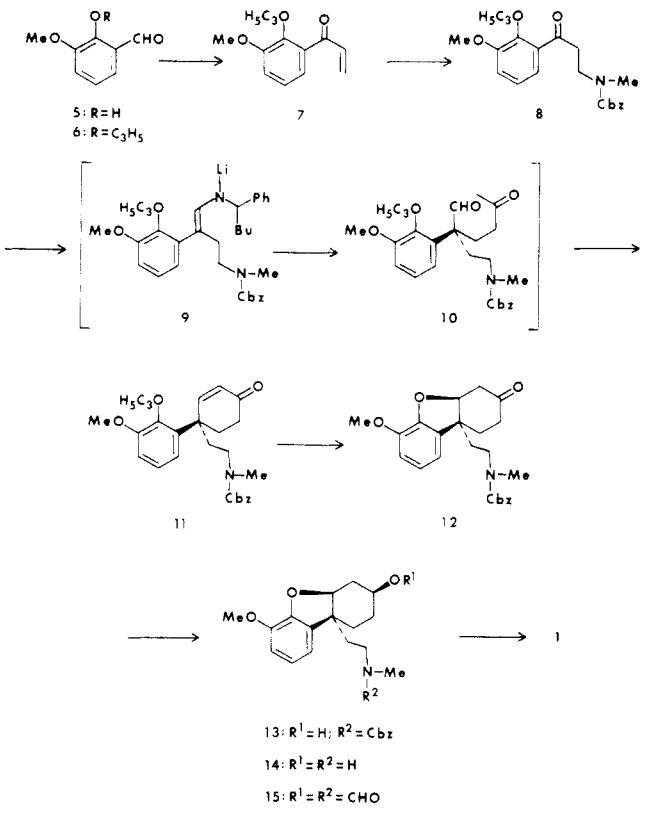
Scheme I



Subsequent removal of the *O*-allyl protecting group from **11** with a catalytic amount (7%) of rhodium trichloride[10] in refluxing ethanol was accompanied by spontaneous cyclization of the intermediate phenol to give **12** in 86% yield. The hydride reduction of the carbonyl functional group of **12** ($LiAlH_4$, glyme, -78 °C) proceeded with a high degree of stereoselectivity (>95%) to afford the alcohol **13**, which was then converted to the amino alcohol **14** by catalytic hydrogenolysis (H_2, 5% Pd-C, HCl/EtOH) in 84% overall yield.

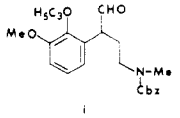
Although it might be possible to convert **14** directly into lycoramine (**1**) by a classical Pictet-Spengler reaction, numerous attempts to effect such a conversion using formaldehyde under a variety of acidic reaction conditions failed to produce significant quantities of lycoramine.[11] Consequently, we turned our attention to the transformation of **14** to lycoramine via a Bischler-Napieralski reaction which has previously been employed for the construction of hydrobenzazepines.[12] Reaction of the amino alcohol **14** with excess acetic formic anhydride in pyridine (80 °C, 6 h) afforded **15** (95% yield), which was smoothly converted to racemic lycoramine (**1**) [as needles, mp 101-102 °C (lit. mp 98-99 °C,[3a] 94-97 °C,[3c])] in 68% yield by cyclization with phosphorus oxychloride (85 °C, 20 h) followed by hydride reduction [$NaBH_4$ (20 equiv), MeOH, -78 °C → 0 °C, 3 h] of the intermediate iminium salt. The synthetic lycoramine, which was thus obtained in 14% overall yield from *o*-vanillin has spectral properties (90 MHz ^1H NMR, IR, low-resolution mass spectra, TLC, VPC) identical with an authentic sample of *dl*-lycoramine.[13]

The application of our general methodology for the construction of quaternary carbon atoms to the syntheses of other natural products is in progress and will be reported independently.

Acknowledgment. We thank the National Cancer Institute, DHEW (Grant CA 21860), and the Robert A. Welch Foundation for their generous support of this work.

Registry No. (±)-**1**, 18797-70-1; **5** sodium salt, 78166-97-9; **6**, 23343-06-8; **7**, 78166-98-0; **8**, 78166-99-1; (±)-**9**, 78167-00-7; (±)-**10**, 78167-01-8; (±)-**11**, 78167-02-9; (±)-**12**, 78167-03-0; (±)-**13**, 78167-04-1; (±)-**14**, 78167-05-2; (±)-**15**, 78167-06-3; (±)-**i**, 78167-07-4; allyl bromide, 106-95-6; vinyl bromide, 593-60-2; benzyl *N*-methylcarbamate, 30379-59-0; 2-(2-bromoethyl)-2-methyl-1,3-dioxolane, 37865-96-6; diethyl [(*N*-benzylidenamino)lithiomethyl]phosphonate, 78167-08-5.

