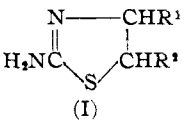
[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

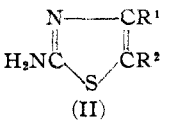
Sulfanilamide Compounds. VII. Thiazoline Derivatives[1]

BY JAMES H. HUNTER AND H. G. KOLLOFF

2-Amino-Δ^2-thiazolines (I) bear a close structural relationship to 2-aminothiazoles (II)



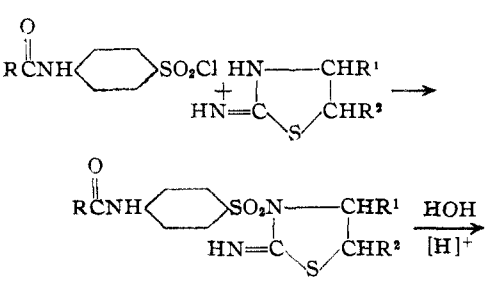
(I)

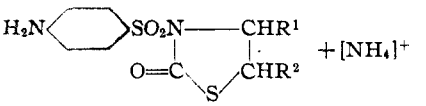


(II)

Since certain sulfanilamidothiazoles have proved efficacious as antibacterial agents, it was considered relevant to investigate a series of sulfanilyl derivatives[2] of type I for the purpose of comparison. Description is herewith given of the preparation and some of the properties of certain N^4-acylsulfanilyl and *p*-nitrobenzenesulfonyl derivatives of 2-amino-Δ^2-thiazoline,[3] 2-amino-4-methyl-Δ^2-thiazoline,[4] 2-amino-5-methyl-Δ^2-thiazoline[5] and 2-amino-5-phenyl-Δ^2-thiazoline,[6] together with their hydrolysis products and proof of the structure of the latter.

The N^4-acylsulfanilyl derivatives were prepared by the action of an ethereal solution of the appropriate N^4-acylsulfanilyl chloride on an aqueous solution of the amine hydrobromide in the presence of sodium carbonate. Contrary to our expectations, these condensation products were alkali-insoluble and upon hydrolysis with dilute sulfuric acid, instead of obtaining 2-sulfanilamido-Δ^2-thiazolines, ammonia was split out and sulfanilylthiazolidones, also insoluble in alkali, were formed. On the basis of these results, the course of the reactions may be formulated as





The structural formulas assigned here to these compounds have received considerable investigation,[7,8,9,10] which, together with the proofs of structure obtained in the present investigation, points to the probable correctness of this formulation. Such a concept is further supported by the studies of Fromm and Kapeller-Adler[11] who found that 4-tolylsulfonyl chloride reacted with 2-amino-Δ^2-thiazoline hydrobromide in the presence of sodium hydroxide to yield 2-imino-3-(4'-tolylsulfonyl)-thiazoline which, upon treatment with dilute sulfuric acid gave 3-(4'-tolylsulfonyl)[2]-thiazolidone.[12]

Elucidation of the structure of the sulfanilylthiazolidenes was found feasible through studies of the mono-*p*-nitrobenzenesulfonyl derivatives of the 2-amino-Δ^2-thiazolines involved. As indicated in the flow sheet below, we have been able to establish the structure of the sulfanilylthiazolidones and, by inference, that of the mono-N^4-acylsulfanilyl- and mono-*p*-nitrobenzenesulfonyliminothiazolines. This method of proof, in the course of which compounds of type V have been prepared, indirectly corroborates the structure of 2-sulfanilamido-Δ^2-thiazoline as reported by Sprague and Kissinger,[7] Jensen[9] and Raiziss and Clemence.[10]

The 3-(*p*-nitrobenzenesulfonyl)-2-iminothiazolines were prepared as described for the corresponding mono-N^4-acylsulfanilyl derivatives, using *p*-nitrobenzenesulfonyl chloride.[13] In the preparation of the mono-*p*-nitrobenzenesulfonyl derivatives of certain of the substituted 2-amino-Δ^2-thiazolines, some di-(*p*-nitrobenzenesulfonyl) derivative was generally formed; however, separation from the mono-compound was effected by fractional crystallization from dilute 1,4-dioxane.

