

7,11-Dithiaazasteroid Analogues (2a)

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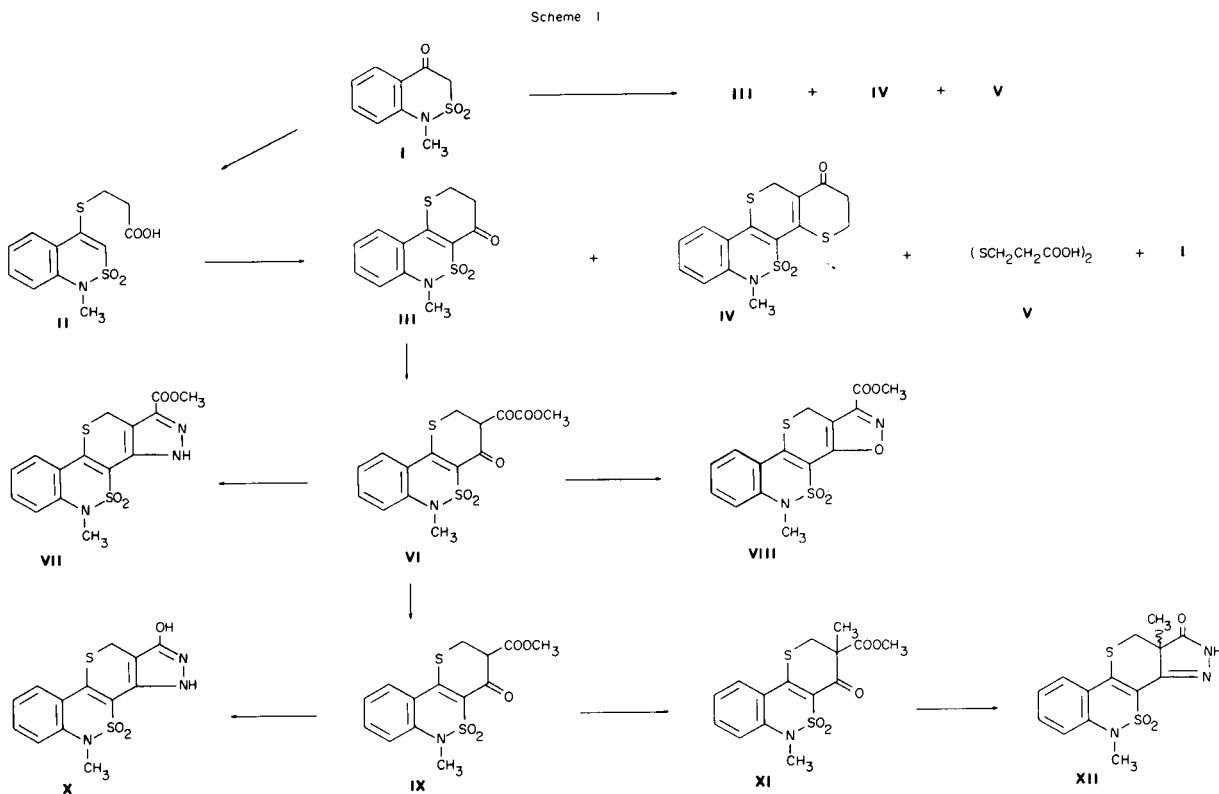
Synthesis of the title compounds has been achieved starting with the new tricyclic ring, 6-methyl-4-oxo-3,4-dihydro-2*H*,6*H*-thiopyrano[3,2-*c*][2,1]benzothiazine 5,5-dioxide (II). This compound was converted to the glyoxylate VI, the β -ketoester IX, a difluoride complex XIII and an enamino ketone XXIV which, by hydrazine, hydroxylamine and glycine treatment, gave 7,11-dithiaazasteroid analogues. Some unexpected products were also obtained from the ketone XVIII and the β -diketone XIX by treatment with chloroacetone and hydrazine respectively.

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Although there has been a great deal of interest in the synthesis of heterocyclic steroids, in view of their biological properties, no report on the synthesis of dithiaazasteroids has yet been made apart from our recent report on the first 6,11-dithiaazasteroids (3). We wish to report the synthesis of the 7,11-dithiaazasteroid analogues, in which the 2,1-benzothiazine moiety forms AB rings whereas the thiopyrane ring forms the C ring of the steroidal skeleton which also carries a 6-methyl substituent. The introduction of a 6-methyl group in steroids has been known to furnish biologically interesting properties (4). The synthetic approach to 7,11-dithiaazasteroids was begun by incorporating a thiopyrane ring to 1-methyl-

1*H*-2,1-benzothiazin-4(3*H*)-one 2,2-dioxide (I) (5), followed by reaction with 3-mercaptopropionic acid, by a procedure previously employed by us (3) as a route to the key ketone III.

