4-Hydroxy-7-(β-carboxyethyl)pyrrolo[2,3-*d*]pyrimidines.—One and one-half grams of the appropriate 4-chloropyrrolopyrimidine ethyl acrylate adduct was refluxed for 3 hr. in 60 ml. of 3.0 *N* hydrochloric acid. The solution was taken to dryness with water pump vacuum in a 60° water bath. The residues were triturated with 5 ml. of water, filtered, and recrystallized from ethanol yielding 0.7–0.8 g. of the desired products. The 4-hydroxy-7-carboxylic compound (referred to as compound C) was compared to its isomer, compound B, for structural proof.

4-Benzylamino-7-(β-cyanoethyl)pyrrolo[2,3-*d*]pyrimidines.—To 0.0113 mole of the appropriate 4-chloro-7-cyanoethyl derivative in 75 ml. of water containing 0.0115 mole (1.6 g.) of anhydrous potassium carbonate was added 0.0123 mole of benzylamine. After heating at slow reflux for 3 hr., the suspension was chilled and the solid was taken up in 200 ml. of ether and dried overnight over anhydrous sodium sulfate. Addition of an equal volume of pentane to the filtered ethereal solutions yielded the pure desired compounds.

4-Benzylamino-7-(β-carbethoxyethyl)pyrrolo[2,3-*d*]pyrimidines.—To 0.0113 mole of the appropriate chloro ester adduct in 100 ml. of absolute ethanol was added 0.034 mole of benzylamine and then heated at 130° for 3 hr. in sealed containers. The solvent was driven off and the thick oils were taken up in ether and dried over anhydrous sodium sulfate. (Paper chromatography on these solutions revealed only one component present.) Addition of pentane to the filtered ethereal solutions gave gums which resisted all attempts to crystallize. They were used as such in the reductions described later. They also were hydrolyzed to the carboxylic acids by the method described earlier for the alkaline hydrolysis of the 4-chloro adducts except that the pH was adjusted carefully to 3.5 for maximum recovery. These 4-benzylamino-7-carboxylic acids also may be prepared as described subsequently.

4-Benzylamino-7-(β-carboxyethyl)pyrrolo[2,3-*d*]pyrimidines.—These may be prepared likewise by the reaction of the 4-chloropyrrolopyrimidine–ethyl acrylate adducts using water as solvent and potassium carbonate with benzylamine as described before for the 4-benzylamino-7-(β-cyanoethyl)-compounds. They may be prepared also by similarly treating the 4-chloro-7-carboxylic acids with aqueous benzylamine and potassium carbonate. These compounds precipitate maximally at pH 3.5–3.8.

4-Benzylamino-7-(γ-hydroxypropyl and γ-aminopropyl)pyrrolo-[2,3-*d*]pyrimidines.—To rapidly stirred suspensions of 0.01 mole (0.38 g.) of lithium aluminum hydride in 300 ml. of anhydrous ether was added, dropwise over 20 min., 0.009 mole of the appropriate 4-benzylamino-7-β-carbethoxy or -β-cyanoethyl compound in 70 ml. of anhydrous ether. After stirring at room temperature for 0.5 hr. longer, 1.0 ml. of water was added dropwise to the vigorously stirred mixtures, followed by 2 ml. of a 25% aqueous sodium hydroxide solution, and finally 2 ml. more of water. After 30 min. of vigorous stirring, the inorganic materials were filtered off and extracted twice with 100 ml. of anhydrous sodium sulfate. The products were best obtained pure as monohydrochlorides by the addition of a slight excess (5–10%) of an ethanolic solution of hydrogen chloride to the previously filtered ethereal solutions and allowing them to stand overnight at room temperature.

Acknowledgment.—The author thanks Miss Lilia Beauchamp for her technical assistance and Dr. S. Blackman and Mrs. R. Purdey for their microanalytical contributions.

Synthesis and Reactions of Some 1,2,4-Pyrimido[4,5-*e*]thiadiazine 1,1-Dioxides[1]

H. M. GILOW AND JOHN JACOBUS[2]

Chemistry Department, Southwestern at Memphis, Memphis 12, Tennessee

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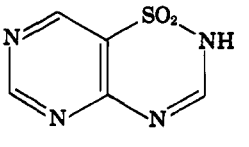
Synthesis of 5,7-dimethyl-1,2,4-pyrimido[4,5-*e*]thiadiazine-6,8-dione 1,1-dioxide and 8-amino-6-methylthio-1,2,4-pyrimido[4,5-*e*]thiadiazine 1,1-dioxide was effected by the cyclization of the corresponding 4-amino-5-pyrimidinesulfonamides with ethyl orthoformate. N-Alkylation of 5,7-dimethyl-1,2,4-pyrimido[4,5-*e*]thiadiazine-6,8-dione 1,1-dioxide was observed giving evidence that the double bond is localized in the 3,4-position. Various reactions of the 1,2,4-pyrimido[4,5-*e*]thiadiazine 1,1-dioxides are reported together with the preparation and reactions of some 5-pyrimidinesulfonic acids and their derivatives.

