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Tuberculostatic Derivatives of 4-Aminobenzoic Acid

IV. Heterocyclic Derivatives of 4-Aminosalicylic Acid (PAS)

KAI ARNE JENSEN and SVEND Å. K. CHRISTENSEN

Chemical Laboratory of the University of Copenhagen, Copenhagen, Denmark

As mentioned in the preceding paper [1] it was attempted to prepare 4-aminosalicylamides with heterocyclic substituents in the amide group by reduction of 4-nitro-2-benzyloxybenzamides. We did not, however, succeed in splitting off the benzyl group when the amides contained heterocyclic substituents. While heterocyclic substituted amides of salicylic acid could easily be prepared by reaction of salicyloyl chloride or acetylsalicyloyl chloride with heterocyclic amines in pyridine solution (Jensen and Linholt [2]), great difficulties were encountered in obtaining well defined compounds by application of this process to the corresponding 4-nitroderivatives. Numerous experiments were performed with the condensation of 2-aminopyridine with 4-nitrosalicyloyl chloride or with 2-acetoxy-4-nitrobenzoyl chloride, with or without excess of 2-aminopyridine, with or without pyridine as condensing agent, at 0° or in boiling benzene or carbon tetrachloride, or in aqueous solution by the Schotten-Baumann procedure. Products were obtained which were obviously inhomogenous, their melting points ranging from 100° to 270°, their nitrogen content from 8 to 14 %, and their colour from almost white to an intense yellow, without any apparent connection between melting point or colour and nitrogen content. On boiling the products with ethanol a certain fractionation could be obtained, but it was impossible to isolate a pure compound, because the products were almost insoluble in the common solvents. In sodium hydroxide they dissolved with an intense reddish-brown colour. When the solution was boiled for a short time and acidified 4-nitrosalicylic acid was obtained.

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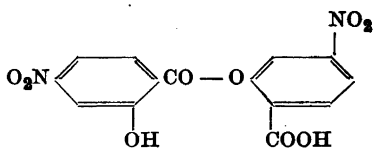
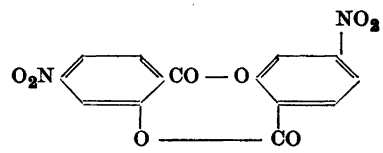
* After completion of this work condensation products of 2-acetoxy-4-nitrobenzoyl chloride with aminoheterocycles have been described by Doub *et al.*[3], but their attempts to reduce these compounds were unsuccessful.

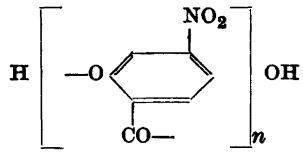
It seems that salicyloyl chloride and acetylsalicyloyl chloride by the action of pyridine or 2-aminopyridine are in part transformed in di- and polysalicylides:



Disalicylide 8.05 % N

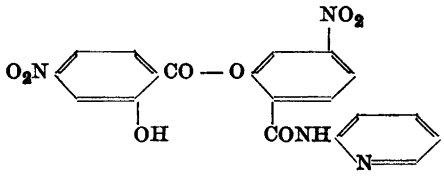


"Diplosal" 8.5 %

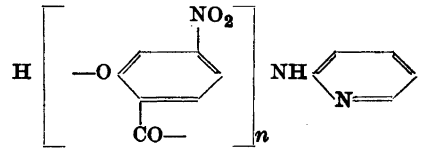


Polysalicylides 8.17 – 8.50 % N

and in part in 2-pyridylamides of these acids:



13.5 % N



11.9 – 8.5 % N

It was observed, however, that a compound having the desired composition (16.2 % N) could be obtained when a solution of 4-nitrosalicyloyl chloride and 2-aminopyridine in pyridine was heated at 120° for some time. Under these circumstances the polymeric anhydrides of 4-nitrosalicylic acid apparently are split by the action of 2-aminopyridine.

Amides of 4-nitrosalicylic acid containing a thiazole, thiadiazole or triazole group were obtained more easily in pure form. In these cases, too, inhomogenous products with low nitrogen content were obtained when the condensation was carried out at lower temperature, but in boiling pyridine products with the calculated composition were formed. No well defined compounds could be obtained from condensations of 4-nitrosalicyloyl chloride with 2-amino-4,6-dimethyl-pyrimidine, 2-amino-4-methyl-pyrimidine, imidazole, indole or 2-methyl-indole. In all these cases the reaction mixture became very dark brown.

