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Research on Alkoxythiobenzamides, III:[2)]

Synthesis of New 3,4,5-Trimethoxythiobenzamides and Related Thiomorpholides with Potential Antisecretory and Antiulcer Activity

Carlo Farina, Renato Pellegata, Mario Pinza and Giorgio Pifferi*

ISF – Laboratories for Biomedical Research – 20090 Trezzano s/N, Milan, Italy
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As a part of a project to synthesize new antisecretory and antiulcer alkoxythiobenzamides, 3,4,5-trimethoxythiobenzamides **2** and **3**, which are analogues of trithiozine, were prepared by reaction of primary amines, acyclic secondary amines and various amino acids with methyl 3,4,5-trimethoxydithiobenzoate **(1a)** or (3,4,5-trimethoxythiobenzoylthio)acetic acid **(1b)**. Some thiomorpholides **7** of alkoxyphenylalkanoic acids were prepared by thionation of the corresponding amides or from the appropriate ketones by the *Willgerodt-Kindler* reaction.

Untersuchungen an Alkoxythiobenzoesäureamiden, 3. Mitt.
Zur Synthese von neuen 3,4,5-Trimethoxythiobenzoesäureamiden und entsprechenden Thiomorpholiden mit potentieller antisekretorischer und ulkushemmender Wirkung

Im Rahmen einer Forschungsarbeit über neue Alkoxythiobenzoesäureamide mit antisekretorischer und anti-Ulkus-Wirkung wurde eine Reihe von 3,4,5-Trimethoxythiobenzoesäureamiden **2** und **3** (Trithiozin-Analoga) hergestellt. Die Synthese dieser Verbindungen erfolgte durch Thioacylierung von primären Aminen, sekundären aliphatischen Aminen und verschiedenen Aminosäuren mit 3,4,5-Trimethoxydithiobenzoesäure-methylester **(1a)** oder -carboxymethylester **(1b)**. Einige Alkoxyphenylalkansäurethiomorpholide **7** wurden auch durch Schwefelung von entsprechenden Amiden oder durch *Willgerodt-Kindler* Reaktion aus den entsprechenden Ketonen dargestellt.

In previous papers on new alkoxythiobenzamides[1,2)], a number of analogues of trithiozine*) were described with different aromatic substitutions and cyclic amine moieties. The main requirements for antisecretory and antiulcer activity are the 3,4,5-trimethoxyphenyl substitution and an oxazolidine or morpholine ring.

For further studies on structure-activity relationships, a number of thiobenzamides derived from non-cyclic amines and some related thiomorpholides, in which the distance between the phenyl ring and the thiocarbonyl group is modified, have been prepared for biological screening. The present paper deals with the synthesis of N-(3,4,5-trimethoxythiobenzoyl) derivatives of primary amines **2a–h**, secondary amines **2i–n** and various amino acids **3a–m**. It should be noted that, unlike most of the other thiobenzamides, compounds **3** can be transformed into hydrosoluble salts.

*) 4-(3,4,5-Trimethoxythiobenzoyl)morpholine, TRESANIL® – I.S.F.

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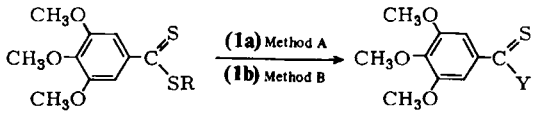
In addition, the syntheses of 3,4,5-trimethoxybenzene-acetic, -propionic and -butyric acid thiomorpholides **7a–c,** alkoxycinnamic acid thiomorpholides **7d–f**** and of the dithiocarbamate **7g** are reported.

Most of the thioamides **2** and **3** (Table 1 and 2) were synthesized by reaction of the suitable amines or amino acids with methyl 3,4,5-trimethoxy-dithiobenzoate **(1a)** in dimethyl sulfoxide (method A) or with the carboxymethyl analogue **1b** in aqueous alkaline solution (method B).



1a: R = CH_3
1b: R = CH_2COOH

2a-n: Y = NR^1R^2
3a-m: Y = NH–X–COOH

Thioacylation accomplished by method B is described as being nonracemizing[3]. This is particularly useful in the case of natural amino acids. However, the derivatives of histidine **3c** and glutamine **3e** were obtained with the same optical purity by method A as well. The derivative of diethanolamine **2m,** not easily prepared by these methods, was synthesized by reaction of 1-(3,4,5-trimethoxythiobenzoyl)imidazole[2] with diethanolamine in dichloromethane. The *Mannich* base **2h** was conventionally prepared from 3,4,5-trimethoxythiobenzamide[4], morpholine and formaldehyde.