Nevertheless, in this case we have found that the treatment of the intermediate acid II with sulfuric acid produced a mixture of four components which were identified as 6-methyl-4-oxo-3,4-dihydro-2*H*-6*H*-thiopyrano[3,2-*c*][2,1]benzothiazine 5,5-dioxide (III) (49%), an unexpected ketone I (23%), a homosteroid IV (8.6%) together with the disulfide V (9.5%). The formation of IV which was rationalized by the subsequent reaction of III with 3-mercaptopropionic acid yielded *in situ* in sulfuric acid cyclization of



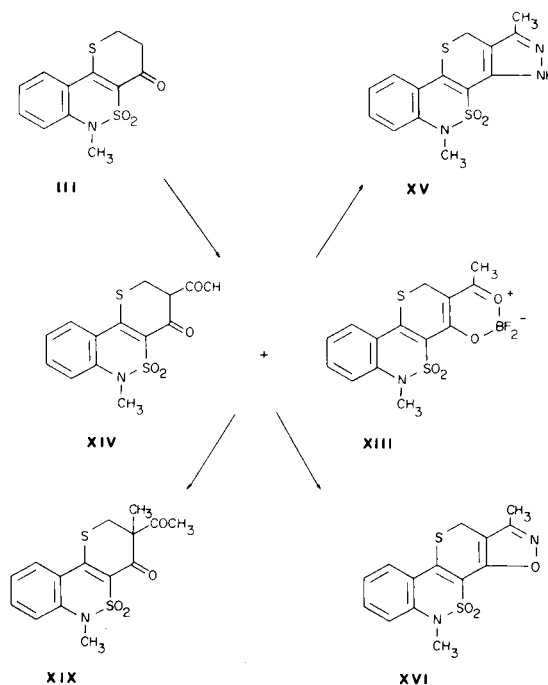
II, is contrary to what we observed in the synthesis of 4-oxo-3,4-dihydro-2*H*,5*H*-thiopyrano[3,2-*c*][1]benzothiopyrano 6,6-dioxide (6). In fact, in the latter case, the reaction of 3-mercaptopropionic acid on benzothiopyrane ketone took place only after oxidation of thiopyranosulphur to sulfoxide. This evidence induced us to attempt the reaction of the starting ketone with 3-mercaptopropionic acid but we observed that the reaction in sulfuric acid produced a mixture of four components which, on separation by column chromatography, furnished III in 21.5% yield. On the contrary cyclization with polyphosphoric acid gave III (56.7%) and IV (31.1%) which could be separated by fractional crystallization.

The successive step consisted in the preparation, by standard procedures, of the glyoxylate (VI) and the difluoride complex (XIII) intermediates, which we used to construct the heterocyclic D ring in the steroidal system. Oxaloylation of ketone III presented many difficulties due to its insolubility in the reaction solvent. It has been found that the solvent in this reaction plays an important role; in xylene, diglyme, pyridine, DMSO, under various conditions, either the reaction failed to occur or the yields were very poor. In nitrobenzene however compound VI was produced in 49% yield. The glyoxylate (VI) furnished 5-methyl-1-carbomethoxy-5,11-dihydro-3*H*-pyrazolo[4,3-*c*]thiopyrano[3,2-*c*][2,1]benzothiazine 4,4-dioxide (VII) and 5-methyl-1-carbomethoxy-5*H*,11*H*-isoxazole[4,5-*c*]thiopyrano[3,2-*c*][2,1]benzothiazine 4,4-dioxide (VIII) by condensation in acetic acid with hydrazine hydrate and hydroxylamine hydrochloride respectively. Compound VI was converted by decarbonylation to the β -ketoester IX which reacted with hydrazine hydrate affording 5-methyl-1-hydroxy-5,11-dihydro-3*H*-pyrazolo[4,3-*c*]thiopyrano[3,2-*c*][2,1]benzothiazine 4,4-dioxide (X) with no C=O absorption in the ir spectrum and an exchangeable proton at δ 12.4 attributable to OH in the pmr spectrum (Ferric chloride test was positive).

The direct carbomethoxylation of III with dimethyl carbonate in nitrobenzene was attempted under basic conditions but a complete failure of the reaction was observed producing a thiopyrano ring cleavage to the acid II. The β -ketoester IX by treatment at room temperature with sodium methoxide and methyl iodide was converted to 3,6-dimethyl-3-carbomethoxy-4-oxo-3,4-dihydro-2*H*,6*H*-thiopyrano[3,2-*c*][2,1]benzothiazine 5,5-dioxide (XI) which on heating with ethanolic solution of hydrazine hydrate, gave racemic 6-methyl-6,15,16-triaza-7,11-dithia-1,3,5,8,14-estrápentaen-17-one 7,7-dioxide (XII) whose structure is in agreement with pmr and ir data. (Scheme 1).

The difluoride complex XIII was obtained as a mixture with the β -diketone XIV by reaction with acetic anhydride and boron trifluoride etherate (7). The compounds 1,5-dimethyl-5,11-dihydro-3*H*-pyrazolo[4,3-*c*]thiopyra-

