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Original paper

Anti-secretory and anti-ulcer activities of some new 2-(2-pyridylmethyl-sulfinyl)-benzimidazoles

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Summary — A series of substituted sulfinyl benzimidazoles were prepared and tested for gastric anti-secretory activity. Following initial screening, two compounds were tested for anti-ulcer activity. The new compounds showed pharmacological properties different from those of omeprazole **1**, since they proved to be weak anti-secretory agents displaying non-specific anti-ulcer activity. Some structural requirements for optimum activity were elucidated.

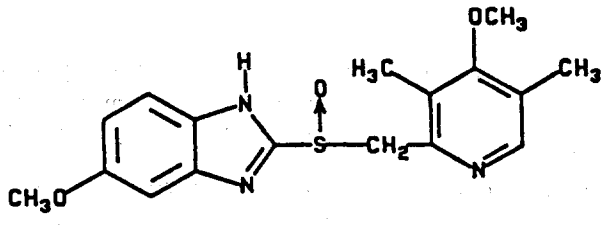
Résumé — **Activités anti-sécrétoire et anti-ulcéreuse de quelques nouveaux (pyridylméthyl-2 sulfinyl)-2 benzimidazoles.** *Une série de dérivés benzimidazoliques de l'oméprazole a été synthétisée et examinée en fonction de l'activité anti-sécrétoire gastrique. Deux composés ont été sélectionnés et essayés sur deux modèles de l'ulcère expérimental. Aucun des nouveaux dérivés ne s'est avéré meilleur que l'oméprazole. On a mis en évidence des corrélations structure—activité.*

gastric anti-secretory activity / anti-ulcer activity / sulfoxides / benzimidazole sulfoxides / pyridylmethyl sulfoxides

Introduction

Peptic ulcer disease is generally thought to be induced by a disturbance in the balance of aggressive factors, such as acid and pepsin, and defensive mechanisms, such as mucus layer and mucosal blood flow [1]. Despite this statement, the research for therapeutically useful anti-ulcer agents has been directed toward the decrease of the aggressive factors according to the famous and old Schwarz's dictum 'no acid — no ulcer' [2]. Different classes of drugs have been discovered and are now available for anti-ulcer therapy from the old anti-acids and anti-cholinergics to the more recent histamine (H_2) receptor antagonists [3], the selective (M_1) AcCh—anti-muscarinics [4] and the recently discovered (H^+/K^+)-ATPase inhibitors [5].

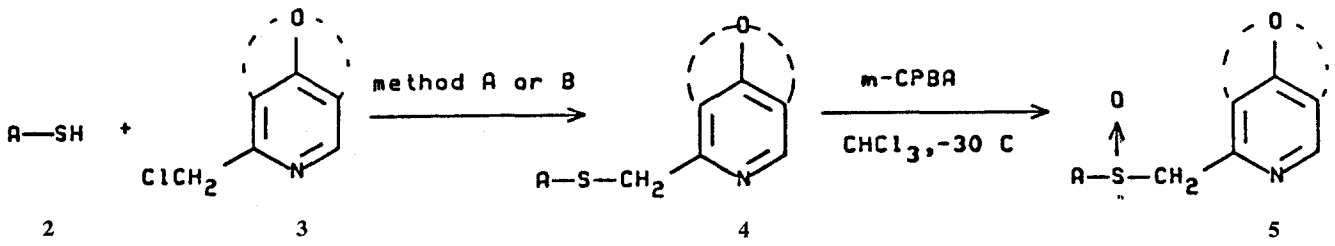
Members of the latter class, the so-called proton pump inhibitors of which omeprazole [6] **1** is the most representative, are now being actively developed [7—9]. The interest in this class of strong and long lasting anti-secretory agents is due to the novel and highly specific mechanism of action, which has been recently elucidated [10, 11]. In addition, sulfinylbenzimidazoles of the omeprazole type have been shown to inhibit gastric lesions induced in animals by the administration of noxious agents [12], thus strengthening the defensive mechanisms. This profile of combined anti-secretory and cytoprotective properties, which is unique in a non-prostaglandin class of drugs, represents, if confirmed in humans, a remarkable advance in the therapy of ulcer disease, since it would address both the aggressive and the defensive aspects of the ulcer etiopathology. Encouraged by these findings, we have synthesized some 2-(2-pyridyl-methyl-sulfinyl)-benzimidazoles having the general formula **5**. The compounds were tested both in anti-secretory and anti-ulcer animal models.



1

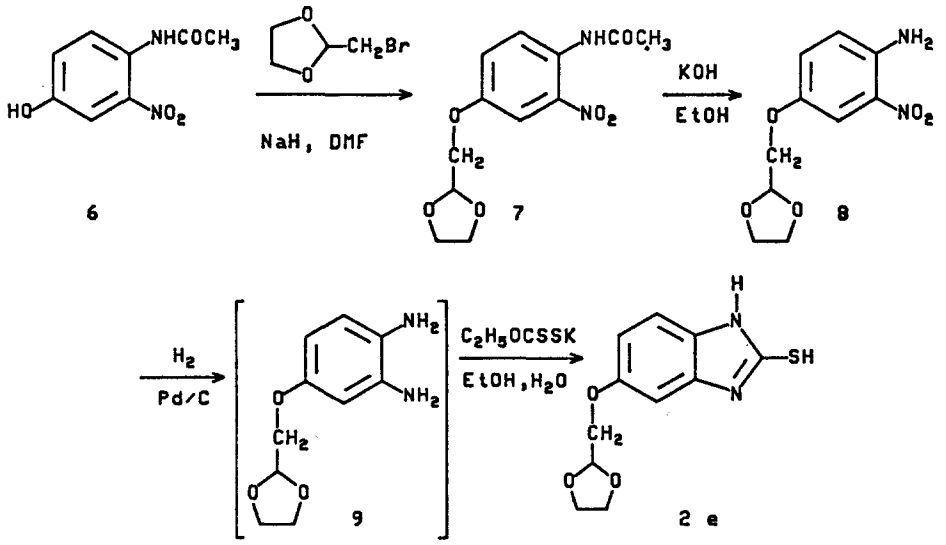
Chemistry

Synthetic pathways for the title compounds are outlined in Schemes 1—5. Benzimidazoline-2-thiones **2** were generally prepared by ring closure of the appropriate *o*-diamino-phenylene derivatives with carbon disulfide in the presence of KOH in warm aqueous ethanol, or with potassium ethyl xanthogenate (Schemes 2—4). Although in Table I the



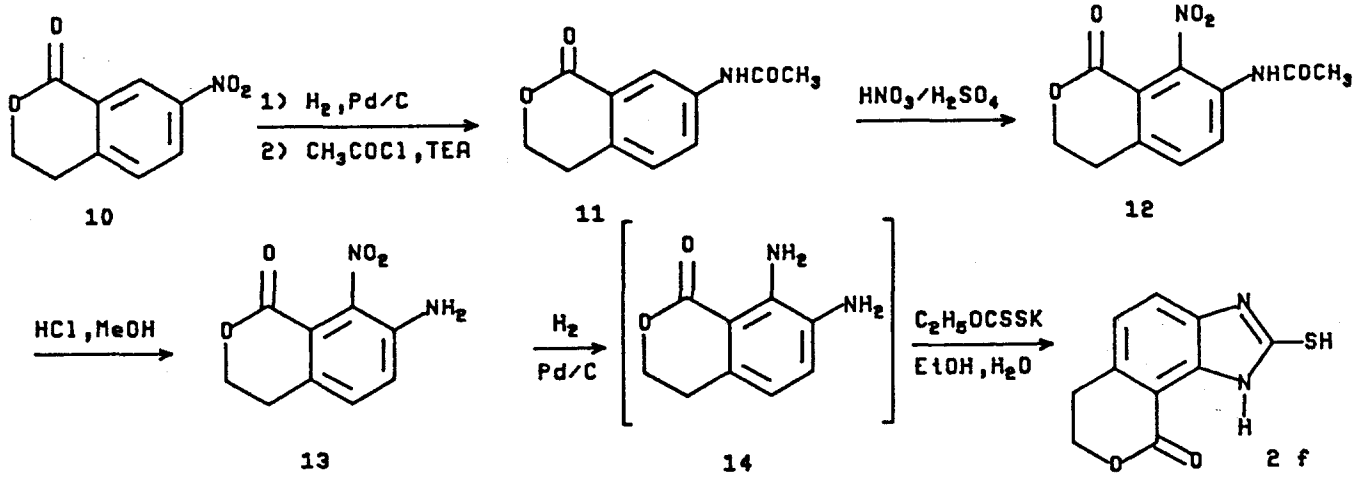
2 3 4 5

Scheme 1.



