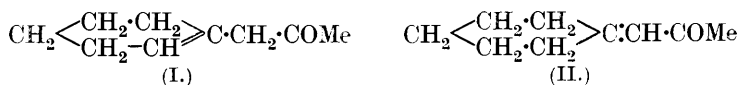CCXXXVII.—*The Chemistry of the Three-carbon System. Part V. The Alkylation of Unsaturated Ketones.*

By George Armand Robert Kon.

By a study of a series of related compounds, from the purely static diphenylpropene (Ingold and Piggott, J., 1922, **121**, 2381) to the highly mobile glutaconic acid and its ester, it is hoped to gain some insight into the conditions governing the mobility of

three-carbon systems; but meanwhile it seems desirable to examine critically some of the reactions used in ascertaining the existence of mobility in a given three-carbon system. In Part I (J., 1923, **123**, 1361), the properties of *cyclo*hexenylacetone were described and the view was put forward that the substance was tautomeric, reacting in the two forms (I) and (II).

$$CH_2 < {}^{CH_2 \cdot CH_2}_{CH_2-CH} \!\!\!> C \cdot CH_2 \cdot COMe \qquad CH_2 < {}^{CH_2 \cdot CH_2}_{CH_2 \cdot CH_2} \!\!\!> C : CH \cdot COMe$$

$$\text{(I.)} \qquad\qquad\qquad\qquad \text{(II.)}$$
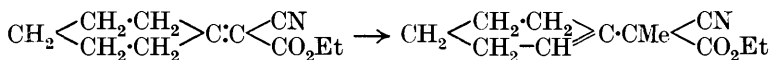
This conclusion rested on the following experimental facts :

(1) *cyclo*Hexenylacetone possesses the βγ-structure (I) under ordinary conditions, as shown by the normal molecular refraction and its behaviour on oxidation.

(2) The ketone possesses the characteristic property of αβ-un-saturated ketones of condensing with ethyl sodiomalonate.

(3) The same ketone is obtained by treating either *cyclo*hexylidene- or Δ¹-*cyclo*hexenyl-acetyl chloride with zinc methyl iodide.

(4) It possesses a hydrogen atom replaceable by sodium which is in turn readily replaced by an alkyl group. The first three of these lines of attack will be amplified on future occasions; the elaboration of the fourth, namely, alkylation, is the object of the present paper.

It is usually assumed that only a " mobile " hydrogen atom is capable of replacement by an alkyl group (compare Ingold and Piggott, *loc. cit.*, p. 2384). In some of the cases previously studied, the formation of an alkyl derivative could not take place unless it was bound up with tautomeric change as in the methylation of ethyl α-cyano*cyclo*hexylideneacetate (Birch and Kon, J., 1923, **123**, 2440) :

$$CH_2 < {}^{CH_2 \cdot CH_2}_{CH_2 \cdot CH_2} \!\!\!> C : C < {}^{CN}_{CO_2Et} \;\rightarrow\; CH_2 < {}^{CH_2 \cdot CH_2}_{CH_2-CH} \!\!\!> C \cdot CMe < {}^{CN}_{CO_2Et}$$

In the alkylation of *cyclo*hexenylacetone it is not necessary for the double bond to move, as even in the αβ-phase the substance has one hydrogen attached to the α-carbon.

It would appear that the alkylation of unsaturated ketones had not been previously attempted and there was no evidence to show whether it was a general property of substances of this class; it was therefore decided to investigate this point and to discover whether the reaction could be used to differentiate between ketones possessing a mobile hydrogen atom and others which are purely static. It was to be expected that the difference, if any, would be one of degree, because, although *cyclo*hexenylacetone and *cyclo*-pentenylacetone alkylate with great ease, it has been shown by Haller that saturated aliphatic and alicyclic ketones can be alkyl-
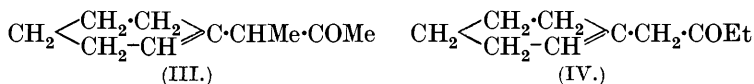
ated, by means of sodamide (compare Claisen, *Ber.*, 1905, **38**, 697), even although they do not possess a mobile hydrogen atom in the accepted sense. The behaviour of a number of unsaturated ketones of different types on alkylation was therefore examined. Far-reaching generalisations would be premature, but the following conclusions can be drawn from the results obtained :—

(1) Static αβ- or βγ-unsaturated ketones do not yield alkyl derivatives under comparatively mild conditions.

