3 W. Saski und S.G. Shah, J. Pharm. Sci. *54*, 277 (1965).
4 G. Levy und K.E. Miller, J. Pharm. Sci. *54*, 1319 (1965).
5 M. Gibaldi und C.H. Nightingale, J. Pharm. Sci. *57*, 226 (1968).
6 C.H. Nightingale und M. Gibaldi, J. Pharm. Sci. *60*, 1360 (1971).
7 S.H. Yalkowsky, O.S. Carpenter, G.L. Flynn und T.G. Slunick, J. Pharm. Sci. *62*, 1949 (1973).
8 Y. Sakiya, N. Umezawa und M. Hanano, Yakugaku Zasshi *94*, 1123 (1974); *96*, 737 (1976); C.A. *82*, 38442 (1975); *85*, 153681 (1976).
9 G.M. Ghaly, S.A. Khalil, M.A. Moustafa, M.W. Gouda und M.M. Motawi, Can. J. Pharm. Sci. *10*, 79 (1975); C.A. *83*, 183345 (1976).
10 S. Feldman, M. De Francisco und P.J. Cascella, J. Pharm. Sci. *64*, 1713 (1975).
11 P.J. Cascella und S. Feldman, J. Pharm. Sci. *68*, 401 (1979).
12 G. Levy und S.P. Gucinski, J. Pharmacol. Exp. Ther. *146*, 80 (1964).
13 J.T. Doluisio und J.V. Swintosky, J. Pharm. Sci. *53*, 597 (1964).
14 E.R. Garrett und P.B. Chemburkar, J. Pharm. Sci. *57*, 944, 949, 1401 (1968).
15 H. Stricker, Arzneim. Forsch. *20*, 391 (1970).
16 H. Stricker, Pharm. Ind. *33*, 157 (1971); *35*, 13 (1973).
17 Documenta Geigy, Wissenschaftliche Tabellen, 7. Ausg. S. 275, Georg Thieme Verlag, Stuttgart 1975.
18 K. Münzel, J. Büchi und O.E. Schultz, Galenisches Praktikum, S. 479, Wissenschaftliche Verlagsgesellschaft mbH, Stuttgart 1959.

[Ph 370]

Arch. Pharm. (Weinheim) *314*, 932–937 (1981)

Syntheses and Configurations of Some Thiomorpholide *S*-Oxides, Trithiozine Metabolites

Carlo Farina*, Marco Visconti, Paolo Ventura, Mario Pinza and Giorgio Pifferi

ISF – Laboratories for Biomedical Research, 20090 Trezzano s/N, Milan, Italy
Eingegangen am 30. Januar 1980

Two metabolites of trithiozine, namely 4-(3,5-dimethoxy-4-hydroxythiobenzoyl)morpholine *S*-oxide **(2a)** and 4-(3,4,5-trimethoxythiobenzoyl)morpholine *S*-oxide **(2b)**, were synthesized by oxidation of the thioamides **1a, b** or, in the case of **2b,** by reaction of *E*- and *Z*-(3,4,5-trimethoxyphenyl)(methylthio)sulfine **(4)** with morpholine. Both procedures afford the compounds **2a, b** as single isomers having the same configuration at the sulfine group. The NMR behaviour of the aromatic ortho protons of **2b,** when compared to that of other aromatic sulfines with known structures in the presence of lanthanide shift reagents, supports the *Z*-configuration.

Synthese und Konfiguration von einigen Thiomorpholid- S-Oxiden, Stoffwechselprodukten des Trithiozins

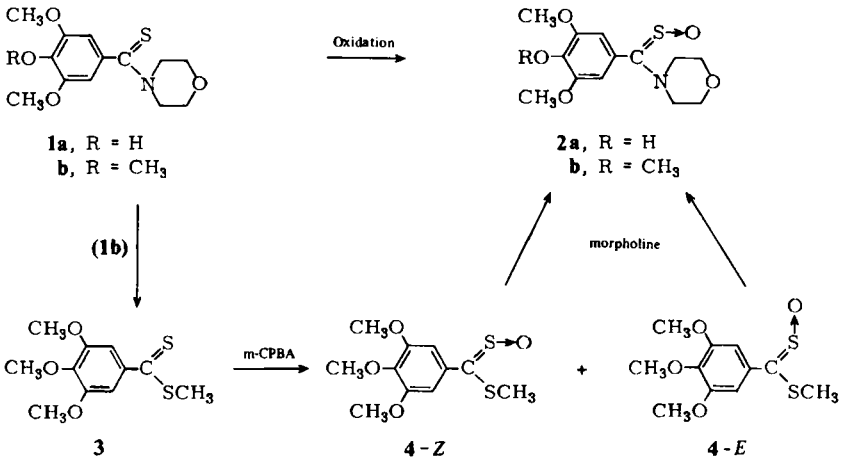
Zwei Stoffwechselprodukte des Trithiozins, nämlich 4-(3,5-Dimethoxy-4-hydroxy-thiobenzoyl)morpholin-S-oxid **(2a)** und 4-(3,4,5-Trimethoxythiobenzoyl)morpholin-S-oxid **(2b)** wurden durch

