42. *Reactions of Aliphatic Diazo-compounds with Carbonyl Derivatives.*

By DONALD W. ADAMSON and J. KENNER.

The action of aliphatic diazo-compounds (either in the free condition or nascent from the corresponding nitroso-derivatives) on carbonyl compounds has been studied, and applied in particular to the preparation of numerous alkyl derivatives of *cyclo*heptanone and *cyclo*octanone. Moreover, the introduction of a side chain carrying a group available for further reaction is also shown to be possible by this method. 2-δ-*Carbethoxybutyl*cyclo*heptanone* has thus been prepared.

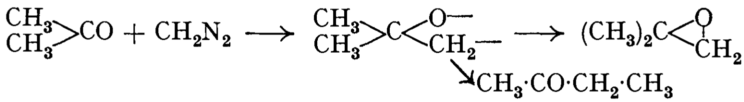
THE facility with which aliphatic diazo-compounds are now available * renders the extended study of their reactions correspondingly feasible. In this large field of work, we have given first place to reactions with carbonyl compounds, on account of the immediate value of the results.

The original discovery by Buchner and Curtius that ethyl benzoylacetate and ethyl trichloroacetoacetate were respectively formed by the action of benzaldehyde and of chloral on ethyl diazoacetate (*Ber.*, 1885, **18**, 2371) was not extended for several years,

$$Ph\cdot CHO + CHN_2\cdot CO_2Et \longrightarrow Ph\cdot CO\cdot CH_2\cdot CO_2Et + N_2$$
$$CCl_3\cdot CHO + CHN_2\cdot CO_2Et \longrightarrow CCl_3\cdot CO\cdot CH_2\cdot CO_2Et + N_2$$

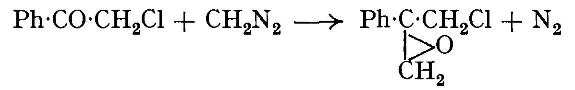
probably owing to the comparatively low reactivity of the diazo-compound. Diazomethane having become available, however, Schlotterbeck was able to prepare methyl ketones from heptaldehyde and *iso*valeraldehyde (*Ber.*, 1907, **40**, 479; 1909, **42**, 2559, 2565). The homologues of diazomethane are still more reactive (J., 1937, 1552), and accordingly almost quantitative yields of propio-, butyro-, and valero-phenones respectively have now been obtained from benzaldehyde and ethereal solutions of the appropriate diazo-compounds.

Owing to their lower reactivity in comparison with aldehydes, ketones were not brought within the scope of this type of reaction until Meerwein and Burneleit (*Ber.*, 1928, **61**, 1840; Meerwein, Bersin, and Burneleit, *ibid.*, 1929, **62**, 999) adopted the device of adding water or alcohol in order to accentuate the dipolar condition of the carbonyl group. About the same time Mosettig, after performing the alkylation of piperonal by diazomethane, observed that some piperonylacetone accompanied the desired acetopiperone (*Ber.*, 1928, **61**, 1391), and later (*Monatsh.*, 1929, **53** and **54**, 427) connected the further alkylation with the presence of methyl alcohol in the reacting medium. Under such conditions, the reaction between diazomethane and a ketone yields a mixture of ketone and ethylenic oxide—a result which Meerwein and Burneleit (*loc. cit.*, p. 1841) expressed by the scheme (compare also Bradley and Robinson, J., 1928, 1314):



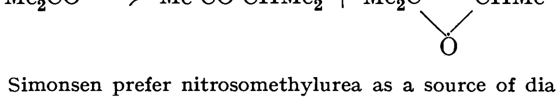
$$\begin{matrix}CH_3\\CH_3\end{matrix}\!>\!CO + CH_2N_2 \longrightarrow \begin{matrix}CH_3\\CH_3\end{matrix}\!>\!C\!<\!\begin{matrix}O-\\CH_2-\end{matrix} \longrightarrow (CH_3)_2C\!<\!\begin{matrix}O\\CH_2\end{matrix}$$
$$\searrow CH_3\cdot CO\cdot CH_2\cdot CH_3$$

This formulation indicates that oxide formation will be diminished by such an anionoid character of R and R^1 as, on the one hand, will not unduly weaken the reactivity of the carbonyl group and, on the other, will facilitate migration by adapting them to satisfy the electronic demand of the methylene group. By contrast, as Arndt and Amende found, groups which enhance reactivity of the carbonyl group conduce to oxide formation (*Ber.*, 1928, **61**, 1122). It is in accordance with this that ω-chloroacetophenone and diazomethane rapidly furnish an excellent yield of *α-phenyl-α-chloromethylethylene oxide*:



$$Ph\cdot CO\cdot CH_2Cl + CH_2N_2 \longrightarrow \begin{matrix}Ph\cdot C\cdot CH_2Cl\\ \vert\!>\!O\\ CH_2\end{matrix} + N_2$$

As Meerwein and his collaborators pointed out (*loc. cit.*), ether restrains the activity of diazomethane. It may therefore on occasion be of value to use the free diazo-compounds, and in this connection we have studied the ethylation of aqueous acetone by free diazoethane. The reaction was rapid at —10° and followed the normal course with formation of methyl *iso*propyl ketone and ααβ-trimethylethylene oxide (following Meerwein, this and all other oxidic products have been isolated in the form of the corresponding glycol):



$$Me_2CO \longrightarrow Me\cdot CO\cdot CHMe_2 + \underbrace{Me_2C\text{——}CHMe}_{O}$$

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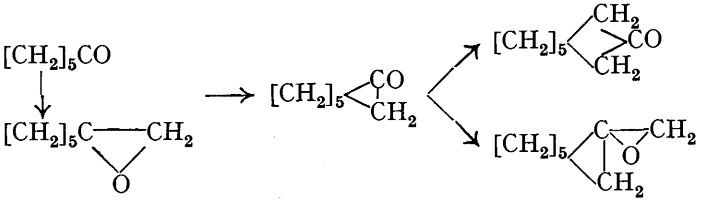
* Owen, Ramage, and Simonsen prefer nitrosomethylurea as a source of diazomethane (J., 1938, 1212). Whereas, however, the instability of this nitroso-derivative is well known (compare, for example, Lipp, Buchkremer, and Seeles, *Annalen*, 1932, **499**, 23, footnote), those derived from mesityl oxide can be kept for years. Mesityl oxide, methylamine, and its homologues are readily available.

