3-(α-Iminoethyl)-4-hydroxy-O^{18}-coumarin (Labeled II). 3-Acetyl-4-hydroxy-O^{18}-coumarin (1.0 g.) and 0.3 g. of ammonium acetate were refluxed in 10 ml. of absolute ethanol for 9 hr. The solid which separated on cooling was recrystallized from absolute ethanol; yield 0.9 g., m.p. 233–235°, O^{18} content, 1.91 atom % excess.

3-Benzoyl-4-hydroxy-O^{18}-coumarin (Labeled IB). A. By the Hydrolysis of III in an O^{18} Enriched Medium.—Acetic acid (3.10 ml.), 1.68 ml. of O^{18} enriched water (6.48 atom % excess), 0.21 ml. of concentrated sulfuric acid, and 0.3 g. of III were refluxed 1.5 hr. The product which separated was crystallized twice from absolute ethanol; yield 0.2 g., m.p. 145°, O^{18} content, 0.667 atom % excess.

This seemingly low O^{18} value results from isotopic exchange with the acetic and sulfuric acids.[17] The theoretical O^{18} content is 0.70 atom % excess.

B. By Equilibration of 3-Benzoyl-4-hydroxycoumarin with an O^{18} Enriched Solution (Control Experiment).—When 0.3 g. of Ib was treated in the same manner as reported for the hydrolysis of III, the product had an O^{18} content of 0.561 atom % excess.

3-Benzyl-4-hydroxycoumarin (IX). A. By Hydrogenolysis of O^{18} Labeled Ib Obtained from III.—Labeled Ib obtained from the hydrolysis of III (80 mg.) was shaken for 3 hr. in 10 ml. of anhydrous methanol with 80 mg. of 10% palladium on charcoal and hydrogen at 38–40 p.s.i. The catalyst was removed and the solvent was evaporated to 1 ml. by a stream of nitrogen. Cooling to −10° yielded 40 mg. of product, m.p. 205°, O^{18} content, 0.085 atom % excess.

B. By Hydrogenolysis of O^{18} Labeled Ib Obtained from Equilibration with O^{18} Water (Control Experiment).—3-Benzoyl-4-hydroxy-O^{18}-coumarin obtained in the exchange experiment with 3-benzoyl-4-hydroxycoumarin and O^{18} water was reduced as in part A. The starting material had an O^{18} content of 0.561 atom % excess; the product was found to have an O^{18} content of 0.089 atom % excess.

Acknowledgment.—The writers are indebted to Professor Karl Paul Link and his associates, Dr. Bruce D. West and Dr. C. H. Schroeder, for valuable suggestions in the development of this work. Professor Laurens Anderson kindly loaned us his apparatus for isotope analysis and also helped with the interpretation of the analytical data and the preparation of the manuscript.

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[17] T. C. Hoering and J. W. Kennedy, *J. Am. Chem. Soc.*, **79**, 56 (1957).

1,2-Dicarbonyl Derivatives Resulting from the Action of Nitrosyl Chloride on Alcohols

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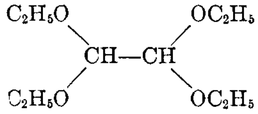
From the synthesis of phenylglyoxal diethyl acetal by the reaction of nitrosyl chloride with acetophenone in ethanol solution, considerable yields of an unknown by-product were isolated. This proved to be 1,1,2,2-tetraethoxyethane and resulted from the action of nitrosyl chloride upon ethanol, presumably by way of oxidation of the intermediate ethyl nitrite. Treatment of a large excess of ethanol with nitrosyl chloride afforded about 50% yields of 1,1,2,2-tetraethoxyethane, assuming four moles of nitrosyl chloride are required for the oxidation, at 30–50° and with a reaction time of three to four hours. The reaction was not accelerated upon illumination with an intense source of visible light. Application of the reaction to 1-propanol led to an inseparable mixture which, however, yielded derivatives of pyruvaldehyde upon treatment with carbonyl reagents. Isopropyl alcohol with nitrosyl chloride afforded a low yield of pyruvohydroxamyl chloride as the only isolable product. Both ethylene glycol and propylene glycol yielded complex mixtures upon treatment with nitrosyl chloride. Although none of the reaction products were positively identified in either case, it was possible to demonstrate the presence of glyoxal-yielding compounds in the ethylene glycol product and pyruvaldehyde-yielding compounds in the propylene glycol product by treatment of the distilled products with 2,4-dinitrophenylhydrazine and identification of the corresponding 2,4-dinitrophenylosazone derivatives.

