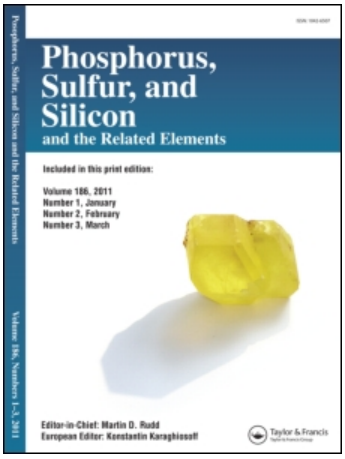

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REACTIONS WITH 6-METHYL-2-THIOURACIL SYNTHESIS OF DIPYRIMIDINO[2,1-b:1',2'-c]THIAZINE. A NEW RING SYSTEM

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REACTIONS WITH 6-METHYL-2-THIOURACIL SYNTHESIS OF DIPYRIMIDINO[2,1-b:1′,2′-c]THIAZINE. A NEW RING SYSTEM

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Bromination of 6-methyl-2-thiouracil (**I**) gave the 5-bromo analogue **II**. Alkylation of each of **I** and **II** yielded the S-alkyl derivatives **IIIa–g**. Cyclisation of **IIIa,c** gave the 3,7-dimethylthiazolo[3,2-a]pyrimidines **VIIa,b**. The 2-arylmethylenethiazolo[3,2-a]pyrimidines **VIa–i** were synthesized via the reaction of either **I** or **II** with a mixture of chloroacetic acid and aromatic aldehydes. The 2-methylthiopyrimidine analogue **VIII** reacted with aromatic amines to produce the 2-arylamino derivatives **IXa,b**. Condensation of the 2-hydrazino analogue **X** with aromatic aldehydes formed the Schiff's bases **XIa–e**. The analogue **XIb** could be cyclised by bromine into the 6-bromo-s-triazolo[4,3-a]pyrimidine derivative **XIII**. The reaction of **X** with each of carbon disulphide and chloroacetyl chloride gave the s-triazolo[4,3-a]pyrimidine **XVII** and pyrimido[2,1-c]-as-triazine **XIX** derivatives, respectively. Also, compound **X** reacted with either 2,4-pentanedione, 3-chloro-2,4-pentanedione or 1,1,1-trifluoro-2,4-pentanedione to form the 2-pyrazolylpyrimidines **XXIa–c**, respectively. Malononitrile added to **XXII** to yield the dipyrimidino-[2,1-b:1′,2′-c]thiazine **XXIII** with a new ring system.

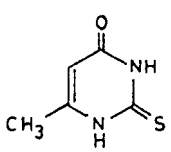
Key words: 2-Thiouracil; thiazolopyrimidine; triazolopyrimidine; dipyrimidinothiazine.

INTRODUCTION

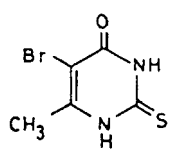
The chemistry and biological activity of pyrimidine functionality fused to heterocyclic ring systems have attracted the attention of many workers,[1–8] and this led our research group to initiate studies with the aim of the synthesis of fused pyrimidines.[9–14] We report here the syntheses of thiazolo[3,2-a], s-triazolo[4,3-a]pyrimidines and pyrimido[2,1-c]-as-triazine. Also, we describe a new synthesis of the dipyrimidino-[2,1-b:1′,2′-c]-1,3-thiazine derivative with a new ring system.

DISCUSSION

Treatment of 6-methyl-2-thiouracil (**I**) with an equimolar amount of bromine in acetic acid yielded the 5-bromo-6-methyl-2-thiouracil (**II**).



I



II

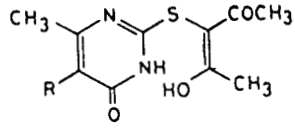
The ir spectrum of **II** displayed absorption bands in the NH and CO regions and the signal corresponding to the pyrimidine-H_5 in its precursor **I** disappeared in the ^{1}H-nmr spectrum (DMSO-d_6).

Alkylation of **I** and **II** with halogeno compounds, in ethanolic sodium ethoxide, gave the corresponding S-alkyl derivatives **IIIa–g**.

III

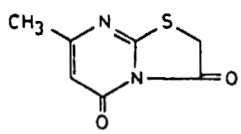
	R	R^1
a	H	CH_2COCH_3
b	H	$CH_2COOC_2H_5$
c	H	$CH(COCH_3)_2$
d	Br	CH_3
e	Br	C_2H_5
f	Br	$CH_2COC_6H_5$
g	Br	$CH(COCH_3)_2$

The assignment of structure **III** to the reaction products was based on analytical and spectral data (see Table I). Derivatives **IIIc,g** most probably exist in the enolic form **III'**, they gave deep violet colour with ferric chloride solution.

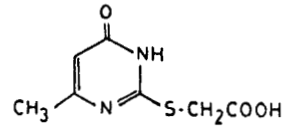


III'

The S-carboxymethyl analogue **V** could be obtained, indirectly, by boiling the 7-methyl-2,3-dihydro-5H-thiazolo[3,2-a]pyrimidine-3,5-dione (**IV**)[15] with water.



IV



V

The ir spectrum of **V** displayed absorption bands at 3120 (broad, OH and NH), 1680 and 1646 cm^{-1} (2CO). Heating a mixture of either **I** or **II**, chloroacetic acid, aromatic aldehydes in acetic acid and acetic anhydride containing sodium acetate afforded the 2-arylmethylene-7-methyl-6-substituted-2,3-dihydro-5H-thiazolo[3,2-a]pyrimidine-3,5-diones (**VIa–i**).

