Bridgehead Nitrogen Heterocycles. III. The 3H-[1,2,4]Thiadiazolo[4,3-*a*]pyridine System[1]

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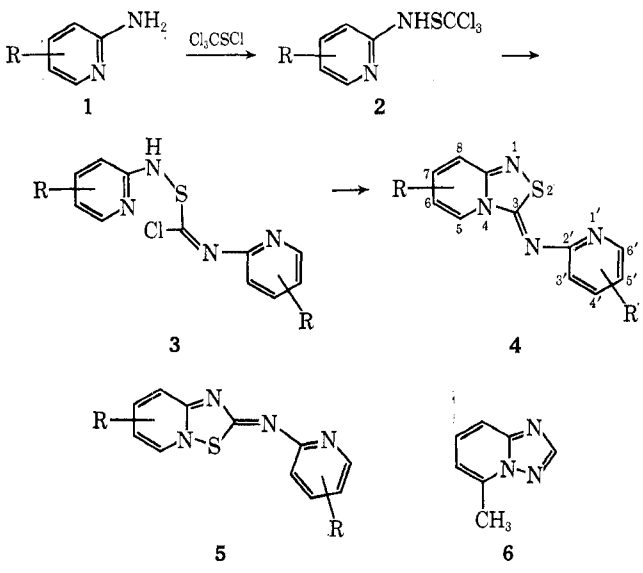
Reaction of 2-aminopyridines with perchloromethyl mercaptan in the presence of base gave 3-(2-pyridylimino)-3H-[1,2,4]thiadiazolo[4,3-*a*]pyridines, a new heterocyclic ring system.

The 1,2,4-thiadiazole ring system, one of the more interesting heterocyclic systems, has been the subject of numerous investigations.[2] A synthetic procedure of considerable utility is the formation of the ring system from amidines and perchloromethyl mercaptan (trichloromethanesulfenyl chloride) developed by Goerdeler,[3] and our interest in bridgehead nitrogen ring systems led us to apply this method to the synthesis of ring-fused 1,2,4-thiadiazoles. There are only two reported examples of ring-fused 1,2,4-thiadiazoles, a [1,2,4]thiadiazolo[4,5-*a*]pyrimidine derivative[4] and a [1,2,4]thiadiazolo[3,4-*b*]benzothiazole derivative.[5]

It was anticipated that the most direct route to the [1,2,4]thiadiazolo[4,3-*a*]pyridine system would be from 2-aminopyridine (**1**, R = H) and perchloromethyl mercaptan. An earlier report[6] described these two reactants as yielding 2-trichloromethylthioaminopyridine (**2**, R = H) which did not undergo ring-closure reactions to bicyclic products. Variation of the reaction conditions as described below led to a cyclization product to which structure **4** (R = H) has been assigned. Structure **5**, resulting from initial condensation at the pyridine nitrogen atom, may be excluded from consideration on the basis of the following data.



Analytical data and molecular weight data (Table I) clearly establish that ring closure occurred. Structure **4** is preferred over that resulting from the alternative mode of ring closure, represented by structure **5**, on spectroscopic and chemical grounds. In bridgehead nitrogen heterocycles of this type,[7] a heteroatom in the five-membered ring adjacent to the bridgehead nitrogen atom has a pronounced effect on the chemical shift of the proton, and substituents, in the *peri* position; *e.g.*, in the *s*-triazolo[1,5-*a*]pyridine system[7a] (**6**) the chemical shift of the 5 proton is τ 1.38 and that of a 5-methyl substituent is τ 7.24, whereas in the indolizine system[7b] the corresponding chemical shifts are τ 1.91 and 7.59, respectively. In the nmr spectra of these cyclization products (Table II), the chemical shift of the 5 proton is τ 1.75 and that of a 5-methyl substituent is τ 6.89, data consistent with structure **4**, in which the shielding is due to the 2-pyridylimino substituent in the 3 position. The synthesis of **4** (R = H) from 2-trichloromethylthioaminopyridine (**2**, R = H) and 2-aminopyridine confirmed the above assignment.

