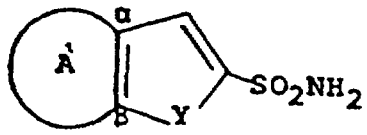
Description

This invention relates to novel aromatic sulfonamides useful in the treatment of elevated intraocular pressure. More particularly this invention relates to compounds having the structural formula:



as hereinafter defined, as well as the pharmaceutically and ophthalmologically acceptable salts thereof. This invention also relates to pharmaceutical compositions and the use thereof for systemic and ophthalmic use employing a novel compound of this invention as active ingredient for the treatment of elevated intraocular pressure, especially when accompanied by pathological damage such as in the disease known as glaucoma.

BACKGROUND OF THE INVENTION

Glaucoma is an ocular disorder associated with elevated intraocular pressures which are too high for normal function and may result in irreversible loss of visual function. If untreated, glaucoma may eventually lead to blindness. Ocular hypertension, i.e., the condition of elevated intraocular pressure without optic nerve head damage or characteristic glaucomatous visual field defects, is now believed by many ophthalmologists to represent the earliest phase of glaucoma.

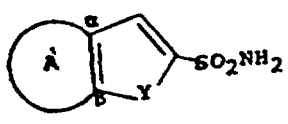
Many of the drugs formerly used to treat glaucoma proved not entirely satisfactory. Indeed, few advances were made in the treatment of glaucoma since pilocarpine and physostigmine were introduced. Only recently have clinicians noted that many β-adrenergic blocking agents are effective in reducing intraocular pressure. While many of these agents are effective in reducing intraocular pressure, they also have other characteristics, e.g. membrane stabilizing activity, that are not acceptable for chronic ocular use. (S)-1-tert-Butylamino-[(4-morpholino-1,2,5-thiadiazol-3-yl)oxy]-2 propanol, a β-adrenergic blocking agent, was found to reduce intraocular pressure and to be devoid of many unwanted side effects associated with pilocarpine and, in addition, to possess advantages over many other β-adrenergic blocking agents, e.g. to be devoid of local anesthetic properties, to have a long duration of activity, and to display minimal tolerance.

Although pilocarpine, physostigmine and the β-blocking agents mentioned above reduce intraocular pressure, none of these drugs manifests its action by inhibiting the enzyme carbonic anhydrase and, thereby, impeding the contribution to aqueous humor formation made by the carbonic anhydrase pathway.

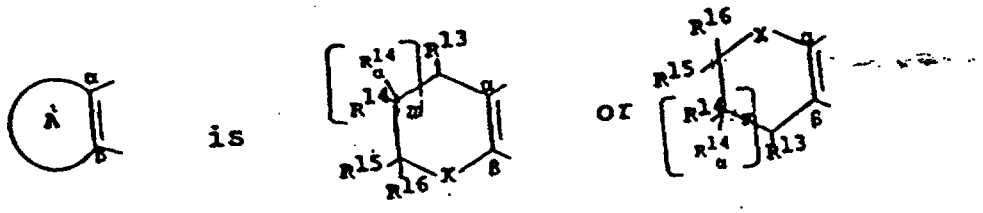
Agents referred to as carbonic anhydrase inhibitors block or impede this inflow pathway by inhibiting the enzyme, carbonic anhydrase. While such carbonic anhydrase inhibitors are now used to treat intraocular pressure by oral, intravenous or other systemic routes, they thereby have the distinct disadvantage of inhibiting carbonic anhydrase throughout the entire body. Such a gross disruption of a basic enzyme system is justified only during an acute attack of alarmingly elevated intraocular pressure, or when no other agent is effective. Despite the desirability of directing the carbonic anhydrase inhibitor only to the desired ophthalmic target tissue, no topically effective carbonic anhydrase inhibitors are available for clinical use.

However, topically effective carbonic anhydrase inhibitors are reported in U.S. Patents 4,386,098; 4,416,890; and 4,426,388. The compounds reported therein are 5 (and 6)-hydroxy-2-benzothiazolesulfonamides and acyl esters thereof.

The novel compounds of this invention are those with structural formula:



wherein



the individual diastereomers, the individual enantiomers or mixtures thereof, or a pharmacologically acceptable salt thereof, wherein:

X is $-SO_2-$;

Y is -S-, -O-, or NR^{19}, wherein R^{19} is H, C_{1-3}-alkyl or benzyl,

m is 0, 1 or 2

R^{13} is

a) hydrogen; or

b) $-NR^{17}R^{18}$, wherein R^{17} and R^{18} are independently selected from:

i) hydrogen or

ii) C_{1-5} alkyl, or

iii) taken together with the nitrogen to which they are attached form a heterocycle such as morpholine, piperidine, pyrrolidine, or piperazine;

R^{14} is hydrogen;

R_α^{14} is hydrogen;

R^{15} is C_{1-5} alkyl; and

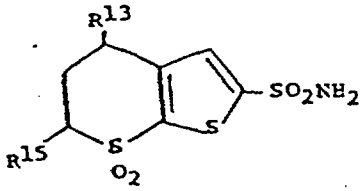
R^{16} is

a) hydrogen, or

b) C_{1-3} alkyl.

A preferred group of compounds are those wherein R^{13} is $-NR^{17}R^{18}$ and R^{16} is hydrogen.

A further preferred group of compounds are compounds of structual formula:



Substitution at R^{13}, R^{14}, R_α^{14}, R^{15} or R^{16} may result in compounds with asymmetric carbons. This invention contemplates all of the enantiomers, and diastereomers and mixtures thereof.

Compounds of formula I which are especially preferred are:

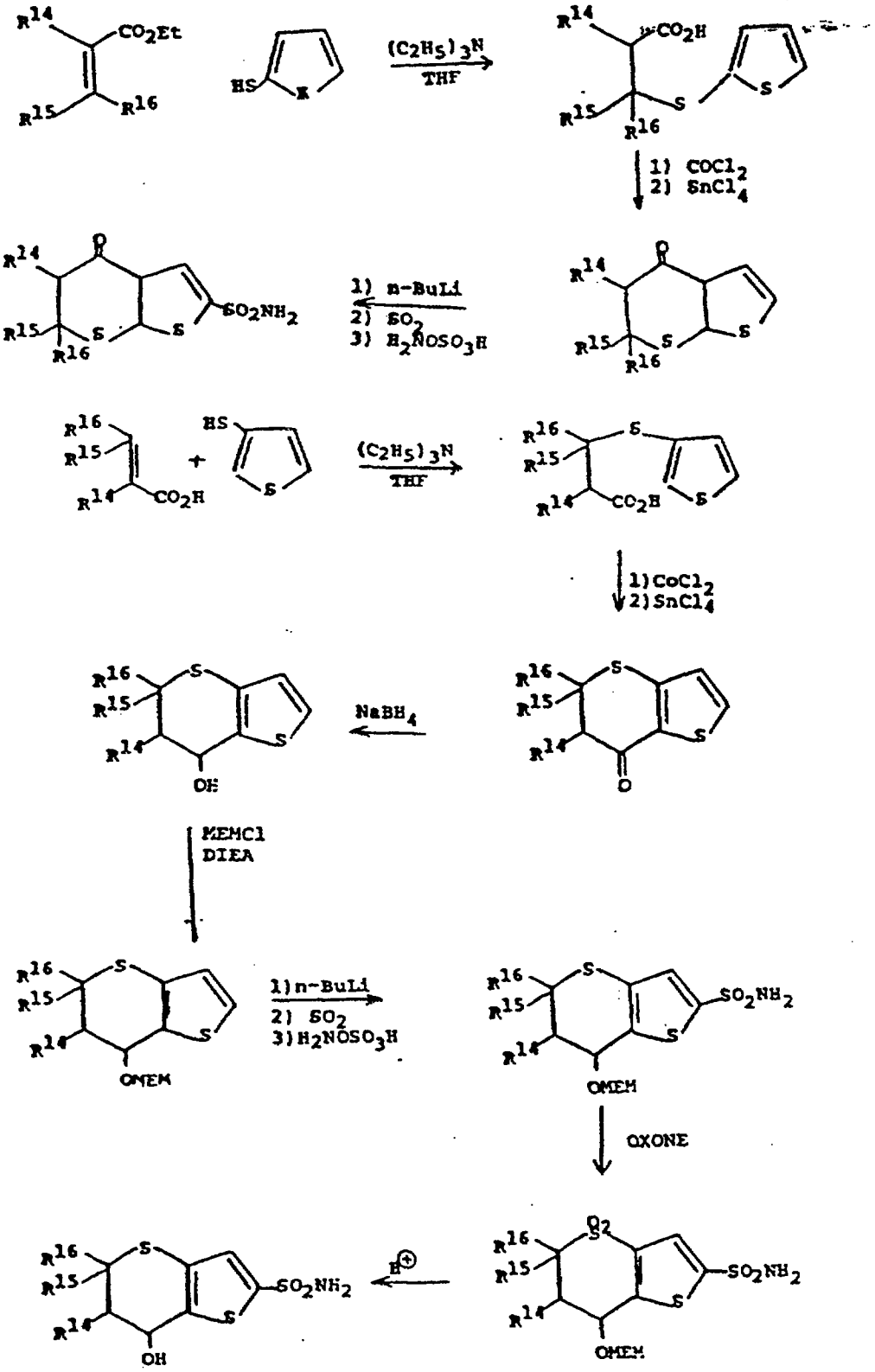
5,6-dihydro-4-ethylamino-6-methyl-4H-thieno[2,3-b]thiopyran-2-sulfonamide-7,7-dioxide;

5,6-dihydro-4-(2-methylpropylamino)-6-methyl-4H-thieno[2 ,3-b]thiopyran-2-sulfonamide-7,7-dioxide;

5,6-dihydro-6,6-dimethyl-4-ethylamino-4H-thieno[2,3-b]thiopyran-2-sulfonamide-7,7-dioxide;

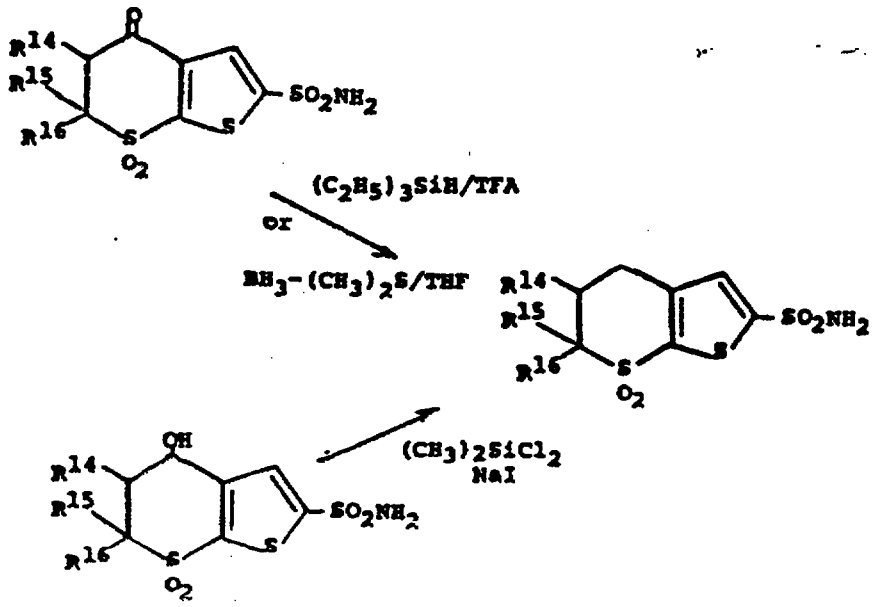
5,6-dihydro-4-ethylamino-6-ethyl-4H-thieno[2,3-b]thiopyran-2-sulfonamide-7,7-dioxide; and cis-or trans-diastereomers and the levo-or dextro-enantiomers of the diastereomers, and mixture of the isomers.

