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Synthesis of the title compounds has been achieved starting from 4-oxo-3,4-dihydro-2*H*,5*H*-thiopyrano[3,2-*c*][1]benzothiopyran 6,6-dioxide (III), which was converted to glyoxylate (IV), β -ketoester (V), difluoride complex (VII) and β -diketone (XII) gave with hydrazine, hydroxylamine and glycine ethyl ester several azadithiasteroid analogues.

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As part of a program on the area of steroid-related heterocyclic systems (2), we now report the synthesis of 6,11-dithiaazasteroidal analogues. Our first approach to the title compounds described herein was the synthesis of unknown precursor 4-oxo-3,4-dihydro-2*H*,5*H*-thiopyrano[3,2-*c*][1]benzothiopyran 6,6-dioxide (III) obtained from thiochroman-4-one 1,1-dioxide by an acid catalyzed reaction with 3-mercaptopropionic acid and subsequent cyclization in 96% sulphuric acid, a procedure previously employed in one route to 6,11-dithiaazasteroid analogues (3). The glyoxylate (IV) together to difluoride complex (VII), both key intermediates, were prepared by acylation of ketone (III) with dimethyl oxalate and sodium methoxide and by treatment with acetic anhydride and boron trifluoride etherate (4), respectively. The glyoxylate (IV), which in solution exists in the tautomeric enol form (5),

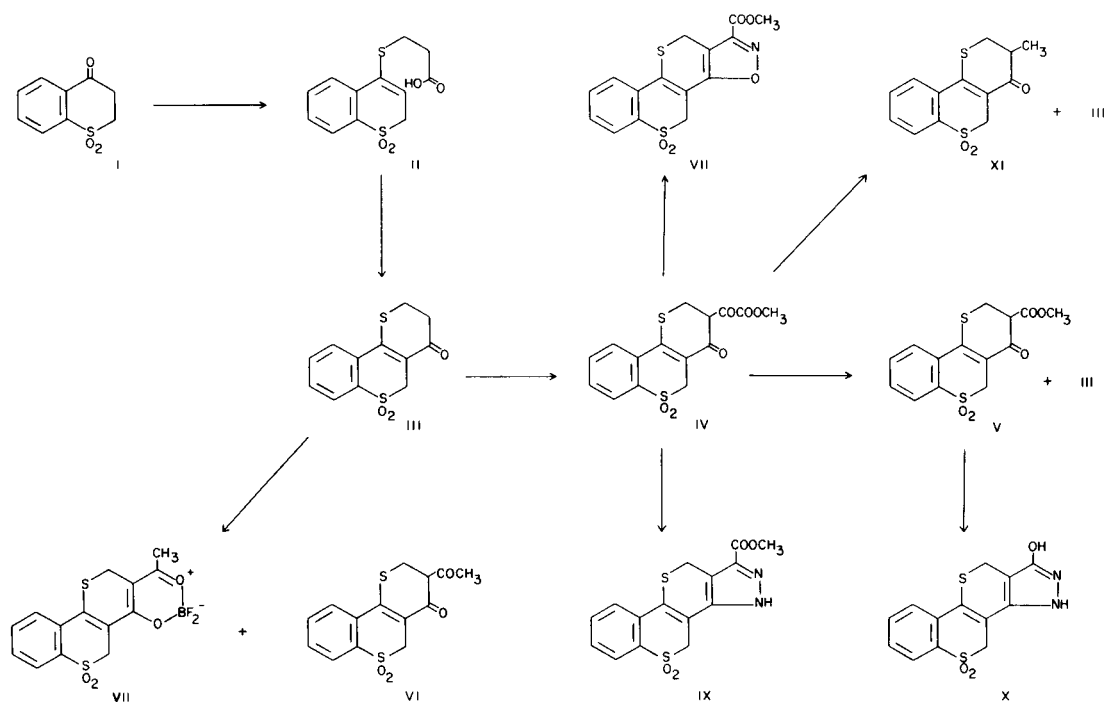
as indicated by ir and pmr spectra, reacts with hydroxylamine in acetic acid at 160° to give the 1-carbomethoxy-4*H*,11*H*-isoxazolo[4,5-*c*]thiopyrano[3,2-*c*][1]benzothiopyran 5,5-dioxide (VIII), while with hydrazine in acetic solution under milder conditions furnished the 1-carbomethoxy-3,11-dihydro-4*H*-pyrazolo[4,3-*c*]thiopyrano[3,2-*c*][1]benzothiopyran 5,5-dioxide (IX). Scheme 1.