Scheme 2

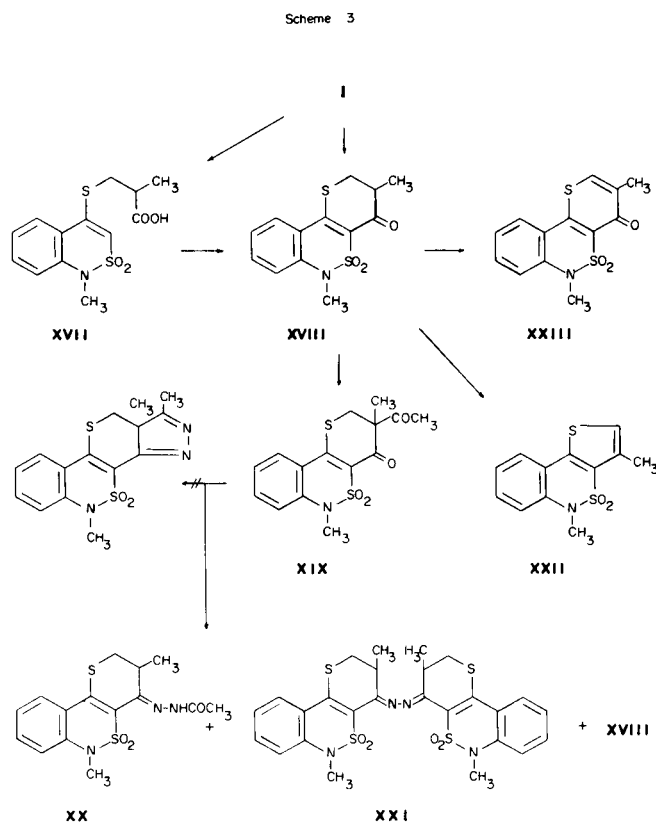


no[3,2-*c*][2,1]benzothiazine 4,4-dioxide (XV) and 1,5-dimethyl-5*H*,11*H*-isoxazole[4,5-*c*]thiopyrano[3,2-*c*][2,1]benzothiazine 4,4-dioxide (XVI) were synthesized by reacting the difluoride complex XIII with hydrazine hydrate and hydroxylamine hydrochloride respectively. (Scheme 2).

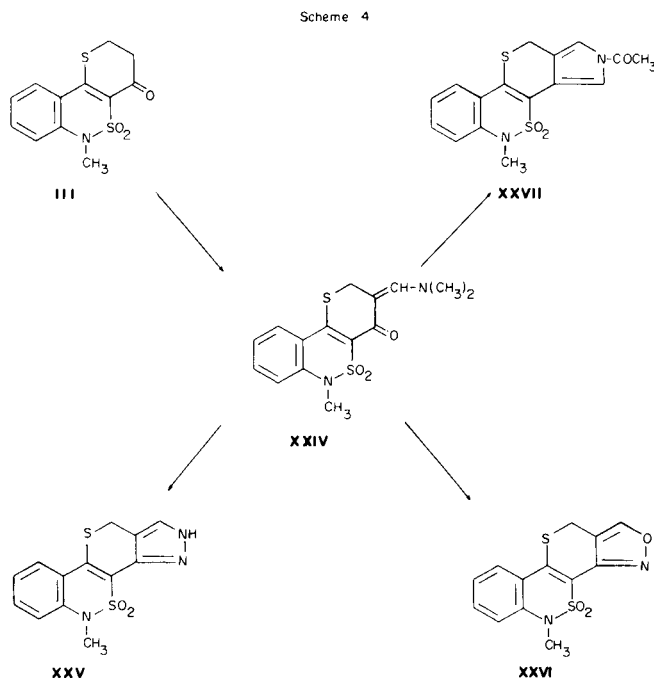
Attempts to introduce a methyl group at C-3 of the β -diketone XIV, under different conditions, were unsuccessful. An alternative route to 3-methyl- β -diketone XIX was therefore sought. The route selected involved the preparation of 3,6-dimethyl-4-oxo-3,4-dihydro-2*H*,6*H*-thiopyrano[3,2-*c*][2,1]benzothiazine 5,5-dioxide (XVIII) and its acetylation at C-3. We obtained the α -methylketone XVIII alone from the starting ketone I by acid catalyzed reaction with β -mercaptoisobutyric acid and subsequent cyclization of intermediate acid XVII in sulfuric acid or directly by reaction of I with β mercaptoisobutyric acid in sulfuric acid. Treatment of XVIII with acetic anhydride and boron trifluoride etherate gave XIX, which however, unexpectedly furnished a mixture of three products by reaction with hydrazine hydrate either in acetic or ethanolic solution. These products were separated by column chromatography on silica gel and identified as the dimer XXI, a hydrazinyl derivative XX and the ketone XVIII. In this connection the acetyl group of XIX was, unfortunately, a leaving group whether in acid or basic conditions thus impeding the reaction we had hypothesized. Subsequently, the bromination of XVIII, by pyridine hydrobromide perbromide (8), was also attempted in order to obtain a useful intermediate, but bromination was followed by the im-

mediate elimination of hydrobromic acid to give only the aromatic α -methylketone XXIII. We then thought of exploiting XVIII to obtain a cyclopentanone in D ring of heterosteroid skeleton through acylation by propargyl bromide (9), but very small yields of unidentifiable products were obtained. On the other hand, the direct reaction with chloroacetone, under basic conditions, unexpectedly furnished a product mp 125° which did not exhibit any C=O band in the ir spectrum while it showed a quartet at δ 6.92 attributable to a vinylic proton, a doublet at δ 2.52 for methyl group and absence of the signal for S-CH₂ group in pmr spectrum deuteriochloroform. On the basis of the above observations and of the parent ion peak at m/e 265 in the mass spectrum which indicated molecular formula C₁₂H₁₁NO₂S₂, the product was identified as 3,4-dimethylthieno[3,2-c][2,1]-benzothiazine 4,4-dioxide (XXII). (Scheme 3).

