cooling, Et_3NHBr was filtered off and the benzene was removed in vacuo. Ac_2O (6.0 g, 0.059 mol) was added to the resulting red oil and the solution was shaken. Ether was added after crystallization started; the product was collected, washed with ether, and dissolved in dry benzene (100 ml). DMAD (3.0 g, 0.013 mol) was added and, after 24-hr reflux, removal of solvent, and chromatography on silica gel with $CHCl_3$ as eluent, methyl 2-(*p*-methoxyphenyl)-5-phenylthiophene-3,4-dicarboxylate, mp 107–109° (80%), was obtained identical with that isolated above.[19]

Registry No.—**2**, 17118-70-6; **6**, 20851-14-3; **10**, 32907-84-9; *N*-methyl-*N*,*N*′-diphenylthiourea, 4949-93-3; phenyl isocyanate, 103-71-9; dimethyl acetylenedicarboxylate, 762-42-5; *p*-methoxythiobenzanilide, 26060-23-1; α-bromophenylacetic acid, 4870-65-9.

References and Notes

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(18) Spectral characterizations were carried out on the following instrumentation: infrared spectra, Perkin-Elmer Model 337 spectrophotometer; ultraviolet spectra, Cary 14 spectrophotometer; NMR spectra, Varian T-60 spectrometer, using Me_4Si as internal standard; mass spectrometer, Hitachi Perkin-Elmer RMU-6E mass spectrometer at 70 eV, with a source temperature of ca. 150°. Melting points were determined in capillaries and all evaporations were carried out using a Rotovap apparatus. Microanalyses were performed by Instranal Laboratories, Inc., Rensselaer, N.Y.

(19) Criteria used to establish identity were superimposable ir spectra, no depression in mixture melting point, and identical R_f values.

Bridgehead Nitrogen Heterocycles. IX. Fused-Ring Systems Derived from Fusion of the 1,2,4-Thiadiazole System with the Isoxazole, 1,3,4-Oxadiazole, Thiazole, 1,2,4-Thiadiazole, and 1,3,4-Thiadiazole Systems[1]

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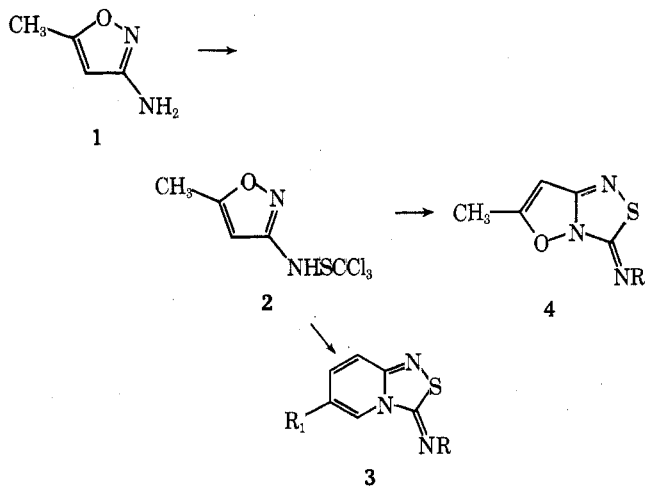
Amino derivatives of the title heterocycles containing the amino group as part of a partial amidine structure reacted with trichloromethanesulfenyl chloride via an isolable trichloromethanesulfenamide intermediate to yield the 3*H*-isoxazolo[3,2-*c*]-, 3*H*-thiazolo[2,3-*c*]-, 3*H*-1,3,4-thiadiazolo[2,3-*c*]-, and the 3*H*-1,2,4-thiadiazolo[4,3-*d*][1,2,4]thiadiazole as well as the 3*H*-1,2,4-thiadiazolo[3,4-*b*][1,3,4]oxadiazole systems. These were characterized by spectral and chemical properties.

In contrast to the large number of substituted, monocyclic 1,2,4-thiadiazoles described in the literature,[2] examples of ring-fused 1,2,4-thiadiazole derivatives remain relatively few. Conceptually there are two general methods for the synthesis of systems containing the ring-fused 1,2,4-thiadiazole moiety. The most direct method involving fusion of an appropriately substituted 1,2,4-thiadiazole has attained only limited usage.[3] The second method, involving ring closure of a 2-amino heterocycle containing a partial amidine structure with a sulfur-containing cyclization agent[4] or by oxidation of an appropriately substituted thiourea,[5] constitutes the most commonly encountered route to these fused ring systems. In earlier publications[6] we have shown that trichloromethanesulfenyl chloride is a particularly efficacious cyclization agent for the synthesis of a variety of six-membered ring systems fused to the 1,2,4-thiadiazole nucleus. This present communication describes the extension of this synthetic route to the preparation of a variety of 5,5-fused ring systems, to a large part unavailable by earlier procedures.

