1,2,4-Triazines. VII (1). 1,3,4-Thiadiazolo[2,3-c]-*as*-triazines and 2-Pyrazolyl-1,3,4-thiadiazoles(2)

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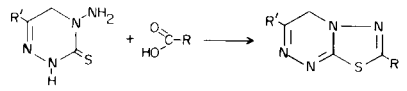
In continuation of our study on the chemistry of sulfur and selenium heterocyclic compounds (3-5) and in view of possible pharmacological activity of new purine analogues, recently, the synthesis of a series of 2-aryl-6-substituted-5-oxo-5*H*-1,3,4-thiadiazolo[2,3-*c*]-*as*-triazines (I) was reported (6) (See Scheme I).

Scheme I



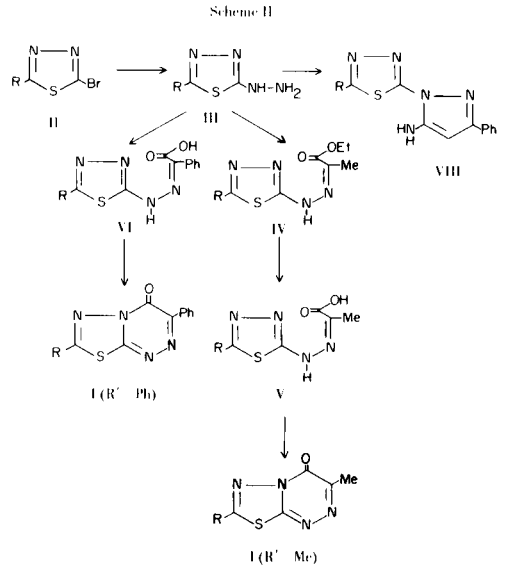
I

In the present work the synthesis of this heterocyclic ring system was achieved in high yield, by an alternative route, starting from the readily available 5-aryl-2-bromo-1,3,4-thiadiazole (II) (7).

5-Substituted-2-bromo-1,3,4-thiadiazole (II) was allowed to react with hydrazine to afford 5-substituted-(1,3,4-thiadiazol-2-yl)hydrazine (III). Treatment of the latter compound with ethyl pyruvate followed by hydrolysis gave the hydrazone (IV).

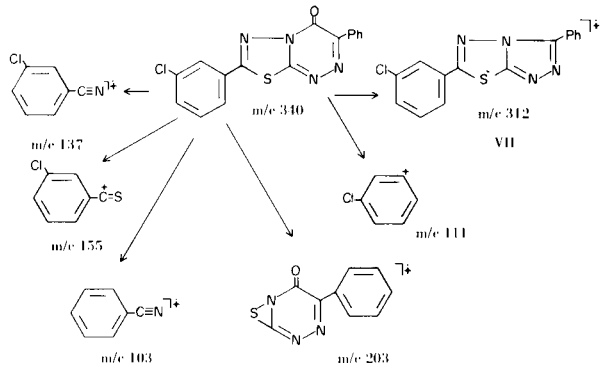
This compound could be directly prepared from the reaction of compound III and pyruvic acid; however, the former sequence had a better yield. Refluxing a solution of compound V in acetic acid, *via* dehydrocyclization reaction, gave the desired compound I ($R' = CH_3$) in high yield. Phenylglyoxylic acid hydrazone of compound III could be directly prepared and subsequently cyclized to compound I ($R' = C_6H_5$) in good yield (See Scheme II).

Scheme II



The structure elucidation was done by analytical, spectroscopic methods and in the cases of known compounds (6) by comparison with the authentic samples. In the uv spectra of compounds I, the higher absorption band (*ca* 340) has greater intensity than the lower absorption band in the region of *ca* 260. This is in agreement with ours and others results that in the case of 5-one series the higher absorption band in very intense (3,8,9).

The mass spectra fragmentation pattern of compound I ($R = m\text{-}ClC_6H_4$, $R' = C_6H_5$) is summarized in Scheme III, and is in good agreement with the structure I.



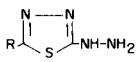
Scheme III

As it could be seen from the above scheme, compound I first loses a carbonyl group and gives *s*-triazolo[3,4-*b*]thiadiazole ion (VII). This led us to examine the possibility of converting the *as*-triazine moiety in compound I to *s*-triazole ring system. However, compound I was found to be quite stable towards heat and light.

The physical data of the intermediates hydrazines, hydrazones and the compounds I are summarized in Table I, II and III.

