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Conversion of 1,2-Aminoalcohols to Carbonyl Compounds

Richard T. Arnold

September 15, 1949

Berkeley, California

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CONVERSION OF 1,2-AMINOALCOHOLS TO CARBONYL COMPOUNDS

by

Richard T. Arnold*

Radiation Laboratory and Department of Chemistry,
University of California, Berkeley**

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ABSTRACT

1. Cyclohexanone has been synthesized in yields of 20-25% from cyclopentanone using the scheme described by Tiffeneau and co-workers.

2. It has been established using radioactive cyanide that all of the C^{14} occupies the C_2 position in the cyclohexanone.

3. No isotope effect was observed.

4. Cycloheptanone has been prepared from cyclohexanone in yields of 45% using the same procedure.

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* While on leave from the University of Minnesota.

** The work described in this paper was sponsored by the Atomic Energy Commission.

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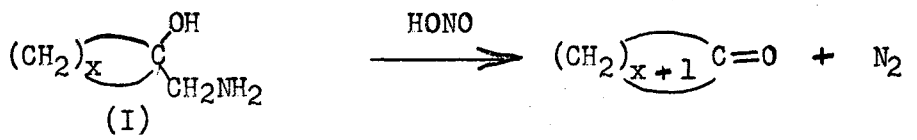
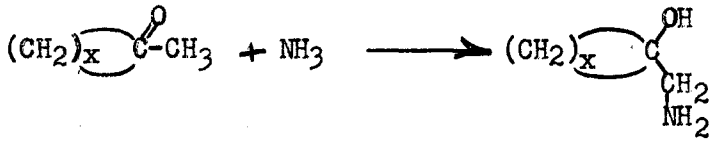
In 1937 Tiffeneau and co-workers (1) reported the formation of cyclic ketones by treatment of 1-hydroxy-1-amino methylcyclokanes (I) with nitrous acid according to the following scheme:



(I)

In the initial work the amino alcohols were prepared by reaction of the appropriate oxide with ammonia



(I)

Later, Goldberg and co-workers (2) prepared compounds of Type I by catalytic hydrogenation of cyanhydrins

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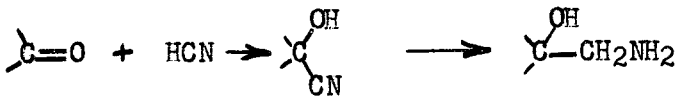
** The work described in this paper was sponsored by the Atomic Energy Commission.

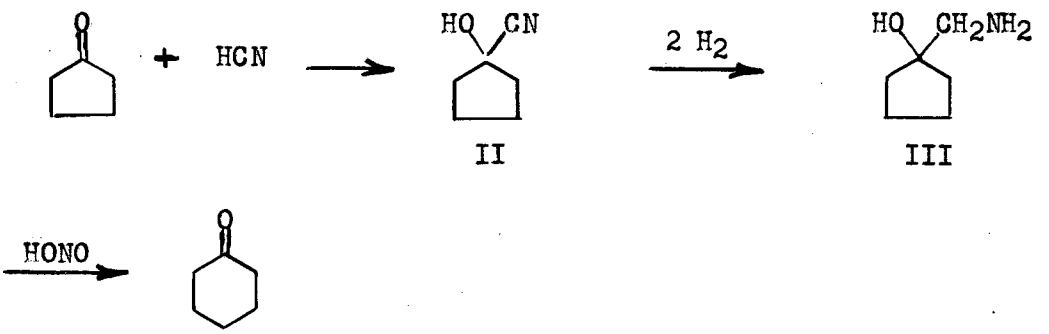
(1) Tiffeneau, Weill and Tchoubar, Compt. rend., 205, 54 (1937).
(2) Goldberg and Monnier, Helv. Chim. Acta, 23, 376 (1940).



and employed the Tiffeneau rearrangement in ring "D" of the steroid series.

More recently the method has been used for the synthesis of cyclononanone (3) and azulenes (4). This rearrangement offers possibilities for the preparation of cyclic ketomes containing isotopic carbon and the present paper deals with this problem.

