of methyl 2,4-dioxo-3,1,4-benzoxazine-5-carboxylate) was suspended in 10 ml. of ethyl alcohol cooled by an ice-bath; 15 ml. of a saturated alcoholic solution of methylamine was added gradually with stirring. After the addition, stirring was continued for half an hour, while intensely yellow colored solid began to appear. The product was removed by filtration and additional product was obtained by evaporation of the mother liquor. The combined products were recrystallized from alcohol; yield 0.85 g., m. p. 158°. The product remained unchanged after refluxing with either concentrated hydrochloric acid or potassium hydroxide.

*Anal.* Calcd. for $C_{10}H_{10}O_2N_2$: N, 14.74. Found: N, 14.70.


## Summary

The 1-methyl-2,4-quinazolinedione, m. p. 147°, reported by Abt was shown to be a mixture of product m. p. 265° and starting material. Scott and Cohen's dimethyl-2,4-quinazolinedione-5-carboxylic acid was identified as the 3-methyl-2,4-quinazolinedione-5-carboxylic acid.

Both the 1-methyl-2,4-quinazolinedione-5-carboxylic acid and its 3-methyl isomer were made by methods which established their structures.


CORVALLIS, OREGON RECEIVED APRIL 22, 1950

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[CONTRIBUTION FROM THE CHEMOTHERAPY DIVISION, STAMFORD RESEARCH LABORATORIES, AMERICAN CYANAMID COMPANY]

# The Preparation of Heterocyclic Sulfonamides[1]

BY RICHARD O. ROBLIN, JR., AND JAMES W. CLAPP

In connection with a study of carbonic anhydrase inhibitors,[2] it occurred to us that heterocyclic sulfonamides might possess a high degree of inhibitory action. This idea was based on the assumption that a competition between carbon dioxide or bicarbonate ion and the sulfonamide group might account for the known inhibitory action of sulfanilamide and other unsubstituted sulfonamides on this enzyme.[3] A direct relationship had been established previously between the acid dissociation constants of sulfanilamide derivatives and their competitive antagonism of *p*-aminobenzoic acid.[4] Consequently, although no evidence for a competitive effect is known in the case of carbonic anhydrase,[5] it was anticipated that heterocyclic sulfonamides would be more highly acidic and might therefore exert a more powerful inhibitory action.

The present report deals with the preparation of heterocyclic sulfonamides unsubstituted on the sulfonamide nitrogen, since unsubstituted derivatives are the only type which have been reported to produce a high degree of enzymic inhibition.[3] The same approach has also been applied to the synthesis of substituted derivatives.

Relatively few heterocyclic sulfonamides in which the sulfur atom is joined directly to a carbon of the heterocyclic ring have been described. They have usually been prepared by chlorosulfonation or conversion of a sulfonic acid to the acid chloride, followed by amidation, methods which are not generally applicable to the synthesis of heterocyclic sulfonamides. On the other hand, the low temperature oxidative chlorination of thio heterocycles, followed by amidation of the sulfonyl chlorides, has been found to be quite widely applicable to the preparation of these compounds. This procedure has been employed previously in the synthesis of aromatic and aliphatic sulfonyl chlorides and 5-acetylaminopyridine-2-sulfonyl chloride.[6]

Some exceptions have been encountered in the general application of the low temperature oxidative chlorination method to the preparation of heterocyclic sulfonyl chlorides. For example, none of the thiouracils or thiotriazines investigated could be converted to the acid chlorides. In the case of 2-thiouracil, only 5-chlorouracil[7] could be identified in the reaction mixture. Similarly, the presence of free amino groups or partially saturated ring systems also appeared to interfere with the normal course of the reaction. The instability of many of the sulfonyl chlorides may account for these exceptions, and for the wide variations in yields obtained in the successful cases. On standing, particularly in an impure state, most of the heterocyclic acid chlorides decompose rapidly with the loss of sulfur dioxide. With the compounds investigated, namely, benzothiazole-2-sulfonyl chloride, 4,6-dimethylpyrimidine-2-sulfonyl chloride and 1-methyltetrazole-5-sulfonyl chloride, the decomposition products were found to be the corresponding chloro derivatives, such as 2-chlorobenzothiazole. This compound has been reported to be the primary product of the chlorination of 2-thiobenzothiazolone when the reaction is carried out for long periods of time at room temperature.[8]