TABLE I

2-Alkylthio-6-methyl-5-substituted-3,4-dihydropyrimidin-4-ones (**IIIa–g**)

Comp. No.	M.p. °C solvent	Yield (%)	R	R'	Formula (M.W.)	Analysis % Calcd. / Found C	H	N	S	IR (cm^{-1})
IIIa	97 Benz./ Pet.ether	69	H	CH_2COCH_3	$C_8H_{10}N_2O_2S$ (198.2)	48.47 48.30	5.08 5.20	14.13 14.00	16.17 16.20	2755 (CH and NH, broad with intermolecular hydrogen bond), 1674, 1662 (2 CO).
IIIb	140 H_2O	67	H	$CH_2CO_2C_2H_5$	$C_9H_{12}N_2O_3S$ (228.3)	47.36 47.50	5.30 5.20	12.27 12.30	14.05 14.00	2760 (CH and NH, broad with intermolecular hydrogen bond), 1750, 1662 (2 CO).
IIIc•	175 EtOH	77	H	$CH(COCH_3)_2$	$C_{10}H_{12}N_2O_3S$ (240.3)	49.99 50.10	5.03 4.80	11.66 11.70	13.34 13.50	3050 (broad, OH and NH with intermolecular hydrogen bond), 1680, 1660 (2 CO).
IIId(1)	240 Dioxane	75	Br	CH_3	$C_6H_7BrN_2OS$ (235.1)	30.65 30.50	3.00 3.10	11.92 12.10	13.64 13.50	2750 (CH and NH, broad with intermolecular hydrogen bond0, 1660 (CO).
IIIe+(2)	187 dil. EtOH	73	Br	C_2H_5	$C_7H_9BrN_2OS$ (249.1)	33.75 33.80	3.64 3.60	11.24 11.30	12.87 13.00	2745 (CH and NH, broad with intermolecular hydrogen bond), 1660 (CO).
IIIf(3)	200 EtOH	78	Br	$CH_2COC_6H_5$	$C_{13}H_{11}BrN_2O_2S$ (339.2)	46.03 45.90	3.27 3.10	8.26 8.10	9.45 9.30	2760 (CH and NH, broad with intermolecular hydrogen bond), 1690, 1670 (2 CO).
IIIg(4)	>300 dil. DMF	76	Br	$CH(COCH_3)_2$	$C_{10}H_{11}BrN_2O_3S$ (319.2)	37.63 37.50	3.47 3.50	8.78 8.80	10.05 10.10	3100 (broad, OH and NH with intermolecular hydrogen bond), 1685, 1665 (2 CO).

Br, Found (Calcd.): (1) 34.10 (33.99); (2) 32.10 (32.07); (3) 23.50 (23.56); (4) 24.90 (25.03).

• ^{1}H-nmr (DMSO-d_6): δ2.01 (s, 3, CH_3), 2.08 (s, 3, CH_3), 2.21 (s, 3, CH_3), 6.09 (s, 1, pyrimidine proton), 7.90 (s, OH, disappeared after deuterium oxide exchange) and 12.56 ppm (broad s, 1, NH, disappeared after deuterium oxide exchange).

+ ^{1}H-nmr (DMSO-d_6): δ1.30 (t, 3, CH_3); 2.38 (s, 3, CH_3); 3.15 (q, 2, CH_2) and 13.05 ppm (broad s, 1, disappeared after deuterium oxide exchange).

TABLE II

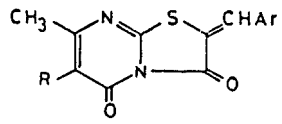
2-Arylmethylene-7-methyl-6-substituted-2,3-dihydro-5H-thiazolo[3,2-a]pyrimidine-3,5-diones (**VIa–i**)

Comp. No.	M.p.°C solvent	Yield (%)	R	Ar	Formula (M.W.)	Analysis % Calcd. / Found C	H	N	S	IR (cm^{-1})
VIa	200 AcOH	75	H	C_6H_5	$C_{14}H_{10}N_2O_2S$ (270.3)	62.21 / 61.90	3.73 / 3.80	10.36 / 10.20	11.86 / 11.90	3080, 2970 (CH), 1750, 1670 (2 CO).
VIb*	235 DMF	78	H	$C_6H_4OCH_3$-p	$C_{15}H_{12}N_2O_3S$ (300.3)	59.99 / 60.00	4.03 / 3.80	9.33 / 9.20	10.68 / 10.70	3090, 2990 (CH), 1740, 1670 (2 CO).
VIc[1]	230 DMF	73	H	C_6H_4Cl-p	$C_{14}H_9ClN_2O_2S$ (304.8)	55.18 / 55.30	2.98 / 3.10	9.19 / 9.00	10.52 / 10.50	3085, 2980 (CH), 1743, 1665 (2 CO).
VId[2]	192 dil. DMF	70	H	C_6H_4Cl-o	$C_{14}H_9ClN_2O_2S$ (304.8)	55.18 / 55.20	2.98 / 2.80	9.19 / 9.30	10.52 / 10.60	3063, 2930 (CH), 1760, 1675 (2 CO).
VIe	269 DMF	80	H	$C_6H_4N(CH_3)_2$-p	$C_{16}H_{15}N_3O_2S$ (313.4)	61.32 / 61.30	4.82 / 4.80	13.41 / 13.50	10.23 / 10.30	3060, 2920 (CH), 1744, 1665 (2 CO).
VIf	267 dil. DMF	70	H	C_4H_3O-2	$C_{12}H_8N_2O_3S$ (260.3)	55.38 / 55.20	3.10 / 3.20	10.76 / 10.80	12.32 / 12.40	3060, 2940 (CH), 1770, 1662 (2 CO).
VIg	242 DMF	72	H	C_4H_3S-2	$C_{12}H_8N_2O_2S_2$ (276.3)	52.16 / 52.20	2.92 / 3.00	10.14 / 10.20	23.21 / 23.20	3070, 2950 (CH), 1767 1662 (2 CO).
VIh+[3]	245 DMF	76	Br	$C_6H_4OCH_3$-p	$C_{15}H_{11}BrN_2O_3S$ (379.2)	47.51 / 47.40	2.92 / 2.80	7.39 / 7.40	8.45 / 8.50	3075, 2990 (CH), 1760, 1670 (2 CO).
VIi[4]	245 DMF	78	Br	$C_6H_4N(CH_3)_2$-p	$C_{16}H_{14}BrN_3O_2S$ (392.3)	48.99 / 49.00	3.60 / 4.50	10.71 / 10.80	8.17 / 8.00	3090, 2920 (CH), 1750, 1660 (2 CO).

