1,2,4-Triazoles. XVI. Derivatives of the *s*-Triazolo[3,4-*b*][1,3,4]thiadiazole Ring System[1]

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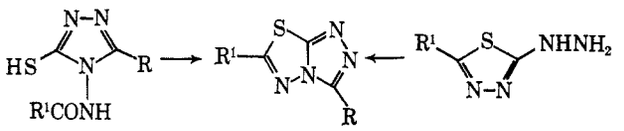
The reaction of 3-alkyl- (or aryl-) 4-amino-*s*-triazole-5-thiols with cyanogen bromide, or carbon disulfide and alkali, results in good yields of 6-amino- or 6-mercapto-3-alkyl- (or aryl-) *s*-triazolo[3,4-*b*][1,3,4]thiadiazoles. 3-Amino- and 3-mercapto-6-phenyl-*s*-triazolo[3,4-*b*][1,3,4]thiadiazole were obtained from the reaction of cyanogen bromide, and carbon disulfide and alkali, on 5-phenyl-1,3,4-thiadiazol-2-yl hydrazine. Some spectral characteristics of these derivatives are described.

The *s*-triazolo[3,4-*b*][1,3,4]thiadiazole ring system (**3**) was initially described by Kanaoka[2] who synthesized alkyl and aryl derivatives of the system by dehydrative ring closure of 4-acylamino-*s*-triazole-5-thiols (**1**) and by ring closure of 1,3,4-thiadiazol-2-ylhydrazines (**2**) with ortho esters. In a continuation of our interests in



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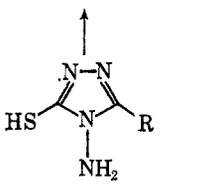

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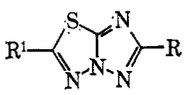

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the chemistry of fused *s*-triazole ring systems,[3] this communication describes new synthetic routes to the *s*-triazolo[3,4-*b*][1,3,4]thiadiazole ring system containing functional groups in the 3 and 6 positions. Some spectral characteristics of these derivatives as well as their chemical properties, are also described.

Cyanogen bromide is finding increasing use in heterocyclic synthesis[4] and we have now found it to be an effective reagent for the ring closure of 4-amino-3-alkyl- (or aryl-) *s*-triazole-5-thiols (**4**) to 3-alkyl- (or aryl-) 6-amino-*s*-triazolo[3,4-b][1,3,4]thiadiazoles (**3**, R^1 = NH_2; Table I). The reaction probably occurred *via* the intermediacy of a thiocyanate[5] and the absence of the thiocyanate band in the 2200-cm^{-1} region in the infrared spectra, together with analytical and ultraviolet spectral data, was taken to indicate that ring closure had occurred. The infrared spectra of these amino compounds showed marked hydrogen-bonding characteristics in the 1700–2500-cm^{-1} region, and this hydrogen bonding most likely accounts for the high melting points of the products. These amino compounds do not undergo the diazonium reaction under standard conditions.

These same substituted *s*-triazole intermediates (**4**)[6] also underwent ready ring closure with carbon disulfide and alkali to 3-alkyl- (or aryl-) *s*-triazolo[3,4-*b*][1,3,4]-thiadiazole-6-thiols (**3**, R^1 = SH; Table I). Analytical and spectral data and the conversion of the thiols into their methylthio ethers established that ring closure to the bicyclic system **3** had occurred. That methylation had taken place at the exocyclic sulfur atom was evident from the nmr spectra of these methylthio ethers; the chemical shifts of the SCH_3 protons were in the range τ 7.16–7.23, in agreement with the chemical shifts of similar protons (τ 7.14–7.27) in substituted 2-methylthiobenzothiazoles.[9] The ring closure most likely involved an intermediate dithiocarbamate and, in this respect, is similar to the formation of *s*-triazolo-[3,4-*b*][1,3,4]thiadiazole-3,6-dithiol (**3**, R = R^1 = SH) from thiocarbohydrazide and carbon disulfide in refluxing pyridine solution.[10]

For spectral studies, products with similar substituents in alternative positions to those above were sought. Ring closure of 5-phenyl-1,3,4-thiadiazol-2-ylhydrazine with cyanogen bromide readily gave in good yield 3-amino-6-phenyl-*s*-triazolo[3,4-*b*][1,3,4]thiadiazole (**3**, R = NH_2; R^1 = Ph), and it was found possible to obtain the corresponding 3-thiol by ring closure of the hydrazine with carbon disulfide and alkali. This thiol was likewise characterized by conversion to its methylthio ether. The scope of these reactions is severely limited by the difficulty in obtaining the intermediate 1,3,4-thiadiazol-2-ylhydrazines with 5-alkyl substituents. Kanaoka[11] found that in the reaction of 2-chloro-5-alkyl-1,3,4-thiadiazoles with hydrazine,

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(2) M. Kanaoka, *J. Pharm. Soc. Japan*, **76**, 113 (1956); *Chem. Pharm. Bull.* (Tokyo), **5**, 385 (1957).

