p. with Δ^{β}-semicarbazone 147—150° (Found : C, 62·7; H, 10·0. $C_{11}H_{21}ON_3$ requires C, 62·5; H, 10·0%).

*2-Methyl*cyclo*hexane Series.*

*2-Methyl*cyclo*hexylideneacetone.*—The acid chloride formed from 2-methyl*cyclo*hexylideneacetic acid (*M*/9) and thionyl chloride not above 40° was treated in dry ether (80 c.c.) with methylmagnesium iodide (*M*/9 in 50 c.c. of ether). The *undistilled* ketonic product readily gave a crystalline *semicarbazone* (10·3 g.), m. p. 194°, sparingly soluble in methyl alcohol, from which it crystallised in light lustrous plates, m. p. 197°; mixed m. p. with Δ^{β}-semicarbazone 159—164° (Found : C, 63·3; H, 9·2. $C_{11}H_{19}ON_3$ requires C, 63·1; H, 9·2%).

In another experiment, the pure Δ^{β}-semicarbazone (m. p. 167—168°) was obtained instead of the pure Δ^{α}-isomeride by treatment of the ketonic product (obtained above) *after distillation*, with semicarbazide acetate. Hence it is essential to convert the undistilled product into the semicarbazone.

2-Methyl*cyclo*hexylideneacetone, regenerated from the pure semicarbazone by Kon's method (*loc. cit.*), had b. p. 99—101°/12 mm., $d_{4^{\circ}}^{20^{\circ}}$ 0·9399, $n_D^{20^{\circ}}$ 1·4908, $[R_L]_D$ 46·86 (calc., 45·82), *J* 5·7% (5 mins.) and 7·0% (10 mins.). Its odour is much less camphoraceous than that of 2-methyl*cyclo*hexenylacetone. On oxidation with permanganate and sodium hydrogen carbonate, it gave 2-methyl*cyclo*hexanone (semicarbazone, m. p. and mixed m. p. 192—193°; mixed m. p. with Δ^{α}-semicarbazone 165—174°).

*2-Methyl*cyclo*hexenylacetone.*—The Δ^{β}-semicarbazone has m. p. 174—175° (rapid heating) and 168—169° (slow heating) (Wallach, *Annalen*, 1912, **394**, 383, gives m. p. 173—174°; Kon and Thakur give m. p. 168°). The regenerated ketone had b. p. 102°/15 mm., $d_{4^{\circ}}^{20^{\circ}}$ 0·9361, $n_D^{20^{\circ}}$ 1·4774, $[R_L]_D$ 45·98 (calc., 45·82).

Reference curve.

% Δ^{α}-Ketone	100	90	75	50	25	10	0
J % (5 mins.)	5·7	19·1	37·1	60·7	80·7	89·3	93·6

Test mixture : 60% Δ^{α}. Found, *J* = 50·4%. From the curve, *J* = 51·3%.

Equilibrations. The following experiments were done on 2-methyl*cyclo*hexylideneacetone under Kon and Linstead's conditions :—

Expt.	Time.	*J* %.	% Δ^{α}-Ketone.	Expt.	Time.	*J* %.	% Δ^{α}-Ketone.	
1	10 mins.	25	85	4	2 hours	68·4	41	
2	30 ,,	48·2	63·5	5†	23 ,,	87·5	12·5	10*
3	60 ,,	60·9	50·0	6 (Δ^{β}-ketone)	42 ,,	90·5	7·5	8*

* Values found by the method of mixtures (Kon and Thakur, *loc. cit.*, p. 2224).

† In (5), the ketone recovered from the first four experiments together with some Δ^{α}-ketone was used.

The equilibrated Δ^{α}-ketone had a strongly camphoraceous odour like that of the Δ^{β}-ketone and gave the Δ^{β}-semicarbazone, m. p. and mixed m. p. 169—170°. All attempts to get the Δ^{α}-semicarbazone from the equilibrated Δ^{α}- or Δ^{β}-ketone failed, the Δ^{β}-semicarbazone, m. p. 170°, always being obtained.

The value at equilibrium may be taken as *ca.* 90% of Δ^{β}-ketone and that of mobility as *ca.* 175 from the first two experiments. The time for half change (*i.e.*, 45% of Δ^{β}) is about 47 minutes from the mobility curve.

*α-Methyl-*trans-*decahydronaphthylidene-2-acetone.*—This was prepared exactly as the 2-methyl*cyclo*hexylideneacetone by the Grignard reaction. The semicarbazone, after crystallisation from methyl alcohol, melted at 214—215° (decomp.) instead of 209—210° as previously recorded (J., 1932, 2146). The ketone regenerated from the semicarbazone (a mixture of semicarbazones, m. p. 205°, 207—208°, 214—215°) had $d_{4^{\circ}}^{20^{\circ}}$ 0·9678, $n_{D}^{20^{\circ}}$ 1·5025, $[R_L]_D$ 62·82 (calc., 62·13), and J 39·7% (10 mins.). The rather high iodine addition indicates the presence of the Δ^{β}-ketone. The Δ^{α}-position of the double bond in the ketone was proved by the fact that it gave *trans*-β-decalone (semicarbazone, m. p. 193°) on oxidation.

After treatment with a large excess of 2*N*-sodium ethoxide for nearly 5 days, the ketone had $n_{D}^{20 \cdot 1^{\circ}}$ 1·4933 and J 70·2% (10 mins.). It gave a semicarbazone, m. p. 194—195°, and 195—196° after crystallisation from methyl alcohol; this depressed the m. p. of the Δ^{α}- but not that of the Δ^{β}-semicarbazone.

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