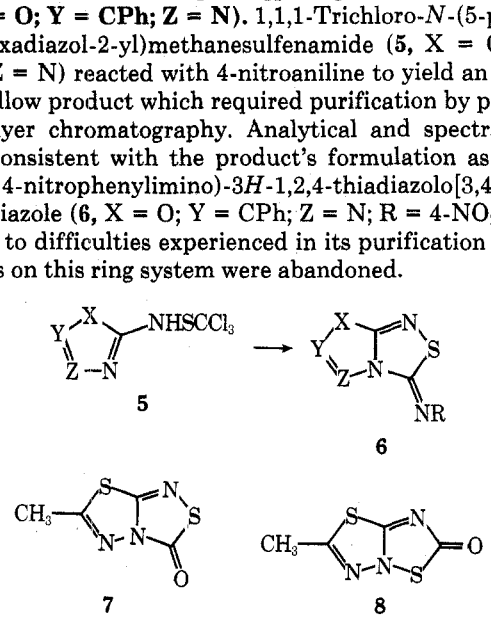
3*H*-Isoxazolo[3,2-*c*][1,2,4]thiadiazole System (4). Reaction of trichloromethanesulfenyl chloride with 2 equiv of 3-amino-5-methylisoxazole (**1**) and 4 equiv of Et_3N proved to be extremely exothermic and resulted in an intractable complex mixture of at least seven components over a range of reaction temperatures (0–20°). However, addition of an aqueous solution of **1** to a stirred, aqueous suspension of trichloromethanesulfenyl chloride, potassium carbonate, Alconox, and crushed ice afforded a cream-colored solid which crystallized from ethanol as colorless needles. Analytical and spectral data (ν_{NH} 3180, $\nu_{C=N}$ 1620 cm^{-1}) supported the product's formulation as the sulfenamide **2**, which was confirmed by the following transformations. Reaction with 2-amino-5-methylpyridine in the presence of Et_3N produced a complex reaction mixture which could be partially resolved using preparative layer chromatography. The major component isolated from this mixture was identified[6] as 6-methyl-3-(5-methyl-2-pyridylimino)-3*H*-1,2,4-thiadiazolo[4,3-*a*]pyridine (**3**, R = 5-CH_3-2-C_5H_3N; R_1 = 6-CH_3) and presumably occurs via a transamination reaction such as was observed in the reactions of 1,1,1-trichloro-*N*-(2-pyrimidyl)methanesulfenamide and 2-aminopyridines.[6] The second component isolated from the mixture crystallized from acetone as cream needles and was

identified as S_8. In contrast to this reaction, condensation of **2** and 3-nitroaniline in the presence of Et_3N proceeded quite cleanly and ultimately afforded a greenish-gold product in 62% yield. This was assigned the structure of 6-methyl-3-(3-nitrophenylimino)-3*H*-isoxazolo[3,2-*c*][1,2,4]thiadiazole (**4**, R = 3-$NO_2C_6H_4$) upon consideration of the analytical and spectral data (Table I).



In a similar fashion, several additional examples of the 3*H*-isoxazolo[3,2-*c*][1,2,4]thiadiazole system have been prepared and the characteristics of these derivatives are described in Table I. It should be noted that examples of this system do not appear to be photostable. This is especially true of **4** (R = 3-$NO_2C_6H_4$), which, if not shielded from light, turns from greenish-gold to orange in less than 1 hr; although isoxazoles are known to be photoreactive,[7] the exact nature of this present decomposition is as yet unknown. Hydrolysis of **4** (R = 3-$NO_2C_6H_4$) in a hot solution of 10% HCl and ethanol resulted in complete disruption of the nucleus to 3-nitroaniline, 3-amino-5-methylisoxazole, and sulfur. Similarly, attempted exchange of the nuclear oxygen atom for sulfur by heating with P_4S_{10} in pyridine was unsuccessful, deep-seated decomposition being observed.

3*H*-1,2,4-Thiadiazolo[3,4-*b*][1,3,4]oxadiazole System (6, X = O; Y = CPh; Z = N). 1,1,1-Trichloro-*N*-(5-phenyl-1,3,4-oxadiazol-2-yl)methanesulfenamide (**5**, X = O; Y = CPh; Z = N) reacted with 4-nitroaniline to yield an insoluble, yellow product which required purification by preparative layer chromatography. Analytical and spectral data were consistent with the product's formulation as 6-phenyl-3-(4-nitrophenylimino)-3*H*-1,2,4-thiadiazolo[3,4-*b*][1,3,4]oxadiazole (**6**, X = O; Y = CPh; Z = N; R = 4-$NO_2C_6H_4$). Owing to difficulties experienced in its purification further studies on this ring system were abandoned.



