SYNTHESIS OF 2,3,5,6,7,8-HEXAHYDRO-3-AMINO-2-THIOXO[1]BENZOTHIENO-[2,3-*d*]PYRIMIDIN-4(1*H*)-ONE AND DERIVATIVES OF THE NEW HETEROCYCLIC SYSTEM 7,8,9,10-TETRAHYDRO-3*H*,11*H*-[1]BENZOTHIENO[2',3':4,5]PYRIMI-DO[2,1-*b*][1,3,4]THIADIAZIN-11-ONE

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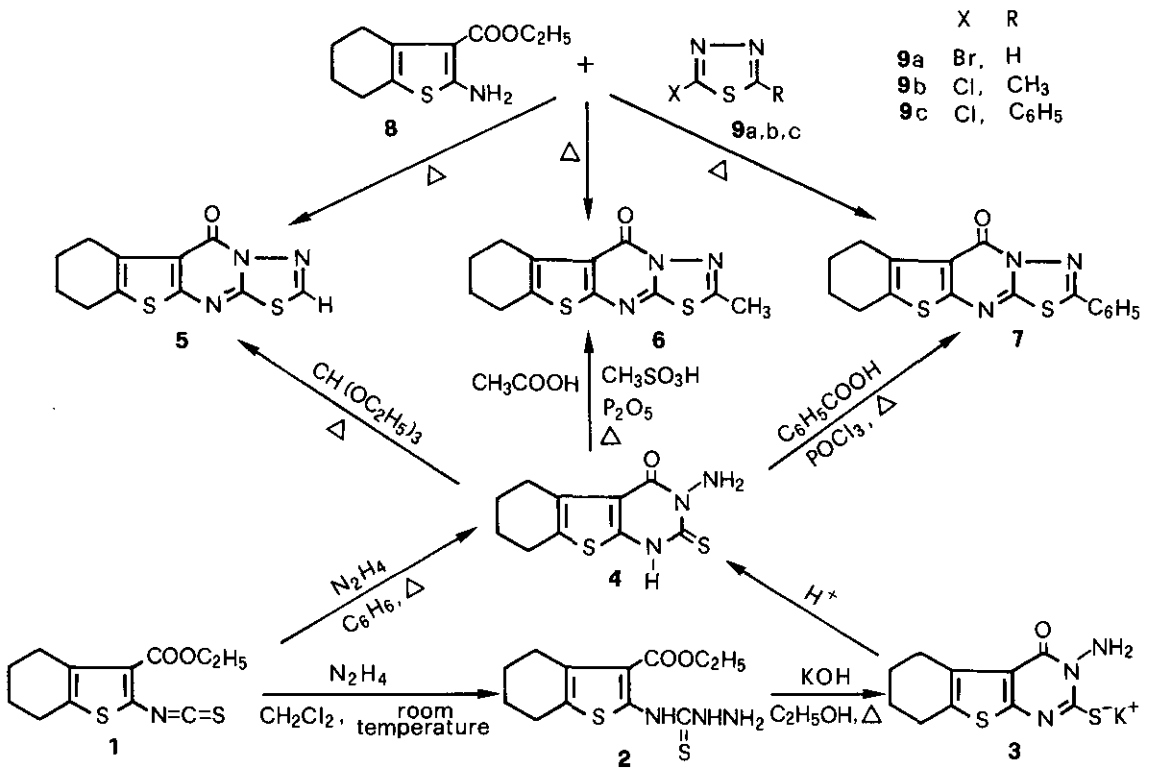
Abstract - A versatile compound, 2,3,5,6,7,8-hexahydro-3-amino-2-thioxo[1]benzothieno[2,3-*d*]pyrimidin-4(1*H*)-one (**4**), was synthesized from ethyl 4,5,6,7-tetrahydro-2-isothiocyanato-1-benzothiophene-3-carboxylate(**1**). Derivatives of a heterocyclic linear system having the 1,3,4-thiadiazine ring were obtained from the key intermediate (**4**).

During the last years we have interested in the synthesis of substituted heterocycles containing the thienopyrimidine system with the aim of finding compounds with anti-inflammatory and analgesic activities.[1-5] In this paper we report the preparations and structural confirmations of 2,3,5,6,7,8-hexahydro-3-amino-2-thioxo[1]benzothieno-[2,3-*d*]pyrimidin-4(1*H*)-one (**4**) and derivatives of the heterocyclic system 7,8,9,10-tetrahydro-3*H*,11*H*-[1]benzothieno[2',3':4,5]pyrimido[2,1-*b*][1,3,4]thiadiazine (**11**), (**12**) and (**13**).

