2-Sulfanilamido-5-methoxy-1,3,4-thiadiazole and Related Compounds

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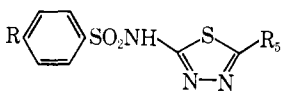
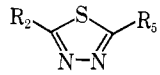
A series of 2,5-disubstituted 1,3,4-thiadiazoles was prepared and converted to benzenesulfonamido derivatives principally by nucleophilic substitution of methylsulfinyl and methylsulfonyl compounds. The antibacterial activity and solubility of the sulfanilamido-1,3,4-thiadiazoles are noted.

In view of the high intrinsic activity of 2-sulfanilamido-1,3,4-thiadiazole based upon blood level data,[1] the synthesis of 5-alkoxy derivatives was undertaken in the hope of applying the effect of alkoxy groups in other sulfa drugs[2-4] in obtaining a persistent, highly active, soluble sulfathiadiazole. The desired 2-sulfanilamido-5-methoxy-1,3,4-thiadiazole was obtained by two related routes which involved nucleophilic displacement of methylsulfonyl and methylsulfinyl groups from various thiadiazoles.

In the most satisfactory variation of our synthesis (Scheme I), 2-(*p*-nitrobenzenesulfonamido)-5-methylthio-1,3,4-thiadiazole (**1**) was prepared by sulfonylation of the amine **17** and then cleanly oxidized by chlorine[5] in aqueous methanol to 2-(*p*-nitrobenzenesulfonamido)-5-methylsulfonyl-1,3,4-thiadiazole (**2**). Reaction of **2** with sodium methoxide in methanol gave 2-(*p*-nitrobenzenesulfonamido)-5-methoxy-1,3,4-thiadiazole (**4**) from which 2-sulfanilamido-5-methoxy-1,3,4-thiadiazole (**5**) was obtained by reduction with





	R	R_5
1	NO_2	SCH_3
2	NO_2	SO_2CH_3
3	CH_3CONH	SCH_3
4	NO_2	OCH_3
5	NH_2	OCH_3
6	NH_2	SO_2CH_3
7	NH_2	$SOCH_3$
8	NH_2	SCH_3
9	NH_2	Br
10	NH_2	Thioxo

	R_2	R_5
11	CH_3S	SCH_3
12	CH_3SO_2	$SOCH_3$
13	CH_3SO_2	SO_2CH_3
14	CH_2SO	$SOCH_3$
15	C_2H_5S	OC_2H_5
16	$C_2H_5SO_2$	OC_2H_5
17	NH_2	SCH_3
18	NH_2	Br
19	CH_3CONH	OC_2H_5
20	$C_2H_5SO_2$	Oxo
21	CH_3S	Oxo

Raney nickel. In contrast to the methylsulfonyl group of **2**, the methylthio groups of **3** and **8** were inert to methoxide displacement (120°, 10 hr). Attempted oxidation of the methylthio group in 2-(*p*-acetamidobenzenesulfonamido)-5-methylthio-1,3,4-thiadiazole (**3**) gave a mixture of products.

A second synthesis of **5** was also investigated. Chlorine oxidation of 2,5-bis(methylthio)-1,3,4-thiadiazole (**11**) gave a mixture of three products: 50% of 2-methylsulfinyl-5-methylsulfonyl-1,3,4-thiadiazole (**12**), 25% of the expected 2,5-bis(methylsulfonyl)-1,3,4-thiadiazole (**13**), and 25% of 2,5-bis(methylsulfinyl)-1,3,4-thiadiazole (**14**). These products were separated by partition chromatography and identified by infrared and nmr spectroscopy and elemental analysis. Reaction of the mixture with sodium sulfanilamide in acetamide at 65° gave two new sulfanilamides in equal amounts, 2-sulfanilamido-5-methylsulfonyl-1,3,4-thiadiazole (**6**) and 2-sulfanilamido-5-methylsulfinyl-1,3,4-thiadiazole (**7**), which were separated by partition chromatography. Reaction of pure 2-methylsulfinyl-5-methylsulfonyl-1,3,4-thiadiazole (**12**) with sodium sulfanilamide gave a 4:3 mixture of **6** and **7**, estimated by paper chromatography. The sulfonamide **6** was also obtained by catalytic reduction of nitro compound **2**, which was a more convenient route. Methoxylation of the sulfanilamide **7** gave **5** which was identical with the sample prepared in the synthesis from the nitro analog **4**.

The facile nucleophilic displacements of a methylsulfinyl group in **7**, **12**, and **14** by either methoxide or sulfanilamide anion show that it is a good leaving group. There are only a few examples of the use of sulfinyl groups in nucleophilic substitution of aromatic compounds and only limited comparison of reactivity to that of other groups.[6] An estimate of the relative reactivity of a methylsulfonyl group *vs.* a methylsulfinyl group was made by comparing the rate of formation of the common product **5** from the reaction of both **6** and **7** with methoxide. The methylsulfinyl group was displaced somewhat faster than the methylsulfonyl group. In amination[7] of 2-substituted purines, methylsulfinyl was less easily displaced than a chloro group. In 1-substituted 2,4-dinitrobenzenes,[8] a 1-phenylsulfinyl group was as reactive toward amines as a chloro group[9] and somewhat more reactive than phenylsulfonyl in a kinetic comparison. Displacements of methylsulfonyl groups, such as in the reaction of **2**, **12**, and **13** with methoxide and sulfanilamide anion, have been more widely investigated.[10] Earlier related work[4,11]

(1) We are indebted to Mrs. N. H. Kuck of the Experimental Therapeutics Research Section for permission to quote her unpublished results showing that it is approximately four times as active as 2-sulfanilamidopyrimidine against a lethal infection of mice with *Diplococcus pneumoniae*, Type I, strain SVI, on the basis of concentrations in blood plasma.

