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Oxidation with Nickel Peroxide. VI.[1] Oxidation of N-Substituted Hydroxylamine Derivatives with Nickel Peroxide

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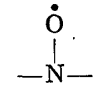
Recently the oxidation with nickel peroxide upon various organic compounds has been studied in our laboratory.

The reaction mechanisms of the nickel peroxide oxidation are in keeping with the assumption that the surface of nickel peroxide acts as a source of hydroxyl radical in an aprotic solvent and abstracts a hydrogen radical from the organic compounds at the favorable position.

De La Mare and Coppinger reported[3] that in the course of oxidation of N,N-dialkyl hydroxylamine with *t*-butyl hydroperoxide there was an intermediate free radical to be defined as follows.



Taylor and Yoneda[4] showed in a short article that diethyl azodicarboxylate was an effective hydrogen-abstracting reagent for the oxidation of hydroxylamines to nitroso compounds.

These experiments suggested that nickel peroxide might play a similar role in the oxidation of hydroxylamine derivatives.

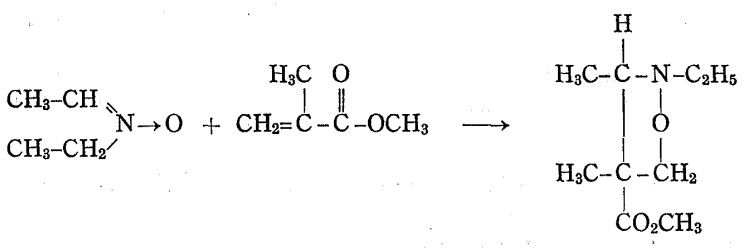
This report describes the products formed by nickel peroxide oxidation of N-substituted hydroxylamines in an aprotic solvent. Phenylhydroxylamines were converted to nitroso compounds by a variety of oxidizing agents, including ferric chloride, chromic acid, perjodate, diethyl azodicarboxylate, *etc.*

However, in the case of nickel peroxide, the nitroso compound which was produced on the surface of the oxidant condensed with hydroxylamine not yet oxidized forming predominantly azoxy compounds. This reaction produced good yields with aromatic hydroxylamines, but was less satisfactory with aliphatic hydroxylamines.

For example, azoxybenzene (89.6%), 4,4′-dimethylazoxybenzene (91.9%), 4,4′-dichloroazoxybenzene (97.3%) and azoxynaphthalene (37.0%) were obtained from the corresponding hydroxylamines in an ether solution at 0°.

Oxidation of N-benzylhydroxylamine gave a poor yield of azoxy compound and α-nitrosotoluene in about 35%.

On the other hand, N,N-dibenzylhydroxylamine was oxidized by nickel peroxide resulting in excellent yield of the corresponding nitron.



1) Part V: K. Nakagawa and H. Onoue, *Tetrahedron Letters*, **1965**, 1433.
2) Location: *Fukushima-ku, Osaka.*
3) H.E. De La Mare and G.M. Coppinger, *J. Org. Chem.*, **28**, 1068 (1963).
4) E.C. Taylor and F. Yoneda, *Chem. Commun.*, **1967**, 199.

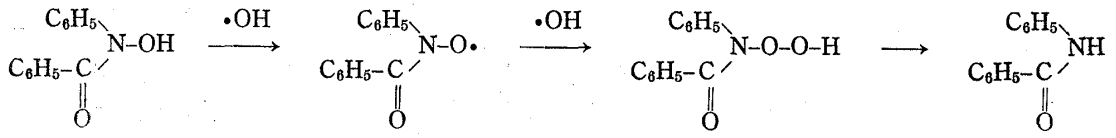
In the case of N,N-diethylhydroxylamine however, the nitron could not be isolated as such but was trapped *in situ* to produce the isoxazolidine by adding methyl methacrylate as shown in the oxidation with *t*-butyl hydroperoxide.[3]

It has previously been known that simple hydroxamic acids gave the corresponding carboxylic acid and nitrogen or nitrous oxide when treated with various oxidizing agents or heated in air,[5-7] and N-substituted hydroxamic acids were oxidized to oxime derivatives or to dimeric nitroso compounds by such reagents as mercuric oxide of periodate.[8,9]

The action of nickel peroxide on benzhydroxamic acid gave N,O-dibenzoylhydroxylamine as the main product, with additional small amounts of benzoic acid under evolution of nitrous oxide. The product, N,O-dibenzoylhydroxylamine, was also obtained by T.F. Emery[10] from potassium benzohydroxamate on periodate oxidation, but the yield was not satisfactory.

H.G. Aurich and F. Baer[11] observed from the oxidation of N-benzoyl-N-phenylhydroxylamine in benzene with nickel peroxide the stable intermediate free radical formed by the abstraction of the hydrogen radical from the hydroxyl group, but the products were not isolated from the reaction mixture.

We carried out this reaction in an ether solution at 20° and obtained benzanilide as a main product with additional small amounts of N,O-dibenzoyl-N-phenylhydroxylamine. The mechanism of the reaction may be envisaged as follows



Experimental

Nickel Peroxide——Nickel peroxide was prepared from nickel sulfate and its available oxygen content was determined by the jodometry as reported in the previous paper.[12] Its quantity used in stoichiometric oxidation was calculated on the basis of the available oxygen content.

Oxidation of β-Phenylhydroxylamine——To a solution of 3.9 g of β-phenylhydroxylamine in 100 ml of ether, 5.5 g of nickel peroxide (1.1 times as much as the theoretical amount) was added under stirring in an ice bath and the heterogeneous mixture was stirred for 1.5 hr at 0°. The reaction mixture was filtered through a glass filter, washed repeatedly with ether, and the combined filtrates were evaporated to remove the solvent. The residue was treated by steam distillation to remove a small amount of nitrosobenzene and chromatographed on alumina to give 3.18 g (89.6%) of pure azoxybenzene.

