New Heterocyclic Structures. [1,3]Thiazino[3,2-*a*]purine and [1,2,3]Triazolo[4,5-*d*][1,3]thiazino[3,2-*a*]pyrimidine

Piergiorgio Pecorari*, Marcella Rinaldi, and Maria Paola Costi

Departimento di Scienze Farmaceutiche, Università di Modena, via S. Eufemia 19, 41100 Modena, Italy

Received December 11, 1988

Derivatives of two new molecular structures, namely, [1,3]thiazino[3,2-*a*]purine and [1,2,3]triazolo[4,5-*d*]-[1,3]thiazino[3,2-*a*]pyrimidine, were synthesized together with other heterocyclic compounds. Retrosynthetic analysis of their molecular skeletons suggested a simple way of obtaining 3,4-dihydro-7,8-diamino-2*H*,6*H*-pyrimido[2,1-*b*][1,3]thiazin-6-one, which is a useful intermediate for their synthesis. This intermediate and the thiazole homologue were obtained directly by reaction of 5,6-diamino-2,3-dihydro-2-thioxo-4(1*H*)-pyrimidinone with 1,3- or 1,2-dibromoalkane, respectively.

J. Heterocyclic Chem., **26**, 1701 (1989).

The polycyclic molecular structures of type **1** (Scheme I), containing pharmacophorous synthons, have not hitherto been studied in any great detail.

Certain derivatives of thiazolo[3,2-*a*]purine (**1**, X = R-C, n = 2) have been the subject of physico-chemical studies [1-3], while others have been investigated for their virucidal, immunoadjuvant and immunosuppressive properties [4].

The polycyclic structure, [1,3]thiazino[3,2-*a*]purine, (**1**, X = R-C, n = 3) is as yet unknown.

The chemical and physico-chemical characteristics of some derivatives of thiazolo[2,3-*b*]pteridine (**1**, X = -C—C-, n = 2) and of [1,3]thiazino[2,3-*b*]pteridine (**1**, X = -C-C-, n = 3) have been studied [5].

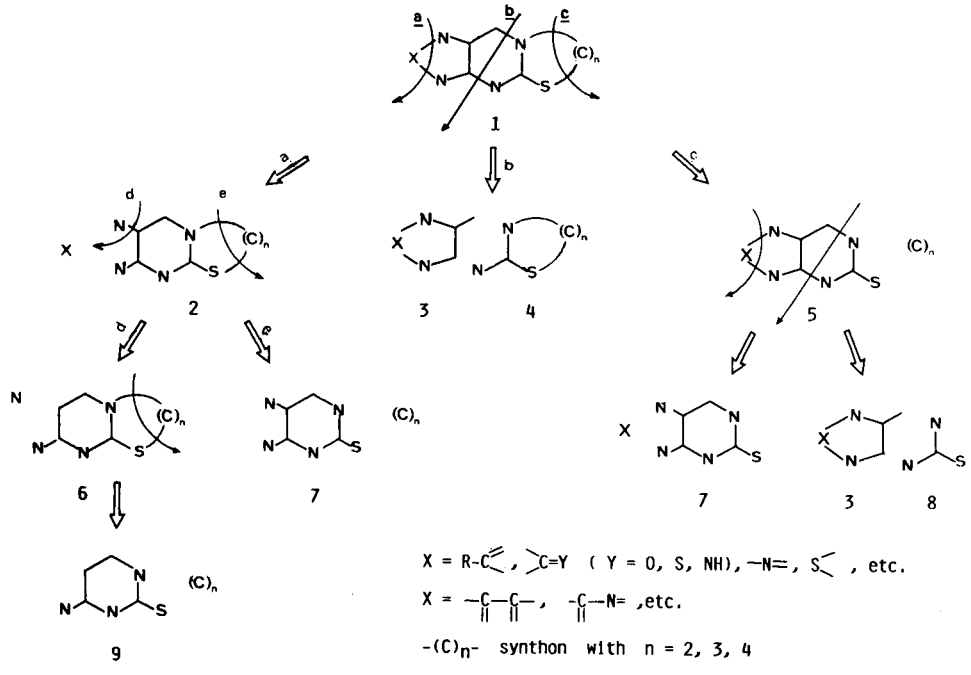
The antiallergic and antihistaminic activity [6,7] of some derivatives of thiazoloazapurine (**1**, X = -N=, n = 2) is known, while no derivative of thiazinoazapurine (**1**, X = -N=, n = 3) is reported in the literature up-to-date.