(2) J. H. Clark, J. P. English, G. R. Jansen, H. W. Marson, M. M. Rogers, and W. E. Taft, *J. Am. Chem. Soc.*, **80**, 980 (1958).

(3) B. A. Koechlin, W. Kern, and R. Engelberg, *Antibiot. Med. Clin. Therapy*, **6** (suppl 1), 22 (1959).

(4) R. G. Shepherd, W. E. Taft, and H. M. Krazinski, *J. Org. Chem.*, **26**, 2764 (1961).

(5) C. W. Noell and R. K. Robins, *J. Am. Chem. Soc.*, **81**, 5997 (1959).

(6) The thiadiazoles **12–14** would not be good substrates for comparison of relative group reactivity since the two leaving groups are subject to unequal activation by the other substitutent present; *cf.* R. G. Shepherd and J. L. Fedrick in "Advances in Heterocyclic Chemistry," Vol. 4, A. R. Katritzky, Ed., Academic Press Inc., New York, N. Y., 1965, pp 211, 216, 251.

(7) R. M. Cresswell and G. B. Brown, *J. Org. Chem.*, **28**, 2560 (1963).

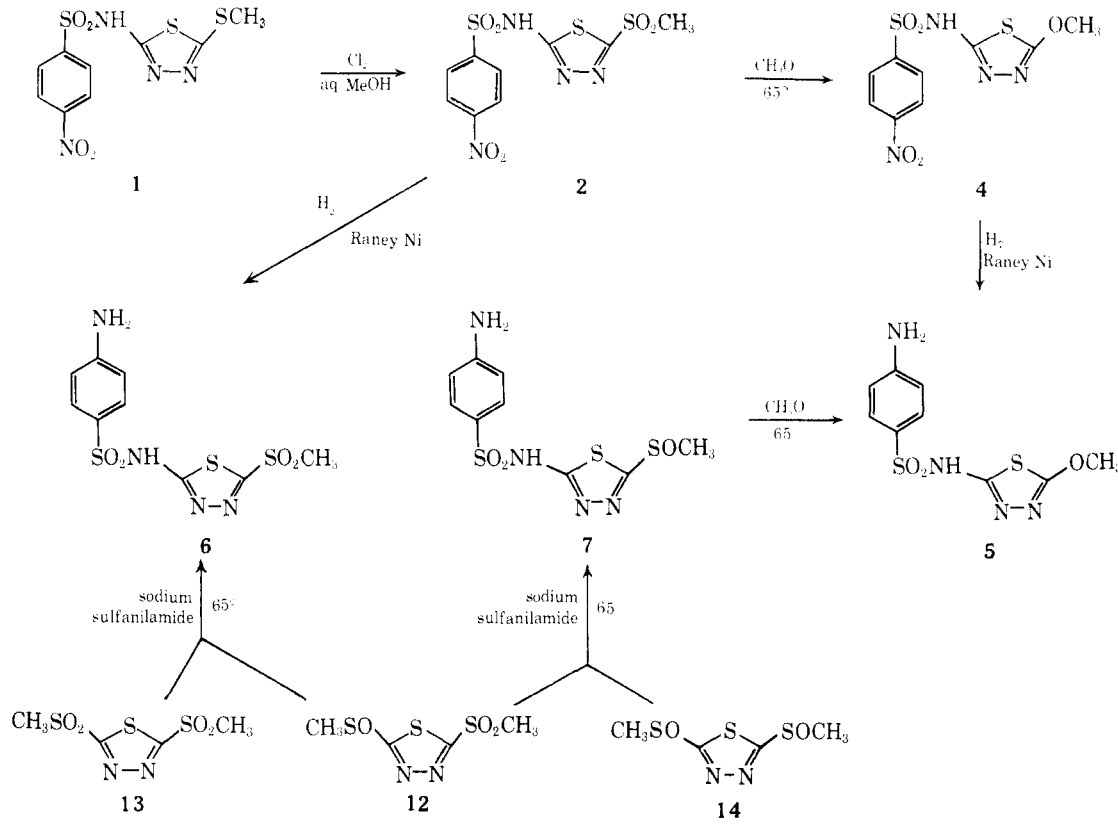
(8) J. F. Bunnett, E. W. Garbisch, Jr., and K. M. Pruitt, *J. Am. Chem. Soc.*, **79**, 385 (1957).

(9) 1-Phenylsulfinyl-2,4-dinitrobenzene is much more reactive than the 1-chloro analog toward thiophenoxide ion: J. F. Bunnett and W. D. Merritt, Jr., *ibid.*, **79**, 5967 (1957).

(10) For a summary of nucleophilic substitution of sulfonyl derivatives of azines, see ref 6, p 211.

(11) W. E. Taft and R. G. Shepherd, *J. Med. Pharm. Chem.*, **5**, 1335 (1962).

SCHEME I



showed that methylsulfonyl is a better leaving group than chloro in reactions of substituted pyrimidines with sulfanilamide anion.

A third variation of the synthesis was attempted. Oxidation of 5-ethoxy-2-ethylthio-1,3,4-thiadiazole (**15**) gave the corresponding 2-ethylsulfonyl compound **16**. In the reaction of **16** with sodium sulfanilamide, ethylation[12] of the sulfanilamide anion and displacement of both substituents on **16** apparently occurred at comparable rates, but more *slowly* than in the case of **12–14**. Dealkylation occurred to a considerably greater extent than methylthio displacement in attempted reaction of methylthio compound **11** with sulfanilamide anion.

