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, $n^{25}\mathrm{D}$ 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.), $n^{25}\mathrm{D}$ 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°, $n^{25}\mathrm{D}$ 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°, $n^{25}\mathrm{D}$ 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°, $n^{25}\mathrm{D}$ 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.

[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

[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.

TABLE I

CHLOROMETHYL ETHERS OF NITRO ALCOHOLS

Nitro hydroxy compound	Chloromethyl ether	Yield, %	B. p., °C.	B. p., Mm.	$n^{20}D$	d^{20}_{20}	Analyses, % Nitrogen Calcd.	Analyses, % Nitrogen Obs.	Analyses, % Chlorine Calcd.	Analyses, % Chlorine Obs.
2-Methyl-2-nitro-1-propanol	1-Chloromethoxy-2-methyl-2-nitropropane	75	85	4	1.4498	1.206	8.37	8.5	21.2	21.0
2-Methyl-2-nitro-1-butanol	1-Chloromethoxy-2-methyl-2-nitrobutane	70	98	3	1.4548	1.175	7.72	7.9	19.5	19.3
2-Nitro-1-butanol	1-Chloromethoxy-2-nitrobutane	69	95	1	1.4510	1.208	8.37	8.6		

TABLE II

MIXED ACETALS

Acetal	Yield, %	B. p., °C.	B. p., Mm.	$n^{20}D$	d^{20}_{20}	Analyses, % Neut. eq. Calcd.	Analyses, % Neut. eq. Obs.	Analyses, % Nitrogen Calcd.	Analyses, % Nitrogen Obs.
2-Methyl-2-nitro-4,6-dioxaheptane	68	65	2	1.4206	1.084			8.59	8.68
2-Methyl-2-nitro-4,6-dioxaoctane	30	72	1	1.4248	1.049			7.92	8.18
3-Methyl-3-nitro-5,7-dioxaoctane	55	75	1	1.4309	1.068			7.92	8.01
2-Amino-2-methyl-4,6-dioxaheptane	72	56	20	1.4158	0.917	133	134.3		
3-Amino-3-methyl-5,7-dioxaoctane	82	60	10	1.4242	0.917	147	148		
2-Methyl-1-(phenoxymethoxy)-2-propanamine	28	100	1	1.4983	1.018	195	196		
2-Methyl-1-(phenoxymethoxy)-2-butanamine	40	102	1	1.500	1.011	209	208		

ether, while the yields of the other amino acetals are based on the nitro acetals.

When the chloromethylation of 2-methyl-2-nitro-1,3-propanediol was attempted, only the acetal, 5-methyl-5-nitro-1,3-dioxane was obtained.[3]

The cyclic acetal was too stable to be split by hydrogen chloride. Support for this hypothesis is given by the fact that bis-(2-methyl-2-nitropropoxy)-methane was found to react with hydrogen chloride and formaldehyde to give 1-chloromethoxy-2-methyl-2-nitropropane.

The effect of structure on the formation of chloromethyl ethers of nitro alcohols is shown by the relative ease of preparation of the chloromethyl ethers. 2-Methyl-2-nitro-1-propanol and 2-methyl-2-nitro-1-butanol reacted smoothly and gave a product which could be distilled at reduced pressure without apparent decomposition. However, the chloromethyl ether of 2-nitro-1-butanol could not be distilled without some decomposition, while no product could be isolated from 2-methyl-2-nitro-3-hexanol.

Experimental

The preparation of the chloromethyl ethers is illustrated by the reaction between hydrogen chloride, formaldehyde and 2-methyl-2-nitro-1-propanol.