Addition at room temperature of the isothiocyanate (**1**) to hydrazine hydrate in dichloromethane afforded the thiosemicarbazide derivative (**2**) which, by subsequent refluxing in ethanolic potassium hydroxide solution, gave the potassium salt of the aminothioxo derivative (**3**). By acidification of an aqueous solution of the potassium salt (**3**) the aminothioxo derivative (**4**) was obtained. Compound (**4**) was also prepared by adding a benzene solution of the isothiocyanate (**1**) to hydrazine hydrate and subsequent prolonged heating of the reaction mixture. By the reaction of compound (**4**) with ethyl orthoformate, acetic acid, or benzoic acid, the corresponding 6,7,8,9-tetrahydro-10*H*-[1]benzothieno[2,3-*d*][1,3,4]thiadiazolo[3,2-*a*]pyrimidin-10-ones (**5**, **6**

and 7) were obtained, respectively. Tetracycles (5), (6)[1] and (7)[1] were proved to be identical with those obtained from the condensation of the ethyl ester (8) with 2-halogeno-1,3,4-thiadiazoles (9a, 9b and 9c)(Scheme 1).



Scheme 1

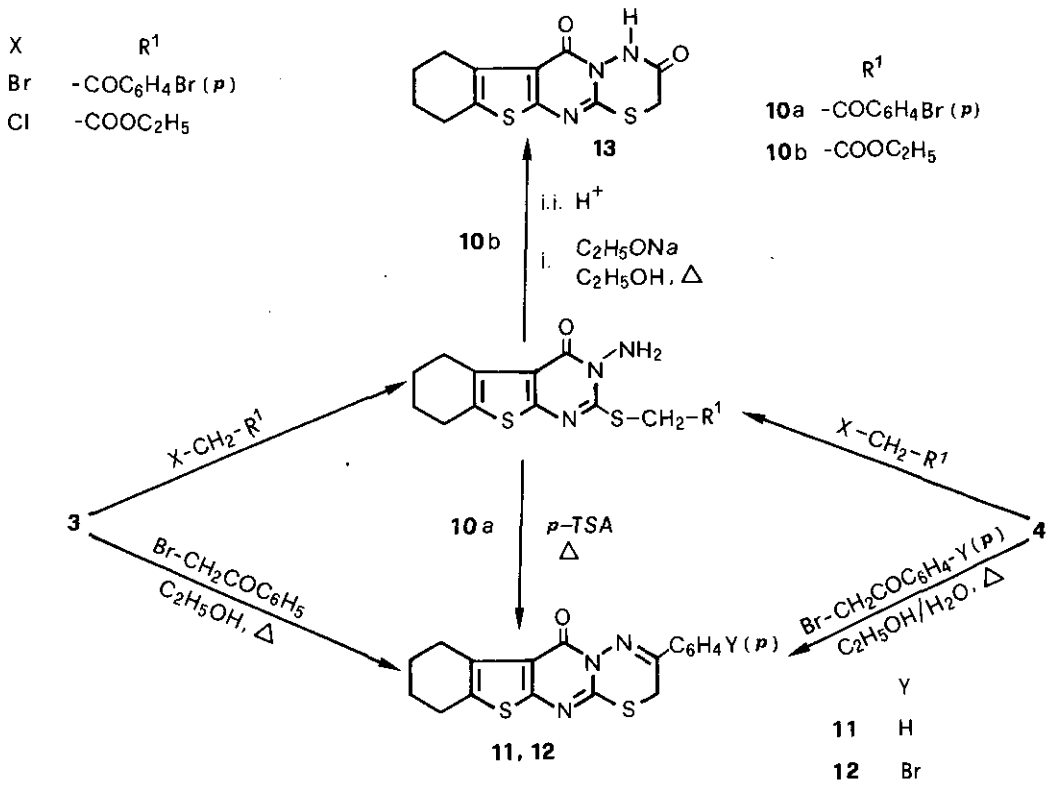
Refluxing in ethanol/water the aminothioxo derivative (4) with 2-bromoacetophenone or with 2,4'-dibromoacetophenone, gave the 2-substituted derivatives of the new heterocyclic ring system (11) and (12), respectively. Compound (11) was also obtained by refluxing in ethanol the potassium salt (3) with 2-bromoacetophenone. Moreover the 2-(4-bromophenyl) derivative (12) was also obtained from cyclization in ethanol of the 2-(4-bromophenyl)-2-oxoethylthio derivative (10a) in presence of the *p*-toluenesulfonic acid (Scheme 2).