TABLE I

PRINCIPAL IONS PRESENT IN THE MASS SPECTRA OF REPRESENTATIVE 3-(2-PYRIDYLIMINO)-3H-[1,2,4]THIADIAZOLO[4,3-*a*]PYRIDINES[a]

Compd no.	*m/e*[b] (relative abundance)
1	228 (42), 227 (12), 136 (18), 124 (27), 78 (100), 51 (31)
2	257 (18), 256 (100), 255 (20), 150 (50), 138 (55), 92 (78)
7	300 (22), 299 (20), 298 (38), 297 (12), 296 (50), 295 (25), 170 (17), 160 (32), 158 (82), 114 (32), 112 (100), 76 (82)
11	365 (19), 364 (100), 363 (24), 362 (100), 245 (11), 244 (24), 243 (10), 242 (34), 182 (10), 181 (10), 151 (33), 106 (100), 79 (35), 78 (35)

[a] Appropriate metastable transitions were observed for the main fragmentations. [b] Ions with a relative abundance >10% only are reported.

The nmr data (Table II) for various derivatives of this ring system are consistent with those for similar heterocycles. Ring coupling constants (determined by first-order analysis) and the *ortho* benzylic coupling constants indicate that considerable bond fixation might be present in this system.

The ring system **4** was stable to hot, dilute acid or base, and no oxidation was observed with excess 30% hydrogen peroxide in acetic acid. Sodium metaperio-

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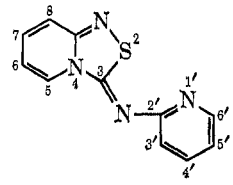
TABLE II

CHEMICAL SHIFTS (τ UNITS) AND COUPLING CONSTANTS (HERTZ) FOR VARIOUS 3H-[1,2,4]THIADIAZOLO[4,3-*a*]PYRIDINE DERIVATIVES[a]



Compd no.	τ_5	τ_6	τ_7	τ_8	$\tau_{3'}$	$\tau_{4'}$	$\tau_{5'}$	$\tau_{6'}$	$J_{5,6}$	$J_{5,7}$	$J_{5,8}$	$J_{6,7}$	$J_{6,8}$	$J_{7,8}$
1[b]	1.75	3.15	m[c]	m	m	m	m	2.55	7.2	1.2	1.2	6.4	1.4	
2[d]	*6.89*[e]	3.91	2.40	3.0[f]	3.0[f]	3.0[f]	3.0[f]	*7.33*[e]	1.0			7.0	1.4	7.0
3[d]	1.75	*7.77*[e]	2.45	2.60	2.85[f]	2.85[f]	*7.67*[e]	1.60	1.4					7.0
7[b]	2.35		3.15[f]	3.15[f]	3.15[f]	3.15[f]		2.07		2.0				
8[b]	1.24		1.82	2.37	2.6[f]	2.6[f]		0.94		2.0				9.0
4[d]	1.67[g]	3.52	*7.70*[e]	2.82	3.15[f]	*7.60*[e]	3.15[f]	1.67[g]	7.2		*h*		1.4	1.0
6[d]	*6.95*[e]	4.15	*7.90*[e]	3.12	3.30	*7.75*[e]	3.45	*7.45*[e]	1.0				1.3	1.3
5[d]	1.75[g]	3.68	2.60	*7.62*[e]	*7.55*[e]	3.15[f]	3.15[f]	1.75[g]	7.3	nr		7.3		1.0
9	1.70	2.70	m[i]	m	m	m		1.85	7.2	1.2	1.2	6.4	1.4	
10	1.40	*7.50*[e]	1.95	2.40		2.10	*7.50*[e]	1.50	1.0	1.0	*h*			
11	*6.70*[e]	3.28	*7.55*[e]	2.55	2.82	*7.41*[e]		*7.12*[e]	1.0					1.3

[a] Spectra were determined using TMS as internal reference except for compound 1 where DSS was used. [b] Determined in CF_3CO_2H. [c] m, very broad overlapping multiplet between τ 1.75 and 3.15. [d] Determined in $CDCl_3$. [e] Methyl resonances italicized. [f] Center of overlapping multiplet. [g] Overlapping multiplet. [h] Not resolvable. [i] Broad overlapping multiplet between τ 1.70 and 2.70.

