[A COMMUNICATION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Diacetoneamine, Diacetonealkamine and 2,4,4,6-Tetramethyl-4,5-dihydro-1,3-oxazine[1]

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Methods apparently are not available for the preparation in quantity of the aliphatic amines which bear the same relationship to primary amines that tertiary alcohols bear to primary alcohols.[2] It seemed possible that such a "tertiary" hexylamine VI could be prepared by a series of reactions beginning with the addition of ammonia to mesityl oxide

$$(CH_3)_2C{=}CHCOCH_3 \xrightarrow{+NH_3} (CH_3)_2CNH_2CH_2COCH_3 \qquad \text{I}$$

$$\xrightarrow{+Ac_2O} (CH_3)_2C(NHAc)CH_2COCH_3 \qquad \text{II}$$

$$\xrightarrow{+H_2} (CH_3)_2C(NHAc)CH_2CHOHCH_3 \qquad \text{III}$$

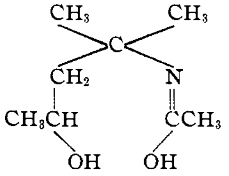
$$\xrightarrow{+H_2O} (CH_3)_2CNH_2CH_2CHOHCH_3 \qquad \text{IV}$$

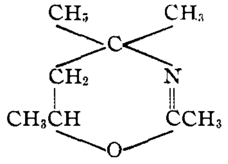
$$\xrightarrow{-H_2O} (CH_3)_2CNH_2CH{=}CHCH_3 \qquad \text{V}$$

$$\xrightarrow{+H_2} (CH_3)_2CNH_2CH_2CH_2CH_3 \qquad \text{VI}$$

The preparation of diacetoneamine as the acid oxalate by the addition of aqueous ammonia to mesityl oxide is well known, but according to Haeseler[3] anhydrous ammonia gave "very poor yields" of diacetoneamine. Anhydrous diacetoneamine, such as is necessary for acetylation, apparently has never been prepared directly from mesityl oxide. Gabriel[4] reported the preparation of 7 g. of N-acetyldiacetoneamine II from a salt of diacetoneamine, but his description indicates at best a very impure amide. None of the other reactions indicated above has been reported, although the reduction of I to IV with sodium amalgam has been described.[5]

We have found that anhydrous ammonia adds to mesityl oxide at room temperatures to give excellent yields of dry diacetoneamine. A procedure has been developed by means of which the reaction mixture obtained as above may be acetylated to acetyldiacetoneamine. The yield of pure ketoamide II was about 44% of the theory based upon the mesityl oxide. The ketoamide II was readily hydrogenated over Raney nickel at 160–170° to give good yields of acetyldiacetonealkamine, III. This compound may be separated by crystallization from dioxane or it may be distilled (with dehydration) at 135–140° 1 mm.). When III was kept at 140–160° it slowly lost water, forming a liquid, b. p. 147° (740 mm.).


III enol


VII

We believe that this liquid has the structure represented in VII, *i. e.*, 2,4,4,6-tetramethyl-5,6-dihydro-1,3-oxazine. Presumably it is formed by the dehydration of the enol of III. The conclusion that the liquid, b. p. 147°, is a cyclic imino ester of the indicated structure is based upon the following facts.

(a) It is a base and gives a neutral equivalent of 140, as compared with a calculated value of 141.

(b) It does not react with methylmagnesium bromide to give methane, nor with *p*-toluenesulfonyl chloride, thus indicating that the nitrogen is tertiary.

(c) It reacts with two moles of hydrogen to give a compound $(CH_3)_2C(NC_2H_5)CH_2CHOH$-$CH_3$, VIII, which Kohn[6] prepared by adding ethylamine to mesityl oxide and then reducing the resulting ketoamine with sodium amalgam in acid.

(d) It is formed by the dehydration of a compound of structure III and is reconverted to III when allowed to stand with water. Crystals of III separate when a moist sample of VII is allowed to stand for a few weeks.

(e) It may be saponified with the formation of sodium acetate and an amino alcohol known to have the structure IV.[5] In fact the preferred method for the preparation of IV involves the hydrolysis of VII rather than III, since VII is obtained more readily in a good yield than is III.

