Bridgehead Nitrogen Heterocycles. V. Some 3*H*-[1,2,4]Thiadiazolo[4,3-*a*]pyridines Derived from 2-Trichloromethylthioaminopyridine

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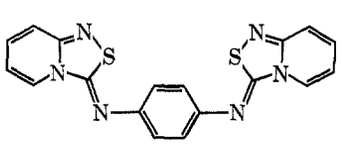
In a previous communication[2] it was shown that 2-aminopyridines underwent ready reaction with perchloromethyl mercaptan to give 3-(2-pyridylimino)-3*H*-[1,2,4]thiadiazolo[4,3-*a*]pyridines. The reaction involved 2-trichloromethylthioaminopyridine (**1**) as an intermediate and, under carefully controlled reaction conditions, **1** was isolated in a pure and relatively stable state.[3] This present communication deals with the use of this trichloro compound in the synthesis of 3*H*-[1,2,4]thiadiazolo[4,3-*a*]pyridines with a variety of substituents in the 3 position.

Condensation of 2-trichloromethylthioaminopyridine (**1**) occurred readily with aromatic primary amines (Table I). The products derived from the corresponding aliphatic amines were unstable, but it was possible to characterize that derived from ammonia by conversion into the *p*-nitrobenzoyl derivative. 2,5-Dichloroaniline (pK_a = 1.5) gave the corresponding 3-(2′,5′-dichlorophenylimino)-3*H*-[1,2,4]thiadiazolo-[4,3-*a*]pyridine (**2**, X = 2,5-$Cl_2C_6H_3N$=) in good yield, whereas 2,6-dichloroaniline did not form the fused system. It is possible that ring closure was prevented by steric hindrance between the 3 substituent and the 5-hydrogen atom but, as other products with comparable steric requirements were prepared, a more likely explanation lies in the low basicity of 2,6-dichloroaniline preventing the formation of the intermediate imidoyl chloride. An aromatic diamine such as *p*-phenylenediamine underwent condensation with two molecules of **1** to form bis(3*H*-[1,2,4]thiadiazolo[4,3-*a*]pyrid-3-ylidene)-*p*-phenylenediamine (**3**).



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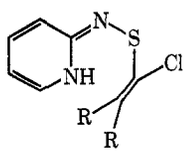

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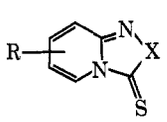

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Sodium sulfhydrate underwent ready reaction with **1** to yield 3*H*-[1,2,4]thiadiazolo[4,3-*a*]pyridine-3-thione (**2**, X = S). These thiones reacted with methyl iodide to form unstable red salts which could not be characterized. The exocyclic sulfur compounds were stable to acid hydrolysis, as was the corresponding *N*-phenylimino compound **2** (X = NPh).

Suitable enolate anions, such as those derived from acetylacetone, acetoacetic ester, diethyl malonate, and ethyl cyanoacetate, also underwent ready condensation with **1** to the fused system **2**. This reaction probably involved displacement of a chloride ion from **1**, followed by elimination of HCl from this product, and subsequent ring closure of the α,β-unsaturated system **4** through a Michael-type addition of the pyridine system. These products, described in Table I, provided strong evidence for the assigned structure of the ring system.

The nmr spectra of the products in Table I were simpler than those of this ring system described earlier[2] and provided confirmation of the earlier assignments. The 3-thione **2** (X = S) and its 5-methyl derivative **2** (X = S; R = 5-CH_3) were particularly informative. The possibility of a Dimroth-type rearrangement[4] occurring in ring systems of this type cannot be overlooked and the alternative structure **5** must be considered. In the case of the 3-thiones **2** (X = S; R = H and 5-CH_3) equivalent structures are produced on rearrangement, whereas with 5-methyl-3-(3′,4′-dichlorophenylimino)-3*H*-[1,2,4]thiadiazolo[4,3-*a*]pyridine (**2**, X = 3,4-$Cl_2C_6H_3N$; R = 5-CH_3) rearrangement would result in 2-(3,4-dichlorophenyl)-2,3-dihydro-5-methyl-*s*-triazolo[4,3-*a*]pyridine-3-thione (**5**, X = 3,4-$Cl_2C_6H_3N$; R = 5-CH_3). If this were the case, the 5-methyl group would be under the strong deshielding influence of the 3-thione group and its chemical shift would be equivalent in both compounds. The nmr data[5] for **2** (X = S; R = 5-CH_3) [τ 6.75 (d, 3, $J_{5,6}$ = 1.2 Hz, 5 CH_3), 3.71 (m, 1, $J_{5,6}$ = 1.2 Hz, $J_{6,7}$ = 5.2 Hz, 6 H), 2.76 (m, 1, $J_{6,7}$ = 5.2 Hz, $J_{7,8}$ = 6.0 Hz, 7 H), 2.85 (m, 1, $J_{7,8}$ = 6.0 Hz, 8 H)] and that for **2** (X = 3,4-$Cl_2C_6H_3N$; R = 5-CH_3) [τ 7.10 (d, 3, $J_{5,6}$ = 1.2 Hz, 5 CH_3), 3.95 (m, 1, $J_{5,6}$ = 1.2 Hz, $J_{6,7}$ = 6.0 Hz, 6 H)] clearly show that in the former the 5-CH_3 group is in a different deshielding environment than in the latter.

