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Bridgehead nitrogen heterocycles **3a, b** and **6a, b** containing the thieno-pyrimidine system have been prepared from the versatile intermediates 3-amino-2,3-dihydro-5,6-dimethyl-2-thioxo-thieno[2,3-*d*]pyrimidin-4(1*H*)-one **1** and its hydrazinium or potassium salts **4**; their structural elucidation is also reported.

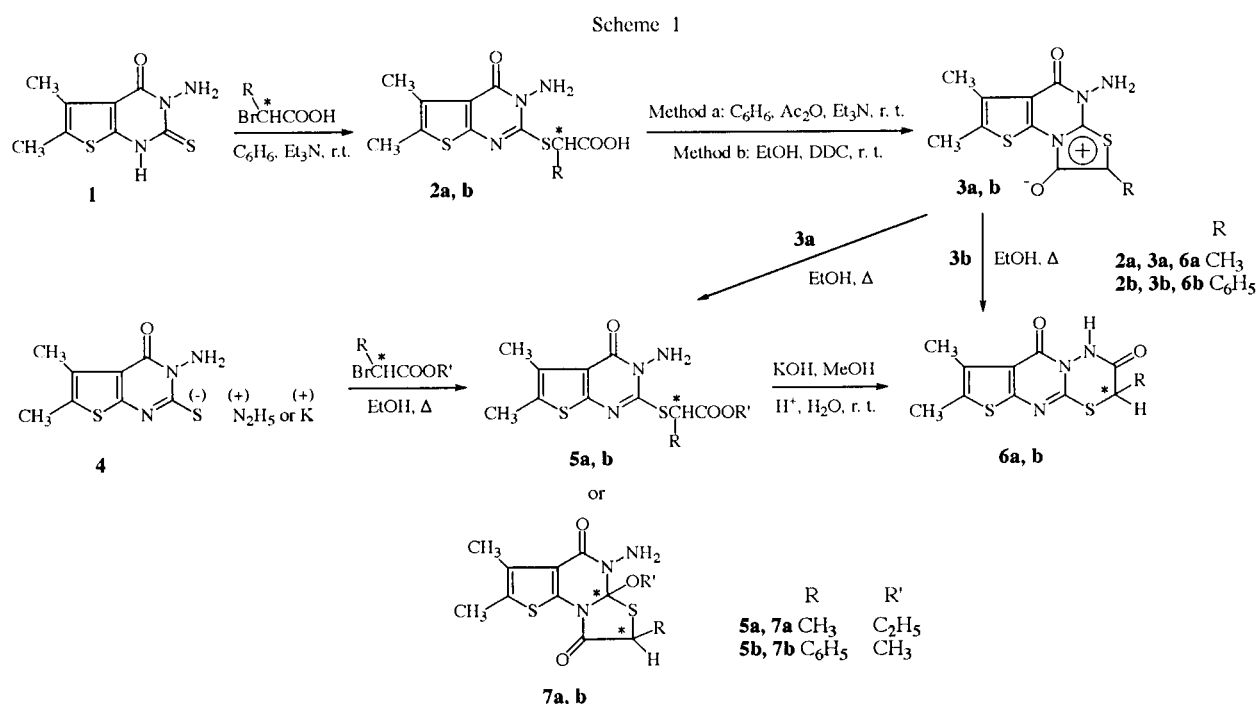
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The derivatives of heterocycles containing the thieno-pyrimidine system are reported to have interesting biological properties [1]. Our interest in this field recently led us to prepare the 3-amino-2,3-dihydro-5,6-dimethyl-2-thioxo-thieno[2,3-*d*]pyrimidin-4(1*H*)-one (**1**) and its hydrazinium (+1) or potassium salts **4** [2, 3]; due to the presence of two adjacent reactive functional groups, as reported for similar compounds [4 - 11], this amino-thioxo derivative **1** and its salts **4** proved to be versatile intermediates for the preparation of bridgehead nitrogen heterocycles.

As our research continues, here we report the synthesis of angular mesoionic compounds **3a, b** and linear tri-cycles **6a, b**, containing the thieno-pyrimidine system with an atom of nitrogen as a bridge, starting from the title thioxo derivatives **1** and **4** (Scheme 1).