3*H*-Thiazolo[2,3-*c*][1,2,4]thiadiazole System (6, X = S; Y = Z = CH). The reaction of 1,1,1-trichloro-*N*-(2-thiazolyl)methanesulfenamide (**5**, X = S; Y = Z = CH) and 3-nitroaniline produced a complex reaction mixture. Partial resolution of this mixture using preparative layer chromatography afforded a yellow product crystallizing from 1,2-dichloroethane as yellow needles. The structure of this material was assigned that of 3-(3-nitrophenylimino)-3*H*-thiazolo[2,3-*c*][1,2,4]thiadiazole (**6**, X = S; Y = Z = CH; R = 3-$NO_2C_6H_4$) upon consideration of the analytical and spectral data. Its ultraviolet spectrum was quite similar to that of 3-(3-nitrophenylimino)-3*H*-thiadiazolo[3,4-*b*]benzothiazole[8] and the NMR spectrum consisted of three sets of absorptions, the first occurring as a doublet at δ 6.68 assigned to H_6 by analogy to derivatives of the pyrrolo[2,1-*b*]thiazole system,[9] the second occurring as a three-proton multiplet in the region of δ 7.35. Within this multiplet a doublet attributable to H-5 could be distinguished at δ 7.38, and the last set occurred as a two-proton multiplet centered at δ 7.88. The mass spectral fragmentation pattern of **6** (X = S; Y = Z = CH; R = 3-$NO_2C_6H_4$) was also in close agreement with the assigned structure. Cleavage of the 2,3 and 3,4 bonds of the fused nucleus gave the 2-thiazolylthionitroso ion as the most intense ion in the spectrum, while cleavage of the 1,2 and 3,4 bonds resulted in the 3-nitrophenylisothiocyanate ion. Similar fragmentations have been observed[6,8] in the 3*H*-1,2,4-thiadiazolo[4,3-*a*]pyridine, -[4,3-*a*]pyrimidine, -[4,3-*a*]pyrazine, and -[3,4-*b*]benzothiazole systems. Additional derivatives of this system are described in Table I.

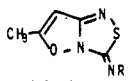
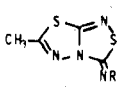
The 3*H*-1,3,4-Thiadiazolo[2,3-*c*][1,2,4]thiadiazole System (6, X = S; Y = CCH_3; Z = N). 1,1,1-Trichloro-*N*-(5-methyl-1,3,4-thiadiazol-2-yl)methanesulfenamide (**5**, X = S; Y = CCH_3; Z = N) reacted with 3-nitroaniline giving 6-methyl-3-(3-nitrophenylimino)-3*H*-1,3,4-thiadiazolo[2,3-*c*][1,2,4]thiadiazole (**6**, X = S; Y = CCH_3; Z = N; R = 3-$NO_2C_6H_4$) in 96% yield. While all available data (Table I) were in agreement with the assigned structure, the ultraviolet and mass spectra are particularly definitive. The ultraviolet spectrum of **6** (X = S; Y = CCH_3; Z = N; R = 3-$NO_2C_6H_4$) (λ_{max} 322, 267, and 245 nm) was almost superimposable with that of the corresponding thiazole derivative (**6**, X = S; Y = Z = CH; R = 3-$NO_2C_6H_4$). The mass spectrum also displayed the characteristic thionitroso and isothiocyanate ions. Rupture of the 1,3,4-thiadiazole moiety could be seen in the thioacylium ion *m/e* 59 (80).

In a similar fashion, two additional examples of the title system were prepared by the reactions of **5** (X = S; Y = CCH_3; Z = N) and primary, aromatic amines. These derivatives are described in Table I.

In an attempt to prepare 6-methyl-3*H*-1,3,4-thiadiazolo[2,3-*c*][1,2,4]thiadiazol-3-one (**7**), whose properties were to be contrasted with those of the isomeric 6-methyl-2*H*-1,3,4-thiadiazolo[3,2-*b*][1,2,4]thiadiazol-2-one[4b] (**8**), **6** (X = S; Y = CCH_3; Z = N; R = 3-$NO_2C_6H_4$) was hydrolyzed in a mixture of 10% HCl in ethanol. Partial resolution of the resulting mixture using preparative layer chromatography afforded three isolatable products, identified as 3-nitroaniline, 2-amino-5-methyl-1,3,4-thiadiazole, and sulfur.

The 3*H*-1,2,4-Thiadiazolo[4,3-*d*][1,2,4]thiadiazole System (6, X = S; Y = N; Z = CCH_3). 1,1,1-Trichloro-*N*-(3-methyl-1,2,4-thiadiazol-5-yl)methanesulfenamide (**5**, X = S; Y = N; Z = CCH_3) reacted with 3-nitroaniline, giving 5-methyl-3-(3-nitrophenylimino)-3*H*-1,2,4-thiadiazolo[4,3-*d*][1,2,4]thiadiazole (**6**, X = S; Y = N; Z = CCH_3; R = 3-$NO_2C_6H_4$) in 72% yield. This structural assignment was based on consideration of the analytical and spectral data. The ultraviolet spectrum of **6** (X = S; Y = N; Z = CCH_3; R

Table I
Some Ring-Fused 1,2,4-Thiadiazoles

R	mp °C	Yield %	Crystal Habit	Formula[a]	M+ (rel int)	Ir, cm⁻¹ C=N-	Ir, cm⁻¹ Thiadiazole ring deformation[b]	uv λmax nm	uv log ε[c]	Nmr Chemical Shift, δ[d]
										
