(H^+-K^+)-ATPase Inhibiting 2-[(2-Pyridylmethyl)sulfinyl]benzimidazoles. 2.[1] The Reaction Cascade Induced by Treatment with Acids. Formation of 5*H*-Pyrido[1′,2′:4,5][1,2,4]thiadiazino[2,3-*a*]benzimidazol-13-ium Salts and Their Reactions with Thiols

Jörg Senn-Bilfinger,* Uwe Krüger, Ernst Sturm, Volker Figala, Kurt Klemm, Bernhard Kohl, Georg Rainer, and Hartmann Schaefer

Byk Gulden Lomberg Chemische Fabrik GmbH, D-7750 Konstanz, FRG

Timothy J. Blake, Dai W. Darkin, Robert J. Ife, Colin A. Leach, Robert C. Mitchell, Edward S. Pepper, Colin J. Salter, and Nicholas J. Viney

Smith Kline & French Research Ltd., The Frythe, Welwyn, Herts., U.K.

Gottfried Huttner† and Laszlo Zsolnai†

Fakultät für Chemie der Universität Konstanz, D-7750 Konstanz, FRG

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The elucidation of the acid catalyzed chemical transformations involved in the inhibition of the gastric (H^+-K^+)-ATPase by 2-[(2-pyridylmethyl)sulfinyl]benzimidazoles **1**, a new class of antiulcer drugs, is reported. Protonation of **1** occurs at the pyridine nitrogen yielding the elusive salts **2**, of which **2d** has been isolated. The ^1H NMR signals for the pyridine 3-methyl groups of **2b–d** are shifted toward higher fields relative to the nonprotonated **1b–d**, suggesting a change in the preferred solution conformation triggered by protonation. The high-field shift is rationalized in terms of the mutual dipole–dipole interaction between the pyridine/pyridinium moiety and the sulfoxide. The solid-state conformation of **8b**·HCl, a stable surrogate of **2d**, was studied by X-ray techniques. Consecutive transformations of **2** in solution give rise to the formation of new, sensitive, and highly thiophilic 5*H*-pyrido[1′,2′:4,5][1,2,4]thiadiazino[2,3-*a*]benzimidazol-13-ium salts **3**. These can be isolated by treatment of **1** with HBF_4 in MeOH. Spectroscopic characterization and the results of an X-ray structure determination of **3b** are presented. In a fast reaction, thiols are added to **3**, yielding the disulfides **12**. These are identical with the previously reported products obtained from the reaction of **1** with thiols in acidic solution. Circumstantial evidence is presented that the sulfoxides **1** are not biologically active per se but require acidic priming to the thiophilic intermediate **3** capable of covalently modifying SH groups on the enzyme.

Introduction

2-[(2-Pyridylmethyl)sulfinyl]benzimidazoles **1a–d** are effective and long-lasting inhibitors of the gastric (H^+-K^+)-ATPase both in vitro and in vivo.[2,3] They exert their inhibitory activity via covalent modification of one or more thiol groups on the enzyme as has been demonstrated by Wallmark et al., using radiolabeled **1d**.[4] In the preceding paper[1] we reported the unequivocally determined structure of a model for the S–S-bonded drug–enzyme complex, represented by a completely rearranged 2-pyridiniobenzimidazolide, containing a disulfide side chain in the 2-position of the pyridine moiety. Furthermore, we described the cleavage of these disulfides by thiols yielding, after a second rearrangement, the reduced form of the sulfoxides **1**, namely, the sulfides **13**. This cleavage reaction parallels the restoration of activity of the inhibited enzyme by 2-mercaptoethanol in isolated gastric glands and purified gastric (H^+-K^+)-ATPase preparations as first reported by Wallmark.[4] Finally, we demonstrated that (H^+-K^+)-ATPase inhibiting efficacy of the sulfoxides **1** was found to be closely related to their acid-catalyzed reactivity toward thiols, suggesting that biological activity of **1** requires acidic priming to a thiophilic intermediate. This is the "active principle" of the sulfoxides **1a–d**. In vivo, the acidic priming is initiated in the acidic compartment of the parietal cell, giving rise to the unique target selectivity of this new class of H^+-secretion blockers.

Recently, Rackur et al.[5] and Im et al.[6] also reported their attempts to elucidate the structure of the disulfides **12** as well as some speculations concerning the chemical reaction pathway of the acid-catalyzed model reaction. Their structural assignment of the disulfides deviates from our unequivocally determined structure and hence their proposed reaction pathway does not meet the needs of the particular chemistry involved.

In this paper, we show, by ^{13}C NMR techniques, that the protonation site of **1** is the pyridine nitrogen and that protonation triggers a different preferred solution conformation, as evidenced by an unexpected high-field shift of the pyridine 3-Me proton signals in **2** relative to nonprotonated **1**. The high-field shift is discussed in terms

† New address, Institut für Anorganische Chemie der Universität Heidelberg, D-6900 Heidelberg 1, FRG.

(1) (a) Part 1: Sturm, E.; Krüger, U.; Senn-Bilfinger, J.; Figala, V.; Klemm, K.; Kohl, B.; Rainer, G.; Schaefer, H.; Blaker, T. J.; Darkin, D. W.; Ife, R. J.; Leach, C. A.; Mitchell, R. C.; Pepper, E. S.; Salter, C. J.; Viney, N. J.; Huttner, G.; Zsolnai, L. *J. Org. Chem.*, preceding paper in this issue. (b) Preliminary details of this work have been presented. See: Figala, V.; Klemm, K.; Kohl, B.; Krüger, U.; Rainer, G.; Schaefer, H.; Senn-Bilfinger, J.; Sturm, E. *J. Chem. Soc., Chem. Commun.* **1986**, 125–127. Figala, V.; Klemm, K.; Kohl, B.; Krüger, U.; Rainer, G.; Schaefer, H.; Senn-Bilfinger, J.; Sturm, E.; Blake, T. J.; Darkin, D. W.; Dawborne, J. S.; Ife, R. J.; Leach, C. A.; Pepper, E. S.; Viney, N. J. *Abstracts of Papers*, 3rd SCI-RSC Medicinal Chemistry Symposium, Cambridge, England, September 1985; Churchill College Cambridge: Cambridge, 1985; Abstract P20. (c) Essentially similar results were presented at the same meeting. See: Wallmark, B.; Carlsson, E.; Larsson, H.; Brändström, A.; Lindberg, P. *Abstracts of Papers*, 3rd SCI-RSC Medicinal Chemistry Symposium, Cambridge, England, September 1985; Abstract S16. See also: Lambert, R. W., Ed. *Proceedings*, 3rd SCI-RSC Medicinal Chemistry Symposium, Cambridge, England, September 1985; pp 293–311. Lindberg, P.; Nordberg, P.; Alminger, T.; Brändström, A.; Wallmark, B. *J. Med. Chem.* **1986**, *29*, 1327–1329.

(2) See ref 1a and references therein.

(3) Brändström, A.; Lindberg, P.; Junggren, U. *Scand. J. Gastroenterol., Suppl.* **1985**, *20*(108), 15–22.

(4) Wallmark, B.; Brändström, A.; Larsson, H. *Biochim. Biophys. Acta* **1984**, *778*, 549.

(5) Rackur, G.; Bickel, M.; Fehlhaber, H.-W.; Herling, A.; Hitzel, V.; Lang, H.-J.; Rösner, M.; Weyer, R. *Biochem. Biophys. Res. Commun.* **1985**, *128*, 477–484.

(6) Im, W. B.; Sih, J. C.; Blakeman, D. P.; McGrath, J. P. *J. Biol. Chem.* **1985**, *260*, 4591–4597.

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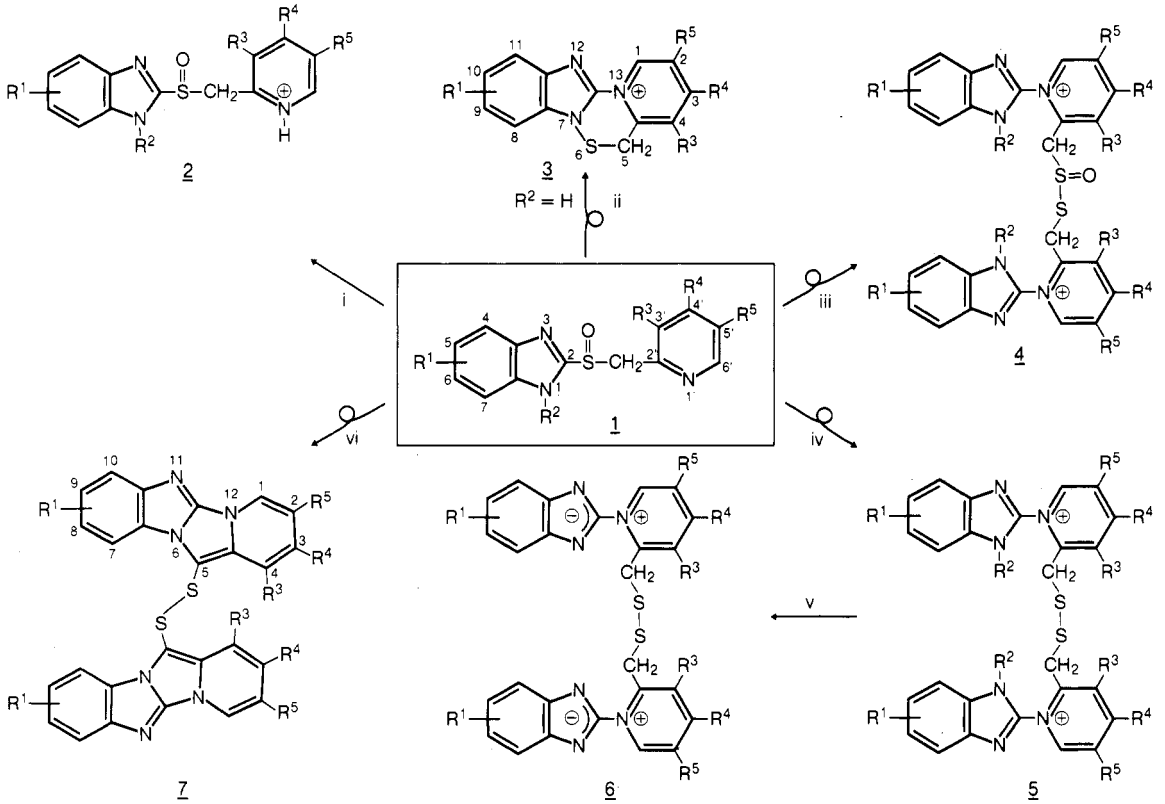
Scheme I. Compounds Derived from Acid Treatment of 1a–e[a]



1a, R^1–R^5 = H; 1b, R^1 = R^2 = R^5 = H, R^3 = Me, R^4 = OMe; 1c, R^1 = 5-CF_3, R^2 = R^5 = H, R^3 = Me, R^4 = OMe; 1d, R^1 = 5-OMe, R^4 = OMe, R^2 = H, R^3 = R^5 = Me; 1e, R^1 = 6-CF_3, R^2 = R^3 = Me, R^4 = OMe, R^5 = H

[a] (i) MeOH, 1 equiv of H^+, –5 °C, 30 min; (ii) MeOH, 1.2–2 equiv of H^+, –5 °C, 2 h; (iii) MeOH, H^+ excess, –40 °C, 2 days; (c = 0.1 mol/L); (iv) MeOH, H^+ excess, room temperature, 20 min; (v) $NaHCO_3$ (aqueous, half-saturated), 0 °C; (vi) HOAc excess, room temperature, 24 h.

of mutual dipole–dipole interactions between the pyridine/pyridinium moiety and the sulfoxide.