(2) The formation of alkyl derivatives is limited to ketones possessing a mobile three-carbon system and can be used to distinguish these substances.

All the ketones which have been alkylated up to the present possess the peculiar structure to which the mobility of *cyclo*hexenylacetone was attributed (see Part I); several such compounds will be described in the near future. The alkylation of compounds exhibiting " retarded mobility " has not yet been thoroughly investigated.

As a preliminary step it was necessary to establish under what conditions *cyclo*hexenylacetone gave the best yield of alkyl derivatives, and so provide a standard of comparison, more especially as certain peculiarities had already been observed in this connexion; *e.g.*, although the action of ethyl iodide in the presence of sodium ethoxide readily gave the ethyl derivative, no trace of the methyl derivative (III) could be prepared by means of methyl iodide and sodium methoxide. *cyclo*Pentenylacetone (Kon and Linstead, *J.*, 1924, **125**, 821) behaved in the same way and so did the ketone (IV) which was prepared by condensing *cyclo*hexanone with methyl

$$CH_2{<}^{CH_2 \cdot CH_2}_{CH_2-CH}{>}C \cdot CHMe \cdot COMe \qquad CH_2{<}^{CH_2 \cdot CH_2}_{CH_2-CH}{>}C \cdot CH_2 \cdot COEt$$
$$\text{(III.)} \qquad\qquad\qquad\qquad \text{(IV.)}$$

ethyl ketone. This failure was found to be due to the dissociating action of methyl alcohol on the sodio-derivative of the ketone; a somewhat similar observation was made by Hope and Perkin (*J.*, 1909, **95**, 2042) regarding the alkylation of ethyl benzoylacetate (compare also Nef, *Annalen*, 1900, **310**, 318). The ketone (III) is actually produced, although in poor yield, in the presence of sodium *ethoxide*, whilst the use of sodium in dry ether leads to the conversion of *cyclo*hexenylacetone into the methyl derivative with the exception of a certain amount which is polymerised to a high-boiling product. Benzene also is a good medium for the reaction; and ethyl, *n*-propyl, *n*-butyl, and allyl derivatives of *cyclo*hexenylacetone have been similarly obtained.

Other unsaturated ketones examined were allylacetone and methylheptenone (γδ-unsaturated), and mesityl oxide, *iso*phorone, piperit-

one, and Δ^1-tetrahydroacetophenone ($\alpha\beta$-unsaturated); in none of these cases could an alkyl derivative be obtained.* Finally, in order to confirm the views already put forward regarding the function of the *cyclo*hexane ring in *cyclo*hexenylacetone, hexahydro-

$$CH_2 \underset{CH_2 \cdot CH_2}{\overset{CH_2 \cdot CH_2}{<}} > CH \cdot CH \text{:} CH \cdot COMe \quad (V.)$$
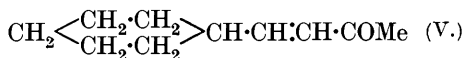
benzaldehyde was condensed with acetone with the object of preparing the ketone (V). The reaction product contained this substance and also the corresponding *aldol* (VI), together with a small

$$CH_2 \underset{CH_2 \cdot CH_2}{\overset{CH_2 \cdot CH_2}{<}} > CH \cdot CH(OH) \cdot CH_2 \cdot COMe \quad (VI.)$$
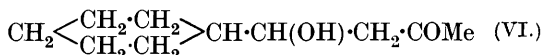
quantity of the $\beta\gamma$-isomeride $C_6H_{10}\text{:}CH \cdot CH_2 \cdot COMe$ (VII). It was subsequently discovered that the last could be readily prepared pure by heating the aldol (VI) with a trace of iodine; the action of oxalic acid or potassium hydrogen sulphate yields the $\alpha\beta$-isomeride (V) only, whilst heating alone appears to give a mixture.

It is a significant fact that neither of the isomerides (V) and (VII) could be alkylated; moreover, whilst *cyclo*hexenylacetone functions both as an $\alpha\beta$- and a $\beta\gamma$-unsaturated ketone, the ketones (V) and (VII) are quite distinct and are only converted one into the other by such means as the addition and elimination of hydrogen bromide. The $\alpha\beta$-isomeride shows a considerable exaltation of the molecular refraction and condenses readily with ethyl sodiomalonate, whilst the $\beta\gamma$-ketone has normal optical properties and does not undergo the Michael reaction. In other words, the two ketones, although formally very closely related to *cyclo*hexenylacetone, are purely static, in complete agreement with the theoretical prediction; and as such they are not alkylated under the standard experimental conditions.

