material and a single spot (R_f 0.7) in $(CH_3)_2CHOH-NH_4OH-H_2O$ (7:1:2). The solution was acidified with 1 N HCl to pH 3-4. The precipitated solid was filtered, washed with water, and dried. **4**: yield 104 mg (78%); mp 187 °C; mass spectrum, *m/e* 765 (M^+, $4Me_3Si$ derivative); UV λ_{max} (ϵ_{max}) pH 1, 293 (23 900) and 277 (24 600); pH 7, 277 (32 400) and 223 (38 200); pH 12, 277 (32 900); ^1H NMR ($(CD_3)_2SO$) δ 7.7 and 6.8 (d of d, 4, C_6H_4), 7.4 (q, 2, C^7H, C^8H), 4.4 (s, 2, $CH_2C{\equiv}C$), 3.2 (s, 1, $HC{\equiv}C$). Anal. ($C_{23}H_{23}N_7O_5{\cdot}2H_2O$) C, H, N.

***N*-[4-[[(2-Amino-3,4-dihydro-4-oxopyrido[3,2-*d*]pyrimidin-6-yl)methyl]propargylamino]benzoyl]-L-glutamic Acid or 8-Deaza-N^{10}-propargylfolic Acid (3).** To a suspension of **9** (84 mg, 0.157 mM) in 2 mL of EtOH was added 0.8 mL of 1 N NaOH. The mixture was stirred for 48 h, at which time reaction appeared to be complete by TLC [$(CH_3)_2CHOH-NH_4OH-H_2O$ (7:1:2)]. The solution was acidified with 1 N HCl to pH 3-4. The precipitated solid was filtered washed with water and dried. **3**: yield 55 mg (73%); mp 202 °C; mass spectrum, *m/e* 766 (M + $4Me_3Si$ derivative); UV λ_{max} (ϵ_{max}) pH 1, 298 nm (18 200) and 250 (11 500); pH 7, 285 (27 400) and 220 (38 500); pH 12, 286 (11 300) and 223 (16 300); ^1H NMR δ 7.6 and 6.8 (d, 2 each, C_6H_4), 7.3 and 7.42 (d, 1 ea, C^7H and C^8H), 6.5 (s, 2-NH_2), 4.8 (s, 2, CH_2N^{10}), 3.2 (s, 1, $HC{\equiv}C$). Anal. ($C_{23}H_{22}N_6O_6{\cdot}H_2O$) C, H, N.

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Registry No. **2**, 101760-45-6; **3**, 106500-88-3; **4**, 106500-89-4; **5**, 76807-56-2; **6**, 76832-41-2; **7**, 76858-72-5; **8**, 106500-90-7; **9**, 106500-91-8; diethyl *N*-(4-aminobenzoyl)-L-glutamate, 13726-52-8; propargyl bromide, 106-96-7; diethyl 8-deazaaminopterin, 76807-59-5; diethyl 8-deazafolate, 76807-65-3; thymidylate synthase, 9031-61-2; folic acid, 59-30-3; 10-methylfolic acid, 2410-93-7; 8-deazafolic acid, 51989-25-4; 8-deaza-10-methylfolic acid, 76807-68-6.

Analogues and Derivatives of Tenoxicam.[1] 1. Synthesis and Antiinflammatory Activity of Analogues with Different Residues on the Ring Nitrogen and the Amide Nitrogen

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The synthesis of tenoxicam, 4-hydroxy-2-methyl-*N*-2-pyridyl-2*H*-thieno[2,3-*e*]-1,2-thiazine-3-carboxamide 1,1-dioxide (**1e**), and of the analogues with various residues on the ring nitrogen and the amide nitrogen is described. This new class of "oxicams" has pronounced antiinflammatory and analgesic properties. The very specific structure–activity relationship of isomeric and isosteric groups at the amide nitrogen has been evaluated. The substituent in position 2 also has a great influence on the pharmacological properties. Tenoxicam is presently undergoing clinical trials.

