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Antitubercular Compounds Related to *p*-Aminosalicylic Acid

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Following the demonstration of the tuberculostatic activity of *p*-aminosalicylic acid (PAS) [1] many investigators have prepared derivatives of *p*-aminosalicylic acid [2a, b and c] with the object of obtaining substances with increased potency against the tubercle bacilli.

Until Freire [3] in 1950 published his communication on the exceptionally high *in vitro* activity of the phenyl ester of *p*-aminosalicylic acid, all the derivatives of PAS which had been prepared had exhibited a lower activity or, at most, the same activity as PAS.

As *in vivo* experiments on mice and guinea pigs have also proved the phenyl ester of *p*-aminosalicylic acid to have a higher activity than PAS [4], we have prepared a number of derivatives of the phenyl esters of PAS and *p*-aminothiolsalicylic acid. In addition to the phenyl esters we have in this communication included the preparation of the *p*-aminosalicylic esters of various alcohols. The results of the testing of the activity of these substances, *in vitro* as well as *in vivo*, will be published elsewhere [5].

Tables 2 and 4 list a number of esters of 4-aminosalicylic acid and 4-aminothiolsalicylic acid, respectively, with various phenols. All these esters were prepared by reduction of the corresponding nitro compounds, which are listed in Tables 1 and 3. The preparation of phenyl esters of 4-nitro- and 4-aminosalicylic acid has been described previously [6, 7, 8]. The latter reference also includes the synthesis of the corresponding *p*-cresyl esters.

The simplest of the nitro esters were prepared by fusing together 4-nitrosalicylic acid and the phenol or thiophenol concerned in the presence of phosphorus oxychloride (method A). Later on we found it more convenient to start with 4-nitrosalicoyl chloride and allow this substance to react with the phenol or thiophenol in boiling toluene (method B). Some of the phenols used were, however, so sparingly soluble in toluene, that the reaction was very

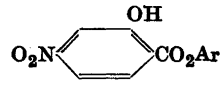


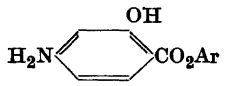
Table 1.

ArOH	Yield %	M. P. °C	Formula	Carbon Calc.	Carbon Found	Hydrogen Calc.	Hydrogen Found	Nitrogen Calc.	Nitrogen Found	Method	Crystallized from
Phenol	79	152 —153.5	$C_{13}H_9NO_5$	60.23	60.35	3.50	3.63	5.40	5.34	A	HAc
p-Cresol	82	123 —124.5	$C_{14}H_{11}NO_5$	61.53	61.78	4.06	4.14	5.13	5.13	A	MeOH
p-(β-Iodoethyl)phenol[a]	67	98 — 99.5	$C_{15}H_{12}JNO_5$	43.57	43.70	2.90	3.24	3.39		B	EtOH
p-Ethoxyphenol	80	108 —109.5	$C_{15}H_{13}NO_6$	59.40	59.21	4.29	4.28	4.62	4.67	B	MeOH
p-Carbomethoxyphenol	80	168 —170	$C_{15}H_{11}NO_7$	56.67	56.77	3.47	3.34	4.41	4.38	B	HAc
p-Carbethoxyphenol	73	115 —118	$C_{16}H_{13}NO_7$	58.00	57.90	3.93	4.12	4.23	4.47	B	EtOH
p-Hydroxypropiophenon	55	96 — 98	$C_{16}H_{13}NO_6$	60.93	61.14	4.16	4.13	4.44	4.13	B	HAc
p-Bromophenol[b]	74	145 —146.5	$C_{13}H_8BrNO_5$	46.14	46.16	2.36	2.51	4.13	4.27	B	HAc
o-Bromophenol[c]	48	122 —123	$C_{13}H_8BrNO_5$	46.14	46.28	2.36	2.49	4.13	4.45	B	Methyl*iso*-butyl-ketone
m-Nitrophenol	73	167 —169	$C_{13}H_8N_2O_7$	51.31	51.47	2.63	2.71	9.22	9.37	B	Methyl*iso*-butyl-ketone
p-Nitrophenol	86	153.5—155	$C_{13}H_8N_2O_7$	51.31	51.34	2.63	2.67	9.22	9.11	A	EtAc
m-Acetaminophenol	55	168.5—169.5	$C_{15}H_{12}N_2O_6$	56.96	57.12	3.79	3.86	8.86	8.90	C	MeOH
p-Acetaminophenol	82	196.5—197.5	$C_{15}H_{12}N_2O_6$	56.96	56.73	3.79	3.87	8.86	9.08	C	HAc
m-Aminophenol	78	158.5—161.5	$C_{13}H_{10}N_2O_5$	56.93	57.35	3.65	3.79	10.22	10.28	—	EtOH
p-Aminophenol	60	177 —179	$C_{13}H_{10}N_2O_5$	56.93	56.87	3.65	3.62	10.22	10.34	—	Acetone-water
m-Succinylaminophenol	46	190 —192	$C_{17}H_{14}N_2O_8$	54.55	54.30	3.75	3.93	7.48	7.76	G	HAc
p-Succinylaminophenol	90	201 —202	$C_{17}H_{14}N_2O_8$	54.55	54.69	3.75	3.77	7.48	7.64	H	Dioxane
p-Phthalylaminophenol		316.5—318.5 (dec.)	$C_{21}H_{14}N_2O_8$	59.72	60.42	3.32	3.48	6.63	6.74	G	HAc
p-Dimethylaminophenol	90	146.5—147	$C_{15}H_{14}N_2O_5$	59.57	59.39	4.64	4.77	9.27	9.50	C	Methyl*iso*-butyl-ketone