There is known to be interest in the pharmacophorus synthon thiazolopyrimidine (**6**, n = 2), which is present in some drugs proposed as immunomodulators (TEI 3096) [8], serotonergic antagonists and anxiolytics (Ritanserin) [9], or as neuroleptics (Setoperone) [10].

There has been scant interest in the framework pyrimido[2,1-*b*][1,3]thiazine (**6**, n = 3) and little has been written about its biological activity.

Retrosynthetic analysis of the molecular skeleton **1**, carried out as indicated in the literature [11-13], produces the

Scheme I



SCHEME II (+)

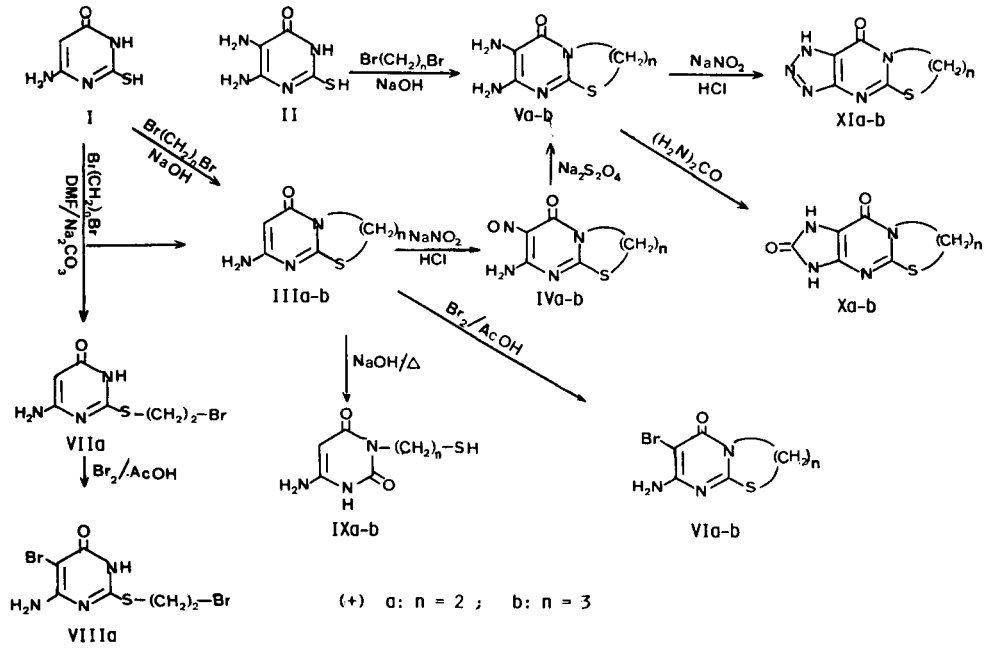


Table 1

Properties of Di- and Tri-heterocyclic Compounds

Compound	Yield (%) [a]	Mp °C	Crystallization solvent [b]	Molecular formula	Analyses Calcd./Found. C	H	N
IIIa	65 [f]	273-274 [c]	DE	$C_6H_7N_3OS$	42.58 42.33	4.17 4.12	24.83 24.72
IIIb	69	258-260	EE	$C_7H_9N_3OS$	45.88 45.80	4.95 4.93	22.93 22.93
IVa	90	239-241 [d]	D	$C_6H_6N_4O_2S$	36.35 36.18	3.05 2.98	28.26 27.98
IVb	93	235-237	DE	$C_7H_8N_4O_2S$	39.61 39.47	3.79 3.74	26.14 25.91
Va	82 [f] 67 [g]	203-205 [e]	W	$C_6H_8N_4OS$	39.11 38.85	4.37 4.33	30.41 30.20
Vb	84 [f] 65 [g]	244-247	W	$C_7H_{10}N_4OS$	42.40 42.64	5.08 5.18	28.26 28.41
VIa	82	219-222	DE	$C_6H_6BrN_3OS$	29.04 28.83	2.43 2.28	16.93 16.70
VIb	90	188-189	DE	$C_7H_8BrN_3OS$	32.07 32.15	3.07 2.88	16.03 15.90
Xa	69	>310	DAE	$C_7H_6N_4O_2S$	39.99 39.99	2.88 3.10	26.65 26.38
Xb	85	>310	DE	$C_8H_8N_4O_2S$	42.85 42.69	3.52 3.51	24.99 24.72
XIa	78	224 dec	DE	$C_6H_5N_5OS$	36.91 36.66	2.58 2.44	35.88 35.49
XIb	77	291-292	W	$C_7H_7N_5OS$	40.18 40.02	3.37 3.17	33.47 33.71

[a] Yield refers to the final product, before crystallization. [b] Crystallization solvents: water (W), dimethylformamide (D), ethanol/ethyl ether (EE), dimethylformamide/ethyl ether (DE), dimetilformamide/ethanol (DEO), dimethylacetamide/ethyl ether (DAE). [c] 274-277° [5] (DEO). [d] 239-243° [5] (D). [e] 204-207° [5] (W). [f] Method A. [g] Method B.

