A General Synthetic System for 1,2,5-Thiadiazoles[1]

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A general model for the synthesis of 1,2,5-thiadiazoles is described in terms of an acyclic NCCN grouping in which the NC functions are varied over the oxidation levels of amine, imine, cyanide, and oxime. Aliphatic compounds containing these functionalities in any combination are converted to appropriately substituted 1,2,5-thiadiazoles by reaction with sulfur monochloride or sulfur dichloride. Acyclic compounds which are applicable in this general synthetic system include α-diamines, α-aminonitriles, alkyl cyanoformimidates, α-amino acid amides, α-aminoamidines, dialkyl oxalimidates, alkyl oxamimidates, α-dioximes, α-isonitrosoamides, α-isonitrosonitriles, cyanogen, and 1-cyanoformamide. Some properties and reactions of the products are described.

Monocyclic derivatives of 1,2,5-thiadiazole (Ia) were first prepared by oxidation of 2,1,3-benzothiadiazoles[2-5] and subsequently by hydrolytic degradation of [1,2,5]-thiadiazolo[3,4-*d*]pyrimidines.[6-9] Derivatives of I

Ia

were also formed by a number of cyclizations, *e.g.*, from diaminomaleonitrile,[10] diethyl oxalimidate,[11] and cyanogen[12] and were also found as major products resulting from the reaction of sulfur dioxide with potassium cyanide[13] and from the reaction of ethyl-substituted aryl hydrocarbons with tetrasulfur tetranitride (S_4N_4).[14] These results, which indicate the inherent stability and driving force toward formation of 1,2,5-thiadiazoles, are in line with the apparent aromatic nature of this ring system. It was shown by gas electron diffraction,[15] microwave spectroscopy,[16] and X-ray diffraction (on the biscarboxamide derivative)[17] that 1,2,5-thiadiazole is a planar ring system with structural parameters very similar to thiophene. The iso-π-electronic relationship between the 1,2,5-thiadiazoles and pyrazines was demonstrated on the basis of ultraviolet spectra, polarographic behavior, and pK_a measurements.[4,10]

We have found that the methods of formation of this aromatic ring system by cyclization reactions encompass several classes of acyclic compounds and that a general model for the structure of aliphatic systems suitable for 1,2,5-thiadiazole syntheses can be devised. This model is defined in terms of an acyclic NCCN grouping in which the N–C functions are varied over the oxidation levels of amine, imine, cyanide, and oxime. Aliphatic compounds which contain these functionalities in any combination react with sulfur monochloride or, in some cases, sulfur dichloride to form an appropriately substituted 1,2,5-thiadiazole.

Based on this model, a large number of readily available acyclic compounds can be constructed which serve as starting materials in these syntheses, *e.g.*, α-diamines,[18a] α-aminonitriles, alkyl cyanoformimidates, α-amino acid amides,[18b] α-aminoamidines, dialkyl oxalimidates, alkyl oxamimidates, α-dioximes, α-isonitrosoamides, and α-isonitrosonitriles. The data now at hand indicate that, with few exceptions, the reactions of these classes of compounds are general over a range of substituents. In addition, two unique starting materials, cyanogen and 1-cyanoformamide, are based on the model described above. The various acyclic compounds employed in these reactions and the derived 1,2,5-thiadiazoles are summarized in Table I.

The yields in these reactions range from about 30 to 90%, depending on the nature of the starting material. The reactions proceed readily at room temperature except in the case of the α-diamine hydrochlorides where slightly elevated temperatures are employed. Since most of the products are volatile they are readily obtained in a state of high purity by steam distillation of the reaction mixture. The nonvolatile products (hydroxy and amino derivatives) are isolated by ether extraction of the water-quenched reaction mixture. Dimethylformamide is the solvent of choice and generally a 100% *M* excess of sulfur monochloride is employed. The stoichiometry of sulfur monochloride is calculated as 1 mole equiv for insertion of the ring sulfur plus 1 mole equiv for each degree of oxidation required to obtain the aromatic form of the ring.

Based on previous work with sulfur monochloride, some remarks on the possible course of these reactions

(1) Preliminary communication, L. M. Weinstock, P. Davis, B. Handelsman, and R. Tull, *Tetrahedron Letters*, 1263 (1966).

(2) A. M. Khaletskii, V. G. Pesin, and T. Chou, *Dokl. Akad. Nauk SSSR*, **114**, 811 (1957); *Chem. Abstr.*, **52**, 4605i (1958); see *Proc. Acad. Sci. USSR, Chem. Technol. Sect.*, **114**, 593 (1957).

(3) V. G. Pesin, A. M. Khaletskii, and T. Chou, *Zh. Obshch. Khim.* **28**, 2089 (1958); *Chem. Abstr.*, **53**, 2214d (1959); see *J. Gen. Chem. USSR*, **28**, 2126 (1958).

(4) L. M. Weinstock, Ph.D. Dissertation, Indiana University, 1958; University Microfilms, Ann Arbor, Mich., Order No. 58-2947; *Dissertation Abstr.*, **19**, 3136 (1959).

(5) M. Carmack, L. M. Weinstock, and D. Shew, Abstracts, 136th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1959, p 37p.

(6) Y. F. Shealy and J. D. Clayton, *J. Org. Chem.*, **28**, 1491 (1963).

(7) Y. F. Shealy and C. A. O'Dell, *ibid.*, **29**, 2135 (1964).

(8) Y. F. Shealy and J. D. Clayton, *ibid.*, **29**, 2141 (1964).

(9) Y. F. Shealy and C. A. O'Dell, *ibid.*, **30**, 2488 (1965).

(10) D. Shew, Ph.D. Dissertation, Indiana University, 1959; University Microfilms, Ann Arbor, Mich., Order No. 59-4037; *Dissertation Abstr.*, **20**, 1593 (1959).

(11) R. Y. Wen, Ph.D. Dissertation, Indiana University, 1962; University Microfilms, Ann Arbor, Mich., Order No. 63-3859; *Dissertation Abstr.*, **23**, 4121 (1963).

(12) R. D. Vest, U. S. Patent 3,115,497 (1963); *Chem. Abstr.*, **60**, 5512*d* (1964).

(13) J. M. Ross and W. C. Smith, *J. Am. Chem. Soc.*, **86**, 2861 (1964).

(14) V. Bertini and P. Pino, *Angew. Chem.*, **77**, 262 (1965).

(15) F. A. Momany and R. A. Bonham, *J. Am. Chem. Soc.*, **86**, 162 (1964).