TABLE III

SOME 3-(1-METHYL-2-PYRIDYLIMINO)-3H-[1,2,4]THIADIAZOLO[4,3-*a*]PYRIDINIUM IODIDES

Salt derived from compd no.	Mp, °C	Yield, %	Color[a]	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
1	214–216	85	Lime green	$C_{12}H_{11}IN_4S \cdot H_2O$[b]	37.12	3.37	14.30	37.92	3.20	14.58
2	240–242	90	Yellow	$C_{14}H_{15}IN_4S$[c]	42.22	3.80	14.07	42.28	3.86	14.06
5	237–238	95	Yellow	$C_{14}H_{15}IN_4S$[d]	42.22	3.80	14.07	42.48	3.78	14.23
4	257–259	90	Orange	$C_{14}H_{15}IN_4S$[e]	42.22	3.80	14.07	42.28	3.67	13.93
6	245	95	Orange	$C_{16}H_{19}IN_4S$[f]	44.97	4.72	13.11	44.94	4.66	12.90

[a] Needles. [b] Registry no. 24097-61-8. [c] 24097-62-9. [d] 24215-63-2. [e] 24097-63-0. [f] 24097-64-1.

date, specific for the oxidation of sulfides to sulfoxides,[8] was also without effect. No reaction was observed with dienophiles such as maleic anhydride and dimethyl acetylenedicarboxylate. Quaternization of **4** occurred sluggishly with methyl iodide at the pyridine nitrogen atom. These salts, described in Table III, are all highly colored, stable products. The nmr spectrum of the methiodide of compound **1** was consistent with alkylation occurring at the position shown. Alkylation at N-1 would have resulted in a considerable upfield shift[9] of the 8 proton, whereas the spectral pattern of the protons at the 5, 6, 7, and 8 positions was very similar to that of the parent system. Also the ultraviolet spectra of the methiodides were practically superimposable on those of the appropriate precursors, providing additional support for methylation at the pyridine nitrogen atom.

Bromination of **4** occurred readily with bromine in glacial acetic acid. Nmr data (Table II) showed that in these bromo products (Table IV) substitution had occurred in the 3-pyridyl substituent. This was confirmed by the synthesis of 3-(5-bromo-2-pyridylimino)-3H-[1,2,4]thiadiazolo[4,3-*a*]pyridine from **2** and 2-amino-5-bromopyridine. Introduction of methyl substituents into the π moiety of the fused system did not alter the bromination pattern and, with the 5,7-dimethyl derivative of **4**, a small amount of dibromo substitution in the 3 substituent was observed.

Several spectral characteristics are worthy of mention. In addition to the infrared >C=N– absorption at *ca.* 1640 cm^{-1} (Table IV), there was always present a characteristic absorption in the region of 1430–1460 cm^{-1}. A similar absorption has been attributed[10] to a 1,2,4-thiadiazole ring deformation and, in this present series, we have found this absorption band to be of diagnostic value. Table I illustrates, for representative 3-(2-pyridylimino)-3H-[1,2,4]thiadiazolo[4,3-*a*]pyridines, the two main fragmentation patterns observed in their mass spectra. The molecular ion fragments by breaking of the C_3–N_4 bond and either the N_1–S or the C_3–S bond. In the former case, the π moiety of the fused system is eliminated as a neutral fragment; in the latter case, 2-pyridyl isocyanide is eliminated. Several other fragmentation pathways, consistent with the variety of substituents in the fused nucleus (Table IV), were observed to a minor degree. An interesting feature of the spectra of the bromo-substituted compounds was the presence of a doubly charged molecular ion whose intensity was dependent on the number of bromo substituents.