6 7 8 9 2e

Scheme 2.



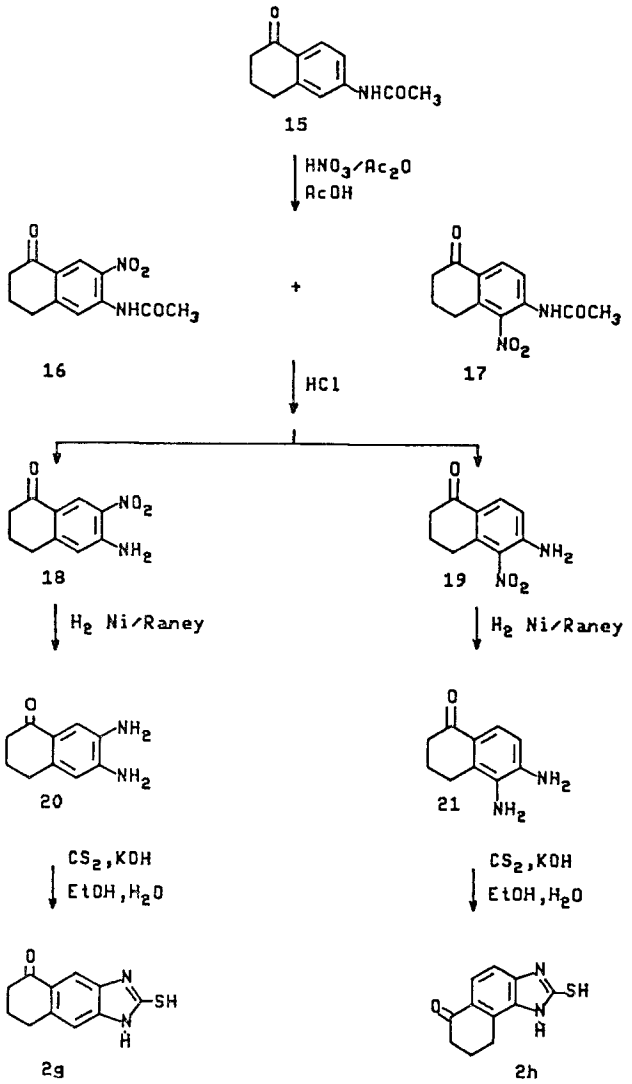
10 11 12 13 14 2f

Scheme 3.

compounds are reported in the thiol form, they are preferentially in their thione form, as evidenced by the characteristic absorptions of the thiourea groups in the IR spectra.

The new chloromethyl pyridines **3** (Table II) were obtained according to Scheme 5. The sulfides **4** (Table III) were prepared by coupling the benzimidazoline-2-thiones with the appropriate chloromethylpyridines either in aqueous ethanol in the presence of NaOH or in anhydrous dimethylformamide (DMF) in the presence of sodium hydride.

Confirmation of the *S*-alkylation comes from NMR and IR evidence (Table IV). Oxidation of the sulfides to the sulfoxides **5** (Tables V and VI) was accomplished by a standard technique employing *m*-chloroperbenzoic acid at —30°C [7, 13].



Scheme 4.

Pharmacology

The pharmacological properties of the new compounds were assessed in the rat, in comparison with omeprazole, by evaluating first their capacities to inhibit gastric acid secretion in two experimental models.

In a preliminary screening, a single dose of 3 mg/kg i.v. was utilized; then the ED_{50} of the two most promising compounds (**5f** and **5g**) was determined. The same two compounds were also tested against gastric erosions induced by different noxious agents. The results are reported in Tables VII and VIII, respectively.

Discussion

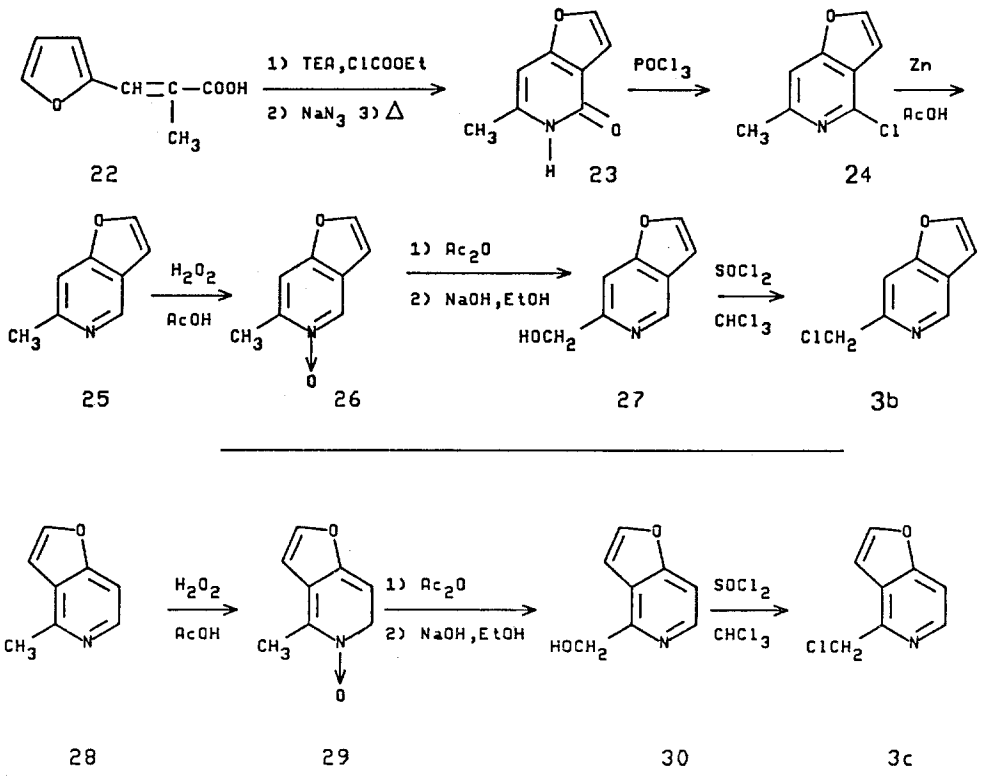
Modifications of the substituents present in the benzimidazole and pyridine moieties of omeprazole **1** were attempted in order to shed light on the structural requirements for optimal anti-secretory and anti-ulcer activities. Although the anti-secretory activity of omeprazole and some of its structural analogues has been evaluated by different authors, as recently described [14], in one *in vitro* and in one *in vivo* model (the isolated gastric gland preparation from the rabbit and the conscious chronic fistula dog), in the present study, selected simple and well-recognized *in vivo* models were used to assess both the anti-secretory and the anti-ulcer activities of our compounds in comparison with omeprazole itself. Rigid requirements seem to be associated with the relative pattern of the methyl and methoxy groups present on the pyridine ring. Actually, the anti-secretory activity of compounds **5j**—**k** in which the methoxy and one of the adjacent methyl groups are restricted in a furo-pyridine system is negatively affected. A possible explanation of the results could be found by considering the pivotal role of the basicity of the pyridine nitrogen which is responsible for the selective accumulation of omeprazole in the secretory glands and in the subsequent transformation into the active principle [11, 15].

