tinic acid) and thionyl chloride is described.

4. The yield of 1,1,1-trichloro-3-(4'-pyridyl)-2-propanol resulting from the condensation of 4-methylpyridine with chloral has been raised from 18 to 42%.

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[CONTRIBUTION FROM THE DIVISION OF MEDICINAL CHEMISTRY, THE SQUIBB INSTITUTE FOR MEDICAL RESEARCH]

Homosulfanilamides[1]

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In 1940 several homosulfanilamides were reported by Miller, Sprague, Kissinger and McBurney[2] as having no significant protective action against experimental streptococcal infections in mice. Similar results had been obtained with 4-homosulfanilamide in this Institute. Later Klarer[3] reported that 4-homosulfanilamide was effective in the treatment of experimental gas gangrene in mice. It appeared desirable to retest some of the homosulfanilamides which we had previously prepared and also to prepare some additional heterocyclic homosulfanilamides for such evaluation. The compounds which we prepared are listed in Table I. They were tested for activity in experimental gas gangrene by the Division of Microbiology and the Division of Pharmacology of this Institute.[4]

TABLE I

HOMOSULFANILAMIDES

Name	M. p., °C.	Empirical formula	Nitrogen, % Calcd.	Found
4-Homosulfanilamide hydrochloride	256[a]	$C_7H_{11}N_2O_2SCl$	12.58	12.28
N^1-Methyl-4-homosulfanilamide hydrochloride	245–247	$C_8H_{13}N_2O_2SCl$	11.83	11.88[b]
2-(4-Homosulfanilamido)-thiazole hydrochloride	276–277	$C_{10}H_{12}N_3O_2S_2Cl$	13.73	13.72[c]
2-(4-Homosulfanilamido)-4,6-dimethylpyrimidine	231–232	$C_{13}H_{16}N_4O_2S$	19.17	18.61[d]
2-(N^4-Acetyl-4-homosulfanilamido)-thiazole	169–170	$C_{12}H_{13}N_3O_3S_2$	13.50	13.28
2-(N^4-Phthaloyl-4-homosulfanilamido)-4,6-dimethylpyrimidine	233–235	$C_{21}H_{18}N_4O_4S$	13.26	13.07
2-(N^4-Phthaloyl-4-homosulfanilamido)-thiazole	207–208	$C_{18}H_{13}N_3O_4S_2$	10.52	10.32
N^4-Sulfanilamido-4-homosulfanilamide	199–201	$C_{18}H_{15}N_3O_4S_2$	12.28	12.37[e]
N^4-(N^4-Acetylsulfanilamido)-4-homosulfanilamide	199–201	$C_{15}H_{17}N_3O_5S_2$	10.96	10.75
N^4-Succinyl-4-homosulfanilamide	147–149	$C_{11}H_{14}N_2O_5S$	9.79	9.96[f]
1-Homosulfanilamide	170[g]	$C_7H_{10}N_2O_2S$		

[a] Reported by Miller, *et al.*, prepared by a different procedure, to have melting point 248–249° (THIS JOURNAL, **62**, 2099 (1940)). [b] Calcd.: Cl, 15.00. Found: Cl, 15.27. [c] Calcd.: S, 20.98. Found: S, 20.43. [d] Calcd.: S, 10.97. Found: S, 10.52. [e] Calcd.: S, 18.76. Found: S, 18.71. [f] Calcd.: S, 11.18. Found: S, 11.15. [g] Prepared in 92% yield by the catalytic reduction procedure of Miller, *et al.*, THIS JOURNAL, **62**, 2099 (1940). Calcd.: S, 17.27. Found: S, 17.36.

Of the compounds tested 4-homosulfanilamide and N^1-methyl-4-homosulfanilamide were the most effective in local treatment of experimental gas gangrene in mice.

For the preparation of 4-homosulfanilamide we found it more convenient if, instead of catalytically reducing *p*-cyanobenzenesulfonamide (Miller, *et al.*[2]), we chlorosulfonated N-acetylbenzylamine, treated the resultant crystalline sulfonyl chloride with ammonia, and finally hydrolyzed the acetyl compound with aqueous alcoholic hydrochloric acid. The hydrochloride salt obtained melted at 256°. Miller, *et al.*, reported a melting point at 248–249°. They mention having chlorosulfonated N-acetylbenzylamine, but did not identify the sulfonyl chloride nor report the hydrolysis of N^4-acetyl-4-homosulfanilamide.

The N^1-heterocyclic homosulfanilamides are not as readily prepared as the corresponding heterocyclic sulfanilamides by the general procedure of treating the required acetamidosulfonyl chloride with an amino heterocycle, followed by hydrolysis. In the preparation of 2-(4-homosulfanilamido) - 4,6 - dimethylpyrimidine, improved yields were obtained by chlorosulfonating α-phthalimidotoluene instead of α-acetamidotoluene.