		Calc.	Found.
a)	J:	30.74	30.44
b)	Br:	23.64	23.60
c)	Br:	23.64	23.72

slow or did not proceed at all. To overcome this difficulty, it was attempted to use pyridine as a solvent, although Libermann [9] has shown, that in the presence of pyridine, 4-nitrosalicoyl chloride is converted into the corresponding disalicylide. However, when anhydrous pyridine was used, the esterification proved to proceed without complications and provide good yields.

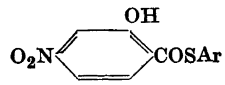
For the preparation of the phenyl esters which contain a free carboxyl group in the phenol component (3′-succinylamino-, 4′-succinylamino- and 4′-phthalylamino phenyl esters) the following method was used:



ble 2.

ArOH	Yield %	M. P. °C	Formula	Carbon Calc.	Carbon Found	Hydrogen Calc.	Hydrogen Found	Nitrogen Calc.	Nitrogen Found	Method	Crystallized from
henol	84	149 —150.5	$C_{13}H_{11}NO_3$	68.12		4.85		6.07	6.12	E	EtOH
Cresol	86	118.5—120.5	$C_{14}H_{13}NO_3$	69.15	68.96	5.41	5.75	5.76	5.73	E	70 % EtOH
(β-Iodoethyl)phenol[a]	66	166 —167.5	$C_{15}H_{14}JNO_3$	47.00	47.32	3.66	3.70	3.66	4.05	F	EtOH
Ethoxyphenol	58	173 —174.5	$C_{15}H_{15}NO_4$	65.94	66.14	5.55	5.53	5.13	5.13	E	*Iso*propanol
Carbomethoxyphenol	91	159 —161	$C_{15}H_{13}NO_5$	62.70	62.65	4.52	4.60	4.87	4.91	E	EtOH
Carbethoxyphenol	73	162 —163	$C_{16}H_{15}NO_5$	63.76	63.40	4.98	5.03	4.65	4.67	F	EtOH
Hydroxypropiophenon	77	167.5—169	$C_{16}H_{15}NO_4$	67.34	67.2	5.31	5.18	4.89	5.02	F	Methyl*iso*butylketone
Bromophenol[b]	77	170.5—171.5	$C_{13}H_{10}BrNO_3$	50.63	50.71	3.24	3.33	4.54	4.99	E	EtOH
Bromophenol[c]	81	133 —135	$C_{13}H_{10}BrNO_3$	50.63	50.50	3.24	3.22	4.54	4.63	F	EtOH
-Aminophenol	67	157 —159	$C_{13}H_{12}N_2O_3$	63.91	63.62	4.96	4.62	11.47	11.25	E	70 % EtOH
Aminophenol	45	183.5—184.5	$C_{13}H_{12}N_2O_3$	63.91	64.20	4.96	5.26	11.47	11.34	E	EtOH
Acetaminophenol	75	203 —204	$C_{15}H_{14}N_2O_4$	62.94	63.16	4.89	5.01	9.80	9.90	E	70 % EtOH
-Succinylaminophenol	70	175 —177	$C_{17}H_{16}N_2O_6$	59.30	59.12	4.65	4.61	8.14	8.16	E	MeOH
Succinylaminophenol	82	191 —192.5	$C_{17}H_{16}N_2O_6$	59.30	59.40	4.65	4.55	8.14	7.93	E	Methylcellosolve-water
Phthalylaminophenol	68	211 —212	$C_{21}H_{16}N_2O_6$	64.28	64.09	4.09	4.30	7.14	7.30	E	Methylcellosolve-water
Dimethylaminophenol	83	185 —186	$C_{15}H_{16}N_2O_3$	66.13	66.13	5.94	5.76	10.28	10.23	E	50 % EtOH