The requirement of a completely aromatic benzimidazole moiety is clearly evidenced by compound **5i**, in which partial saturation of the aromatic moiety leads to a loss of activity.

As far as modifications of the benzimidazole nucleus are concerned, both electron releasing and withdrawing groups have been considered, either as simple substituents or inserted into additional rings fused with the benzimidazole moiety. Some of these modifications have already been taken into account in [14] and our results may supplement the conclusions inferred therein. Simple electron releasing groups were inserted at position 5 and the compounds obtained (**5a**—**e**) are practically inactive. This fact was rather unexpected, since omeprazole itself carries an electron releasing group, but, since it has been shown that a proper lipophilicity is beneficial for good activity, the high hydrophilic character of the selected substituents might be the cause of the observed loss of activity. A steric parameter might also be taken into account for compound **5e**. The low anti-secretory activity of compound **5b** is substantially in agreement with the above disclosed results: a different dose and a different experimental model might explain the low anti-secretory activity that we found.

Electron withdrawing groups (ketone and ester) have been inserted into fused structures (compounds **5f**—**h**). The fairly good activity found confirms that this type of substitution can lead to active compounds, but in the present case, a steric effect might be responsible for the lower activity in comparison with omeprazole. Therefore, it can be said that for optimum anti-secretory activity, the substitution pattern of the pyridine ring and the aromaticity of the benzimidazole nucleus are of fundamental importance. Electron withdrawing and releasing groups are tolerated on the benzimidazole nucleus, but particular attention should be given to the lipophilic and steric parameters.

Considering now the effect on the anti-ulcer activity, as tested in the stress plus acetylsalicylic acid (ASA) model, compounds **5f**—**g** appear to be as active as omeprazole.



Scheme 5.

The two compounds considered here, however, were not able to prevent the lesions induced by ethanol. It can be concluded that the present compounds show pharmacological properties different from those of omeprazole, with their anti-secretory activities being only in some cases comparable to that of the reference compound and not associated with cytoprotective properties, at least as intended by Robert *et al.* [16]. Only a non-specific anti-ulcer activity underlies the pharmacological profile of these new 2-(2-pyridylmethyl-sulfinyl)-benzimidazoles.

Experimental protocols

Pharmacology

The anti-secretory activities of the compounds were investigated in both the pylorus-ligated rat [17] and in the anesthetized rat with continous perfusion of the stomach lumen [18] whose acid secretion was elicited by histamine (1 mg/kg/h, i.v.).

The protective action of the compounds against gastric erosions was determined according to two experimental models: ethanol-induced gastric ulcer [12] and acetylsalicylic acid (ASA)-induced gastric damage in stressed rats [19]. The activity of the selected and the reference compounds was determined after bolus i.v. administration.

Chemistry

Melting points are uncorrected and were obtained on a Büchi capillary melting point apparatus. Infrared spectra were run in nujol on a Perkin—Elmer 337 spectrophotometer. ^{1}H NMR spectra were recorded on a Varian T-60 spectrometer in the indicated solvent and the chemical shifts are given in ppm (δ) against the internal standard tetramethylsilane. The new compounds were analyzed for C, H, N (Cl and S) and the analytical data were within $\pm$ 0.4% of the theoretical values. The indicated yields have not been optimized. The reactions were monitored by thin—layer chromatography (TLC) on Silicagel 60 F-254 plates (Merck) eluted by appropriate solvents. Column chromatographies were performed on Silicagel 60 (Merck, 70—230 mesh) and were eluted by appropriate solvents. Melting points, yields, crystallization solvents and analytical data of compounds **2** (**a**—**j**), **3** (**a**—**c**), **4** (**a**—**k**) and **5** (**a**—**k**) are summarized in Tables I—VI.

Synthesis of the fused mercaptoimidazoles **2** *(a—j)*

5-Amino-benzimidazoline-2-thione **2a**, *4,5,6,7-tetrahydrobenzimidazoline-2-thione* **2i** and *5-methoxy-benzimidazoline-2-thione* **2j** were synthesized according to described procedures [20—22].

5-Acetamido-benzimidazoline-2-thione **2b**

Acetic anhydride (1.36 g, 13.3 mmol) in anhydrous tetrahydrofuran (THF) (5 ml) was dropped at room temperature into a suspension of **2a** (2 g, 12.1 mmol) and NEt_3 (1.85 ml, 13.3 mmol) in anhydrous THF (20 ml). Within 30 min a clear solution was obtained, from which a white solid slowly crystallized out. The suspension was stirred overnight and then the solid was filtered and dried. Yield 1.8 g.

Table I. Physicochemical data of the benzimidazole-2-thiones **2a—j**. A—S—H

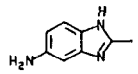
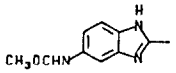
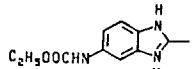
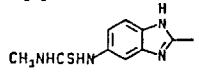
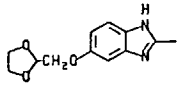
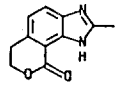
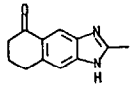
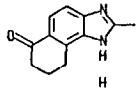
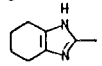
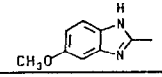
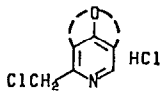
2	A	M.p. °C	Cryst.Solv.	Yield %	Analysis	IR (cm^{-1})	^{1}H-NMR (solvent: $CDCl_3$ - d_6-DMSO 2:5) δ (ppm)
a		276-278 (280)[20]	-	-	-	-	-
b		290 (300-307)[20]	THF	72	$C_9H_9N_3OS$	1660 ($CH_3\underline{CO}$), 1620 (phenyl), 1490 (NHCSNH)	2.1 (s, 3H); 7 (d, 1H); 7.2 (m, 1H); 7.7 (d, 1H); 9.9 (s, 1H); 12.3 (bs, 2H)
c		280	Et_2O	36	$C_{10}H_{11}N_3O_2S$	1690 (NH$\underline{COO}$), 1620 (phenyl), 1490 (NHCSNH)	1.3 (t, 3H); 4.2 (q, 2H); 6.9-7.2 (m, 2H); 7.5 (d, 1H); 9.4 (s, 1H); 12.3 (bs, 2H)
d		224-225	THF	68	$C_9H_{10}N_4S_2$	1620 (phenyl), 1480 (NHCSNH)	3.0 (d, 3H); 6.9-7.4 (m, 3H); 7.5 (q, 1H); 9.4 (s, 1H); 12.4 (s, 2H)
e		265-266	EtOH-H_2O	83	$C_{11}H_{12}N_2O_3S$	1635 (phenyl), 1500 (NHCSNH)	3.8-4.0 (m, 6H); 5.2 (t, 1H); 6.7-6.8 (m, 2H); 7.0 (d, 1H); 12.3 (s, 2H)
f		240-241	EtOH-H_2O	76	$C_{10}H_8N_2O_2S$	1705 (CO); 1625 (phenyl), 1490 (NHCSNH)	3.1 (t, 2H); 4.6 (t, 2H); 7.1 (d, 1H); 7.4 (d, 1H); 11.7 (b, 1H); 12.8 (b, 1H)
g		290	EtOH-H_2O	86	$C_{11}H_{10}N_2OS$	1665 (CO), 1625 (phenyl), 1500 (NHCSNH)	2.1 (m, 2H); 2.6 (t, 2H); 3.0 (t, 2H); 7.0 (s, 1H); 7.6 (s, 1H); 12.6 (b, 2H)
h		240-241	EtOH-H_2O	65	$C_{11}H_{10}N_2OS$	1660 (CO), 1610 (phenyl), 1505 (NHCSNH)	2.1 (m, 2H); 2.6 (t, 2H); 3.0 (t, 2H); 7.0 (d, 1H); 7.7 (d, 1H); 12.6 and 12.7 (2b, 2H)
i		300 (282-283)[21]	EtOH-H_2O	-	-	-	-
j		(266)[22]		-	-	-	-

Table II. Physicochemical data of the chloromethyl pyridines hydrochlorides **3a—c**.