geneological tree represented in Scheme I.

The most immediate disconnections *a* and *c* determine, in a synthetic sense, known reactions of cyclization and interconversion of functional groups.

Disconnection *b* generates synthon **3**, the synthetic equivalents of which appear to be only slightly reactive.

Taking this analysis as its starting point, the present study sets out to synthesize new molecular skeletons, namely, new condensed thiazino-derivatives, by means of easy and efficient processes.

Scheme II is a detailed representation of the reactions corresponding to disconnection *a*.

In order to obtain the required heterocycles **Xa-b** and **XIa-b**, the essential intermediates are the compounds **Va-b**.

These intermediates can be obtained in two ways: **I** → **IIIa-b** → **IVa-b** → **Va-b** corresponding to disconnection *d*, or **II** → **Va-b** corresponding to disconnection *e*.

It is known that the cyclization of non-symmetrical derivatives of 2-thiouracil with 1,2-difunctional reagents gives rise to the formation of the two isomers, thiazolo-[3,2-*a*]pyrimidin-5-one and 7-one [14-16]; on the other hand, cyclization of 6-amino-2,3-dihydro-2-thioxo-4(1*H*)pyrimidinone (6-amino-2-thiouracil) (**I**) with 1,2-dibromoethane yields only the isomer 5-oxo **IIIa** [5].

Previous research [17] showed that reaction of 5,6-diamino-2,3-dihydro-2-thioxo-4(1*H*)-pyrimidinone (**II**) with two equivalents of alkyl halide produces alkylation only at S and at N^3. No trace of alkylated product at S and N^1 or at S and at the amino groups was found.

These observations showed **II** → **Va-b** to be the shortest route to the required intermediates.

The reaction **II** → **Va-b** was carried out and the structures of **Va-b** were confirmed by means of the sequence **I** → **IIIa-b** → **IVa-b** → **Va-b**.