Experimental Part[5]

N-Acetyl-4-homosulfanilyl Chloride.—Ten grams of acetylbenzylamine was added to 30 cc. of chlorosulfonic acid while maintaining the temperature below 15°. The temperature was then raised to 50–60° and held at this point

(1) The nomenclature used in this paper conforms in general to that accepted for sulfanilamides. Structure (I) $NH_2C_6H_4SO_2NH_2$ has been designated 4-homosulfanilamide and structure (II) $NH_2C_6H_4CH_2SO_2NH_2$ 1-homosulfanilamide. The nitrogen of the sulfonamido group is N^1 and that in the group para to the sulfonamido group is N^4.

(2) E. Miller, J. M. Sprague, L. W. Kissinger and L. F. McBurney, THIS JOURNAL, **62**, 2099 (1940).

(3) J. Klarer, *Klin. Wochschr.*, **20**, 1250 (1941); *cf.* Klarer, U. S. Patent 2,288,531 (1942).

(4) Dorothy M. Hamre, H. A. Walker, Wolcott B. Dunham, H. B. van Dyke and Geoffrey Rake, *Proc. Soc. Exp. Biol. Med.*, **55**, 170–173 (1944).

(5) All melting points are uncorrected.

for half an hour, after which the mixture was poured upon cracked ice. The oily product which precipitated crystallized. It was washed once by decantation with ice water, and then allowed to stand in a second wash water for one hour. The crude wet product was then dissolved in chloroform, dried with magnesium sulfate, and precipitated with 3–4 volumes of hexane, m. p. 95–97°, yield 7.4 g. (44.6%). It did not keep well and analysis showed it to be somewhat low in chlorine content. *Anal.*[6] Calcd. for $C_9H_{10}ClNO_3S$: Cl, 14.34. Found: Cl, 13.06.

4-Homosulfanilamide.—Four hundred grams of acetylbenzylamine was converted to the crude acetyl homosulfanilyl chloride as indicated above. The latter was then added to one liter of concentrated ammonium hydroxide keeping the temperature below 15°. After stirring for two hours at this temperature the mixture was stored in a refrigerator overnight, the crystalline solid filtered off and washed with water. Additional product was obtained by concentrating the filtrate to dryness and recrystallizing the residual solid from 95% alcohol. The total yield was 250 g. (36.9%) of N^4-acetyl-4-homosulfanilamide m. p. 168–169°. The 250 g. of acetyl compound was then hydrolyzed by refluxing for six hours with 2.5 liters of alcohol and 2.5 liters of 10% hydrochloric acid, the solution filtered, and concentrated to dryness *in vacuo*. The crude product thus obtained was recrystallized from 95% alcohol yielding 184 g. (83.6%) 4-homosulfanilamide hydrochloride, m. p. 256°. Klarer[3] used alkaline hydrolysis of the acetyl compound and isolated 4-homosulfanilamide as the free base.

N^1-Methyl-N^4-acetyl-4-homosulfanilamide.—This compound was prepared by the procedure described by Klarer,[3] m. p. 98–99°; yield 76.7%.

N^1-Methyl-4-homosulfanilamide.—Fifty-five grams of N^1-methyl-N^4-acetyl 4-homosulfanilamide was hydrolyzed by boiling for three hours with 1100 cc. of 50% aqueous alcohol containing 5% hydrochloric acid and recrystallized from 95% alcohol. The yield of hydrochloride salt was 13.5 g. (25.1%), m. p. 245–247°. Klarer[3] used alkaline hydrolysis of the acetyl compound and isolated the N^1-methyl-4-homosulfanilamide as the free base.

N^4-(N^4-Acetylsulfanilamido)-4-homosulfanilamide.—Four grams of 4-homosulfanilamide was mixed thoroughly in a mortar with 4.9 g. of N-acetyl-4-homosulfanilyl chloride and 2.5 cc. of pyridine. The mixture was heated on a steam-bath for one-half an hour, added to about 50 cc. of acidulated water, and the yellow precipitate thus formed filtered off and washed with water; m. p. 178–185°; yield 7 g. (87.5%). After recrystallization from 50% alcohol the product melted at 199–201°.

N^4-Sulfanilamido-4-homosulfanilamide.—The above acetyl compound (6.35 g.) was hydrolyzed by refluxing for one-half an hour with a solution of 53 cc. of 10% hydrochloric acid and 20 cc. of 95% alcohol. The hot solution was treated with charcoal, filtered, cooled, and made just alkaline to congo red with sodium hydroxide. The precipitate was filtered, and recrystallized from 50% alcohol; m. p. 198–200°; yield 4 g. (70%). After recrystallizing from 95% alcohol it melted at 199–201°. A mixed m. p. with the acetyl compound from which it was made was 177–180°. A nitrite titration on 100 mg. of the deacetylated compound gave 3.25 cc. of 0.1 *N* KNO_2; calcd., 3.18 cc. of 0.1 *N* KNO_2.