The formation of compound XXII demonstrates a ring contraction of the thiopyrano ring to thiophene as was observed for the ring contraction of thiochromans to benzo[*b*]thiophenes under different conditions (10). Finally XXV and XXVI were synthesized by treatment of hydrazine hydrate and hydroxylamine hydrochloride respectively with enamine ketone XXIV obtained from III on reaction with dimethylformamide dimethylacetal while base-catalyzed reaction of XXIV with glycine and acetic anhydride according to the procedure of Zav'yalov (11),



furnished 5-methyl-2-acetyl-5*H*,11*H*-pyrrolo[4,3-*c*]thiopyrano[3,2-*c*][2,1]benzothiazine 4,4-dioxide (XXVII). (Scheme 4).



EXPERIMENTAL

Melting points were determined in capillary tubes (Electrothermal melting point apparatus) and are uncorrected. The ir spectra were measured with a Perkin-Elmer (model 247) spectrophotometer in chloroform unless otherwise specified. The pmr spectra were obtained with a JOEL Model C60 HL 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 F₂₅₄). The chromatographic separations have been carried out on silica gel Merck (Kieselgel 60,70-230 mesh) column.

β -(1-Methyl-1*H*-2,1-benzothiazin-4-ylthio-2,2-dioxide)propionic Acid (II).

The reaction of 1-methyl-1*H*-2,1-benzothiazin-4(3*H*)-one 2,2-dioxide (5) (0.100 mole), 3-mercaptopropionic acid (0.100 mole) and *p*-toluenesulfonic acid monohydrate (0.005 mole) by previously reported procedure (3) gave II, mp 188-190° (64.2% yield).

Anal. Calcd. for C₁₂H₁₃NO₂S₂: C, 48.16; H, 4.35; N, 4.68. Found: C, 48.24; H, 4.28; N, 4.71.

Cyclization of II With Sulfuric Acid.

6-Methyl-4-oxo-3,4-dihydro-2*H*,6*H*-thiopyrano[3,2-*c*][2,1]benzothiazine 5,5-Dioxide (III); 6-Methyl-1-oxo-2,3-dihydro-1*H*,6*H*,12*H*-thiopyrano[3,2-*c*]thiopyrano[3,2-*c*][2,1]benzothiazine 5,5-dioxide (IV).

The acid (II) (17.6 g) was added to 96% sulfuric acid (90 ml) and the mixture allowed to stand at room temperature overnight. The resulting red solution was poured into crushed ice and the solid which separated was filtered, washed well with 10% aqueous sodium carbonate and then with water. The crude product was recrystallized from acetic acid to give 6.73 g of III, mp 254-255° (40.7% yield); pmr (trifluoroacetic acid): δ 3.40 (A₂) and 3.20 (B₂) [m, 4H (A₂B₂ system), CH₂CH₂] and 3.53 (s, 3H, N-CH₃); ir: 1665 cm⁻¹ (C=O).

Anal. Calcd for C₁₂H₁₁NO₂S₂: C, 51.24; H, 3.91; N, 4.98. Found: C, 50.98; H, 3.93; N, 5.06.

Acidification of the combined alkaline washings gave 1.2 g (9.8 %) of the disulphide V. Concentration of the mother liquor after crystallization produced 7.50 g of very impure material (the tlc exhibited three evident spots) which on separation by chromatography on silica gel eluting with cyclohexane-ethyl acetate (98/2), gave additional III (9%), the ketone I (23%) and the homosteroid IV (8.54%). Compound IV was recrystallized from acetic acid, mp 215-217°; pmr (deuteriochloroform): δ 3.22 (A₂) and 2.88 (B₂) [m, 4H (A₂B₂ system) CH₂-CH₂], 3.57 (s, 3H, N-CH₃) and 3.90 (s, 2H, S-CH₂); ir: 1630 cm⁻¹ (C=O); ms: m/e 352 [M⁺].

Anal. Calcd for C₁₅H₁₃NO₃S₂: C, 51.28; H, 3.70; N, 3.98. Found: C, 51.03; H, 3.74; N, 3.91.

Treatment of I With Mercaptopropionic Acid in Polyphosphoric Acid.

Polyphosphoric acid (30 g) was heated to 80° in a beaker. Ketone I (5 g) together with 3-mercaptopropionic acid (5 g) was added and the mixture was maintained at that temperature for 2 hours. After cooling, the dark-red syrup was poured into crushed ice and the yellowish solid which separated was filtered and washed, first with 10% aqueous sodium carbonate and then with water, to yield 7.2 g of crude product which by fractionated crystallization from acetic acid gave III (56.7%) and IV (31.1%).

6-Methyl-3-carbomethoxycarbonyl-4-oxo-3,4-dihydro-2H,6H-thiopyrano[3,2-c][2,1]benzothiazine 5,5-Dioxide (VI).

Ketone III (4 g, 0.014 mole) was dissolved in 200 ml of anhydrous nitrobenzene and slowly added under nitrogen to a mixture of sodium methoxide (1.52 g, 0.028 mole) and dimethyl oxalate (3.35 g, 0.028 mole) in 100 ml of anhydrous nitrobenzene. As the condensation proceeded, a reddish-brown solid gradually precipitated. After stirring the reaction mixture for 30 minutes at room temperature, tlc indicated the disappearance of starting ketone. Then the mixture was hydrolyzed with ice-cold water. To the emulsion produced was added a saturated solution of sodium chloride and the nitrobenzene layer was separated and washed with 10% sodium hydroxide. Acidification of the combined alkaline aqueous solutions gave a yellowish product which was collected, washed several times (water) and recrystallized from ethyl acetate, mp 165-167° (59.6% yield); pmr (deuteriochloroform): δ 3.50 (s, 3H, N-CH₃), 3.92 (s, 3, COOCH₃), 4.38 (s, 2H, S-CH₂) and 14 (broad s, 1H, OH); ir: 1600 (chelated C=O), 1730 (ester C=O) and 3550 cm⁻¹ (chelated OH).