Because of the instability of the sulfonyl chlorides, the crude products were usually converted directly to the more stable sulfonamides by amidation in liquid ammonia. In this manner, a num-

(1) Presented in part before the Division of Medicinal Chemistry at the Philadelphia Meeting of the American Chemical Society, April 10, 1950.

(2) Miller, Dessert and Roblin, THIS JOURNAL, **72**, 4893 (1950).

(3) Mann and Keilin, *Nature*, **146**, 164 (1940); Krebs, *Biochem. J.*, **43**, 525 (1948).

(4) Bell and Roblin, THIS JOURNAL, **64**, 2905 (1942).

(5) *Cf.* Davenport, *J. Biol. Chem.*, **158**, 567 (1945).

(6) Schiller and Otto, *Ber.*, **9**, 1638 (1876); Zincke and Frohneberg, *ibid.*, **42**, 2722 (1909); Douglass and Johnson, THIS JOURNAL, **60**, 1486 (1938); Caldwell and Kornfeld, *ibid.*, **64**, 1695 (1942).

(7) Johnson, *Am. Chem. J.*, **40**, 19 (1908).

(8) Findlay and Dougherty, THIS JOURNAL, **68**, 1666 (1946).

TABLE I

PROPERTIES OF HETEROCYCLIC SULFONAMIDES

| | Sulfonamide | M. p.,[a] °C. | % yield[d] | Formula | Carbon, %[i] Calcd. | Carbon, %[i] Found | Hydrogen, %[i] Calcd. | Hydrogen, %[i] Found | Nitrogen, %[i] Calcd. | Nitrogen, %[i] Found |
|---|---|---|---|---|---|---|---|---|---|---|
| I | Imidazole-2- | 236–236.5 | 6*[e] | $C_3H_4N_2O_2S$ | 24.5 | 24.3 | 3.4 | 3.4 | 28.6 | 28.4 |
| II | 1-Methylimidazole-2- | 148.5–149.5 | 7*[f] | $C_4H_7N_2O_2S$ | 29.8 | 30.0 | 4.4 | 4.4 | 26.1 | 26.4 |
| III | 1-Phenylimidazole-2- | 170–170.5 | 74[e] | $C_9H_8N_2O_2S$ | 48.4 | 48.4 | 4.1 | 4.0 | 18.8 | 18.9 |
| IV | Benzimidazole-2- | 214[b] | 43[e] | $C_7H_7N_2O_2S$ | 42.6 | 42.6 | 3.6 | 3.7 | 21.3 | 21.2 |
| V | 1,2,4-Triazole-3- | 224.5–225.5[b] | 20[e] | $C_2H_4N_4O_2S$ | 16.2 | 16.2 | 2.7 | 2.6 | 37.8 | 38 1 |
| VI | Pyrido[2,1-c]-s-triazole-3- | 242–242.5[c] | 36[e] | $C_6H_6N_4O_2S$ | 36.4 | 36.5 | 3.1 | 3.2 | 28.3 | 28.0 |
| VII | 3-Hydroxy-4-phenyl-4,1,2-triazole-5- | 257–259[c] | 32*[e] | $C_8H_8N_4O_3S$ | 40.0 | 39.9 | 3.4 | 3.5 | 23.3 | 23.1[k] |
| VIII | 4-Phenyl-4,1,2-triazole-3,5-di- | 242.5–243.5[c] | 24[e] | $C_8H_8N_6O_4S_2$ | 31.7 | 31.7 | 3.0 | 2.9 | 23.1 | 23.0 |
| IX | 1-Methyltetrazole-5- | 139–140 | 23[g] | $C_2H_4N_6O_2S$ | 14.7 | 14.6[l] | | | 42.9 | 42.7 |
| X | 1-Phenyltetrazole-5- | 157–158 | 38*[e] | $C_7H_7N_5O_2S$ | 37.3 | 37.6 | 3.1 | 3.4 | 31.1 | 31.1 |
| XI | Thiazole-2- | 120.5–121 | 27[e,g] | $C_3H_4N_2O_2S_2$ | 21.9 | 22.2 | 2.5 | 2.7 | 17.1 | 17.2 |
| XII | 4-Methylthiazole-2- | 166–167 | 10*[g] | $C_4H_6N_2O_2S_2$ | 27.0 | 27.2 | 3.4 | 3.5 | 15.7 | 15.7 |
