Bridgehead Nitrogen Heterocycles. VI. The Synthesis and Characterization of Some Ring-Fused 3-Substituted 3*H*-[1,2,4]Thiadiazolopyrimidines, -pyrazines, and -pyridazines[1a]

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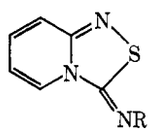
Condensation of the trichloromethylthioamino derivatives of pyridazines, pyrimidines, and pyrazines derived from the corresponding amino compound and perchloromethyl mercaptan with primary aromatic amines gave a variety of 3-substituted derivatives of the new, title ring systems. In several instances transaminations were observed. Spectral characteristics of these derivatives are described.

The 3*H*-[1,2,4]thiadiazolo[4,3-*a*]pyridine ring system **1** was synthesized recently from 2-aminopyridines and perchloromethyl mercaptan.[2a] Isolation of the intermediate trichloromethylthioaminopyridine, followed by reaction with primary, aromatic amines, enabled a wide variety of substituents to be introduced into the 3 position.[2b] Reaction with sodium sulfhydrate and suitable enolate anions greatly extended the scope of this route to this fused-ring system.[2b] The isomeric ring system, 2-substituted 2*H*-[1,2,4]thiadiazolo[2,3-*a*]pyridine (**2**), has also been prepared



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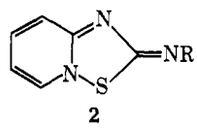

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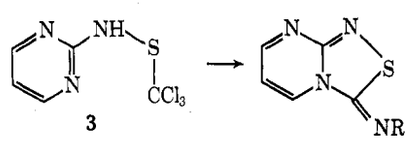
recently[3] by the oxidation of *N*-(2-pyridyl)thioureas with bromine or sulfuryl chloride, and 2-aminobenzothiazole and perchloromethyl mercaptan were found to yield the corresponding [1,2,4]thiadiazolo[3,4-*b*]-benzothiazole system.[4] It was of interest to establish whether the reaction of an appropriate amino heterocycle with perchloromethyl mercaptan is a general route to ring-fused [1,2,4]thiadiazole derivatives, and results obtained in the pyridazine, pyrimidine, and pyrazine systems are described in this communication.

3*H*-[1,2,4]Thiadiazolo[4,3-*a*]pyrimidine (4).—2-Aminopyrimidine has been reported[5] to react with perchloromethyl mercaptan giving 2-trichloromethylthioaminopyrimidine (**3**). Treatment of this sulfenamide with a variety of primary, aromatic amines in chloroform solution gave in moderate yields the 3*H*-[1,2,4]thiadiazolo[4,3-*a*]pyrimidine derivatives **4** described in Table I. Reaction of 2-aminopyrimidine and perchloromethyl mercaptan in the ratio of 2:1 gave a small quantity of 3-(2-pyrimidylimino)-3*H*-[1,2,4]-thiadiazolo[4,3-*a*]pyrimidine characterized only by a molecular ion, *m/e* 230, and an infrared absorption at 1620 cm^{-1} (C=N). With 2-amino-4-methylpyridine and **3**, the desired product **4** (R = 4-CH_3-2-C_5H_3N) was obtained together with an equal amount of a product identified as 7-methyl-3-(4-methyl-2-pyridylimino)-3*H*-[1,2,4]thiadiazolo[4,3-*a*]pyridine (**5**). This could also be prepared directly from 2-amino-4-methylpyridine and perchloromethyl mercaptan (2:1) as described previously.[2a] This no doubt arose by a transamination reaction in which the more basic 2-amino-4-methylpyridine (pK_a = 7.48)[6] displaced 2-aminopyrimidine (pK_a = 3.45)[7] from **3** forming the corresponding 4-methyl-2-trichloromethylthioaminopyridine (**6**), which then underwent ring closure with 2-amino-4-methylpyridine to **5**. In this study transamination was always observed to some extent when closure was attempted using 2-aminopyridine derivatives, being easily detected by tlc, but only with 2-amino-4-methylpyridine was the quantity of product sufficient for isolation. Related amine exchange in sulfenamides has also been observed[8] with 2-*tert*-butylaminothiobenzothiazole and morpholine on heating in an inert solvent to 100°.