0365-6233/81/1111-0932 $ 02.50/0

Oxidation der entsprechenden Thioamide **1a, b** oder, im Fall des **2b**, durch Reaktion von *E*- und *Z*-3,4,5-Trimethoxyphenyl-methylthiosulfin **(4)** mit Morpholin synthetisiert. Die beiden synthetischen Verfahren ergeben die Verbindungen **2a, b** als Isomere mit der gleichen Konfiguration der Sulfin Gruppe.

Das NMR Verhalten der ortho aromatischen Protonen von **2b** im Vergleich zu denjenigen anderer aromatischer Sulfine bekannter Struktur in Gegenwart von Lanthaniden Shift-Reagenzien ergibt die *Z*-Konfiguration.

Previous metabolic studies[1a,b] on trithiozine **(1b)**, a new antisecretory and antiulcer drug[1c], showed, among others metabolites, the formation of 4-(3,5-dimethoxy-4-hydroxythiobenzoyl)morpholine S-oxide **(2a)** and 4-(3,4,5-trimethoxythiobenzoyl)morpholine S-oxide **(2b)** (Scheme 1).



Scheme 1: Synthesis of thiomorpholide S-oxides **2a, b**.

These compounds may be regarded as aminosulfines, whose bent heterocumulenic system may assume the *E* and *Z* configurations. Both isomers were already isolated for chlorosulfines[2], alkylthiosulfines[3] and aromatic sulfines[4].

Oxidation of *N*-unsubstituted and *N*-monosubstituted thioamides affords the corresponding S-oxides in the *Z* configuration, owing to hydrogen bonding stabilization between the sulfine oxygen and the amide hydrogen[5]. The spatial configuration of *N,N*-disubstituted thioamide S-oxides, so far prepared[6,7], has not been reported.

The present work deals with the synthesis and the configuration assignment of metabolites **2a, b** by means of lanthanide NMR shift reagents.

Oxidation of thioamides **1a**[8] and **1b** with monoperphthalic acid in dichloromethane (method A) or with hydrogen peroxide in acetic acid (method B) afforded the corresponding S-oxides **2a, b.** The analogues **6** and **8** were also synthesized (Table 1) as reference standards from thiobenzoylpiperidine **(5)**[9] and thiobenzoylmorpholine **(7)**[10] according to method B. The formation of only one of the two possible isomers was established by chromatography and NMR spectroscopy. Since mild methylation of **2a** with

diazomethane afforded **2b**, the oxidation of **1a** and **1b** seems to proceed with the same stereochemistry.

To obtain both *E* and *Z* isomers of **2b**, an alternative synthesis was undertaken. Methyl 3,4,5-trimethoxydithiobenzoate **(3)*** was oxidized with 3-chloroperbenzoic acid (m-CPBA) and a mixture of *E*- and *Z*-3,4,5-trimethoxyphenyl methylthio sulfines **(4)** was obtained. The stereoisomers were then separated by silica gel chromatography. However, reaction of sulfines **4**-*E* and **4**-*Z* with morpholine, afforded only the same isomer **2b**. Since this condensation is slow (especially in the case of **4**-*Z*) and the resulting thioamide S-oxide is instable[1a,6] in the reaction medium, **2b** is obtained in poor yield along with its decomposition products: thioamide **1b** and 4-(3,4,5-trimethoxybenzoyl)morpholine. Thioamide S-oxides **2a, b** as well as dithioester S-oxides **4** can be stored without appreciable degradation only at low temperature. For this reason, compounds **2** and **4** were purified by column chromatography and thermal procedures were avoided. Purity was checked by TLC and, in the case of **2b**, also by HPLC[11].

The configuration of compound **2b** has been defined on the basis of the changes in the NMR chemical shifts of phenyl and morpholine protons induced by tris (dipivalomethanato)europium [Eu(DPM)$_3$]. It is known that for aromatic sulfines Eu(DPM)$_3$ complexation takes place at the oxygen atom of the CSO bent system and this induces a larger shift for protons in the *syn* position than for those in the *anti* position[12].