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[1] This investigation was supported in part by grants from the Wisconsin Alumni Research Foundation.

[2] Bewad, *J. prakt. Chem.*, [2] **63**, 233 (1901); Khouin, *J. Russ. Phys.-Chem. Soc.*, **41**, 327; *C. A.*, **6**, 881 (1911); Montagne, *Ann. chim.*, [10] **13**, 30 (1930).

[3] "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, 1932, p. 191; Haeseler, THIS JOURNAL, **47**, 1195 (1925).

[4] Gabriel, *Ann.*, **409**, 305 (1915).

[5] Heintz, *Ann.*, **183**, 291 (1876); Kahan, *Ber.*, **30**, 1318 (1897); Kohn, *Monatsh.*, **25**, 141 (1904).

[6] Kohn, *ibid.*, **25**, 841 (1904), **28**, 479 (1907).

(f) Gabriel obtained 2,4,4,6-tetramethyl-1,3-oxazine in a similar way by heating acetyldiacetoneamine.[7]

All attempts to dehydrate the amino alcohol, IV, to the unsaturated amine, V, or reduce it to the saturated amine, VI, have been unsuccessful. It appears that the amino group on the tertiary carbon is more readily removed than the hydroxyl group in the secondary carbon atom. All attempts to remove the hydroxyl group resulted either in the loss of the amino group or the recovery of the amino alcohol unchanged. The dehydration of III, IV or VII was attempted with phosphorus pentoxide, sulfuric acid, oxalic acid, iodine, phosphoric acid and with alumina at 320 to 350°. The reduction of the hydroxy group was attempted with hydriodic acid, tin and hydriodic acid, phosphorus and hydriodic acid, phosphorus and iodine, and iodine and tetralin.

Attempts to decrease the number of stages in the synthesis of the desired tertiary hexylamine through the use of catalytic hydrogenation were unsuccessful. Diacetoneamine would not react with hydrogen over Raney nickel under the conditions (below 30°) at which it is stable.[4] Attempts to eliminate the oxygen in II, III, or VII by hydrogenolysis, and thus obtain the acetyl derivative of VI, resulted in the formation of VIII. Diacetonealkamine, IV, is very inactive toward hydrogen. When it reacted (250°) none of the desired compound VI was obtained. The negative results in these experiments show the great difference between 1,3-glycols and 1,3-amino alcohols in their behavior toward hydrogen.

Experimental Part

Diacetoneamine.—One mole (98 g.) of mesityl oxide was placed in a test-tube (3 × 25 cm.) and cooled by placing the test-tube in a Dewar flask containing liquid ammonia and stirring for ten minutes. Liquid ammonia (17–18 g.) was then added to the mesityl oxide. During the addition, the mesityl oxide was churned with a glass rod having a glass disk, 2.5 cm. in diameter, sealed on the lower end. The test-tube, and contents, together with the stirrer, were removed from time to time from the Dewar flask and weighed in order to ascertain when sufficient ammonia had been added. The test-tube containing mesityl oxide and ammonia was then placed in a steel bomb of the type used in catalytic hydrogenation, and allowed to stand at a temperature of 10–23° for three days. The reaction mixture, obtained by the above method, was used directly in the preparation of acetyldiacetoneamine. The reaction may be carried out on a much larger scale if facilities for cooling the mesityl oxide and holding the mixture during the period of reaction are available. The pressure developed when the reaction mixture first warms up to room temperature is not great and glass pressure bottles could probably be used with safety. There is practically no internal pressure after the reaction mixture has stood for two days.

The acid oxalate of diacetoneamine was prepared for the sake of comparison with Haeseler's method by adding the above reaction mixture to 126 g. of oxalic acid dihydrate dissolved in 600 cc. of 95% alcohol at a temperature of 15–20°. The product was filtered and dried at room temperature and 25 to 30 mm. pressure. The diacetoneamine acid oxalate, m. p. 125°, so obtained weighed 168 g., and represents a yield of 75% based upon the mesityl oxide. The yield is better than previously reported and the process is much shorter and simpler.

