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THE CLEMMENSEN AND WOLFF-KISHNER REDUCTIONS OF DIMETHYLKETENE DIMER

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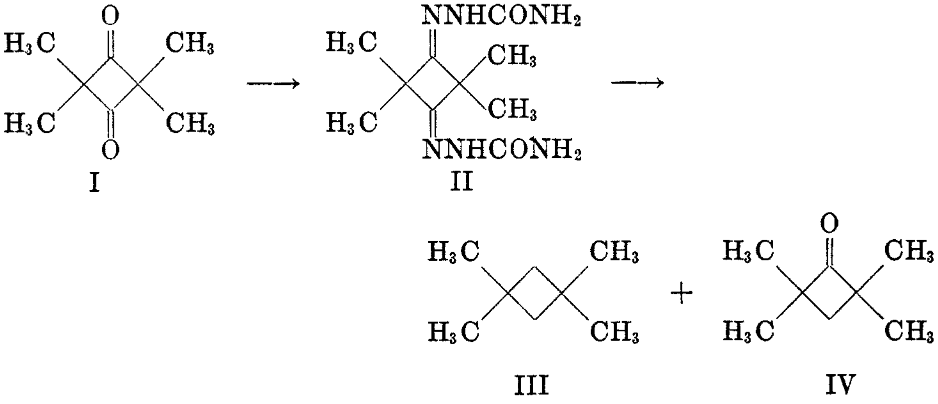
In connection with the development of methods for the synthesis of spiranes derived from cyclobutane, *e.g.* dispiro[3.1.3.1]decane, we have been interested in the reduction of the carbonyl groups of tetrasubstituted-1,3-cyclobutanedione derivatives to the corresponding methylene groups.

There are no data in the literature on the reduction of 1,3-cyclobutanediones by the Clemmensen or Wolff-Kishner methods (1, 2), those customarily used to accomplish the desired change. Therefore we undertook to study the behaviour of the simplest, readily available, model compound, 2,2,4,4-tetramethyl-1,3-cyclobutanedione (dimethylketene dimer) (I), under Wolff-Kishner and Clemmensen-type conditions.

Dimethylketene dimer (I), which is readily prepared in good yield from isobutyryl chloride by the action of triethylamine (3), is known to form a disemicarbazone (II) (4). It has now been shown that the disemicarbazone decomposes in a solution of sodium in diethylene glycol at 210–230° to yield, as the principal products, 1,1,3,3-tetramethylcyclobutane (III), and an intermediate reduction product, which on acid hydrolysis gives 2,2,4,4-tetramethylcyclobutanone (IV). The amount of hydrocarbon (III) formed depends on the duration of the heating period, a 12% yield resulting after one hour, and a 19% yield after four hours. The yield of intermediate was reduced from 42% after one hour to 20% after four hours of heating. This reaction sequence represents a practical synthesis of IV, as well as of 1,1,3,3-tetrasubstituted cyclobutane derivatives in general.



Evidence which supports the assignment of the cyclobutane structure to the saturated C_8H_{16} hydrocarbon (III) resulting from Wolff-Kishner reduction of I

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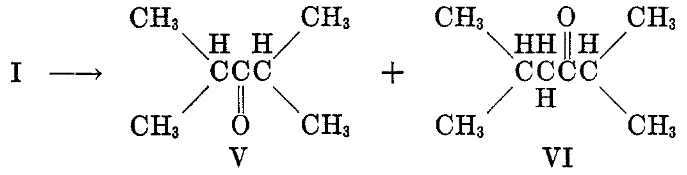
has been obtained from a closely related series of reactions. Dispiro[3.1.3.1]decane has been prepared by the Wolff-Kishner reduction of the disubstituted ketene dimer, dispiro[3.1.3.1]decane-5,10-dione (5). This product of reduction has been shown to be identical (5) with material which had been obtained from the same diketone by conversion to the *bis*-mercaptole followed by reductive desulfurization (5a). From the identity of the products from the two reduction sequences it seemed likely that no rearrangement of the carbon skeleton of I had occurred during the Wolff-Kishner reduction.