The structures of products (11) and (12) were confirmed by elemental analyses and ir, ^{1}H-nmr and mass spectra. In particular, signals attributable to NH or NH_2 group were absent in both ir and ^{1}H-nmr spectra. Moreover signals at δ 3.94 for the 2-phenyl derivative (11) and at δ 3.90 for the 2-(4-bromophenyl) derivative (12), at-

tributable to the two methylene protons in position 3, were observed in ^{1}H-nmr spectra.

By reaction of the potassium salt (**3**) or of an alkaline solution of the aminothioxo derivative (**4**) with ethyl chloroacetate, the ethyl ester (**10b**) was obtained. Heating in ethanol of the ester (**10b**) in presence of sodium ethoxide and subsequent acidification of the resulting mixture with hydrochloric acid or acetic acid afforded the 7,8,9,10-tetrahydro-3*H*,11*H*-[1]benzothieno[2',3':4,5]pyrimido[2,1-*b*][1,3,4]thiadiazine-2-(1*H*),11-dione (**13**). The structure of compound (**13**) was substantiated by elemental analysis and ir, ^{1}H-nmr and mass spectra. In particular, the ir spectrum showed a band at 3180 cm^{-1} attributable to N-H stretching and a broad band at 1680 cm^{-1} due to overlapping bands of the two carbonyl groups. Moreover, the ^{1}H-nmr spectrum exhibited a broad signal at δ 11.71, confirming the presence of NH group, and a signal at δ 3.84 attributable to the two methylene protons in position 3 (Scheme 2).

Scheme **2**



EXPERIMENTAL

All melting points were taken in open capillaries using a Gallemkamp melting point apparatus with a digital

thermometer MFB-595 and are uncorrected. The ir spectra were recorded with a Perkin-Elmer 281 spectrophotometer in KBr disks. Elemental analyses for C, H, N and S were obtained on an EA1108 Elemental Analyzer Fisons-Carlo Erba instruments. 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, 70eV; source temperature 250-300°C; trap current 60 μA. The sample temperature ranged from room temperature to 300°C. The ^{1}H-nmr spectra were recorded on Bruker AC-80 spectrometer. Chemical shifts are reported in δ ppm from TMS as internal standard.

4-(4,5,6,7-Tetrahydro-3-carboethoxy-1-benzothien-2-yl)thiosemicarbazide(2).

To a stirred solution of hydrazine hydrate (1.55 g, 31.0 mmol) in dichloromethane (100 ml) a solution of isothiocyanate (1)[6] (8.3 g, 31.0 mmol) in dichloromethane (100 ml) was added dropwise at room temperature. The suspension was stirred at room temperature for 2 h and then the solid was collected, washed with dichloromethane, dried and recrystallized from dioxane/ethanol to give 2 (3.7 g, 40%) as colourless microcrystals, mp 200-202°C(decomp.); ir: ν 3370, 3200 and 3160(NH_2 or NH), 1670(C=O) cm^{-1}; Anal. Calcd for $C_{12}H_{17}N_3O_2S_2$: C,48.16; H,5.68; N,14.04; S,21.40. Found: C,48.40; H,5.80; N,13.90; S,21.70.

Potassium salt of 2,3,5,6,7,8-hexahydro-3-amino-2-thioxo[1]benzothieno[2,3-*d*]pyrimidin-4(1*H*)-one(3).

To a hot ethanolic solution (80 ml) of potassium hydroxide (1.2 g, 21.4 mmol) compound (2) (6.0 g, 20.0 mmol) was added and the resulting mixture was refluxed for 30 min. The hot suspension was then filtered and the solid collected was washed with warm dioxane and dried to give 3 (5.5 g, 95%) as white powder; ir: ν 3230(NH_2), 1640(C=O) cm^{-1} ; Anal. Calcd for $C_{10}H_{10}N_3OKS_2$: C,41.23; H,3.43; N,14.43; S,21.99. Found: C,41.20; H,3.40; N,14.20; S,21.75.