During this work we briefly investigated a number of thiadiazole reactions in attempts to furnish the desired sulfonamide **5** or suitable thiadiazole intermediates. Acid-catalyzed exchange of methylthio groups for methoxy in **8**, **11**, or **17** did not occur at 65° (72 hr) or at 140° (24 hr) in methanol. Reaction of **3** and **17** with methoxide failed at 120° (10 hr). Even under meticulously anhydrous conditions (65°, 5 hr), the bis(methylthio) compound **11** with methoxide ion gave only the 5-oxo compounds **21** in good yield;[13] the latter was produced also by hydroxide ion as expected. The reaction (65°, 22 hr) of 2-amino-5-bromo-1,3,4-thiadiazole (**18**) with methoxide ion resulted in both ring cleavage and aminothiadiazolone formation.

Two alternative routes to **5**, requiring the unknown 5-bromo compound **9**, failed. Reaction of 2,5-dibromo-1,3,4-thiadiazole[14] with either sodium sulfanilamide or methoxide ion produced tar and ring-opened decomposition products even at low temperature. Coupling of *p*-nitrobenzenesulfonyl chloride with 2-amino-5-bromo-1,3,4-thiadiazole **18** in pyridine at 80° produced the sulfonamido derivative of 2-amino-5-pyridinium-1,3,4-thiadiazole (the predominant product at 20°). The 5-bromo displacement did not occur in the absence of the sulfonyl chloride, suggesting that this reagent provided electrophilic catalysis of the nucleophilic substitution of the 5-bromo group *via* a 3- (or 4-) sulfonylthiadiazolium ion. Similarly, electrophilic catalysis of nucleophilic substitution by chloride ion occurred on heating 2-amino-5-bromo-1,3,4-thiadiazole (**18**) with acid, resulting in the formation of the 5-chloro analog[14] instead of the desired 5-oxo compound.

Synthesis of 2-amino-5-ethoxy-1,3,4-thiadiazole by hydrolysis[15] of the acetylamino derivative **19** failed. Under both alkaline and acidic conditions,[16,17] decomposition occurred. No reaction occurred in attempting to sulfonylate the amide nitrogen of 2-acetamido-5-ethoxy-1,3,4-thiadiazole **19** by heating solutions of its anion in various solvents at 70–100° for several hours with *p*-nitrobenzenesulfonyl chloride.

After this work was completed, two independent reports appeared describing two different syntheses[16,18]

(12) This nucleophilic attack at the alkyl–oxygen bond and effects of structure and reaction temperature (only 70° in this instance) on such alkylation have been discussed[4] for pyridazines and pyrimidines. In the reaction of 3-methoxy-6-methylsulfonylpyridazine with sulfanilamide anion only a small amount of demethylation occurs.

(13) The reaction course is presumed to be formation of the 5-methoxy compound which is then demethylated by the methylmercaptide ion produced in the initial reaction step.

(14) R. Stollé and K. Fehrenbach, *J. Prakt. Chem.*, [2] **122**, 306 (1929).

(15) This work was carried out by Dr. A. S. Kende, of these laboratories; **19**, recently reported from acetylation of the amine,[18] was prepared by thermal cyclization of ethyl 3-(N-acetylthiocarbamyl)thionocarbazate and by refluxing ethyl 3-thiocarbamylthionocarbazate with acetic anhydride.

(16) E. Åkerblom and K. Skagius, *Acta Chem. Scand.*, **18**, 174 (1964).

(17) Instability of the amine to alkali and acid has recently been reported.[15]

(18) R. Clarkson, British Patents 916,061 (1963), 916,062 (1963); *Chem. Abstr.*, **59**, 1649*h*, 1650*c* (1963).

of 2-amino-5-alkoxy-1,3,4-thiadiazoles and their conversion[18] to the corresponding sulfanilamides *via* acetylsulfanilyl chloride.

Table I records the relative antibacterial activities and the solubilities at urinary pH of the 2-sulfanilamido-5-substituted 1,3,4-thiadiazoles prepared. Compounds **8** and **10** were prepared by condensation of the corresponding amines with acetylsulfanilyl chloride and hydrolysis.

TABLE I
2-SULFANILAMIDO-5-SUBSTITUTED 1,3,4-THIADIAZOLES

Compd	Solubility,[a] mg/100 ml	Relative activity[b] *S. aureus, in vivo*
5	125–250	1/4
6	500–1000	<1/4 i
7	500–1000	<1/4 i
8	125–250	1/32
10	125–250	<1/4 i

[a] Rough estimations[4] at 37° in 0.1 *M* acetate pH 6 buffer. [b] These data, supplied by G. S. Redin and E. McCoy of our Experimental Therapeutics Research Section, represent the approximate relative antibacterial activities of the compounds against a lethal infection with *S. aureus*, strain Smith, in mice based on comparisons of per cent survivals using graded (two-fold) doses given by single oral tubing (immediately after injection) with per cent survival produced by graded doses of standard (sulfadiazine) taken as unity. The symbol "<1/4 i" means that the compound was tested at only one level (approximately four times the median effective dose of sulfadiazine) and was found inactive at this level.

Experimental Section[19]

2-Amino-5-methylthio-1,3,4-thiadiazole (17) was prepared in 77% yield by methylation[20] of the 5-thione and recrystallized from ethanol (12 ml/g), mp 178.9–179.6° (lit.[20] 176–178°).