Using 50% HBF_4 as the acid, we were able to isolate, in the consecutive transformation reactions of **2**, a new intermediate **3**, which was unambiguously assigned the 5*H*-pyrido[1′,2′:4,5][1,2,4]thiadiazino[2,3-*a*]benzimidazol-13-ium structure, according to the spectroscopic data and an X-ray structure determination of **3b**. Consistent with the almost planar structure of **3**, these compounds possess a long wavelength absorption in their UV spectra relative to **1** and **12**.[1] This was also referred to in the preceding publication. The life span of **3** depends on the solvent, the pH of the medium, and, surprisingly, on the concentration of the solutions. Compounds **3** show very high reactivity toward thiols forming the above-mentioned rearranged disulfides, identical with those obtained from the reaction of **1** with thiols under acidic conditions (see preceding paper[1]).

In a short qualitative structure discussion, it will be shown that minor structural modifications in **1**, which hamper the formation of the intermediate **3**, exert great influence on the inhibition of the (H^+–K^+)-ATPase, as well as the model reaction of **1** with thiols. This indicates that the sulfenamide **3** represents the "active principle" of this class of inhibitors of gastric acid secretion.

Results and Discussion

Protonation of 1a–e and the Consecutive Cascade of Transformations. In Scheme I, an overview of the structures of compounds derived from acid treatment of the sulfoxides **1** under different conditions is given. As can be seen from this scheme, the outcome of the transformation reactions induced by acids is extremely dependent on the conditions applied. Thus, in aqueous acidic solutions, the formation of the dark red-colored tetracyclic disulfides **7**,[5] the most stable compounds derived from **1**, is a significant reaction. The structural elucidation of these compounds was very difficult since compounds **7** are in equilibrium with their corresponding monomer sulfenyl radicals which caused extreme line broadening in the ^1H NMR.

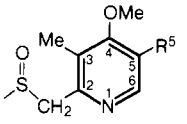
The formation of **7** could be circumvented by using nonaqueous acidic solutions, e.g., methanol. This enabled us to isolate and characterize the elusive intermediates involved in the acid-induced reaction cascade. The fate of **1**, under acidic conditions, not only depends on the reaction time and temperature but also on the pH value of the reaction mixture and, notably, on the concentration of the solution. This explains the difficulties encountered in the elucidation of the reaction mechanism of **1** under aqueous conditions. Scheme I gives examples of some of the conditions used to study the various transformations.

In this section, protonation of **1** to form the reactive salts **2** as well as the formation of the completely rearranged compounds **3** and **7** is described. The thiolsulfinates **4** and the symmetric disulfides **5** and **6** will be the subject of a forthcoming paper.[7]

Formation of the Salts 2 and Conformational Changes Involved. The sulfoxides **1** are weakly basic compounds, e.g., pK_a of **1d**, 3.97,[3] and are reversibly protonated by acids to form **2**. Since the salts **2** are short-lived intermediates in aqueous solution, the identification of the site of protonation was performed in cooled acidified methanolic solutions in which **2** could be "frozen out"

(7) Part 3 in this series, publication to be submitted.

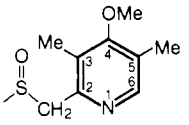
Table I. Carbon-13 NMR Chemical Shifts (δ) of the Pyridine Parts of (A) Neutral and (B) Protonated 1d and 8b



	1d			8b		
	A[a]	B[b]	Δδ	A[a]	B[c]	Δδ
C-2	149.66	142.95	+6.71	150.07	141.41	+8.66
C-3	126.41	130.83	-4.42	126.46	130.98	-4.52
C-4	163.51	170.04	-6.53	163.43	169.83	-6.40
C-5	125.36	128.99	-3.63	125.18	128.66	-3.48
C-6	148.96	142.32	+6.64	148.93	141.86	+7.07
2-CH_2	60.26	53.95	+6.31	62.96	54.42	+8.54
3-Me	10.38	10.50	-0.12	10.35	10.56	-0.21
4-OMe	59.18	60.79	-1.61	59.14	60.66	-1.52
5-Me	12.08	13.41	-1.33	12.09	13.47	-1.38

[a] From a DMF-d_7 solution at 20 °C. [b] From a stoichiometric HBF_4 salt dissolved at -40 °C in DMF-d_7 and recorded at -40 °C. [c] From a stable stoichiometric HBF_4 salt recorded in DMF-d_7 at -40 °C.

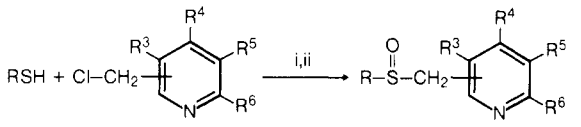
Table II. Partial ^1H NMR Chemical Shifts of the Pyridine Part Signals and Shift Differences Obtained after Protonation of Selected 1 and 8 with DCl[a]



	1c		1d[b]		8a		8b	
	δ	Δδ	δ	Δδ	δ	Δδ	δ	Δδ
2-CH_2	4.81	+0.20	4.74	+0.38	4.29	+0.31	4.36	+0.28
3-CH_3	2.19	-0.18	2.15	-0.12	2.27	+0.20	2.04	-0.23
4-OCH_3	3.90	+0.23	3.68	+0.22	3.80	+0.37	3.73	+0.27
R^5 = H	6.94	+0.60						
R^5 = CH_3			2.23	+0.22	2.33	+0.18	2.26	+0.21
H-6	8.13	+0.43	8.11	+0.46	8.21	+0.36	8.18	+0.37

[a] From CD_3OD solutions at room temperature; the acidic solutions contained 10–15 μL of 20% DCl/D_2O per mL of solution. [b] Recorded immediately after dissolution.

Scheme II. Preparation of the Stable Sulfoxides 8a–d[a]



8a-d

8a, R = R^3 = R^5 = Me, R^4 = OMe, R^6 = H, 2-py; **8b**, R = Ph, R^3 = R^5 = Me, R^4 = OMe, R^6 = H, 2-py; **8c**, R = 5-(trifluoromethyl)-1*H*-benzimidazol-2-yl, R^3 = R^5 = H, R^4 = OMe, R^6 = Me, 2-py; **8d**, R = 5-(trifluoromethyl)-1*H*-benzimidazol-2-yl, R^3–R^6 = H, 3-py

[a] (i) EtOH/2 N NaOH; (ii) CH_2Cl_2, MCPBA, -30–0 °C.

below -40 °C. However, addition of 1 equiv of aqueous 50% HBF_4 to a methanolic solution of **1d** at -5 °C gave solid **2d** (X = BF_4^-), which was stable enough to be isolated. Analogues of **1**, in which the benzimidazole moiety is replaced by a phenyl or methyl group (**8a** and **8b** in Scheme II), do not suffer acid-induced transformations, and the salts thereof are easily obtained.

Protonation of **1d** and **8b** is accompanied by similar ^{13}C NMR chemical shift changes (Table I), clearly indicating that **1d** is protonated at the pyridine nitrogen.

This is further supported by the ^1H NMR chemical shifts for the protons of the pyridine moieties, obtained immediately after dissolution of racemic **1b**, **1c**, or **1d** in acidified MeOH (Table II).

Surprisingly, however, the signals due to the methyl groups in position 3 of the pyridine moieties are shifted toward higher field compared to their shifts in the nonprotonated sulfoxides. The high-field shift is also observed with the phenyl sulfoxide **8b** but not with the methyl-substituted sulfoxide **8a** and also not with the sulfides **13**. Furthermore, we found that the high-field shift was enhanced at low temperatures as can be seen from Figure 1, where the shift differences between **1d**/**2d** and **8b** and **8b**·HCl are plotted against temperature. The methyl sulfoxide **8a** does not show this behavior.

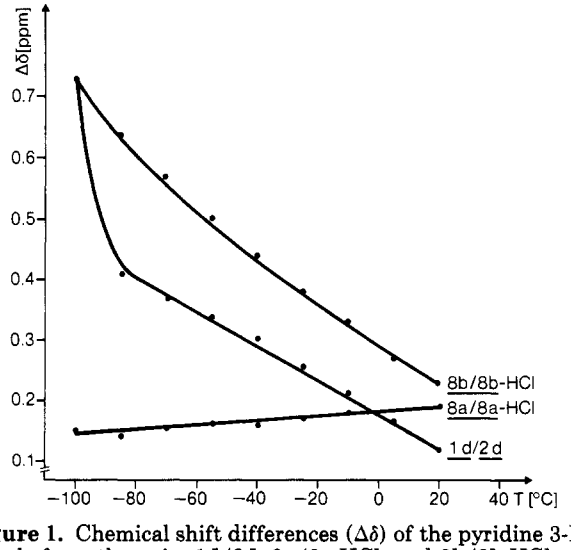


Figure 1. Chemical shift differences (Δδ) of the pyridine 3-Me signals from the pairs **1d**/**2d**, **8a**/**8a**·HCl, and **8b**/**8b**·HCl.

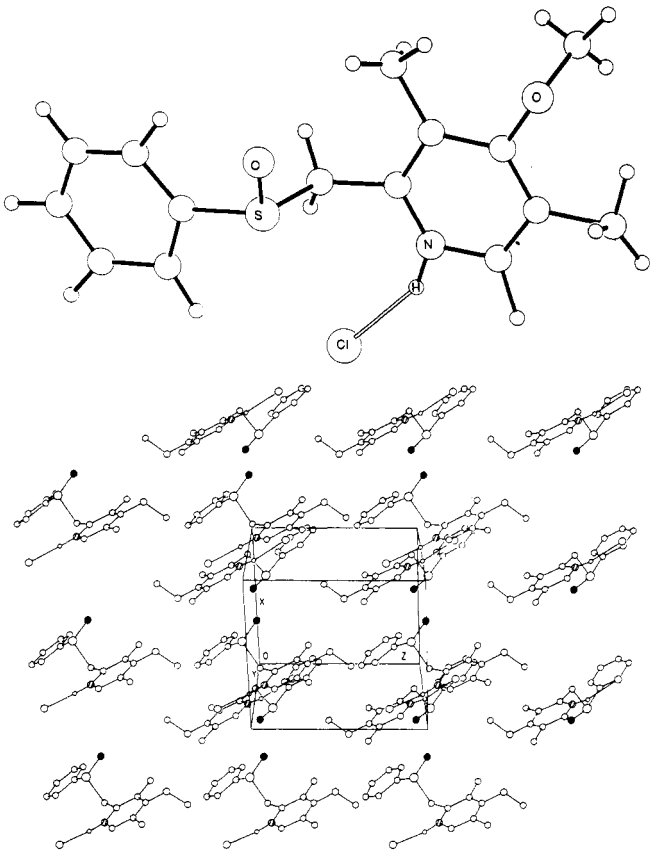


Figure 2. Top: perspective drawing of **8b**·HCl derived from the X-ray coordinates. Bottom: packing of **8b**·HCl in the crystal [(●) nitrogen atoms, (●) sulfoxide oxygens].