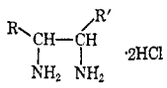
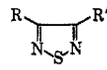
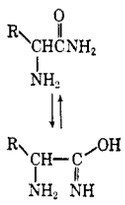
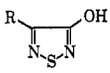
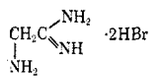
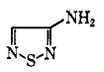
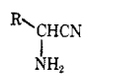
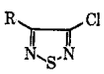
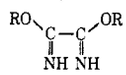
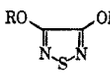
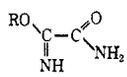
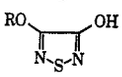
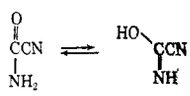
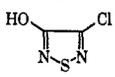
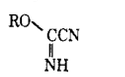
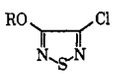
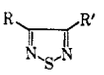
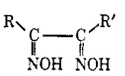
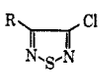
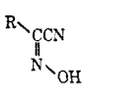
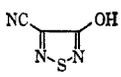
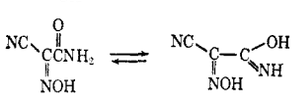
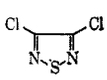
(16) V. Dobyns and L. Pierce, *ibid.*, **85**, 3553 (1963).

(17) R. R. McDonald, Ph.D. Dissertation, Indiana University, 1962; University Microfilms, Ann Arbor, Mich., Order No. 62-5054; *Dissertation Abstr.*, **23**, 1897 (1962).

(18) Soon after the publication of the preliminary communication concerning this work, two related reactions were reported. (a) V. Bertini and P. Pino, *Angew. Chem. Intern. Ed. Engl.*, **5**, 514 (1966), prepared 1,2,5-thiadiazoles by the reaction of α-diamines with sulfur nitride (N_4S_4). Since N_4S_4 is prepared by the reaction of sulfur monochloride with ammonia, the method holds no advantage over the direct use of sulfur monochloride. (b) An alternate synthesis of hydroxy-1,2,5-thiadiazole derivatives from α-amino acid amides employing thionyl chloride or thionyl aniline was reported by S. A. Mizsak and M. Perelman, *J. Org. Chem.*, **31**, 1964 (1966), and by G. R. Collins, *Dissertation Abstr.*, **27**, 403-B (1966).

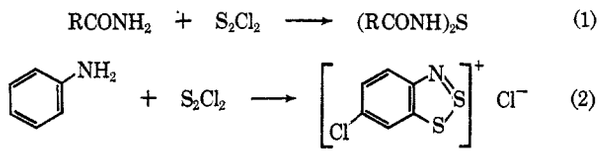
TABLE I

SYNTHESIS OF 1,2,5-THIADIAZOLES BY REACTION OF SULFUR CHLORIDES WITH ALIPHATIC COMPOUNDS

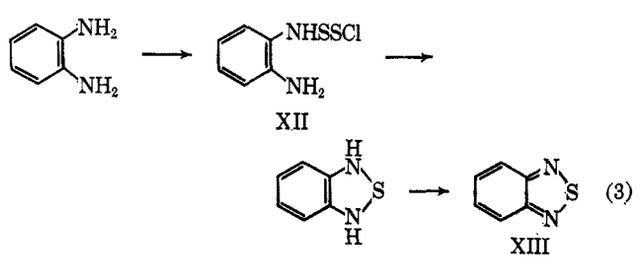
Aliphatic starting material	Name or type	Product	Sulfur chloride used
	α-Diamine dihydrochloride	 Ia, R = R′ = H; Ib, R = H; R′ = Me; Ic, R = H; R′ = COOH; Id, R = R′ = $(CH_2)_4$	S_2Cl_2
	α-Amino acid amide	 IIa, R = H; IIb, R = Me; IIc, R = Et; IId, R = *n*-Pr; IIe, R = *i*-Pr; IIf, R = *n*-Bu; IIg, R = *i*-Bu; IIh, R = C_6H_5; IIi, R = $C_6H_5CH_2$	S_2Cl_2
	α-Aminoacetamidine dihydrobromide	 III	S_2Cl_2
	α-Aminonitrile	 IVa, R = H; IVb, R = C_6H_5	S_2Cl_2
	Dialkyl oxalimidate	 Va, R = Me; Vb, R = Et	SCl_2[a]; S_2Cl_2
	Alkyl oxamimidate	 VI, R = Et	S_2Cl_2
	1-Cyanoformamide	 VII	S_2Cl_2
	Alkyl cyanoformimidate	 VIIIa, R = Me; VIIIb, R = Et; VIIIc, R = *i*-Pr	S_2Cl_2
NCCN	Cyanogen	 IX	SCl_2[b]; S_2Cl_2
	α-Dioxime	 Ia, R = R′ = H; X, R = R′ = CH_3	S_2Cl_2
	α-Isonitrosonitrile	 IVb, R = C_6H_5	S_2Cl_2
	α-Isonitrosocyanoacetamide	 XI[c]	SCl_2

[a] See ref 11. [b] See ref 12. [c] See ref 13.

can be made. The reactions of sulfur monochloride suggest that the molecule can be polarized as $ClSS^{\delta+}Cl^{\delta-}$ and in several instances compounds containing the chlorodithio group (ClSS–) have been isolated.[19] Chlorodithio compounds have also been postulated as intermediates in the reaction of aliphatic amides with sulfur monochloride leading to bisamidosulfides[20] (eq 1) and in the Herz reaction[21] (eq 2). It has recently been reported that, under conditions of the Herz reaction, *o*-phenylenediamine is converted to 2,1,3-benzo-



thiadiazole[22] (XIII) and in this case it appears that the N-chlorodithio intermediate (XII) is cleaved at the S–S bond by nucleophilic attack of the *ortho* amino group (eq 3). A similar process is proposed for the



formation of monocyclic 1,2,5-thiadiazoles from aliphatic compounds and sulfur monochloride. The

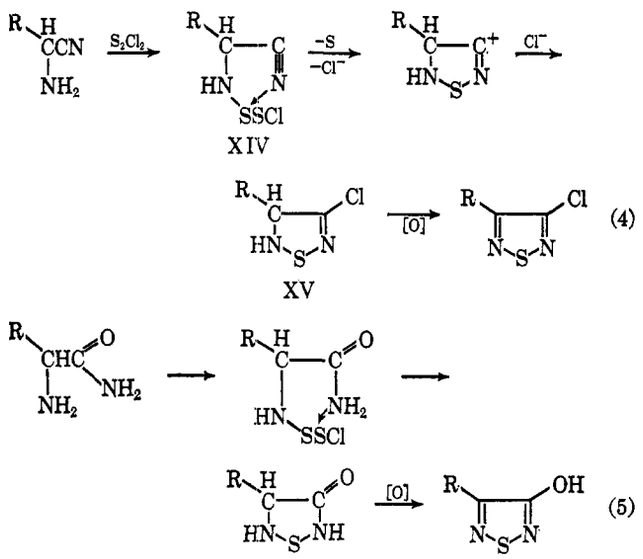
(19) Z. S. Ariyan and L. A. Wiles, *J. Chem. Soc.*, 4510 (1961); 1725 (1962); 755 (1963).

(20) P. Hope and L. A. Wiles, *ibid.*, 5679 (1964).

(21) P. Hope and L. A. Wiles, *Chem. Ind.* (London), 32 (1966).