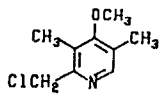
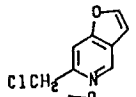
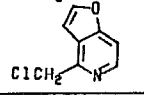
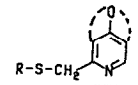
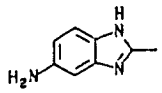
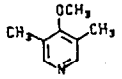
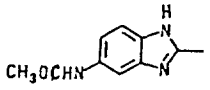
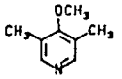
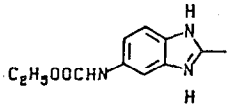
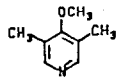
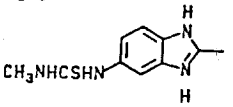
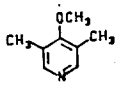
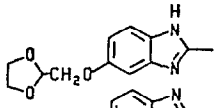
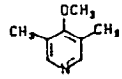
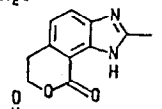
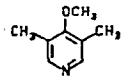
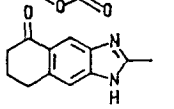
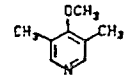
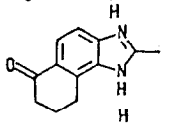
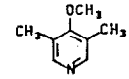
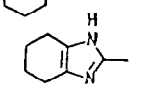
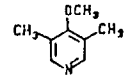
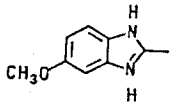
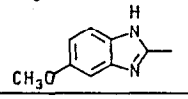
3		M.p. °C	Cryst.Solv.	Analysis	IR (cm^{-1})	^{1}H-NMR (solvent: $CDCl_3$ - d_6-DMSO 2:5) δ (ppm)
a		127-128 (128)[26]	-	-	-	-
b		181-183	Et_2O	C_8H_6ClNO . HCl	1520-1610 (pyridine)	5.0 (s, 2H); 7.3 (d, 1H); 8.2 (s, 1H); 8.3 (d, 1H) 9.3 (bs, 1H); 9.4 (s, 1H)
c		202-204	Et_2O	C_8H_6ClNO . HCl	1520-1610 (pyridine)	5.3 (s, 2H); 6.6-9.0 (bs, 1H); 7.6 (d, 1H); 8.2 (d, 1H); 8.5 (d, 1H); 8.7 (d, 1H)

Table III. Physicochemical data of sulfides **4a—k**.



comp	R		Method	M.p. °C	Cryst. Solv.	Yield %	Analysis
4a			A	84–86	Et_2O	64	$C_{16}H_{18}N_4OS$
4b			A	114–115	Et_2O	89	$C_{18}H_{20}N_4O_2S$
4c			A	102–103	Et_2O	61	$C_{19}H_{22}N_4O_3S$
4d			A	200–201	Et_2O	76	$C_{18}H_{21}N_5OS_2$
4e			B	114–115	Et_2O	57	$C_{20}H_{23}N_3O_4S$
4f			B	125–126	AcOEt	73	$C_{19}H_{19}N_3O_3S$
4g			A	126–128	EtOH	51	$C_{20}H_{21}N_3O_2S$
4h			A	141–142	EtOH	68	$C_{20}H_{21}N_3O_2S$
4i			A	125–126	CH_3CN	85	$C_{16}H_{21}N_3OS$
4j			A	135–137	Et_2O	59	$C_{16}H_{13}N_3O_2S$
4k			A	143–144	Et_2O	65	$C_{16}H_{13}N_3O_2$

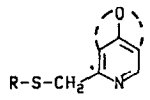
5-[(Ethoxycarbonyl)amino]-benzimidazoline-2-thione **2c**
Ethylchloroformiate (0.33 g, 3 mmol) in anhydrous THF (5 ml) was dropped into a suspension of **2a** (0.5 g, 3 mmol) and NEt_3 (0.3 g, 3 mmol) in anhydrous THF (10 ml). The suspension was stirred overnight at room temperature and then evaporated to dryness. The pure title compound was obtained after purification of the residue utilizing flash chromatography. (Eluant: methylenedichloride—methanol, 9:1.) Yield 0.4 g.

5-(3-Methylthioureido)-benzimidazoline-2-thione **2d**
A suspension of **2a** (1.8 g, 10.89 mmol) and methylisothiocyanate (0.87 g, 11.98 mmol) in THF (25 ml) was refluxed for 2 h. The white solid was filtered and dried to give the title compound. Yield 1.87 g.

2-[(4-Acetamido-3-nitro-phenoxy)-methyl]-1,3-dioxolane **7**
To a solution of 4-acetamido-3-nitro-phenol **6** [23] (2.9 g, 14.8 mmol) in dry DMF (10 ml) was added portionwise 80% NaH in oil (0.44 g, 14.8 mmol). The resulting solution was stirred at room temperature for 30 min and then 2-bromomethyl-1,3-dioxolane (2.46 g, 14.8 mmol) was added. The reaction mixture was heated to 90°C overnight under continuous stirring, then poured into water and extracted with ethyl acetate. The organic layer was washed with water, dried over $MgSO_4$ and concentrated to dryness. **7** was obtained as a yellow—orange solid. Yield 2.37 g (57%). An analytical sample was crystallized from methanol. mp: 85—87°C. IR ($CHCl_3$) (cm^{-1}): 3370 (N—H); 1705 (CONH); 1510 (NO_2). NMR ($CDCl_3$, DMSO-d_6), δ (ppm): 2.2 (s, 3H); 4.0 (b, 4H); 4.1 (d, 2H); 5.3 (t, 1H); 7.2 (dd, 1H); 7.6 (d, 1H); 8.0 (d, 1H); 9.9 (b, 1H).

2-[(4-Amino-3-nitro-phenoxy)-methyl]-1,3-dioxolane **8**
A solution of **7** (2.1 g, 7.4 mmol) in ethanol (50 ml) was reacted with 85% KOH (0.98 g, 14.8 mmol) for 3 h under stirring at room temperature. The reaction mixture was then concentrated to dryness and taken up in ethylacetate. The organic layer was washed with water and dried over $MgSO_4$. After evaporation of the solvent, crude **8** was purified by flash column chromatography. (Eluant: toluene—ethylacetate, 7:3). Yield 1.5 g (84%). mp: 95—96°C. IR (cm^{-1}): 3480—3370 (NH_2); 1515 (NO_2). NMR ($CDCl_3$), δ (ppm): 3.9—4.2 (m, 6H); 5.3 (t, 1H); 5.7 (b, 2H); 6.8 (d, 1H); 7.2 (dd, 1H); 7.6 (d, 1H).