2-bromopropionic or α -bromophenylacetic acid, to give the acid derivatives **2a** and **2b**, respectively; these derivatives **2a** and **2b**, stirred at room temperature in benzene with a mixture of acetic anhydride and triethylamine (v/v 1:1) (method a) or phenyl derivative **2b** stirred at room temperature in ethanol with an equimolar amount of *N,N'*-dicyclohexylcarbodiimide (DCC) (method b), cyclized to give the mesoionic compounds **3a, b** (Scheme 1). In the cyclization of the phenyl derivative **2b** the preferred endo-cyclization at the N1 atom of the pyrimidine ring in the presence of DCC under our reaction conditions must be emphasized. These mesoionic compounds were isolated at high degrees of purity and recrystallization decreased very much the yields.

Prolonged heating in ethanol of the mesoionic compound **3a** gave the ethyl ester **5a**, while in the case of the



The amino-thioxo derivative **1** reacted in benzene, at room temperature, in the presence of triethylamine with

mesoionic compound **3b** it gave the linear dione **6b** which was identical to the product obtained from methanolic

alkaline hydrolysis of the methyl ester **5b** easily obtained from the hydrazinium or potassium ester **4**.

The linear dione **6a** was only obtained from the methanolic alkaline hydrolysis of the ethyl ester **5a**.

Talukdar *et al.* [12] prepared the same mesoionic system with the phenyl in the 5 and 7 positions and, according to their synthetic route, the reaction of the thioxo derivative with the appropriate halo-ester gave a product with γ -lactam structure instead of the ester derivatives, on the basis of the ir data, C=O 1745 cm^{-1} [12]; thus, compounds **5a, b** showing in the ir spectra signals at 1750 and 1740 cm^{-1} , respectively, may be proposed with the alternative lactam structures **7a, b**.

Moreover the same authors [12, 13] reported that the above γ -lactam structure was also obtained by heating these thiazole mesoionic systems in ethanol, as a formation of an ethanol adduct from the mesoionic system.

Analytical and spectral data are in accordance with the proposed structure for compounds **2a, b, 3a, b, 5a, b** and **6a, b**.

The mesoionic compounds **3a, b** exhibit in the ir and ^1H nmr spectra signals attributable to the presence of an amino group; in the mass spectra, the molecular ions at m/z 281 (60%) for the 7-methyl derivative **3a** and at m/z 343 (25%) for the 7-phenyl derivative **3b** are confirmed, while the presence of a signal at m/z 121 (41%) for the 7-phenyl derivative **3b**, attributable to the fragment $[\text{PhCS}^+]$, corroborates the reaction of the thioxo group with α -bromophenyl acetic acid.

The linear structures of the dione derivatives **6a, b**, as opposed to the angular ones, are confirmed in the ^1H nmr by the presence of an amidic hydrogen as a sharp signal at δ 11.76 for the 3-methyl derivative **6a** and as a broad one at δ 12.18 for the 3-phenyl derivative **6b**, and of C2-proton as a quartet signal at δ 4.23 for the 3-methyl derivative **6a** and as a singlet at δ 5.54 for the 3-phenyl derivative **6b**; in the ir spectra, the amidic hydrogen is confirmed by a broad signal at 3185 cm^{-1} for the 3-methyl derivative **6a** and at 3210 cm^{-1} for the 3-phenyl derivative **6b**.

EXPERIMENTAL

Melting points are uncorrected and were determined in open capillary tubes on a Gallenkamp melting points apparatus. The ir spectra were recorded on a Perkin Elmer 1600 Series FT-IR in potassium bromide disks. Elemental analyses for C, H, N, and S were obtained on an EA1108 elemental analyzer Fisons-Carlo Erba instrument. The low resolution mass spectra were recorded by direct insertion into ion source on a VG-2AB2SE mass spectrometer under the following conditions: ionization energy, 70 eV; source temperature 250-300°C; trap current 60 μA . The ^1H nmr spectra were recorded at 200 MHz on a Varian Inova-Unity 200 spectrometer; chemical shifts (δ) are reported in ppm from TMS as internal standard; coupling constants (J) are in Hertz. The purity of compounds was checked by tlc on Merck

silica gel 60 F-254 plates. All commercial chemicals were purchased from Aldrich, Fluka, Merck and Carlo Erba and were used without further purification.