As a part of the intensive current effort to find more effective anticancer agents, considerable attention has been given to the fields of pyrimidine and purine chemistry in a search for potential antimetabolites of the naturally occurring pyrimidines and purines involved in biosyntheses. A large number of pyrimidine and purine derivatives containing sulfur have been reported and also tested for anticancer properties. 6-Mercaptopurine is one of the more effective of this group.[3] It is felt that pyrimidine and purine derivatives containing sulfur in some of its higher oxidation states have been neglected. The first synthesis of a purinesulfonamide was described recently by Beaman and Robins.[4] Kromov-Borisov and Karlinskaya[5] have shown that derivatives of pyrimidine-5-sulfonic acids display antileukemic activity. This prompted us to prepare various purine and pyrimidine derivatives containing sulfonic acid and sulfonamide groups so that their anticancer properties could be evaluated.

Two examples of a 1,2,4-thiadiazine 1,1-dioxide ring system fused to a heterocyclic system have been reported. Blicke and Lee[6] reported the fusion of this system to an imidazole ring while Yale, Losee, and Bernstein[7] have fused it to a pyridine ring. If the 1,2,4-thiadiazine 1,1-dioxide ring system also could be fused to a pyrimidine ring, two general types of derivatives could be formed (**1** and **2**).[8]



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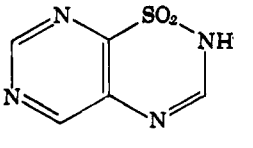

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(1) This investigation was supported by the National Cancer Institute, National Institutes of Health, contract no. CY-5252.

(2) Undergraduate Research Participant supported by a grant, NSF G-12070, from the National Science Foundation.

(3) H. E. Skipper, J. A. Montgomery, J. R. Thomson, and F. M. Schabel Jr., *Cancer Res.*, **19**, No. 4, 425 (1959).

(4) A. G. Beaman and R. K. Robins, *J. Am. Chem. Soc.*, **83**, 4038 (1961).

(5) N. V. Khromov-Borisov and R. L. Karlinskaya, *Zh. Obschch. Khim.*, **24**, 2212 (1954); *Chem. Abstr.*, **50**, 355 (1956).

(6) F. F. Blicke and C.-M. Lee, *J. Org. Chem.*, **26**, 1861 (1961).

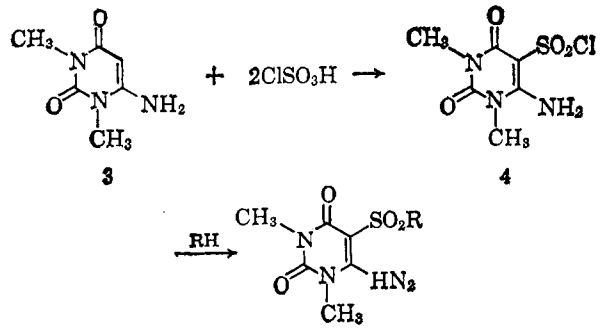
(7) H. L. Yale, K. Losee, and J. Bernstein, *J. Am. Chem. Soc.*, **82**, 2044 (1960).

(8) It has been shown by F. C. Novello, *et al.*, (ref. 15), Ekbom [*Bih. Svensk Velenskakad Handl.*, **27**, II, 3 (1902)], and H. L. Yale and J. T. Sheehan (ref. 14) that the 1,2,4-thiadiazine 1,1-dioxide system exists as a tautomeric equilibrium in which the hydrogen resides on either the 2- or 4-position. This would indicate that I and II also might exist as a tautomeric equilibrium; however, for simplicity only one of the tautomers is shown in each case.

The preparation of derivatives of **1** has been accomplished and will be reported here.

In order to obtain derivatives of **1** it appeared that the easiest approach would be the cyclization of some 4-amino-5-pyrimidinesulfonamides. Direct introduction of a sulfonyl chloride group in the 5-position of various pyrimidines has been reported by numerous authors.[5,9-12]

6-Amino-1,3-dimethyluracil (**3**) reacted with chlorosulfonic acid to form the relatively stable 5-sulfonyl chloride **4**. The 5-sulfonyl chloride **4** reacted with water, methanol, ammonia, methylamine, and ethylamine in a manner characteristic of sulfonyl chlorides to form **5**, **6**, **7**, **8**, and **9**, respectively.



3 **4**

5. R = OH
6. R = OCH_3
7. R = NH_2
8. R = $NHCH_3$
9. R = $NHCH_2CH_3$

Preparation of 5,7-dimethyl-1,2,4-pyrimido[4,5-*e*]-thiadiazine-6,8-dione 1,1-dioxide (**10**) and 2,5,7-trimethyl-1,2,4-pyrimido[4,5-*e*]thidiazine-6,8-dione 1,1-dioxide (**11**) was effected by heating **7** and **8**, respectively, in an excess of triethyl orthoformate or trimethyl orthoformate. Cyclization could not be effected when the sulfonamides were heated with formic acid or formaldehyde. It also has been observed by Freeman and Wagner[13] that triethyl orthoformate can bring about cyclization more readily than does formic acid. N - Ethyl - 6 - amino - 1,3 - dimethyl - 5 - pyrimidinesulfonamide (**9**), when treated with triethy lorthoformate, did not form the corresponding N-ethylthiadiazine **12**. Freeman and Wagner[13] and also Blicke and Lee[6] have observed similar difficulty in cyclization of N-alkylsulfamoyls.