		Calc.	Found.
a)	J:	33.1	32.33
b)	Br:	25.98	26.94
c)	Br:	25.98	26.40



ble 3.

ArSH	Yield %	M. P. °C	Formula	Carbon Calc.	Carbon Found	Hydrogen Calc.	Hydrogen Found	Nitrogen Calc.	Nitrogen Found	Sulfur Calc.	Sulfur Found	Method	Crystallized from
Thiophenol	73	196—198	$C_{13}H_9NO_4S$	56.70	56.8	3.28	3.33	5.09	5.26	11.62	11.40	A	HAc
-Ethoxythiophenol	66	126—127	$C_{15}H_{13}NO_5S$	56.41	56.6	4.08	3.80	4.39	4.43	10.03	9.71	B	HAc

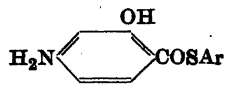


Table 4.

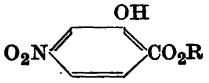
ArSH	Yield %	M. P. °C	Formula	Carbon Calc.	Carbon Found	Hydrogen Calc.	Hydrogen Found	Nitrogen Calc.	Nitrogen Found	Sulfur Calc.	Sulfur Found	Method	Crystallized from
Thiophenol	55	142–144	$C_{13}H_{11}NO_2S$	63.64	63.69	4.49	4.63	5.71	5.59	13.05	12.73	F	EtOH
p-Ethoxythiophenol	70	165–166	$C_{15}H_{15}NO_3S$	62.26	62.01	5.19	5.20	4.84	4.73	11.07	11.06	F	EtOH

4-nitrosalicylic acid was esterified with *m*- or *p*-acetaminophenol. The acetyl group was removed by mild hydrolysis, and the product was finally acylated by means of the anhydride of the appropriate dibasic acid.

The nitro compounds were reduced to the corresponding amino compounds either catalytically by means of Adam's catalyst (method E) or by means of stannous chloride (method F). Most nitro compounds can be reduced according to both methods, but in some cases the stannous chloride method is to be preferred, particularly in the case of the sulphur-containing compounds. In spite of the fact that the reduction with stannous chloride takes place in a liquid of fairly high acidity, the esters are not appreciably hydrolyzed.

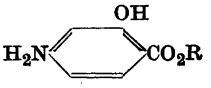
The six esters of 4-aminosalicylic acid with different alcohols which are listed in Table 6 have likewise been prepared by reduction of the corresponding nitro compounds. The reduction was effected catalytically according to method E, with one exception (the benzyl ester) in which the stannous chloride method (method F) proved more convenient. All the nitro compounds which are listed in Table 5 were prepared by treating 4-nitrosalicoyl chloride with an excess of the appropriate alcohol. The ethyl- and *n*-butyl esters of 4-nitrosalicylic acid and 4-aminosalicylic acid have previously been described by Jensen *et al.*[2a]

Table 7 comprises a number of N-substituted compounds of phenyl 4-aminosalicylate. Apart from phenyl 4-carbethoxyaminosalicylate, which was prepared by fusing together 4-carbethoxyaminosalicylic acid and phenol in the presence of phosphorus oxychloride, they were all prepared from phenyl 4-aminosalicylate; the tosyl compound by treatment with toluenesulphochloride in pyridine, the other acyl compounds by the action of the appropriate acid anhydride in boiling glacial acetic acid (method G) or in acetone (method H). Incidentally the acetyl compound has previously been prepared by Marauyama and Imamura [8] by treating N,O-diacetyl-4-aminosalicoyl chloride with phenol.



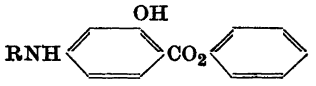
ible 5.