There was also evidence of some further ethylation of the ketone, just as diethyl and methyl propyl ketones were detected among the products from diazomethane and acetone (Meerwein and Burneleit, *loc. cit.*). This is also exemplified in the production of *cyclo*octanone, as well as *cyclo*heptanone and pentamethylene-ethylene oxide (I) from *cyclo*hexanone (Mosettig and Burger, *J. Amer. Chem. Soc.*, 1930, **52**, 3456; Schering-Kahlbaum A.G., D.R.-P. 579,309):

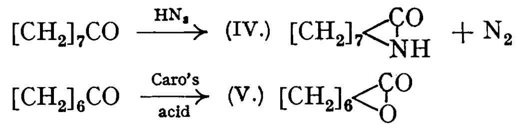
(I.)



(II.)

In this instance, however, we have found that *cyclo*octanone formation is almost completely suppressed by using only a slight excess of diazomethane over that theoretically requisite.

*cyclo*Octanone together with hexamethylene-ethylene oxide (II) is in turn obtainable in fair yield from *cyclo*heptanone, and readily separated from unchanged ketone by its indifference towards sodium bisulphite. This also serves as an indication, which experiment confirms, that *cyclo*octanone will not be attacked by diazomethane. It would be a mistake to connect this result with the extraordinary difficulty in synthesising *cyclo*nonanone (Ruzicka, Brugger, Pfeiffer, Schinz, and Stoll, *Helv. Chim. Acta*, 1926, **9**, 499; Ziegler and Aurnhammer, *Annalen*, 1934, **513**, 43), because, as the scheme shows, the methods of ring enlargement by hydrazoic acid (Schmidt, *Ber.*, 1924, **57**, 704; Ruzicka, Goldberg, Hürbin, and Boekenoogen, *Helv. Chim. Acta*, 1933, **16**, 1323) or by Caro's acid (Baeyer and Villiger, *Ber.*, 1899, **32**, 3625) are clearly analogous:

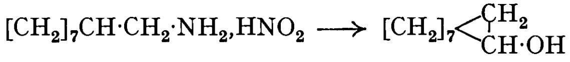


$$[CH_2]_7CO \xrightarrow{HN_3} \text{(IV.)}\ [CH_2]_7\!<\!\begin{matrix}CO\\|\\NH\end{matrix} + N_2$$

$$[CH_2]_6CO \xrightarrow[\text{acid}]{\text{Caro's}} \text{(V.)}\ [CH_2]_6\!<\!\begin{matrix}CO\\|\\O\end{matrix}$$

Similarly Ruzicka and Brugger obtained *cyclo*nonanol from *cyclo*octylmethylamine nitrite (VI) (*Helv. Chim. Acta*, 1926, **9**, 399):

(VI.)

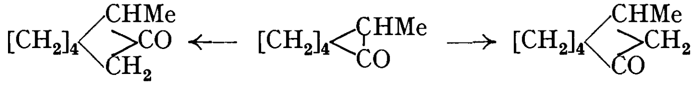


$$[CH_2]_7CH{\cdot}CH_2{\cdot}NH_2,HNO_2 \longrightarrow [CH_2]_7\!<\!\begin{matrix}CH_2\\|\\CH{\cdot}OH\end{matrix}$$

It is thus evident that the method of ring enlargement constitutes the best approach to the *cyclo*nonane and *cyclo*decane series. Stimulation of the carbonyl group by proton, on which the successful production of (IV) and (V) depends, is however clearly not permissible in presence of diazo-compounds, and, as we have found, this restriction is not compensated by use of a more reactive diazo-compound. Thus diazoethane also has no action on *cyclo*octanone under the conditions we have employed.

Our further experiments with carbonyl compounds have been designed as preparatory to the systematic development of the chemistry of derivatives of the cyclic ketones. Thus, from *cyclo*hexanone, 2-*methyl*- as well as 2-n-*heptyl*-cyclo*heptanone* was readily prepared, accompanied by small proportions of ethylene oxide derivatives. The 2-alkyl derivatives of cyclic ketones are recognised to be almost inert towards such ketonic reagents as hydrogen cyanide. This naturally applies also to sodium bisulphite and permits their separation by its means from any unalkylated ketone remaining from the above reactions. On the other hand, semicarbazone formation can be carried out, though slowly, and permits the further purification of the 2-alkyl derivatives. Since, further, the reactivity of these ketones towards diazo-compounds is almost negligible under ordinary conditions, there is no complication owing to formation of *cyclo*octanone derivatives. Very satisfactory results were also obtained by use of 4-methyl-, 4-ethyl-, 3 : 5-dimethyl-, and 4-methoxy-*cyclo*hexanones.