Decarbonylation of IV on heating with soft glass powder gave in very poor yield (12%) the β -ketoester (V) (6) together with III.

Compound V on treatment with an acetic solution of hydrazine afforded 1-hydroxy-3,11-dihydro-4*H*-pyrazolo[4,3-*c*]thiopyrano[3,2-*c*][1]benzothiopyran 5,5-dioxide (X).

Attempts to introduce a methyl group at C-3 of the glyoxylate (IV), under different conditions, were unsuccessful. The mixture obtained from reaction of IV with

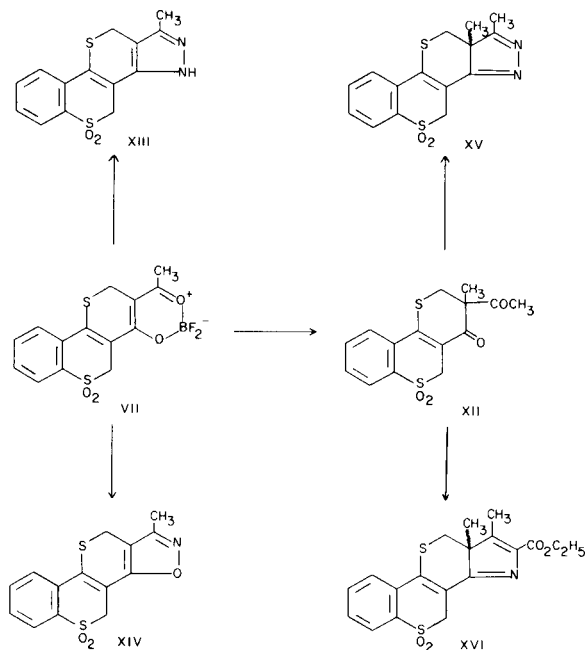
Scheme 1



methyl iodide and sodium methoxide was found to be mainly three products (tlc) which were separated by column chromatography on silica gel and identified as starting glyoxylate (IV), ketone (III) (22%) and 3-methyl-4-oxo-3,4-dihydro-2*H*,5*H*-thiopyrano[3,2-*c*][1]benzothiopyran 6,6-dioxide (XI) (42.3%). The pmr spectrum of the latter exhibits a complex multiplet for the protons at C-2 and C-3 and the methyl group appears as a doublet, thus confirming the assigned structure.

The boron complex intermediate (VII) directly on heating with acetic acid solutions of hydrazine and hydroxylamine gave 1-methyl-3,11-dihydro-4*H*-pyrazolo[4,3-*c*]thiopyran 5,5-dioxide (XIII) and 1-methyl-4*H*,11*H*-isoxazolo[4,5-*c*]thiopyrano[3,2-*c*]benzothiopyran 5,5-dioxide (XIV), respectively. Scheme 2.

Scheme 2



Finally, VII was converted with sodium methoxide and methyl iodide into 3-acetyl-3-methyl-4-oxo-3,4-dihydro-2*H*,5*H*-thiopyrano[3,2-*c*][1]benzothiopyran (XII), which with an acetic acid solution of hydrazine afforded racemic 17-methyl-15,16-diaza-6,11-dithia-1,3,5,8,14,16-estrahexaen 6,6-dioxide (XV) while with a pyridine solution of glycine ethyl ester furnished racemic 17-methyl-16-carbomethoxy-15-aza-6,11-dithia-1,3,5,8,14,16-estrahexaen 6,6-dioxide (XVI).