Unfortunately, no detailed directions were published by Tchoubar (5) for the conversion (via the cyanhydrins) of cyclopentanone and cyclohexanone into cyclohexanone and cycloheptanone, respectively. In the current work, cyclopentanone was converted into its cyanhydrin (II), the latter hydrogenated (without purification) to an amino alcohol (III) and this, in turn, (without purification) transformed into cyclohexanone through treatment with nitrous acid.



The reaction mechanism probably involves an intermediate diazonium cation which rearranges spontaneously

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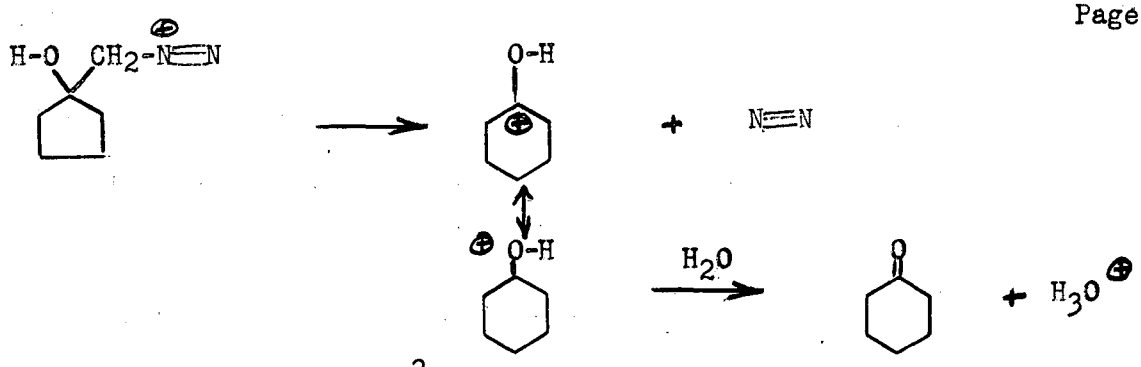
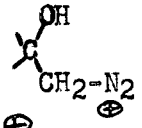
(3) Ruzicka, Plattner and Wild, Helv. Chim. Acta, 26, 1631 (1943).

(4) Plattner, Furst and Studer, Helv. Chim. Acta, 30, 1091 (1947).

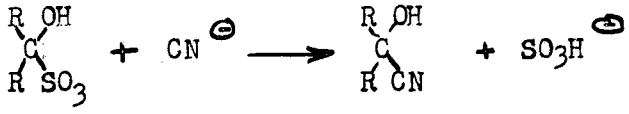
(5) Ellis, Org. Syn., Coll. Vol. I, p. 18.



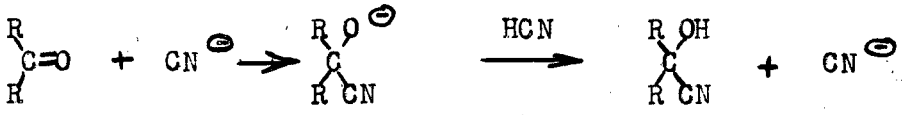
according to an intramolecular S_N2 reaction in which a methylene group (bonded to the  group) makes a back attack against the methylene group of $-CH_2-\overset{\oplus}{N}\equiv N$, the nitrogen molecule being eliminated from the front of the tetrahedron. Dewar (6) assumes the formation of a primary carbonium ion.

Preparation of Crude Cyanhydrin: - Several routes to cyanhydrin are in common use:

(a) Direct reaction between cyanide ion and bisulfite addition compounds (7)



(b) Direct addition of anhydrous hydrogen cyanide to carbonyl compounds in the presence of cyanide ion as a catalyst (7)



(c) A modification of method (b) in which the carbonyl compound (dissolved in ether) is supported over a solution of aqueous cyanide and HCN is liberated slowly at low temperature by the dropwise addition of a strong acid (4).