The difficulty of alkylating 2-methyl*cyclo*hexanone was overcome by using Meerwein's device of treating the ketone with nitrosomethylurethane in alcoholic solution in presence of potassium carbonate (Schering-Kahlbaum A.G., *loc. cit.*), whereby a mixture of 2- and 3-methyl*cyclo*heptanones, separable by sodium bisulphite, was obtained in 37% yield, together with an equal quantity of ethylene oxide derivative :



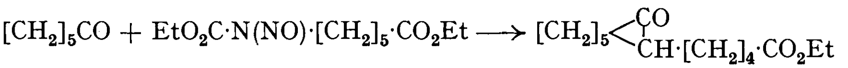
$$[\mathrm{CH_2}]_4\!\left\langle\begin{array}{l}\mathrm{CHMe}\\ \quad >\mathrm{CO}\\ \mathrm{CH_2}\end{array}\right. \longleftarrow [\mathrm{CH_2}]_4\!<\!\begin{array}{l}\mathrm{CHMe}\\ \mathrm{CO}\end{array} \longrightarrow [\mathrm{CH_2}]_4\!\left\langle\begin{array}{l}\mathrm{CHMe}\\ \quad >\mathrm{CH_2}\\ \mathrm{CO}\end{array}\right.$$

The 2-derivative is, of course, more conveniently prepared from diazoethane (or nitrosoethylurethane) and *cyclo*hexanone, but the 3-isomeride is not otherwise easily available in the pure condition, since, for example, 3-methyl*cyclo*hexanone and diazomethane furnish a mixture—obviously of 3- and 4-*methyl*cyclo*heptanones.* The latter, however, being accessible from 4-methyl*cyclo*hexanone, the three possible methyl*cyclo*heptanones have now been isolated. Surprisingly, *cyclo*pentanone furnished comparatively poor results with diazoethane.

Meerwein's procedure is further applicable to the higher urethanes, and in our experience, apart from the above instance, furnishes the same results as the free diazo-compounds. Our nitrosoalkylamino-ketones may naturally also be used in place of the urethanes, but the liability to formation of pyrazoline derivatives from mesityl oxide (J., **1937**, 1551) may be a disadvantage in isolating the desired products.

The general trend of our results is to indicate that the greater anionoid reactivity of the homologues of diazoethane corresponds to a proportionately greater yield of ketones as compared with oxide.

A most important further extension of the general reaction we have here exploited would obviously be achieved if, in place of simple alkyl groups, others containing a reactive centre could be introduced into carbonyl compounds. This also we have successfully accomplished in the first case selected, namely, that of the δ-carbethoxybutyl group. *cyclo*Hexanone was successively converted into ε-leucinelactam, ε-carboxy-*n*-amylamine hydrochloride, ε-carbethoxy-*n*-amylamine, and the corresponding nitrosourethane. The last reacted with *cyclo*hexanone under Meerwein's conditions, yielding 2-*δ-carbethoxybutyl*cyclo*heptanone* (VII), characterised by its 2 : 4-dinitrophenylhydrazone and viscous *oxime* and by the *semicarbazone* of the free acid :



$$[\mathrm{CH_2}]_5\mathrm{CO} + \mathrm{EtO_2C{\cdot}N(NO){\cdot}[CH_2]_5{\cdot}CO_2Et} \longrightarrow [\mathrm{CH_2}]_5\!<\!\begin{array}{l}\mathrm{CO}\\ \mathrm{CH{\cdot}[CH_2]_4{\cdot}CO_2Et}\end{array} \qquad \text{(VII.)}$$

It remains to draw attention to the indications of stereoisomerism among the semicarbazones of several of the ketones now described. Whereas those prepared from *cyclo*heptanone and its various 4-substituted derivatives at once exhibited sharp melting points, 2-alkyl derivatives furnished products which melted indefinitely and required repeated crystallisation for purification. The matter was examined in detail in the case of 2-methyl*cyclo*heptanone. At the ordinary temperature a *derivative*, m. p. 177—178·5° after purification, was obtained, and at 60° an *isomer*, m. p. 134·5—136°, was formed. The ketone regenerated from each afforded the other isomer under the appropriate conditions and the same 2 : 4-*dinitrophenylhydrazone*, m. p. 102—111°. The range of this melting point was much diminished (121—122°) by repeated crystallisation and was perhaps also an indication of the existence of isomeric forms. Such indications were noted in a number of instances. Stereoisomeric semicarbazones of cyclic ketones have previously been observed by Wallach in the cases of α-and β-thujones (*Annalen*, 1904, **336**, 247), *iso*thujone and carvenone (*Ber.*, 1895, **28**, 1955), and by Rupe and Dorschky in the case of *d*-carvone (*Ber.*, 1906, **39**, 2112).

EXPERIMENTAL.

A. *Action of Diazo-derivatives on Benzaldehyde.*—(1) A solution of diazoethane (7·1 g., from 40 g. of crude nitrosoethyldiacetoneamine) in dry ether (1300 c.c.) was added to a solution of benzaldehyde (10·6 g.) in a small volume of ether, cooled in ice. When nitrogen evolution had ceased (24 hours), ether and the excess of diazoethane were removed by distillation, and the colourless residue shaken with sulphuric acid (0·1%; 60 c.c.) for 8 hours. After neutralisation with N/20-barium hydroxide, steam distillation, extraction with ether, and drying over sodium sulphate, the product was recovered by evaporation and shaken with saturated sodium bisulphite solution for 5 hours. The unchanged oil, separated in the usual manner, yielded propiophenone (12·6 g.), b. p. 100—100·5°/24 mm., m. p. 17·5—19°. Its semicarbazone, m. p.180—180·5°, did not depress the m. p. of a sample from the authentic ketone.

(2) Diazo-*n*-propane (4·3 g., from 23 g. of crude nitroso-*n*-propyldiacetoneamine) in dry ether (1400 c.c.) and benzaldehyde (6·0 g.) after 48 hours yielded butyrophenone (7·5 g.), b. p. 111—112°/24 mm.; semicarbazone, m. p. 190—190·5°.

(3) Diazo-*n*-butane (2·5 g.), in dry ether (35 c.c.) and benzaldehyde (3·5 g.), after 2 hours, yielded valerophenone (4·8 g.), b. p. 129—131°/23 mm.; semicarbazone, m. p. 166·5°.