2-[(3-Amino-3,4-dihydro-5,6-dimethyl-4-oxo-thieno[2,3-*d*]-pyrimidin-2-yl)thio]-propionic acid (**2a**).

A mixture of amino-thioxo derivative **1** [2, 3] (0.40 g, 1.8 mmol), 2-bromopropionic acid (0.16 ml, 99%, $d = 1.70$, 1.8 mmol) and triethylamine (0.25 ml) in benzene (30 ml) was stirred at room temperature for 30 hours. After filtration the resulting solution was extracted with a sodium bicarbonate 5% solution. The aqueous solution was dropwise acidified with hydrochloric acid to pH 5-6: the solid was collected, washed with water and dried to give **2a** as a light yellow powder. Yield: 22%; mp 200-203° dec.; ir: ν 3320 and 3260 (NH_2), 1695 and 1670 (C=O) cm^{-1} ; ^1H nmr (dimethylsulfoxide- d_6): δ 1.45 (d, $J = 7.4$ Hz, 3H, CH_3), 2.28 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 4.17 (q, $J = 7.4$ Hz, 1H, -CH-), 5.70 (s, 2H, NH_2), 12.70 (br s, 1H, OH).

Anal. Calcd. for $\text{C}_{11}\text{H}_{13}\text{N}_3\text{O}_3\text{S}_2$: C, 44.15; H, 4.35; N, 14.04; S, 21.40. Found: C, 44.00; H, 4.20; N, 14.30; S, 21.15.

α -[(3-Amino-3,4-dihydro-5,6-dimethyl-4-oxo-thieno[2,3-*d*]-pyrimidin-2-yl)thio]-phenylacetic acid (**2b**).

A mixture of amino-thioxo derivative **1** [2, 3] (0.30 g, 1.3 mmol), α -bromophenylacetic acid (0.28 g, 98%, 1.3 mmol) and triethylamine (0.20 ml) in benzene (25 ml) was stirred at room temperature for 2 days. After filtration, the resulting solution was extracted with a sodium bicarbonate 5% solution. The aqueous solution, after filtration, was dropwise acidified with hydrochloric acid to pH 6-7: the solid was collected, washed with water and dried to give **2b** as a white amorphous powder. Yield: 44%; mp 127-29° dec.; ir: ν 3300 and 3205 (NH_2), 1730 and 1675 (C=O) cm^{-1} ; ^1H nmr (dimethylsulfoxide- d_6): δ 2.34 (s, 3H, CH_3), 2.36 (s, 3H, CH_3), 5.28 (s, 1H, -CH-), 5.76 (s, 2H, NH_2), 7.35-7.53 (m, 5H, ArH), 13.10 (br s, 1H, OH).

Anal. Calcd. for $\text{C}_{16}\text{H}_{15}\text{N}_3\text{O}_3\text{S}_2$: C, 53.18; H, 4.15; N, 11.63; S, 17.72. Found: C, 53.40; H, 4.05; N, 11.50; S, 17.50.

5-Amino-2,3,7-trimethyl-8-hydroxy-4-oxo-4*H*-thiazolo[3,2-*a*]-thieno[3,2-*e*]pyrimidinium inner salt (**3a**).

Method a

A mixture of acetic anhydride (0.5 ml) and triethylamine (0.5 ml) was added to a stirred suspension of the acid derivative **2a** (0.13 g, 0.43 mmol) in benzene (2 ml): the mixture was stirred at room temperature for 2 hours. The yellow resulting mixture was diluted with diethyl ether and the solid collected, washed with diethyl ether and dried to give **3a** as a yellow powder; the product resulted pure at tlc; a sample was recrystallized from dioxane/benzene. Yield: 33%; mp 120-23° dec.; ir: ν 3280 and 3125 (NH_2), 1695 and 1630 (C=O) cm^{-1} ; ms: m/z 281 (60%) $[\text{M}^+]$; ^1H nmr (dimethylsulfoxide- d_6): δ 1.39 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 6.11 (s, 2H, NH_2).