N-Acetyldiacetoneamine.—The reaction product of ammonia and mesityl oxide (292 g., 3 moles) was placed in a liter three-necked flask provided with a motor-driven stirrer, a dropping funnel, and a thermometer. While the mixture was stirred rapidly, air was drawn through the flask for several minutes by a suction pump in order to remove any unreacted ammonia. The mixture was then cooled down to −2 or −3° in an ice–salt mixture, and three hundred ml. of acetic anhydride was added during a period of six hours. The temperature of the reaction mixture was maintained in the neighborhood of 0° (±3°). The first third of the acetic anhydride was added very slowly since the reaction is strongly exothermic. The first 100 ml. of acetic anhydride was diluted with an equal volume of benzene in order that heating at the point of reaction might be minimized. The second and third 100-ml. portions of acetic anhydride were added more rapidly without dilution. The reaction mixture was stirred and maintained at a temperature of 0–10° for one or two hours after the addition of the last of the acetic anhydride.

The mixture was then transferred to a liter flask having a ground glass joint and the lower boiling products were removed by distillation through a Widmer column (spiral, 15 cm. in length) at a pressure of 6 to 20 mm. Products distilling below 70° at 1 mm.[7] were discarded, approximately 300 g. of material distilled between 70 and 100° at 1 mm., leaving a residue of 30 to 40 g. The fraction boiling from 70 to 92° at 1 mm. contained a good deal of acetamide which crystallized out. The crystals were removed by filtration through a sintered glass funnel and washed with benzene for the removal of the ketoamide. In case this fraction solidified completely, it was warmed in benzene before filtration. The benzene solution was then combined with the fraction of ketoamide boiling at 92–100° (1 mm.), the benzene removed under the water pump, and the residue refractionated. By the repetition of this process a total of about 55 g. of acetamide and about 210 g. of acetyldiacetoneamine, b. p. 93–97° (1 mm.), m. p. 46–46.5°, was obtained. Contrary to Gabriel's results the distillate of even the crude material solidified. Analysis for N: calcd. for $C_8H_{15}O_2N$, 8.91%; found, 9.02%.

Hydrogenation of Acetyldiacetoneamine.—Acetyldiacetoneamine (70 g., 0.45 mole) in 60 ml. of dioxane was al-

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(7) The method and apparatus for fractionation are to be described in a paper by Martha E. Smith and Homer Adkins entitled "The Relative Reactivity of Amines in the Aminolysis of Amides" to be published in THIS JOURNAL.

lowed to react with hydrogen in the presence of Raney nickel catalyst (5 g.) at 100 to 200 atmospheres pressure and a temperature of 160–170°, until 0.5 mole of hydrogen was taken up. This required one to two hours. The hydrogenation may be carried out on a much larger scale but it proved more convenient to make several successive hydrogenations on the scale indicated. The catalyst was not removed from the bomb after a hydrogenation, but another quantity of ketoamide and dioxane and a little catalyst were added.

The procedure for isolating the product depended upon whether the acetyldiacetonealkamine or the tetramethyldihydroöxazine was desired. For the isolation of acetyldiacetonealkamine, the dioxane was partially removed by distillation under reduced pressure and the acetyldiacetonealkamine allowed to crystallize from the remaining solvent. If the tetramethyldihydroöxazine was desired, the reaction mixture was submitted to fractional distillation through a modified Widmer column.[7]

4-Methyl-4-acetylaminopentanol-2, or N-Acetyldiacetonealkamine.—After removal of the catalyst by centrifuging, the dioxane solution was concentrated by distillation at 20 to 30 mm. pressure. When the solution was sufficiently concentrated, it was allowed to cool to room temperature and the acetyldiacetonealkamine crystallized out. No attempt was made to secure maximum yield of this compound, since the dihydroöxazine was in general the desired product. However, in one experiment 195 g. of the hydroxy amide was obtained from 450 g. of the ketoamide. This represents a yield of 42%. A corresponding yield of 42% of the tetramethyldihydroöxazine was obtained by fractional distillation of the mother liquors from the crystallization of the acetyldiacetonealkamine. The acetyldiacetonealkamine was recrystallized from dioxane for the purpose of analysis; m. p. 87.5–89°; N, calcd. for $C_8H_{17}O_2N$, 8.80%; found, 8.88%.

