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1,2,3-Thiadiazoles as Potential Antineoplastic Agents. I. Synthesis of Novel 4-Monosubstituted and 4,5-Disubstituted Derivatives (1,2)

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1,2,3-Thiadiazole-4-carboxylic acid (IV) has been synthesized by oxidation of 5-(2-furyl)-1,2,3-thiadiazole-4-carboxylic acid (IIb), and converted *via* the acid chloride (V) to the amide (VI), ethyl ester (VII) and azide (IX). Rearrangement of the azide (IX) in ethanol led to ethyl N-(1,2,3-thiadiazol-4-yl)carbamate (X) and in benzene or toluene to a complex substance, possibly N,N,N-*tris*-(1,2,3-thiadiazol-4-yl)-isocyanurate (XI). Ethyl 5-phenoxy-1,2,3-thiadiazole-4-carboxylate (XIII), prepared from ethyl (phenoxyacetyl)diazoacetate (XII), has been converted to ethyl 5-formyl-1,2,3-thiadiazole-4-carboxylate methyl phenyl acetal (XVI) *via* the α-halo ether (XIV). The acetal (XVI) underwent partial hydrolysis in dilute acid to yield ethyl 5-formyl-1,2,3-thiadiazole-4-carboxylate phenyl hemiacetal (XVII) as an oil. Vacuum distillation of XVII gave ethyl 5-formyl-1,2,3-thiadiazole-4-carboxylate (XVIII) as an oil. The aldehyde XVIII, but not the hemiacetal XVII, formed a crystalline oxime (XIX) with hydroxylamine.

Until very recently, the chemistry of 1,2,3-thiadiazoles has been a relatively unexplored field since the first synthesis of a 1,2,3-thiadiazole, 5-anilino-1,2,3-thiadiazole (3), and the pioneer researches of Wolff (4), and of Staudinger and co-workers (5). The methods employed in these original researches have remained the only procedures available for preparation of this nucleus, with the exception of the novel reaction observed by Hurd and Mori (6) some ten years ago. The loss of nitrogen by 1,2,3-thiadiazoles upon irradiation with light has been reported (7), and formation of dithiafulvenes and dithiadienes as products noted. Quite recently the interconversion of 5-mercapto-1-phenyl-1,2,3-thiazole and 5-anilino-1,2,3-thiadiazole has been reported (8), an observation interesting on several counts, including that of base-lability of the 1,2,3-thiadiazole nucleus. The synthetic utility of the original synthesis from diazomethane and an isothiocyanate has been extended to include diazoethane (9) and phenyldiazomethane (10). The spectral properties of certain 5-(substituted)-amino-1,2,3-thiadiazoles have been examined (10), and the conclusion drawn that the nucleus is similar to aromatic nuclei in its ultraviolet absorption spectral properties. In the infrared spectrum, several band-structure assignments were made. We noted several years ago (11) the difference in the spectra of methyl benzoyldiazoacetate and 5-phenyl-1,2,3-thiadiazole-4-carboxylic acid derivatives (free acid, ester, and amide). Very recently, a modification of the original synthesis of 1,2,3-thiadiazoles has led to 5-amino-1,2,3-thiadiazole (12).

Ethyl (2-furoyl)diazoacetate (I) (Chart I) is readily available from the commercially available materials, 2-furoyl chloride and ethyl diazoacetate, by the usual method of direct interaction of reactants with a second mole of ethyl diazoacetate acting as a base (13). Ethyl 5-(2-furyl)-1,2,3-thiadiazolecarboxylate (IIa) was prepared in satisfactory yield by reaction of I with ammoniacal hydrogen sulfide. Saponification of IIa led to the free acid (IIb). The oxidation of IIb was investigated, since it is apparent that oxidative removal of the furan ring offers a new potential route to 1,2,3-thiadiazole-4,5-dicarboxylic acid (III)