EXPERIMENTAL.

Alkylation of cyclo*Hexenylacetone.* [With LAURENCE FREDERICK SMITH.]—1. *Methylation.* The ketone (1/10 g.-mol.) was added to a cooled solution of 2·3 g. of sodium in 30 c.c. of methyl alcohol, and 20 g. of methyl iodide were gradually added. The red colour of the solution was quickly discharged, gas was briskly evolved, and the solution became neutral to litmus in $\frac{1}{2}$ hour. A further quantity of sodium methoxide was then added, followed by methyl iodide, and the solution boiled. These operations having been repeated

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* This result is somewhat unexpected in view of the work of Baker (this vol., p. 663). The experiments were carefully repeated, but no trace of an alkyl derivative was isolated; a considerable quantity of the diketone, m. p. 162°, and some dihydro*iso*phorone were the only ketonic compounds present.

once more, water was added, the ketone taken up in ether, carefully washed, dried, and freed from ether. The residue on distillation consisted of the unchanged ketone together with 1 g. of high-boiling by-product; all fractions of the reaction product gave with semicarbazide the semicarbazone of *cyclo*hexenylacetone.

The methylation was repeated, "molecular" sodium in dry ether being used to form the sodio-derivative of the ketone. The reaction was vigorous, a dark orange, semi-solid mass being produced. On addition of an excess of methyl iodide and warming, the solution gradually became lighter and sodium iodide separated : the reaction was complete in about 2 hours. The reaction product was isolated as in the previous case and distilled under reduced pressure, the greater part boiling below $110°/20$ mm.; there was a certain quantity of high-boiling by-products. The low fraction was obtained in 40—45% yield and readily gave the *semicarbazone* of α-*methyl*-Δ^1-*cyclohexenylacetone* (III), which crystallised from methyl alcohol in silky needles, m. p. 169°; it also crystallised very well from acetone, in which it is but sparingly soluble (Found : C, 63·1; H, 9·3. $C_{11}H_{19}ON_3$ requires C, 63·2; H, 9·1%). The *ketone* was regenerated from it by means of oxalic acid and had b. p. $101°/20$ mm., 209—$210°/762$ mm., $d_4^{19\cdot9°}$ 0·92766, $n_D^{19\cdot9°}$ 1·47153, $[R_L]_D$ 45·88 (calc., 45·72); it has a strong odour of camphor.

The methylation was also carried out in benzene solution with a similar result, except that a little of the original material was isolated (in the form of its semicarbazone). A very poor yield of the methylated ketone was obtained with dry sodium methoxide in benzene or with sodium ethoxide in ethyl alcohol; with sodium butoxide in butyl alcohol, scarcely any methylated ketone was obtained, the product consisting mainly of high-boiling oils.

2. *Ethylation.* The reaction was carried out in ethereal solution exactly as described above, but required a longer time for completion ; the semicarbazone, m. p. 185°, already described (*loc. cit.*) was isolated in good yield. The reaction was also carried out with sodamide in benzene solution ; the yield of ketone was, however, greatly diminished owing to the formation of high-boiling by-products.

3. *Propylation* was carried out with *n*-propyl iodide in benzene solution ; the reaction was sluggish and twelve hours' boiling was required to complete it. From 13·8 g. of initial material about 8 g. of liquid boiling below 230° were obtained, and from this, with some difficulty, a *semicarbazone* was formed which crystallised from acetone in glistening plates, m. p. 152° (Found : C, 65·7; H, 9·3. $C_{13}H_{23}ON_3$ requires C, 65·8; H, 9·8%). The same ketone was obtained, although in very poor yield, by means of propyl iodide

and sodium ethoxide; in ether the reaction did not proceed to any extent.

4. *Butylation.* The reaction with *n*-butyl iodide in benzene solution took 15 hours to complete. The *semicarbazone* of the new ketone was formed with difficulty; after several crystallisations from acetone, small, rhombic crystals, m. p. 125°, were obtained (Found : C, 66·8; H, 10·5. $C_{14}H_{25}ON_3$ requires C, 66·9; H, 10·0%).