When the cyclization reactions were run at higher temperatures both cyclization and N-alkylation of the thiadiazine nucleus occurred. For example, when **7** was heated with triethyl orthoformate at 150° instead of the usual 120–130°, a 74% yield of 2-ethyl-5,7-dimethyl-1,2,4-pyrimido[4,5-*e*]thiadiazine-6,8-dione 1,1-dioxide (**12**) was formed. Similar treatment of **7** with trimethyl orthoformate yielded a 76% yield of 2,5,7-trimethyl-1,2,4-pyrimido[4,5-*e*]thiadiazine-6,8-dione 1,1-dioxide (**11**) together with a 15% yield of **10**. The fact that none of the 4-alkylthiadiazines was isolated in the reactions carried out and the relatively high yield of 2-alkylthiadiazines indicates that very little, if any, of the 4-alkyl product was formed in these cases. Yale and Sheehan have observed the reaction of triethyl orthoformate and benzothiadazines at 150° and report the formation of both the 2- and 4-alkylthiadiazines.[14]

Both **11** and **12** readily undergo cleavage of the thiadiazine ring when crystallized from water to form 1,3-dimethyl - 5 - methylsulfamoyl - 6 - uracilformamide (**13**) and 1,3-dimethyl-5-ethylsulfamoyl-6-uracilformamide (**14**), respectively. Cleavage of 2-alkylthiadiazines is known to take place with hydroxylic solvents; however, 4-alkylthiadiazines are stable to hydroxylic solvents[14] and are cleaved only under basic conditions.[15] This together with the fact that the preparation of **11** also was accomplished by the reaction of triethyl orthoformate and **8**, which was identical with the product obtained from the reaction of **7** and trimethyl orthoformate at the higher temperature, indicated that **11** and probably **12** were the 2-alkylthiadiazines and not the 4-alkylthiadiazines. The ultraviolet spectra of **11** and **12** were similar, also indicating that both thiadiazines were alkylated in the same position.

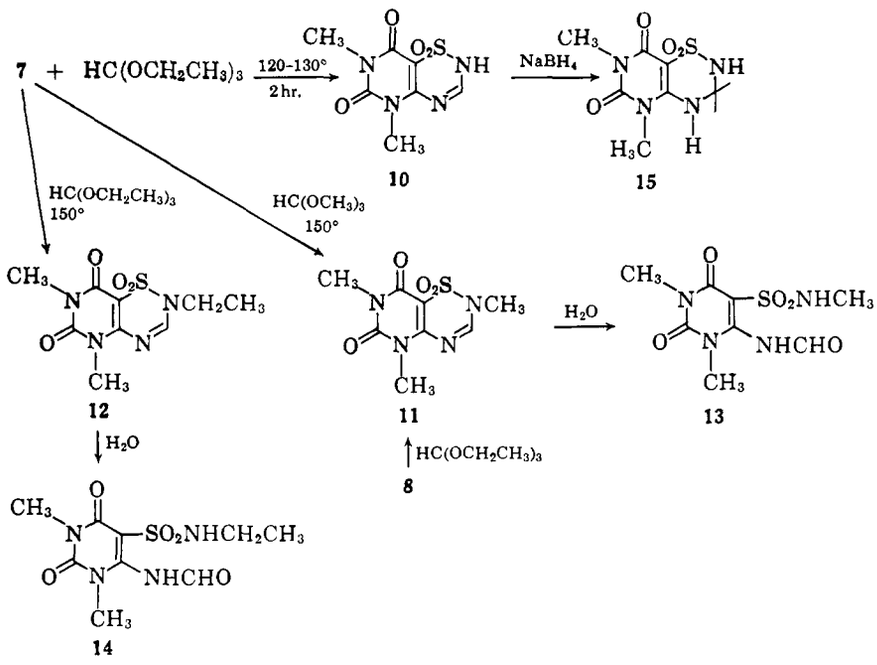
Cyclization of **7** with trimethyl orthoformate and triethyl orthoformate to form the corresponding 2-alkylthiadiazine in a 78 and 74% yield, respectively, indicates that the double bond of **10** exists predominantly, if not entirely, in the 3,4-position under these conditions. This is different from the results obtained with the benzothiadiazines where the major product was the 4-alkyl product.[14,15]

The ultraviolet spectra also support these findings since **10** shows maxima at 308 mμ and 258 mμ similar to the 2-alkylthiadiazine, **11** and **12**, both of which have maxima at 309 mμ and 263 mμ. This is in agreement with Yale and Sheehan[14] who found that the 1,2,4-thiadiazine with the double bond in the 2,3-position has only one absorption maximum at 278 mμ with a shoulder at 295 mμ.

The reaction of **7** with formaldehyde did not form the desired 5,7-dimethyl-3,4-dihydro-1,2,4-pyrimido[4,5-*e*]-thiadiazine-6,8-dione 1,1-dioxide (**15**). However, **15** was prepared by the reaction of **10** with an excess of sodium borohydride.