CHART I

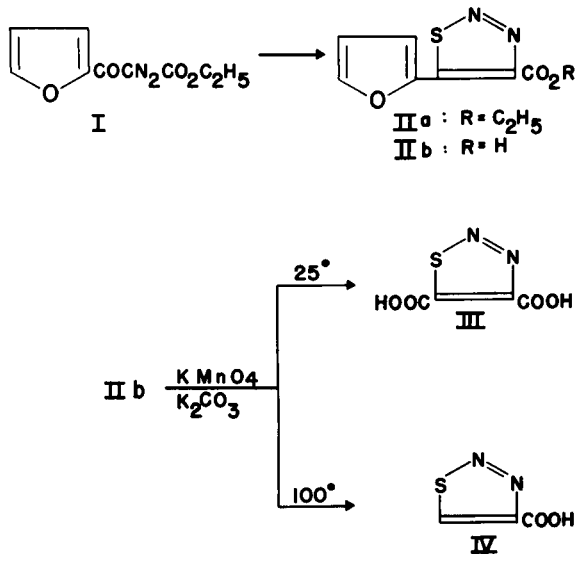

CHART II

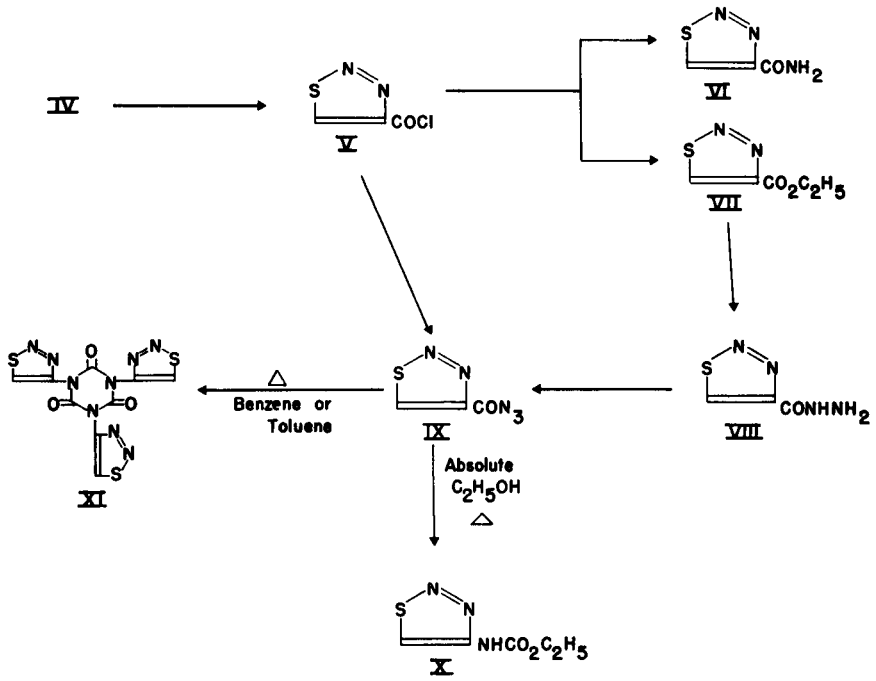

CHART III

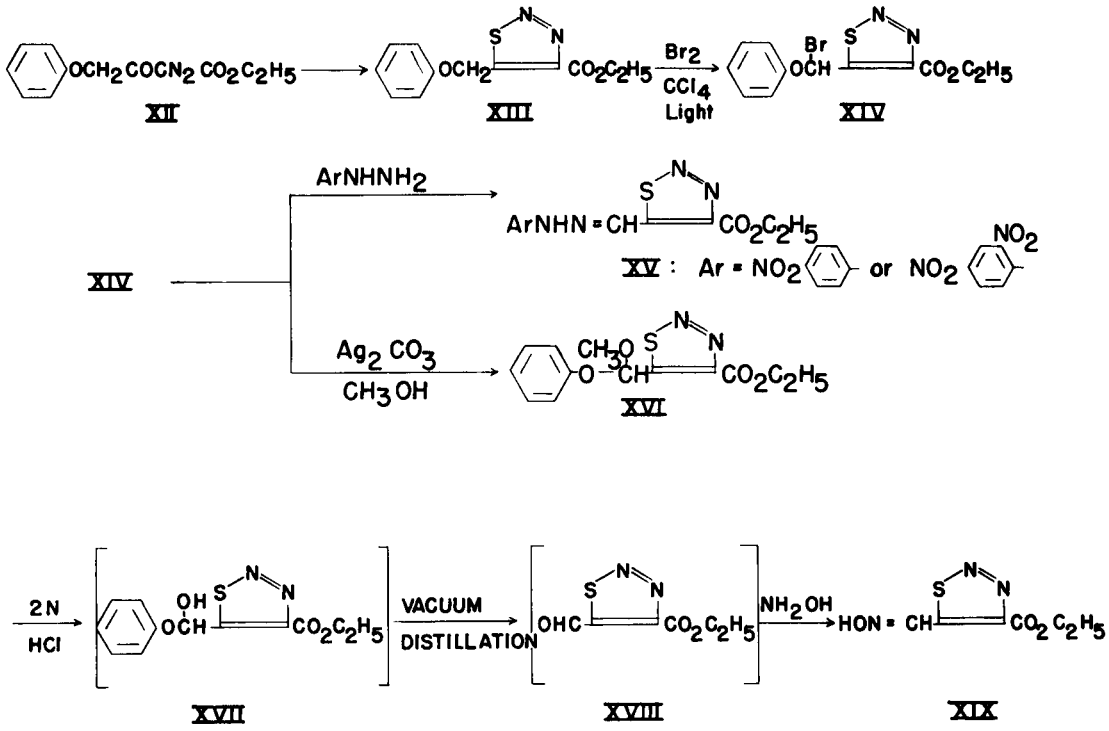

TABLE I

5-Aryl- and 5-Benzyloxymethyl-1,2,3-Thiadiazole-4-Carboxylic Acid Derivatives

Substituents			Analyses							
			% Carbon		% Hydrogen		% Nitrogen		% Sulfur	
4-Position	5-Position	M.P.,°C	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
$-COOC_2H_5$	$C_6H_5CH_2OCH_2-$	82.2- 83.0	56.10	55.67	5.07	4.97	10.07	10.47	11.52	11.05
-COOH	$C_6H_5CH_2OCH_2-$	162.5-163.0	52.79	52.48	4.03	3.95	11.20	11.02	12.81	12.76
$-CONH_2$	$C_6H_5CH_2OCH_2-$	113-114	53.00	52.69	4.45	4.41	16.86	16.52	12.84	12.62
$-COOCH_3$	*m*-Br-C_6H_4-	91.4-92.0	40.14	39.82	2.36	2.41	-	-	10.71	10.79
$-COOCH_3$	*m*-NO_2-C_6H_4-	149.6-150.5	45.28	45.53	2.66	2.68	-	-	12.08	11.94
$-COOC_2H_5$	*m*-Br-C_6H_4-	83.5-84.5	42.18	42.11	2.90	3.01	-	-	10.24	10.56
$-COOCH_3$	$C_6H_5OCH_2-$	72.0-73.5	52.79	52.82	4.03	4.00	-	-	12.81	12.94

TABLE II

Antineoplastic Activity: Amide (VI) and Hydrazide (VIII) of 1,2,3-Thiadiazole-4-carboxylic Acid