Cl, Foung (Calcd.): (1) 11.50 (11.63); (2) 11.70 (11.63); Br, Found (Calcd.): (3) 20.90 (21.07); (4) 20.50 (20.37).

* ^{1}H-nmr (DMSO-d_6): δ 2.15 (s, 3, CH_3); 3.90 (s, 3, OCH_3), 6.18 (s, 1, pyrimidine proton), 7.25 (d,2, aromatic protons), 7.65 (d, 2, aromatic protons) and 8.25 ppm (s, 1, methylenic proton).

+ ^{1}H-nmr (DMSO-d_6): δ 2.40 (s, 3, CH_3), 3.85 (s, 3, OCH_3), 7.18 (d, 2, aromatic protons), 7.73 (d, 2, aromatic protons), and 8.08 ppm (s, 1, methylenic proton).

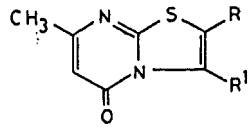


VI

	R	Ar
a,	H	C_6H_5
b,	H	$C_6H_4OCH_3$-p
c,	H	C_6H_4Cl-p
d,	H	C_6H_4Cl-o
e,	H	$C_6H_4N(CH_3)_2$-p
f,	H	C_4H_3O-2
g,	H	C_4H_3S-2
h,	Br	$C_6H_4OCH_3$-p
i,	Br	$C_6H_4N(CH_3)_2$-p

Structure **VI** was inferred from the following (a) Compound **VIa** could be obtained from each of **IV** and **V** by the reaction with benzaldehyde in acetic acid and acetic anhydride. (b) The ir spectra of **VIa–i** displayed characteristic bands. The ^{1}H-nmr spectra (DMSO-d_6) agreed with the proposed structure (Table II).

Cyclisation of **IIIa,c**, by heating at 120°C with polyphosphoric acid, formed the thiazolo[3,2-a]pyrimidine derivatives **VIIa,b**.

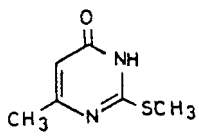


VII

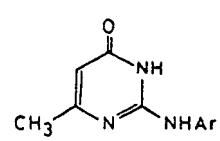
	R	R^1
a	H	CH_3
b,	$COCH_3$	CH_3

Structure **VII** was based on: (a) It was reported in the literature that compound **I** reacted with ethyl bromoacetate to produce **IV**.[15] (b) The ir spectra of **VIIIa,b** were compatible with structure **VII**. The ir spectra of both **VIIa** and **b** displayed carbonyl absorption at 1700 cm^{-1} value which is higher in frequency compared with **V** and **VIII**. This is in agreement with the fact that carbonyl groups attached to a tertiary nitrogen atom absorb at a higher frequency than those attached to a secondary one.[19]

Heating 6-methyl-2-methylthio-3,4-dihydropyrimidin-4-one (**VIII**)[16] with aromatic amines, at 140°C till evolution of methanethiol ceased, the 2-arylamino derivatives **IXa,b** were obtained.



VIII



IX

a, Ar = C_6H_5
b, Ar = C_6H_4Cl-p

TABLE III

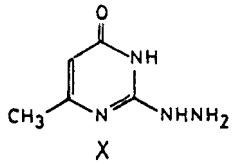
2-Arylmethylenehydrazino-6-methyl-3,4-dihydropyrimidin-4-ones (**XIa–e**)

Comp. No.	M.p.°C solvent	Yield (%)	Ar	Formula (M. W.)	Analysis % Calcd. / Found C	H	N	IR (cm^{-1})
XIa	240 dil. DMF	69	C_6H_5	$C_{12}H_{12}N_4O$ (228.3)	63.14 63.20	5.30 5.20	24.55 24.50	3120 (broad NH), 1660 (CO).
XIb*	220 dil. EtOH	63	$C_6H_4OCH_3$-p	$C_{13}H_{14}N_4O_2$ (258.3)	60.45 60.30	5.46 5.50	21.69 21.70	3150 (broad, NH), 1662 (CO).
XIc+	280 dil. DMF	65	C_6H_4Cl-p	$C_{12}H_{11}ClN_4O$ (262.7)	54.87 54.80	4.22 4.20	21.33 21.40	3130 (broad, NH), 1666 (CO).
XId	215 dil. dioxane	66	$C_6H_4N(CH_3)_2$-p	$C_{14}H_{17}N_5O$ (271.3)	61.98 62.00	6.32 6.20	25.81 25.90	3150 (broad, NH), 1666 (CO).
XIe	175 dil. DMF	70	C_4H_3O-2	$C_{10}H_{10}N_4O_2$ (218.2)	55.04 55.00	4.62 4.50	25.68 25.70	3120 (broad, NH), 1665 (CO).

