refluxed for one hour, diluted with water and extracted with ether. Crystallization of the resulting oil from isopropanol gave trimesitylfuran VIII exclusively, no saturated diketone being detected.

In one experiment the dienolate-B was decomposed in cold dilute acetic acid and only traces of the furan were isolable from the oily product which could be distilled in the vacuum oven. This oil is very evidently the 1-monoenolate-B.

From the fact that the two samples of the dienolate-B give the furan rather than the saturated diketone, it is certain that they both have the same configuration at the 1-enol group as indicated in formula VIB. Both samples, of course, must have the same configuration at the 4-enol group (corresponding to that of the 4-monoenolate-A) since this group was formed in both experiments before enolization occurred at the 1-carbonyl group.

Summary

1,2,4-Trimesitylbutanedione-1,4 was obtained as the result of 1,4-addition of mesitylmagnesium bromide to di-(trimethylbenzoyl)-ethylene. The 4-monoenolate-A was first formed (proved by halogenation) and was further enolized to the dienolate (proved by oxidation).

1,2,4-Trimesityl-2-butenedione-1,4 was obtained by oxidation of the dienols and by elimination of halogen acid from the 3-halogeno-1,2,4-trimesitylbutane-1,4-diones.

2,3,5-Trimesitylfuran and its mononitro derivative are described.

The 3-halogeno-1,2,4-trimesityl-1,4-butanediones have been obtained each in diastereoisomeric forms.

The existence of two 4-monoenolates, A and B, was demonstrated: A was formed by the addition of mesitylmagnesium bromide to di-(trimethylbenzoyl)-ethylene or by the action of any Grignard reagent on the 3-halogeno-1,2,4-trimesitylbutane-1,4-diones, and B by the enolization of the saturated 1,4-diketone. They were characterized by halogenation to the stereoisomeric halogeno diketones. A basis for assignment of configurations is discussed.

The 1-monoenol-A (m. p. 145°) was obtained by partial ketonization of the dienolate. It lacked most of the usual enolic properties. Ketonization gave the saturated diketone. Enolization gave a crystalline dienol which was metastable and easily oxidized to the unsaturated 1,4-diketone.

The existence of two dienolates, A and B, was demonstrated. A was obtained from the 4-monoenolate-A by enolization with mesitylmagnesium bromide, and was converted by hydrolysis and ketonization to the saturated diketone. B was obtained by the action of phenylmagnesium bromide on the 4-monoenolate-A and was characterized by hydrolysis with spontaneous formation of trimesitylfuran.

Configurations at the 1-enol group are assigned on the basis of the relative ease of furan formation and ketonization.

The mechanism of furan ring closure is discussed in the light of this work.

Charlottesville, Virginia
Received October 17, 1939

[Contribution from the Research Laboratories of the Calco Chemical Division of the American Cyanamid Company]

Sulfanilamide Derivatives. V. Constitution and Properties of 2-Sulfanilamidopyridine[1]

By M. L. Crossley, E. H. Northey and Martin E. Hultquist

Although 2-sulfanilamidopyridine[2] (now named "sulfapyridine" by the American Medical Association) has received wide publicity as a result of its use in the treatment of pneumonia,[3] attention has been drawn to the fact that practically nothing has been published on its physical and chemical properties, and no evidence has been given in support of the assigned structure.[4]

We had independently synthesized this compound as part of our program on N^1-substituted sulfanilamides and had made a pharmacological study, but the announcements from England were made before we were prepared to publish our information. We offer the following evidence on constitution as well as data on the properties of the carefully purified compound.

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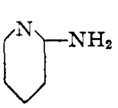
(1) Presented in part before the Division of Medicinal Chemistry, A. C. S. Meeting, Baltimore, Md., April, 1939.

(2) See Sulfanilamide Derivatives I, This Journal, **60**, 2217 (1938), for nomenclature.

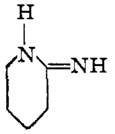
(3) Whitby, *Lancet*, **1**, 1210 (1938); synthesized by J. A. Ewins and M. A. Phillips.

(4) Marshall, *J. Am. Med. Assoc.*, **112**, 352 (1939).

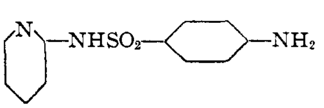
2-Sulfanilamidopyridine was synthesized by reaction of N-acetylsulfanilyl chloride with 2-aminopyridine, followed by hydrolysis of the acetyl group. 2-Aminopyridine is a well-known compound, but can exist in tautomeric forms having the structures I and II, so that it is necessary to decide which form represents the structure of its sulfanilyl derivative. Structures III, IV and V represent the possibilities through replacement of a hydrogen attached to nitrogen in formulas I and II. 2-Aminopyridine derivatives having structure II undergo hydrolysis on boiling in sodium hydroxide solution with evolution of ammonia and production of pyridone.[5]



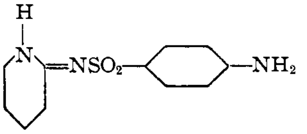
I



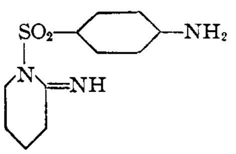
II



III



IV



V

Actually, no hydrolysis of 2-sulfanilamidopyridine occurred on boiling with 50% sodium hydroxide, or weaker strengths. When hydrolyzed by boiling with 36% hydrochloric acid, practically quantitative yields of sulfanilic acid and 2-aminopyridine were obtained. This evidence supports structure III and is against IV and V.