Natural amino acids or their derivatives were employed for the synthesis of compounds **3a–i** (Table 2), except for 4-amino-3-hydroxybutyric acid which was used as the racemic mixture. In particular, N,N-dimethylglutamine[5] and N,N-dipropylglutamine were prepared from glutamic acid by the method of *Weygand* et al.[6] and the aqueous solution of their sodium salts was directly reacted with **1b** according to method B. Glutamic acid 5-methyl ester, N^{α}- and N^{ε}-formyl derivatives of lysine[7] were thioacylated by method A in the presence of one equivalent of triethylamine to afford **3d, 3h** and **3i,** respectively. In this case method A was preferred because the reaction with **1b** in aqueous solution was very slow. Compound **3j** was obtained by acid hydrolysis of its N^{α}-formylated precursor **3h,** while the isomer **3k** had to be prepared by alkaline hydrolysis of **3i.** In fact, treatment of **3i** with hydrochloric acid in ethanol-water (Scheme 1) gave the thiazolone **4b** as the dihydrochloride. The same cyclization was also performed in anhydrous acidic medium as described for similar compounds[8].

It should be noted that the thiazolone **4b** cannot be reconverted to the amino acid **3k** by means of bases such as NaOH, NH_4OH, etc. The intramolecular nucleophilic attack of the free amino group on the carbonyl is favoured so that the caprolactam derivative **2f** was the only product isolated. The easy formation of this seven-membered ring was already observed by *Terashima* et al.[9], who obtained α-amino-ε-caprolactam from methyl lysinate in the presence of Cu^{2+}.

**Some thioacryloylamines with potential anti-H_2 activity have been recently reported by F. Guerrera et al., I Convegno Nazionale, Div. Chim. Farm., Soc. Chim. It., Dec. 13, *1979,* Abs. n. 50.

Tab. *1: N-Mono and N,N-Disubstituted 3,4,5-Trimethoxythiobenzamides* **2**

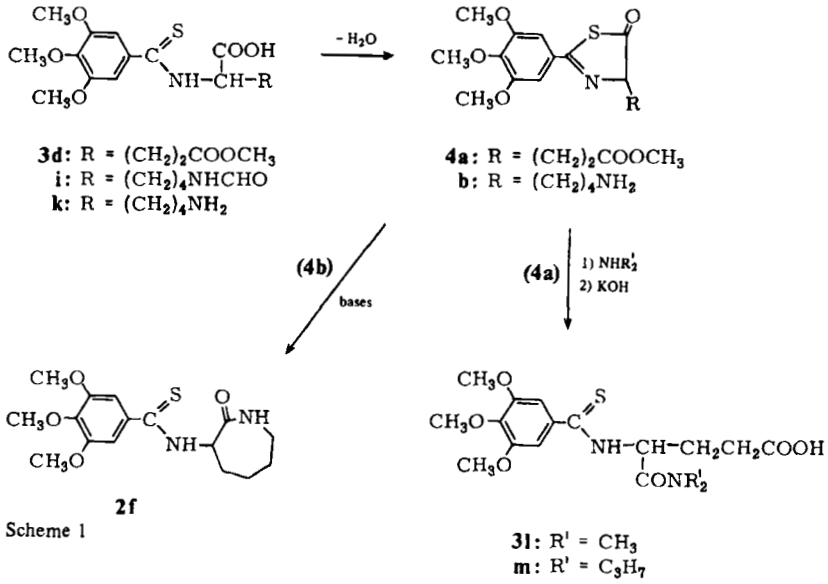
Comp. n°	R^1	R^2	Yield %[a] (Method)	M.p.°[b]	Formula[c] (M.W.)
2a	H	CH_3	52(B)	125–128	$C_{11}H_{15}NO_3S$ (241.3)
b	H	C_2H_5	63(B)	113–114	$C_{12}H_{17}NO_3S$ (255.3)
c	H	CH_2CH_2OH	40(A)	130–131	$C_{12}H_{17}NO_4S$ (271.4)
d	H	$CH_2CH_2OCH_3$	42(A)	76–77	$C_{13}H_{19}NO_4S$ (285.4)
e	H	CH_2CH_2-4(5)-imidazolyl	58(B)	159–161	$C_{15}H_{19}N_3O_3S$ (321.4)
f	H	$(CH_2)_4$–NH | –CH–CO[d]	40(A)	129–131	$C_{16}H_{22}N_2O_4S$ (338.4)
g	H	NH_2	38(B)	126–128	$C_{10}H_{14}N_2O_3S$ (242.3)
h	H	CH_2-4-morpholinyl	43[e]	140–141	$C_{15}H_{22}N_2O_4S$ (326.4)
i	CH_3	CH_3	78(B)	101–102	$C_{12}H_{17}NO_3S$ (255.3)
j	CH_3	CH_2CH_2OH	30(A)	119–120	$C_{13}H_{19}NO_4S$ (285.4)
k	C_2H_5	C_2H_5	75(B)	95–96	$C_{14}H_{21}NO_3S$ (283.4)
l	C_2H_5	CH_2CH_2OH	27(A)	110–112	$C_{14}H_{21}NO_4S$ (299.4)
m	CH_2CH_2OH	CH_2CH_2OH	35[e]	121–123	$C_{14}H_{21}NO_5S$ (315.4)
n	$CH_2CH_2OCH_3$	$CH_2CH_2OCH_3$	48(A)	55–56	$C_{16}H_{25}NO_5S$ (343.4)