Compound	Test System	Dose mg./kg.	Survivors	Animal Wt. Diff. (T-C) (a)	Tumor Wt. T/C (a)	% T/C (a)	Status
VI	HS 1 (b)	20	2/6	-0.5 (c)	193/1012	--	Toxic test
VI	HS 1	10	4/6	0.0 (c)	50/621	8	Active (d)
VI	HS 1	10	0/6	---	---	--	Toxic test
VI	HS 1	10	4/6	-0.4 (c)	347/682	50	Active (e)
VI	HS 1	10	2/6	-0.3 (c)	50/780	--	Toxic test
VIII	LL (f)	50	6/6	-1.6	812/1657	49	Active (d)
VIII	LL	50	6/6	-1.0	657/459	143	Inactive (e)

(a) T = test, C = control. (b) Human Sarcoma, HS 1, embryonated egg as host. (c) Average weight of test embryos minus that of control embryos. (d) At Stage 1 of sequential screen. (e) At Stage 2 of sequential screen. (f) Lewis lung carcinoma.

and the 4-monoacid (IV). Both III and IV were prepared and characterized by Wolff. Although IIb could be oxidized to III with alkaline permanganate at 25°, III was obtained in only about 8% yield. At 100°, both oxidation of the furyl group and subsequent decarboxylation of the 5-carboxyl group occurred to give 1,2,3-thiadiazole-4-carboxylic acid (IV), in 12% yield. In this particular sequence, the furyl derivative (IIb) obviously was not a satisfactory source of either III or IV.

In order to obtain 1,2,3-thiadiazole-4-carboxylic acid in quantity sufficient for the reactions shown in Chart II, the synthetic procedure of Hurd and Mori (6) was employed. We obtained the acid chloride (V) as a clear viscous oil from interaction of thionyl chloride and IV when a small amount of ethyl acetate was used as solvent. Reaction of V with ammonia gave the previously undescribed 1,2,3-thiadiazole-4-carboxamide (VI), and with ethanol the known ethyl ester (VII). Attempted application of either the Hofmann reaction to VI or the Schmidt reaction to IV was unsatisfactory as a route to 4-amino-1,2,3-thiadiazole. In order to study the Curtius rearrangement as a route to the 4-amino derivative, 1,2,3-thiadiazole-4-carboxazide was prepared by two methods: reaction of the acid chloride (V) with sodium azide and interaction of the hydrazide (VIII) with nitrous acid. The previously reported melting point for VIII was confirmed. In our hands, the azide was found to melt 113.5-114.5°, some 25° higher than previously reported (14). The azide (IX) gave satisfactory analytical values for carbon-hydrogen, nitrogen, and sulfur, and possessed the expected azide infrared band in the 2100-2200 cm^{-1} region. In addition, the infrared spectrum contained a carboxazide carbonyl band at 1680 cm^{-1}, a carbon-hydrogen stretching band at 3097 cm^{-1} and, in the 1500-650 cm^{-1} region, virtually all of the bands recently cited (10) as associated with ring-stretching and ring-breathing modes of the 1,2,3-thiadiazole nucleus. In absolute ethanol, Curtius rearrangement of IX occurred to give ethyl N-(1,2,3-thiadiazole-4-

yl)carbamate (X) in 38% yield. Analytical and infrared spectral data support the indicated structure. This urethan (X) was resistant to hydrolysis in both dilute and concentrated hydrochloric acid. Accordingly, an alternative Curtius rearrangement procedure was employed, in which the azide is heated in an inert solvent like benzene or toluene, and the product isocyanate often is isolable. When IX was heated in benzene, a product, m.p. 145-150°, was obtained, but also approximately 50% of the starting azide. In boiling toluene, only the product m.p. 145-150° was formed. Although analysis is in fair agreement with theory for the isocyanate, infrared spectral data do not support the isocyanate structure. The most significant part of the infrared spectral data involves the absence of a band in the 2300-2100 cm^{-1} region, characteristic of isocyanates, and presence of two bands in the carbonyl region. Isocyanates show no carbonyl absorption. The product was insoluble in most common organic solvents, and was stable towards acid-hydrolysis. The insolubility of the product made its purification difficult, and its degree of purity is not known. However, the infrared spectral data and stability towards acid hydrolysis provide conclusive evidence that the product is not an isocyanate. The analytical data and spectra would support postulation of a dimerization, trimerization, or polymerization product of the isocyanate. The trimerization product, an isocyanurate (XI), is depicted in Chart II. Isocyanurates similar to XI have been previously observed from Curtius rearrangement with *m*-nitrobenzoyl azide and phenylacetyl azide (15).