2-(*p*-Nitrobenzenesulfonamido)-5-methylthio-1,3,4-thiadiazole (1).—A solution of 9.5 g (0.042 mole) of *p*-nitrobenzenesulfonyl chloride in 10 ml of pyridine was added rapidly to a stirred, ice-cooled slurry of 5.86 g (0.04 mole) of **17** in 10 ml of pyridine. The ice bath was removed and the reaction became mildly exothermic for about 1 hr. After 17 hr at 25°, the mixture was heated for 0.5 hr on a steam bath. The excess pyridine was removed at the vacuum pump and the residue was taken up in 130 ml of water. Neutralization with acetic acid to pH 4 gave a crude solid which was reprecipitated from 200 ml of dilute alkali by acidification. Recrystallization from ethanol (100 ml/g), using charcoal, gave a tan solid, 7.4 g (53%), mp 221.2–223.8° dec; R_f 0.69 (quenching); infrared maxima at 7.61, 7.71, 8.65 μ (sulfonamide SO_2 bands).

Anal. Calcd for $C_9H_8N_4O_4S_3$: C, 32.6; H, 2.4; N, 16.9; S, 29.0. Found: C, 32.9; H, 2.5; N, 16.9; S, 29.0.

2-(*p*-Nitrobenzenesulfonamido)-5-methylsulfonyl-1,3,4-thiadiazole (2).—A cooled suspension of 3.0 g (0.009 mole) of **1** in 75 ml of 80% aqueous methanol was treated[5] with a fast stream of Cl_2 for 2 hr at about 8°. The filtered solid weighed 3 g (91%), mp 194–201.3° dec, mixture melting point with starting material 189.7–196° dec. Paper chromatography showed a slight difference between the product (R_f 0.68) and starting material (R_f 0.72). The infrared spectrum showed introduction of sulfone absorptions at 7.52 and 8.72 μ in addition to sulfonamide SO_2 peaks at 7.64, 7.71, and 8.85 μ. The crude product was recrystallized from 35% aqueous ethanol (150 ml/g) several times to give material (50% yield) melting at 220.3–222.5°.

Anal. Calcd for $C_9H_8N_4O_6S_3$: C, 29.7; H, 2.2; N, 15.4; S, 26.4. Found: C, 29.8; H, 2.4; N, 15.4; S, 26.0.

When this oxidation was performed on 2-(*p*-acetamidobenzenesulfonamido)-5-methylthio-1,3,4-thiadiazole (**3**), rapid dissolution occurred and a complex mixture of products was noted [R_f values 0.4, 0.53 (starting material, faint), 0.68, 0.74, and 0.84]. Only gums were isolated and not further characterized.

2-(*p*-Nitrobenzenesulfonamido)-5-methoxy-1,3,4-thiadiazole (4).—A methanolic solution of 135 mg (0.0025 mole) of freshly prepared sodium methoxide (5 ml) was added to 0.455 g (0.00125 mole) of **2** and the solution was refluxed for 3.5 hr. Paper chromatography revealed only one component [R_f 0.65, indistinguishable from starting material (R_f 0.65)]. The reaction mixture was cooled and acidified to pH 4.8 with glacial acetic acid and then evaporated to a small volume. Addition of 5 ml of cold water precipitated a yellow solid (0.21 g, 53%), mp 190–194° dec, which depressed the melting point of **2** to 183–187°. New infrared maxima at 6.2, 7.2, 7.8, and 10.5 μ and disappearance of the sulfone bands distinguished this product from starting material. Although this product was analytically pure, material identical in infrared spectrum but having a higher melting point (206.5–209.1°, lit.[18] 192–195°) was obtained in 50% yield from a subsequent experiment.

Anal. Calcd for $C_9H_8N_4O_5S_2$: C, 34.2; H, 2.6; N, 17.7; S, 20.3; OCH_3, 4.8. Found: C, 34.0; H, 2.4; N, 17.3; S, 19.9; OCH_3, 4.4.

2-Sulfanilamido-5-methoxy-1,3,4-thiadiazole (5).—A slurry of 0.7 g of wet Raney nickel in 120 ml of a solution of 1.4 g (0.00442 mole) of **4** in acetone was shaken under 2 kg/cm^2 (2 atm) of hydrogen for 22 hr (86% of the theoretical hydrogen uptake). The filtrate was evaporated nearly to dryness and allowed to crystallize in the cold. The off-white crystals (0.94 g, 74%) melted at 164.5–170.5°, and had R_f 0.77 in an 18:1:1:16 BuOH–AcOH–NH_4OH–H_2O system (sulfanilamide R_f 0.52). Recrystallization from 1:1 methanol–water (14 ml/g) gave product (55%) with mp 172.6–174.5° (lit.[18] 181–182°), NH_2 doublet at 2.83 and 2.92 μ.

Anal. Calcd for $C_9H_{10}N_4O_3S_2$: C, 37.8; H, 3.5; N, 19.6; S, 22.4; OCH_3, 5.3. Found: C, 38.1; H, 3.7; N, 19.6; S, 22.4; OCH_3, 5.2.

2-(*p*-Acetamidobenzenesulfonamido)-5-methylthio-1,3,4-thiadiazole (3).—Acetylsulfanilyl chloride (4.90 g, 0.021 mole) was added in several portions to a slurry of 2.94 g (0.02 mole) of **17** in 10 ml of dry pyridine. The reaction mixture was stirred and cooled until most of the solids dissolved (15 min), then briefly heated to 46° to dissolve the remaining solids, and stirred overnight at room temperature. The solution was heated at 65–70° for 0.5 hr and the pyridine was removed at the vacuum pump. The gummy residue was triturated with several milliliters of hot methanol giving tan solid. This was recrystallized from 30 ml of boiling ethanol (0.3 g of charcoal), giving 4.1 g (60%) of off-white solid, mp 188.1–189° (lit.[21] 218°), R_f 0.56 (quenching).