The ultraviolet absorption spectral data listed in Table IV also reveal some interesting information about

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(9) W. W. Paudler and L. S. Helmick, *J. Heterocycl. Chem.*, **5**, 691 (1968).
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TABLE IV

SOME DERIVATIVES OF THE 3H-[1,2,4]THIADIAZOLO[4,3-*a*]PYRIDINE SYSTEM (**4**)[a]

Compd no.	R	3-Pyridylimino substituent	Mp, °C	Color[b]	Yield, %	Uv data, λ_{max}, nm (log ϵ)	Ir data, $\nu C{=}N$, cm^{-1}
1	H	H	174–176	A	75	392 (4.00), 378 (4.03), 338 (4.43), 328 (4.20), 280 (4.08), 240 (4.26)	1640
2	5-CH_3	6′-CH_3	173	B	85	395 (3.75), 380 (3.81), 347 (4.16), 337 (3.97), 280 (3.69), 230 (4.08)	1630
3	6-CH_3	5′-CH_3	194–196	C	65	395 (3.93), 380 (3.96), 343 (4.28), 333 (4.17), 285 (4.09), 245 (4.26)	1645
4	7-CH_3	4′-CH_3	189–191	C	80	375 (4.78), 365 (4.79), 323 (5.06), 312 (4.97), 270 (4.82), 228 (5.09)	1640
	7-CH_3	4′-CH_3	228[c]	D	90	370 (3.93), 328 (4.17), 318 (4.09), 273 (3.94), 238 (4.23)	1630
5	8-CH_3	3′-CH_3	150–151	D	85	390 (4.01), 375 (3.99), 339 (4.17), 327 (4.08), 277 (3.90), 230 (4.11)	1630
6	5,7-$(CH_3)_2$	4′,6′-$(CH_3)_2$	164–165	A	80	380 (4.28), 343 (4.53), 330 (4.40), 275 (4.15), 230 (4.52)	1640
7	6-Cl	5′-Cl	205–207	D	35	405 (3.82), 387 (3.88), 348 (4.34), 336 (4.23), 288 (4.17), 250 (4.32), 225 (4.26)	1640
8	6-Br	5′-Br	230–232	D	40	408 (4.05), 388 (4.11), 348 (4.46), 337 (4.37), 290 (4.37), 252 (4.45)	1620
9	H	5′-Br	172–174	D	90	393 (4.06), 377 (4.08), 347 (4.22), 290 (4.07), 240 (4.28), 225 (4.32)	1640
10	6-CH_3	3′-Br,5′-CH_3	224–225	D	90	395 (3.98), 378 (4.00), 348 (4.18), 293 (3.98), 242 (4.17)	1650
11	5,7-$(CH_3)_2$	5′-Br,4′,6′-$(CH_3)_2$	213–214	D	85	390 (4.04), 378 (4.07), 348 (4.22), 280 (3.90), 240 (4.24)	1650
12	5,7-$(CH_3)_2$	3′,5′-$(Br)_2$,4′,-6′-$(CH_3)_2$	270	D		395 (4.09), 380 (4.11), 348 (4.37), 337 (4.22), 288 (3.99), 247 (4.28), 230 (4.31)	1640

[a] Satisfactory analytical data (±0.3% for C, H, and N) were reported for all compounds in this table. [b] Needles: A, rust; B, gold; C, orange; D, yellow. [c] Perchlorate.

this ring system. The absorptions can be divided into four general bands. The first band, centered around 390 nm, is assigned to the ring-fused portion of the molecule. The second, and the most structured band, occurs at about 340–350 nm while a third band occurs at about 280–290 nm. These last two bands are assigned to the exocyclic π moiety, substitution of bromine into the 5 position of the exocyclic π moiety causing a strong shift in the second and third bands without affecting the first band. Furthermore, a bromine substituent in the 6 position of the fused-ring system shifts the first band while leaving the second and third bands unaffected. It was observed that the second band lost most of its fine structure when the exocyclic π moiety contained either methyl, bromine, or chlorine substituents, and this change was of considerable help in structural assignments. The fourth band centered at 240–250 nm was also assigned to the ring-fused portion of the system. It shifted only on introduction of substituents into the thiadiazolo[4,3-*a*]pyridine nucleus.