During a recent study[1] of the preparation of phenylglyoxal diethyl acetal by the reaction of nitrosyl chloride with acetophenone in ethanol solution, a by-product [b.p. 80–84° 10 (mm.)] was observed in yields amounting to as much as one-third of the weight of the desired phenylglyoxal acetal. Elemental and infrared analyses and molecular weight determination suggested the identity of the by-product to be 1,1,2,2-tetraethoxyethane (I). Confirmation of the structure then was obtained



I

by acid hydrolysis of the by-product to ethanol and glyoxal followed by conversion of the latter to glyoxime by reaction with hydroxylamine. The possibility that the glyoxal acetal (I) arose solely from reaction of nitrosyl chloride with the solvent then was considered. Nitrosyl chloride was fed to a large excess of ethanol while maintaining the solution at slightly above room temperature. Upon warming to 38° a vigorous reflux of ethyl nitrite occurred and an exothermic reaction began, accompanied by rapid evolution of a mixture of nitric oxide, nitrous oxide, and nitrogen. The reaction mixture was allowed to stand for several hours and, after treatment with hot aqueous sodium hydroxide to remove any acidic or ester by-products, was distilled to give 1,1,2,2-tetraethoxyethane in an amount equivalent to 38.5% of the weight of nitrosyl chloride employed. In subsequent trials the time required for completion of the nitrosyl chloride reaction was found to be as short as three to four hours. Despite the uncertainty surrounding the mechanism, it is likely that at least three and possibly four moles of nitrosyl chloride are required for oxidation of the methyl and methylol groups of ethanol, the latter situation being represented by the following over-all equation.

$$4NOCl + 5C_2H_5OH \longrightarrow (C_2H_5O)_2CHCH(OC_2H_5)_2 + 2H_2O + 2NO + N_2O + 4HCl \quad (1)$$

A requirement of three moles of nitrosyl chloride corresponds to a yield of 37% while a four-mole requirement would indicate a 49% yield.

Study of this surprising oxidation occurring under the mild condition of a ketone nitrosation was then

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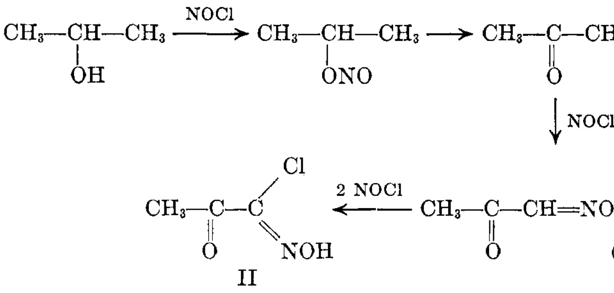
[1] David T. Manning and Harry A. Stansbury, Jr., *J. Org. Chem.*, **26**, 3755 (1961).

extended to other alcohols. The reaction of nitrosyl chloride with a large excess of 1-propanol for five hours at 30–52° yielded a complex liquid mixture, b.p. 45–120° (3 mm.), amounting to approximately 38% by weight of the nitrosyl chloride employed. Infrared analysis of the distillate revealed the presence of carbonyl, ether, and acetal-type functions. The presence of pyruvaldehyde derivatives in the distillate was confirmed by acid hydrolysis of the combined fractions followed by reaction with hydroxylamine, yielding methylglyoxime. In another similar experiment, material distilling at 63–73° (5 mm.) yielded the 2,4-dinitrophenylosazone of pyruvaldehyde upon treatment with 2,4-dinitrophenylhydrazine.

The reaction of nitrosyl chloride with isopropyl alcohol proceeded in a different manner. Distillation of the reaction mixture afforded no high-boiling liquid fraction. The bulk of the reaction product occurred in a rather sizeable residue from which was isolated a low yield of pyruvohydroxamyl chloride (II), probably arising from the following sequence.



II (2)

Reaction of both ethylene glycol and propylene glycol with nitrosyl chloride produced complex mixtures which could not be resolved by fractional distillation. The presence of glyoxal-yielding compounds in the product from ethylene glycol and of pyruvaldehyde-yielding compounds in the propylene glycol product was demonstrated, however, by treatment of the distilled reaction mixtures with 2,4-dinitrophenylhydrazine and isolation of the appropriate 2,4-dinitrophenylosazones.

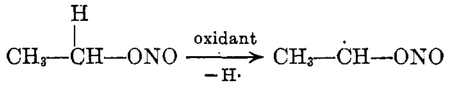
The reaction of nitric acid with ethanol to give glyoxal has been reported.[2] Nitrosyl chloride, however, is known to react rapidly with ethanol[3] yielding ethyl nitrite and hydrogen chloride according to the following equilibrium.

$$C_2H_5OH + NOCl \rightleftharpoons C_2H_5ONO + HCl \qquad (3)$$

No further decomposition of this system, under mild conditions, apparently has been observed. Previous preparations of 1,1,2,2-tetraethoxyethane have involved the acid-catalyzed reactions of glyoxal[4] or of a derivative[5] thereof with ethanol and have resulted in low (23–26%) yields even after prolonged reaction periods.