Into a mixture of 238 g. of 2-methyl-2-nitro-1-propanol, 90 g. of trioxymethylene and 175 ml. of concentrated hydrochloric acid in a 1-liter beaker was passed a rapid stream of HCl from a cylinder of liquefied hydrogen chloride. The beaker was in an ice-bath which kept the temperature below 30° during the addition of the hydrogen chloride. The contents of the beaker were stirred vigorously and the hydrogen chloride was added through a disperser of sintered glass. After about one hour the addition was stopped, 50 ml. of benzene was added, and the layers were separated. Dry air was passed through the top layer until no more hydrogen chloride was evolved and then the product was distilled, first at atmospheric pressure and then at 5 mm. to remove the chloromethyl ether. This came off at 90–94°, wt. 228 g.

The preparation of a mixed acetal is illustrated by the following experiment.

One-hundred and sixty grams of methanol was placed in a 500 ml. round-bottomed flask equipped with a sealed stirrer, a dropping funnel and a reflux condenser. One mole (23 g.) of sodium was added slowly and when all had reacted, 145 g. (0.8 mole) of 1-chloromethoxy-2-methyl-2-nitrobutane was added dropwise to the refluxing mixture. After one-half hour of refluxing the mixture was cooled and filtered. Then 500 ml. of water was added and the methanol was stripped off. The oil which separated from the water was distilled. The main cut (81.4 g.) came off at 75° at 1–1.5 mm.

Reduction of the nitro mixed acetals is illustrated by the following experiment.

2-Methyl-2-nitro-4,6-dioxaheptane (78.6 g.) was dissolved in 400 ml. of methanol and reduced with hydrogen in a rocking bomb at 50–60° and 1000 lb. pressure in the presence of 5 g. of Raney nickel. The methanol was stripped off and the product was distilled at 10 mm. The weight of the product was 53.5 g.

Reaction between an acetal and hydrogen chloride was carried out as follows.

To 63 g. (0.25 mole) of bis-(2-nitroisobutoxy)-methane was added 1 mole of formalin. Dry hydrogen chloride was passed into this mixture at room temperature for three hours. The mixture was then extracted with benzene and the high boiling product was rectified under reduced pressure. A middle cut of 27 g. was taken which boiled at 104–106° at 13 mm. and contained 21.5% of chlorine. Theory for 1-chloromethoxy-2-methyl-2-nitropropane is 21.2%.

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[3] The fact that this acetal was formed from the diol while chloromethyl ethers were formed from the monohydroxy compounds suggests that the chloromethyl ethers were formed through the acetals as intermediates and that the cyclic acetal was too stable to be split by hydrogen chloride. Thus the equations might be written to account for the formation of the chloromethyl ethers. Support for this hypothesis is given by the fact that bis-(2-methyl-2-nitropropoxy)-methane was found to react with hydrogen chloride and formaldehyde to give 1-chloromethoxy-2-methyl-2-nitropropane.

$$2ROH + HCHO \xrightarrow{H^+} (RO)_2CH_2 + H_2O$$

$$(RO)_2CH_2 + HCl \longrightarrow ROCH_2Cl + ROH$$

Summary

The chloromethyl ethers of three nitro alcohols have been prepared.

Evidence suggests that the formation of these chloromethyl ethers takes place through the formal as an intermediate.

Several mixed acetals have been prepared from chloromethyl ethers of nitro alcohols and the nitro groups in these compounds have been reduced to amino groups.

TERRE HAUTE, INDIANA RECEIVED JANUARY 2, 1948

[CONTRIBUTION FROM THE INSTITUTE OF PAPER CHEMISTRY]

Reactions of Vanillin and its Derived Compounds. VI.[1] The Reaction of Vanillin with Mercuric Oxide[2,3]

BY IRWIN A. PEARL

The high yields of vanillic acid obtained when vanillin is treated with alkali and 0.5 mole of silver oxide in aqueous solution[4,5] and the interesting reactions of vanillin with alkali in the presence of silver oxide and silver metal[6] led to a study of the reaction of vanillin with alkali and other metallic oxides. This paper reports the study with mercuric oxide.