Inasmuch as syntheses from IV involving reaction at the carboxyl group could lead ultimately only to 4-substituted-1,2,3-thiadiazoles, other 1,2,3-thiadiazole derivatives were investigated. One of the more interesting was 5-phenoxymethyl-1,2,3-thiadiazole-4-carboxylic acid (XIII in Chart III), prepared by interaction of ethyl phenoxyacetyldiazoacetate (XII) with ammoniacal hydrogen sulfide. Diazoketo esters like XII, with the diazo group flanked by two carbonyl groups, are unusually stable and can be handled with complete safety in relatively large amounts. The preparation of XII involved direct interaction of the readily available substances, ethyl diazoacetate and phenoxyacetyl chloride. The reaction involving ethyl diazoacetate must be carried out cautiously but XII crystallizes from the reaction mixture in 52% yield, minimizing hazards otherwise associated with removal of unreacted ethyl diazoacetate by vacuum distillation. Several procedures for cleavage of the ether function were investigated, including attempted hydrogenolysis over palladium-on-charcoal and rhodium. All procedures failed. Presumably hydrogenolysis procedures were unsuccessful because of poisoning of the catalyst by the bivalent sulfur of the thiadiazole nucleus. As a potential intermediate for aldehyde synthesis, an α-halo ether appeared of interest in view of a recent report of synthesis of benzaldehyde from benzylmethyl ether by bromination (16). Bromine reacted with XIII satisfactorily in carbon tetrachloride solution under illumination with either a 150- or 300-watt lamp. The illumination was essential. The product, obtained in 92% yield, was a light yellow solid with a very sharp, irritating odor. The substance was unstable in moist air and gave positive Beilstein and alcoholic silver nitrate tests for halogen. Analysis in fair agreement with theory was obtained, but in view of the loss of weight of the substance upon heating (presumably from loss of hydrogen bromide), completely satisfactory analytical results could not be expected. With either *p*-nitro- or 2,4-dinitrophenylhydrazine, arylhydrazones (XV) of ethyl 5-formyl-1,2,3-thiadiazole-4-carboxylate were obtained. However, the derivatives (XV) were quite resistant towards acid hydrolysis and the free aldehyde (XVIII) was not obtained in this way. Reaction of XIV with absolute methanol and silver carbonate gave ethyl 5-formyl-1,2,3-thiadiazole-4-carboxylate methyl phenyl acetal (XVI) as a colorless, odorless, low-melting solid in virtually quantitative yield. Hydrolysis of XVI in dilute ethanolic hydrochloric acid at reflux temperature gave an oily product, to which structure XVII is ascribed on the basis of infrared spectral analysis. The spectrum contained an O-H stretching band at 3375 cm^{-1}, carbonyl stretching band at 1725 cm^{-1}, and phenyl bands at 1620 and 1595 cm^{-1}. Attempted distillation of XVII under high vacuum gave two fractions, the first of which was purified XVII with a melting point of approximately 20°. The second higher-boiling fraction (XVIII) did not solidify upon cooling, and its infrared spectrum contained two carbonyl bands. In addition to the ester band at 1725 cm^{-1}, there was present a second carbonyl band at 1685 cm^{-1} which was attributed to the aldehyde carbonyl group. Both XVII and XVIII reacted with 2,4-dinitrophenylhydrazine reagent to give a 2,4-dinitrophenylhydrazone, identical with that obtained from the α-halo ether (XIV). However, only the aldehyde fraction containing XVIII gave the aldoxime (XIX) with hydroxylamine; XVII was unreactive under the same conditions. In its present state of development, the distillation of XVII *in vacuo* can not be regarded as a preparative procedure, since *ca.* 85% of the material decomposed during the distillation, which occurred at temperatures above 200°.

In order to study possible ether cleavage reactions, the benzyl analog of XIII was prepared from ethyl benzyloxyacetyldiazoacetate, which was obtained as a crystalline solid, m.p. 31.5-32.5°, but not otherwise characterized. Reaction of the latter with ammoniacal hydrogen sulfide gave ethyl 5-benzyloxy-1,2,3-thiadiazole-4-carboxylate. Repeated attempts to cleave the benzyloxy group in various acidic media did not lead to a pure product. Reaction appeared to occur, but the products were either reddish-colored solids or oils which were difficult to purify. Attempted hydrogenolysis failed, presumably because the thiadiazole poisoned the catalyst. Reaction with aluminum chloride gave a complex of undetermined structure. The properties

of ethyl 5-benzyloxy-1,2,3-thiadiazole-4-carboxylate, the free acid, and the amide are given in Table I. Properties of certain other thiadiazoles prepared from acyl- or aroyldiazoacetic esters available in this laboratory also are given in Table I.

Several of the compounds prepared during the present study have been screened against three tumor systems (Sarcoma 180, Adenocarcinoma 755, and Leukemia 1210) in mice by the Cancer Chemotherapy National Service Center (17). The compounds screened include the last six entries in Table I; I (Chart I); VI, VII, VIII, and X (Chart II); and XII, XIII (and the free acid and amide corresponding to XIII), XV, where Ar = 2,4-dinitrophenyl, and XVI (Chart III). All substances were inactive *vs.* the mouse tumor systems. Additional tests were carried out with the amide (VI) and hydrazide (VIII) with results as indicated in Table II. The activity of the amide (VI) is interesting, but its ultimate significance must, of course, await the results of additional screening studies.

EXPERIMENTAL (18)

1,2,3-Thiadiazole-4,5-dicarboxylic Acid (III) and 1,2,3-Thiadiazole-4-carboxylic Acid (IV) from 5-(2-Furyl)-1,2,3-thiadiazole-4-carboxylic Acid (IIb).

Two grams (0.01 mole) of 5-(2-furyl)-1,2,3-thiadiazole-4-carboxylic acid and 8.6 g. (0.054 mole) of potassium permanganate were dissolved in 200 ml. of water containing 10.0 g. of potassium carbonate. The resulting solution was stirred for one-half hour at room temperature, the manganese dioxide removed by filtration, and the filtrate acidified with hydrochloric acid. After standing at room temperature overnight, the solution was evaporated to dryness under reduced pressure. The residual solid was extracted with three 50-ml. portions of ether, which were combined, dried over anhydrous magnesium sulfate, and evaporated to dryness. The white solid 1,2,3-thiadiazole-4,5-dicarboxylic acid was left as residue after solvent removal in 0.152 g. (7.8%) yield; m.p. 96-98° [lit. (4b) m.p., 98°].

