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Derivatives and Reactions of Sulfanilhydrazide *

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Sulfanilhydrazide was first described, in 1926, by Curtius and Stoll [1], who prepared it by the action of concentrated hydrochloric acid for only a few minutes on 4-acetamido-benzenesulfonyl-hydrazide (acetylsulfanilhydrazide). Unaware of this publication we tried to hydrolyze acetylsulfanilhydrazide by boiling with dilute hydrochloric acid, but in this way the hydrazide was decomposed. We therefore sought for another method of preparing sulfanilhydrazide and found that it could very conveniently be prepared from sulfanilyl fluoride, which we had previously found useful in the preparation of esters of sulfanilic acid [2], where deacetylation would involve also hydrolysis of the ester group. The sulfanilhydrazide prepared from sulfanilylfluoride had, of course, the same properties as that prepared by the method of Curtius and Stoll, but the fluoride method is more convenient and gives a better yield.

Sulfanilhydrazide may be recrystallized from water or dilute ethanol and is a beatifully crystalline substance with m.p. 133°. It is difficultly soluble in cold water, but dissolves as well in acids as in alkalis. It reduces Fehling's solution, Tollen's reagent, an iodine solution by warming (or in the cold by addition of NaOH), and it combines with different carbonyl compounds: a solution of the hydrazide in dilute hydrochloric acid gives white crystalline precipitates with benzaldehyde, acetone, pyruvic acid *etc.* With glucose and glyoxal it forms water soluble condensation products and with *p*-dimethylamino-benzaldehyde it gives a yellow colour. With isatin slightly soluble, yellow isatin-sulfanilylhydrozone is formed. This compound was prepared with a view to using it at an intestinal antiseptic. It was found, however, that both this compound and the other derivatives of sulfanilhydrazide had

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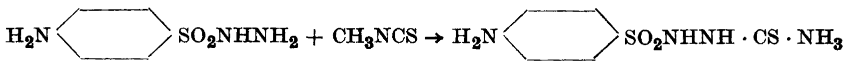
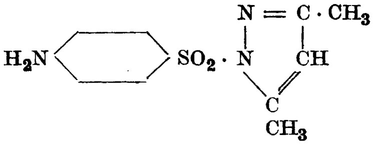
* This investigation was completed in 1943–45. Since then a few of the compounds here described have been reported by other workers (Seppi [3], Roth and Degering [4]).

only a slight bacteriostatic eefect ($^1/_4$—1/10 of the effect of sulfanilamide against pneumococci *).

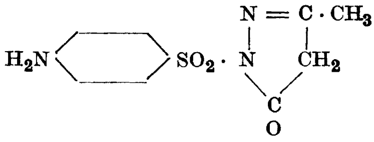
As sulfonylhydrazines have not been very thoroughly investigated, we have studied in more detail the reactions of sulfanilhydrazide. With methylisothiocyanate it reacts slowly with formation of a thiosemicarbazide:



With potassium cyanate and acetic acid a semicarbazide is formed. With acetylacetone and with ethyl acetoacetate the following pyrazole derivatives are formed:

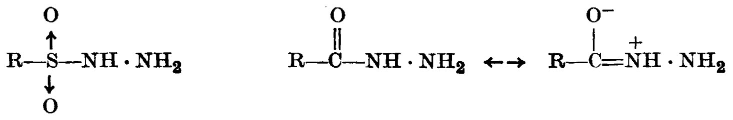


1-Sulfanilyl-3,5-dimethylpyrazole



1-Sulfanilyl-3-methyl-pyrazolone(5)

It is evident that sulfanilhydrazide more resembles a monosubstituted alkylhydrazine than an acylated hydrazine, and this is without doubt due to the fact that the influence of the sulfonyl group on the hydrazine residue is purely inductive, whereas in a carboxylic acid hydrazide resonance is possible:



$$R\text{—}\underset{\underset{O}{\downarrow}}{\overset{\overset{O}{\uparrow}}{S}}\text{—}NH\cdot NH_2 \qquad R\text{—}\overset{\overset{O}{\|}}{C}\text{—}NH\cdot NH_2 \longleftrightarrow R\text{—}\overset{\overset{O^-}{|}}{C}{=}\overset{+}{N}H\cdot NH_2$$

The inductive effect of the sulfonyl group, however, makes sulfanilhydrazide less reactive than an alkylhydrazine. No reaction took place with carbon disulfide and potassium hydroxide, with methylthiuronium sulfate, or with cyanamide. No thiadiazole could be prepared from the thiosemicarbazide.