2,3,5,6,7,8-Hexahydro-3-amino-2-thioxo[1]benzothieno[2,3-*d*]pyrimidin-4(1*H*)-one(4).

To a stirred solution of potassium salt (3) (3.1g, 10.65 mmol) in water (150 ml) 37% hydrochloric acid (0.9 ml) was added dropwise : a white solid separated. The solid was collected, washed with water, dried and recrystallized from dioxane to give 4 (1.35 g, 50%) as colourless microcrystals, mp 266-267°C(decomp.); ir: ν 3320, 3260, 3140 and 3100(NH_2 or NH), 1670(C=O) cm^{-1}; ms: (m/z) 253(M^+); Anal. Calcd for $C_{10}H_{11}N_3OS_2$: C,47.43; H,4.34; N,16.60; S,25.29. Found: C,47.50; H,4.45; N,16.60; S,25.40.

Compound (4) was also prepared by adding a solution of isothiocyanate (1) (1.0 g, 3.74 mmol) in benzene (15 ml) dropwise at room temperature to a stirred solution of hydrazine hydrate (1.0 g, 20.0 mmol) in benzene (5 ml). The suspension was refluxed under stirring for 8 h. After cooling, the solid was collected, washed with ethanol, dried and recrystallized from dioxane to give 4 (0.38 g, 40%) as colourless microcrystals, mp 266-267°C(decomp.)

6,7,8,9-Tetrahydro-10*H*-[1]benzothieno[2,3-*d*][1,3,4]thiadiazolo[3,2-*a*]pyrimidin-10-one(5).

A mixture of 4 (0.80 g, 3.16 mmol) and triethyl orthoformate (15 ml, 88.3 mmol) was refluxed for 14 h. After cooling, the solid was collected, washed with warm dioxane and recrystallized from dioxane to give 5 (0.66 g, 79%) as white powder, mp 284-286°C(decomp.); ir: ν 1680(C=O) cm^{-1}; ms: (m/z) 263 (M^+) Anal. Calcd for $C_{11}H_9N_3OS_2$: C,50.19; H,3.42; N,15.96; S,24.33. Found: C,50.40; H,3.50; N,15.80; S,23.90.

Compound (5) was also obtained according the synthetic method used by Russo *et al.*[1] : a mixture of ethyl ester (8)[7] (2.25 g, 10.0 mmol) and bromothiadiazole (9a)[8] (1.65 g, 10 mmol) was heated at 140°C on an oil bath for 30 min under stirring until the evolution of hydrogen bromide was complete. After cooling, the mixture was treated with warm dioxane and filtered. The solid collected was poured into about 100 ml of 5% $NaHCO_3$ and the resulting precipitate was filtered off, washed with water, dried and recrystallized from dioxane to give 5 (50 mg, 2%) as white powder, mp 284-286C°(decomp.); ir: ν 1680(C=O) cm^{-1}; Anal. Calcd for $C_{11}H_9N_3OS_2$: C,50.19; H,3.42; N,15.96; S,24.33. Found: C,49.90; H,3.45; N,16.20; S,23.95.

6,7,8,9-Tetrahydro-2-methyl-10*H*-[1]benzothieno[2,3-*d*][1,3,4]thiadiazolo[3,2-*a*]pyrimidin-10-one(6).

A mixture of 4 (1.0 g, 3.95 mmol), phosphorus pentoxide (0.6 g, 4.22 mmol), acetic acid (0.3 ml, 5 mmol) and methanesulfonic acid (1.3 ml, 19.8 mmol) was heated at 80°C on an oil bath for 9 h. After cooling, the mixture was treated with water and 10% sodium hydroxide and the resulting solid was collected, washed with water, dried and recrystallized from ethanol to give 6 (0.66 g, 60%) as white powder, mp 204-205°C ; ir: ν 1690(C=O) cm^{-1}; ms: (m/z) 277(M^+); Anal. Calcd for $C_{12}H_{11}N_3OS_2$: C,51.98; H,3.97; N,15.16; S,23.10. Found: C,51.70; H,4.10; N,15.25; S,22.90.

Compound (6) was identical with respect to mp, ir and mass spectra and tlc with a sample obtained by Russo *et al.*[1], by condensation of ethyl ester (8)[7] with 2-chloro-5-methyl derivative (9b).[9] The mp indicated by Russo *et al.*[1] has a higher value because it was taken using a different apparatus.