The thieno-dihydrothiopyran ring systems are prepared following the reaction schemes outlined below:



The novel compounds of this invention wherein R^{13} is hydrogen can be prepared by treating the corresponding 4 oxo compound with triethylsilane in trifluoracetic acid, or from the corresponding carbinol in organic solvent such as acetonitrile with dimethyldichlorosilane and sodium iodide at about 75-100 °C for

about 1 to 4 hours as exemplified below.

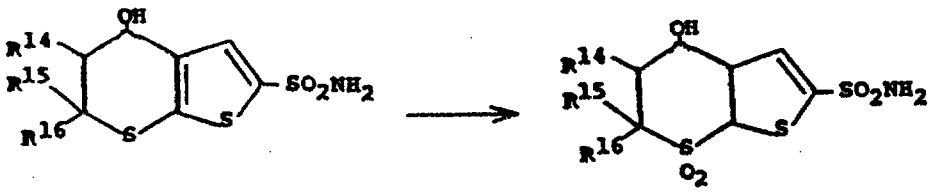


Reduction of the oxo compound is best conducted in an inert atmosphere by adding triethylsilane dropwise to a solution of the ketone in the trifluoracetic acid (TFA) at room temperature. The triethylsilane and ketone are used in a molar ratio of about 3:1 to 5:1 preferably 4:1. The mixture is heated at about 60 °C to reflux for about 2 to 6 hours. After cooling the excess TFA is neutralized by addition of aqueous base such as sodium bicarbonate. The aqueous solution is extracted with an inert organic solvent such as ethyl acetate and the extract is dried and evaporated to dryness.

Alternatively, reduction of the oxo compound is also accomplished using boranedimethylsulfide in THF as solvent and heating the mixture at reflux for about 3 hours.

The carbinol is reduced by heating at reflux with the dimethyldichlorosilane and NaI in acetonitrile for about 0.5 to 4 hours followed by quenching with water.

The 7,7-dioxide group in most of the novel compounds is generated by heating a C_{1-3}alkanolic, preferably methanolic, solution of the corresponding thiopyran with aqueous OXONE®

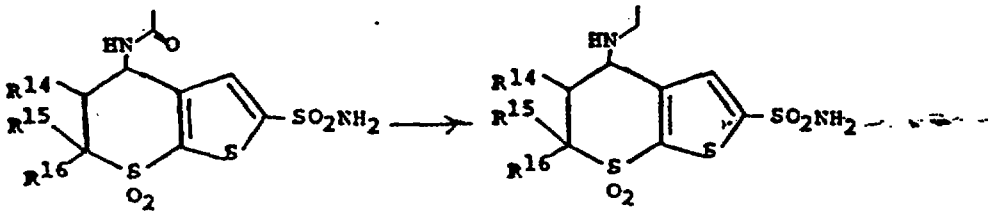


at about room temperature for about 12 to 24 hours.

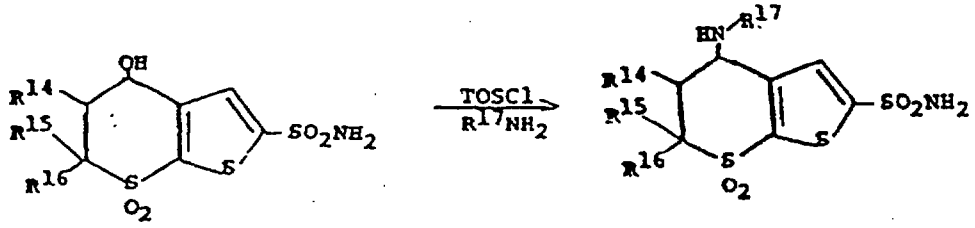
The 4-hydroxy group present in the thiopyran ring is prepared by reduction of the corresponding 4-keto group with a complex metal hydride, such as sodium borohydride. The reduction is conducted in a C_{1-3}alkanol, preferably ethanol at about room temperature for about 0.5 to 3 hours.

A free 4-amino group is achieved by hydrolysis of an N-acyl group such as acetyl with a strong acid such as hydrochloric acid in an aqueous alcohol, preferably methanol at about 75 °C to reflux for about 12 to 24 hours.

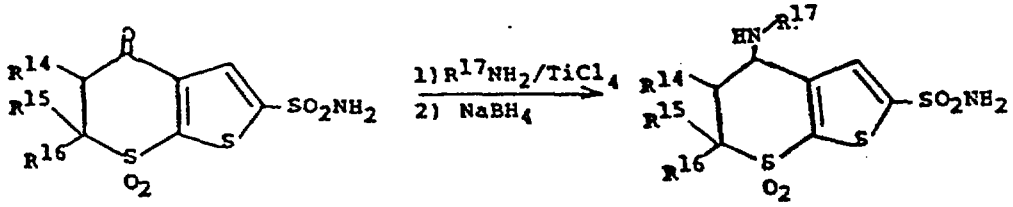
Reduction of the N-acyl group with borane-dimethylsulfide complex in an ethereal solvent such as THF, diethylether, or 1,2-dimethoxyethane provides an alkylamino as exemplified below by reduction of acetamido to ethylamino. The amide starting materials can be prepared by acylation of the 4-amino compounds.



Alkylamino groups are also available from the corresponding 4-hydroxy compounds by treatment of the 4-hydroxy with toluenesulfonyl chloride in pyridine at about -20°C to 5°C for about 3 to 10 hours followed by the addition of an alkylamine at a temperature below about 15°C followed by warming to about 30-60°C for about 5 to 16 hours as shown below:



4-Alkylamines are also prepared from the 4-oxo compounds by the following scheme:



In this process a solution of the keto compound in a solvent such as diethylether, THF, 1,2-dimethoxyethane, benzene, toluene or mixtures thereof at about -20°C to 0°C is treated quickly with about a one molar excess of an amine of formula $R^{17}NH_2$ followed by titanium tetrachloride dropwise. After about 1 to 5 hours the mixture is filtered and evaporated. The residue is treated with a complex metal hydride, such as sodium borohydride, in excess in a C_{1-3}alkanol, preferably methanol, at about room temperature for up to 24 hours. Excess hydride is destroyed with aqueous acid and the product is isolated by standard techniques.

Aromatic ethers are cleaved by standard procedures such as with boron tribromide, pyridine•HCl, $C_2H_5S^-$ or the like.

Compounds in which m = 0 are prepared by the process described in the attached scheme.

In this process, a 2,2-disubstituted-2-bromoacetate derivative 1 is treated with a 2-mercaptooxazole of the type 2 in a solvent such as ether, THF, CH_3OH, H_2O, C_2H_5OH, DMF or mixtures thereof at about -20°C to the reflux temperature of the solvent to yield a 2-(2-mercaptoxazolyl)-2,2-disubstituted acetate 3. In turn, the ester is hydrolyzed to the acid under acid conditions such as aq. HCl, CH_3COOH, aq. H_2SO_4 and aq. H_3PO_4, and basic conditions such as NaOH, KOH, LiOH in solvents such as H_2O, alcohol, DMF, THF in a temperature range of 0° to the reflux temperature of the solvent.

The resulting acid 4 is then transformed to the N,O-dimethylhydroxamide by treating the acid with carboxyl group activating reagents such as carbonyldiimidazole followed by treatment with N,O-dialkylhydroxylamine such as dimethylhydroxylamine in solvents such as DMF, THF, methylene chloride, or ether.

The hydroxamides 5 are then transformed into furano[2,3-b]dihydrothiophenes 6 by the following 3-step sequence. Reaction of the N,O-dimethyl hydroxamides with the Li salt of acetylene or trimethylsilyl acecylene gives rise to acetylenic ketones which are desilylated by treatment with alkanols such as methanol and then cyclized by heating in a solvent such as benzene, toluene, ethyl benzene, xylenes, or

mesitylene from 50° to the reflux temperature of the solvent.

The resulting furano[2,3-b]thiophenes are sulfonylated by standard methods such as treatment with sulfuric acid and acetic anhydride in solvents such as CH_2Cl_2 at temperatures ranging from -20 to ambient followed by treatment of the sulfonic acids with halogenating reagents such as PCl_5 to form the sulfonyl chlorides which are reacted with NH_4OH in acetone or ethyl acetate to form the sulfonamides 7.

The reduction of the carbonyl can be achieved by standard hydride reduction methods and is best effected by the reaction of $NaBH_4$ in an alcoholic solvent at temperatures ranging from 0° to ambient to give the hydroxyl derivatives 8.

Compounds of the types 7 and 8 can be converted to the 4-alkylamino compounds by standard methods.

Preparation of the 6,6-dioxides are also carried out by treating an alcoholic solution of the dihydro furano[2,3-b]thiophenes with aqueous OXONE(R)

The novel pharmaceutical formulations of this invention are adapted for oral administration such as tablets, capsules or the like; for nasal administration, especially in the form of a spray; for injection, in the form of a sterile injectable liquid; or for topical ocular administration in the form of solutions, ointments, solid water soluble polymeric inserts, or gels.

This invention is particularly concerned with formulations adapted for topical ocular administration for the treatment of glaucoma and other stages of elevated intraocular pressure and contain about 0.1% to 15% by weight of medicament, especially about 0.5 to 2% by weight of medicament, the remainder being comprised of carriers and other excipients well known in the art.

The medicament in the novel topical ocular formulations comprises one of the novel compounds of this invention either alone or in combination with a β-adrenergic blocking agent such as timolol maleate or a parasympathomimetic agent such as pilocarpine. In such combinations the two active agents are present in approximately equal amounts.

The present invention also provides the use of a novel compound of this invention or a pharmaceutical formulation thereof for the manufacture of a medicament useful for treating elevated intraocular pressure and/or ocular hypertension. Of primary concern is the treatment by topical ocular administration of about 0.1 to 25 mg and especially 0.2 to 10 mg of such compound per day, either by single dose or on a 2 to 4 dose per day regimen.

PREPARATION 1

5,6-Dihydro-4H-4-hydroxy-6-(p-methoxyphenyl)thieno[2,3-b]thiopyran-2-sulfonamide-7,7-dioxide

Step A: Preparation of 3-(p-Methoxyphenyl)-2-(2-mercaptothiophene)propanoic acid

A solution of 2-mercaptothiophene (6.5 g, 0.056 mol), THF (75 ml), p-methoxycinnamic acid (10 g, 0.056 mol), and $(C_2H_5)_3N$ (12.1 g, 0.12 mol) was heated at reflux under N_2. After 19 hours, another quantity of 2-mercaptothiophene (0.6 g, .0055 mol) was added to the reaction mixture. After an additional 5 hours at reflux, the reaction was poured into 3N HCl and the aqueous phase extracted with ethyl acetate (3x). The organic extracts were dried, filtered and concentrated to dryness. The residue was triturated with hexane and filtered to yield 15.7 g (95%) of product; m.p. 112-114°C (CH_3CN).

Employing the procedure substantially as described in Step A but starting with ethyl 4-bromopentanoate in place of the p-methoxycinnamic acid, there is produced ethyl 4-(2-thienylthio) pentanoate.

Saponification with potassium hydroxide in aqueous ethanol provides 4-(2-thienylthio) pentanoic acid.

Step B: Preparation of 5,6-Dihydro-4H-6-(p-methoxyphenyl)thieno[2,3-b]thiopyran-4-one

Under N_2 in a 3-neck flask was placed product from Step A (70 g 0.24 mol), DMF (1 ml) and CH_2Cl_2 - (500 ml). To the stirred solution oxalyl chloride (33 g 0.26 mol) was added dropwise at room temperature . After 1 hour, the solution was cooled to -10°C and a solution of $SnCl_4$ (31.4 g, 0.12) in CH_2Cl_2 (14 ml) was added dropwise. The mixture was then stirred at 0°C and after 0.5 hours, H_2O (250 ml) was added. The mixture was separated and the organic extract was washed with 5% NaOH solution, H_2O, dried, filtered and concentrated to dryness. The residue was chromatographed on silica gel (1L) and the product eluted with CH_2Cl_2 to yield 49.4 g (75%) of product; m.p. 82-83°C (CH_2Cl_2-ligroin).