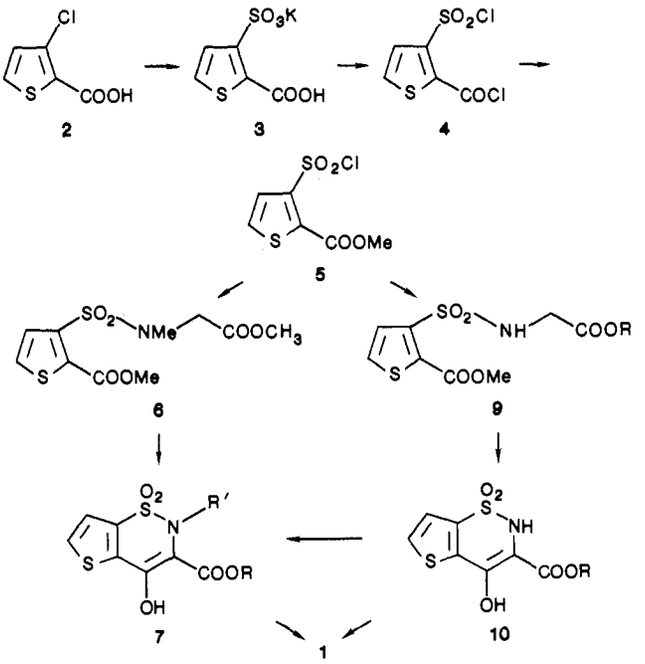
Around 1968 Lombardino and Wiseman discovered the benzo-1,2-thiazine enolamide 1,1-dioxides as a new class of potent nonsteroidal antiinflammatory agents.[2] By variation of the residues at the ring and at the amide nitrogen atoms, piroxicam has been identified as the most active derivative (Figure 1). The favorable pharmacological and pharmacokinetic properties of this compound make a "once a day dose" of 20 mg optimal to relieve pain and other symptoms of arthritic patients.[3] The potency is about 5 and 10 times higher, respectively, than that of indomethacin and phenylbutazone, the two best known drugs of the 1960s for this indication.

Recognizing the outstanding antiinflammatory potency of some of these enolamides in rats, we decided in 1973 to study the synthesis and the pharmacological activity of analogues in which the annulated benzene ring is replaced by a heterocyclic unit (Figure 1, A). It appeared to be plausible that this variation of the molecule could exert a pronounced influence on activity, similar to that found previously for the residues at the two nitrogen atoms. This paper deals with the synthesis of 4-hydroxy-2*H*-thieno-[2,3-*e*]-1,2-thiazine-3-carboxamide 1,1-dioxides **1**.[4]

Chemistry

Synthesis of the title compounds **1a–q** (Table I) started from the acid **2**, which was obtained by a "Fiesselmann" thiophene synthesis, followed by substitution of the hydroxy group by chlorine.[5] A sulfite-exchange reaction of **2** yielded the potassium sulfonate **3**, which was transformed into the bis(acid chloride) **4**, with phosphorus pentachloride in phosphorus oxychloride. Selective methanolysis

Scheme I

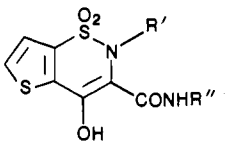


[†] Technischen Universität Wien.
[‡] F. Hoffmann-La Roche & Co. Ltd.

(1) Trademark: Tilcotil (F. Hoffmann-La Roche & Co. Ltd.).
(2) Lombardino, J. G.; Wiseman, E. H. *Med. Res. Rev.* **1982**, *2*, 127.

0022-2623/87/1830-0678$01.50/0

Table I. Antiinflammatory, Analgesic, and Ulcerogenic Properties and Preparation of 4-Hydroxy-2*H*-thieno[2,3-*e*]-1,2-thiazine-3-carboxamide 1,1-Dioxides



1

no.	R″	R′	antiinflammation, kaolin edema rat[a] inhibn edema: ED_{30},[c] mg/kg po	antiinflammation, kaolin edema rat[a] increase pain threshold: ED_{100},[c] mg/kg po	ulcerogenicity, rat:[b] ED_{50},[d] mg/kg po	rctn time, h	yield, %	crystn solvent	mp, °C dec
1a	phenyl	Me	>100	ca. 75		7	75	xylene	248–251
1b	3-methylphenyl	Me	43.4 (5.7–333.8)	3.9 (3.0–385.2)	7 (2.7–14.4)	7	70	benzene	197–199
1c	4-hydroxyphenyl	Me	ne	ne		7	75[e]	dioxane	287–290
1d	3-chlorophenyl	Me	>100	>100		7	70	xylene	241–243
1e	2-pyridyl	Me	2.6 (0.5–13.8)	5.3 (0.4–67.1)	0.7 (0.4–1.1)	7	75	xylene	209–213
1f	3-pyridyl	Me	63.7 (1.4–2798.7)	>100	6.3 (1.5–19.0)	7	70[e]	pyridine	241–244
1g	4-pyridyl	Me	ne	ne		7	43[e,f]	DMF[g]	263–267
1h	6-methyl-2-pyridyl	Me	ca. 30	27.4 (0.1–5988.4)	0.5 (0.2–1.1)	7	63[h]	benzene	216–218
1i	2-pyrimidinyl	Me	ne	ne		18	26[i]	ethanol	221–223
1j	2-pyrazinyl	Me	ca. 70	ca. 56	1.8 (0.09–4.5)	7	70	xylene	245–248
1k	2,4-dimethyl-6-pyrimidyl	Me	ne	ne		7	63[j]	xylene	270–271
1l	5-methyl-3-oxazolyl	Me	ca. 20	ca. 24		7	71	xylene	239–243
1m	3,4-dimethyl-5-oxazolyl	Me	ne	ne		14	65[j]	benzene	206–208
1n	2-thiazolyl	Me	ca. 20	ca. 14	2.2 (0.9–5.1)	7	85	xylene	225
1o	2-pyridyl	H	>100	>100		*k*	*k*	*k*	201–202
1p	2-pyridyl	Et	ne	ca. 24		*l*	*l*	*l*	184–188
1q	2-pyridyl	4-OMe-benzyl				8	64	acetone/hexane	191
piroxicam			1.9 (0.06–6.1)	4.0 (0.7–24.1)	0.5 (0.05–1.2)				