Table IV. Spectroscopic data of sulfides **4a—k.**



A	IR (cm^{-1}) (nujol)	^1H-NMR (solvent: A: $CDCl_3$, B: $CDCl_3$-d_6-DMSO 2:5) (ppm)
4a	3360- 3440(NH); 1630-1610-1520 (benzimidazole and pyridine)	2.2-2.3 (2s, 6H); 3.7 (s, 3H); 4.4 (s, 2H); 5.8 (bs, 3H); 6.5 (m, 1H) 6.8 (d, 1H); 7.3 (d, 1H); 8.2 (s, 1H); A
4b	1660 (CONH); 1600-1560-1510 (benzimidazole and pyridine)	2.1 (s, 3H); 2.2-2.3 (2s, 6H); 3.7 (s, 3H); 4.6 (s, 2H); 7.0 (d, 1H); 7.3 (d, 1H); 7.8 (bs, 1H); 8.0 (bs, 1H); 9.9 (bs, 1H); B
4c	3210 (NHCOO), 1730 (OCO), 1600-1550-1510 (benzimidazole and pyridine)	1.3 (t, 3H); 2.3 (2s, 6H); 3.8 (s, 3H); 4.3 (q, 2H); 4.4 (s, 2H); 6.9-7.2 (bs, 1H); 7.1 (dd, 1H); 7.5 (d, 1H); 7.8 (d, 1H); 8.3 (s, 1H); A
4d	1600-1570-1510 (benzimidazole and pyridine); 1480 (NHCSNH)	2.2-2.3 (2s, 6H); 3.0 (d, 3H); 3.7 (s, 3H); 4.7 (s, 2H); 6.9-7.6 (m, 4H); 8.2 (s, 1H); 9.4 (s, 1H); 12.5 (bs, 1H); B
4e	1620-1590-1510 (benzimidazole and pyridine)	2.2 (2s, 6H); 3.8 (s, 3H); 4.0 (d, 2H); 4.4 (s, 2H); 5.3 (t, 1H); 6.8 (dd, 1H); 7.0 d, 1H); 7.4 (d, 1H); 8.2 (s, 1H); A
4f	1705 (COO); 1620-1590-1500 (benzimidazole and pyridine)	2.3 (2s, 6H); 3.1 (t, 2H); 3.8 (s, 3H) 4.4 (s, 2H); 4.6 (t, 2H); 7.0 (d, 1H); 7.8 (d, 1H); 8.6 (s, 1H); 12.1 (b, 1H); A
4g	1670 (CO); 1620-1580-1500 (benzimidazole and pyridine)	2.2 (m, 2H); 2.3 (2s, 6H); 2.7 (t, 2H); 3.1 (t, 2H); 3.8 (s, 3H); 4.4 (s, 2H); 7.3 (s, 1H); 8.2 (s, 1H); 8.3 s, 1H); A
4h	1665 (CO); 1610-1585-1500 (benzimidazole and pyridine)	2.0-2.5 (m, 2H); 2.2 and 2.3 (2s, 6H); 2.7 (t, 2H); 3.3 (t, 2H); 3.8 (s, 3H); 4.4 (s, 2H); 7.4 (d, 1H); 7.9 (d, 1H); 8.3 (s, 1H); 12.8-14.0 (b, 1H); A
4i	1600-1590 (C=N and pyridine); 1560 (C=C)	1.8 (b, 4H); 2.3 (s, 6H); 2.6 (b, 4H); 3.8 (s, 3H); 4.2 (s, 2H); 8.2 (s, 1H); 9.3 (b, 1H); A
4j	1600-1590-1500 (benzimidazole and pyridine)	3.8 (s, 3H); 4.5 (s, 2H); 6.6-7.2 (m, 3H); 7.3-7.7 (m, 3H); 8.9 (s, 1H); 11.3 (bs, 1H); A
4k	1600-1590-1500 (benzimidazole and pyridine)	3.8 (s, 3H); 5.2 (s, 2H); 6.8 (dd, 1H); 7.0 (d, 1H); 7.4 (d, 1H); 7.4 (s, 1H); 7.7 (d, 1H); 8.1 (d, 1H); 8.4 (d, 1H); B

5-[(1,3-Dioxolan-2-yl)-methoxy]-benzimidazoline-2-thione **2e**
An ethanolic solution of **8** (1.5 g, 6.24 mmol) was hydrogenated at room temperature and atmospheric pressure over 10% Pd/C (0.15 g). After hydrogen uptake was complete, the reaction mixture was filtered and the clear solution of **9** was diluted with water. Potassium ethylxanthogenate (2.0 g, 12.5 mmol) was added and the reaction mixture was gently refluxed for 4 h. After cooling to 40°C, glacial acetic acid (7 ml) was added, followed by water. Pure **2e** crystallized immediately as a yellow solid.

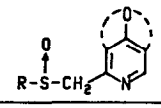
7-Acetamido-isochroman-1-one **11**
A suspension of 7-nitro-isochroman-1-one **10** [24] (18.0 g, 93.19 mmol) in ethylacetate (200 ml) was hydrogenated at room temperature and atmospheric pressure over 10% Pd/C (0.9 g). After the theoretical absorption, the reaction mixture was filtered and transferred into a three-necked round-bottomed flask. Triethylamine (14.14 g, 0.14 mmol) was added and the solution was cooled to 0°C. Acetyl chloride (7.68 g, 98 mmol) was added dropwise under vigorous stirring and the reaction mixture was further stirred for 15 min at 0°C and then for 2 h at room temperature. The suspension was then washed with diluted HCl and dried over $MgSO_4$. Upon concentration, **11** crystallized and was recovered by filtration. Yield 13.5 g (71%). mp: 174—175°C. IR (cm^{-1}): 3360—3335 (N—H); 1720 (COO); 1685 (CONH). NMR ($CDCl_3$, DMSO-d_6), δ (ppm): 2.1 (s, 3H); 3.0 (t, 2H); 4.5 (t, 2H); 7.3 (d, 1H); 7.9 (dd, 1H); 8.2 (d, 1H); 10.1 (b, 1H).

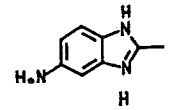
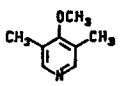
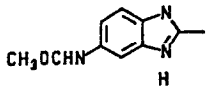
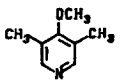
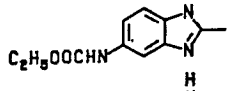
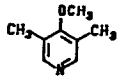
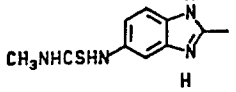
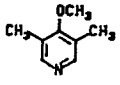
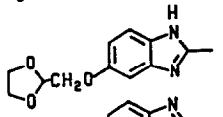
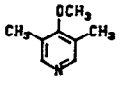
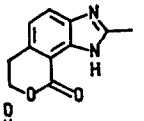
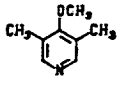
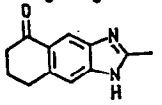
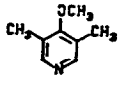
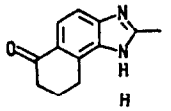
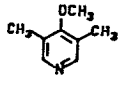
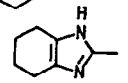
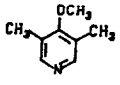
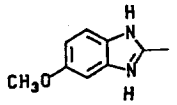
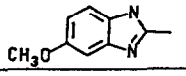
7-Acetamido-8-nitro-isochroman-1-one **12**
To a stirred solution of **11** (12.0 g, 5.84 mmol) in conc. H_2SO_4 (48 ml) 65% HNO_3 (48 ml) was added dropwise at —10°C under stirring. Stirring was continued for 1.5 h at the same temperature, then the reaction mixture was poured onto ice. A dark yellow solid soon separated and was recovered by filtration. Crude **12** (10.38 g, 71%) was sufficiently pure; an analytical sample was crystallized from 50% EtOH. mp: 214—215°C. IR (cm^{-1}): 3280—3180 (N—H); 1725 (COO); 1670 (CONH); 1515 (NO_2). NMR ($CDCl_3$, DMSO-d_6), δ (ppm): 2.1 (s, 3H); 3.1 (t, 2H); 4.6 (t, 2H); 7.6 (d, 1H); 7.9 (d, 1H); 9.8 (b, 1H).