(1) Presented in part before the Division of Medicinal Chemistry of the American Chemical Society at Atlantic City, N. J., Sept. 8-12, 1941.

(2) Since this work was undertaken, Jensen and Thorsteinsson (*Dansk Tids. Farm.*, **15**, 41 (1941); *cf. Chem. Abst.*, **35**, 5109 (1941), have reported the synthesis of several of these derivatives.

(3) Gabriel, *Ber.*, **22**, 1141 (1889).

(4) Gabriel and Ohle, *ibid.*, **50**, 813 (1917).

(5) Hirsch, *ibid.*, **23**, 965 (1890).

(6) Gabriel and Colman, *ibid.*, **47**, 1872 (1914).

(7) Sprague and Kissinger, THIS JOURNAL, **63**, 578 (1941).

(8) Hartmann and Druey, *Helv. chim. acta*, **24**, 536 (1941).

(9) Jensen, *ibid.*, **24**, 1249 (1941).

(10) Raiziss and Clemence, THIS JOURNAL, **63**, 3124 (1941).

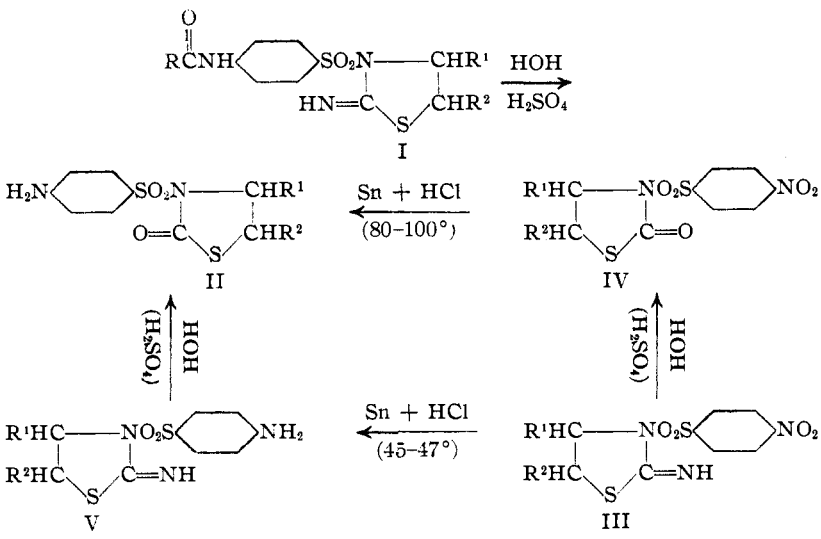
(11) Fromm and Kapeller-Adler, *Ann.*, **467**, 240 (1928).

(12) Fromm and Kapeller-Adler name these compounds as 2-imino-thiazolinyl-3-tolylsulfonate and thiazolidonyl-3-tolylsulfonate, respectively.

(13) Ekbom, *Ber.*, **35**, 653 (1902).

The di-(*p*-nitrobenzenesulfonyl) derivatives, which were produced in small yield as by-products when the condensation was carried out in aqueous sodium carbonate–ether mixtures, could be prepared in good yield as the main product by utilizing the free amino-thiazoline in pyridine. Since the procedures are essentially the same for the four compounds under consideration, details will be given for the proof of the structure of only one of these, *i. e.*, 3-sulfanilyl-5-methyl-2-thiazolidone.

Preliminary biologic evaluation[14] of these thiazolidine and thiazolidone derivatives is incomplete at present. On the basis of the data now available, the compounds possess a higher degree of activity against experimental β-hemolytic streptococcal infections than they do against Type I pneumococcal infections. It is of interest to note that of the compounds thus far tested against experimental infections in mice, 3-(*p*-nitrobenzenesulfonyl)-2-thiazolidone and its 4- or 5-methyl substituted derivatives have shown moderate to good activity against β-hemolytic streptococcal infections, although their anti-pneumococcal activity is but slight; and that in general these derivatives possess much more activity than the corresponding 3-sulfanilyl-2-thiazolidones.



