point determination. Check runs, with longer reaction periods, were made to check the completeness of the reaction. It is apparent from the analyses that, under the conditions used in this work, there is no tendency for the salts to form crystalline ammines with the excess ammonia gas present.

Procedure.—The melting point of the salts is obtained by raising the temperature of the glycerol-bath rapidly to within 15–20° of the melting point of the salt. The difference between t^1 and t^2 is about 8° at this point. Retarding the rate of heating reduced this difference to within 2° in a few minutes. At this point the temperature of the system is slowly raised until the white salt melts.[7] The flow of ammonia gas is continued throughout the melting point determinations.

The hygroscopicity was estimated by placing a few crystals of the salt on very dry days on a watch glass and observing the rate at which it absorbed moisture and liquefied.

The results obtained with the twelve acids used in these experiments appear in Table I. The melting points are uncorrected.

The accuracy of these results is established by the exact agreement of the observed melting points of ammonium formate and ammonium acetate with the previously reported values.[1,2,3] Duplicate measurements agreed to within ±1°. In general the hygroscopicity decreases with increase in molecular weight.

(7) The melting points reported were all taken at atmospheric pressure. When taken at a pressure of 1.5 mm. they were about 7–8° lower and inconsistent. No immediate brisk evolution of ammonia was observed, but on heating considerably above the m. p. decomposition can be seen to take place readily.

TABLE I

Ammonium salt of acid	M. p., °C.	Hygroscopic	Analyses, % NH Calcd.	Found
Formic	116	Very	26.98	26.63
Acetic	114	Very	22.07	21.81
Propionic	107	Extremely	18.68	18.19
n-Butyric	108	Very	16.18	15.72
Isobutyric	118	Slightly	16.18	15.69
n-Valeric	108	Very	14.27	13.93
Isovaleric	91	Extremely	14.27	13.77
n-Caproic	108	Moderately	12.77	12.48
Isocaproic	102	Moderately	12.77	12.52
n-Heptylic	112	Slightly	11.56	11.31
n-Caprylic	114	Slightly	10.56	10.17
n-Pelargonic	115	Slightly	9.72	9.46

The salts of lower molecular weight show a greater tendency to sublime than do those of higher molecular weight. Although no accurate solubility determinations were made, it was obvious from washing out the tubes that the solubility of the salts in water decreases rapidly with increase in molecular weight.

Summary

1. An apparatus for preparing the anhydrous ammonium salts of aliphatic carboxylic acids and determining their melting points is described.

2. The melting points of the anhydrous ammonium salts of twelve of the lower aliphatic acids are reported.

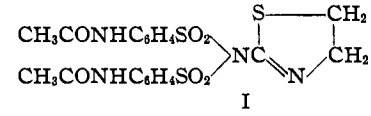
BOSTON, MASSACHUSETTS RECEIVED JUNE 12, 1941

[CONTRIBUTION FROM THE DERMATOLOGICAL RESEARCH LABORATORIES, DIVISION OF ABBOTT LABORATORIES]

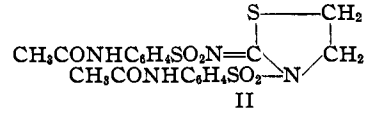
2-Sulfanilyl-aminothiazoline

BY GEORGE W. RAIZISS AND LEROY W. CLEMENCE

In a series of N^1-heterocyclic sulfanilamide derivatives[1] which we prepared and are investigating biologically one of the compounds, 2-sulfanilyl-aminothiazoline, proved to be of particular interest, both chemically and therapeutically. It was prepared by the condensation of *p*-acetylsulfanilyl chloride with 2-aminothiazoline. This reaction produced a bisacetylsulfanilyl derivative,[2] regardless whether one or two moles of the sulfonyl chloride was used. 2-(Di-acetsulfanilyl)-aminothiazoline (I) and 2-acetsulfanilylimino-3-acetsulfanilylthiazolidene (II) are the possible structures of the products formed in this reaction.



I



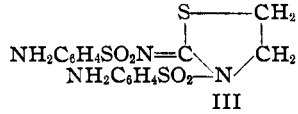
II

After hydrolysis of the diacetyl compound with boiling 10% hydrochloric acid, we obtained on cooling a small amount of insoluble material which was shown to be sulfanilic acid. The acid soluble material, precipitated by neutralization, showed

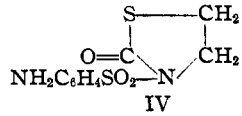
(1) Raiziss, Clemence and Freifelder, THIS JOURNAL **63**, 2739 (1941).

