The reaction of butyraldoxime with nitrous acid without excess mineral acid must follow, in part, a different pathway because the major off-gas is NO (67%). As in the excess mineral acid catalyzed reaction, both the N_2 and N_2O show a 50% enrichment in ^{15}N. Thus these gases come equally from nitrous acid and oxime. The fact that so much NO is produced and that it all comes from the nitrous acid forms the basis for our considerations in this case. It should be emphasized that this NO does indeed come from a reaction of nitrous acid with the oxime. Under the same conditions of solvents, concentration, and temperature, nitrous acid does not react in a self-decomposition to give NO as an off-gas. Only when the oxime is added is NO produced.

One possibility that might explain the difference is as follows. In the presence of mineral acid a rapid reaction takes place to give the nitrosonium ion, and it is this NO^+ which is doing the reacting at an extremely

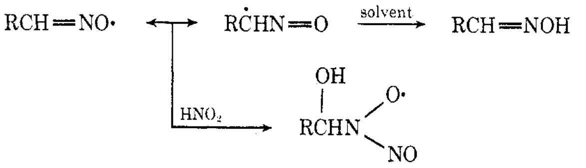
$$H^+ + HNO_2 \rightleftharpoons H_2NO_2^+$$
$$H_2NO_2^+ \rightleftharpoons H_2O + NO^+$$

rapid rate. On the other hand, when there is no excess mineral acid present, it is nitrous acid, HNO_2, which is reacting as an oxidizing agent.

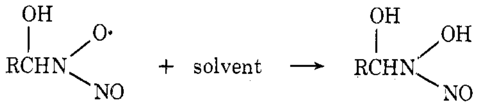
Other oxidizing agents that have been reported to react with oximes are ceric ion,[7] palladium(IV) acetate,[8] lead tetraacetate,[8] and NO_2.[8] The proposed intermediate product of these reactions is the iminoxyl radical, RCH=NO·. We similarly propose that, in the absence of mineral acid, nitrous acid reacts with butyraldoxime to give the iminoxyl radical, NO, and water.[9]

$$RCH{=}NOH + HNO_2 \longrightarrow RCH{=}NO\cdot + NO + H_2O$$

In compliance with our observations, the NO thus produced will come only from the nitrous acid. The iminoxyl radical thus produced can now react in one of two ways. It can abstract a hydrogen from the solvent to give back the starting oxime, or it can react with more nitrous acid in an addition across the double bond to give another radical.

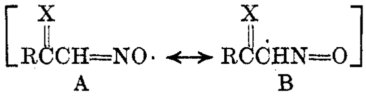


This new radical can abstract a hydrogen from the solvent to give the precursor already postulated to give the aldehyde and N_2O.

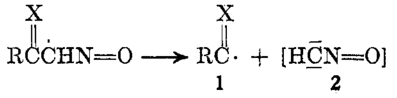


The remaining N_2O and N_2 would be derived from a scheme similar to those proposed above for the reactions carried out in strong acid.

The major difference between the foregoing butyraldoxime reaction with nitrous acid and the reaction of phenylglyoxaldoxime or glyoxime seems to lie in the degree to which either the free radical (iminoxyl) or ionic (nitrosonium ion) enters reaction. In the case of the iminoxyl route, the intermediate would be



The above resonance hybrid could react with nitrous acid either as A or B. If it reacts as A, the reaction would follow the same course as previously described. On the other hand, B would be highly prone to acyl cleavage and might therefore react as follows.



Further oxidation and hydrolysis of **1** or **2** would give the observed cleavage products, formic acid and benzoic acid. The glyoxylic acids observed are most probably derived *via* oxidation of the parent aldehydes.

Registry No.—Nitrous acid, 7782-77-6; butyraldoxime, 110-69-0; phenylglyoxaldoxime, 522-34-9; glyoxime, 557-30-2.

Acknowledgment.—We should like to thank Dr. M. P. Doyle for his help in formulating some of the mechanisms described herein.