(22) P. Hope and L. A. Wiles, *J. Chem. Soc.*, 1283 (1966). These workers obtained a 27% yield of XIII by this reaction in refluxing benzene. In the course of this work, we found that XIII is formed in 81% yield when carried out in dimethylformamide.

reaction of α-aminonitriles (eq 4) and α-amino acid amides (eq 5) serve to illustrate the role of the amine, amide, and cyanide functions in these cyclizations. The formation of thiadiazoles from oximes is less easily rationalized.



From eq 4 it is clear that amine functions applicable in these syntheses must be primary and bear at least one α-hydrogen atom. This allows oxidation to the aromatic form of the thiadiazole, presumably *via* an N-chloro or N-chlorodithio intermediate. Sulfur monochloride or adjacent N-chlorodithio groups, such as in XIV, react with nitrile groups by addition leading to chloro substituted 1,2,5-thiadiazoles.

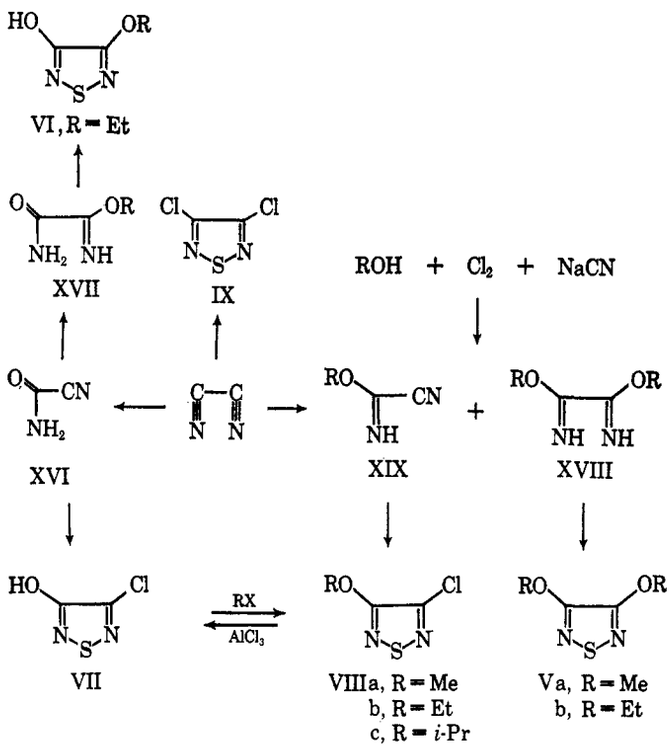
Since sulfur dichloride is in equilibrium with sulfur monochloride and chlorine, these reagents behave in the same manner except that the presence of chlorine leads to the introduction of an additional chlorine atom in the thiadiazole in certain cases where the dichloride is employed.

The synthesis of 1,2,5-thiadiazoles from α-diamines was investigated as early as 1897 when Michaelis[23] attempted the synthesis of the parent compound by reaction of ethylenediamine with sulfur dioxide. In this case, the reagent exhibits no oxidative effect and the product was formulated as 2-aminoethylsulfimic acid. In the present work, the reaction of four α-diamine dihydrochlorides with sulfur monochloride was examined and each yielded the corresponding 1,2,5-thiadiazole (Ia–d). Noteworthy in this series is the one-step synthesis of the parent 1,2,5-thiadiazole (Ia) in 50% yield from ethylenediamine dihydrochloride.

The reaction of α-amino acid amides with sulfur monochloride in dimethylformamide serves as a general synthesis of 3-alkyl-4-hydroxy-1,2,5-thiadiazoles.[18b] Nine amino acid amides were examined in this reaction, producing the hydroxy thiadiazoles IIa–i in 40–60% yield. In a related synthesis, α-aminoacetamidine dihydrobromide was converted to 3-amino-1,2,5-thiadiazole (III). The relative inaccessability of substituted α-aminoamidines limits the usefulness of this method.

α-Aminoacetonitrile bisulfate was found to be a convenient starting material for the synthesis of both 3-chloro-1,2,5-thiadiazole (IVa) and 3,4-dichloro-1,2,5-thiadiazole (IX). Reaction of the aminonitrile with sulfur monochloride produces the monochloro compound in 74% yield while the use of commercial sulfur dichloride leads to a 1:1 mixture of IVa and IX. However, if excess chlorine is added to the latter reaction, the dichloro compound is formed exclusively in 82% yield. It was subsequently shown that IX is not formed *via* chlorination of IVa under the reaction conditions employed. Introduction of the second chloro group therefore must take place prior to aromatization, possibly on an intermediate such as XV (R = H). Substituted α-aminonitriles were also found to undergo thiadiazole formation. For example, α-aminophenylacetonitrile was transformed into 3-chloro-4-phenyl-1,2,5-thiadiazole (IVb).

SCHEME I



Cyanogen and a number of its derivatives are starting materials based on the general model for 1,2,5-thiadiazole syntheses. Cyanogen has been reported by Vest[12] to react with sulfur dichloride to form 3,4-dichloro-1,2,5-thiadiazole (IX) and we have found that the reaction is also smoothly effected with sulfur monochloride. Unlike sulfur dichloride, the reaction with sulfur monochloride is not exothermic and is readily carried out by passing cyanogen into a solution of the sulfur chloride at 80°. Compound IX is isolated in pure form in 90% yield by steam distillation. 1-Cyanoformamide (XVI) formed in quantitative yield by the acid-catalyzed reaction of cyanogen with water[24] is converted into 3-chloro-4-hydroxy-1,2,5-thiadiazole (VII) on treatment with sulfur monochloride. Prior conversion of XVI to the imino ether (XVII)[24] leads to 3-ethoxy-4-hydroxy-1,2,5-thiadiazole (VI, R = Et) (Scheme I).

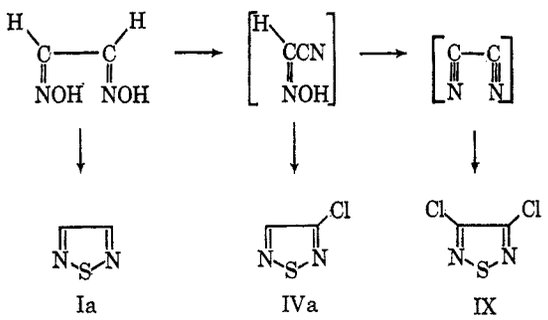
The reaction products of cyanogen with alcohols, dialkyl oximidates (XVIII), and alkylcyanoformimidates (XIX), also available through the reaction

(23) A. Michaelis and P. Graentz, *Chem. Ber.*, **30**, 1009 (1897).