(a) Isolated yields; no efforts were made to optimize these yields. (b) All compounds, except **2h**, were recrystallized from ethanol. (c) All compounds were analyzed for N and S. (d) Compound **2f** $[\alpha]_D^{20}$ = +118,5° (c = 1.9, DMF)] was prepared from L-α-amino-ε-caprolactam (see ref.[16]). (e) See experimental section.

Tab. *2: N-(3,4,5-Trimethoxythiobenzoyl)aminoacids* **3**

Comp. n°	X–COOH	Yield %[a] (Method)	M.p.°	Crystn. solvent	$[\alpha]_D^{20}$, deg.[b] (solvent)	Formula[c] (M.W.)
3a	$(CH_2)_3$-COOH	72(B)	146–147	H_2O	–	$C_{14}H_{19}NO_5S$ (313.4)
b	$CH_2CH(OH)CH_2COOH$	70(B)	169–171	H_2O	–	$C_{14}H_{19}NO_6S$ (329.4)
c	$CHCH_2$-4(5)-imidazolyl | COOH	71(B) [24(A)]	220 (d.)	EtOH	+27.8 (c=0.8, 0.1N-HCl)	$C_{16}H_{19}N_3O_5S$ (365.4)
d	$CH(CH_2)_2COOCH_3$ | COOH	84(A)	152–154[d]	i-PrOH	+18.9[d] (c=1.3, H_2O)	$C_{16}H_{21}NO_7S$ (371.4)
e	$CH(CH_2)_2CONH_2$ | COOH	83(B) [28(A)]	147–148	H_2O	+54.2 (c=1,0, EtOH)	$C_{15}H_{20}N_2O_6S$ (356.4)
f	$CH(CH_2)_2CONMe_2$ | COOH	26(B)	160–171	i-Pr_2O	+55.7 (c=0.9, EtOH)	$C_{17}H_{24}N_2O_6S$ (384.4)
g	$CH(CH_2)_2CONPr_2$ | COOH	23(B)	123–125	i-Pr_2O	+6.3 (c=0.8, EtOH)	$C_{21}H_{32}N_2O_6S$ (440.6)
h	$(CH_2)_4$-CHCOOH | NHCHO	78(A)	156–158	EtOH-H_2O	+15.1 (c=0.7, EtOH)	$C_{17}H_{24}N_2O_6S$ (384.4)
i	$CH(CH_2)_4$-NHCHO | COOH	65(A)	83–85	EtOH-H_2O	+19.3 (c=0.9, EtOH)	$C_{17}H_{24}N_2O_6S$ (384.4)
j	$(CH_2)_4$-CHCOOH | NH_2	30[e]	230–235 (d.)	EtOH-Et_2O	+14.7 (c=1.9, 0.1N-HCl)	$C_{16}H_{24}N_2O_5S$ (356.4)
k	$CH(CH_2)_4$-NH_2 | COOH	42[e]	145[d.]	–	+20.4 (c=0.9, EtOH)	$C_{16}H_{24}N_2O_5S$ (356.4)
l	$CH(CH_2)_2$-COOH | $CONMe_2$	56[e]	185–186	EtOH	–	$C_{17}H_{24}N_2O_6S$ (384.4)
m	$CH(CH_2)_2$-COOH | $CONPr_2$	25[e]	149–151	EtOH	–	$C_{21}H_{32}N_2O_6S$ (440.6)

(a) Isolated yields; no efforts were made to optimize these yields. (b) All compounds for which optical activity was measured were prepared from L-amino acids. (c) All compounds were analyzed for N and S. (d) As dicyclohexylamine salt. (e) See experimental section.