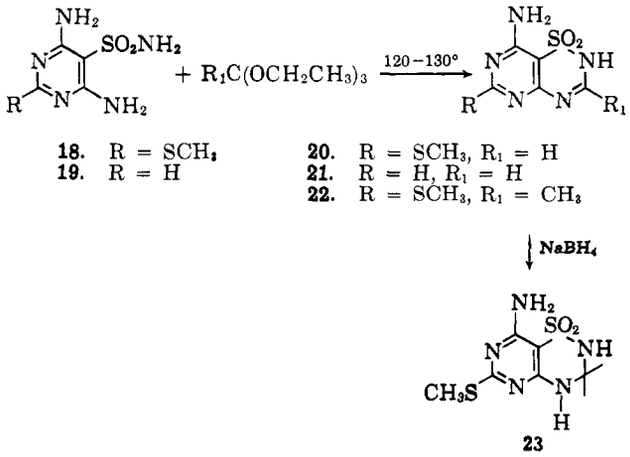
Preparation of other pyrimido-1,2,4-thiadiazines 1,1-dioxides was limited by the difficulty encountered in the preparation of other 4-amino-5-pyrimidinesulfonamides needed to form thiadiazines of type **1**. Pyrimidines such as 4,6-diamino-2-methylthiopyrimidine, 4,6-diamino - 2 - hydroxypyrimidine, 2,6 - diamino - 4 - hydroxypyrimidine, 4-amino-6-hydroxy-2-methylpyrimidine, or 2,6-diamino-4-chloropyrimidine were sulfonated with chlorosulfonic acid to form the corresponding 5-pyrimidinesulfonic acids. In no case was the corresponding sulfonyl chloride isolated. 4,6-Diamino-2-methylthio-5-pyrimidinesulfonic acid (**16**) was converted to 4,6-diamino-2-methylthio-5-pyrimidinesulfonyl chloride with phosphorus oxychloride. The relatively unstable sulfonyl chloride formed 4,5-diamino-2 - methylthio - 5 - pyrimidinesulfonamide (**18**) when treated with ammonia. None of the other sulfonic acids could be converted to the corresponding sulfonamides in this way.

(9) G. R. Barker, N. G. Luthy, and M. M. Dhar, *J. Chem. Soc.*, 4206, (1954).
(10) R. C. Elderfield and R. N. Prasad, *J. Org. Chem.*, **26**, 3863 (1961).
(11) R. R. Herr, T. Enklji, and R. J. Bardo, *J. Am. Chem. Soc.*, **78**, 401 (1956).
(12) N. V. Khromov-Borisov and R. S. Karlinskaya, *Zh. Obshch. Khim.*, **27**, 2518 (1957); *Chem. Abstr.*, **52**, 7327 (1958).
(13) J. H. Freeman and E. C. Wagner, *J. Org. Chem.*, **16**, 815 (1951).
(14) H. L. Yale and J. T. Sheehan, *ibid.*, **26**, 4315 (1961).
(15) F. C. Novello, S. C. Bell, E. L. A. Abrams, C. Ziegler, and J. M. Sprague, *ibid.*, **25**, 970 (1960).



4,6 - Diamino - 5 - pyrimidinesulfonamide (**19**) was formed when the methylthio group of sulfonamide **18** was replaced by a hydrogen in refluxing Raney nickel. Oxidation of the methylthio group of **18** to the methylsulfonyl group with chlorine or hydrogen peroxide could also be effected without affecting the sulfonamide group. These reactions could not be carried out on the corresponding sulfonic acid or sulfonyl chloride.

When 4,6-diamino-2-methylthio-5-pyrimidinesulfonamide (**18**) or 4,6-diamino-5-pyrimidinesulfonamide (**19**) was heated with an excess of triethyl orthoformate ring closure was effected to form 8-amino-6-methylthio-1,2,4-pyrimido[4,5-*e*]thiadiazine 1,1-dioxide (**20**) and 8-amino - 1,2,4 - pyrimido[4,5-*e*]thiadiazine 1,1 - dioxide (**21**), respectively, with no N-alkylation being observed. Ring closure of **18** also was effected with refluxing trimethyl orthoformate to form **20** or with triethyl orthoacetate to form **22**. Sodium borohydride reduced **20** to form 8-amino-3,4-dihydro-6-methylthio-1,2,4-pyrimido-[4,5-*e*]thiadiazine 1,1-dioxide (**23**).



18. R = SCH_3
19. R = H

20. R = SCH_3, R_1 = H
21. R = H, R_1 = H
22. R = SCH_3, R_1 = CH_3

All of the sulfonamides prepared showed characteristic absorption bands at 1134–1177 cm.$^{-1}$ and at 1020–1043 cm.$^{-1}$. The sulfonamides of substituted uracils also showed characteristic bands at 1372–1385 cm.$^{-1}$. The sulfonic acids and the one methylsulfonate **6** showed characteristic absorption bands at 1030–1051 cm.$^{-1}$ and at 1204–1220 cm.$^{-1}$.[16]

Tests for anticancer activity of the compounds reported in this paper are being obtained by the National Cancer Chemotherapy Service Center, Bethesda, Maryland. Significant results of these tests will be reported elsewhere.

Experimental[17]

Sulfonation of Substituted Pyrimidines.—To 25 ml. of freshly distilled chlorosulfonic acid, which was cooled on ice, was added 10 g. of 6-amino-1,3-dimethyluracil (**3**) at such a rate so that the temperature of the reaction mixture did not go above 20°. After addition was complete the reaction mixture was heated on a water bath for 2 hr. or refluxed for 1 hr., cooled, and poured on 300 g. of crushed ice with vigorous stirring. The excess ice was removed and the sulfonyl chloride was rapidly filtered. The light tan precipitate was washed with a little cold water and sucked as dry as possible. This product was never purified but was used as such in subsequent reactions.

4,6-Diamino-2-methylthiopyrimidine, 4,6-diamino-2-hydroxypyrimidine, 2,6-diamino-4-hydroxypyrimidine, and 4-amino-6-hydroxy-2-methylpyrimidine were sulfonated by the same procedure as was **3**. In all cases the only product isolated was the 5-sulfonic acid. Analytical data for these sulfonic acids are given in Table I.