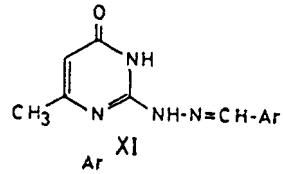
+ Cl, Found (Calcd.): 13.40 (13.50).

* ^{1}H-nmr (DMSO-d_6): δ 2.06 (s, 3, CH_3), 3.80 (s, 3, OCH_3), 5.57 (s, 1, pyrimidine proton), 7.00 (d, 2, aromatic protons), 7.85 (d, 2, aromatic protons), 8.00 (s, 1, methylenic proton) and 11.65 ppm (broad s, 2, 2NH, disappeared after deuterium oxide exchange).

Structure **IX** was based on analytical and ir spectral data. The 2-hydroazino derivative **X**[17] condensed with aromatic aldehydes, in refluxing ethanol, to yield the Schiff's bases **XIa–e**.



X



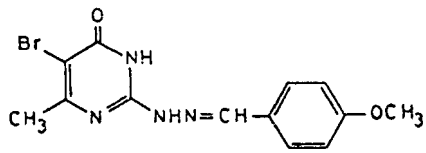
XI

Ar

a , C_6H_5
b , $C_6H_4OCH_3$-p
c , C_6H_4Cl-p
d , $C_6H_4N(CH_3)_2$-p
e , C_4H_3O-2

The ir spectra of **XIa–e** displayed absorption bands around 3130 (NH) and 1660 cm^{-1} (CO). The ^{1}H-nmr spectrum (DMSO-d_6), as an example, of **XIb** showed signals at δ 2.06 (s, 3, CH_3), δ 3.80 (s, 3, OCH_3), δ 5.57 (s, 1, pyrimidine-H_5), δ 7.00 (d, 2, aromatic protons), δ 7.85 (d, 2, aromatic protons), δ 8.00 (s, 1, methylenic protons) and δ 11.65 ppm (broad s, 2, 2NH; disappeared after deuterium oxide exchange) (Table III).

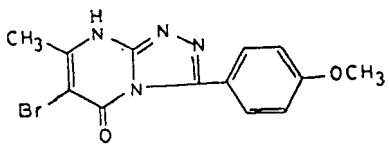
Attempted cyclisation of **XIb**, by treatment with an equivalent of bromine in acetic acid and in the presence of sodium, acetate formed only the 5-bromoanalogue **XII**.



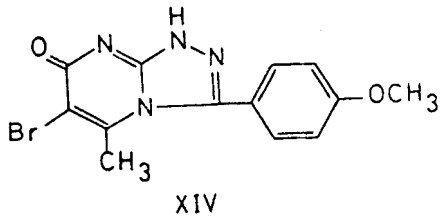
XII

The ir spectrum of **XII** displayed compatible absorption bands. ^{1}H-nmr spectrum (DMSO-d_6) revealed the absence of the signal characteristic of the pyrimidine-H_5, but showed the methylenic signal at δ 8.00 ppm. (Experimental).

Cyclisation of **XIb** could be effected, by treatment with two equivalents of bromine in acetic acid and in the presence of sodium acetate, and afforded the 6-bromo-7-methyl-3-*p*-methoxyphenyl-1H,5H-s-triazolo[4,3-a]pyrimidin-5-one (**XIII**), rather than the isomeric structure **XIV**.



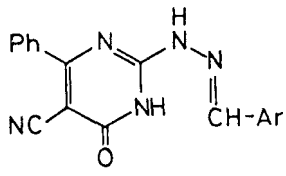
XIII



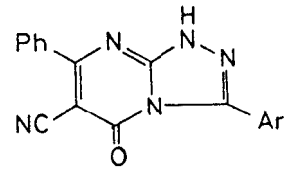
XIV

Structure **XIII** was established for the reaction product based on (a) Treatment of the 2-arylmethylenehydrazino-4-oxo-6-phenyl-3,4-dihydropyrimidine-5-carbonitrile (**XV**) with bromine, in acetic acid and in the presence of sodium acetate,

yielded **XVI**.[18] (b) The ir spectrum of **XIII** displayed an absorption band at 1715 cm^{-1} (CO). The carbonyl absorption band suffered a high frequency shift compared with that of **XIb** which absorbed at 1660 cm^{-1}. This shift favors structure **XIII** over the isomeric structure **XIV**. That is due to the fact that the carbonyl group attached to a tertiary nitrogen atom absorbs at a higher frequency than one attached to a secondary nitrogen.[19] The ^{1}H-nmr spectrum (DMSO-d_6) of **XIII** revealed the absence of a signal characteristic of the methylenic proton (see Experimental).

