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CONTENTS

STUDIES IN ANTIMALARIALS

PART IV. AMMONOLYSIS OF ALIPHATIC KETONES WITH HYDROGENATION

BY HARKRISHAN LAL BAMI, BALKRISHNA HARIHAR IYER
AND
PRAPHULLA CHANDRA GUHA

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Part IV. Ammonolysis of Aliphatic Ketones with Hydrogenation*

BY HARKRISHAN LAL BAMI, BALKRISHNA HARIHAR IYER
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During the course of our work (Bami, Iyer and Guha, *J. Indian Inst. Sci.*, 1947, **29** A, 1, *cf.*, *Science and Culture*, 1947, **12**, 448) on the preparation of Paludrine (Curd and Rose, *J.C.S.*, 1946, 729), a recent synthetic antimalarial of repute, considerable difficulty was encountered in obtaining isopropylamine, one of the essential intermediates for the preparation of this drug. Hofmann's method and Gabriel's method for the preparation of isopropylamine were found to give poor yields and involved a number of operations. Considering the importance of this intermediate, it was thought worth while to explore various methods for finding out a convenient and direct method for its preparation.

Direct ammonolysis of acetone in presence of hydrogen was one of the possible approaches to the problem. Accordingly, acetone was converted into isopropylamine quantitatively by using aqueous or alcoholic ammonia in presence of hydrogen under pressure and a suitable hydrogenation catalyst like Raney's nickel. The success achieved in the preparation of isopropylamine from acetone by this method stimulated interest in extending its application for the preparation of aliphatic amines from ketones with a view to their utilisation for the synthesis of substituted biguanides of the paludrine type as potential antimalarials. Various other ketones (*vide* Table) have also been successfully converted into the corresponding aliphatic primary amines.

A survey of the literature showed that isopropylamine was usually prepared by the reduction of acetoxime catalytically (Paul, *Bull. Soc. Chim.*, 1937, (5), **4**, 1121) or by other methods (Goldschmidt, *Ber.*, 1887, **20**, 728; Tafel and Pfefferman, *Ber.*, 1902, **35**, 1514; Tseng and Chang, *Science Reports Natl. Univ. Reports*, 1936, **1**, No: 3, 19, *cf.*, *Amer. Chem. Abst.*, 1937, **31**, 95; Takaki and Ueda, *J. Pharm. Soc. Japan*, 1938, **58**, 296). This had also been prepared from dioxyacetoxime (Piloty and Ruff, *Ber.*, 1897, **30**, 1664), isopropylcarbylamine (Siersch, *Ann.*, **148**, 263; Gautier, *Ann. de Chim.*, 1869, (4), **17**, 251), α-amino-isobutyro nitrile (Gulewitsch and Wasmus,

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* A note on this work has been published in *Current Science*, 1947, **16**, 253.

Ber., 1906, **39**, 1187) isobutyramide (Hofmann, *Ber.*, 1882, **15**, 768) aceto phenyl hydrazone (Tafel, *Ber.*, 1886, **19**, 1926) and isopropyl halide (Gabriel, *Ber.*, 1891, **24**, 3104). Acetone itself has been reduced by sodium in presence of alcoholic ammonia by Loffler (*Ber.*, 1910, **43**, 2032) to give isopropylamine while isopropyl alcohol has also been ammonolysed by passing its vapours with ammonia over ThO_2 at 300° by Sabatier and Mailhe (*Compt. rend.*, 1911, **153**, 1205). Ketazines (Mailhe, *Compt. rend.*, 1920, **170**, 1265) have also been hydrogenated in vapour phase catalytically to give isopropylamine. George Mignonac (*Compt. rend.*, 1921, **172**, 223) has also prepared this amine from acetone by the action of ammonia and hydrogen in the presence of *finely divided nickel at ordinary temperature and pressure.*

2-Amino-butane has been obtained from methyl-ethyl-ketoxime (Pope, *J.C.S.*, **101**, 1702; Mailhe, *Compt. rend.*, 1905, **141**, 114; Freylon, *Ann. de Chim.*, 1908, (8), **15**, 285; Sabatier, *ibid.*, 1909, **16**, 104), secondary butyl halides (Hofmann, *Ber.*, 1874, **7**, 513; Sheverdina and Kocheschkov, *J. Gen. Chem., U.S.S.R.*, 1938, **8**, 1825), butyl mustard oil (Reymann, *Ber.*, 1874, **7**, 1289) and isobutyloxy-methylethylketoximes (Blaise and Picard, *Ann. de Chim.*, 1912, (8), **26**, 268). Andree (*Bull. Soc. Chim.*, 1939, (5), **6**, 1576) has prepared the same from methyl ethyl ketone by catalytic methods.