As derivatives of this system decompose near their melting point, difficulties in purification occur with lower melting products. This was especially true in the reactions of **3** with aniline derivatives. For example,



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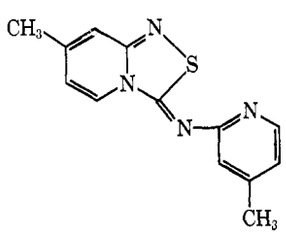

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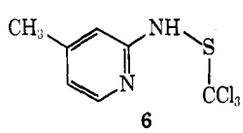

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while those derivatives presented in Table I were easily purified, reaction of **3** with either *p*-toluidine or *p*-chloroaniline yielded products which decomposed upon attempted recrystallization.

The analytical and spectral data described in Tables I and II clearly show that ring closure had occurred to these [1,2,4]thiadiazolo[4,3-*a*]pyrimidines. The possibility that ring closure had occurred in an alternative sense to yield a 2-substituted 2*H*-[1,2,4]thiadiazolo-[2,3-*a*]pyrimidine (**7**) (such would be the case if in **3** the trichloromethylthio group were attached to a ring

(1) (a) Support of this work by U. S. Public Health Service Research Grant CA 08495, National Cancer Institute, is gratefully acknowledged; (b) NDEA Trainee, 1970–1972.

(2) (a) K. T. Potts and R. Armbruster, *J. Org. Chem.*, **35**, 1965 (1970); (b) *ibid.*, **36**, 1846 (1971).

(3) R. L. N. Harris, *Aust. J. Chem.*, **25**, 993 (1972).

(4) (a) F. von Strum and W. Hans, *Angew. Chem.*, **67**, 743 (1955); (b) K. T. Potts and J. Kane, unpublished results.

(5) J. Goerdeler and E. R. Erbach, *Chem. Ber.*, **95**, 1637 (1962).

(6) F. N. Fastier and M. A. McDowell, *Austr. J. Exptl. Biol.*, **36**, 491 (1968).

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(8) J. J. D'Amico and D. D. Mullins, *Int. J. Sulfur Chem.*, in press; see also F. A. Davis, R. B. Wetzil, T. J. Devon, and J. F. Starkhouse, *J. Org. Chem.*, **36**, 799 (1971); F. A. Davis, S. Divald, and A. H. Cohn, *Chem. Commun.*, 294 (1971).

TABLE I

SOME RING-FUSED 1,2,4-THIADIAZOLES

Structure	R	Method	Mp, °C[a]	Yield, %	Crystal habit[b]	Solvent[c]	Analysis: Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	M·+ m/e (rel intensity)	Ir, cm⁻¹: C=N–	Ir, cm⁻¹: Thiadiazole ring deformn	Uv: λmax, nm	Uv: Log ε
4	2-Pyridyl	A	226–228	40	N	A	52.38	3.08	30.55	52.30	3.04	30.40	229 (100)	1640	1455	423	3.51
																407	3.53
																337	4.16
																324	4.10
																273	4.02
																252	4.14
4	4-Methyl-2-pyridyl	A	201–202	13	N	B:E	54.30	3.73	28.79	54.22	3.67	28.54	243 (100)	1630	1470	396	3.34
																376	3.29
																329	3.87
																321	3.82
																270	3.75
																247	3.81
4	4,6-Dimethyl-2-pyridyl	A	217–218	10	P	B	56.01	4.31	27.22	55.86	4.15	27.19	257 (100)	1630	1450	415	3.49
																333	4.16
																321[d]	4.15
																308	3.90
																272	4.00
																250	4.11
4	5-Chloro-2-pyridyl	A	249–250	28	Y	A	45.54	2.29	26.56	45.69	2.30	26.55	263 (95)	1640	1475	400	3.68
																341	4.20
																330[d]	4.13
																280	4.12
																247	4.23
4	5-Iodo-2-pyridyl	A	255–256	24	X	C	33.81	1.70	19.72	33.71	1.67	19.65	355 (100)	1630	1460	398	3.77
																343	4.31
																333[d]	4.23
																285	4.15
																245	4.21
4	2,5-Dichlorophenyl	A	199–200	57	N	F	44.46	2.04	18.85	44.42	2.03	18.80	296 (59)	1640	1470	415	3.40
																335[d]	3.52
																292	3.96
																239	4.32
4	3,4-Dichlorophenyl	A	182–184	81	N	F	44.46	2.04	18.85	44.65	2.04	19.16	296 (44)	1630	1470	420	3.46
																332[d]	3.62
																302	4.09
																244	4.24
4	*p*-Nitrophenyl	A	243–244	44	N	G	48.34	2.58	25.63	48.15	2.50	25.47	273 (80)	1630	1470	413	3.99
																360	4.16
																285[d]	3.90
																247	4.33
4	*m*-Nitrophenyl	A	189–191	66	N	G	48.34	2.58	25.63	48.24	2.53	25.53	273 (92)	1630	1470	405	3.49
																300[d]	4.04
																277[d]	4.13
																247	4.33

