containing 150 cc. of dioxane, 32 g. of isopropyl bromide, and 2 g. of potassium iodide was refluxed for fourteen hours. After distilling off most of the dioxane, ether and water were added, and the ether layer, after washing with alkali and with water and then drying over calcium chloride, yielded on distillation 13 g. (38% yield) of the desired product; b. p. 147–148° at 12 mm., $n^{20}D$ 1.5764, d^{25}_4 1.017. Nitration yielded a mononitro derivative (1-isopropoxy-2-methyl-4-nitronaphthalene), light yellow needles, m. p. 45°. *Anal.* Calcd. for $C_{14}H_{15}O_3N$: N, 5.71; Found: N, 5.69.

α-Naphthyl Isopropyl Ether.—This was prepared by a procedure similar to the preceding, from the sodium salt of α-naphthol and isopropyl bromide in 21% yield; b. p. 139–140° at 9 mm., $n^{20}D$ 1.5848, d^{25}_4 1.025. On nitration a mononitro derivative was obtained which yielded 4-nitro-1-naphthol on treatment with alcoholic potassium hydroxide for one hour on the steam-bath and is thus identified as 1-isopropoxy-4-nitronaphthalene; dark yellow needles, m. p. 69°. *Anal.* Calcd. for $C_{13}H_{13}O_3N$: N, 6.06; Found: N, 6.15.

Summary

It is shown that hydrogen atoms *ortho* and *para* to the hydroxyl or alkoxyl group in phenols and phenol ethers exchange with deuteroalcohol in the presence of small amounts of sulfuric acid. Exceptions are β-naphthol and derivatives thereof in which exchange occurs only at the α-position. The unsymmetrical phenols, 5-hydroxyhydrindene and 6-hydroxytetralin, which couple at a preferred *ortho* position (Mills–Nixon effect), show two active nuclear hydrogens in the exchange reaction.

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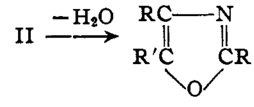
[CONTRIBUTION FROM THE VENABLE CHEMICAL LABORATORY OF THE UNIVERSITY OF NORTH CAROLINA]

Conversion of α-Amino Acids to Acylamido Ketones and Oxazoles

BY RICHARD H. WILEY AND OLIN H. BORUM[1]

A previous communication[2] described a method for the conversion of α-amino acids (I) to acetamidoketones (II, R' = CH_3) by reaction with acetic anhydride in pyridine, and of the acetamidoketones to oxazoles (III).

$$\underset{\text{I}}{RCH(NH_2)CO_2H} + 2(R'CO)_2O \xrightarrow{\text{pyr.}} \underset{\text{II}}{RCH(NHCOR')COR'} + 2RCO_2H + CO_2$$



III

The present paper describes the anomalous course of this reaction with glycine, the substitution of propionic for acetic anhydride in the formation of a propionamidoketone, and a modified procedure for obtaining yields of 70–90% of the acylamidoketone.

The reaction product obtained on refluxing glycine and acetic anhydride in pyridine can be fractionated to give a principal fraction boiling at 105–108° at 2 mm. The analytical data show that this compound is not acetamidoacetone, the product which would be formed if the reaction were analogous to that with alanine. The data agree with values calculated for an acetyl derivative of acetamidoacetone. This is substantiated by the hydrolysis of this acetyl derivative to acetamidoacetone b. p. 101–105° (0.5 mm.) in 76% yield. The structure of the acetyl derivative cannot be assigned on the basis of the available information. It is noted in this connection that previous attempts to bring about this reaction with glycine[3] were less successful because the reaction is very slow at steam-bath temperatures.

Improved yields of 3-acetamido-2-butanone are obtained by stirring during the reaction period to aid in evolution of carbon dioxide. The preferred procedure, in which the product is separated by fractionation of the reaction mixture, gives 88% of redistilled product as described in the experimental part. Using this procedure aminophenylacetic acid and propionic anhydride give a 75% yield of 1-phenyl-1-propionamido-2-butanone.

Dehydration of the acylamidoketones to oxazoles with potassium bisulfate and other reagents has been accomplished but with no advantage over the previously described[2] sulfuric acid dehydration.