| XIII | Benzothiazole-2- | 177[b] | 58[g] | $C_7H_6N_2O_2S_2$ | 39.2 | 39.0 | 2.8 | 2.9 | 13.1 | 13.3 |
| XIV | 2-Amino-1,3,4-thiadiazole-5- | 215.5–216[c] | 63[e,h] | $C_2H_4N_4O_2S_2$ | 13.3 | 13.6 | 2.3 | 2.4 | 31.1 | 31.3 |
| XV | 2-Acetylamino-1,3,4-thiadiazole-5- | 258–259[b] | 85[e] | $C_4H_6N_4O_3S_2$ | 21.6 | 21.5 | 2.7 | 2.8 | 25.2 | 25.2 |
| XVI | 1,3,4-Thiadiazole-2,5-di- | 184–185[c] | 11*[e] | $C_2H_4N_4O_4S_2$ | 9.8 | 9.9 | 1.7 | 1.6 | 22.9 | 23.0 |
| XVII | Pyrimidine-2- | 180.5–181[b] | 10[e] | $C_4H_5N_3O_2S$ | 30.2 | 30.2 | 3.2 | 3.1 | 26.4 | 26.2 |
| XVIII | 4,6-Dimethylpyrimidine-2- | 200–200.5[b] | 46[e] | $C_6H_9N_3O_2S$ | 38.5 | 38.6 | 4.9 | 4.7 | 22.5 | 22.2 |
| XIX | 5-Chloropyrimidine-2- | *ca.* 135–140 | 3*[e] | $C_4H_4ClN_3O_2S$ | 24.8 | 24.8[l] | | | 21.7 | 21.6 |
| XX | Pyrazine-2- | 166–166.5 | 18[e] | $C_4H_5N_3O_2S$ | 30.2 | 30.1 | 3.2 | 3.3 | 26.4 | 26.2 |

[a] Corrected. [b] With bubbling. [c] With dec. [d] Crude, from thio compound; purified yields indicated by *. [e] Recrystallization solvent water. [f] Ethyl acetate. [g] Ethylene chloride. [h] By hydrolysis of XV with ethanol–hydrochloric acid (20:3). [i] Average of two check results not differing from calculated values by more than ±0.3%. These microanalyses were carried out under the direction of Dr. J. A. Kuck. [k] Single value. [l] Van Slyke carbon analyses.

ber of new types of heterocyclic sulfonamides have been prepared (Table I). These compounds are quite stable and can be recrystallized from water or organic solvents. They are fairly resistant to hot 0.1 *N* hydrochloric acid, but with 6 *N* acid many of the sulfonamides are largely converted to the hydroxy derivatives. Of the following sulfonamides, IX, X, XIII and XVIII, only IX was recovered unchanged after heating on a steam-bath for one to two hours with 6 *N* hydrochloric acid.

As had been anticipated from the greater electronegativity associated with hetero atoms such as nitrogen and sulfur, a number of these unsubstituted sulfonamides are relatively strong acids, the acid strength usually increasing with an increase in the number of hetero atoms. Some of the $pK_a$ values and the carbonic anhydrase inhibitory activity of these compounds are recorded in an accompanying paper.[2] In general, practically all of the heterocyclic sulfonamides investigated proved to be highly effective inhibitors, a few of them having 100–2000 times the activity of sulfanilamide.