Sulfanilyl fluoride reacts only slowly with phenylhydrazine, and no pure phenylhydrazide could be prepared in this way. Acetylsulfanilyl chloride on the other hand reacts easily with phenylhydrazine to give the corresponding phenylhydrazide. This could be oxidized with mercuric oxide to a yellow azo

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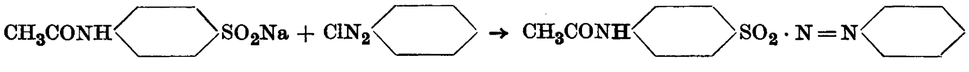
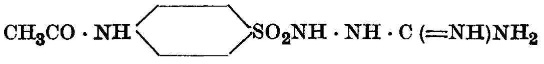
* We thank Dr. K. Schmith of the State Serum Institute, Copenhagen, for making these measurements.

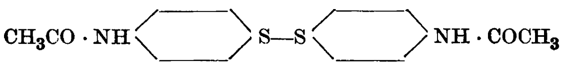
compound. The same compound could also be prepared (but in less pure state) by the reaction of sodium-4-acetylamino-benzenesulfinate and benzenediazonium chloride:



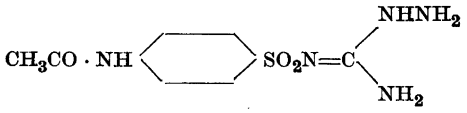
By reaction of acetylsulfanilhydrazide with cyanamide we hoped to prepare an acetylsulfanilylaminoguanidine with the formula:



The only pure product which could be isolated from the reaction mixture was, however, di-*p*-acetylaminodiphenyl-disulfide:



By reaction of acetylsulfanilylcyanamide with hydrazine we prepared an aminoguanidine with the formula:



The compound is only slowly in sodium hydroxide and therefore has no hydrogen at the nitrogen atom bound to the SO_2-group. By reaction of this aminoguanidine with nitrous acid a tetrazole is formed, which was shown to be identical with the compound prepared from aminotetrazole and acetylsulfanilyl chloride (Jensen[5]). By treatment with dilute sodium hydroxide this tetrazole is transformed into the isomeric compound of Veldstra and Wiardi[6]. The constitution of these acetylsulfanilylaminotetrazoles have been subjected to a closer investigation which will be published in another paper.

EXPERIMENTAL

Sulfanilhydrazide. Sulfanilylfluoride (8.75 g) is suspended in ethanol (15 ml) and hydrazine hydrate (5 ml) is added. By warming a reaction sets in and the solution begins to boil. After the reaction has finished the solution is cooled and water (10—20 ml) is added. The crystals which separate are filtered, washed with water, and recrystallized from water or dilute (30 %) ethanol. Yield 7 g = 75 %. M. p. 133—135° with destruction (colour change to yellow, formation of nitrogen, sulfur dioxide and aniline). The hydrazide forms long, colourless needles.

$C_6H_9O_2N_3S$ (187.2) Calc. N 22.45 Found N 22.52

Acetylsulfanilhydrazide. Acetylsulfanilyl chloride (11.5 g) is dissolved in a mixture of abs. ethanol (100 ml) and hydrazine hydrate (5 ml). White crystals separate, which are filtered and washed with ethanol. Yield 11.0 g = 96 %. The compound can be recrystallized from water, but as it is gradually decomposed by heating with water, it should be dissolved in boiling water, the solution filtered and cooled rapidly. The melting point is 176—178° (dec.) by slow heating, but is 191—192° on a preheated block.