6,7,8,9-Tetrahydro-2-phenyl-10*H*-[1]benzothieno[2,3-*d*][1,3,4]thiadiazolo[3,2-*a*]pyrimidin-10-one(7).

A mixture of 4 (0.30 g, 1.18 mmol), benzoic acid (0.29 g, 2.36 mmol) and phosphorus oxychloride (2 ml, 21.4 mmol) was refluxed for 20 min. After cooling, phosphorous oxychloride was evaporated under reduced pressure and the residue was treated with 10% sodium hydroxide. The resulting solid was collected, washed with water, dried and recrystallized from dioxane to give 7 (0.10 g, 25%) as green microcrystals, mp 246-247°C ; ir: ν 1700(C=O) cm^{-1}; ms: (m/z) 339(M^+) ; Anal. Calcd for $C_{17}H_{13}N_3OS_2$: C,60.17; H,3.83; N,12.39; S,18.87. Found: C,59.90; H,3.75; N,12.20; S,18.80.

Compound (7) was identical with respect to mp, ir and mass spectra and tlc with a sample obtained by Russo *et al.*[1], by condensation of ethyl ester (8)[7] with 2-chloro-5-phenyl derivative (9c).[10] The mp indicated by Russo *et al.*[1] has a higher value because it was taken using a different apparatus.

3,4,5,6,7,8-Hexahydro-3-amino-2-[[2-(4-bromophenyl)-2-oxoethyl]thio]-[1]benzothieno[2,3-*d*]pyrimidin-4(3*H*)-one(10a) from aminothioxo derivative(4): 2,4'-dibromoacetophenone (0.55 g, 1.98 mmol) was added, at room temperature and under stirring, to a suspension of 4 (0.5 g, 1.97 mmol) in 10% sodium hydroxide (10 ml) and ethanol (5 ml). After stirring at room temperature for 30 min, the mixture was poured into water (100 ml). The resulting solid was collected, washed with water, dried and recrystallized from dioxane/water to give 10a (0.26 g, 29%) as white product, mp 217-218°C(decomp.); ir: ν 3300 and 3190(NH_2), 1680(C=O) cm^{-1}; Anal. Calcd for $C_{18}H_{16}N_3O_2BrS_2$: C,48.01; H,3.55; N,9.33; S,14.22. Found: C,47.95; H,3.60; N,9.10; S,14.15.

from potassium salt(3): 2,4'-dibromoacetophenone (0.55 g, 1.97 mmol) was added to a suspension of **3** (0.57 g, 1.96 mmol) in ethanol (25 ml). The mixture was stirred at room temperature for 2 h. The resulting solid was collected, washed with water, dried and recrystallized from dioxane/water to give **10a** (0.62 g, 70%) as white product, mp 217-218°C(decomp.).

Ethyl ester of [(3,4,5,6,7,8-hexahydro-3-amino-4-oxo[1]benzothieno[2,3-*d*]pyrimidin-2-yl)thiolacetic acid(10b).

from aminothioxo derivative(4): Ethyl chloroacetate (0.2 ml, 2.31 mmol) was added to a hot suspension of **4** (0.5 g,1.97 mmol) in ethanolic potassium hydroxide solution (0.15 g in 20 ml). The mixture was refluxed for 2 h and then filtered while hot. The white solid separated at room temperature from the ethanolic filtrate was collected, washed with ethanol, dried and recrystallized from ethanol to give **10b** (0.13 g, 19%) as white needles, mp 162-163°C; ir: ν 3320 and 3210(NH_2), 1735 and 1680(C=O) cm^{-1}; ms: (m/z) 339(M^+); Anal. Calcd for $C_{14}H_{17}N_3O_3S_2$: C,49.55; H,5.01; N,12.38; S,18.87. Found C,49.25; H,5.00; N,12.30; S,18.80.

from potassium salt(3): Ethyl chloroacetate (0.6 ml, 6.93 mmol) was added to a suspension of **3** (1.5 g, 5.15 mmol) in ethanol (50 ml). The suspension was refluxed for 1 h and filtered while hot. The white solid separated at room temperature from the filtrate was collected, washed with ethanol, dried and recrystallized from ethanol to give **10b** (0.78 g, 45%) as white needles, mp 162-163°C.