3d: R = $(CH_2)_2COOCH_3$
i: R = $(CH_2)_4NHCHO$
k: R = $(CH_2)_4NH_2$

4a: R = $(CH_2)_2COOCH_3$
b: R = $(CH_2)_4NH_2$

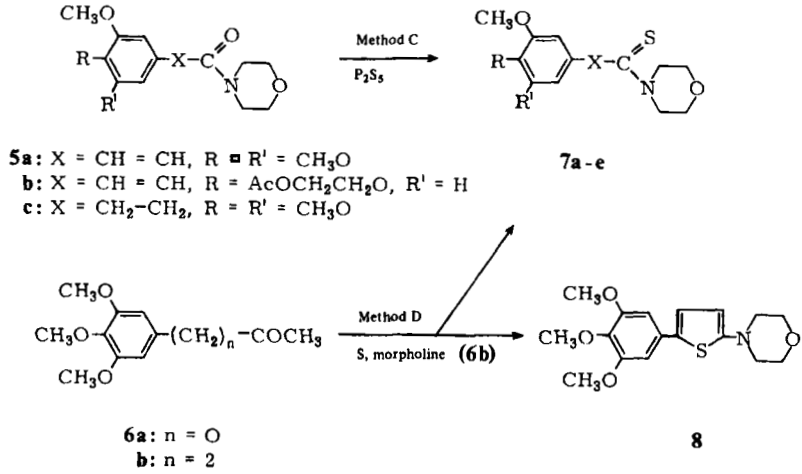
2f

3l: R' = CH_3
m: R' = C_3H_7

Scheme 1

The two isoglutamine derivatives **3l** and **3m** were not easily obtainable by amidation of **3d**, therefore the thiazolone **4a** was readily prepared by acid cyclization of **3d** and employed as an intermediate. Reaction of **4a** with dimethyl- and dipropylamine and subsequent hydrolysis gave the corresponding thioamides **3l** and **3m**, obviously as racemic mixtures.

Among the thiomorpholides listed in Table 3, compounds **7b, d, e** were prepared by thionation of the suitable amides **5a**[10], **5b** and **5c** with phosphorus pentasulfide (Scheme 2,



5a: X = CH = CH, R = R' = CH_3O
b: X = CH = CH, R = $AcOCH_2CH_2O$, R' = H
c: X = CH_2–CH_2, R = R' = CH_3O

7a-e

6a: n = O
b: n = 2

8

Scheme 2

method C). Compound **7f** was obtained by deacetylation of **7e**. The *Willgerodt-Kindler* reaction (method D) on ketones **6a** and **6b** (the latter prepared by the reduction of 3,4,5-trimethoxybenzylideneacetone[11]), afforded the thioamides **7a**[12] and **7c**. Together with **7c**, 2-(4-morpholinyl)-5-(3,4,5-trimethoxyphenyl)thiophene **(8)** was also isolated as a by-product. A similar cyclization was already observed by *Purrello*[13]. Finally, the dithiocarbamate **7g** was prepared by reacting 3,4,5-trimethoxybenzyl chloride with sodium 4-morpholinecarbodithioate in ethanol.

All compounds listed in the Tables were characterized as crystalline solids whose structures were confirmed by elemental analyses, IR spectroscopy and, when necessary, by NMR and mass spectrometry.