Steps C: Preparation of 5,6-Dihydro-4H-6-(p-methoxyphenyl)thieno[2,3-b]thiopyran-4-one-2-sulfonamide

To an ice cooled solution of product from Step B (20.0 g, 0.072 mol) and acetic anhydride (21.2 g, 0.02 mol) in ethyl acetate (100 ml) there was added dropwise under N_2, concentrated H_2SO_4 (4.5 ml, 0.084 mol. After 1 hour, the solution was stirred at room temperature and a solution of potassium acetate (8.0 g, 0.082 mol) in 95% ethanol (40 ml) was added. After 2 hours, the solid was collected on a filter and dried in vacuo to yield 28 g of potassium salt.

To a suspension of the potassium salt (20 g, 0.05 mol) and 18-crown-6 (1g) in CH_3CN (200 ml), PCl_5 - (21 g, 0.1 mol) was added and the mixture heated at 60 °C with stirring. After 21 hours, the mixture was concentrated to dryness. The residue was partitioned between H_2O and CH_2Cl_2 (3 x). The organic extract was dried, filtered and concentrated to dryness. The residue was dissolved in acetone and poured into concentrated NH_4OH. The solution was concentrated to dryness and the residue dry packed with silica gel. The dry pack was placed on a Still column (100 mm) and the product eluted with 3-5% CH_3OH-CH_2Cl_2 to yield 5.3 g (30%) of product; m.p. 228-230 °C (CH_3CN).

Step D: Preparation of 5,6-Dihydro-4H-4-hydroxy-6-(p-methoxyphenyl)thieno[2,3-b]thiopyran-2-sulfonamide

To a suspension of the product from Step C (5.0 g, 0.014 mol) in absolute ethanol (75 ml) was added portionwise $NaBH_4$ (2.0 g, 0.05 mol). The mixture was heated at reflux with stirring. After 1 hour, the suspension was cooled, and the ethanol removed under reduced pressure (20 mm). Water was added to the residue and the pH adjusted to 8.5 with dilute acid (3N HCl). The suspension was extracted with ethyl acetate (3x) and the organic extract dried, filtered and concentrated to dryness. The residue was crystallized from CH_3OH-CH_3CN and filtered through a pad of filter aid and charcoal to yield 3.1 g (62%) of product; m.p. 215-217 °C.

Step E: Preparation of 5,6-Dihydro-4H-4-hydroxy-6-(p-methoxyphenyl)thieno[2,3-b]thiopyran-2-sulfonamide-7,7-dioxide

To a suspension of product from Step D (2.45 g, 0.0069 mol) in CH_3OH (75 ml) stirred at room temperature was added dropwise a solution of "OXONE" (6,2 g, 0.01 mol) in H_2O (75 ml). After the addition, the mixture was heated at reflux for 1 hour, and stirred at room temperature for 1 hour. The CH_3OH was then removed under reduced pressure and the resulting aqueous layer extracted with ethyl acetate (4x). The organic extracts were dried, filtered and concentrated to dryness. The residue was recrystallized from CH_3CN to yield 1.8 g (67%) of product; m.p. 247-248 °C.

Employing the procedures substantially as described in Preparation 1, Steps A through E, but substituting for the 3-(4-methoxyphenyl)acrylic acid used in Step A, the 3-R^3-acrylic acids depicted in Table I, there are produced the 5,6-dihydro-4H-4-hydroxy-6-R^3-thieno[2,3-b]thiopyran-2-sulfonamide-7,7-dioxides also depicted in Table I by the following reaction scheme:

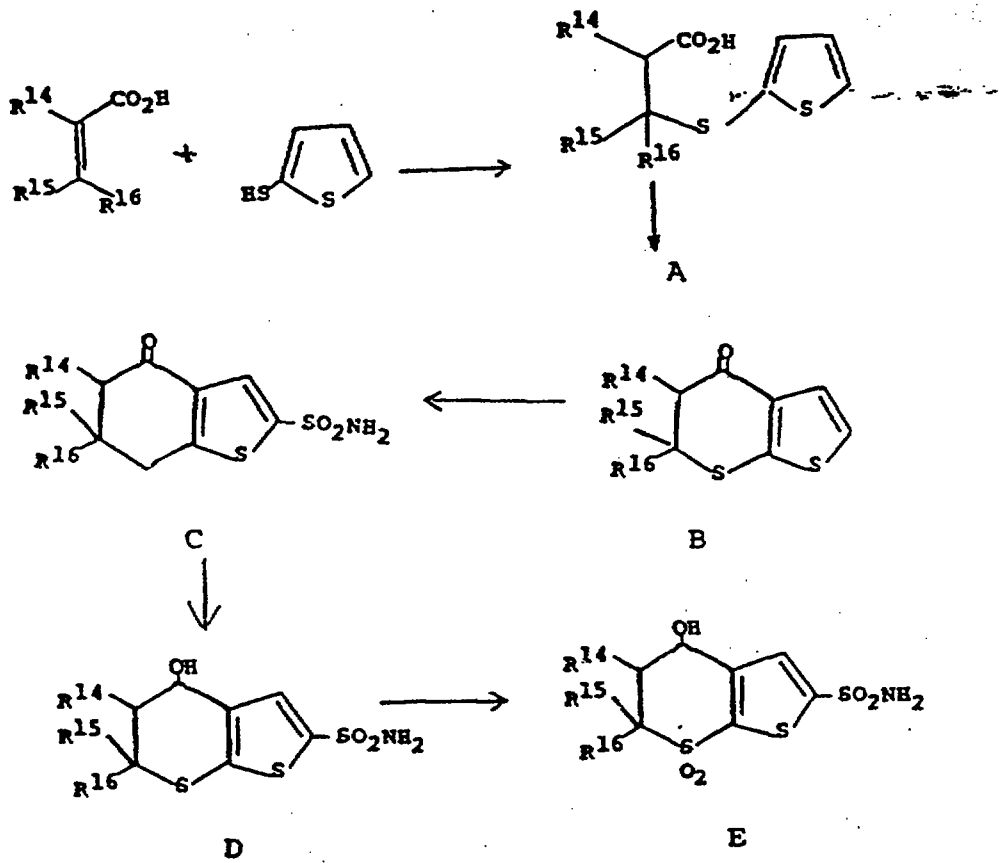


TABLE I

m.p.(°C) of Product of Step							
R^{14}	R^{15}	R^{16}	A	B	C	D	E
H	CH_3-	CH_3	129*	74.5-75	185.5-186.5	146-147	210-211
H	C_2H_5-	C_2H_5-	-	-	-	-	-
H	C_2H_5-	CH_3	-	-	-	-	-
H	CH_3-	m-C_3H_7	-	-	-	-	-

*b.p. at 0.4 mm Hg.

Employing the procedures substantially as described in Preparation 1, Steps A through E, but starting with 4-(2-thienylthio) pentanoic acid, there is produced 5,6-dihydro-7-methyl-4-hydroxy-4H-thieno [2,3-b] thiepin-2-sulfonamide-8,8-dioxide.

PREPARATION 2

5,6-Dihydro-4H-4-isobutylamino-6-(p-methoxyphenyl)thieno[2,3-b]thiopyran-2-sulfonamide-7,7-dioxide (α-isomer hydrochloride and β-isomer hydrogen maleate)

Under N_2, a mixture of 5,6-dihydro-4H-4-hydroxy-6-(p-methoxyphenyl)thieno[2,3-b]thiopyran-2-sulfonamide-7,7-dioxide (4.9 g 0.014 mol) in pyridine (20 ml) was cooled to -10°C while p-toluene-sulfonyl chloride (5.3 g, 0.028 mol) was added portionwise. The resulting brown solution was stirred at -10 to 0°C. After 6 hours, isobutylamine (45 ml) was added at 0-4°C dropwise at a rate that the internal temperature did not exceed 15°C. After 2 hours, the temperature was raised to 50°C and stirred overnight. The volatiles were removed first at reduced pressure (20 mm) and then high vacuum (1 mm). The residue was treated

with 10% aqueous NaOH and ether and separated. The aqueous layer was adjusted to pH 8.5 and extracted with ethyl acetate (3x). The extracts were concentrated to dryness, the residue was dry packed with silica and placed on a Still column (100 mm). The mixture of diasteriomers was eluted from the column with 2-3% CN_3OH-$CHCl_3$ to yield 0.7 g of β-isomer, 1.8 g of $\alpha+\beta$ isomers and 1.3 g of α-isomer (61%). The α-isomer was treated with 4.5 N NCl-C_2H_5OH and crystallized from isopropanol-ethanol to yield product; m.p. 211-214°C.

^{1}H NMR (DMSO) δ 1.0 (t, 6H), 2.12 (m, 1H), 2.65 (m, 1H), 2.0 (bd, 1H), 3.05 (bs, 1H), 3.19 (q, 1H), 3.82 (s, 3H), 5.05 (bs, 1H), 5.28 (d, 1H), 7.06 (d, 2H), 7.44 (d, 2H), 8.23 (bs, 2H exch), 8.28 (s, 1H).

Analysis: Calc'd for $C_{18}H_{24}N_2O_5S_3$·NCl.			
Found:	C, 44.94; C, 45.15;	H, 5.24; H, 5.12;	N, 5.82 N, 5.80.

The β-isomer was crystallized as the maleate salt from CH_3CN to yield product, m.p. 190-192°C. ^{1}H NMR (DMSO) δ 0.94 (t, 6H), 1.88 (m, 1H), 2.65-3.5 (m, 4H), 3.81 (s, 3H), 4.65 (bs, 1H), 5.34 (d, 1H), 6.1 (s, 2H), 7.07 (d, 2H), 7.39 (d, 2H), 7.82 (bs, 1H), 8.19 (bs, 2H each).

Analysis: Calc'd for $C_{18}H_{24}N_2O_5S_3$·$C_4N_4O_4$.			
Found:	C, 47.13; C, 47.09;	H, 5.03; H, 5.05;	N, 5.00 N, 5.03.

EXAMPLE 1

Following the procedures substantially as described in Preparation 2, but using the 4-hydroxy-compounds and amines depicted in Table II, there are produced the 4-substituted amino compounds also depicted in Table II by the following reaction scheme:



TABLE II

$R^{17}R^{18}N$-	R^{14}	R^{15}	R^{16}
n-C_3H_7NH-	H	CH_3-	CH_3-
C_2H_5NH-	H	C_2H_5-	C_2H_5-
$(CH_3)_2CHCH_2NH$-	H	C_2H_5-	CH_3-
C_2H_5NH-	H	CH_3	n-C_3H_7-

Following the procedures substantially as described in Preparation 2 but using as starting materials 5,6-dihydro- 7-methyl-4-hydroxy-4H-thieno [2,3-b]thiepin-2-sulfonamide-8,8-dioxide and isobutylamine, there is produced the α- and β-diastereomersof 5,6-dihydro-4-isobutylamino-4H-7-methylthieno-[2,3-b]thiepin-2-sulfonamide-8,8-dioxide hydrochloride.