(24) R. P. Welcher, M. E. Castellion, and V. P. Wystrach, *J. Am. Chem. Soc.*, **81**, 2541 (1959).

of sodium cyanide and chlorine with aqueous alcohol,[25] both react with the sulfur chloride forming the appropriately substituted thiadiazole. The conversion of XVIII (R = Me and Et) to the corresponding 3,4-dialkoxy-1,2,5-thiadiazole (Va and Vb) can be effected with sulfur dichloride[11] or sulfur monochloride. Three examples of XIX were converted to the 3-alkoxy-4-chloro-1,2,5-chloro-1,2,5-thiadiazoles (VIIIa–VIIIc). Compound VII was also obtained by the aluminum chloride dealkylation of VIIIc (Scheme I).

The synthesis of a 1,2,5-thiadiazole from an oxime was reported by Ross and Smith,[13] who obtained 3-cyano-4-hydroxy-1,2,5-thiadiazole (XI) from α-isonitrosocyanoacetamide and sulfur dichloride. We find that α-dioximes can also be converted to 1,2,5-thiadiazoles; *e.g.*, dimethylglyoxime yields 3,4-dimethyl 1,2,5-thiadiazole (X) plus a trace of dimethylfurazan. The reaction of aldoximes are complicated by partial dehydration to nitriles which lead in turn to chlorinated thiadiazoles. Thus, glyoxime on reaction with sulfur monochloride formed a mixture consisting of 1,2,5-thiadiazole (Ia), 3-chloro-1,2,5-thiadiazole (IVa), and 3,4-dichloro-1,2,5-thiadiazole (IX).

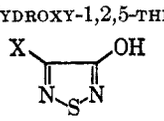


Ia IVa IX

3-Hydroxy-1,2,5-thiadiazole exhibits marked acidic properties consistent with the known strongly electron-withdrawing nature of this ring system.[4,10] The pK_a of the compound (5.10) is similar to that of acetic acid. Alkyl substituents exert no effect on the pK_a in water, but negative substituents greatly increase the degree of ionization (see Table II).[26] The absence of absorption in the carbonyl region of infrared spectra taken in chloroform solution indicates that they exist essentially in the hydroxy form as opposed to the oxo form. Furthermore, alkylation of hydroxy thiadiazoles proceeds *via* *o*-alkylation. Thus, ethylation of 3-chloro-4-hydroxy-1,2,5-thiadiazole provides VIIIb, the same product obtained by cyclization of ethyl cyanoformimidate (XIX, R = Et).

TABLE II

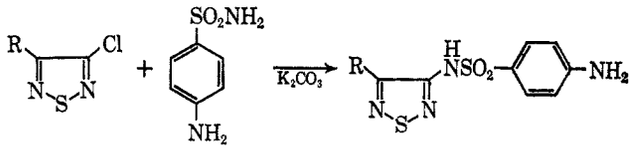
pK_a CONSTANTS FOR HYDROXY-1,2,5-THIADIAZOLES IN WATER



X	pK_a
H	5.10[a]
CH_3	5.10
CH_2CH_3	5.10
OH	4.68 (pK_{a_2} 7.50)[b]
OCH_2CH_3	4.40
Cl	3.65
CN	2.97[c]

[a] pK_a 5.2.[13] [b] See ref 11. [c] See ref 13.

Chloro substituents in the 1,2,5-thiadiazoles are reactive toward nucleophilic substitution and both 3-chloro-1,2,5-thiadiazole and 3-chloro-4-ethoxy-1,2,5-thiadiazole were converted into the corresponding sulfonamides on heating with sulfanilamide in presence of potassium carbonate.



R = H, OEt

Experimental Section[27]

1,2,5-Thiadiazole.—Ethylenediamine dihydrochloride (53.2 g, 0.4 mole) was added to a solution of 194 ml (2.4 moles) of sulfur monochloride in 380 ml of DMF and the mixture was gradually heated to 75–80° (mildly exothermic reaction). After 5 hr the mixture was cooled to 10°, 300 ml of water was slowly added, and the mixture was distilled until the vapor temperature reached 100°. The distillate, consisting of an azeotropic mixture of water and 1,2,5-thiadiazole, was extracted with pentane. The pentane extracts were washed once with a small amount of water, dried, and distilled at atmospheric pressure through a short Vigreux column. After removal of the solvent, there was obtained 17.3 g (50%) of 1,2,5-thiadiazole: bp 94°; λ_{max}^{MeOH} 253, 256, and 260 mμ (ε 7680, 7550, and 5360, respectively); nmr showed a single peak at τ 1.39 (5% in CCl_4); $\nu_{max}^{CHCl_3}$ 3000, 1365, 1340, 1210, 1035, 885, 830, and 790 cm^{-1}; analytical glpc indicated a purity of 99%. An analytical sample was obtained through preparative glpc.

Anal. Calcd for $C_2H_2N_2S$: C, 27.89; H, 2.34; N, 3.254; S, 37.24. Found: C, 27.76; H, 2.40; N, 32.71; S, 37.09.

The spectral properties and gas chromatographic behavior were identical with those of 1,2,5-thiadiazole obtained by decarboxylation of 1,2,5-thiadiazole-3,4-dicarboxylic acid as previously reported.[4]

3-Methyl-1,2,5-thiadiazole.—The procedure above for 1,2,5-thiadiazole was repeated using 1,2-diaminopropane dihydrochloride. There was obtained 28.1 g (70%) of 3-methyl-1,2,5-thiadiazole distilling at 120–122°: λ_{max}^{MeOH} 258 mμ (ε 8640). The infrared spectrum was identical with that recorded by Gill[28] for this compound.

Anal. Calcd for $C_3H_4N_2S$: C, 35.98; H, 4.03; N, 27.97; S, 32.02. Found: C, 36.16; H, 4.06; N, 27.84; S, 31.91.

4,5,6,7-Tetrahydro-2,1,3-benzothiadiazole.—*trans*-1,2-Diaminocyclohexane sulfate (21–22 g, 0.1 mole) was added to a solution of 24.3 ml (0.3 mole) of sulfur monochloride in 50 ml of DMF. An ice bath was used as needed to maintain the temperature of the reaction at 45–50°. After 2.5 hr, 150 ml of water was added and the mixture distilled until the vapor temperature reached 100°. The product was extracted from the distillate with hexane and dried; the solvent was removed by distillation at at-

(25) J. V. Nef, *Ann.*, **287**, 265 (1895).

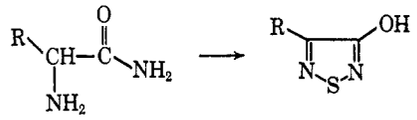
(26) The pK_a values of 3-alkyl-4-hydroxy-1,2,5-thiadiazoles carried out in 66% aqueous dimethylformamide (DMF) fall in the range of 6.4–7.3.[13b]

(27) All melting points are corrected. Infrared spectra were obtained with a Perkin-Elmer 421 spectrophotometer. Ultraviolet spectra were obtained in methanol solutions using a Carey Model 11 recording spectrophotometer. Nmr spectra were measured on a Varian A-60 instrument. For analytical gas–liquid partition chromatography (glpc), a Aerograph A90P2 gas chromatograph was used with a thermal conductivity detector. The column was 20% Carbowax 1540 on Chromosorb W. The stainless steel column was 5 ft long, 4-mm i.d. Operating conditions were column temperature, 110°; injector block, 186°; detector, 230°. Helium flow rate was 120 ml/min. For preparative glpc, an Aerograph Autoprep gas chromatograph was used. The column (20% DC 200 on Gas Chrom P) was 20 ft long, 10-mm i.d. Operating conditions were column temperature 200°; injector block, 250°; detector; 250°. Helium flow rate was 200 ml/min. Commercial grade sulfur monochloride and reagent trade dimethylformamide were employed. Extracts were dried with anhydrous magnesium sulfate.