5. *Allylation. cyclo*Hexenylacetone in sodium ethoxide solution reacted very vigorously with allyl bromide, so that the latter had to be added in several portions; otherwise high-boiling by-products were formed. The reaction proceeds better in benzene solution. The *semicarbazone* of the new ketone crystallised from acetone in plates, m. p. 163° (Found : C, 66·2; H, 8·7. $C_{13}H_{21}ON_3$ requires C, 66·3; H, 9·0%); the yield, however, was rather poor.

α-Δ^1-*cycloHexenylmethyl Ethyl Ketone* (IV).—Methyl ethyl ketone was condensed with *cyclo*hexanone exactly as described by Wallach for the preparation of the lower homologue (*Annalen*, 1912, **394**, 376); the yield was rather poorer. The fraction, b. p. 200—225°, was refractionated under reduced pressure; a considerable fraction, b. p. 90°/9 mm., was then obtained. This had $d_4^{15·7°}$ 0·93303, $n_D^{15·7°}$ 1·47697, $[R_L]_D$ 46·07 (calc., 45·72). The *semicarbazone* of this ketone was an extremely intractable substance; after repeated crystallisations from acetone it was possible to isolate plates, m. p. 153° (Found : C, 63·3; H, 8·9. $C_{11}H_{19}ON_3$ requires C, 63·2; H, 9·1%). The synthesis of this ketone is now in progress.

The new ketone, like its lower homologue, could not be methylated in the presence of sodium methoxide; but ethylation was successful in benzene solution or in the presence of sodium ethoxide. The *semicarbazone* of the ethylated ketone forms glistening plates, m. p. 115° (Found : C, 65·7; H, 9·8. $C_{13}H_{23}ON_3$ requires C, 65·8; H, 9·8%). A small amount of the same ketone was synthesised from α-Δ^1-*cyclo*hexenylbutyric acid (compare Part I) and gave a semicarbazone identical with the above.

Condensation of Hexahydrobenzaldehyde with Acetone.—Hexahydrobenzaldehyde was prepared as described by Sabatier and Mailhe (*Bull. Soc. chim.*, 1905, **33**, 74). In view of the scanty details given in their paper, the following description may be found useful :

*cyclo*Hexyl chloride (80 c.c.), in 300 c.c. of ether, was treated with 16 g. of magnesium and a little magnesium methyl iodide. When the vigorous reaction had subsided, the mixture was heated for $\frac{1}{2}$ hour and 90 c.c. of ethyl orthoformate were gradually added. The ether was then boiled off, great care being necessary because a

violent reaction began as soon as most of it had been removed; the reaction could be controlled by plunging the flask in ice-water. The product, consisting of an almost solid, grey mass, was allowed to cool and decomposed with ice-water and dilute sulphuric acid. The crude acetal, which was isolated by means of ether, was hydrolysed without further purification by boiling for $1\frac{1}{2}$ hours with five times its volume of sulphuric acid $(1 : 4)$. The aldehyde was distilled off in steam and isolated in the form of the bisulphite compound, which was purified by grinding with ether and decomposed by heating with excess of aqueous sodium carbonate in a current of steam. The aldehyde was separated from the aqueous distillate and used immediately; a further small quantity was recovered by extracting the aqueous layer with ether. The aldehyde polymerises very rapidly and should be used the same day. Yield 40%.

Hexahydrobenzaldehyde (84 g.) was shaken with pure acetone (250 c.c.) and 1% aqueous sodium hydroxide (250 c.c.) for 24 hours; the aqueous layer was then separated off, extracted with a small volume of ether, and the combined oil and extract were dried with a little potassium carbonate. The ether was removed under reduced pressure, and the residue fractionated; unless a good vacuum is maintained, some water is split off at this stage. The small fraction collecting below $105°/15$ mm. was mainly unchanged aldehyde and was again condensed with acetone. The bulk (38 g.) boiled between $105°$ and $125°$, another fraction (23 g.) being obtained between $130°$ and $160°$, together with an intermediate fraction. On refractionation, about 50 g. and 27 g. of the low and the high fraction respectively were obtained.