EXAMPLE 2

5,6-Dihydro-4-ethylamino-6,6-dimethyl-4H-thieno[2,3-b]thiopyran-2-sulfonamide-7,7-dioxide

Step A: Preparation of 5,6-Dihydro-4-ethylamino-6,6-dimethyl-4H-thieno[2,3-b]thiopyran-2-sulfonamide

A solution of 5,6-dihydro-6,6-dimethyl-4H-thieno[2,3-b]thiopyran-4-one-2-sulfonamide (3.00 g, 0.011 mol) in dry tetrahydrofuran (40 ml) and benzene (40 ml) was cooled to -10° C and condensed ethylamine (15 ml, 10.8 g, 0.24 mol) was added rapidly with stirring. Titanium tetrachloride 1.14 g, 0.006 mol) was added over 20 minutes while maintaining the temperature below 0° C. The mixture was stirred at ambient temperature for 2.5 hours, filtered, and the solid was washed with tetrahydrofuran. The combined filtrate and washings were evaporated in vacuo and the residue was suspended in absolute methanol (105 ml). With stirring under nitrogen, sodium borohydride (0.53 g, 0.014 mol) was added portionwise over 15 minutes and the mixture was stirred at ambient temperature for 21 hours. After acidification with concentrated hydrochloric acid, the mixture was concentrated in vacuo. The residue was distributed between water (100 ml) and ethyl acetate (100 ml), and the aqueous layer was separated and extracted with ethyl acetate (2 x 50 ml). The water layer then was basified with saturated sodium bicarbonate solution and extracted with ethyl acetate (3 x 250 ml). The combined extracts were washed with water (3x), dried over sodium sulfate, and evaporated in vacuo. The residue was crystallized as the hydrochloride salt from ethanolic hydrogen chloride to afford 2.60 g (69%) of pure product.

An analytical sample melted at 210-211.5° C after recrystallization from ethanol.

Anal. Calc'd for $C_{11}H_{18}N_2O_2S_3 \cdot HCl$:			
Found:	C, 38.53; C, 38.49,	H, 5.58, H, 5.53;	N, 8.17; N, 8.03.

Step B: Preparation of 5,6-Dihydro-4-ethylamino-6,6-dimethyl-4H-thieno[2,3-b]thiopyran-2-sulfonamide-7,7-dioxide

A solution of 5,6-dihydro-4-ethylamino-6,6-dimethyl-4H-thieno[2,3-b]thiopyran-2-sulfonamide (3.95 g, 0.013 mol) in methanol (85 ml) was acidified with 6.25 N methanolic hydrogen chloride (2.1 ml). With stirring, a solution of 'OXONE' (11.68 g, 0.019 mol) in water (65 ml) was added over 15 minutes. After stirring at ambient temperature for 17.5 hours, the mixture was filtered and the solid was washed with methanol. The combined filtrate and washings were concentrated in vacuo below 55° C to remove methanol and the cloudy aqueous solution was basified with saturated sodium bicarbonate solution. The mixture was extracted with ethyl acetate (150 ml and 2 x 100 ml), and the combined extracts were washed twice with water, dried over sodium sulfate and evaporated in vacuo. The amorphous residue was converted to the crystalline hydrochloride salt using ethanolic hydrogen chloride to yield 2.16 g (44%) of analytically pure product melting at 255-255.5° C.

Anal. Calc'd for $C_{11}H_{18}N_2O_4S_3 \cdot HCl$:			
Found:	C, 35.24; C, 35.31,	H, 5.11, H, 5.00;	N, 7.47; N, 7.53.

Employing the procedures substantially as described in Example 7, Steps A and B, but using as starting materials 6-(R^3R^4)-4-oxo compounds and R^5R^6NH depicted in Table VII there are produced the 6-R^3R^4)-4-amino compounds also depicted in Table VII by the following reaction scheme:

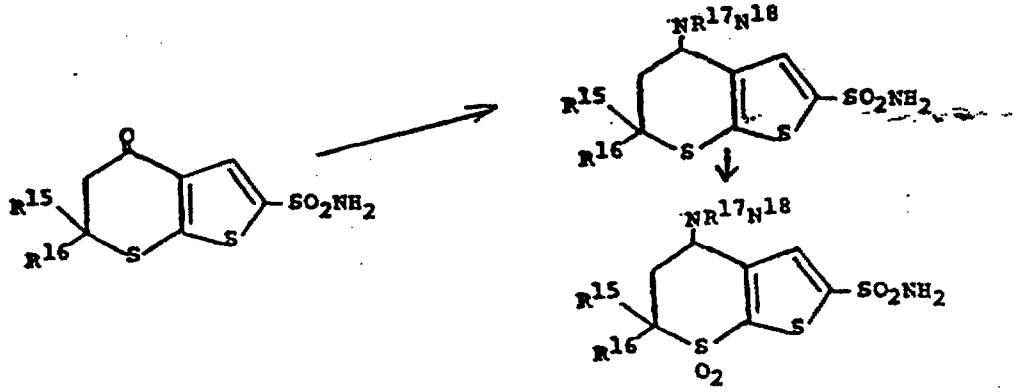


TABLE III

$R^{17}R^{18}N-$	R^{15}	R^{16}
$(CH_3)_2CHCH_2NH-$	CH_3-	CH_3-
$(CH_3)_2CHCH_2NH-$	C_2H_5-	C_2H_5-
$(CH_3)_2CHCH_2NH-$	C_2H_5-	CH_3-
$(CH_3)_2CHCH_2NH-$	CH_3-	$n-C_3H_7-$
C_2H_5NH-	C_2H_5-	C_2H_5-
C_2H_5NH-	C_2H_5-	CH_3-
C_2H_5NH-	CH_3-	$n-C_3H_7-$

PREPARATION 3

6,7-Dihydro-5H-7-hydroxy-5-methylthieno[3,2-b]thiopyran-2-sulfonamide-4,4-dioxide

Step A: Preparation of 3-(3-mercaptothiophene)-3-methylpropionic acid

A mixture of crotonic acid (2.7 g., 0.28 mol), THF (40 ml), $(C_2H_5)_3N$ (1.45 g, 0.14 mol) and 3-mercaptothiophene (3.6 g, 0.03 mol) was heated at reflux under N_2. After 21 hours, the solution was poured into dilute aqueous HCl and extracted with ethyl acetate (3x). The organic extracts were dried, filtered and concentrated to dryness to yield the title compound in 93% yield.

Step B: Preparation of 6,7-Dihydro-5H-7-oxothieno[3,2-b]thiopyran

Under N_2 in a three-necked flask was placed product from Step A (59.3 g, 0.29 mol), DMF (1.5 ml) and CH_2Cl_2 (450 ml). To the stirred solution was added dropwise at ambient temperature oxalyl chloride (40.7 g 0.32 mol). After 1 hour, the solution was cooled to -10°C and a solution of $SnCl_4$ (40 g, 0.15 mol) in CH_2Cl_2 (100 ml) was added dropwise. The mixture was stirred at 0°C and after 0.5 hour H_2O (300 ml) was added. The mixture was separated and the organic extract is washed with saturated Na_2CO_3 H_2O, and brine, dried, filtered and concentrated to dryness to yield the title compound in quantitative yield.

Step C: Preparation of 6,7-Dihydro-5H-7-hydroxy-5-methylthieno[3,2-b]thiopyran

Under N_2, a mixture of product from Step B (11 g, 0.06 mol), ethanol (75 ml) and $NaBH_4$ (2.5 g, 0.065 mol) was stirred at room temperature. After 0.5 hour, the mixture was heated at reflux for 1 hour, cooled and then concentrated to dryness. The residue was partitioned between H_2O and $CHCl_3$ (3x) and the organic extracts were dried, filtered and concentrated to dryness to yield the title compound in 87% yield.

Analysis calc'd for $C_8H_{10}OS_2$:	C, 51.63;	H, 5.41.
Found:	C, 51.37;	H, 5.54.

Step D: Preparation of 6,7-Dihydro-5H-7-(methoxyethoxymethoxy)-5-methylthieno[3,2-b]thiopyran

To a solution of product from Step C (26 g, 0.14 mol) under N_2, diisopropylethylamine (28.2 g, 0.21 mol) and CH_2Cl_2 (300 ml) was added dropwise a solution of methoxyethoxymethylchloride (25 ml, 0.22 mol) and the solution was stirred at room temperature. After 72 hours, the reaction was washed with 1N HCl, saturated $NaHCO_3$ solution and H_2O. The organic layer was dried, filtered and concentrated to dryness. The residue was chromatographed on a Still column (100 mm) and the product eluted with 20% ethylacetate-hexane to provide the title compound in 18% yield.

Step E: Preparation of 6,7-Dihydro-5H-7-(methoxyethoxymethoxy)-5-methylthieno[3,2-b]thiopyran-2-sulfonamide

Under N_2, a solution of product from Step D (39.7 g, 0.145 mol) in THF (500 ml), was cooled to -78°C and a solution of n-BuLi (1.6 M, 100 ml, 0.16 mol) was added dropwise. After 0.5 hour, SO_2 gas was passed over the surface for 40 minutes. After the addition, the mixture was stirred for 2 hours at room temperature. The mixture was then treated with H_2O (560 ml), sodium acetate $3H_2O$ (45 g, 0.54 mol) and hydroxylamine-o-sulfonic acid (30.5 g, 0.27 mo]). After stirring overnight at room temperature, the aqueous suspension was extracted with ethyl acetate (3x). The organic extracts were dried, filtered and concentrated to dryness. The residue was chromatographed on a Still column (100 mm) and the product was eluted with 4% CH_3OH-$CHCl_3$ to yield the title compound in 21% yield.

Step F: Preparation of 6,7-Dihydro-5H-7-(methoxyethoxymethoxy)-5-methylthieno[3,2-b]thiopyran-2-sulfonamide-4,4-dioxide

To a solution of oxone (10.4 g, 0.017 mol) in H_2O (100 ml) is added dropwise a solution of product from Step E (4.0 g, 0.011 mol) in CH_3OH (100 ml). After stirring at room temperature overnight, the mixture was cooled to -10°C and sulfuric acid (100 ml) was added. After a 0.5 hour in the cold and 1 hour at room temperature, the mixture was added to H_2O and extracted with ethyl acetate (5x). The organic extracts were dried, filtered and concentrated to dryness. The residue was chromatographed on a Still column (40 mm) and the product eluted with 5% CH_3OH-$CHCl_3$ to provide the title compound in 19% yield; m.p. 219-221°C.

Analysis Calc'd for $C_8H_{11}NO_5S_3$:			
	C, 32.34;	H, 3.73;	N, 4.71.
Found:	C, 32.26;	H, 3.67;	N, 4.72.

EXAMPLE 3

6,7-Dihydro-5H-7-(ethylamino)-5-methylthieno[3,2-b]thiopyran-2-sulfonamide-4,4-dioxide (9)

Step A: Preparation of 6,7-Dihydro-5H-7-acetamido-5-methylthieno[3,2-b]thiopyran-2-sulfonamide-4,4-dioxide

To a cooled solution (0.7°C) of product from Preparation 3 Step G (3.6 g, 0.012 mol) in CH_3CN (75 ml) is added dropwise concentrated H_2SO_4 (12.3 ml). After addition, the mixture is stirred at room temperature overnight and then poured onto ice (300 g). After stirring for 1 hour, the mixture is extracted with ethyl acetate (3x). The organic extracts are dried, filtered and concentrated to yield the title compound.

Step B: Preparation of 6,7-Dihydro-5H-7-(ethylamino)-5-methylthieno[3,2-b]thiopyran-2-sulfonamide-4,4 dioxide

Into a 2-necked flask fitted with a short path distillation head is added product from Step A (2.5 g, .0075 mol) and THE (40 ml). The mixture is heated at gentle reflux and a solution of BH_3. $(CH_3)_2S$ (2.4 ml of 10 M, 24 mmol) is added very carefully. The mixture is heated at reflux for 0.5 hour and then treated with 6N HCl (20 ml). The mixture is concentrated to dryness to yield the title compound as the hydrochloride salt.

EXAMPLE 4

6,7-Dihydro-5H-7-amino-5-methylthieno[3,2-b]thiopyran-2-sulfonamide-7,7-dioxide

A mixture of product from Example 3 (5.2 g, 0.015 mol), CH_3OH (50 ml) and 12 N HCl (50 ml) is heated at reflux. After 6 hours, the mixture is concentrated to dryness to yield the title compound as the hydrochloride salt.