The mechanism of the present reaction, though unclear, may involve the general steps 4–6.

It was felt that hydrogen abstraction (step 4) might be accomplished by a chlorine atom as in the photonitrosation of hydrocarbons by nitrosyl chloride.[6]

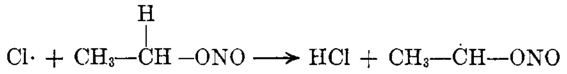


$$CH_3-\overset{H}{\overset{|}{C}}H-ONO \xrightarrow[-H\cdot]{\text{oxidant}} CH_3-\dot{C}H-ONO \qquad (4)$$

$$CH_3-\dot{C}H-ONO \longrightarrow CH_3CHO + NO \qquad (5)$$

$$CH_3CHO \xrightarrow[C_2H_5OH]{NOCl} HON{=}CHCHO \xrightarrow[C_2H_5OH]{NOCl} I + N_2O \qquad (6)$$

$$NOCl \xrightarrow{h\nu} NO\cdot + Cl\cdot \qquad (7)$$



$$Cl\cdot + CH_3-\overset{H}{\overset{|}{C}}H-ONO \longrightarrow HCl + CH_3-\dot{C}H-ONO \qquad (8)$$

Exposure of our reaction system to intense visible light failed, however, either to increase the yield or rate of acetal formation, or to accelerate the decomposition of nitrosyl chloride as judged by disappearance of brown color from the reaction mixture. Other possible means of accomplishing step 4 include oxidation (a) by molecular chlorine generated from the thermal decomposition of nitrosyl chloride and (b) by dinitrogen tetroxide, present as an impurity in the nitrosyl chloride.

Experimental[7]

Identification of the Low-Boiling By-product from the Synthesis of Phenylglyoxal Diethyl Acetal.—In a series of preparations of phenylglyoxal diethyl acetal by the reaction of nitrosyl chloride with acetophenone and ethanol, various samples of the reaction product were found to contain, in addition to phenylglyoxal diethyl acetal, low-boiling fractions (approximately 76–130° (10 mm.), amounting to 19–27% of the total weight of organic product. Several of the low-boiling fractions were combined (weight 295.6 g.) and redistilled to yield a main fraction weighing 197.4 g., b.p. 80–84° (10 mm.), $n^{20}\text{D}$ 1.4074. The material showed no aromatic absorption upon infrared analysis which revealed only two strong bands at 8.9 and 9.2 μ in addition to aliphatic C–H absorption. Elemental and molecular weight analysis gave the following results in accord with the empirical formula $C_{10}H_{22}O_4$.

Anal. Calcd. for $C_{10}H_{22}O_4$: C, 58.22; H, 10.75; mol. wt., 206.3. Found: C, 58.26; H, 10.70; mol. wt., 210.

The reported boiling point of 1,1,2,2-tetraethoxyethane ($C_{10}H_{22}O_4$) is 88–89° (14 mm.) or close to that odserved. A comparison of the previously mentioned infrared scan with a scan of 1,1,2,2-tetrabutoxyethane showed them to be almost identical.

A 41.3-g. (0.2 mole) sample of the material was hydrolyzed by refluxing under a still with 200 ml. of water containing 15 drops of concentrated sulfuric acid for a 2-hr. period. Ethanol was then recovered by distilling the mixture, which gave an aqueous solution containing 59% ethanol, by weight. The yield of ethanol (28.3 g.) was 76.8% and the composition of the aqueous ethanol solution was confirmed by mass spectrometric analysis.

The distillation residue was then filtered and to it was added 28 g. (0.403 mole) of hydroxylamine hydrochloride and 40 g. of anhydrous sodium acetate. The resulting mixture was heated on the steam bath for 1 hr. and worked up to give, upon drying, 9.5 g. of white crystalline glyoxime, m.p. 177–177.5° (reported[8] m.p. 178°). An additional crop of 2.3 g. was obtained from the filtrate. The total yield of glyoxime was 67.1%.