The effect is seen in highly polar proton-bridge weakening solvents (DMSO or MeOH), indicating that the shift is not associated with intramolecular hydrogen bonding. In summary, the high-field shift is associated with the pyridine and sulfoxide moieties. It can only be observed if an anisotropic group (phenyl or benzimidazolyl) is linked to the sulfur, suggesting that the pyridine 3-Me group approaches the anisotropic unit through a conformational change associated with protonation.

Such an approach is not found in the solid state of **8b**·HCl, as was revealed from an X-ray analysis of **8b**·HCl, which was chosen as a stable analogue of **2d** (Figure 2).

The solid-state conformation of **8b**·HCl cannot account for the observed high-field effect found in solution, since the two aromatic rings are arranged in parallel planes and in a "trans" manner with respect to the linking S–CH_2 unit. Furthermore, a strong H bond between the oppositely charged ions is present which must be weakened or absent in highly polar solvents such as MeOH or DMSO. In addition, from the crystal packing diagram (Figure 2b), it can be seen that pairs of **8b**·HCl are orientated in such a manner that strong *intermolecular* sulfoxide–dipole/sulfoxide–dipole interactions are possible.

The preferred solution conformations of **1/8** and **2/8**-H^+ may also be accounted for by considering the mutual *intramolecular* dipole–dipole interactions between the pyridine/pyridinium moiety and the sulfoxide.

Protonation of pyridine causes an inversion of the dipole moment from D = 2.12 D to D = −2.97 D.[8] Thus, in **2/8**-H^+ we postulate that, realignment of the pyridinium and sulfoxide dipoles, following protonation, necessitates a rotation about the CH_2–S bond and gives rise to a conformation in which the pyridine 3-Me group approaches the anisotropic benzimidazole or phenyl (Figure 3). The upfield shift in **2/8b**-H^+ is therefore accounted for by the 3-methyl group being forced to lie within the shielding region of the benzimidazole or phenyl. The lack of such an effect in **8a/8a**-H^+ is consistent with the absence of an anisotropic group. Furthermore, the enhancement of the effect at low temperature reflects the increased contribution of this low-energy conformation under these conditions.

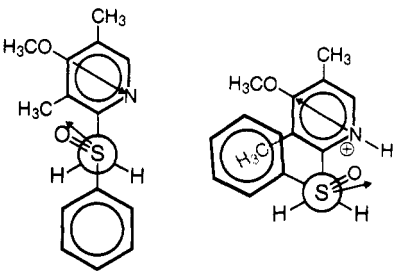


Figure 3. Newman projections of **8b** and **8b**-H^+ through the CH_2–S bond.

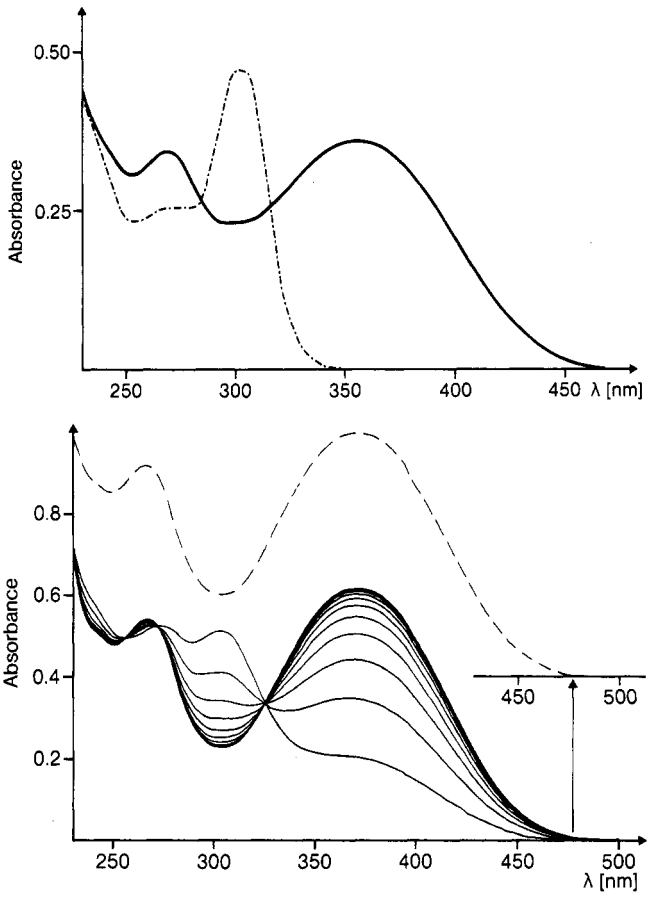


Figure 4. UV spectra derived from **1d** (at 20 °C). Top: **1d** in MeOH (-·--·-), $c = 2.9 \times 10^{-5}$ mol L^{-1}, d = 1 cm; **1d** 10 min after dissolution in 0.1 mol L^{-1} HCl (—), $c = 3.1 \times 10^{-5}$ mol L^{-1}, d = 1 cm. Bottom: **1d** in MeOH containing 0.4% (v/v) 1 mol L^{-1} HCl (—), $c = 5.3 \times 10^{-5}$ mol L^{-1}, d = 1 cm, first cycle 4 min after dissolution, other cycles each 6 min; isolated **3d** in MeOH/HCl (- - -), $c = 2.6 \times 10^{-4}$ mol L^{-1}, d = 0.2 cm.

Formation and Characterization of the Long Wavelength Absorbing Intermediate 3. Treatment of **1a–d** with aqueous acids in the absence of thiols gives rise to the development of a long wavelength absorbing species; the maximum bathochromic absorption being reached

(8) CNDO and INDO Molecular Orbital Program; CNINDO: Dobosh, P. A. "QCPE Program" No. 223, calculated on CDC 6500, Fides Rechenzentrum Zürich, Switzerland.

within a few minutes (e.g., **1d** dissolved in 0.1 N HCl, Figure 4).

However, the rapid decrease of this maximum, observed at concentrations of 10^{-4} mol/L or higher, reveals the elusive character of the intermediate species in aqueous solution. In more dilute aqueous acidic solutions (less than 10^{-4} mol/L) or in acidified MeOH, even at concentrations higher than 10^{-4} mol/L, the life time of this intermediate is dramatically prolonged. Thus we were able to follow the development of UV spectra characterized by isosbestic points starting from **1** even in less acidified solution.

In the case of **1d**, the elusive intermediate could be enriched from dilute aqueous solutions by HPLC techniques using a buffer of pH 2.1 as eluant. Isolation of analytically pure **3b–d** was achieved by dissolution of **1b–d** in a mixture of a slight molar excess of aqueous 50% HBF_4 in MeOH at −5 °C. The yellowish precipitates gave UV spectra virtually superimposable with those obtained from the treatment of **1b–d** with acid in aqueous solution (Figure 4). On the basis of spectroscopic data, the new 5*H*-pyrido[1′,2′:4,5][1,2,4]thiadiazino[2,3-*a*]benzimidazol-13-ium structure **3**[9] was assigned to this intermediate.

The charged compounds **3** result from a new far-reaching rearrangement of the precursor sulfoxides **1**. The pyridine nitrogen is now linked to the 2-position of a benzimidazole moiety; a molecular arrangement which is also found in the disulfides **12** (Scheme V) and described in the preceding paper.[1,10] However, in contrast to **12**, in which almost free rotation is possible around the bond connecting the two heterocycles, the additional bridge in **3**, linking the benzimidazole and pyridinium moieties, enforces a more coplanar arrangement. The long-wavelength UV absorption of **3**, which is not observed in spectra of **12**, arises as a consequence of this increased coplanarity (cf. Discussion in the preceding paper in this series[1]).

The ^{1}H NMR spectra of **3b–d** are characterized by an extreme downfield shift of the signal for the proton at position 1 (δ >9). This is due to a combination of the delocalized positive charge and the anisotropic field of the lone-pair electrons of N-12 caused by the almost planar arrangement of the molecule. This extreme shift is not seen with the charged disulfide **12**.

The structure **3** also accounts for the fact that substituents in position 5 of **1** give rise to regioisomeric mixtures of isolated **3c** and **3d** (1:1 and 6:4, respectively). As might be expected, the largest ^{1}H NMR chemical shift differences in the isomeric pairs are observed for the signals of H-8 and H-11. In isomer-free **3b**, H-8 and H-11 appear as two separate signals (δ 7.80 and 7.60, respectively) which is in accordance with the presence of benzimidazole nitrogen substitution. The corresponding protons, H-4 and H-7, in the precursor sulfoxides **1** have identical chemical shifts due to a tautomeric equilibration in polar solvents.[11] The expected chemical shift differences were also observed for C-8 and C-11 in the ^{13}C NMR spectrum of **3b**.

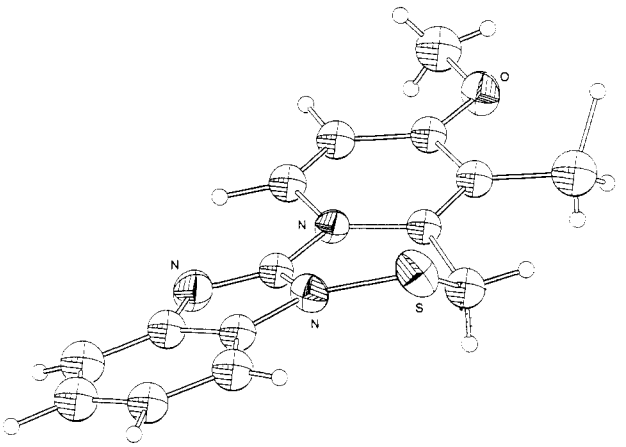
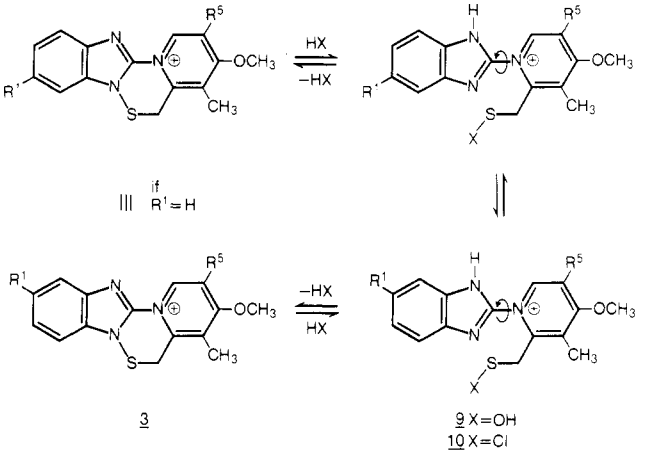


Figure 5. Perspective drawing of **3b** derived from the X-ray coordinates.