Experimental

3-(N^4-Acylsulfanilyl)-2-iminothiazolidines.—The preparation of these derivatives may be suitably illustrated by the following example.

3-(N^4-Acetylsulfanilyl)-2-iminothiazoline.—Nine and fifteen hundredths grams (0.05 mole) of 2-amino-Δ^2-thiazoline hydrobromide and 10.6 g. (0.1 mole) of anhydrous sodium carbonate were dissolved in 50 cc. of water, the solution covered with 25 cc. of ether and, with vigorous stirring, 11.67 g. (0.05 mole) of N^4-acetylsulfanilyl chloride slowly added. The mixture was stirred for two hours and allowed to stand overnight. The precipitate was collected and air-dried; yield, 14.0 g. (93.6%). A small amount of the crude product, upon crystallization from aqueous acetone, gave a white amorphous material melting at 183°.[15]

Anal. Calcd. for $C_{11}H_{13}N_3O_3S_2$: N, 14.05. Found: N, 14.25.

3-Sulfanilyl-2-thiazolidones.—As described in the example below, these were obtained by the acid hydrolysis of the corresponding N^4-acetylsulfanilyl derivatives.

3-Sulfanilyl-5-phenylthiazolidone.—A mixture of 1.4 g. (0.00373 mole) of 3-(N^4-acetylsulfanilyl)-5-phenyl-2-iminothiazolidine, 25 cc. of water and 1 cc. of concentrated sulfuric acid was heated for three hours on a steam-bath, then allowed to stand overnight. The white precipitate was collected, washed with water and air dried; yield, 1.1 g. (88.4%). The presence of ammonia in the filtrate was readily shown with Nessler reagent. The crude product, after repeated crystallizations from dilute alcohol, gave white crystals melting constantly at 168–170°.

Anal. Calcd. for $C_{15}H_{14}N_2O_3S_2$: N, 8.38. Found: N, 8.56.

3-(*p*-Nitrobenzenesulfonyl)-5-methyl-2-iminothiazoline.—A solution of 19.7 g. (0.1 mole) of 2-amino-5-methyl-Δ^2-thiazoline hydrobromide,[5] m. p. 110–111°, in 75 cc. of water was covered with 50 cc. of ether and 10.6 g. (0.1 mole) of anhydrous sodium carbonate added with vigorous mechanical stirring. When solution was complete, 22.15 g. (0.1 mole) of *p*-nitrobenzenesulfonyl chloride,[13] m. p. 87.5–88°, was added slowly and stirring continued for two hours. The precipitate was collected, washed with water and dried in air; yield, 33 g. When the crude product was added to 300 cc. of boiling alcohol, 8.5 g. remained undissolved. After repeated crystallizations from dilute 1,4-dioxane, this alcohol-insoluble product yielded pale yellow needles, m. p. 219.5–220.5°.

Anal. Calcd. for $C_{16}H_{14}N_4O_5S_2$: N, 11.52. Found: N, 11.36.

Upon chilling, 7.2 g. of light yellow crystals was obtained from the alcoholic filtrate; m. p. 114–114.5°. From the mother liquor an additional 4.8 g. of a somewhat less pure product was obtained; total yield, 12 g. (39.9%).

Anal. Calcd. for $C_{10}H_{11}N_3O_4S_2$: N, 13.95. Found: N, 13.85.

3-Sulfanilyl-5-methyl-2-iminothiazolidine.—Fifty cubic centimeters of 10% hydrochloric acid was added to a well-stirred mixture of 6.02 g. (0.02 mole) of once-crystallized 3-(*p*-nitrobenzenesulfonyl)-5-methyl-2-iminothiazoline, 50

(14) By Dr. D. W. McKinstry.

(15) All melting points are uncorrected.