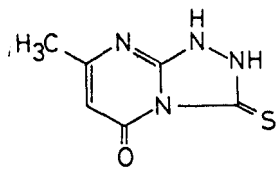


XV

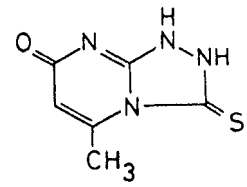


XVI

The 2-hydrazino derivative **X** was converted into the 7-methyl-3-thioxo-2,3-dihydro-1H,5H-s-triazolo[4,3-a]pyrimidin-5-one (**XVII**), by the action of carbon disulphide in ethanolic potassium hydroxide solution.



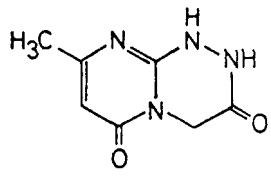
XVII



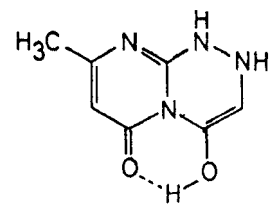
XVIII

The ir spectrum of **XVII** displayed a carbonyl absorption band at 1710 cm^{-1}. Again the high frequency shift of the carbonyl group in **XVII** compared with those of **I**, **II** and **IIId,e** which absorbed around 1660 cm^{-1}, supported structure **XVII** over **XVIII**. Moreover, the ^{1}H-nmr spectrum (DMSO-d_6) of **XVII** showed a pattern that could be intelligibly interpreted in terms of this structure.

Also, compound **X** reacted with chloroacetyl chloride, in cold anhydrous dioxane, and formed the 8-methyl-1,2,3,4-tetrahydro-6H-pyrimido[2,1-c]-as-triazine-3,6-dione (**XIX**) hydrochloride rather than the isomeric structure **XX**. The free base **XIX** was liberated by treatment with sodium acetate solution.



XIX

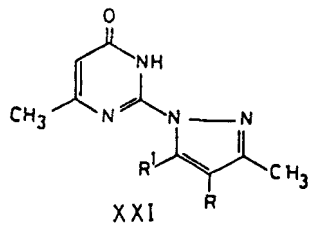


XX

Structure **XIX** was assigned to the reaction product based on ir-study. The ir spectrum of **XIX** displayed absorption bands at 1700 and 1670 cm^{-1} (2CO). The absence of any absorption band at the region 2500–3000 cm^{-1}, indicated that there

was no hydrogen bonds which would have been expected if the reaction product had structure **XX**. The ^{1}H-nmr spectrum (DMSO-d_6) of **XIX** showed agreement (Experimental).

The reaction of **X** with either 2,4-pentanedione, 3-chloro-2,4-pentane-dione or 1,1,1-trifluoro-2,4-pentanedione in ethanol yielded the 2-(4′,5′-disubstituted-3′-methylpyrazol-1′-yl)-6-methyl-3,4-dihydropyrimidin-4-ones (**XXIa–c**), respectively.

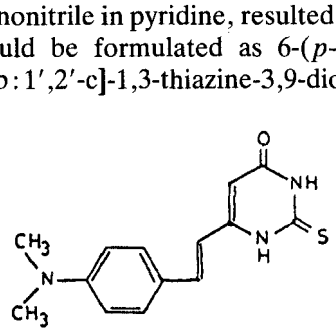


XXI

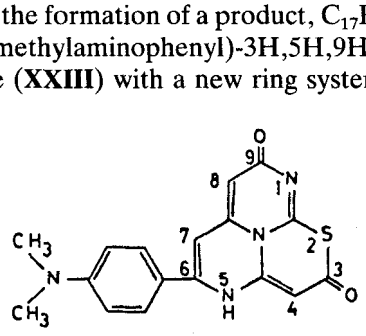
	R	R^1
a,	H	CH_3
b,	Cl	CH_3
c,	H	CF_3

Structure **XXI** was suggested for the reaction products based on correct analytical and ir spectral data (Experimental).

Prolonged refluxing of mixture of 6-(*p*-dimethylaminostyryl)-2-thiouracil (**XXII**)[20] and malononitrile in pyridine, resulted in the formation of a product, $C_{17}H_{14}N_4O_2S$, which could be formulated as 6-(*p*-dimethylaminophenyl)-3H,5H,9H-dipyrimidino[2,1-b:1′,2′-c]-1,3-thiazine-3,9-dione (**XXIII**) with a new ring system.



XXII



XXIII

Assignment of structure **XXIII** to the reaction product is based on analytical and spectroscopic data. The ir spectrum of **XXIII** displayed absorption bands at 3170 (NH), 1665 and 1640 cm^{-1} (2CO), but revealed no cyano group absorption. Its ^{1}H-nmr spectrum (DMSO-d_6) revealed signals at 3.00 (s, 6, $2CH_3$), 6.08 (s, 1, pyrimidine-H_8), 6.65 (d, 2, aromatic protons), 6.80 (s, 1, pyrimidine-H_7), 7.62 (d, 2, aromatic protons), 7.65 (s, 1, thiazine-H_4) and 12.23 ppm (broad s, 1, NH, disappeared after deuterium oxide exchange); a pattern that could be reasonably interpreted in terms of structure **XXIII**.

EXPERIMENTAL

All melting points are uncorrected. Ir spectra were recorded (KBr) on a Perkin Elmer 1430 spectrophotometer. ^{1}H-nmr spectra were determined in $(CD)_3SO$ with a Varian ^{1}H Gemini 200 spectrometer

and chemical shifts were expressed as δ values against $SiMe_4$ as internal standard. Microanalytical data were performed by the Microanalytical Center at Cairo University.