7-Amino-8-nitro-isochroman-1-one **13**
A suspension of **12** (7.2 g, 28.77 mmol) in 3.5% methanolic HCl (115 ml) was warmed at 60°C under stirring for 15 h. After cooling, the reaction mixture was concentrated and allowed to stand overnight at room temperature. **13** was isolated as yellow—orange crystals. Yield 3.5 g (50%). mp: 182—185°C. IR (cm^{-1}): 2600—2400 broad; 1725 (COO); 1530 (NO_2). NMR ($CDCl_3$, DMSO-d_6), δ (ppm): 2.9 (t, 2H); 4.5 (t, 2H); 7.2 (s, 2H); 8.5 (s, 3H).

2-Thioxo-6,7-dihydropyrano[3,4-e]benzimidazolin-9-one **2f**
A solution of **13** free base (2.2 g, 10.57 mmol) (obtained from 2.8 g of the hydrochloride salt by alkalinization with 17% Na_2CO_3 and extraction with ethylacetate, mp: 195—198°C) in methanol (50 ml) was hydrogenated at room temperature and atmospheric pressure over 10% Pd/C (0.2 g). After the absorption was complete, the reaction mixture was filtered and the clear solution of **14** was transferred into a round-bottomed flask. Water was added, followed by potassium ethylxanthogenate (3.4 g, 21.2 mmol) and the reaction mixture was gently refluxed for 3.5 h. After usual workup, crystalline **2f** was recovered by filtration.

Table V. Physicochemical data of sulfoxides 5a—k.



comp	R		M.p. °C	Cryst. Solv.	Yield %	Analysis
5a			172-174	EtOH	61	$C_{16}H_{18}N_4O_2S$
5b			105-106	EtOH-CH_3COCH_3	53	$C_{18}H_{20}N_4O_3S$
5c			179-181	EtOH	81	$C_{19}H_{22}N_4O_4S$
5d			118-120	EtOH-Et_2O	59	$C_{18}H_{21}N_5O_2S_2$
5e			160-161	AcOEt	75	$C_{20}H_{23}N_3O_5S$
5f			135-137	AcOEt-Et_2O	68	$C_{19}H_{19}N_3O_4S$
5g			175-176	AcOEt	54	$C_{20}H_{21}N_3O_3S$
5h			194-195	AcOEt	49	$C_{20}H_{21}N_3O_3S$
5i			158-159	CH_3CN	70	$C_{16}H_{21}N_3O_2S$
5j			185-187	EtOH	66	$C_{16}H_{13}N_3O_3S$
5k			143-144	CH_3CN	60	$C_{16}H_{13}N_3O_3S$

6-Acetamido-7-nitro-1,2,3,4-tetrahydronaphthalen-1-one **16** *and 6-acetamido-5-nitro-1,2,3,4-tetrahydronaphthalen-1-one* **17**

Finely ground 6-acetamido-1,2,3,4-tetrahydronaphthalen-1-one **15** (5.0 g, 24.6 mmol), prepared by known procedures [25], was added to acetic anhydride (30 ml) and the resulting suspension was cooled to 5°C. Under vigorous stirring, a solution of concentrated nitric acid (d = 1.4, 2.8 ml) in glacial acetic acid (4.75 ml) was added at the same temperature and the suspension was then allowed to come to room temperature. After 2 h, a dark solution was obtained. The reaction mixture was poured onto ice—water containing diluted H_2SO_4 and then extracted with ethylacetate. The organic layer was washed several times with water, diluted $NaHCO_3$ and then water again until neutrality. After drying over $MgSO_4$ and evaporation of the solvent, a thick brown oil was obtained which was induced to solidify by treatment with diethyl ether. Yield 3.1 g (51%) of a mixture of **16** and **17**. TLC analysis (CH_2Cl_2—MeOH, 95:5) showed two main spots R_f = 0.7 (**17**) and R_f = 0.8 (**16**). Pure samples of **16** and **17** were obtained by flash column chromatography. (Eluant: ethylacetate—cyclohexane, 1:1.) **17** was eluted first and was recrystallized from ethanol. Red crystals. mp: 198—200°C. IR (cm^{-1}): 3350 (N—H); 1705 (CO); 1685 (CONH); 1510 (NO_2). NMR ($CDCl_3$), δ (ppm): 2.2 (m, 2H); 2.2 (s, 3H); 2.7 (t, 3H); 3.0 (t, 2H); 8.2 (d, 1H); 8.4 (d, 1H); 8.5 (b, 1H).

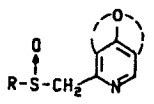
16 was recrystallized from aqueous ethanol as an orange amorphous powder. mp: 140—142°C. IR (cm^{-1}): 3350 (N—H); 1710 (CO); 1670 (CONH); 1525 (NO_2). NMR ($CDCl_3$), δ (ppm): 2.2 (m, 2H); 2.3 (s, 3H); 2.7 (t, 2H); 3.0 (t, 3H); 8.7 (s, 1H); 8.9 (s, 1H); 10.5 (b, 1H).

6-Acetamido-7-amino-1,2,3,4-tetrahydronaphthalen-1-one **18** *and 6-acetamido-5-amino-1,2,3,4-tetrahydronaphthalen-1-one* **19**

1.0 g of the above mixture of **16** and **17** was suspended in 6 N HCl (30 ml) and heated on the steam bath under manual stirring. After 50 min, the dark solution was cooled, poured onto ice—water, neutralized with 17% Na_2CO_3 and finally extracted with ethylacetate. After drying, the solvent was removed under vacuum and the raw material (0.75 g) subjected to flash column chromatography. (Eluant: ethylacetate—cyclohexane, 1:1.) **19** was eluted first and after evaporation of the solvent, 0.4 g (48%) of a yellow—orange solid was obtained, which was recrystallized from a mixture of ethylacetate—cyclohexane. mp: 190—191°C. IR (cm^{-1}): 3340—3235 (NH_2); 1660 (CO); 1520 (NO_2). NMR ($CDCl_3$, DMSO-d_6), δ (ppm): 2.0 (m, 2H); 2.5 (t, 2H); 2.9 (t, 2H); 6.9 (d, 1H); 7.0 (s, 2H); 7.8 (d, 1H).