Some 6-Methyl-3-substituted-3H-isoxazolo[3,2-c][1,2,4]thiadiazoles										
2,5-$Cl_2C_6H_3$	117-118[e]	22	Cream needles[f]	$C_{11}H_7Cl_2N_3OS$	299 (17)	1630	1470	312	3.84	2.43 (d, 3, 6-CH_3, $J_{6,7}$ = 1.2 Hz)
								268	3.87	5.90 (d, 1, H_7)
								238	4.08	6.97 (dd, 1, H_4', $J_{3',4'}$ = 7.6 Hz)
										7.08 (dd, 1, H_6', $J_{4',6'}$ = 2.3 Hz)
										7.36 (dd, 1, H_3', $J_{3',6'}$ = 1.0 Hz)
2-$NO_2C_6H_4$	142-143[e]	12	Gold plates[f]	$C_{11}H_8N_4O_3S$	276 (19)	1650	1440	305	3.89	2.47 (d, 3, 6-CH_3, $J_{6,7}$ = 1.2 Hz)
								260	4.09	5.93 (d, 1, H_7)
								238	4.18	7.53 (m, 4, aromatic)
3-$NO_2C_6H_4$	139-141[e]	62	Greenish-gold needles[g]	$C_{11}H_8N_4O_3S$	276 (20)	1640	1410	318	3.98	2.48 (d, 3, 6-CH_3, $J_{6,7}$ = 1.2 Hz)
								272	4.20	5.96 (d, 1, H_7)
								241	4.14	7.72 (m, 4, aromatic)
4-$NO_2C_6H_4$	167[h]	43	yellow, irreg. prisms[i]	$C_{11}H_8N_4O_3S$	276 (46)	1630	1410	372	4.17	2.48 (d, 3, 6-CH_3, $J_{6,7}$ = 1.2 Hz)
								290	3.92	5.97 (d, 1, H_7)
								238	4.03	7.18 (d, 2, H_2' and H_6', $J_{2',3'} = J_{5',6'}$ = 9.2 Hz)
										8.22 (d, 2, H_3' and H_5')
										
Some 3-Substituted-3H-thiazolo[2,3-c][1,2,4]thiadiazoles										
3-$NO_2C_6H_4$	140-142[e]	18	yellow needles[j]	$C_{10}H_6N_4O_2S_2$	278 (63)	1610	-	331	4.18	6.68 (d, 1, H_6, $J_{5,6}$ = 5.0 Hz)
								270[k]	4.04	7.35 (m, 2, aromatic)
								248	4.13	7.38 (d, 1, H_5), 7.88 (m, 2, aromatic)
4-$NO_2C_6H_4$	240-242[e]	11	orange needles[l]	$C_{10}H_6N_4O_2S_2$	278 (72)	1640	-	390	4.26	-
								283	4.05	-
										
Some 6-Methyl-3-substituted-3H-1,3,4-thiadiazolo[2,3-c][1,2,4]thiadiazoles										
2,5-$Cl_2C_6H_3$	146-147	54	cream prisms[m]	$C_{10}H_6Cl_2N_4S_2$	316 (90)	1620	1470	310	3.92	2.64 (s, 3, 6-CH_3)
								238	4.06	6.99 (dd, 1, H_4', $J_{3',4'}$ = 8.0 Hz)
										7.07 (dd, 1, H_6', $J_{4',6'}$ = 2.5 Hz)
										7.34 (dd, 1, H_3', $J_{3',6'}$ = 0.8 Hz)
3-$NO_2C_6H_4$	178-179	96	yellow, matted needles[n]	$C_{10}H_7N_5O_2S_2$	293 (100)	1630	1430	322	4.11	2.70 (s, 3, 6-CH_3)
								267	4.05	7.53 (m, 2, aromatic)
								245	4.13	8.04 (m, 2, aromatic)
4-$NO_2C_6H_4$	240-242	38	yellow, irreg. prisms[o]	$C_{10}H_7N_5O_2S_2$	293 (96)	1620	1450	370	4.23	2.71 (s, 3, 6-CH_3)
								275	3.91	7.24 (d, 2, H_2' and H_6', $J_{2',3'} = J_{5',6'}$ = 9.2 Hz)
								237	3.93	8.27 (d, 2, H_3' and H_5')
										
Some 5-Methyl-3-substituted-3H-1,2,4-thiadiazolo[4,3-d][1,2,4]thiadiazoles										
2,5-$Cl_2C_6H_3$	185-187	36	cream needles[p]	$C_{10}H_6Cl_2N_4S_2$	316 (81)	1630	1470	335[k]	3.82	2.87 (s, 3, 5-CH_3)
								319	3.87	7.22 (m, 4, aromatic)
								270	3.67	
								239	3.98	
3-$NO_2C_6H_4$	181-183	72	yellow, matted needles[q]	$C_{10}H_7N_5O_2S_2$	293 (100)	1630	1470	330	4.04	2.85 (s, 3, 5-CH_3)
								260[k]	4.03	7.56 (m, 4, aromatic)
								245	4.10	