Reaction of Nitrosyl Chloride with Ethanol.—To 1 l. of ethanol was added, with stirring, 114 g. (1.74 moles) of nitrosyl chloride[9] through a gas diffuser over a period of approximately 1 hr. while maintaining a temperature of 23–31°. Upon completing the feed, the temperature of the mixture was raised to 38° whereupon a vigorous reflux of ethyl nitrite occurred and a colorless gas was evolved which had the composition: nitric oxide, 86.6%; nitrogen, 10.3%; nitrous oxide, 3.2%.

The reaction mixture was held at 38–43° for 21 min. and then stored overnight. The solution was then stirred and heated to 58°, 667 g. of 20% sodium hydroxide solution was added, and

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[2] A. Hantzsch, *Ann.*, **222**, 65 (1884).

[3] L. J. Beckham, W. A. Fessler, and M. A. Kise, *Chem. Rev.*, **48**, 366 (1951).

[4] C. Harries and P. Temme, *Ber.*, **40**, 165 (1907).

[5] H. Fiesselmann and F. Hörndler, *Chem. Ber.*, **87**, 906 (1954).

[6] M. A. Naylor and A. W. Anderson, *J. Org. Chem.*, **18**, 115 (1953).

[7] All temperatures are uncorrected.

[8] Heilbron, "Dictionary of Organic Compounds," Oxford University Press, New York, N. Y., 1953.

[9] Purchased from the Matheson Co. and used without further purification.

the mixture then refluxed for 1.5 hr. After removing ethanol at reduced pressure, the residue was extracted with ether and the extract evaporated to give the crude liquid product. Distillation of the latter afforded 43.9 g. of 1,1,2,2-tetraethoxyethane, b.p. 65–79° (10 mm.), which had an infrared spectrum identical to that of the material previously established as 1,1,2,2-tetraethoxyethane. The main portion distilled at 78.5–79° (10 mm.) and gave the following analysis.

Anal. Calcd. for $C_{10}H_{22}O_4$: C, 58.22; H, 10.75. Found: C, 58.47; H, 10.65.

The following yields would correspond to the requirement of either 3 or 4 moles of nitrosyl chloride per mole of acetal: for 3 moles, 36.8% yield; for 4 moles, 49.0% yield.

The possible influence of light upon the nitrosyl chloride–ethanol reaction then was studied as follows: nitrosyl chloride (114 g., 1.74 moles) was fed, with stirring, to 1 l. of ethanol over a 1-hr. period while illuminating the system with three 275-watt sun lamps placed close to and surrounding the reaction flask. The temperature of the exothermic reaction was maintained at 25–28° during the feed period by external cooling. Following the feed period, the reaction mixture was allowed to warm to 31° and then gradually to 51°, with stirring over a 3.68-hr. interval at which time the brown color of nitrosyl chloride had disappeared. The reaction mixture was then worked up in the previously described manner. A total yield of 49.5 g. (0.24 mole) of crude 1,1,2,2-tetraethoxyethane, boiling over the range of 62–78° (10 mm.), was obtained.

The previous procedure was repeated in identical fashion, but without the illumination. Following the 1-hr. feed period the disappearance of nitrosyl chloride color was actually somewhat faster than in the presence of light, requiring only 2.87 hr. at 29–50°. Working up the reaction mixture at this point yielded 55.2 g. (0.269 mole) of crude acetal, b.p. 57–78° (10 mm.).

Reaction of 1-Propanol with Nitrosyl Chloride.—To 1 l. of 1-propanol was added, with stirring, 2 moles of nitrosyl chloride (92 ml. at −30°) over a period of 69 min. while maintaining a temperature of 24–28° with cooling. The reaction mixture was allowed to warm to 32° over a 19-min. period and then, in sequence, held at 30–36° for a period of 2.58 hr. and at 51–52° for 1 hr. Volatile materials (788 g.) were then flashed from the mixture leaving 91 g. of residue. The latter was extracted with ligroin (most of it dissolved) and the extract distilled to give 49.9 g. of liquid, b.p. 45–120° (3 mm.). This was redistilled to give a total of fourteen fractions boiling over the range of 63–141° (5 mm.) and fairly uniform in size. The fractions possessed remarkably similar infrared spectra including strong carbonyl absorption at 5.6–5.7 μ and bands at 8.9 and 9.3 μ similar to those of 1,1,2,2-tetraethoxyethane.

In order to demonstrate the presence of pyruvaldehyde-yielding compounds in the distillation fractions, eleven of the cuts, totaling 33.1 g., were combined and refluxed with a solution of 10 drops of concentrated sulfuric acid in 200 ml. of water for a 14-hr. period to hydrolyze the acetal and/or ketal linkages. At the end of this time, a solution of 28.0 g. (0.403 mole) of hydroxylamine hydrochloride and 40 g. (0.488 mole) of anhydrous sodium acetate in 100 ml. of water was added to the mixture and the new mixture refluxed, with stirring, for a period of 7 hr. Working up the mixture gave a small amount of pyruvaldehyde dioxime which was purified by vacuum sublimation to give fine white crystals, m.p. 146–147° (reported[8] m.p. 153°, 157°).