B. *Action of Diazo-derivatives on Ketones.*—(1) *Acetone.* Dry gaseous diazoethane (0·05 g.-mol. from 0·1 g.-mol. of nitrosoethyldiacetoneamine) was passed into a mixture of acetone (0·14 g.-mol.) and water (2 g.) at −50° in the receiver D (J., 1937, 1555). Rapid evolution of nitrogen occurred when the temperature was allowed to rise to −10°, and decolorisation occurred after 2—3 minutes. The mixture having been cooled again to −50°, the process was repeated with a similar quantity of diazoethane. This time, the maximum temperature was 0° and the mixture separated into two layers. Following on a third and similar additions of diazoethane, decolorisation was complete after 5 hours at −10°. The product, having been shaken for 14 hours with 0·1% sulphuric acid (50 c.c.) and neutralised with barium hydroxide, was distilled under atmospheric pressure until the residue amounted to only 25 c.c. (R). Saturation of the distillate with potassium carbonate caused separation of an oil (9·2 g.), from which, after its ethereal solution had been dried with potassium carbonate, the following fractions were obtained: (1) 0·85 g., b. p. 72—87°; (2) 1·15 g., b. p. 87—93°; (3) 3·4 g., b. p. 93—96·5°; (4) 1·9 g., b. p. 96·5—97·5°; (5) 0·4 g., b. p. 97·5—125°; (6) 1·0 g., b. p. 125—165°. On redistillation, fractions (2), (3), and (4) yielded methyl *iso*propyl ketone (4·5 g.), b. p. 94—95·5° (Clarke, *J. Amer. Chem. Soc.*, 1911, **33**, 528, gives 95—95·3°), of which the semicarbazone, m. p. 113·5—114·5°, did not depress the m. p. of an authentic specimen. Fraction (6), after being shaken with water to remove any glycol, dried, and redistilled, furnished a few drops of ketonic material, b. p. 135—145° (semicarbazone, m. p. 104—108° after recrystallisation from light petroleum, b. p. 40—60°, which depressed the m. p. of the above semicarbazone). From the residue (R), trimethylethylene glycol (1·15 g.), b. p. 85°/26 mm., 177·5—178·5°/750 mm. (Henry, *Compt. rend.*, 1907, **144**, 1404, gives 177—178°), was obtained (Found: C, 57·3; H, 11·3. Calc. for $C_5H_{12}O_2$: C, 57·7; H, 11·6%).

(2) *ω-Chloroacetophenone.* The ketone (3·1 g.) in dry ether (20 c.c.) and methyl alcohol (20 c.c.) was treated with diazomethane (1·05 g.) in dry ether (100 c.c.). After 12 hours, a non-lachrymatory, non-ketonic oil (3·0 g.), b. p. 135—137°/17 mm., was isolated: it was deemed to be *α-phenyl-α-chloromethylethylene oxide* (Found: Cl, 20·9. C_9H_9OCl requires Cl, 21·1%).

(3) cyclo*Hexanone.* (a) The action of free diazomethane on this ketone has already been studied (Mosettig and Bürger, *loc. cit.*; Robinson and Smith, J., 1937, 372). *cyclo*Heptanone was, however, more conveniently prepared on the lines of D.R.-P. 579,309 by adding nitrosomethylurethane (69 g.) in the course of 2 days to a well-stirred ice-cooled mixture of *cyclo*hexanone (49 g.), absolute alcohol (100 c.c.), and anhydrous potassium carbonate (5 g.). About 11 l. of nitrogen having been evolved, the liquid was filtered and shaken with saturated sodium bisulphite solution for 12 hours. Suberone (22·3 g.), b. p. 178—179° (semicarbazone, m. p. 162·5—163·5°), was thus obtained. The material inert to bisulphite was similar to that obtained by the workers mentioned. After being shaken for 12 hours with 0·5% sulphuric acid and fractionated at 25 mm., it furnished 1-hydroxymethyl-1-*cyclo*hexanol (15 g.), m. p. 75—75·5°, together with impure *cyclo*octanone (4·8 g.). Suberone (34 g.) was also obtained by using nitrosomethyldiacetoneamine (100 g.), absolute alcohol (110 c.c.), and anhydrous potassium carbonate (27 g.) and maintaining the temperature below 30° for 5 days. The presence of pyrazoline derivative, however, was obstructive to the isolation of the glycol.

(b) The product from *cyclo*hexanone (33 g.) and nitrosoethylurethane * (1·05 g.-mol.), isolated after treatment with dilute sulphuric acid,† was resolved into the following fractions

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* A preliminary account of the action of diazoethane on *cyclo*hexanone has been published by Giraitis and Bullock (*J. Amer. Chem. Soc.*, 1937, **59**, 951), but this reaction and the greater part of the work now described had been embodied in a thesis by one of us in November, 1936.

† In this and succeeding instances of the use of nitrosoalkylurethanes, the procedure corresponded to that detailed later for the case of 4-methyl*cyclo*hexanone and nitrosomethylurethane. This technique is the most satisfactory, but other instances had been studied before it was evolved.

at 22—23 mm. pressure: (1) 5·2 g., b. p. 55—70°; (2) 28.8 g., b. p. 70—79°; (3) 1·3 g., b. p. 79—125°; (4) 4·6 g., b. p. 125—158°, a small tarry residue being left. From (1), (2), and (3), *cyclo*hexanone (1·0 g.) was removed by sodium bisulphite, and fractionation under ordinary pressure then yielded (1) 1·6 g., b. p. to 170°; (2) 2·7 g., b. p. 170—180°; (3) 17·5 g., b. p. 180—186°; (4) 8·3 g., b. p. 186—190°; (5) residue, 1·6 g. From (2) and (3), 2-methyl*cyclo*heptanone (16·5 g., b. p. 186—189°) was isolated. Alternatively, the entire original product, after acid treatment (29·5 g., b. p. 170—192°), yielded a semicarbazone (29 g.), from which the ketone, b. p. 187—187·5°, was recovered (Godchot and Cauquil, *Compt. rend.*, 1929, **188**, 794, found 185—186°) (Found: C, 76·1; H, 10·9. Calc. for $C_8H_{14}O$: C, 76·2; H, 11·1%). Similar results were obtained by use of ethereal diazoethane or of nitrosoethyldiacetoneamine.