The formation of compound **9** from **2** and 2-amino-5-bromopyridine indicates that the fused-ring system is most likely formed *via* the intermediates **2** and **3**. As **3** is an imidoyl chloride, it would be expected to undergo an extremely facile ring closure to **4**.

Experimental Section[11]

General Procedure for the Preparation of 3-(2-Pyridylimino)-3H-[1,2,4]thiadiazolo[4,3-*a*]pyridines.—The aminopyridine (0.04 mol) in chloroform (200 ml) and Et_3N (0.1 mol) were stirred at 0° while Cl_3CSCl (3.6 g, 0.02 mol) was added dropwise over 1 hr. After the mixture was stirred at room temperature for 3 hr, the solvent was removed and the residue was washed with methanol. Crystallization from acetone (for the Br derivative chloroform was used) afforded the products described in Table IV.

(11) All evaporations were done under reduced pressure using a Rotavap apparatus. Spectral characterizations were performed with the following instrumentation: ir and uv spectra, Perkin-Elmer Model 337 and Cary Model 14 spectrophotometers, respectively; nmr, Varian A-60 spectrometer; mass spectra, Hitachi Perkin-Elmer RMU-6E mass spectrometer. Melting points were taken in capillaries and microanalyses were by Galbraith Laboratories, Inc., Knoxville, Tenn.

General Procedure for the Preparation of 3-(1-Methyl-2-pyridylimino)-3H-[1,2,4]thiadiazolo[4,3-*a*]pyridinium Iodides.—A 1:1 mixture of the above bases and CH_3I was refluxed in chloroform. The salt crystallized from the hot reaction mixture and, on recrystallization from ethanol, gave the products described in Table III.

Bromination of 3-(2-Pyridylimino)-3H-[1,2,4]thiadiazolo-[4,3-*a*]pyridines.—The fused-ring system (0.02 mol) in glacial acetic acid (200 ml) was stirred at room temperature while a solution of Br_2 (0.02 mol) in glacial acetic acid (10 ml) was added slowly. An immediate reaction occurred and the reaction mixture was heated at 100° for 1 hr during which time it became a bright yellow color. The reaction mixture was poured over ice and the precipitate recrystallized from acetone.

Registry No.—1, 24097-57-2; 2, 24097-94-7; 3, 24097-95-8; 4, 24097-96-9; 4 (perchlorate), 24097-74-3; 5, 24162-35-4; 6, 24097-97-0; 7, 24097-98-1; 8, 24097-99-2; 9, 24162-36-5; 10, 24097-58-3; 11, 24097-59-4; 12, 24097-60-7.

Thiapyrone Chemistry. III.[1] The Reaction of 2,6-Dimethylthio-3,5-diphenylthiapyrone with Hydroxide Ion