A similar procedure utilizing 8.8 g. of potassium permanganate in 800 ml. of water at the reflux temperature for four hours, with product isolation as immediately above, gave 0.26 g. (12.6%) of 1,2,3-thiadiazole-4-carboxylic acid, m.p. and lit. (4b) m.p. 227-228° (dec.). The major part of the 1,2,3-thiadiazole-4-carboxylic acid required in this investigation was prepared by the method of Hurd and Mori (6).

1,2,3-Thiadiazole-4-carboxamide (VI).

1,2,3-Thiadiazole-4-carboxylic acid (1.10 g.) was heated under reflux with 25 ml. of ethyl acetate and 12 ml. of thionyl chloride for 3.5 hours. Excess thionyl chloride and ethyl acetate were removed by vacuum distillation to leave the acid chloride as a clear, viscous liquid. The acid chloride was poured into 25 ml. of ice-cold concentrated ammonium hydroxide. The resulting solid (0.90 g., 90%) was collected by filtration and recrystallized from 95% ethanol to give 0.70 g. of 1,2,3-thiadiazole-4-carboxamide, m.p. 219.5-220.5°.

The infrared spectrum contained bands at 3365 (N-H stretch), 3180, 3110 (C-H stretch), 1670 (carbonyl stretch), 1505 (N-H in-plane deformation), 1375, 1100, 970, 890, 798, and 680 cm^{-1}.

Anal. Calcd. for $C_3H_3N_3OS$: C, 27.90; H, 2.34; N, 32.54; S, 24.80. Found: C, 28.09; H, 2.53; N, 32.86; S, 24.78.

Ethyl 1,2,3-Thiadiazole-4-carboxylate (VII).

1,2,3-Thiadiazole-4-carboxylic acid (6.11 g.) was added to 10 ml. of ethyl acetate and 15 ml. of thionyl chloride and the mixture heated under reflux until no more 1,2,3-thiadiazole-4-carboxylic acid remained undissolved. The mixture then was refluxed for an additional hour. The solution was cooled, and then excess thionyl chloride and solvent were removed by vacuum distillation. Absolute ethanol (100 ml.) was added to the residue, and the resulting mixture heated under reflux for two hours. The hot solution was poured over ice and diluted with 200 ml. of water. Upon cooling and further dilution, a solid crystallized, which was collected by filtration and recrystallized from petroleum ether, b.p. 88-98°. Ethyl 1,2,3-thiadiazole-4-carboxylate was obtained in 4.37 g. (59%) yield, m.p. 88-90°, lit. m.p. 86-86.5° (6).

The infrared spectrum contained bands at 3085 (C-H stretch) 2995 (C-H str.), 2905 (C-H str.), 1725 (carbonyl str.), 1480, 1465, 1375, 1340, 1225, 1100, 1025, 960, 905, 880, 845, and 780 cm^{-1}.

1,2,3-Thiadiazole-4-carboxyhydrazide (VIII).

Ethyl 1,2,3-thiadiazole-4-carboxylate (4.37 g., 0.0277 mole) was suspended in 50 ml. of absolute ethanol and the mixture heated until all of the ester dissolved. Hydrazine (95%; 1.76 g., 0.055 mole) in 5 ml. of absolute ethanol was added all at once to the hot alcoholic solution. The resulting mixture was heated under reflux, with stirring, for one hour. The hydrazide, which was insoluble in the hot ethanol and precipitated as it was formed, was collected by filtration and dried; yield, 3.70 g. (92.8%), m.p. and lit. (14) m.p. 210° (dec.).

1,2,3-Thiadiazole-4-carboxazide (IX).

Procedure A.

Two grams (0.014 mole) of 1,2,3-thiadiazole-4-carboxhydrazide was dissolved in diluted hydrochloric acid (prepared by adding 5.7 ml. of 6 *N* hydrochloric acid to 50 ml. of water). The resulting solution was covered with 250 ml. of ether and the mixture chilled to 0° in an ice-salt bath. A solution of sodium nitrite (1.05 g. in 10.0 ml. of water) was added with stirring in small portions so that the temperature of the mixture remained below 5°. After sodium nitrite addition was complete, the reaction mixture was stirred for an additional ten minutes. The ether layer was separated, and the aqueous layer washed with 50 ml. of ether. The combined ether extracts were washed with dilute sodium bicarbonate, and dried over anhydrous magnesium sulfate. Ether removal under reduced pressure gave the azide as a white solid, yield 1.76 g. (81.8%), m.p. 113.5-114.5°.

The infrared spectrum contained bands at 3097 (C-H str.), 2190, 2155 (azide str.), 1680 (carbonyl str.), 1475, 1300, 1260, 1200, 1140, 935, 890, 860, and 750 cm^{-1}.

Anal. Calcd. for C_3HN_5OS: C, 23.22; H, 0.65; N, 45.14; S, 20.65. Found: C, 23.31; H, 1.01; N, 46.30; S, 20.04.

Procedure B.

One gram of 1,2,3-thiadiazole-4-carboxylic acid, 10 ml. of ethyl acetate, and 30 ml. of thionyl chloride were heated together under reflux for two hours. Excess thionyl chloride and solvent were removed by vacuum distillation and reagent acetone (25 ml.) added to the residue. An aqueous solution of sodium azide (0.7 g. in 2.0 ml. water) was added to the acetone solution, chilled in an ice bath, with fast mechanical stirring. Stirring was continued for ten minutes, and then 50 ml. of water was added. The azide, which precipitated from the aqueous acetone solution, was collected by filtration and dried at room temperature in a vacuum desiccator; yield, 0.62 g., m.p. 113.5-114.5°.

Curtius Rearrangement of 1,2,3-Thiadiazole-4-carboxazide.

