

Tuberculostatic Derivatives of *p*-Aminobenzoic Acid

V. 4-Aminosalicilyl Derivatives of Sulfanilamide and Related Compounds

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With the purpose of investigating their tuberculostatic activity some compounds which at the same time are derivatives of *p*-aminosalicylic acid (PAS) and sulfonamides or sulfones were prepared.

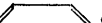

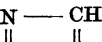

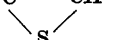
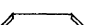

From the reaction of *p*-nitrosalicyloyl chloride with aniline a well defined product could more easily be obtained than from the reaction of this acid chloride with heterocyclic amines (*cf.* the preceding paper¹). Analogously *p*-nitrosalicyloyl derivatives of sulfanilamide, sulfathiazole *etc.* were obtained without difficulty and generally in good yields. The nitro compounds form intensely yellow powders which are very slightly soluble in most solvents.

The following compounds were prepared ($R = O_2N \text{---} \text{C}_6\text{H}_3(\text{OH}) \text{---} \text{CO--}$):

I	$RNH \text{---} \text{C}_6\text{H}_4 \text{---} \text{SO}_2\text{NH}_2$	PNS-Derivative of: Sulfanilamide
II	$RNH \text{---} \text{C}_6\text{H}_4 \text{---} \text{SO}_2\text{NH} \text{---} \text{C}_5\text{H}_4\text{N}$	Sulfapyridine
III	$RNH \text{---} \text{C}_6\text{H}_4 \text{---} \text{SO}_2\text{NH} \text{---} \text{C}_4\text{H}_2\text{N}_2\text{S}$	Sulfathiazole
IV	$RNH \text{---} \text{C}_6\text{H}_4 \text{---} \text{SO}_2\text{NH} \text{---} \text{C}_4\text{H}_2\text{N}_2\text{S} \text{---} \text{C}(\text{CH}_3)=\text{N}$	Sulfamethylazole
V	$RNH \text{---} \text{C}_6\text{H}_4 \text{---} \text{SO}_2\text{NH} \text{---} \text{C}_6\text{H}_3\text{N}_2$	Sulfadiazine
VI	$RNH \text{---} \text{C}_6\text{H}_4 \text{---} \text{SO}_2\text{NH} \text{---} \text{C}_6\text{H}_3\text{N}_2 \text{---} \text{CH}_3$	Sulfamerazine

$(\text{RNH} \text{---} \text{C}_6\text{H}_4)_2\text{SO}_2$ VII	$\text{RNH} \text{---} \text{CH}_2 \text{---} \text{C}_6\text{H}_4 \text{---} \text{SO}_2\text{NH}_2$ VIII	$\text{RNHCH}_2\text{CH}_2\text{COOH}$ IX
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$$\begin{array}{c} \diagup \\ \text{CO—} \end{array} \text{);}$$

X	$R'NH$  SO_2NH_2	Sulfanilamide
XI	$R'NH$  SO_2NH 	Sulfathiazole
XII	$R'NH$  SO_2NH 	Sulfamethylizole
XIII	$(R'NH$  $)_2SO_2$	4,4'-Diamino-diphenylsulfone
XIV	$R'NHCH_2$  SO_2NH_2	Marfanil

p-Nitrosalicylanilide (2-Hydroxy-4-nitrobenzanilide). *p*-Nitrosalicyloyl chloride (2 g) was added with cooling to aniline (5 ml) and the reaction product recrystallized from benzene. Yield 2.1 g (80 %). M. p. 238°.

$C_{13}H_{10}O_4N_2$ (258.2) Calc. N 10.85 Found N 10.65

By catalytic hydrogenation at room temperature and atmospheric pressure (*cf.* Jensen, Rosdahl and Ingvorsen²) this compound was transformed into *p*-aminosalicylanilide (m. p. 143°) identical with the product prepared by Jensen and Ingvorsen³.

***N*⁴-(*p*-Nitrosalicyloyl)-sulfanilamide (I).** Sulfanilamide (0.005 mole; 0.85 g) dissolved in 10 ml of pyridine was added to *p*-nitrosalicyloyl chloride (1 g) and the solution heated for ½ hour at 120°. The mixture was diluted with water and the precipitate filtered and washed thoroughly with water. Yield of crude product 1.55 g (89%). Recrystal-

lized from ethanol it formed orange-yellow crystals which turned almost white at 200° and melted at 249—50°.