3-Aminopentane (α-ethyl-propylamine) has been prepared from diethylketoxime (Mailhe, *Bull. Soc. Chem.*, (4), **15**, 327; Noyes, *Amer. Chem. J.*, 1893, **15**, 540), ketazines (Mailhe, *loc. cit.*), diethylketone (with ammonium formate and acetic acid) (Wallach, *Ann.*, 1905, **343**, 59) and diethyl carbinol (Andree, *loc. cit.*); while 2-aminopentane has been prepared from methyl propyl ketoxime (Pope, *loc. cit.*; Freylon, *loc. cit.*; Kursanoff, *J. Phys. Chem., U.S.S.R.*, **30**, 269), methyl-propyl-ketone-phenyl-hydrazone (Tafel, *Ber.*, 1886, **19**, 1927) and methylpropylketone (sodium and alcoholic ammonia) (Loffler, *loc. cit.*).

β-Isohexylamine has been prepared from α-mesityl oxime (Kerp, *Ann.*, **290**, 149) and α-amino-α-methyl-isobutylaceto-nitrile (Gulewitsch and Wasmus, *loc. cit.*); while 2-aminoheptane has been prepared from 2-nitro or 2-bromo heptane (Konowalow, *J. Phy. Chem., U.S.S.R.*, **25**, 488; Clarke, *J. Amer. Chem. Soc.*, 1899, **21**, 1027). 2-Amino-octane has been prepared from 2-iodo or 2-nitro octane (Squire, *Ann.*, **92**, 400; Cahours, *Compt. rend.*, 1854, **39**, 254; Konowalow, *J. Phys. Chem., U.S.S.R.*, **25**, 294), methyl-*n*-hexylketoxime (Kishner, *J. Phys. Chem., U.S.S.R.*, **31**, 878) and methyl-*n*-hexylcarbinol (Merz and Gasiorowski, *Ber.*, 1884, **17**, 634).

For the present work, the choice of catalyst fell on Raney's nickel mainly due to its ease of availability, cheapness and efficiency. Raney's nickel is best suited for low temperature and low pressure work in contrast to metal oxides or mixed catalysts like copper chromium oxide (Covert, *J. Amer. Chem. Soc.*, 1932, **54**, 4116) which require high temperature and pressure; and has the advantage of converting the secondary amine formed in the system back into the primary one [I. G. Farb, D. R. P. 551436 (1930)], thus giving a product of uniform purity in good yields. A variety of catalysts like activated alumina [Temmler, B.P. 508756 (1939)], heavy metal oxides [I. G. Farb., B.P. 436214 (1935)] and other metals [Pratt and Moriss, B.P. 542609 (1942)] have been used to reduce an oxime, nitrile [Pratt and Moriss, *loc. cit.*; *Fab. de products de Chim.*, B.P. 282083 (1926)] or a ketone itself (with ammonia) (Olin and Schwoegler, U.S.P. 2278372 and 2278373 (1942)) in liquid or vapour phase at elevated temperatures with hydrogen under pressure.

Raney's catalyst was prepared according to the method of Raney [U.S.P. 1628190 (1927)], and Paul and Hilley [*Bull. Soc. Chim.*, 1936, (series 5), **3**, 2331] and used in quantities of nearly 10 per cent. of the weight of ketone.

Ammonia has been used in the form of its aqueous solution or dissolved in methyl or ethyl alcohol. But in all these experiments the amount of ammonia used has been in large excess for the reason that excess of ammonia helps to give primary amines as the chief product at low temperature and during a short period of reaction (Vorozhtzov and Kobelev, *J.C.S., U.S.S.R.*, 1934, **4**, 310; Groggins and Stirton, *Ind. Eng. Chem.*, 1936, **28**, 1051). In case of ammonolysis and reduction of acetone into isopropylamine (Expts. II–VI) liquor ammonia has given the best results. As hydrogenation is facilitated by homogeneity of the mass, in the case of the higher ketones, the use of solvents has been found necessary due to their immiscible character.