EXAMPLE 5

6,7-Dihydro-5H-7-isobutylamino-5-methylthieno[3,2-b]-thiopyran-2-sulfonamide 4,4-dioxide

A mixture of product from Example 4 (3.3g, 0.01 mol), THF (100 ml), and Et_3N (3 ml) is stirred at room temperature while a solution of isobutyryl chloride (1.1 g, 0.01 mol) in THF (10 ml) is added dropwise. The mixture is stirred at room temperature overnight and then treated with saturated $NaHCO_3$ solution. The mixture is extracted with ethyl acetate (3x). The organic extracts are dried, filtered, and concentrated to dryness to yield the amide. Reduction of the amide as described in Example 3 , Step B provides the title compound.

EXAMPLE 6

trans-5,6-Dihydro-4H-4-ethylamino-6-methylthieno[2,3-b] thiopyran-2-sulfonamide-7,7-dioxide and cis-5,6-Dihydro-4H-4-ethylamino-6-methylthieno[2,3-b] thiopyran-2-sulfonamide-7,7-dioxide

Step A: Preparation of 3-(2-mercaptothiophene) butanoic acid

To a solution of thiophenethiol (20.0 g, 0.17 mol) in THF (283 ml) was added crotonic acid (13.2 g, 0.15 mol) and triethylamine (11.8 ml, 0.085 mol) and the mixture was refluxed for 22 hours. The solution was concentrated, acidified with 3N HCl and it was extracted with ethyl acetate. The organic layers were washed with 3N HCl, water, and brine. Drying and solvent evaporation gave an oil (37.2 g); distillation (107°C, 0.02 mmHg) gave the title compound (30.3 g, 100%).

Step B: Preparation of 5,6-Dihydro-4H-6-methylthieno [2,3-b]thiopyran-4-one

To a solution of product from Step A (30.3 g 0.15 mol) in CH_2Cl_2 (231 ml) and DMF (0.7 ml) was added oxalyl chloride (14.0 ml, 0.16 mol) dropwise and the mixture was stirred at room temperature for 1 hour. The mixture was cooled to -10°C and a solution of stannic chloride (8.8 ml, 0.075 mol) in CH_2Cl_2 (42 ml) was added dropwise maintaining the temperature below 0°C. The reaction was stirred at 0°C for 1 hour and water (116 ml) was then added dropwise maintaining the temperature below 10°C. The layers were separated, the aqueous phase was extracted with CH_2Cl_2 and the organic layers were washed with water, saturated bicarbonate solution and brine. Drying and solvent evaporation gave the title compound (26.9 g, 97%).

Step C: Preparation of 5,6-Dihydro-4H-6-methylthieno [2,3-b]thiopyran-4-one-2-sulfonic acid

To a solution of product from Step B (26.9 g, 0.14 mol) in CH_2Cl_2 (224 ml), cooled to -5°C, was added acetic anhydride (39.6 ml, 0.42 mol) followed by dropwise addition of sulfuric acid (8.0 ml, 0.15 mol) maintaining the temperature below 0°C. The reaction was stirred at room temperature for 1.5 hours. The solid was collected under nitrogen and dried to give the title compound (36.3 g, 98%).

Step D: Preparation of 5,6-Dihydro-4H-6-methylthieno [2,3-b]thiopyran-4-one-2-sulfonylchloride

To a suspension of product from Step C (36.3 g, 0.14 mol) in CH_2Cl_2 (175 ml), cooled to -8°C was added a suspension of PCl_5 (45.8 g, 0.22 mol) in CH_2Cl_2 (733 ml) dropwise maintaining the temperature below 0°C. The mixture was stirred at 0°C for 1/2 hour and then poured into ice water (250 ml). The layers were separated, the aqueous phase further extracted with CH_2Cl_2 and the organic layers were washed with water and treated with decolorizing carbon. Drying and solvent evaporation gave the title compound (40.7g).

Step E: Preparation of 5,6-Dihydro-4H-6-methylthieno [2,3-b]thiopyran-4-one-2-sulfonamide

To ammonium hydroxide (106 ml), cooled to -30°C was added a solution of product from Step D (39.6 g, 0.14 mol) in acetone (140 ml) dropwise, maintaining the temperature between -20°C and -30°C. The mixture was stirred at 0°C for 1 hour, concentrated, the solid collected, washed with water and dried to give the title compound (31.6 g, 86%).

Step F: Preparation of 5,6-Dihydro-4H-4-hydroxy-6-methylthieno[2,3-b]thiopyran-2-sulfonamide

To a suspension of product from Step E (30.0 g, 0.11 mol) in absolute ethanol (1100 ml) was added sodium borohydride (5.3 g, 0.14 mol). The mixture was refluxed for 2 hours and then stirred at room temperature overnight. The mixture was cooled to 0°C, acidified with 1N HCl, basified with saturated bicarbonate solution, concentrated and extracted with ethyl acetate. Drying and solvent evaporation gave the title compound (26.8 g, 92%).

Step G: Preparation of 5,6-Dihydro-4H-4-hydroxy-6-methylthieno[2,3-b]thiopyran-2-sulfonamide-7,7 -dioxide

To a solution of product from Step F (26.8 g, 0.10 mol) in methanol (500 ml) was added a solution of oxone (104.5 g, 0.17 mol) in water (567 ml) dropwise and the resulting suspension was stirred at room temperature overnight. The mixture was concentrated, diluted with water and extracted with ethyl acetate. Drying and solvent evaporation gave the product as a solid, (27.9 g, 94%). An analytical sample was prepared by recrystallization from acetonitrile; mp 195-197°C.
Anal. Calc'd. for $C_8H_{11}NO_5S_3$: C, 32.31; H, 3.73; N, 4.71. Found: C, 32.34; H, 3.80; N, 5.02.

Step H: Preparation of trans-5,6-dihydro-4H-4-ethylamino-6-methylthieno[2,3-b]thiopyran-2-sulfonamide-7,7-dioxide and cis-5,6-dihydro-4H-4-ethylamino-6-methylthieno[2,3-b]thiopyran-2-sulfonamide-7,7-dioxide

Under N_2, a suspension of product from Step G (13.5 g, 0.045 mol) in pyridine (80 ml) was cooled to -10°C and p-toluenesulfonyl chloride (19.2 g, 0.1 mol) was added portionwise. After 5 hours at 0°C, 70% aqueous ethylamine (190 ml) was added dropwise while keeping the temperature below 15°C. After complete addition, the solution was allowed to stir at room temperature for 2 hours and then heated at 50°C overnight. The deep purple solution was concentrated to dryness. The residue was partitioned between saturated $NaHCO_3$ and ethyl acetate (3x), and the organic layers were dried, filtered and concentrated to dryness. The residue was dry packed in silica gel (70-230 mesh) and placed on a Still column of silica gel (230-400 mesh). The column was eluted with 4% CH_3OH-$CHCl_3$ to yield 5.6 g (38%) of trans-isomer and then elution with 5% CH_3OH-$CHCl_3$ yielded 5.6 g (38%) of cis-isomer. The compounds were converted to their hydrochloride salts yielding the trans-hydrochloride mp 272-273°C and the cis-hydrochloride mp 270-273°C.

Step I: Alternate preparation of trans-5,6-dihydro-4H-4-ethylamino-6-methylthieno[2,3-b] thiopyran-2-sulfonamide-7,7-dioxide

To a solution of product from Step G (9.2 g, 0.31 mol) in CH_3CN (110 ml) cooled to -10°C was added dropwise 95.5% H_2SO_4 (32 ml, 0.31 mol). After the addition, the suspension was allowed to warm to room temperature. After stirring overnight, the solution was poured onto ice and stirred for 1 hour. The solution was then extracted with ethyl acetate (4x) and the organic extracts were backwashed with $NaHCO_3$, dried, filtered and concentrated to dryness to yield 9.1 g (87%) of 5,6-dihydro-4H-4-acetylamino-6-methylthieno-[2,3-b]thiopyran-2-sulfonamide-7,7-dioxide.

A suspension of the acetylamino compound (8.8 g, 0.026 mol) in THF (180 ml) was fitted with a short path distillation head and the mixture was heated at reflux while a solution of borane-dimethylsulfide (9.0 ml, 0.09 mol) was added dropwise with stirring (the short path distillation head was utilized to collect the volatile dimethylsulfide). After 1.5 hours, the reaction mixture was concentrated to dryness, the residue treated with 12 N HCl, and the mixture heated at reflux. After 0.5 hour, the suspension was concentrated to dryness and the residue was treated with $NaHCO_3$. The mixture was extracted with ethyl acetate (4x) and the organic layers were dried, filtered and concentrated to dryness to yield 8.1 g (96%) of a mixture of trans- and cis-isomers (HPLC analysis 87/13 trans:cis). Chromatography as described in Step H provided pure trans-isomer.

Employing the procedure substantially as described in Example 6 , Steps A-H, the following compounds are prepared:

α-5,6-Dihydro-4H-4-isobutylamino-6-methylthieno [2,3-b]thiopyran-2-sulfonamide-7,7-dioxide maleate; mp 218°C. (from CH_3OH/2-propanol);

β-5,6-Dihydro-4H-4-isobutylamino-6-methylthieno[2,3-b] thiopyran-2-sulfonamide-7,7-dioxide hydrochloride hemihydrate; mp 210-213°C. (from 2-propanol);

trans-5,6-dihydro-4H-4-ethylamino-6-ethylthieno[2,3-b] thiopyran-2-sulfonamide-7,7-dioxide hydrochloride; mp 172-6°C. (from CH_3OH/2-propanol);

cis-5,6-dihydro-4H-4-ethylamino-6-ethylthieno[2,3-b] thiopyran-2-sulfonamide-7,7-dioxide hydrochloride; mp 250°C. (from CH_3OH/2-propanol);

cis- and trans-5,6-dihydro-4H-4-methylamino-6-methylthieno[2,3-b]-thiopyran-2-sulfonamide-7,7-dioxide;

cis- and trans-5,6-dihydro-4H-4-methylamino-6-ethylthieno[2,3-b]-thiopyran-2-sulfonamide-7,7-dioxide;

cis- and trans-5,6-dihydro-4H-4-methylamino-6-(1-propyl)[2,3-b]-thiopyran-2-sulfonamide-7,7-dioxide;

cis- and trans-5,6-dihydro-4H-4-methylamino-6-isobutyl [2,3-b]-thiopyran-2-sulfonamide-7,7-dioxide.

Step J: Resolution of trans-5,6-dihydro-4H-4-ethyl amino-6-methylthieno[2,3-b]thiopyran-2-sulfonamide-7,7-dioxide

A mixture of the title compound (2.8 g, 0.0086 mol) and di-p-toluoyl-D-tartaric acid monohydrate (0.85 g, 0.0021 mol) in n-propanol (300 ml) was heated to boiling and the hot solution filtered through a filter-aid pad with a layer of charcoal (Norite and Darco). The filtrate was concentrated by boiling to a volume of about 75 ml and then allowed to crystallize. After standing overnight, the crystals were filtered off and the material recrystallized twice more from n-propanol (75 ml) to yield a 2:1 salt of free base to acid. The combined mother liquors from these recrystallization were saved for Step B. The salt was then treated with a saturated solution of $NaHCO_3$ and the mixture extracted with ethyl acetate (5x). The organic extracts were dried, filtered and concentrated to dryness to yield 0.6 g of free base. The hydrochloride salt was prepared from 5.6 N HCl ethanol and crystallized from CH_3OH-isopropanol to yield 0.53 g of the (+) isomer; $[\alpha]_D^{24}$ = 8.23 (C, 0.9 CH_3OH); mp 283-285°C. The combined mother liquors were treated with a saturated solution of $NaHCO_3$ and the mixture extracted with ethyl acetate (5x). The organic extracts were dried, filtered and concentrated to dryness. The residue was treated with di-p-toluoyl-L-tartaric acid monohydrate (0.85, 0.0021 mol) and n-propanol (200 ml) and the isomers separated by the process described previously to give 0.7 g of the (-) isomer; $[\alpha]_D^{24}$ = -8.34 (C, 1.0 CH_3OH); mp 283-285°C.

