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Tuberculostatic Derivatives of *p*-Aminobenzoic Acid

III. Heterocyclic Derivatives of 4-Aminosalicylic Acid

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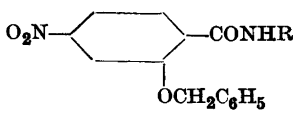
In a preceding paper [1] some amides of 4-aminosalicylic acid (PAS) were prepared for the purpose of investigating their tuberculostatic activity. The method applied, *viz.* the reaction of ethyl 4-nitrosalicylate with amines and reduction of the nitro compounds formed, is only applicable to amines having not too weak a basic character, *i. e.* mainly aliphatic amines. While the piperidide and morpholide could be prepared in the same way as the aliphatic derivatives, 2-aminopyridine and similar compounds did not react with ethyl 4-nitrosalicylate. As heterocyclic derivatives of this type would be similar to the most strongly bacteriostatically active sulphonamides, their investigation was deemed to be of interest.

The acid chloride of 4-nitrosalicylic acid, like salicylic acid chloride, is rather unstable. By reaction with aniline the corresponding anilide could be prepared, and this could be reduced to 4-aminosalicylanilide. By reaction of the acid chloride with 2-aminopyridine, 2-aminothiazole and other heterocyclic amino compounds, however, a more complex reaction took place, and at first it was not possible to isolate the desired compounds (*cf.* the following paper).

It was then investigated whether the corresponding compounds with the hydroxyl group protected by benzylation would be more easily obtainable. 2-Benzyloxy-4-nitrobenzoic acid gave a quite stable acid chloride, which by reaction with heterocyclic amines in pyridine gave well-defined and beautifully crystalline amides of the type:



R = 2-pyridyl, 2-thiazolyl etc.

By catalytic hydrogenation the nitrogroup was easily reduced, but, contrary to our expectation, the benzyl group was not split off, even by prolonged hydrogenation. This is very remarkable, the more so because it was found that 4-nitro-2-benzyloxybenzoic acid and the corresponding amide and anilide were easily transformed into 4-aminosalicylic acid, 4-aminosalicylamide and 4-aminosalicylanilide respectively. In these cases the benzyl group was split off so easily that a reduction of the nitro group alone by catalytic hydrogenation could only be carried out with some difficulty.

The difficulty of reductive splitting off of the benzyl group is therefore a peculiarity of the heterocyclic derivatives. Even with the use of a considerable amount of platinum as a catalyst or by hydrogenation at 100° and 150 atmospheres no toluene was formed. These findings have been examined further and will be discussed in a subsequent paper.

EXPERIMENTAL

4-Nitro-salicylmorpholide. A mixture of 3 g of ethyl 4-nitrosalicylate and 3 g of morpholine was heated in a sealed tube at 120° for 5 hours. The excess of morpholine was removed in vacuo at 100°. The residue was dissolved in hot water acidified with acetic acid. On cooling crystals separated which were recrystallized from 50 % ethanol after treatment with activated carbon. Yield 50 %. The morpholide forms yellow needles with m.p. 247—248°.

$C_{11}H_{12}O_5N_2$ (252.2) Calc. N 11.11 Found N 10.97

4-Nitro-salicylpiperidide. Prepared in the same way as the morpholide. M. p. 230—232°.

$C_{12}H_{14}O_4N_2$ (250.2) Calc. N 11.20 Found N 11.10

4-Amino-salicylmorpholide. The above mentioned nitro compound was hydrogenated (0.5 g of the nitro compound and 0.01 g PtO_2 in 25 ml of ethanol). The ethanol was removed in vacuo leaving an oil which crystallized by rubbing. The compound was extremely soluble in ethanol and easily soluble also in water. For purification it was dissolved in dry benzene and fractionally precipitated by addition of petroleum ether, the first fractions being discarded. By cooling in ice and rubbing almost colourless crystals separated. Yield 0.2 g. M. p. 161—162°.

$C_{11}H_{14}O_3N_2$ (222.2) Calc. N 12.61 Found N 12.77

4-Amino-salicylpiperidide. Prepared and purified in the same way as the morpholide. M. p. 134—135°.