Finally, in view of the potent pharmacological activity

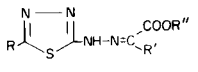
Table I



R	M.p., °C (a)	Yield %	Formula	C% Calcd.	C% Found	H% Calcd.	H% Found	N% Calcd.	N% Found
C_6H_5	183 (b)	97	$C_8H_8N_4S$	50.00	50.14	4.17	4.02	29.17	29.34
o-ClC_6H_4	198	96	$C_8H_7ClN_4S$	42.38	42.45	3.09	3.21	24.72	24.89
m-ClC_6H_4	228	95	$C_8H_7ClN_4S$	42.38	42.27	3.09	3.18	24.72	24.90
p-ClC_6H_4	308-310	94	$C_8H_7ClN_4S$	42.38	42.09	3.09	3.01	24.72	24.63
p-BrC_6H_4	268	92	$C_8H_7BrN_4S$	35.42	35.29	2.58	2.63	20.66	20.83
o-$CH_3C_6H_4$	162-163	73	$C_9H_{10}N_4S$	52.43	52.57	4.85	4.99	27.18	27.02
p-$CH_3C_6H_4$	208-210	90	$C_9H_{10}N_4S$	52.43	52.61	4.85	4.94	27.18	27.23
m-$CH_3OC_6H_4$	164	97	$C_9H_{10}N_4OS$	48.65	48.49	4.50	4.63	25.23	25.08
p-$CH_3OC_6H_4$	189	96	$C_9H_{10}N_4OS$	48.65	48.52	4.50	4.67	25.23	25.38

(a) All compounds were crystallized from ethanol. (b) J. Sandstrom, *Arkiv Kemi*, 9, 225 (1956); through *Chem. Abstr.*, 50, 15516[i] (1956) gives m.p. 190-191°.

Table II



R	R′	R″	M.p., °C (a)	Yield %	Formula	C% Calcd.	C% Found	H% Calcd.	H% Found	N% Calcd.	N% Found
o-ClC_6H_4	CH_3	C_2H_5	237-238	86	$C_{13}H_{13}ClN_4O_2S$	48.07	48.20	4.01	4.17	17.26	17.37
m-ClC_6H_4	CH_3	C_2H_5	209-210	94	$C_{13}H_{13}ClN_4O_2S$	48.07	48.01	4.01	3.98	17.26	17.32
p-ClC_6H_4	CH_3	C_2H_5	241-242	96	$C_{13}H_{13}ClN_4O_2S$	48.07	48.25	4.01	4.14	17.26	17.02
m-$CH_3OC_6H_4$	CH_3	C_2H_5	214-215	90	$C_{14}H_{16}N_4O_3S$	52.50	52.64	5.00	5.12	17.50	17.41
p-$CH_3OC_6H_5$	CH_3	C_2H_5	219-220	94	$C_{14}H_{16}N_4O_3S$	52.50	52.62	5.00	5.09	17.50	17.39
p-$CH_3C_6H_4$	CH_3	C_2H_5	246-247	97	$C_{14}H_{16}N_4O_2S$	55.26	55.34	5.26	5.32	18.42	18.30
C_6H_5	CH_3	H	219-220	88	$C_{11}H_{10}N_4O_2S$	50.38	50.19	3.82	3.89	21.37	21.41
o-ClC_6H_4	CH_3	H	246-247	60	$C_{11}H_9ClN_4O_2S$	44.52	44.67	3.04	3.14	18.89	18.71
m-ClC_6H_4	CH_3	H	217-218	76	$C_{11}H_9ClN_4O_2S$	44.52	44.39	3.04	3.01	18.89	18.89
p-ClC_6H_4	CH_3	H	245-246	90	$C_{11}H_9ClN_4O_2S$	44.52	44.48	3.04	3.17	18.89	18.63
m-$CH_3OC_6H_4$	CH_3	H	221-222	75	$C_{12}H_{12}N_4O_3S$	49.32	49.45	4.11	4.23	19.18	19.23
p-$CH_3OC_6H_4$	CH_3	H	227-228	88	$C_{12}H_{12}N_4O_3S$	49.32	49.20	4.11	4.05	19.18	19.02
p-$CH_3C_6H_4$	CH_3	H	233-234	88	$C_{12}H_{12}N_4O_2S$	52.17	52.31	4.35	4.47	20.29	20.12
C_6H_5	C_6H_5	H	234-235	98	$C_{16}H_{12}N_4O_2S$	59.26	59.05	3.70	3.76	17.28	17.42
o-ClC_6H_4	C_6H_5	H	237-238	84	$C_{16}H_{11}ClN_4O_2S$	53.56	53.64	3.07	3.21	15.62	15.75
m-ClC_6H_4	C_6H_5	H	236-237	96	$C_{16}H_{11}ClN_4O_2S$	53.56	53.42	3.07	3.02	15.62	15.49
p-ClC_6H_4	C_6H_5	H	227-228	94	$C_{16}H_{11}ClN_4O_2S$	53.56	53.64	3.07	3.01	15.62	15.46
p-BrC_6H_4	C_6H_5	H	242-243	96	$C_{16}H_{11}BrN_4O_2S$	47.64	47.73	2.73	2.87	13.90	13.82
m-$CH_3OC_6H_4$	C_6H_5	H	226-227	87	$C_{17}H_{14}N_4O_3S$	57.63	57.71	3.95	3.99	15.82	15.84
p-$CH_3OC_6H_4$	C_6H_5	H	229-230	92	$C_{17}H_{14}N_4O_3S$	57.63	57.49	3.95	3.81	15.82	15.69
p-$CH_3C_6H_4$	C_6H_5	H	230-231	98	$C_{17}H_{14}N_4O_2S$	60.36	30.18	4.14	3.94	16.57	16.39

