*Anal.* Calcd. for $C_8H_{17}O_2Br$: Br, 35.55. Found: Br, 35.48.

**Dimethylcarbamylphthalimide.**—Ten grams (0.11 mole) of *unsym*-dimethylurea and 22.2 g. (0.11 mole) of phthalyl chloride were heated in an oil-bath at 135° until the evolution of hydrogen chloride ceased. The mass was triturated with sodium carbonate solution and the undissolved portion recrystallized from dilute alcohol; m. p. 144–145°; yield 16 g. (70%); M. L. D. 1000; M. H. D. 1000.

*Anal.* Calcd. for $C_{11}H_{10}O_3N_2$: N, 12.84. Found: N, 12.68.

**Diethylcarbamylphthalimide.**—M. p. 116–117° after recrystallization from dilute alcohol; M. L. D. 1000; M. H. D. 600.

*Anal.* Calcd. for $C_{13}H_{14}O_3N_2$: N, 11.38. Found: N, 11.52.

**Dibutylcarbamylphthalimide.**—M. p. 179–180° after recrystallization from toluene; M. L. D. 1000; M. H. D. 1000.

*Anal.* Calcd. for $C_{17}H_{22}O_3N_2$: N, 9.27. Found: N, 9.10.

## Summary

A number of disubstituted acetamides have been described in which the substituents are alkyl, arylalkyl, alkoxyalkyl and aryloxyalkyl, and their hypnotic and lethal doses for experimental animals have been reported.

ANN ARBOR, MICHIGAN RECEIVED JULY 17, 1941

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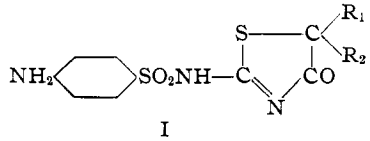
[CONTRIBUTION FROM THE MEDICAL-RESEARCH DIVISION, SHARP AND DOHME, INC.]

# Sulfonamidothiazolones*

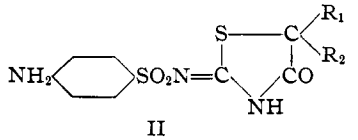
BY MAURICE L. MOORE AND CHARLES S. MILLER

In continuation of our studies of various derivatives of sulfanilamide and their chemotherapeutic activity,[1] we have prepared a series of sulfonamidothiazolones which possess considerable interest in view of the results recently reported in the synthesis and study of other heterocyclic derivatives.[2–5] We were particularly interested also in the substituted products obtained by the introduction of alkyl groups into the 5-position on the thiazolone ring. This paper describes the preparation, properties and chemotherapeutic activity of these compounds.

The acyl derivatives of 2-sulfanilamido-4-thiazolone, I or II

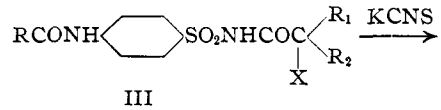


I

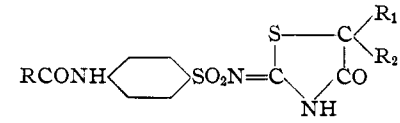


II

were prepared by the reaction of the appropriate *p*-acylaminobenzenesulfonyl chloride with the desired 2-amino-4-thiazolone in a pyridine solution or by the reaction of potassium thiocyanate with the necessary $N^4$-acyl-$N^1$-α-haloacylsulfanilamide, III, according to the equation



III



The nitro derivatives were prepared from *p*-nitrobenzenesulfonyl chloride and the 2-aminothiazolone in pyridine solution. The 2-sulfanilamido-4-thiazolones were obtained by the acid hydrolysis of the corresponding $N^4$-acetylsulfanilamidothiazolones.

These compounds are assigned structure I on the basis of Dains'[6] recent work on the stable form of some aryl-substituted 2-iminothiazolidones although Wheeler and Johnson[7] originally suggested structure II for the stable form of aryl-substituted pseudo-thiohydantoins. A study of some of the reactions of the sulfonamidothiazolones suggests that they exist in tautomeric form.

## Experimental[8]

The 2-amino-4-thiazolones used in this investigation were prepared by the reaction of the α-haloacid or α-haloacid halide with thiourea according to the usual procedures. All are reported in the literature except the following:

* These compounds may exist in tautomeric form and therefore could be called "Sulfonyliminothiazolidones."