In this work all three procedures were examined and (c) was finally chosen as being best adapted to the current problem. Cyanhydrin prepared from bisulfite

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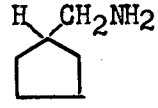
(6) M.J.S. Dewar "The Electronic Theory of Organic Chemistry," Oxford Press, 1949, p.211

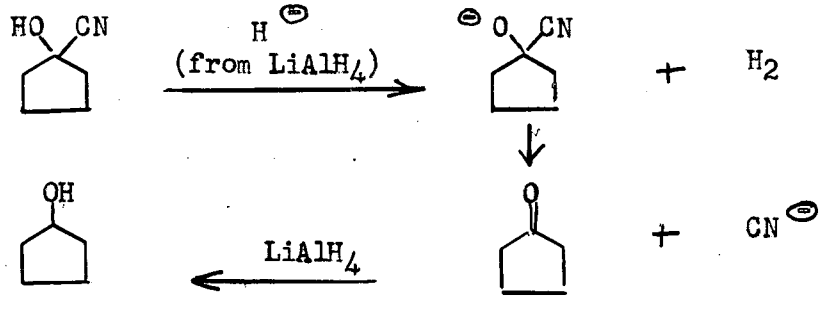
(7) Cook and Linstead, J. Chem. Soc., 959 (1934).

addition compounds contained some poison which interfered with the subsequent reaction. Method (b) gave mechanical difficulties and inconsistent results were obtained.

Hydrogenation of Cyanhydrin: - During the catalytic hydrogenation of cyanhydrins in acetic acid solution containing hydrochloric acid, considerable hydrogenolysis of the tertiary hydroxyl group occurs (3,4) and, in the present case, leads to the formation of cyclohexanone (from  + HONO) and this contaminates the final ketone unless a careful fractionation is carried out after the hydrogenation step. It is believed that less reductive cleavage occurs and a more pure cyclohexanone obtained when the cyanhydrins were reduced in ethanol (with either platinum or Raney nickel) containing acetic acid, but no concentrated hydrochloric acid.

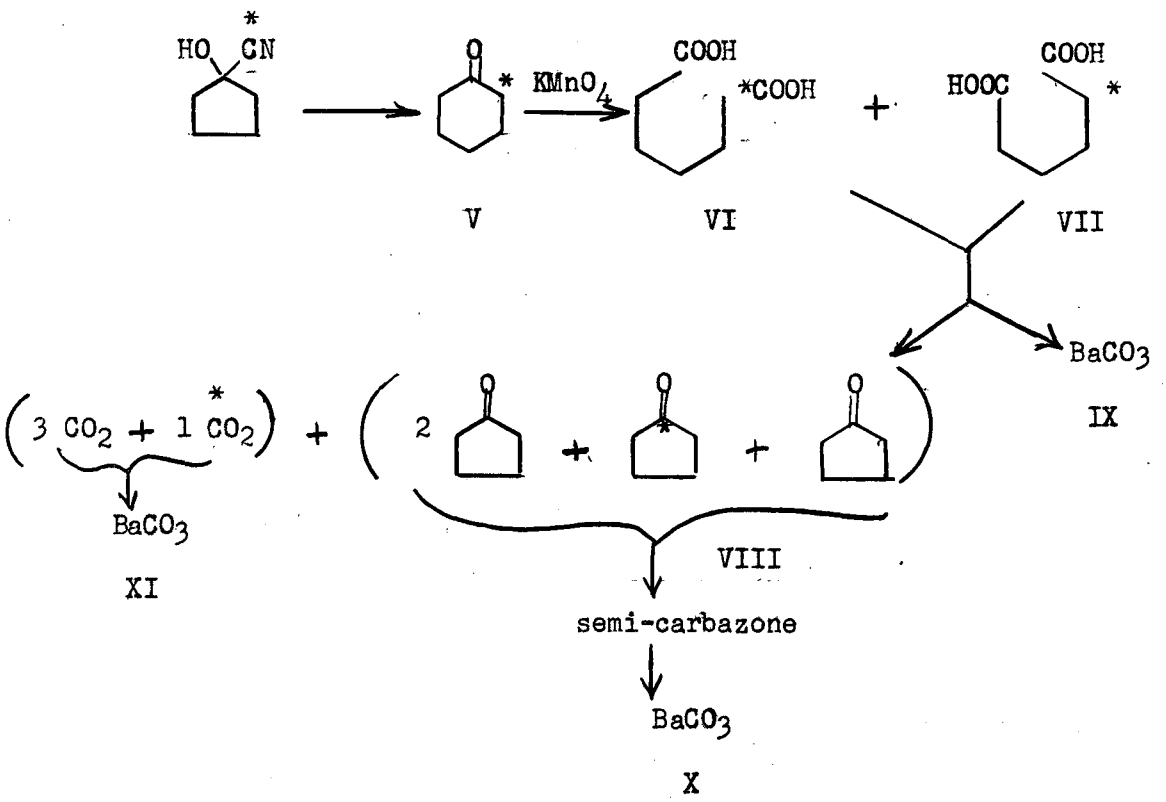
For reasons of which the writer is not certain, cyanhydrin prepared from synthetic cyanide samples gave considerable trouble in the hydrogenation step and the high specific activity preparation was a failure on this account.