[a] Satisfactory analytical values (±0.4% for C, H, N) were reported for all compounds in table: Ed.; [b] KBr; [c] $CHCl_3$; [d] $CDCl_3$; [e] Decomposition; [f] Method B, prep. layer chromatography, $CHCl_3$: EtOAc:: 80:20, recrystallized from EtOH; [g] Method A, recrystallized from EtOH; [h] Violent decomposition; [i] Method A, recrystallized from EtOAc; [j] Purified by prep. layer chromatography, $CHCl_3$: EtOAc:: 70:30, recrystallized from 1,2-dichloroethane; [k] Shoulder; [l] Purified by prep. layer chromatography, $CHCl_3$: EtOAc:: 80:20, recrystallized from 1,2-dichloroethane; [m] Method B, recrystallized from EtOH; [n] Method A, recrystallized from EtOH; [o] Method A, recrystallized from 1,2-dichloroethane; [p] Recrystallized from EtOAc; [q] Recrystallized from 1,2-dichloroethane.

= 3-$NO_2C_6H_4$) (λ_{max} 330, 260, and 245 nm) compared very favorably with that of its 1,3,4 isomer. In addition, the infrared spectrum displayed a C=N absorption at 1630 cm^{-1} and a thiadiazole ring deformation at 1470 cm^{-1}. The NMR spectrum, in addition to a complex aromatic multiplet centered at δ 7.56, exhibited a methyl absorption at δ 2.85 which was shifted downfield relative to that observed for the methyl group of 5-amino-3-methyl-1,2,4-thiadiazole at δ 2.54. This downfield shift presumably reflects the 1,3 relationship between the methyl group and the exocyclic imine function.

In a similar fashion, the 2,5-dichloro analog **6** (X = S; Y = N; Z = CCH_3; R = 2,5-$Cl_2C_6H_3$) was prepared from **5** (X = S; Y = N; Z = CCH_3) and 2,5-dichloroaniline. The analytical and spectral data were entirely consistent with those of its predecessor (Table I).

Experimental Section[10]

Preparation of the Intermediate Sulfenamides.[11] A. 1,1,1-Trichloro-*N*-(5-methyl-3-isoxazolyl)methanesulfenamide (2). $ClSCCl_3$ (18.6 g) was suspended in a stirred solution of K_2CO_3 (13.8 g), Alconox[12] (1 g), H_2O (300 ml), and crushed ice. A solution of 3-amino-5-methylisoxazole (9.80 g) and H_2O (100 ml) was then added over 15 min. The precipitated product was collected, washed with H_2O, and dried by suction. This was sufficiently pure for further use. Additional purification by crystallization from EtOH gave colorless needles: 14.8 g (60%); mp 140–142° dec; ir (KBr) 3180 (NH), 1620 cm^{-1} (C=N); λ_{max} (CH_3OH) 223 nm (log ϵ 3.86); NMR ($CDCl_3$) δ 2.38 (s, 3, CH_3), 6.09 (s, 1, H_4), 7.99 (broad s, 1, NH); mass spectrum *m/e* (rel intensity) $M^{\cdot+}$ 246 (35).

Anal. Calcd for $C_5H_5Cl_3N_2OS$: C, 24.26; H, 2.04; N, 11.32. Found: C, 24.24; H, 2.01; N, 11.36.

B. 1,1,1-Trichloro-*N*-(5-phenyl-1,3,4-oxadiazol-2-yl)methanesulfenamide (5, X = O; Y = CPh; Z = N). A solution of $ClSCCl_3$ (4.65 g) in $CHCl_3$ (50 ml) was added over 30 min to a stirred suspension of 2-amino-5-phenyl-1,3,4-oxadiazole (8.05 g) and $CHCl_3$ (500 ml). After stirring for 4 hr, the precipitate was collected, washed with H_2O, and dried by suction, 5.9 g (76%), mp 147–150° dec. This was sufficiently pure for further use.

C. 1,1,1-Trichloro-*N*-(2-thiazolyl)methanesulfenamide (5, X = S; Y = Z = CH). A solution of $ClSCCl_3$ (5.58 g) in Et_2O (25 ml) was added over 15 min to a stirred solution of 2-aminothiazole (6.0 g) and Et_2O (400 ml). After stirring for 10 min the solvent was removed from the reaction mixture and the residue was washed with aqueous EtOH. Filtration gave an orange solid which was dried by suction, 3.3 g (44%), mp 53–59° dec. Although attempts to purify the material further resulted in complete decomposition, it was sufficiently pure for further use.

D. 1,1,1-Trichloro-*N*-(5-methyl-1,3,4-thiadiazol-2-yl)methanesulfenamide (5, X = S; Y = CCH_3; Z = N). A solution of $ClSCCl_3$ (7.44 g) and $CHCl_3$ (50 ml) was added over 15 min to a stirred solution of 2-amino-5-methyl-1,3,4-thiadiazole (9.2 g) and $CHCl_3$ (450 ml). After stirring for 1 hr the reaction mixture was evaporated to dryness, yielding a cream product which was washed with EtOH and dried by suction: 6.5 g (61%); mp 126–129° dec; mass spectrum *m/e* (rel intensity) $M^{\cdot+}$ 263 (18). Although this material could be partially purified by crystallization from benzene, it was sufficiently pure for further use.