Anal. Calcd. for C₁₅H₁₃NO₄S₂: C, 49.04; H, 3.54; N, 3.81. Found: C, 49.11; H, 3.69; N, 3.80.

5-Methyl-1-carbomethoxy-5,11-dihydro-3H-pyrazolo[4,3-c]thiopyrano[3,2-c][2,1]benzothiazine 4,4-Dioxide (VII).

The glyoxylate VI (1.1 g, 0.003 mole) was dissolved in 20 ml of acetic acid and 98% hydrazine hydrate (0.5 ml) was added. The resulting solution was refluxed for 30 minutes. On cooling, a yellow crystalline precipitate was separated. The product was filtered, washed with methanol and recrystallized from acetic acid, mp 285-286° (0.42 g, 38.9% yield); pmr (trifluoroacetic acid): δ 3.60 (s, 3H, N-CH₃), 4.12 (s, 3H, COOCH₃) and 4.50 (s, 2H, S-CH₂).

Anal. Calcd. for C₁₅H₁₃N₃O₄S₂: C, 49.58; H, 3.58; N, 11.57. Found: C, 49.51; H, 3.63; N, 11.63.

5-Methyl-1-carbomethoxy-5H,11H-isoxazolo[4,5-c]thiopyrano[3,2-c][2,1]benzothiazine 4,4-Dioxide (VIII).

To a solution of VI (0.300 g, 0.0008 mole) in acetic acid (10 ml) was added hydroxylamine hydrochloride (0.120 g, 0.0017 mole). The reaction mixture was heated in an oil-bath at 180° for 15 minutes, then allowed to cool at room temperature. The yellow solid that separated was collected by filtration, washed with ethanol and recrystallized from acetic acid, mp 244-245° (0.180 g, 62% yield); pmr (trifluoroacetic acid): δ 3.61 (s, 3H, N-CH₃), 4.11 (s, 3H, COOCH₃) and 4.45 (s, 2H, S-CH₂).

Anal. Calcd. for C₁₅H₁₂N₂O₄S₂: C, 49.45; H, 3.29; N, 7.69. Found: C, 49.47; H, 3.33; N, 7.81.

6-Methyl-3-carbomethoxy-4-oxo-3,4-dihydro-2H,6H-thiopyrano[3,2-c][2,1]benzothiazine 5,5-Dioxide (IX).

The decarbonylation procedure of glyoxylate VI was identical to that

reported previously (3) except that acetone extracted was chromatographed on silica gel (cyclohexane-ethyl acetate 9/1) to give IX in 69% yield, which was recrystallized from ethyl acetate, mp 163-165°; pmr (trifluoroacetic acid): δ 3.60 (s, 3H, N-CH₃), 3.94 (s, 3H, COOCH₃) and 3.65-4.30 (complex m, 3H, CH₂-CH); ir: 1670 (conjugated C=O), 1735 cm⁻¹ (ester C=O).

Anal. Calcd. for C₁₄H₁₃NO₃S₂: C, 49.56; H, 3.83; N, 4.13. Found: C, 49.61; H, 3.80; N, 4.27.

5-Methyl-1-hydroxy-5,11-dihydro-3H-pyrazolo[4,3-c]thiopyrano[3,2-c][2,1]benzothiazine 4,4-Dioxide (X).

To the solution of IX (0.680 g, 0.002 mole) in acetic acid (10 ml) was added 98% hydrazine hydrate (0.35 ml). The reaction mixture was refluxed for 15 minutes and then allowed to cool. The yellow crystalline solid formed quickly was filtered and recrystallized from acetic acid, mp 292-294° (40% yield); pmr (DMSO-d₆): δ 3.42 (s, 3H, N-CH₃), 4.06 (s, 2H, S-CH₂) and 12.4 (broad s, 1H, OH); ir (nujol): 3400 cm⁻¹ (NH), no (C=O) band.

Anal. Calcd. for C₁₃H₁₁N₃O₃S₂: C, 48.60; H, 3.43; N, 13.08. Found: C, 48.66; H, 3.41; N, 12.96.

3,6-Dimethyl-3-carbomethoxy-4-oxo-3,4-dihydro-2H,6H-thiopyrano[3,2-c][2,1]benzothiazine 5,5-Dioxide (XI).

To a solution of sodium methoxide (0.5 g sodium in 80 ml of dry methanol) was added IX (0.9 g) and methyl iodide (10 ml). The mixture was stirred for 12 hours at room temperature followed by boiling for 3 hours. After cooling, the mixture was diluted with water and acidified with acetic acid. The acid solution was extracted with chloroform and the combined extracts were washed with water and dried over sodium sulphate to give 1.1 g of an oily residue which was chromatographed on silica gel. Elution with benzene-ethyl acetate (9.8/0.2) yielded XI which was recrystallized from ethyl acetate, mp 165-167° (0.310 g, 33%); pmr (deuteriochloroform): 1.60 (s, 3H, CH₃ at C-3), 3.70 (A) and 3.34 (B) [q, 2H (AB system), J = 15 Hz, S-CH₂], 3.50 (s, 3H, N-CH₃) and 3.75 (s, 3H, COOCH₃).

