NEW HETEROCYCLIC RING SYSTEMS. XIV.[1] 7,11-DITHIAOXASTEROIDS ANALOGUES

Violetta Cecchetti, Arnaldo Fravolini,* Renata Fringuelli, and Fausto Schiaffella

Istituto di Chimica Farmaceutica e Tecnica Farmaceutica, Università degli Studi, Via del Liceo, 06100 Perugia, Italy

Abstract - By reaction of 1,2-benzooxathiin-4(3H)-one 2,2-dioxide (**II**) with mercaptopropionic acid the new tricycle 4-oxo-3,4-dihydro-2H-thiopyrano[3,2-c][1,2]benzooxathiin 5,5-dioxide (**IV**) together with tetracycle **V** and pentacycle **VII** were obtained. The key ketone **IV** was then converted to ß-diketone **IX**, enamino ketone **XVI** and α-bromoketone **XX** intermediates to give with nucleophilic reagents 7,11-dithiaoxasteroids analogues.

In continuation of our work in the area of heterosteroids and related model systems, we now wish to report the synthesis of 6-oxa-7,11-dithiasteroid analogues.

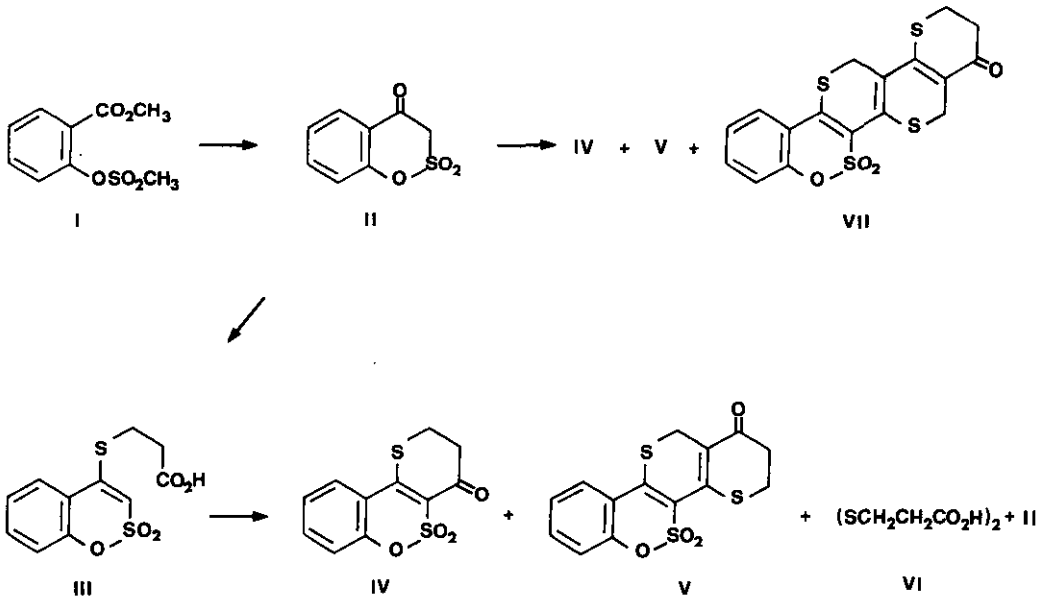
The synthetic approach to new heterosteroidic systems follows the one previously achieved by us for the synthesis of 6,11-[2] and 7,11-dithiaazasteroids,[1] namely annelation of a thiopyrane nucleus by mercaptopropionic acid to a bicyclic ketone, in this case 1,2-benzooxathiin-4(3H)one 2,2-dioxide (**II**) to give 4-oxo-3,4-dihydro-2H-thiopyrano [3,2-c][1,2]benzooxathiin 5,5-dioxide (**IV**) which was *first bifunctionalized so as to obtain* 6-oxa-7,11-dithiasteroidic systems by nucleophilic reagents. Therefore, the ketone **IV**, key intermediate in the projected synthesis, was prepared by PPA cyclodehydration of ß-(1,2-benzooxathiin-4-ylthio)propionic acid **III**.