TABLE I

DERIVATIVES OF THIAZOLIDINES

3-Substituent (S)	2-Iminothiazolidine (S)—N——CH₂ / HN=C, S, CH₂				2-Imino-4-methylthiazolidine (S)—N——CH—CH₃ / HN=C, S, CH₂			
	M. p., °C. (uncor.)	Formula	Nitrogen, % Calcd.	Found	M. p., °C.	Formula	Nitrogen, % Calcd.	Found
N⁴-Acetylsulfanilyl	183	$C_{11}H_{13}N_3O_3S_2$[a]	14.05	14.25	178–179	$C_{12}H_{15}N_3O_3S_2$[b]	13.42	13.19
N⁴-Caproylsulfanilyl	160–160.5	$C_{16}H_{21}N_3O_3S_2$[a]	11.83	11.99	145–146	$C_{16}H_{23}N_3O_3S_2$[d]	11.38	11.30
p-Nitrobenzenesulfonyl	135–137	$C_9H_8N_3O_4S_2$[b]	14.63	14.64	133–134.5	$C_{10}H_{11}N_3O_4S_2$[f]	13.95	14.17
Sulfanilyl	144–145	$C_9H_{11}N_3O_2S_2$[b]	16.34	16.59	137–138	$C_{10}H_{13}N_3O_2S_2$[d]	15.50	15.31

3-Substituent (S)	2-Imino-5-methylthiazolidine (S)—N——CH₂ / HN=C, S, CH—CH₃				2-Imino-5-phenylthiazolidine (S)—N——CH₂ / HN=C, S, CH—C₆H₅			
N⁴-Acetylsulfanilyl	162–163	$C_{12}H_{15}N_3O_3S_2$[c]	13.42	13.26	181–183	$C_{17}H_{17}N_3O_3S_2$[b]	11.20	11.38
N⁴-Caproylsulfanilyl	164–165	$C_{16}H_{23}N_3O_3S_2$[b]	11.38	11.41	203–204	$C_{21}H_{25}N_3O_3S_2 \cdot C_2H_5OH$[b,e]	8.85	8.67
p-Nitrobenzenesulfonyl	114–114.5	$C_{10}H_{11}N_3O_4S_2$[b]	13.95	13.85	139.5–140.5	$C_{15}H_{13}N_3O_4S_2$[b]	11.57	11.78
Sulfanilyl	153–153.5	$C_{10}H_{13}N_3O_2S_2$[b]	15.50	15.28				

3-Substituent (S)	2-Ketothiazolidine (S)—N——CH₂ / O=C, S, CH₂				2-Keto-4-methylthiazolidine (S)—N——CH—CH₃ / O=C, S, CH₂			
p-Nitrobenzene sulfonyl	182–183	$C_9H_8N_2O_5S_2$[h]	9.72	9.99	139–141	$C_{10}H_{10}N_2O_5S_2$[d]	9.27	9.52
Sulfanilyl	209–210	$C_9H_{10}N_2O_3S_2$[b]	10.85	10.99	134.5–135.5	$C_{10}H_{12}N_2O_3S_2$[d]	10.30	10.50

3-Substituent (S)	2-Keto-5-methylthiazolidine (S)—N——CH₂ / O=C, S, CH—CH₃				2-Keto-5-phenylthiazolidine (S)—N——CH₂ / O=C, S, CH—C₆H₅			
p-Nitrobenzenesulfonyl	177	$C_{10}H_{10}N_2O_5S_2$[b]	9.27	9.33	165.5–168	$C_{15}H_{12}N_2O_5S_2$[h]	7.69	7.88
Sulfanilyl	190.5–191.5	$C_{10}H_{12}N_2O_3S_2$[d]	10.30	10.35	168–170	$C_{15}H_{14}N_2O_3S_2$[d]	8.38	8.56

Di-substituted derivatives	(3)—N——CH₂ / (2)=C, S, CH₂				(3)—N——CH—CH₃ / (2)=C, S, CH₂			
2-(*p*-Nitrobenzenesulfonylimino)-3-(*p*-nitrobenzenesulfonyl)	268.5–270.5	$C_{16}H_{12}N_4O_8S_3$[g]	11.85	11.75	242–242.5	$C_{16}H_{14}N_4O_8S_3$[h]	11.52	11.71