## Experimental

In a majority of cases, the intermediate thio heterocycles were available from a previous investigation in this Laboratory.[9] References to the methods of preparation employed are given in Table II. The following new compounds were also used as intermediates.

**2-Pyrimidinethiol.**[10]—To a solution of 3.3 g. of sodium hydroxide in 115 ml. of methanol which had been saturated with hydrogen sulfide was added 10 g. of 2-chloropyrimidine.[11] The mixture was refluxed for thirty minutes, filtered, diluted with 2 volumes of water, and acidified. The yellow precipitate was filtered and dried; crude yield 3.0 g. (30%). It was recrystallized from water; m. p. 219–220° dec.

*Anal.* Calcd. for $C_4H_4N_2S$: C, 42.8; H, 3.6; N, 25.0. Found: C, 42.6; H, 3.8; N, 25.0.

**2-Pyrazinethiol.**[12]—Forty-five grams of 2-chloropyrazine,[13] 30 g. of potassium acid sulfide and 250 ml. of anhydrous ethanol were heated at 110° in a shaking autoclave for six hours. The dark reaction mixture was filtered and the filter cake extracted three times with 50–75-ml. portions of anhydrous ethanol. The filtrates were combined and evaporated to dryness, and the residue recrystallized from hot water to give about 8 g. of a substance which was probably dipyrazinyl sulfide (m. p. 106–107.3°) as the principal product of the reaction. The filter cake was extracted with hot water and the aqueous solution treated with activated carbon. On evaporation there was obtained a mixture of potassium chloride and 2-pyrazinethiol which after drying and grinding was separated by extraction with ether using a Soxhlet apparatus. Evaporation of the ether and recrystallization from water gave a small amount of a product having a m. p. of 215–218°.

*Anal.* Calcd. for $C_4H_4N_2S$: C, 42.8; H, 3.6; N, 25.0. Found: C, 42.8; H, 3.7; N, 25.5.

**Sulfonyl chlorides** (Table II) were prepared in aqueous hydrochloric or acetic acid depending on the solubility of the thio compounds and the disulfides formed during the oxidative chlorination. Water alone seemed to be too poor a solvent to permit the reaction to proceed as rapidly as desired. In many instances only small quantities of the intermediate thio heterocycles were available and no attempt was made to establish optimum conditions for each compound. Consequently, many of the low over-all yields recorded in Table I could probably be improved considerably by a further study of the individual cases.

The general procedure for the preparation of the sulfonyl chlorides was to dissolve or suspend the powdered thio compound in 10 or more parts of dilute acid and stir the mixture rapidly in an ice-bath while chlorine was being introduced through a capillary tube at a moderately rapid rate for the required time. The time interval was dependent on the scale of the reaction and the rate of chlorine input. Care was exercised to keep the temperature

(9) *Cf.* Astwood, Bissell and Hughes, *Endocrinology*, **37**, 456 (1945).

(10) Prepared by Miss A. M. Dessert in these laboratories.

(11) Howard, U. S. Patent 2,477,409 (1949).

(12) Prepared by Mr. R. P. Germann, Calco Chemical Division, Bound Brook, N. J.

(13) Sayward, U. S. Patent 2,391,745 (1945).