The course of this reaction confirms what we had observed before in the analogous synthesis of 6-methyl-4-oxo-3,4-dihydro-2H,6H-thiopyrano[3,2-c][2,1]benzothiazine 5,5-dioxide.[1]

As a matter of fact in this case as well the expected tricyclic ketone **IV** (69.5%) is accompanied by starting ketone **II** (11.6%) disulphide **VI** (10.9%) and a D-homosteroid **V** (8.0%) as a consequence of liberation of mercaptopropionic acid in the cyclization reaction.

The direct reaction of ketone **II** with mercaptopropionic acid in PPA gave rise to an original sequential polyannelation affording tricycle **IV** (22.2%) together with tetracyclic D-homosteroid **V** (35.3%) and an unexpected red product (3.9%) (M^+ 408), which was then identified as the pentacycle 4-oxo-3,4,5,14-tetrahydro-2H-thiopyrano[3,2-c]thiopyrano[3,2-c]thiopyrano[3,2-c][1,2]benzooxathiin 7,7-dioxide (**VII**). (Scheme I).

SCHEME I



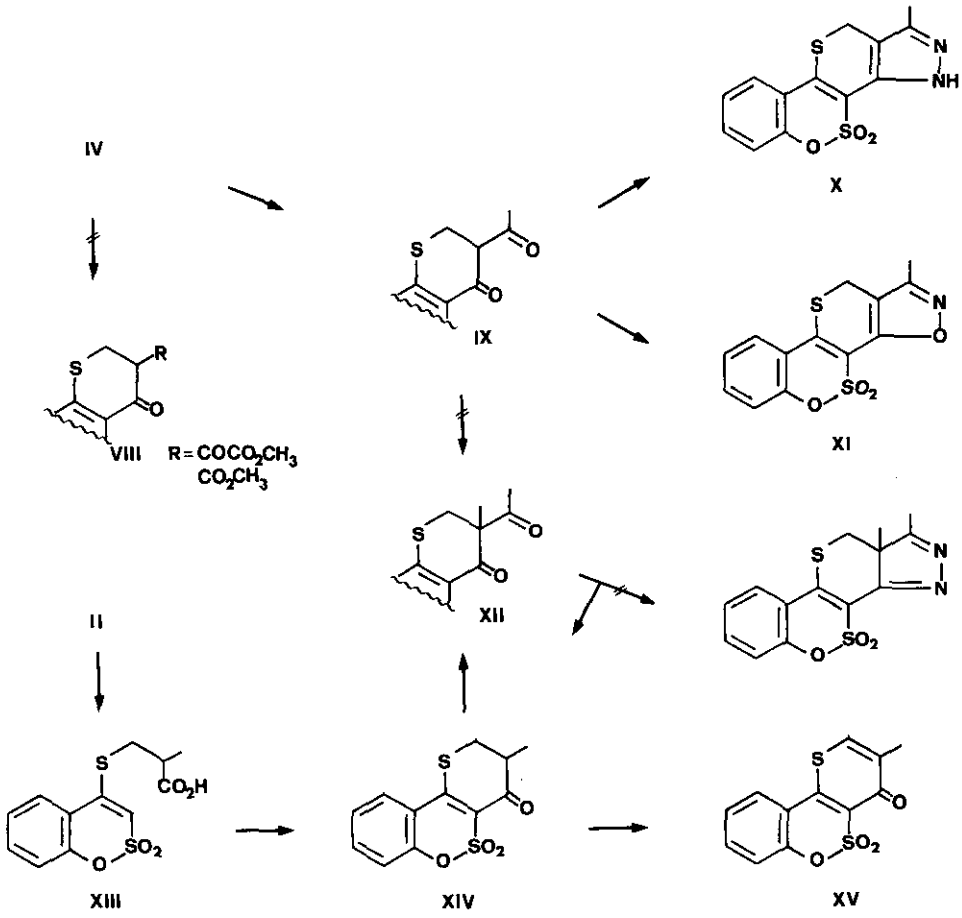
The first step for bifunctionalization of tricyclic ketone **IV** consisted in the attempt to prepare the ß-ketoester **VIII**, a versatile intermediate for the construction of the D-ring of the steroidic system, but all attempts to carboxymethylate **IV** with methyl carbonate, magnesium methylcarbonate or indirectly with dimethyl oxalate under different conditions unfortunately are unsuccessful.