9	2,6-Dimethyl-4-pyrimidyl	B	182–184	32	Z	D	54.52	4.93	29.35	54.29	4.85	29.18	286 (100)	1640	1440	370	328	317	255[d]	226	385[d]	358	278	253[d]	242	425	368	253	425	338	336	327	315[d]	270[d]	363
10	2-Pyrazinyl	B	287–289	30	Y	B	46.94	2.63	36.50	46.78	2.49	36.39	230 (100)	1620	1470																			
12	6-Chloro-3-pyridazinyl	B	240–243	12	Y	B:E	36.13	1.35	28.10	36.22	1.34	28.12	298 (63)	1610	1480																			
12	5-Methyl-2-pyridyl	A	252–254	16	N	S	47.57	2.90	25.22	47.65	3.02	25.16	277 (100)	1610	1470																			

[a] All decomposed at melting point except **9**. [b] N = orange needles; P = orange prisms; Y = yellow, irregular prisms; X = brown, irregular prisms; Z = yellow, matted needles. [c] A = acetone; B = benzene; C = chloroform; D = cyclohexane; E = petroleum ether (bp 60–80); F = ethyl acetate; G = 1,2-dichloroethane; S = sublimed. [d] Shoulder.

TABLE II

NMR DATA FOR SOME REPRESENTATIVE RING-FUSED 1,2,4-THIADIAZOLES

Structure	R	Chemical shift, δ[a]
4	4,6-Dimethyl-2-pyridyl	2.35 (s, 3, 4′-CH_3), 2.60 (s, 3, 6′-CH_3), 6.55 (q, 1, 6-H), 6.70 (m, 1, 5′-H), 7.02 (m, 1, 3′-H), 8.66 (m, 1, 7-H), 8.80 (m, 1, 5-H)
9	2,6-Dimethyl-4-pyrimidyl	2.30 (d, 3, 7-CH_3), 2.48 (s, 3, 6′-CH_3), 2.72 (s, 3, 2′-CH_3), 3.20 (s, 3, 5-CH_3), 6.62 (m, 1, 8-H), 6.88 (m, 1, 5′-H)
10	2-Pyrazinyl	8.02 (m), 8.45 (m), 8.93 (m), 9.02 (m), 9.34 (m), 9.50 (m)
12	5-Methyl-2-pyridyl	2.38 (s, 3, 5′-CH_3), 7.35 (m), 8.40 (m)

[a] All spectra were determined in $CDCl_3$ except **10**, where CF_3CO_2D was used.

nitrogen) can be excluded on the basis of the close relationship of the spectral data to that of derivatives of the 3*H*-[1,2,4]thiadiazolo[4,3-*a*]pyridine system.[2]

Steric considerations clearly exert an influence on the ring closure to the fused system, as 2-amino-4,6-dimethylpyrimidine failed to yield a product with perchloromethyl mercaptan in a 2:1 ratio. In contrast to 2-trichloromethylthioaminopyridine, the pyrimidine derivative **3** did not react with sodium sulfhydrate or a variety of enolate anions such as sodium acetylacetonate, most likely owing to ring opening under the alkaline reaction conditions.

3*H*-[1,2,4]Thiadiazolo[4,3-*c*]pyrimidine (9).—This ring system could only be prepared from the reaction

7 **8** **9**

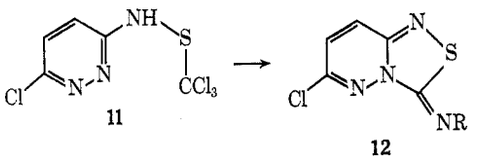
of 4-amino-2,6-dimethylpyrimidine[9] with perchloromethyl mercaptan (2:1) in the presence of triethylamine. All attempts to isolate the postulated 2,6-dimethyl-4-trichloromethylthioaminopyrimidine (**8**) intermediate were unsuccessful. The nmr spectrum of **9** showed four clearly separated methyl resonances at δ 2.30, 2.48, 2.72, and 3.20 and the assignments made in Table II are based on decoupling experiments and on the downfield shift expected for protons or methyl groups adjacent to nitrogen.

3*H*-[1,2,4]Thiadiazolo[4,3-*a*]pyrazine (10).—As with the 4-aminopyrimidine derivative above, 2-aminopyrazine could only be converted into 3-(2-pyrazinylimino)-3*H*-[1,2,4]thiadiazolo[4,3-*a*]pyrazine (**10**) by reaction with perchloromethyl mercaptan in the presence of triethylamine. The intermediate 2-trichloromethylthioaminopyrazine also proved too unstable for isolation and **10** could only be purified by numerous preparative layer chromatograms.