$C_8H_{11}O_3N_3S$ (229.2) Calc. N 18.33 Found N 18.54

Benzaldehyde sulfanilhydrazone. Sulfanilhydrazide (2.0 g) is suspended in ethanol (20 ml), benzaldehyde (1.0 g) is added. The mixture is heated to boiling and on diluting with water the hydrazone is precipitated. It is recrystallized from 50 % ethanol. Yield 2.4 g = 87 %. M. p. 172—73°.

$C_{13}H_{13}O_2N_3S$ (275.3) Calc. N 15.26 Found N 15.20

Isatin β-sulfanilhydrazone. Sulfanilhydrazide (0.94 g) and isatin (0.73 g) are dissolved together in hot ethanol (25 ml) and the solution heated to boiling for a few minutes. On cooling yellow crystals form. Yield 1.45 g = 92 %. The compound was recrystallized from dilute ethanol (50 %). It is very slightly soluble in abs. ethanol, insoluble in acids and bases.

$C_{14}H_{12}O_3N_4S$ (316.3) Calc. N 17.71 Found N 17.84, 17.66

Acetylsulfanil-phenylhydrazide. A mixture of acetylsulfanilyl chloride (12 g), ethanol (100 ml) and phenylhydrazine (10.8 g) is heated to boiling. On cooling a precipitate of phenylhydrazine hydrochloride separates and is filtered off. By dilution with water (200 ml) the filtrate gives a precipitate of the phenylhydrazide. Yield 14 g = 90 %. Recrystallized from dilute ethanol. White crystals with m. p. 160—61° (dec.). Insoluble in water, very soluble in ethanol. The compound has also been described by Seppi[3].

$C_{14}H_{15}O_3N_3S$ (305.3) Calc. N 13.77 Found N 13.72, 13.83

We tried to prepare sulfanil phenylhydrazide by reaction of sulfanilyl fluoride with phenylhydrazine (either in alcoholic solution or by direct heating of the fluoride with phenylhydrazine to 180°), but we did not succeed in isolating a pure compound. The melting point is practically constant (67—69°) after a few recrystallizations from benzene + ligroin (the product being very soluble in benzene or in ethanol). The nitrogen was much too low, however, and the product gave positive reaction for fluorine.

Acetylsulfanilyl-azo-benzene. Acetylsulfanil-phenylhydrazide (0.5 g) is dissolved in boiling ethanol (10 ml), benzene (20 ml) is added. The solution is heated to boiling, shaken vigourously with mercuric oxide (5 g) and filtered. The solvent is removed *in vacuo* at room temperature and the residue is dissolved in 10 ml hot ethanol. The solution is filtered and cooled in ice and on rubbing orange-yellow crystals separate. Yield 0.20 g = 40 %. Decompose by heating at 100—110°.

$C_{14}H_{13}O_3N_3S$ (303.3) Calc. N 13.85 Found N 13.90

The same compound was prepared by mixing a solution of sodium acetamidobenzenesulfinate with a solution of benzenediazoniumchloride.

1-Acetylsulfanilyl-4-methyl-thiosemicarbazide. A mixture of acetylsulfanilhydrazide (7.6 g), methyl isothiocyanate (2.5 g) and ethanol (50 ml) is boiled for 1 hour. Without going into solution the precipitate is altered. Yield 5.5 g = 55 %. M. p. ca. 230°. Very slightly soluble in most solvents. A small portion was recrystallized from ethanol (80 %) in which it is also slightly soluble. M. p. 248° (dec.). The compound is soluble in dilute sodium hydroxide.

$C_{10}H_{14}O_3N_4S_2$ (302.4) Calc. N 18.53 Found N 18.51

1-Sulfanilyl-4-methyl-thiosemicarbazide. A mixture of sulfanilhydrazide (1.9 g). methyl isothiocyanate (0.75 g) and ethanol (20 ml) is boiled for 2 hours. The solution is cooled and diluted with 20 ml of water. White crystals separate and are recrystallized from dilute ethanol (30—40 %). Colourless needles. M. p. 195—96°. Yield 75 %. The compound is soluble both in acids and bases and contains a free aminogroup (diazotates and couples).