(1) Moore, Miller and Miller, THIS JOURNAL, **62**, 2097 (1940).
(2) Foshbinder and Walters, *ibid.*, **61**, 2032 (1939).
(3) Lott, *et al.*, *ibid.*, **61**, 3593 (1939); **62**, 1873 (1940).
(4) Roblin, *et al.*, *ibid.*, **62**, 2002 (1940).
(5) Sprague and Kissinger, *ibid.*, **63**, 578 (1941).
(6) Roberts and Dains, *Univ. Kansas Sci. Bull.* **25**, 213 (1938).
(7) Wheeler and Johnson, *Amer. Chem. J.*, **28**, 121 (1902).
(8) All melting points reported are uncorrected.

TABLE I

2-$N^4$-ACETYLSULFANILAMIDO-5-SUBSTITUTED-4-THIAZOLONES

| No. | 5-Substituent | Yield,[a] % | M. p., °C. (uncor.) | Formula | Nitrogen analyses,[h] % Calcd. | Found |
|---|---|---|---|---|---|---|
| 1[b] | -H | 50 | 266.5 | $C_{11}H_{11}O_4N_3S_2$ | 13.42 | 13.39 |
| 2[c] | $-CH_3$ | 45 | 244–245 | $C_{12}H_{13}O_4N_3S_2$ | 12.84 | 12.69 |
| 3 | $-CH_2CH_3$ | 50 | 200–201 | $C_{13}H_{15}O_4N_3S_2$ | 12.32 | 12.35 |
| 4 | $-(CH_2)_2CH_3$ | .. | 187–188 | $C_{14}H_{17}O_4N_3S_2$ | 11.83 | 11.73 |
| 5[d] | $-(CH_2)_3CH_3$ | 40 | 184–185 | $C_{15}H_{19}O_4N_3S_2$ | 11.38 | 11.31 |
| 6 | $-(CH_2)_4CH_3$ | 60 | 190–191 | $C_{16}H_{21}O_4N_3S_2$ | 10.97 | 10.83 |
| 7[e] | $-(CH_2)_{15}CH_3$ | .. | 143[e] | $C_{27}H_{43}O_4N_3S_2$ | 7.81 | 7.67 |
| 8[f] | $(-CH_3)_2$ | 65 | 247–248 | $C_{13}H_{15}O_4N_3S_2$ | 12.32 | 12.22 |
| 9[g] | $(-CH_2CH_3)_2$ | 70 | 210–211.5 | $C_{15}H_{19}O_4N_3S_2$ | 11.38 | 11.33 |

[a] The yields are based upon crude solid. [b] The 2-amino-4-thiazolone used in the preparation of this compound is insoluble in pyridine. Therefore, the sulfonyl chloride was added gradually to a hot suspension of it in pyridine, following which solution resulted before the final addition of the sulfonyl chloride. The compound was purified by recrystallization from a mixture of methyl cellosolve and water, and melted with decomposition. [c] Two equivalents of 2-amino-5-methyl-4-thiazolone were used in the preparation of this compound. It was recrystallized from 50% methyl cellosolve. [d] The crude product was obtained as a taffy-like material which was difficult to purify. The yield is calculated on one recrystallization from dilute alcohol. [e] Recrystallized from ethyl alcohol. The melting point is indefinite as it softens at 130° and melts up to 143°. However, three recrystallizations gave the same results. [f] Fifty per cent. excess of sulfonyl chloride was used. [g] Yields up to 98% have been obtained by the use of 50% excess of sulfonyl chloride. [h] The analyses were carried out in these laboratories with the coöperation of Mr. John P. Lutz.

**2-Amino-5-propyl-4-thiazolone,** m. p. 182° after recrystallization from alcohol, prepared from α-bromovaleric acid.

*Anal.* Calcd. for $C_6H_{10}ON_2S$: N, 17.72. Found: N, 17.70.

**2-Amino-5-amyl-4-thiazolone,** m. p. 191°, prepared from α-bromoheptanoic acid.

*Anal.* Calcd. for $C_8H_{14}ON_2S$: N, 15.05. Found: N, 14.97.

**Sulfonamidothiazolones.**—(1) To 112.1 g. (0.78 mole) of 2-amino-5-ethyl-4-thiazolone dissolved in 500 cc. of dry pyridine by heating was added with stirring 200 g. (0.86 mole) of recrystallized *p*-acetaminobenzenesulfonyl chloride over a period of one-half hour. In the case of 2-amino-4-thiazolone complete solution did not occur before the addition of the sulfonyl chloride. However, as the reaction proceeded all of the material dissolved in the pyridine. After the addition was complete and the heat of the reaction began to subside, the solution was heated below the reflux temperature for one-half hour on the steam-bath. The pyridine was removed under reduced pressure and the sirupy residue triturated with 500 cc. of 1:2 hydrochloric acid. Water was added slowly to the mixture as long as precipitation occurred and the crude product thus obtained was filtered and washed several times with water. A yield of 130 g. (50%) was obtained and after purification by crystallization from dilute alcohol with decolorization with charcoal (Norite) it melted at 200–201°.