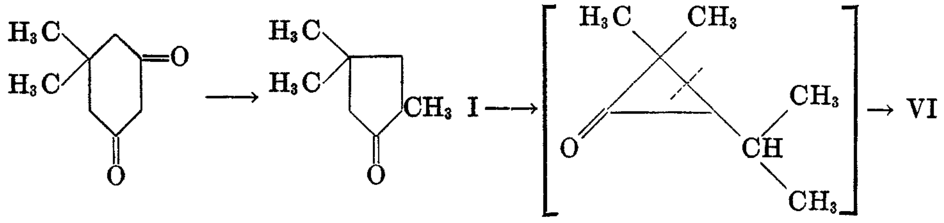
According to Wolff (1, 6) the first step in the reduction of a semicarbazone by heating with alkali is the conversion to the corresponding hydrazone. Analysis indicated that the nitrogenous, intermediate reduction product was probably a mixture consisting predominantly of the hydrazone of IV. Acid hydrolysis of the intermediate occurred almost instantaneously at room temperature, yielding a monoketone, $C_8H_{14}O$, which has been assigned the structure IV. The isolation of the intermediate reduction product under such relatively severe conditions probably resulted from its pronounced volatility (b.p. 90–93°/45 mm.), which caused it to be removed from the site of the reaction and remain largely in the vapor phase.

Reduction of I by refluxing for 48 hours in methanol solution with amalgamated zinc and hydrochloric acid (Clemmensen conditions) resulted in the formation of two readily isolable ketones, 2,4-dimethyl-3-pentanone (V) and 2,5-dimethyl-3-hexanone (VI). An authentic sample of VI for comparison purposes was prepared by the reaction of isobutyryl chloride with isobutylmagnesium bromide in the inverse manner at 0°.



It has been reported that dimers of ketoketenes, on being heated in the presence of aqueous base, undergo hydrolytic opening of the four-membered ring to yield the appropriate β-keto acids, which are then decarboxylated readily (7). It appears that this cleavage is also acid-catalyzed, since refluxing I with methanol-hydrochloric acid, in the absence of zinc, resulted solely in hydrolysis and decarboxylation; V was the only product isolated.

The mode of formation of VI under Clemmensen conditions is less obvious. It is conceivable that the necessary rearrangement occurred after the fashion observed by Dey and Linstead (8) in the Clemmensen reduction of 5,5-dimethyl-



1,3-cyclohexanedione to 2,4,4-trimethylcyclopentanone; the resulting substituted cyclopropanone could then have undergone hydrogenolysis of the bond between the α-carbon atoms to yield VI. A number of instances of Clemmensen reduction of cyclic β-diketones without rearrangement have been reported (2), most of these studies predating the observation of Dey and Linstead. There is as yet insufficient information available to describe the structural features of the parent cyclic β-diketone which lead to rearrangement under Clemmensen reduction conditions.

Attempted Clemmensen reduction of IV under the same conditions employed in the reduction of I yielded only unreacted starting material.

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EXPERIMENTAL[2]

All melting points are uncorrected.

Dimethylketene dimer (I). Dimethylketene dimer was prepared in the manner described by Miller and Johnson (3), with the exception that benzene was used as the solvent in place of ether. A 69% yield of crude dimer, m.p. 111.5–113.5°, was obtained [the pure dimer melts at 115–116° (3)].

Wolff-Kishner reduction of dimethylketene dimer (I). Dimethylketene dimer (I) was converted to the corresponding disemicarbazone according to the method of Wedekind and Weisswange (4). The reaction rate was accelerated by boiling the reaction mixture until precipitation began. Crude, air-dried disemicarbazone (39.4 g.) was added, all at once, to a solution of 30 g. of sodium in 250 cc. of diethylene glycol (Eastman Kodak "Practical") at 130° and the temperature was raised rapidly to 210°, where it was maintained for one hour. Initially there was copious evolution of gas and considerable frothing. To the cooled reaction mixture, 200 cc. of water was added, and the products were separated by steam-distillation. The distillate contained 11.0 g. of a separate phase with a piperidine-like odor; an additional 2.0 g. of crude product was extracted from the 100 cc. of aqueous distillate. Distillation gave 2.0 g. (11%) of 1,1,3,3-tetramethylcyclobutane (III) as a colorless, mobile liquid, b.p. 75–80°/745 mm. and 9.2 g. (42% calculated as hydrazone of IV) of a yellow liquid, b.p. 90–93°/45 mm. From 22.5 g. of semicarbazone after four hours at 210° there were obtained 1.9 g. (19%) of (III) and 2.5 g. (20%) of the higher-boiling fraction. The lower-boiling product did not decolorize bromine in carbon tetrachloride solution and was largely insoluble in concentrated sulfuric acid. Washing with the latter removed traces of amine-like impurities. A sample of the purified III boiled at 86–87°/748 mm.; n_D^{25} 1.3930.