TABLE II

HETEROCYCLIC SULFONYL CHLORIDES

| No.[a] | Ref. to thio cmpd. | Thio cmpd., g. | Ml. of reacn. med. | Time, min. |
|---|---|---|---|---|
| I[b] | *l* | 1.0 | 10, 1 *N* HCl | 70 |
| II | *m* | 2.0 | 10, 2 *N* HCl | 60 |
| III | *n* | 1.5 | 20, 1 *N* HCl | 25 |
| IV | *p* | 0.250 | 10, 20% acetic | 50 |
| V[c] | *q* | 4.6 | 80, 2 *N* HCl | 60 |
| VI | *r* | 0.6 | 20, 1 *N* HCl | 50 |
| VII | *s* | 0.20 | 10, 1 *N* HCl | 35 |
| VIII | *s* | 0.19 | 10, 20% acetic | 50 |
| IX[d] | *t* | 1.55 | 20, 0.2 *N* HCl | 45 |
| X[e] | *u* | 1.0 | 10, 1 *N* HCl | 75 |
| XI | *v* | 2.5 | 25, 1.6 *N* HCl | 60 |
| XII[f] | *w* | 0.58 | 10, 1 *N* HCl | 75 |
| XIII[g] | *x* | 110 | 1650, 33% acetic | 180 |
| XV[h] | *y* | 40 | 660, 33% acetic | 120 |
| XVI[i] | *z* | 2.76 | 45, 33% acetic | 90 |
| XVII | *aa* | 0.300 | 7, 1.5 *N* HCl | 20 |
| XVIII | *bb* | 2.0 | 25, 1 *N* HCl | 20 |
| XIX | *cc* | 0.40 | 10, 1 *N* HCl | 75 |
| XX[k] | *aa* | 0.200 | 5, 1 *N* HCl | 55 |

[a] Numerals correspond to those of the respective sulfonamides of Table I. [b] M. p. 183° (cor.) bubbl., from ether. *Anal.* Calcd. for $C_3H_3ClN_2O_2S$: C, 21.6; H, 1.8; N, 16.8. Found: C, 21.9; H, 2.1; N, 17.0. [c] Run in water gave only disulfide. [d] Disulfide used; thio compound gave poor yield. [e] Disulfide gave anomalous results. [f] Brown gum first formed during chlorination. [g] Prod. unstable; m. p. 108–110° (cor.) from pet. ether. [h] M. p. 194° (cor.) dec. on rapid heating, from ethylene chloride. *Anal.* Calcd. for $C_4H_4ClN_3O_3S_2$: N, 17.4. Found: N, 17.3. [i] Prod. unstable, m. p. 71.5–75° (cor.) from pet. ether. [k] Prod. liquefied on attempted filtration. [l] Marckwald, *Ber.*, **25**, 2354 (1892). [m] Jones, *et al.*, THIS JOURNAL, **71**, 4000 (1949). [n] Wohl and Marckwald, *Ber.*, **22**, 568 (1889). [p] Lellman, *Ann.*, **221**, 1 (1883). [q] Freund, *Ber.*, **29**, 2483 (1896). [r] Tarbell, *et al.*, THIS JOURNAL, **70**, 1381 (1948). Prof. Tarbell kindly provided us with a generous sample. [s] Arndt, Milde and Tschenscher, *Ber.*, **55B**, 341 (1922). [t] Stollé and Henke-Stark, *J. prakt. Chem.*, [2] **124**, 261 (1930). [u] Stollé and Strittmatter, *ibid.*, [2] **133**, 60 (1932). [v] Mathes and Beber, THIS JOURNAL, **70**, 1451 (1948). [w] Buchman, Reims and Sargent, *J. Org. Chem.*, **6**, 764 (1941). [z] Calco Chemical Division, American Cyanamid Company, Bound Brook, N. J. [y] Guha, THIS JOURNAL, **44**, 1502 (1922). [x] Söderbäck, *Svensk. Kem. Tid.*, **57**, 62 (1945); *C.A.*, **40**, 4719 (1946). [aa] See Experimental. [bb] Evans, *J. prakt. Chem.*, [2] **48**, 503 (1893). [cc] English and Leffler, THIS JOURNAL, **72**, 4324 (1950).

below 7–8° in order to minimize decomposition of the product. The reaction, which is exothermic, was usually continued until a good excess of dissolved chlorine colored the mixture. With XIII and XVI, chlorination had to be carried further, until a test of the suspended solid showed it to be mostly soluble in ethylene chloride. A high degree of conversion never was attained in the case of XIX. On the other hand, a few compounds (XVII, XVIII, XX) were so sensitive that chlorination had to be stopped as soon as the first excess was present, since the amount of solid in the mixture was obviously diminishing.