3*H*-[1,2,4]Thiadiazolo[4,3-*b*]pyridazine (12).—2-Amino-6-chloropyridazine reacted with perchloromethyl mercaptan to give 6-chloro-2-trichloromethylthioaminopyridazine (**11**), sufficiently pure for further reaction. With 2-amino-5-methylpyridine, ring closure

(9) A. R. Ronzio and W. B. Cook, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 71.

occurred to 6-chloro-3-(5-methyl-2-pyridylimino)-3*H*-[1,2,4]thiadiazolo[4,3-*b*]pyridazine (**12**, R = 5-CH_3-2-C_5H_3N). However, using a 2:1 ratio of the aminopyridazine and perchloromethyl mercaptan gave 6-chloro-3-(6-chloro-3-pyridazinylimino)-3*H*-[1,2,4]thiadiazolo[4,3-*b*]pyridazine (**12**, R = 6-Cl-3-$C_4H_2N_2$). Preparative layer chromatography was necessary to effect satisfactory purification of both derivatives.



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Spectral Characteristics.—Infrared bands common to all compounds were observed at 1610–1640 and 1440–1480 cm^{-1} and may be assigned to the C=N group and a thiadiazole ring deformation,[2,10] respectively. In contrast to derivatives of the 3*H*-[1,2,4]-thiadiazolo-[4,3-*a*]pyridine system,[11] all the members of these present systems, with the exception of 5,7-dimethyl-3-(2,6-dimethyl-4-pyrimidylimino)-3*H*-[1,2,4]thiadiazolo-[4,3-*c*]pyrimidine (**9**), showed no fluorescence and, in one or two instances, gave as yet unidentified photoproducts. In derivatives of the two fused-ring systems with exocyclic pyridyl substituents at the 3 position, the ultraviolet spectra consisted of four main bands centered at approximately 400, 330, 275, and 250 nm with the bands at 330 and 275 nm associated with the pyridine nucleus as in the 3*H*-[1,2,4]thiadiazolo[4,3-*a*]-pyridine system. Variation of substituents had predictable effects on the absorptions which are shown in Table I.

Representative nmr data for these compounds are described in Table II. In compounds containing the exocyclic 2-pyridylimino moiety, assignments for this substituent were made by analogy to related derivatives in the 3*H*-[1,2,4]thiadiazolo[4,3-*a*]pyridine system[2] and in those derivatives containing the thiadiazolo[4,3-*a*]pyrimidine nucleus, assignments are based on the downfield shift expected for protons adjacent to nitrogen and by comparison with derivatives of the *s*-triazolo[1,5-*a*]pyrimidine system.[12]

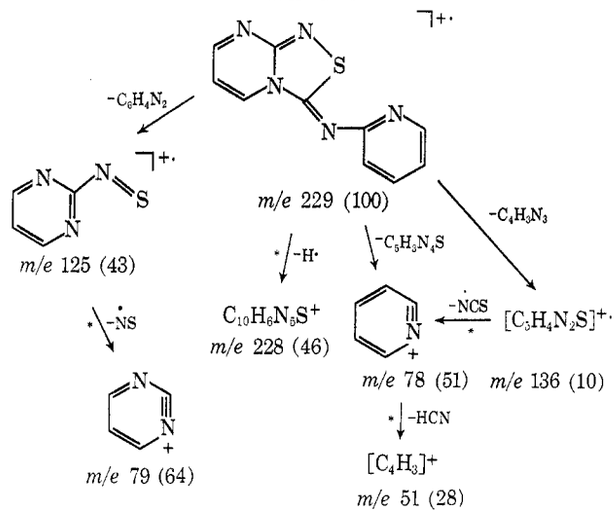
The stability of these compounds is reflected in the intensity of the molecular ions (frequently >90%) in their mass spectra. In all products derived from 2-aminopyrimidine and 2-aminopyrazine, a major fragmentation pathway of the bicyclic systems is the formation of a 2-pyrimidyl or 2-pyrazinylthionitroso ion. Other pathways are shown in Scheme I. In contrast, derivatives of the 3*H*-[1,2,4]thiadiazolo[4,3-*c*]pyrimidine system undergo a much more complicated fragmentation in which the only definitive feature is the loss of acetonitrile from the molecular ion. Similarly the 3*H*-[1,2,4]thiadiazolo[4,3-*b*]pyridazines lose a chlorine radical from the molecular ion in addition to the elimination of $C_6H_2ClN_6S$. In the latter case a $[C_3H_2Cl]^+$ ion, possibly a chlorocyclopropenium ion, is formed.

