

Conformationally and Configurationally Stabilized Benzaldoxime

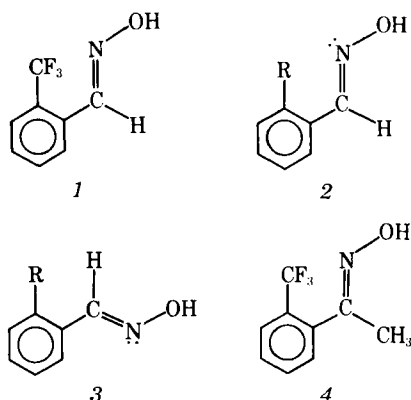
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Abstract □ The unusual behavior of *syn-o*-trifluoromethylbenzaldoxime is noted. The data collected are consistent with the interpretation that an interaction occurs between the electron pair on the oxime nitrogen and the *o*-trifluoromethyl group.

Keyphrases □ Benzaldoxime—synthesis □ *syn-o*-Trifluoromethylbenzaldoxime—conformation, configuration stability □ NMR spectroscopy—structure □ UV spectrophotometry—structure

In the synthesis of various trifluoromethylbenzaldoximes as potential muscle relaxants, the unusual behavior of *syn-o*-trifluoromethylbenzaldoxime (*1*) was observed (1). It is the purpose of this report to establish and explain the cause of this behavior.

Benzaldoximes can exist as two isomers (*syn* and *anti*) and will react with hydrogen chloride gas in diethyl ether to form hydrochloride salts. This reactivity is also true of *o*-substituted benzaldoximes (e.g., *o*-CH₃, *o*-NO₂, *o*-Cl, and *o*-F). Although hydrochloride salt formation could be precluded by the sterically unfavorable, in-plane conformer 2, these oximes may rotate about the carbon-carbon single bond to the more sterically favorable, in-plane conformer 3 and then react.



Conformer *1* is an exception, because it exists only in the *syn* configuration and will not react with hydrogen chloride (in diethyl ether or in refluxing aqueous ethanol). This unusual stability is attributed to an interaction between the electron pair of the oxime nitrogen and the *o*-trifluoromethyl group. Precedence for such an interaction comes from many sources. The inductive effects of fluorine are well known (2). Streitwieser has shown that inductive field effects, rather than hyperconjugative effects operate in fluoroalkyl anions (3).

The NMR data (Table I) are consistent with the *syn* assignment for *1*. The H_c protons (in tetrahydrofuran) of *syn-o*-chloro- and *syn-o*-nitrobenzaldoximes were reported at 1.5 and 1.43 τ , respectively (4).

The *anti*-isomers of each had the H_c at 2.37 τ . In *1* the quartet observed for the R_b proton ($J = 2$ c.p.s.) re-

sults from long-range coupling (F¹⁹ - H¹) via conformer 2 (5). Long-range coupling of an aldehydic proton through five bonds has been observed in benzene and heterocyclic derivatives (6).

In order to test whether the electron pair on nitrogen of *1* were truly unavailable, the preparation of oxime ethers was undertaken. Buchler reported that during the synthesis of the *O*-methyl ether of benzaldoxime, a small amount of the *N*-methyl product (nitron) was formed (7).

The *syn-o*-methyl- and *syn-p*-trifluoromethylbenzaldoximes reacted in the manner described by Buchler. These results show that the former compound can rotate to 3 if 2 hinders nitron formation. In the case of the latter, a trifluoromethyl group in the molecule, but distant from the oxime, does not affect the reaction. With *1*, no traces of nitron could be isolated or detected, a situation consistent with an interaction between the electron pair of nitrogen and the *o*-trifluoromethyl group.

In search of other oximes which might exhibit the same reactivity as *1*, *o*-trifluoromethylacetophenone oxime (4) was considered a likely possibility. However, it is known that acetophenone is not completely analogous to benzaldehyde, since the former has only one oxime isomer (8).

Compound 4 was found to exist as a single isomer which formed a hydrochloride salt. The single oxime isomer was expected, but the salt formation would appear to contradict the interaction proposed in this paper. The UV data for *1* and 4 showed this not to be the case: 4 ($\lambda_{\max.} = 263$, ϵ 1,482, and 270 $m\mu$, ϵ 1,400, ethanol) is consistent with an out-of-plane conformation. *1* ($\lambda_{\max.} = 250$ $m\mu$, ϵ 13,800, ethanol) compares favorably with acetophenone