(3) References to earlier work can be found in K. T. Potts, H. R. Burton, and S. K. Roy, *J. Org. Chem.*, **31**, 265 (1966).

(4) See, *e.g.*, N. J. Leonard, D. Y. Curtin, and J. M. Beck, *J. Am. Chem. Soc.*, **69**, 2459 (1947); J. T. Cassaday and E. I. Hoegberg, U. S. Patent, 2,575,6147 (Nov 20, 1951); *Chem. Abstr.*, **46**, 6158*d* (1952); P. Pierron, *Ann. Chim. Phys.*, **11**, 316 (1919); B. Abramovitch, U. S. Patent, 2,443,062 (June 8, 1948); *Chem. Abstr.*, **43**, 252*e* (1949); A. Richardson, *J. Org. Chem.*, **28**, 2581 (1963); I. C. I., Ltd., Belgian Patent, 619,606 (Dec 31, 1962); *Chem. Abstr.*, **59**, 10091*c* (1963).

(5) J. Kinugawa, M. Ochiai, C. Matsumura, and H. Yamamoto, *Chem. Pharm. Bull.* (Tokyo), **12**, 433 (1964).

(6) Modifications, which resulted in increased yields of products, of the two most practical methods[7,8] for the synthesis of these intermediates are described in the Experimental Section.

(7) H. Beyer and C. F. Kröger, *Ann.*, **637**, 135 (1960).

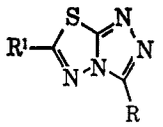
(8) E. Hoggarth, *J. Chem. Soc.*, **4811** (1952).

(9) P. E. Todesco and P. Vevarelli, *Bull. Sci. Fac. Chem. Ind. Bologna*, **20**, 125 (1962); *Chem. Abstr.*, **59**, 8562 (1963); see also G. R. Pettit, I. B. Douglas, and R. A. Hill, *Can. J. Chem.*, **42**, 2357 (1964).

(10) J. Sandstrom, *Acta Chem. Scand.*, **15**, 1297 (1961).

(11) M. Kanaoka, Ph.D. Dissertation, University of Toyama, Japan. We are indebted to Dr. Kanaoka for the gift of a copy of his dissertation and wish to acknowledge many stimulating discussions with him (1962–1963).