Anal. Calcd. for C₁₅H₁₅NO₃S₂: C, 50.99; H, 4.24; N, 3.96. Found: C, 51.07; H, 4.24; N, 3.92.

Racemic 6-Methyl-6,15,16-triaza-7,11-dithia-1,3,5,8,14-estrpentaen-17-one 7,7-Dioxide (XII).

The β ketoester XI (0.300 g) was dissolved in ethanol (20 ml) and 0.3 ml 98% hydrazine hydrate was added and the mixture boiled for 4 hours. Cooling produced a crystalline precipitate which was filtered and recrystallized from acetic acid, mp 339-340° (0.070 g, 24% yield); pmr (DMSO-d₆): δ 1.35 (s, 3H, CH₃ at C-13), 3.42 (s, 3H, N-CH₃), 3.61 (A) and 3.28 (B) [q, 2H (AB system), J = 13.5 Hz, S-CH₂] and 11.7 (broad s, 1H, NH); ir (nujol): 3320 (NH), 1720 cm⁻¹ (NH-C=O).

Anal. Calcd. for C₁₄H₁₃N₃O₃S₂: C, 50.15; H, 3.88; N, 12.54. Found: C, 50.15; H, 3.94; N, 12.41.

3,3-Difluoro-1,6-dimethyl-3H,6H,11H-1,3,2-dioxaborino[5,6-c]thiopyrano[3,2-c][2,1]benzothiazine 5,5-Dioxide (XIII); 6-Methyl-3-acetyl-4-oxo-3,4-dihydro-2H,6H-thiopyrano[3,2-c][2,1]benzothiazine 5,5-Dioxide (XIV).

To a solution of III (2.81 g, 0.010 mole) in acetic anhydride (50 ml) was added boron trifluoride etherate (4.26 g, 0.030 mole). The mixture, after heating on a steam bath for 1 hour, was cooled and the orange precipitate was filtered. The crude product, that tlc showed to consist of two main components, was extracted with boiling ethanol at reflux temperature. The ethanolic extract yielded XIV (25%) which was recrystallized from ethanol, mp 193-194°; pmr (DMSO-d₆): δ 2.30 (s, 3H, COCH₃), 3.40 (s, 3H, N-CH₃), and 4.08 (s, 2H, S-CH₂).

Anal. Calcd. for C₁₄H₁₃NO₄S₂: C, 52.01; H, 4.02; N, 4.33. Found: C, 52.16; H, 4.07; N, 4.21.

The residue after extraction with ethanol yielded compound XIII after recrystallization from acetic acid mp 267-270° (70.8 yield).

Anal. Calcd. for C₁₄H₁₂BF₂NO₄S₂: C, 45.30; H, 3.24; N, 3.77. Found: C, 45.53; H, 3.33; N, 3.56.

1,5-Dimethyl-5,11-dihydro-3*H*-pyrazolo[4,3-*c*]thiopyrano[3,2-*c*][2,1]benzothiazine 4,4-Dioxide (XV).

The crude mixture of XIII and XIV (0.500 g) and 98% hydrazine hydrate (0.4 ml) in acetic acid (50 ml) was refluxed for 7 hours. Evaporation of two-thirds of the solvent furnished a crystalline solid (0.310 g) and recrystallization from acetic acid afforded XV, mp 274-276° (69.5% yield); pmr (DMSO-*d*₆): δ 2.25 (s, 3H, CH₃), 3.43 (s, 3H, N-CH₃), 4.14 (s, 2H, S-CH₂) and 12.60 (s, 1H, NH).

Anal. Calcd. for C₁₄H₁₃N₃O₂S₂: C, 53.65; H, 4.07; N, 13.16. Found: C, 52.44; H, 4.16; N, 13.24.

1,5-Dimethyl-5*H*,11*H*-isoxazolo[4,5-*c*]thiopyrano[3,2-*c*][2,1]benzothiazine 4,4-Dioxide (XVI).

The crude mixture of XIII and XIV (0.500 g) and hydroxylamine hydrochloride (0.250 g) in acetic acid (30 ml) was heated on an oil-bath at 180° for 45 minutes. The yellow solution was allowed from cool and the solid that separated was collected and recrystallized from acetic acid, mp 204-205° (70% yield); pmr (DMSO-*d*₆): δ 2.28 (s, 3H, CH₃), 3.45 (s, 3H, N-CH₃) and 4.25 (s, 2H, S-CH₂).

Anal. Calcd. for C₁₄H₁₃N₂O₃S₂: C, 52.50; H, 3.75; N, 8.75. Found: C, 52.31; H, 3.88; N, 8.96.

β-(1-Methyl-1*H*,2,1-benzothiazin-4-ylthio 2,2-Dioxide)isobutyric Acid (XVII).

By an identical procedure for II, using β-mercaptoisobutyric acid (12), XVII was obtained which was recrystallized from aqueous ethanol, mp 173-174° (57.9% yield).