Anal. Calcd for $C_{11}H_{13}N_4O_3S_3$: C, 38.4; H, 3.5; N, 16.3; S, 28.0. Found: C, 38.3; H, 3.5; N, 16.1; S, 27.4.

2-Sulfanilamido-5-methylthio-1,3,4-thiadiazole (8).—A slurry of 1 g of **3** in 30 ml of 2 *N* HCl was boiled for 15 min. The resulting solution was treated with 50 mg of charcoal and the cooled filtrate was added to a solution of 10 g of sodium acetate in 40 ml of water. The suspension formed was stirred for 15 min, giving product (0.82 g, 88%) with mp 206.5–207.5° and R_f 0.39 (arylamine). Recrystallization from 75% aqueous ethanol (20 ml/g) using charcoal gave a 68% recovery of material melting at 209.7–210.7 (lit.[21] 198°); infrared maxima at 7.86 and 8.84 μ (SO_2 stretching doublet).

Anal. Calcd for $C_9H_{10}N_4O_2S_3$: C, 35.8; H, 3.3; N, 18.5; S, 31.8. Found: C, 35.8; H, 3.7; N, 18.7; S, 31.6.

2,5-Bis(methylthio)-1,3,4-thiadiazole (11) was prepared in 43% yield, bp 102–105° (0.15 mm), $n^{23.5}$D 1.6559 (lit.[22] 1.6530), by methylation of 2-mercapto-1,3,4-thiadiazole-5-thione.

Oxidation of 2,5-Bis(methylthio)-1,3,4-thiadiazole (11) to Form 12, 13, and 14.—Chlorine gas was bubbled for 2 hr into a cooled, stirred solution of 21 g (0.118 mole) of 2,5-bis(methylthio)-1,3,4-thiadiazole in 210 ml of 70% aqueous methanol. During this time the temperature rose from 10 to 20° and dropped slowly to 10°. The white precipitate (20 g, 67% yield, mp 130.3–134.7°) was recrystallized twice from methanol (30 ml/g) to give 14.5 g of material with mp 137.3–144.6°. This material was chromatographed using a cyclohexane–dioxane–water (40:60:8) partition system: three components at hold-back volumes (hbv) of 1, 2, and 4, respectively, in a ratio of 1:2:1 were ob-

(19) Melting points are corrected. R_f values were obtained in a 9:1:8 butanol–ammonia–water descending paper chromatographic system unless otherwise noted. Spots were detected by ultraviolet quenching and arylamine visualization.[4]

(20) G. Pala, *Farmaco* (Pavia), *Ed. Sci.*, **13**, 650 (1958); *Chem. Abstr.*, **53**, 18947c (1959).

(21) P. C. Guha and D. B. Das-Gupta, *J. Indian Chem. Soc.*, **22**, 79 (1945). The melting points of **3** and **8** may be reversed in this reference, and therefore our experimental details are given.

(22) G. D. Thorn, *Can. J. Chem.*, **38**, 1439 (1960).

served by ultraviolet monitoring of the effluent. The column cuts were evaporated to small volumes and cooled to collect products which were recrystallized from methanol. In this manner the following compounds were obtained.

(a) **2,5-Bis(methylsulfonyl)-1,3,4-thiadiazole (13):** hbv 1; mp 176.8–178.5°; infrared maxima at 7.50 and 8.70 (sulfone stretching doublet) and 10.36, 12.76, 13.1 μ; nmr τ 6.20 (in DMSO-d_6). By cooling the original filtrate, an additional 3.5% yield of this component was obtained.

Anal. Calcd for $C_4H_6N_2O_4S_3$: C, 19.7; H, 2.5; N, 11.6; S, 39.7. Found: C, 20.1; H, 2.8; N, 11.5; S, 39.6.

(b) **2-Methylsulfinyl-5-methylsulfonyl-1,3,4-thiadiazole (12):** hbv 2; mp 151.3–153.4°; infrared sulfone doublet (7.55 and 8.55 μ), sulfoxide band (9.42 μ), others at 9.07, 10.4 and 12.8 μ; nmr equal singlets at τ 6.24 (CH_3SO_2) and 6.68 (CH_3SO).

Anal. Calcd for $C_4H_6N_2O_3S_3$: C, 21.3; H, 2.7; N, 12.4; S, 42.5. Found: C, 21.5; H, 3.0; N, 12.5; S, 42.2.

(c) **2,5-Bis(methylsulfinyl)-1,3,4-thiadiazole (14):** hbv 4; mp 161.5–163.5°; no sulfonyl bands in the infrared but strong maxima at 9.46 (sulfoxide stretching) and at 7.22, 7.68, 9.2, 9.56, 10.32 μ; nmr τ 6.71 singlet.

Anal. Calcd for $C_4H_6N_2O_2S_3$: C, 22.8; H, 2.9; N, 13.3. Found: C, 23.2; H, 2.6; N, 13.0.