*Anal.* Calcd. for $C_{13}H_{15}O_4N_3S_2$: N, 12.32; S, 18.77. Found: N, 12.35; S, 18.82.

The properties of the homologous $N^4$-acetyl compounds are summarized in Table I.

The higher acyl derivatives (Table II) were prepared by the same general procedure although they were obtained in lower yields and were isolated as crude taffy-like products which presented some difficulties in purification. The *p*-nitrobenzene and *p*-toluenesulfonamidothiazolones (Table III) were obtained in satisfactory yields by the same method.

Attempts to improve the yields of the acetyl derivatives by condensation of the sulfonyl chloride with the appropriate 2-amino-4-thiazolones in aqueous solution, using sodium carbonate as a neutralizing agent, failed to give the desired products. Direct condensations of the sulfonyl chloride with two equivalents of the 2-amino-thiazolones in the absence of any solvent were successful, but the yields were not any higher and the products were difficult to purify. Similar yields were obtained by carrying out the condensations in the presence of one equivalent of pyridine.

(2) To $N^4$-acetylsulfanilamide, 21.4 g., (0.1 mole), dissolved in 200 cc. of *N* sodium hydroxide, was added, dropwise with stirring, 11.3 g. (0.1 mole) of chloroacetyl chloride. After the heat of the reaction had subsided, the solution was neutralized with concentrated hydrochloric acid and the crude $N^4$-acetyl-$N^1$-α-chloroacetylsulfanilamide purified by crystallization from methyl cellosolve and water, m. p. 241–242° with decomposition.

*Anal.* Calcd. for $C_{10}H_{11}O_4N_2SCl$: N, 9.64. Found: N, 9.56.

**$N^4$-Acetyl-$N^1$-α-bromobutyrylsulfanilamide,** m. p. 230–232° with decomposition, was prepared in the same manner from α-bromobutyryl bromide and $N^4$-acetylsulfanilamide.

*Anal.* Calcd. for $C_{12}H_{15}O_4N_2SCl$: N, 7.72. Found: N, 7.72.

The above products were refluxed for four hours in alcohol with 20% excess of potassium thiocyanate according to the procedure of Dains and Eberly.[9] **2-$N^4$-Acetylsulfanilamido-4-thiazolone,** m. p. 264–266° dec., and **2-$N^4$-acetylsulfanilamido-5-ethyl-4-thiazolone,** m. p. 200–201°, were prepared in this manner. The products were isolated from the reaction mixture by dilution with water and were purified by crystallization from water or dilute alcohol.

(9) Dains and Eberly, THIS JOURNAL, **55**, 3859 (1933).

TABLE II

2-$N^4$-ACYLSULFANILAMIDO-5-SUBSTITUTED-4-THIAZOLONES

| No. | Acyl group | 5-Substituent | M. p., °C. (uncor.) | Formula | Nitrogen analyses,[b] % Calcd. | Found |
|---|---|---|---|---|---|---|
| 1 | $CH_3CO$- | -$CH_2CH_3$ | 200–201 | $C_{14}H_{15}O_4N_3S_2$ | 12.32 | 12.35 |
| 2 | $CH_3(CH_2)_4CO$- | -$CH_2CH_3$ | 174–175 | $C_{17}H_{23}O_4N_3S_2$ | 10.58 | 10.52 |
| 3 | $CH_3(CH_2)_5CO$- | -$CH_2CH_3$ | 140–141 | $C_{18}H_{25}O_4N_3S_2$ | 10.22 | 10.17 |
| 4[a] | $CH_3(CH_2)_4CO$- | -$(CH_2)_3CH_3$ | 134–135 | $C_{19}H_{27}O_4N_3S_2$ | 9.88 | 9.80 |
| 5[a] | $CH_3(CH_2)_5CO$- | -$(CH_2)_3CH_3$ | 139–140 | $C_{20}H_{29}O_4N_3S_2$ | 9.57 | 9.61 |

[a] Recrystallized from dioxane and water. [b] Analyses carried out with the coöperation of Mr. John P. Lutz and Mr. John R. Taylor.

