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**SYNTHESIS OF NEW SULFANILAMIDE DERIVATIVES
AS SULFANILAMIDOUREA, SULFANILAMIDOTHIOUREA
AND OTHER RELATED COMPOUNDS**

**A Thesis Presented by EWA NIEMIEC in Partial Fulfilment
of the Requirements for the Degree of Master of Arts.**

**American University of Beirut
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1941
1940

I. Introduction

The stimulus for this work was a lecture entitled "Recent Advances in Chemotherapy With Special Reference to the Sulphonamide Drugs", delivered by Lt. Col. Pulvertoft at the A.U.B. on Dec. 30, 1943(1). In this lecture mention was made of the bacteriostatic effect of urea, - the old country practice of treating wounds with urine being "the first hint of the truth". Urea was also described as being effective when given along with sulfanilamide in the treatment of purulent wounds, the action of urea being to counteract the antibacteriostatic effect of pus extracts, such as amino acids a.t.c.

It seemed of interest then to study compounds in which urea or its derivatives form part of the sulfanilamide molecule; to prepare such compounds and test their antibacterial properties. This appeared all the more desirable as the related sulfanilylthiourea was claimed to be efficacious against tubercle bacilli (2). More recently these results were confirmed (3) and even thiourea itself has been claimed to have the same action (4).

The synthesis of the following compounds was contemplated: sulfanilamidourea, sulfanilamidothiourea, sulfanilylhydrazines, sulfanilylhydrazides and sulfanilylhydrazidines.

Martanil or 4-homosulfanilamidourea, first used in the German army during this war, possessed the remarkable property of not being counteracted by para-aminobenzoic acid or pus extracts. It also appeared of interest to prepare the corresponding 4-homosulfanilylurea and study its properties.

The compound sulfanilylurea had been prepared in 1942 (5) (6), and the corresponding thiourea derivative in 1941 (7) and 1945 (8). These compounds are often wrongly named sulfanilamidourea and sulfanilamidothiourea although they contain NH group less than the latter.

Abstract

Sulfanilamidourea, sulfanilamidothiourea and 4-homosulfanilamidourea were synthesized and tested in vitro for antibacterial properties. All three compounds showed a marked activity against Clostridia, the activities of the urea derivatives being superior to that of sulfathiazole. Sulfanilamidourea and sulfanilamidothiourea had also inhibiting effects on Streptococcus viridans but to a lesser degree than sulfathiazole.

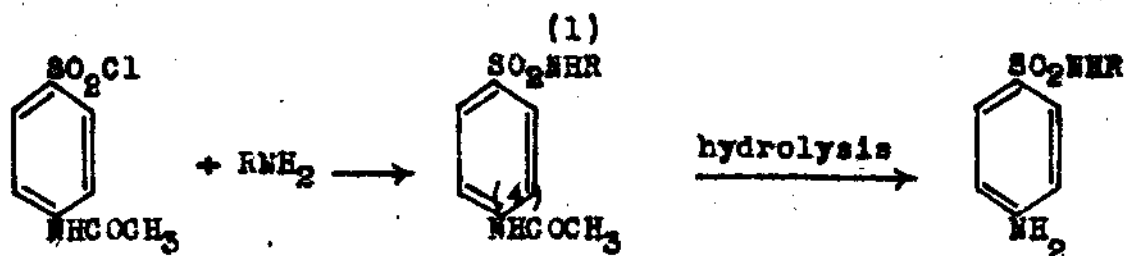
Other related sulfanilamide derivatives prepared could not be tested since they were obtained in the therapeutically inactive form. These were: N⁴-acetylsulfanilylphenylhydrazine, N⁴-acetylsulfanilylmonoacethydraside, N⁴-acetylsulfanilyldiacethydraside and p-nitrobenzenesulfonyltolonylhydrazidine.

The acethydraside compounds were obtained from N⁴-acetylsulfanilylhydrazine for the preparation of which a convenient method was developed.

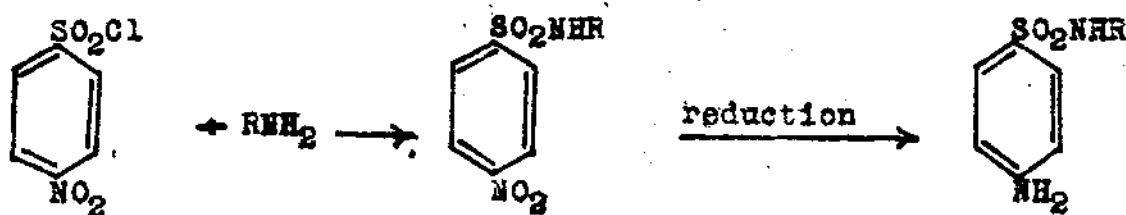
N⁴-Acetylsulfanilylhydrazine was also made use of in the synthesis of sulfanilylbenzhydrazide, a compound already described but prepared from a different starting material.