Scheme III. Isomerization of 3



If DCl but not DBF_4 or trifluoroacetic acid is added to **3** dissolved in CD_3OD, coalescence of the ^{1}H NMR signals for H-8 and H-11 is observed. Thus, in **3b** (R^1 = H) the two doublets for H-8 and H-11 merge to one broad signal for both protons. In the case of **3c** and **3d** (R^1 = CF_3 and OMe, respectively), the singlets due to H-8 and H-11 of each regioisomer coalesce to one broad singlet. The corresponding doublets for H-8 and H-11 of each regioisomer of both compounds are not fully resolved. These experiments suggest a rapid ring opening–rotation–ring closure process (Scheme III). This is probably due to the high nucleophilicity of the chloride anion combined with the relatively high stability of the sulfenic acid chloride **10**, allowing sufficient time for rotation around the linking bond.[12]

Water-induced equilibration is too slow to be observed within the NMR time scale. Indirect evidence for sulfenic acid **9** formation[13] by an analogous nucleophilic attack of water is discussed below and will be described in detail in the forthcoming publication.[7]

The positive ion DISIMS spectra confirmed the molecular weight of the cationic species, which yielded the base peak for all three compounds (m/z 284 for **3b**, m/z 352 for **3c**, and m/z 328 for **3d**). Since **3b** cannot form regioisomers, it was chosen for the growth of single crystals for X-ray analysis. Suitable crystals of this sensitive compound could be obtained by in situ preparation of **3b** from **1b** at −20 °C by dissolution of **1b** in a cold mixture

(9) For reviews on the chemistry of sulfenamides, see: (a) Schubart, R. "Sulfensäuren und deren Derivative, Sulfensäure-N-Derivate" *Methoden der Organischen Chemie (Houben-Weyl)*; Klamann, D., Ed.; Thieme: Stuttgart, 1985; Vol. E11, p 107. (b) Hogg, D. R. *Compr. Org. Chem.* **1979**, *3*, 277. (c) The involvement of cyclic sulfenamides in the rearrangement of allyl sulfenates has been discussed by: Hoffmann, R. W.; Goldmann, S. *Chem. Ber.* **1978**, *111*, 2716.

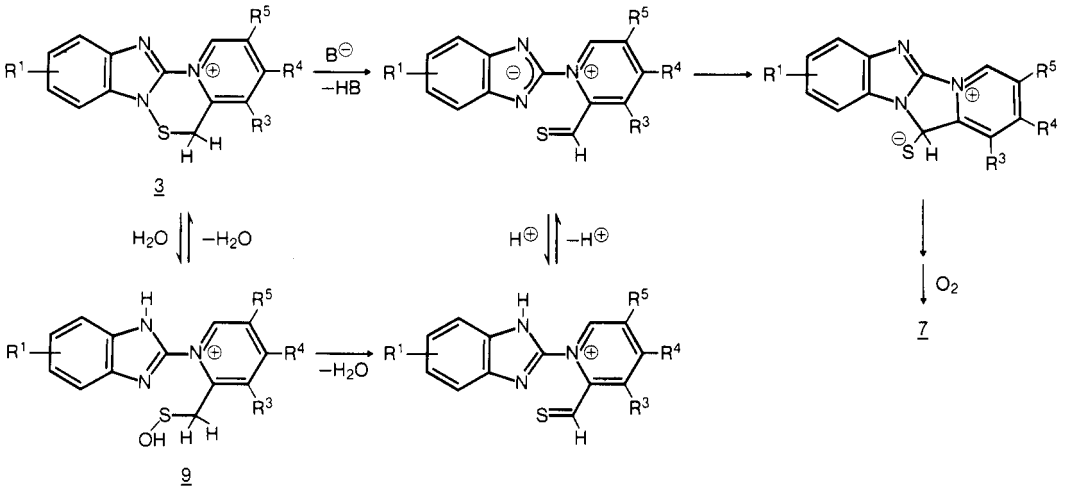
(10) (a) 2-Pyridiniobenzimidazolide, the backbone of **12**, was first reported by: Boyd, G. V. *Tetrahedron Lett.* **1966**, 3369. Recently analogues thereof have been communicated by: Alcalde, E.; Dinarès, I.; Fayet, J.-P.; Vertut, M.-C.; Elguero, J. *J. Chem. Soc., Chem. Commun.* **1986**, 734–735. (b) See also: Figala, V. Ph.D. Thesis, Universität München, 1970.

(11) They show tautomeric equilibria in nonaqueous solvents such as $CDCl_3$, e.g., **1d** has a ^{13}C NMR spectrum showing pairs of peaks for benzimidazole carbons. The ^{1}H NMR spectrum shows line broadening for H-4, H-6, and H-7.

(12) For a recent review of sulfenic acid halides, see ref 9a, p 68.

(13) Davis, A. F.; Jenkins, L. A.; Billmers, R. L. *J Org. Chem.* **1986**, *51*, 1033 and references therein.

Scheme IV. Formation of 7



of MeOH containing a slight excess of aqueous 50% HBF_4. The results of the X-ray analysis (Figure 5) are in complete accord with the spectroscopic data discussed above.

The X-ray analysis corroborated the conclusions drawn from the UV and NMR data, namely, that **3** exists in an almost coplanar arrangement. This is indicated by the torsion angle C4a–N13–C12a–N7 = 18°. All pyridinium linked atoms, with the exception of ring carbon C5, are located within a common plane containing the pyridinium moiety (C5 deviates by 22.6 pm).

Chemical Reactivity of 3. The chemical reactivity of **3** is governed by the weakness of the sulfenamide-like S6–N7 bond and the enhanced mobility of the H-5 protons, due to the acidifying influence of the pyridinium moiety. Even weak nucleophiles, e.g., H_2O, are capable of opening the S6–N7 bond reversibly by a nucleophilic attack on S6, thus forming sulfenic acid derivatives. In the presence of water, a concentration-dependent equilibrium is observed between **3** and the thiolsulfinate **4**, the expected condensation product of the sulfenic acid **9**.[7,14]

Reaction of 3 with Thiols. In the preceding paper,[1] we described the formation of the disulfides **12**, obtained from the reaction of the sulfoxides **1** with thiols such as 2-mercaptoethanol under acidic conditions. We discussed this reaction with respect to the covalent inhibition of the gastric (H^+–K^+)-ATPase.

As indicated in the above discussion, the sulfenamides **3** are also formed from **1** under these acidic conditions in the absence of thiols, suggesting that **3** may be the reactive thiophilic intermediate. Since **3b–d** are easily prepared in analytically pure form as BF_4 salts, we were able to study the reaction of **3b–d** with thiols under acidic as well as neutral conditions. The reaction products **12**, whose structure elucidation has been discussed previously,[1] result from nucleophilic attack of the thiol sulfur on S6 of **3** with concomitant cleavage of the weak S6–N7 bond.[15]

The rapid reaction can easily be followed spectrophotometrically in stopped-flow experiments, as the long wavelength absorption of **3** is not superimposed by other absorptions. Thus, the second-order rate constants were found to be 62.1 ± 2.2 L mol^{-1} s^{-1} and 77.3 ± 5.7 L mol^{-1} s^{-1} for the reaction of **3c** and **3d**, respectively, with 2-mercaptoethanol in 0.1 N HCl at 20 °C.

As can be seen from these data, substituents in position 9(10) of **3** only marginally influence the formation of **12**. The weakness of the sulfenamide-like bond between S6 and N7, as well as the excellent leaving group ability of the benzimidazole part, is a prerequisite for this very fast reaction.

Formation of 7. Recently, Rackur et al. described the formation of the tetracyclic disulfide **7a** (R^{1-5} = H) from a solution of **1a** in 0.1 N HCl at room temperature and discussed the prospective involvement of compounds **7** in the inhibitory process of the (H^+-K^+)-ATPase. According to their postulated reaction pathway, compounds **7** are formed via putative thioaldehydes (Scheme IV) which rapidly react with the benzimidazole nitrogen to form the disulfides **7** after oxidation by air. Extreme signal broadening in the ^1H NMR spectrum of **7a**, as well as faint signals in the ESR spectrum, suggests that, in solution, **7a** is in equilibrium with the corresponding monomer sulfenyl radical. Osmometric molecular weight determinations confirmed that **7a** is only dissociated by a trace amount and accounts for the weak ESR signals observed.

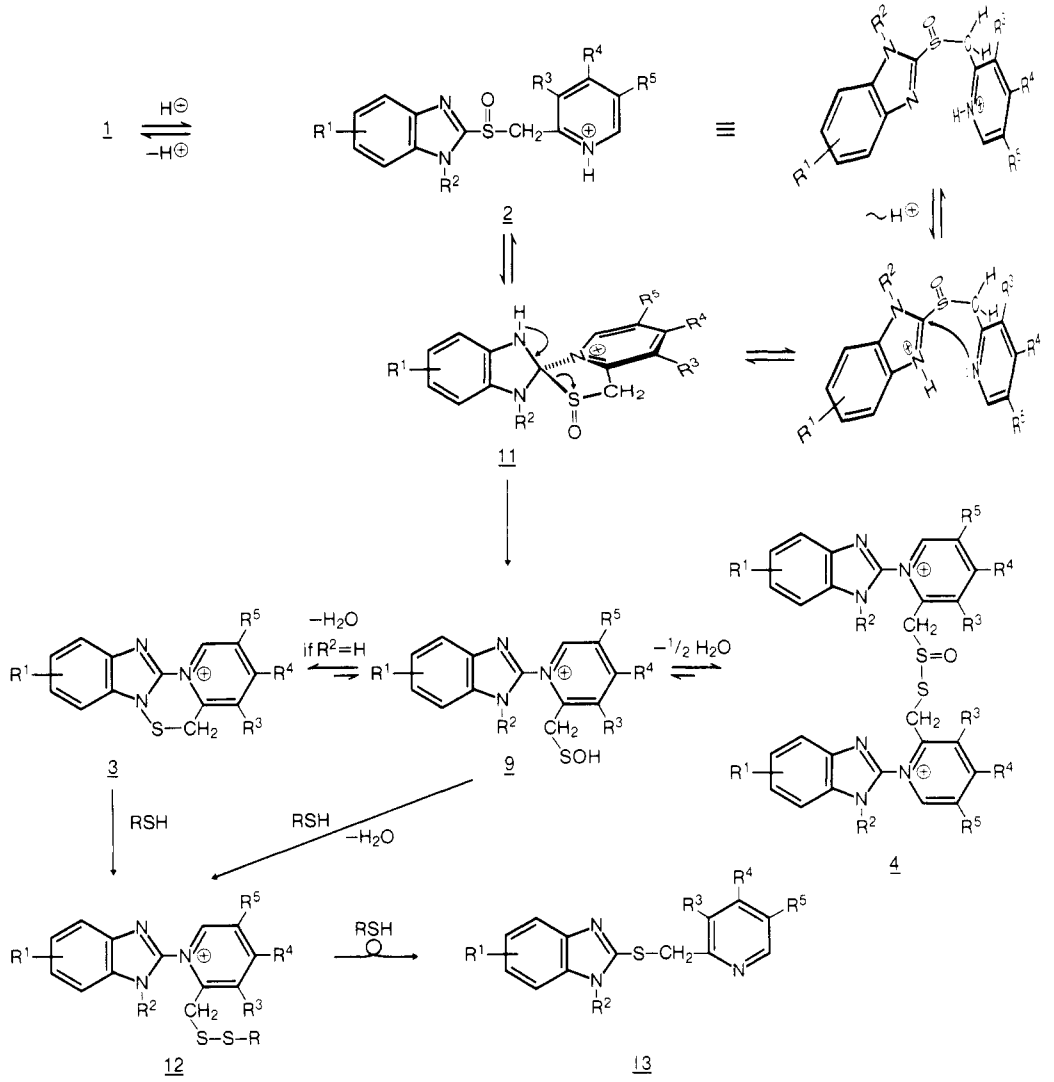
Since the sulfenamide-like compounds **3** are formed under these acidic conditions they should also be regarded as potential precursors of thioaldehydes. The protons H-5 in **3** are easily removed, due to the acidifying influence of both the adjacent pyridinium moiety and sulfur atom, thus yielding the putative thioaldehyde in a smooth fragmentation reaction (Scheme IV). The ease of this fragmentation reaction is further enhanced by the weakness of the sulfenamide like S6–N7 bond and the excellent leaving group ability of the benzimidazole moiety, which may be further enhanced by protonation. The thioaldehydes can also be formed by deprotonation induced fragmentation of the disulfides **12** or **5** which already contain the rearranged molecular backbone, albeit that the applied base must have a higher basicity (data not included). Since the methoxy substituent R^4 in the pyridine part of **3b–d** greatly stabilizes these compounds, the reaction to **7** is of minor relevance during the acid treatment of these sulfoxides.