Other spectral data provided confirmation of these structures, in particular the extended conjugation evident in the ultraviolet spectra (Table I) and the carbonyl absorption of those compounds derived from **2** and enolate ions. Thus, in 3-(diacetylmethylidene)-3*H*-[1,2,4]thiadiazolo[4,3-*a*]pyridine (**6**) the carbonyl absorption occurred at 1660 cm^{-1}, indicative of an α,β-unsaturated ketone. Such an absorption is incompatible with the corresponding isomeric structure **5**. Similar absorptions were observed with the other compounds of this type.

An interesting feature of the nmr spectrum of 3-(diacetylmethylidene)-3*H*-[1,2,4]thiadiazolo[4,3-*a*]pyridine was the appearance of the methyl resonance as an extremely sharp, ringing-out singlet at τ 7.50. This could not be split into two peaks at −28° or by the addition of pyridine. This symmetry may be explained

(1) (a) Partial support of this work by U. S. Public Health Service Research Grant CA 08495, National Cancer Institute, is gratefully acknowledged. (b) National Dairy Fellow, 1969–1970.

(2) K. T. Potts and R. Armbruster, *J. Org. Chem.*, **35**, 1965 (1970).

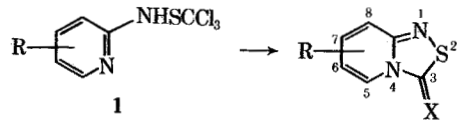
(3) J. Goerdeler, H. Groschopp, and U. Sommerbad, *Chem. Ber.*, **96**, 182 (1957).

(4) For a recent review, see M. Wahren, *Z. Chem.*, **7**, 241 (1969).

(5) The nmr spectra of the two 3-thiones were calculated from the observed chemical shifts and coupling constants using a LAOCN-3 program (A. A. Bothner-by and S. Castellano, Program 111, Quantum Chemistry Program Exchange, Indiana University, 1968). The chemical shifts and peak intensities of the calculated spectra were in close agreement with the experimental spectra.