For compound **2b**, morpholine and methoxy oxygens must also be considered as other possible coordination centers. In order to verify that Eu(DPM)$_3$ actually complexes at sulfine moiety, the LIS values of **1b, 5** and **7** were compared to those of **2b, 6** and **8** (Table 1).

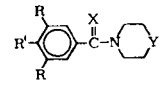
As compound **5** does not contain oxygen atoms, it cannot bind Eu(DPM)$_3$. The comparison among the LIS values of the methylenes α and β to nitrogen in **6, 7** and **8** shows that the complexation at the sulfine oxygen is preferred with respect to that at morpholine oxygen. The LIS values of the protons β to nitrogen for compounds **1b** and **7** indicate that the morpholine oxygen binds Eu(DPM)$_3$ more than methoxy groups. Finally, the low LIS values of the methylenes β to nitrogen in **2b** (2.0 ppm compared with 15–20 ppm for **1b** and **7**) and the 0.8 ppm LIS value of methoxy groups for **2b** with respect to 5.3 and 2.1 ppm for **1b** demonstrate that the complexation of Eu(DPM)$_3$ takes place preferentially at the CSO moiety.

It is also apparent that for thioamide S-oxides **2b, 6** and **8** the aromatic protons undergo a LIS of similar magnitude (2.4–3.5 ppm); the same is true for the protons α (5.3–6.3 ppm) and β (1.9–2.0 ppm) to nitrogen. This suggests that such compounds have the same stereochemistry.

The *E*–*Z* geometry of **2b, 6, 8** was determined by comparing $\Delta\delta$ values ($\Delta\delta = \delta[CDCl_3 + 0.3\text{ eq Eu(DPM)}_3] - \delta[CDCl_3]$) of ortho aromatic protons to that of sulfines with known configuration (Table 2). Compounds **2b, 6** and **8** have $\Delta\delta$ values in the range 0.8 – 1.1 ppm which are consistent with the shifts of ortho protons *anti* to CSO observed in **4**-*Z* and reported[12] for diphenyl sulfine and *Z*-phenyl phenylthio sulfine. From these data it can be argued that all examined thioamide S-oxides exist in the *Z*-configuration.

* obtained by reaction of **1b** with methyliodide and hydrogen sulfide[8]

Table 1: *Chemical and LIS data of thiobenzamides and their S-oxides*



Comp. n°	R	R'	X	Y	Yield % (Method)	M.p.°	Formula[a] (M.W.)	LIS (ppm)			
								Ortho aromatic H	α to N CH_2	β to N CH_2	R and R'
1a	CH_3O	HO	S	O	(b)	172–174	$C_{13}H_{17}NO_4S$ (283.3)	–(f)	–	–	–
1b	CH_3O	CH_3O	S	O	(c)	139–141	$C_{14}H_{19}NO_4S$ (297.4)	4.8	7.1 and 7.5	15.5	5.3 and 2.1
2a	CH_3O	HO	SO	O	46(B)	148–151 d.	$C_{13}H_{17}NO_5S$ (299.3)	–(f)	–	–	–
2b	CH_3O	CH_3O	SO	O	57(A)	124–125 d.	$C_{14}H_{19}NO_5S$ (313.4)	3.5	6.3	2.0	0.8
5	H	H	S	CH_2	(d)	63– 64	$C_{12}H_{15}NS$ (205.3)	0	0	0	0
6	H	H	SO	CH_2	51(B)	52– 55	$C_{12}H_{15}NOS$ (221.3)	2.4	5.3	1.9	0.9
7	H	H	S	O	(e)	137–139	$C_{11}H_{13}NOS$ (207.3)	2.7	8.6	20.2	1.1
8	H	H	SO	O	47(B)	104–106 d.	$C_{11}H_{13}NO_2S$ (223.3)	2.8	6.4	2.0	1.0

a) Mass spectra of all new compounds showed M^+ corresponding to their molecular weight. b) see ref.[8] c) see ref.[1c], d) see ref.[10], e) see ref.[11], f) The acidity of the phenolic group causes the decomposition of $Eu(DPM)_3$.

Table 2: △ δ *values of ortho aromatic protons of sulfines*

Sulfine	Δδ [a]	
	Z	*E*
Diphenyl[b]	1.0	2.8
Phenyl phenylthio[b]	1.1	2.9
4	1.4	2.1
2b	1.1	
6	0.8	
8	0.9	

a) △ δ = δ[$CDCl_3$ + 0.3 eq $Eu(DPM)_3$] – δ[$CDCl_3$]; b) see ref.[12].