Overall Reaction Pathway to 13. Disulfides of type **12** have been described in the preceding paper as a model for the covalently inhibited (H^+–K^+)-ATPase. A simplified proposal for the unique chemistry involved in their formation is depicted in Scheme V.

The most general aspect of the reaction cascade is the acid-catalyzed transformation of the sulfoxides into highly thiophilic species, the sulfenic acid **9**, and derivatives thereof, via a new type of rearrangement. From a mechanistic point of view, the key step in this process is the formation of the putative spiro sulfoxide **11** arising from

(14) Block, E.; O'Connor, J. *J. Am. Chem. Soc.* **1974**, *96*, 3929. See also ref 13.
(15) See ref 9a, p 126, and ref 9b.

Scheme V. Proposed Pathway for the Reaction of 1a-e with Thiols (RSH) under Acidic Conditions



nucleophilic attack of the pyridine nitrogen on the activated 2-position of the benzimidazole moiety.

We suggest that formation of **11** is induced by protonation of **1** on the pyridine nitrogen to form, in the first instance, the salts **2**. Protonation initiates a conformational change, due to different internal dipole–dipole interactions of free and protonated **1** as evidenced by the ^{1}H NMR high-field shift of the signal for the pyridine 3-methyl group. In the conformation assumed by **2**, both reactive centers involved in the formation of **11** approach each other. However, to facilitate the reaction, the benzimidazole must become protonated and the pyridine nitrogen demasked, giving a species which will only be present to a small extent under acidic conditions. This proton transfer may take place via an intramolecular or an intermolecular process. The subsequent attack by the pyridine on the benzimidazole 2-position, however, must occur rapidly, before CH_2–S bond rotation, since the adopted conformation may no longer be of low energy for this species.

This sequence of transformations offers a possible explanation for the seemingly paradoxical finding, that the transformation of **1** to rearranged products is faster, the lower the pH of the reaction mixture. The formation of **11** is, however, hampered in highly concentrated acids, e.g., in 90% H_2SO_4, and this, we believe, is due to the permanent masking of the pyridine nitrogen under these conditions.

We suggest that the postulated spiro form **11** rearranges to the very unstable sulfenic acid **9**. **9** can be stabilized by an intramolecular loss of water if R^2 = H, forming the tetracyclic sulfenamides **3a–d** which, in cases **3c–d** ($R^1 \neq$ H), exist as of mixtures of two regioisomers.[16] In the case of the sulfoxide **1e**, where R^2 = Me, stabilization via **3** is impossible and, therefore, an intermolecular loss of water occurs to form the thiolsulfinate **4e**.[14] **4e** is the expected dimeric anhydride of the sulfenic acid **9**. The ^{1}H NMR coalescence experiment with isolated **3b** and DCl discussed above shows that the equilibrium between **3b** and the corresponding sulfenic acid chloride **10b** is almost completely in favor of the cyclic form. The corresponding sulfenic acid **9b** itself is even more disfavored. However, at high concentrations of **3** and low temperature, the conditions for the dimerization of **9** or derivatives thereof to the thiolsulfinates **4** are dramatically improved.[7]

The reaction of sulfenamides with thiols to form disulfides is a well-documented reaction.[15] In the case of the planar cyclic sulfenamides **3** both the release of steric repulsion and the excellent leaving group ability of the benzimidazole moiety contribute to the fast formation of **12**.

If the acid-induced treatment of **1** is performed in the presence of thiols, the disulfides **12** may also be formed

(16) Due to the sensitivity of **3**, separation of the regioisomers was not attempted.

by trapping the putative sulfenic acids **9** prior to their cyclization to **3**. In support of this, the sulfoxide **1e** (R^2 = Me), which is unable to form **3**, cleanly gives the corresponding disulfide **12e**. However, a dramatic difference in the thiol reaction is seen if acid treatment of **1** is performed prior to thiol addition. Whereas, the N-unsubstituted sulfoxides **1b–d** still give **12b–d**, **1e** is rapidly transformed to **4e**, which is slowly reduced to **5e** by thiols.[7] This chemical feature is reflected by the high in vitro activity of **1b–d** in contrast to **1e** which is almost inactive. The rapid stabilization of the sulfenic acid **9** to the sulfenamide **3** renders a highly thiophilic species with an extended life span, available for diffusion to the target enzyme. This is especially the case if the concentration of **3** is very low, thus disfavoring dimerization to **4**.[14] The lifetime of **3**, even in aqueous acid, is in the range of hours if the concentration is below 10^{-6} mol/L. The physiological concentration of **3** reached in the parietal cells may be of the same order.

The (H^+–K^+)-ATPase activity of the sulfoxides **1** can, therefore, be discussed in terms of the formation of the long-lived sulfenamides **3**, the "active principle". Thus, as can be seen from Scheme V, analogues in which the pyridine is attached to the 3- or 4-position would not be expected to readily undergo the rearrangement to **3** since the distance between the pyridine nitrogen and the benzimidazole 2-position would be too great. Similarly, the formation of the spiro intermediate **11** is hampered in **8c** (Scheme II) due to the steric effect of the methyl group in the 6-position which can be readily seen from space-filling models. Consistent with their inability to form **3**, these compounds do not inhibit the (H^+–K^+)-ATPase. On the other hand, the 4-MeO group in the sulfenamides **3b–d** exerts a stabilizing influence and this may, in part, account for the high activity of the precursor sulfoxides **1b–d** in contrast to **1a**.

The disulfides **12** can easily be cleaved with thiols to the sulfides **13**. This reduction, in which a second rearrangement of the molecule backbone occurs, was discussed in depth in the preceding paper.[1] Formally, the overall reaction of the sulfoxides **1** with excess thiol is, therefore, a simple reduction to the corresponding sulfides **13**. This apparently trivial reaction, however, hides a unique acid-induced cascade, involving two far-reaching rearrangements of the molecular backbone.

Conclusions. The sulfoxides **1a–d** are potent and long-lasting inhibitors of gastric acid secretion and elicit their activity by the covalent modification of thiol groups on the gastric (H^+–K^+)ATPase. The disulfides **12** are a model for the covalently inhibited enzyme. Under conditions which resemble those of the parietal cell, (e.g., 0.1 N HCl), **1a–d** are transformed in a cascade of unique and fast reactions. These reactions are induced by protonation of **1a–d** and thus account for the high selectivity of these drugs in vivo. Since all intermediates involved are highly polar charged compounds, they probably accumulate in the vicinity of the target enzyme.

We have presented evidence that the sulfenamide **3** is the long-lived "active principle" of the highly active precursor sulfoxides **1**. **3** is identical with the thiophilic intermediate deduced in the preceding paper.[1] Furthermore, we have demonstrated that biological activity of congeners of **1** can be explained in terms of the proposed reaction pathway outlined in Scheme V. In summary, the reactions described render the sulfoxides **1a–d** a unique class of gastric (H^+–K^+)-ATPase inhibiting drugs with high selectivity.

Experimental Section

Melting points are uncorrected and were determined with a Büchi 510 apparatus (heating rate 3 °C/min). Microanalyses were performed by Dr. W. Rozdzinski, Institut für Organische Chemie, Biochemie und Isotopenforschung der Universität, Pfaffenwaldring 55, D-7000 Stuttgart 80, West Germany. IR spectra were recorded with a Perkin-Elmer 257 grating spectrometer. ^1H and ^{13}C NMR spectra were recorded at 200.13 (or 360.13) MHz and 50.32 (or 90.56) MHz, respectively, by using selective 5 mm diameter probes on a Bruker AC 200 (or AM 360) superconducting high-resolution FT-NMR spectrometer. TMS was used as internal standard in organic solvents (TSP in D_2O). Mass spectra were obtained by using a VG MM 7070 F spectrometer interfaced to a VG 2035 data system or on a Finnigan 4610 mass spectrometer interfaced to an Incos 2300 data system. The latter instrument was used to obtain positive ion DISIMS (discharge ionization secondary ion mass spectrometry) spectra. The sample matrix employed was 3-nitrobenzyl alcohol. The bombarding gas was xenon, and the system was operated by using a discharge potential of 3.5 kV. Molecular weights (MW) were determined in chloroform with a Knauer vapor pressure osmometer calibrated with benzil. ESR spectra were recorded on a Bruker B-ER 420 spectrometer operating in X band. UV–vis spectra were obtained by using a Perkin-Elmer Model 555 photometer.

Synthesis of the Sulfoxides 1, 2, and 8. The syntheses of the sulfoxides **1a,b,d**[17] and **1c**[18] were previously described. The methyl-substituted sulfoxide **1e**, as well as the derivatives **8c,d**, is described in the preceding paper.[1] The sulfoxides **8a,b** were prepared according to Scheme II via the corresponding sulfides which were converted to the sulfoxides by oxidation with 3-chloroperoxybenzoic acid in CH_2Cl_2.