$C_{12}H_{16}O_2N_2$ (220.2) Calc. N 12.73 Found N 12.83

2-Benzyloxy-4-nitrobenzoic acid. To a suspension of 50 g of 4-nitrosalicylic acid in 100 ml of ethanol were added 35 g of benzyl chloride and 50 ml of 20 % sodium hydroxide. The mixture was heated to boiling and on refluxing the reddish brown colour faded after some time. A 2-N solution of sodium hydroxide was then added until the reddish brown colour reappeared. On addition of the alkali the solution became turbid and ethanol was therefore added, until it was clear. These steps were repeated until the colour remained permanent on continued refluxing. After 1—2 hours the reaction was complete. The ethanol was then partially removed by distillation and replaced by water. Dilute hydrochloric acid was then added, until the precipitation of the benzyl compound was complete. The precipitate was recrystallized from boiling 60 % ethanol. Yield 40 g or 55 %. M. p. 170°.

$C_{14}H_{11}O_5N$ (273.2) Calc. N 5.22 Found N 5.13

2-Benzyloxy-4-amino-benzoic acid. By hydrogenation of the above compound (1 g in 20 ml of ethanol + 0.05 g of PtO_2) toluene and 4-aminosalicylic acid were formed. When the hydrogenation was stopped as soon as the amount of hydrogen calculated for reduction of the nitro group had been absorbed 2-benzyloxy-4-amino-benzoic acid could be isolated. The filtrate from platinum was evaporated in vacuo until crystallization occurred and the product was recrystallized from benzene. M. p. 160°.

$C_{14}H_{13}O_3N$ (243.2)	Calc.	N	5.76	Equiv. wt.	243.2
	Found	»	5.48	» »	245.4

2-Benzyloxy-4-nitrobenzoyl chloride. A mixture of 10 g of 2-benzyloxy-4-nitrobenzoic acid and 10 ml of thionyl chloride was refluxed for 1—1 ½ hour on a water bath. Excess of thionyl chloride was removed in vacuo and the residue was recrystallized from benzene after treatment with dried carbon. The acid chloride separated as large yellow crystals. Yield 9.2 g or 86 %. M. p. 122°.

$C_{14}H_{10}O_4NCl$ (291.7)	Calc.	N	4.80	Cl	12.16
	Found	»	4.71	»	12.12

2-Benzyloxy-4-nitrobenzamide. Two grams of the acid chloride was added to 10 ml of ice-cold, concentrated aqueous ammonia, 30 ml of water was added and the solution neutralized with acetic acid. The yellow crystals which separated were recrystallized from 90 % ethanol acidified with a few drops of concentrated acetic acid. Yield 1.3 g. M. p. 178°.

$C_{14}H_{12}O_4N_2$ (272.3) Calc. N 10.30 Found N 10.14

By catalytic hydrogenation 4-aminosalicylamide was obtained.

2-Benzyloxy-4-nitrobenzanilide. A solution of 1 g of aniline in 5 ml of pyridine was added to 2.9 g of 2-benzyloxy-4-nitrobenzoyl chloride. The mixture became warm, but cooling was unnecessary and the acid chloride dissolved on stirring. After slow cooling, during which some anilide crystallized, the mixture was poured into 300 ml of water. The anilide, which separated, was filtered and recrystallized from acetic acid. Yellow crystals; slightly soluble in ethanol and benzene. Yield 2.2 g. M. p. 201°.

$C_{20}H_{16}O_4N_2$ (348.3) Calc. N 8.04 Found N 8.13

4-Aminosalicylanilide. A hot suspension of 1 g of the preceding compound and 100 mg of PtO_2 in 25 ml of ethanol was hydrogenated. The precipitate gradually dissolved, and after 2 hours the calculated amount of hydrogen had been absorbed. The solution, which had an odour of toluene, was filtered and part of the ethanol was removed *in vacuo*. Water was added and the solution was heated to boiling, so that the precipitate formed was dissolved. Charcoal was added and the hot solution filtered. On cooling the anilide separated as colourless crystals. M. p. 143°. The compound gives a violet colour with ferric chloride.