E. 1,1,1-Trichloro-*N*-(3-methyl-1,2,4-thiadiazol-5-yl)methanesulfenamide (5, X = S; Y = N; Z = CCH_3). A solution of $ClSCCl_3$ (0.93 g) and CH_3OH (15 ml) was added over 10 min to a stirred solution of 5-amino-3-methyl-1,2,4-thiadiazole (1.15 g) and CH_3OH (50 ml). After stirring for 3 hr the solvent was removed from the reaction mixture and the residue was washed with H_2O. Filtration gave a cream product which was dried by suction, 0.38 g (29%), mp 128–130° dec. This was sufficiently pure for further use.

General Procedure for the Preparation of Some 3-Substituted 3*H*-Isoxazolo[3,2-*c*][1,2,4]thiadiazoles (4). 1,1,1-Trichloro-*N*-(5-methyl-3-isoxazolyl)methanesulfenamide (0.01 mol) was added portionwise to a stirred solution of an aromatic amine (0.01 mol), Et_3N (0.03 mol), and $CHCl_3$ (150 ml). After stirring for 14 hr the reaction mixture was evaporated to dryness. Reaction work-up was by either of two procedures. **A.** The residue, after washing with CH_3OH, was purified as indicated. **B.** The residue was washed with H_2O, yielding an oil which was extracted with $CHCl_3$. Drying over $MgSO_4$ and removal of the $CHCl_3$ gave a solid which was purified as indicated (Table I).

Reaction of 2 with 2-Amino-5-methylpyridine. 1,1,1-Trichloro-*N*-(5-methyl-3-isoxazolyl)methanesulfenamide (2, 2.48 g) was added portionwise to a stirred solution of 2-amino-5-methylpyridine (1.08 g), Et_3N (3.04 g), and $CHCl_3$ (150 ml). After stirring for 24 hr the reaction mixture was evaporated to dryness and the residue was resolved by preparative layer chromatography [1.00 mm, $CHCl_3$–EtOAc (90:10)]. One component crystallized from $(CH_3)_2CO$ as orange prisms and was identified as 3 (R = 5-CH_3-2-C_5H_3N; R_1 = 6-CH_3) being identical in all respects with an authentic sample, mp 194–196°, mmp 194–196°. A second component crystallized from $(CH_3)_2CO$ as cream needles and was identified as S_8 from its mass spectrum: *m/e* (rel intensity) $M^{\cdot+}$ 256 (100).

Acid Hydrolysis of 4 (R = 3-$NO_2C_6H_4$). 6-Methyl-3-(3-nitrophenylimino)-3*H*-isoxazolo[3,2-*c*][1,2,4]thiadiazole (0.25 g) was refluxed 2 hr in a solution of HCl (10%, 10 ml) and EtOH (15 ml). Neutralization with $NaHCO_3$ and evaporation to dryness gave a solid which was extracted with a $CHCl_3$–H_2O mixture. The $CHCl_3$ layer was separated and dried over Na_2SO_4 before being evaporated to dryness. TLC [$CHCl_3$–CH_3OH (80:20)] of the residue indicated a complex mixture, with unreacted starting material, 3-nitroaniline, 3-amino-5-methylisoxazole, and S_8 shown by comparison of R_f values with those of authentic samples. Trituration of the residue with $(CH_3)_2CO$ gave a cream solid which was identified as S_8 from its mass spectrum: *m/e* (rel intensity) $M^{\cdot+}$ 256 (100).

6-Phenyl-3-(4-nitrophenylimino)-3*H*-1,2,4-thiadiazolo[3,4-*b*][1,3,4]oxadiazole (6, X = O; Y = CPh; Z = N; R = 4-$NO_2C_6H_4$). Sulfenamide **5** (X = O; Y = CPh; Z = N) (3.10 g) was added portionwise to a stirred solution of 4-nitroaniline (1.38 g), Et_3N (3.04 g), and $CHCl_3$ (150 ml). After stirring for 14 hr, the solvent was removed from the reaction mixture, yielding an orange product which, after washing with CH_3OH, was purified by preparative layer chromatography (1.00 mm, $CHCl_3$). Subsequent crystallization from $CHCl_3$ gave yellow prisms: 0.48 g (14%); mp 238–240°; ir (KBr) 1660, 1630 (C=N), 1560, 1340 (NO_2), 1460 cm^{-1} (thiadiazole ring deformation); λ_{max} ($CHCl_3$) 373 nm (log ϵ 4.34), 258 (4.43); mass spectrum *m/e* (rel intensity) $M^{\cdot+}$ 339 (100).

Anal. Calcd for $C_{15}H_9N_5O_3S$: C, 53.09; H, 2.67; N, 20.64. Found: C, 52.93; H, 2.56; N, 20.48.