R	Yield %	M. P. °C	Formula	Carbon Calc.	Carbon Found	Hydrogen Calc.	Hydrogen Found	Nitrogen Calc.	Nitrogen Found	Method	Crystallized from
Ethyl	70	88	$C_9H_9NO_5$							D	EtOH
i-Butyl	68	33.5— 34.5	$C_{11}H_{13}NO_5$							D	EtOH
*Iso*hexyl		oil	$C_{13}H_{17}NO_5$							D	
*Cyclo*hexyl	50	92 — 93.5	$C_{13}H_{15}NO_5$	58.83	58.87	5.71	5.71	5.27	5.27	D	HAc
Benzyl	64	69 — 70	$C_{14}H_{11}NO_5$	61.51	61.30	4.03	4.11	5.12	5.34	D	HAc



ible 6.

R	Yield %	M. P. °C	Formula	Carbon Calc.	Carbon Found	Hydrogen Calc.	Hydrogen Found	Nitrogen Calc.	Nitrogen Found	Method	Crystallized from
Ethyl	80	114 —116	$C_9H_{11}NO_3$							E	EtOH
i-Butyl	70	92.5— 93.5	$C_{11}H_{15}NO_3$							E	70 % EtOH
*Iso*hexyl		42	$C_{13}H_{19}NO_3$	65.77	65.94	8.09	7.81	5.91	6.13	E	
*Cyclo*hexyl	89	131 —132.5	$C_{13}H_{17}NO_3$	66.35	66.22	7.30	7.36	5.96	5.85	E	EtOH
Benzyl	79	98 — 99	$C_{14}H_{13}NO_3$	69.10	69.31	5.40	5.35	5.76	5.88	F	EtOH



ble 7.

R	Yield %	M. P. °C	Formula	Carbon Calc.	Carbon Found	Hydrogen Calc.	Hydrogen Found	Nitrogen Calc.	Nitrogen Found	Sulfur Calc.	Sulfur Found	Method	Crystallized from
p-Toluenesulfonyl	57	169 —171	$C_{20}H_{17}NO_5S$	62.66	62.61	4.44	4.54	3.66	3.46	8.35	8.10		
Acetyl	76	181.5—183	$C_{15}H_{13}NO_4$	66.42	66.29	4.84	4.84	5.16	5.14			G	EtOH
Carbethoxy	65	149 —151	$C_{16}H_{15}NO_5$	63.78	63.86	4.98	5.10	4.65	4.74				EtOH
Lactosyl *	20	208 —212	$C_{25}H_{39}NO_{17}$	48.00	48.01	6.30	6.44	2.24	2.02				
Mannosyl	70	191.5—193	$C_{19}H_{21}NO_8$	58.31	58.37	5.42	5.56	3.58	3.83				
Glucosyl **	60	117 —120	$C_{19}H_{33}NO_9$	55.75	55.87	5.67	6.00	3.42	3.26				
Phthalyl	59	181.5—182.5	$C_{21}H_{15}NO_6$	66.83	66.76	3.98	4.09	3.71	3.80			H	Acetone
Succinyl	57	179 —181	$C_{17}H_{15}NO_6$	61.95	62.03	4.56	4.45	4.25	4.40			G	70 % EtOH
Maleinyl	66	188 —191	$C_{17}H_{13}NO_6$	62.37	62.42	3.97	4.12	4.28	4.26			H	EtOH

* Obtained as the tetrahydrate.
** » » » monohydrate.

The catalyst applied for the glucoside formation in the preparation of the three N-glucosides mentioned in the table was either ammonium chloride, as devised by Kuhn [10], or glacial acetic acid, as described by Weygand [11]. The corresponding N-glucosides of 4-aminosalicylic acid have recently been prepared by Haberland [12] in a similar manner.

EXPERIMENTAL

Microanalyses by G. Cornali. All melting points are corrected.

Intermediates. 4-Nitrosalicylic acid was prepared as described by Mc Ghie *et al.*[13], and 4-nitrosalicoyl chloride was prepared by treating 4-nitrosalicylic acid with thionyl chloride [14].

4-Aminosalicylic acid and most of the phenols used were commercially available. The following phenols were prepared according to methods previously described: *p*-(β-iodoethyl)-phenol [15], *p*-ethoxyphenol [16], *p*-propiophenol [17], *p*-dimethylaminophenol [18], and *p*-ethoxythiophenol [19].