(2) Sprague and Kissinger in a recent paper, *ibid.*, **63**, 578 (1941), published while this paper was being written, also observed the formation of a di-substituted derivative and hydrolysis to 2-sulfanilylaminothiazoline.

analyses for nitrogen and sulfur which corresponded to a mono-sulfanilylaminothiazoline. However, such a compound, having an available sulfonamido hydrogen, should dissolve in dilute sodium hydroxide. The product of hydrolysis did not show complete solubility in alkaline solution. The insoluble material, after filtration and drying, amounted to about 10–15% of the total hydrolysis product. The substance obtained by neutralization of the alkaline solution was recrystallized from 50% alcohol. Nitrogen and sulfur analyses agreed with the values for 2-sulfanilylaminothiazoline and the product was completely soluble in alkaline solution. The alkali insoluble portion, which we first assumed was only the di-sulfanilylamino derivative, gave low nitrogen analyses for such a compound (10.5–11% instead of 13.59%). By fractional crystallization from 50% alcohol or pyridine–water mixture we were able to separate two substances, the di-sulfanilyl derivative,[3] 2-sulfanilylimino-3-sulfanilylthiazolidene (Formula III) and a compound for which we proposed[4] the structure in Formula IV, 3-sulfanilylthiazolidene-2-one.



III



IV

The analytical and molecular weight data agree with the theoretical values.

It would therefore seem that Formula II is the probable one for the di-acetyl compound since on hydrolysis cleavage could take place both at the ring nitrogen to give the 2-sulfanilylaminothiazoline and sulfanilic acid and at the 2-imino nitrogen to give the structure in Formula IV, with formation of the di-sulfanilyl derivative (III) by simply splitting off the acetyl groups.

The 2-aminothiazoline was prepared by a modification of Gabriel's[5] method using β-bromoethylamine hydrobromide and potassium thiocyanate. We also used β-chloroethylamine hydrochloride, for which we developed a new synthesis, with good results.

In tests on various species of animals, 2-sulfanilyl-aminothiazoline (sulfathiazoline)[6] was found to be of low toxicity. When given by mouth, it is absorbed quickly into the blood stream. The therapeutic effect of sulfathiazoline in mice with Types II and III pneumococcus infection was about the same as observed with sulfathiazole. In *Staphylococcus aureus* infection, sulfathiazoline proved to be superior to sulfathiazole.

(3) Jensen and Thorsteinsson, *Dansk Tidskrift for Farmaci*, **15**, 41 (1941), also published while this paper was being written, showed the formation of the di-sulfanilyl compound but did not mention the keto derivative (Formula IV).

(4) The suggestion for this formula was given to us by Mr. Norman Hansen of Abbott Laboratories, North Chicago, Ill.

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

(6) Sulfathiazoline is the name given to 2-sulfanilylaminothiazoline for common usage.

Experimental Part

Preparation of 2-Aminothiazoline.—Gabriel[5] obtained this compound by evaporating an aqueous solution of β-bromoethylamine hydrobromide[7] and potassium thiocyanate to dryness and extraction of the residue with anhydrous alcohol. The 2-aminothiazoline hydrobromide obtained was fairly pure. The base was liberated by alkalinizing a concentrated solution of the hydrobromide and extracting with ether.

By refluxing the aqueous reaction mixture instead of evaporating, we obtained the same yields. The use of β-chloroethylamine hydrochloride, which was simpler to produce, according to the following method, than the bromo compound, gave slightly higher yields.

Sixty grams of monoethanolamine was dissolved in 150 cc. of chloroform in a 2-liter three-neck flask to which was attached a reflux condenser and a stirrer. Dry hydrogen chloride was introduced below the surface of the liquid through a wide inlet tube (about 15 mm. inside diameter) with good mixing. After one hour the mixture separated in two layers and shortly thereafter crystals commenced to form. Gradually the whole mass became thick with crystals. Hydrogen chloride gas was passed through for several hours longer, care having been taken that the inlet tube did not become clogged. This tube was then substituted by a dropping funnel and 120 g. of thionyl chloride was added dropwise over a period of several hours; the mixture was heated to gentle reflux on the steam-bath after half of the chloride addition. The refluxing was continued until the oily layer which formed began to crystallize; the mass was then heated under vacuum to remove the chloroform and traces of thionyl chloride. The crystalline mush remaining in the flask was very hygroscopic and difficult to recrystallize from solvents. The yield of this crude β-chloroethylamine hydrochloride was 115 g. (99%).

The crude hydrochloride was dissolved in 200 cc. of water and filtered; after addition of 100 g. of potassium thiocyanate, the solution was refluxed for nine hours. After cooling, 100 cc. of 40% sodium hydroxide was added and the solution thoroughly extracted with 1500 cc. of ether (in about five 300-cc. portions). The ether extracts were dried over sodium sulfate, filtered and the ether distilled off. The residue was an oil which crystallized on standing, yield 72 g. (70%).