Further evidence in support of III is that the compound forms a monosodium salt which hydrolyzes in water to give a *p*H of 10 to 11. This is characteristic of all sulfonamides of the structure —SO_2NH—.[6] While structures IV and V might conceivably give rise to monosodium salts, it would be predicted from the behavior of the sodium salt of 2-aminopyridine that these would be more highly hydrolyzed in water and would give rise to higher *p*H values than those found.

These facts and deductions lead one to the conclusion that structure III is correct and justify the name 2-sulfanilamidopyridine.

Physical Properties of 2-Sulfanilamidopyridine.—2-Sulfanilamidopyridine is soluble to the extent of approximately 1.05 g./100 cc. in water at 100°; 0.11 g./100 cc. at 40°; 0.05 g./100 cc. at 20°.

It melts with slight decomposition in a capillary tube, over the range: 190.4 (first shrinking)—190.9 (first meniscus)—191.5° (complete melting). On the Dennis block a value of 192.8° was obtained on warming from room temperature, and the same value was obtained by placing the material in contact with the hot bar.

The compound crystallizes from alcohol in small, glistening rhombs. It is white, odorless and tasteless.

Chemical Properties.—2-Sulfanilamidopyridine dissolves readily in strong hydrochloric acid, presumably forming a hydrochloride or dihydrochloride. Potentiometric titration on addition of hydrochloric acid, however, gives a smooth curve without indication of salt formation, so that it is evident that the hydrochloride is highly dissociated. 2-Sulfanilamidopyridine forms a sodium salt which may be isolated and purified.[7]

The solution in hydrochloric acid may be titrated quantitatively by diazotization with sodium nitrite. The reaction is in equimolecular proportions and involves only the amino group of the sulfanilamide part of the molecule.

On heating a sample of the material in a test-tube to about 220° decomposition occurs with development of a brown color and evolution of sulfur dioxide and aniline (a similar but slower decomposition occurs at the melting point and explains the wide range). This is in contrast to sulfanilamide, which develops a blue or violet color and evolves ammonia and aniline.

Purified 2-sulfanilamidopyridine had the following microanalysis[8]: Calcd. for $C_{11}H_{11}O_2N_3S$: C, 52.99; H, 4.45; N, 16.86; S, 12.86. Found: C, 53.02, 53.06; H, 4.66, 4.55; N, 16.72, 16.72; S, 12.76, 12.93.

When assayed by titration with 0.1 *N* sodium nitrite to an end-point on starch iodide paste, the results were 100.2, 100.0. Molecular weight determinations using *m*-dinitrobenzene (K_f 12.49, setting point 89.70°) gave: 251.5, 251.5, 251.0, 248.0. Calcd. 249.29.

Experimental Part

2-(N^4-Acetylsulfanilamido)-pyridine.—18.8 g. (0.2 mole) of 2-aminopyridine (purified by double vacuum fractionation and three recrystallizations from 1 part benzene and 2 parts hexane; melting range 57.0–58.0°; setting point 57.90°) was dissolved in 75 cc. of anhydrous dioxane; 23.5 g. (0.1 mole) of N-acetylsulfanilyl chloride (recrystallized twice from toluene and once from chloroform; m. p. 148.5–149.5°) was added. The mixture was warmed to 95° and held fifteen min. On cooling and stirring, the oily layer crystallized. The crystals were filtered and washed with 25 cc. of dioxane, then 25 cc. of alcohol, and finally with 150 cc. of water. The dry weight was 27 g. or 92.8% based on N-acetylsulfanilyl chloride.

The crude 2-(N^4-acetylsulfanilamido)-pyridine was recrystallized from 200 cc. of dioxane and 125 cc. of water with use of activated charcoal and the crystals were washed with dilute dioxane. On drying, the material partially melted and changed crystalline form indicating loss of

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[5] H. Maier-Brode and J. Altpeter, "Das Pyridin und seine Derivate in Wissenschaft und Technik," Verlag Wilhelm Knapp, Halle, 1934, p. 99.

[6] For structure of such salts see N. V. Sidgwick, "The Organic Chemistry of Nitrogen," Clarendon Press, Oxford, 1937, p. 158.

[7] Marshall, Bratton and Litchfield, *Science*, **88**, 597 (1938).

