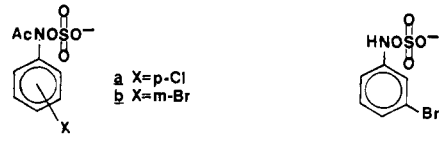
The second reduction pathway for **25** may not be very important in the presence of sufficient Fe^{2+}. A 5-fold molar excess of thiophenol has a barely discernable effect on the yield of **2a** observed during the reduction of **1a** in 10^{-3} M Fe^{2+} at pH 4.7, increasing the yield from 39.7 ± 2.2% to 42.6 ± 1.9%. This is not unexpected since both neutral and cationic arylamino radicals are relatively poor $H^{\bullet}$ abstracting agents.[33]

N-Acylated materials similar to **1a–d** are not subject to rapid reduction by Fe^{2+}. *N*-(Sulfonatooxy)-4-chloroacetanilide (**26a**) yields only 4.4% of the reduction product 4-chloroacetanilide in 0.25 M $FeCl_2$ at pH 4.6.[2a] *N*-(Pivaloyloxy)-3-bromoacetanilide (**4b**) undergoes little reduction (ca. 2–4%) over a period of 48 h in 10^{-3} M Fe^{2+} at pH 4.7. Neither of these materials undergoes rapid decomposition under these conditions, so competition between Fe^{2+}-mediated reduction and other processes cannot explain their lack of reduction. It is likely that these species do not chelate Fe^{2+} well since the electron pair on N will not be as readily available as in **1**. Surprisingly *N*-(3-bromophenyl)hydroxylamine-*o*-sulfonate (**27b**), which is generated during the hydrolysis of *N*-



26 **27b**

(sulfonatooxy)-3-bromoacetanilide (**26b**) in 0.1 M HCl,[3] is also relatively inert to reduction by Fe^{2+}. At 80 °C in 10^{-3} M Fe^{2+} at pH 1.0, the decomposition of **26b** yields only 4.8 ± 0.8% of **2b**. We have previously shown that >90% of **26b** is converted into **27b** at this pH and temperature.[3] At 40 °C similar yields of **2b** were obtained. In the absence of Fe^{2+} no reduction product is observed.[3] The low yield of **2b** may be due to competition between reduction and unassisted N–O bond heterolysis since **27b** decomposes in aqueous solution about 10^3-fold more rapidly than **1b**. Electron transfer from Fe^{2+} to the anionic sulfate ester may also be more difficult than to the neutral pivalic acid ester. We are continuing our studies on the reduction reactions of **1a–d** with other transition metal ions to test the generality of the reaction.

Our results indicate that the potentially carcinogenic polycyclic analogues[1] of **1a–d** will decompose in aqueous media via heterolysis of the N–O bond to produce nitrenium ion intermediates in the absence of reducing agents. As a result of investigations on a number of related systems including sulfuric, sulfonic, and carboxylic acid esters of *N*-hydroxyacetanilides and *N*-chloroaniline derivatives,[2–4,14,15] it is clear that the predominant mode of reaction of these species is heterolytic formation of *N*-arylnitrenium ions. These electrophilic species remain the most likely candidates for reactions with DNA that lead to cancer. However, we have discovered different modes of reaction, including the Fe^{2+}-mediated reductions demonstrated here, that lead to other reactive species including radicals[6] and quinone imines.[2a,b] Whether these species play a role in the carcinogenic properties of metabolites of aromatic amines and amides is not currently known, but this possibility cannot be dismissed. We have previously pointed out that not all adducts from in vivo and in vitro experiments are easily explainable in terms of the properties of *N*-arylnitrenium ions.[2a]

Acknowledgment. We are grateful for grant support provided by the American Cancer Society (BC-348).

Supplementary Material Available: Synthesis, isolation, and characterization of the hydrolysis products **3c**, **5a–d**, **6b**, **6c**, **9a** (4 pages). Ordering information is given on any current masthead page.

(32) A referee has suggested that metal ion catalyzed dismutation of **25** may lead to reduced (anilines) and oxidized products (azo and azoxy products). However, no such oxidation products were detected in the presence of Fe^{2+} in the two cases (**1a**, **1d**) in which such products were sought.