The reaction vessel used for these experiments was shaken at an angle of 30° at moderate speed in all the cases. Application of temperature was found very necessary for these reactions, activity of ammonia being a function of its partial pressure which increases with temperature. Higher temperatures also help to keep the ketones in solution and increase their internal energies. Conversion of acetone into corresponding amine did not take place in the absence of heating (*vide* Expt. VII).

Pressure of nearly 90 lbs./sq. in. and a temperature of upto 100° were maintained for these experiments. It might have been possible to shorten the period of reaction by using higher pressures, and temperatures, but the equipment used was not suitable for experiments with higher pressures and temperatures.

TABLE

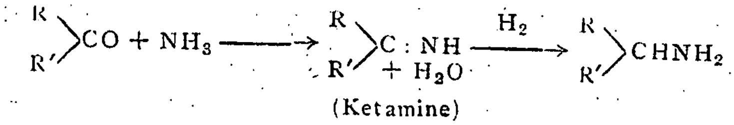
Conversion of aliphatic ketones into corresponding amines

(Pressure of 90 lbs./sq. in. has been used in all these experiments)

No.	Ketone	Quantity in grams	Ammonia with or without solvent	Raney's nickel in grams	Time in hours	Temperature °C.	Amine	B.P. at 685 mm.	Yield in grams	Remarks
I	Acetone (dimethyl ketone)	75	Acetone saturated with ammonia at 0°	10	7	50–60	Isopropylamine $CH_3 \cdot CH(NH_2) \cdot CH_3$	32–34°	Traces	Mixture of isopropyl alcohol and acetone recovered
II	do	25	Methyl alcohol saturated with ammonia at 0° 50 c.c.	8	5	do	do	do	20	..
III	do	21	Liquor ammonia 30 ,,	6	3½	do	do	do	18	..
IV	do	42	Alcohol saturated with ammonia at 0° 70 ,,	6	3½	do	do	do	20	..
V	do	35	do 70 ,,	10	8	90–100	do	do	20	..
VI	do	68	Liquor ammonia, 100 ,,	7	11	50–60	do	do	62	..
VII	do	40	do 75 ,,	5	12	25	do	do	3	Ammonolysis feeble
VIII	Diethyl-ketone	40	do 80 ,,	5	4	50–60	3-Aminopentane $CH_3CH_2 \cdot CH(NH_2) \cdot CH_2CH_3$	84–86°	30	..
IX	Ethylmethyl-ketone	40	do 80 ,,	6	6	do	2-Aminobutane $CH_3CH_2 \cdot CH(NH_2) \cdot CH_3$	60–62°	35	..
X	Methyl *n*-propyl ketone	40	Methyl alcohol 70 ,, Liquor ammonia 80 ,,	10	12	50–60	2-Aminopentane $CH_3 \cdot CH(NH_2) \cdot CH_2 \cdot C_2H_5$	88–89°	35	..
XI	Methyl-isobutyl-ketone	50	Methyl alcohol 70 ,, Liquor ammonia 80 ,,	8	9	90–100	β-Isohexylamine $CH_2 \cdot CH(NH_2) \cdot CH_2 \cdot CH(CH_3)_2$	99–102°	40	..
XII	Methyl-*n*-amyl ketone	35	Alcoholic ammonia 100 ,, Liquor ammonia 50 ,,	10	12	do	2-Aminoheptane $CH_3 \cdot CH(NH_2) \cdot (CH_2)_4CH_3$	136–138°	16	..
XIII	Methyl-*n*-hexyl ketone	50	Alcoholic ammonia 125 ,, Liquor ammonia 40 ,,	10	14	do	2 Aminooctane $CH_3 \cdot CH(NH_2) \cdot (CH_2)_5CH_3$	164–165°	30	..

The ketones have been converted into the corresponding amines under the conditions described in the Table. For isolation, the amines were first converted into their hydrochlorides and after removal of unreacted products and solvents, the amines were regenerated, from the residual solids, separated and purified by repeated fractional distillations. The yield of secondary and tertiary amines as by-products were negligibly small and yields of the desired amines usually varied from 75–95 per cent.