(28) J. M. Gill, Ph.D. Dissertation, Indiana University, 1963; University Microfilms, Ann Arbor, Mich., Order No. 64-468; *Dissertation Abstr.*, **24**, 2690 (1964).

TABLE III

REACTION OF α-AMINO ACID AMIDES WITH SULFUR MONOCHLORIDE



R	Mp, °C	λ_{max}^{MeOH}, mμ (ε)	Purification method[a]	Formula	Calcd, % C	H	N	S	Found, % C	H	N	S
H	127.5–128.5[b]	273 (7420)	E	$C_2H_2N_2OS$	23.52	1.97	27.43	31.40	23.88	2.16	27.35	31.27
Me	151–153[c]	275 (8340)	A	$C_3H_4N_2OS$	31.02	3.47	24.12	27.61	31.30	3.63	23.87	27.49
Et	96–98	275 (8780)	A, B	$C_4H_6N_2OS$	36.90	4.65	21.53	24.63	37.35	4.62	21.30	24.60
n-Pr	62–63	276 (8700)	C	$C_5H_8N_2OS$	41.65	5.59	19.43	...	41.93	5.30	19.22	...
i-Pr	84–86[d]	275 (8890)	C	$C_5H_8N_2OS$	41.65	5.59	19.43	...	41.85	5.32	19.03	...
n-Bu	42–44	276 (8950)	B, C	$C_6H_{10}N_2OS$	45.55	6.37	17.71	...	45.95	6.16	17.94	...
i-Bu	37.5–38.5	277 (8750)	B, C	$C_6H_{10}N_2OS$	45.55	6.37	17.71	20.27	45.60	6.26	17.58	20.19
C_6H_5	166–168[e]	304 (15,800)	D	$C_8H_6N_2OS$	53.92	3.39	15.72	17.99	54.20	3.39	15.50	17.84
$C_6H_5CH_2$	137–139[f]	303 (2430) 279 (8520)	A, B	$C_9H_8N_2OS$	56.23	4.20	14.57	16.68	56.04	4.00	14.46	16.96

[a] Purification methods: A, recrystallization from water; B, sublimation *in vacuo;* C, precipitation from charcoaled alkaline solutions by addition of hydrochloric acid; D, recrystallization from cyclohexane. [b] Mp 128.5–130.[13] [c] Mp 146.[18b] [d] Mp 84–85.[18b] [e] Mp 165–166.[18b] [f] Mp 139–140.[18b]

mospheric pressure. The oil residue was distilled under reduced pressure to yield 3.4 g (24.2%) of 4,5,6,7-tetrahydro-2,1,3-benzothiadiazole: bp 65–65° (1 mm), λ_{max}^{MeOH} 268 and 265 mμ (both (ε 10,300).

Anal. Calcd for $C_6H_8N_2S$: C, 51.40; H, 5.75; N, 19.98; S, 22.87. Found: C, 51.56; H, 5.55; N, 19.63; S, 22.94.

1,2,5-Thiadiazole-3-carboxylic Acid.—2,3-Diaminopropionic acid (416 mg, 4 mmoles) was added to a mixture of 2.0 ml (0.025 mole) of sulfur monochloride and 4.0 ml of DMF at 5°. The mixture was warmed to 20°, stirred for 2 hr, quenched onto ice, and extracted with three 50-ml portions of ether. The ether extracts were washed once with water, dried, and evaporated to dryness *in vacuo*. The yellow solid was dissolved in aqueous sodium bicarbonate and extracted with carbon disulfide. The aqueous phase was acidified and extracted with ether. The ether extracts were dried and evaporated to yield 190 mg (36%) of 1,2,5-thiadiazole-3-carboxylic acid, mp 164–166° (lit.[4] mp 162–164°). The infrared spectrum was identical with that previously reported for this acid.[4]

Reaction of α-Amino Acid Amides with Sulfur Monochloride. Preparation of 3-Alkyl-4-hydroxy-1,2,5-thiadiazoles.—The α-amino acid amide (0.1 mole, free base or amine salt) was added to a solution of 24.3 ml (0.3 mole) of sulfur monochloride in 50 ml of DMF, stirred 5 hr at room temperature, and poured into 250 ml of ice water. The mixture was filtered to remove the precipitate sulfur; the filtrate was extracted four times with 100-ml portions of ether. The combined ether extracts were washed once with a small amount of water, dried, and evaporated *in vacuo* to yield 40–60% of the crude 3-alkyl-4-hydroxy-1,2,5-thiadiazole. Purification methods and properties are summarized in Table III.

Alkyl Cyanoformimidates.—These products were prepared according to the procedure of Nef.[25] Chlorine gas was passed into a solution of 4.7 moles of the alcohol, 1.94 moles of sodium cyanide, and 800 ml of water maintained at −10 to −15°. The chlorine was added at a rate of 1.5 g/min for 48 min (72 g, 1.0 mole). After the addition, the mixture was stirred 3 hr at −5 to −10° and extracted three times with ethyl ether. The ether extracts were washed three times with aqueous saturated sodium chloride, dried, and distilled to yield the alkyl cyanoformimidates given in Table IV.

TABEL IV

$$ROH + NaCN + Cl_2 \longrightarrow ROCCN \quad (\parallel NH)$$

R	Yield, %	Bp (mm), °C
Me	12	24–25 (17)
Et	28	36–39 (10)
i-Pr	24	35–38 (15)

Reaction of Alkyl Cyanoformimidates with Sulfur Monochloride. Preparation of 3-Alkoxy-4-chloro-1,2,5-thiadiazoles.—The alkyl cyanoformimidate (0.1 mole) was added dropwise under 20° to a solution of 24.3 ml (0.3 mole) of sulfur monochloride in 50 ml of DMF. After 16 hr at room temperature, the mixture was added to 200 ml of water and internally steam distilled. The product was extracted from the distillate with petroleum ether (bp 30–60°), dried, and distilled to yield the 3-chloro-4-alkoxy-1,2,5-thiadiazoles listed in Table V. The products were 99% pure according to analytical glpc. Analytical samples were obtained through preparative glpc.