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Oxidation of *O*-Alkylhydroxylamines with Bis[[(*m*-(trifluoromethyl)phenyl]sulfonyl] Peroxide

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Received March 31, 1988

A series of *O*-alkylhydroxylamines was oxidized with [*m*-(trifluoromethyl)phenyl]sulfonyl peroxide to give the corresponding alcohol and carbonyl compound. The evidence presented suggests that these products of N–O cleavage arise from decomposition of a hyponitrite ester intermediate produced by nucleophilic trapping of an *N*-alkoxy nitrenium ion.

In attempts to prepare electrophilic aminating agents, we examined the oxidations of O-substituted hydroxylamines, **1**, with [*m*-(trifluoromethyl)phenyl]sulfonyl peroxide (**2**, *m*-TFBSP). We hoped by this method to access O-substituted *N*-(arylsulfonoxyl)hydroxylamines, **3**, that might be useful as aminating agents toward π-electron donors (eq 1). Early results suggested that the intermediate arylsulfonoxylamines, **3**, were quite reactive. We thus undertook an investigation of the oxidation to learn more of their chemistry.

$$\underset{\mathbf{1}}{2RONH_2} + \underset{\mathbf{2}}{(3\text{-}CF_3C_6H_4SO_2O)_2} \rightarrow \underset{\mathbf{3}}{RONHOSO_2C_6H_4CF_3} + \underset{\mathbf{4}}{RONH_3^+ArSO_3^-} \quad (1)$$

Results and Discussion

O-Benzylhydroxylamine, **1a**, was chosen as a typical *O*-alkylhydroxylamine. Oxidation with **2** in methylene chloride at −30 °C gave benzyl alcohol, **5**, and *O*-benzylbenzaldoxime, **6**, as the major products in addition to the

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Table I. Products from the Oxidation of O-Substituted Hydroxylamines with *m*-TFBSP in Dichloromethane at −30 °C

hydroxylamine $R_1R_2CHONH_2$	equiv[a]	alcohol, %[b] R_1R_2CHOH	carbonyl prod, %[b,c] $R_1R_2C{=}O$	salt 4, %
1a: R_1 = H; R_2 = C_6H_5	2.1	16	17	53
	2.5	27	16	66
	3.0	35	17	85
	3.5	43	18	87
	4.0	27	21	80
1b: R_1 = H; R_2 = n-C_5H_{11}	3.0	90	7	
1c: R_1, R_2 = $-(CH_2)_5-$	3.0	94	6	
1d: R_1R_2CH = t-Bu	3.0	76		
1e: R_1 = R^2 = C_6H_5	3.0	42[d]	30[e]	

[a] Moles of hydroxylamine per mole of *m*-TFBSP. [b] Yields were determined by gas chromatography of the crude products using an internal standard. Reported yields were the average of two or more experiments and have a variance of +3%. The yields are based on the moles of peroxide according to the stoichiometry of Scheme III, which gives 0.5 mol of hyponitrite ester per mole of peroxide. Thus the maximum yield of alcohol, or carbonyl, or their sum is 1 mol. [c] The carbonyl product is the O-substituted oxime derivative of the initially formed aldehyde or ketone. [d] This yield is the sum of benzhydrol and bis(benzhydryl ether). [e] This is the yield of benzophenone, which was not converted to the oxime under the reaction conditions.

hydroxylammonium trifluoromethylbenzenesulfonate salt byproduct, **4** (eq 2). These products result from cleavage of the N–O bond in the reactant. Precedent established in the oxidation of **1a** by lead tetraacetate[1-4] suggested that a hyponitrous ester could be an intermediate product in the oxidation.

$$\underset{\mathbf{1a}}{C_6H_5CH_2ONH_2} + 2 \rightarrow \underset{\mathbf{5}}{C_6H_5CH_2OH} + \underset{\mathbf{6}}{C_6H_5CH{=}NOCH_2C_6H_5} + \underset{\mathbf{4}}{C_6H_5CH_2ONH_3^+ArSO_3^-} \quad (2)$$

Several observations were made that substantiate this hypothesis. The stoichiometry of the reaction was determined by measuring the product yields as a function of reactant ratios. Maximum yields were obtained at 3:1 molar ratio of **1a** to **2** (Table I). If 2.1 equiv of **1a** was used, then 24% of *m*-TFBSP remained in solution, and if 3.5 equiv of **1a** was used, then excess **1a** could be detected in the reaction mixture. A balanced reaction involving a hyponitrous ester intermediate requires a 3:1 stoichiometry, as is observed.