(9) The unalkylated aldehyde **i** was also obtained 10-20% yield from this sequence. Despite numerous attempts, we have not yet found



reaction conditions which would allow complete alkylation of the intermediate metalloenamine **9**.

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(11) However, we know of only one example of the formation of a seven-membered ring by a Pictet-Spengler reaction: Kametani, T.; Terui, T.; Ogino, T.; Fukumoto, K. *J. Chem. Soc. C* **1969**, 874. For a related process, see Wittekind, R. R.; Lazarus, S. *J. Heterocycl. Chem.* **1971**, *8*, 495.

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(13) We thank Professor A. G. Schultz for the 90-MHz ^1H NMR and IR spectra and also an authentic sample of racemic lycoramine.

(14) Recipient of a National Institutes of Health (National Cancer Institute) Research Career Development Award, 1980-1985.

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Received April 27, 1981

Azetidinone Antibiotics. 22. A Rearrangement of Oxoazetidinesulfinic Acids to Haloazetidinones[1]

Summary: Treatment of the oxoazetidinesulfinic acid **3** with a positive halogen source gave trans and cis 4-haloazetidinones **5**; the trans isomers of **5** are easily converted to oxazoline **6** by chromatography on silica gel, while the cis isomers are transformed into **6** by reacting with PbF_2 in Me_2SO.

Sir: Earlier reports have shown that sulfinic acid **3** is a useful intermediate in the synthesis of 3-methylenecepham sulfoxide **4**.[2] We now report that further investigation into the chemistry of this sulfinic acid has demonstrated a unique reactivity which leads to the formation of other synthetically useful azetidinone derivatives.

Treatment of the penicillin sulfoxide **1** in refluxing toluene with NCS (1 equiv. 90 min) gave the sulfinyl chloride **2**[2] (Scheme I), which upon hydrolysis (aqueous 1 N HCl, toluene, 1 h) provided sulfinic acid **3** in 70% yield as a colorless amorphous solid; NMR ($CDCl_3$) δ 1.9 (s, 3, CH_3), 4.46 (s, 2, side-chain CH_2), 4.88 (d, 1, J = 5.0 Hz,

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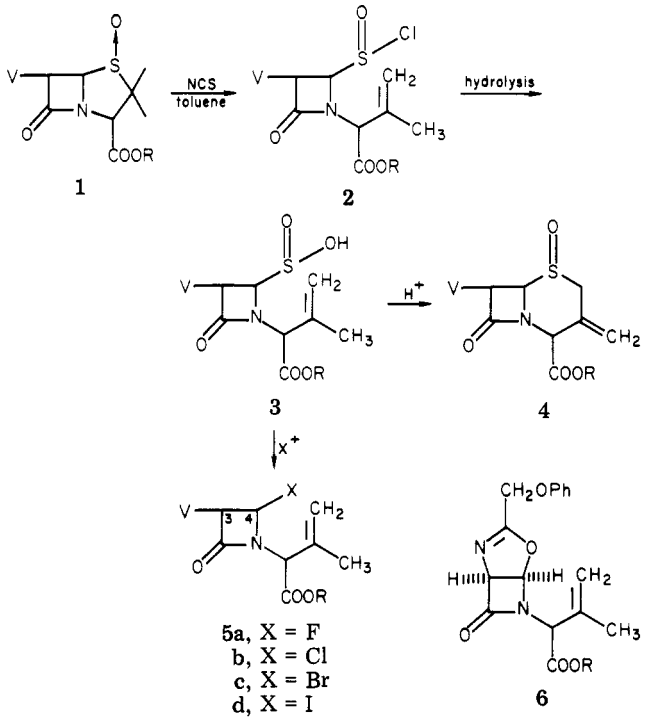
Scheme I[a]



[a] V = $C_6H_5OCH_2CONH$; R = $CH_2C_6H_4$-*p*-NO_2

azet H), 5.0 (s, 1, CHCOOpNB), 5.2 (m, 2, CH_2=), 5.3 (s, 2, CH_2 ester), 5.8 (dd, 1, J = 5.0 and 8.0 Hz), 6.8–8.4 (m, 9, Ar H), and 8.4 (d, 1, J = 8.0 Hz NH).[3]