TABLE I

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



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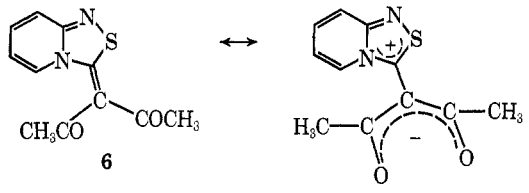
R	Substituents, 3 position	Registry no.	Mp, °C	Color	Crystal habit	Recrystn solvent[a]	Method of preparation[b]	Yield, %	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	$\nu_{C=N}$ (KBr), cm^{-1}	$\lambda_{max}^{CH_3OH}$ nm (log ϵ)
H	N-C_6H_5	28912-70-1	104–105	Yellow green	Plates	E	IB	60	$C_{12}H_9N_3S$	63.41	3.99	18.49	63.47	4.10	18.77	1630	390 (3.83), 295 (4.20), 238 (4.30), 220 (4.25)
H	N-*p*-$CH_3C_6H_4$	28912-71-2	108–109	Yellow	Rhombs	E	IB	65	$C_{13}H_{11}N_3S$	64.70	4.61	17.41	64.92	4.53	17.34	1625	395 (3.96), 295 (4.35), 242 (4.42)
H	N-(2,5-$Cl_2C_6H_3$)	28912-72-3	123–124	Yellow	Needles	E	IA	50	$C_{12}H_7Cl_2N_3S$	48.66	2.38	14.19	48.76	2.49	14.15	1620	385 (4.04), 300 (4.25), 240 (4.50)
5-CH_3	N-(3,4-$Cl_2C_6H_3$)	28912-73-4	149–150	Pale green	Needles	E	IA	70	$C_{13}H_9Cl_2N_3S$	50.36	2.93	13.55	50.53	2.88	13.68	1640	400[c] (4.15), 385 (4.19), 313 (4.44), 242 (4.72)
			248[d]	Green	Needles	F	ID	40	$C_{18}H_{12}N_6S_2 \cdot {}^1/_4CH_3COOH$	56.76	3.28	21.72	56.78	3.28	21.72	1610	410 (4.25), 325 (4.47), 240 (4.52)
H	N-(1-$C_{10}H_7$)	28912-74-5	121	Green	Irregular prisms	G	IB	35	$C_{16}H_{11}N_3S$	69.29	4.00	15.15	68.95	3.90	14.62	1610	400 (3.18), 328 (3.72), 240 (4.15)
H	N-($CH_2C_6H_5$)	28912-75-6	80–82	Yellow	Needles	G	IC	50	$C_{13}H_{11}N_3S$	64.70	4.60	17.41	64.15	4.56	17.85	1640	395[c] (3.58), 380 (3.62), 285 (3.78), 240 (4.30)
H	N-(*p*-$NO_2C_6H_4CO$)	28912-76-7	>300	Lime green	Irregular prisms	H	II	15	$C_{13}H_9N_4SO_3$	51.99	2.68	18.66	51.54	2.61	18.58	1640	370 (4.68), 265 (4.65)
H	S	28912-77-8	145–147	Golden brown	Plates	G	III	35	$C_6H_4N_2S_2$	42.83	2.40	16.65	42.72	2.36	16.56	1625	388 (3.83), 322 (3.72), 368 (3.72), 265 (3.50), 235 (4.07)
5-CH_3	S	28912-78-9	112–113	Yellow	Needles	G	III	45	$C_7H_6N_2S_2$	46.13	3.31	15.37	45.92	3.12	14.98	1645	395 (3.83), 340 (3.68), 328 (3.65), 240 (2.99)
H	$C(COCH_3)_2$	28912-79-0	146	Yellow	Irregular prisms	I	IV	30	$C_{11}H_{10}N_2O_2S$	56.39	4.30	11.96	56.14	4.20	11.86	1630	403 (4.29), 330 (4.00), 285 (3.92), 240 (4.27)
H	$C(COCH_3)COOEt$	28912-80-3	140	Yellow	Irregular prisms	I	IV	50	$C_{12}H_{12}N_2O_3S$	54.53	4.58	10.60	54.53	4.57	10.58	1640	395 (4.00), 333 (3.85), 255[c] (3.80), 242 (4.02)
H	$C(COOEt)_2$	28912-81-4	124	Yellow	Irregular prisms	I	IV	40	$C_{13}H_{14}N_2O_4S$	53.09	4.79	9.52	52.97	4.74	9.27	1635	400 (3.95), 330 (4.02), 320 (4.05), 242 (4.34)
H	C(CN)COOEt	28912-82-5	187–189	Pale yellow	Irregular prisms	I	IV	10	$C_{11}H_9N_3O_2S$	53.43	3.67	16.99	53.23	3.67	17.23	1645	410 (3.83), 393 (4.01), 378 (3.95), 328 (3.98), 318 (3.97), 240 (4.10)
7-Br	N-(2-C_6H_4N)	28912-83-6	204–205	Bright yellow	Needles	E	V	60	$C_{11}H_7N_4SBr \cdot {}^1/_2H_2O$	41.78	2.55	17.22	41.75	2.20	17.57	1630	345 (4.22), 328 (4.15), 275 (3.99), 250 (4.22)
7-I	N-(5-I,2-C_6H_4N)	28966-92-9	229–230	Greenish gold	Needles	E	IC	50	$C_{11}H_6I_2N_4S$	27.46	1.47	11.65	27.37	1.23	11.41	1625	385 (4.04), 350 (4.30), 340 (4.21), 288 (4.14)

[a] E = acetone; F = acetic acid; G = ethanol; H = DMF; I = sublimation at 80° (0.5 mm). [b] See Experimental Section. [c] Shoulder. [d] Bis(3*H*-[1,2,4]thiadiazolo[4,3-*a*]pyrid-3-ylidene)-*p*-phenylenediamine.

in terms of a significant amount of single bond character in the exocyclic double bond, resulting in rotation of the exocyclic moiety as shown in **7**. A similar aver-



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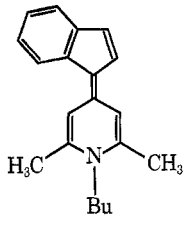

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aging effect has been observed[6] for the methyl groups in 1-butyl-1,4-dihydro-2,6-dimethyl-4-inden-1-ylidenepyridine (**8**) where the methyl resonance was a sharp singlet until −20°.