2,4-Diamino-6-chloropyrimidine (2.9 g.) could be sulfonated only when refluxed with chlorosulfonic acid (10 ml.) for 1 hr. When the reaction mixture was poured on ice an immediate precipitate of starting material formed. The filtrate yielded 2,4-diamino-6-chloro-5-pyrimidinesulfonic acid in a 31% yield (1.4 g.) on standing overnight. The sulfonic acid was crystallized from water to give a pure sample which did not melt below 330°. A satisfactory C–H analysis could not be obtained on 2,4-diamino-6-chloro-5-pyrimidinesulfonic acid, but it could be converted to 2,4,6-triamino-5-pyrimidinesulfonic acid by heating at 150° in an excess of alcoholic ammonia which did give acceptable analytical data (Table I).

6-Amino-1,3-dimethyl-5-uracilsulfonamide (**7**).—6-Amino-1,3-dimethyl-5-uracilsulfonyl chloride (**4**), obtained from the chlorosulfonation of 10 g. of **3**, was added to 200 ml. of anhydrous ammonia. Evaporation of the excess ammonia left a tan solid which was dissolved in a small amount of water, decolorized with animal charcoal, and cooled to give 5.05 g. (31% yield based on 10 g. of **3**) of the monohydrate as white needles, m.p. 117–119°. After several crystallizations from water the anhydrous product, m.p. 218–220°, was obtained when the monohydrate was heated at 150° under reduced pressure overnight.

Anal. Calcd. for $C_6H_{10}N_4O_4S$: C, 30.76; H, 4.30; N, 23.92; S, 13.69. Found: C, 30.60; H, 4.32; N, 23.71; S, 13.30.

6-Amino-N-methyl-1,3-dimethyl-5-uracilsulfonamide (**8**) **and 6-Amino-N-ethyl-1,3-dimethyl-5-uracilsulfonamide** (**9**).—6-Amino-1,3-dimethyl-5-uracilsulfonyl chloride (**4**), obtained from the chlorosulfonation of 10 g. of **3**, was added to 100 ml. of anhydrous methylamine, or 100 ml. of anhydrous ethylamine if **9** was the desired product, and kept at the temperature of Dry Ice. After all of the solid had gone into solution it was removed from the Dry Ice and the excess amine evaporated. (If the mixture is removed from the Dry Ice before all of the solid had gone into solution the mixture becomes hot and the product isolated is mainly the corresponding amine salt of the sulfonic acid.) A 25% yield (4.0 g.) of the pure N-methylsulfonamide

(16) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1954, pp. 363, 364.

(17) All *melting points* are uncorrected. All ultraviolet spectra were made in water unless otherwise noted using a Beckman DB spectrophotometer. The infrared spectra were taken with potassium bromide pellets using a Perkin-Elmer Infracord spectrophotometer.

TABLE I

2,4,6-TRISUBSTITUTED 5-PYRIMIDINESULFONIC ACIDS AND DERIVATIVES

Compound	Yield, %	M.p.,[a] °C.	Formula[b]	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
4,6-Diamino-2-methylthio-5-pyrimidinesulfonic acid	33	265–267	$C_5H_{10}N_4O_3S_2$[c]	23.62	23.57	3.96	3.73	22.04	22.23	25.22	25.44
4,6-Diamino-2-hydroxy-5-pyrimidinesulfonic acid	23	>330	$C_4H_6N_4O_3S$	23.30	23.49	2.94	3.10	27.17	27.18	15.55	15.64
2,4-Diamino-6-hydroxy-5-pyrimidinesulfonic acid	34	>330	$C_4H_9N_5O_4S$[d]	21.57	21.67	4.06	3.94	31.38	31.48	14.37	14.33
4-Amino-6-hydroxy-2-methyl-5-pyrimidinesulfonic acid	43	305–306	$C_5H_7N_3O_4S$	29.26	29.01	3.44	3.51	20.48	20.62	15.63	15.51
2,4-Diamino-6-chloro-5-pyrimidinesulfonic acid	31	>330	$C_4H_5ClN_4O_3S$	21.34		2.24		24.94	25.01	14.28	14.54
2,4,6-Triamino-5-pyrimidinesulfonic acid	82	>310	$C_4H_7N_5O_3S$	23.41	23.39	3.44	3.69	34.13	34.06	15.63	15.66
4,6-Diamino-2-methylthio-5-pyrimidinesulfonamide	59	198–199	$C_5H_9N_5O_2S_2$	25.52	25.28	3.81	3.77	29.77	29.66	27.26	27.19
4,6-Diamino-5-pyrimidinesulfonamide	31	217–218	$C_4H_7N_5O_2S$	25.39	25.55	3.72	3.87	37.02	37.28	16.95	16.83
4,6-Diamino-2-methylsulfonyl-5-pyrimidinesulfonamide	79	238–239	$C_5H_9N_5O_4S_2$	22.47	22.61	3.39	3.28	26.20	26.46	24.00	24.00

[a] All melting points are uncorrected. [b] All samples were crystallized from water except 4,6-diamino-2-hydroxy-5-pyrimidinesulfonic acid which was dissolved in 5% sodium hydroxide and precipitated by the addition of acetic acid. [c] Formula and calculations based on monohydrate. [d] Formula and calculation based on ammonium salt.