When sulfinic acid **3** was treated with a positive halogen source, an immediate desulfonation occurred to form a new product, the nature of which depended upon the halogen employed. For example, when a methylene chloride solution of **3** was treated with positive fluorine ($FClO_3$/DMF, 1 equiv, −78 °C), a rapid reaction led to the formation of the corresponding *cis*-4-fluoroazetidinone **5a**: colorless foam; IR ($CHCl_3$) 1795 cm^{-1}; NMR ($CDCl_3$) δ 1.87 (s, 3, CH_3), 4.56 (s, 2, CH_2OPh), 5.01 and 5.18 (m, 2, CH_2=), 5.05 (s, 1, CHCOOpNB), 5.31 (s, 2, CH_2 of pNB), 5.55 (m, 1, azet H), 5.90 and 6.66 (dd, 1, azet H), 6.85–8.34 (m, 10, aromatic H and NH). Similarly, treatment of **3** with NCS (1 equiv. CH_2Cl_2, 22 °C, 5 min) gave *cis*-4-chloroazetidinone **5b** in quantitative yield: colorless crystals, mp 131–132 °C (ethyl acetate);[4] IR ($CHCl_3$) 1782 cm^{-1}; NMR ($CDCl_3$) δ 1.91 (s, 3, CH_3), 4.50 (s, 2, CH_2OPh), 4.88 (s, 1, CHCOOpNB), 5.00 and 5.16 (m, 2, CH_2=), 5.3 (s, 2, CH_2 ester), 5.75 (dd, 1, J = 5.0 and 8.0 Hz, azet H), 6.15 (d, 1, J = 5.0 Hz, azet H), and 6.74–8.27 (m, 10, aromatic H and NH).[3]

Treatment of the cis chloroazetidinone derivative **5b** with lithium chloride in acetone at 22 °C for 1 h resulted in epimerization of the chlorine to give the mixture of cis and trans isomers in the ratio of ca. 2:3.[5] On preparative TLC,[6] the trans isomer was completely converted to oxazoline **6**:[7] colorless amorphous solid; NMR ($CDCl_3$) δ 1.8 (s, 3, CH_3), 4.73 (s, 2, CH_2OPh), 4.93 (d, 1, J = 4.00 Hz, azet H), 5.05 and 5.15 (m, 3, CHCOOpNB and CH_2=), 5.4 (s, 2, CH_2 ester), 6.25 (d, 1, J = 4.0 Hz, azet H), and 6.9–8.3 (m, 9, ArH).[3] An alternative preparation of this oxazoline can easily be performed by reacting the cis chloroazetidinone **5b** with an excess of PbF_2 in Me_2SO at room temperature for 4 h.

When a positive bromine source (NBS) was added to the sulfinic acid **3** (CH_2Cl_2, 1 equiv, 0 °C, 5 min), the corresponding 4-bromoazetidinone was obtained in high yield. In this case, however, cis and trans isomers were present as a mixture.[8] Preparative TLC of the mixture led to formation of oxazoline **6**.[9] Likewise, when the sulfinic acid **3** was treated with positive iodine (NIS, 1 equiv, CH_2Cl_2, 0 °C, 5 min), both cis and trans iodo isomers were obtained, contaminated by a small amount of oxazoline **6**.

The facile desulfonation of sulfinic acid **3** is probably due to the presence of an adjacent nitrogen whose free electron pair is available to help stabilize a developing positive charge at carbon atom 4. Kwart and Body[10] have observed that certain imino conjugated chlorosulfonyl compounds having N=CSO_2Cl functionality are unstable and readily desulfonate to form the corresponding chloro derivative. They report that the desulfonation reaction is enhanced "when the imino nitrogen acquires a threshold magnitude of positive character". A similar situation would result in our case as the azetidinone nitrogen begins to donate its electron pair.

We believe that the halogenation products observed can be rationalized by mechanisms similar to those suggested for the chlorination of alcohols by thionyl chloride.[11] The retention of configuration observed in the case of fluorine and chlorine is probably the result of an S_Ni reaction. The mixture of cis and trans isomers arising with positive bromine and iodine reactions might be attributed to a combination of pathways: S_Ni, S_N1, and S_N2.

A β,γ-unsaturated 3-phthalimido-4-chloroazetidinone similar to compound **5** has previously been prepared by a tedious route by Wolfe and co-workers.[12] The method employed allylic bromination of the corresponding α,β-unsaturated olefin with *N*-bromosuccinimide to make the dibromo compound, which was converted to the β,γ-unsaturated olefin with zinc in acetic acid. The product was obtained as a 1:1 mixture of epimers (epimeric at the α carbon) and in low yield. According to our method described above, compound **5** as well as compound **6** is readily prepared as a single isomer by a simple procedure and in high yield. Both compounds have already proved to be key intermediates in the synthesis of oxygen analogues of penicillins and cephalosporins.[12,13]

Acknowledgment. We are thankful to Professor Leo A. Paquette of the Ohio State University for many helpful discussions and to R. Thomas of the Lilly Research Lab-

(3) All new compounds have satisfactory elemental analyses and/or mass spectra.