TABLE I



R	Mp, °C	Solvent[a]	Yield, %	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
3-SUBSTITUTED 6-AMINO-s-TRIAZOLO[3,4-b][1,3,4]THIADIAZOLES, $R^1 = NH_2$										
H	230	A	83	$C_3H_3N_5S$	25.5	2.1	49.6	25.4	2.2	49.8
CH_3[b]	270	B	40	$C_4H_5N_5S \cdot {}^1/_3H_2O$	29.8	3.1	43.5	30.1	3.6	43.7
CH_3CH_2	259–261	C	81	$C_5H_7N_5S$	35.5	4.2	41.4	35.7	4.2	41.6
C_6H_5	256–257	A	74	$C_9H_7N_5S$	49.8	3.2	32.2	49.9	3.1	32.0
o-ClC_6H_4	243	A	53	$C_9H_6ClN_5S$	43.0	2.4	27.8	43.0	2.5	27.6
p-$CH_3OC_6H_4$	268	A	53	$C_{10}H_9N_5OS$	48.6	3.7	28.3	48.4	3.6	28.1
$C_6H_5CH_2$	190	A	45	$C_{10}H_9N_5S$	51.8	4.2	30.2	51.7	4.0	30.2
p-$CH_3C_6H_4$	295	A	50	$C_{10}H_9N_5S$	51.8	4.2	30.2	51.8	4.1	29.9
3-Substituted s-Triazolo[3,4-b][1,3,4]thiadiazole-6-thiols,[c] $R^1 = SH$										
H	220	D	77	$C_3H_2N_4S_2$	22.8	1.3	35.4	23.0	1.4	35.2
CH_3	225	D	45	$C_4H_4N_4S_2$	27.9	2.3	32.5	28.0	2.5	32.9
CH_3CH_2	222	D	30	$C_5H_6N_4S_2$	32.2	3.2	30.0	32.2	3.3	30.3
C_6H_5	210	D	84	$C_9H_6N_4S_2$	46.1	2.6	23.9	46.3	2.7	24.0
p-$CH_3C_6H_4$	227	D	84	$C_{10}H_8N_4S_2$	48.4	3.2	22.6	48.6	3.0	22.9
p-$CH_3OC_6H_4$	225	D	45	$C_{10}H_8N_4OS_2$	45.4	3.1	27.1	45.6	3.1	27.4
3-Substituted 6-Methylthio-s-triazolo[3,4-b][1,3,4]thiadiazoles,[c] $R^1 = SCH_3$										
H	206	E	82	$C_4H_4N_4S_2$	27.9	2.3	32.5	28.1	2.4	32.5
CH_3	173	E	87	$C_5H_6N_4S_2$	32.2	3.2	30.1	32.1	3.4	30.1
C_6H_5	168	E	62	$C_{10}H_8N_4S_2$	48.4	3.2	22.6	48.1	3.5	22.8
p-$CH_3C_6H_4$	227	E	59	$C_{11}H_{10}N_4S$	50.4	3.8	21.4	50.6	4.0	21.7
p-$CH_3OC_6H_4$	195	E	94	$C_{11}H_{10}N_4OS_2$	47.5	3.6	20.1	47.8	3.6	20.4

[a] A = EtOH; B = H_2O–EtOH; C = H_2O; D = pyridine–ethyl acetate; E = ethyl acetate. [b] Picrate, crystallized from ethanol as plates, mp 217°. *Anal.* Calcd for $C_{10}H_8N_8O_7S$: C, 31.25; H, 2.1; N, 29.1. Found: C, 31.2; H, 2.1; N, 29.2. [c] Colorless plates.

the major product obtained was a 4-amino-3-alkyl-s-triazole-5-thiol, formed by ring opening of the thiadiazole nucleus with hydrazine followed by ring closure to the s-triazole under the basic reaction conditions. Similar results were obtained in the present study, though it was possible to effect displacement of the chlorine atom with hydrazine in 2-chloro-5-phenyl-1,3,4-thiadiazole without ring opening occurring.

5-Phenyl-1,3,4-thiadiazol-2-ylhydrazine readily formed a benzoyl derivative that, along with phosphoryl chloride in xylene, underwent ring closure to 3,6-diphenyl-s-triazolo[3,4-b][1,3,4]thiadiazole (**3**, R = R^1 = Ph) contrary to reports in the literature.[2] This product was identical with that formed by ring closure of 4-benzamido-3-phenyl-s-triazole-5-thiol. It is interesting to note that this 3,5-diphenyl product was not formed in an attempted reaction of 2-chloro-5-phenyl-1,3,4-thiadiazole with 5-phenyltetrazole under reaction conditions that resulted in condensation and ring closure to the fused s-triazole system with 2-chloro-5-nitropyridine, 4-chloroquinazoline, and cyanuric chloride.[12]

The two general methods above were investigated as possible routes to the bicyclic system with no substituent in the 6 position. 4-Amino-3-methyl-s-triazole-5-thiol readily formed the corresponding N-formyl compound but all attempts to effect cyclization to the fused system were unsuccessful. Reaction of this s-triazole intermediate with ethyl orthoformate gave only the corresponding imidate whose structure was assigned on the basis of analytical and spectral data, as well as by analogy.

(12) R. Husigen, H. T. Sturm, and M. Seidel, *Chem. Ber.*, **94**, 1555 (1961).

The ultraviolet absorption spectral data for the compounds described in Table I are listed in Table II. The ultraviolet absorption of the s-triazolo[3,4-b]-[1,3,4]thiadiazole nucleus, as represented by the 3,6-dimethyl product,[2] occurs at 251 mμ (log ε 3.45). The introduction of a 6-amino substituent results in a 13-mμ hypsochromic shift of the absorption maximum, whereas a 6-thiol group causes a shift to 285 mμ. The increase in conjugation resulting from the introduction of a 3-aryl substituent gives the expected shift of the absorption maximum to longer wavelength and it is interesting to note that in the 3-o-chlorophenyl product the inability of the substituent to achieve complete coplanarity with the fused system owing to steric crowding is reflected in the absorption data for the system. The effect of various substituents, as well as conversion into the cation or anion form, on the absorption maximum of the system can be ascertained from Table II.