[8] Purification and determination of physical constants were carried out by W. J. Mader. Microanalyses were made under the direction of G. L. Royer.

dioxane of crystallization. After two recrystallizations from 70% alcohol, the melting range was 225.2° (first softening), 226.6° (first meniscus), 228.1° (final melting). This value was unchanged by recrystallization from 30% acetic acid, diacetone alcohol, and 70% alcohol. On the Dennis block, the material melted at 230.5° when placed on the hot bar or at 229.0° when warmed from room temperature. When a sample was heated at 230° for five minutes, then remelted, the range was 190.0–227.5°, indicating thermal decomposition.

Anal. Calcd. for $C_{13}H_{13}O_3N_3S$: C, 53.59; H, 4.50; N, 14.43; S, 11.00. Found: C, 53.47; H, 4.56; N, 14.53; S, 10.95.

The condensation was also run in pyridine in which case equimolecular amounts of 2-aminopyridine and N-acetylsulfanilyl chloride were used. The crude product so obtained contained a yellow impurity which was difficult to remove.

2-Sulfanilamidopyridine.—The acetyl derivative was hydrolyzed by boiling 29.1 g. (0.1 mole) with 10 g. (0.25 mole) of sodium hydroxide and 150 cc. of water for two hours. The excess sodium hydroxide was neutralized to *p*H 11, activated charcoal was added, and the hot mixture clarified, giving a colorless solution. On acidifying to *p*H 6, 23.1 g. of colorless crystals was obtained equal to 92.5%.

After two recrystallizations from 70% alcohol, the compound had the properties noted above, which remained unchanged on further recrystallizations from alcohol and chlorobenzene.

Hydrolysis of 2-Sulfanilamidopyridine.—Seventy-five grams (0.3 mole) of 2-sulfanilamidopyridine was boiled with 300 cc. of concentrated hydrochloric acid for one hour. After twenty min. crystals started to separate. The mixture was cooled to 15°, the crystals filtered, and washed with a little cold water; weight of crystals: 46.7 g. Titration by nitrite gave 100.2% purity, calculated as sulfanilic acid. The material decomposed gradually above 300°.

The mother liquor was evaporated to 50 cc. and a little more sulfanilic acid removed. Sodium hydroxide was then added in great excess and the oil layer separated. The aqueous layer was extracted with toluene. The toluene extract combined with the oil was dried over solid sodium hydroxide and distilled. The cut from 205 to 212° amounted to 21.0 g., with 2.0 g. of forerun and 1.3 g. of still residue; the total was 24.3 g. or 86% calculated as 2-aminopyridine. The setting point of the main cut was 57.9°, unchanged by admixture with 2-aminopyridine. The material did not resemble ordinary 2-aminopyridine in odor when freshly distilled, but on standing in the air for twenty-four hours the normal odor returned.

The aqueous mother liquors were titrated with sodium nitrite and accounted for 2.7 g. calculated as sulfanilic acid. Total recovery was 49.4 g. or 95.4%.

Melting Range Behavior.—Capillary melting ranges were determined by immersing the tube in a bath preheated to 180°. The values given are corrected. No difference was noted in melting range through use of sealed tubes filled with nitrogen. Some decomposition occurred on melting, as shown by heating a sample at 193° for five minutes in air and in nitrogen. The resulting melting ranges then were: sample melted in air, 154.0–184.5–189.9°; sample melted in nitrogen, 165.0–186.0–190.5°. This would indicate that decomposition on melting was both thermal and oxidative.

Summary

1. The preparation of 2-sulfanilamidopyridine and its physical and chemical properties are described.

2. Evidence in favor of the accepted formula for this compound is given.

BOUND BROOK, N. J. RECEIVED NOVEMBER 16, 1939

[CONTRIBUTION FROM RYERSON PHYSICAL LABORATORY, UNIVERSITY OF CHICAGO]

X-Ray and Optical Properties of Built-up Films

BY SEYMOUR BERNSTEIN

The discrepancy of about 3.6% between X-ray and optical measurements of the thickness per layer of barium–copper stearate films has been reported by C. Holley and S. Bernstein[1] and by C. Holley.[2] Investigations of refraction corrections in the X-ray measurements and possible phase change corrections in the optical measurements show that these cannot account for the discrepancy. Further investigation indicates that the discrepancy must be explained in terms of the structure of the films.

Phase Changes on Reflection

The film thicknesses were measured optically by measuring the fringe displacement between a step of 100 layers to 1000 or more layers of film deposited on an optical flat, as described by Mr. Holley.[2] In order to determine whether the phase change on reflection from the surface of the 100 layer portion was different from the phase change on reflection from the surface of the thicker portion of the films, a 1900-100 layer film was coated with aluminum by evaporation. Before having been covered with aluminum the

[1] C. Holley and S. Bernstein, *Phys. Rev.*, **52**, 525 (1937).

[2] C. Holley, *ibid.*, **53**, 534 (1938).