TABLE III

2-SULFANILAMIDO-5-SUBSTITUTED-4-THIAZOLONES

| No. | 5-Substituent | Yield,[a] % | M. p., °C. (uncor.) | Formula | Nitrogen analyses,[g] % Calcd. | Found |
|---|---|---|---|---|---|---|
| 1[b] | -H | 45 | 235–238[b] | $C_9H_9O_3N_3S_2$ | 15.50 | 15.44 |
| 2 | -$CH_3$ | 77 | 167–168 | $C_{10}H_{11}O_3N_3S_2$ | 14.73 | 14.71 |
| 3[c] | -$CH_2CH_3$ | 83 | 184–184.5 | $C_{11}H_{13}O_3N_3S_2$ | 14.05 | 13.87 |
| 4 | -$(CH_2)_2CH_3$ | | 160–161 | $C_{12}H_{15}O_3N_3S_2$ | 13.42 | 13.48 |
| 5 | -$(CH_2)_3CH_3$ | 76 | 206.5–207.5 | $C_{13}H_{17}O_3N_3S_2$ | 12.84 | 12.83 |
| 6 | -$(CH_2)_4CH_3$ | 63 | 167–168 | $C_{14}H_{19}O_3N_3S_2$ | 12.32 | 12.34 |
| 7[d] | -$(CH_2)_{15}CH_3$ | | 129–131 | $C_{25}H_{41}O_3N_3S_2$ | 8.49 | 8.43 |
| 8 | $(-CH_3)_2$ | 82 | 210–211 | $C_{11}H_{13}O_3N_3S_2$ | 14.05 | 13.98 |
| 9 | $(-CH_2CH_3)_2$ | 80 | 198–199 | $C_{13}H_{17}O_3N_3S_2$ | 12.84 | 12.76 |
| 10[e] | 2-*p*-Nitrobenzenesulfonamido-5-ethyl-4-thiazolone | 73 | 192–193 | $C_{11}H_{11}O_5N_5S_2$ | 12.77 | 12.67 |
| 11[f] | 2-*p*-Nitrobenzenesulfonamido-5-butyl-4-thiazolone | 38 | 186–187 | $C_{13}H_{15}O_5N_5S_2$ | 11.76 | 11.62 |
| 12 | 2-*p*-Toluenesulfonamido-5-ethyl-4-thiazolone | | 139–140 | $C_{12}H_{14}O_2N_2S_2$ | 9.40 | 9.44 |

[a] The yields are based upon crude solid. [b] Recrystallized from methyl cellosolve and water. Melted with decomposition. [c] Sulfur analysis: calcd., 21.40; found, 21.35. [d] Hydrolysis was carried out by refluxing 15.85 g. of the acetyl derivative for forty-five minutes in a solution of 10 cc. conc. hydrochloric acid and 100 cc. alcohol. Solution was complete within five minutes and in ten minutes a precipitation of the hydrochloride began. However, a small amount of unhydrolyzed material was recovered on working up the product. Recrystallized from alcohol. [e] Ten per cent. excess of the aminothiazolone was used. Recrystallized from anhydrous alcohol. [f] Equivalent quantities of the sulfonyl chloride and aminothiazolone were used. Recrystallized from anhydrous alcohol. [g] Analyses carried out with the coöperation of Mr. John P. Lutz.

**Hydrolysis.**—The acid hydrolysis of the $N^4$-acetylsulfanilamidothiazolones was carried out by refluxing a suspension of the crude material in 1:7 hydrochloric acid (8 cc. per g.) and alcohol (0.5–2.0 cc. per g.) until all of the solid dissolved. The hot solution was decolorized with charcoal (Norite) and upon cooling, the product crystallized from the solution as the free amine or as a mixture of the hydrochloride and the free amine. In those cases where attempts were made to recrystallize the hydrochloride, it was converted into the free amine. The crude solid was redissolved in dilute ammonia solution and again decolorized with charcoal. Slow neutralization of the solution with dilute hydrochloric acid gave a product which was easily purified by crystallization from alcohol and water.

The sulfanilamido-4-thiazolones are slightly acidic in their properties; for example, a saturated aqueous solution of 2-sulfanilamido-5-ethyl-4-thiazolone has a *p*H of 4.9. Therefore, they are usually obtained in the form of the free amines from the acid hydrolysis solution. However, if the acidity of the solution is increased, the compounds are obtained as a mixture of the hydrochloride and the free amine. The ammonium salt of 2-sulfanilamido-5-ethyl-4-thiazolone was obtained by dissolving the free amine in a minimum of dilute aqueous ammonia and salting out with excess of concentrated aqueous ammonia. A 1% solution of the ammonium salt in water has a *p*H of 7.3.