In the nmr spectra of the 6-amino products [determined in $(CD_3)_2SO$], the chemical shifts of the amino protons fell in the range τ 1.97 (3-p-tolyl) to 2.27 (3-methyl) while the methyl protons of the corresponding methylthio derivatives were in the range τ 7.16 (3-p-methoxyphenyl) to 7.22 (3-methyl). No simple relationship between the chemical shift of the amino protons and the π-electron density at the amino group (calculated using the Hückel LCAO method) was apparent. The 3 proton in 6-amino-s-triazolo[3,4-b][1,3,4]thiadiazole occurred at τ 0.95 and in the 6-methylthio derivative it occurred at τ 1.21, both being at considerably lower field than the corresponding proton in s-triazole (τ 1.88).

As it is of great interest to study the effect of changing the position of the nitrogen atom on the properties

TABLE II

ULTRAVIOLET ABSORPTION SPECTRAL DATA FOR CERTAIN *s*-TRIAZOLO[3,4-*b*][1,3,4]THIADIAZOLES

Substituent		
R	R^1	λ_{max}, mμ (log ε)
H	NH_2	238 (3.79);[a] 243 (3.88)
CH_3	NH_2	238 (3.83);[a] 241 (3.90)
Et	NH_2	238 (3.80);[a] 242 (3.69)
$C_6H_5CH_2$	NH_2	236 (3.99);[a] 243 (4.06)
p-$CH_3C_6H_4$	NH_2	267 (4.39);[a] 246[b] (4.15)
		272[b] (4.38) 278 (4.41)
		287 (4.11)
p-$CH_3OC_6H_4$	NH_2	274 (4.50);[a] 293 (4.52)
		292[b] (4.30) 309 (4.37)
o-ClC_6H_4	NH_2	249 (4.12);[a] 255 (4.10)
C_6H_5	NH_2	257 (4.34);[a] 256 (4.30)
		269[b] (4.26) 274[b] (4.20)
		284[b] (4.05) 287[b] (3.08)
		312[b] (3.31)
H	SH	285 (4.06);[c] 287 (4.09)
H	SCH_3	259 (4.11)
CH_3	SH	290 (4.18);[c] 288 (4.18)
CH_3	SCH_3	259 (4.06)
Et	SH	287 (4.04);[c] 291 (3.98)
C_6H_5	SH	275 (4.26);[c] 273 (4.17)
C_6H_5	SCH_3	265 (4.21)[c]
p-$CH_3C_6H_4$	SH	275 (4.33)
p-$CH_3C_6H_4$	SCH_3	260 (4.31)
p-$CH_3OC_6H_4$	SH	287 (4.12);[c] 287 (4.08)
p-$CH_3OC_6H_4$	SCH_3	264 (4.35)
		281 (4.27)
NH_2	C_6H_5	240[c] (4.26);[a] 263 (4.32)
		267 (4.29) 295[b] (3.84)
SH	C_6H_5	258 (4.19);[c] 242[b] (4.19)
		267 (4.28)
SCH_3	C_6H_5	271 (4.51)

[a] Cation. [b] Shoulder. [c] Anion.

of these ring systems, attempts were made to prepare the isomeric system, *s*-triazolo[1,5-*b*][1,3,4]thiadiazole (**5**). Cyclodehydrogenation of suitably substituted amidines is now a well-established route[13] to fused *s*-triazole systems containing a 1,5 point of fusion. However, N-[alkyl- (or aryl-), 1,3,4-thiadiazol-2-yl]-benzamidines, described in the Experimental Section, did not undergo ring closure with lead tetraacetate under a variety of conditions.

Experimental Section[14]

3-Alkyl-4-amino-*s*-triazole-5-thiols.—Thiocarbohydrazide[15] (10.6 g, 0.1 mole) was stirred with the appropriate carboxylic acid (20 ml) and heated to boiling for 5–10 min. Cooling the reaction mixture and dilution with ethyl acetate gave the 3-alkyl-4-amino-*s*-triazole-5-thiols in yields of 75–80%.