8 was obtained by decolorizing with animal charcoal and three crystallizations from water, m.p. 203–204°.

Anal. Calcd. for $C_7H_{12}N_4O_4S$: C, 33.87; H, 4.88; N, 22.57; S, 12.92. Found: C, 33.55; H, 4.86; N, 22.32; S, 12.96.

The N-ethylsulfonamide **9** was dissolved in methanol, decolorized with animal charcoal, and cooled to yield 4.5 g. (26% yield based on 10 g. of **3**), m.p. 260–263°.

Anal. Calcd. for $C_8H_{14}N_4O_4S$: C, 36.63; H, 5.38; N, 21.36; S, 12.23. Found C, 36.38; H, 5.68; N, 21.35; S, 12.52.

Methyl 6-amino-1,3-dimethyl-5-uracilsulfonate (**6**).—Crude **4**, obtained from 10 g. of **3**, was stirred in 350 ml. methanol overnight at room temperature. Enough methanol was added to the mixture so that on heating the ester went into solution. Upon cooling the crude methylsulfonate **6** was obtained in a 46% yield (7.4 g.), m.p. 204–206°. Further crystallization from methanol yielded a product which began to soften at 193°, m.p. 206–208°. When water was used as a solvent, only a very small portion of the ester could be reclaimed.

Anal. Calcd. for $C_7H_{11}N_4O_5S$: C, 33.73; H, 4.45; N, 16.88; S, 12.88. Found: C, 33.59; H, 4.63; N, 16.94; S, 13.07.

5,7-Dimethyl-1,2,4-pyrimido[4,5-e]thiadiazine-6,8-dione 1,1-Dioxide (**10**).—6-Amino-1,3-dimethyl-5-pyrimidinesulfonamide (**7**) (4 g.) was added to 50 ml. of triethyl orthoformate and kept at 120–130° for 2 hr. with stirring. It is best to carry out this reaction in an open container in order to allow the ethanol to escape as the reaction proceeds. After the reaction was complete, it was cooled and diluted with 50 ml. of ether to assure complete precipitation of the product. A 67% yield (2.8 g.) of the thiadiazine **10** was obtained by dissolving in N,N-dimethylformamide and then diluting with methanol, m.p. 271–272°. Further purification gave an analytical sample, m.p. 274–275°; ν_{max} 1219, 1162, 1134, and 1031 cm.$^{-1}$; λ_{max} 308 mμ (ε 7100) and 258 mμ (ε 8490).

Anal. Calcd. for $C_7H_8N_4O_4S$: C, 34.43; H, 3.30; N, 22.95; S, 13.13. Found: C, 34.53; H, 3.62; N, 22.82; S, 13.10.

2-Ethyl-5,7-dimethyl-1,2,4-pyrimido[4,5-e]thiadiazine-6,8-dione 1,1-Dioxide (**12**).—6-Amino-1,3-dimethyl-5-pyrimidinesulfonamide (**7**) (1 g.) was heated in 25 ml. of triethyl orthoformate for 3 hr. at 150°. Upon cooling a 74% yield (0.86 g.) of the N-ethylthiadiazine **12** was isolated, m.p. 180–181°. Two crystallizations from triethyl orthoformate yielded white needles, m.p. 182–183°; ν_{max} 1232, 1166, 1134, 1041, and 1022 cm.$^{-1}$; $\lambda_{max}^{HC(OEt)_3}$ 309 mμ (ε 4050) and 263 mμ (ε 12,200).

Anal. Calcd. for $C_8H_{12}N_4O_4S$: C, 39.70; H, 4.48; N, 20.58, S, 11.78. Found: C, 39.83; H, 4.43; N, 20.37; S, 12.03.

5-Ethylsulfamoyl-1,3-dimethyl-6-uracilformamide (**14**).—A 96% yield (0.31 g.) of formamide **14** was obtained when 0.30 g. of the thiadiazine **12** was dissolved in a minimum amount of hot water. The product melted 181–182° and showed a depression to 148–158° when mixed with **12**; λ_{max} 250 mμ (ε 17,300) and 230 mμ (ε 10,600).

Anal. Calcd. for $C_9H_{14}N_4O_4S$: C, 37.23; H, 4.86; N, 19.30; S, 11.12. Found: C, 37.09; H, 4.91; N, 19.38; S, 11.05.

2,5,7-Trimethyl-1,2,4-pyrimido[4,5-e]thiadiazine-6,8-dione 1,1-Dioxide (**11**).—N-Methyl-6-amino-1,3-dimethyl-5-pyrimidinesulfonamide (**8**) (1 g.) was heated with stirring at 120–130° for 6 hr. in 100 ml. of triethyl orthoformate. On cooling a 78% yield (0.82 g.), m.p. 235–237°, of the 2-alkylthiadiazine **11** was obtained. The analytical sample was crystallized twice from triethyl orthoformate, m.p. 243–244°; ν_{max} 1233, 1166, 1132, 1064, and 1088 cm.$^{-1}$; $\lambda_{max}^{HC(OEt)_3}$ 309 mμ (ε 4480) and 263 mμ (ε 12,300).

Anal. Calcd. for $C_8H_{10}N_4O_4S$: C, 37.22; H, 3.90; N, 21.70; S, 12.42. Found: C, 36.92; H, 4.04; N, 21.68; S, 12.64.