Tab. *3: Various Thiomorpholides* **7**

Comp. n°	R	R^1	X	Yield %[a] (Method)	M.p.°[b]	Formula[c] (M.W.)
7a	CH_3O	CH_3O	CH_2	25(D)	109–110[d]	$C_{15}H_{21}NO_4S$ (311.4)
b	CH_3O	CH_3O	$(CH_2)_2$	54(C)	104–105	$C_{16}H_{23}NO_4S$ (325.4)
c	CH_3O	CH_3O	$(CH_2)_3$	20(D)	85–86	$C_{17}H_{25}NO_4S$ (339.5)
d	CH_3O	CH_3O	CH=CH	41(C)	181–182	$C_{16}H_{21}NO_4S$ (323.4)
e	$AcOCH_2CH_2O$	H	CH=CH	85(C)	104–107	$C_{18}H_{23}NO_5S$ (365.5)
f	$HOCH_2CH_2O$	H	CH=CH	80[e]	128–130	$C_{16}H_{21}NO_4S$ (323.4)
g	CH_3O	CH_3O	CH_2S	58[e]	143–145	$C_{15}H_{21}NO_4S_2$ (343.5)

(a) Isolated yields; no efforts were made to optimize these yields. (b) All compounds were recrystallized from ethanol. (c) All compounds were analyzed for N and S. (d) Ref.[12]: m.p. 110–111°. (e) See experimental section.

Experimental

Melting points: Büchi capillary apparatus, uncorr. Omitted *elemental analyses* were within ± 0.4 % of the theoretical values. *IR spectra:* as oil mull, Perkin-Elmer 157. *NMR spectra*: in $CDCl_3$, Perkin-Elmer R12B, the chemical shifts (δ) are stated in parts per million downfield from tetramethylsilane used as int. ref. *Mass spectra:* by direct introduction, Varian Mat 112 (electron energy 70 eV, emission 1.5 mA). *Optical rotations:* Perkin-Elmer 141 polarimeter. Omitted IR, NMR

and mass spectra were consistent with the assigned structures. *Materials.* N,N-Dipropylglutamine was prepared by reaction of N-trifluoroacetylglutamic anhydride[6] with dipropylamine in tetrahydrofuran at 0° and subsequent removal of the trifluoroacetyl group with sodium borohydride in ethanol. The sodium salt was used in aqueous solution without isolation. N^{α}-formyllysine, m.p. 182–184° (d.) (lit. 185–186°) and N^{ε}-formyllysine, m.p. 219–222° (d.) (lit. 214–215°, d.) were prepared according to *Hofmann* et al.[7].

4-(2-Acetoxyethoxy)-3-methoxycinnamic acid (m.p. 175–179°) was obtained by acetylation of cinnametic acid[14] and converted via the acid chloride into 4-[4-(2-acetoxyethoxy)-3-methoxycinnamoyl]morpholine **(5b)**, m.p. 108–111°. $C_{18}H_{23}NO_6$ (349.4) Calcd.: N 4.0 Found: N 4.0.
4-(3,4,5-Trimethoxybenzenepropionyl)morpholine **(5c)** was prepared by catalytic hydrogenation of *4-(3,4,5-trimethoxycinnamoyl)morpholine* **(5a)**[10], m.p. 117–118°. $C_{16}H_{23}NO_5$ (309.4) Calcd. N 4.5 Found N 4.5.

[(3,4,5-Trimethoxyphenylthioxomethyl)thio]acetic acid **(1b)**

A solution of 20 g (67.3 mmol) 4-(3,4,5-trimethoxythiobenzoyl)morpholine[1] and 25 g (134 mmol) iodoacetic acid in 135 ml acetone was refluxed for 2 h. After cooling, the precipitate was collected, washed with acetone and dried, yielding 31 g (94 %) of *4-[α-carbpoxymethylthio-3,4,5-trimethoxybenzylidene]morpholinium iodide,* m.p. 155 ° (d.). $C_{16}H_{22}INO_6S$ (483.3) Calcd.: I 26.3 N 2.9 S 6.6 Found: I 26.3 N 2.9 S 6.7.
A stream of dry hydrogen sulfide was bubbled through an ice-cold solution of the above morpholinium iodide (30 g, 62 mmol) in 80 ml pyridine for 6 h. The red solution was then poured into 10 % sulfuric acid and extracted with ether. Acid-base work up and crystallization from water gave 10.5 g (56 %) of **1b**, m.p. 122–124°. $C_{12}H_{14}O_5S_2$ (302.4) Calcd.: S 21.2 Found: S 21.4.

3,4,5-Trimethoxythiobenzamides **(2a–n)** *and* **(3a–m)**

Method A.