4-Amino-3-aryl-*s*-triazole-5-thiols were prepared by the procedure described by Hoggarth.[8] Excellent yields of the potassium 2-substituted dithiocarbazinates were obtained by carrying out the reaction at reflux temperature and isolating the salts by pouring the reaction mixture into ether. The following new esters, isolated as colorless needles, were prepared: methyl 2-*o*-chlorobenzoyldithiocarbazinate (30%), mp 132° (*Anal.* Calcd for $C_9H_9ClN_2OS_2$: C, 41.8; H, 3.5; N, 10.7. Found: C, 41.7; H, 3.6; N, 11.0.); methyl 2-*p*-toluoyldithiocarbazinate (75%), mp 150° (*Anal.* Calcd for $C_{10}H_{12}N_2OS_2$: C, 50.0; H, 5.0; N, 11.6. Found: C, 50.1; H, 5.1; N, 11.5.); methyl 2-phenylacetyldithiocarbazinate (65%), mp 143° (*Anal.* Calcd for $C_{10}H_{12}N_2OS_2$: C, 50.0; H, 5.0; N, 11.6. Found: C, 49.8; H, 4.9; N, 11.9.).

These methyl 2-substituted dithiocarbazinates gave the following new *s*-triazole derivatives as colorless, irregular prisms: 4-amino-3-*p*-tolyl-*s*-triazole-5-thiol (51%) from ethyl acetate, mp 213° (*Anal.* Calcd for $C_9H_{10}N_4S$: C, 52.4; H, 4.8; N, 27.1. Found: C, 52.2; H, 4.7; N, 27.1.); 4-amino-3-*o*-chlorophenyl-*s*-triazole-5-thiol (54%), from ethanol, mp 152° (*Anal.* Calcd for $C_8H_7ClN_4S$: C, 42.4; H, 3.1; N, 24.7. Found: C, 42.5; H, 3.1; N, 24.5.); 4-amino-3-benzyl-*s*-triazole-5-thiol (26%) from ethanol, mp 180° (*Anal.* Calcd for $C_9H_{10}N_4S$: C, 52.4; H, 4.8; N, 27.1. Found: C, 52.6; H, 4.7; N, 27.4).

2-Amino-5-phenyl-1,3,4-thiadiazole.—Benzoic acid (114.0 g, 0.94 mole) and concentrated sulfuric acid (225 ml, 98%) were mixed thoroughly and, with cooling and rapid stirring, thiosemicarbazide (78.0 g, 0.86 mole) was added in small amounts. After the addition was completed, the solution was heated on a steam bath for 8 hr. The mixture was cooled and mixed with ice and concentrated ammonium hydroxide to precipitate the free base. 2-Amino-5-phenyl-1,3,4-thiadiazole crystallized from ethanol as colorless needles, 84.5 g (56%), mp 225° (lit.[16] mp 225°).

2-Chloro-5-phenyl-1,3,4-thiadiazole.—2-Amino-5-phenyl-1,3,4-thiadiazole (5.0 g, 0.03 mole), dissolved in hydrochloric acid (150 ml, 37%) at −5°, was treated dropwise with sodium nitrite (7.0 g, 0.01 mole) in water (25 ml) over a period of 45 min. The 5-phenyl-1,3,4-thiadiazol-2-yl diazonium chloride began to separate as yellow crystals and, after an additional 2 hr, the reaction mixture was transferred to a steam bath and heated for 15 min, when a dark red oil separated from the solution. On cooling, the oil crystallized from aqueous ethanol as colorless plates: 4.0 g (73%); mp 84.5°; infrared spectrum ($CHCl_3$) 3021, 2433, 1471, 1326, 1222, 1138, 1131, and 1064 cm^{-1}; $\lambda_{max}^{CH_3OH}$ 277 mμ (log ε 4.12).

Anal. Calcd for $C_8H_5ClN_2S$: C, 48.8; H, 2.6. Found: C, 48.9; H, 2.5.

5-Phenyl-1,3,4-thiadiazol-2-ylhydrazine.—2-Chloro-5-phenyl-1,3,4-thiadiazole (5.0 g, 0.03 mole) and hydrazine hydrate (5 ml, 85%) were mixed with ethanol (50 ml) and refluxed for 45 min. On cooling, the 5-phenyl-1,3,4-thiadiazol-2-ylhydrazine separated as golden plates: 1.0 g (21%); mp 184–186°; infrared spectrum (Nujol) 3125, 2882, 2793, 1623, 1567, 1502, 1464, 1443, 1376, 1316, 1261, 1133, 1056, 1001, 984, 758, 750, and 674 cm^{-1}; $\lambda_{max}^{CH_3OH}$ 305 mμ (log ε 3.95).