Reaction of 12, 13, and 14 Mixture with Sodium Sulfanilamide.—A mixture of 4.1 g (0.021 mole) of sodium sulfanilamide and 6.0 g of acetamide was heated to 100° to effect solution and cooled to 60°. Then 2.42 g (0.01 mole) of the mixture of thiadiazoles **12**, **13**, and **14** described above was added. A solution quickly resulted and the reaction was held at 55–60° for 1 hr. Paper chromatography showed arylamines at R_f 0.26 and 0.36 in equal amounts, unchanged sulfanilamide (R_f 0.57) and a trace component at R_f 0.10. After adding 50 ml of water and cooling, the solution was adjusted to pH 6.5 with concentrated HCl. Continued stirring for 45 min precipitated unchanged sulfanilamide. The filtrate was adjusted to pH 2.8 precipitating a gum, which was crystallized by trituration with ethanol to yield 1.3 g (41%) of tan solid, which contained approximately equal amounts of 2-sulfanilamido-5-methylsulfonyl-1,3,4-thiadiazole (R_f 0.36) and 2-sulfanilamido-5-methylsulfinyl-1,3,4-thiadiazole (R_f 0.26) by chromatography. Partition chromatography of the crude product containing some sulfanilamide in a heptane–ethyl acetate–methanol–water system separated the following sulfonamides.

(a) **2-Sulfanilamido-5-methylsulfinyl-1,3,4-thiadiazole (7):** R_f 0.26; mp 208.7–209.7° dec; infrared maxima at 7.71 and 8.81 (SO_2 stretching doublet) and at 9.46 μ (sulfoxide stretching).

Anal. Calcd for $C_9H_{10}N_4O_3S_3$: C, 34.0; H, 3.2; N, 17.6; S, 30.2. Found: C, 34.0; H, 3.1; N, 17.7; S, 30.3.

(b) **2-Sulfanilamido-5-methylsulfonyl-1,3,4-thiadiazole (6):** R_f 0.36; mp 213–214°; identical in infrared spectrum (7.69 and 8.83 sulfonamide SO_2 stretching and 7.52 and 8.70 μ sulfone SO_2 stretching doublets) and paper chromatographic R_f to a sample prepared from **2** by reduction.

A mixture of 0.41 g (1.1 mmoles) of sodium sulfanilamide and 0.6 g of acetamide was melted and cooled to 70°. Pure **12** (0.226 g, 1 mmole) was added and the mixture was kept at 70° for 1 hr. Paper chromatography of an aliquot of the reaction removed at this time, spotted alongside of **6** and **7** for reference showed formation of **6** and **7** in a ratio of 4:3.

2-Sulfanilamido-5-methylsulfonyl-1,3,4-thiadiazole (6) by Reduction of 2.—Raney nickel catalyst (0.8 g) was added to a solution of 0.3 g (8.25 mmoles) of 2-(*p*-nitrobenzenesulfonamido)-5-methylsulfonyl-1,3,4-thiadiazole (**2**) in 50 ml of acetone containing 0.6 ml of acetic acid. The pH 4.5 solution was shaken under 2 kg/cm^2 of hydrogen for 23 hr (75% of theoretical uptake). The filtrate was evaporated to a small volume and a crystalline slurry was produced by addition of 5 ml of water and cooling. The off-white solid (0.098 g, 40%) was identical in infrared spectrum and R_f with the compound isolated from the above displacement reaction. Recrystallization from 1:1 ethanol–water (100 ml/g) raised the melting point 222.9–224.9°.

Anal. Calcd for $C_9H_{14}N_4O_4S_3$: C, 32.4; H, 3.0; N, 16.8; S, 28.8. Found: C, 32.8; H, 3.1; N, 16.6; S, 29.1.

Synthesis of 5 from 2-Sulfanilamido-5-methylsulfinyl-1,3,4-thiadiazole (7) and Sodium Methoxide.—A solution of 0.0696 g (0.2 mmole) of **7** in 0.667 ml (0.6 mmole) of 0.91 *M* methanolic sodium methoxide was gently refluxed for 1.6 hr. Paper chromatography showed a gradual transformation of the starting material (R_f 0.24) to a new arylamine (R_f 0.35) with about 75% conversion at 1.6 hr. The new product was isolated by evaporation to dryness and addition of 1 *N* HCl to the residue. A white solid was obtained in 78% yield which was identical with sulfonamide **5** in the infrared spectrum and R_f in two systems (R_f 0.35 in 9:1:8 BuOH–NH_4OH–H_2O, R_f 0.77 in 18:1:1:16 BuOH–AcOH–NH_4OH–H_2O).

Comparison of Reactivity of 6 and 7.—Solutions of either 3.2 mg (0.01 mmole) of **6** or **7** in 2 ml of dry methanol containing 0.09 mmole of sodium methoxide were refluxed for 72 hr. After thin layer chromatography (silica gel, 2:1 chloroform–methanol), the spots of **6**, **7**, and **5** in aliquots were detected as before.[4,19] After 24 hr about 25% of sulfone **6** and about 35% of sulfoxide **7** had been converted to the common product **5**, and at 72 hr about 50% conversion of **6** and 65% conversion of **7** was observed.

2-Ethylthio-5-ethoxy-1,3,4-thiadiazole (15) was made by the method of Sandström,[23] bp 98–101° (1.5 mm) [lit.[9] 100° (4 mm)].

2-Ethoxy-5-ethylsulfonyl-1,3,4-thiadiazole (16).—Chlorine was bubbled slowly into a well-stirred solution of 2 g (10.5 mmoles) of **15** in 100 ml of 80% aqueous methanol at 0–5° for 0.75 hr. The solution was evaporated to a syrup which was dissolved in about 100 ml of ether. The ether was washed with 10 ml water and dried (Na_2SO_4). Evaporation gave 1.5 g (65%) off-white product, which was recrystallized from 1:1 ethanol–hexane (8 ml/g), mp 51.7–52.7° (30% yield); infrared sulfone maxima at 7.55 and 8.7 μ.

Anal. Calcd for $C_6H_{10}N_2O_3S_2$: C, 32.5; H, 4.5; N, 12.6; S, 28.9. Found: C, 32.7; H, 4.5; N, 12.9; S, 28.9.