Vanillin gradually reacts with an excess of mercuric oxide in a boiling aqueous solution containing at least two moles of alkali to give a clear alkaline solution which may be treated by various procedures to give several different reaction products. All forms of mercuric oxide are operative, but the more reactive, freshly precipitated forms require less time. The reaction time is also dependent, to a considerable extent, upon the temperature of boiling which, in turn, is dependent upon dilution. The reaction of vanillin with mercuric oxide is much slower than that with silver oxide.

Acidification of the alkaline reaction mixture with a non-reducing acid (such as sulfuric acid) gives a high yield of 5-hydroxymercurivanillin and minor amounts of oxidized mercurated compounds. Acidification with hydrochloric acid yields 5-hydroxymercurivanillin as the chief product, together with minor quantities of 5-chloromercurivanillin and other mercurated compounds, including oxidized and bis derivatives.

Treatment of the alkaline solution with sulfur dioxide, followed by short boiling, decomposes the organic mercury compounds and gives a 60–70% yield of vanillic acid and a 25–35% yield of recovered vanillin. No mercurated products are obtained after the sulfur dioxide treatment, and most of the mercury is recovered as the free metal.

When only one mole of vanillin is employed in the above reaction, the vanillic acid yield is very low, and almost all the initial vanillin is recovered after the sulfur dioxide treatment.

Long boiling of vanillin with technical dry mercuric oxide and excess alkaline solution resulted in considerable decarboxylation of the originally formed vanillic acid to yield 11% of guaiacol. This was an unexpected result, because earlier work[7,8] on the caustic fusion of vanillin to yield protocatechuic acid indicated that the carboxyl group was much more resistant to removal by drastic alkaline treatment than was the methoxyl group. All attempts to oxidize vanillin by means of mercuric oxide without alkali in a non-aqueous solvent were unsuccessful.

5-Hydroxymercurivanillin was identified by converting it successively to 5-acetoxymercurivanillin, 5-chloromercurivanillin, and 5-iodovanillin, which compounds were compared with the corresponding compounds prepared according to Paolini,[9] who obtained acetoxymercurivanillin by treating vanillin with mercuric oxide in boiling glacial acetic acid. Paolini's compound was proved to be 5-acetoxymercurivanillin by Henry and Sharp.[10] 5-Iodovanillin was also compared with the iodovanillin prepared according to Carles[11] which Raiford and Wells[12] proved to be 5-iodovanillin.

Paolini's[9] 5-acetoxymercurivanillin, upon boiling with *N* potassium hydroxide solution and acidifying with hydrochloric acid, yielded 5-chloromercurivanillin, but all attempts to isolate 5-hydroxymercurivanillin from 5-acetoxymercurivanillin failed.

5-Hydroxymercurivanillin possesses remarkable toxicity toward representative microörganisms, such as sporeforming and non-sporeforming aerobic bacteria and molds and compares favorably with such outstanding antiseptics as ethylmercury and phenylmercury derivatives. On the other

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[1] For paper V of this series, see Pearl and McCoy, THIS JOURNAL, **69**, 3071 (1947).

[2] Presented before the Division of Organic Chemistry at the 112th meeting of The American Chemical Society, New York, N. Y., September 15–19, 1947.

[3] This paper represents a portion of the results obtained in the research program sponsored by the Sulphite Pulp Manufacturers' Research League and conducted for the League by The Institute of Paper Chemistry. Acknowledgment is made by the Institute for permission on the part of the League to publish these results.

[4] Pearl, THIS JOURNAL, **68**, 429 (1946).

[5] Pearl, *ibid.*, **68**, 1100 (1946).

[6] Pearl, *J. Org. Chem.*, **12**, 79 (1947).

[7] Tiemann, *Ber.*, **8**, 512 (1875).

[8] Pearl, THIS JOURNAL, **68**, 2180 (1946).

[9] Paolini, *Gazz. chim. ital.*, **51**, II, 188 (1921).

[10] Henry and Sharp, *J. Chem. Soc.*, 8288 (1930).

[11] Carles, *Bull. soc. chim.*, **17**, 14 (1872).

[12] Raiford and Wells, THIS JOURNAL, **57**, 2500 (1935).