Anal. Calcd for $C_8H_8N_4S$: C, 50.0; H, 4.2; N, 29.1. Found: C, 49.9; H, 4.2; N, 28.8.

The picrate crystallized from ethanol–benzene as yellow needles, mp 219–222°.

Anal. Calcd for $C_{14}H_9N_7O_7$: C, 39.9; H, 2.6; N, 23.3. Found: C, 39.9; H, 2.4; N, 22.85.

2-Benzoyl-1-(5-phenyl-1,3,4-thiadiazol-2-yl)hydrazine.—5-Phenyl-1,3,4-thiadiazol-2-ylhydrazine (10.0 g, 0.052 mole) was treated with benzoyl chloride and pyridine in the standard manner, and the benzoyl compound crystallized from ethanol as colorless needles, 9.0 g (67%), mp 219–222°.

Anal. Calcd for $C_{15}H_{12}N_4OS$: C, 61.0; H, 4.0; N, 18.9. Found: C, 61.2; H, 4.0; N, 19.0.

3,5-Diphenyl-*s*-triazolo[3,4-*b*][1,3,4]thiadiazole.—2-Benzoyl-1-(5-phenyl-1,3,4-thiadiazol-2-yl)hydrazine (3.0 g, 0.01 mole) was mixed with phosphorus oxychloride (50.0 g, 0.3 mole) and xylene (50 ml). The reaction mixture was refluxed until solution was complete and it was then evaporated to dryness under reduced pressure and mixed with ice water. The product was recrystallized from benzene, from which it formed colorless needles, 1.0 g (37%), mp 200°. The infrared spectrum of this compound was superimposable with that of an authentic sample.

The benzenesulfonate crystallized from methanol–ether as colorless plates, mp 219°.

Anal. Calcd for $C_{18}H_{16}N_4O_3S_2$: C, 57.8; H, 3.8; N, 12.8. Found: C, 57.6; H, 3.7; N, 12.5.

(13) J. D. Bower and F. P. Doyle, *J. Chem. Soc.*, 729 (1957); K. T. Potts, H. R. Burton, and J. Bhattacharyya, *J. Org. Chem.*, **31**, 260 (1966).

(14) Evaporations were done under reduced pressure on the steam bath using a rotavap apparatus and melting points were taken in capillaries. Infrared spectra were measured on Baird 1R2 and Perkin-Elmer 421 spectrophotometers and ultraviolet spectra were determined on a Beckmann DK-2 spectrophotometer. Nmr spectra were measured on a Varian A-60 spectrometer and also on a Varian V-4302 dual-purpose, 60-Mc spectrometer using tetramethylsilane as internal standard and usual methods of calibration. We are indebted to Dr. T. Crawford and Mr. J. Rosene for their assistance in determining these spectra. Microanalyses were performed by Galbraith Laboratories Inc., Knoxville, Tenn.

(15) L. F. Audrieth, E. S. Scott, and P. S. Kippur, *J. Org. Chem.*, **19**, 733 (1954).

(16) G. Young and W. Eyre, *J. Chem. Soc.*, **79**, 54 (1901).

3-Substituted 6-Amino-*s*-triazolo[3,4-*b*][1,3,4]thiadiazoles.—The following general procedure was used. Cyanogen bromide (5.0 g, 0.05 mole) and the 3-substituted 4-amino-*s*-triazole-5-thiols (0.04 mole) were refluxed in 75% aqueous alcohol for 2–3 hr. The initial red solution gradually turned yellow in color. The reaction mixture was evaporated to one-fourth volume and diluted with a saturated solution of sodium acetate. The precipitated amine was collected and purified by crystallization from the solvent listed in Table I.