5-Bromo-6-methyl-2-thiouracil (**II**): A solution of 1.60 g (0.01 mol) of bromine in 20 ml of glacial acetic acid was gradually added, with shaking, to a suspension of 1.42 g (0.01 mol) of **I** in 40 ml of acetic acid. The reaction mixture was heated on a water bath for 1 h with occasional shaking, then cooled and poured into water. The white precipitate was filtered off, washed thoroughly with water, dried and crystallised from dilute dimethylformamide to give 1.55 g (70%) of **II**; mp 260°C; ^{1}H-nmr spectrum (DMSO-d_6): 2.22 ppm (s, 3, CH_3) and 12.80 (broad s, 2, 2NH; disappeared after deuterium oxide exchange); ir (KBr): 3130 (NH), 2920 (CH) and 1660 cm^{-1} (CO). Anal. Found (Calcd.): C, 27.20 (27.16); H, 2.30 (2.28); Br, 35.90 (36.14); N, 12.50 (12.67); S, 14.50 (14.50).

2-Alkylthio-6-methyl-3,4-dihydropyrimidin-4-ones (**IIIa–c**) *and 2-Alkylthio-5-bromo-6-methyl-3,4-dihydropyrimidin-4-ones* (**IIId–g**). *General procedure A*: To an ethanolic sodium ethoxide solution (prepared by dissolving 0.23 g, 0.01 mol, of sodium metal in 50 ml of absolute ethanol), 0.01 mol of either **I** (1.42 g) or **II** (2.21 g) was added and refluxed for 15 minutes. The mixture was treated with an equimolecular amount of each of chloropropanone (0.93 g), ethylbromoacetate (1.67 g), 3-chloro-2,4-pentanedione (1.35 g), methyl iodide (1.42 g), ethyl iodide (1.56 g) or phenacyl bromide (1.99 g), and refluxed for 1 h. Compounds **IIIb–g** were separated by pouring the reaction mixture into ice water, the white solid, thus formed, was collected, washed with water and crystallised from the proper solvent. Compound **IIIa** was obtained by evaporating the reaction mixture till dryness, the resulting residue was triturated with petroleum ether (90–100°C), the solid, so obtained, filtered off and crystallised (cf. Table I).

Bromination of VIII. Preparation of **IIId**. *Method B*: A solution of 0.78 g (0.005 mol) of **VIII** in 25 ml of glacial acetic acid was gradually treated with a solution of 0.80 g (0.005 mol) of bromine in 10 ml of acetic acid. The whole was shaked and heated on a water bath for 1 h. The reaction mixture was cooled, poured into water, the solid that separated, was collected, washed with water and crystallised from dioxane to yield 1.02 g (87%) of **IIId**; m.p. 240°C, not depressed when mixed with that obtained by method A.

2-Carboxymethylthio-6-methyl-3,4-dihydropyrimidin-4-one (**V**): One g of IV[15] in 30 ml of water was heated under reflux for 3 h, concentrated and left to cool whereby colourless crystals separated. Recrystallisation from water gave 0.72 g (65%) of V; m.p. >300°C; which was acidic to aqueous sodium carbonate. ir (KBr): 3120 (broad OH and NH), 1680 and 1646 cm^{-1} (2CO). Anal. Found (Calcd.): C, 41.80 (41.99); H, 4.00 (4.03); N, 14.10 (13.99); S, 16.00 (16.01).

2-Arylmethylene-7-methyl-6-substituted-2,3-dihydro-5H-thiazolo[3,2-a]pyrimidine-3,5-diones (**VIa–i**): *General procedure A*: A mixture of 0.01 mol of each of **I** (1.42 g) or **II** (2.21 g), 0.011 mol (1.04 g) of chloroacetic acid, 0.01 mol of the appropriate aldehyde and 2 g of anhydrous sodium acetate was refluxed in 30 ml of glacial acetic acid and 15 ml of acetic anhydride for 3 h. The reaction mixture was poured into water, the deposited precipitate thus formed, was filtered off, washed thoroughly with water, dried and crystallised from the proper solvent to produce **VIa–i** (cf. Table II).

Method B: A mixture of 0.91 g (0.005 mol) of **V**,[15] 0.53 g (0.005 mol) of benzaldehyde and 1 g of anhydrous sodium acetate was refluxed in 20 ml of glacial acetic acid and 10 ml of acetic anhydride for 3 h. The reaction mixture was poured into water, the solid that separated was collected, washed with water, dried and crystallised from acetic acid to give 1.08 g (80%) of **VIa**, m.p. 200°C no depression was observed when mixed with that prepared by method (A).

Method C: A mixture of 1 g (0.005 mol) of **IV**, 0.53 g (0.005 mol) of benzaldehyde, 1 g of anhydrous sodium acetate, 20 ml of glacial acetic acid and 10 ml of acetic anhydride was heated under reflux for 3 h. The reaction mixture was poured into water, the solid that formed, was filtered off, washed with water, dried and crystallised from acetic acid to yield 1.04 g (77%) of **VIa**, identical (m.p. and m.m.p.) with those obtained by methods (A) and (B).

Cyclisation of **IIIa–c**. *Synthesis of* **VIIa,b**. *General procedure*: A suspension of 2 g of each of **IIIa.c** in 10 g of polyphosphoric acid (prepared by dissolving 5 g of phosphorus pentoxide in 5 ml of orthophosphoric acid) was heated at 100–120°C on an oil bath for 1 h. The solution was left to cool, poured with stirring into ice water and basified with ammonium hydroxide solution. The solid that formed, was collected, washed with water and crystallised from the proper solvent to give **VIIa,b**.