N-(3,4,5-trimethoxythiobenzoyl)glutamic acid 5-methyl ester **(3d)**

A mixture of 9.1 g (35.2 mmol), methyl 3,4,5-trimethoxydithiobenzoate **(1a)**[2], 7.5 g (47 mmol) glutamic acid 5-methyl ester and 4.7 g (47 mmol) triethylamine in dimethyl sulfoxide was stirred at 50° for 16 h. The resulting dark yellow suspension was poured into water, washed with ether, acidified with dil. hydrochloric acid and extracted with ether. The organic extracts were washed with water, dried and evaporated to dryness. The residual oil (11 g) was characterized as the dicyclohexylamine salt, m.p. 152–154° (from 2-propanol). $C_{16}H_{21}NO_7S \cdot C_{12}H_{23}N$ (552.7) Calcd.: N 5.1 S 5.8 Found: N 5.1 S 5.8.

Method B.

N^{α}-(3,4,5-trimethoxythiobenzoyl)histidine **(3c)**

A solution of 5 g (16.5 mmol) **1b** and 2.6 g (16.5 mmol) histidine in 33 ml 1N-NaOH was stirred at room temp. for 24 h. The solution was acidified with hydrochloric acid and the resulting suspension was washed with chloroform. The aqueous layer was adjusted to pH 5 with sodium hydrogen carbonate and the precipitate was collected to yield 4.2 g of **3c**, m.p. 220° (d.). $C_{16}H_{19}N_3O_5S$ (365.4) Calcd.: N 11.5 S 8.8 Found: N 11.5 S 8.8.

N,N-Bis(2-hydroxyethyl)-3,4,5-trimethoxythiobenzamide **(2m)**

A solution of 10 g (41 mmol) 1-(3,4,5-trimethoxythiobenzoyl)imidazole[2] and 9 g (82 mmol) diethanolamine in dichloromethane was stirred at room temp. for 16 h. The solution was washed with 20 % hydrochloric acid in brine, dried and evaporated to dryness. Chromatography over silica gel (chloroform-methanol 95 : 5) and subsequent crystallization from ethanol afforded 4.5 g of **2m**, m.p. 121–123°. $C_{14}H_{21}NO_5S$ (315.4) Calcd.: N 4.4 S 10.2 Found: N 4.4 S 10.2 IR: 3470, 3370, 1585, 1510, 1485 and 1125 cm^{-1}.

N-(4-Morpholinylmethyl)-3,4,5-trimethoxythiobenzamide **(2h)**

A solution of 11.4 g (50 mmol) 3,4,5-trimethoxythiobenzamide[4], 4.8 g (55 mmol) morpholine and 5 ml 40 % formaldehyde in dioxane was stirred at room temp. for 2 d. The solvent was evaporated under vac., the residue was dissolved in 10 % hydrochloric acid and washed with chloroform. Precipitation with sodium hydrogen carbonate yielded 7.1 g of **2h**, m.p. 140–141°. $C_{15}H_{22}N_2O_4S$ (326.4) Calcd.: N 8.6 S 9.8 Found: N 8.6 S 9.8.

N^{ε}-(3,4,5-Trimethoxythiobenzoyl)lysine **(3j)**

A solution of 5 g (13 mmol) **3h** and 10 ml 10 % hydrochloric acid in 95 % ethanol was refluxed for 2 h; the solvent was removed under vac. and the residue, taken up with water, was purified through a column of Amberlite IR-45 (OH). Yield: 1.4 g of **3j**, m.p. 230–235° (d.). $C_{16}H_{24}N_2O_5S$ (356.4) Calcd.: N 7.9 S 9.0 Found: N 7.9 S 9.0. IR: 3280, 1600, 1580, 1540, 1500 and 1125 cm^{-1}.

N^{α}-(3,4,5-Trimethoxythiobenzoyl)lysine **(3k)**

A solution of 5 g (13 mmol) **3i** in 50 ml 0.5 N -NaOH was refluxed for 3 h. After cooling, dil. hydrochloric acid was added to bring the pH to about 7, and water was removed under vac. The residue was dissolved in ethanol, filtered from the insoluble material and evaporated to dryness. The crude product was purified by elution on Amberlite IR-45 (OH), yielding 1.95 g of **3k**, m.p. 145° (d.). $C_{16}H_{24}N_2O_5S$ (356.4) Calcd.: N 7.9 S 9.0 Found: N 7.9 S 9.0. IR: 3200, 1600, 1590, 1540–1530, 1500 and 1125 cm^{-1}.