$C_{20}H_{18}O_2N_2$ (318.3) Calc. N 12.28 Found N 12.18

The following compounds were prepared in the same way as the anilide of 2-benzyloxy-4-nitrobenzoic acid with the exception that the reaction went more slowly, and in the case of the pyrimidine compound slight warming was appropriate. In each case 2.9 g of the acid chloride was employed.

2-(2'-Benzyloxy-4'-nitrobenzoyl)-aminopyridine. Yield 2.2 g. M. p. 144°. Recrystallized from acetic acid (90 %).

$C_{19}H_{15}O_4N_3$ (349.3) Calc. N 12.03 Found N 11.99

2-(2'-Benzyloxy-4'-nitrobenzoyl)-aminothiazole. Yield 2.7 g. M. p. 201°. Recrystallized from acetic acid.

$C_{17}H_{13}O_4N_3S$ (355.3) Calc. N 11.83 Found N 11.95

2-(2'-Benzyloxy-4'-nitrobenzoyl)-amino-5-methyl-1,3,4-thiadiazole. For the preparation 2-amino-1,3,4-thiazole was dissolved in boiling pyridine. Yield 1.7 g. M. p. 196°. Recrystallized from acetic acid (90 %).

$C_{17}H_{14}O_4N_4S$ (370.4) Calc. N 15.13 Found N 15.03

2-(2'-Benzyloxy-4'-nitrobenzoyl)-amino-4,6-dimethylpyrimidine. Yield 1.7 g. M. p. 206°. Recrystallized from 70 % acetic acid.

$C_{20}H_{18}O_4N_4$ (378.4) Calc. N 14.81 Found N 15.05

All these compounds form yellow crystals which are only slightly soluble in benzene and ethanol.

By catalytic hydrogenation the following compounds were prepared:

2-(2'-Benzyloxy-4'-aminobenzoyl)-amino-pyridine. One gram of the nitro compound and 50 mg of PtO_2 were suspended in 40 ml of hot ethanol and hydrogenated. In the course of 2 hours the nitro compound dissolved and the amino derivative was isolated in the same way as the anilide. Almost white crystals with m. p. 183°.

$C_{19}H_{17}O_2N_3$ (319.3) Calc. N 13.16 Found N 13.49

2-(2'-Benzyloxy-4'-aminobenzoyl)-amino-thiazole. This compound is less soluble in ethanol than the preceding compound and crystallized directly from the ethanol solution without addition of water. The compound is light yellow. M. p. 214—215°. Yield 0.50 g.

$C_{17}H_{15}O_2N_3S$ (325.3) Calc. N 12.92 Found N 12.97

2-(2'-Benzyloxy-4'-aminobenzoyl)-amino-5-methyl-1,3,4-thiazole. Prepared in the same way as the thiazole derivative. Slightly soluble in ethanol. Light yellow. Yield 0.58 g. M. p. 110—111°.

$C_{17}H_{16}ONS$ (340.4) Calc. N 16.46 Found N 16.56

By catalytic hydrogenation at 100° and 150 atmospheres the benzyloxy-compounds were reisolated. No toluene was formed and the reacting mixture gave no colour with ferric chloride, showing that no hydroxy compound had been formed. A difference from the hydrogenations at low pressure was, however, that the solutions formed by hydrogenation of the nitro compounds on exposition to air deposited some intensely yellow precipitates, which were almost insoluble in all common solvents. It seems that these compounds are azoxy compounds corresponding to the nitro compounds used.

Thiazole compound:

$C_{34}H_{26}O_5N_6S_2$ (662.7)	Calc.	N 12.68	C 61.60	H 3.95
	Found	» 12.70	» 62.23	» 3.98

SUMMARY

Some heterocyclic derivatives of 4-nitrosalicylic acid and 4-aminosalicylic acid have been described, including derivatives of 4-nitro-2-benzyloxybenzoic acid. By catalytic hydrogenation the benzyl group could easily be split of from the free acid, from the amide and the anilide, but not from the heterocyclic derivatives.

REFERENCE

1. Jensen, K. A., Rosdahl, K.-G., and Ingvorsen, H. *Acta Chem. Scand.* **2** (1948) 220.

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