On the contrary the treatment of **IV** with boron trifluoride etherate in acetic anhydride afforded in good yield the 3-acetyl-4-oxo-3,4-dihydro-2H-thiopyrano[3,2-c][1,2]benzooxathiin 5,5-dioxide (**IX**) which by reaction with hydrazine and hydroxylamine gave pyrazole **X** and isoxazole **XI** derivatives respectively.

Attempts to introduce a methyl group at C-3 of the ß-diketone **IX**, in order to obtain hetero-steroidic systems methylated at C-13, failed.

The hypothesized 3-methyl-3-acetyl-3,4-dihydro-4-oxo-2H-thiopyrano[3,2-c][1,2]benzooxathiin 5,5-dioxide (**XII**) was then obtained by an alternative route by first preparing the 3-methyl-4-oxo-3,4-dihydro-2H-thiopyrano[3,2-c][1,2]benzooxathiin 5,5-dioxide (**XIV**) through the reaction of II with mercaptoisobutyric acid, and then by acetylation to C-3. However, the treatment of ß-diketone **XII**, with hydrazine under different conditions afforded again **XIV**, showing how the acetyl group is a leaving group. The bromination of **XIV**, by pyridine hydrobromide perbromide, was also unsuccessful, yielding the aromatic α-methyl ketone **XV** rather than the expected bromine derivative. (Scheme II).