Employing the procedure substantially as described in Step J, but using trans- and cis-5,6-dihydro-4-ethylamino-6-ethyl-4H-thieno[2,3-b]thiopyran-2-sulfonamide-7,7-dioxide there are produced the following compounds:

trans (+)-5,6-dihydro-4H-4-ethylamino-6-ethylthieno [2,3-b]thiopyran-2-sulfonamide-7,7-dioxide hydrochloride, mp 275-277°C, 99% optically pure by HPLC. From di-p-toluoyl-D-tartaric acid (DPTDTA);

trans (-)-5,6-dihydro-4H-4-ethylamino-6-ethylthieno [2,3-b]thiopyran-2-sulfonamide-7,7-dioxide hydrochloride, mp 277-280°C, $[\alpha]_D^{24}$ = -9.43, 97.6% optically pure by HPLC, from di-p-toluoyl-L-tartaric acid (DPTLTA);

cis (+)-5,6-dihydro-4H-4-ethylamino-6-ethylthieno [2,3-b]thiopyran-2-sulfonamide-7,7-dioxide hydrochloride, mp 252-253°C, 99% optically pure by HPLC, from DPTDTA;

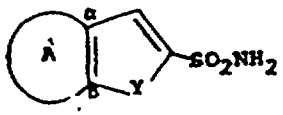
cis (-)-5,6-dihydro-4H-4-ethylamino-6-ethylthieno [2,3-b]thiopyran-2-sulfonamide-7,7-dioxide-hydrochloride, mp 248-250°C, 99% optically pure by HPLC from DPTLTA.

Similarly, each of the other cis- and trans-diastereomers described after Step I of this Example 6 , can be resolved into its enantiomers by procedures substantially as described in Step J.

Claims

Claims for the following Contracting States : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

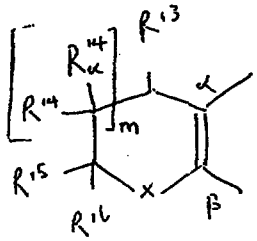
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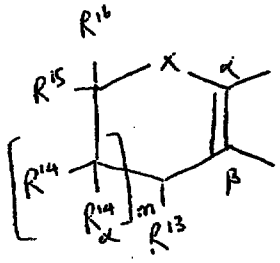
wherein



is



or



the individual diastereomers, the individual enantiomers or mixtures thereof,

or an ophthalmologically acceptable salt thereof, wherein:

X is $-SO_2-$;

Y is -S-, -O-, or NR^{19}, wherein R^{19} is H, C_{1-3}alkyl or benzyl,

m is 0, 1 or 2;

R^{13} is

a) hydrogen; or

b) $-NR^{17}R^{18}$, wherein R^{17} and R^{18} are independently selected from:

i) hydrogen or

ii) C_{1-5}alkyl, or taken together with the nitrogen to which they are attached form a heterocycle selected from morpholine, piperidine, pyrrolidine, and piperazine;

R^{14} is hydrogen;

$R^{14}\alpha$ is hydrogen;

trans (-)-5,6-dihydro-4H-4-ethylamino-6-ethylthieno [2,3-b]thiopyran-2-sulfonamide-7,7-dioxide hydrochloride, mp 277-280°C; $[\alpha]_D^{24}$ = -9.43, 97.6% optically pure by HPLC, from di-p-toluoyl-L-tartaric acid (DPTLTA);

cis (+)-5,6-dihydro-4H-4-ethylamino-6-ethylthieno [2,3-b]thiopyran-2-sulfonamide-7,7-dioxide hydrochloride, mp 252-253°C, 99% optically pure by HPLC, from DPTDTA;

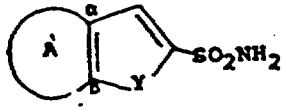
cis (-)-5,6-dihydro-4H-4-ethylamino-6-ethylthieno [2,3-b]thiopyran-2-sulfonamide-7,7-dioxide-hydrochloride, mp 248-250°C, 99% optically pure by HPLC from DPTLTA.

Similarly, each of the other cis- and trans-diastereomers described after Step I of this Example 6 , can be resolved into its enantiomers by procedures substantially as described in Step J.

Claims

Claims for the following Contracting States : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

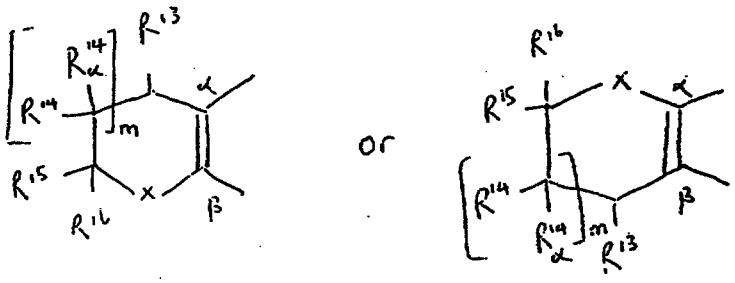
1. A compound of structural formula:



wherein



is



the individual diastereomers, the individual enantiomers or mixtures thereof,

or an ophthalmologically acceptable salt thereof, wherein:

X is $-SO_2-$;

Y is -S-, -O-, or NR^{19}, wherein R^{19} is H, C_{1-3}alkyl or benzyl,

m is 0, 1 or 2;

R^{13} is

a) hydrogen; or

b) $-NR^{17}R^{18}$, wherein R^{17} and R^{18} are independently selected from:

i) hydrogen or

ii) C_{1-5}alkyl, or taken together with the nitrogen to which they are attached form a heterocycle selected from morpholine, piperidine, pyrrolidine, and piperazine;

R^{14} is hydrogen;

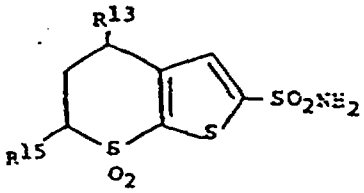
$R^{14}\alpha$ is hydrogen;

R^{15} is C_{1-5} alkyl; and
R^{16} is

a) hydrogen, or
b) C_{1-3}alkyl.

2. A compound as claimed in Claim 1 wherein R^{13} is $-NR^{17}R^{18}$ and R^{16} is hydrogen.

3. A compound as claimed in Claim 2, of structural formula:



4. The cis- or trans-diastereomers or the levo- or dextro enantiomers of the diastereomers, or mixtures of the isomers of the compound:
5,6-dihydro-4-ethylamino-6-methyl-4H-thieno[2,3-b]-thiopyran-2-sulfonamide-7,7-dioxide;
5,6-dihydro-4-(2-methylpropylamino)-6-methyl-4H-thieno [2,3-b]thiopyran-2-sulfonamide-7,7-dioxide;
5,6-dihydro-4-ethylamino-6-ethyl-4H-thieno[2,3-b]thiopyran-2-sulfomanide-7,7-dioxide; or
5,6-dihydro-6,6-dimethyl-4-ethylamino-4H-thieno[2,3-b]thiopyran-2-sulfonamide-7,7-dioxide.

5. The cis- or trans-diastereomers or the levo- or dextro-enantiomers of the diastereomers or mixtures of the isomers of the compound 5,6-dihydro-4-ethylamino-6-methyl-4H-thieno[2,3-b]thiopyran-2-sulfonamide-7,7-dioxide.

6. The cis- or trans-diastereomers or the levo- or dextro-enantiomers of the diastereomers or mixtures of the isomers of the compound 5,6-dihydro-4-ethylamino-6-ethyl-4H-thieno[2,3-b]thiopyran-2-sulfonamide-7,7-dioxide.

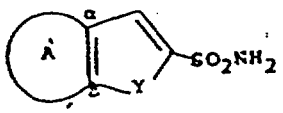
7. An ophthalmological formulation for the treatment of ocular hypertension comprising an ophthalmologically acceptable carrier and an effective ocular antihypertensive amount of a compound of Claim 1.

8. The use of a compound as claimed in Claim 1 for the manufacture of a medicament useful for treating elevated intraocular pressure.

9. The use of a compound as claimed in Claim 1 for the manufacture of a medicament useful for treating ocular hypertension.

Claims for the following Contracting States: ES, GR

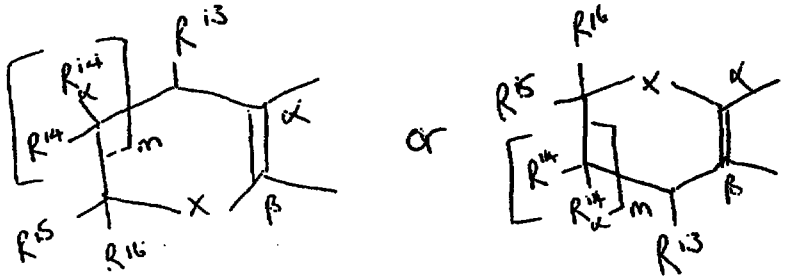
1. A process for preparing substituted aromatic sulfonamides of structural formula (I)



wherein



is



the individual diastereomers, the individual enantiomers or mixtures thereof,

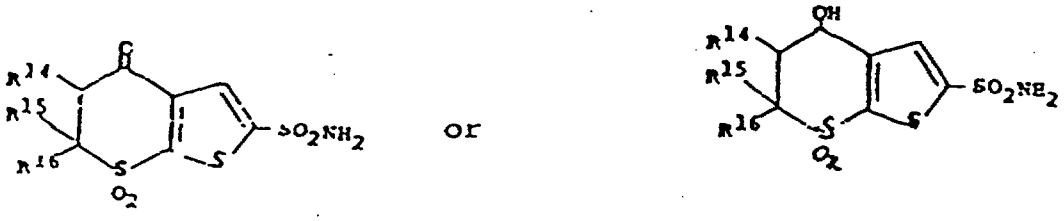
or an ophthalmologically acceptable salt thereof, wherein:
X is $-SO_2-$;
Y is -S-, -O-, or NR^{19}, wherein R^{19} is H, C_{1-3}alkyl or benzyl,
m is 0, 1 or 2;
R^{13} is

a) hydrogen; or
b) $-NR^{17}R^{18}$, wherein R^{17} and R^{18} are independently selected from:
i) hydrogen or
ii) C_{1-5}alkyl, or taken together with the nitrogen to which they are attached form a heterocycle selected from morpholine, piperidine, pyrrolidine, and piperazine;

R^{14} is hydrogen;
R_α^{14} is hydrogen;
R^{15} is C_{1-5} alkyl; and
R^{16} is

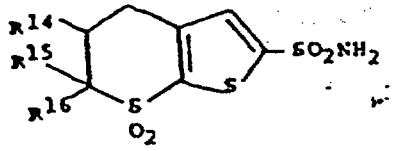
a) hydrogen, or
b) C_{1-3}alkyl;

which comprises
(A) treating the corresponding compound of formula (I) wherein X is sulphur with aqueous OXONE in an organic solvent;
(B) For preparing compounds of formula I in which R^{13} is H;
by treating the corresponding 4-oxo compound (a) or carbinol (b) of formulae



(a) (b)

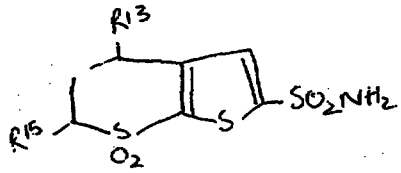
wherein R^{14}, R^{15} and R^{16} are those previously defined with triethylsilane in TFA or with dimethyldichlorosilane and sodium iodide in an organic solvent respectively to render a compound in which R^{13} is H of formula



(C) For preparing a compound of formula (I) wherein R^{17} and R^{18} each represents hydrogen, by hydrolysis of the corresponding derivative having an N-acyl group;
(D) For preparing a compound of formula (I) wherein R^{13} represents an alkylamino group,
D.1) by reducing the corresponding derivative having an N-acyl-group; or
D.2) by treatment of the corresponding compound wherein R^{13} represents hydroxy with toluenesulfonyl chloride followed by the addition of the desired alkylamine; or
D.3) by treatment of the corresponding compound wherein R^{13} is a carbonyl group with an amine in the presence of titanium tetrachloride followed by reduction of the resulting intermediate with a complex metal hydride.