II. Synthesis of Sulfanilamides in General

The general method of preparing sulfanilamides is to react N - acetylsulfanilyl chloride with the amine compound, with or without the use of condensing agent, and subsequent removal of the N⁴ - acetyl group by acid or alkaline hydrolysis:



For compounds that do not resist treatment with acids and alkalis the p - nitrobenzenesulfonyl chloride is condensed with the amino compound followed by reduction:



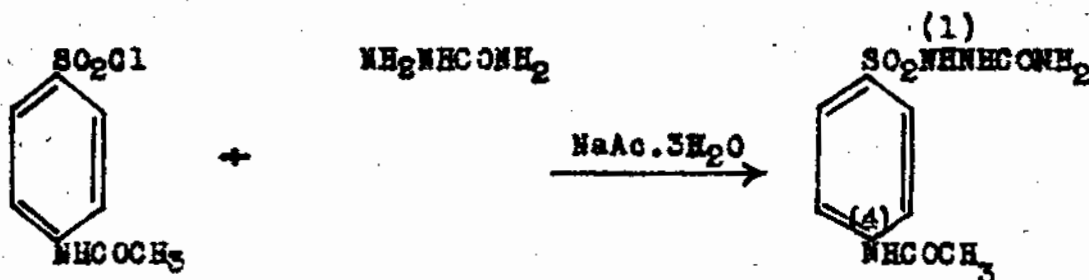
The condensation of the sulfanilyl chloride reagent with strong bases requires no condensing agent, but simply an excess of the base. With less basic amino compounds sodium acetate or sodium carbonate is used. With neutral amino compounds a strong base such as sodium hydroxide or pyridine is usually required.

III. New Sulfanilamide Derivatives

1. Sulfanilamidourea and Sulfanilamidothiourea

N - Acetylsulfanilyl chloride does not react with urea to form N⁴- acetylsulfanilylurea. Sulfanilylurea has therefore been prepared by indirect methods, namely from sulfanilylcyanamide (5), and sulfanilylethylisourea (6). Semicarbazide however, on account

of its primary amino group, would be expected to react with the sulfanilyl reagent. Indeed, the reaction goes smoothly using as mild a condensing agent as sodium acetate, although semicarbazide itself is neutral:



The routine procedure consists of grinding dry or wet acid chloride with semicarbazide hydrochloride and crystalline sodium acetate (usually equimolecular amounts of the acid chloride and semicarbazide are used, or slight excess of the latter, and an excess of sodium acetate). The reaction is completed by heating the product with some water for 30 minutes at 60°C. The resulting compound is very slightly soluble in water, from which it is recrystallized with difficulty.

On hydrolysis in aqueous NaOH the N⁴-acetylsulfanilamidourea thus obtained undergoes decomposition with liberation of ammonia. On the other hand it is very resistant to acid hydrolysis in aqueous solution. Refluxing for several hours with concentrated HCl causes only partial hydrolysis. Complete saponification was finally achieved by the use of alcoholic aqueous HCl solution.

When thiosemicarbazide was used instead of semicarbazide hydrochloride under the same conditions, a product was obtained which resembled thiosemicarbazide in its physical properties and showed no depression of melting point when mixed with thiosemicarbazide. It was therefore assumed that no reaction had taken place and recourse was had to a different method of condensation using pyridine.

But here the same product was obtained in even smaller yield. When, however, the elementary analysis was performed on these compounds, it was clear, that they represented the correct product, namely N⁴- acetylsulfanilamidothiourea. The above fact gives an illustration of how even a mixed melting point can leave one in the lurch.

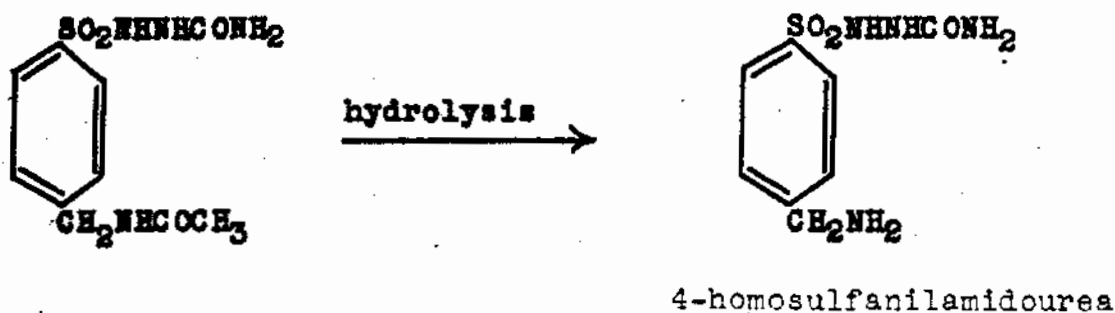
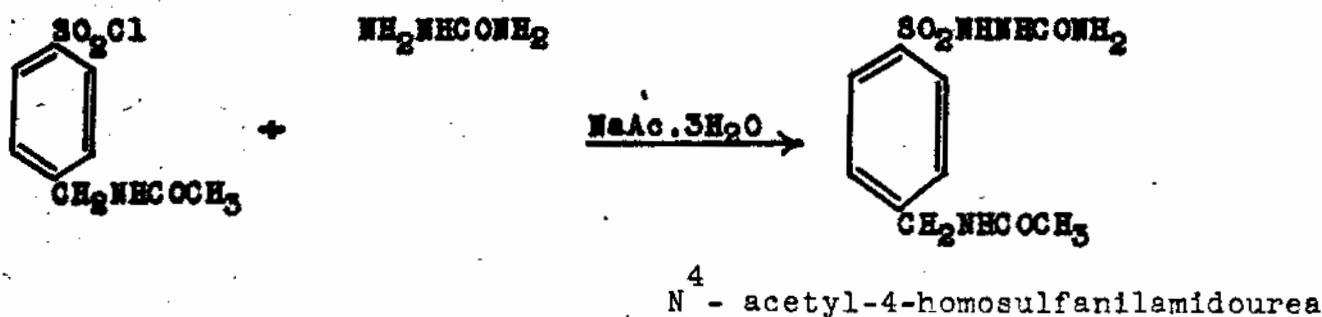
The hydrolysis of this compound was performed exactly as described for sulfanilamidourea.