The pmr spectra of the reported compounds are in agreement with the assigned structures. However, in some cases the pmr spectra show for methylene protons α to a sulfone group a twofold behaviour. While the com-

pounds V, XI, XII, XV and XVI exhibit a well-defined AB system owing to the magnetic nonequivalence of these methylene protons in different solvents, for other ones no *geminal* coupling was observed and thus these protons appeared to be equivalent. This led us to findings that the electronic character of the substituent in the *peri* position, as observed for methylene protons adjacent to a sulfoxide function (7), plays an important role in determining the magnetic equivalence and nonequivalence of the methylene protons, producing a different molecular conformation.

EXPERIMENTAL

Melting points were determined in capillary tubes (Büchi melting point apparatus) and are uncorrected. Ir spectra were measured with a Perkin-Elmer (Model 247) spectrophotometer in chloroform unless otherwise specified. 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 (silica gel).

β -(2*H*-[1]Benzothiopyran-4-ylthiopropionic Acid 1,1-Dioxide (II).

A solution of thiochroman-4-one 1,1-dioxide (8) (19.6 g., 0.100 mole), 3-mercaptopropionic acid (13.8 g., 0.130 mole) and *p*-toluenesulfonic acid monohydrate (1 g., 0.0058 mole) in dry benzene (150 ml.) was refluxed for 12 hours under a Dean-Stark trap. The remaining procedure was similar to that reported (3) for analogous compound. Recrystallization of crude product from ethanol gave II, m.p. 121-123° (88.5% yield).

Anal. Calcd. for $C_{12}H_{12}O_4S_2$: C, 50.70; H, 4.22. Found: C, 50.79; H, 4.11.

4-Oxo-3,4-dihydro-2*H*,5*H*-thiopyrano[3,2-*c*][1]benzothiopyran 6,6-Dioxide (III).

The acid (II) (10 g.) was dissolved in 96% sulphuric acid (30 ml.) and the mixture was allowed to stand at room temperature overnight, then poured into crushed ice. The solid precipitate was filtered and washed first with 10% aqueous sodium carbonate and then with water. The crude product was purified with boiling ethyl acetate and successively recrystallized from acetic acid, m.p. 230-232° (64.5% yield); pmr (trifluoroacetic acid): δ 3.30 (A_2) and 3.18 (B_2) [m, 4*H* (A_2B_2 system), CH_2-CH_2] and 4.53 (s, 2*H*, SO_2-CH_2), ir: ν 1650 cm^{-1} (conjugated C=O).

Anal. Calcd. for $C_{12}H_{10}O_3S_2$: C, 54.13; H, 3.76. Found: C, 54.15; H, 3.91.

3-Carbomethoxycarbonyl-4-oxo-3,4-dihydro-2*H*,5*H*-thiopyrano[3,2-*c*][1]benzothiopyran 6,6-Dioxide (IV).

To a suspension of sodium methoxide (5.4 g., 0.10 mole) in dry pyridine (100 ml.) in a dry system under nitrogen was added a solution of dimethyl oxalate (11.8 g., 0.10 mole) in dry pyridine (70 ml.). Ketone (III) (13.3 g., 0.05 mole) in dry pyridine (200 ml.) was then added dropwise to the reaction mixture at room temperature. After the addition was completed, the reaction mixture was stirred for 5 hours and then diluted with ice-water and acidified with dilute hydrochloric acid. The glyoxylate (IV) which separated as a yellowish precipitate was filtered and recrystallized from acetic acid, m.p. 181-183° (72% yield); pmr (DMSO-

d_6): δ 3.76 (s, 3H, COOCH₃), 4.08 (s, 2H, SCH₂), 4.46 (s, 2H, SO₂-CH₂) and \sim 8.70 (broad s, 1H, OH); ir: ν 1610-1590 (chelated C=O), 1730 (ester C=O) and 3550 cm⁻¹ (chelated OH).

Anal. Calcd. for C₁₅H₁₂O₆S₂: C, 51.14; H, 3.41. Found: C, 51.00; H, 3.34.