The semicarbazone was obtained in two, presumably stereoisomeric, forms. Prepared at 60°, in presence of sufficient methyl alcohol for homogeneity, the crude material obtained after 5 days melted at 122—125°, and after four recrystallisations from light petroleum (b. p. 40—60°), at 134·5—136° (Found: N, 23·1. Calc. for $C_9H_{17}ON_3$: N, 23·0%). At the ordinary temperature a product, m. p. 164—168°, resulted after 5 days, and after four recrystallisations from methyl alcohol melted at 177—178·5° (Found: N, 23·4%). The semicarbazone, m. p. 176—177°, of acetyl*cyclo*hexane (b. p. 180—181°) (Nenitzescu and Cioranescu, *Ber.*, 1936, **69**, 1820) depressed the m. p. of the product now described to 143—153°. A mixture of the two semicarbazones derived from diazoethane melted at 118—153°, and the ketone regenerated from each form was convertible into the other form under the appropriate conditions. Godchot and Cauquil (*loc. cit.*) and Wallach (*Annalen*, 1906, **345**, 146) record m. p. 117—118° and 129—131° respectively. The ketone from each form afforded the same 2 : 4-*dinitrophenylhydrazone*, m. p. 121—122° after repeated crystallisation from alcohol (Found: N, 18·1. $C_{14}H_{18}O_4N_4$ requires N, 18·3%). Again, the oxime, b. p. 127°/22 mm. (Godchot and Cauquil, *loc. cit.*, record 126°/16 mm.), was converted into its phenylurethane, m. p. 97—100° after crystallisation from light petroleum (Found: N, 11·1. Calc. for $C_{15}H_{20}O_2N_2$: N, 10·8%) (Godchot and Cauquil record 96—97°); the m. p. was raised to 125—127° after three further crystallisations.

(c) The nitrosation of n-*octylurethane*, b. p. 152—155°/19 mm. (Found: N, 7·0. $C_{11}H_{23}O_2N$ requires N, 7·0%), was performed in the usual manner, but the nitroso-derivative could not be distilled under 0·5 mm. pressure without decomposition. The crude material (43 g.) and *cyclo*hexanone (19 g.) furnished a product, from which, after the usual treatment, the following fractions were obtained at 20 mm. pressure: (1) at 75—135°, 0·9 g.; (2) b. p. 135—145°, 2·0 g.; (3) b. p. 145—150°, 1·9 g.; (4) b. p. 150—156°, 22·2 g.; (5) b. p. 156—160°, 3·7 g.; (6) b. p. 160—210°, 2·5 g.; residue, 1·5 g. 2-n-*Heptyl*cyclo*heptanone* (20·3 g.), further purified by redistillation of fraction (4), boiled at 153—157°/21 mm.; a solid semicarbazone was not isolated even after 8 weeks under the usual conditions, but a very viscous colourless *oxime* (7·8 g.), b. p. 145—148°/0·8 mm. (Found: N, 6·0. $C_{14}H_{27}ON$ requires N, 6·2%), was obtained from the ketone (9 g.). It did not afford a solid phenylurethane, but from the ketone, b. p. 174—178°/32 mm. (Found: C, 79·5; H, 12·4. $C_{14}H_{26}O$ requires C, 80·0; H, 12·4%), regenerated by oxalic acid, a 2 : 4-*dinitrophenylhydrazone* was prepared, m. p. 54—60°, and 65° after four recrystallisations from ethyl alcohol (Found: N, 14·1. $C_{20}H_{30}O_4N_4$ requires N, 14·4%).

(d) ε-Leucinelactam (Schmidt, *Ber.*, 1924, **57**, 704; 1925, **58**, 2413; E.P. 331,947) was converted into ε-aminohexoic acid hydrochloride (compare "Organic Syntheses," XVII, 7), from which the ethyl ester, b. p. 105°/18 mm., was prepared. The corresponding *urethane*, b. p. 185°/20 mm. (Found: N, 6·3. $C_{11}H_{21}O_4N$ requires N, 6·1%), furnished a nitroso-derivative, which could not be distilled under 0·5 mm. pressure without decomposition. The crude material (13 g.) and *cyclo*hexanone (5 g.) under the usual conditions finally yielded a product, from which the following fractions were obtained: (1) 1·05 g., b. p. 75—175°/25 mm.; (2) 6·7 g., b. p. 145—150°/0·7 mm.; (3) 1·6 g., b. p. 150—200°/0·7 mm., leaving a deep red, tarry residue (1·4 g.). 2-δ-*Carbethoxybutyl*cyclo*heptanone* (6·1 g.), b. p. 144—148°/0·7 mm. (Found: C, 69·2; H, 9·7. $C_{14}H_{24}O_3$ requires C, 70·0; H, 10·0%), obtained by redistillation of fraction (2), was not quite pure; it afforded no solid semicarbazone but a viscous *oxime*, b. p. 169—174°/0·7 mm. (Found: N, 5·3. $C_{14}H_{25}O_3N$ requires N, 5·5%). Boiling the ketonic ester for 2 hours with aqueous sodium hydroxide (10%; 20 c.c.) sufficed for its hydrolysis. The resulting acid (1·3 g.) was characterised by a *semicarbazone*, m. p. 146—152°, from which a uniform product, m. p. 157—158°, ensued after three recrystallisations from methyl alcohol (Found: C, 58·4; H, 9·0; N, 15·5. $C_{13}H_{23}O_3N_3$ requires C, 58·0; H, 8·6; N, 15·6%).