A Simple High Yield Synthesis of Methanol-^{18}O and Ethanol-^{18}O[1]

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In the course of studies of kinetic oxygen isotope effects, we developed a simple high yield method for the synthesis of methanol-^{18}O and ethanol-^{18}O with negligible dilution of the label from starting $H_2{}^{18}O$. To our knowledge, no method affording these alcohols in good yield and not requiring $H_2{}^{18}O$ in large excess has yet appeared in the literature.[2] These isotopically labeled alcohols are available commercially, but a recent quotation[3] shows methanol-^{18}O (80 atom %) at $1170 per gram, and ethanol-^{18}O (80 atom %) at $950 per 0.5 g, or 5.6 and 12.8 times the molar cost of $H_2{}^{18}O$ (80 atom %), respectively.

Methanol-^{18}O was prepared by the hydrolysis of tri-*n*-butyl orthoformate (in excess) by $H_2{}^{18}O$ in the presence of HCl, followed by lithium aluminum hydride

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(7) J. W. Bird and D. G. M. Diaper *Can. J. Chem.* **47**, 145 (1969).

(8) M. M. Frojomovic and G. Just, *Can. J. Chem.*, **46**, 3719 (1968).

(9) A similar bimolecular hydrogen abstraction has been proposed for the oxidation of formic acid by nitrous acid in dilute acidic media: J. V. L. Longstaff and K. Singer, *J. Chem. Soc.*, 2604 (1954).

(1) Supported by NIH Grant No. GM 12278 and NSF Grant No. GB 8529 to J. F. Kirsch, and by PHS Training Grant No. 5 T01 GM 31-12.

(2) For a review, see J. L. Borowitz, A. Raviv, P. Rona, D. Sadeh, D. Samuel, and F. S. Klein, *J. Label. Compounds*, **1**, 259 (1966). The yield reported for their preparation of labeled methanol amounts to 20% based on labeled water consumed. The total amount of water used was 16 times the molar yield of methanol, which had 95% of the ^{18}O excess of the water.

(3) Miles Laboratories, Inc., Research Products Division, Catalog C, Kankakee, Ill.

reduction of the resulting butyl formate-*carbonyl*-^{18}O. Similarly, ethanol-^{18}O was prepared by the acid-catalyzed hydrolysis of 1,1-dipropoxyethane with removal of the acetaldehyde-^{18}O as formed, followed by reduction to the alcohol.[4] Within the experimental error of ±0.2% of the ^{18}O excess, there was no isotopic dilution in the preparations. Overall yields were about 85%.

Experimental Section[5]

Tri-*n*-butyl Orthoformate.[6]—A mixture of 11 ml of redistilled trimethyl orthoformate and 30 ml of 1-butanol was refluxed with 100 mg of *p*-toluenesulfonic acid monohydrate while the theoretical amount of methanol (12 ml, bp 65–67°) was slowly removed by distillation through a Vigreux column. The remaining material was distilled and, after removal of the excess butanol, 20 g was collected, bp 120–124° (15 mm). Only the last 10 g collected was used in the following preparation.

***n*-Butyl Formate-*carbonyl*-^{18}O.**—A mixture of 7.5 ml (28.2 mmol) of tri-*n*-butyl orthoformate, 5 ml of diglyme (distilled at 15 mm from $LiAlH_4$), and 0.5 ml (27.6 mmol) of $H_2{}^{18}O$[7] (1.530 ± 0.001 atom %) was protected from atmospheric moisture as 2.5 ml of anhydrous HCl was introduced from a syringe onto the surface with magnetic stirring. The mixture immediately became homogeneous and was distilled through a small Vigreux column. *n*-Butyl formate-*carbonyl*-^{18}O and 1-butanol were collected over the range bp 107–118° for use in the following step.