Table 2

^{1}H-NMR, UV and IR Spectral Data of the Di- and Tricyclic Compounds

Compound	^{1}H-NMR (δ ppm) [a]	UV λ max nm (log ε) [b]	IR (cm^{-1}) [f] NH_2,	C=O
(IIIa)	3.41 (t, 2H, SCH_2), 4.17 (t, 2H, NCH_2), 4.79 (s, 1H, 6-H), 6.47 (s, 2H, 7-NH_2)	220.9 (4.29) 270.1 (3.62)	3390 3180	1630 1600
(IIIb)	2.06 (m, 2H, CCH_2C), 3.11 (t, 2H, SCH_2), 3.80 (t, 2H, NCH_2), 4.86 (s, 1H, 7-H), 6.37 (s, 2H, 8-NH_2)	217.7 (4.31) 233.7 (4.29) 280.9 (3.75)	3400 3165	1640 1620
(IVa)	3.55 (t, 2H, SCH_2), 4.38 (t, 2H, NCH_2), 9.06 and 11.17 [c]	212.7 (4.22) 277.4 (3.82) 342.6 (4.24)	3260 3150	1680 1630
(IVb)	2.19 (m, 2H, CCH_2C), 3.19 (t, 2H, SCH_2), 4.01 (t, 2H, NCH_2), 8.81 and 10.75 [c]	216.6 (4.24) 273.1 (3.77) 346.8 (4.32)	3280 3140	1690 1630
(Va) [d]	3.44 (t, 2H, SCH_2), 4.21 (t, 2H, NCH_2), 5.72 (s, 2H, 7-NH_2)	219.1 (4.29) 293.4 (3.92)	3330 3160	1670 1625
(Vb)	2.07 (m, 2H, CCH_2C), 3.09 (t, 2H, SCH_2), 3.52 (s, 2H, 7-NH_2), 3.88 (t, 2H, NCH_2), 5.68 (s, 2H, 8-NH_2)	230.2 (4.15) 305.7 (3.79)	3350 3180	1660 1620
(VIa)	3.48 (t, 2H, SCH_2), 4.24 (t, 2H, NCH_2), 6.81 (s, broad band, 7-NH_2)	223.0 (4.34) 272 (sh) (3.75) 287.8 (3.85)	3400 3150	1640 1605
(VIb)	2.09 (m, 2H, CCH_2C), 3.12 (t, 2H, SCH_2), 3.86 (t, 2H, NCH_2), 6.71 (s, 2H, 8-NH_2)	218.1 (4.30) 233.8 (4.29) 291.6 (3.94)	3400 3150	1640 1610
(Xa)	3.53 (t, 2H, SCH_2), 4.35 (t, 2H, NCH_2), 10.85 and 11.20 (s, NH)	213.1 (4.32) 267.6 (4.00) 301.6 (3.88)		1730
(Xb)	2.12 (m, 2H, CCH_2C), 3.17 (t, 2H, SCH_2), 3.99 (t, 2H, NCH_2), 10.80 and 11.24 (s, NH)	214.8 (4.28) 268.7 (3.40) 308.6 (3.88)		1730 1665
(XIa) [e]	3.59 (t, 2H, SCH_2), 4.39 (t, 2H, NCH_2)	204.9 (4.15) 227.6 (4.00) 266.7 (3.97)		1705
(XIb)	2.18 (m, 2H, CCH_2), 3.21 (t, 2H, SCH_2), 4.05 (t, 2H, NCH_2)	206.0 (3.83) 230 (sh) (3.71) 275.3 (3.75)		1690

[a] Dimethyl sulfoxide-d_6. [b] In ethanol. [c] Two large singlets, attributable to intramolecular hydrogen bond N-H--O=N. [d] Large band between 3.50-3.33 ppm, attributable to 6-NH_2. [e] Broadest and low band between 8.50-6.00 ppm. [f] Frequency ranges (ν).

Cyclization of **I** and **II** with 1,2- or 1,3-dibromoalkane was carried out both in alkaline aqueous solution and in DMF. In the latter solvent, the reaction proved more complex; for example, reaction of **I** with 1,2-dibromoethane yielded the alkylthiouracil derivative **VIIa** in addition to the cyclized product **IIIa**.

The cyclized compound **IIIa-b** were confirmed by means of the physico-chemical characteristics of their hydrolysis products **IXa-b**, obtained according to [18].

The polyheterocyclic compounds **Xa-b** and **XIa-b** were prepared from **Va-b** by means, respectively, of fusion with urea or of reaction with sodium nitrite-hydrochloric acid.

The structures of all the synthesized compounds were also confirmed by means of their ir, uv and ^{1}H-nmr spectra (Table II).