The 2-alkylthiadiazine **11** also was prepared by heating 0.5 g. of 6-amino-1,3-dimethyl-5-pyrimidinesulfonamide (**7**) and 25 ml. of trimethyl orthoformate at 150° in a pressure bottle for 6 hr. Upon cooling 15% yield (0.08 g.) of the thiadiazine **10**, m.p. 273–275°, was obtained. The thiadiazine **10** was the same in all respects as the product obtained from the reaction of triethyl orthoformate and the sulfonamide **7**. When the filtrate was diluted with 75 ml. of ether a 76% yield (0.42 g.) of the 2-alkylthiadiazine **11** was obtained, m.p. 242–243°. Mixture melting point with the 2-alkylthiadiazine **11** obtained from the reaction of the N-methylsulfonamide **8** and triethyl orthoformate showed no depression.

1,3-Dimethyl-5-methylsulfamoyl-6-uracilformamide (**13**).—An 88% yield (0.39 g.) of the formamide **13** was obtained when 0.40 g. of the thiadiazine **11** was dissolved in a minimum amount of hot water. The product melted 238–239° and showed a depression to 213–227° when mixed with **10**; λ_{max} 250 mμ (ε 16,100) and 230 mμ (ε 9000).

Anal. Calcd. for $C_8H_{12}N_4O_5S$: C, 34.78; H, 4.38; N, 20.28; S, 11.61. Found: C, 34.74; H, 4.63; N, 20.34; S, 11.84.

3,4-Dihydro-5,7-dimethyl-1,2,4-pyrimido[4,5-e]thiadiazine-6,8-dione 1,1-Dioxide (**15**).—To 0.1 g. of sodium borohydride dissolved in 2 ml. of water was added slowly 0.8 g. of 5,7-dimethyl-1,2,4-pyrimido[4,5-e]thiadiazine-6,8-dione 1,1-dioxide (**10**). After 2 hr. a small amount of precipitate formed which was removed and then acidified with acetic acid. Upon filtration of the acidic mixture the dihydro product **15** was isolated in a 37% yield (0.3 g.). After one crystallization from water an analytical sample was obtained, m.p. 298–299°; ν_{max} 1240, 1148, 1089, 1065, 1022, and 1000 cm.$^{-1}$; λ_{max} 259 mμ (ε 11,500).

Anal. Calcd. for $C_7H_{10}N_4O_4S$: C, 34.14; H, 4.09; N, 22.76; S, 13.02. Found: C, 34.17; H, 4.31; N, 22.91; S, 13.19.

4,6-Diamino-2-methylthio-5-pyrimidinesulfonamide (**18**).—4,6-Diamino-2-methylthio-5-pyrimidinesulfonic acid trihydrate (**16**) (20 g.) was refluxed for 1 hr. with 75 ml. of phosphorus oxychlo-

ride. The excess phosphorus oxychloride was distilled by heating the sample on a water bath under reduced pressure. Heating was continued until the solution became a thick sirup. If heating was continued for a longer period of time the sulfonyl chloride decomposed to a crystalline material and the desired product was not obtained. The thick sirup was added to 400 ml. of ammonia. Evaporation of the ammonia left a tan solid which was decolorized with animal charcoal and crystallized from water yielding 9.7 g. (59% yield) of long white needles, m.p. 195–197°. Further crystallization from water increased the m.p. to 198–199°. Analytical data are given in Table I.

4,6-Diamino-5-pyrimdinesulfonamide (19).—4,6-Diamino-2-methylthio-5-pyrimidinesulfonamide (**18**) (2.5 g.) was dissolved in 50 ml. water to which 5 g. of Raney nickel[18] was added. This reaction mixture was refluxed for 3 hr. with vigorous stirring. Longer refluxing also will remove the sulfonamide group while a shorter reflux time leaves too much starting material. A 31% yield (0.63 g.) of **19** was obtained upon evaporation of the filtrate and crystallization of the residue from a small amount of water, m.p. 215–216.5°. Further crystallization from water gave an analytical sample, m.p. 221–222°. Analytical data are given in Table I.

4,6-Diamino-2-methylsulfonyl-5-pyrimidinesulfonamide.—4,6-Diamino-2-methylthio-5-pyrimidinesulfonamide (**18**) (2 g.) was added to 50 ml. water and cooled to 0° in an ice bath. Chlorine was slowly bubbled through this suspension until all of the solid went into solution and the solution was light yellow in color. (This takes a few minutes depending on how rapidly the chlorine is bubbled through the suspension. A large excess of chlorine should be avoided or the yield will be reduced greatly.) The product begins to separate shortly after the solid goes into solution. After standing in an ice bath for 0.5 hr. the mixture was filtered and after one crystallization from water yielded 1.6 g. (70% yield), m.p. 235–237°, with evolution of a gas. Further crystallization from water gave a sample that turns yellow at 235°, m.p. 249–250° dec.

4,6-Diamino-2-methylsulfonyl-5-pyrimidinesulfonamide also was prepared by dissolving **18** (0.9 g.) in 10 ml. of acetic acid and 10 ml. of acetic anhydride. To this solution was added 1 ml. of 30% hydrogen peroxide. After a short time the reaction mixture became hot and the product separated from the solution. A 79% yield (0.81 g.) of crude product was obtained upon filtration. Two crystallizations from water gave material that was identical with that from the oxidation with chlorine. Analytical data are given in Table I.