After the synthesis of these 2 compounds was completed my attention was drawn to an abstract which appeared in December issue of Chemical Abstracts 1943 and which owing to the war arrived in Beirut late in 1944. This was an abstract of an article published by Guha and Handa in an unavailable Indian journal simply stating the synthesis of sulfanilylsemicarbazide and thiosemicarbazide without giving any data whatsoever (9). Still later (1944) an American patent appeared claiming the synthesis of these 2 compounds (10). More recently (1945) Roth and Degering without referring to the work of the Indian chemists or the patent literature described the preparation of the acetyl derivatives (11). It is clear that the latter authors were not successful in hydrolyzing them to the corresponding sulfanilamido compounds.

2. 4 - Homosulfanilamidourea

The logical method to synthesize homosulfanilamides would be to treat the amino compounds with N - acetyl-4-homosulfanilyl chloride, the latter being prepared by chlorosulfonating N-acetylbenzylamine. It was found that the reaction of N-acetyl-4-homosulfanilyl chloride with semicarbazide hydrochloride using crystalline sodium

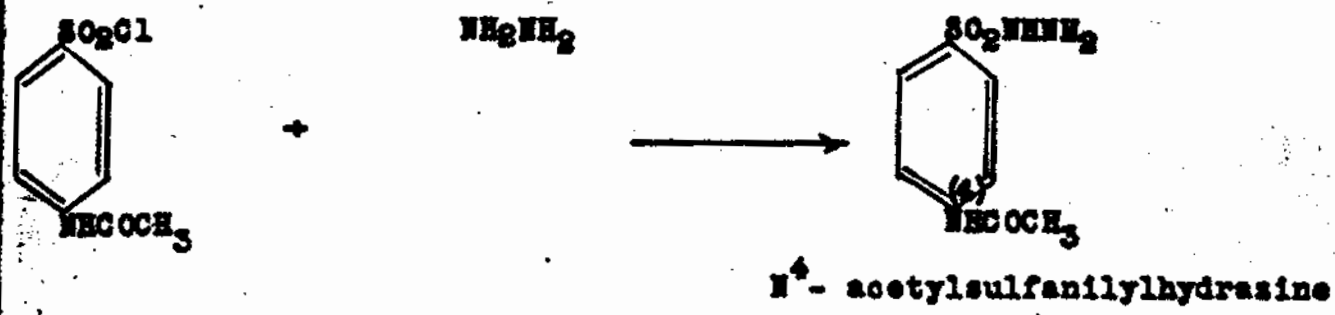
acetate as condensing agent proceeds smoothly and with good yield. The product which is more soluble than the corresponding lower homologue can be hydrolyzed without difficulty by the method mentioned above. Absolute instead of 95% alcohol is used for this purpose, because the 4-homosulfanilamidourea hydrochloride as it crystallizes, is characterized by its extreme solubility in water.



3. Sulfanilylhydrazines

In connection with this work it was important to prepare sulfanilylhydrazine and study its properties, not only for its own sake, but because it was intended to be used as starting material for the preparation of the corresponding hydrazides. Since sulfanilamide literature after 1935 made no mention of sulfanilylhydrazine, it was assumed that the compound had hitherto not been prepared.

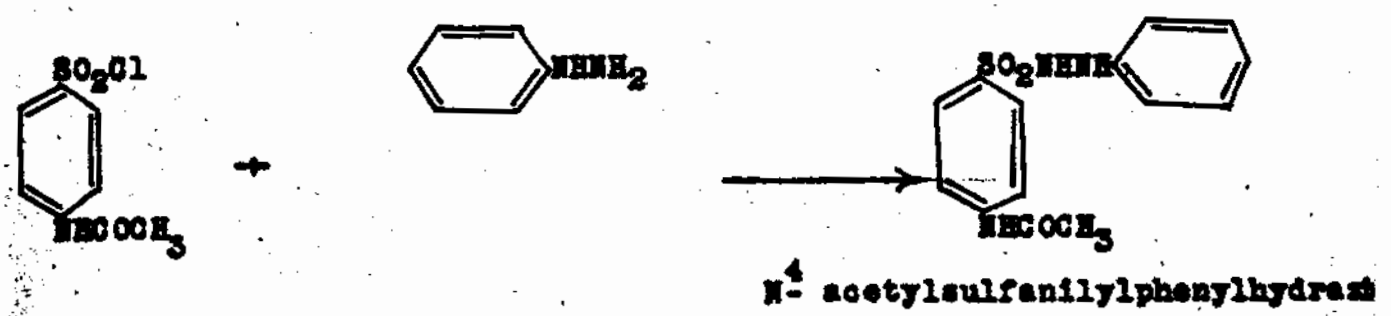
Treatment of hydrazine dihydrochloride with dry N-acetyl-sulfanilyl chloride using crystalline sodium acetate in the usual manner resulted in the formation of the expected N⁴-acetyl-sulfanilylhydrazine



When however wet sulfanilyl chloride reagent was used the yields were extremely poor and capricious. They could be improved by using crystalline sodium carbonate instead of acetate. By far the best results gave the condensations of hydrazine with acetylsulfanilyl chloride in its dry state with crystalline sodium carbonate.