A. Rearrangement in Ethanol. Preparation of Ethyl N-1,2,3-Thiadiazole-4-yl)carbamate (X).

1,2,3-Thiadiazole-4-carboxhydrazide (4.39 g.) was dissolved in dilute hydrochloric acid solution (prepared by adding 5.7 ml. of 6 *N* hydrochloric acid to 50 ml. of water). The resulting solution was covered with 350 ml. of ether and the mixture chilled to 0° in an ice-salt bath. An aqueous solution of sodium nitrite (2.76 g. in 10 ml. water) was added in small portions with vigorous stirring so that the temperature remained below 5°. After addition of the nitrite solution was complete, stirring was continued for ten minutes. The ether layer was separated, and the aqueous layer was extracted with an additional 100 ml. of ether. The combined ethereal extracts were washed with dilute sodium bicarbonate solution and dried over anhydrous magnesium sulfate for thirty minutes. The dry extract then was concentrated to one-half the original volume by distillation of required quantity of ether, and 150 ml. of absolute ethanol added. Then the remainder of the ether was removed by distillation. The residual ethanol solution was heated under reflux on a steam bath for three hours, cooled slightly, poured over crushed ice, and diluted with 400 ml. of water. After the solution stood overnight, there was present a solid which was collected by filtration and recrystallized from ethanol-water; yield of ethyl N-(1,2,3-thiadiazol-4-yl)carbamate, 2.0 g. (38%), m.p. 110.5-112.0°).

The infrared spectrum contained bands at 3210 (N-H str.), 3050 (C-H str.), 1715 (carbonyl str.), 1590 (N-H in-plane deformation), 1570, 1310, 1270, 1220, 1075, 990, and 890 cm^{-1}.

Anal. Calcd. for $C_5H_7N_3O_2S$: C, 34.67; H, 4.08; N, 24.26; S, 18.51. Found: C, 34.69; H, 4.29; N, 24.82; S, 18.94.

B. Rearrangement in Toluene and Benzene.

1,2,3-Thiadiazole-4-carboxhydrazide (2 g.) was dissolved in dilute hydrochloric acid (5.7 ml. 6 *N* hydrochloric acid in 50 ml. water). The resulting solution was covered with 250 ml. ether and cooled to 0° in an ice-salt bath. Aqueous sodium nitrite (1.05 g. in 10 ml. water) was added in small portions with stirring so as to maintain a temperature of less than 5°. After nitrite addition was complete the solution was stirred an additional ten minutes, the ether layer was separated, and the aqueous layer was extracted with 50 ml. of ether. The combined ether extracts were washed with dilute sodium bicarbonate solution and then dried over anhydrous magnesium sulfate thirty minutes. Dry toluene (150 ml.) was added to the dry ether solution and the ether then removed by distillation. Then the toluene solution was heated under reflux for three hours. A brown solid was present in the mixture. The solvent was removed by evaporation under reduced pressure and the brown solid collected. The brown solid was added to petroleum ether (b.p. 88-98°), heated to boiling, but proved insoluble and was collected by filtration; yield, 1.51 g., m.p. 145-150°. No azide proved isolable from the petroleum ether mother liquor.

The infrared spectrum contained bands at 3105 (C-H str.), 1770 (carbonyl str.), 1677, 1570, 1365, 1330, 1230, 1225, 855, and 755 cm^{-1}.

Anal. Calcd. for $(C_3HN_3OS)x$: C, 28.35; H, 0.79; N, 33.10; S, 25.20. Found: C, 28.48; H, 2.08; N, 34.38; S, 25.98.

The identical procedure with 150 ml. of benzene in place of toluene resulted in 0.91 g. of product, m.p. 145-150°, and recovery of 0.98 g. of the azide, m.p. 113-114°, from the benzene mother liquor.

Ethyl Phenoxyacetyldiazoacetate (XII).

Phenoxyacetyl chloride (16 g., 0.094 mole) was added dropwise to ethyl diazoacetate (21.4 g., 0.188 mole), cooled to 10°. The reaction mixture was shaken continuously. There was an immediate evolution of gas. As the reaction mixture became warm with continued addition of phenoxyacetyl chloride, it was cooled in an ice-bath. When the addition was complete, shaking of the reaction mixture was continued until gas-evolution became moderate. The reaction mixture then stood at room temperature for twenty-four hours, and subsequently in a freezer for twenty-four hours. Scratching of the sides of the reaction vessel caused crystallization of the product, which was collected by filtration (two crops from the mother liquor were obtained by cooling) and recrystallized from petroleum ether to give 12.2 g. (52%) of the yellow ethyl phenoxyacetyldiazoacetate, m.p. 53.5-54.0°.

The infrared spectrum contained bands at 2145 (aliphatic diazo str.), 1704 (ester carbonyl str.), 1678 (keto carbonyl str.), 1606 (phenyl in-plane skeletal mode), 1500, 1378, 1317, 1235, 1154, 996, 763, 746, and 700 cm^{-1}.

Anal. Calcd. for $C_{12}H_{12}N_2O_4$: C, 56.05; H, 4.87; N, 11.28. Found: C, 57.95; H, 4.77; N, 11.85.

Ethyl 5-Phenoxymethyl-1,2,3-thiadiazole-4-carboxylate (XIII).

Ethyl phenoxyacetyldiazoacetate (1.0 g.) was dissolved in 50 ml. of warm methanol, a 20 ml. quantity of concentrated ammonium hydroxide was added and the resulting solution saturated with hydrogen sulfide. The saturated solution then was poured slowly into 600 ml. of ice-water with vigorous stirring. The precipitate which formed was collected, washed three times with water, and recrystallized from ethanol-water to give the colorless ethyl 5-phenoxymethyl-1,2,3-thiadiazole-4-carboxylate, m.p. 57-58°, in 0.8 g. (75%) yield. The compound was not light-sensitive.