2. The process of claim 1, wherein R^{13} is $-NR^{17}R^{18}$ and R^{16} is hydrogen.

3. The process of claim 2, wherein the compounds obtained have the following structural formula:



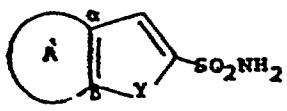
4. The process of claim 1, wherein the compounds obtained are selected from the cis- or trans-diastereomers or the levo- or dextro enantiomers of the diastereomers, or mixtures of the isomers of the compound:
5,6-dihydro-4-ethylamino-6-methyl-4H-thieno[2,3-b]-thiopyran-2-sulfonamide-7,7-dioxide;
5,6-dihydro-4-(2-methylpropylamino)-6-methyl-4H-thieno[2,3-b] thiopyran-2-sulfonamide-7,7-dioxide;
5,6-dihydro-4-ethylamino-6-ethyl-4H-thieno[2,3-b]thiopyran-2-sulfonamide-7,7-dioxide;or
5,6-dihydro-6,6-dimethyl-4-ethylamino-4H-thieno[2,3-b]-thiopyran -2-sulfonamide-7,7-dioxide.

5. The process of claim 1 wherein the compounds obtained are the cis- or trans-diastereomers or the levo- or dextro-enantiomers of the diastereomers or mixtures of the isomers of the compound
5,6-dihydro-4-ethylamino-6-methyl-4H-thieno[2,3-b]thiopyran-2-sulfonamide-7,7-dioxide.

6. The process of claim 1 wherein the compounds obtained are the cis- or trans-diasteraomers or the levo- or dextro-enantiomers of the diastereomers or mixtures of the isomers of the compound
5,6-dihydro-4-ethylamino-6-ethyl-4H-thieno[2,3-b]thiopyran-2-sulfonamide-7,7-dioxide.

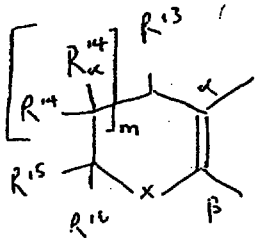
Patentansprüche
Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Verbindung der Strukturformel:

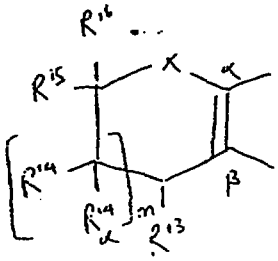


worin





oder



die einzelnen Diastereomere, die einzelnen Enantiomere oder Gemische davon oder ein ophthalmologisch annehmbares Salz davon bedeutet, worin:

X -für SO_2- steht;

Y -S-, -O-oder NR^{19} ist, worin R^{19} H, C_{1-3}-Alkyl oder -Benzyl bedeutet,

m 0,1 oder 2 ist;

R^{13}

a) Wasserstoff; oder

b) $NR^{17}R^{18}$ ist, worin R^{17} und R^{18} unabhängig voneinander aus

i) Wasserstoff oder

ii) C_{1-5}-Alkyl ausgewählt sind oder zusammen mit dem Stickstoff, an den sie gebunden sind, einen Heterocyclus, ausgewählt aus Morpholin, Piperidin, Pyrrolidin und Piperazin, bilden;

R^{14} Wasserstoff bedeutet,

$R^{14}{}_{\alpha}$ Wasserstoff ist;

R^{15} für C_{1-5}-Alkyl steht; und

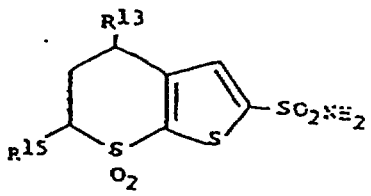
R16

a) Wasserstoff oder

b) C_{1-3}-Alkyl bedeutet.

2. Verbindung nach Anspruch 1, worin R^{13} für $-NR^{17}R^{18}$ steht und R^{16} Wasserstoff ist.

3. Verbindung nach Anspruch 2 der Strukturformel:



4. Cis- oder trans-Diastereomere oder lävo- oder dextro-Enantiomere der Diastereomeren oder Gemische der Isomeren der Verbindung:

5,6-Dihydro-4-ethylamino-6-methyl-4H-thieno[2,3-b]thiopyran-2-sulfonamid-7,7-dioxid;
5,6-Dihydro-4-(2-methylpropylamino)-6-methyl-4H-thieno[2,3-b]thiopyran-2-sulfonamid-7,7-dioxid;
5,6-Dihydro-4-ethylamino-6-ethyl-4H-thieno[2,3-b]thiopyran-2-sulfonamid-7,7-dioxid oder
5,6-Dihydro-6,6-dimethyl-4-ethylamino-4H-thieno[2,3-b]thiopyran-2-sulfonamid-7,7-dioxid.

5. Cis- oder trans-Diastereomere oder lävo- oder dextro-Enantiomere der Diastereomeren oder Gemische der Isomeren der Verbindung:
5,6-Dihydro-4-ethylamino-6-methyl-4H-thieno[2,3-b]thiopyran-2-sulfonamid-7,7-dioxid.

6. Cis- oder trans-Diastereomere oder lävo- oder dextro-Enantiomere der Diastereomeren oder Gemische der Isomeren der Verbindung:
5,6-Dihydro-4-ethylamino-6-ethyl-4H-thieno[2,3-b]thiopyran-2-sulfonamid-7,7-dioxid.

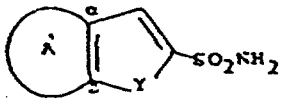
7. Ophthalmologische Rezeptur zur Behandlung der okularen Hypertension umfassend einen ophthalmologisch annehmbaren Träger und eine wirksame okular-antihypertensive Menge einer Verbindung nach Anspruch 1.

8. Verwendung einer Verbindung nach Anspruch 1 zur Herstellung eines Medikaments, das für die Behandlung des erhöhten intraokularen Druckes geeignet ist.

9. Verwendung einer Verbindung nach Anspruch 1 zur Herstellung eines Medikaments, das für die Behandlung der okularen Hypertension geeignet ist.

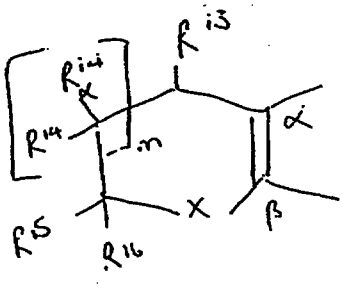
Patentansprüche für folgende Vertragsstaaten: ES, GR

1. Verfahren zur Herstellung substituierter aromatischer Sulfonamide der Strukturformel (I)

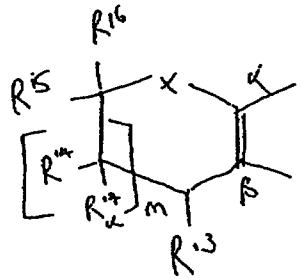


worin





oder



die einzelnen Diastereomere, die einzelnen Enantiomere oder Gemische davon, oder ein ophthalmologisch annehmbares Salz davon bedeutet, worin:
X -für SO_2- steht;
Y -S-, -O-oder NR^{19} ist, worin R^{19} H, C_{1-3}-Alkyl oder -Benzyl bedeutet,
m 0,1 oder 2 ist;
R^{13}

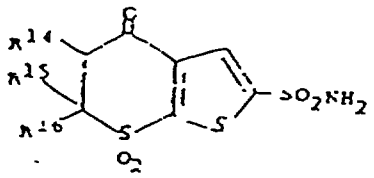
a) Wasserstoff; oder
b) $NR^{17}R^{18}$ ist; worin R^{17} und R^{18} unabhängig voneinander aus
i) Wasserstoff oder
ii) C_{1-5}-Alkyl ausgewählt sind oder zusammen mit dem Stickstoff, an den sie gebunden sind, einen Heterocyclus, ausgewählt aus Morpholin, Piperidin, Pyrrolidin und Piperazin, bilden;

R^{14} Wasserstoff bedeutet,
R_α^{14} Wasserstoff ist;
R15 für C_{1-5}-Alkyl steht; und
R16
a) Wasserstoff oder
b) C_{1-3}-Alkyl bedeutet,

umfassend

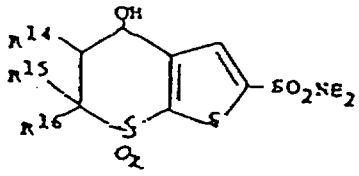
(A) die Behandlung der entsprechenden Verbindung der Formel (I), worin X Schwefel bedeutet, mit einem wäßrigen OXON in einem organischen Lösungsmittel;

(B) zur Herstellung von Verbindungen der Formel (I), in der R^{13} H bedeutet, die Behandlung der entsprechenden 4-Oxo-Verbindung (a) oder des Carbinols (b) der Formeln



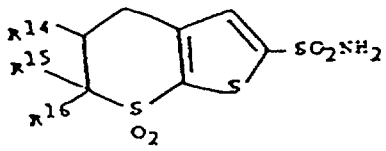
(a)

oder



(b)

worin R^{14}, R^{15} und R^{16} die zuvor gegebene Definition besitzen, mit Triethylsilan in TFA bzw. mit Dimethyldichlorsilan und Natriumiodid in einem organischen Lösungsmittel, um eine Verbindung, in der R^{13} H ist, der Formel



herzustellen;

(C) zur Herstellung einer Verbindung der Formel (I), worin R^{17} und R^{18} jeweils Wasserstoff darstellen, Hydrolyse des entsprechenden Derivates, das eine N-Acylgruppe besitzt;

(D) zur Herstellung einer Verbindung der Formel (I), worin R^{13} für eine Alkylaminogruppe steht,

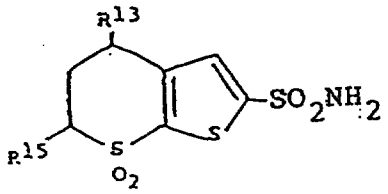
D.1) die Reduktion des entsprechenden Derivates, das eine N-Acylgruppe besitzt; oder

D.2) die Behandlung der entsprechenden Verbindung, worin R^{13} Hydroxy darstellt, mit Toluolsulfonylchlorid, gefolgt von der Addition des gewünschten Alkylamins; oder

D.3) die Behandlung der entsprechenden Verbindung, worin R^{13} eine Carbonylgruppe darstellt, mit einem Amin in Gegenwart von Titantetrachlorid, gefolgt von der Reduktion des erhaltenen Zwichenproduktes mit einem komplexen Metallhydrid.

2. Verfahren nach Anspruch 1, bei dem R^{13} für $-NR^{17}R^{18}$ steht und R^{16} Wasserstoff ist.

3. Verfahren nach Anspruch 2, bei dem die erhaltenen Verbindungen die folgende Strukturformel besitzen:



4. Verfahren nach Anspruch 1, bei dem die erhaltenen Verbindungen aus den cis- oder trans-Diastereomeren oder den lävo- oder dextro-Enantiomeren der Diastereomeren oder aus den Gemischen der Isomeren der Verbindung:
5,6-Dihydro-4-ethylamino-6-methyl-4H-thieno[2,3-b]thiopyran-2-sulfonamid-7,7-dioxid;
5,6-Dihydro-4-(2-methylpropylamino)-6-methyl-4H-thieno[2,3-b]thiopyran-2-sulfonamid-7,7-dioxid;
5,6-Dihydro-4-ethylamino-6-ethyl-4H-thieno[2,3-b]thiopyran-2-sulfonamid-7,7-dioxid oder
5,6-Dihydro-6,6-dimethyl-4-ethylamino-4H-thieno[2,3-b]thiopyran-2-sulfonamid-7,7-dioxid, ausgewählt werden.