The sulfonyl chloride was filtered with suction, washed well with ice-cold water, and pressed damp-dry on the funnel. It was used without delay for reaction with ammonia. When the acid chloride was a liquid (XI, XII), it was extracted from the reaction mixture with a little ether, and the extract washed with ice-cold water, dried, and used at once. In one instance (II) the acid chloride crystallized from solution only after partial neutralization with sodium hydroxide.

Decomposition of many of the sulfonyl chlorides occurred when they were allowed to stand at room temperature; sulfur dioxide could be easily detected. In the following cases, the decomposition product was taken up in petroleum ether, washed with water, dried, and recovered by removal of the solvent.

Benzothiazole-2-sulfonyl chloride gave 2-chlorobenzothiazole, m. p. 20–21°, yielding a 6-nitro derivative, m. p. 192–193°[14]; 4,6-dimethylpyrimidine-2-sulfonyl chloride gave 2-chloro-4,6-dimethylpyrimidine, m. p. 35.5–37°.[15] The product from 1-methyltetrazole-5-sulfonyl chloride crystallized from petroleum ether to a white solid, volatile *in vacuo*, m. p. 35–35.5°, which by analogy is 5-chloro-1-methyltetrazole.

*Anal.* Calcd. for $C_2H_3ClN_4$: N, 47.3. Found: N, 47.7.

**Sulfonamides** were prepared by adding the crude damp sulfonyl chlorides gradually, with swirling, to a large excess of liquid ammonia in a Dewar flask. In most cases, the reaction was vigorous and the acid chlorides dissolved rapidly and practically completely. Routinely, the solution was allowed to stand for a short time, then poured into a beaker for evaporation of the excess ammonia. The dry residue was taken up in a little dilute ammonium hydroxide, treated with Darco, filtered, made slightly acidic and chilled. The solid (if any) was filtered and dried; occasionally a second passage through dilute base and reprecipitation were employed. If the product did not precipitate, the acidified solution was evaporated to dryness *in vacuo*. Purification was effected by recrystallization.

Concentrated ammonium hydroxide can also be employed for amidation. The yield of XV was essentially the same in either case, but the yield of XIII was about three-fourths of that obtained by the use of liquid ammonia.

**Acid Hydrolysis of Sulfonamides.**—X (25 mg.), heated two hours on a steam-bath with 2.7 ml. of 6 *N* hydrochloric acid, gave 8 mg. of 5-hydroxy-1-phenyltetrazole, m. p. 184.5–187.5° (cor.)[16]; 0.50 g. of XIII heated two hours on a steam-bath with 50 ml. of 6 *N* acid gave 0.35 g. of 2-hydroxybenzothiazole, m. p. 137–138° (cor.)[17]; 25 mg. of XVIII heated one hour on a steam-bath with 2.5 ml. of 6 *N* acid gave a few mg. of 2-hydroxy-4,6-dimethylpyrimidine, m. p. 194–196° (cor.),[18] with browning, mixed m. p. with XVIII 157–183° (cor.) dec. IX (25 mg.) heated two hours on a steam-bath with 2.5 ml. of 6 *N* hydrochloric acid was recovered unchanged in 80% yield.

## Summary

The preparation and properties of a series of new heterocyclic sulfonamides have been described. These compounds were synthesized from thio heterocycles by low temperature oxidative chlorination followed by amidation of the sulfonyl chlorides. This method was quite generally applicable to the preparation of heterocyclic sulfonamides which were not readily obtainable by other procedures.

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(14) Hofmann, *Ber.*, **13**, 8 (1880), reported m. p. *ca.* 24° and m. p. 192°, respectively.

(15) Angerstein, *ibid.*, **34**, 3956 (1901), reported m. p. 38°.

(16) Dimroth and de Montmollin, *ibid.*, **43**, 2904 (1910), reported m. p. 187°.

(17) Hunter, *J. Chem. Soc.*, 125 (1930), reported m. p. 138°.

(18) Wheeler and Jamieson, *Am. Chem. J.*, **32**, 342 (1904), reported m. p. 198–199°.