(a) All Compounds were crystallized from ethanol-water.

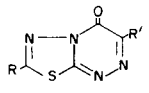
of pyrazole ring system, it was also of our interest to incorporate the pyrazole moiety in the 1,3,4-thiadiazoles. Therefore, 5-substituted-[1,3,4-thiadiazol-2-yl]hydrazones (III) were allowed to react with α-cyanoacetophenone in acid medium to give the desired compound VIII in high yield (See Scheme II).

The pyrazolyl-1,3,4-thiadiazoles prepared are summarized in Table IV.

EXPERIMENTAL

Melting points were determined on a Kofler hot stage microscope and are uncorrected. Nmr spectra were determined using Varian T60A spectrometer and chemical shifts (δ) are in ppm relative to tetramethylsilane. The ir spectra were obtained from a Leitz Model III spectrograph. Mass spectra were run on a Varian MAT CH_5 instrument. Uv spectra were obtained using a Pye Unicam SP800 instrument.

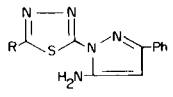
Table III



R	R′	M.p., °C (a)	Yield %	Formula	C% Calcd.	C% Found	H% Calcd.	H% Found	N% Calcd.	N% Found	λ max (b) (nm)	log ε
m-ClC_6H_4	CH_3	211-212	84	$C_{11}H_7ClN_4OS$	47.39	47.42	2.51	2.66	20.11	20.26	332 263	3.88 3.86
p-ClC_6H_4	CH_3	299-230 (c)	84	$C_{11}H_7ClN_4OS$	47.39	47.32	2.51	2.45	20.11	20.29	356 270	4.34 4.23
m-$CH_3OC_6H_4$	CH_3	244-245	87	$C_{12}H_{10}N_4O_2S$	52.55	52.67	3.64	3.73	20.43	20.59	334 264	4.28 4.13
p-$CH_3OC_6H_4$	CH_3	227-228 (d)	79	$C_{12}H_{10}N_4O_2S$	52.55	52.73	3.64	3.82	20.43	20.49	354 272	4.15 2.07
p-$CH_3C_6H_4$	CH_3	216-217 (e)	84	$C_{12}H_{10}N_4OS$	55.81	55.93	3.87	3.79	21.71	21.69	354 276	3.98 3.82
C_6H_5	C_6H_5	240-242 (f)	94	$C_{16}H_{10}N_4OS$	62.74	62.85	3.26	3.16	18.30	18.35	356 276	4.39 3.98
o-ClC_6H_4	C_6H_5	197-198	78	$C_{16}H_9ClN_4OS$	56.38	56.58	2.64	2.53	16.45	16.57	359 250	4.13 3.78
m-ClC_6H_4	C_6H_5	192-193	88	$C_{16}H_9ClN_4OS$	56.38	56.38	2.64	2.69	16.45	16.59	360 254	4.26 4.15
p-ClC_6H_4	C_6H_5	252-253 (g)	91	$C_{16}H_9ClN_4OS$	56.38	56.55	2.64	2.57	16.45	16.39	358 258	4.39 4.37
p-BrC_6H_4	C_6H_5	266-267	88	$C_{16}H_9BrN_4OS$	49.87	49.73	2.34	2.45	14.55	14.63	356 264	4.27 4.03
m-$CH_3OC_6H_4$	C_6H_5	222-223	84	$C_{17}H_{12}N_4O_2S$	60.71	60.81	3.57	3.48	16.67	16.52	358 282	4.07 3.78
p-$CH_3OC_6H_4$	C_6H_5	244-245 (h)	90	$C_{17}H_{12}N_4O_2S$	60.71	60.81	3.57	3.62	16.67	16.73	352 276	4.15 3.87
p-$CH_3C_6H_4$	C_6H_5	243-245 (i)	94	$C_{17}H_{12}N_4OS$	63.75	63.66	3.75	3.90	17.50	17.61	358 256	4.09 4.10