The crude 2-aminothiazoline melted at 76–78°, and after recrystallization from benzene at 80–82°.

Reaction between 2-Aminothiazoline and *p*-Acetylsulfanilyl Chloride.—Fifty-one grams (0.5 mole) of 2-aminothiazoline was dissolved in 80 cc. of pyridine and 200 cc. of acetone and 234 g. (1 mole) of *p*-acetylsulfanilyl chloride

(7) "Organic Syntheses," **18**, 13 (1938).

added gradually with stirring and cooling to keep the temperature below 60°. The mixture was allowed to stand overnight and precipitated by adding it with good mixing to 5 liters of water containing 50 cc. of concd. hydrochloric acid. The precipitate was filtered and washed well with water. After drying the yield was 182 g. (78%) and this crude product melted at 155–156°. After two recrystallizations from 50% alcohol it melted at 164–165° with foaming up the tube.

Anal. Calcd. for $C_{19}H_{20}O_6N_4S_3 \cdot H_2O$ (Formula I or II): N, 10.89; S, 18.68; H_2O, 3.50. Found: N, 10.88; S, 18.92; H_2O, 3.43.

The anhydrous substance, obtained by drying in vacuum over phosphorus pentoxide for seventy-two hours, melted at 205–206°.

Hydrolysis of Diacetyl Compound.—The crude acetyl derivative obtained above was hydrolyzed by refluxing in 10 volumes of 10% hydrochloric acid for one-half hour and then cooled. A small amount of material crystallized out and was filtered off. After recrystallization it was identified as sulfanilic acid. The clear acid filtrate was neutralized by the addition of sodium carbonate and the precipitate which formed was filtered and washed with water. The yield of this crude material was about 70%.

This was suspended in 10 volumes of normal sodium hydroxide solution and stirred well for one hour. The alkali insoluble material, which amounts to 10–15% of the total, was filtered off and washed well with water. It was recrystallized from 50% alcohol or a mixture of equal volumes of pyridine and water. A product which was difficultly soluble in 50% alcohol was filtered off and recrystallized several times from much larger volumes of 50% alcohol. It was more readily soluble in the pyridine mixture but separated immediately on cooling and was recrystallized several times. It melted at 259–261°.[8]

Anal. Calcd. for $C_{15}H_{16}O_4N_4S_3$ (Formula III): N, 13.59; S, 23.30. Found: N, 13.77; S, 23.46.

On further cooling and inducing crystallization of the alcohol or pyridine filtrates from above by stirring, a precipitate is obtained which after further crystallization melts at 206–208°.

(8) Jensen (*loc. cit.*) gave the melting point 265° for this compound.

Anal. Calcd. for $C_9H_{10}O_3N_2S_2$ (Formula IV): N, 10.85; S, 24.80; mol. wt., 258. Found: N, 10.80; S, 24.24; mol. wt., 263.9.

The alkali-soluble substance was precipitated by neutralization with dilute hydrochloric acid. After filtration and washing with water, it was recrystallized from 50% alcohol using "darco." The yield of this product, 2-sulfanilylaminothiazoline, was slightly below 50%. On heating it melted at 209–210° with preliminary shrinking at 207°.

Anal. Calcd. for $C_9H_{11}O_2N_3S_2$: N, 16.34; S, 24.90. Found: N, 15.88; S, 24.70.

The compound is slightly soluble in water (0.02%); it is very soluble in dilute sodium hydroxide and dilute hydrochloric acid.

Mono-acetylsulfanilylaminothiazoline.—The above compound was treated in dilute hydrochloric acid solution with an excess of acetic anhydride. The insoluble crystalline precipitate which separated was recrystallized from 50% alcohol. On heating it melted at 256–258°. It was soluble in dilute sodium hydroxide solution.

Anal. Calcd. for $C_{11}H_{13}O_3N_3S_2$: N, 14.04; S, 21.40. Found: N, 13.60; S, 20.77.

Summary

1. 2-Sulfanilylaminothiazoline (sulfathiazoline) and related compounds have been described.

2. The reaction between *p*-acetylsulfanilyl chloride and 2-aminothiazoline results in the di-substituted acetyl derivative which, upon hydrolysis, yields sulfathiazoline, 2-sulfanilylimino-3-sulfanilylthiazolidene and 3-sulfanilylthiazolidene-2-one.

3. 2-Sulfanilylaminothiazoline (sulfathiazoline) in experimental pneumococcic infection in mice was found to be about equal to sulfathiazole. The effect in staphylococcic infection was found to be superior to that of sulfathiazole.

PHILADELPHIA, PA. RECEIVED JULY 22, 1941