(4) The corresponding benzhydryl ester of *cis*-4-chloroazetidinone, mp 71–73 °C (ether), was also prepared by the same procedure in 65% yield.

(5) The ratio was determined from the NMR spectrum.

(6) Merck silica gel prep plate with indicator was eluted with ethyl acetate and hexane (3:2).

(7) The cis isomer **5b** was recovered unchanged from the chromatography.

(8) For cis bromoazetidinone **5c**, the NMR spectrum in $CDCl_3$ is: 1.96 (s, 3, CH_3), 4.58 (s, 2, CH_2OPh), 4.83 (s, 1, CHCOOpNB), 5.05–5.2 (m, 2, CH_2=)), 5.7 (dd, 1, J = 5.0 Hz, azet H), 6.3 (d, 1, J = 5.0 Hz, azet H), and 6.9–8.3 (m, 10, aromatic H and NH).

(9) No cis isomer could be isolated by chromatography. However, in the case of the corresponding methyl esters of 3-phthalimido-4-chloroazetidinones, both cis and trans isomers were isolated by chromatography. The cis isomer melts at 107.5–109 °C (ether); NMR ($CDCl_3$) δ 2.05 (s, 3, CH_3), 3.86 (s, 3, CH_3 ester), 5.06 (d, 2, J = 1.5 Hz, CH_2=), 5.18 (m, 1, $CHCOOCH_3$), 5.66 (d, 1, J = 4.2 Hz, azet H), 6.33 (d, 1, J = 4.2 Hz, azet H), 7.83 (m, 5, ArH). The trans isomer melts at mp 110–111 °C (ether); NMR δ 2.0 (s, 3, CH_3), 3.83 (s, 3, CH_3 ester), 4.83 (s, 1, $CHCOOCH_3$), 5.26 (m, 2, CH_2=), 5.5 (d, 1, J = 2.0 Hz, azet H), 5.96 (d, 1, J = 2.0 Hz, azet H), 7.83 (m, 5, ArH).[12]

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oratories for technical assistance.

Registry No. 1, 29707-62-8; 2, 78183-91-2; 3, 78109-48-5; 5a, 78109-49-6; 5b, 78183-92-3; 5b benzhydryl ester, 70982-50-2; 5c, 78109-50-9; 5d, 78109-51-0; 6, 78183-93-4.

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Relative Nucleophilicities of Oxanions, Thianions, Carbanions, and Halide Ions in Dimethyl Sulfoxide Solution

Summary: Extrapolations of Brønsted-type plots have revealed that thiophenoxide ions are about 10^2–10^3 times more nucleophilic toward alkyl halides in dimethyl sulfoxide solution than fluorenyl carbanions and 10^4–10^5 times more nucleophilic than 2-naphthoxide ions of the same basicity.

Sir: The order of nucleophilicities of oxanions vs. thianions and of fluoride ion vs. chloride ion, as defined by relative rates of S_N2 reaction with alkyl halides, has long been a topic of interest and some controversy.[1,2] In hydroxylic solvents such as methanol the order is $RS^- > RO^-$ and $Cl^- > F^-$, and the high nucleophilicities of RS^-, Cl^-, and other highly polarizable anions (Br^-, RSe^-, I^-, etc.) have been attributed to the ability of their nonbonded electrons to initiate bonding at greater distances ("early transition states") and/or the availability of low-lying d orbitals[1b] or low-energy HOMO's.[1c] In dipolar nonhydroxylic solvents such as acetone or DMF, the order of nucleophilicities of halide ions is reversed, however.[2] This is true also in the gas phase where the order of nucleophilicities F^-, $CH_3O^- > CH_3S^- \gg Cl^- > CN^- > Br^-$ has been found, and the conclusion has been drawn that the high nucleophilicity of highly polarizable anions in solution is not an intrinsic factor but is instead an artifact caused by solvation.[3] This conclusion is supported by the observation of the same nucleophilicity order, i.e., F^-, $CH_3O^- > PhO^- > Cl^- > Br^-$, toward PrOTs in Me_2SO, although data allowing a direct comparison of oxanions and thianions are missing.[4]