(4) 4-*Methyl*cyclo*hexanone*. (a) To a stirred mixture of the ketone (30 g.), absolute alcohol (60 c.c.), ether (60 c.c.), and potassium carbonate (6 g.), cooled by ice, nitrosomethylurethane (35 g.) was gradually added during 3 days. The theoretical volume of nitrogen having been

evolved, the liquid was filtered after the fourth day. Following on removal of ether and alcohol, shaking with 0·5% sulphuric acid for 5 days, neutralisation, saturation with ammonium sulphate, extraction with ether, and removal of ether and ethyl carbonate, fractionation under 26 mm. pressure yielded (1) 2·85 g., b. p. 62—83° (essentially unchanged ketone); (2) 9·95 g., b. p. 83—87°; (3) 6·55 g., b. p. 87—90°; (4) 1·6 g., b. p. 90—100°; (5) 1·6 g., b. p. 100—137°; (6) 7·15 g., b. p. 137—142°; residue, 1·6 g. From fractions (2), (3), and (4), *4-methyl*cyclo*heptanone* (14·6 g.), b. p. 84·5°/25 mm., 194·5°/762 mm. (Found: C, 75·7; H, 11·2. $C_8H_{14}O$ requires C, 76·2; H, 11·1%), was isolated through its bisulphite compound. Its *semicarbazone* had m. p. 158—160° after two crystallisations from methyl alcohol (Found: C, 59·1; H, 9·1; N, 22·9. $C_9H_{17}ON_3$ requires C, 59·0; H, 9·3; N, 22·9%). The portion of fractions (2), (3), and (4) inert to sodium bisulphite (1·7 g.) had the odour of *cyclo*octanone, and was presumed to be a mixture of the 4- and the 5-methyl derivative. Fraction (6) solidified and separated from light petroleum in lustrous plates, m. p. 85·5—86·5° (Found: C, 66·5; H, 10·9. Calc. for $C_8H_{16}O_2$: C, 66·7; H, 11·1%). Wallach and Evans (*Annalen*, 1906, **347**, 346) record 87—88° as the m. p. of 1-hydroxymethyl-4-methyl*cyclo*hexanol.

Ethereal diazomethane afforded similar products.

(b) The ketone and a 5% excess of nitrosoethylurethane were treated as in the case of *cyclo*hexanone, and the following fractions finally separated: (1) 7·0 g., b. p. 130—170°; (2) 28·5 g., b. p. 170—203°, both under ordinary pressure; (3) 8·0 g., b. p. to 95°; (4) 0·5 g., b. p. 95—115°; (5) 3·0 g., b. p. 115—137°, under 20 mm. pressure. From fractions (1), (2), (3), and (4), the original ketone (2·0 g.) was removed by sodium bisulphite, and the residue (30·4 g.) converted into its *semicarbazone* (27·3 g.), m. p. 124—131°. The regenerated *ketone* boiled at 204°/757 mm. (Found: C, 76·8; H, 11·4. $C_9H_{16}O$ requires C, 77·1; H, 11·4%). Alternatively an essentially pure sample of the ketone (19·8 g.), b. p. 201·5—204·5°, was derived from the residue by fractionation. The semicarbazone just described (Found: N, 21·7. $C_{10}H_{19}ON_3$ requires N, 21·4%) was apparently a mixture of stereoisomers, since after five recrystallisations from methyl alcohol its m. p. was 162·5—164·5° (Found: N, 21·6%). Similarly its 2 : *4-dinitrophenylhydrazone*, at first sticky, after six recrystallisations from ethyl alcohol, melted at 135—137° (Found: N, 17·6. $C_{15}H_{20}O_4N_4$ requires N, 17·5%). The viscous *oxime*, b. p. 132°/23 mm. (Found: N, 9·2. $C_9H_{17}ON$ requires N, 9·0%), did not yield a solid phenylurethane.

The use of ethereal diazoethane led to similar results.

(5) *3-Methyl*cyclo*hexanone*. The fractions derived from this ketone (10 g.) and nitrosomethylurethane (5% excess) were: (1) 0·8 g., b. p. 170—187°; (2) 4·4 g., b. p. 188—194°, both under atmospheric pressure; (3) 1·3 g., b. p. to 145°; (4) 2·7 g., b. p. 145—155°, both under 40 mm. pressure; residue, 0·6 g. The semicarbazone from fraction (2) melted over a wide range, 135—161°, as though derived from a mixture of ketones. Since Wallach and Evans (*loc. cit.*) described 1-hydroxymethyl-3-methyl*cyclo*hexanol as an oil, b. p. 150—153°/39 mm., this was presumed to be the essential composition of fraction (4).

(6) *2-Methyl*cyclo*hexanone*. Ethereal diazomethane was only decolorised after 10 days in presence of the ketone, and no *cyclo*heptanone derivative could be isolated from the product. When, however, the ketone (38 g.) was treated with nitrosomethylurethane (5% excess), 8·5 l. of nitrogen were evolved in 5 days. Fractions were separated as follows: (1) 4·4 g., b. p. 140—161° (inert to bisulphite, essentially unchanged ketone); (2) 4·15 g., b. p. 161—180°; (3) 11·5 g., b. p. 180—210°, under ordinary pressure; (4) 2·2 g., to 110°; (5) 2·5 g., 110—140°; (6) 12·7 g., 140—143°, under 28 mm.; residue, 1·5 g. A ketone (3·1 g.), b. p. 188·5—190·5°, was separated from fractions (2) and (3) through its bisulphite compound. Although the results of analysis were not entirely satisfactory (Found: C, 74·4, 74·1; H, 11·5, 11·4%), the material was evidently essentially *3-methyl*cyclo*heptanone*, since it at once yielded a definite *semicarbazone*, m. p. 179—181° after crystallisation from benzene (Found: N, 23·1. $C_9H_{17}ON_3$ requires N, 23·0%). Fractionation of the unreactive material from fractions (2) and (3) furnished (1) 1·95 g., b. p. 164—184°; (2) 2·5 g., b. p. 184—192°; (3) 1·9 g., b. p. 192—215°; residue, 4 g. From a portion, b. p. 187—191°, of the second fraction, a semicarbazone, m. p. 165—169°, was prepared and identified with that derived from 2-methyl*cyclo*heptanone (from diazoethane and *cyclo*hexanone) by direct comparison. The third fraction was probably a mixture of methyl*cyclo*octanone derived from 3-methyl*cyclo*heptanone (which would react preferentially to its 2-isomeride with diazomethane), since the material did not react with semicarbazide.