Anal. Calcd. for C₁₃H₁₃NO₄S₂: C, 49.84; H, 4.79; N, 4.47. Found: C, 50.02; H, 4.91; N, 4.41.

3,6-Dimethyl-4-oxo-3,4-dihydro-2*H*,6*H*-thiopyrano[3,2-*c*][2,1]benzothiazine 5,5-Dioxide (XVIII).

Method A. By Cyclization of the Acid XVII.

The reaction mixture was worked up in an identical fashion to III. The α-methyl ketone XVIII that was obtained was recrystallized from acetic acid, mp 202-204° (48.6% yield); pmr (trifluoroacetic acid): δ 1.45 (d, 3H, J = 6 Hz, CH₃), 3.0-3.5 (complex m, 3H, CH₂-CH) and 3.58 (s, 3H, N-CH₃).

Anal. Calcd. for C₁₃H₁₃NO₃S₂: C, 55.93; H, 4.41; N, 4.75. Found: C, 55.99; H, 4.30; N, 4.97.

Method B. By Treatment of I With β-Mercaptoisobutyric Acid in Sulfuric Acid.

To the solution of ketone I (4.22 g, 0.020 mole) in 96% sulfuric acid (10 mole) was added β-mercaptoisobutyric acid (2.12 g, 0.020 mole) and the mixture allowed to stand at room temperature overnight. It was then poured onto ice water and the precipitate was collected to give XVIII in 70% yield.

3,6-Dimethyl-3-acetyl-4-oxo-3,4-dihydro-2*H*,6*H*-thiopyrano[3,2-*c*][2,1]benzothiazine 5,5-Dioxide (XIX).

To a solution of XVIII (0.600 g, 0.002 mole) in acetic anhydride (10 ml) was added boron trifluoride etherate (0.600 g, 0.004 mole). The reaction mixture was stirred at room temperature for 2 hours and then diluted with hexane (20 ml) to give an oily product. On standing, the oily product crystallized and an analytical sample was recrystallized from ethanol, mp 171-173° (29.3% yield); pmr (trifluoroacetic acid): 1.96 (s, 3H, CH₃), 2.44 (s, 3H, COCH₃) δ 3.50 (s, 3H, N-CH₃) and 3.60 (broad s, 2H, S-CH₂).

Anal. Calcd. for C₁₅H₁₅NO₄S₂: C, 53.41; H, 4.45; N, 4.15. Found: C, 53.61; H, 4.39; N, 4.17.

Reaction of XIX With Hydrazine Hydrate.

A mixture of XIX (0.340 g, 0.001 mole) and 98% hydrazine hydrate (0.2 ml) in acetic acid (10 ml) was refluxed and after 20 minutes an orange precipitate was obtained (13). Crystallization of the precipitate from acetic gave 0.100 g (16% yield) of 4,4'-azino-bis(3,6-dimethyl-3,4-dihydro-2*H*,6*H*-thiopyrano[3,2-*c*][2,1]benzothiazine 5,5-dioxide (XXI), mp

335-336°; pmr (trifluoroacetic acid): δ 1.85 (d, 3H, J = 7.5 Hz, CH₃), 3.36 (s, 3H, N-CH₃) and 3.20-3.92 (complex m, 3H, S-CH₂-CH); ir (nujol): no (C=O) band; ms: m/e 587 [M⁺].

Anal. Calcd. for C₂₆H₂₆N₄O₄S₄: C, 53.24; H, 4.43; N, 9.55. Found: C, 52.42; H, 4.62; N, 9.36.

By concentration of the acetic acid filtrate and additional solid was separated which was chromatographed on silica gel (benzene-ethyl acetate 9.8/0.2) to give XVIII (0.076 g, 24.2% yield) and 0.132 g (35.6% yield) of 3,6-dimethyl-4-acetohydrazone-3,4-dihydro-2*H*,6*H*-thiopyrano[3,2-*c*][2,1]benzothiazine 5,5-dioxide (XX). It was recrystallized from ethanol, mp 257-258°; pmr (DMSO-*d*₆): δ 1.12 (d, 3H, J = 6.7 Hz, CH₃), 1.9 (s, 3H, COCH₃), 3.38 (s, 3H, N-CH₃), 3.2-3.92 (complex m, 3H, CH₂-CH) and 10.9 (broad s, 1H, NH).

Anal. Calcd. for C₁₅H₁₇N₃O₃S₂: C, 51.28; H, 4.48; N, 11.97. Found: C, 51.50; H, 4.96; N, 11.69.

Attempted Preparation of Acetonyl Derivative XVIII.

To a solution of sodium methoxide (0.450 g of sodium in 20 ml of dry methanol) was added 1.5 g (0.005 mole) of XVIII and the mixture was refluxed for 15 minutes. The evaporation of the reaction mixture *in vacuo* gave the sodium salt which was dissolved in dry DMSO (30 ml) and then chloroacetone (0.920 g, 0.01 mole) was added. The reaction mixture was stirred under nitrogen at room temperature overnight, then poured into water, acidified (2*N* hydrochloric acid) and extracted with chloroform. The combined chloroform layers were washed with water and dried over sodium sulfate to give 0.810 g of oily residue which was chromatographed on silica gel. Elution with benzene yielded 3,5-dimethylthieno[3,2-*c*][2,1]benzothiazine 4,4-dioxide (XXII) (0.600 g, 44.5% yield), which was recrystallized from hexane-cyclohexane, mp 124-125°; pmr (deuteriochloroform): δ 2.52 (d, 3H, CH₃), 3.46 (s, 3H, N-CH₃) and 6.92 (q, 1H, S-CH); ir: no (C=O) band; ms: m/e 265 [M⁺].