Control reactions showed that benzaldehyde rapidly reacts with salt **4** under the reaction conditions to give *O*-benzylbenzaldoxime, **6**, thus accounting for its production. On the other hand, neither benzaldoxime nor α-nitrosotoluene dimer, other possible products of oxidation, gave **6** under these conditions, and thus they should have been observed if they had been produced. Therefore the primary products of the oxidation are benzyl alcohol and benzaldehyde. These are well-known products of decomposition of benzyl hyponitrite.[1] Thermolysis gives benzyloxy radicals, which can either disproportionate to give **5** and benzaldehyde or which can abstract hydrogen from solvent to give only **5**.

Other O-substituted hydroxylamines, **1b–e**, behaved similarly. The major product was the corresponding alcohol. Lesser amounts of the carbonyl product, as its O-substituted oxime, were also observed (Table I). *O*-Benzhydrylhydroxylamine, **1e**, is an exception in that benzophenone, which is not converted to the oxime derivative under the reaction conditions, was present in the products (30%). Evidently escape from the solvent cage by alkoxy radicals is faster than their cage disproportionation in most cases.

The ratio of benzyl alcohol to benzaldehyde from **1a** is similar to that found in the lead tetraacetate/dichloromethane oxidation of *O*-benzylhydroxylamine, 31% and 18%, respectively, where hyponitrite esters are also presumed intermediates.[1] The ratio of alcohol to carbonyl products for **1b–e** changes markedly as the *O*-alkyl substituent is changed, in contrast to literature reports that the thermal decomposition of *O*-alkyl hyponitrites give very little variation of this ratio for different *O*-alkyl substituents.[5]

The difference may lie in the reaction conditions. The thermolysis data are for purified hyponitrite esters in hydrocarbon solvents, whereas the present data were obtained for hyponitrite esters decomposing in an acidic and complex reaction mixture. Walling reported that the partitioning between hydrogen abstraction and disporportionation is very solvent dependent for hyponitrite decompositions,[6] and Carey found that product mixtures in the lead tetraacetate oxidation of *O*-benzylhydroxylamine were very dependent on the solvent.[4] Thus it is likely that the reaction environment plays an important, but unknown, role in determining the ultimate products from the hyponitrite ester.

On several occasions reaction mixtures of **1a** were examined by ^1H NMR, but in no case was the hyponitrite ester observed, even though the half-life of the purified compound in hydrocarbon solvents is ~2.5 h at 35 °C.[2] Likewise hyponitrite esters have not been observed in lead tetraacetate oxidations of hydroxylamines.[1,4] The products strongly suggest their intermediacy; however, the reaction medium may also play a role in the rate of their decomposition.

If the reaction between hydroxylamines and *m*-TFBSP is analogous to the reactions of simple amines and *m*-TFBSP,[7] then *N*-[[(trifluoromethyl)phenyl]sulfonoxyl]-*N*-alkoxyamines, **3**, are first-formed intermediates. The present data do not exclude the possibility of an electron-transfer reaction between the hydroxylamine and the peroxide, but the products and stoichiometry are consistent with the formation of *N*-(sulfonyloxy)hydroxylamines by nucleophilic attack on the O–O bond.

The production of hyponitrous esters requires that a nitrogen–nitrogen bond be formed during the course of the oxidation. Several reactions of **3** can be envisioned, which lead to N–N bond formation, and thence products. Reaction of **3** with the starting hydroxylamine could yield a 1,2-dialkoxy hydrazine, **7**, which could be further oxidized to the hyponitrous ester (Scheme I). Alternatively **3** could undergo ionization to yield an alkoxy-stabilized nitrenium ion, **8**. Capture of **8** by **3** followed by elimination could give the hyponitrous ester (Scheme II). Finally capture of **8** by starting hydroxylamine could also yield **7**, which could give the hyponitrous ester upon further oxidation