The infrared spectrum contained bands at 1741 (ester carbonyl str.), 1604 (skeletal in-plane phenyl mode), 1494, 1381, 1347, 1251, 1203, 1061, 1029, 760, and 695 cm^{-1}.

Anal. Calcd. for $C_{12}H_{12}N_2O_3S$: C, 54.53; H, 4.59; N, 10.60; S, 12.13. Found: C, 54.81; H, 4.52; N, 10.79; S, 11.78.

Saponification of 1 g. of the ester in 100 ml. of 5% sodium hydroxide (two hours at room temperature and then heated on the steam bath until solution complete), followed by acidification with concentrated hydrochloric acid and recrystallization of the precipitated product from water gave 5-phenoxymethyl-1,2,3-thiadiazole-4-carboxylic acid m.p. 171-172° in 0.82 g. (93%) yield.

The infrared spectrum contained bands at 3000, 2900, 1688 (acid carbonyl str.), 1604 (in-plane skeletal phenyl mode), 1533, 1495, 1450, 1244, 760, and 690 cm^{-1}.

Anal. Calcd. for $C_{10}H_8N_2O_3S$: C, 50.84; H, 3.41; N, 11.86; S, 13.57. Found: C, 50.98; H, 3.36; N, 12.16; S, 13.57.

The free acid (0.5 g.), prepared as outlined immediately above, was heated under reflux with 8 ml. of thionyl chloride for 1.5 hours after the solid acid had gone into solution. Excess thionyl chloride was removed by vacuum distillation, the solid residue dissolved in 20 ml. of ethanol, and 10 ml. of concentrated ammonium hydroxide added. The resulting mixture stood at room temperature for 24 hours. The colorless product was collected by filtration and recrystallized from 95% ethanol to give 5-phenoxymethyl-1,2,3-thiadiazole-4-carboxamide, m.p. 152.5-153.5°, in 0.31 g. (63%) yield.

The infrared spectrum contained bands at 3388 (N-H str.), 3080 (C-H str.), 1680 (carbonyl str.), 1604 (in-plane skeletal phenyl mode), 1502, 1245, 1049, 987, 757, 693, 678 cm^{-1}.

Anal. Calcd. for $C_{10}H_9N_3O_2S$: C, 51.05; H, 3.86; N, 17.86; S, 13.63. Found: C, 50.94; H, 3.79; N, 18.23; S, 13.67.

Bromination of Ethyl 5-Phenoxymethyl-1,2,3-thiadiazole-4-carboxylate.

Thirty grams of ethyl 5-phenoxymethyl-1,2,3-thiadiazole-4-carboxylate was dissolved in 300 ml. of carbon tetrachloride and the resulting solution heated to boiling. Bromine (19.2 g.) in 50 ml. of carbon tetrachloride was added dropwise while the refluxing solution was illuminated with a 300-watt white light. After bromine addition was complete, the reflux period was extended for 30 minutes under continued illumination. The reaction mixture was cooled slightly, and then the solvent was evaporated under reduced pressure. The residual product was dissolved in boiling petroleum ether (b.p. 66-76°). Upon cooling, phenyl [α-bromo-(4-carbethoxy-1,2,3-thiadiazol-4-yl)-carbinyl] ether (XIV) separated from solution as a very pale yellow solid, m.p. 74.5-76.0°, in 36 g. (92%) yield. The substance evolved fumes of hydrogen bromide upon contact with moist air.

The infrared spectrum contained bands at 2965 (C-H str.), 1745 (carbonyl str.), 1590 (in-plane skeletal phenyl mode), 1485, 1225, 1197, 1085, 1070, 765, and 655 cm^{-1}.

Anal. Calcd. for $C_{12}H_{11}BrN_2O_3S$: Br, 23.28. Found: Br, 21.27; loss in weight at 100° in one hour, 1.08%.

Ethyl 5-Formyl-1,2,3-thiadiazole-4-carboxylate Methyl Phenyl Acetal (XVI).

Phenyl [α-bromo-(4-carboethoxy-1,2,3-thiadiazol-4-yl)-carbinyl] ether (36.0 g.) and 29.0 g. of silver carbonate were added to 800 ml. of absolute methanol and the resulting mixture stirred at room temperature for 18 hours. Excess silver carbonate and silver bromide were removed by filtration. The filtrate was cooled and diluted with sufficient ice to precipitate the product acetal. Recrystallization was effected by solution in ethanol and addition of ice to give ethyl 5-formyl-1,2,3-thiadiazole-4-carboxylate methyl phenyl acetal as a colorless solid, m.p. 38.0-40.0° in 27.7 g. (89.6%) yield.

The infrared spectrum contained bands at 2980 (C-H str.), 2820 (C-H str.), 1725 (carbonyl str.), 1590 (in-plane skeletal phenyl mode), 1490, 1215, 850, 750, and 685 cm^{-1}.

Anal. Calcd. for $C_{13}H_{14}N_2O_4S$: C, 53.05; H, 4.80; N, 9.51; S, 10.89. Found: C, 53.10; H, 4.87; N, 9.80; S, 10.77.

Acid-Catalyzed Hydrolysis of Ethyl 5-Formyl-1,2,3-thiadiazole-4-carboxylate Methyl Phenyl Acetal. Isolation of Hemiacetal and Aldehyde Fractions.