5-Methoxy-2-[((4-methoxy-3,5-dimethyl-2-pyridyl)methyl)sulfinyl]-1*H*-benzimidazole Tetrafluoroboric Acid Salt (2d·BF_4^-). To a stirred suspension of **1d** (500 mg, 1.4 mmol) in methanol (15 mL) at −5 °C was added HBF_4 (50% in water, 0.2 mL). Immediately after acid addition a yellowish solution was formed. After the mixture was stirred for 10 min, colorless crystals precipitated, which were collected by filtration after further 20 min of stirring. The crystals were dried (vacuum, 40 °C, 5 h) to give **2d**·BF_4^-, 200 mg (40%): mp 130 °C dec; IR (KBr) 3270, 2940, 1622 cm^{-1}; ^1H NMR (DMF-d_7, −40 °C) δ 8.78 (s, 1 H, H-6′), 7.64 (d, 1 H, $J_{7,6}$ = 8.9 Hz, H-7), 7.19 (d, 1 H, $J_{4,6}$ = 2.2 Hz, H-4), 7.03 (dd, 1 H, H-6), 5.13 (s, 2 H, 2′-CH_2), 4.00 (s, 3 H, 4′-OCH_3), 3.88 (s, 3 H, 5-OCH_3), 2.46 (s, 3 H, 5′-CH_3), 2.14 (s, 3 H, 3′-CH_3); ^{13}C NMR (DMF-d_7, −40 °C) δ 170.04 (s, C-4′), 157.07 (s, C-5), 150.40 (s, C-2), 142.95 (s, C-2′), 142.32 (d, J_{CH} = 189.3 Hz, C-6′), 138.28 (s, C-7a), 134.54 (s, C-3a), 130.83 (s, C-3′), 128.99 (s, C-5′), 117.99 (d, J_{CH} = 164.5 Hz, C-7), 114.32 (d, J_{CH} = 161.9 Hz, C-6), 95.94 (d, J_{CH} = 159.9 Hz, C-4), 60.79 (q, J_{CH} = 147.4 Hz, 4′-OCH_3), 54.95 (q, J_{CH} = 144.0 Hz, 5-OCH_3) 53.95 (t, J_{CH} = 145.0 Hz, 2′-CH_2), 13.41 (q, J_{CH} = 133.2 Hz, 5′-CH_3), 10.50 (q, J_{CH} = 130.3 Hz, 3′-CH_3); MS [DISIMS (+)], m/z (relative intensity) 346 (16, M^+), 330 (32), 328 (100), 326 (71), 296 (46), 282 (32). Anal. Calcd for $C_{17}H_{19}N_3O_3S$·HBF_4: C, 47.13; H, 4.65; N, 9.70; S, 7.40. Found: C, 47.17; H, 4.82; N, 9.70; S, 7.35.

General Procedure for 8a,b. The thiols (0.01 mol) were reacted with the corresponding (chloromethyl)pyridine derivatives[18] (see Scheme II) in 50 mL of EtOH containing 10 mL of aqueous 2 N NaOH at 50 °C until the reactions were complete. After evaporation to dryness, the organic materials were extracted twice with ethylacetate (30 mL each) and the combined extracts dried over Na_2SO_4 and evaporated to dryness. The residues, without further purification, were dissolved in CH_2Cl_2 (100 mL), cooled to −30 °C and oxidized by the addition of 0.01 mol of 3-chloroperoxybenzoic acid in one portion. After 2 h at −30 °C the temperature of the reaction mixture was allowed to rise to 0 °C (30 min). It was extracted twice with half-saturated aqueous Na_2CO_3 solution (20 mL each), and the combined extracts were washed with water, dried over Na_2SO_4, and evaporated to dryness. **8a** was recrystallized from hot cyclohexane; **8b** was obtained as an oil, pure enough for our purposes.

(17) Junggren, U. K.; Sjöstrand, S. E. Eur. Pat. 005 129, 1979.
(18) Senn-Bilfinger, J.; Schaefer, H.; Figala, V.; Klemm, K.; Rainer, G.; Schudt, Chr.; Simon, W. Ger. Offen. DE 3 240 248, 1981.

Table III. Temperature Dependency of the ^1H NMR Chemical Shift (δ) of the Pyridine 3-Methyl Group[a]

temp, °C	1d	2d		8a	8a·HCl	8b	8b·HCl
+30			2.05				
+20	2.15		2.03	2.28	2.47	2.04	1.81
+5	2.14		1.97	2.28	2.46	2.03	1.76
−10	2.13		1.91	2.28	2.46	2.03	1.70
−25	2.12		1.86	2.28	2.45	2.02	1.64
−40	2.10	1.78	1.80	2.28	2.44	2.01	1.57
−55	2.09	1.72	1.75	2.28	2.44	2.01	1.51
−70	2.06	1.66	1.69	2.28	2.43	2.00	1.43
−85	2.04	1.59	1.63	2.28	2.42	1.99	1.35
−90			1.52				
−95			1.32				
−97			1.31				
−100	2.00	1.27	1.27	2.27	2.42	1.99	1.26

[a] For conditions, see text.

4-Methoxy-3,5-dimethyl-2-[(methylsulfinyl)methyl]-pyridine (8a): yield, 1.7 g (80%); mp 72–73 °C (cyclohexane); IR (KBr) 2995, 1570, 1470, 1275, 1080, 1040 cm^{-1}; ^1H NMR (CD_3OD) δ 8.21 (s, 1 H, H-6), 4.29 (AB, 2 H, $\Delta\nu$ = 0.06 Hz, J_{AB} = 13.26 Hz, 2-CH_2), 3.80 (s, 3 H, 4-OCH_3), 2.71 (s, 3 H, $SOCH_3$), 2.33 (s, 3 H, 5-CH_3), 2.27 (s, 3 H, 3-CH_3). Anal. Calcd for $C_{10}H_{15}NO_2S$: C, 56.31; H, 7.09; N, 6.56; S, 15.04. Found: C, 56.20; H, 7.04; N, 6.36; S, 15.27.

4-Methoxy-3,5-dimethyl-2-[(phenylsulfinyl)methyl]-pyridine (8b): yield, 2.2 g (81%); oil; IR (KBr) 3460, 1570, 1420, 1440, 1270, 1090, 1045 cm^{-1}; ^1H NMR (CD_3OD) δ 8.18 (s, 1 H, H-6), 7.55 (s, 5 H, Ph), 4.36 (AB, 2 H, $\Delta\nu$ = 0.25 Hz, J_{AB} = 12.72 Hz, 2-CH_2), 3.73 (s, 3 H, 4-OCH_3), 2.26 (s, 3 H, 5-CH_3), 2.04 (s, 3 H, 3-CH_3); ^{13}C NMR (DMF-d_7) δ 163.43 (C-4), 150.07 (C-2), 148.93 (C-6), 144.57 (Ph C-1), 130.56 (Ph C-4), 128.69 (Ph C-2 and C-6), 126.46 (C-3), 125.18 (C-5), 123.66 (Ph C-3 and C-5), 62.96 (2-CH_2), 59.14 (4-OCH_3), 12.09 (5-CH_3), 10.35 (3-CH_3). Anal. Calcd for $C_{15}H_{17}NO_2S$: C, 65.43; H, 6.22; N, 5.08; S, 11.63. Found: C, 65.63; H, 6.17; N, 4.82; S, 11.72.

4-Methoxy-3,5-dimethyl-2-[(phenylsulfinyl)methyl]-pyridine Hydrochloride (8b·HCl). **8b** (1.88 g, 0.0068 mol) was dissolved in 1 N HCl (6.84 mL) and evaporated to dryness. The crystalline residue was recrystallized from hot acetonitrile, yielding 1.2 g (56.7%) **8b**·HCl: mp 146–147 °C; IR (KBr) 3440 (br), 2620, 1630, 1620, 1470, 1295, 1270, 1090, 1050 cm^{-1}; ^1H NMR (CD_3OD) δ 8.55 (s, 1 H, H-6), 7.49–7.65 (m, 5 H, phenyl), 4.64 (AB, 2 H, $\Delta\nu$ = 0.087 Hz, J_{AB} = 13.98 Hz, 2-CH_2), 4.00 (s, 3 H, 4-OCH_3), 2.46 (s, 3 H, 5-CH_3), 1.81 (s, 3 H, 3-CH_3). ^{13}C NMR (DMF-d_7) δ 168.45 (s, C-4), 145.20 (s, Ph C-1), 142.80 (s, C-2), 142.63 (d, J_{CH} = 179.6 Hz, C-6), 131.14 (d, J_{CH} = 162.2 Hz, Ph C-4), 129.95 (s, C-3), 128.85 (d, J_{CH} = 163.1 Hz, Ph C-2 and C-6), 127.82 (s, C-5), 123.85 (d, J_{CH} = 165.1 Hz, Ph C-3 and C-5), 60.29 (q, J_{CH} = 147.1 Hz, 4-OCH_3), 57.54 (t, J_{CH} = 144.6 Hz, 2-CH_2), 12.85 (q, J_{CH} = 129.6 Hz, 5-CH_3), 10.68 (q, J_{CH} = 129.9 Hz, 3-CH_3). Anal. Calcd for $C_{15}H_{17}NO_2S$·HCl: C, 57.78; H, 5.82; N, 4.49; S, 10.28; Cl, 11.37. Found: C, 57.68; H, 5.79; N, 4.22; S, 10.23; Cl, 11.44.

Single-Crystal X-ray Structure of (*R*)-8b·HCl. Colorless crystals of **8b**·HCl suitable for analysis were prepared by slow crystallization from acetonitrile at −20 °C. They were monoclinic, space group $P2_1$, with a = 835 (1) pm, b = 937 (1) pm, c = 938 (1) pm, β = 92.1 (1)°, and d_{calcd} = 1.41 g cm^{-3} for Z = 2 ($(C_{15}H_{18}N_1O_2S_1)^+Cl^-$, M_r 311.8). The randomly chosen crystal was of R configuration.

Collection of the diffraction data was carried out on a Syntex-Nicolet P3 diffractometer equipped with a graphite monochromated Mo Kα radiation source. The size of the crystal used for data collection was 0.10 × 0.15 × 0.20 mm. A total of 1083 independent reflections were measured for $2.0° \le 2\theta \le 44°$, of which 920 were considered to be observed [$I_0 \ge 2\sigma(I_0)$]. The structures were solved by direct methods using the SHELXTL[19] package and refined by least-squares techniques. The positions of the hydrogen atoms were derived from difference Fourier syntheses. The final agreement factors were R = 0.0868 and R_w = 0.0831. The agreement factors for the enantiomer with S configuration were somewhat worse (R = 0.087 and R_w = 0.0836).

^1H NMR Studies on the Temperature Dependency of the Chemical Shift of the Pyridine 3-Me Signals in 1d/2d, 8a/8a·HCl and 8b/8b·HCl. The chemical shifts of the pyridine 3-Me signals in the free bases **1d**, **8a**, and **8b** were obtained from CD_3OD solutions (10 mg each in 0.5 mL, prepared at room temperature), which were successively cooled to −100 °C. The same procedure, but with addition of 20% DCl/D_2O solution (10 μL), was applied for **8a**·HCl and **8b**·HCl. In the case of the acid labile **1d**, consecutive transformations during formation of **2d** were circumvented by preparing the CD_3OD solution at −78 °C, addition of the acid and warming up to −40 °C. The left column relating to **2d** in Table III consists of the shifts obtained by successive cooling to −100 °C, whereas the right column contains the corresponding data obtained by rewarming of this solution. At temperatures higher than +5 °C increasing amounts of transformation products were observed.