The amines are volatile ammoniacal smelling liquids and considerable care was necessary for the isolation of isopropylamine to avoid mechanical and evaporation losses. Special care was taken to purify the ketones and the solvents before using them for these reactions. It has been observed that the lower ketones give the best results with liquor ammonia while it is necessary to use a solvent and higher temperature and pressure in the case of ketones of higher molecular weight. The mechanism of reaction has been explained by Loffler (*loc. cit.*) and Mignonia (*loc. cit.*), as follows:



$$\begin{matrix} R \\ R' \end{matrix}\!\!>CO + NH_3 \longrightarrow \underset{\text{(Ketamine)}}{\begin{matrix} R \\ R' \end{matrix}\!\!>C:NH + H_2O} \xrightarrow{H_2} \begin{matrix} R \\ R' \end{matrix}\!\!>CHNH_2$$

Experimental

Raney's nickel.—Aluminium metal pieces (2 mols., 54 g.) were melted in a fire-clay crucible at 1200° in a charcoal furnace and to the molten mass one of the nickel cubes was added when it got dissolved with considerable evolution of heat. Remaining metal pieces in the form of cubes were then added in such a way that the heat of reaction was enough to dissolve the nickel and keep it molten. In this way nickel (59 g., 1 mol.) was dissolved in aluminium and the mass after stirring was allowed to cool. The nickelaluminium alloy was powdered and sieved through a 60-mesh sieve.

The alloy powder was added in small quantities to a dish having sodium hydroxide solution (30%, 600 c.c.) with stirring and external cooling. When the reaction subsided, the liquid was decanted off and fresh quantities of sodium hydroxide solution (400 c.c.) were added again. The mixture was heated on a water-bath till the evolution of hydrogen ceased. The akaline solution was decanted and the catalyst repeatedly washed with distilled water in similar manner till the alkali was removed completely. It was filtered on an asbestos filter paper, washed first with water (distilled) and later with alcohol and benzene. Care was taken not to expose the catalyst to air any time by keeping it always covered with water or solvent. Finally it was bottled under absolute alcohol; yield 55 grams.

Isopropylamine from acetone.—Acetone (68 g., b.p. 54°) along with liquor ammonia (30%, 100 c.c.) and Raney's catalyst (7 g.) was charged into the autoclave (capacity 600 c.c.). The autoclave was evacuated by means of a water pump and hydrogen was introduced to obtain a pressure of 90 lbs./sq. in. The autoclave was fixed into the mechanical shaker and electrically heated for 11 hours. Hydrogen absorption started after an hour when the temperature reached 50–60°. Hydrogen was introduced periodically to replenish what was consumed in the reaction. The hydrogenation and ammonolysis were considered over when the absorption of hydrogen stopped. After 11 hours of heating and shaking the autoclave was allowed to cool and after releasing the hydrogen pressure, the product was decanted into hydrochloric acid solution (18%; 200 c.c.) so as to fix the amine as its hydrochloride. The solution was evaporated to dryness, redissolved in water (150 c.c.) and transferred into a distillation flask (750 c.c.). The amine was regenerated by sodium hydroxide solution (40%; 200 c.c.) added through a dropping funnel and the amine was driven off by application of heat and condensed by an efficiently cooled double surface condenser. The amine which distilled off first was dried over potassium hydroxide and fractionally distilled twice; b.p. 32–34°; yield, 62 grams.

β-Isohexylamine from methylisobutyl-ketone.—Methyl isobutyl-ketone (B.P. 115°; 50 g.) was charged into the autoclave with methyl alcohol (70 c.c.), liquor ammonia (80 c.c.) and Raney's nickel (5. g.). The mixture was shaken for 9 hours at 90–100° at 90 lbs./sq. in. Hydrogen was introduced from time to time and when the absorption was over, the reaction was stopped. The mixture was decanted and the amine was fixed as its hydrochloride as described above. The hydrochloride solution was evaporated to dryness and the amine regenerated with sodium hydroxide solution (40%) under cooling. The amine separated as an oily layer which was mechanically separated and the ethereal extract of the aqueous portion also added to the same. The amine solution was dried over sodium hydroxide and after removal of ether the amine was fractionally distilled twice. Isohexylamine, b.p. 99–102° (40 g.) was obtained.

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