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Scheme I

$$\mathbf{1a} + 2 \xrightarrow{k_1} 3 + 4$$

$$3 + \mathbf{1a} \xrightarrow{k_2} \underset{\mathbf{7}}{RONH{-}{-}NHOR}$$

$$7 + 2 \xrightarrow{fast} RON{=}{=}NOR$$

Scheme II

$$\mathbf{1a} + 2 \xrightarrow{k_1} 3 + 4$$

$$3 \xrightarrow{k_2} \underset{\mathbf{8}}{RO^+{=}{=}NH}$$

$$8 + 3 \xrightarrow{k_3} RONHN(OSO_2Ar)OR$$

$$RONHN(OSO_2Ar)OR \xrightarrow{fast} RON{=}{=}NOR$$

Scheme III

$$\mathbf{1a} + 2 \xrightarrow{k_1} 3 + 4$$

$$3 \xrightarrow{k_2} 8$$

$$8 + \mathbf{1a} \xrightarrow{k_3} 7$$

$$7 + 2 \xrightarrow{fast} RON{=}{=}NOR$$

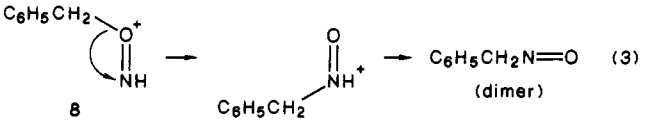
$$61\mathbf{a} + 22 \longrightarrow 44 + RON{=}{=}NOR$$

by *m*-TFBSP (Scheme III). All of these scenarios require the observed 3:1 stoichiometry to obtain 0.5 equiv of hyponitrite ester. This product in turn would give 1 equiv of alcohol, or carbonyl, or their sum. Subsequent conversion of the carbonyl to the oxime is not considered in the stoichiometry.

A further consideration for Schemes I–III is whether the reaction between the hydroxylamine and peroxide (k_1) is fast, and a subsequent step (k_2) is rate determining, or whether k_1 is the slow step, and subsequent steps are fast. The evidence discounts the former possibility. If k_1 is a fast step, only 2 equiv of hydroxylamine are required to convert all of the peroxide to **3**, thus no peroxide should remain in solution if at least 2 equiv of hydroxylamine are used. This is contrary to the observation that 24% of *m*-TFBSP remains after reaction with 2.1 equiv of **1a** as determined by iodometric titration. Secondly, Schemes I and III require free hydroxylamine to be present to give N–N bond formation. If k_1 is fast, then using only 2 equiv of hydroxylamine would give **3** and the salt **4**, with little or no free hydroxylamine present as is required in Schemes I and III, and formation of the N–N bond would be suppressed. If k_1 is fast for Scheme II, in which product formation depends only on **3**, maximum yields of N–N bond formation would be observed at 2:1 equivalency. It is thus probable that the reaction between **1** and *m*-TFBSP is the slow step of the process.

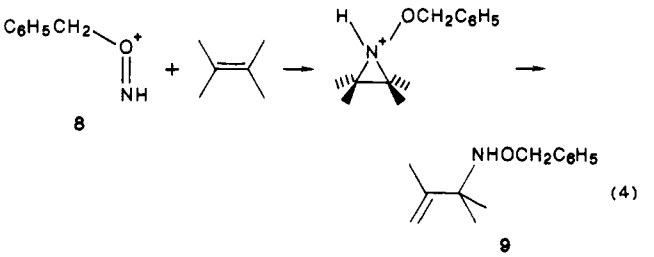
Given that k_1 is rate determining in Schemes I–III, then Scheme III is the more likely mechanistic alternative. For Scheme I to be operative requires that hydroxylamine **1** react faster with adduct **3** than with *m*-TFBSP. This is highly unlikely since the peroxide is much more electrophilic than **3**.[8] The remaining possibilities, Schemes II and III, are similar in that both involve ionization of **3** to an alkoxy nitrenium ion, k_2, but they are different in that Scheme II utilizes trapping of the nitrenium ion (k_3) by **3** to give the N–N bond, while Scheme III has trapping of the nitrenium ion (k_3) by hydroxylamine **1**. Scheme III is the preferred mechanism since it predicts that the yields of products from N–N bond formation should increase as the concentration of the hydroxylamine increases. This is the observed result for **1a** (Table I). Furthermore hydroxylamine **1** is expected to be a much better nucleophile both sterically and electronically than the N-(arylsulfonoxy)hydroxylamine **3** so its ability to trap the nitrenium ion should be greater. Thus N–N bond formation by hydroxylamine trapping (Scheme III) is the major pathway to products, although Scheme II cannot be excluded absolutely. In fact Scheme II may partially account for the formation of N–O cleavage products when less than stoichiometric quantities of hydroxylamine are employed.