(a) All Compounds were crystallized from ethyl acetate-chloroform. (b) In methanol. (c) Reference (6) m.p. 230°. (d) Reference (6) m.p. 277°. (e) Reference (6) m.p. 215°. (f) Reference (6) m.p. 240-242°. (g) Reference (6) m.p. 257°. (h) Reference (6) m.p. 217°. (i) Reference (6) m.p. 246°.

Table IV



R	M.p., °C (a)	Yield %	Formula	C% Calcd.	C% Found	H% Calcd.	H% Found	N% Calcd.	N% Found
C_6H_5	171-172	94	$C_{17}H_{13}N_5S$	63.95	63.99	4.08	4.22	21.94	21.78
o-ClC_6H_4	185-186	86	$C_{17}H_{12}ClN_5S$	57.71	57.65	3.39	3.45	19.80	19.68
m-ClC_6H_4	180-181	80	$C_{17}H_{12}ClN_5S$	57.71	57.85	3.39	3.28	19.80	19.65
p-ClC_6H_4	243-244	89	$C_{17}H_{12}ClN_5S$	57.71	57.83	3.39	3.42	19.80	19.78
p-BrC_6H_4	218-219	84	$C_{17}H_{12}BrN_5S$	51.26	51.14	3.02	3.12	17.59	17.63
m-$CH_3OC_6H_4$	193-194	90	$C_{18}H_{15}N_5OS$	61.89	61.93	4.30	4.15	20.06	20.21
o-$CH_3C_6H_4$	138-139	82	$C_{18}H_{15}N_5S$	64.86	64.79	4.50	4.62	21.02	21.21
p-$CH_3C_6H_4$	230-231	93	$C_{18}H_{15}N_5S$	64.86	64.92	4.50	4.63	21.02	21.14

(a) All compounds were crystallized from ethanol.

5-*p*-Chlorophenyl[1,3,4-thiadiazol-2-yl]hydrazine (III, R = *p*-ClC_6H_4).

A solution of 2-bromo-5-*p*-chlorophenyl-1,3,4-thiadiazole (2.75 g., 0.01 mole) and hydrazine hydrate (2.5 g., 0.05 mole) in 20 ml. of ethanol was refluxed for five hours. After cooling the precipitate was filtered to give 2.12 g. (94%) of III (R = *p*-ClC_6H_4), m.p. 308-310°; molecular weight (by mass spectroscopy) 226.

Other 5-substituted-[1,3,4-thiadiazol-2-yl]hydrazines were prepared similarly (See Table I).

Ethyl α-Oxopropionate 5-*p*-Chlorophenyl[1,3,4-thiadiazol-2-yl]-hydrazone (IV, R = *p*-ClC_6H_4).

A solution of 5-*p*-chlorophenyl[1,3,4-thiadiazol-2-yl]hydrazine (III, R = *p*-ClC_6H_4) (2.26 g., 0.01 mole) and ethyl α-oxopropionate (1.28 g., 0.011 mole) in 50 ml. of ethanol was refluxed for six hours. The solvent was evaporated and the residue was crystallized from ethanol to give 3.11 g. (96%) of IV (R = *p*-ClC_6H_4); m.p. 241-242°; nmr (deuteriochloroform): 7.62 (q, 4H, aromatic), 4.35 (q, 2H, OCH_2), 2.45 (s, 3H, CH_3), and 1.38 (t, 3H, CH_3); ir (potassium bromide): 1700 cm^{-1} (ester); molecular weight (by mass spectroscopy) 324.

Anal. Calcd. for $C_{13}H_{13}ClN_4O_2S$: C, 48.07; H, 4.01; N, 17.26. Found: C, 48.25; H, 4.14; N, 17.02.