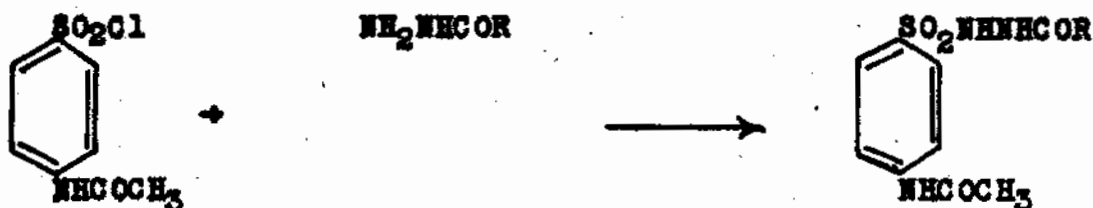
Repeated attempts to hydrolyze this compound were unsuccessful. Later it was learned that the acetyl compound as well as the hydrolyzed product had been prepared by Curtius and Stoll in 1926 (12). My method for the preparation of the acetyl derivative differs in that the more available hydrazine hydrochloride instead of the hydrazine hydrate is utilized. The product which I obtained melted 6° higher.

Using the same method with sodium acetate as condensing agent, N⁴- acetylsulfanilylphenylhydrazine was also prepared in good yield. This compound was described later by Roth and Degering (11), but neither these authors nor I succeeded in deacetylating it.

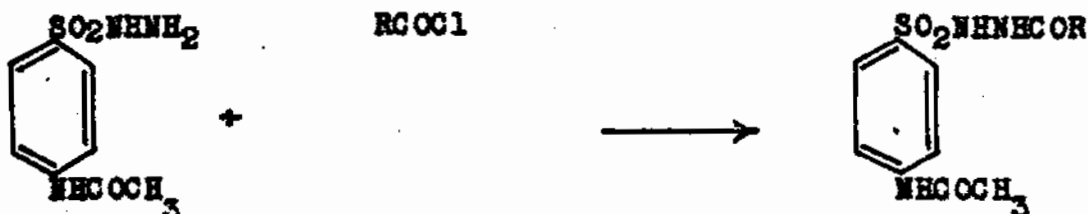


4. Sulfanilylhydrazides

Two ways are theoretically possible for the preparation of N^4 -acetylsulfanilylhydrazides. Either N -acetylsulfanilyl chloride is made to react with an acid hydrazide:



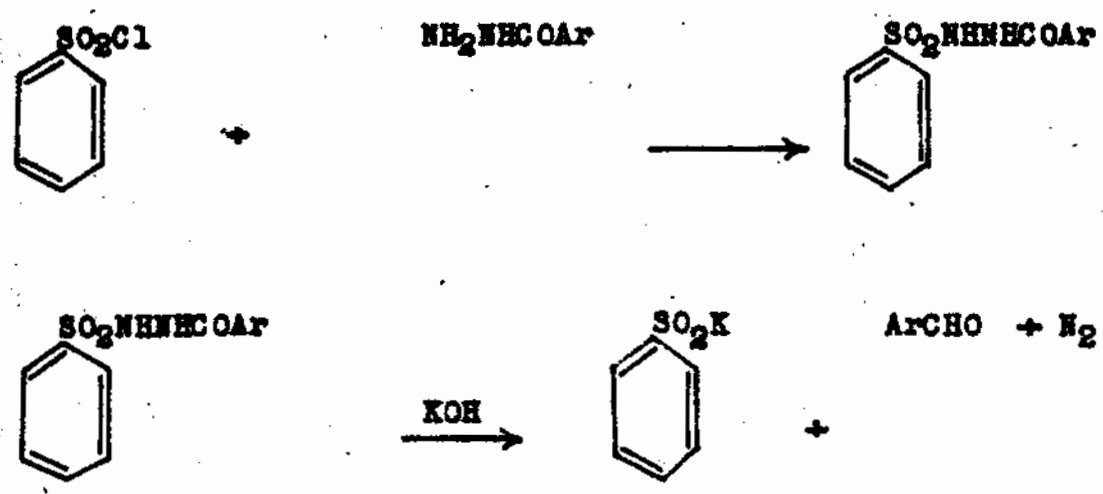
or N^4 -acetylsulfanilylhydrazine is acylated:



Haslewood (13) used the first method for his benzhydrazide derivative. Saponifying the acetyl compound with sodium hydroxide, he got as a "byproduct" benzaldehyde which he characterized by preparing its 2,4 - dinitrophenylhydrazone. I repeated Haslewood's experiments and confirmed his findings.

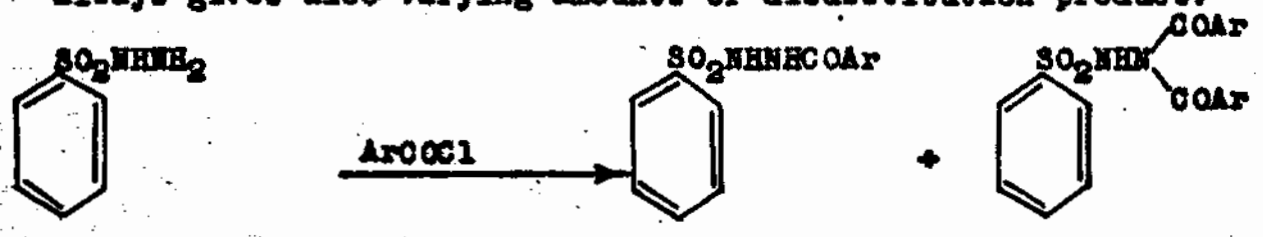
The second method which I used consisted of treating N^4 -acetylsulfanilylhydrazine with benzoyl chloride or acetic anhydride in pyridine solution. The product obtained by the use of benzoyl chloride gave the same melting point as Haslewood's product, but the conditions of benzoylation had to be controlled in order not to get a mixture of mono - and dibenzhydrazides. The mono substituted compound as well as the mixture of mono - and dibenzhydrazide derivatives were hydrolyzed by Haslewood's method to sulfanilylmonobenzhydrazide, which was again identical with that of Haslewood.