18 (0.31 g, 37%) was recrystallized from ethanol as a brownish

Table VI. Spectroscopic data of sulfoxides **5a—k**.



comp	IR (cm^{-1}) (nujol)	^{1}H-NMR (solvent: A: $CDCl_3$, B: $CDCl_3$-d_6-DMSO 2:5) δ (ppm)
5a	3330-3470 (NH_2), 1020 (S→O)	2.2 (2s, 6H); 3.7 (s, 3H); 4.5-4.7 (2d, 2H); 5.0 (bs, 2H); 6.6 (d, 1H); 6.7 (s, 1H); 7.3 (d, 1H); 8.2 (s, 1H); 12.9 (bs, 1H); B
5b	3330 (CONH), 1660 (CONH), 1050 (S→O)	2.1 (s, 3H); 2.2-2.3 (2s, 6H); 3.7 (s, 3H); 4.7 (bs, 2H); 7.3 (dd, 1H); 7.6 (d, 1H); 8.2 (m, 2H); 10.0 (s, 1H); B
5c	3210 (NH-COO), 1730 (-OCO), 1040 (S→O)	1.3 (t, 3H); 2.2 (2s, 6H); 3.7 (s, 3H); 4.2 (q, 2H); 4.5 (bs, 1H); 4.7 (s, 2H); 7.3-7.5 (m, 2H); 8.0 (d, 1H); 8.2 (s, 1H); 12.3-13.6 (bs, 1H); B
5d	1480 (NHCSNH), 1040 (S→O)	2.2 (s, 6H); 3.1 (d, 3H); 3.7 (s, 3H); 4.6-4.8 (2d, 2H); 6.2 (bq, 1H); 7.1-7.7 (m, 3H); 7.9 (s, 1H); 8.2 (s, 1H); B
5e	1040 (S→O)	2.2 (s, 6H); 3.7 (s, 3H); 3.9 (b, 4H); 4.0 (d, 2H); 4.6 (s, 2H); 5.2 (t, 1H); 6.8 (dd, 1H); 7.0 (d, 6H); 7.4 (d, 1H); 8.1 (s, 1H); 13.4 (b, 1H); B
5f	1720 (COO), 1025 (S→O)	2.3 (2s, 6H); 3.2 (t, 2H); 3.8 (s, 3H); 4.6 and 4.9 (2d, gem, 2H); 4.7 (t, 2H); 7.2 (d, 1H); 8.0 (d, 1H); 8.4 (s, 1H); 13.0 (b, 1H); A
5g	1675 (CO), 1055 (S→O)	2.0-2.3 (m, 2H); 2.2 (2s, 6H); 2.7 (t, 2H); 3.1 (t, 2H); 3.7 (s, 3H); 4.6 and 4.9 (2d, gem, 2H); 7.4 (b, 1H); 8.2 (s, 1H); 8.4 (6, 1H); A
5h	1675 (CO), 1045 (S→O)	2.1-2.4 (m, 2H); 2.2 (s, 6H); 2.7 (t, 2H); 3.3 (b, 3H); 3.7 s, 3H); 4.6 and 4.9 (2d, gem, 2H); 7.3 (db, 1H); 8.1 (d, 1H); 8.2 (s, 1H); A
5i	1010 (S→O)	1.8 (b, 4H); 2.1 (2s, 6H); 2.6 (b, 4H); 3.7 (s, 3H); 4.6 (s, 2H); 8.2 (s, 1H); 11.7 (b, 1H); A
5j	1580-1510 (pyridine) 1040 (S→O)	3.8 (s, 3H); 4.6-4.9 (dd, 2H); 6.8 (dd, 1H); 6.8 (bs, 1H); 6.9 (dd, 1H); 7.3 (d, 1H); 7.3 (m, 1H); 7.6 (d, 1H); 8.8 (d, 1H); 11.7 (bs, 1H); A
5k	1580-1500 (pyridine) 1040 (S→O)	3.8 (s, 3H); 4.8-5.0 (dd, 2H); 6.7 (dd, 1H); 6.8 (bs, 1H); 6.9 (dd, 1H); 7.4 (m, 2H); 7.6 (d, 1H); 8.4 (d, 1H); 10.0 (bs, 1H); A

solid. mp: 209—210°C. IR (cm^{-1}): 3475—3200 (NH_2); 1665 (CO); 1500 (NO_2). NMR ($CDCl_3$, DMSO-d_6), δ (ppm): 2.0 (m, 2H); 2.5 (t, 2H); 2.8 (t, 2H); 6.8 (s, 1H); 7.8 (s, 2H); 8.5 (s, 1H).

6,7-Diamino-1,2,3,4-tetrahydronaphthalen-1-one **20**
A solution of **18** (2.4 g, 11.64 mmol) in THF (150 ml) was hydrogenated at room temperature and atmospheric pressure over Ni/Raney (0.24 g). After the hydrogen uptake was complete, the reaction mixture was filtered and concentrated to dryness. Crude **20** (2.0 g, 98%) was used for the next step without further purification. mp: 153—156°C. IR (cm^{-1}): 3400—3200 (NH_2); 1660 (CO). NMR ($CDCl_3$, DMSO-d_6), δ (ppm): 2.0 (m, 2H); 2.4 (t, 2H); 2.7 (t, 2H); 4.4 and 5.3 (2b, 4H); 6.4 (s, 1H); 7.1 (s, 1H).

2-Thioxo-5,6,7,8-tetrahydronaphth[2,3-d]imidazolin-5-one **2g**
A solution of **20** (2.3 g, 13.05 mmol) was dissolved in a 1:1 mixture of water and ethanol (100 ml). To this solution, 85% KOH (1.0 g, 15.18 mmol) was added, followed by carbon disulfide (2.02 g, 26.5 mmol). The reaction mixture was gently refluxed for 1.5 h and then was allowed to cool to 40°C. Glacial acetic acid (10 ml) was added with stirring which was continued at that temperature for an additional 30 min. Upon cooling, **2g** crystallized out as a brown solid.

5,6-Diamino-1,2,3,4-tetrahydronaphthalen-1-one **21**
A solution of **19** in THF was hydrogenated over Ni/Raney with the same procedure previously described for **20**. Crude **21** was obtained in 78% yield. mp: 176—177°C. IR (cm^{-1}): 3410—3200 (NH_2); 1665 (CO). NMR ($CDCl_3$, DMSO-d_6), δ (ppm): 2.0 (m, 2H); 2.4 (t, 2H); 2.6 (t, 2H); 4.2 and 5.3 (2b, 4H); 6.5 (d, 1H); 7.2 (d, 1H).

2-Thioxo-6,7,8,9-tetrahydronaphth[1,2-d]imidazolin-6-one **2h**
Compound **2h** was obtained from **21** in 65% yield with the same procedure previously employed for **2g**. Brown solid.

Synthesis of the chloromethylpyridines **3** *(a—c)*

2-Chloromethyl-3,5-dimethyl-4-methoxy-pyridine **3a** was prepared according to the described procedure [26].

6-Methyl-4,5-dihydrofuro[3,2-c]pyridin-4-one **23**
To a solution of 2-methyl-3-(2-furyl)-propenoic acid **22** [27] (15.2 g, 0.1 mol) in acetone (100 ml) cooled at 0°C were added simultaneously NEt_3 (11.13 g, 0.11 mol) and ethylchloroformiate (13.2 g, 0.12 mol). After 30 min of stirring, a solution of sodium azide (4.75 g, 0.15 mol) in water (25 ml) was added dropwise and then poured onto ice—water

Table VII. Anti-secretory activity of sulfoxides **5** (a—k).

Compd	Pylorus ligation[a] (i.v.)	Stomach perfused rat[b] (agonist: histamine) (i.v.)
5a	±	±
5b	++	++
5c	±	±
5d	++	±
5e	+++	++
5f	++	+++
5g	+++	+++
5h	±	++
5i	±	±
5j	++	++
5k	++	++
Omeprazole	+++	+++

[a]Statistically significant activity is assessed on the following scale: ±: < 35% inhibition at 3 mg/kg; ++: 35—50% inhibition at 3 mg/kg; +++: > 50% inhibition at 3 mg/kg.
[b]Statistically significant activity is assessed on the following scale: ±: < 50% inhibition at 3 mg/kg; ++: 50—70% inhibition at 3 mg/kg; +++: > 70% inhibition at 3 mg/kg.