3-Chloro-4-ethoxy-1,2,5-thiadiazole.—A mixture of 3-chloro-4-hydroxy-1,2,5-thiadiazole (13.6 g, 0.1 mole), 11.7 g (0.11 mole) of sodium carbonate, 20.2 g (0.13 mole) of ethyl iodide, and 250 ml of DMF was heated at 55–60° for 2 hr. Water (500 ml) was added and the thiadiazole ether separated by azeotropic distillation and extraction as described above. The product, obtained in 73% yield, exhibited infrared and ultraviolet spectra identical with those of 3-chloro-4-ethoxy-1,2,5-thiadiazole obtained from the cyclization of ethyl cyanoformimidate. 3-Chloro-4-isopropoxy-1,2,5-thiadiazole was prepared in a similar manner in 63% yield.

3-Chloro-4-hydroxy-1,2,5-thiadiazole. A. By Cyclization of 1-Cyanoformamide.—1-Cyanoformamide[24] (7.0 g, 0.1 mole) was added over a 10-min period at room temperature to a solution of 32.4 ml (0.4 mole) of sulfur monochloride in 60 ml of DMF. After stirring 4 hr, the mixture was added to 320 ml of ice water and filtered to remove the precipitated sulfur; the filtrate was extracted with four 75-ml portions of ether. The ether extracts were washed once with a small amount of water, dried, and evaporated *in vacuo* to a residue of 3-chloro-4-hydroxy-1,2,5-thiadiazole (12.0 g, 88%), mp 106–109°. Recrystallization from water produced the pure material: mp 110–112°, λ_{max}^{MeOH} 282 mμ (ε 8300).

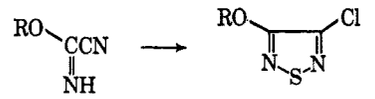
Anal. Calcd for C_2HClN_2OS: C, 17.59; H, 0.74; Cl, 25.96; N, 20.51; S, 23.48. Found: C, 17.71; H, 0.80; Cl, 25.70; N, 20.74; S, 23.29.

B. From 3-Chloro-4-isopropoxy-1,2,5-thiadiazole.—A mixture of 1.0 g of 3-chloro-4-isopropoxy-1,2,5-thiadiazole, 1.28 g of aluminum chloride, and 10 ml of toluene was refluxed for 2 hr. The cooled mixture was added to cold 4 *N* hydrochloric acid. The layers were separated and the aqueous layer was washed twice with 30 ml of warm toluene. The combined toluene solutions were evaporated to dryness *in vacuo*, providing 0.65 g (85%) of 3-chloro-4-hydroxy-1,2,5-thiadiazole, mp 109–112°. The product exhibited an infrared spectrum identical with that of the product prepared by procedure A.

3-Ethoxy-4-hydroxy-1,2,5-thiadiazole.—Ethyl oxamimidate hydrochloride was prepared according to the procedure of Welcher, *et al.*[24] This imino ether (31.6 g, 0.208 mole) was added immediately after isolation and rapid drying to a mixture of 132 ml (1.72 moles) of sulfur monochloride and 276 ml of DMF at 20°. The mixture was stirred 16 hr, quenched onto 300 g of ice, and extracted twice with 200-ml portions of ether. The ether extracts were backwashed once with 50 ml of water, dried, and evaporated *in vacuo* to 29.0 g of a white solid, mp 92–96°. Re-

TABLE V

REACTION OF ALKYL CYANOFORMIMIDATES WITH SULFUR MONOCHLORIDE



R	Yield, %	λ_{max}^{MeOH}, mμ (ε),	Bp (mm) or mp, °C	Calcd, %					Found, %				
				C	H	Cl	N	S	C	H	Cl	N	S
Me	80	278 (9120)	63 (17), 53–54	23.94	2.01				24.16	1.91			
Et	83	278 (9200)	86.5–87.5 (17)	29.19	3.06	21.54	17.02	19.48	29.34	2.90	21.28	17.33	19.47
i-Pr	95	280 (9280), 283 (9350)	68–69 (15)	33.62	3.95	19.85	15.68	17.95	33.85	4.01	20.09	15.66	17.95

crystallization from benzene provided 15.4 g (51%) of 3-ethoxy-4-hydroxy-1,2,5-thiadiazole: mp 106–107°, λ_{max}^{MeOH} 278 mμ (ε 8760).

Anal. Calcd for $C_4H_6N_2O_2S$: C, 32.87; H, 4.14; N, 19.17; S, 21.94. Found: C, 33.24; H, 3.92; N, 19.20; S, 21.82.

3-Chloro-1,2,5-thiadiazole. A. By Cyclization of α-Aminoacetonitrile Bisulfate.—α-Aminoacetonitrile bisulfate (154 g, 1.0 mole) was added over a 0.5-hr period at 0–5° to a solution of 243 ml (3.0 moles) of sulfur monochloride in 450 ml of DMF. After stirring at 0° for 16 hr, 450 ml of water was slowly added with good cooling. The mixture was distilled until the vapor temperature reached 107° and the distillate, consisting of a two-phase azeotrope of chlorothiadiazole and water, was extracted with petroleum ether. The petroleum ether extracts were washed with water, dried, and distilled at atmospheric pressure through a 10-in. Vigreux column. After removal of the solvent (30–60°), 89 g (74%) of 3-chloro-1,2,5-thiadiazole distilling at 123–124° was obtained: λ_{max}^{MeOH} 260, 263, 267, and 270 mμ (ε 8000, 8630, 8080, and 6550, respectively); nmr exhibited a single peak at τ 1.60 (5% $CDCl_3$);[29] $\nu_{max}^{CDCl_3}$ 3100, 3000, 1445, 1320, 1300, 1280, 1145, 940, 860, 820, and 645 cm^{-1}. The product was found 99.5% pure by analytical glpc, the remaining 0.5% being 3,4-dichloro-1,2,5-thiadiazole. An analytical sample was obtained through preparative glpc.

Anal. Calcd for C_2HClN_2S: C, 19.92; H, 0.84; Cl, 29.41; N, 23.24; S, 26.60. Found: C, 20.12; H, 0.84; Cl, 29.39; N, 23.31; S, 26.87.

B. From 3-Hydroxy-1,2,5-thiadiazole.—A mixture of 2.06 g (0.02 mole) of 3-hydroxy-1,2,5-thiadiazole and 4.0 ml of phosphorus oxychloride was heated at 80° in an open Carius tube until the evolution of hydrogen chloride ceased (about 0.5 hr). The tube was sealed and heated at 150° for 12 hr. The contents of the tube were poured onto ice water, made alkaline with concentrated aqueous ammonium hydroxide, and extracted with petroleum ether. The dried extracts were distilled through a short column to produce 1.38 g (57%) of 3-chloro-1,2,5-thiadiazole, identical on the basis of infrared and ultraviolet spectra, boiling point, and glpc behavior with the product formed in procedure A.