At the time this was finished I was not aware of the work of Mc Padyen and Stevens (14) in which they devise a method for the preparation of aromatic aldehydes. This method consists of the treatment of an aromatic hydrazide with benzenesulfonyl chloride and subsequent decomposition of the resulting benzenesulfonylhydrazide with alkali:



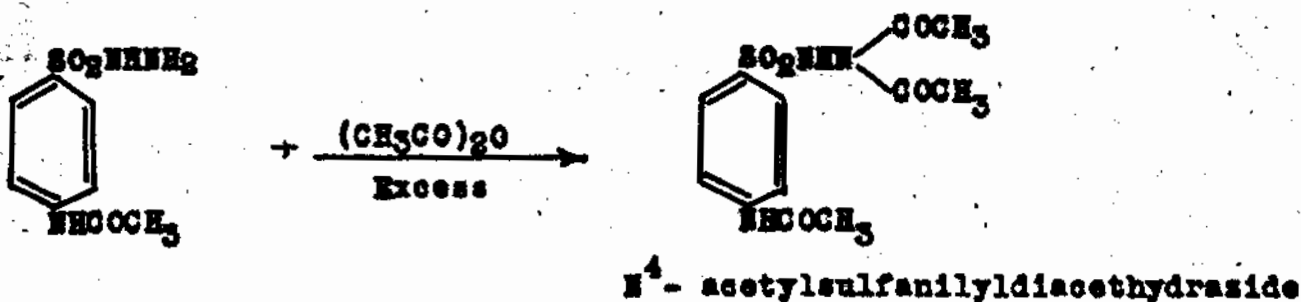
Haslewood also appears not to have been acquainted with Mc Padyen and Stevens, because he was surprised at the appearance of benzaldehyde after alkaline hydrolysis.

Mc Padyen and Stevens prepared their benzenesulfonylhydrazides by both methods described, but they gave preference to the first starting with acid hydrazide inasmuch as the second method almost always gives also varying amounts of disubstitution product:

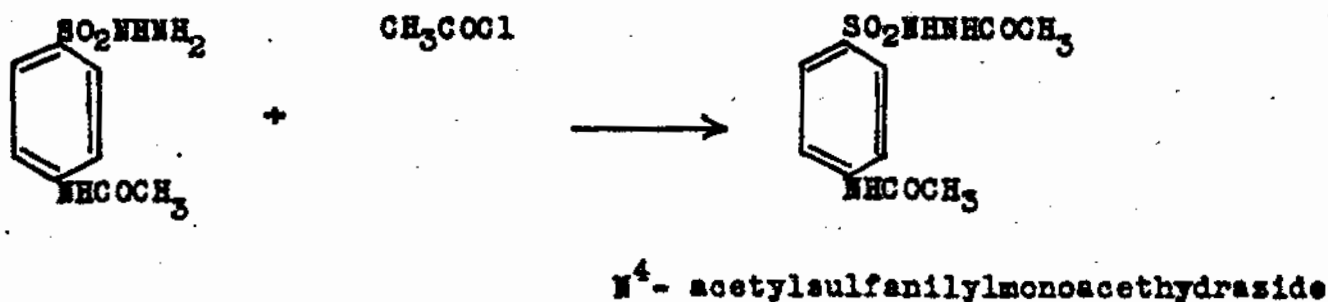


For the preparation of sulfanilylacethydrazide the second method appeared more desirable on account of the difficulty of preparing acethydrazide itself. Treatment of N⁴-acetylsulfanilylhydrazine with an excess of acetic anhydride in pyridine solution gave a nice crystalline product, which however as the elementary

analysis showed, was a diacethydrazide derivative:



When the conditions were modified and an exact amount of the acetylating agent necessary to form the mono derivative was used (preferably acetyl chloride), the monoacethydrazide was obtained:



Both compounds, the N⁴- acetylsulfanilylmonoacethydrazide and the N⁴- acetylsulfanilyldiacethydrazide were hydrolyzed by the method of Curtius and Stoll (12) to sulfanilylhydrazine. Hydrolyses with HCl of lower concentrations including 3N HCl lead to the same end product. These results indicate that all the acetyl groups are very labile and therefore a still milder saponification method should be used. Another possibility would be to prepare the corresponding nitro compounds and reduce them.

5. Sulfanilylhydrazidine

Aliphatic hydrazidines are not known. Of the aromatic hydrazidines the best characterized is tolenyl derivative prepared by Pinner (15). It was expected that sulfanilylhydrazidines in analog to the corresponding amidines (16) would not resist acid or alkali hydrolysis, so p- nitrobenzenesulfonyl chloride was used instead

of acetylsulfanilyl chloride. Tolonylhydrazidine prepared according to Pinner (15) by the action of hydrazine on the corresponding imidoether was made to react with p-nitrobenzenesulfonyl chloride in pyridine solution. The product after purification appeared to be the correct compound, but it was not further studied.

IV. Bacteriological Findings *

The Antibacterial properties of sulfanilamidourea, sulfanilamidothiourea and 4-homosulfanilamidourea were studied in vitro against a variety of bacteria. The activities of these new drugs were determined and compared with those of common sulfanilamides.

The results showed that sulfanilamidourea and 4-homosulfanilamidourea were superior to sulfathiazole in their inhibitory action upon *Clostridium welchii*, *Cl. tetani*, *Cl. sporogenes*, and *Cl. chauvei*. Sulfanilamidothiourea showed a much less activity than sulfathiazole.