Methanol-^{18}O.—A mixture of 40 ml of anhydrous diglyme and 1.6 g (42 mmol) of lithium aluminum hydride in small lumps was gently warmed with magnetic stirring under nitrogen in a 250-ml flask until the lumps disintegrated. The mixture of *n*-butyl formate-*carbonyl*-^{18}O and 1-butanol from above was added slowly with stirring while the reaction mixture was cooled in ice. After 20 min at room temperature, the resulting suspension was again cooled in ice and stirred as 0.8 ml of water was carefully dropped in. Then 5 ml of ethylene glycol was added.[8] Distillation through a small Vigreux column afforded methanol-^{18}O (bp 64.5–65.6°), yield 0.76 g (86% based on starting $H_2{}^{18}O$).

Methyl Formate-*methoxy*-^{18}O.—Methanol-^{18}O was refluxed with eight times the theoretical amount of redistilled 98% formic acid while methyl formate-*methoxy*-^{18}O (bp 31.5–32.5°) was collected. Typical yields were 90%. Mass spectrometry showed 1.531 ± 0.002% ^{18}O in the methoxyl position.

This preparation was repeated starting with 0.100 ml of $H_2{}^{18}O$ (65.1 atom %).[9] The resulting methyl formate (0.240 g, 72%) showed 66 ± 1 atom % label in the methoxyl position.

Acetaldehyde-^{18}O.—To a stirred mixture of 3.1 ml (17.5 mmol) of freshly distilled 1,1-dipropoxyethane[10] and 0.25 ml (12.8 mmol) of water-^{18}O (65.1 atom %) was added 0.8 ml of dry HCl as before. Slow distillation through a Vigreux column afforded acetaldehyde-^{18}O (bp 21–24°), yield 0.60 g (95%). The receiver was cooled to −78°, and the product was kept cold until used.

Ethanol-^{18}O.—A suspension of 0.15 g (3.9 mmol) of lithium aluminum hydride in 10 ml of anhydrous diglyme was prepared as before and stirred under nitrogen at 0° while a solution of 0.56 g (12 mmol) of acetaldehyde-^{18}O in 6 ml of anhydrous diglyme was slowly added. After the cautious addition of 0.6 ml of water, distillation through a Vigreux column afforded 0.53 g of ethanol-water azeotrope (bp 78–79°), yield 90%. Mass spectrometry showed the ethanol to be 65.1 ± 0.1 atom % ^{18}O.

Analysis.—Mass spectra were obtained on a CEC Model 21-614 residual gas analyzer modified for use as a mass spectrometer. Water was assayed by the method of Boyer.[11] Methyl formate and ethanol were assayed by examination of the parent peaks P and P + 2. The presence of a P − 2 fragment for ethanol was compensated for. The position of the label in methyl formate was confirmed by examination of the fragments at m/e 31 and 33.[12] The relative error in determination of isotopic excess was ±0.2% for the low ^{18}O content material.

Registry No.—*n*-Butyl formate-*carbonyl*-^{18}O, 36794-39-5; methanol-^{18}O, 5770-05-8; methyl formate-*methoxy*-^{18}O, 36794-41-9; acetaldehyde-^{18}O, 3752-37-2; ethanol-^{18}O, 36794-43-1.

Acknowledgment.—The author wishes to thank Dr. Jack F. Kirsch for many helpful discussions.

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[4] This method can be generalized to the preparation of many primary and secondary alcohols by use of the appropriate ethylene acetal or ketal.

[5] All temperatures are uncorrected.

[6] Available from Fisher Scientific Co., Pittsburgh, Pa.

[7] Yeda Research and Development Co., Ltd., Rehovoth, Israel.

[8] The use of ethylene glycol to liberate methanol from the alkoxides avoids the problem of separating methanol from large amounts of butanol-water azeotrope (bp 93°).

[9] Bio-Rad Laboratories, Richmond, Calif.

[10] Preparation analogous to that of acetal as described by Adkins and Nissen in "Organic Syntheses," Collect. Vol. I, Wiley, New York, N. Y., 1941, p 1.

[11] P. D. Boyer, D. J. Graves, C. H. Suelter, and M. E. Dempsey, *Anal. Chem.*, **33**, 1906 (1961).

[12] H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, San Francisco, Calif., 1967, pp 174, 175.