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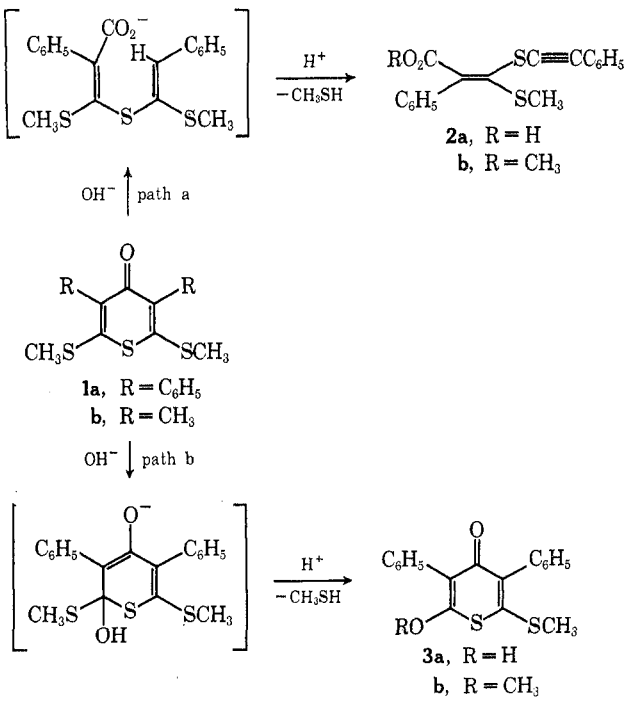
The reaction of 2,6-dimethylthio-3,5-diphenylthiapyrone (**1a**) with hydroxide ion has been reinvestigated. The major product of the reaction is shown to be the hydroxythiapyrone **3a**, which on treatment with diazomethane gives the isomeric enol ethers **3b** and **4b**. Spectral and chemical evidence used to support these conclusions are discussed.

In the course of our studies on the chemistry of thiapyrones, we have had occasion to reinvestigate the reaction of 2,6-dimethylthio-3,5-diphenylthiapyrone (**1a**) with hydroxide ion. Schönberg and Asker[2] described this reaction as leading to the complex thio ether **2a** *via* ring cleavage followed by the acid-catalyzed elimination of methanethiol. This sequence is indicated in path a. However, the only evidence offered in support of the assigned structure was an elemental analysis and demonstration of the acidic character of the product by its solubility properties and its reaction with diazomethane to form the "ester" **2b**.

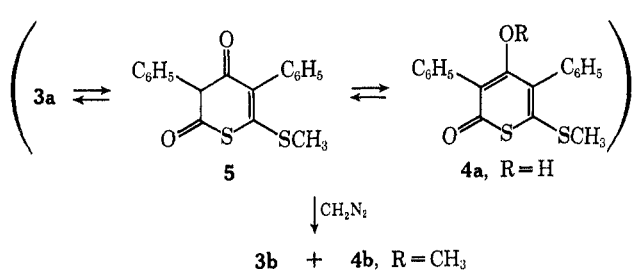


Our investigation of this reaction has revealed that the product is not **2a** but rather is the thiapyrone derivative **3a**, existing in solution in equilibrium with its tautomeric forms **4a** and **5**. When treated with diazomethane, this mixture produces the isomeric enol ethers **3b** and **4b**. The structural assignments of these products based on chemical and spectroscopic data are the subject of this report.

Results and Discussion

2-Methylthio-3,5-diphenyl-6-hydroxy-4-thiapyrone (**3a**) is produced in 38% yield by treatment of **1a** with alcoholic potassium hydroxide by the procedure described by Schönberg.[2] Path b, involving a Michael addition of hydroxide ion to **1a** followed by acidification and consequent elimination of methanethiol, suggests a possible route for its formation. This yellow crystalline material has the same melting point and other properties previously attributed to the incorrectly assigned structure **2a**.[2]

A key to the characterization of the acidic thiapyrone **3a** was its reaction with diazomethane. Since it seemed likely that **3a** should also exist as **4a**,[3] both tautomeric forms of the parent thia-2,4-pyrone **5**, methylation of



the tautomeric mixture was expected to produce the isomeric enol ethers **3b** and **4b**.[4] Careful chromatographic separation of the total reaction mixture afforded

(1) Paper II of this series: H. J. Teague and W. P. Tucker, *J. Org. Chem.*, **32**, 3144 (1967).

(2) A. Schönberg and W. Asker, *J. Chem. Soc.*, 604 (1946).

(3) The yellow hydrolysis product probably exists mainly as tautomer **4a** in both the solid state and in solution. Its visible absorption maximum (370 mμ) closely resembles that (380 mμ) of the α-thiapyrone ether **4b** (Table I).

(4) D. Herbert, W. B. Mors, O. R. Gottlieb, and C. Djerassi, *J. Amer. Chem. Soc.*, **81**, 2427 (1959).