$C_{13}H_{11}O_6N_3S$ (337.3) Calc. N 12.46 Found N 12.54

In a similar way the other nitro compounds (Table I) were prepared. In preparing the comp. no. VIII the hydrochloride of Marfanil instead of the free amine was used. Yields in most cases were 70—90 %. The crude products were recrystallized from ethanol or acetic acid. The derivatives of the heterocyclic sulfonamides and comp. no. VII are very slightly soluble in the common solvents, whereas the other compounds were rather soluble in hot ethanol. The compounds form light yellow crystals.

By reaction of *p*-nitrosalicyloyl chloride with 4,4'-diaminodiphenylsulfone a bis-*p*-nitrosalicyloyl derivative was obtained. With 4-aminophenyl-5'-amino-2'-thiazolyl-sulfone (Promizole) on the other hand a product was obtained which apparently is a mono-*p*-nitrosalicyloyl derivative (calc. 13.34 % N, found 13.10 %). Other preparations, however, gave lower nitrogen values and the compound was not examined further.

The derivative of β -alanine was prepared by using a Schotten-Bauman procedure in the same way as salicyloyl- β -alanine (Moss *et al.*⁴).

Reduction was performed with tin and hydrochloric acid in acetic acid solution in the same way as described in the preceding paper.

*N*⁴-(*p*-Aminosalicyloyl)-sulfanilamide. On recrystallizing from dilute ethanol (70 %) the compound separated as white shiny plates. Slightly soluble in hot ethanol, easily soluble in acetone. M. p.: decomposes gradually at 270—300°.

$C_{13}H_{13}O_4N_3S$ (307.3) Calc. N 13.74 S 10.64
Found " 13.70 " 10.64

In a similar way the other amino compounds (Table 2) were prepared.

Table 1. *p*-Nitrosalicylic acid derivatives of sulfanilamide etc.

No.	Empirical formula	M. p.	% N	
			calc.	found
I	$C_{13}H_{11}O_6N_3S$	250°	12.46	12.50
II	$C_{18}H_{14}O_6N_4S$	205° (dec.)	13.52	13.45
III	$C_{16}H_{12}O_6N_4S_2$	290° (dec.)	13.36	13.80
IV	$C_{16}H_{13}O_6N_5S_2$	296° (dec.)	16.08	16.60
V	$C_{17}H_{13}O_6N_5S$	295° (dec.)	16.86	16.63
VI	$C_{18}H_{15}O_6N_5S$	270° (dec.)	16.31	16.45
VII	$C_{26}H_{18}O_{10}N_4S$	245° (dec.)	9.68	9.97
VIII	$C_{14}H_{13}O_6N_3S$	254°	11.94	11.96
IX	$C_{10}H_{10}O_6N_2S$	212—13°	11.03	11.15

Nos. III and IV were recrystallized from acetic acid, the others from ethanol. No. VI melts first at ca. 160° but solidifies again.

Table 2. *p*-Aminosalicyloyl derivatives of sulfanilamide etc.

No.	Empirical formula	M. p.	% N	
			calc.	found
X	$C_{13}H_{13}O_4N_3S$	dec.	13.74	13.70
XI	$C_{16}H_{14}O_4N_4S_2$	270° (dec.)	14.35	13.82
XII	$C_{16}H_{15}O_4N_5S_2$	280° (dec.)	17.50	18.07
XIII	$C_{26}H_{20}O_8N_4S$	264°	10.81	10.68
XIV	$C_{14}H_{15}O_4N_3S$	219°	13.08	12.98

SUMMARY

p-Nitrosalicylic acid derivatives of sulfanilamide and substituted sulfanilamides, of diaminodiphenylsulfone and *p*-aminomethylbenzenesulfonamide (Marfanil, Sulfamylon) were prepared by the reaction of *p*-nitrosalicyloyl chloride with the appropriate amino compound in pyridine solution. The corresponding *p*-amino derivatives were obtained by reduction of the nitro compounds with tin and hydrochloric acid in acetic acid solution.

REFERENCES

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3. Jensen, K. A., and Ingvorsen, H. *Acta Chem. Scand.* **6** (1952) 161.
4. Moss, J. N., Urist, H., and Martin, G. J. *Arch. Biochem.* **19** (1948) 213.

Received August 18, 1951.