α-Hydroxy-α-cyclohexylbutan-γ-one (VI).—The high fraction obtained in the condensation consists mainly of the above ketone. The portion boiling at 140—$146°/15$ mm. had $d_4^{20·0°}$ $0·99795$, $n_D^{20·0°}$ $1·47604$, $[R_L]_D$ $47·98$ (calc., $47·72$) (Found : C, $71·3$; H, $10·6$. $C_{10}H_{18}O_2$ requires C, $70·5$; H, $10·6\%$). The high carbon content is probably due to the presence of some unsaturated ketone. The *semicarbazone* is very sparingly soluble; it crystallises from alcohol in thick, transparent crystals, m. p. 171—$172°$ (Found : C, $58·4$; H, $9·2$; N, $18·7$. $C_{11}H_{21}O_2N_3$ requires C, $58·1$; H, $9·3$; N, $18·5\%$). The ketone could not be regenerated from the *semicarbazone*, as it underwent dehydration, the ketone (V) being produced, even though oxalic acid was used. The ketone so obtained has b. p. 112—$114°/$ 17 mm., $d_4^{19°}$ $0·9304$, n_D $1·48376$, and gave a semicarbazone, m. p. $168°$ (see below).

Hexahydrobenzylideneacetone (V).—The low fraction obtained in the condensation consisted of the above ketone accompanied by a small quantity of the βγ-isomeride and a trace of the hydroxy-

ketone; the presence of the last was shown by the fact that some water was split off on redistilling the liquid under atmospheric pressure.

The mixture of semicarbazones obtained from this fraction can be readily separated into a soluble and an insoluble portion. The latter melts with decomposition at about 235° after sintering at 205° and is best purified by extraction with alcohol. It is evidently the *semicarbazide-semicarbazone* of *hexahydrobenzylideneacetone* (Found : N, 30·0. $C_{12}H_{24}O_2N_4$ requires N, 29·6%). The soluble constituent crystallised well from dilute methyl alcohol and also from benzene in flattened needles, m. p. 168°, and consisted of the normal semicarbazone (Found : C, 63·3; H, 9·2; N, 20·2. $C_{11}H_{19}ON_3$ requires C, 63·1; H, 9·1; N, 20·1%).

The *ketone* regenerated from either of these compounds by means of oxalic acid had b. p. 230—232°/765 mm. (thermometer in the vapour up to the 100° mark), 103°/9 mm., $d_4^{19\cdot6°}$ 0·92228, $n_D^{19\cdot6°}$ 1·48424, whence $[R_L]_D$ 47·21 (calc., 45·72). The pure ketone gives the high-melting semicarbazone if left in contact with excess of semicarbazide acetate and an excess of alcohol, which prevents the immediate separation of the normal semicarbazone; the latter is formed if the mixture is " seeded " and scratched. Hexahydrobenzylideneacetone is readily formed from the aldol (VI) by the action of potassium hydrogen sulphate or hydrated oxalic acid; on distilling the aldol at ordinary pressure, a mixture of the αβ-ketone with its βγ-isomeride is formed (see below).

Hexahydrobenzylideneacetone (6 c.c.) was added to a solution of 6 c.c. of ethyl malonate in 20 c.c. of alcohol containing 1 g. of sodium, and the mixture warmed for 24 hours. Water was then added, a little unchanged neutral oil removed by means of ether, and the aqueous layer acidified. A heavy oil was precipitated which rapidly solidified and was collected and re-crystallised from dilute alcohol or benzene, plates, m. p. 140°, being obtained. They consisted of *ethyl* 1-cyclo*hexyl*-3 : 5-*diketocyclohexane-6-carboxylate* (Found : C, 67·7; H, 8·3. $C_{15}H_{22}O_4$ requires C, 67·6; H, 8·3%); the yield was about 80%. The ester gave a faint brown colour with ferric chloride and behaved as a strong acid. On hydrolysis with barium hydroxide in the usual way, it passed into 1-cyclo*hexyl*-3 : 5-*diketo*cyclo*hexane*, which crystallised from dilute alcohol in fine needles, m. p. 162° (Found : C, 74·2; H, 9·5. $C_{12}H_{18}O_2$ requires C, 74·2; H, 9·3%).

No definite products were isolated, in spite of repeated attempts, when hexahydrobenzylideneacetone was oxidised by means of ozone. On oxidation with 3% potassium permanganate in the presence of sodium hydrogen carbonate, small quantities of hexa-

hydrobenzaldehyde and the corresponding acid were obtained. All attempts to alkylate the ketone both in the presence of alcohol and in indifferent solvents led to the production of a very viscous, yellow resin of high boiling point, evidently the product of polymerisation or internal condensation. The ketone appears to be very sensitive to the action of sodium ethoxide.