Other α-oxopropionate 5-substituted[1,3,4-thiadiazol-2-yl]-hydrazones (IV) were prepared similarly (See Table II).

α-Oxopropionic Acid 5-*p*-Chlorophenyl[1,3,4-thiadiazol-2-yl]-hydrazine (V, R = *p*-ClC_6H_4).

A solution of ethyl α-oxopropionate 5-*p*-chlorophenyl[1,3,4-thiadiazol-2-yl]hydrazone (3.24 g., 0.01 mole) and sodium hydroxide (0.8 g., 0.02 mole) in 100 ml. of ethanol-water (50:50) was refluxed for four hours. The solution was acidified (hydrochloric acid). The precipitate was filtered and crystallized from ethanol to give 2.67 g. (90%) of V (R = *p*-ClC_6H_4), m.p. 245-246°.

Anal. Calcd. for $C_{11}H_9ClN_4O_2S$: C, 44.52; H, 3.04; N, 18.89. Found: C, 44.48; H, 3.17; N, 18.63.

Other α-oxopropionic acid 5-substituted[1,3,4-thiadiazol-2-yl]-hydrazones (V) were prepared similarly (See Table II).

Phenylglyoxylic Acid 5-*p*-Chlorophenyl[1,3,4-thiadiazol-2-yl]-hydrazone (VI, R = *p*-ClC_6H_4).

A solution of 5-chlorophenyl[1,3,4-thiadiazol-2-yl]hydrazine (2.26 g., 0.01 mole) and phenylglyoxylic aicd (1.5 g., 0.01 mole) in 50 ml. of ethanol was refluxed for four hours. The mixture was cooled and the precipitate was filtered to give 3.37 g. (94%) of VI (R = *p*-ClC_6H_4), m.p. 227-228°.

Anal. Calcd. for $C_{16}H_{11}ClN_4O_2S$: C, 53.56; H, 3.07; N, 15.62. Found: C, 53.64; H, 3.01; N, 15.46.

Other phenylglyoxylic acid 5-substituted[1,3,4-thiadiazol-2-yl]-hydrazones were prepared similarly (See Table II).

2-*m*-Chlorophenyl-6-methyl-5-oxo-5*H*-1,3,4-thiadiazolo[2,3-*c*]-*as*-triazine (I, R = *m*-ClC_6H_4, R' = CH_3).

A solution of α-oxopropionic acid 5-*p*-chlorophenyl[1,3,4-thiadiazol-2-yl]hydrazone (V, R = *p*-ClC_6H_4, 2.965 g., 0.01 mole) in 100 ml. of acetic acid was refluxed for 48 hours. The solvent was evaporated and the residue was crystallized from ethyl acetate-chloroform to give 2.4 g. (84%) of I (R = *m*-ClC_6H_4, R = CH_3), m.p. 211-212°; ir (potassium bromide): 1665 (C=O), 1515, 1470, 1370, 1282, 1252, 1184, 1063, 1000, 952, 854, 800, 782, 750, and 675 cm^{-1}.

Anal. Calcd. for $C_{11}H_7ClN_4OS$: C, 47.39; H, 2.51; N, 20.11. Found: C, 37.42; H, 2.66; N, 20.26.

Other 2-substituted-6-methyl (or 6-phenyl)-5-oxo-5*H*-1,3,4-thiadiazo[2,3-*c*]-*as*-triazines were prepared similarly (See Table III).

2-(3-Phenyl-5-aminopyrazolyl)-5-phenyl-1,3,4-thiadiazole (VIII, R = C_6H_5).

A solution of 5-phenyl[1,3,4-thiadiazol-2-yl]hydrazine (0.184 g., 0.01 mole), and α-cyanoacetophenone (0.145 g., 0.001 mole) in 2.5 ml. of ethanol-acetic acid (8:2) was refluxed for one hour. The solvent was evaporated and the residue was crystallized from ethanol to give 0.3 g. (94%) of VIII (R = C_6H_5), m.p. 171-172°; molecular weight (by mass spectroscopy) 319.

Anal. Calcd. for $C_{17}H_{13}N_5S$: C, 63.95; H, 4.08; N, 21.94. Found: C, 63.99; H, 4.22; N, 21.78.

Other 2-(3-phenyl-5-aminopyrazolyl)-5-aryl-1,3,4-thiadiazoles were prepared similarly (See Table IV).

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