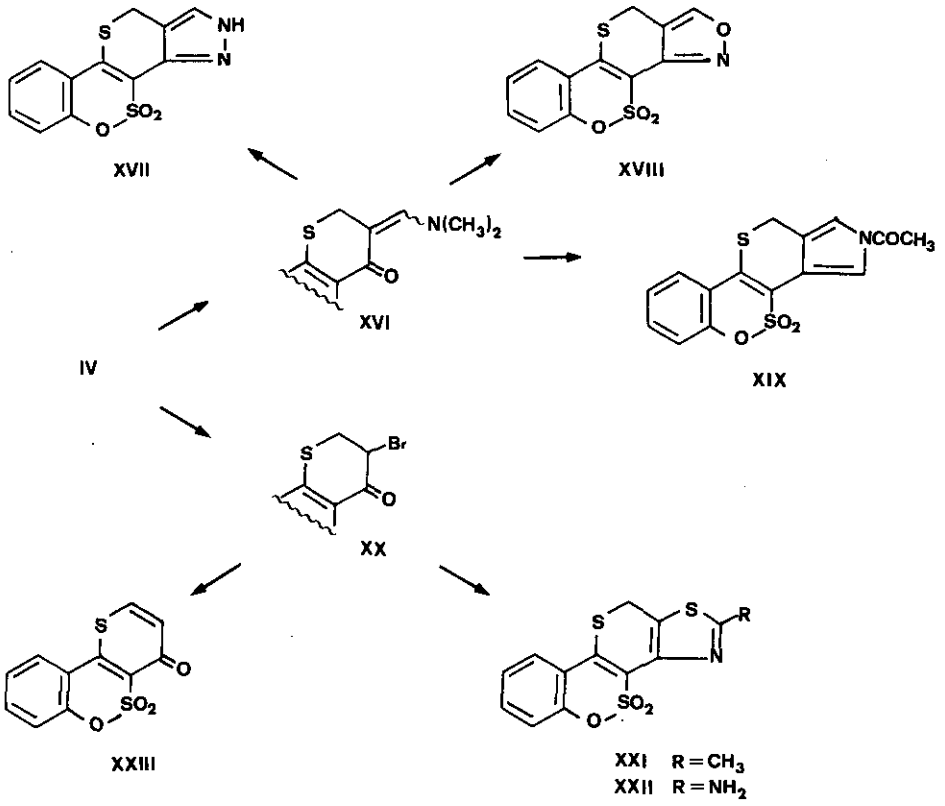
SCHEME II



Other pyrazole and isoxazole heterosteroids **XVII** and **XVIII** were prepared, respectively, through the reaction of hydrazine and hydroxylamine with enamino ketone **XVI**. In a similar fashion with glycine and acetic anhydride according to the procedure of Zav'yalov[3] 2-acetyl-11H-pyrrolo[3,4-c][1,2]benzooxathiin 4,4-dioxide (**XIX**) was obtained.

Finally thiazole derivatives **XXI** and **XXII** were synthesized from α-bromoketone **XX** and thiamides. Cyclization to give thiazole heterosteroids proceeds in moderate yields. The reaction of **XX** with *urea failed instead*, affording 4-oxo-4H-thiopyrano [3,2-c][1,2]benzooxathiin 5,5-dioxide (**XXIII**). (Scheme III).

SCHEME III



EXPERIMENTAL

Melting points were determined in capillary tubes (Electrothermal melting point apparatus) and are uncorrected. The ^{1}H-NMR spectra were obtained with a 90 MHz Varian EM 390 spectrometer in the indicated solvents. Chemical shifts and coupling constants were measured in ppm (δ) and J (Hz) with respect to TMS. The mass spectrum was obtained on a Varian MAT 311 A. The purity of the analytical samples was checked by tlc on silica gel Merck (Kieselgel 60 F_{254}). The chromatographic separations were carried out on silica gel Merck (Kieselgel 60,70-230 mesh) column.

1,2-Benzooxathiin-4(3H)-one 2,2-Dioxide (II).

To a suspension of sodium hydride (80% mineral oil suspension) (1.5 g, 50 mmole) in DMF (60 ml) was added a solution of methyl o-methanesulfonyloxy salicilate[4] (10 g, 43.5 mmole) in DMF (50 ml), the temperature being maintained at 0°C. The mixture was stirred under nitrogen at this temperature for 1 h. The resulting yellow solution was poured into cold water, acidified with 2N HCl and the precipitate that formed was filtered (5.2 g, 60.4% yield) and recrystallized from ethanol, mp 96-97°C (Lit.[5] mp 88°C; Lit.[6] mp 90°C; Lit.[7] mp 90-92°C). Anal. Calcd for $C_8H_6O_4S$: C, 48.49;

H, 3.03. Found: C, 48.30; H, 3.00.

ß-(1,2-Benzooxathiin-4-ylthio 2,2-Dioxide)propionic Acid (III).

To a solution of **II** (10 g, 50.5 mmole) in dry benzene (70 ml) was added 3-mercaptopropionic acid (6.4 g, 60.4 mmole) and 0.4 g of p-toluensulfonic acid monohydrate. The resulting mixture was refluxed for 15 h under a Dean-Stark trap. Acid **III** (5.0 g, 34.6% yield) was obtained by previously reported procedure[2a] and recrystallized from n-hexane/ethyl acetate, mp 165-167°C. Anal. Calcd for $C_{11}H_{10}O_5S_2$: C, 46.15; H, 3.50. Found: C, 45.98; H, 3.39.

Cyclization of III with Polyphosphoric Acid.

4-Oxo-3,4-dihydro-2H-thiopyrano[3,2-c][1,2]benzooxathiin 5,5-Dioxide (IV); 1-Oxo-1,2,3,12-tetrahydro-thiopyrano[3,2-c]thiopyrano[3,2-c][1,2]benzooxathiin 5,5-Dioxide (V).