An inverse addition experiment (slow addition of **1a** to mTFBSP) supports this interpretation. In this experiment the concentration of **1a** is low at all times during the course of the reaction. In addition to N–O cleavage products, a small amount of α-nitrosotoluene dimer[1] could be detected in the reaction mixture. Presumably the lowered trapping efficiency results in some O to N rearrangement in the intermediate nitrenium ion **8** (eq 3).



(3)

Furthermore if the same experiment is carried out in the presence of tetramethylethylene, a new product is detected in low yields (8.5%) that was identified on the basis of spectral information as 3-[(*O*-benzylhyroxyl)amino]-2,3-dimethyl-1-butene, **9**. This product could arise from the reaction of **8** with tetramethylethylene followed by proton loss (eq 4), thus supporting the hypothesis that *O*-alkyl nitrenium ions are intermediates in the oxidation. The low yields, however, discouraged further investigation of this method as a potential amination process.



(4)

Comparison of the results obtained here with those obtained in the lead tetraacetate oxidation of *O*-alkylhydroxylamines reveals distinct differences. The major products in both cases are N–O cleavage products; however, the LTA oxidations give a much greater proportion of O to N rearrangement than seen with **2**.[1-4] Furthermore, in the presence of olefins, LTA oxidation of *O*-alkylhydroxylamines is a viable method for the preparation of *N*-alkoxyaziridines.[4,10] One reason for this difference in chemistry might be attributed to differences in the first-formed (hydroxyamino)lead species, **10**, and the hydroxyamino arenesulfonate, **3**. The arenesulfonate group is a much better leaving group than $Pb(OAc)_3$ when they are attached to nitrogen,[11] and thus ionization of **3** occurs readily to give the highly reactive nitrenium ion. Nucleophilic trapping gives ultimately the N–O cleavage products. On the other hand, the poorer leaving ability of lead results in slower ionization and greater amounts

(8) For example, amines typically react conveniently with *O*-(mesitylenesulfonyl)hydroxylamine at 0 °C,[9] whereas they react readily with **2** at −78 °C.[5]

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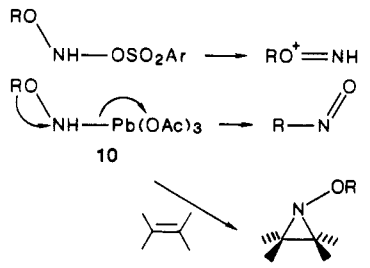
Scheme IV



of migration assisted ionization (hence rearranged products) and greater amounts of nucleophilically assisted ionization to give aziridines (Scheme IV).

Experimental Section

Melting points are uncorrected. Proton NMR spectra were recorded on either JEOL PS-100 or Varian XL-200 instruments; chemical shifts are reported for chloroform-*d* solutions in ppm relative to Me_4Si. Infrared spectra were recorded on a Perkin-Elmer 1310 spectrometer as potassium bromide disks for solids or as thin films for neat liquids. Mass spectra were obtained on a Hitachi RMU-6E or a Hewlett-Packard 5995 spectrometer. Analytical VPC was carried out on a HP-5890 gas chromatograph with bonded silica columns (Alltech): A, 0.53 mm × 10 m Superox (polyethylene glycol); B, 0.53 × 10 m RSL-300 (phenyl methyl silicone); and C, 0.53 mm × 10 m RSL-150 (methyl silicone). GC yields were determined by introduction of an internal standard to the crude product mixture, injection on the appropriate column, and calculating the yields of volatile products from peak area measurements after correcting for differential detector response to the various components. Reaction products were isolated by flash chromatography or preparative VPC, which was carried out on a Varian Aerograph 920 gas chromatograph with packed columns: D, 6 mm × 3 m 10% Carbowax–2% KOH, and E, 6 mm × 2 m 10% QF-1, or HPLC (Waters) and compared with authentic samples.