3-Substituted *s*-Triazolo[3,4-*b*][1,3,4]thiadiazole-6-thiols.—The following general procedure was used. The 3-substituted 4-amino-*s*-triazole-5-thiols (0.09 mole) and potassium hydroxide (5.0 g, 0.09 mole) were dissolved in methanol (100 ml) and, after the addition of carbon disulfide (20 ml), the solution was refluxed for 24 hr. During this time, the odor of hydrogen sulfide was noticeable. The solution was then evaporated to dryness and aqueous hydrochloric acid (50 ml) was added. The crude 3-substituted *s*-triazolo[3,4-*b*][1,3,4]thiadiazole-6-thiols were collected and recrystallized from pyridine–ethyl acetate and these products are described in Table I.

3-Amino-6-phenyl-*s*-triazolo[3,4-*b*][1,3,4]thiadiazole.—5-Phenyl-1,3,4-thiadiazol-2-ylhydrazine (2.0 g, 0.01 mole) and cyanogen bromide (1.0 g, 0.01 mole) were refluxed for 3 hr in aqueous methanol (100 ml, 75%) and the solution was then poured into ether (*ca.* 300 ml). The solid that precipitated was collected and dissolved in boiling water and, after filtering, sodium acetate was added. The precipitated amine crystallized from methanol–ethyl acetate as yellow prisms: 1.0 g (47%); mp 260°; infrared spectrum (Nujol) 3125, 2994, 2841, 1634, 1582, 1529, 1508, 1484, 1451, 1381, 1319, 1304, 1232, 1160, 1127, 1065, 946, and 916 cm^{-1}; $\lambda_{max}^{CH_3OH}$ 267 mμ (log ε 4.29) and 240 mμ (sh) (log ε 4.26).

Anal. Calcd for $C_9H_7N_5S$: C, 49.8; H, 3.25; N, 32.25. Found: C, 49.6; H, 3.2; N, 32.4.

6-Phenyl-*s*-triazolo[3,4-*b*][1,3,4]thiadiazole-3-thiol.—5-Phenyl-1,3,4-thiadiazol-2-ylhydrazine (1.9 g, 0.01 mole) and potassium hydroxide (0.55 g, 0.01 mole) were dissolved in methanol (100 ml) and, after adding carbon disulfide (5 ml), the reaction mixture was refluxed for 24 hr. The methanol was then removed under reduced pressure and the product was precipitated by the addition of aqueous hydrochloric acid (50 ml, 1 *N*). The thiol was recrystallized from benzene–methanol and separated as stout, colorless needles: 1.2 g (60%); mp 262°; infrared spectrum (Nujol) 2882, 1534, 1508, 1462, 1379, 1330, 1314, 1255, 1092, 1019, 952, and 920 cm^{-1}; $\lambda_{max}^{CH_3OH}$ 258 mμ (log ε 4.19).

Anal. Calcd for $C_9H_6N_4S_2$: C, 46.1; H, 2.6; N, 23.9. Found: C, 46.3; H, 2.8; N, 23.7.

3-Methylthio-6-phenyl-*s*-triazolo[3,4-*b*][1,3,4]thiadiazole.—The thiol (0.2 g, 0.0001 mole) and a few drops of sodium hydroxide solution (50%) were mixed in water and shaken with methyl iodide (5 ml). The excess methyl iodide was removed by heating and the crude methylthio ether was separated. It crystallized as colorless plates: 0.21 g (97%); mp 146°; infrared spectrum ($CHCl_3$) 2950, 2907, 1603, 1471, 1453, 1441, 1377, 1311, 1229, 1036, and 1026 cm^{-1}; $\lambda_{max}^{CH_3OH}$ 271 mμ (log ε 4.51); nmr spectrum ($CDCl_3$), τ 7.20 (SCH_3), 2.14, and 2.46 (aromatic).

Anal. Calcd for $C_{10}H_8N_4S_2$: C, 48.4; H, 3.25; N, 22.6. Found: C, 48.6; H, 3.6; N, 22.8.

4-Formamido-3-methyl-*s*-triazole-5-thiol.—4-Amino-3-methyl-*s*-triazole-5-thiol (4.8 g, 0.04 mole) was refluxed in formic acid (100 ml, 100%) for 24 hr. The excess acid was evaporated, and the residue crystallized from methanol as stout, colorless needles: 2.0 g (34%); mp 233°; infrared spectrum (Nujol) 2967, 1650, 1585, 1575, 1486, 1441, 1368, 1351, 1332, 1189, 1112, 1074, 1021, 981, 886, 817, and 761 cm^{-1}; $\lambda_{max}^{CH_3OH}$ 257 mμ (log ε 4.23).