Experimental Part

3-Acetamido-2-butanone (II, R = CH_3, R' = CH_3).—A mixture of 159 ml. (1.98 moles) of pyridine (J. T. Baker C. P.), 224 ml. (2.35 moles) of acetic anhydride (95% min. assay), and 35.11 g. (0.39 mole) of vacuum-dried alanine (Merck) was heated with stirring on the steam-bath for six hours after solution was complete. The excess pyridine and acetic anhydride were removed at reduced pressure and the residue distilled through a short column to obtain 47.5 g., 93.2% of the theoretical amount of crude 3-acetamido-2-butanone, b. p. 110–125° at 3 mm. On refractionation 88% of the theoretical amount, 45 g., b. p. 102–106° at 2 mm., was obtained, $n^{25}D$ 1.4558.

Anal. Calcd. for $C_6H_{11}NO_2$: C, 55.79; H, 8.59; N, 10.85. Found: C, 55.81; H, 8.48; N, 10.90.

Without stirring the yield dropped to 46%. Reducing the molar ratio of pyridine or anhydride also reduced the yield.

1-Phenyl-1-propionamido-2-butanone (II, R = C_6H_5, R' = C_2H_5).—A mixture of 60 g. (0.4 mole) of aminophenylacetic acid (E. K. Co.), 250 ml. (2.0 moles) of propionic anhydride (Carbide and Carbon Co.), and 165

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[1] The work reported in this paper was taken in part from the Master's Thesis submitted by Olin H. Borum to the Graduate School of the University of North Carolina.

[2] Richard H. Wiley, *J. Org. Chem.*, **12**, 43 (1947).

[3] Dakin and West, *J. Biol. Chem.*, **78**, 91–105 (1928).

ml. of pyridine were heated to solution and then at gentle reflux for one and a half hours. On vacuum distillation a fraction, b. p. 159–162° at 3–4 mm., weighing 66 g., 75% of the theoretical amount of 1-phenyl-1-propionamido-2-butanone, was collected. This fraction solidified on standing and was recrystallized from xylene, m. p. 69.7–70.7 (cor.).

Anal. Calcd. for $C_{13}H_{17}O_2N$: C, 71.20; H, 7.82; N, 6.39. Found: C, 71.33; H, 7.89; N, 6.65.

Acetyl Acetamidoacetone.—A mixture of 1.1 liters (11 moles) of acetic anhydride (95% min. assay), 485 ml. (6 moles) of pyridine (J. T. Baker C. P.), and 75 g. (1 mole) of vacuum-dried glycine (E. K. Co) was refluxed with stirring for six hours. The excess pyridine and acetic anhydride were removed at reduced pressure and the residue distilled to obtain 95 g., 60% of the theoretical amount, of crude acetyl acetamidoacetone, b. p. 118–128° at 3 mm. On refractionation 85 g., 54% of the theoretical amount of purified acetyl acetamidoacetone, b. p. 105–108° at 2 mm., was separated, $n^{25}\text{D}$ 1.4668; d^{25}_{25} 1.1275.

Anal. Calcd. for $C_7H_{11}O_3N$: C, 53.49; H, 7.05; N, 8.91. Found: C, 53.54; H, 7.17; N, 9.17.

Acetyl acetamidoacetone reacts immediately with neutral potassium permanganate solution to give a heavy precipitate. Acetamidoacetone does not. Both decolorize bromine in carbon tetrachloride solution.

Acetamidoacetone (II, R = H, R' = CH_3).—Thirty-two grams of acetyl acetamidoacetone was dropped into 500 ml. of boiling water over a thirty-minute period. The mixture was steam distilled for five hours, the remaining water and acetic acid removed under reduced pressure, and the residue fractionated to give 17.8 g., 76% of the theoretical amount of acetamidoacetone, b. p. 104–109° (1–2 mm.), $n^{25}\text{D}$ 1.4600 (supercooled). This fraction solidified to an extremely hygroscopic solid, m. p. 39–41°.