Preparation of 3. **3a** was too unstable to be isolated as the BF_4 salt according to the general procedure described for the preparation of **3b–d**. Thus, it was generated in solution by dissolution of **1a** (10^{-6} mol/L) either in MeOH with the addition of aqueous 1 N HCl (4 μL/mL) or in 0.1 N HCl and detected by UV. The characteristic long wavelength absorption λ_{max} = 355 (in MeOH/HCl) and 348 nm (in HCl) developed slowly and reached their maximal intensity after 2 h (MeOH/HCl) and 1 h (HCl), respectively, standing at room temperature.

General Procedure for the Preparation of 3b–d as BF_4 Salts. The sulfoxides **1b–d** (13.5 mmol) were dissolved in stirred mixtures of MeOH and 50% aqueous HBF_4 at −5 °C and kept for 2 h. The yellowish precipitates formed were filtered off, washed with little cold MeOH, and dried under reduced pressure (50 °C, 72 h) to yield the analytically pure sulfenamides **3**.

3-Methoxy-4-methyl-5*H*-pyrido[1′,2′:4,5][1,2,4]thiadiazino[2,3-*a*]benzimidazol-13-ium tetrafluoroborate (3b·BF_4^-): from MeOH (57 mL) and HBF_4 (1.7 mL) according to the above general procedure; yield, 2.5 g of **3b**·BF_4^- (50.0%); mp 186 °C dec; IR (KBr) 1625 cm^{-1}; UV (MeOH acidified with 1 N aqueous HCl (4 μL/mL)) λ_{max} 330 nm (ϵ 15000 L mol^{-1} cm^{-1}); ^1H NMR (DMF-d_7) δ 9.73 (d, 1 H, $J_{1,2}$ = 7.6 Hz, H-1), 8.12 (d, 1 H, H-2), 7.88 (d, 1 H, $J_{8,9}$ = 7.1 Hz, H-8[20]), 7.70 (d, 1 H, $J_{11,10}$ = 7.7 Hz, H-11), 7.51 (dd, 2 H, H-9 superimposed with H-10), 5.36 (s, 2 H, H-5), 4.48 (s, 3 H, 3-OCH_3), 2.55 (s, 3 H, 4-CH_3); ^{13}C NMR[21] (MeCN-d_3, −40 °C) δ 171.67 (s, C-3), 145.78 (s, C-4a), 142.77 (s, C-12a), 141.35 (d, J_{CH} = 199.8 Hz, C-1), 123.20 (s, C-4), 107.71 (d, J_{CH} = 175.3, C-2), 58.12 (q, OCH_3), 31.34 (t, C-5), 9.80 (q, CH_3) [singlets not assigned, δ 138.54, 134.38 (C-7a, C-11a); doublets not assigned, δ 123.3, 119.3, 116.8, 110.7 (C-8, C-9, C-10, C-11)]; MS [DISIMS (+)], m/z (relative intensity) 284 (100, M^+), 286 (44), 282 (69), 253 (62), 252 (63), 238 (33). Anal. Calcd for

(19) Sheldrick, G. M. "SHELXTL, an integrated system of solving, refining, and displaying crystal structures from diffraction data", Universität Göttingen: Göttingen 1981; Revision 3.0.

(20) Assignment analogous to **3c**·BF_4^-; see ref 22.

(21) Since **3b** is rapidly transformed into the disulfide **5b** via the thiolsulfinate **4b**, carefully controlled conditions to obtain a ^{13}C NMR spectrum of **3b** are required. The conditions used were as follows: **3b** (20 mg) was dissolved in dry MeCN-d_3 (0.5 mL) and the solution immediately cooled to −40 °C. Under these conditions almost no transformations were observed as revealed by a ^1H NMR spectrum after the accomplished ^{13}C recording.

$C_{15}H_{14}N_3OS{\cdot}BF_4$: C, 48.54; H, 3.80; N, 11.32; S, 8.64. Found: C, 48.24; H, 4.00; N, 11.25; S, 8.46.

Single-Crystal X-ray Structure of 3b·BF_4^-. Yellowish needles of 3b·BF_4^-, suitable for analysis, were obtained by in situ generation of 3b·BF_4^- from **1b** according the following procedure: **1b** (129.1 mg) was dissolved in cold (0 °C) MeOH (49.4 mL) and 50% aqueous HBF_4 (0.056 mL) added; thereafter, the cold solution was transferred to a refrigerator (−20 °C) and kept at this temperature for 2 days. The needles were carefully removed by filtration and dried under vacuum at 40 °C (2 h). They were monoclinic, space group $P2_1/c$, with a = 949.4 (4) pm, b = 1714 (1) pm, c = 950.4 (5) pm, β = 90.11 (4)°, and d_{calcd} = 1.59 g cm^{-3} for Z = 4 ($(C_{15}H_{14}N_3O_1S_1)^+BF_4^-$, M_r 371.2).

Collection of the diffraction data was carried out on a Syntex-Nicolet P3 diffractometer equipped with a graphite monochromated Mo Kα radiation source. The size of the crystal used for data collection was 0.3 × 0.2 × 0.4 mm. A total of 1474 independent reflections were measured for $2° \le 2\theta \le 44°$, of which 1033 were considered to be observed [$I_0 \ge 2\sigma(I_0)$]. The structures were solved by direct methods using the SHELXTL[19] package and refined by least-squares techniques. The positions of the hydrogen atoms were derived from difference Fourier syntheses. The final agreement factors were R = 0.069 and R_w = 0.068.

Isomeric mixture (1/1) of 3-methoxy-4-methyl-9(10)-(trifluoromethyl)-5*H*-pyrido[1′,2′:4,5][1,2,4]thiadiazino[2,3-*a*]benzimidazol-13-ium tetrafluoroborate (3c·BF_4^-): according to the general procedure from MeOH (135 mL) and HBF_4 (3.55 mL); yield, 4.9 g of 3c·BF_4^- (82.6%); mp 150 °C dec; IR (KBr) 1625 cm^{-1}; UV (MeOH acidified with 1 N aqueous HCl (4 μL/mL)) λ_{max} 319 nm (ϵ 16700 L mol^{-1} cm^{-1}); ^{1}H NMR (MeCN-d_3) [partially separated signals of two isomers with the ratio of 1/1] δ 9.41 and 9.40 (not completely separable, 1 H, $J_{1,2}$ = 7.6 Hz, H-1), 8.17 (s, 0.5 H, H-8 of the first isomer[22]) and 7.98 (s, 0.5 H, H-11 of the second isomer), 7.77–7.68 (m, 2 H, H-10 and H-11 of the first isomer and H-8 and H-9 of the second isomer), 7.70 (d, 1 H, H-2), 4.89 (s, 2 H, H-5), 4.31 (s, 3 H, 3-OCH_3), 2.45 (s, 3 H, 4-CH_3); ^{1}H NMR (Me_2SO-d_6) δ 9.61 and 9.59 (d, 0.5 H and 0.5 H, $J_{1,2}$ = 7.4 Hz, H-1), 8.28 and 8.19 (s, 0.5 H and 0.5 H, H-8 and H-11 of both isomers), 8.0–7.7 (m, 2 H, H-10 and H-11 of the first isomer and H-8 and H-9 of the second isomer), 7.90 (d, 1 H, H-2), 5.13 (s, 2 H, H-5), 4.34 (s, 3 H, 3-OCH_3), 2.43 (s, 3 H, 4-CH_3); ^{1}H NMR (CD_3OD) δ 9.61 (d, 1 H, $J_{1,2}$ = 7.6 Hz, H-1), 8.16 and 7.98 (s, 0.5 H and 0.5 H, H-8 and H-11), 7.90 (d, 1 H, H-2), 7.8–7.7 (m, 2 H, H-10 and H-11 of the first isomer and H-8 and H-9 of the second isomer), 5.06 (s, 2 H, H-5), 4.39 (s, 3 H, 3-OCH_3), 2.52 (s, 3 H, 4-CH_3); MS [DISIMS (+)], m/z (relative intensity) 352 (100, M^+), 350 (31), 320 (16). Anal. Calcd for $C_{16}H_{13}F_3N_3OS{\cdot}BF_4$: C, 43.76; H, 2.98; N, 9.57; S, 7.30. Found: C, 43.56; H, 3.21; N, 9.48; S, 7.10.

Isomeric mixture (66/34) of 3,9(10)-dimethoxy-2,4-dimethyl-5*H*-pyrido[1′,2′:4,5][1,2,4]thiadiazino[2,3-*a*]benzimidazol-13-ium tetrafluoroborate (3d·BF_4^-): from MeOH (150 mL) and HBF_4 (3.5 mL) according to the general procedure; yield, 4.3 g of 3d·BF_4^- (76.7%); mp 150 °C dec; IR (KBr) 1625 cm^{-1}; UV (MeOH acidified with 1 N aqueous HCl (4 μL/mL)) λ_{max} 370 nm (ϵ 11700 L mol^{-1} cm^{-1}); ^{1}H NMR (DMF-d_7) [partially separated signals of two isomers[20]]; major isomer (66%, 10-OCH_3); minor isomer (34%, 9-OCH_3)] (major isomer) δ 9.57 (s, 0.66 H, H-1), 7.78 (d, 0.66 H, $J_{8,9}$ = 8.9 Hz, H-8), 7.26 (d, 0.66 H, $J_{11,9}$ = 2.2 Hz, H-11), 7.09 (dd, 0.66 H, H-9), 4.49 (s, 3 × 0.66 H, 3-OCH_3), 3.98 (s, 3 × 0.66 H, 10-OCH_3), (minor isomer) δ 9.59 (s, 0.34 H, H-1), 7.62 (d, 0.34 H, $J_{11,10}$ = 9.0 Hz, H-11), 7.40 (d, 0.34 H, $J_{8,10}$ = ca. 2 Hz, H-8), 7.18 (dd, 0.34 H, H-10), 4.51 (s, 3 × 0.34 H, 3-OCH_3), 3.94 (s, 3 × 0.34 H, 9-OCH_3), (superimposed signals of both isomers) δ 5.34 (s, 2 H, H-5), 2.77 (s, 3 H, 2-CH_3), 2.61 (s, 3 H, 4-CH_3); MS [DISIMS (+)], m/z (relative intensity) 328 (100, M^+), 326 (27), 296 (18). Anal. Calcd for $C_{17}H_{18}N_3O_2S{\cdot}BF_4$: C, 49.18; H, 4.37; N, 10.12; S, 7.72. Found: C, 49.12; H, 4.38; N, 10.13; S, 7.95.

(22) This assignment denotes the first isomer as the 10-trifluoromethyl-substituted regioisomer. The H-8 singlet of the 9-substituted regioisomer was expected at lower field than the corresponding H-11 singlet of the 10-substituted isomer. This order of singlets is found in the spectra of the N-1 methylated 6-(trifluoromethyl)benzimidazole 1e and its unambiguously synthesized 1-methyl-5-trifluoromethyl isomer, see ref 1a.