When this reaction was carried out at 15°, the ethoxy group was displaced and **2-ethylsulfonyl-1,3,4-thiadiazol-5-one**[24] **(20)** (mp 96.6–97.6° from 100 ml of benzene) was formed. Infrared maxima were present at 5.85 (C=O), 3.0 (NH), and 7.5 and 8.5 μ (sulfone doublet).

Reaction of Sodium Sulfanilamide with 2-Ethylsulfonyl-5-ethoxy-1,3,4-thiadiazole.—A mixture of 0.5 g of acetamide and 0.174 g (0.90 mmole) of sodium sulfanilamide was heated and the melt was cooled to 70° and 0.100 g (0.45 mmole) of **16** was added. Reaction at 70° for 5 and 20 min and at 80° for 1 hr produced a mixture [R_f 0.10 (10%), 0.37 (10%), 0.57 (70%, sulfanilamide), 0.86 (5%), 0.93 (5%) after 1 hr at 80°] of products from which no pure material was isolated. Apparently displacement of both substituents (products, R_f 0.10, 0.37) and deethylation[4,12] of the ethoxy group (ethylated sulfanilamide, R_f 0.86, 0.93) took place at comparable rates.

2-Sulfanilamido-1,3,4-thiadiazole-5-thione (10).—A slurry of 0.7 g (2.11 mmoles) of 2-(*p*-acetamidobenzenesulfonamido)-1,3,4-thiadiazole-5-thione[25] in 5 ml of concentrated HCl and 25 ml of ethanol was heated at reflux for 20 min. The resulting solution was evaporated to a small volume and diluted with 20 ml of water. After cooling for 1 hr, the slurry was filtered to give 0.5 g (90%) of product, mp 216.2–216.5° dec, R_f 0.05 (arylamine), whose infrared spectrum did not show the NAc band at 5.98 μ present in starting material. Recrystallization from 1:1 ethanol–water (35 ml/g) gave analytical material (70% yield), mp 220.3–221° dec, lit.[26] mp 210°.

Anal. Calcd for $C_3H_2N_4O_2S_3$: C, 33.3; H, 2.8; N, 19.4; S, 33.4. Found: C, 33.8; H, 3.0; N, 19.5; S, 33.1.

2-Methylthio-1,3,4-thiadiazol-5-one (21).—A solution of 0.565 g (0.0032 mole) of 2,5-bismethylthio compound **11** was prepared in 5 ml of methanolic sodium methoxide [freshly prepared from 0.1455 g (0.00634 g-atom) of sodium and methanol distilled into the flask from Mg]. An aliquot removed after 5.5 hr of refluxing showed a single new spot (R_f 0.81) in the 0.5% Na_2CO_3 paper chromatography system and no starting material at R_f 0.68. About 80% conversion was calculated from the extinction coefficient of the pure compound at 262 mμ. The reaction mixture was vacuum evaporated to dryness and from the white residue of sodium salt neutral **21** was obtained in 30% yield by dissolving in 5 vol of cold water and acidifying to pH 5 with glacial acetic acid. The product was recrystallized from boiling hexane (18 ml/g) to give white needles (25% yield): mp 95.7–

(23) J. Sandström, *Arkiv Kemi*, **4**, 305 (1952).

(24) *Anal.* Calcd for $C_4H_6N_2O_3S_2$: C, 24.7; H, 3.0; N, 14.4; S, 32.6. Found: C, 25.1; H, 3.2; N, 14.8; S, 32.6.

(25) This compound, mp 243–244° dec and R_f 0.12, was made by condensation of 2-amino-1,3,4-thiadiazole-5-thione with acetylsulfanilyl chloride in pyridine; lit.[26] mp 188°.

(26) K. Dostal, K. Kolbach, and B. Stavric [*Acta Pharm. Jugoslav.*, **9**, 81 (1959); *Chem. Abstr.*, **59**, 11493*b* (1963)] disclosed these compounds after our work was completed.

96.0° (lit.[27] mp 96–97°); R_f 0.81; infrared maxima at 2.9–3.2 (NH), 6.15 μ (C=O in the thiadiazolone); nmr, $CDCl_3$ at τ −0.1 (NH bonded) and 7.38 (SCH_3) with relative weight 1:3; λ_{max}^{MeOH} 262 mμ (ϵ 6430), $\lambda_{max}^{0.1NNaOH}$ 278 mμ (ϵ 6970).

Anal. Calcd for $C_3H_3N_2OS_2$: C, 24.3; H, 2.7; N, 19.0; S, 43.3. Found: C, 24.6; H, 2.7; N, 19.1; S, 43.4.

Refluxing 1 hr with 2 moles of KOH in methanol gave the identical product in similar yield. When refluxed with 0.1 equiv of methoxide in methanol, mostly starting material was left after 12 hr by paper chromatography.

2-Amino-5-chloro-1,3,4-thiadiazole.—Heating 2-amino-5-bromo-1,3,4-thiadiazole[28] (**18**) on the steam bath with excess concentrated HCl for 15 hr caused disappearance of infrared absorption at 9.75 μ and appearance of strong absorption at 9.15 μ. Differential halogen analysis of the isolated material demonstrated conversion to 2-amino-5-chloro-1,3,4-thiadiazole:[14] 0.80 g-atom of chlorine and 0.21 g-atom of bromine. The bromo compound was unchanged after 0.5 hr, at 20° or by refluxing 2 *N* ethanolic HCl for 1 hr.