Anal. Calcd. for $C_3H_6O_2N_2$: C, 35.29; H, 5.92; N, 27.44. Found: C, 35.87; H, 6.57; N, 26.57.

The infrared spectrum confirmed the structure as that of pyruvaldehyde dioxime.

The previous run was repeated on a larger scale giving, upon work-up, 95 g. of a flashed distillate, b.p. 35–109° (1 mm.). Fractional distillation of this gave thirteen cuts of fairly uniform size, several of which were tested for the presence of pyruvaldehyde derivatives by reacting samples of them with 2,4-dinitrophenylhydrazine reagent. Only the first two cuts, boiling over the combined range of 63–75° (5 mm.), gave pyruvaldehyde 2,4-dinitrophenylosazone. The derivative of cut 1, b.p. 63–68° (5 mm.), melted at 298° (reported[8] for pyruvaldehyde 2,4-dinitrophenylosazone, m.p. 299–300°), and gave the following analysis.

Anal. Calcd. for $C_{15}H_{12}N_8O_8$: N, 25.92. Found: N, 25.33.

Reaction of Isopropyl Alcohol with Nitrosyl Chloride.—One liter of isopropyl alcohol was stirred while 2 moles (92 ml. at −30°) of nitrosyl chloride were fed over a period of 1.27 hr., maintaining a temperature of 26–29°. Evolution of nitric oxide became apparent at the end of the feed period and the stirred mixture was allowed to warm to 30–33° where it was held, with gentle reflux, for a 1.67-hr. period. At this time, the reaction mixture was heated to 50–51° and stirred at this temperature for a 1-hr. period.

Volatile material (777 g.) then was removed from the reaction mixture under reduced pressure leaving a residue, weight 65 g. Attempted distillation of the latter led to partial decomposition and some crystalline material sublimed into the lower part of the column. A portion (0.6 g.) of this material was recrystallized from benzene and further purified by vacuum sublimation to give crystals of pyruvohydroxamyl chloride, m.p. 106–107° (reported[10] m.p. 105–106°).

Anal. Calcd. for $C_3H_4NO_2Cl$: C, 29.65; H, 3.32; N, 11.53; Cl, 29.17. Found: C, 29.70; H, 3.51; N, 11.46; Cl, 29.73.

The infrared spectrum was identical to that of an authentic sample of pyruvohydroxamyl chloride.

Reaction of Ethylene Glycol with Nitrosyl Chloride.—To 1 l. of ethylene glycol was added, with stirring and cooling, 131 g. (2.0 moles) of nitrosyl chloride over a period of 1.78 hr. The mixture then was warmed to 35° and held at this temperature, where a mildly exothermic reaction occurred, for a 2-hr. period. The reaction mixture was then heated to 61° and stirred at this temperature for a period of 1.25 hr.

The reaction mixture was then distilled to give a series of fractions (total wt., 1101 g.) boiling over the approximate range of 40–93° (0.5 mm.). All the fractions reacted with 2,4-dinitrophenylhydrazine to give the crude 2,4-dinitrophenylosazone of glyoxal, m.p. 311–317° dec. (reported[11] m.p. 318° dec).

Reaction of Propylene Glycol with Nitrosyl Chloride.—To 1 l. of propylene glycol was added, with stirring, 131 g. (2.0 moles) of nitrosyl chloride over a 1.67-hr. period with cooling to maintain the temperature at 25–26°. The reaction mixture was allowed to warm, exothermically, to 35–38°, where it was stirred for 1 hr. at which time the brown reaction solution had become colorless. The mixture was then heated to 60° and stirred at this temperature for 1 hr.

The reaction mixture was next distilled at reduced pressure to give a series of fractions [final b.p. 110° (0.5 mm.)] all of which reacted with 2,4-dinitrophenylhydrazine to give the 2,4-dinitrophenylosazone of pyruvaldehyde. The identity of the material from two recrystallized (nitrobenzene) preparations (both melting at 297°) was verified by determining the melting point upon mixture with authentic material.

Acknowledgment.—The authors are indebted to Mr. C. M. Lovell and Dr. H. F. White for the infrared studies performed.

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(10) H. Reinboldt and O. Schmitz-Dumont, *Ann.*, **444**, 113 (1925).

(11) C. Neuberg and E. Simon, *Biochem. Z.*, **256**, 485 (1932).