Anal. Calcd. for $\text{C}_{11}\text{H}_{11}\text{N}_3\text{O}_2\text{S}_2$: C, 46.97; H, 3.91; N, 14.94; S, 22.77. Found: C, 46.65; H, 4.20; N, 14.70; S, 22.40.

5-Amino-2,3-dimethyl-8-hydroxy-4-oxo-7-phenyl-4*H*-thiazolo[3,2-*a*]thieno[3,2-*e*]pyrimidinium inner salt (**3b**).

Method a

A mixture of acetic anhydride (1 ml) and triethylamine (1 ml) was added to a stirred suspension of the acid derivative **2b** (0.30 g, 0.83 mmol) in benzene (2 ml): the mixture was stirred at room temperature for 2 hours. The orange resulting mixture was diluted with diethyl ether and the solid was collected, washed with diethyl ether and dried to give **3b** as an orange powder; the product resulted pure at tlc; a sample was recrystallized from dioxane/benzene. Yield: 52%; mp 260-263° dec.; ir: ν 3295 and 3195 (NH₂), 1690 and 1655 (C=O) cm⁻¹; ms: *m/z* 343 (25%) [M⁺], 121 (41%) [PhCS⁺]; ¹H nmr (dimethylsulfoxide-*d*₆): δ 2.44 (s, 6H, 2CH₃), 6.26 (s, 2H, NH₂), 6.94-7.73 (m, 5H, ArH).

Anal. Calcd. for C₁₆H₁₃N₃O₂S₂: C, 55.97; H, 3.79; N, 12.24; S, 18.65. Found: C, 55.80; H, 3.65; N, 11.90; S, 18.25.

Method b

A mixture of the acid derivative **2b** (0.060 g, 0.17 mmol) and DDC (0.35 g, 0.17 mmol) in ethanol (10 ml) was stirred at room temperature for 2 hours. The solid separated was collected, washed with ethanol and dried to give **3b** as an orange powder; the product resulted pure at tlc; a sample was recrystallized from dioxane/benzene. Yield: 65%.

Ethyl ester of 2-[(3-amino-3,4-dihydro-5,6-dimethyl-4-oxo-thieno[2,3-*d*]pyrimidin-2-yl)thio]-propionic acid (**5a**).

A mixture of hydrazinium or potassium salt **4** [2, 3] (2.6 mmol) and ethyl 2-bromopropionate (0.35 ml, 99%, *d* = 1.394, 2.7 mmol) in ethanol (40 ml) was refluxed for 2 hours. The resulting solution was filtered and cooled to room temperature. The solid separated was collected, washed with ethanol, dried and recrystallized from ethanol to give **5a** as light brown microcrystals. Yield 50%; mp 138-40°; ir: ν 3310 and 3195 (NH₂), 1750 and 1655 (C=O) cm⁻¹; ¹H nmr (dimethylsulfoxide-*d*₆): δ 1.31 (t, *J* = 7 Hz, 3H, CH₃), 1.50 (d, *J* = 7.2 Hz, 3H, CH₃), 2.32 (s, 3H, CH₃), 2.35 (s, 3H, CH₃), 4.28 (q, *J* = 7.2 Hz, 1H, CH), 4.30 (q, *J* = 7 Hz, 2H, CH₂), 5.78 (s, 2H, NH₂).

Anal. Calcd. for C₁₃H₁₇N₃O₃S₂: C, 47.70; H, 5.20; N, 12.85; S, 19.55. Found: C, 47.55; H, 5.00; N, 12.70; S, 19.35.

The mesoionic compound **3a** (35 mg) in ethanol (10 ml) was heated at reflux for 20 minutes. The solution was concentrated under vacuum and the residue was collected, washed with methanol, dried and recrystallized from ethanol to give a brown solid identical with respect ir, ¹H nmr and mp to ethyl ester **5a**.

Methyl ester of α -[(3-amino-3,4-dihydro-5,6-dimethyl-4-oxo-thieno[2,3-*d*]pyrimidin-yl)thio]-phenylacetic acid (**5b**).