^{1}H NMR Studies of the Chloride-Induced Isomerizations of 3b and 3c. Rapid isomerizations of **3b** and **3c** indicated by the coalescence of the signals for H-8 and H-11 in their ^{1}H NMR spectra could be brought about by the addition of DCl. Additions of CF_3CO_2D or HBF_4 gave no similar results.

3b: two signals (δ 7.88 (d, 1 H, H-8) and 7.70 (d, 1 H, H-11)) were observed from a DMF-d_7 solution (1.5 mg of 3b·BF_4^-, 0.5 mL DMF-d_7); they coalesced to one signal (δ 7.74 (br, 2 H)) by the addition of DCl (50 μL of 20% DCl/D_2O).

3c: in this case only the signals H-8 of the 9-trifluoromethyl regioisomer (δ 8.16 (s, 0.5 H)) and H-11 of the 10-trifluoromethyl regioisomer (δ 7.98 (s, 0.5 H)) were sufficiently separated (1.5 mg of 3c·BF_4^-, 0.5 mL CD_3OD); both signals of both isomers coalesced to one signal (δ 8.04 (br, 1 H)) by the addition of DCl (40 μL of 20% DCl/D_2O).

Reactions of 3 with 2-Mercaptoethanol. (A) Isolation of 2-[2-(5-Hydroxy-2,3-dithiapentyl)-4-methoxy-3-methyl-1-pyridinio]-5-(trifluoromethyl)benzimidazolide (Neutral Form of 12c, R = CH_2CH_2OH). This compound was obtained on a preparative scale from 3c·BF_4^- as follows. To 3c·BF_4^- (0.01 mol) dissolved at room temperature in MeOH (500 mL) was added immediately after dissolution the equivalent amount of 2-mercaptoethanol. After 30 min, ice–water (1 L) was added and the pH of the yellowish solution adjusted to 8 by means of a saturated aqueous $NaHCO_3$ solution. Two extractions with ethyl acetate (400 mL each) and drying of the combined extracts over K_2CO_3 gave, after evaporation to dryness and recrystallization of the solid residue from hot acetonitrile, pure neutral form of **12c** (R = CH_2CH_2OH), identical in every respect with the previously prepared compound,[1] in 73% yield.

(B) UV-Monitored Reactions under Stopped-Flow Conditions. Stopped-flow measurements were performed in 0.1 N HCl at 20 °C. The buildup of **3** from acidified aqueous solutions of **1** (about 10^{-4} mol/L) was controlled photometrically (**3c**, 10 min, 314 nm; **3d**, 10–15 min, 359 nm).

When a plateau value for the concentration of **3** was reached, the reaction was initiated by mixing with a solution of 2-mercaptoethanol in 0.1 N HCl (about 10^{-2} mol/L, mixing ratio 1:1) in the stopped-flow device. For calculating the second-order rate constant k_2, it was assumed that all sulfoxide **1** in the acidic solution had been converted to **3**, without any loss to decomposition products. This is well fulfilled in methanolic solution and sufficiently in aqueous solution, if the time periods for the build up of **3** and for the measurement are not too long. Fresh solutions of **3** were prepared for each measurement. From the known concentration of the reactants and the measured rate of the decay of **3**, k_2 was calculated by using the expression[23]

$$k_2 = -\frac{1}{c(\mathrm{RSH})} \cdot \frac{\ln c(3)}{t} \quad [\mathrm{L\ mol^{-1}\ s^{-1}}]$$

Stopped-flow measurements were performed with a device built up from a Hi-Tech (SF 2A 557) stopped-flow mixing unit, a source for monochromatic chopped light (Metrospec grating monochromator with D_2 lamp and Brookdeal Electronics light chopper), and a phase-sensitive detection unit (RCA 4840 photomultiplier powered by Keithley Instr. 244 high voltage supply in connection with a Brookdeal Electronics lock-in amplifier Model 9503). For measurement processing and data storage and handling a Kontron PSI 80 computer was used in direct connection with the stopped-flow device. Curves for decaying reactants and pseudo-first-order kinetic plots were plotted for each experiment on a Houston Instrument digital plotter (HI PLOT). The dead time of the device for mixing reactants in one and the same solvent was determined as 6 ms by chromate oxidation of hydrogen peroxide.

Bis(pyrido[1,2-*c*]imidazo[1,2-*a*]benzimidazol-5-yl) Disulfide (7a).[5] **1a** (10 mmol) was dissolved at room temperature in acetic acid (100 mL). After the mixture stood overnight, shiny dark crystals precipitated, which were filtered off and dried under vacuum at 95 °C for 24 h, yielding **7a**, 1.5 g (62.5%); the product contained, according to the ^{1}H NMR and the elemental analysis,

(23) Frost, A. A.; Pearson, R. G. *Kinetics and Mechanism. A Study of Homogeneous Chemical Reactions*, 2nd ed.; Wiley: New York, 1961; p 19.

1.75 equiv of acetic acid, which could not be removed without decomposition of **7a**: ^{1}H NMR (CF_3COOD)[24] δ 8.28 (d, 1 H, $J_{1,2}$ = 7.2 Hz, H-1), 7.6–7.7 (m, 3 H, H-2, H-3, H-4), 7.5–7.6 (m, 1 H, H-7), 7.3–7.45 (m, 1 H, H-10), 7.05–7.25 (m, 2 H, H-8, H-9). ESR: The paramagnetism of solutions of **7a** was demonstrated unambiguously by ESR. A solution of **7a** in chloroform or toluene shows an ESR signal of low intensity without hyperfine splitting, indicating low radical concentration and rapid exchange processes between the monomer radical and the disulfide dimer. MW determination: MW (chloroform) 495 g/mol (expected 476 g/mol for the dimer). MS (70 eV), m/z (relative intensity) 238 (100, $C_{13}H_8N_3S^+$), 122 (11, $C_6H_4NS^+$), 119 (14, $C_{13}H_8N_3S^{2+}$), 78 (28%, $C_5H_4N^+$); UV (chloroform) λ_{max} 510 nm (ϵ 7000), 422 (7800), 264 (42 800); based on MW 476. Anal. Calcd for $C_{26}H_{16}N_6S_2 \cdot 1.75$ HOAc: C, 60.91; H, 3.98; N, 14.44; S, 11.02. Found: C, 60.98; H, 4.15; N, 14.67; S, 11.04.

(24) Neutral solvents gave pronounced signal broadening due to the accompanied sulfenyl radical. **7a** is believed to be protonated in CF_3COOD solution, forming the corresponding bis cation of **7a**. This is indicated by the low field lying shifts of the C-1 proton signals. The assignment is analogous to **3b**.

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Asymmetric Additions to Chiral Naphthalenes. 4. An Asymmetric Synthesis of the AB-Ring of Aklavinone

A. I. Meyers* and Kimio Higashiyama

Department of Chemistry, Colorado State University, Ft. Collins, Colorado 80523

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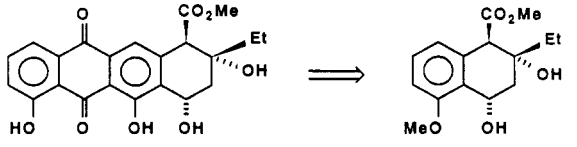
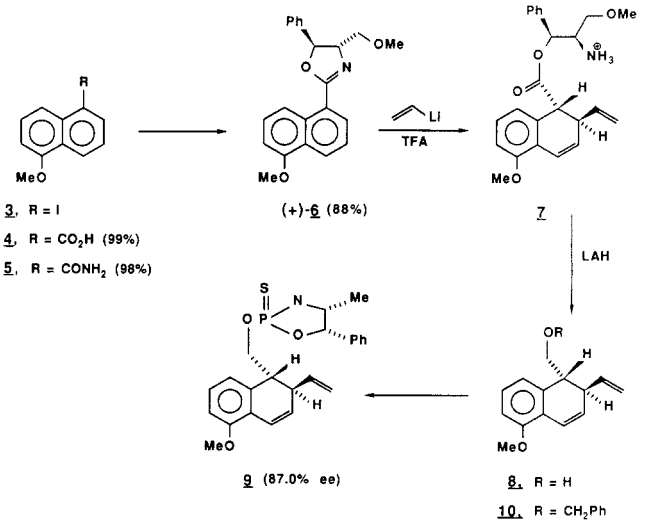
The chiral 1-naphthyloxazoline (+)-**6**, prepared from known 1-iodo-5-methoxynaphthalene, was treated with vinyllithium to afford the dihydronaphthalene **8**, after quenching and reductive removal of the chiral auxiliary. Introduction of the tertiary hydroxyl group followed by bromination–hydrolysis gave the appropriately substituted AB-ring of aklavinone **2** in 84–88% ee. The absolute configuration and relative configuration were confirmed by X-ray single-crystal analysis.

The extensive effort to reach the anthracycline antitumor antibiotics by total synthesis has culminated in a number of efficient and sometimes elegant routes to aklavinone and 11-deoxyanthracyclinones.[1] Our recent studies involving chiral naphthalenes have opened an asymmetric route to a variety of dihydronaphthalenes containing two simultaneously introduced stereocenters,[2] and it is the application of this methodology to the anthracyclinones we now wish to describe. Our approach to the problem addresses the stereochemically endowed AB-ring of aklavinone (**1**) which, if simplified into the bicyclic system **2**, becomes the objective of our chiral naphthalene methodology. Once accomplished, with hopefully high enantiomeric excess, **2** can be appropriately substituted to allow annulation[3] to the final anthracyclinone alkavinone.



1 **2**

Our synthetic sequence leading to the AB-ring **2**, anticipated to provide the correct absolute stereochemistry, began with transforming the known 5-methoxy-1-iodonaphthalene (**3**)[4] into the carboxylic acid **4** (*n*-BuLi, THF, CO_2) in 99% yield. Transformation to the amide **5** was accomplished by using oxalyl chloride, CH_2Cl_2, and ammonia affording the product in 98% yield. The chiral oxazoline (+)-**6** was formed from the amide **5** by first converting it into the imidate (Meerwein's reagent, 1,2-dichloroethane), followed by addition of (*S*,*S*)-(+)-1-methoxy-2-amino-3-phenyl-3-hydroxypropane.[5] Thus, the requisite starting material **6** was prepared from **3** in three steps in 85% yield. The crucial asymmetric addition was



performed by using vinyllithium (THF, –60 °C), which added from the top (*re*) face[2] of **6**, and the resulting adduct was quenched with trifluoroacetic acid. In this manner, the oxazoline ring opened, affording the dihydro-

(1) Bauman, J. G.; Hawley, R. C.; Rappaport, H. *J. Org. Chem.* **1985**, *50*, 1569. A complete list of references to earlier synthetic work is given.
(2) Meyers, A. I.; Barner, B. A. *J. Org. Chem.* **1986**, *51*, 120 and earlier references cited.
(3) Kende, A. S.; Rizzi, J. P. *J. Am. Chem. Soc.* **1981**, *103*, 4247.
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(5) Meyers, A. I.; Knaus, G.; Kamata, K.; Ford, M. E. *J. Am. Chem. Soc.* **1976**, *98*, 567.

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