In the mass spectrometer the compounds described above all underwent fission of the 2,3 and 3,4 bonds of the nucleus and gave a 2-thionitrosopyridinium ion which lost NS· forming the pyridyne ion. However, the 3-methylidene derivatives underwent fragmentation of the exocyclic substituents prior to fragmentation of the fused-ring system.

Experimental Section[7]

Synthesis of 2-Trichloromethylthioaminopyridines.—The 2-aminopyridine (0.5 mol) in water (200 ml) was added dropwise with rapid stirring to a water (1000 ml)–ice (500 g) mixture of Cl_3CSCl (0.5 mol), K_2CO_3 (0.5 mol), and 1 g of Alconox. The product precipitated rapidly and was filtered cold in a sintered glass funnel and air-dried. The yield was 70%, with further purification being unnecessary and the stability of the product depending on its dryness and storage in the cold.

(6) G. V. Boyd, A. W. Ellis, and M. D. Harns, *J. Chem. Soc. C*, 800 (1970); see also H. Kessler, *Angew. Chem., Int. Ed. Engl.*, **9**, 219 (1970).

(7) 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 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., and Instranal Laboratory, Inc., Rensselaer, N. Y.

I. Reaction of 2-Trichloromethylthioaminopyridines with Primary Amines.—The following variety of procedures result in reproducible yields of the products reported in Table I.

A.—The 2-trichloromethylthioaminopyridine (0.02 mol), the amine (0.02 mol), and a large excess of K_2CO_3 (anhydrous) were refluxed in ethanol (300 ml) for 24 hr. After the insoluble material was filtered off, the solvent was removed yielding an oil which crystallized from the appropriate solvent listed in Table I.

B.—The above reactants were stirred at room temperature for 24 hr and the reaction mixture was worked up as in A.

C.—The 2-trichloromethylthioaminopyridine (0.02 mol) and the amine (0.02 mol) were stirred in ethanol (200 ml) at 0° in the presence in Et_3N (0.06 mol) for 2 hr. The solvent was removed and water (50 ml) was added. The resultant oil was extracted with ether and the product finally crystallized from ethanol.

D.—The reaction mixture obtained as in A above was added to water (300 ml) and the residue filtered and recrystallized from glacial acetic acid.

II. Preparation of 3-(*p*-Nitrobenzimido)-3*H*-[1,2,4]thiadiazolo[4,3-*a*]pyridine (9).—A stream of ammonia was passed into a chloroform (300 ml) solution of 2-trichloromethylthioaminopyridine (0.05 mol) at 0°. After 2 hr, the NH_4Cl was filtered off and the solvent removed to yield a yellow oil which was dissolved in acetone and *p*-nitrobenzoyl chloride, and K_2CO_3 (anhydrous) was added. After 24 hr at room temperature the precipitate was filtered, washed with water, and then recrystallized from DMF.

III. Preparation of 3*H*-[1,2,4]Thiadiazolo[4,3-*a*]pyridine-3-thiones.—The appropriate 2-trichloromethylthioaminopyridine (0.02 mol) was dissolved in ethanol (200 ml) and a solution of NaSH (0.02 mol) was added dropwise with stirring at 0°. After 1 hr the solution was allowed to come to room temperature and, after an additional 3 hr, the solution was filtered and the solvent removed. The resultant oil crystallized from methanol and the product was further purified by sublimation at 100° (bath temperature) (0.03 mm).

IV. Reaction of 2-Trichloromethylthioaminopyridine with Carbanions.—A solution of the active methylene compound (0.02 mol) and KOH (0.02 mol) in ethanol (100 ml) was added dropwise at room temperature to the 2-trichloromethylthioaminopyridine (0.02 mol) in ethanol (400 ml) in the presence of excess K_2CO_3 (anhydrous). After 24 hr the solution was filtered and the solvent removed to yield a dark residue which was dissolved in benzene and passed over an alumina column (1 × 6 in). The effluent solution was evaporated to yield a yellow solid which was sublimed at 130° (bath temperature) (0.03 mm).

V. *In Situ* Generation of 5-Bromo-2-trichloromethylthioaminopyridine and Its Reaction with 2-Aminopyridine.—A solution of 2-amino-5-bromopyridine (0.02 mol) and triethylamine (0.02 mol) in chloroform (50 ml) was added dropwise to a solution of Cl_3CSCl (0.02 mol) in chloroform (300 ml) at 0°. After the addition was completed a solution of 2-aminopyridine (0.02 mol) and triethylamine (0.06 mol) in chloroform (100 ml) was added dropwise and the solution was warmed to room temperature. After 3 hr the solvent was removed and the residue washed with MeOH to yield a yellow solid which was purified by preparative tlc.

Registry No.—**1**, 28913-69-8; **3**, 28912-84-7.