4-Carbethoxyaminosalicylic acid was prepared by carbethoxylation of 4-aminosalicylic acid as described by Doub *et al.*[2c]

Method A. A mixture of 0.5 mole of 4-nitrosalicylic acid and 0.75 mole of the appropriate phenol was heated to a temperature of 80—100° C. 30 ml of phosphorus oxychloride was added and the temperature raised to 140° C and this temperature maintained until the evolution of gas had ceased. The mixture was then cooled to 115° C and 10 ml of toluene was added to keep the mixture in a fluid condition during the subsequent cooling process. When the mixture had been cooled to 60° C, 75 ml of methanol was added, and the cooling was continued until room temperature had been reached. The resulting crystalline 4-nitrosalicylic acid ester was filtered and washed on the filter with 75 ml of methanol. After drying, the compound was recrystallized from the solvent mentioned.

Method B. A suspension was made of 0.05 mole of the appropriate phenol in 50 ml of dry toluene and 0.05 mole of 4-nitrosalicoyl chloride was added. The mixture was refluxed until the evolution of hydrogen chloride had ceased (½—2 hours) and was then cooled to room temperature. In most cases the ester separates on standing; if not, 50 ml of petroleum ether should be added. The crystals which separated were filtered, washed with 10 ml of methanol, 10 ml of a saturated sodium bicarbonate solution and 25 ml of water and subsequently recrystallized.

Method C. A solution was prepared of 0.15 mole of 4-nitrosalicoyl chloride and 0.15 mole of the appropriate phenol in 100 ml of dry pyridine *. The mixture was heated to the boiling point and kept at this temperature for 5 minutes.

After cooling to room temperature, 200 ml of water was added to precipitate the crystalline ester. The ester was filtered, washed with saturated sodium bicarbonate solution and water and recrystallized.

Method D. 4-Nitrosalicoyl chloride was suspended in 3—6 times the equivalent amount of the appropriate alcohol. The mixture was heated on the steam-bath until the evolution of hydrogen chloride had ceased (½—2 hours) and subsequently cooled to room temperature. The crystals which separated were filtered, washed with methanol and recrystallized from a suitable solvent. The *iso*-hexylester, which was an oil, was isolated

* Dried by azeotropic distillation with benzene, according to Mitchell and Smith [20].

by removing the excess of *iso*-hexanol *in vacuo*, and hydrogenated without further purification.

Method E. A suspension was made of 0.03 mole of the 4-nitrosalicylic acid ester in 100 ml of methylcellosolve; 0.1 g of Adam's platinum oxide was added, and the mixture was reduced at room temperature and at a hydrogen pressure of 3 at., until the theoretical amount of hydrogen had been absorbed (1—2 hours). After removal of the platinum by filtration, about 50 mg of sodium dithionite was added and the amino compound precipitated by slowly adding 200 ml of water. The 4-aminosalicylate which separated was filtered and recrystallized, if required.

Method F. A solution was prepared of 20 g of stannous chloride dihydrate in a mixture of 55 ml of ethanol and 20 ml of conc. hydrochloric acid. The mixture was heated to the boiling point and 0.025 mole of the nitro compound was added gradually. The reaction mixture was refluxed for a further 5—10 minutes, and then 250 ml of water * (heated to about 50° C) was added. After cooling to room temperature the separated amino compound was filtered and washed with water.

Method G. A solution was prepared of 0.05 mole of the amino compound and 0.066 mole of the appropriate acid anhydride by heating in 75 ml of glacial acetic acid. The mixture was refluxed for 1 hour, cooled to room temperature, and 150 ml of water was added. The solution was allowed to stand, and when the acyl amino compound had crystallized, it was filtered, washed with water and recrystallized.

Method H. A mixture of 0.05 mole of the amino compound and 0.066 mole of the acid anhydride in 150 ml of acetone was refluxed. After a period of about 20 minutes the acyl amino compound begins to crystallize from the clear solution. After refluxing for 2 hours the mixture was cooled, the solid which separated was filtered and washed with acetone.

As regards the phenyl ester of 4-phthalylaminosalicylic acid, the reaction product is not clearly soluble in sodium bicarbonate solution. Consequently it was extracted with 150 ml of a saturated sodium bicarbonate solution at 50° C. A small amount of insoluble material was removed by filtration, the filtrate was acidified with 4 *N* hydrochloric acid, and the phenyl 4-phthalylaminosalicylate which crystallized was filtered and washed with water.

Phenyl 4-(mannosylamino)-salicylate. A mixture of 4.6 g (0.02 mole) of phenyl 4-aminosalicylate and 3.6 g (0.02 mole) of D(—)mannose in 25 ml of absolute ethanol was refluxed for 1 hour, 0.2 g of ammonium chloride being added as a catalyst. After half an hour crystals of the mannoside begin to separate from the hot solution. After cooling, the solid was filtered, washed with absolute ethanol and recrystallized from 70 per cent ethanol.