The present study describes the synthesis of two new heterocyclic rings, shows that the intermediates **Va-b** can be obtained rapidly and in good yield (65-70%) by means of reaction **II** → **Va-b**, and, furthermore, that 5,6-diamino-2,3-dihydro-2-thioxo-4(1*H*)-pyrimidinone reacts with 1,2- and 1,3-dihalogenated electrophiles first at S and then at N^3.

EXPERIMENTAL

Substances (**I**) and (**II**) were purchased from Sigma Chemical Co.. Melting points were determined on a Büchi 510 apparatus and are uncorrected. The ir spectra were recorded in potassium bromide pellets or in Nujol suspension on a Perkin Elmer spectrophotometer Model 681. The uv specta were obtained with a Perkin Elmer spectrophotometer Model Lambda 5, using 1 cm quarz cells in 10^{-5} *M* ethanolic solution. The absorption maxima are reported in nanometers. The ^{1}H-nmr spectra were recorded with a Varian spectrometer Model XL 200 (Centro Interdipartimentale Grandi Strumenti, Università di Modena) in DMSO-d_6 solution. Chemical shifts are reported in ppm from tetramethylsilane used as internal standard and are given in δ units. The following abbreviations were used to designate the multiplicity of individual signals: s = singlet, t = triplet and m = multiplet.

Microanalyses were carried out by Miss S. Selmi, to whom we are grateful, in the Microanalysis Laboratory of Dipartimento di Scienze Farmaceutiche, Università di Modena.

7-Amino-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (**IIIa**), 8-Amino-3,4-dihydro-2*H*,6*H*-pyrimido[2,1-*b*][1,3]thiazin-6-one (**IIIb**).

Method A.

Propan-2-ol (40 ml) was added to an equal volume of a 2*N* sodium hydroxide solution containing 6-amino-2,3-dihydro-2-thioxo-4(1*H*)-pyrimidinone (6-amino-2-thiouracil) (**I**) (5 g, 35 mmoles) and then either 1,2-dibromoethane or 1,3-dibromopropane (40 mmoles) were stirred in dropwise at room temperature. The solution was stirred at room temperature for 5 hours and then at 60° for another 4 hours. After being left to stand overnight at room temperature, it was saturated with carbon dioxide, whereupon it yielded **IIIa** or **IIIb**, respectively.

The mother waters were dried out under rotary evaporation and the resultant residue was finely powdered and repeatedly extracted with boiling propan-2-ol. Evaporation of the alcoholic fraction left a substance which, when treated with a solution of sodium carbonate, was found to consist of **IIIa** or **IIIb**, **IIIa**, 3.8 g, and **IIIb**, 4.5 g.

Method B.

6-Amino-2-thiouracil (**I**) (5 g, 35 mmoles) was added slowly into a stirred mixture of DMF (15 ml), 1,2-dibromoethane (40 mmoles) and sodium carbonate decahydrate (4.5 g). After two hours at room temperature the reaction mixture was heated under stirring for 10-12 hours at 60-65° and then refrigerated.

The insoluble fraction of the reaction liquid was suspended in water and treated with sodium carbonate until the *p*H reached 9-10. The insoluble residue consisted of **IIIa**. Acidification of the soluble fraction in sodium carbonate with concentrated acetic acid separated a compound which was crystallized from boiling water, mp 310° dec (H_2O), 1.3 g, yield 15%; ir: ν max cm^{-1} 3380, 3165 (NH_2), 1660, 1610 (C=O), 1195, 720; uv (ethanol): λ max, nm (log ϵ) 267 (3.68), 217.4 (4.08); ^{1}H-nmr (DMSO-d_6): δ 8.46 (s, 2H, 6-NH_2), 5.72 (s, 1H, 5-H), 4.43 (t, 2H, $BrCH_2$), 3.68 (t, 2H, SCH_2).

Anal. Calcd. for $C_6H_8BrN_3OS$: C, 28.81; H, 3.22; N, 16.80. Found: C, 28.73; H, 2.92; N, 16.70.