3-Carbomethoxy-4-oxo-3,4-dihydro-2H,5H-thiopyrano[3,2-c][1]-benzothiopyran 6,6-Dioxide (V).

The decarbonylation procedure of IV was similar to that described previously (3) except that the acetone residue obtained was chromatographed on alumina to give (benzene-ethyl acetate 9/1) III, (ethyl acetate, ethanol) an impurifiable mixture and finally (ethanol-2N hydrochloric acid 9.9/0.1) V (12% yield), which was recrystallized from ethanol, m.p. 165-167°; pmr (deuteriochloroform): δ 3.76 (s, 3H, COOCH₃), 3.2-3.9 (complex m, 3H, CH₂-CH) and 4.28 (A) and 4.22 (B) [q, 2H (AB system), J = 15 Hz, SO₂-CH₂]; ir: ν 1652 (conjugated C=O), 1730 cm⁻¹ (ester C=O); ms: M⁺ 324.

Anal. Calcd. for C₁₄H₁₂O₅S₂: C, 51.85; H, 3.70. Found: C, 51.99; H, 3.60.

3,3-Difluoro-1-methyl-3H,5H,12H-1,3,2-dioxaborino[5,6-c]thiopyrano[3,2-c][1]-benzothiopyran 6,6-Dioxide (VII).

Boron trifluoride etherate (5.68 g., 0.040 mole) was added to a solution of III (2.66 g., 0.010 mole) in acetic anhydride (80 ml.). The mixture was heated on a steam bath for 1 hour, then refluxed for 2 hours during which time the color became deep orange and red crystalline material separated from the solution. The solution was cooled, filtered and the resulting boron complex was washed with ether and recrystallized from acetic acid, m.p. 294-297° (86.4% yield).

Anal. Calcd. for C₁₄H₁₁BF₂O₄S₂: C, 47.21; H, 3.09. Found: C, 47.02; H, 3.18.

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

The above reaction was carried out at room temperature for 48 hours. By dilution of the reaction mixture with diethyl ether, a precipitate consisting of VI and VII (tlc) was obtained. Extraction of the solid precipitate with boiling ethanol at reflux yielded VI (31%) while the residue was VII (27%). The β -diketone (VI) was recrystallized from ethanol, m.p. 226-228°; pmr (trifluoroacetic acid): δ 2.50 (s, 3H, COCH₃), 4.00 (s, 2H, SCH₂) and 4.66 (s, 2H, SO₂-CH₂).

Anal. Calcd. for C₁₄H₁₂O₄S₂: C, 54.54; H, 3.89. Found: C, 54.40; H, 3.84.

3-Acetyl-3-methyl-4-oxo-3,4-dihydro-2H,5H-thiopyrano[3,2-c][1]-benzothiopyran 6,6-Dioxide (XII).

To a solution of sodium methoxide (0.8 g. sodium in 70 ml. of dry methanol) was added boron complex (VII) (2 g.) followed by methyl iodide (18 ml.). The resulting mixture was heated at 60° for 12 hours. After the addition of an additional amount of methyl iodide (10 ml.), the mixture was refluxed an additional 8 hours. The solvent volume was reduced *in vacuo* and the solution was diluted with water. The yellowish precipitate was filtered and recrystallized from ethanol, m.p. 208-210° (1.35 g., 75% yield); pmr (trifluoroacetic acid): δ 1.68 (s, 3H, CH₃), 2.45 (s, 3H, COCH₃), 3.72 (A) and 3.68 (B) [q, 2H (AB system), J = 14 Hz, SCH₂], 4.68 (A) and 4.56 (B) [q, 2H (AB system), J = 15 Hz, SO₂-CH₂].

Anal. Calcd. for C₁₅H₁₄O₄S₂: C, 55.90; H, 4.35. Found: C, 55.97; H, 4.24.

1-Carbomethoxy-4H,11H-isoxazolo[4,5-c]thiopyrano[3,2-c][1]-benzothiopyran 5,5-Dioxide (VIII).