2,4,4,6-Tetramethyl-5,6-dihydro-1,3-oxazine.—In order to obtain this compound, the reaction mixture from the hydrogenation of acetyldiacetoneamine was fractionated at atmospheric pressure through a modified Widmer column with a 15-cm. spiral.[7] After the removal of most of the dioxane, the temperature at the head of the column dropped from 100 to about 90° and remained in this vicinity for some time. During this time the acetyldiacetonealkamine was being dehydrated with the formation of tetramethyldihydroöxazine, and therefore the distillation was carried out very slowly. The tetramethyldihydroöxazine began to come over at 130°, and the distillation temperature varied in the range 130–145°, depending upon the extent to which water resulting from the dehydration was being formed. The latter portion of the dihydrooxazine distilled over very slowly, and distillation was continued as long as anything came over at 150° or less. The crude tetramethyldihydroöxazine was refractionated immediately in order to remove water, as otherwise the latter reacted with the formation of acetyldiacetonealkamine. In a typical preparation from 280 g. of acetyldiacetoneamine, 201 g. of the tetramethyldihydroöxazine, b. p. 143–145°, was obtained. This represents a yield of 80% of the theoretical.

Refractionation of the product yielded a fraction boiling constantly at 146.8–147.0° (737 mm.), or 50–51° (17 mm.); n^{25}D 1.4358. Neutral equivalent: calcd. 141; found, 140. Analysis for N: calcd. for $C_8H_{15}ON$, 9.94%; found, 9.93%. M. p. of picrate, 152–153°. Picrate analyzed for N, calcd. for $C_{14}H_{17}O_8N_4$: 15.18%; found, 15.21%.

N-Ethyldiacetonealkamine is produced if the hydrogenation of N-acetyldiacetoneamine is allowed to proceed beyond the absorption of one mole of hydrogen per mole of ketoamide. A sample of the oxazine, VII, (0.16 mole in 25 ml. of dioxane) was allowed to take up 0.16 mole of hydrogen within sixty minutes over Raney nickel (3 g.) at 170°. From the reaction mixture were isolated 0.06 mole of VII and 0.08 mole of N-ethyldiacetonealkamine, VIII. The pure compound had a b. p. of 84–85° (17 mm.). A sample gave a neutral equivalent of 143 (calcd. 145), and evolved two moles of methane per mole of VIII in a Grignard machine. The picrate had a m. p. of 158–159°.

Diacetonealkamine, or 4-Methyl-4-aminopentanol-2.—The tetramethyldihydroöxazine (156 g., 1.1 moles) or acetyldiacetonealkamine was refluxed with 600 ml. of 10% sodium hydroxide solution for eight and one-half hours. The reaction mixture was saturated with sodium chloride, extracted with ether five times, and the ether extract dried with solid potassium hydroxide. The ether was removed by distillation at atmospheric pressure and the residue distilled under reduced pressure. The entire amount, 103 g. (80% yield), boiled at 74.5–75.5° (15 mm.), or 61–61.5° (7 mm.). A sample after refractionation evolved when treated with methylmagnesium bromide two moles of methane per mole of IV and showed a neutral equivalent of 118 (calcd. 117).

Summary

Procedures have been described for the preparation of the following compounds in quantities of 100 to 200 g.: (a) diacetoneamine by the addition of anhydrous ammonia to mesityl oxide; (b) acetyldiacetoneamine by the reaction of acetic anhydride with diacetoneamine; (c) acetyldiacetonealkamine by the catalytic hydrogenation of acetyldiacetoneamine; (d) 2,4,4,6-tetramethyl-5,6-dihydro-1,3-oxazine by heating acetyldiacetonealkamine; (e) diacetonealkamine by the hydrolysis of acetyldiacetonealkamine, or 2,4,4,6-tetramethyl-5,6-dihydro-1,3-oxazine.

Many unsuccessful attempts have been made to reduce or dehydrate these compounds to a *t*-hexylamine.

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