Ethyl 5-formyl-1,2,3-thiadiazole-4-carboxylate methyl phenyl acetal (10 g.) was dissolved in an ethanolic hydrochloric acid solution (prepared by adding 20 ml. of concentrated hydrochloric acid to 100 ml. of 95% ethanol). The resulting solution was heated under reflux for 4 hours. The hot reaction mixture was poured onto crushed ice, and an additional 250 ml. quantity of water added. An immiscible liquid separated from the aqueous mixture. The total mixture was extracted with three 100-ml. portions of ether, which were combined and dried over anhydrous magnesium sulfate for thirty minutes. Solvent removal by vacuum distillation gave a residual yellow liquid in approximately 9 ml. yield. The infrared spectrum of the liquid (no solvent) contained, among other bands, bands at 3375 (O-H str.), 1725 (ester carbonyl str.), 1620 (in-plane phenyl mode), and 1595 cm^{-1} (in-plane phenyl mode). These infrared spectral data support formulation of the hydrolysis product as ethyl 5-formyl-1,2,3-thiadiazole-4-carboxylate phenyl hemiacetal (XVII).

The above hemiacetal was distilled under high vacuum (*ca.* 50 microns Hg). Two fractions were collected with the aid of a micro distilling head: Fraction 1, boiling range 40-70°, solidified in the water-cooled condenser and melted at approximately 22°. The infrared spectrum of Fraction 1 was identical with that of the starting hemiacetal. Fraction 2, boiling range 140-170°, yield 2 ml., did not solidify upon cooling. The infrared spectrum of Fraction 2 contained only very weak bands at 3390 and 1595 cm^{-1}, assumed to be due to small quantities of the hemiacetal fraction, and contained strong bands at 1725 cm^{-1} (ester carbonyl str.) and 1685 cm^{-1} (aldehyde carbonyl str.). These spectral data, and formation of a crystalline

oxime (following section) support the postulate that this fraction is impure ethyl 5-formyl-1,2,3-thiadiazole-4-carboxylate (XVIII).

Ethyl 5-Formyl-1,2,3-thiadiazole-4-carboxylate Oxime (XIX).

Approximately 1 ml. of ethyl 5-formyl-1,2,3-thiadiazole-4-carboxylate (boiling range 140-170° at 50 microns) was dissolved in 5 ml. of 10% sodium hydroxide. Excess hydroxylamine hydrochloride was added to the stirred mixture, and then ethanol until a homogeneous solution resulted. The solution then was heated on a steam bath for 30 minutes. The hot solution was diluted with 20 ml. of water and the mixture cooled in an ice-bath. After 1 hour, ethyl 5-formyl-1,2,3-thiadiazole-4-carboxylate oxime separated from solution, and was recrystallized from 95% ethanol; yield, 0.337 g., m.p. 192-193°.

The infrared spectrum contained bands at 3090 (C-H str.), 2950, 2755, 1710 (imine str.), 1490, 1320, 1205, 1015, 925, 845, and 780 cm^{-1}.

Anal. Calcd. for $C_6H_7N_3O_3S$: C, 35.81; H, 3.50; N, 20.88; S, 15.93. Found: C, 36.05; H, 3.59; N, 20.93; S, 15.81.

Ethyl 5-Formyl-1,2,3-thiadiazole-4-carboxylate 2,4-Dinitrophenylhydrazone.

Phenyl [α-bromo-(4-carboethoxy-1,2,3-thiadiazol-4-yl)-carbinyl] ether (2 ml. of crude product obtained as residue upon removal of excess bromine and carbon tetrachloride) was dissolved in ethanol. The ethanolic solution was poured into hot excess 2,4-dinitrophenylhydrazine reagent (2,4-dinitrophenylhydrazine in ethanolic sulfuric acid) (19). After 5 minutes, the yellow 2,4-dinitrophenylhydrazone precipitated from solution and was collected by filtration. After recrystallization from 95% ethanol, the substance was obtained as yellow needles, m.p. 189-191°, in 1.05 g. yield.

The infrared spectrum contained bands at 3270 (N-H str.), 3100 (C-H str.), 1712 (imine str.), 1615, 1602, 1505, 1495, 1348, 1220, 1130, 825, 740, and 700 cm^{-1}.

Anal. Calcd. for $C_{12}H_{10}N_6O_6S$: C, 39.34; H, 2.75; N, 22.94; S, 8.75. Found: C, 39.51; H, 2.73; N, 22.88; S, 8.78.

Ethyl 5-Formyl-1,2,3-thiadiazole-4-carboxylate *p*-Nitrophenylhydrazone.

Phenyl [α-bromo-(4-carboethoxy-1,2,3-thiadiazol-4-yl)carbinyl] ether (1.5 ml. of crude product obtained as residue upon removal of excess bromine and solvent) was dissolved in 10 ml. of 95% ethanol. Water was added dropwise to incipient cloudiness. *p*-Nitrophenylhydrazine (1.17 g.) and five drops of glacial acetic acid were added, and the resulting solution warmed on a steam bath for 10 minutes. Twenty ml. of water was added to the warm solution, which then was cooled in an ice bath. The brownish yellow *p*-nitrophenylhydrazone crystallized, and was collected by filtration and recrystallized from the minimal quantity of 95% ethanol; yield, 0.52 g., m.p. 225° (dec.).

The infrared spectrum contained bands at 3265 (N-H str.), 1705 (imine str.), 1600 (phenyl in-plane skeletal mode), 1540, 1485, 1325, 1270, 1110, 835, and 750 cm^{-1}.

Anal. Calcd. for $C_{12}H_{11}N_5O_4S$: C, 44.85; H, 3.45; N, 21.80; S, 9.98. Found: C, 44.95; H, 3.60; N, 21.19; S, 9.78.

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