Anal. Calcd. for $C_5H_9O_2N$: C, 52.16; H, 7.88; N, 12.16. Found: C, 51.87; H, 7.92; N, 12.10.

Acetamidoacetone was converted to 2,5-dimethyloxazole by the process previously described.[3] Ten to fifteen per cent. of 2,5-dimethyloxazole, b. p. 116–117°, $n^{25}\text{D}$ 1.4365 was obtained. The reported[4] boiling point is 117°.

Anal. Calcd. for C_5H_7ON: N, 14.42. Found: N, 14.60.

2,5-Dimethyloxazole picrate, m. p. 122–122.5°, was prepared in alcohol solution. The reported m. p. is 124°.[4]

Anal. Calcd. for $C_{11}H_{10}O_8N_4$: N, 17.17. Found: 17.34.

Dehydration of 3-Acetamido-2-butanone to 2,4,5-Trimethyloxazole.—Thirty grams of 3-acetamido-2-butanone was dropped over a thirty-minute period onto 87.5 g. of potassium bisulfate in a distilling flask at 220°. A total of 21.10 g. of distillate was collected in the receiver. This material on fractionation gave a total of 17.8 g., b. p. 70–147°. A center cut of 7.8 g., b. p. 141–143°, $n^{25}\text{D}$ 1.4280 gave a picrate, m. p. 110–111.5°, which did not lower the m. p. when mixed with a sample of previously prepared[2] picrate. When 11.7 g. of the crude reaction mixture, b. p. 142–150°, was washed with 33% aqueous sodium hydroxide and dried over solid potassium hydroxide 1.7 g. of oxazole, b. p. 133–135°, $n^{25}\text{D}$ 1.4391, was obtained. Other pyrolyses with alumina, anhydrous zinc sulfate, lime, boron oxide and phosphorus pentoxide at 200–300°, but not thermal pyrolysis at 500°, dehydrate the ketone to the oxazole in low yields.

Summary

Glycine reacts with acetic anhydride in pyridine to form acetyl acetamidoacetone which is readily hydrolyzed to acetamidoacetone. Improved yields in the conversion of alanine to 3-acetamido-2-butanone, the conversion of aminophenylacetic acid to 1-phenyl-1-propionamido-2-butanone, and a potassium bisulfate dehydration of 3-acetamido-2-butanone to 2,4,5-trimethyloxazole are reported.

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[4] Wrede and Feuerriegel, *Z. physiol. Chem.*, **218**, 129 (1933).

Chapel Hill, N. C. Received September 6, 1947

[Contribution from the Research and Development Division, Commercial Solvents Corporation]

Some Chloromethyl Ethers of Nitro Alcohols and the Preparation of Mixed Acetals from Them

By E. B. Hodge

The reaction between formaldehyde, hydrogen chloride and an alcohol to form a chloromethyl ether was first reported by Henry.[1] Since then, the reaction has become very well known and is frequently used in synthetic work. The chlorine atom in these compounds is quite reactive, and it was thought to be of interest to see if the chloromethyl ethers of nitro alcohols would form. These compounds would make available a new tool in the preparation of derivatives containing aliphatic nitro groups. The aromatic nitro group is known to hinder the chloromethylation reaction.[2]

The success of the chloromethylation reaction as applied to nitro hydroxy compounds was found to vary with the structure of the nitro hydroxy compound. The chloromethyl ethers prepared were mobile liquids with sharp odors. They were soluble in benzene and the usual oxygenated solvents, but were insoluble in petroleum ether and water. On being shaken for a short time with water they decomposed.

Properties and yields of the chloromethyl ethers prepared are listed in Table I. The yields are based on the nitro alcohol.

The chloromethyl ethers prepared were found to react smoothly with sodium phenoxide and alkoxides to give mixed acetals. The nitro group in these could be reduced catalytically to the amino group. Properties and yields of these mixed acetals are given in Table II.

Yields of the nitro acetals and of the amino acetals from phenol are based on the chloromethyl

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[1] L. Henry, *Bull. acad. roy. Belg.*, 3, **25**, 439 (1893).

[2] "Organic Reactions," Vol. I, John Wiley and Sons, New York, N. Y., 1942, p. 65.