The reduction of the nitro derivatives were beset by great difficulties. Catalytic hydrogenation of the nitro compounds were first attempted, using PtO_2 as a catalyst. The pyridine compound could be hydrogenated in hot acetic acid, where it is fairly soluble, but no well defined product could be isolated. The products prepared from 2-aminothiazole and 2-amino-5-methylthiadiazole on the other hand are almost insoluble in all common solvents and although hydrogen was slowly absorbed by suspensions of the compounds in ethanol no amino compounds were formed: the yellow compounds turned white without going in solution and the reaction products were amorphous, insoluble in all solvents except concentrated acids and bases, gave no reaction for an aromatic amino group and could not be purified to give a well defined product. Only in the case of the nitrosalicyloyl derivative of 2-amino-4,5-dimethylthiazole could an amino compound of the desired composition be isolated from the hydrogenation mixture. In this case the nitro compound is fairly soluble in ethanol.

Several other means of reduction had been tried with no success when it was found that reduction proceeded smoothly with tin and hydrochloric acid in acetic acid solution. Under these conditions also the difficultly soluble nitrosalicyloyl derivatives of 2-aminothiazole and 2-amino-5-methylthiadiazole went into solution in few minutes. The amino compounds could be isolated after precipitation of tin with hydrogen sulfide. The amino compounds form colourless crystals and are soluble even in dilute ethanol. They dissolve easily in alkali and in dilute hydrochloric acid but form slightly soluble hydrochlorides with concentrated hydrochloric acid. With ferric chloride they give a violet colour.

The compounds have been found to possess tuberculostatic activity but less than the parent compound, PAS (experiments by J. Lehmann, to be published later).

EXPERIMENTAL

Microanalyses by Mr. A. Grossmann

2-Acetoxy-4-nitrobenzoic acid. A mixture of 183 g of 4-nitro-salicylic acid, 110 g of acetic anhydride and 500 ml of benzene was refluxed for 4 hours. The solution was concentrated to half the volume *in vacuo*. On cooling light yellow crystals deposited, which were filtered and recrystallized from dry benzene. Yield 198 g (88 %). M. p. 156°.

$C_9H_7O_6N$ (225.1) Calc. N 6.22 Found N 6.27

On boiling with water the compound is easily hydrolyzed to 4-nitrosalicylic acid.

2-Acetoxy-4-nitrobenzoyl chloride. A mixture of the acid (11.2 g) and thionyl chloride (10 ml) was heated on a water bath for 15 minutes. The excess of thionyl chloride was

removed *in vacuo* and the residue recrystallized from hexane. Yield 8 g (66 %). Light yellow crystals; m. p. 57.5°.

$C_9H_6O_5NCl$ (243.6) Calc. N 5.75 Found N 6.14

2-Hydroxy-4-nitrobenzoyl chloride (4-nitrosalicyloyl chloride). A mixture of 5 g of 4-nitrosalicylic acid, 20 ml of benzene and 4 ml of thionyl chloride was heated to 90° for 1—2 hours. Generally the acid dissolved in the course of ½ hour (depending on the fineness of the powder). After removing of benzene and excess of thionyl chloride in vacuo the acid chloride crystallized in yellow rosettes which were washed with dry petroleum ether and dried *in vacuo* over paraffin and phosphorus pentoxide. Humidity should be excluded very cautiously during the preparation. Yield quantitative. M. p. 59—60°.

$C_7H_4O_4NCl$ (201.5) Calc. N 6.95 Found N 6.97

4-Nitrosalicylamides. Condensation of heterocyclic amines with 4-nitrosalicyloyl chloride or 2-acetoxy-4-nitrobenzoyl chloride at lower temperature gave products with low nitrogen content. Products with the desired nitrogen content were obtained in the following way: 0.01 mole of 4-nitrosalicyloyl chloride was melted and a solution of 0.01 mole of the amino compound in 15 ml of dry pyridine was added at one time. A vigourous reaction took place. The solution was heated to 120° for ½ hour, cooled and poured into water. The precipitation was completed by addition of acetic acid, and after filtration the precipitate was washed thoroughly with water and digested with 20 ml of hot ethanol. The crude products (yields 50—70 %) were used directly for reduction. They are far from pure, but with exception of compounds nos. II and III their solubility was so extremely slight that it was inconvenient to recrystallize more than small portions for analysis. At least two recrystallizations were necessary to obtain pure products. With exception of compound no III they have no sharp melting points but decompose before melting, the melting point therefore being very dependent on the heating rate.