The sulfonamidothiazolones were tested for chemotherapeutic activity against experimental streptococcal and pneumococcal infections in a standard stock strain of white mice.[10] The antistreptococcal activity of these compounds was determined by the oral administration of daily doses of 5 mg. for four days to 20-g. mice experimentally infected with one thousand lethal doses of a virulent strain of β-hemolytic streptococcus. The initial dose of compound was given at the same time as the intraperitoneal injection of the infective culture. The antipneumococcal activity was determined by the oral administration of 20 mg. doses to mice infected with one hundred lethal doses of type I pneumococci at the time of the first dose of compound. Five additional doses were administered orally at seven, twenty-four, forty-eight, seventy-two and ninety-six hours.

(10) We are indebted to Dr. Bettylee Hampil and Mr. G. W. Webster for the testing of these compounds.

The results indicate that six compounds, the 5-propyl, 5-butyl, 5-amyl, 5,5-diethyl, and the $N^4$-hexanoyl and heptanoyl substituted 5-butyl derivatives of sulfanilamidothiazolone, possess promising antistreptococcal activity. Favorable antipneumococcal activity was shown by the 5-ethyl, 5-butyl, 5,5-dimethyl, 5,5-diethyl and the $N^4$-hexanoyl substituted 5-butyl derivatives.

TABLE IV

MAXIMUM BLOOD CONCENTRATIONS[a]

| Compound | Dose 0.25 g./kg. per mouse | Dose 1.0 g./kg. per mouse |
|---|---|---|
| Sulfanilamide | 14[b] | 50[b] |
| Sulfapyridine | 15[c] | 19[c] |
| Sulfathiazole | 16[d] | 21[d] |
| 2-Sulfanilamido-5-ethyl-4-thiazolone | 25[e] | 50[e] |

[a] The results are given as mg. per 100 cc. as determined by the Marshall method (*J. Biol. Chem.*, **128**, 537 (1939)) and represent the average from three separate determinations. Each determination was made from the pooled blood of five mice.

[b] These results were obtained from blood samples taken one hour after administration of the drug. It is probable that the maximum blood concentration had been passed.

[c] These concentrations were maintained from one to four hours after administration of the drug, after which they fell off rapidly. However, significant concentrations remained after twelve hours.

[d] This blood concentration at the lower dose level was obtained in one hour and fell off rapidly thereafter. At the higher dose, this blood concentration was maintained for about three hours. The compound was eliminated almost entirely from the blood within twelve hours after administration.

[e] The blood concentration at the lower dose reached its maximum in two hours after administration of the drug and maintained a relatively high level for eight hours. The maximum was reached in four hours at the higher dose and the concentration remained above 40 mg. per cent. for eight hours. However, the blood was free of the drug in twelve hours after both doses.

Preliminary tests on the antistaphylococcal activity of the 5-ethyl and 5,5-diethyl compounds indicate that they have activity against this organism.

In order to correlate the chemotherapeutic effect of these compounds, we have determined the relative absorption and blood concentration of 2-sulfanilamido-5-ethyl-4-thiazolone for comparison with sulfanilamide, sulfapyridine and sulfathiazole in mice at a dosage of 0.25 g. and 1.0 g. per kilogram of body weight according to the Marshall method.[11,12] The maximum blood concentrations at the two dose levels of these compounds are recorded in Table IV. It should be pointed out that 2-sulfanilamido-5-ethyl-4-thiazolone is absorbed as rapidly and its maximum concentration is higher on both dose levels than for the other three compounds. It also appeared to be completely eliminated from the blood between eight and twelve hours after administration at both dose levels.

## Summary

The preparation and properties of a number of sulfonamidothiazolones are described. Sixteen 2-sulfanilamido-4-thiazolones have been tested for their chemotherapeutic effect against experimental streptococcic and pneumococci infections in mice. This group of compounds shows promising chemotherapeutic activity.

GLENOLDEN, PA. RECEIVED AUGUST 13, 1941

(11) Bratton and Marshall, *J. Biol. Chem.*, **128**, 537 (1939).

(12) These tests were conducted in coöperation with Mr. G. W. Webster, Mr. Lloyd G. Colio and Mr. John P. Lutz.