Di-substituted derivatives	(3)—N——CH / (2)=C, S, CH—CH₃				(3)—N——CH₂ / (2)=C, S, CH—C₆H₅			
2-(*p*-Nitrobenzenesulfonylimino)-3-(*p*-nitrobenzenesulfonyl)	219.5–220.5	$C_{16}H_{14}N_4O_8S_3$[h]	11.52	11.36	215.5–218	$C_{21}H_{16}N_4O_8S_3$[h]	10.22	9.95

[a] From aqueous acetone. [b] From alcohol. [c] From acetone–petroleum ether. [d] From aqueous alcohol. [e] *Anal.* Calcd. for $C_{21}H_{25}N_3O_8S_2$: C, 57.86; H, 6.5. Found: C, 57.76; H, 6.33. [f] From benzene. [g] From pyridine, followed by pulverizing and extracting first with hot alcohol, then hot acetone. [h] From dilute 1,4-dioxane.

cc. of alcohol and 7.12 g. (0.06 atom) of granulated tin. After stirring for four hours at 45–47°, the mixture was filtered, washed with a little water and tin salts removed from the filtrate by repeatedly saturating with hydrogen sulfide. Excess hydrogen sulfide was removed by aeration and the clear solution made alkaline with saturated sodium bicarbonate. The white crystalline precipitate was collected, washed with water and air-dried; yield, 2.6 g. (48%); m. p. 148–149°. When crystallized twice from dilute and once from undiluted alcohol, the product melted sharply at 153–153.5°.

Anal. Calcd. for $C_{10}H_{13}N_3O_2S_2$: C, 44.28; H, 4.79; N, 15.50. Found: C, 44.20; H, 4.62; N, 15.28.

3-(*p*-Nitrobenzenesulfonyl)-5-methyl-2-thiazolidone.—A mixture of 1.51 g. (0.005 mole) of 3-(*p*-nitrobenzenesulfonyl)-5-methyl-2-iminothiazoline, 50 cc. of water and 1 cc. of concentrated sulfuric acid was heated on a steam-bath for thirty-five minutes. When cold, the voluminous precipitate was collected, washed with water and dried in air; yield, 1.2 g. (79.5%); m. p. 174–175°. Ammonia was shown to be present in the filtrate by means of Nessler reagent. The crude compound was crystallized twice from alcohol; m. p. 177°.

Anal. Calcd. for $C_{10}H_{10}N_2O_5S_2$: N, 9.27. Found: N, 9.33.

3-Sulfanilyl-5-methyl-2-thiazolidone

A. By Reduction of 3-(*p*-Nitrobenzenesulfonyl)-5-methyl-2-thiazolidone.—A mixture of 2.6 g. (0.0086 mole) of 3-(*p*-nitrobenzenesulfonyl)-5-methyl-2-thiazolidone, 50 cc. of alcohol, 15 cc. of concentrated hydrochloric acid and 10 g. of granulated tin was refluxed on a steam-bath for thirty minutes. The clear, colorless solution was filtered from excess tin, the filtrate diluted with 50 cc. of water and chilled. The white crystals, after collecting, washing and drying, were crystallized from 50 cc. of alcohol; yield, 0.8 g. (34.2%); m. p. 189–190°. Recrystallization from alcohol gave a product melting at 190–190.5°.

Anal. Calcd. for $C_{10}H_{12}N_2O_3S_2$: N, 10.30. Found: N, 10.50.

When mixed with 3-sulfanilyl-5-methyl-2-thiazolidone,[16] m. p. 190.5–191°, the mixture melted at 190–190.5°.

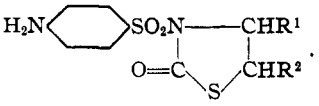
B. By Hydrolysis of 3-Sulfanilyl-5-methyl-2-iminothiazolidine.—One gram (0.0037 mole) of 3-sulfanilyl-5-methyl-2-iminothiazolidine was suspended in a solution of 20 cc. of water and 0.7 cc. of concentrated sulfuric acid and heated on a steam-bath for three hours. When cold, the crystalline precipitate was collected, washed with water and dried. The presence of ammonia in the filtrate was shown by a positive reaction with Nessler reagent. The crude product was crystallized from 60 cc. of alcohol; yield, 0.5 g. (49.6%), m. p. 190.5–191.5°.