3,4-Dichloro-1,2,5-thiadiazole. A. From α-Aminoacetonitrile Bisulfate.—Chlorine gas (3 g/min) was passed into a stirred mixture of 450 ml of DMF and 190 ml of sulfur dichloride at 0° for 15 min. The chlorine addition was continued as 154 g (1.0 mole) of α-aminoacetonitrile bisulfate was added over a 0.5-hr period. After another 0.5 at 0–5°, the mixture was warmed to 25° and stirred for an additional 5 hr (after 1 hr at 25° the chlorine addition was stopped). Water (450 ml) was slowly added with cooling and the mixture worked up as described in procedure A for the synthesis of 3-chloro-1,2,5-thiadiazole. In this case, there was obtained 124 g (80%) of 3,4-dichloro-1,2,5-thiadiazole distilling at 101–102° (122 mm): bp 154–155° (760 mm); λ_{max}^{MeOH} 271, and 275 mμ (ε 9600 and 9450, repectively); $\nu_{max}^{CHCl_3}$ 1440, 1320, 1275, 1020, 830, and 810 cm^{-1}. Glpc analysis indicated the product consisted of 99% 3,4-dichloro-1,2,5-thiadiazole and 1% monochlorothiadiazole. An analytical sample was obtained through preparative glpc. The material was identical with 3,4-dichloro-1,2,5-thiadiazole obtained according to the procedure of Vest.[12]

Anal. Calcd for $C_2Cl_2N_2S$: C, 15.50; H, 0.00; Cl, 45.75; N, 18.07. Found: C, 15.68; H, 0.00; Cl, 45.53; N, 18.08.

The same procedure carried out without the addition of chlorine resulted in a 75% yield of a 45:65 mixture (by glpc) of 3-chloro- and 3,4-dichloro-1,2,5-thiadiazole.

B. From Cyanogen.—Cyanogen was bubbled at the rate of about 1–2 g/min into a solution of 40.5 ml (0.5 mole) of sulfur monochloride in 80 ml of DMF at 80° for 5 hr. The reaction mixture was cooled, treated with 200 ml of water, and the product was isolated by azeotropic distillation and extraction as above. There was obtained 69.7 g (90%) of 3,4-dichloro-1,2,5-thiadiazole with spectral properties and glpc behavior identical with those of the product described in procedure A.

3,4-Dimethyl-1,2,5-thiadiazole.—Dimethylglyoxime (29 g, 0.25 mole) was added in small portions to a solution of 81 ml (1.0 mole) of sulfur monochloride in 160 ml of DMF, maintaining the temperature at 20–25° with external cooling. Two hours after the addition was complete, 400 ml of water was added and the mixture distilled to a vapor temperature of 100°. The distillate was neutralized with sodium carbonate and extracted with pentane; the pentane extracts were backwashed with a small amount of water, dried, and distilled at atmospheric pressure. There was obtained 10.95 g (38%) of 3,4-dimethyl-1,2,5-thiadiazole, bp 146–148°. Analytical glpc indicated that the product was 97% pure, the remainder being 3,4-dimethylfurazan. An analytical sample was obtained through preparative glpc: λ_{max}^{MeOH} 263 mμ (ε 9850).

Anal. Calcd for $C_4H_6N_2S$: C, 42.08; H, 5.30; N, 24.54; S, 28.08. Found: C, 42.15; H, 5.27; N, 24.36; S, 27.93.

Reaction of Glyoxime with Sulfur Monochloride.—Glyoxime (8.8 g, 0.1 mole) was added to a mixture of 24.3 ml (0.3 mole) of sulfur monochloride in 50 ml of DMF at 25°. The temperature of the reaction was maintained with the aid of an ice bath. After 2 hr, 100 ml of water was added and the mixture distilled until the vapor temperature reached 100°. The distillate was extracted with pentane. The pentane solution was dried and distilled through a short Vigreaux column. After removal of the solvent, 5.1 g of an oil, bp 90–115°, was obtained. Glpc analysis of this oil indicated that it was a mixture of 44% 1,2,5-thiadiazole, 36% 3-chloro-1,2,5-thiadiazole, and 20% 3,4-dichloro-1,2,5-thiadiazole.

N′-[1,2,5-thiadiazole-3-yl]sulfanilamide.—A stirred mixture of 12.0 g (0.1 mole) of 3-chloro-1,2,5-thiadiazole, 41.4 g (0.3 mole) of potassium carbonate, 51.6 g (0.3 mole) of sulfanilamide, and 10 g of acetamide was heated at 145° for a 25-min period. The mixture was cooled to 90°, 300 ml of water was added, and the mixture was distilled to a vapor temperature of 100° to remove some unchanged chloro compound. The pH of the cooled mixture was adjusted to 8.8 with concentrated hydrochloric acid and the unchanged sulfanilamide was removed by filtration. The filtrate was acidified to pH 3–4 to precipitate the crude product which was purified by recrystallization from 50% acetic acid with charcoal treatment. There was obtained 7.6 g (30%) of N′-[1,2,5-thiadiazole-3-yl]sulfanilamide:[30] mp 198–200°, λ_{max}^{MeOH} 268 mμ (ε 22,600).

Anal. Calcd for $C_8H_8N_4O_2S$: C, 37.49; H, 3.15; N, 21.86; S, 25.02. Found: C, 37.61; H, 3.13; N, 21.71; S, 25.09.

The use of 3-chloro-4-ethoxy-1,2,5-thiadiazole in the procedure above produced 62% of N′-[3-ethoxy-1,2,5-thiadiazole-4-yl]-sulfanilamide:[31] mp 115–116°, λ_{max}^{MeOH} 268 mμ (ε 21,200).

Anal. Calcd for $C_{16}H_{12}N_4O_3S$: C, 39.99; H, 4.03; N, 18.65; S, 21.35. Found: C, 40.08; H, 3.81; N, 18.39; S, 21.22.

3-Amino-1,2,5-thiadiazole.—α-Aminoacetamidine dihydrobromide (2.35 g, 0.01 mole) was added to a mixture of 2.5 ml of sulfur monochloride and 5 ml of DMF. The mixture was stirred 2 hr at 25° and then quenched onto ice water. The mixture was extracted three times with ether and the ether extracts were washed with a small amount of water and with saturated sodium bicarbonate. The dried ether solution was concentrated to an

(29) In the preliminary communication it was incorrectly reported that the nmr was taken of the neat liquid.

(30) M. Carmack and L. M. Weinstock, U. S. Patent 3,066,147 (1962); *Chem. Abstr.*, **58**, 7949b (1963).

(31) K. Menzyl, German Patent 1,175,683 (1963); *Chem. Abstr.*, **61**, 12009h (1964).

oil residue consisting of 670 ml (66%) of 3-amino-1,2,5-thiadiazole, λ_{max}^{MeOH} 295 mμ (ε 11,900). The infrared spectrum was identical with that recorded by Collins.[18b] The material was not further purified but was converted directly to N′-[1,2,5-thiadiazole-3-yl]sulfanilamide by standard procedures. The sulfa product, mp 197–200°, was identical with the material prepared above from 3-chloro-1,2,5-thiadiazole and sulfanilamide.