A strain of *Streptococcus viridans* was completely inhibited by 10 mg percent sulfathiazole in veal infusion broth; sulfanilamidourea and sulfanilamidothiourea exerted a partial inhibition under the same experimental conditions, but were completely bacteriostatic in concentrations of 100 mg percent. 4-Homosulfanilamidourea had no inhibitory effect.

Sulfathiazole had a definite and marked bacteriostatic effect on one of the three strains of *Corynebacterium diphtheriae* tested. Sulfanilamidourea, sulfanilamidothiourea and 4-homosulfanilamidourea exhibited it irregularly and to a lesser degree than sulfathiazole.

Sulfathiazole in concentrations of 10 mg percent exerted a marked inhibitory action on the growth of virulent human *Mycobacter*

* Abstracted from the thesis of Miss Aida Djanian -

The Bacteriostatic Effect of Sulfonamide-Urea Compounds

tuberculosis in a synthetic medium. Under similar conditions all three urea derivatives gave negative results.

Two strains of *Staphylococcus aureus* exhibited no alterations of their growth in a synthetic medium containing the sulfanilamides and the new urea compounds.

The urea derivatives had also no effect on *Escherichia coli*, *Eberthella typhosa*, *Salmonella paratyphi* (Schottmüller) and various other gram-negative rods; sulfathiazole exerted slight bacteriostatic effect on some of the gram-negative rods.

V. Experimental

N-Acetylsulfanilyl chloride.

This intermediate was prepared according to H. Gilman, Organic Syntheses, Collective Volume I, p.8. The wet product was spread on filter papers in thin layers, and dried slowly in the air. When almost dry, it was extracted with chloroform in a simplified Soxhlet apparatus. On evaporation of the solvent N-acetylsulfanilyl chloride crystallized from the remaining portion. Its melting point was 146-147°C. This purification seemed to be not necessary in the preparation of the compounds described below, because when crude product was used, the resulting substances did not appear to be less pure. The only advantage of the recrystallization was, that the purified material could be kept indefinitely, while in its crude state it had to be used at once. The crude material was used either without drying in the form of wet paste, or dried in a desiccator.

N⁴-Acetylsulfanilamideurea.

5 gm of semicarbazide hydrochloride, 10,5 gm of dry N-acetylsulfanilyl chloride (1 mol per 1 mol), and 30 gm of crystalline sodium acetate (5 mols) were thoroughly ground in a mortar. A little water was usually added to start the reaction. (When the corresponding amount of wet N-acetylsulfanilyl chloride was used, no addition of water was necessary.) The thick mass was then transferred with a minimum amount of water to a flask, and heated on water bath for 30 min. at 60°C. After cooling, the precipitate was filtered and extracted with boiling water in which N⁴-acetylsulfanilamideurea is soluble with difficulty. White needles came down

which melted at 223-224°C with decomposition. Yield 6 gm.

Sulfanilamidourea

6 gm of N⁴- acetylsulfanilamidourea were treated with 21 cc concentrated HCl (density 1,19), and then with 70 cc of 95% alcohol in a round-bottom flask, fitted to a condenser with a normal glass joint. The contents were refluxed for 3 hours on a steam bath. On cooling crystals separated. They were filtered and dissolved in the minimum amount of hot water. The solution was filtered while hot and neutralized with sodium carbonate solution until just neutral to litmus paper. On cooling needles separated, which when once more recrystallized from boiling water melted at 229°C with decomposition. Yield 4,5 gm.

N⁴- Acetylsulfanilamidothiourea.

5 gm of thiosemicarbazide, 13 gm of dry N-acetylsulfanilyl chloride, or the corresponding amount of wet product (1 mol per 1 mol), and 23 gm of crystalline sodium acetate (3 mols) were made to react in the same manner as in the case of the urea derivative. The so obtained substance could also be recrystallized from boiling water. After two recrystallizations the needles melted at 186°C with decomposition. Yield was around 2 gm and could be increased by using an excess of N-acetylsulfanilyl chloride.

Sulfanilamidothiourea

2 gm of N⁴- acetylsulfanilamidothiourea were treated with 18 cc of concentrated HCl (density 1,19) and then with 60 cc of 95% alcohol. The further procedure was the same as in the case of the urea derivative. Needles melting at 224-225°C were obtained. Yield 1 gm

N-Acetyl-4-homosulfanilyl chloride

This was obtained by chlorosulfonation of N-acetylbenzylamine according to the method used by Frank H. Bergheim and William Braker, J.A.C.S. 66, 1459 (1944). N-Acetylbenzylamine was obtained from benzylbromide and acetamide (Ber. 59, 2667); benzylbromide from toluene by bromination in sunlight (Ber. 18, 606). The product did not keep well and had to be used the same day it was prepared.

N⁴-Acetyl-4-homosulfanilamidourea

7 gm of semicarbazide hydrochloride, 7 gm of N-acetyl-4-homosulfanilyl chloride, and 20 gm of crystalline sodium acetate were ground in a mortar. The sirupy product, formed at the beginning, solidified to a cream, which was as usually transferred with little water to a flask, heated, for 30 min. at 60°C, filtered and recrystallized from water. This compound was found to be much more soluble in water, than its lower homologue. It crystallized in the form of rods melting at 193°C with decomposition. Yield 5 gm. When analysed after being dried in the air it showed to contain one water of crystallization which could be removed when the substance was dried in vacuum (in the drying pistol) over P₂O₅ at 100°C (loss in weight 18 gm. per mol)

4-Homosulfanilamidourea

1 gm of N⁴-acetyl-4-homosulfanilamidourea was dissolved in 14 cc of concentrated HCl (density 1,19) and then 4 volumes (56 cc) of absolute alcohol were added. The solution was refluxed for 8-9 hours on a steam bath. On cooling the hydrochloride of the homo-compound crystallized in the form of clusters melting at 226°C with

decomposition. It was too soluble in water to be recrystallized from it. Yield 0,7 gm.