$C_8H_{12}O_2N_4S_2$ (260.3) Calc. N 21.53 Found N 21.56

1-Sulfanilyl-semicarbazide. Sulfanilhydrazide (1.9 g) is dissolved in acetic acid (20 %; 5 ml) by warming. The solution is then cooled and a solution of 1 g of potassium cyanate in 2 ml of water is added with stirring. After half an hour the mixture is filtered, and the precipitate is recrystallized from water (easily soluble in hot water). Yield 1.3 g = 56 %. The compound decomposes with evolution of gas above 200°, without a sharp melting point.

$C_7H_{10}O_3N_4S$ (230.2) Calc. N 24.34 Found N 25.12

1-Sulfanilyl-3,5-dimethyl-pyrazole. A mixture of sulfanilhydrazide (4.4 g), acetylacetone (3 g) and ethanol (15 ml) is heated on steam bath for 2 hours. The ethanol is evaporated, whereupon the reaction product crystallizes in leaves. These are filtered off, washed with ethanol and ether, and recrystallized from ethanol. Yield 3.1 g = 53 %. M. p. 182°. Diazotation shows the presence of free amino group.

$C_{11}H_{13}O_2N_3S$ (251.3) Calc. N 16.72 Found N 16.78

1-Sulfanilyl-3-methyl-pyrazolone (5). A mixture of sulfanilhydrazide (1.9 g), ethyl acetoacetate (1.3 g) and ethanol (10 ml) is refluxed for one hour. When cool the solution was diluted with water, and the precipitate was recrystallized from water with the addition of activated carbon. Yield 1.7 g = 67 %. M. p. 148°. White needles, easily soluble in ethanol and in hot water.

$C_{10}H_{11}O_3N_3S$ (253.3) Calc. N 16.59 Found N 16.60

4-Acetylsulfanilylaminoguanidine. Ten grams of the calcium salt of acetylsulfanilylcyanamide, 2.5 g of hydrazine sulfate and 0.7 g of hydrazine hydrate were thoroughly mixed together and the mixture heated in an oil bath at 160—70° for one hour. The reaction mixture was extracted with boiling water; after filtering and cooling a finely crystalline white precipitate separated. It was recrystallized from boiling water with addition of activated carbon. M. p. 256°.

$C_9H_{13}O_3N_5S$ (271.3) Calc. N 25.90 Found N 25.56

4-Sulfanilylaminoguanidine. The acetyl compound (2 g) was dissolved in hot 2N NaOH (50 ml) and the solution boiled for 15 min. The hot solution was neutralized to pH 6, carbon was added and the solution filtered. On cooling colourless crystals separated. Recrystallized from water. M. p. 202°. Yield 0.9 g or 53 %.

$C_7H_{11}O_2N_5S$ (229.3) Calc. N 30.54 Found N 30.07

Acetylsulfanilylaminotetrazole. 4-Acetylsulfanilylaminoguanidine (0.7 g) was dissolved in 15 ml 4N H_2SO_4 and a solution of sodium nitrite (0.3 g) in 2 ml of water was slowly added. Yellowish crystals separated. On recrystallization from hot water under addition of activated carbon they became almost colourless. M. p. 172—73° (dec.). Yield 0.5 g.

$C_9H_{10}O_3N_6S$ (282.3) Calc. N 29.77 Found N 29.46

According to the melting point this compound is identical with the acetylsulfanilylaminotetrazole previously described. It also gave azoimide by hydrolysis with hot sodium hydroxide and on treatment with cold 0.1 N sodium hydroxide was transformed into an isomer with m. p. 202°.

SUMMARY

Sulfanilhydrazide has been prepared by reaction of sulfanilylfluoride with hydrazine and some of its reactions have been studied.

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