Table VIII. Anti-secretory and anti-ulcer activities of the selected sulfoxides.

Compd	Anti-secretory activity (i.v.) ED_{50} mg/kg	Anti-ulcer activity (*os*) ED_{50} mg/kg	
	stomach perfused rat	stress + ASA	ethanol
5f	1.39	8.9	NA[a]
5g	1.30	10.0	NA
Omeprazole	0.31	9.4	3.1

[a]NA = $ED_{50} \geqslant 10$ mg/kg.

(500 g) under stirring. The separated solid was collected by filtration and dried. A solution of this solid in benzene (120 ml) was dropped slowly into a solution of tributylamine (15 ml) in diphenyl methane (100 ml) heated at 200°C. The reaction mixture was cooled and diethyl ether (200 ml) was added. The separated solid was filtered and dried. Yield 12.6 g (84%). mp: 239—240°C. IR (cm^{-1}): 3100 (NH); 1660 (CONH). NMR data are not available owing to the insolubility of the compound. Anal. $C_8H_7NO_2$; C calcd 64.42, found 64.21; H calcd 4.73, found 4.85; N calcd 9.39, found 9.19.

4-Chloro-6-methyl-furo[3,2-c]pyridine ***24***
A mixture of **23** (5 g, 33.5 mmol) and $POCl_3$ (10 g) was refluxed for 4 h. The solution was cooled at room temperature and poured onto ice—water (500 g) and the oily product which separated was extracted into ethylacetate. The organic solution was washed several times with water, dried and evaporated to dryness to give the title compound as a white solid sufficiently pure to be used in the next step. Yield 3.7 g (66%). mp: 59—60°C [28]. NMR ($CDCl_3$), δ (ppm): 2.6 (s, 3H); 6.8 (d, 1H); 7.2 (s, 1H); 7.6 (d, 1H).

6-Methyl-furo[3,2-c]pyridine ***25***
Zn dust (30 g) was added portionwise to a solution of **24** (12.4 g, 74 mmol) in glacial acetic acid (120 ml). The solution was refluxed overnight, cooled at room temperature and filtered. The solution was evaporated to dryness, 30% NaOH solution was cautiously added under cooling and the oily product was extracted into diethyl ether. The organic solution was washed several times with water, dried and evaporated to dryness to give a white solid. Yield 7.4 g (75%). mp: 52—53°C. NMR ($CDCl_3$), δ (ppm): 2.7 (s, 3H); 6.8 (d, 1H); 7.3 (s, 1H); 7.6 (d, 1H); 8.8 (s, 1H).

6-Methyl-furo[3,2-c]pyridine N-*oxide* ***26***
Into a solution of **25** (8.6 g, 64 mmol) in glacial acetic acid (75 ml), 33% H_2O_2 (13 ml) was added dropwise at room temperature. Then the temperature was raised to 100°C and kept for 18 h. The solution was cooled and evaporated to dryness. The crude title compound was purified by crystallization from diethyl ether. Yield 7.5 g (77%). mp: 83—84°C. IR (cm^{-1}): 1590—1500 (pyridine); 1220 (N → O). Anal. $C_8H_7NO_2$; C calcd 64.42, found 64.66; H calcd 4.73, found 4.68; N calcd 9.39, found 9.52.

6-Hydroxymethyl-furo[3,2-c]pyridine ***27***
A solution of **26** (7.3 g, 48.9 mmol) in acetic anhydride (73 ml) was heated at 100°C for 4 h. The reaction mixture was cooled at room temperature and evaporated to dryness. The residue was dissolved into a solution of NaOH (3.9 g, 97.8 mmol) and 95% ethanol (80 ml). The reaction mixture was heated at 80°C for 20 min, cooled and evaporated to dryness. The residue was taken up into ethylacetate; this solution was washed with an NaCl solution and evaporated to dryness. The oily yellow residue was dissolved into methyl ethyl ketone and gaseous HCl was introduced. The hydrochloride of the title compound was obtained as a crystalline solid. Yield 5.3 g (58%). mp: 162—163°C. IR (cm^{-1}): 3190 (CH_2OH); 1600—1520 (pyridine). Anal. $C_8H_7NO_2 \cdot HCl$; C calcd 51.76, found 51.48; Cl calcd 19.10, found 18.93.

6-Chloromethyl-furo[3,2-c]pyridine ***3b***
Thionyl chloride (4.12 ml, 57.2 mmol) was added to a suspension of **27** (2.5 g, 13.4 mmol) in chloroform (50 ml) cooled at —10°C. After 2 h of stirring at room temperature, the clear yellowish solution was evaporated to dryness and from the crude residue after crystallization from anhydrous diethyl ether, the title compound was obtained as hydrochloride salt. Yield 2.5 g (98%).

4-Methyl-furo[3,2-c]pyridine N-*oxide* ***29***
The title compound was obtained starting from the known **28** [29] (2.3 g, 17.27 mmol) following the procedure described for **26**. Yield 1.5 g (58%). mp: 106—107°C. IR (cm^{-1}): 1590—1510 (pyridine); 1230 (N → O). Anal. $C_8H_7NO_2$; C calcd 64.42, found 64.18; H calcd 4.73, found 4.81; N calcd 9.39, found 9.22.

4-Hydroxymethyl-furo[3,2-c]pyridine ***30***
This compound was obtained from **29** (3 g, 20.11 mmol) following the procedure described for **27**. Yield 1.8 g (56%). mp: 203—205°C (as hydrochloride salt). IR (cm^{-1}): 3200 (CH_2OH); 1600—1510 (pyridine). Anal. $C_8H_7NO_2 \cdot HCl$; C calcd 51.76, found 51.59; Cl calcd 19.10, found 19.38.

4-Chloromethyl-furo[3,2-c]pyridine ***3c***
The title compound was prepared from **30** (1.8 g, 9.69 mmol) following the procedure described for **3b**. Yield 1.93 g (91%).

General method for the preparation of sulfides ***4*** *(**a**—**k**)*

Method A
A suspension of a mercapto derivative **2** (25 mmol) in water (20 ml), ethanol (65 ml) and NaOH (50 mmol) was stirred at room temperature until a clear solution resulted.
A suspension of the suitable chloromethylpyridine **3** as hydrochloride salt (27.5 mmol) in ethanol (80 ml) was then introduced and the reaction mixture was heated at 90°C for 1 h. After cooling, the ethanol was evaporated and the residue was dissolved between water and ethylacetate. The organic solution was washed with water, dried and evaporated. The desired compound was obtained and purified by crystallization from the suitable solvent.

Method B
A solution of a mercapto derivative **2** (25 mmol) in dry DMF (90 ml) was added dropwise to a suspension of 80% sodium hydride (50 mmol) in dry DMF (15 ml) at room temperature under stirring. After 15 min, the appropriate chloromethylpyridine hydrochloride **3** was added at once and stirring continued for 3 h. The reaction mixture was poured into water (1 l), pH was adjusted to 7.5 and the raw material was extracted into ethylacetate. After drying over $MgSO_4$, the crude sulfide was obtained by evaporation of the solvent under vacuum. Pure sulfide was obtained by crystallization from the suitable solvent.

General method for the preparation of sulfoxides ***5*** *(**a—k**)*

To a solution of the suitable sulfide derivative **4** (10 mmol) in chloroform (120 ml) cooled at — 30°C, 66% 3-chloroperbenzoic acid (10 mmol) in chloroform (60 ml) was added dropwise. The solution was stirred for 1 h, then gaseous NH_3 was bubbled into it at — 30°C. The separated salts were filtered off and the solution was evaporated to dryness. The pure compounds were generally obtained by crystallization from the suitable solvent.

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