N⁴- Acetylsulfanilylhydrazine

5 gm of hydrazine dihydrochloride, 12 gm of dry N-acetylsulfanilyl chloride (1 mol per 1 mol) and 28 gm of crystalline sodium carbonate (2 mols) were ground in a mortar. The reaction started without addition of water and was marked by strong evolution of gas. When gas stopped evolving, some water was added, ground more, and left standing for 1 hour at room temperature to complete the reaction. The product was filtered, washed well with water and recrystallized from approximately 500 cc of boiling water (the proper amount of water should be used in order to boil the solution too long, since it results in decomposition of the N⁴-acetylsulfanilylhydrazine and causes therefore low yields.) Crystalline plates melting at 183-184° with decomposition were obtained. Yield 7-8 gm.

N⁴- Acetylsulfanilylphenylhydrazine

5 gm of phenylhydrazine hydrochloride (recrystallized from dilute HCl and then from 95% alcohol), 8,1 gm of dry N-acetylsulfanilyl chloride (1 mol per 1 mol) and 19 gm of crystalline sodium acetate (4 mols) were made to react by grinding with addition of little water. A sticky mass resulted which hardened upon standing in the refrigerator. This was ground, filtered, and recrystallized from watery alcohol. The phenylhydrazine derivative crystallized in the form of yellow needles melting at 157-159°C d. When recrystallized once more with addition of charcoal a white product melting at 161-162°C. d. was obtained. Yield 4,1 gm.

N⁴- Acetylsulfanilylmonobenzhydrazide

To 1 gm of N⁴-acetylsulfanilylhydrazine dissolved in dry pyridine 0,5 cc of benzoyl chloride (1 mol per 1 mol) was slowly introduced with cooling. After 24 hours of standing at room temperature the solution was evacuated over sulfuric acid in order to remove most of the pyridine. The residue was treated with dilute HCl, precipitate collected and recrystallized from watery alcohol. After the next two recrystallizations the product melted at 219-220°C with decomposition. Yield: 0,5 gm.

N⁴- Acetylsulfanilylmonoacethydraside.

To the solution of 3 gm of N⁴- acetylsulfanilylhydrazine in dry pyridine 0,93 cc of acetyl chloride (1 mol per 1 mol) were slowly introduced with cooling. After 24 hours most of the pyridine was removed by vacuum distillation, the residue treated with dilute HCl and kept in the refrigerator to make the substance precipitate. The precipitate was then collected and recrystallized twice from water. The pure product melted at 205-206°C with decomposition. Yield 1,2 gm.

The same substance was obtained when acetic anhydride was used, but the product melted at a somewhat lower temperature.

N⁴- Acetylsulfanilyldiacethydraside.

To the solution of 3 gm of N⁴- acetylsulfanilylhydrazine in pyridine 3 cc of acetic anhydride (1 mol per 2,5 mols) were introduced. Cooling was not necessary. The further procedure was the same as for the monoderivative. Two recrystallizations from water gave needles melting at 191-192°C with decomposition. Yield 2-2,5

Hydrolyses of N⁴-acetylsulfanilylmono- and -diacetylhydrazides

1. Method of Curtius and Stell (12).

0,3 gm of the monoacetylhydrazide derivative was kept on a steam bath for 5 minutes in 3 cc of 12 N HCl. After cooling the solution was neutralized with sodium carbonate care being taken not to increase the volume too much (at first solution and then solid sodium carbonate was used for that purpose.) After filtering the solution was left for crystallization. Long thick needles came down which when recrystallized from water melted at 129°C. with decomposition. Nitrogen percentage of this substance was found to be 20,25.

The same was repeated with the diacetylhydrazide derivative. The hydrolysis product appeared to be the same as in the above case. It had the same melting point, showed no depression of melting point when mixed with it, and its nitrogen percentage was 19,84.

These results indicate that both substances were hydrolyzed by concentrated HCl to sulfanilylhydrazine, which melts at 131°C with decomposition and its calculated nitrogen is 19,91%.

2. 0,3 gm of mono-and-diacetylhydrazide derivatives were kept on a steam bath for 10 minutes with 4 cc 6 N HCl. After neutralization with solid sodium carbonate in both cases products melting at 130-131°C (d) were obtained.

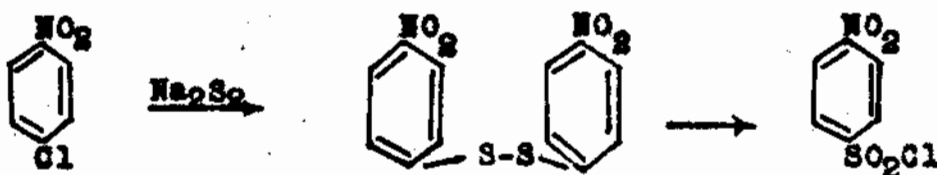
3. 0,3 gm of both compounds were treated as in 2, with 5 cc of 3 N HCl and gave the same products melting at 130-131°C (d.)

p-Nitrobenzenesulfonyl chloride

This intermediate was prepared from di-p-nitrophenyl disulfide according to a modified method which was used for the ortho isomer: Blatt, Org. Synth. Col. Vol II, p. 471. Di-p-nitrophenyl disulfide was suspended in acetic acid and chlorine was bubbled through.