[a] Female albino rats of the Füllinsdorf strain of about 70 g received a subcutaneous injection of 0.1 mL of a 10% kaolin (bolus alba) suspension into the right hind paw. Drugs suspended in a 0.5% tragacanth solution were administered orally 0.5 h before and 3.5 h after the kaolin injection. The paw diameters and the pressure pain threshold were determined after the kaolin injection. The inhibition of the edema and the increase of the pain threshold were calculated in percent of control animals. In each experimental set, a group receiving 30 mg/kg po phenylbutazone was included for validation purpose. Without an inhibition of the edema by this standard drug compared to control within predetermined limits, the results of the whole set were discarded. [b] Female albino rats of the Füllinsdorf strain of about 160 g were starved for 24 h. Drugs suspended in a 0.5% gum of tragacanth were administered orally. Thereafter the animals were exposed to a cold-water stress (22.5 °C) for 2 h. The rats were sacrificed and the animals with macroscopically recognizable erosions of the gastric mucosa were counted. [c] For drugs where at least one dose group produced a significant effect, the group mean values were used for graphical determination of the ED_{30} or ED_{100}. The graphical method does not allow the determination of confidence limits. For drugs with measurement of effects at three different dose levels, a logit analysis has been carried out. For the dose–effect relationship, a logit curve was adapted. This allows the calculation of the 95% confidence interval of the ED. (In the logit model the upper asymptote—as one of the assessment parameters—was computed separately for each compound and adapted with the least-square method.) >100 is given if an effect was observed that did not allow estimation of an ED_{30} or ED_{100}, respectively. ne = no effect up to 100 mg/kg. [d] The ED_{50} is defined as the dose that induces lesions in 50% of the animals. The ED_{50} with 95% confidence interval was calculated by probit analysis. [e] Product precipitates from the reaction mixture. Addition of active carbon in recrystallization only. [f] No distillation from the reaction mixture, because amine is too volatile. [g] Considerable decrease in yield due to decomposition. [h] First the hygroscopic amine is dissolved in 500 mL of xylene, 100 mL of which is distilled off to remove water before **7a** is added. From the reaction mixture 200 mL of solvent is distilled. [i] Volume of the reaction mixture is kept constant by addition of dry xylene at the same rate as solvent is distilled from the reaction mixture. [j] Only 100 mL of solvent is distilled from the reaction mixture. [k] Prepared by debenzylation of **1q**; see Experimental Section. [l] Modified reaction sequence; see Experimental Section.

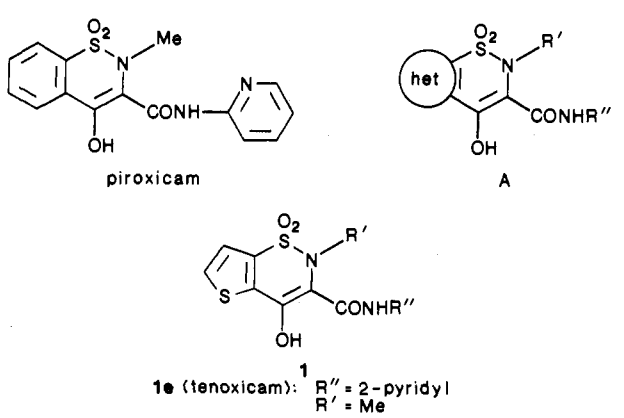


Figure 1.

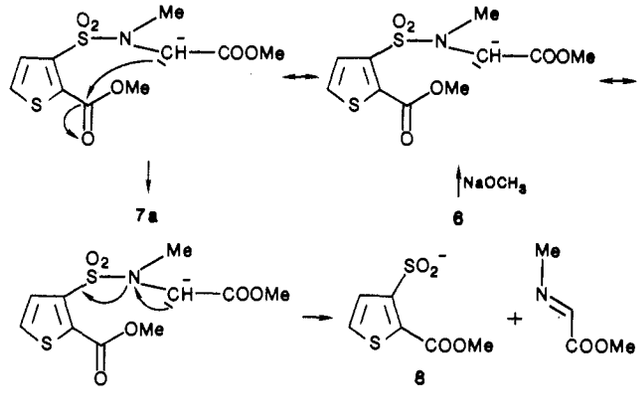
gave the ester **5**, which is the key intermediate for the annulation sequence (Scheme I).