A mixture of glyoxylate (IV) (0.50 g., 0.0014 mole) and hydroxylamine hydrochloride (0.2 g., 0.0029 mole) in acetic acid (20 ml.) was quickly heated on an oil-bath maintained at 170° for 15 minutes and then allowed to cool at room temperature. The crystalline solid separated (0.180 g.) was filtered and washed with ethanol. The solid was then chromatographed on silica gel (benzene-chloroform 1/1) to give VIII (0.150 g., 30.7%), which was recrystallized from acetic acid, m.p. 229-231°; pmr (trifluoroacetic acid): δ 4.08 (s, 3H, COOCH₃), 4.30 (s, 2H, SCH₂) and 4.63 (s, 2H, SO₂-CH₂).

Anal. Calcd. for C₁₅H₁₁NO₅S₂: C, 51.57; H, 3.15; N, 4.01. Found: C, 51.28; H, 3.26; N, 3.90.

1-Carbomethoxy-3,11-dihydro-4H-pyrazolo[4,3-c]thiopyrano[3,2-c][1]-benzothiopyran 5,5-Dioxide (IX).

To a solution of IV (0.8 g., 0.0023 mole) in acetic acid (25 ml.) was added 95% hydrazine hydrate (0.3 ml.) and the reaction mixture was refluxed for 3 hours. On cooling, a yellow crystalline precipitate was separated. The product was filtered, washed with ethanol and recrystallized from acetic acid, m.p. 283-285° (0.200 g., 25.3% yield); pmr (trifluoroacetic acid): δ 4.13 (s, 3H, COOCH₃), 4.44 (s, 2H, SCH₂) and 4.70 (s, 2H, SO₂-CH₂); ir (nujol): ν 3290 cm⁻¹ (NH).

Anal. Calcd. for C₁₅H₁₂N₂O₄S₂: C, 51.72; H, 3.45; N, 8.04. Found: C, 51.46; H, 3.44; N, 7.86.

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

To a solution of V (0.120 g.) in acetic acid (5 ml.) was added 95% hydrazine hydrate (0.3 ml.). An exothermic reaction ensued with darkening of the yellow solution. The mixture was refluxed for 3 hours, and after cooling, the solid which separated was collected and recrystallized from acetic acid, m.p. 296-299° (0.040 g., 35.3%); pmr (DMSO-d₆): δ 3.95 (s, 2H, SCH₂) and 4.57 (s, 2H, SO₂-CH₂); ir (nujol): ν 3280 cm⁻¹ (NH), no band (C=O).

Anal. Calcd. for C₁₃H₁₀N₂O₃S₂: C, 50.98; H, 3.27; N, 9.15. Found: C, 60.12; H, 3.39; N, 9.28.

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

To a solution of sodium methoxide (0.3 g. sodium in 20 ml. of dry methanol) was added 1 g. of IV, followed by methyl iodide (12 ml.), and the mixture was refluxed for 24 hours. The cold reaction mixture was diluted with water and acidified with acetic acid. The acid solution was extracted with ethyl acetate, and the combined organic layers were washed with water and dried over sodium sulphate to give 0.720 g. of an oily residue, which was chromatographed on silica gel. Elution with benzene-ethyl acetate (9.8/0.2) yielded XI (0.330 g., 42.3%). Further elution with benzene-ethyl acetate (9/1) and finally with ethyl acetate afforded III (0.163 g., 22%) and starting IV respectively. The product XI was recrystallized from ethyl acetate m.p. 166-168°; pmr (deuteriochloroform): δ 1.35 (d, 3H, J = \sim 6.5 Hz, CH₃), 2.6-3.4 (complex m, 3H, CH₂-CH), 4.33 (A) and 4.27 (B) [q, 2H (AB system), J = 15 Hz, SO₂-CH₂].

Anal. Calcd. for C₁₃H₁₂O₃S₂: C, 55.71; H, 4.28. Found: C, 55.83; H, 4.23.

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

To a solution of VII (0.250 g.) in acetic acid (40 ml.) was added 95% hydrazine hydrate (0.2 ml.). Subsequently the reaction mixture was refluxed for 5 hours and then concentrated to one-half volume *in vacuo* and diluted with water. The crystalline product that separated was filtered and recrystallized from ethanol, m.p.