The above fraction (6) solidified, and melted at 55—58° after crystallisation from light petroleum (b. p. 40—60°) (Found: C, 66·9; H, 10·9. Calc. for $C_8H_{16}O_2$: C, 66·7; H, 11·1%). Wallach and Beschke found that 1-hydroxymethyl-2-methyl*cyclo*hexanol melts at 59—60° (*Annalen*, 1906, **347**, 338).

(7) 4-*Ethyl*cyclo*hexanone*. (a) The reaction between the ketone (15·5 g.) in methyl alcohol (100 c.c.) and diazomethane (5·6 g.) in absolute ether (650 c.c.) was complete after 5 days. After removal of alcohol and ether, and treatment with sulphuric acid, fractionation at 20 mm. pressure yielded (1) 5·9 g., b. p. 96—100°; (2) 5·2 g., b. p. 100—107°; (3) 1·1 g., b. p. 107—120°; (4) 0·3 g., b. p. 120—140°; (5) 3·8 g., b. p. 140—148°. 4-*Ethyl*cyclo*heptanone* (9·2 g.), b. p. 214—215°, was separated from fractions (1), (2), and (3) by means of its bisulphite compound (Found: C, 76·7; H, 11·2. $C_9H_{16}O$ requires C, 77·1; H, 11·4%), and at once yielded a *semicarbazone*, m. p. 125—127°, and 130° after crystallisation from benzene (Found: N, 21·8. $C_{10}H_{19}ON_3$ requires N, 21·4%). The viscous straw-coloured oil (1·2 g.), b. p. 125—129°/0·6 mm., was presumed to be essentially 1-hydroxymethyl-4-ethyl*cyclo*hexanol.

(b) The ketone (11·6 g.) and ethereal diazoethane (33% excess) in a similar experiment yielded (1) 10·0 g., b. p. 95—100°; (2) 2·1 g., b. p. 100—110°; (3) 0·65 g., 110—135°; (4) 1·5 g., b. p. 135—150°, at 19 mm. Bisulphite treatment removed unchanged ketone (0·2 g.) from fractions (1), (2), and (3), and the residual 2-*methyl*-4-*ethyl*cyclo*heptanone* (11·4 g.) boiled at 102—106°/26 mm. or 220—224°/754 mm. (Found: C, 78·3; H, 11·4. $C_{10}H_{18}O$ requires C, 77·9; H, 11·7%). Its *semicarbazone*, obtained after 10 days under low temperature conditions (compare 2-methyl*cyclo*heptanone), melted at 105—112°, but after four recrystallisations from methyl alcohol, at 153·5—154·5° (Found: N, 20·3. $C_{11}H_{21}ON_3$ requires N, 19·9%). The regenerated ketone boiled at 224—226°/763 mm. The sticky crude 2 : 4-*dinitrophenylhydrazone* melted at 100—102° after five recrystallisations from ethyl alcohol (Found: N, 16·7. $C_{16}H_{22}O_4N_4$ requires N, 16·8%).

(8) 3 : 5-*Dimethyl*cyclo*hexanone*. The ketone prepared from the reduction product of *m*-5-xylenol by means of hydrogen and a nickel catalyst at 197—200° was essentially one substance, since the m. p. of its crude semicarbazone was only raised from 196—204° to 200—204° after two recrystallisations from methyl alcohol.

(a) From the ketone (32 g.) and nitrosomethylurethane (5% excess) were obtained (1) 2·2 g., b. p. 50—73°; (2) 2·2 g., b. p. 73—90°; (3) 18·45 g., b. p. 90—100°; (4) 2·25 g., b. p. 100—135°, under 22 mm. pressure; (5) 1·2 g., b. p. to 110°; (6) 7·4 g., b. p. 110—112°, under 0·8 mm. pressure; residue, 2·0 g. The bisulphite-reactive ketone (17·1 g.), b. p. 87—91°/23 mm., from fractions (1), (2), and (3) afforded 3 : 5-*dimethyl*cyclo*heptanone* (14·0 g.), b. p. 88·5—90·5°/23 mm., from which a single *semicarbazone* was easily obtained in theoretical yield, m. p. 166·5° after one recrystallisation from methyl alcohol (Found: N, 21·8. $C_{10}H_{19}ON_3$ requires N, 21·4%). The regenerated ketone boiled at 205—206°/753 mm. (Found: C, 77·1; H, 11·5. $C_9H_{16}O$ requires C, 77·1; H, 11·4%). 1-*Hydroxymethyl*-3 : 5-*dimethyl*cyclo*hexanol*, m. p. 68—70°, was obtained by recrystallising the solidified fraction (6) from light petroleum (b. p. 40—60°) (Found: C, 68·6; H, 11·2. $C_9H_{18}O_2$ requires C, 68·4; H, 11·4%).

The same products were obtained by use of diazomethane.