Oxidation of N-Benzylhydroxylamine——To a solution of 3.69 g of N-benzylhydroxylamine in 100 ml of ether, 9.30 g of nickel peroxide was added under stirring at 0°. The reaction mixture was stirred for one hour at 0° and filtered. The filtrate was concentrated and distilled to give 1.18 g of α-nitrosotoluene, bp 70—75° (1 mmHg) and from the residue a trace of azoxy compound was obtained.

Oxidation of N,N-Diethylhydroxylamine——To a solution of 5.8 g of N,N-diethylhydroxylamine in 200 ml of benzene, 22 g of nickel peroxide was added under stirring at 10° and anhydrous magnesium sulfate (about 3 g) was added directly to the reaction mixture. The heterogeneous mixture was allowed to react for one hr at 10°. The reaction mixture was filtered through a glass filter, washed with benzene, and 15.3 g of methyl methacrylate was added to the combined filtrate. The mixture was heated at 60° for 20 hr and concentrated by distillation. The concentrate was fractionated and yielded 6.71 g (55.1%) of isoxazolidine, bp 97—101° (25 mmHg). *Anal.* Calcd. for $C_9H_{17}O_3N$: C, 57.73; H, 9.15; N, 7.48. Found: C, 57.56; H, 9.21; N, 7.30.

Oxidation of Benzhydroxamic Acid——To a solution of 2.05 g of benzhydroxamic acid in 150 ml of acetonitrile, 4.73 g of nickel peroxide was added under stirring in an ice bath and the mixture was stirred

5) F. Klages, R. Heinle, H. Sitz, and E. Specht, *Chem. Ber.*, **96**, 2387 (1963).
6) M. Schenck, *Chem. Ber.*, **77**, 29 (1944).
7) I. De Paolini, *Gazz. Chim. Ital.*, **56**, 757 (1926).
8) T. Emery and J.B. Neilands, *J. Am. Chem. Soc.*, **82**, 4903 (1960).
9) O. Exner, *Collection Czech. Chem. Commun.*, **21**, 1500 (1956).
10) T. Emery and J.B. Neilands, *J. Org. Chem.*, **27**, 1075 (1962).
11) H.G. Aurich and F. Baer, *Tetrahedron Letters*, **1965**, 3879.
12) K. Nakagawa, R. Konaka, and T. Nakata, *J. Org. Chem.*, **27**, 1597 (1962).

for 3 hr at 5°. The reaction mixture was filtered, washed repeatedly with acetonitrile and the combined filtrates were evaporated to give a crude product. Recrystallization from chloroform gave 1.04 g (57.5%) of pure N,O-dibenzoylhydroxylamine, mp 160—161°. A small amount of benzoic acid was obtained from the oxidant by dissolving in hydrochloric acid.

Oxidation of N-Benzoyl-N-Phenylhydroxylamine——To a solution of 6.39 g of N-benzoyl-N-phenylhydroxylamine in 400 ml of ether, 21.1 g of nickel peroxide was added at 10°. The mixture was stirred for about 5 hr at 10° until the unreacted material could not be detected by TLC. The reaction mixture was filtered and washed with ether and benzene, and the combined filtrates were evaporated to remove the solvent. The residue was recrystallized from benzene to give 1.73 g (29.2%) of benzanilide, mp 160—160.5°.

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Effect of Combination of Pharmaceuticals on Gastrointestinal Absorption. II.[1] Combination of Caffeine with Non-absorbable Drugs

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In previous paper[1] it has been shown that the gastric absorption rates on the relatively absorbable drugs were remarkably depressed by simultaneous administration with caffeine, and there was a proportional relationship between the apparent absorption rate constants for drugs and existing ratio of caffeine complexes in administered solution. The effect of caffeine on drug absorption was remarkable for more absorbable drugs but was so little for poorly absorbable drugs. And it was also conceivable that the apparent absorption rate constants for drugs approached to intermediate values between those of free drugs and caffeine with increasing of caffeine.

Accordingly, as the further extension of the previous study[1] summarized above, it is followed that caffeine may act as a means of enhancing the gastric absorption for non-absorbable drugs which have the complexing tendency to caffeine. Since the gastric absorption rate usually increases with increasing lipid solubility, it is of interest to investigate the possibility of enhancing the absorption of certain drugs by formation of drug complexes which are more lipid-soluble than the drug itself.

The purpose of the present investigation is to explore the effect of caffeine on gastric absorption of non-absorbable drugs, sulfathiazole[3] (ST) and *p*-aminobenzoic acid[3] (PABA).

Experimental

Materials——Caffeine and PABA were recrystallized from distilled water. ST was recrystallized from ethanol. A diluted hydrochloric acid (0.1N) was used as the solvent for materials, and phenol red or ST was dissolved in the administered solution as the volume change indicator.

Analytical Procedures——Sulfathiazole: To 10 ml of sample solution added 0.5 ml of 0.1% sodium nitrite solution. After 3 minutes' shaking, 0.5 ml of 0.4% ammonium sulfamate was added to the sample

1) Part I: S. Goto, R. Takamatsu, M. Shibao, and S. Iguchi, *Chem. Pharm. Bull.* (Tokyo), **16**, 332 (1968).
2) Location: *Katakasu, Fukuoka.*
3) The result of our experiments using rabbit stomach showed that the gastric absorption of these compounds were almost zero at pH 1.0.