In defining an order of relative nucleophilicities it is important, however, to compare anions of the same basicity. Although this is generally recognized, the necessary data are usually lacking. In hydroxylic solvents it is difficult because the range of basicities that can be measured is narrow (about 10 pK units). For example, weakly basic anions, such as halide ions, all have the same apparent basicity in H_2O or MeOH, and strongly basic anions, such as carbanions or nitranions, cannot be generated in high enough concentration to permit rate studies to be made. In dipolar nonhydroxylic solvents, such as Me_2SO, anions of a much wider range of basicities can be studied (about 30 pK units). By placing remote substituents in the benzene rings in thiophenoxide (PhS^-), 2-naphthoxide (2-NpO^-), and 9-(carbomethoxy)fluorenyl (9-CO_2Me-Fl^-) anions, Brønsted-type plots can be obtained (e.g., Figure 1),[5] which allow such comparisons for nucleophilicities of thianions, carbanions, and oxanions. The present study shows that toward $PhCH_2Cl$, BuCl, and BuI the order of relative nucleophilicities in Me_2SO solution is $ArS^- \gg$ 9-G-$Fl^- >$ 2-NpO^- for anions of the same basicity.

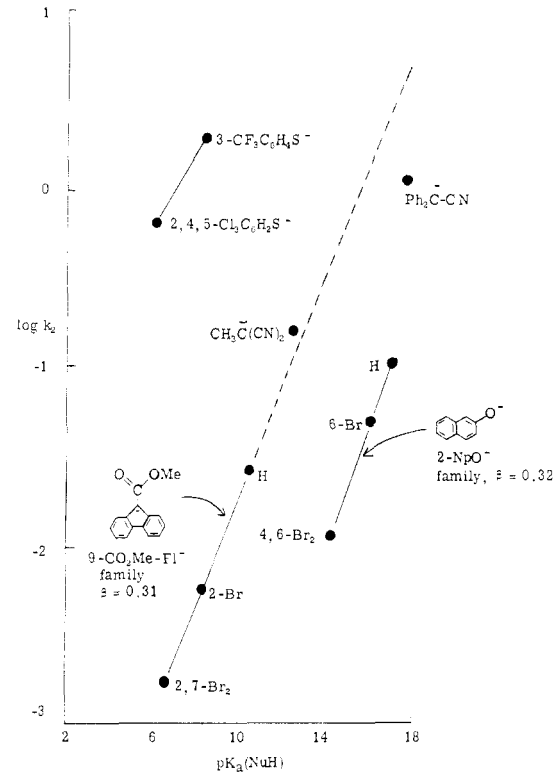

Figure 1. Brønsted-type plots for the reactions of thiophenoxide ions, 9-(carbomethoxy)fluorenyl carbanions (9-CO_2Me-Fl^-) and 2-naphthoxide ions (2-NpO^-) with $PhCH_2Cl$ in Me_2SO solution at 25 °C.

Examination of Figure 1 shows that 9-CO_2Me-Fl^- carbanions reacting with $PhCH_2Cl$ in Me_2SO solution exhibit essentially the same sensitivity to changes in basicity (β_{Nu} = 0.31) as do 2-NpO^- ions (β_{Nu} = 0.32). The fact that the points for $MeC(CN)_2^-$ and Ph_2CCN^- carbanions fit near to the line for 9-CO_2Me-Fl^- anions supports our earlier conclusion that steric demands of 9-CO_2Me-Fl^- anions are low[5] and suggests that carbanion nucleophilicities do not vary much for carbanions of different structural types. The vertical gap between the two Brønsted lines corresponds to about a 25-fold greater nucleophilicity for carbanions vs. oxanions of equal basicity.

Most thiophenoxides react too rapidly with $PhCH_2Cl$ for the rates to be measured by our spectrophotometric method. We have observed, however, that the conjugate base of 2,4,5-$Cl_3C_6H_2SH$ (pK_a = 6.0) reacts 318 times faster than the conjugate base of 9-CO_2Me-2,7-Br_2-FlH (pK_a = 6.5) and that the conjugate base of 3-$CF_3C_6H_4SH$ (pK_a = 8.1) reacts 360 times faster than the conjugate base of 9-CN-FlH (pK_a = 8.3). It follows that, toward $PhCH_2Cl$ in Me_2SO, thiophenoxide ions are about 10^4 times more nucleophilic than 2-naphthoxide ions of the same basicity (Figure 1).

Similar Brønsted-type plots have been made for these nucleophiles reacting with BuCl and/or BuI. The vertical

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(6) Hughes, D. L., unpublished results.

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