(10) J. Goerdeler and M. Budnowski, *Chem. Ber.*, **94**, 1682 (1961).

(11) K. T. Potts, H. H. Richtol, and R. Armbruster, *Anal. Chem.*, **43**, 1304 (1971).

(12) Y. Makisumi, H. Watanabe, and K. Tori, *Chem. Pharm. Bull.*, **12**, 204 (1964).

SCHEME I[a]



[a] Denotes metastable transition.

Experimental Section[13]

The following procedures illustrate the general methods employed.

2-Trichloromethylthioaminopyrimidine (**3**).—Perchloromethyl mercaptan (37.2 g) was suspended in a stirred solution of potassium carbonate (30 g), Alconox (1 g), water (600 ml), and crushed ice. A solution of 2-aminopyrimidine (19.0 g) in water (200 ml) was then added over 30 min. The precipitated product was collected, washed with water, and dried by suction. This was sufficiently pure for further use.

Method A. 3-(2-Pyridylimino)-3*H*-[1,2,4]thiadiazolo[4,3-*a*]-pyrimidine (4, R = 2-C_5H_4N).—A solution of 2-trichloromethylthioaminopyrimidine (4.0 g) in chloroform (100 ml) was added at room temperature to a stirred solution of 2-aminopyridine (1.54 g), triethylamine (5.0 g), and chloroform (250 ml). After stirring for 24 hr the solvent was removed from the reaction mixture, giving a brown solid which, after washing with methanol, crystallized from acetone as orange needles, 1.5 g (40%), mp 226–228° dec.

Method B. 5,7-Dimethyl-3-(2,6-dimethyl-4-pyrimidylimino)-3*H*-[1,2,4]thiadiazolo[4,3-*c*]pyrimidine (**9**).—A solution of perchloromethyl mercaptan (3.72 g) in chloroform (50 ml) was added over 30 min to a stirred solution of 4-amino-2,6-dimethylpyrimidine (4.93 g), triethylamine (8.1 g), and chloroform (150 ml). After stirring for 24 hr at room temperature, the reaction mixture was evaporated to dryness and the residue was leached with several portions of boiling benzene. The benzene was evaporated, and the residue was dissolved in a small volume of chloroform and then added to a column of Florisil (*ca.* 10 × 6.5 cm) and eluted with ethyl acetate. The resulting yellow solid crystallized from cyclohexane as matted, yellow needles, 1.9 g (33%), mp 182–184°.

Registry No.—**3**, 40899-18-1; **4** (R = 2-pyridyl), 40899-19-2; **4** (R = 4-methyl-2-pyridyl), 40899-20-5; **4** (R = 4,6-dimethyl-2-pyridyl), 40899-21-6; **4** (R = 5-chloro-2-pyridyl), 40899-22-7; **4** (R = 5-iodo-2-pyridyl), 40899-23-8; **4** (R = 2,5-dichlorophenyl), 40899-24-9; **4** (R = 3,4-dichlorophenyl), 40899-25-0; **4** (R = *p*-nitrophenyl), 40899-26-1; **4** (R = *m*-nitrophenyl), 40899-27-2; **9** (R = 2,6-dimethyl-4-pyrimidyl), 40899-23-3; **10** (R = 2-pyrazinyl), 40899-29-4; **12** (R = 6-chloro-3-pyridazinyl), 40899-30-7; **12** (R = 5-methyl-2-pyridyl), 40899-31-8; perchloromethylmercaptan, 75-70-7; 2-aminopyrimidine, 109-12-6; 2-aminopyridine, 504-29-0; 4-amino-2,6-dimethylpyrimidine, 461-98-3.

(13) All evaporations were done under reduced pressure using a rotatory evaporator. Spectral characterizations were performed with the following instrumentation: ir and uv spectra, Perkin-Elmer Model 337 and Cary Model 14 spectrophotometers; mass spectra, Hitachi Perkin-Elmer RMU-6E mass spectrometer. Melting points were taken in capillaries and microanalyses were by Galbraith Laboratories, Inc., Knoxville, Tenn., and Instranal Laboratory, Inc., Rensselaer, N. Y. Plc was carried out on 20 × 20 nm plates using a 1-mm layer of silica gel PF 254 containing $CaSO_4$ with chloroform–ethyl acetate (80:20) as developing agent.