Reaction of 2-Amino-5-bromo-1,3,4-thiadiazole with *p*-Nitrobenzenesulfonyl Chloride.—A solution of 0.222 g (0.001 mole) of *p*-nitrobenzenesulfonyl chloride in 1 ml of dry pyridine added rapidly to a slurry of 0.180 g (0.001 mole) of 2-amino-5-bromo-1,3,4-thiadiazole[23] (**18**) in 1 ml of pyridine gave a slight exotherm and heavy precipitation. An additional 3 ml of dry pyridine was added and the mixture was stirred for 2 hr. The yellow product (0.25 g, mp 222–226.5° dec) was very soluble in water, insoluble in ether, and gave a positive silver nitrate test. Elemental analyses (C, 35.2; H, 3.2; N, 20.3; S, 12.4; ionic Br, 28.7) and the infrared spectrum (NH_2, 3.05, 3.20 μ; NO_2, 6.5, 7.4 μ) suggested that this product was 1-(2-aminothiadiazol-5-yl)pyridinium bromide containing about 25% of the corresponding sulfonylated product. 2-Amino-5-bromo-1,3,4-thiadiazole was recovered unchanged from pyridine after 24 hr at 25° in the absence of the sulfonyl chloride.

Complete sulfonylation was achieved by running the reaction[29] at 80° for 20 min (negative Bratton–Marshall test for starting amine). The yellow product (67%, mp 250–253° dec) was isolated as the chloride by pouring the reaction mixture into 3 *N* HCl. A pyridinium moiety was indicated by the analyses below and by the formation of a red precipitate (mp 165°) of a glutacondialdehyde anil[30] from acidification of its solution in alkali. Recrystallization from glacial acetic acid gave a halogen-free light yellow solid (mp 290°) whose analysis agreed with the 1-[2-(*p*-nitrobenzenesulfonamido)-1,3,4-thiadiazol-5-yl]pyridinium zwitterion (sulfonamide anion). Characteristic infrared bonds were present at 6.15, 6.25, 6.65, 7.0, 7.4, 9.25, 10.6, 12.8, 14.45 (pyridine, N-pyridinium), 6.52, 7.43 (NO_2), 7.72, 8.66 (sulfonamide SO_2), 11.63, 13.55 μ (*para*-substituted phenyl).

Anal. Calcd for $C_{13}H_9N_5O_4S_2$: C, 43.0; H, 2.5; N, 19.3. Found: C, 42.4; H, 2.6; N, 19.3.

Acknowledgments.—We thank Mr. W. Fulmor and staff for nmr spectra, Mr. L. Brancone and staff for microanalyses, and Mr. C. Pidacks and staff for partition chromatographic separations.

(27) P. C. Guha and S. C. Guha, *Quart. J. Indian Chem. Soc.*, **4**, 239 (1927).

(28) Prepared by R. B. Angier, J. Semb, and K. Cyr (132nd National Meeting of the American Chemical Society, New York, N. Y., Sept 1957, p 31-O) from 2-amino-1,3,4-thiadiazole and bromine in acetic acid, mp 180–181°.

(29) Carried out by Dr. J. L. Fedrick, of these laboratories.

(30) T. Zincke, *Ann. Chem.*, **330**, 367 (1904).

Novel Broad-Spectrum Anthelmintics. Tetramisole[1] and Related Derivatives of 6-Arylimidazo[2,1-*b*]thiazole

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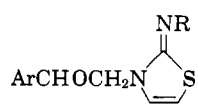
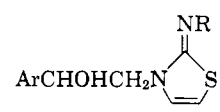
In a critical screening test in chickens, 2-acetylimino-3-[2-hydroxy-2-(2-thienyl)ethyl]thiazoline (IV, thiazothienol) was found to be active against heterakids, ascarids, and capillarids. IV was also active against various nematodes in sheep, but not in rats or in mice. In chickens and in sheep, but not in mice or in rats, IV undergoes metabolic ring closure to 5,6-dihydro-6-(2-thienyl)imidazo[2,1-*b*]thiazole (VII, thiazothielite), which is active as an anthelmintic in all four species. A large series of imidazothiazole derivatives related to VII were prepared and screened. From these studies emerged tetramisole (XII), the stable, water-soluble hydrochloride of 2,3,5,6-tetrahydro-6-phenylimidazo[2,1-*b*]thiazole, as the most promising novel broad-spectrum anthelmintic of the series. Tetramisole is active at low, atoxic oral and parenteral dose levels against all adult and immature gastrointestinal and pulmonary nematodes tested in 14 different hosts.

The purpose of this paper is to describe briefly the experiments which led to the discovery of tetramisole, a novel broad-spectrum anthelmintic.[1]

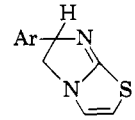
The first relevant experiments involved the synthesis of new derivatives of 2-aminothiazole as potential anthelmintics. The condensation of a bromomethyl aryl ketone with 2-aminothiazole proceeded easily to give the hydrobromide of a 3-aroylmethyl-2-iminothiazoline (Ia)[2–4] (Table I). Acylation of Ia with acetic anhydride in the presence of pyridine gave the corresponding 3-aroylmethyl-2-acetyliminothiazoline (Ib)



Ia, R = H
b, R = $COCH_3$



IIa, R = H
b, R = $COCH_3$



III

(Table I), which was reduced to the racemic 2-acetylimino-3-(2-hydroxyarylethyl)thiazoline (IIb) with sodium borohydride at reflux temperature (Table II). The imino ketones Ia were similarly reduced, preferably at lower temperature, to the imino alcohols IIa (Table II). These four reactions proceeded in high yield and without unexpected preparative difficulties.

In a routine critical screening test for anthelmintic activity in naturally infected chickens, one of these

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