β-cyclo*Hexylidene-ethyl Methyl Ketone* (α-cyclo*Hexylidenebutan-γ-one*) (VII).—This ketone occurs, as already mentioned, in the low fraction obtained in the condensation of hexahydrobenzaldehyde and acetone, more especially if sufficient care is not taken to prevent the dehydration of the aldol. It can be isolated in the form of its semicarbazone, this being very sparingly soluble in ethyl acetate, whilst that of the αβ-ketone is readily soluble. The ketone is best prepared by slowly distilling the aldol with a trace of iodine. As the distillate could not be freed from traces of halogenated compounds which rapidly caused discoloration, the ketone was converted into the *semicarbazone*, which separated immediately and crystallised from much ethyl acetate in small, sparkling plates, m. p. 162—162·5°; when pure, it also crystallised well from acetone, less so from methyl alcohol (Found : N, 20·5. $C_{11}H_{19}ON_3$ requires N, 20·1%). The *ketone* regenerated from the semicarbazone by means of oxalic acid boiled at 101°/9 mm. (thermometer in the vapour), and had $d_4^{18\cdot0°}$ 0·93706, $n_D^{18\cdot0°}$ 1·47683, whence $[R_L]_D$ 45·86 (calc., 45·72); another, smaller batch showed b. p. 224—226°/764 mm., $d_4^{26\cdot0°}$ 0·93157, $n_D^{26\cdot0°}$ 1·47310, $[R_L]_D$ 45·82. Its odour is practically indistinguishable from that of the ketone (V) and is reminiscent of benzylideneacetone.

The ketone could not be oxidised by means of ozone either in a neutral solvent or in acetic acid, although the production of an explosive ozonide was observed. Oxidation with potassium permanganate led to adipic acid. The structure of the ketone is, however, apparent from its method of formation not only from the aldol but also from the αβ-ketone by the addition and removal of hydrogen bromide (see below).

The ketone could not be made to condense with ethyl sodiomalonate. It was recovered unchanged in an attempt to ethylate it with ethyl iodide and sodium ethoxide. Reaction occurred with " molecular " sodium and ethyl iodide in warm ether, but no ethylated ketone was obtained, the material recovered being, apparently, a reduction product.

Addition of Hydrogen Bromide to the Isomeric Ketones.—The βγ-ketone (5 c.c.) was added drop by drop to ice-cold hydrobromic acid (3 c.c.) with continuous shaking. The dark bromo-ketone was isolated by means of ether and boiled with 10% aqueous sodium

hydrogen carbonate without further purification; the colour changed through dark green to light yellow. The unsaturated ketone formed was isolated by means of steam and was easily recognised as the βγ-ketone by its characteristic semicarbazone; no trace of the αβ-isomeride could be detected.

The experiment was repeated starting with the αβ-ketone; the βγ-ketone was again the sole volatile product; there was in each case a fair amount of a viscous, yellow, oily residue after the steam distillation.

Experiments on Other Unsaturated Ketones.—*iso*Phorone was recovered unchanged after treatment with sodium ethoxide and ethyl iodide, except for a small amount of high-boiling by-product. It was also treated with " molecular " sodium in dry ether, followed by ethyl iodide; the product was distilled, when about 30% boiled below 125°/20 mm., for the most part lower than *iso*phorone itself. From this fraction the semicarbazone of dihydro*iso*phorone, m. p. 205° (decomp.), was obtained in quantity (Found : C, 60·7; H, 9·7. Calc., C, 60·9; H, 9·7%), but no other ketonic product could be isolated. The residue in the distilling flask solidified and after crystallisation from ethyl acetate melted at 162° (yield about 60%); its identity with the compound prepared by Hess and Munderloh (*Ber.*, 1918, **51**, 377) was shown by means of the di-semicarbazone described by Baker (*loc. cit.*).

Tetrahydroacetophenone, prepared by Darzens's method (*Compt. rend.*, 1910, **150**, 707) and regenerated from its semicarbazone (m. p. 216—217° after three crystallisations from methyl alcohol), had b. p. 81°/13 mm., $d_4^{20\cdot0°}$ 0·9685, $n_D^{20\cdot0°}$ 1·49042, $[R_L]_D$ 37·09 (compare Auwers and Eisenlohr, *J. pr. Chem.*, 1910, **82**, 133). Attempts to alkylate the ketone both in the presence of sodium ethoxide and in neutral solvents were unsuccessful.

The condensation of the ketone with ethyl sodiomalonate proceeds readily; the products formed will be the subject of a further communication.