Yield: 5.45 g ~ 70 %. M.p. 191.5—193° C. $[\alpha]_D^{20}$ in pyridine: $-194° \pm 3°$ ($c = 1$).

Phenyl 4-(lactosylamino)-salicylate. A mixture of 4.6 g (0.02 mole) of phenyl 4-aminosalicylate and 7.2 g (0.02 mole) of lactose in 70 ml of dry methanol was refluxed for 40 hours, 0.2 ml of glacial acetic acid being added as a catalyst. The reaction mixture was filtered while hot, and the filtrate was cooled to room temperature. The lactoside which separated was recrystallized from 70 per cent ethanol.

Yield: 2.55 g ~ 20 %. M.p. 208—212° C (decomp.) $[\alpha]_D^{20}$ in pyridine: $-69° \pm 3°$ ($c = 1$).

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* In the preparation of phenyl 4-aminothiolsalicylate it was necessary, before the addition of water, to remove a certain amount of undissolved substance by filtration.

The analysis corresponds to the tetrahydrate, a finding which was confirmed through a determination of the weight loss by drying at 0.01 mm Hg and 40° C.

Phenyl 4-(glucosylamino)-salicylate. A mixture of 4.6 g (0.02 mole) of phenyl 4-aminosalicylate and 3.6 g (0.02 mole) of glucose in 70 ml of dry methanol was refluxed for 24 hours, 0.25 ml of glacial acetic acid being added as a catalyst. After cooling 70 ml of water was added to precipitate the glucoside. The latter was washed with water and recrystallized from 70 per cent ethanol.

Yield: 9.9 g ~ 60 %. M.p. 117—120° C (decomp.) $[\alpha]_D^{20}$ in pyridine: $-111° \pm 3°$ ($c = 1$).

The analysis corresponds to the monohydrate, a finding which was confirmed through a determination of the weight loss by drying at 0.01 mm Hg and 40° C.

Phenyl 4-toluenesulphonaminosalicylate. Phenyl 4-aminosalicylate, 3.45 g (0.015 mole) and toluenesulphochloride, 3.00 g (0.0158 mole) was dissolved in 25 ml of pyridine. The solution was kept at a temperature of about 50° C for 1 hour, after which dilute hydrochloric acid was added to precipitate the sulphonamide. After recrystallisation from ethanol, the melting point was 169—170° C.

Yield: 3.25 g ~ 57 %.

4'-Aminophenyl 4-nitrosalicylate. A mixture of 9.48 g (0.03 mole) of 4'-acetaminophenyl 4-nitrosalicylate and 100 ml of *N* ethanolic hydrogen chloride was refluxed. After a few minutes a clear solution results, but shortly afterwards the hydrochloride of 4'-aminophenyl 4-nitrosalicylate begins to precipitate. After refluxing for 1 hour, the mixture was cooled, and the hydrochloride filtered off and washed with ether. The hydrochloride was stirred into 60 ml of *N*/2 sodium acetate solution to liberate the base. The latter was filtered, washed with water and reprecipitated from acetone-water.

Yield: 4.9 g ~ 60 %. M.p. 177—179° C.

3'-Aminophenyl 4-nitrosalicylate. This compound was prepared from 3'-acetaminophenyl 4-nitrosalicylate in analogy with the preparation of 4'-aminophenyl 4-nitrosalicylate.

Yield: 78 %. M.p. 158.5—161.5° C.

Phenyl 4-carbethoxyaminosalicylate. A mixture of 9.0 g (0.04 mole) of 4-carbethoxyaminosalicylic acid and 7.5 g (0.08 mole) of phenol was heated to about 100° C, and 2.4 ml of phosphorus oxychloride was added. The temperature was raised to 120—130° C and kept here until the evolution of gas had ceased. The mixture was now cooled to room temperature and 20 ml of methanol was added. The ester which separated was filtered, washed with methanol and recrystallized from ethanol.

Yield: 7.8 g ~ 65 %. M.p. 149—151° C.

SUMMARY

The preparation of a number of esters of 4-nitrosalicylic acid and 4-aminosalicylic acid with various phenols and thiophenols and with a few simple alcohols is described. A number of N-substituted compounds of the phenyl ester of 4-aminosalicylic acid have also been prepared.

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