The authors gratefully acknowledge Mr. *V. Colzani* for recording the NMR spectra, Dr. *L. Simonotti* for recording the mass spectra and Dr. *M. Moggia* for assistance in the redaction of the manuscript.

Experimental

MP: Büchi capillary apparatus, uncorr. *IR spectra:* as oil mull, Perkin-Elmer 177. *Mass spectra:* by direct introduction, Varian MAT 112 (electron energy 70 eV, emission 1.5 mA). *UV spectra:* Beckman DB-GT (MeOH). *^{1}H-NMR spectra:* Perkin-Elmer R 12B 60 MHz. The LSR used was $Eu(DPM)_3$, Solvent $CDCl_3$, TMS int. ref. The runs were performed using the "incremental dilution" technique[13]. The LIS values (ppm) were obtained plotting δ versus $Eu(DPM)_3$/substrate ratio and determining the slope of the straight line obtained.

Thioamide S-oxides by Oxidation of Thioamides

Method A

4-(3,4,5-Trimethoxythiobenzoyl)morpholine S-oxide (**2b**)

To a cold (−50°) solution of 3 g (10 mmol) **1b** in 15 ml dichloromethane were added 18 ml (10 mmol) of a 0.56 M solution of monoperphthalic acid in diethylether. The reaction temp. was then brought to 0° and the precipitate was filtered. The filtrate was evaporated i. vac. and the residue was chromatographed over Florisil (50 g, dichloromethane/methanol 98 : 2) to afford 1.8 g (57 %) of **2b**, m.p. 124–125° dec. $C_{14}H_{19}NO_5S$ (313.4). MS: m/e = 313 (M^+); IR: 1580, 1510 (sh), 1493, 1420, 1335, 1200, 1130, 1110, 1000, 980 cm^{-1}; ^{1}H-NMR: δ (ppm) = 6.60 (s, 2H, ArH), 3.83 (s, 17H, OCH_3 and morpholine); UV λ max: 329, 288 (sh), 277 and 240 (sh) nm. The purity was checked by HPLC[11] which showed 86 % of **2b**, 4 % of **1b** and 10 % of 4-(3,4,5-trimethoxybenzoyl)morpholine.

Method B

4-(3,5-Dimethoxy-4-hydroxythiobenzoyl)morpholine S-oxide (**2a**)

A suspension of 5 g (17.6 mmol) **1a**[8] and 5 g sodium acetate in 50 ml acetic acid was heated at 50° until solution, then 1.4 ml (24 mmol) 50 % hydrogen peroxide was added. After 5 min the solution was poured into 1.5 l 6.9 % sodium hydrogen carbonate and extracted with chloroform. The organic phase was thoroughly washed with water, dried and evaporated i. vac. The residue was chromatographed over Florisil (80 g, dichloromethane/methanol 97 : 3) to afford 2.4 g (46 %) of **2a**, m.p. 148–151° dec. $C_{13}H_{17}NO_5S$ (299.3). MS: m/e = 299 (M^+); IR: 3200, 1590, 1520 (sh), 1500, 1110, 965 cm^{-1}; ^{1}H-NMR: δ (ppm) = 6.62 (s, 2H, ArH), 3.91 (s, 14H, OCH_3 and morpholine); UV λmax: 322, 244 (sh) nm.

4-(3,4,5-Trimethoxythiobenzoyl)morpholine S-oxide (**2b**) *from* (**2a**)

A solution of 600 mg (2 mmol) **2a** in 20 ml dichloromethane was treated at 0° with an excess of diazomethane (from 1 g of N-nitrosomethylurea). The solution was stirred for 30 min at room temp., then the excess of diazomethane and the solvent were removed i. vac. The residue was chromatographed over Florisil (20 g, dichloromethane/methanol 98 : 2) yielding 250 mg (40 %) of **2b**, m.p. 122–124° dec., identical with the sample obtained by method A.

