

## Tuberculostatic Derivatives of *p*-Aminobenzoic Acid

### VI. Preparation of Amides of *p*-Aminosalicylic Acid (PAS) by Means of 2-Acetoxy-4-acetamido-benzoyl Chloride

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The difficulties encountered in preparing heterocyclic derivatives of *p*-aminosalicylamide (Jensen and Ingvorsen<sup>1</sup>, Jensen and Christensen<sup>2</sup>) via 4-nitrosalicylic acid caused us to investigate the possibility of preparing compounds of this type more directly from 4-aminosalicylic acid (PAS). To transform this acid into an acid chloride the amino group, and probably also the hydroxy group, should be protected, for instance by introduction of a carbobenzyloxy group or an acetyl group. The first possibility would offer the advantage that the carbobenzyloxy group might be removed by hydrogenolysis, whereas the acetyl group has to be removed by hydrolysis which will also involve the other amide group. After some preliminary experiments with 4-carbobenzyloxyamino-2-hydroxybenzoic acid we, however, concentrated our efforts on the reactions of 2-acetoxy-4-acetamidobenzoyl chloride, which turned out to be rather easily accessible. This acid chloride couple easily with amines to give 4-acetamidosalicylamides. By hydrolysis these give the corresponding amides of *p*-aminosalicylic acid, although not in good yields, because the hydrolysis of course attacks both the acetamido and the benzamido group. Because of the easy accessibility of the acid chloride this method of preparing amides of *p*-aminosalicylic acid nevertheless seems to be preferable to their preparation via 4-nitrobenzoyl chloride.

## EXPERIMENTAL

Microanalyses by Mr. A. Grossmann.

*2-Hydroxy-4-acetamidobenzoic acid* \*. 2-Hydroxy-4-aminobenzoic acid (7.7 g) was dissolved in 2 N NaOH (25 ml) and acetic anhydride (10.2 g) was added successively with stirring, sodium hydroxide being added to maintain the pH at 7. When the acetic anhydride had dissolved the solution was acidified strongly with hydrochloric acid (19 ml). The solid was filtered off and recrystallized from 50 % ethanol. Yield 7.3 g (74 %). M. p. 231° (dec.).

$C_9H_9O_4N$  (195.2) Calc. N 7.18 Found N 7.36

*2-Acetoxy-4-acetamidobenzoic acid* \*. 2-Hydroxy-4-aminobenzoic acid (10 g) was suspended in a mixture of dry benzene (30 ml) and acetic anhydride (25 ml) and the mixture refluxed for 2 hours. After cooling the solid was filtered off (yield 15.5 g or 100 %) and recrystallized from acetic acid containing 20 % acetic anhydride. Yield of recrystallized product: 12 g (78 %). M. p. 195°.

$C_{11}H_{11}O_5N$  (237.2) Calc. N 5.91 Found N 5.93

*2-Hydroxy-4-carbobenzoyloxyaminobenzoic acid*. To an icecold solution of 2-hydroxy-4-aminobenzoic acid (1 g) in 1 N sodium hydroxide (6.5 ml) was added alternately and with thorough stirring 6.5 ml of 1 N sodium hydroxide and a solution of benzyl chloroformate (2 g) in toluene. After standing for one hour in an ice bath the solution was extracted with ether and to the aqueous solution was added concentrated hydrochloric acid until pH = 2. The precipitate was recrystallized from dilute ethanol (1:1). Yield 1.8 g (69 %). M. p. 187–88°.

$C_{15}H_{13}O_5N$  (287.3) Calc. C 62.69 H 4.62 N 4.88  
Found " 62.72 " 4.53 " 4.71

Even by application of a large excess of benzyl chloroformate only the mono-derivative was formed.

*2-Acetoxy-4-acetamidobenzoyl chloride*. Finely powdered 2-acetoxy-4-acetamidobenzoic acid (1 g) was mixed with thionyl chloride (2 ml). After standing for about one hour at room temperature a reaction set in: hydrogen chloride was evolved and the solid went in solution; separation of another solid began as a rule before all had dissolved. After two hours a homogenous, almost white precipitate of the acid chloride had formed. The process can be considerably accelerated by addition of a trace of pyridine, but the product then becomes yellow. After removing of excess thionyl chloride *in vacuo*, addition of dry benzene and evaporating again, the product could be directly used for preparation of the amides. When working with larger amounts 1 ml of thionyl chloride for each g of the acid is sufficient.

For analysis the acid chloride was prepared in the following way: 1 g of the acid was suspended in 5 ml of chloroform and 1 ml of thionyl chloride was added. After 2–3

\* While this work was in progress these two acids were also reported by Drain *et al.*<sup>4</sup>.

hours all had dissolved with evolution of hydrogen chloride. After standing for 24 hours colourless prismatic crystals had separated, which were filtered off and washed with chloroform. M. p. 144°.