On the basic of its ir, uv and ^{1}H-nmr spectra and of the data of elementary analysis, this product proved to be 6-amino-2-(2-bromoethylthio)-4(3*H*)-pyrimidinone (**VIIa**).

The soluble fraction in the reaction liquid was concentrated to near-dryness and the residue treated with a solution of sodium carbonate until alkaline *p*H. The insoluble fraction consisted of 2.42 g of **IIIa**, yield 41%.

7-Amino-2,3-dihydro-6-nitroso-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (**IVa**) and 8-Amino-3,4-dihydro-7-nitroso-2*H*,6*H*-pyrimido[2,1-*b*]-[1,3]thiazin-6-one (**IVb**).

Compound **IIIa** or **IIIb** (1 g, 6 mmoles), finely powdered, was added slowly into a stirred solution of 15% acetic acid (40 ml) at 35-40°, until it dissolved. The solution was cooled to room temperature and sodium nitrite (0.45 g, 6.5 mmoles in 2 ml of water) was slowly added dropwise, stirring at the same temperature for another 6 hours. The blue product formed was collected and crystallized from an appropriate solvent, **IVa**, 1.05 g and **IVb**, 1.07 g.

6,7-Diamino-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (**Va**) and 7,8-Diamino-3,4-dihydro-2*H*,6*H*-pyrimido[2,1-*b*][1,3]thiazin-6-one (**Vb**).

Method A.

Recently purchased sodium hydrosulfite was added slowly to a suspension of nitrose derivative **IVa** (0.5 g, 25 mmoles) or (**IVb**) (0.54 g, 25 mmoles) in boiling water (25 ml) until the blue colour completely disappeared. The pale-yellow solution was refluxed for 5 minutes and then refrigerated for 2 hours. The resultant precipitate consisted of **Va** (0.385 g) or **Vb** (0.390 g), respectively.

Method B.

5,6-Diamino-2,3-dihydro-2-thioxo-4(1*H*)-pyrimidinone (**II**) (5 g, 31 mmoles) was dissolved in 2*N* sodium hydroxide (32 ml) and propan-2-ol (32 ml) was then added. A light precipitate was immediately formed. 1,2-Dibromoethane or 1,3-dibromopropane (38 mmoles) were then slowly stirred into the reaction mixture at room temperature, stirring continuing at the same temperature

for 2 hours and then at 60-70° for a further 5 hours. In the reaction with 1,2-dibromoethane, a first precipitate was obtained by cooling the mixture and saturating it with carbon dioxide; in the reaction with 1,3-dibromopropane, the precipitate was formed simply cooling. When the precipitate was treated with a solution of sodium carbonate, it yielded an insoluble fraction which, when crystallized from an appropriate solvent, exhibited physical and physico-chemical characteristics identical to those of **Va** and **Vb**, respectively.

The soluble fraction in sodium carbonate solution consisted of a mixture of hitherto unidentified compounds.

When the residue obtained by concentration to near-dryness was similarly treated with sodium carbonate, it yielded further **Va** or **Vb**, **Va**, 3.8 g and **Vb**, 4.03 g.

7-Amino-6-bromo-2,3-dihydro-5*H*-thiazolo[3,2-*a*]pyrimidin-5-one (**VIa**) and 8-Amino-7-bromo-3,4-dihydro-2*H*,6*H*-pyrimido[2,1-*b*]-[1,3]thiazin-6-one (**VIb**).

Bromine (7.5 mmoles) at room temperature was stirred dropwise into solution of **IIIa** (1 g, 6 mmoles) or **IIIb** (1 g, 6 mmoles) in glacial acetic acid (24 ml). The reaction mixture was stirred at room temperature for 8 hours and left to stand overnight. The resultant precipitate was collected, washed with ethyl ether and proved to consist of **VIa·HBr** (1.84 g) and **VIb·HBr** (1.81 g), respectively. **VIa·HBr**, yield 95%, mp 268-270° (methanol/ethyl ether); ^{1}H-nmr (DMSO-d_6): δ 7.29 (large band, 2H, 7-NH_2); 4.24 (t, 2H, NCH_2), 3.47 (t, 2H, SCH_2).