Anal. Calcd. for $C_{10}H_{12}N_2O_3S_2$: N, 10.30. Found: N, 10.35.

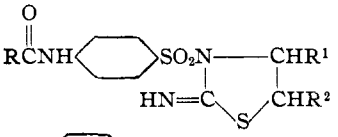
The above compound, when mixed with 3-sulfanilyl-5-methyl-2-thiazolidone[16] and the product obtained by reduction of 3-(*p*-nitrobenzenesulfonyl)-5-methyl-2-thiazolidone, melted at 190–190.5°.

Summary

The preparation and some properties of a series of mono-N^4-acylsulfanilylthiazolines and their hydrolysis products, sulfanilylthiazolidones, have been described. These sulfanilylthiazolidones have been proved to be of the general type



By inference, the mono-N^4-acylsulfanilyl and mono-*p*-nitrobenzenesulfonyl derivatives of the corresponding 2-amino-Δ^2-thiazolines have the structures,



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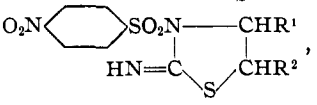
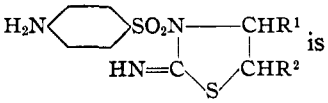
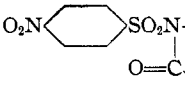


respectively. The preparation of several derivatives of the type



is described. Based on the limited biological data available at the time of writing, in this series of compounds, derivatives of the type



appear to be the most efficacious against experimental β-hemolytic streptococcal infections.

(16) From hydrolysis of 3-(N^4-acetylsulfanilyl)-5-methyl-2-iminothiazolidine.

KALAMAZOO, MICHIGAN RECEIVED OCTOBER 1, 1942

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

The Action of Aliphatic Diazo Compounds upon α,β-Unsaturated Ketones. II.[1] *cis-* and *trans*-Dibenzoylethylene

BY LEE IRVIN SMITH AND KENNETH L. HOWARD[2]

An aliphatic diazo compound, such as diazomethane, will react with simple α,β-unsaturated esters to give, as the first product, a Δ^1-pyrazoline in which the nitrogen atom is always linked to the α-carbon atom of the carbonyl compound. These Δ^1-pyrazolines rearrange under the influence of certain reagents (such as halogen acids), to give Δ^2-pyrazolines; whenever possible, the product of this rearrangement will contain a carbon to nitrogen double bond which is conjugated with the carbonyl group. When pyrolyzed, the usual decomposition of the pyrazolines involves loss of nitrogen with formation of a homolog, usually the β-alkyl derivative of the original unsaturated carbonyl compound, a cyclopropane or a mixture of the two; but frequently the pyrolysis also involves merely a dehydrogenation, and gives rise to the pyrazole.[3]

In general, in the reaction with aliphatic diazo compounds, the α,β-unsaturated ketones parallel the esters; thus from the reaction between benzalacetophenone and diazomethane, both pyrazolines were obtained; on pyrolysis, the pyrazolines gave the alkylated ethylene and the pyrazole, but not the cyclopropane.[1] Even when a quinone is used as the unsaturated carbonyl compound, the products conform, in so far as it is possible, with these same types. Thus Fieser and Peters[4] obtained the Δ^1-pyrazoline and from it by oxidation, the pyrazole, when 1,4-naphthoquinone

(1) First paper, Smith and Pings, *J. Org. Chem.*, **2**, 23 (1937).

(2) Abstracted from a thesis by K. L. Howard, presented to the Graduate Faculty of the University of Minnesota in partial fulfillment of the requirements for the Ph.D. Degree, July, 1942.

(3) von Auwers, *Ann.*, **470**, 284 (1929); **496**, 27, 252 (1902); *Ber.*, **66**, 1198 (1933); von Pechmann, *ibid.*, **33**, 3590, 3594, 3597 (1900).

(4) Fieser and Peters, THIS JOURNAL, **53**, 4080 (1931).