1,3,4-Thiadiazolo[2,3-c]-*as*-triazines and *s*-Triazolo[3,4-*b*]-1,3,4-thiadiazoles (1)

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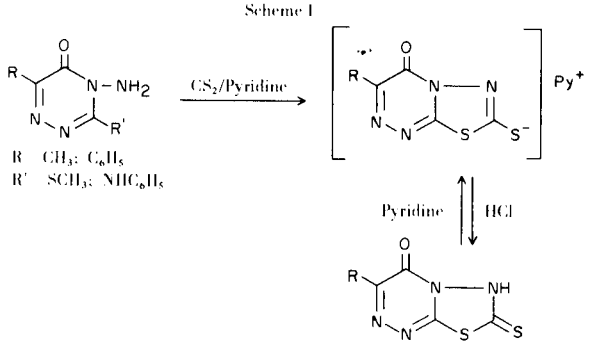
In view of possible pharmacological activity of new purine analogues, a series of 1,3,4-thiadiazolo[2,3-*c*]-*as*-triazines as well as *s*-triazolo[3,4-*b*]-1,3,4-thiadiazoles have been synthesized.

It has been reported (2) that 6-substituted-4-amino-3-methylmercapto-4,5-dihydro-*as*-triazin-5-ones or their 3-anilino analogues when treated with carbon disulfide in pyridine, afforded 7-oxo-2-thioxo-6-methyl-1,2-dihydro-7*H*-1,3,4-thiadiazolo[2,3-*c*]-*as*-triazines (See Scheme I).

Scheme I

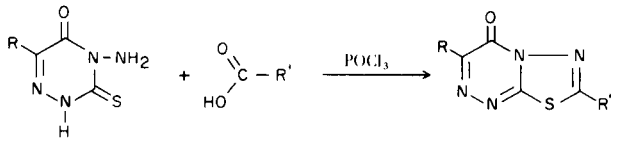


R = CH_3; C_6H_5
R' = SCH_3; NHC_6H_5

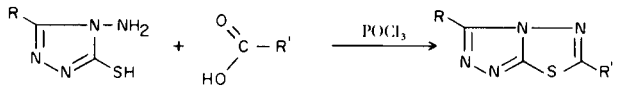
6-Substituted-4-amino-2,3,4,5-tetrahydro-*as*-triazin-5-one-3-thiones were allowed to react with a number of carboxylic acids in the presence of phosphorus oxychloride, similar to the method of preparation of 2-amino-1,3,4-thia and selenadiazoles (3). The reaction failed to give thiadiazole derivatives, unless the acids used were aromatic or conjugated. The only product which separated in the case of aliphatic acids were the amide of the starting aminotriazines which could not be cyclized by further treatment with boiling phosphorus oxychloride or with cold concentrated sulfuric acid.

However, a similar reaction conducted with 3-substituted-4-amino-3-mercapto-1,2,4-triazoles and aromatic, conjugated as well as aliphatic carboxylic acids, gave good yields of *s*-triazolo[3,4-*b*]-1,3,4-thiadiazoles (See Scheme II).

Scheme II



R = CH_3; C_6H_5
R' = aryl, styryl, and propenyl

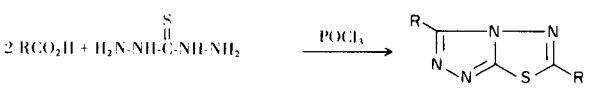


R = H; CH_3; C_2H_5; C_6H_5; CF_3; C_2F_5; C_3F_7
R' = CH_3; C_2H_5; C_6H_5; $CH_2C_6H_5$; $CH{=}CHC_6H_5$; CF_3; C_2F_5; C_3F_5

Interaction between amino-*as*-triazine derivatives and acid chlorides led to the formation of the corresponding amide. Ring closure of the acyl amides attempted by phosphorus oxychloride, was successful only in cases of conjugated or aromatic acyl amides.

All *s*-triazolo[3,4-*b*]-1,3,4-thiadiazoles in which the two substituents were identical were also prepared by a one step synthesis through heating of an excess of the appropriate carboxylic acid with thiocarbohydrazide in the presence of phosphorus oxychloride (See Scheme III).

Scheme III

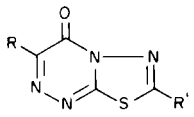


The structure elucidation in both cases was done by analytical and spectroscopical methods.

The infrared spectrum of the *s*-triazolo[3,4-*b*]-1,3,4-thiadiazole series, showed strong bands near 1688 cm^{-1}, supporting this structure rather than the possible isomeric form, *i.e.*, oxadiazolo-*as*-triazine derivatives.

All compounds prepared are reported in Tables I, II, and III.