Reaction of compound **5** with sarcosinate gave the diester **6** in a very good yield, which was then cyclized to the thieno[2,3-*e*]-1,2-thiazinecarboxylates **7a** and **7b**. Although extensive variations of the reaction conditions were examined—best results were obtained with sodium methoxide in methanol—a yield of about 20% of **7a** could not be exceeded. Compound **7a** represents a precursor for the target molecules described in this paper (**1a–n**); they were obtained individually by aminolysis of **7a** in xylene with the desired primary amine.

A closer examination of the cyclization step led to the isolation of sulfinic acid **8** (Scheme II) in appreciable amounts. Thus, we concluded that a reductive sulfon-

(3) Hobbs, D. C. *Eur. J. Rheumatol. Inflammation* **1983**, *6*, 46.
(4) Hromatka, O.; Binder, D.; Pfister, R.; Zeller, P. Swiss Pat. Appl. 11582, 1974; *Chem. Abstr.* **1976**, *85*, 63077*f*.
(5) Steinkopf, W.; Köhler, W. *Justus Liebigs Ann. Chem.* **1937**, *532*, 250.

Scheme II



amide cleavage had occurred as a side reaction under ring-closure conditions. To avoid this, the diester **9a** was prepared from **5** and glycine methyl ester. It could be argued that under the basic cyclization conditions **9a** might be deprotonated at the nitrogen and subsequently also at the methylene group, which would then undergo the Dieckmann cyclization. The negatively charged nitrogen would be less prone to attract the electron pair of the carbanion, eliminating the cause for reductive sulfonamide cleavage and favoring ring closure over cleavage. In fact, this concept turned out to be valid, and ring closure of **9** resulted in a 58% yield of **10a**.

Compound **10a** could be methylated to **7a** in very good yield. Apart from doubling the total yield of the cyclization sequence, this modified ring closure to **10a** allows free choice of the substituent at the ring nitrogen (**1p**, **1q**).

Compound **1o**, which bears no substituent at the ring nitrogen, was not obtained by direct amidation of **10b**, but in a modified reaction sequence, in which **10a** was first protected at the ring nitrogen with a 4-methoxybenzyl group to yield **7d**, which after amidation gave **1q**, from which the protective group was removed by treatment with acid.

Pharmacology

For the assessment of antiinflammatory and analgesic activity, a kaolin-induced edema in the rat hind paw was used.[6] The differences in the diameter of the inflamed vs. the uninflamed paw and in the pressure on the paws necessary to elicit a threshold pain response were compared in animals with and without orally applied compounds (Table I). The main side effect of nonsteroidal antiinflammatory compounds is their ulcerogenic activity. The ulcerogenic potential was assessed in a rat model by the enhancement of stress-induced gastric mucosal lesions after oral administration of the compounds[7] (Table I).

Discussion

Some thieno[2,3-*e*]thiazine enolamide 1,1-dioxides exhibit very interesting antiinflammatory and analgesic properties. As Table I illustrates, the influence of the substituents R′ and R″ in the thienothiazines **1a–p** on the activity is remarkable.

The anilides **1a–d** are less active than the heterocyclic amides **1e–p**. In the 2-position (R′), only methyl is allowed; hydrogen and ethyl practically eliminate the activity (cf. compounds **1e**, **1o**, and **1p**). The isomeric 2-, 3- or 4-pyridyl amides **1e**, **1f**, and **1g** differ substantially in their antiinflammatory and analgesic properties. The homologous 6′-methyl derivative **1h** of the 2-pyridyl amide **1e** is much less active. The amides with two heteroatoms in their N-substituent R″ (**1i–n**) are less interesting than the 2-pyridyl amide, resulting in an unusual difference between compounds with isosteric residues such as pyridyl and thiazolyl. The most potent substance in this series is the 2-methyl-*N*-2-pyridyl derivative **1e**. The ulcerogenicity of antiinflammatory drugs usually corresponds with their antiinflammatory activity because both effects are due to lower plasma prostaglandin levels. This parallelism is also true in this series (Table I).

Conclusion

Thieno[2,3-*e*]-1,2-thiazine-3-carboxamide 1,1-dioxides **1** can be prepared in a similarly economic mode as the benzothiazine analogues.

The variations of the residues in positions 2 and 3 of **1** provide compounds with a pronounced structure–activity relationship concerning their antiinflammtory, analgesic, and ulcerogenic properties. In comparison with the piroxicam derivatives with analogous substitution patterns, the biological activities are similar.[2] This can be seen in Table I, by comparing the results of **1e** with those of piroxicam. It indicates that the replacement of the benzo ring of piroxicam by thiophene influences the pharmacological properties neither positively nor negatively, which is somewhat surprising, considering the sensitivity of isomeric, homologous, and isosteric residues at the other half of the molecule.