Methyl 4,5-dihydro-5-oxo-2-(3,4,5-trimethoxyphenyl)-4-thiazolepropionate **(4a)** *hydrobromide*

A solution of 11 g (29.6 mmol) **3d** and 30 ml of 10 % hydrobromic acid in acetic acid was stirred for 2h at room temp. The reaction mixture was diluted with 100 ml diisopropyl ether and the precipitate was crystallized from ethanol, yielding 10.5 g (82 %) of **4a**, m.p. 184–188° (d.). $C_{16}H_{19}NO_6S \cdot HBr$ (434.3) Calcd.: Br 18.4 N 3.2 S 7.4 Found: Br 18.3 N 3.2 S 7.4. IR: 2700, 2650, 1740, 1625, 1580, 1530, 1500 and 1125 cm^{-1}.

4,5-Dihydro-5-oxo-2-(3,4,5-trimethoxyphenyl)-4-thiazolebutylamine **(4b)** *dihydrobromide* was similarly prepared in 85 % yield from **3k**, m.p. 231° (d.). $C_{16}H_{22}N_2O_4 \cdot S2HBr$ (500.3) Calcd.: Br 32.0 N 5.5 S 6.4 Found: Br 32.0 N 5.5 S 6.4.

(±)-α-*(3,4,5-Trimethoxythiobenzoylamino)ε-caprolactam* **(2f)**

A solution of 500 mg (1 mmol) **4b** in 20 ml methanol was saturated with dry ammonia. After standing for 3 h, the solution was concentrated under vac. The precipitate was washed with water and crystallized from ethanol to yield 200 mg (59 %) of **2f** m.p. 206–207°. $C_{16}H_{22}N_2O_4S$ (338.4) Calcd.: N 8.3 S 9.5 Found: N 8.3 S 9.4. IR: 3290, 3210, 3100, 1680, 1590, 1520, 1495 and 1125 cm^{-1}.

(±)-5-(Dipropylamino)-5-oxo-4-(3,4,5-trimethoxythiobenzoylamino)pentanoic acid **(3m)**

A solution of 3.5 g (8 mmol) **4a** and 10 ml (73 mmol) dipropylamine in 50 ml trichloroethylene was refluxed for 3 h. After cooling, the solution was washed with dil. hydrochloric acid and water, dried and evaporated to dryness. After chromatography over silica gel (chloroform) 2 g of the methyl ester of **3m,** were obtained. This was dissolved in 30 ml ethanol with 5 ml 1N-KOH and stirred at room temp. for 36 h. The solution was diluted with water, washed with ether, acidified and extracted with ether. Removal of the solvent and crystallization from ethanol gave 0.9 g of **3m,** m.p. 149–151°. $C_{21}H_{32}N_2O_6S$ (440.6) Calcd.: N 6.4 S 7.3 Found: N 6.4 S 7.3. IR: 3400, 1740, 1630, 1590, 1520, 1490 and 1125 cm^{-1}.

Thiomorpholides **(7a–f)**

Method C.

4-[4-(2-Acetoxyethoxy)-3-methoxythiocinnamoyl]morpholine **(7e)**

A solution of 9.5 g (27.2 mmol) **5b** and 6 g (27.2 mmol) phosphorus pentasulfide was heated in anhydrous pyridine at 95° for 2.5 h. After cooling, the brown solution was poured into 500 ml of cold 10 % hydrochloric acid. The precipitate was collected, dissolved in chloroform and washed with aqueous sodium carbonate and water. The organic layer was dried, evaporated under vac. and the residue was crystallized from 2-propanol to yield 8.5 g of **7e,** m.p. 104–107°. $C_{18}H_{23}NO_5S$ (365.5) Calcd.: N 3.8 S 8.8 Found: N 3.8 S 8.8.

4-[4-(2-Hydroxyethoxy)-3-methoxythiocinnamoyl]morpholine **(7f)**

A solution of 4.5 g (12.3 mmol) **7e** in 80 ml ethanol and 20 ml 10 % potassium hydroxide was stirred at room temp. for 0.5 h. Hydrochloric acid was then added and the precipitate was crystallized from ethanol to yield 3.2 g of **7f.** $C_{16}H_{21}NO_4S$ (323.4) Calcd.: N 4.3 S 9.9 Found: N 4.3 S 9.9.

Method D.