Anal. Calcd. for $C_6H_7Br_2N_3OS$: C, 21.90; H, 2.14; N, 12.77. Found: C, 22.20; H, 2.04; N, 12.90.

Compound **VIb·HBr** was obtained in a yield of 97%, mp 269-272° dec.

Anal. Calcd. for $C_7H_9Br_2N_3OS$: C, 25.70; H, 2.77; N, 12.85. Found: C, 25.43; H, 2.70; N, 12.98.

When the hydrobromide **VIa·HBr** (0.5 g) or **VIb·HBr** (0.5 g) was treated with a solution of sodium carbonate until *p*H 10, it yielded a product consisting of **VIa** (0.34 g, 91%) or **VIb** (0.35 g, 93%), respectively.

6-Amino-5-bromo-2(2-bromoethylthio)-3*H*,4*H*-pyrimidin-4-one (**VIIIa**).

Compound **VIIIa** was obtained from **VIIa** (0.20 g) operating under the same conditions as for synthesis of **VIa**, (0.23 g, yield 88%) mp 270° dec (methanol/ethyl ether); ir: ν max cm^{-1} 3420, 3160 (NH_2), 1630 (C=O), 1190, 720; uv (ethanol): λ max nm (log ϵ) 275 (3.98), 227 (4.28); ^{1}H-nmr (DMSO-d_6): 8.35 (s, 2H, 6-NH_2), 4.51 (t, 2H, $BrCH_2$), 3.70 (t, 2H, SCH_2).

Anal. Calcd. for $C_6H_7Br_2N_3OS$: C, 21.90; H, 2.14; N, 12.77. Found: C, 22.18; H, 2.22; N, 13.00.

6-Amino-3-(2-mercaptoethyl)-2,4-(1*H*,3*H*)-pyrimidinedione (**IXa**) and 6-Amino-3-(3-mercaptopropyl)-2,4-(1*H*,3*H*)-pyrimidinedione (**IXb**).

A suspension of **IIIa** or **IIIb** (0.5 g, 3 mmoles) in 2*N* sodium hydroxide solution was refluxed for 2 hours. The resultant solution was acidified with hydrochloric acid (1:1 v:v) until *p*H 3 and left to stand overnight. The precipitate was collected and crystallized from an appropriate solvent, **IXa**, 0.3 g, yield 55%, mp 247-249° (H_2O); ir: ν max cm^{-1} 3400, 3180 (NH_2), 1710, 1650 (C=O), 1285, 785; uv (ethanol): λ max nm (log ϵ) 263 (4.24), 202 (3.93); ^{1}H-nmr (DMSO-d_6): δ 10.41 (s, 1H, NH), 6.22 (s, 2H, 6-NH_2), 4.52 (s, 1H, 5-H), 3.77 (t, 2H, NCH_2), 2.50 (t, 2H, SCH_2).

Anal. Calcd. for $C_6H_9N_3O_2S$: C, 38.49; H, 4.44; N, 22.56. Found: C, 38.21; H, 4.64; N, 22.32.

Compound **IXb**, (0.27 g), yield 50% had mp 248-250° dec (ethanol); ir: ν max cm^{-1} 3380, 3190 (NH_2), 1690, 1655 (C=O), 1280, 780; uv (ethanol): λ max nm (log ϵ) 264 (4.25), 202 (4.00), ^{1}H-nmr (DMSO-d_6): δ 10.42 (s, 1H, NH), 6.26 (s, 2H, 6-NH_2), 4.52 (s, 1H, 5-H), 3.71 (t, 2H, NCH_2), 2.38 (t, 2H, SCH_2), 1.71 (m, 2H, CCH_2C).

Anal. Calcd. for $C_7H_{11}N_3O_2S$: C, 41.77; H, 5.51; N, 20.88. Found: C, 41.51; H, 5.39; N, 20.61.

1,3,6,7-Tetrahydrothiazolo[3,2-*a*]purine-2,9-dione (**Xa**) and 1,3,7,8-Tetrahydro[1,3]thiazin[3,2-*a*]purine-2,10-dione (**Xb**).