5. Verfahren nach Anspruch 1, bei dem die erhaltenen Verbindungen die cis- oder trans-Diastereomere oder die lävo- oder dextro-Enantiomere der Diastereomeren oder Gemische der Isomeren der Verbindung:
5,6-Dihydro-4-ethylamino-6-methyl-4H-thieno[2,3-b]thiopyran-2-sulfonamid-7,7-dioxid sind.

6. Verfahren nach Anspruch 1, bei dem die erhaltenen Verbindungen die cis- oder trans-Diastereomere oder lävo- oder dextro-Enantiomere der Diastereomeren oder Gemische der Isomeren der Verbindung:
5,6-Dihydro-4-ethylamino-6-ethyl-4H-thieno[2,3-b]thiopyran-2-sulfonamid-7,7-dioxid sind.

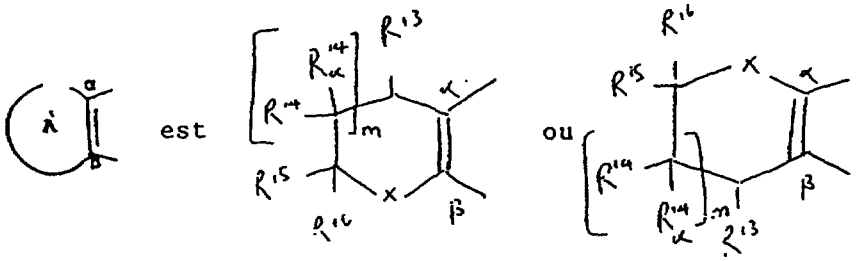
Revendications

Revendications pour les Etats contractants suivants : AT, BE, DE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Composé de formule développée :



dans laquelle



ses diastéréoisomères particuliers, ses énantiomères particuliers ou leurs mélanges,
ou un de ses sels ophtalmologiquement acceptables,
où :
X est $-SO_2-$;
Y est -S-, -O-, ou NR^{19} où R^{19} est H, un groupe alkyle en C_{1-3} ou benzyle,
m vaut 0, 1 ou 2 ;

R^{13} est

a) un atome d'hydrogène ; ou

b) $-NR^{17}R^{18}$, où R^{17} et R^{18} sont choisis de manière indépendante parmi :

i) un atome d'hydrogène ; ou

ii) un groupe alkyle en C_{1-5}, ou pris conjointement avec l'atome d'azote au quel ils sont fixés, forment un hétérocycle choisi parmi la morpholine, la pipéridine, la pyrrolidine et la pipérazine ;

R^{14} est un atome d'hydrogène ;

$R^{14}{}_{\alpha}$ est un atome d'hydrogène ;

R^{15} est un groupe alkyle en C_{1-5} ; et

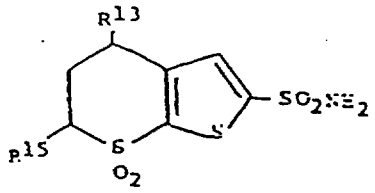
R^{16} est

a) un atome d'hydrogène, ou

b) un groupe alkyle en C_{1-3}.

2. Composé selon la revendication 1, dans lequel R^{13} est $-NR^{17}R^{18}$ et R^{16} est un atome d'hydrogène.

3. Composé selon la revendication 2, de formule développée :



4. Diastéréoisomères cis ou trans ou les énantiomères lévogyres ou dextrogyres des diastéréoisomères ou des mélanges des isomères du composé :
5,6-dihydro-4-éthylamino-6-méthyl-4H-thiéno(2,3-b)thiopyran-2-sulfonamide-7,7-dioxyde ;
5,6-dihydro-4-(2-méthylpropylamino)-6-méthyl-4H-thiéno(2,3-b)thiopyran-2-sulfonamide-7,7-dioxyde ;
5,6-dihydro-4-éthylamino-6-éthyl-4H-thiéno(2,3-b)thiopyran-2-sulfonamide-7,7-dioxyde ; ou
5,6-dihydro-6,6-diméthyl-4-éthylamino-4H-thiéno(2,3-b)thiopyran-2 -sulfonamide-7,7-dioxyde.

5. Diastéréoisomères cis ou trans ou les énantiomères lévogyres ou dextrogyres des diastéréoisomères ou des mélanges des isomères du composé 5,6-dihydro-4-éthylamino-6-méthyl-4H-thiéno(2,3 -b)-thiopyran-2-sulfonamide-7,7-dioxyde.

6. Diastéréoisomères cis ou trans ou les énantiomères lévogyres ou dextrogyres des diastéréoisomères ou des mélanges des isomères du composé 5,6-dihydro-4-éthylamino-6-éthyl-4H-thiéno(2,3-b)-thiopyran-2-sulfonamide-7,7-dioxyde.

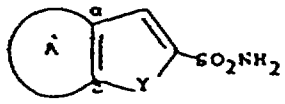
7. Formulation ophtalmologique pour le traitement de l'hypertension oculaire qui comprend un véhicule ophtalmologiquement acceptable et une quantité efficace antihypertensive oculaire d'un composé selon la revendication 1.

8. Utilisation d'un composé selon la revendication 1 pour la préparation d'un médicament utile pour traiter la pression intra-oculaire élevée.

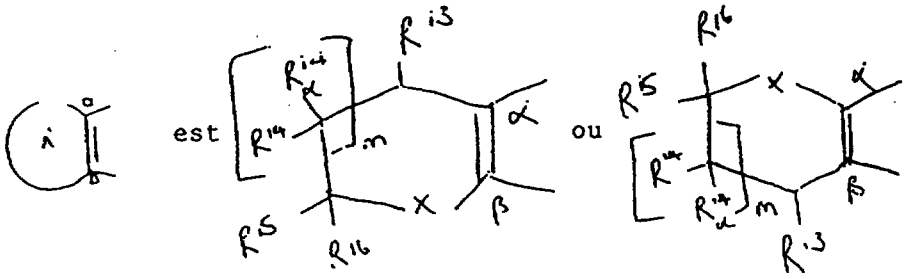
9. Utilisation d'un composé selon la revendication 1, pour la préparation d'un médicament utile pour le traitement de l'hypertension oculaire.

Revendications pour les Etats contractants suivants : ES, GR

1. Procédé pour la préparation de sulfonamides aromatiques substitués de formule développée (I) :



dans laquelle



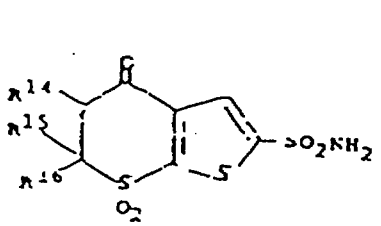
de ses diastéréoisomères particuliers, de ses énantiomères particuliers ou leurs mélanges, ou d'un de ses sels ophtalmologiquement acceptables,
où :
X est $-SO_2-$; Y est -S-, -O-, ou NR^{19} où R^{19} est H, un groupe alkyle en C_{1-3} ou benzyle,
m vaut 0, 1 ou 2 ;
R^{13} est

a) un atome d'hydrogène ; ou
b) $-NR^{17}R^{18}$, où R^{17} et R^{18} sont choisis de manière indépendante parmi :
i) un atome d'hydrogène ; ou
ii) un groupe alkyle en C_{1-5}, ou pris conjointement avec l'atome d'azote au quel ils sont fixés, forment un hétérocycle choisi parmi la morpholine, la pipéridine, la pyrrolidine et la pipérazine ;

R^{14} est un atome d'hydrogène ;
$R^{14}{}_\alpha$ est un atome d'hydrogène ;
R^{15} est un groupe alkyle en C_{1-5} ; et
R^{16} est

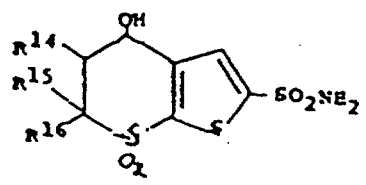
a) un atome d'hydrogène, ou
b) un groupe alkyle en C_{1-3}

qui comprend
(A) le traitement du composé correspondant de formule (I) dans laquelle X est un atome de soufre avec de l'OXONE aqueuse dans un solvant organique ;
(B) pour la préparation des composés de formule (I) dans laquelle R^{13} est H, le traitement du composé correspondant 4-oxo (a) ou carbinol (b) de formules



(a)

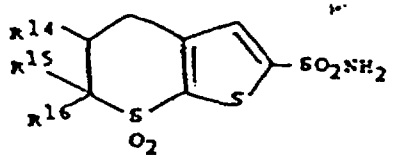
ou



(b)

* C L M S *

où R^{14}, R^{15} et R^{16} sont ceux précédemment définis, avec le triéthylsilane dans TFA ou avec le diméthyldichlorosilane et l'iodure de sodium dans un solvant organique respectivement pour donner un composé dans lequel R^{13} est H de formule



(C) pour la préparation d'un composé de formule (I) dans laquelle R^{17} et R^{18} représentent chacun un atome d'hydrogène, l'hydrolyse du dérivé correspondant ayant un groupe N-acyle ;

(D) pour la préparation d'un composé de formule (I) dans laquelle R^{13} représente un groupe alkylamino,

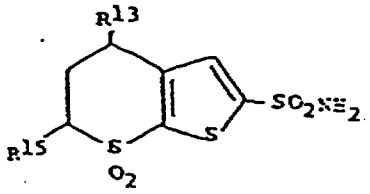
D.1.) la réduction du dérivé correspondant ayant un groupe N-acyle ; ou

D.2.) le traitement du composé correspondant dans lequel R^{13} représente un groupe hydroxyle avec le chlorure de toluène-sulfonyle suivi de l'addition de l'alkylamine souhaitée;ou

D.3.) le traitement du composé correspondant dans lequel est un groupe carbonyle avec une amine en présence de tétrachlorure de titane suivi de la réduction de l'intermédiaire résultant avec un hydrure métallique complexe.

2. Procédé selon la revendication 1, dans lequel R^{13} est $-NR^{17}R^{18}$ et R^{16} est un atome d'hydrogène.

3. Procédé selon la revendication 2, dans lequel les composés obtenus possèdent la formule développée suivante :



4. Procédé selon la revendication 1, dans lequel les composés obtenus sont choisis parmi les diastéréoisomères cis ou trans ou les énantiomères lévogyres ou dextrogyres des diastéréoisomères ou des mélanges des isomères du composé :
5,6-dihydro-4-éthylamino-6-méthyl-4H-thiéno(2,3-b)thiopyran-2-sulfonamide-7,7-dioxyde ;
5,6-dihydro-4-(2-méthylpropylamino)-6-méthyl-4H-thiéno(2,3-b)thiopyran-2-sulfonamide-7,7-dioxyde ;
5,6-dihydro-4-éthylamino-6-éthyl-4H-thiéno(2,3-b)thiopyran-2-sulfonamide-7,7-dioxyde ; ou
5,6-dihydro-6,6-diméthyl-4-éthylamino-4H-thiéno(2,3-b)thiopyran-2 -sulfonamide-7,7-dioxyde.

5. Procédé selon la revendication 1, dans lequel les composés obtenus sont les diastéréoisomères cis ou trans ou les énantiomères lévogyres ou dextrogyres des diastéréoisomères ou des mélanges des isomères du composé 5,6-dihydro-4-éthylamino-6-méthyl-4H -thiéno(2,3-b)thiopyran-2-sulfonamide-7,7-dioxyde.

6. Procédé selon la revendication 1, dans lequel les composés obtenus sont les diastéréoisomères cis ou trans ou les énantiomères lévogyres ou dextrogyres des diastéréoisomères ou des mélanges des isomères du composé 5,6-dihydro-4-éthylamino-6-éthyl-4H-thiéno(2,3-b)thiopyran-2-sulfonamide-7,7-dioxyde.