3,7-Dimethyl-5H-thiazolo[3,2-a]pyrimidin-5-one (**VIIa**): was crystallised from water to yield 1.60 g (88%); m.p. 135°C.—ir (KBr): 2990 (CH) and 1700 cm^{-1} (CO). Anal. Found (Calcd.): C, 53.40 (53.31); H, 4.50 (4.47); N, 15.60 (15.54); S, 17.70 (17.79).

2-Acetyl-3,7-dimethyl-5H-thiazolo[3,2-a]pyrimidin-5-one (**VIIb**): was crystallised from dilute ethanol

to yield 1.65 g (89%); m.p. 119°C; ir (KBr): 2920 (CH); 1730 and 1700 cm^{-1} (2 CO). Anal. Found (Calcd.): C, 54.10 (54.04); H, 4.40 (4.54); N, 12.50 (12.60); S, 14.50 (14.43).

2-Arylamino-6-methyl-3,4-dihydropyrimidin-4-ones (**IXa,b**): A mixture of 0.01 mol (1.56 g) of **VIII** and 0.01 mol of either aniline (0.93 g) or *p*-chloroaniline (1.28 g) was heated at 140°C till methanethiol stopped. The residue was triturated with ethanol and the solid so obtained, was filtered off, washed with ethanol, dried and crystallised from dilute dimethylformamide to give **IXa,b**.

Compound **IXa** was prepared in 69% (1.39 g); m.p. 255°C; ir (KBr): 2930 (CH and NH) broad, with intermolecular hydrogen bond, and 1660 cm^{-1} (CO). Anal. Found (Calcd.): C, 65.50 (65.66); H, 5.60 (5.51); N, 21.00 (20.88).

Compound **IXb** was obtained in 72% (1.70 g); m.p. 300°C; ir (KBr): 2870 (CH and NH, broad with intermolecular hydrogen bond), and 1662 cm^{-1} (CO). Anal. Found (Calcd.): C, 56.10 (56.06); H, 4.30 (4.28); Cl, 15.00 (15.04); N, 17.80 (17.83).

2-Arylmethylenehydrazino-6-methyl-3,4-dihydropyrimidin-4-ones (**XIa–e**). *General procedure*: A mixture of 0.01 mol (1.40 g) of X[17] and an equimolecular amount of the appropriate aldehyde in 50 ml of absolute ethanol was refluxed for 5 h. The solid that formed, on dilution with water was collected dried and crystallized from the proper solvent to yield **XIa–e** (cf. Table III).

5-Bromo-6-methyl-2-p-methoxyphenylmethylenehydrazino-3,4-dihydropyrimidin-4-one (**XII**): To a solution of 1.29 g (0.005 mol) of **XIb** in 30 ml of glacial acetic acid containing 1 g of anhydrous sodium acetate, 0.80 g (0.005 mol) of bromine in 15 ml of acetic acid was gradually added with shaking. The whole was heated on a water bath for 3 h, left to cool and poured into water. The precipitate that separated, was collected, washed thoroughly with water, dried and crystallised from dilute dimethylformamide to yield 1.10 g (65%) of **XII**; m.p. 240°C; ^{1}H nmr spectrum (DMSO-d_6): δ 2.25 (s, 3, CH_3), 3.76 (s, 3, OCH_3), 7.20 (d, 2, aromatic protons), 7.75 (s, 1, methylenic proton), 7.88 (d, 2, aromatic protons) and 11.60 ppm (broad s, 1, NH, disappeared after deuterium oxide exchange; ir (KBr): 3150 (broad NH) and 1670 cm^{-1} (CO). Anal. Found (Calcd.): C, 46.20 (46.31); H, 3.90 (3.89); Br, 23.70 (23.70); N, 16.70 (16.62).

6-Bromo-7-methyl-3-p-methoxyphenyl-1H,5H-s-triazolo[4,3-a]pyrimidin-5-one (**XIII**): 1.29 g (0.005 mol) of **XIb** was dissolved in 30 ml of glacial acetic acid containing 1 g of anhydrous sodium acetate. To the resulting solution was gradually added 1.60 g (0.01 mol) of bromine in 20 ml of acetic acid with stirring. The whole was heated on a water bath for 3 h, cooled and poured into water. The solid so formed, was filtered off, washed with water, dried and crystallised from dilute dimethylformamide to give 1.06 g (63%) of **XIII**; m.p. 300°C; ^{1}H-nmr spectrum (DMSO-d_6): δ 2.45 (s, 3, CH_3), 3.83 (s, 3, OCH_3), 7.11 (d, 2, aromatic protons), 8.07 ppm (d, 2, aromatic protons) and (the NH, proton spreads over all the spectrum); ir (KBr): 2995 (broad, NH with hydrogen bond) and 1715 cm^{-1} (CO). Anal. Found (Calcd.): C, 46.60 (46.59); H, 3.20 (3.31); Br, 23.90 (23.84); N, 16.60 (16.72).