10 g (34.9 mmole) of acid **III** were added to 50 g of PPA prewarmed to 90-100°C. Heating was continued for 1 h, then the mixture reaction was poured into crushed ice, the resulting precipitate was filtered and washed with 10% aqueous sodium carbonate and then with water.

Recrystallization from acetic acid gave 6.0 g (64.1% yield) of **IV**, mp 242-244°C; ^{1}H-NMR (TFA): δ 3.55 (A_2) and 3.15 (B_2) [m, 4H, (A_2B_2 system) SCH_2CH_2]. Anal. Calcd for $C_{11}H_8O_4S_2$: C, 49.25; H, 2.98. Found: C, 49.60; H, 3.01.

Acidification of the combined alkaline washings gave disulfide **VI** (0.4 g, 10.9% yield). The residue from mother liquor of crystallization of **IV** was chromatographed on silica gel. Elution with cyclohexane/ethyl acetate (98:2) afforded additional ketone **IV** (0.5 g, 5.4% yield) together with starting ketone **II** (0.8 g, 11.6% yield) and D-homosteroid **V** (0.95 g, 8.1% yield). Compound **V** was recrystallized from acetic acid, mp 212-215°C; ^{1}H-NMR (DMSO-d_6): δ 3.40 (A_2) and 2.80 (B_2) [m, 4H (A_2B_2 system) SCH_2CH_2] and 3.98 (s, 2H, SCH_2). Anal. Calcd for $C_{14}H_{10}O_4S_3$: C, 49.70; H, 2.96. Found: C, 50.04; H, 2.81.

Reaction of II with Mercaptopropionic Acid in Polyphosphoric Acid.

To warmed polyphosphoric acid (15 g), ketone **II** (3 g, 15.1 mmole) and mercaptopropionic acid (2 g, 18.9 mmole) were added and the mixture was maintained on a steam bath for 1 h. After cooling, the reaction mixture was poured into crushed ice and precipitate was first filtered and washed with 10% aqueous sodium carbonate, then with water and finally chromatographed on silica gel. Elution with cyclohexane/ethyl acetate (8:2) gave the recovery of 0.9 g (30.0% yield) of ketone **II** together with 0.9 g (22.2% yield) of **IV**, 1.8 g (35.3% yield) of **V** and 0.24 g (3.9% yield) of 4-oxo-3,4,5,14-tetrahydro-2H-thiopyrano[3,2-c]thiopyrano[3,2-c]thiopyrano[3,2-c][1,2]benzooxathiin 7,7-dioxide (VII), which was recrystallized from cyclohexane/ethyl acetate, red needles, mp 250-251°C; ^{1}H-NMR ($CDCl_3$): δ 3.53 (A_2) and 2.70 (B_2) [m, 4H, (A_2B_2 system) SCH_2CH_2], 3.73 and 3.86 (each s, 2H, SCH_2); ms: m/e 408 M^+. Anal. Calcd for $C_{17}H_{12}O_4S_4$: C, 50.00; H, 2.94. Found: C, 49.45; H, 2.85.

3-Acetyl-4-oxo-3,4-dihydro-2H-thiopyrano[3,2-c][1,2]benzooxathiin 5,5-Dioxide (**IX**).

To a solution of **IV** (2.5 g, 9.3 mmole) in acetic anhydride (100 ml) was added boron trifluoride etherate (5 g, 35.2 mmole) and the mixture was heated at 90°C for 4 h. After cooling, the yellow precipitate (2 g) which formed was collected. ß-Diketone **IX** was obtained by heating the solution of the above precipitate and sodium acetate (7.2 g, 87.8 mmole) in 100 ml of acetic acid for 5 min at 140°C. The resulting solution was then concentrated and diluted with water, the precipitate was collected (1.4 g, 48.4% yield) and recrystallized from acetic acid, mp 225-227°C; ^{1}H-NMR (DMSO-d_6): δ 2.33 (s, 3H, CH_3) and 4.20 (s, 2H, SCH_2). Anal. Calcd for $C_{13}H_{10}O_5S_2$: C, 50.32; H, 3.23. Found: C, 50.20; H, 3.18.