Anal. Calcd. for C₁₂H₁₁NO₂S₂: C, 54.34; H, 4.15; N, 5.28. Found: C, 54.51; H, 4.31; N, 5.20.

Attempted Bromination of XVIII.

Pyridine hydrobromide perbromide (1.6 g, 0.005 mole) was added to a solution of XVIII (0.600 g, 0.002 mole) in acetic acid (8 ml) and the mixture was stirred at 60° for 2 hours. Water was then added to the mixture and the resulting precipitate filtered and washed with water. Recrystallization from acetic acid gave 0.450 g (76.3% yield) of 3,6-dimethyl-4-oxo-4*H*,6*H*-thiopyrano[3,2-*c*][2,1]benzothiazine 5,5-Dioxide (XXIII), mp 279°; pmr (deuteriochloroform): 2.20 (d, 3H, CH₃), 3.46 (s, 3H, N-CH₃) and 7.44 (q, 1H, S-CH).

Anal. Calcd. for C₁₃H₁₁NO₃S₂: C, 53.24; H, 3.75; N, 4.78. Found: C, 53.51; H, 3.74; N, 4.72.

6-Methyl-3[(dimethylamino)methylene]-4-oxo-3,4-dihydro-2*H*,6*H*-thiopyrano[3,2-*c*][2,1]benzothiazine 5,5-Dioxide (XXIV).

To a solution of III (1.4 g, 0.005 mole) in 100 ml of dry toluene was added dimethylformamide dimethylacetal (10 ml) and refluxed for 1 hour under a Dean-Stark trap. The solution was cooled and the precipitate that formed was filtered and recrystallized from acetic acid, mp 243-244° (67.3% yield); pmr (DMSO-*d*₆): δ 3.19 [s, 6H, N(CH₂)₂], 3.32 (s, 3H, N-CH₃), 4.25 (s, 2H, S-CH₂) and 7.43 (s, 1H, CH).

Anal. Calcd. for C₁₅H₁₆N₂O₃S₂: C, 53.57; H, 4.76; N, 8.33. Found: C, 53.37; H, 4.95; N, 8.27.

5-Methyl-5,11-dihydro-2*H*-pyrazolo[4,5-*c*]thiopyrano[3,2-*c*][2,1]benzothiazine 4,4-Dioxide (XXV).

A solution of XXIV (0.500 g, 0.0015 mole) and 98% hydrazine hydrate (0.3 ml) was stirred at room temperature for 2 hours. The yellow precipitate that was formed was recrystallized from acetic acid, mp 245° (53% yield); pmr (DMSO-*d*₆): δ 3.45 (s, 3H, N-CH₃), 4.20 (s, 2H, S-CH₂), 7.64 (1H, t-like, pyrazole proton) and 13 broad s, 1H, NH exchangeable with deuterium oxide).

Anal. Calcd. for C₁₅H₁₁N₃O₂S₂: C, 51.15; H, 3.61; N, 13.77. Found: C, 50.98; H, 3.63; N, 13.51.

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

A mixture of XXIV (0.500 g, 0.0015 mole) and hydroxylamine hydrochloride (0.200 g, 0.003 mole) in acetic acid (10 ml) was heated on an oil-bath at 180° and refluxed continually for 15 minutes. The cool solution gave 0.320 g of XXVI, which was recrystallized from acetic acid, mp 205° (70.2% yield); pmr (DMSO-*d*₆): δ 3.55 (s, 3H, N-CH₃), 4.44 (s, 2H, S-CH₂) and 8.78 (s, 1H, isoxazole proton).

Anal. Calcd. for C₁₃H₁₀N₂O₃S₂: C, 50.98; H, 3.27; N, 9.15. Found: C, 51.07; H, 3.23; N, 9.17.

5-Methyl-2-acethyl-5*H*,11*H*-pyrrolo[4,3-*c*]thiopyrano[3,2-*c*][2,1]benzothiazine 4,4-Dioxide (XXVII).

Glycine (0.135 g, 0.0018 mole) and potassium hydroxide (0.100 g, 0.0018 mole) were dissolved in dry methanol (20 ml). The enamine ketone XXIV (0.500 g, 0.0015 mole) was added, and the resulting solution was heated at reflux temperature under nitrogen for 2 hours. After cooling, ether was added and the potassium salt that precipitated (very hygroscopic) was filtered and added to 70 ml of acetic anhydride. The suspension was heated at reflux temperature under nitrogen for 75 minutes and then concentrated *in vacuo*. The crystalline residue was washed with boiling ethanol and then recrystallized from acetic acid, mp 230° (39% yield); pmr (DMSO-*d*₆): δ 2.62 (s, 3H, COCH₃), 3.50 (s, 3H, N-CH₃), 4.15 (s, 2H, S-CH₂) and 7.20 (s, 2H, pyrrole protons).

Anal. Calcd. for C₁₆H₁₄N₂O₃S₂: C, 55.49; H, 4.05; N, 8.09. Found: C, 55.36; H, 4.07; N, 8.17.

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