4-(3,4,5-Trimethoxybenzenethiobutyryl)morpholine **(7c)**

A mixture of 38 g (0.16 mol) **6b,** 5.75 g (0.18 mol) sulfur and 26 g (0.30 mol) morpholine was heated at 130° for 3 h. After cooling, the mixture was dissolved in chloroform, washed with dil. hydrochloric acid, sodium hydrogen carbonate and water. The organic layer was evaporated under vac., the residue chromatographed over silica gel (ether) and crystallized from ethanol to yield 10.6 g of **7c,** m.p. 85–86°. $C_{17}H_{25}NO_4S$ (339.5) Calcd.: N 4.1 S 9.5 Found: N 4.2 S 9.4. IR: 1590, 1510, 1490, 1240, 1130, 1005, 850 and 820 cm^{-1}. NMR: 6.59 (s, 2H, ArH), 4.50–4.20 and 3.80–3.60 (complex abs., 8H, morpholine), 3.85 (s, 6H, m-OCH_3), 3.80 (s, 3H, p-OCH_3), 3.10–2.50 (complex abs., 4H, Ar-CH_2 and CH_2CS), 2.30–1.80 (complex abs., $CH_2CH_2CH_2$).

The first eluates contained another product (2.5 g), m.p. 115–117° (ethanol), which was shown to be *2-(4-morpholinyl)-5-(3,4,5-trimethoxyphenyl)thiophene* **(8)** $C_{17}H_{21}NO_4S$ (335.4) Calcd.: C 60.9 H 6.31 N 4.2 S 9.6 Found: C 60.7 H 6.29 N 4.2 S 9.5. IR: 1580, 1505, 1490, 1130, 1015, 900, 820 and 770 cm^{-1}. NMR: 6.74 (s, 2H, ArH), 6.93 and 6.07 (two d, 2H, J = 4Hz, thiophene protons), 3.86 (s, 9H, $ArOCH_3$), 3.7–3.8 and 3.0–3.2 (complex abs., 8H, morpholine). MS: m/e 335 (M^+, 80 %), 320 ($[M-CH_3]^+$, 100 %).

3,4,5-Trimethoxybenzyl 4-morpholinecarbodithioate (**7g**)

A solution of 4.4 g (20 mmol) sodium 4-morpholinecarbodithioate dihydrate[15] and 4.3 g (20 mmol) 3,4,5-trimethoxybenzyl chloride was refluxed in ethanol for 0.5 h. After cooling, the precipitate was collected and recrystallized from ethanol to yield 4 g of **7g**, m.p. 143–145°. $C_{15}H_{21}NO_4S_2$ (343.5) Calcd.: N 4.1 S 18.7 Found: N 4.1 S 18.6.

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References

1 G. Pifferi, R. Monguzzi, S. Banfi and C. Carpi, Eur. J. Med. Chem. Chim. Ther. *8*, 462 (1973).
2 II: C. Farina, M. Pinza, A. Gamba and G. Pifferi, Eur. J. Med. Chem. Chim. Ther. *14*, 27 (1979).
3 G. C. Barret, J. Chem. Soc. *1965*, 2825.
4 R. B. Moffett, J. Med. Chem. *7*, 319 (1964).
5 A. Meister, J. Biol. Chem. *210*, 17 (1954).
6 F. Weygand and E. Leising, Chem. Ber. *87*, 248 (1954).
7 K. Hofmann, E. Stutz, G. Spühler, H. Yajima and E. T. Schwartz, J. Am. Chem. Soc. *82*, 3727 (1960).
8 G. C. Barret and A. R. Khokhar, J. Chromatogr. *39*, 47 (1969).
9 S. Terashima, M. Wagatsuma and S. Yamada, Tetrahedron *29*, 1487 (1973).
10 G. Cerbai, G. Di Paco and G. Dell'Omodarme, Boll. Chim. Farm. *101*, 211 (1962).
11 T. Nakada and K. Nishihara, J. Pharm. Soc. Japan *64*, 74 (1944).
12 E. Kasztreiner, J. Borsy and L. Vargha, Biochem. Pharmacol. *11*, 651 (1962).
13 G. Purrello, Gazz. Chim. Ital. *97*, 35 (1967).
14 Fr. M. 6380 (Nov. 18, 1968); C. A. *76*, 140232w (1972).
15 D. De Filippo and C. Preti, Gazz. Chim. Ital., *95*, 707 (1965).
16 R. Pellegata, M. Pinza and G. Pifferi, Synthesis *1978*, 614.

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