O-Benzylhydroxylamine **1a** was available commercially (Aldrich) as the hydrochloride salt. Treatment with concentrated potassium hydroxide and extraction (CH_2Cl_2) gave the free base. Hydroxylamines **1b,c** were prepared by the method of Chimiak[12] by alkylation of *N*-hydroxyphthalimide with *n*-hexyl iodide and cyclohexyl iodide, respectively, followed by hydrazinolysis. Hydroxylamine **1d** was prepared from *tert*-butyl acetate and *N*-hydroxyphthalimide by the method of Chimiak.[13] Hydroxylamine **1e** was prepared by the method of Schumann.[14] *m*-TFBSP, **2**, was prepared by the method of Dannley.[15]

Reaction of *O*-Benzylhydroxylamine, 1a, with *m*-TFBSP, 2. General Procedure. In a typical experiment, a stirred solution of *O*-benzylhydroxylamine, **1a**, (520 mg, 4.2 mmol) in dichloromethane (5 mL) was cooled to −28 °C (CCl_4/dry ice) under a nitrogen atmosphere to preclude the facile reaction of the hydroxylamine with carbon dioxide, which gives unreactive carbamate salts. A solution of **2** (900 mg, 2 mmol) in dichloromethane (6 mL) was added dropwise. A yellow color developed, and a fine white solid precipitated. The heterogeneous mixture was stirred at −28 °C for 1 h and at room temperature for 2 h. The reaction mixture was cooled to −28 °C and filtered. The solid was identified as *O*-benzylhydroxylammmonium *m*-(trifluoromethyl)benzenesulfonate (733 mg, 2.1 mmol) by comparison with an authentic sample of the salt prepared from *O*-benzylhydroxylamine and *m*-(trifluoromethyl)benzenesulfonic acid. The filtrate was washed with 10% aqueous potassium hydroxide (3 × 15 mL). The aqueous washes were extracted with dichloromethane (10 mL), and the combined organic layers were dried ($MgSO_4$). Analysis by gas chromatography showed the presence of two volatile products. These were isolated by flash chromatography and shown to be benzyl alcohol, **5**, and *O*-benzylbenzaldoxime, **6**, by comparison with authentic samples. Benzyl alcohol (16%) was quantified by HPLC with a μ-Porasil column (Waters) and *p*-nitroaniline as an internal standard. *O*-Benzylbenzaldoxime (17%) was quantified by VPC with use of column A and mesitylene as an internal standard.

Also isolated by flash chromatography of the crude products was a very small amount of a compound identified as *N*-benzyloxy-*m*-(trifluoromethyl)benzenesulfonamide (NMR ($CDCl_3$) δ 5.04 (s, 2 H), 7.08 (s, 1 H), 7.4 (m, 5 H), 8.0 (m, 4 H)) by comparison with an authentic sample. This product probably arises by attack by the hydroxylamine on a sulfonyl center, rather than on the O–O bond of **2**. The yield of this product was <1% and was not of further concern.

By the same procedure, various ratios of **1a** to **2** were reacted. The results are found in Table I.

***O*-*n*-Hexylhydroxylamine, 1b.** By use of the same procedure, **1b** (470 mg, 4 mmol) was reacted with **2** (600 g, 1.33 mmol). Examination of the crude products by VPC showed the presence of two volatile components. These were isolated by preparative VPC (column E) and shown to be *n*-hexanol and *O*-(*n*-hexyl)-hexaldoxime by comparison with authentic samples. These products were quantified in subsequent runs by VPC using column A with mesitylene as an internal standard (Table I).

***O*-Cyclohexylhydroxylamine, 1c.** By the same procedure, **1c** (230 mg, 2 mmol) was reacted with **2** (300 mg, 0.67 mmol). Examination of the crude products by VPC revealed only two volatile components present. These were isolated by preparative VPC (column E) and shown to be cyclohexanol (94%) and *O*-cyclohexylcyclohexanone oxime (6%) by comparison with authentic samples. These products were quantitated in subsequent runs by VPC with column A with mesitylene as an internal standard.