Compound **Va** or **Vb** (1 g, 52 mmoles), mixed with urea (0.7 g, 116 mmoles), was heated at 180-185° and 190-195°, respectively, until resolidification was complete (60 minutes). The cooled solid was treated with 0.5*N* sodium hydroxide solution. The resultant solution was acidified and yielded a crystalline precipitate consisting of **Xa** (0.78 g) and **Xb** (0.96 g), respectively.

6,7-Dihydrothiazolo[3,2-*a*][1,2,3]triazolo[4,5-*d*]pyrimidin-9(1*H*)-one (**XIa**) and 7,8-Dihydro-[1,2,3]triazolo[4,5-*d*][1,3]thiazino-[3,2-*a*]pyrimidin-10(1*H*)-one (**XIb**).

Crystalline sodium nitrite (0.22 g, 32 mmoles) was added slowly into a stirred suspension of **Va** (0.5 g, 27 mmoles) or **Vb** (0.5 g, 25 mmoles), respectively, in 20 ml of hydrochloric acid (1:1 v:v) in an ice bath.

In the case of **Va**, the solution was left to stand at room temperature for a day, heated at 50° for 40 minutes and then concentrated to half volume and cooled. The resultant product consisted of **XIa** (0.41 g). In the case **Vb**, after being continuously stirred at room temperature for some hours, the solution precipitated a crystalline substances which, recovered after being left to stand overnight, proved to consist of **XIb** (0.41 g).

REFERENCES AND NOTES

[1] R. W. Balsiger, A. L. Fikes, T. P. Johnston, and J. A. Montgomery, *J. Org. Chem.*, **26**, 3446 (1961).

[2] R. Marumoto, Y. Yoshioka, and M. Honjo, *Chem. Pharm. Bull.*, **22**, 342 (1974).

[3] J. A. Montgomery and H. J. Thomas, *J. Heterocyclic Chem.*, **17**, 583 (1980).

[4] J. W. Hadden, L. N. Simon, and A. Giner-Sorolla, European Patent Appl. EP 73,490; *Chem. Abstr.*, **99**, 105273p (1983).

[5] E. Falch, *Acta Chem. Scand.*, **B31**, 167 (1977).

[6] P. Chaplen, E. Lunt, S. Marshall, D. Pain, and K. Wooldridge, *Eur. J. Med. Chem., Chim. Ther.*, **10**, 447 (1975).

[7] S. Isoda, N. Suzuki, T. Miwa, and S. Aibara, European Patent Appl. EP 159707; *Chem. Abstr.*, **104**, 168482 (1986).

[8] E. Arrigono-Martelli, *Drugs of the Future*, **9**, 591 (1984).

[9] Chemical Editorial Staff (CES), *Drugs of the Future*, **11**, 391 (1986).

[10] *Anu. Drug Data Rep.*, **6**, 156 (1984); Ref [9].

[11] E. J. Corey, *Pure Appl. Chem.*, **14**, 19 (1967), and his further papers on the same topic.

[12] S. Warren, "Organic Synthesis: The Disconnection Approach", John Wiley, NY 1982.

[13] J. Fuhrhop and G. Penzlin, "Organic Synthesis, Concepts, Methods, Starting Materials", Verlag Chemie, Weinheim, 1983.

[14] G. R. Brown and W. R. Dyson, *J. Chem. Soc. (C)*, 1527 (1971).

[15] E. Campaigne, J. C. Huffman, and T. P. Selby, *J. Heterocyclic Chem.*, **16**, 725 (1979).

[16] K. Undheim in "Comprehensive Heterocyclic Chemistry", Vol **6**, A. R. Katrinksy and C. W. Rees, eds, Pergamon press, London 1984, pp 613-748.

[17] P. Pecorari, M. Melegari, M. Rinaldi, and M. P. Costi, *Boll. Chim. Farm.*, **127**, 71 (1988).

[18] E. Falk and T. Natvig, *Acta Chem. Scand.*, **24**, 1423 (1970).