The present work has led to the selection of compound **1e**, now known as tenoxicam, for further development.[8–10] Tenoxicam is presently undergoing clinical trials[11] with arthritic patients. A daily dose of 20 mg in man is sufficient because of its long plasma half-life.[12] The metabolism of tenoxicam differs to some extent from that of piroxicam.[13]

Experimental Section

Melting points were determined with a Kofler melting point apparatus. The melting points are not corrected. The ^{1}H NMR spectra were determined with a Perkin-Elmer R 12A spectrometer using tetramethylsilane as an internal standard. The abbreviation s refers to singlet, and the number in parentheses refers to the number of protons represented by the given signal. All compounds analyzed within ±0.3% of theoretical values for C, H, and N. In most cases the reported yields for the products were not optimized.

Synthesis of Compounds 1 from 7a. General Procedure. A suspension of 2.5 g (9 mmol) of **7a** and 11 mmol of the corresponding amine in 300 mL of dry xylene is stirred at reflux temperature while 200 mL of solvent is slowly distilled from the reaction mixture. Then active carbon is added. The reaction mixture is boiled once more for a short time and filtered hot. After cooling, the filtrate is allowed to rest at −20 °C for 4 h. Precipitated **1** is filtered off and recrystallized. The product is washed with petrol ether and dried in vacuo.

Compounds **1a–n** and **1q** were prepared according to this procedure (see Table I).

4-Hydroxy-*N*-2-pyridyl-2*H*-thieno[2,3-*e*]-1,2-thiazine-3-carboxamide 1,1-Dioxide (1o). A solution of 4.3 g (9.7 mmol)

(6) Strub, K. M.; Aeppli, L.; Müller, R. K. M. *Eur. J. Rheumatol. Inflammation* **1982**, *5*, 478.
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of **1q** and 8.6 mL of anisole in 170 mL trifluoroacetic acid is kept under argon at 50 °C for 16 h. The acid is removed in vacuo and the residue is partitioned between 0.1 N sodium hydroxide solution (500 mL) and ether (500 mL). The aqueous phase is acidified with 0.1 N hydrochloric acid and the precipitated product filtered and washed with water. After drying in vacuo at 80 °C, 2.88 g (92%) of yellow product **1o** is obtained, mp 201–202 °C.

2-Ethyl-4-hydroxy-*N*-2-pyridyl-2*H*-thieno[2,3-*e*]-1,2-thiazine-3-carboxamide 1,1-Dioxide (1p). A solution of 2.35 g (8.12 mmol) of **7c** and 2.3 g (24.4 mmol) of 2-pyridinamine in 250 mL of *o*-xylene is kept at reflux temperature under an atmosphere of argon for 7 h. Then the solvent is removed in high vacuo and the residue is recrystallized from hexane/acetone to yield 2.5 g of yellow product, mp 143–144 °C (enamine of **1p** with 2-pyridinamine). This compound is dissolved in 65 mL of 2 N hydrochloric acid at reflux temperature. On cooling, eventually with an ice bath, **1p** crystallizes from the yellow aqueous solution. After filtration, several washings with water, and drying in high vacuo at 90 °C 1.77 g (62%, overall) of intensely yellow crystals of **1p** is obtained, mp 184–188 °C.

3-Sulfo-2-thiophenecarboxylic Acid, Potassium Salt (3). A solution of 120 g (1.15 mol) of anhydrous sodium bisulfite in 330 mL of water is added to a solution of 179 g (1.1 mol) of 3-chloro-2-thiophenecarboxylic acid (**2**) and 44 g (1.1 mol) of sodium hydroxide in 475 mL of water. The mixture is adjusted to pH 7.6 by addition of 30% soda lye. After addition of 9 g of finely ground cuprous chloride, the solution is kept in an autoclave at 143 °C[14] for 16 h. After cooling to 40 °C, the mixture is filtered and 150 mL of concentrated hydrochloric acid is added. Unreacted **2** precipitates and is removed by filtration.[15] Potassium chloride (240 g) is added to the filtrate with heating. On slow cooling **3** precipitates as anhydrous cubic crystals.[16] The mixture is kept at 5 °C for 16 h and filtered by suction, and the crystals are dried at 110 °C. The finely ground crystals are heated twice in anhydrous acetone to remove the remaining impurities of **2**. The solvent is removed by filtration, and the crystals are dried in vacuo at 70 °C; yield, 210 g of **3** (40 g of **2** can also be recovered); mp 275–283 °C dec. Anal. ($C_5H_3KO_5S_2$) C, H, S.

3-(Chlorosulfonyl)-2-thiophenecarbonyl Chloride (4). To a suspension of 50 g (203 mmol) of **3** in 250 mL of phosphorus oxychloride is added 85 g (406 mmol) of phosphorus pentachloride, which results in spontaneous effervescence (hydrogen chloride). After being stirred and heated on a boiling water bath for 90 min, the reaction mixture is allowed to cool to room temperature, the inorganic salts are removed by suction, and the filtrate is evaporated to remove phosphorus oxychloride. The oily residue is dissolved in 400 mL of anhydrous chloroform, filtered, and evaporated. On cooling, **4** crystallizes and can be used for the next reaction step without further purification; yield 48.5 g (98%) of **4**; mp 42–43 °C (from ether at −20 °C). Anal. ($C_5H_2Cl_2O_3S_2$) C, H.