1-Methyl-3,11-dihydro-pyrazolo[4,3-c]thiopyrano[3,2-c][1,2]benzooxathiin 4,4-Dioxide (**X**).

To the solution of **IX** (0.31 g, 1 mmole) in acetic acid (50 ml) was added 98% hydrazine hydrate (0.4 ml) and the mixture was refluxed for 1 h. After concentration to one-half volume in vacuo the solution was diluted with water. The resulting precipitate was filtered (0.18 g, 58.8% yield) and recrystallized from acetic acid, mp 292-293°C; ^{1}H-NMR (DMSO-d_6): δ 2.23 (s, 3H, CH_3), 4.20 (s, 2H, SCH_2) and 12.85 (broad s, 1H, NH). Anal. Calcd for $C_{13}H_{10}N_2O_3S_2$: C, 50.98; H, 3.27; N, 9.15. Found: C, 50.62; H, 3.15; N, 9.00.

1-Methyl-11H-isoxazolo[4,5-c]thiopyrano[3,2-c][1,2]benzooxathiin 4,4-Dioxide (**XI**).

Hydroxylamine hydrochloride (0.15 g, 2.1 mmole) was added to a solution of **IX** (0.31 g, 1 mmole) in acetic acid (50 ml). The reaction mixture after heating on an oil-bath at 180°C for 3 h was concentrated to one-half volume in vacuo and then diluted with water. The solid precipitate was collected (0.18 g, 58.6% yield) and recrystallized from acetic acid, mp 225-227°C; ^{1}H-NMR (DMSO d_6): δ 2.30 (s, 3H, CH_3) and 4.38 (s, 2H, SCH_2). Anal. Calcd for $C_{13}H_9NO_4S_2$: C, 50.81; H, 2.93; N, 4.56. Found: C, 50.99; H, 2.70; N, 4.48.

ß-(1,2-Benzooxathiin-4-ylthio 2,2-Dioxide)isobutyric Acid (**XIII**).

This compound was obtained according to procedure for the preparation of **III**, using ß-mercaptoisobutyric acid.[8] It was recrystallized from ethyl acetate/n-hexane, mp 158-160°C (42.9% yield). Anal. Calcd for $C_{12}H_{12}O_5S_2$: C, 48.00; H, 4.00. Found: C, 47.89; H, 3.90.

3-Methyl-4-oxo-3,4-dihydro-2H-thiopyrano[3,2-c][1,2]benzooxathiin 5,5-Dioxide (**XIV**).

A mixture of **XIII** (5.0 g, 16.7 mmole) and PPA (25 g) was heated on an oil-bath at 140°C for 1 h. After cooling, the syrupy material was poured into crushed ice and the precipitate was collected by filtration. This solid was first washed with 10% aqueous sodium bicarbonate and then with water (2.0 g, 42.6% yield). It was recrystallized from acetic acid, mp 214-216°C; ^{1}H-NMR (DMSO-d_6): δ 1.20 (d, 3H, J=6 Hz, CH_3), 2.80 and 3.68 (m, 3H, SCH_2CH). Anal. Calcd for $C_{12}H_{10}O_4S_2$: C, 51.06; H, 3.55. Found: C, 50.96; H, 3.41.

3-Methyl-3-acetyl-3,4-dihydro-4-oxo-2H-thiopyrano[3,2-c][1,2]benzooxathiin 5,5-Dioxide (**XII**).