A mixture of hydrazinium or potassium salt **4** [2, 3] (2.6 mmol) and methyl α -bromophenylacetate (0.42 ml, 97%, *d* = 1.457, 2.6 mmol) in ethanol (40 ml) was refluxed under stirring for 30 minutes and then stirred at room temperature for 1.5 hours. The reaction mixture was poured into water (300 ml): the solid separated was collected, dried and recrystallized from ethanol to give **5b** as a light yellow amorphous solid. Yield 85%; mp

218-20°; ir: ν 3310 and 3210 (NH₂), 1740 and 1680 (C=O) cm⁻¹; ¹H nmr (dimethylsulfoxide-*d*₆): δ 2.36 (s, 6H, 2CH₃), 3.67 (s, 3H, OCH₃), 5.41 (s, 1H, CH), 5.82 (s, 2H, NH₂), 7.38-7.54 (m, 5H, ArH).

Anal. Calcd. for C₁₇H₁₇N₃O₃S₂: C, 54.40; H, 4.53; N, 11.20; S, 17.06. Found: C, 54.40; H, 4.40; N, 10.95; S, 17.25.

3,7,8-Trimethyl-3*H*,9*H*-thieno[2',3':4,5]pyrimido[2,1-*b*]-[1,3,4]thiadiazin-2,9-(4*H*)-dione (**6a**).

A suspension of ethyl ester **5a** (0.34 g, 1.0 mmol) in a solution of sodium hydroxide (40 mg, 1.0 mmol) in methanol (10 ml) and water (2 ml) was stirred at room temperature for 24 hours; the mixture was poured into water (100 ml): by acidification of the resulting solution with hydrochloric acid until pH 4-5 a white solid separated; this solid was collected, washed with water, dried and recrystallized from ethanol/water to give **6a** as colourless needles. Yield 55%; mp 208-10°; ir: ν 3185 (br NH), 1695 and 1675 (C=O) cm⁻¹; ¹H nmr (dimethylsulfoxide-*d*₆): δ 1.39 (d, *J* = 7 Hz, 3H, CH₃), 2.36 (s, 3H, CH₃), 2.38 (s, 3H, CH₃), 4.23 (q, *J* = 7 Hz, 1H, CH), 11.76 (br s, 1H, NH).

Anal. Calcd. for C₁₁H₁₁N₃O₂S₂: C, 46.97; H, 3.91; N, 14.94; S, 22.77. Found: C, 46.65; H, 4.05; N, 14.70; S, 22.65.

7,8-Dimethyl-3-phenyl-3*H*,9*H*-thieno[2',3':4,5]pyrimido[2,1-*b*]-[1,3,4]thiadiazin-2,9-(4*H*)-dione (**6b**).

A suspension of methyl ester **5b** (0.39 g, 1.0 mmol) in a solution of sodium hydroxide (40 mg, 1.0 mmol) in methanol (10 ml) and water (2 ml) was stirred at room temperature for 24 hours; the mixture was filtered and the filtrate poured into water (100 ml): by acidification with hydrochloric acid until pH 4-5 a white solid separated; this solid was collected, washed with water, dried and recrystallized from dioxane/water to give **6b** as an amorphous white solid. Yield 50%; mp 273-75° dec.; ir: ν 3210 broad (NH), 1675 broad (C=O) cm⁻¹; ¹H nmr (dimethylsulfoxide-*d*₆): δ 2.39 (s, 6H, 2CH₃), 5.54 (s, 1H, CH), 7.27-7.41 (m, 5H, ArH), 12.18 (br s, 1H, NH).

Anal. Calcd. for C₁₆H₁₃N₃O₂S₂: C, 55.97; H, 3.79; N, 12.24; S, 18.65. Found: C, 55.80; H, 3.75; N, 12.10; S, 18.30.

The mesoionic compound **3b** (35 mg) in ethanol (10 ml) was heated under reflux for 20 minutes. The resulting solution was cooled to room temperature: the white solid separated was collected, washed with methanol, dried and recrystallized by dioxane/water to give a product that was identical with respect to ir, ¹H nmr and mp to dione derivative **6b**.

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