7-Methyl-3-thioxo-2,3-dihydro-1H,5H-s-triazolo[4,3-a]pyrimidin-5-one (**XVII**): One g of **X**, 0.5 g of potassium hydroxide and 3 ml of carbon disulphide were refluxed in 50 ml of ethanol for 4 h. After removal of ethanol, water was added and the alkaline solution was filtered. The clear filtrate was acidified with dilute hydrochloric acid and the formed precipitate was collected and crystallised from dilute dimethylformamide to yield 0.78 g (60%) of **XVII**; m.p. 292°C; ^{1}H-nmr spectrum (DMSO-d_6): 2.86 (s, 3, CH_3); 5.82 (s, 1, pyrimidine proton), 12.60 (broad, s, 1, NH; disappeared after deuterium oxide exchange) and 13.73 ppm (broad, s, 1, NH; disappeared after deuterium oxide exchange); ir (KBr): 3120 (broad NH), 2820 (CH) and 1710 cm^{-1} (CO). Anal. Found (Calcd.): C, 39.50 (39.55); H, 3.30 (3.32); N, 30.80 (30.75); S, 17.50 (17.60).

8-Methyl-1,2,3,4-tetrahydro-6H-pyrimido[2,1-c]-as-triazine-3,6-dione (**XIX**) *hydrochloride*: A solution of 1.40 g (0.01 mol) of **X** in 40 ml of anhydrous dioxane was gradually treated with 1.13 g (0.01 mol) of chloroacetyl chloride with stirring. The reaction solution was left overnight where upon colourless crystals were separated and recrystallised from ethanol to give 1.52 g (70%) of **XIX**. HCl; m.p. 198°C; which was acidic to sodium carbonate solution; ir (KBr): 3250 (broad NH), 2920 (CH), 1710 and 1675 cm^{-1} (2CO). Anal. Found (Calcd.): C, 39.00 (38.82); H, 4.20 (4.19); Cl, 16.30 (16.37); N, 25.70 (25.87).

The free base **XIX**: A solution of 1.08 g (0.005 mol) of **XIX** HCl in 50 ml of water was treated with a solution of 0.5 g of sodium acetate in 10 ml of water and warmed for 5 minutes. The solid thus separated, was collected, washed with water, dried and crystallised from ethanol to give 0.68 g (75%) of **XIX**; m.p. 220°C; ^{1}H-nmr spectrum (DMSO-d_6); 2.19 (s, 3, CH_3); 4.18 (s, 2, CH_2); 5.57 (s, 1, pyrimidin proton) and 10.24 ppm (broad s, 2, 2NH; disappeared after deuterium oxide exchange); ir (KBr): 3290 (broad NH), 2860 (CH), 1700 and 1670 cm^{-1} (2CO). Anal. Found (Calcd.): C, 46.70 (46.67); H, 4.40 (4.48); N, 31.20 (31.10).

2-(4',5'-Disubstituted-3'-methylpyrazol-1'-yl)-6-methyl-3,4-dihydropyrimidin-4-ones (**XXIa–c**). *General Procedure*: To a solution of 1.40 g (0.01 mol) of **X** in 50 ml of absolute ethanol, 0.01 mol of each of 2,4-pentanedione (1.00 g), 3-chloro-2,4-pentanedione (1.35 g) or 1,1,1-trifluoro-2,4-pentane-dione (1.54 g) was added. The reaction mixture was refluxed for 5 h, concentrated and cooled. The crystalline solid separated was filtered off and recrystallised to yield **XXIa–c**. Compound **XXIa** was crystallised from petroleum ether (90–100°) to give 1.43 g (70%); m.p. 130°C; ir (KBr): 3110 (broad NH), 2990 (CH) and 1670 cm^{-1} (CO). Anal. Found (Calcd.): C, 58.90 (58.81); H, 5.80 (5.92); N, 27.50 (27.43). Compound **XXIb** was crystallised from ethanol to give 1.63 g (68%); m.p. 220°C; ir (KBr): 3120 (broad NH), 2930 (CH) and 1680 cm^{-1} (CO). Anal. Found (Calcd.): C, 50.30; (50.32); H, 4.70 (4.65); N, 23.50 (23.47); Cl, 14.90 (14.85). Compound **XXIc** was crystallised from dilute ethanol to give 1.78 g (69%); m.p. 160°C; ir (KBr): 3115 (broad NH), 2915 (CH) and 1670 cm^{-1} (CO). Anal. Found (Calcd.): C, 46.60 (46.52); H, 3.60 (3.51); N, 21.60 (21.70).

6-(p-Dimethylaminophenyl)-3H,5H,9H-Dipyrimidino[2,1-b:1',2'-c]-1,3-thiazine 3,9-dione (**XXIII**): A mixture of 2.73 g (0.01 mol) of 6-(*p*-dimethylaminostyryl)-2-thiouracil (**XXII**)[20] and 0.66 g (0.01 mol) of malononitrile in 50 ml of pyridine was refluxed for 30 h. The reaction mixture was poured into water, the precipitate that formed, was collected, washed thoroughly with water, dried and crystallised from dilute dimethylformamide to yield 2.47 g (73%) of **XXIII**; m.p. >300°C; ^{1}H-nmr spectrum (DMSO-d_6): δ 3.00 (s, 6, $2CH_3$); 6.08 (s, 1, pyrimidine H-8), 6.65 (d, 2, aromatic protons), 6.80 (s, 1, pyrimidine-H-7); 7.62 (d, 2, aromatic protons), 7.65 (s, 1, thiazine H-4) and 12.23 ppm (broad s, 1, NH; disappeared after deuterium oxide exchange); ir (KBr): 3170 (broad NH), 2910 (CH), 1665 and 1640 cm^{-1} (2CO). Anal. Found (Calcd.): C, 60.30 (60.34); H, 4.20 (4.17); N, 16.40 (16.56); S, 9.50 (9.48).

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