Anal. Calc'd for C_8H_{16}: C, 85.63; H, 14.37.

Found: C, 85.72; H, 14.20.

The higher-boiling fraction with the amine-like odor gave a qualitative test for nitrogen and was completely and rapidly soluble in hydrochloric acid, whereupon an oil, 2,2,4,4-tetramethylcyclobutanone (IV) precipitated within a few seconds; IV boiled at 77°/150 mm.; 128.5–129°/745 mm.

Anal. Calc'd for $C_8H_{14}O$: C, 76.14; H, 11.18.

Found: C, 76.12; H, 11.19.

The *semicarbazone* of IV was prepared according to the method of Shriner and Fuson (9). After recrystallization from methanol the glistening plates melted at 193–194°. From 0.5 g. of amine-like intermediate by acid hydrolysis and conversion of the resulting ketone to semicarbazone there resulted 0.43 g. of derivative.

Anal. Calc'd for $C_9H_{17}N_3O$: C, 58.98; H, 9.35.

Found: C, 59.00; H, 9.24.

The *2,4-dinitrophenylhydrazone* of IV was prepared by dissolving 2.5 g. of 2,4-dinitro-

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[2] Analyses are by Dr. Adalbert Elek, 4763 W. Adams Blvd., Los Angeles, California.

phenylhydrazine in 15 cc. of concentrated sulfuric acid and adding 1 g. of IV. The solution was allowed to stand for one-half hour, was poured into 200 cc. of water, and the resulting mixture was allowed to stand overnight. Four recrystallizations of the precipitated solid from methanol yielded orange-red plates, m.p. 115–116°.

Anal. Calc'd for $C_{14}H_{18}N_4O_4$: C, 54.89; H, 5.92.

Found: C, 54.92; H, 5.99.

Clemmensen reduction of dimethylketene dimer (I). To a mixture containing 200 g. of amalgamated, mossy zinc, 200 cc. of concentrated hydrochloric acid, and 240 cc. of methanol was added 22.4 g. of I. The reaction mixture was refluxed for 48 hours. Gases leaving the reaction were passed through a Dry-Ice trap to remove volatile organic products. At the end of the reaction period the solution was decanted, combined with the trap contents, diluted with 2 l. of water, and extracted with ether. The ether extracts were concentrated and to the residue was added 200 cc. of concentrated hydrochloric acid and 240 cc. of methanol. The resulting solution was refluxed for 36 hours to decompose unreacted starting material (when this was not done objectionable amounts of unreacted starting material appeared in the higher-boiling product fractions), diluted with 2 l. of water, and extracted with ether. The dried ethereal solution was concentrated, the residues were distilled through an eight-inch, helices-packed column, with partial take-off head, at a reflux ratio of about ten to one, and the following fractions were collected:

NUMBER	B.P., °C.	YIELD, G.	n_D^{25}
1	85–120	2.3	—
2	120–125	1.1	1.3972
3	125–130	2.2	1.3990
4	130–135	2.1	1.4000
5	135–138.5	0.9	1.4010
6	138.5–142	2.8	1.4030
residue	—	2.5	1.4085

2,4-Dimethyl-3-pentanone is described as a liquid, with a somewhat camphoraceous odor, b.p. 123–125° (10); n_D^{20} 1.4007 (11); semicarbazone, m.p. 160° (corr.) (10); 2,4-dinitrophenylhydrazone, m.p. 91–92° (12).

Cuts nos. 2 and 3 possessed camphoraceous odors; 2,4-dinitrophenylhydrazone of each (prepared by the method described for IV and crystallized, as orange plates, from methanol), m.p. 92.5–94°; mixed m.p. with an authentic sample of 2,4-dinitrophenylhydrazone of VI (m.p. 92.5–93.5°) showed no depression; semicarbazone of cuts nos. 2 and 3, m.p. 154–155°.