I. 2-(p-Nitrosalicyloyl)-aminothiazole. Light yellow crystals from acetic acid. M. p. ca. 300° (dec.). Almost insoluble in ethanol.

$C_{10}H_7O_4N_3S$ (265.3) Calc. C 44.60 H 2.62 N 15.84
Found » 44.20 » 3.12 » 15.96—16.04—15.87 *

II. 2-(p-Nitrosalicyloyl)-4,5-dimethylthiazole. Yellow crystals from ethanol (fairly soluble). M. p. ca. 300° (dec.).

$C_{12}H_{11}O_4N_3S$ (293.3) Calc. N 14.33 Found N 14.20—13.94—13.97 *

III. 2-(p-Nitrosalicyloyl)-amino-4-methyl-5-carbethoxy-thiazole. Light yellow crystals from ethanol or acetic acid. M. p. 237—38°.

$C_{14}H_{13}O_6N_3S$ (351.3) Calc. N 11.96 Found N 11.53

* Different preparations.

IV. 2-(p-Nitrosalicyloyl)-aminopyridine. Intensely brownish yellow crystals from propanol; almost insoluble in ethanol. M. p. ca. 240° (dec.).

$C_{12}H_9O_4N_3$ (259.2) Calc. N 16.21 Found N 16.05—16.39—16.49 *

V. 3-(p-Nitrosalicyloyl)-amino-1,2,4-triazole. Light yellow crystals from ethanol. M. p. ca. 315 (dec.).

$C_9H_7O_4N_5$ (249.2) Calc. N 28.10 Found N 27.81

VI. 2-(p-Nitrosalicyloyl)-amino-5-methyl-1,3,4-thiadiazole. Light yellow (almost white) crystals from acetic acid (very slightly soluble). Insoluble in most solvents. M. p. ca. 300° (dec.).

$C_{10}H_8O_4N_4S$ (280.3) Calc. C 42.87 H 3.62 N 19.99
Found » 43.02 » 3.28 » 19.77—19.72—20.16—20.26 *

4-Aminosalicylamides. Reduction of the nitro compounds was performed in the following way: The nitro compound (1 g) was mixed well with 100 g of granulated tin and 20 ml of acetic acid and 5 ml of conc. hydrochloric acid were added. The mixture was heated to 100° for 10 minutes, the compounds usually dissolving in 1 or 2 minutes. The solution was decanted from the tin (which was used for the next preparation), diluted with 150 ml of water and precipitated with hydrogen sulfide. After filtration the solution was brought to pH = 5, the precipitates filtered and washed with water. They were recrystallized from 50 % ethanol and dried at 100°. Yields 0.60—0.70 g. The products form colourless crystals.

2-(p-Aminosalicyloyl)-aminothiazole. M. p. 252° (dec.), 266° on the Kofler-stage.

$C_{10}H_9O_2N_3S$ (235.3) Calc. C 51.09 H 3.85 N 17.85
Found » 50.86 » 4.04 » 17.60

2-(p-Aminosalicyloyl)-amino-4,5-dimethylthiazole. M. p. 253—54°, 268° on the Kofler stage.

$C_{12}H_{13}O_2N_3S$ (263.3) Calc. N 15.95 Found N 16.33

2-(p-Aminosalicyloyl)-aminopyridine. M. p. 185—86°, 190° on the Kofler stage.

$C_{12}H_{11}O_2N_3$ (229.3) Calc. N 18.33 Found N 17.98

2-(p-Aminosalicyloyl)-amino-5-methyl-1,3,4-thiadiazole. M. p. ca. 300° (dec.).

$C_{10}H_{10}O_2N_4S$ (250.2) Calc. N 22.40 Found N 21.94

* Different preparations.

SUMMARY

Condensation of *p*-nitrosalicyloyl chloride with heterocyclic amines in pyridine solution at 120° gave the corresponding heterocyclic substituted *p*-nitrosalicylamides. At lower temperature more complicated products were formed.

By reduction of the nitro compounds with tin and hydrochloric acid in acetic acid solution the corresponding heterocyclic substituted *p*-aminosalicylamides were obtained.

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3. Doub, L., Schaeffer, J. J., Bambas, L. L., and Walker, C. T. *J. Am. Chem. Soc.* **73** (1951) 903.

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