3-Chloro-4-phenyl-1,2,5-thiadiazole. A. From α-Amino-α-phenylacetonitrile Hydrochloride.—α-Amino-α-phenylacetonitrile hydrochloride (16.8 g, 0.1 mole) was added over a 0.5-hr period to a solution of 24.3 ml (0.3 mole) of sulfur monochloride in 45 ml of DMF. The mixture was stirred 16 hr at 25° and 200 ml of water was slowly added. The mixture was extracted with ether and the ether extracts were dried and evaporated to an oil residue which distilled at 109–111°, (1 mm). There was obtained 9.23 g (47%) of 3-chloro-4-phenyl-1,2,5-thiadiazole which was over 99% pure by glpc: λ_{max}^{MeOH} 287 and 232 mμ (ε 12,000 and 8900). An analytical sample was obtained through preparative glpc, mp 33°.

Anal. Calcd for $C_8H_5ClN_2S$: C, 48.86; H, 2.56; Cl, 18.03; N, 14.25; S, 16.31. Found: C, 48.89; H, 2.54; Cl, 18.16; N, 14.01; S, 16.17.

B. From Isonitrosophenylacetonitrile.—α-Isonitrosophenylacetonitrile (10.46 g, 0.073 mole) was added to a solution of 17.4 ml (0.217 mole) of sulfur monochloride in 35 ml of DMF. The mixture was warmed slowly to 50° whereupon the reaction became slightly exothermic. After 2.5 hr at 50° the mixture was cooled and added to 200 ml of ice water. The mixture was extracted with petroleum ether and the organic layer backwashed with water. After drying the petroleum ether, extracts were evaporated to a residue consisting of 1.95 g (15%) of 3-chloro-4-phenyl-1,2,5-thiadiazole. The infrared spectrum and glpc behavior of this material were identical with those of the material prepared by procedure A.

2,1,3-Benzothiadiazole.—To a solution of 16.2 ml (0.2 mole) of sulfur monochloride in 30 ml of DMF was added 5.4 g (0.05 mole) of *o*-phenylenediamine over a 10-min period under 10°. The mixture was warmed to 25° and stirred for 2 hr. The reaction was quenched by the addition of 50 ml of water and the mixture internally steam distilled until the vapor temperature reached 100°. The crystallized 2,1,3-benzothiadiazole was removed from the filtrate by filtration and washed with water. After air drying, the product weighed 5.5 g (81%), mp 42.5–43.5 (lit.[32] mp 44°).

Registry No.—Ia, 288-39-1; Ib, 5728-06-3; Ic, 13368-86-0; Id, 5970-14-9; IIa, 5728-07-4; IIb, 5728-08-5; IIc, 5933-67-5; IId, 5728-09-6; IIe, 5933-68-6; IIf, 5728-10-9; IIg, 5728-11-0; IIh, 5728-12-1; IIi, 5933-69-7; III, 6504-55-8; IVa, 5097-45-0; IVb, 5728-14-3; VI, 13350-98-6; VII, 5728-15-4; VIIIa, 5728-16-5; VIIIb, 5728-17-6; VIIIc, 5728-18-7; IX, 5728-20-1; X, 5728-21-2; XIII, 273-13-2; methyl cyanoformimidate, 13369-03-4; ethyl cyanoformimidate, 13369-04-5; isopropyl cyanoformimidate, 13369-05-6; N′-[1,2,5-thiadiazole-3-yl]sulfanilamide, 5097-43-8; N′-[3-ethoxy-1,2,5-thiadiazole-4-yl]sulfanilamide, 13369-07-8.

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Ozonolysis of Polycyclic Aromatics. XIV. Ozonation of Pentaphene and Benzo[*rst*]pentaphene[1-3]

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Ozonation of pentaphene (**1**) in methylene chloride at −78° with 1 mole equiv of ozone led to a peroxidic mixture which on reductive work-up (sodium iodide in acetic acid) gave 2,2′-binaphthyl-3,3′-dicarboxaldehyde (**5**, 25%); oxidative work-up (sodium hydroxide, hydrogen peroxide) led to **5** (16%), phthalic acid (**8**, 2%), and 2,2′-binaphthyl-3,3′-dicarboxylic acid (**9**, 16%). In both instances, 28% of unreacted **1** was recovered. Dialdehyde **5** was also obtained from **1** *via* osmium tetroxide oxidation to *cis*-6,7-dihydroxy-6,7-dihydropentaphene (**12**) followed by aqueous sodium periodate oxidation. Chromic acid oxidation of **5** gave **9** (14%), while the latter was independently prepared in 71% yield *via* cuprous oxide coupling of the diazonium salt of 2-aminonaphthalene-3-carboxylic acid (**11**). Dialdehyde **5** in base underwent an intramolecular Cannizzaro reaction to 2,2′-binaphthyl-3-hydroxymethyl-3′-carboxylic acid (**6**) which lactonized on treatment with strong acid or mild heat to the ε-lactone **7**. Ozonation of **1** with 4 mole equiv of ozone followed by oxidative work-up gave **8** (9%) and 2,2′,4,4′,5,5′-hexacarboxybiphenyl (**14**, 53%). The hexamethyl ester (**15**) obtained from **14** was independently synthesized by an Ullman coupling of 5-bromo-1,2,4-tricarbomethoxybenzene (**18**). Ozonation of benzo[*rst*]pentaphene (**2**) in methylene chloride at −78° with 3.5 mole equiv of ozone followed by oxidative work-up led to benzo[*rst*]pentaphene-5,8-dione (**3**, 14%), **8** (4%), *p*-terphenyl-2,2′,3′,2″-tetracarboxylic acid 2′,3′-anhydride (**19**, 10%), and 2-(*o*-carboxyphenyl)-1,10-phenanthrenedicarboxylic acid anhydride (**20**, 3%), with a 56% recovery of unreacted **2**. A comparison of the reactivity to ozone of the noncarcinogenic **1** and related pentacyclic and hexacyclic hydrocarbons of increasing carcinogenicity indicate that there is no simple, consistent correlation between carcinogenicity, K- and L-region additivity toward ozone, and the Pullmans' electronic theory of carcinogenesis.

During the past decade, we have actively investigated the reaction between ozone and some 18 aromatic polycyclics, aza aromatics, and aza aromatic N-oxides. One of our continuing objectives has been the search for any substantive correlation between K- and L-region additivity[4a] of these polycyclic aromatics toward ozone and their relative carcinogenicity. Aside from its obvious significance in the carcinogenic process, the ob-

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(3) Taken entirely from the Ph.D. thesis of L.S.

(4) (a) As defined by A. Pullman and B. Pullman, *Advan. Cancer Res.*, **3**, 117 (1955); (b) A. Pullman and B. Pullman, "Cancérization par les Substances Chimiques et Structure Moléculaire," Masson & Cie, Paris, 1955.