To a solution of **XIV** (1.0 g, 3.6 mmole) in acetic anhydride (50 ml) was added boron trifluoride

etherate (2.0 g) and the mixture was heated at 100-110°C for 8 h. The solution was concentrated under reduced pressure, diluted with chloroform, washed with water and then dried over sodium sulfate. The gummy dark residue was purified on silica gel column (eluent cyclohexane/chloroform 1:1) to afford **XII** (0.5 g, 43.6% yield) which was recrystallized from ethanol, mp 164-166°C; ^{1}H-NMR (TFA): δ1.93 (s, 3H, CH_3), 2.40 (s, 3H, $COCH_3$) and 3.60 (s, 2H, SCH_2). Anal. Calcd for $C_{14}H_{12}O_5S_2$: C, 51.85; H, 3.70. Found: C, 52.20; H, 3.76.

Attempted Bromination of **XIV**.

To a solution of **XIV** (0.5 g, 1.8 mmole) in acetic acid (20 ml) was added pyridine hydrobromide perbromide (0.67 g, 2.1 mmole) and the mixture was boiled for 1 h. Cooling produced a crystalline precipitate which was filtered to give 3-methyl-4-oxo-4H-thiopyrano[3,2-c][1,2]benzooxathiin 5,5-dioxide **(XV)** (0.35 g, 70.5% yield). It was recrystallized from acetic acid, mp 316-318°C; ^{1}H-NMR (TFA) : δ 1.80 (s, 3H, CH_3) and 6.78-7.48 (m, 5H, aromatic protons and SCH). Anal. Calcd for $C_{12}H_8O_4S_2$: C, 51.43; H, 2.86. Found: C, 51.25; H, 2.81.

3-[(Dimethylamino)methylene]-3,4-dihydro-4-oxo-2H-thiopyrano[3,2-c][1,2]benzooxathiin 5,5-Dioxide **(XVI)**.

To a solution of **IV** (1.0 g, 3.7 mmole) in dry toluene (100 ml) was added dimethylformamide dimethyl acetal (10 ml) and the mixture was refluxed for 1 h under nitrogen. After cooling at room temperature the resultant brown precipitate was filtered (0.8 g, 66.4% yield) and recrystallized from acetic acid, mp 236-238°C; ^{1}H-NMR (DMSO-d_6): δ 3.27 [s, 6H, $N(CH_3)_2$], 4.45 (s, 2H, SCH_2) and 7.58 (s, 1H, CH). Anal. Calcd for $C_{14}H_{13}NO_4S_2$: C, 52.01; H, 4.02; N, 4.33. Found: C, 51.84; H, 3.98; N, 4.40.

2,11-Dihydro-pyrazolo[4,3-c]thiopyrano[3,2-c][1,2]benzooxathiin 4,4-Dioxide **(XVII)**.

To a solution of **XVI** (0.5 g, 1.6 mmole) in acetic acid (20 ml) was added 98% hydrazine hydrate (0.1 ml) and the mixture was boiled for 30 min. After cooling the resulting solid was collected (0.4 g, 88.5% yield) and recrystallized from acetic acid, mp 287-288°C; ^{1}H-NMR (DMSO-d_6): δ 4.30 (s, 2H, SCH_2), 7.73 (t-like, 1H, pyrazole proton) and 13.1 (broad s, 1H, NH). Anal. Calcd for $C_{12}H_8N_2O_3S_2$: C, 49.32; H, 2.74; N, 9.59. Found: C, 49.62; H, 2.68; N, 9.45.

11H-Isoxazolo[4,3-c]thiopyrano[3,2-c][1,2]benzooxathiin 4,4-Dioxide **(XVIII)**.

A mixture of **XVI** (0.5 g, 1.5 mmole) and hydroxylamine hydrochloride (0.22 g, 3.2 mmole) in acetic acid (20 ml) was heated on an oil-bath at 160°C for 15 min. The solution was cooled and the solid that was obtained was filtered (0.28 g, 61.7% yield) and recrystallized from acetic acid, mp 206-208°C; ^{1}H-NMR (DMSO-d_6): δ 4.48 (s, 2H, SCH_2) and 8.70 (s, 1H, isoxazole proton). Anal. Calcd for $C_{12}H_7NO_4S_2$: C, 49.15; H, 2.39; N, 4.78. Found: C, 48.91; H, 2.35; N, 4.68.