Methyl 3-(Chlorosulfonyl)-2-thiophenecarboxylate (5). After addition of 9.6 g (0.3 mol) of methanol to a solution of 48 g (196 mmol) of **4** in 500 mL of anhydrous chloroform, the mixture is refluxed for 3 h. On evaporation of the solvent, crystalline **5** is obtained; yield, 44.8 g (95%); mp 60–63 °C. Anal. ($C_6H_5ClO_4S_2$) C, H.

Methyl 3-[[*N*-[(Ethoxycarbonyl)methyl]-*N*-methylamino]sulfonyl]-2-thiophenecarboxylate (6). A mixture of 24 g (0.1 mol) of **5** and 15.4 g (0.1 mol) of sarcosine ethyl ester hydrochloride in 50 mL of dry pyridine is allowed to react for 2 h at room temperature. The solvent is removed in vacuo, and the residue is taken up in 100 mL of 2 N hydrochloric acid and extracted with dichloromethane several times. The combined organic layers are dried and evaporated. The crystalline residue is triturated in a small amount of cold ethanol; yield, 27 g (84%) of **6**; mp: 83–85 °C (ethanol). Anal. ($C_{11}H_{15}NO_6S_2$) C, H, N.

Methyl 4-Hydroxy-2-methyl-2*H*-thieno[2,3-*e*]-1,2-thiazine-3-carboxylate 1,1-Dioxide (7a). (**A**) A suspension of 64.3 g (0.2 mol) of **6** in 210 mL of 1 N sodium methoxide in methanol is stirred at room temperature under nitrogen for 15 min. A clear solution is obtained, which is refluxed for 25 min. After cooling, the reaction mixture is neutralized with concentrated hydrochloric acid and evaporated. The residue is taken up in 100 mL of 2 N hydrochloric acid and extracted with dichloromethane several times. The combined organic layers are first extracted with a 10% solution of sodium acetate and then with a 10% solution of sodium carbonate. The latter phase is acidified with hydrochloric acid and extracted with dichloromethane several times. The combined organic layers are dried, stirred with active carbon, filtered, and evaporated. The crystalline residue is triturated with a small amount of cold ethanol; yield, 11 g (20%) of **7a**; mp 193–195 °C. Anal. ($C_9H_9NO_5S_2$) C, H, N.

(**B**) A solution of 4.9 g (18.8 mmol) of **10a** in 25 mL of anhydrous DMF is added to a suspension of 1.79 g (74.6 mmol) of sodium hydride in 16 mL of anhydrous DMF at 0 °C during 2 h. After the mixture is stirred for 1 h at room temperature, 4.65 mL (74.7 mmol) of methyl iodide is added during 1 h and the reaction mixture is stirred at room temperature for 16 h. The solvent is removed in vacuo. The residue is treated with 30 mL of 0.5 N hydrochloric acid and 40 mL of dichloromethane. The aqueous phase is extracted six times with 10 mL of dichloromethane. The combined organic layers are washed with water, dried (sodium sulfate), and evaporated. The crude product is dissolved in 5 mL of ethanol with heating. After the mixture is cooled to 0 °C, **7a** is filtered by suction, washed with 5 mL of cold ethanol, and dried in vacuo at 60 °C; yield, 4.05 g (78.5%) of **7a**; mp 191–195 °C.

Methyl 3-Sulfino-2-thiophenecarboxylate (8). The sodium acetate phase from the synthesis of **7a** (process A) is acidified with excess hydrochloric acid and extracted with dichloromethane several times. The combined organic layers are dried, stirred with active carbon, filtered, and concentrated in vacuo at a temperature below 30 °C, which results in crystallization of 15.2 g of **8** from the solution; mp 98–100 °C (ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 9.69 (s, 1 H, OH), 7.73 (s, 2 H, H thiophene), 3.92 (s, 3 H, OCH_3).

Ethyl 4-Hydroxy-2-methyl-2*H*-thieno[2,3-*e*]-1,2-thiazine-3-carboxylate 1,1-Dioxide (7b). (**A**) A solution of 3.2 g (10 mmol) of **6** in 11 mL of 1 N sodium ethoxide in ethanol is kept at 65 °C for 1 h. The reaction mixture is hydrolyzed with 70 mL of ice-cooled 2 N hydrochloric acid and extracted with dichloromethane several times. The combined organic layers are washed with a solution of sodium bicarbonate, dried, stirred with active carbon, filtered, and evaporated. The oily residue crystallizes upon trituration with ether. The crystals are filtered and recrystallized from ethanol; yield, 0.35 g (12%); mp 161–163 °C (change of crystal structure at 151–153 °C). Anal. ($C_{10}H_{11}NO_5S_2$) C, H, N.