N^4-Succinyl-4-homosulfanilamide.—Seventeen grams of 4-homosulfanilamide was dissolved in one liter of dioxane and to this solution there was added with stirring 9 g. of succinic anhydride dissolved in 100 cc. of dioxane. The solution was refluxed for two hours after which it was concentrated to a volume of about 75 cc. On standing in the refrigerator overnight a crystalline product separated. This was filtered off, redissolved in absolute alcohol and precipitated with benzene. A second recrystallization from alcohol and benzene gave a product m. p. 147–149°; yield 8 g. (35%). It was soluble to the extent of 2–3% in water.

2-(N^4-Acetyl-4-homosulfanilamido)-thiazole.—One hundred thirty-two grams of N-acetyl-4-homosulfanilyl chloride was added gradually to 52.7 g. of 2-aminothiazole dissolved in 185 cc. of pyridine at a temperature below 35°. The mixture was heated one hour at 70–80° and allowed to stand overnight. The bulk of the pyridine was removed under reduced pressure after which one equivalent of normal sodium hydroxide was added, the mixture warmed for one-half hour at 70–80° and concentrated to dryness *in vacuo*. The residue was treated with a small amount of water and evaporated to dryness, and this operation repeated once again. Finally the residue was washed with ethyl acetate and then extracted with boiling dioxane. On cooling the dioxane the 2-(N^4-acetyl-4-homosulfanilamido)-thiazole separated as white needles; m. p. 154–165°; yield 83.9 g. (50.6%). A sample recrystallized from dioxane melted at 169–170°.

2-(4-Homosulfanilamido)-thiazole.—Hydrolysis of 2-(N^4-acetyl-4-homosulfanilamido)-thiazole using aqueous alcoholic hydrochloric acid in the same manner as described above for the hydrolysis of N^4-acetyl-4-homosulfanilamide gave a 51% yield of 2-(4-homosulfanilamido)-thiazole hydrochloride which after recrystallization from alcohol melted at 276–277°.

N^4-Phthaloyl-4-homosulfanilyl Chloride.—Thirty cc. of chlorosulfonic acid was cooled to 10° and 26.5 g. of benzyl phthalimide added with stirring at 10° during twenty minutes. The reaction mixture was then heated for one-half an hour at 55–60° when it was cooled to 35° and poured on 400 g. of ice. The gummy product which separated was extracted with chloroform, the extract dried over magnesium sulfate, filtered, and concentrated to small volume under reduced pressure. From this residual solution the product was precipitated as a white powder with petroleum ether; m. p. 124–125°, yield 25.5 g. (68%). *Anal.* Calcd. for $C_{18}H_{10}ClNO_4S$: Cl, 10.56. Found: Cl, 9.92.

2-(N^4-Phthaloyl-4-homosulfanilamido)-4,6-dimethylpyrimidine.—Twenty-four grams of 2-amino-4,6-dimethylpyrimidine was dissolved in 75 cc. of pyridine and the solution cooled to 5°; 65 g. of N^4-phthaloyl-4-homosulfanilyl chloride was added with stirring. The mixture was then heated on a steam-bath for two hours, cooled to 25°, poured into 600 cc. of water, and acidified. The precipitate which separated was crystallized from alcohol yielding 24 g. (29.4%) of product of m. p. 233–235°. A sample further recrystallized from alcohol melted at 235–236°.

2-(4-Homosulfanilamido)-4,6-dimethylpyrimidine.—Thirty-six grams of 2-(N^4-phthaloyl-4-homosulfanilamido)-4,6-dimethylpyrimidine, 10 cc. of hydrazine hydrate (85%) and 250 cc. of absolute alcohol were refluxed for three hours. Upon cooling, the precipitated material was filtered, washed with alcohol and dried; yield 27 g., m. p. 194–198°. The latter was dissolved in 500 cc. of boiling water, and hydrolyzed with 100 cc. of 10% hydrochloric acid. After filtering off the phthalylhydrazide, the filtrate was made alkaline with dilute sodium hydroxide. The precipitated product, 10 g., after crystallization from 95% alcohol melted at 231–232°.

2-(N^4-Phthaloyl-4-homosulfanilamido)-thiazole.—Five grams of 2-aminothiazole was dissolved in 20 cc. of pyridine. The solution was cooled to 5–10° and 16.5 g. of N^4-phthaloyl-4-homosulfanilyl chloride added with stirring. The reaction mixture was heated on a steam-bath for two hours, then cooled and diluted with water. This mixture was acidified, the precipitated material filtered, washed and dried; m. p. 174–8°; yield 11.5 g. (58.7%). Recrystallization from alcohol gave 4.0 g. of m. p. 207–208°. Attempts to hydrolyze this product failed to give the desired homosulfanilamide.

Summary

Several new homosulfanilamides have been prepared.

Of the homosulfanilamides prepared, 4-homosulfanilamide and N^1-methyl-4-homosulfanilamide were the most effective in local treatment of experimental gas gangrene in mice.

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(6) All micro analyses were carried out by Mr. J. F. Alicino of this Institute.