***O*-*tert*-Butylhydroxylamine, 1d.** By the same procedure, **1d** (100 mg, 1.1 mmol) was reacted with **2** (170 mg, 0.37 mmol). Examination of the crude products by VPC showed only one volatile component, which was identified as *tert*-butyl alcohol by retention time and its NMR spectrum. This product was quantitated by addition of mesitylene as an internal standard and integration of the NMR spectrum of the mixture (Table I).

***O*-(Diphenylmethyl)hydroxylamine, 1e.** In a large scale reaction using the same procedure, **1e** (2 g, 10 mmol) was reacted with **2** (1.5 g, 3.3 mmol). After a standard workup the products were separated by flash chromatography on silica gel with chloroform/hexane (60:40) as the eluting solvent. The products were identified by comparison of melting points and NMR spectra with authentic samples. The major products were benzhydrol and benzophenone. Also present in lesser amounts were bis(diphenylmethyl ether), **11**,[16] *O*-(diphenylmethyl)benzophenone oxime, **12**,[17] and a very small amount of *N*-(diphenylmethoxy)-*N'*-(diphenylmethyl)diazine *N'*-oxide, **13**.[4] This last product has been postulated to arise from the condensation of **1e** with nitrosodiphenylmethane.[4] It was found that each of these products gave a unique signal in the NMR that could be used for quantitation purposes. By the same procedure **1e** (200 mg, 1 mmol) was reacted with **2** (300 mg, 0.33 mmol). After workup and evaporation, mesitylene was added to the product mixture, and the products were quantitated by NMR. A control experiment showed that benzhydrol is converted to the bis(ether) **11** under the reaction conditions, so the yield of alcohol reported in Table I includes the yield of ether product (×2). The yield of **13** was too small to measure.

Inverse Addition of 2 to 1a. A solution of **1a** (520 mg, 4.2 mmol) in dichloromethane (30 mL) was added dropwise to a cooled (−28 °C) solution of **2** (900 mg, 2 mmol) in dichloromethane (30 mL). After a normal workup and evaporation, examination by NMR showed that in addition to the normal benzyl alcohol and *O*-benzylbenzaldoxime products, a small singlet at 5.42 ppm was also present in the spectrum. This signal was identical with that of α-nitrosotoluene dimer, as determined by comparison with an authentic sample.[1] TLC comparison supported the assignment, but the yield was very low, and this product was not pursued further.

Reaction of 1a with 2 in the Presence of Tetramethylethylene. A solution of **2** (300 mg, 0.65 mmol) in dichloromethane

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(5 mL) was added dropwise to a cold (−28 °C) solution of **1a** (250 mg, 2 mmol) and tetramethylethylene (109 mg, 1.3 mmol) in dichloromethane (10 mL). After the addition was complete, the reaction mixture was stirred for 1 h at −28 °C and for 2 h at room temperature. The mixture was cooled to −50 °C and filtered to remove the precipitated salt (85%). The filtrate was extracted with 10% aqueous potassium hydroxide (3 × 15 mL) and then with 2 N HCl (2 × 15 mL). The organic layer was dried ($MgSO_4$) and evaporated. Kugelrohr distillation separated benzyl alcohol and *O*-benzylbenzaldoxime from a third component. The unknown compound was isolated by preparative TLC (silica gel/chloroform) and purified by preparative VPC (OV-101). The clear oil was identified as 3-[(*O*-benzylhydroxyl)amino]-2,3-dimethyl-1-butene, **9**: NMR δ 1.26 (s, 6 H, $(CH_3)_2$), 1.85 (broadened s, 3 H, allylic CH_3), 4.76 (s, 2 H, benzylic CH_2), 4.94 (m, 1 H, vinyl H), 4.99 (m, 1 H, vinyl H), 7.40 (s, 5 H, C_6H_5); IR (neat) 3080, 3060, 3020, 2870, 1640, 1490, 1450, 1170, 1060 cm^{-1}; MS, *m/e* 205 (parent), 190 (P − 15), 123, 105, 77. In a repeat experiment, mesitylene was added to the crude product mixture. NMR analysis showed **9** to be present in a yield of 8.5%. The low yield discouraged further investigation of **9**.