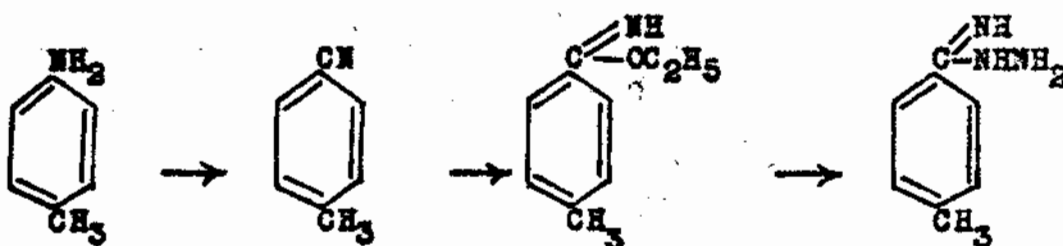
When all the yellow solid dissolved, the solution was pored into ice water. The precipitate was filtered and recrystallized from aviation benzine.

Di-p-nitrophenyl disulfide was obtained from p-nitrochlorobenzene and sodium disulfide according to Gilman, Org. Synth. Col. Vol. I p.215. Directions were slightly modified from those given for the ortho isomer.



P-Tolenylhydrazidine

This compound was prepared according to the scheme given below:



Tolunitrile was obtained from p-toluidine by the Sandmeyer react according to -Gattermann, p.288; p-tolenylimidoether according to Gustav Glock - Ber. 21, 2650; p-tolenylhydrazidine according to A. Pinner - Lieb. An. 297, 240 and Lieb. An. 298, 1.

P-Nitrobenzenesulfonyltolenylhydrazidine.

To the solution of 0,3 gm of p-tolenylhydrazidine 0,45 gm of nitrosulfonyl chloride was introduced. After 15 min. the mixture was treated with dilute HCl and the precipitate collected. The product was purified by dissolving it in hot acetone with subsequent addition of hot water. Yellow rods came down, melting at 151-155°C.

TABLE

Compound	Formula	Melting range, °C. #	Analysis in % **					
			Calculated			Found		
			C	H	N	C	H	N
N ⁴ -Acetylsulfanil- amidourea	C ₉ H ₁₂ N ₄ O ₄ S	223-4 d.			20,58			20,06
Sulfanilamidourea	C ₇ H ₁₀ N ₄ O ₃ S	229 d.	36,51	4,38	24,34	37,1	4,8	24,25
N ⁴ -Acetylsulfanil- amidothiourea	C ₉ H ₁₂ N ₄ O ₃ S ₂	186 d.	37,49	4,20	19,43	37,1	4,6	18,8
Sulfanilamidothio- urea	C ₇ H ₁₀ N ₄ O ₂ S ₂	224-5 d.	34,13	4,09	22,76	34,45	4,3	23,0
N ⁴ -Acetyl-4-homo- sulfanilamidourea.	C ₁₀ H ₁₄ N ₄ O ₄ S.H ₂ O	193 d.	39,46	5,30	18,41	40,4	5,3	18,5
4-Homosulfanilamido- urea.HCl	C ₈ H ₁₃ N ₄ O ₃ SO ₁	223 d.	34,23	4,67	19,96	35,4	5,2	19,8
N ⁴ -Acetylsulfanilyl- hydrazine	C ₈ H ₁₁ N ₃ O ₃ S	103-4 d.	41,91	4,84	18,33	41,9	4,9	18,2
N ⁴ -Acetylsulfanil- lylphenylhydra- zine	C ₁₄ H ₁₅ N ₃ O ₃ S	161-2 d.	55,07	4,95	13,76	55,15	5,5	13,47
N ⁴ -Acetylsulfanil- lylmonooacethydra- side	C ₁₀ H ₁₃ O ₄ N ₃ S	205-6 d.			15,49			15,79
N ⁴ -Acetylsulfanil- lydiacethydra- side	C ₁₂ H ₁₅ N ₃ O ₅ S	191-2 d.	46,00	4,83	13,41	45,8	4,8	13,6

* All melting points are uncorrected

** Analyses for N were done in Biochemistry Department first and then they were repeated and also analyzed for C and H in Rehovoth, Slef Institute.



Nitrogen determinations did not show consistent values and thus it was concluded that the compound was not obtained in its pure form. Calculated N for the hydrochloride = 15.11%; found: 15.59%, 14.19%

VI. Summary

Sulfanilamidourea, sulfanilamidothiourea and 4-homosulfanilamidourea were synthesized and tested in vitro for antibacterial properties. All three compounds showed a marked activity against Clostridia, the activities of the urea derivatives being superior to that of sulfathiazole. Sulfanilamidourea and sulfanilamidothiourea had also inhibiting effects on Streptococcus viridans but to a lesser degree than sulfathiazole.

Other related sulfanilamide derivatives prepared could not be tested since they were obtained in the therapeutically inactive form. These were: N⁴-acetylsulfanilylphenylhydrazine, N⁴-acetylsulfanilylmonoacethydrazide, N⁴-acetylsulfanilyldiacethydrazide and p-nitrobenzenesulfonyltolonylhydrazidine.

The acethydrazide compounds were obtained from N⁴-acetylsulfanilylhydrazine for the preparation of which a convenient method was developed.

N⁴-Acetylsulfanilylhydrazine was also made use of in the synthesis of sulfanilylbenshydrazide, a compound already described but prepared from a different starting material.

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