8-Amino-6-methylthio-1,2,4-pyrimido[4,5-*e*]thiadiazine 1,1 Dioxide (20) and 8-Amino-1,2,4-pyrimido[4,5-*e*]thiadiazine 1,1 Dioxide (21).—4,6-Diamino-2-methylthio-5-pyrimidinesulfonamide (**18**) (1 g.) was heated for 2 hr. at 120–130° in 20 ml. of triethyl orthoformate. Upon cooling the thiadiazine **20** was obtained in an 86% yield (0.9 g.), m.p. 315–317°. An analytical sample was obtained by two crystallizations from N,N-dimethylformamide and water, m.p. 321–322° dec.; ν_{max} 1204, 1136, and 1079 cm.$^{-1}$; λ_{max} 249 mμ (ϵ 26,700).

Anal. Calcd. for $C_6H_7N_5O_2S_2$: C, 29.34; H, 2.86; N, 28.39; S, 26.15. Found: C, 29.16; H, 3.06; N, 28.24; S, 26.17.

Cyclization of sulfonamide **18** also was effected with refluxing trimethyl orthoformate yielding **20** in a 62% yield.

To 4,6-diamino-5-pyrimidinesulfonamide (**19**) (1.8 g.) was added 50 ml. of triethyl orthoformate and treated in a manner similar to **18**. Thiadiazine **21** was obtained in a 97% yield (1.76 g.). Two crystallizations from N,N-dimethylformamide and water gave an analytical sample, m.p. 308–309°; ν_{max} 1219, 1159, 1078, 1020, and 1002 cm.$^{-1}$; λ_{max} 244 mμ (ϵ 11,200) and 223 mμ (ϵ 22,000).

Anal. Calcd. for $C_5H_5N_5O_2S$: C, 30.15; H, 2.53; N, 35.16; S, 16.10. Found: C, 29.88; H, 2.71; N, 35.02; S, 16.30.

8-Amino-3-methyl-6-methylthio-1,2,4-pyrimido[4,5-*e*]thiadiazine 1,1-Dioxide (22).—4,6-Diamino-2-methylthio-5-pyrimidinesulfonamide (**18**) (1 g.) was heated for 1 hr. at 120–130° with stirring in 15 ml. of triethyl orthoacetate. Upon cooling the thiadiazine **22** was obtained in a 54% yield, m.p. 314–315°; ν_{max} 1149, 1099, 1050, and 1020 cm.$^{-1}$; λ_{max} 247 mμ (ϵ 28,300).

Anal. Calcd. for $C_7H_9N_5O_2S_2$: C, 32.42; H, 3.50; N, 27.01; S, 24.73. Found: C, 32.27; H, 3.61; N, 27.29; S, 24.90.

8-Amino-3,4-dihydro-6-methylthio-1,2,4-pyrimido[4,5-*e*]thiadiazine 1,1-Dioxide (23).—8-Amino-6-methylthio-1,2,4-pyrimido [4,5-*e*]thiadiazine 1,1-dioxide (**20**) (0.5 g.) was added slowly to 0.1 g. of sodium borohydride in 5 ml. of water. After standing for 3 hr. the reaction mixture was filtered to obtain the dihydro product **23** in an 81% yield (0.41 g.). One crystallization from water gave an analytical sample, m.p. 261–262°; ν_{max} 1202 and 1148 cm.$^{-1}$; λ_{max} 230 mμ (ϵ 26,600) and 255 mμ (sh).

Anal. Calcd. for $C_6H_9N_5O_2S_2$: C, 29.14; H, 3.67; N, 28.32; S, 25.93. Found: C, 29.11; H, 3.69; N, 28.41; S, 25.81.

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9-Aminoacridines and 4-Aminoquinolines. Steric Effects of N,N-Disubstitution[1]

RICHARD M. PECK

The Institute for Cancer Research, Philadelphia 11, Pennsylvania

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N,N-Disubstitution was found to labilize the aromatic amino bond of 9-aminoacridine to permit a previously unreported type of reaction with alcohols, yielding 9-acridinyl ethers. An analogous reaction in similarly N,N-disubstituted 4-aminoquinolines was not found; however, a pronounced effect on base strength and ultraviolet spectra upon increasing the bulk of the substituents was noted.

N,N-Disubstitution of 9-aminoacridine and 4-aminoquinoline derivatives was initially attempted to reduce intramolecular reactivity to other groups which were to be introduced at the end of an alkyl side chain; these objectives were abandoned in the quinoline series due to an unexpected rearrangement[2] and now in the acridine series due to inherent instability of the compounds to the conditions of subsequent reactions. In an attempt at synthesis of compound III, the reaction was carried out in refluxing Methyl Cellosolve, a procedure often found useful in moderating the sometimes destructively exothermic nature of such reactions,[3] and a compound subsequently identified as IV was isolated. Compound III was then synthesized in the absence of Methyl Cellosolve and its reactivity to or the alcohols near the boiling point of Methyl Cellosolve was investigated with a series of simple glycols, with ethylene chlorohydrin, and with diethylene glycol. The reactions all occurred rapidly near 115° and apparently were uncomplicated by side reactions, except in the case of ethylene chlorohydrin, where too long a reaction time led to alkylation of the nucleus. No attempt was made, however, to obtain optimum yields. Table I lists the products which are stable in the absence of active hydro-

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