7,8,9,10-Tetrahydro-2-phenyl-3*H*,11*H*-[1]benzothieno[2',3':4,5]pyrimido[2,1-*b*][1,3,4]thiadiazin-11-one(11).

from aminothioxo derivative(4): A mixture of compound (**4**) (0.15 g, 0.59 mmol) and 2-bromoacetophenone (0.14 g, 0.7 mmol) in ethanol/water (8:2)(100 ml) was refluxed for 3 h. Within 2 h yellow microcrystals separated. After cooling, the solid was collected, washed with water, dried and recrystallized from dioxane/ethanol to give **11** (70 mg, 33%) as yellow microcrystals, mp 252-253°C(decomp.); ir: ν 1680(C=O) cm^{-1}; ms: (m/z) 353(M^+); ^{1}H-nmr($CDCl_3$): 7.48-7.96(m, 5H), 3.94(s, 2H), 3.04(m, 2H), 2.77(m, 2H), 1.87(m, 4H); Anal. Calcd for $C_{18}H_{15}N_3OS_2$: C,61.18; H,4.25; N,11.89; S,18.13. Found: C,60.90; H,4.30; N,11.90; S,18.30.

from potassium salt(3): A mixture of 2-bromoacetophenone (0.35 g, 1.76 mmol) and compound (**3**) (0.5 g, 1.72 mmol) in ethanol (25 ml) was refluxed for 2 h. After cooling, the resulting solid was collected, washed with water, dried and recrystallized from dioxane/ethanol to give **11** (0.40 g, 66%) as yellow microcrystals, mp 252-253°C (decomp.).

7,8,9,10-Tetrahydro-2-(4-bromophenyl)-3*H*,11*H*-[1]benzothieno[2',3':4,5]pyrimido[2,1-*b*][1,3,4]thiadiazin-11-one(12)

from aminothioxo derivative(4): A mixture of compound (**4**) (0.15 g, 0.59 mmol) and 2,4'-dibromoacetophenone (0.20 g, 0.72 mmol) in ethanol/water (8:2) (100 ml) was refluxed for 3 h. Within 2 h yellow microcrystals separated. After cooling, the resulting solid was collected, washed with water, dried and recrystallized from dioxane to give **12** (0.13 g, 51%) as yellow microcrystals, mp 279-280°C(decomp.); ir: ν 1690(C=O) cm^{-1}; ms: (m/z) 431(M^+) and 433(M^+); 1H-nmr($CDCl_3$): 7.58-7.92(m, 4H), 3.90(s, 2H), 3.06(m, 2H), 2.80(m, 2H), 1.87(m, 4H); Anal. Calcd for $C_{18}H_{14}N_3OBrS_2$: C,50.01; H,3.24; N,9.72; S,14.82. Found: C,50.20; H,3.30; N,9.80; S,14.70.

from (4-bromophenyl)-2-oxoethylthio derivative(10a): To a refluxed solution of compound (**10a**) (0.2 g, 0.44 mmol)

in ethanol (150 ml), *p*-toluenesulfonic acid (60 mg) was added: a yellow solid separated. The mixture was refluxed for 2 h. After cooling, the solid was collected, washed with warm ethanol, dried and recrystallized from dioxane to give 12 (40 mg, 21%) as yellow powder, mp 278-280°C(decomp.).

7,8,9,10-Tetrahydro-3*H*,11*H*-[1]benzothieno[2',3':4,5]pyrimido[2,1-*b*][1,3,4]thiadiazine-2(1*H*),11-dione(13).

To a hot solution of sodium (0.07 g, 3.04 mmol) in ethanol (20 ml) thioacetate derivative (10b) (1.0 g, 2.95 mmol) was added over 5 min. The solution, after refluxing for 5 min, was stirred at room temperature for 1 h and then concentrated under reduced pressure. The resulting mixture was acidified with glacial acetic acid (0.2 ml) or 10% hydrochloric acid (1.1 ml) and then stirred for 30 min. The resulting solid was collected, washed with water, dried and recrystallized from dioxane/water to give 13 (0.34 g, 39%) as white powder, mp 258-259°C; ir:ν 3180(NH), 1680(C=O) cm^{-1}; ms: (m/z) 293(M^+); 1H-nmr(DMSO-d_6): 11.71(br s, 1H), 3.84(s, 2H), 2.85(m, 2H), 2.74(m, 2H), 1.78(m, 4H); Anal. Calcd for $C_{12}H_{11}N_3O_2S_2$: C,49.14; H,3.75; N,14.33; S,21.84. Found: C,49.10; H,3.70; N,13.95; S,21.60.

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