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Periodate Oxidation of Hydroxylamine Derivatives. Products, Scope and Application[1,2]

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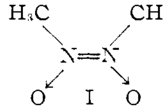
Periodate was found to cleave primary and secondary hydroxamic acids very rapidly to yield a carboxylic acid and an oxidized derivative of hydroxylamine. N-substituted (*i.e.*, secondary) hydroxamic acids and N-methylhydroxylamine gave on periodate oxidation an intensely ultraviolet-absorbing substance. From N-methylhydroxylamine, *cis*-nitrosomethane dimer was isolated in good yield. The effectiveness of hydroxylamine as a carboxyl-blocking reagent was tested by conversion of N-hydroxysuccinamic acid to methyl N-hydroxysuccinamate and subsequent periodate oxidation of the latter to methylhydrogensuccinic acid.

In a communication concerning the structure of the ferrichrome compounds we reported[3] a reaction of periodate with hydroxamic acids. It was concluded that periodate rapidly and quantitatively cleaves these substances to liberate the acyl group as the free acid. In this paper we wish to describe (a) the oxidation product of the hydroxylamine moiety and (b) the use of hydroxylamine as a carboxyl-blocking reagent.

Both N-methylacethydroxamic acid and N-methylhydroxylamine yielded, on periodate oxidation, material with a very strong absorption band at 264 mμ. Since N-methylhydroxylamine is readily available, it was utilized as the starting material for the preparation of the ultraviolet-absorbing compound. The latter, which was obtained as a white, crystalline solid, was shown to be *cis*-nitrosomethane dimer (I).



I

Compound I was characterized by ultraviolet absorption properties, positive diphenylamine–sulfuric acid test, reduction to methylamine and by conversion to the *trans* isomer following simple dissolution in chloroform. Dimer I was prepared for the first time by Gowenlock and Trotman[4] through the pyrolysis of *t*-butyl nitrite, and it has very recently been reported[5] as a minor product in the photolysis of azomethane and nitric oxide. Previous attempts to prepare nitrosoalkane dimers by oxidation of the N-substituted hydroxylamines have failed, presumably because of a rapid tautomerism of the nitroso compounds to the oximes. Possibly the oxidation with periodate succeeds through the formation of an intermediate similar to that which occurs in the oxidation of glycols and which forces the alkyl radicals into the *cis* configuration. The reaction with N-substituted hydroxamic acids may proceed through a similar mechanism, but in this case the product was not isolated and the configuration of the dimer was not established. Although no attempt was made to use as starting material alkyl hydroxylamines other than N-methylhydroxylamine, it appears that the reaction may have general applicability for the synthesis of *cis*-nitrosoalkane dimers. From the latter, the *trans* isomers are obtained very easily.[6] The yield is very good, the starting materials are readily available and the need for special apparatus is eliminated.

The adaptation of the reaction to the structural study of complex hydroxamic acids of natural origin is self evident. After periodate oxidation the acyl part is separated by ether extraction and the hydroxylamine moiety identified after catalytic hydrogenation to the corresponding amine. A search of the literature reveals the existence of several naturally-occurring iron-binding compounds of microbial origin which are very likely hydroxamic acids. The structures of nocardamine[7] and mycobactin[8] already have been determined. We established that the former reacts with periodate to give the characteristic absorption peak. Since grisein,[9] terregens factor[10] and coprogen[11] have ferrichrome-like activity and all bind ferric ion, it appears probable that these, too, are N-substituted hydroxamic acids. Terregens factor, nocardamine and ferrichrome all show a similar reaction with periodate. The other compounds have not been tested. The immediate appearance of the intense ultraviolet absorption band of the nitroso dimer after periodation is a simple and sensitive test for an N-alkyl hydroxylamine or an N-substituted hydroxamic acid.

In order to examine the effectiveness of hydroxylamine as a carboxyl-blocking reagent, succinic anhydride was converted successively to methylhydrogensuccinic acid,[12] N-hydroxysuccinamic acid[13] and methyl N-hydroxysuccinamate. The latter, which was obtained as a clear oil, was oxidized with periodate in the usual way to give methylhydrogensuccinic acid in satisfactory yield.

Under the conditions used for the above synthesis, diazomethane apparently did not react with the hydroxyl of the hydroxamic function to any appreciable extent. Although the experiments reported here do not exclude the possibility of an N-methylation, the latter event would have no impor-

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(1) Abstracted from the doctoral dissertation of Thomas Emery, University of California, Berkeley, 1960.

(2) This research was sustained by a grant from the Office of Naval Research.

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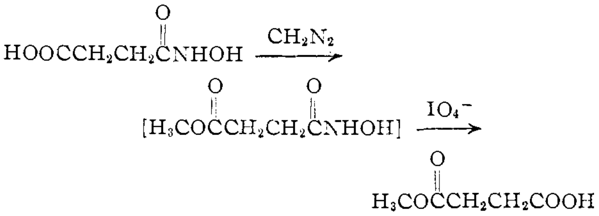

$$HOOCCH_2CH_2\overset{O}{\overset{\|}{C}}NHOH \xrightarrow{CH_2N_2} [H_3CO\overset{O}{\overset{\|}{C}}CH_2CH_2\overset{O}{\overset{\|}{C}}NHOH] \xrightarrow{IO_4^-} H_3CO\overset{O}{\overset{\|}{C}}CH_2CH_2COOH$$

tant bearing on the course of the hydroxamic–periodate reaction. The stability of the hydroxamic function is greatly augmented (even against periodate oxidation[3]) by the addition of ferric ion. In the case of the ferrichrome compounds,[3] the iron was most conveniently set free through reduction and removal with cyanide or a chelating resin.