2-Acetyl-11H-pyrrolo[3,4-c]thiopyrano[3,2-c][1,2]benzooxathiin 4,4-Dioxide **(XIX)**.

To a solution of glycine (0.56 g, 7.5 mmole) and potassium hydroxide (0.42 g, 7.5 mmole) in dry methanol (60 ml) was added enamino ketone **XVI** (2.0 g, 6.2 mmole). The resulting mixture was

refluxed under nitrogen for 2 h and worked up by the previously reported procedure.[1] Recrystallized from acetic acid, mp 202-204°C (0.3 g, 14.5% yield); ^{1}H-NMR ($CDCl_3$): δ 2.55 (s, 3H, $COCH_3$), 4.00 (s, 2H, SCH_2) and 7.80 (s, 2H, pyrrole protons). Anal. Calcd for $C_{15}H_{11}NO_4S_2$: C, 54.05; H, 3.30; N, 4.20. Found: C, 53.88; H, 3.10; N, 3.99.

3-Bromo-3,4-dihydro-4-oxo-2H-thiopyrano[3,2-c][1,2]benzooxathiin 5,5-Dioxide (**XX**).

By same procedure carried out for **XV**. Crystallized from acetic acid, mp 208-209°C (77.2 % yield); ^{1}H-NMR (DMSO-d_6): δ 3.85 (dd, 1H, J=6 and 15 Hz, SCH_2CH), 4.32 (dd, 1H,J=3 and 15 Hz, SCH_2CH) and 5.22 (dd, 1H, J=3 and 6 Hz, SCH_2CH). Anal. Calcd for $C_{11}H_7BrO_4S_2$: C, 38.05; H, 2.02. Found: C, 37.85; H, 1.90.

2-Methyl-11H-thiazolo[5,4-c]thiopyrano[3,2-c][1,2]benzooxathiin 4,4-Dioxide (**XXI**).

To a solution of **XX** (5.0 g, 1.4 mmole) in DMF (10 ml) was added thioacetamide (0.22 g, 2.9 mmole) and the mixture was refluxed for 2 h. After cooling the reaction mixture was poured into water and the collected precipitate (0.5 g) purified by silica gel column chromatography (eluent cyclohexane/ chloroform 1:1) it was recrystallized from acetic acid, mp 200-202°C (21.5% yield); ^{1}H-NMR ($CDCl_3$): δ 2.72 (s, 3H, CH_3) and 4.21 (s, 2H, SCH_2). Anal. Calcd for $C_{13}H_9NO_3S_3$: C, 48.30; H, 2.79; N, 4.33. Found: C, 48.01; H, 2.71; N, 4.02.

2-Amino-11H-thiazolo[5,4-c]thiopyrano[3,2-c][1,2]benzooxathiin 4,4-Dioxide (**XXII**).

By same procedure for **XXI**, using thiourea. It was recrystallized from acetic acid, mp 256-258°C (42.8% yield); ^{1}H-NMR (DMSO-d_6): δ 4.35 (s, 2H, SCH_2) and 7.30 (s, 2H, NH_2). Anal. Calcd for $C_{12}H_8N_2O_3S_3$: C, 44.44; H, 2.47; N, 8.64. Found: C, 44.09; H, 2.30; N, 8.55.

4-Oxo-4H-thiopyrano[3,2-c][1,2]benzooxathiin 5,5-Dioxide (**XXIII**).

By same procedure reported above for **XXI** and **XXII**, using urea. It was recrystallized from acetic acid, mp 218-220°C (52.2% yield); ^{1}H-NMR (DMSO-d_6): δ 7.40 and 8.73 (d, 2H, J=10.5 Hz, H-2 and H-3). Anal. Calcd for $C_{11}H_6O_4S_2$: C, 49.62; H, 2.26. Found: C, 49.30; H, 2.18.

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