Attempts to reduce the cyanhydrin with lithium aluminum hydride failed. This is probably due to rapid anion formation in the presence of a strong base and elimination of cyanide ion (7).



Location of Labeled Carbon Atom: - Using C^{14}-labeled cyanide, the previously proposed scheme should lead to C_2^{14} isotopically homogeneous cyclohexanone (V). In order to establish this fact, (V) was oxidized to the two isotopic adipic acids (VI) and (VII) and these cyclized to the mixture of isotopic cyclopentanones (VIII). The carbon dioxide liberated was collected in alkali and precipitated as barium carbonate (XI) for measurement of activity.

If "X" represents the total activity per mole of adipic acid cyclized, "3X/4" should be present in the cyclopentanones (VIII) and "X/4" in the carbon dioxide liberated (assuming no isotope effect.) For measurement the adipic acid (VI + VII) and cyclopentanone semi-carbazone were converted to barium carbonate, giving (IX) and (X).*



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* The writer is indebted to Mr. V. H. Tashinian, University of California, Berkeley, for these combustions.

From the above it can be seen that the activities expressed in terms of dis./min./mg. of $BaCO_3$ in (IX), (X) and (XI) should be found in the following ratios:

$$X/IX = 0.750; \qquad XI/IX = 1.50$$

Two sets of data on differently combusted samples and measured separately are as follows:

IX	982 982	aver. = 982 dis/min/mg	IX	1026 1004 1005 986	aver. = 1005 dis/min/mg
X	754 730	aver. = 742 dis/min/mg	X	713 761 776 769	aver. = 755 dis/min/mg
XI	1487 1508 1481 1457	aver. = 1482 dis/min/mg	XI	1491 1496 1530	aver. = 1506 dis/min/mg
	X/IX = 0.756; XI/IX = 1.509			X/IX = 0.751; XI/IX = 1.499	

There can be little doubt that all of the C^{14} is in the 2-position in the synthetic cyclohexanone.

Synthesis of Cyclohexanone and Cycloheptanone: - Both cyclohexanone and cycloheptanone were prepared by essentially the same procedure in overall yields (based on cyanide) of 20-25% and 44.5%, respectively. The lower yield of cyclohexanone is attributed to less favorable cyanhydrin formation from cyclopentanone (8,9) and greater mechanical difficulties due to the tendency for cyclohexanone to co-distill with ether.

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(8) Lapworth and Manske, J. Chem. Soc., 2533 (1928).
(9) Prelog and Kobelt, Helv. Chim. Acta, 32, 1187 (1949).

EXPERIMENTAL

Cyclopentanone cyanhydrin: - A bulk sample of crude cyclopentanone cyanhydrin was prepared (4) and aliquot portions were used in studying the subsequent steps.

Cyclopentanone (18 g., redistilled b.p. 129-130°) was dissolved in 40 ml. ether and placed in a three-necked flask equipped with stirrer, dropping funnel and condenser along with 20 g. potassium cyanide and 30 ml. water. Concentrated hydrochloric acid (23 ml.) was introduced over a period of two hours with good stirring while the mixture was held at 0° to -5°. Stirring at this temperature was continued for four additional hours after which the reaction mixture was stored in a refrigerator for two days.

Ether (100 ml.) was used for extraction of the cold mixture. Removal of the ether using a water aspirator gave a crude water-white oil; wt. 30 g.; theoretical based on pure cyanhydrin, 25 g.