TABLE I



R	R′	M.p., °C	Yield %	Formula	C% Calcd.	C% Found	H% Calcd.	H% Found
CH_3	$CH{=}CHCH_3$	220	20	$C_8H_8N_4OS$	46.15	46.12	3.84	3.83
CH_3	$CH{=}CHC_6H_5$	275	90	$C_{13}H_{10}N_4OS$	57.77	57.74	3.70	3.70
CH_3	C_6H_5	265	50	$C_{11}H_8N_4OS$	54.09	54.08	3.28	3.27
CH_3	p-$CH_3C_6H_4$	215	87	$C_{12}H_{10}N_4OS$	55.81	55.77	3.87	3.85
CH_3	p-$CH_3OC_6H_4$	227	58	$C_{12}H_{10}N_4O_2S$	52.55	52.50	3.64	3.62
CH_3	p-FC_6H_4	266	68	$C_{11}H_7FN_4OS$	50.38	50.30	2.67	2.66
CH_3	p-ClC_6H_4	230	50	$C_{11}H_7ClN_4OS$	47.48	47.42	2.51	2.50
CH_3	p-$NO_2C_6H_4$	270	41	$C_{11}H_7N_5O_3S$	45.67	45.63	2.42	2.41
C_6H_5	$CH{=}CHCH_3$	225	92	$C_{13}H_{10}N_4OS$	57.77	57.72	3.70	3.69
C_6H_5	$CH{=}CHC_6H_5$	293	92	$C_{18}H_{12}N_4OS$	65.06	65.08	3.61	3.60
C_6H_5	C_6H_5	238	86	$C_{16}H_{10}N_4OS$	62.74	62.70	3.26	3.23
C_6H_5	p-$CH_3C_6H_4$	246	86	$C_{17}H_{12}N_4OS$	63.75	63.71	3.75	3.74
C_6H_5	p-$CH_3OC_6H_4$	217	85	$C_{17}H_{12}N_4O_2S$	60.71	60.73	3.57	3.56
C_6H_5	p-FC_6H_4	335	92	$C_{16}H_9FN_4OS$	59.25	59.23	2.77	2.79
C_6H_5	p-ClC_6H_4	257	86	$C_{16}H_9ClN_4OS$	56.47	56.49	2.64	2.62
C_6H_5	p-$NO_2C_6H_4$	322	76	$C_{16}H_9N_5O_3S$	54.70	54.72	2.56	2.55

EXPERIMENTAL

Melting points were taken on a Kofler hot stage microscope and are uncorrected. The ir spectra were determined on a Leitz model III spectrograph using potassium bromide discs. Mass spectra were recorded on a Varian-Mat 111 spectrometer. Nmr spectra were taken on a Varian A60A instrument.

2,6-Diphenyl-7-oxo-7*H*-1,3,4-thiadiazolo[2,3-*c*]-*as*-triazine.

6-Phenyl-4-amino-2,3,4,5-tetrahydro-*as*-triazin-5-one-3-thione (2) (1.10 g., 5 mmoles) benzoic acid (1.22 g., 10 mmoles), and 10 ml. of phosphorus oxychloride were refluxed for ½ hour. Excess phosphorus oxychloride was distilled under reduced pressure. The residue was triturated with dilute sodium hydroxide solution to remove unreacted materials. The solid residue was recrystallized from acetic acid to give 1.3 g. (86%) of the title compound, m.p. 238°; molecular weight (by mass spectroscopy) 306; ν max cm^{-1} 1688, 1525, 1494, 1445, 1412, 1325, 1275, 788, 767, 743, and 680.

2-Phenyl-6-methyl-7-oxo-7*H*-1,3,4-thiadiazolo[2,3-*c*]-*as*-triazine.

6-Methyl-4-amino-2,3,4,5-tetrahydro-*as*-triazin-5-one-3-thione (2) (1.74 g., 10 mmoles), benzoic acid (2.24 g., 20 mmoles), and 15 ml. of phosphorus oxychloride were refluxed for ½ hour. The reaction mixture was worked up as indicated for the preparation of the 2,6-diphenyl analogue to give 1.22 g. (50%) of the desired compound, m.p. 265°; molecular weight (by mass spectroscopy), 244.

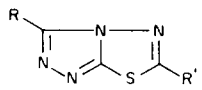
This compound was also prepared by ring closure of 6-methyl-4-benzoylamino-2,3,4,5-tetrahydro-*as*-triazin-5-one-3-thione (see below), by ½ hour refluxing with an excess of phosphorus oxychloride. The yield of the bicyclic compound in this way was 65%.

6-Methyl-4-benzoylamino-2,3,4,5-tetrahydro-*as*-triazine-5-one-3-thione.

A mixture of (0.78 g., 5 mmoles) 6-methyl-4-amino-2,3,4,5-tetrahydro-*as*-triazin-5-one-3-thione and 5 ml. of benzoyl chloride was refluxed for 1 hour. Excess benzoyl chloride was removed under reduced pressure and the residue was recrystallized from acetic acid to give 1 g. of amide (77%), m.p. 225°; molecular weight (by mass spectroscopy), 262.