Acknowledgment. This project was supported in part by the National Science Foundation (Grants CHE-8304000 and CHE-8709853) whom we would like to thank.

Registry No. **1a**, 622-33-3; **1b**, 4665-68-3; **1c**, 4759-21-1; **1d**, 37477-16-0; **1e**, 1782-38-3; **2**, 35673-10-0; **4**, 116006-92-9; **5**, 100-51-6; **6**, 17146-21-3; **12**, 65311-52-6; **13**, 30542-59-7; $C_5H_{11}CH_2OH$, 111-27-3; *t*-BuOH, 75-65-0; $C_6H_5CH(OH)C_6H_5$, 91-01-0; $C_6H_5CH_2OCH_2C_6H_5$, 574-42-5; *O*-(*n*-hexyl)hexaldoxime, 116006-90-7; cyclohexanol, 108-93-0; *O*-cyclohexylcyclohexanone, 116006-91-8; oxime benzophenone, 119-61-9; tetramethylethylene, 563-79-1; 3-[(*O*-benzylhydroxy)amino]-2,3-dimethyl-1-butene, 116006-93-0.

Synthesis of 1-*O*-Methyl-β,D-ezoaminuroic Acid†

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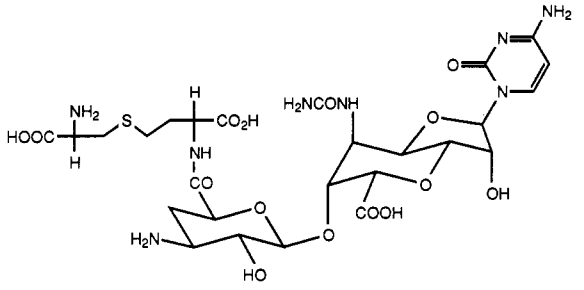
Received April 4, 1988

The synthesis of the title compound from the Diels–Alder adduct of diethyl ketomalonate and 1,3-butadiene (nine steps, 13% overall yield) is described. The key step is a transannular "bromolactamization" reaction, which sets up the stereocontrolled functionalization of the pyran ring. The use of resolved *p*-methoxyphenethylamine as the source of the amino group allows the synthesis of both the D (natural) and L (unnatural) series amino sugars.

Ezomycin A_1 (**1**) is an antifungal antibiotic isolated by Takaoka, Sakata, and co-workers from a *Streptomyces*[1] and shown by Sakata to possess the structure shown below: an amino sugar (ezoaminuroic acid, **2**) linking an octosyl nucleoside and a pseudodipeptide (cystathionine).[2] Several groups have studied approaches to the synthesis of the octose,[3–6] and Suami recently completed the synthesis of the octose nucleoside portion in protected form.[6c] An early synthesis of a derivative (**24**) of **2** from 1,6-anhydro-β,D-glucopyranose, reported by Ogawa,[7] required 12 steps and proceeded in about 2% overall yield.



1, ezomycin A_1

We undertook the synthesis of ezoaminuroic acid to showcase the "iodolactamization" procedure we have developed over the last few years.[8–10] As the accompanying retrosynthetic analysis of **2** illustrates, the logical precursor, lactam **3**, should be makable by a transannular cyclization of unsaturated amide **5**, followed by several functional group modifications. We describe in this article not only the successful synthesis that indeed gives the methyl glycoside of **2** according to the prescribed path but also the difficulties with the "iodolactamization" procedure and with lactam nitrogen protection that we were forced to circumvent in order to arrive at the target amino sugar.

Results and Discussion

Halolactamization Studies. The carboxamide **10**, which contains all the pyranose carbons and the functional groups appropriate for cyclization studies, was prepared with good efficiency on a multigram scale as shown below. Diels–Alder reaction of diethyl ketomalonate (**6**) with excess 1,3-butadiene in a sealed tube afforded the diester **8**,[11] which was hydrolyzed and decarboxylated to give the dihydropyrancarboxylic acid **9**. Conversion of **9** to its acid

† This paper is dedicated to Prof. E. J. Corey on the occasion of his 60th birthday.

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