Representative Procedure for the Preparation of Some 3-Substituted 3*H*-Thiazolo[2,3-*c*][1,2,4]thiadiazoles. 3-(3-Nitrophenylimino)-3*H*-thiazolo[2,3-*c*][1,2,4]thiadiazole (6, X = S; Y = Z = CH; R = 3-$NO_2C_6H_4$). Sulfenamide **5** (X = S; Y = Z = CH) (2.5 g) was added portionwise to a stirred solution of 3-nitroaniline (1.38 g), Et_3N (3.04 g), and $CHCl_3$ (150 ml). After stirring for 14 hr, the solvent was removed from the reaction mixture, giving a brown product which, after washing with CH_3OH, was purified by preparative layer chromatography [1.00 mm, $CHCl_3$–EtOAc (70:30)]. Subsequent crystallization from 1,2-dichloroethane gave yellow needles, 0.50 g (18%), mp 140–142° dec (Table I).

General Procedure for the Preparation of Some 3-Substituted 3*H*-1,3,4-Thiadiazolo[2,3-*c*][1,2,4]thiadiazoles (6, X = S; Y = CCH_3; Z = N). Sulfenamide **5** (X = S; Y = CCH_3; Z = N) (0.01 mol) was added portionwise to a stirred solution of a primary, aromatic amine (0.01 mol), Et_3N (0.03 mol), and $CHCl_3$ (150 ml). After stirring for 14 hr the reaction mixture was evaporated to dryness. **A.** The residue was washed with CH_3OH and purified by crystallization from a suitable solvent. **B.** The residue was washed with H_2O yielding a semisolid which was extracted with $CHCl_3$. Separation and drying of the $CHCl_3$ over $MgSO_4$ and evaporation to dryness afforded a solid which was purified by crystallization from a suitable solvent (Table I).

Acid Hydrolysis of 6 (X = S; Y = CCH_3; Z = N; R = 3-$NO_2C_6H_4$). 6-Methyl-3-(3-nitrophenylimino)-3*H*-1,3,4-thiadiazolo[2,3-*c*][1,2,4]thiadiazole (0.50 g) was refluxed in HCl (10%, 20 ml) and EtOH (40 ml). After 24 hr the solvent was removed from the reaction mixture and the residue was neutralized with aqueous $NaHCO_3$. The aqueous phase was extracted with $CHCl_3$ which was subsequently separated and dried over Na_2SO_4. The $CHCl_3$ was then removed and the residue, after preparative layer chromatography [1.00 mm, $CHCl_3$–EtOAc (80:20)], afforded three components which were identified as 3-nitroaniline, 2-amino-5-methyl-1,3,4-thiadiazole, and S_8. All three were identical in all respects with authentic samples.

Representative Procedure for the Preparation of Some 3-Substituted 3*H*-1,2,4-Thiadiazolo[4,3-*d*][1,2,4]thiadiazoles (6, X = S; Y = N; Z = CCH_3). 5-Methyl-3-(2,5-dichlorophenylimino)-3*H*-1,2,4-thiadiazolo[4,3-*d*][1,2,4]thiadiazole (6, X = S; Y = N; Z = CCH_3; R = 2,5-$Cl_2C_6H_3$). Sulfenamide **5** (X = S; Y = N; Z = CCH_3) (0.53 g) was added portionwise to a stirred solution of 2,5-dichloroaniline (0.32 g), Et_3N (0.61 g), and $CHCl_3$ (50 ml).

After stirring for 14 hr, the solvent was removed from the reaction mixture, yielding a cream product which, after washing with CH_3OH, crystallized from EtOAc as cream needles, 0.23 g (36%), mp 185–187° (Table I).

Registry No.—6-Methyl-3-substituted 3*H*-isoxazolo[3,2-*c*]-[1,2,4]thiadiazoles, 55723-65-4 (R = 2,5-$Cl_2C_6H_3$), 55723-66-5 (R = 2-$NO_2C_6H_4$), 55723-67-6 (R = 3-$NO_2C_6H_4$), 55723-68-7 (R = 4-$NO_2C_6H_4$; 3-substituted 3*H*-thiazolo[2,3-*c*][1,2,4]thiadiazoles, 55723-69-8 (R = 3-$NO_2C_6H_4$), 55723-70-1 (R = 4-$NO_2C_6H_4$); 6-methyl-3-substituted 3*H*-1,3,4-thiadiazolo[2,3-*c*][1,2,4]thiadiazoles, 55723-71-2 (R = 2,5-$Cl_2C_6H_3$), 55723-72-3 (R = 3-$NO_2C_6H_4$), 55723-73-4 (R = 4-$NO_2C_6H_4$); 5-methyl-3-substituted 3*H*-thiadiazolo[4,3-*d*][1,2,4]thiadiazoles, 55723-74-5 (R = 2,5-$Cl_2C_6H_3$), 55723-75-6 (R = 3-$NO_2C_6H_4$); **1**, 1072-67-9; **2**, 55723-76-7; **3** (R = 5-CH_3-2-C_5H_3N; R_1 = 6-CH_3), 24097-95-8; **5** (X = O; Y = CPh; Z = N), 55723-77-8; **5** (X = S; Y = Z = CH), 55723-78-9; **5** (X = S; Y = CCH_3; Z = N), 55723-79-0; **5** (X = S; Y = N; Z = CCH_3), 55723-80-3; 2-amino-5-phenyl-1,3,4-oxadiazole, 1612-76-6; 2-aminothiazole, 96-50-4; 2-amino-5-methyl-1,3,4-thiadiazole, 108-33-8; 5-amino-3-methyl-1,2,4-thiadiazole, 17467-35-5; 2-amino-5-methylpyridine, 1603-41-4; trichloromethanesulfenyl chloride, 594-42-3.