Anal. Calcd. for $C_{11}H_{10}N_4O_2S$: C, 50.38; H, 3.81. Found: C, 50.49; H, 3.69.

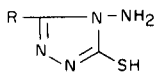
TABLE II



R	R′	M.p., °C	Yield %	Formula	C%		H%		N%	
					Calcd.	Found	Calcd.	Found	Calcd.	Found
H	C_6H_5	187-190	51	$C_9H_6N_4S$	53.46	53.44	2.97	2.96	27.72	27.73
CH_3	$CH{=}CHC_6H_5$	196-199	63	$C_{12}H_{10}N_4S$	59.51	59.48	4.13	4.10	23.14	23.10
CH_3	C_6H_5	176-177	53	$C_{10}H_8N_4S$	55.55	55.51	3.70	3.67	25.92	25.88
CH_3	CF_3	130-132	20	$C_5H_3F_3N_4S$	28.84	28.80	1.44	1.43	26.92	26.94
C_2H_5	$CH{=}CHC_6H_5$	164-166	50	$C_{13}H_{12}N_4S$	60.93	60.89	4.64	4.66	21.87	21.82
C_2H_5	CF_3	108-109	33	$C_6H_5F_3N_4S$	32.43	32.41	2.25	2.23	25.22	25.20
C_6H_5	C_6H_5	201 (a)	90	$C_{15}H_{10}N_4S$	64.74	64.70	3.59	3.52	20.14	20.11
CF_3	CH_3	74-75	73	$C_5H_3F_3N_4S$	28.84	28.78	1.44	1.40	26.92	26.94
CF_3	C_2H_5	45-48	65	$C_6H_5F_3N_4S$	32.43	32.45	2.25	2.24	25.22	25.20
CF_3	$CH_2C_6H_5$	63-66	90	$C_{11}H_7F_3N_4S$	46.47	46.44	2.46	2.44	19.71	19.65
CF_3	$CH{=}CHC_6H_5$	195	63	$C_{12}H_7F_3N_4S$	48.64	48.66	2.36	2.33	18.91	18.88
CF_3	CF_3	157-160	85	$C_5F_3N_4S$	22.90	22.85			21.37	21.34
CF_3	C_2F_5	63-66	46	$C_6F_8N_4S$	23.07	23.01			17.94	17.71
C_2F_5	C_2F_5	96-97	40	$C_7F_{10}N_4S$	23.20	23.15			15.46	15.50
C_3F_7	C_3F_7	89-90	45	$C_9F_{14}N_4S$	23.37	23.32			12.12	12.09

(a) Ref. (5) m.p. 199.5-200°.

TABLE III



R	M.p., °C	Yield %	Formula	C% Calcd.	C% Found	H% Calcd.	H% Found	N% Calcd.	N% Found
CF_3	130-132	40	$C_3H_3F_3N_4S$	19.56	19.53	1.63	1.62	30.43	30.40
C_2F_5	143-145	40	$C_4H_3F_5N_4S$	20.51	20.45	1.28	1.26	23.93	23.86
C_3F_7	73-77	45	$C_5H_3F_7N_4S$	21.12	21.07	1.05	1.01	19.71	19.65

3-Heptafluoropropyl-4-amino-5-mercapto-1,2,4-triazole.

A mixture of (1 g., 0.01 mole) thiocarbohydrazide (4) and 1.2 ml. of heptafluorobutyric acid was refluxed gently for 15 minutes. A crystalline mass was obtained after cooling of the reaction mixture which was recrystallized from water to give 1.25 g. (45%) of the title compound, m.p. 74-76°; molecular weight (by mass spectroscopy) 284; ν max cm^{-1} 3200, 3090, 2905, 1610, 1540, 1500, 1450, 1345, 1315, 1218, 1186, 1123, 1032, 1020, 955, 918, 883, 858, 785, 753, and 723.

2,5-Diheptafluoropropyl-*s*-triazolo[3,4-*b*]-1,3,4-thiadiazole.

A mixture of 0.57 g. of 3-heptafluoropropyl-4-amino-5-mercapto-1,2,4-triazole and 0.85 g. of heptafluorobutyric acid and 2 ml. of phosphorus oxychloride was gently refluxed for ½ hour. To the reaction mixture ice water was added and the crystalline mass was recrystallized from ethanol to give 0.41 g. (45%) of white flakes, m.p. 89-90°; molecular weight (by mass spectroscopy) 462; ν max cm^{-1}, 1580, 1450, 1342, 1270, 1235, 1220, 1205, 1165, 1112, 1065, 1010, 885, 855, 749, and 734.

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