$C_{11}H_{10}O_4NCl$  (255.7)    Calc. Cl 13.87    Found Cl 13.84

*Amides of 2-hydroxy-4-aminobenzoic acid.* To the acid chloride prepared from 1 g of the acid was added 10 ml of dry benzene and either 2.5 mole of the amine or 1 mole of the amine and 1.5 mole of pyridine. The mixture was cooled and stirred well. After ½ hour 10–20 ml of warm (40°) 2-N sodium hydroxide was added and the mixture shaken in separatory funnel. The aqueous layer was separated and acidified. The acetamido compound was filtered off and either recrystallized or hydrolyzed directly. Hydrolysis of the acetoxy group was attained by boiling with 25 ml of 6-N sulfuric acid for 10–15 minutes (or until the solid had dissolved); when the cooled solution was brought to pH 5–6 the amino compound separated. Yields of the crude acetamido compounds were 80–100 %, yields of the hydrolysed products 40–60 %. Identity of the amino compounds with those prepared via the nitro compounds was shown by mixed melting points.

In this way the following amides were prepared:

*2-Hydroxy-4-acetamidobenzoic isopropylamide.* Recrystallized from 50 % ethanol. Melts at 185°, solidifies and melts again at 210°.

$C_{12}H_{16}O_3N_2$  (236.7)    Calc. N 11.84    Found N 11.94

By hydrolysis 2-hydroxy-4-aminobenzoic isopropylamide was obtained. M. p. 161°, with no depression on mixing with a product prepared via the nitro compound <sup>3</sup>.

*2-Hydroxy-4-acetamidobenzoic diethylamide.* Recrystallized from water.

$C_{13}H_{18}O_3N_2$  (250.3)    Calc. N 11.20    Found N 11.09

Melts at 214°, solidifies and melts again at 230°; no depression on mixing with a product prepared by acetylation of the amino compound obtained via the corresponding nitro compound <sup>3</sup>.

*2-Hydroxy-4-aminobenzanilide.* Recrystallized from ethanol. M. p. 143°.

*N<sup>2</sup>-(2-Hydroxy-4-aminobenzoyl)-sulfanilamide.* Recrystallized from ethanol. Decomposes at about 300°. N 13.36 %, calc. 13.70 %.

*2-(2'-Hydroxy-4'-aminobenzoyl)-aminopyridine.* Recrystallized from 50 % ethanol. M. p. 186°. N 17.98 %, calc. 18.30 %.

*2-(2'-Hydroxy-4'-aminobenzoyl)-amino-5-methyl-1,3,4-thiadiazole.* Recrystallized from 50 % ethanol. M. p. 300° (dec.). N 21.94 %, calc. 22.40 %.

*2-(2'-Hydroxy-4'-aminobenzoyl)-aminothiazole.* To the acid chloride prepared from 2 g of 2-acetoxy-4-acetamidobenzoic acid was added a solution of 1 g of 2-aminothiazole in 5 ml of pyridine with good mixing. After 2 hours 100 ml of water was added and the precipitate was filtered. After recrystallization from acetic acid containing 20 % acetic anhydride 0.75 g of 2-(2'-acetoxy-4'-acetamidobenzoyl)-aminothiazole was obtained. M. p. 294–95°.

$C_{14}H_{13}O_4N_3S$  (319.3)    Calc. N 13.13    Found N 13.23

On hydrolysis 0.35 g of the deacetylated compound was obtained. This compound is slightly soluble in boiling water; on cooling colourless needles were obtained. When dried at room temperature over  $\text{CaCl}_2$  the composition corresponds to a hemihydrate:

$\text{C}_{10}\text{H}_9\text{O}_2\text{N}_3\text{S} \cdot \frac{1}{2}\text{H}_2\text{O}$  (244.3)    Calc. C 49.18    H 4.22    N 17.10    S 13.11  
   Found » 49.18    » 4.10    » 17.21    » 13.05

After drying at  $100^\circ$  the composition corresponds to an anhydrous compound:

$\text{C}_{10}\text{H}_9\text{O}_2\text{N}_3\text{S}$  (235.3)            Calc. N 17.84            Found N 17.50

M. p.  $266^\circ$  (dec.) in accordance with the value found for the product prepared via the nitro compound <sup>2</sup>.

#### SUMMARY

2-Acetoxy-4-acetamidobenzoic acid, prepared by acetylation of *p*-aminosalicylic acid (PAS), has been transformed into the acid chloride. By condensation of this with different amino compounds and subsequent hydrolysis of the acetoxy group the corresponding substituted *p*-aminosalicylamides have been obtained.

#### REFERENCES

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