References and Notes

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(10) Spectral characterizations were carried out on the following instrumentation: infrared spectra, Perkin-Elmer Model 337 spectrophotometer; ultraviolet spectra, Cary 14 spectrophotometer; NMR spectra, Varian T-60 and HA-100 spectrometers, using Me_4Si as an internal standard; mass spectra, Hitachi Perkin-Elmer RMU-6E mass spectrometer at 70 eV, utilizing the direct insertion probe technique with a source temperature of ca. 150°. All melting points were determined in capillaries using a Thomas-Hoover capillary melting point apparatus or a Mel-Temp apparatus. Evaporations were carried out under reduced pressure using a Buchi Rotovap apparatus. PLC was carried out on 20 × 20 mm plates using silica gel PF 254 with $CaSO_4$ (thickness and solvent as indicated). Microanalyses were by Galbraith Laboratories, Knoxville, Tenn., and Instranal Laboratory, Inc., Rensselaer, N.Y.

(11) Generally, partial decomposition of these sulfenamides during purification resulted in unsatisfactory analytical data.

(12) Alconox is the registered trade name of a phosphorus base wetting agent and detergent manufactured by Alconox Inc., New York, N.Y.

Reaction of 2-Arylhydrazono-3-oxonitriles with Hydroxylamine. Synthesis of 3-Amino-4-arylazoisoxazoles

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Whereas the 2-arylhydrazono-3-oxonitriles **1a–e** react with hydroxylamine hydrochloride and sodium acetate in refluxing ethanol to yield the amidoximes **2a–e**, 3-amino-4-arylazo 5-substituted isoxazoles (**3a–e**) are formed when **1a–e** are treated with hydroxylamine in aqueous ethanol. On the other hand, treatment of **1a–e** with hydroxylamine in the presence of excess methanolic sodium methoxide has resulted in the formation of the 5-amino-4-arylazo 3-substituted isoxazoles **4a–e**. Ethyl arylazocyanoacetate (**11a–e**) reacts with hydroxylamine hydrochloride and sodium acetate to yield the amidoximes **12a–e**, which could be readily cyclized into the 3-aminoisoxazoles **13a–e** by the action of methanolic sodium methoxide. The behavior of **2** toward the action of thionyl chloride, benzaldehyde, and hydrazines is reported.

Although several recent papers have dealt with the synthesis and biological evaluation of 4-arylazo-5-isoxazolones,[1-3] 4-arylazo-5-aminoisoxazoles have been neglected. We have now studied the reaction of some 2-arylhydrazono-3-oxonitriles with hydroxylamine as a source of aminoarylazoisoxazoles.

Treatment of the β-ketonitriles **1a–e** with NH_2OH·HCl and sodium acetate in refluxing ethanol led to amidoximes **2a–e**. Cyclization of these products with H_2SO_4 or sodium ethoxide gave the 3-aminoisoxazoles **3a–e**; these compounds were also obtained directly from the reaction of **1a–e** with NH_2OH in aqueous ethanol. The preferential attack of NH_2OH at the C≡N group in these reactions is in contrast to other findings,[4,5] which indicate that the CO group in **1a–e** is the more reactive electrophilic center in nonprotic media. The enhanced reactivity of the C≡N group in the hydroxylamine reactions is attributed to protonation. Consistent with this view are the findings that at pH 11, no reaction with NH_2OH occurred, and that in the presence of alkoxides, the 5-amino compounds **4a–e** were formed in good yield. Compounds **4a–d** were also obtained via action of aryldiazonium salts on 5-amino-3-phenylisoxazole (**5**). Although ethyl cyanoacetate derivatives have been shown to react with NH_2OH to yield either 3- or 5-aminoisoxazoles depending on reaction conditions,[6] 5-aminoisoxazoles or 5-isoxazolones are the only reported products from reaction of 3-oxonitriles with NH_2OH under a variety of acidic and basic conditions.[7-11]

In contrast to the behavior of **1a–e**, the methylarylhydrazones **6a–d** reacted with NH_2OH·HCl and sodium acetate in refluxing ethanol to yield the 5-imino-2-isoxazolines **7a–d**. Compound **7a** was converted into 4-methylphenylhydrazono-3-phenyl-2-isoxazolin-5-one (**8**) by the action of ACOH–HCl mixture.

Similar to the behavior of **1a–e** toward the action of NH_2OH, the 2-phenylhydrazono-3-iminonitriles **9a,b**