Thiomorpholide S-oxide 2b through Methylthio Sulfines 4

E- and Z-3,4,5-Trimethoxyphenyl methylthio sulfines (**4**)

To a stirred solution of 2 g (7.7 mmol) **3**[8] in 30 ml dichloromethane, 1.6 g (7.7 mmol) 85 % m-CPBA was added and stirring was continued for 20 min at room temp. The yellow solution was washed with 1N-NaOH and water, dried and evaporated i. vac. The residue was chromatographed over silica gel

(30 g, ethyl ether/hexane 4 : 1). The first eluates (Rf = 0.43, same eluent) afforded 600 mg (28 %) of **4-*E***, m.p. 87–89°; $C_{11}H_{14}O_4S_2$ (274.4); MS: m/e = 274 (M^+); IR: 1575, 1500, 1330, 1240, 1125, 1100, 1060, 990, 850 cm^{-1}; ^{1}H-NMR: δ (ppm) = 7.62 (s, 2H, ArH), 3.94 (s, 3H, 4-OCH_3), 3.92 (s, 6H, 3,5-OCH_3), 2.32 (s, 3H, SCH_3); UV λmax: 356, 273 and 244 nm. The second fraction (Rf = 0.24, same eluent) yielded 300 mg (14 %) of **4-*Z***, m.p. 123–125°, $C_{11}H_{14}O_4S_2$ (274.4). MS: m/e = 274 (M^+); IR: 1585, 1500, 1340, 1240, 1135, 1125, 1110, 1010, 995, 835, 820 and 805 cm^{-1}; ^{1}H-NMR: δ (ppm) = 6.63 (s, 2H, ArH), 3.90 (s, 9H, OCH_3), 2.56 (s, 3H, SCH_3).

4-(3,4,5-Trimethoxythiobenzoyl)morpholine S-oxide **(2b)**

A solution of 270 mg (1 mmol) **4-*E*** and 0.3 ml (3.5 mmol) morpholine in dichloromethane was stirred at room temp. for 2 d. The solvent was evaporated and the residue* was chromatographed over Florisil (15 g, dichloromethane). The fractions containing crude **2b** were evaporated and rechromatographed over Florisil (10 g, dichloromethane/methanol 98 : 2), yielding 30 mg (9.6 %) of pure **2b**, m.p. 124–125° dec., identical with the sample from **1b**.

The isomer **4-*Z*** was reacted in the same way to give only traces of **2b** together with starting **4-*Z*** and decomposition products. The TLC spot* corresponding to **2b** (Rf = 0.19 chloroform/methanol 95 : 5) was scraped off, eluted with methanol and analyzed by NMR, UV and Mass spectrometry.

* Thioamide S-oxides may be visualized on TLC by spraying silica plates with an aqueous solution of $FeCl_3$[6]. In any case only one spot was revealed by this reagent.

References

1 a) G. Pifferi, P. Ventura, C. Farina and A. Frigerio in Mass Spectrometry in Drug Metabolism, A. Frigerio and L. Ghisalberti Ed., p. 45, Plenum Press, New York *1977;* b) P. Ventura, U. Cornelli and G. Pifferi, Farmaco, Ed. Sci. *32*, 640 (1977); c) G. Pifferi, R. Monguzzi, S. Banfi and C. Carpi, Chim. Ther. *8*, 462 (1973).

2 J. F. King and T. Durst, J. Am. Chem. Soc. *85*, 2676 (1963).

3 B. Zwanenburg, L. Thys and J. Strating, Tetrahedron Lett. *1967*, 3453.

4 B. Zwanenburg, L. Thys and J. Strating, Rec. Trav. Chim. Pays-Bas *86*, 577 (1967).

5 W. Walter and G. Maerten, Justus Liebigs Ann. Chem. *712*, 46 (1968).

6 W. Walter, J. Curts and H. Pawelzik, Justus Liebigs Ann. Chem. *643*, 29 (1961).

7 W. Walter and O. H. Bauer, Justus Liebigs Ann. Chem. *1976*, 1584.

8 C. Farina, M. Pinza, A. Gamba and G. Pifferi, Eur. J. Med. Chem. Chim. Ther. *14*, 27 (1979).

9 W. Walter and M. Radke, Justus Liebigs Ann. Chem. *739*, 201 (1970).

10 E. J. Hedgley and H. G. Fletcher Jr., J. Org. Chem. *30*, 1282 (1965).

11 P. Ventura, M. Zanol, T. Crolla and G. Pifferi in Recent Development in Chromatography and Electrophoresis, Ed. A. Frigerio and L. Renoz, Vol. 1, p. 87, Elsevier Publ. Co., Amsterdam 1979.

12 A. Tangerman and B. Zwanenburg, Tetrahedron Lett. *1973*, 79.

13 B. L. Shapiro and M. D. Johnston Jr., J. Am. Chem. Soc. *94*, 8185 (1972)