Table I—NMR Data of Various Oximes^a

Oxime Configuration	R _a	R _b	1 ^b	2 ^c	H _c	
					1 ^b	2 ^c
<i>syn</i>	<i>p</i> -CF ₃	H	1.82	1.84	1.04	-1.56
<i>syn</i> ^e	<i>o</i> -CF ₃	H ^d	1.46	1.44	0.58	-2.04
<i>syn</i>	<i>o</i> -CH ₃	H	1.56	1.60	0.38	—
<i>syn</i>	<i>o</i> -Cl	H	1.40	—	0.84	—
<i>anti</i> HCl	<i>o</i> -Cl	H	—	1.70	—	-1.60
<i>syn</i>	<i>o</i> -NO ₂	H	1.66	—	1.50	—
<i>anti</i> HCl	<i>o</i> -NO ₂	H	—	1.70	—	-0.22
<i>syn</i>	<i>o</i> -F	H	1.60	—	0.74	—
<i>anti</i> HCl	<i>o</i> -F	H	—	1.74	—	0.64
<i>syn</i>	<i>o</i> -CF ₃	CH ₃	7.80	—	1.85	—

^a Spectra were run (Varian A60a) with TMS as the internal standard. ^b Solvent: CDCl₃. ^c Solvent: *d*₆-DMSO. ^d A quartet ($J = 2$ c.p.s.), all other peaks in this table are singlets. ^e The F¹⁹ spectra were run (Varian HA 100) at temperatures from 20 to -70° with trifluoroacetic acid as the external standard, a singlet 8.0 p.p.m. upfield from the standard was observed.

oxime ($\lambda_{\text{max.}} = 245 \text{ m}\mu$, $\log \epsilon = 4.02$) which indicates an in-plane conformation (9).

The reason for the different conformations for 1 and 4 is not apparent. The stability of 1 appears to be a unique property associated with the *o*-trifluoromethyl group and the aldoxime function.

EXPERIMENTAL

Nitrone Formation—The procedure of Buchler for the synthesis and isolation of nitrones and *o*-methyl benzaldoxime ethers was used (7).

***o*-Trifluoromethylacetophenone oxime (4)**—Compound 4 was prepared by Bachmann's procedure using hydroxylamine hydrochloride in pyridine and absolute ethanol (10). Yield 75%, m.p. 118–120°.

Anal.—Calcd. for $\text{C}_9\text{H}_8\text{F}_3\text{NO}$: C, 53.20; H, 3.94; N 6.90. Found: C, 53.44; H, 4.08; N, 6.85.

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Kinetics of the Reaction of 1,3-Dihydro-1-hydroxy-3-oxo-1,2-benziodoxole with Cysteine

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Abstract □ The kinetics of the oxidation of cysteine by 1,3-dihydro-1-hydroxy-3-oxo-1,2-benziodoxole were studied in buffered solutions at pH 6.8, 7.2, 7.6, and 8.0 by means of a rapid stop flow system. The second-order rate constants obtained were 50 moles/l. sec., 150 moles/l. sec., 835 moles/l. sec., and 1175 moles/l. sec., respectively. One or more reactive intermediates are postulated and their possible structure and the mechanisms involved are discussed, involving the intermediate formation of an (unstable) iodine-sulfur bond.

Keyphrases □ Cysteine oxidation—kinetics □ 1,3-Dihydro-1-hydroxy-3-oxo-1,2-benziodoxole—cysteine oxidation □ UV spectrophotometry—analysis

"*o*-Iodosobenzoic acid" has been used for some time as a reagent for mercapto groups, and the reaction that occurs has a stoichiometry of 1 mole of oxidizing agent to 2 moles of the thiol (1). Since it has been proven that "*o*-iodosobenzoic acid" has a cyclic structure, namely, 1,3-dihydro-1-hydroxy-3-oxo-2-benziodoxole (I) (2), it was of interest to investigate the kinetics of this reaction, to determine if this reaction occurred as a three-center process involving 2 moles of cysteine and one of benziodoxole; or as a two-center reaction, involving 1 mole of benziodoxole and 1 mole of cysteine, to give

in a first, rate-determining step, a reactive species. It had been noted before that the mechanism of oxidation of thiols depends upon the nature of the oxidant, and that the rate-determining step is the oxidation of the thiol to a reactive intermediate (3). The kinetics of this reaction have been studied by using potassium ferricyanide (3), potassium persulfate (4), hydrogen peroxide (5), and sodium 2,6-dichlorobenzophenone indophenol (6). Therefore a study to determine the kinetics of the oxidation of cysteine with 1,3-dihydro-1-hydroxy-3-oxo-1,2-benziodoxole was undertaken, in the pH range 6.8–8.0, in order to compare the action of 1,3-dihydro-1-hydroxy-3-oxo-1,2-benziodoxole, a radiomimetic agent, with that of the above-mentioned, more conventional oxidizing agents.

EXPERIMENTAL

A mixing chamber, built by Nieman¹ was utilized. First, however, it had to be modified because of the easy formation of air bubbles in this type of manual-injection system. The authors, therefore, designed a simplified version (Fig. 1) consisting of a

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