(**B**) A solution of 1.93 g (7 mmol) of **10b** in 4 mL of dry DMF is added to a suspension of 185 mg (7.7 mmol) of sodium hydride in 2 mL of DMF during 30 min. After the mixture is stirred for 1 h, 1.2 g (8.45 mmol) of methyl iodide is added, and after another 30 min, 565 mg (4 mmol) of methyl iodide is added. After 1 h the solvent is removed in vacuo and the residue treated with 30 mL of 0.5 N hydrochloric acid and 30 mL of dichloromethane. The aqueous phase is extracted twice with dichloromethane. The combined organic layers are dried and evaporated. The crystalline residue is triturated with a small amount of cold ethanol; yield, 1.76 g (87%) of **7b**; mp 161–163 °C.

Methyl 2-Ethyl-4-hydroxy-2*H*-thieno[2,3-*e*]-1,2-thiazine-3-carboxylate 1,1-Dioxide (7c). A solution of 6.70 g (25.6 mmol) of **10a** in 40 mL of DMF is slowly added to a stirred suspension of 1.35 g (56.4 mmol) of sodium hydride in 40 mL of dry DMF. The suspension is stirred at room temperature for 90 min. With cooling with ice, 16 g (8.2 mL, 102.6 mmol) of ethyl iodide is added during 5 min. After another 4 h at 20 °C, the solvent is removed in high vacuo, the residue is partitioned between ethyl acetate and 0.1 N hydrochloric acid, the organic phase is dried (sodium sulfate), and the solvent is removed in vacuo. The residue of 14 g of colorless solid is filtered over 60 g of silica gel, eluting with dichloromethane. The 8.4 g of **7c** thus obtained are recrystallized from dichloromethane/*n*-hexane, affording 5.4 g (73%) of white crystals; mp 172–173 °C. Anal. ($C_{10}H_{11}NO_5S_2$) C, H, N.

Methyl 4-Hydroxy-2-[(4-methoxyphenyl)methyl]-2*H*-thieno[2,3-*e*]-1,2-thiazine-3-carboxylate 1,1-Dioxide (7d).

(14) Lower temperatures result in incomplete reaction, higher temperatures in decarboxylation.

(15) Addition of acid at lower temperatures results in coprecipitation of the sodium salt.

(16) If cooling proceeds too fast, **3** precipitates as needles which cannot be easily filtered.

From **10a** and 4-methoxybenzyl bromide as given for **7a** (procedure B); colorless crystals, mp 180 °C. Anal. ($C_{16}H_{15}NO_5S_2$) C, H, N.

Methyl 3-[[[(Methoxycarbonyl)methyl]amino]sulfonyl]-2-thiophenecarboxylate (9a). A solution of 6 g (25 mmol) of **5** and 6.3 g (50 mmol) of glycine methyl ester hydrochloride in 20 mL of pyridine is stirred at room temperature for 4 h. The reaction mixture is worked up as given for **6**; yield, 5.2 g (71%); mp 93–94 °C (methanol). Anal. ($C_9H_{11}NO_6S_2$) C, H, N.

Methyl 3-[[[(Ethoxycarbonyl)methyl]amino]sulfonyl]-2-thiophenecarboxylate (9b). From 12 g (50 mmol) of **5** and 7 g (50 mmol) of glycine ethyl ester hydrochloride following the procedure given for **9a**; yield, 12 g (78%); bp 193 °C (0.05 mm); mp 51 °C. Anal. ($C_{10}H_{13}NO_6S_2$) C, H, N.

Methyl 4-Hydroxy-2*H*-thieno[2,3-*e*]-1,2-thiazine-3-carboxylate 1,1-Dioxide (10a). A sodium methoxide solution of 90 g (3.9 mol) of sodium in 1.3 L of anhydrous methanol is diluted with 5 L of *n*-hexane. After addition of 500 g (1.7 mol) of **9a**, the reaction mixture is stirred at reflux temperature for 6 h. After the mixture is cooled to room temperature, 1 L of water and then 2 L of 10% hydrochloric acid are added. The precipitate is filtered by suction and thoroughly washed with 15 L of water. After drying in vacuo at 60 °C, 260 g (58%) of **10a** is obtained; mp 191–193 °C. Anal. ($C_8H_7NO_5S_2$) C, H, N.

Ethyl 4-Hydroxy-2*H*-thieno[2,3-*e*]-1,2-thiazine-3-carboxylate 1,1-Dioxide (10b). A solution of 9.2 g (30 mmol) of **9b** in 30 mL of 2 N ethanolic sodium ethoxide solution is stirred at 60 °C for 2 h. The reaction mixture is poured on 200 mL of 2 N hydrochloric acid and extracted with dichloromethane several times. The combined organic layers are first extracted with 10% aqueous sodium acetate solution and then with sodium carbonate solution several times. From the organic layer 2.5 g of **9b** is recovered. The combined carbonate phases are acidified with hydrochloric acid and extracted with dichloromethane several times. The combined organic layers are dried, stirred with active carbon, filtered, and evaporated. The residue is recrystallized from ether to yield 3.5 g (42.5%) of **10b**; mp 148–150 °C. Anal. ($C_9H_{11}NO_6S_2$) C, H, N.