Experimental[14]

Synthesis of *cis*-Nitrosomethane Dimer (I).—Five grams (0.06 mole) of N-methylhydroxylamine hydrochloride[15] was dissolved in 200 ml. of water. To this was added, with stirring, a solution of 16.0 g. of H_5IO_6 dissolved in 200 ml. of water. The precipitated iodine was filtered off at once and the filtrate extracted several times with chloroform in order to remove the remaining soluble iodine. The solution then was passed through a 2.5 × 40 cm. Dowex AG1-X10, 200–400 mesh, formate column at a flow rate of approximately 4 ml./min. This procedure quantitatively removed both periodate and iodate. After passage through a 1 × 20 cm. column of hydrogen form Dowex 50, 200–400 mesh resin the solution was then frozen and lyophilized overnight. The resulting white, crystalline solid was dried 2 days over P_2O_5 at room temperature and then for 6 hours at 56° *in vacuo*. The yield was 2.2 g. (80%) with m.p. 93.5–95°. In water log ϵ_{max} at 264 mμ was 3.98; in ethanol λ_{max} was at first at 269 mμ and after 36 hours at room temperature 282 mμ. The product gave a blue color with diphenylamine–sulfuric acid.[16] These properties are in good agreement with those reported in the literature.[6]

Reduction of I.—Exactly 30 mg. (333 μmoles) of I was hydrogenated in 12 ml. of glacial acetic acid using about 10 mg. of PtO_2; 3.9 moles of H_2 was consumed per mole dimer. The catalyst was filtered off and the filtrate quantitatively transferred to a 5-ml. volumetric flask and made up to the mark with water. A 1.0-ml. aliquot was analyzed by automatic electrometric titration[17] and found to contain 133 (100% theor.) microequivalents of a volatile amine with a pK_a' of 10.7. The pK_a' found for authentic methylamine under identical conditions was also 10.7.[18]

Synthesis of *trans*-Nitrosomethane Dimer.—Approximately 200 mg. of I was suspended in 15 ml. of redistilled chloroform and the suspension shaken gently overnight. At the end of this period the solution was filtered and the filtrate allowed to slowly evaporate at room temperature. The large, needle-like crystals were recrystallized from ethanol and air-dried. The m.p. was 120–121° (lit.,[6] 122°) and the diphenylamine–sulfuric acid test[16] was positive. The ultraviolet absorption properties were essentially identical with those reported by Gowenlock and Trotman.[6]

Anal. Calcd. for $C_2H_6N_2O_2$: C, 26.66; H, 6.66; N, 31.11. Found: C, 26.82; H, 6.81; N, 30.96.

Synthesis and Periodate Oxidation of Methyl N-Hydroxysuccinamate.—Methylhydrogensuccinic acid was converted to the monohydroxamic acid through the procedure of Blatt[19] and the use of an additional equivalent of KOH. The product titrated electrometrically[17] as a divalent acid with pK_{a1}' of 4.5 and pK_{a2}' of 9.7; neut. equiv. (to pH 6.5) 132 (theor. 133). The prisms melted at 105° (lit.[13] 105–106°).

A solution was prepared containing 1.33 g. (0.01 mole) of N-hydroxysuccinamic acid in 10 ml. of dry methanol. An ethereal solution of diazomethane was added dropwise with constant shaking until a faint yellow color persisted for a few seconds. Electrometric titration of a small aliquot of the solution showed that the carboxyl group had been eliminated completely. The solvent was removed to yield a clear, colorless, neutral oil. The intensity of the ferric ion reaction was approximately 80% of that of acethydroxamic acid, on a molar basis, at 500 mμ in the presence of excess ferric chloride at pH 2.5. The oil was taken up in 10 ml. of water and aqueous 10% periodic acid added until no more iodine precipitated upon further addition. The iodine was filtered off and the solution adjusted to pH 6.5 with 2 *N* NaOH. The bulk of the dissolved iodine then was extracted with chloroform.

The solution was adjusted to pH 3 by addition of dilute HCl and then filtered to remove some additional precipitated iodine. The filtrate was evaporated to dryness, the half-ester extracted from the salt with benzene and recrystallized from benzene–cyclohexane. The neutral equivalent was 132; after 1 hour at room temperature with a slight excess of KOH, 66. The yield of methylhydrogensuccinic acid was 900 mg. (68%), m.p. 58°, not depressed by admixture with an authentic specimen.

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[14] Melting points uncorrected. Microanalyses by Chemistry Department, University of California, Berkeley. Ultraviolet spectra were measured with the Process and Instruments spectrophotometer.

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[18] Under similar conditions, M. S. Kharasch, T. H. Meltzer and W. Nudenberg, *J. Org. Chem.*, **22**, 37 (1957), reported quantitative reduction of *trans*-nitrosomethane dimer to methylamine.

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