Synthesis of cyclohexanone: - Approximately 20 mmoles of the above crude cyanhydrin was dissolved in 25 ml. of 95% ethanol and 10 ml. of acetic acid and reduced with hydrogen at 40 pounds pressure in the presence of platinum made from 100 mg. platinum oxide. Reduction was complete in twelve hours with approximately 40 mmoles of hydrogen being absorbed. After removing the catalyst by filtration the excess ethanol was removed under vacuum with a water aspirator. Then, 30 ml. of water was added and the solution cooled to -5°. Sodium nitrite (1.37 g.) dissolved in 3 ml. water was added and the solution allowed to stand at 0° for thirty minutes. Ether (100 ml.) was added and the two-phase system was allowed to reflux on a steam cone under an efficient condenser for three hours. At this point, nitrogen had ceased to be liberated and the ether layer was washed with 10% potassium bicarbonate, dried and evaporated to give a mobile liquid residue. This was volatilized at 80° and 1 mm./Hg into a dry ice trap; volume 1.2 ml.

The crude cyclohexanone was oxidized to adipic acid in the following manner. The crude ketone (1.2 ml.) was added dropwise to warm nitric acid (6 ml., conc.) containing 10 mg. ammonium vanadate as catalyst. After the rapid oxidation had ceased, the mixture was kept warm on a steam bath for thirty minutes; 2 ml. water was added and the mixture cooled. Adipic acid (m.p. 144-147°) weighing 0.8 g. after being dried at 110° was isolated.

Assuming a 52% yield (5) (which was confirmed by a separate oxidation on pure cyclohexanone) the yield of cyclohexanone was approximately 50%. Yields of this size were never obtained on small runs starting from cyclopentanone.

Synthesis of cycloheptanone: - Crude cyclohexanone cyanhydrin (20 mmoles) prepared by treating 20 mmoles cyclohexanone in ether with acidified KCN solution at 0° was dissolved in 25 ml. ethanol and 10 ml. acetic acid and hydrogenated at 40 lbs. pressure in the presence of platinum made from 100 mg. platinum oxide. Approximately theoretical uptake of hydrogen (40 mmoles) was complete in fifteen hours. The mixture was worked up exactly as in the cyclohexanone synthesis described above.

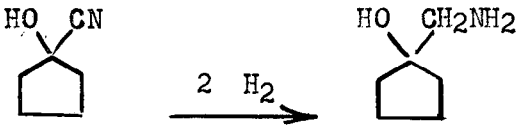
The volatilized crude product was redistilled and the fraction boiling between 179-181° collected as pure cyclopentanone: n_D^{21} 1.4575. (Reported n_D^{21} 1.4604). Yield, 44.5%.

The above yield was obtained whether one started on a small run with cyclohexanone or took an aliquor portion of crude cyanhydrin (from a storage bottle)for the reduction. This is in contrast to the cyclopentanone to cyclohexanone example. In the latter case good yields of cyanhydrin formation were more difficultly achieved on small runs.

Low activity run, cyclopentanone to cyclohexanone: - Solid potassium cyanide (2.7 g., 40 mmoles of 96.5%) was placed in a 50 ml. Erlenmeyer flask equipped with a standard taper joint. To this was added 1 mmole of KCN-C^{14} containing approximately 17 c activity (10) dissolved in 5 ml. water. Over this aqueous solution was placed 3.4 g. cyclopentanone (b.p. 130°) dissolved in 15 ml. ether. While this two-phase system was being stirred magnetically at 0° to -5°, 4.5 g. of 90% formic acid was added dropwise from a capillary pipette over a period of two

(10) Prepared by R. Selff of this laboratory.

hours. Stirring at 0° was continued for four additional hours and the mixture was stored in a refrigerator for two days to assure equilibration. An ether extract of this mixture was washed with water and the ether evaporated under a column on a steam bath. The resulting crude cyanhydrin was dissolved in 50 ml. of 95% ethanol and 20 ml. acetic acid and reduced with hydrogen at 40 pounds pressure in the presence of platinum made from 400 mg. platinum oxide. The reduction started rapidly but stopped after one-third of the expected uptake of hydrogen. An additional 200 mg. of platinum oxide was added and 0.7 pounds of hydrogen absorbed. At this point there was little question about the presence of catalyst poison. The solution was filtered and the reduction was then effected with excess Raney nickel (ca. 2 g.). Numerical details on the reduction are shown below.