(b) The ketone (28 g.) and nitrosoethylurethane (10% excess) yielded a product, from which, after sulphuric acid treatment, the following fractions were obtained under 27 mm. pressure: (1) ethyl carbonate, b. p. to 70°; (2) 1·85 g., b. p. 70—85°; (3) 6·2 g., b. p. 85—89°; (4) 9·0 g., b. p. 89—92°; (5) 5·0 g., b. p. 92—94°; (6) 5·0 g., b. p. 94—100°; (7) 2·9 g., b. p. 100—120°; (8) 3·2 g., b. p. 120—135°. From fractions (1) to (6), unchanged ketone (4·2 g.) was removed with the aid of sodium bisulphite; the inert material under 22 mm. pressure afforded (1) 8·45 g., b. p. 83·5—85°; (2) 7·45 g., b. p. 85—90°; (3) 5·3 g., b. p. 90—93·5°; residue, 1·5 g. Fractions (1) to (3), after 10 days under low temperature conditions, yielded a *semicarbazone* (21 g.), m. p. 152—183°, and 204—208° after six recrystallisations from methyl alcohol (Found: N, 19·9. $C_{11}H_{21}ON_3$ requires N, 19·9%). From this, 2 : 3 : 5-*trimethyl*cyclo*heptanone*, b. p. 215°/763 mm. (Found: C, 78·2; H, 11·6. $C_{10}H_{18}O$ requires C, 77·9; H, 11·7%), was obtained; its 2 : 4-*dinitrophenylhydrazone*, m. p. 73—80° when first prepared, melted at 91—93° after five recrystallisations from methyl alcohol (Found: N, 17·0. $C_{16}H_{22}O_4N_4$ requires N, 16·8%).

(9) 4-*Methoxy*cyclo*hexanone*. This yielded a semicarbazone, m. p. 183—185° (Helfer, *Helv. Chim. Acta*, 1924, **7**, 950, recorded 178°), from which the ketone, b. p. 91·5°/24 mm., was regenerated. The 2 : 4-*dinitrophenylhydrazone* had m. p. 141·5—142·5° (Found: N, 18·0. $C_{13}H_{16}O_5N_4$ requires N, 18·2%).

The reaction between the ketone (10·4 g.) and nitrosomethylurethane (5% excess) was carried out in the usual manner except that no ether was employed. Fractionation of the ultimate product under 21 mm. pressure yielded (1) 0·75 g., b. p. 90—109°; (2) 5·8 g., b. p. 109—114°; (3) 0·5 g., b. p. 114—155°; (4) 4·5 g., b. p. 155—185°. From fraction (2), somewhat impure 4-*methoxy*cyclo*heptanone* (4·8 g.), b. p. 111·5—114°/24 mm., was obtained (Found: C, 65·6, 65·9; H, 10·1, 10·1. $C_8H_{14}O_2$ requires C, 67·6; H, 10·0%). The *semicarbazone*, m. p. 175·5°

after two crystallisations from methyl alcohol (Found : N, 21·4. $C_9H_{17}O_2N_3$ requires N, 21·1%), and the 2 : 4-*dinitrophenylhydrazone*, twice recrystallised from ethyl alcohol, m. p. 115—117° (Found : N, 17·3. $C_{14}H_{18}O_5N_4$ requires N, 17·4%), were prepared. The bisulphite compounds of both the original and the new ketone were readily soluble in water. From fraction (4), a very viscous, colourless oil, presumably 4-methoxy-1-hydroxymethyl*cyclo*hexanol (3·0 g.), b. p. 130—140°/1·5 mm., was derived.

(10) *cyclo*Pentanone. The product from the ketone (10·2 g.) and nitrosoethylurethane (10% excess) on fractionation yielded (1) 5·75 g., b. p. 120—135°, containing ethyl carbonate; (2) 4·4 g., b. p. 135—146°; (3) 3·3 g., b. p. 146—170°; (4) 2·5 g., b. p. 170—190°; residue, 1·4 g. The mixture of semicarbazones (9·2 g.), m. p. 165—213°, prepared from fractions (1) to (4), yielded ketonic material, from which were obtained (1) 2·2 g., b. p. 128—135° (*cyclo*pentanone); (2) 1·3 g., b. p. 135—162°; (3) 1·1 g., b. p. 162—168°; residue, 0·4 g. The semicarbazone, m. p. 192—193·5°, from fraction (3) did not depress the m. p. of that prepared from 2-methyl*cyclo*hexanone. Similar results were obtained by use of ethereal diazoethane at 0°, whether in concentrated solution prepared at $-50°$, or in dilute solution.

(11) *cyclo*Heptanone. The product from the ketone (11·2 g.), absolute alcohol (20 c.c.), dry ether (20 c.c.), potassium carbonate (2 g.), and nitrosomethylurethane (20 g.) after 6 days (3·5 l. of nitrogen evolved) yielded the following fractions under 18 mm. pressure : (1) 1·8 g., b. p. to 75°; (2) 5·5 g., b. p. 75—95°; (3) 0·8 g., b. p. 95—135°; (4) 4·35 g., b. p. 135—142°. From fractions (1), (2), and (3), *cyclo*heptanone (1·3 g.) was recovered by means of sodium bisulphite. The unreactive material (4·1 g.), b. p. 196—199°, m. p. 26—30°, was characterised as *cyclo*octanone by its semicarbazone, m. p. 169—171° (Found : N, 23·1. Calc. for $C_9H_{17}ON_3$: N, 23·0%). Fraction (4) solidified, and separated from light petroleum (b. p. 40—60°) in leaflets, m. p. 49—51° (Found : C, 66·9; H, 10·8. Calc. for $C_8H_{16}O_2$: C, 66·7; H, 11·1%). Wallach (*Annalen*, 1906, **345**, 148) records b. p. 135—140°/16 mm. and m. p. 50—51° for 1-hydroxymethyl*cyclo*heptanol.

(12) *cyclo*Octanone in methyl-alcoholic solution was unattacked either by dilute ethereal diazomethane or by concentrated ethereal diazoethane at $-50°$.

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