3-[[[(Ethoxycarbonyl)methyl]amino]sulfonyl]-2-thiophenecarboxylic Acid (9c). The sodium acetate phase is acidified with concentrated hydrochloric acid and extracted with ether several times. The combined extracts are dried, treated with active carbon, filtered, and evaporated. The residue is recrystallized to yield 0.7 g of **9c**; mp 180–182 °C. Anal. ($C_9H_{11}NO_6S_2$) C, H, N.

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Registry No. **1a**, 59804-36-3; **1b**, 59804-41-0; **1c**, 59804-40-9; **1d**, 59804-42-1; **1e**, 59804-37-4; **1f**, 59804-38-5; **1g**, 59804-39-6; **1h**, 59804-45-4; **1i**, 59804-47-6; **1j**, 59821-96-4; **1k**, 59804-44-3; **1l**, 106820-65-9; **1m**, 106820-66-0; **1n**, 59804-26-1; **1o**, 106820-67-1; **1p**, 106820-68-2; **1q**, 106820-69-3; **2**, 59337-89-2; **3**, 59337-90-5; **4**, 59337-91-6; **5**, 59337-92-7; **6**, 106820-59-1; **7a**, 59804-25-0; **7b**, 98827-42-0; **7c**, 106820-60-4; **7d**, 106820-61-5; **8**, 106820-62-6; **9a**, 106820-63-7; **9b**, 59804-28-3; **9c**, 106820-64-8; **10a**, 98827-44-2; **10b**, 59804-48-7; 2-aminopyrazine, 5049-61-6; 2,4-dimethyl-6-aminopyrimidine, 461-98-3; 5-methyl-2-aminooxazole, 33124-04-8; 3,4-dimethyl-2-aminooxazole, 45529-92-8; sarcosine ethyl ester hydrochloride, 52605-49-9; 4-methoxybenzyl bromide, 2746-25-0; glycine methyl ester hydrochloride, 5680-79-5; glycine ethyl ester hydrochloride, 623-33-6; aniline, 62-53-3; 3-toluidine, 108-44-1; 4-hydroxyaniline, 123-30-8; 3-chloroaniline, 108-42-9; 2-aminopyridine, 504-29-0; 3-aminopyridine, 462-08-8; 4-aminopyridine, 504-24-5; 2-amino-6-methylpyridine, 1824-81-3; 2-aminopyridine, 109-12-6; 2-aminothiazole, 96-50-4.

Leukotriene Receptor Antagonists. 1. Synthesis and Structure–Activity Relationships of Alkoxyacetophenone Derivatives†

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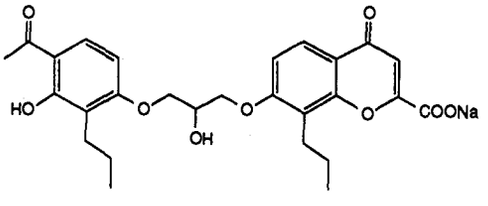
A series of derivatives of 2,4-dihydroxy-3-propylacetophenone (1) were prepared and examined for their ability to block leukotriene D_4 (LTD_4) induced contraction of guinea pig ileum. Straight-chain carboxylic acids where the carboxyl group was separated from the acetophenone moiety by varying numbers of methylenes were evaluated, and maximum activity was obtained with the pentamethylene acid (**6**). Examination of ring substitution showed that the 2-propyl-3-hydroxy-4-acetyl substitution pattern was required for maximum LTD_4 antagonist activity. Additional chain terminal groups were examined, and the acidic 5-tetrazolyl group separated from the acetophenone moiety by four to seven methylenes (**26**, **23**, **27**, **28**) gave excellent in vitro and in vivo activities. Compound **26** (LY171883) had the best balance of in vitro and in vivo activity. It lacked bronchospastic activity at the doses administered and has been chosen for clinical evaluation.

Since the discovery of slow reacting substance of anaphylaxis (SRS-A), a number of investigators have hypothesized the importance of this family of mediators in human diseases.[1-3] SRS-A is now recognized as a mixture of leukotrienes C_4, D_4, and E_4 (LTC_4, LTD_4 and LTE_4).[3-5] Recent studies have implicated leukotrienes in the pathogenesis of hypersensitive airways in sheep,[6] monkeys[7] and human asthmatics.[8] A clinical trial of a leukotriene antagonist in asthma will help to identify the role of leukotrienes in this human disease. Lack of bioavailability and a short biological half-life of the best known leukotriene antagonist, FPL 55712,[9-11] have hindered clinical evaluation of this compound. Though structure–activity



FPL 55712

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