(a) In presence of platinum made from 400 mg. platinum oxide:

Time	Pressure
3:00 p.m.	44.7
3:30 p.m.	43.2
5:00 p.m.	42.8

(b) An additional 200 mg. of platinum oxide added:

5:15 p.m.	40.2
8:30 p.m.	39.5

(c) Platinum filtered and about 2 g. Raney nickel added:

8:45 p.m.	40.2
9:05 p.m.	36.7
9:30 p.m.	36.5
10:00 p.m.	36.2

Total uptake of hydrogen was approximately correct for a theoretical value of 80 mmoles.

The Raney nickel was removed by filtration, 3 ml. acetic acid added and the excess ethanol removed under vacuum. Water (50 ml.) was added, the solution cooled to 0° to -5° and 3.0 g. sodium nitrite dissolved in 5 ml. water added. After allowing the solution to remain at 0° to -5° for twenty minutes, the mixture was warmed on the at approximately 70° for one and one-half hours at which time nitrogen had ceased to be eliminated. Ether extraction with two 100 ml. portions followed by extraction of the ether layer with 10% potassium bicarbonate, drying with sodium sulfate and evaporation of the ether gave an oil which was transferred with a small pipette to a small distillation apparatus and all the material volatile at 80° and 1 mm./Hg collected in a dry ice trap. A volume of 1.5 ml. was collected and redistilled at atmospheric pressure. The portion boiling at a bath temperature between $145\text{-}162^{\circ}$ weighed 0.989 g.

Oxidation to adipic acid: - The above radioactive cyclohexanone (0.989 g.) was oxidized by stirring overnight with a solution containing 3.2 g. potassium permanganate, 2 pellets potassium hydroxide and 50 ml. water. A small quantity of unused permanganate was destroyed by dropwise addition of sodium bisulfite solution. A small amount of Norite ($\sim$0.5 g.) was added and the solution filtered. The residue was washed thoroughly with water and the washings combined with the main filtrate. This was evaporated under a hood by means of an infra-red lamp to a crystalline residue which was then dissolved in 6 ml. water, acidified with 2 ml. concentrated hydrochloric acid and kept in a refrigerator overnight. From this solution 0.83 g. of adipic acid was isolated which melted at $145.5\text{-}147^{\circ}$ with recrystallization.

Since in previous runs with authentic cyclohexanone an equal weight of adipic acid could be isolated from a given weight of ketone, the distilled ketone used in this oxidation must contain at least 85% by weight of cyclohexanone.

Therefore, the yield of cyclohexanone based on cyanide is approximately 21%.

Cyclization of adipic acid, low activity in C^{14}: - Adipic acid (0.775 g.) from the above oxidation was treated with 4 ml. barium hydroxide solution containing 0.265 g. barium hydroxide/ml. and this solution evaporated to a dry crystalline mass under an infra-red lamp. This solid was pyrolyzed at 280-290° for two and one-half hours. The distilled cyclopentanone was caught in a dry ice trap (and later converted to its semi-carbazone for purification) and the carbon dioxide evolved was absorbed in 12 ml. sodium hydroxide containing 4 g. sodium hydroxide/150 ml. From the latter there was obtained 0.584 g. barium carbonate (XI) by addition of 7 ml. of 2 N ammonium nitrate and 15 ml. of 1 N barium chloride.

From the cyclopentanone obtained above there was formed 0.431 g. of a semi-carbazone (m.p. 206-207°).

SUMMARY

1. Cyclohexanone has been synthesized in yields of 20-25% from cyclopentanone using the scheme described by Tiffeneau and co-workers (1, 11).
2. It has been established using radioactive cyanide that all of the C^{14} occupies the C_2 position in the cyclohexanone.
3. No isotope effect was observed.
4. Cycloheptanone has been prepared from cyclohexanone in yields of 45% using the same procedure.

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(11) Tchoubar, Compt. rend., 212, 195 (1941).