Anal. Calcd for $C_4H_6N_4OS$: C, 30.4; H, 3.8; N, 35.4. Found: C, 30.4; H, 3.8; N, 35.2.

Ethyl N-(3-Methyl-5-mercapto-*s*-triazol-2-yl)formimidate.—Triethyl orthoformate (100 ml) and 3-methyl-4-amino-*s*-triazole-5-thiol (5.0 g, 0.039 mole) were refluxed for 24 hr and the excess ortho ester was then removed under reduced pressure. The gummy residue was mixed with petroleum ether (500 ml) and the precipitate that formed crystallized from benzene–petroleum ether as colorless needles, 1.2 g (17%), mp 145°.

Anal. Calcd for $C_6H_{10}N_4OS$: C, 38.8; H, 5.4; N, 30.8. Found: C, 39.3; H, 5.5; N, 30.6.

N-(5-Phenyl-1,3,4-thiadiazol-2-yl)benzamidine.—2-Amino-5-phenyl-1,3,4-thiadiazole (36.0 g, 0.20 mole) was mixed with benzonitrile (21.0 g, 0.25 mole) and aluminum chloride (26.6 g, 0.25 mole). Solution occurred with evolution of heat and the reaction mixture was then heated in an oil bath at 180–190° for 15 min. After cooling, ice water was added, followed by a 10% sodium hydroxide solution and the precipitated product was collected and dried. Recrystallization from benzene afforded colorless needles: 36.0 g (63%); mp 183°; infrared spectrum ($CHCl_3$) 2801, 1621, 1449, 1379, 1071, 1002, and 989 cm^{-1}; $\lambda_{max}^{CH_3OH}$ 240 mμ (log ε 4.64).

Anal. Calcd for $C_{15}H_{12}N_4S$: C, 64.3; H, 4.3; N, 20.0. Found: C, 63.8; H, 4.6; N, 19.6.

N-(5-Methyl-1,3,4-thiadiazol-2-yl)benzamidine was prepared in a similar manner from 2-amino-5-methyl-1,3,4-thiadiazole, and was obtained as colorless needles: 8.3 g (29%); mp 177°; infrared spectrum (Nujol) 3155, 3012, 3817, 1637, 1527, 1497, 1460, 1377, 1326, 1195, 1149, 1070, and 975 cm^{-1}; $\lambda_{max}^{CH_3OH}$ 302 mμ (log ε 4.26) and 235 mμ (log ε 3.99).

Anal. Calcd for $C_8H_{10}N_4S$: C, 55.0; H, 4.6; N, 25.7. Found: C, 55.0; H, 4.4; N, 25.5.

Sulfostyril (2,1-Benzothiazine 2,2-Dioxide). II.[1] Synthesis

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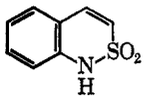
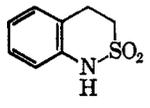
The synthesis of sulfostyril (**1**), the parent member of the 2,1-benzothiazine dioxide ring system, is described. The critical step in the successful synthesis, reduction of an intermediate ketone (**8**), could not be carried out by the usual chemical or catalytic means. It was finally transformed to the olefin by the Bamford–Stevens reaction. No carbon skeleton rearrangements were observed in this tosylhydrazone decomposition.

In a previous paper[1] we described the synthesis of 3,4-dihydrosulfostyril (dihydro-2,1-benzothiazine 2,2-dioxide) (**2**), which was prepared as a potential intermediate to the hitherto unknown aromatic sultam sulfostyril[2] (**1**). All attempts to convert **2** to **1** by thermal, oxidative, or other chemical methods failed; consequently, it became necessary to devise an alternate route.



1



2

In this paper, we describe the successful synthesis of sulfostyril (Scheme I). Sulfoacetic acid (**3**) was converted to the half-ester **4** and then to the sulfonyl chloride[3] (**5**). Attempts to prepare **5** or chlorosul-

(1) Part I of this series: B. Loev and M. F. Kormendy, *J. Org. Chem.*, **30**, 3163 (1965).

(2) Compound **1** can be systematically named as 2,1-benzothiazine 2,2-dioxide or, less satisfactorily, as *o*-aminostyrene-β-sulfonic acid sultam; for convenience, we prefer the name "sulfostyril," by analogy with the name "carbostyril" used for the carbonyl analog.

(3) R. Viellefosse, *Bull. Soc. Chim. France*, 351 (1947).