278-280° (82% yield); pmr (DMSO- d_6): δ 2.20 (s, 3H, CH₃), 4.03 (s, 2H, SCH₂), 4.60 (s, 2H, SO₂-CH₂) and \sim 10 (broad s, 1H, NH).

Anal. Calcd. for C₁₄H₁₂N₂O₂S₂: C, 55.26; H, 3.95; N, 9.21. Found: C, 54.98; H, 4.07; N, 9.30.

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

A mixture of VII (0.5 g., 0.0014 mole) and hydroxylamine hydrochloride (0.20 g., 0.0028 mole) in acetic acid (70 ml.) was heated in an oil-bath at 180° for 4 hours. The solution was then evaporated to about 20 ml. and poured into ice-water. The gummy precipitate was collected, washed with water, dried and then chromatographed on alumina. Elution with benzene-ethyl acetate 95/5 afforded 0.310 g. (72.5%) of XIV, which was recrystallized from ethyl acetate, m.p. 219-221°; pmr (deuteriochloroform): δ 2.24 (s, 3H, CH₃), 3.98 (s, 2H, SCH₂) and 4.32 (s, 2H, SO₂-CH₂).

Anal. Calcd. for C₁₄H₁₁NO₃S₂: C, 55.08; H, 3.61; N, 4.59. Found: C, 55.21; H, 3.66; N, 4.71.

Racemic 17-Methyl-15,16-diaza-6,11-dithia-1,3,5,8,14,16-estrahex-aene 6,6-Dioxide (XV).

To a solution of XII (0.2 g., 0.00062 mole) in acetic acid (5 ml.) was added 95% hydrazine hydrate (0.1 ml.), and the mixture was refluxed for 2 hours. After cooling, the reaction mixture was poured into 50 ml. of water and alkalized with 10% aqueous sodium bicarbonate solution. The yellow precipitate was collected and crystallized from acetic acid m.p. 225-227° (0.13 g., 66% yield); pmr (deuteriochloroform): δ 1.46 (s, 3H, CH₃ at C-13), 2.23 (s, 3H, CH₃ at C-17), 3.18 (A) and 3.10 (B) [q, 2H (AB system), J = \sim 12 Hz, SCH₂], 4.52 (A) and 4.40 (B) [q, 2H (AB system), J = \sim 15 Hz, SO₂-CH₂]; ms: M⁺ 318.

Anal. Calcd. for C₁₅H₁₄N₂O₂S₂: C, 56.60; H, 4.40; N, 8.80. Found: C, 56.73; H, 4.53; N, 8.65.

Racemic 16-Carbethoxy-17-methyl-15-aza-6,11-dithia-1,3,5,8,14,16-estrahexaene 6,6-Dioxide (XVI).

Glycine ethyl ester hydrochloride (0.5 g., 0.0036 mole) was added to a stirred solution of XII (0.8 g., 0.0025 mole) in dry pyridine (30 ml.). After 60 hours at reflux, tlc on an aliquot of the reaction solution indicated a mixture of starting XII and a

more polar material. The reaction solution was concentrated, and after cooling was poured into ice water. The solid that separated was filtered, dried and chromatographed on alumina. Elution with benzene-ethyl acetate 9/1, gave XVI (0.180 g., 18.5% yield), which was recrystallized from ethanol, m.p. 183-185°; pmr (deuteriochloroform): δ 1.42 (s, 3H, CH₃ at C-13), 2.26 (s, 3H, CH₃ at C-17), 3.02 (A) and 2.94 (B) [q, 2H (AB system), J = \sim 12 Hz, SCH₂], 4.52 (A) and 4.34 (B) [q, 2H (AB system), J = \sim 15 Hz, SO₂-CH₂]; ms: M⁺ 389.

Anal. Calcd. for C₁₉H₁₉NO₄S₂: C, 58.61; H, 4.88; N, 3.60. Found: C, 58.77; H, 4.93; N, 3.41.

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