2,5-Dimethyl-3-hexanone (VI) is described as a liquid with a menthone-like odor, b.p. 147–148° (13); n_D^{20} 1.4049 (14); m.p. of semicarbazone, 144° (14).

Cuts no. 5, no. 6, and residue had terpene-like odors; semicarbazone from no. 5, no. 6, and residue, m.p. 144–145°.

Anal. Calc'd for $C_9H_{17}N_3O$: C, 58.35; H, 10.34.

Found: C, 58.53; H, 10.27.

An authentic sample of VI was prepared by the inverse addition of isobutylmagnesium bromide to isobutyryl chloride, and converted to the semicarbazone, m.p. 145–146°; mixed m.p. with semicarbazone from no. 5, no. 6, and residue, 143.5–145°.

The rates of semicarbazone formation of V and VI are such that it was possible to separate VI from a mixture of the two ketones by boiling with semicarbazide hydrochloride and sodium acetate in methanol-water for two or three minutes. If the reaction mixture was then diluted with a large volume of water only the semicarbazone of VI precipitated. To regenerate VI it was necessary only to steam-distil a suspension of the semicarbazone in 10% oxalic acid. To convert V to its semicarbazone in good yield it was found desirable to reflux the reaction mixture for one hour or longer.

The *2,4-dinitrophenylhydrazone* of VI (from synthetic material or from Clemmensen reduction) melted at 67–68°. There was no depression of the mixed melting point of the derivatives from the two sources.

Anal. Calc'd for $C_{14}H_{20}N_4O_4$: C, 54.53; H, 6.54.
Found: C, 54.58; H, 6.53.

From several of the early preparations of the 2,4-dinitrophenylhydrazone of VI there was isolated a yellow-orange solid, m.p. 38–39° after crystallization from methanol-water.

Anal. Calc'd for $C_{14}H_{20}N_4O_4$: C, 54.53; H, 6.54.
Found: C, 53.60; H, 6.61.

It was not possible to reproduce these experiments at a later date; only the derivative m.p. 67–68°, was isolated.

Hydrolysis and decarboxylation of dimethylketene dimer (I). A solution containing 100 cc. of concentrated hydrochloric acid, 120 cc. of methanol, and 10 g. of I was refluxed for 48 hours. Carbon dioxide was evolved rapidly at the start, and evolution of gas was complete after 19 hours. The reaction mixture was diluted with water and extracted with ether. After the ethereal extracts had been dried over magnesium sulfate, they were concentrated and the residue was distilled, yielding 3.6 g. (45%) of V, b.p. 123–125° ($n_D^{23.5}$ 1.3983) and 0.5 g. of residue ($n_D^{23.5}$ 1.4000).

Both the principal fraction and residue yielded 2,4-dinitrophenylhydrazones, m.p. 93–94°, which did not depress the melting point of an authentic sample of the 2,4-dinitrophenylhydrazone of V.

Clemmensen reduction of 2,2,4,4-tetramethylcyclobutanone (IV). A mixture of 4.7 g. of IV, 50 cc. of methanol, 50 cc. of concentrated hydrochloric acid, and 50 g. of zinc amalgam was refluxed for 48 hours. At the end of that time it was diluted with water and extracted with ether. The dried ethereal extracts were concentrated, and the residue was distilled, yielding 0.9 g., b.p. 55–100°; 0.7 g., b.p. 100–129°; and 1.15 g. of residue. The first fraction was completely soluble in concentrated sulfuric acid, and hence contained no hydrocarbon (III). Both the second fraction and the residue gave semicarbazones, m.p. 193–194°, which were identical with that of the starting material.

SUMMARY

The Wolff-Kishner reduction of dimethylketene dimer has been shown to yield 1,1,3,3-tetramethylcyclobutane and an intermediate reduction product, which on acid hydrolysis gives 2,2,4,4-tetramethylcyclobutanone.

The Clemmensen reduction of dimethylketene dimer yields 2,4-dimethyl-3-pentanone and 2,5-dimethyl-3-hexanone. The Clemmensen method fails to reduce 2,2,4,4-tetramethylcyclobutanone.

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