N-Aralkylsalicylamides

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The N-benzylsalicylamides described in Table I were prepared for evaluation as anthelmintics. The compounds were synthesized by the general methods which have been described for the preparation of N-arylsalicylamides,[1-5] with occasional minor modifications.

Experimental Section[6]

Method A.[1-3]—Phosphorus trichloride (1 equiv) was added dropwise to a mixture of salicylic acid (3 equiv) and the amine (3 equiv) without external cooling. After the addition was complete, the reaction mixture was heated at 180° until the evolution of HCl ceased. The product was isolated by stirring the reaction mixture in aqueous Na_2CO_3 solution.

N-Benzyl-2-mercaptobenzamide.—Phosphorus trichloride (9.2 g, 0.06 mole) was added dropwise to a mixture of thiosalicylic acid (30.8 g, 0.20 mole) and benzylamine (21.4 g, 0.20 mole). The reaction mixture was heated at 180° for 45 min and the product was isolated as previously described; yield 30.0 g (62%), mp 208–209°.

Anal. Calcd for $C_{14}H_{13}NOS$: C, 69.11; H, 5.38; N, 5.76; S, 13.18. Found: C, 68.91; H, 5.18; N, 5.89; S, 13.16.

Method B.[4]—Phenyl salicylate and the amine (1:1) were heated at 180–200° for 2 hr. The product was isolated by treatment with dilute ethanol.

N-(4-Chlorobenzyl)salicylamide was obtained by a modification[5] of method B in which 1,2,4-trichlorobenzene was used as solvent.

N-(β-Phenoxyethyl)salicylamide.—A solution of β-phenoxyethylamine (6.88 g, 0.05 mole) and phenyl salicylate (10.71 g, 0.05 mole) in 10 ml of 1,2,4-trichlorobenzene was heated at 190–200° for 30 min. Removal of solvent and phenol under vacuum yielded a residue which was treated with dilute alcohol; yield 11.0 g (85.5%), mp 115–116°. The analytical sample (mp 116–117°) was crystallized from CCl_4.

Anal. Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.45. Found: C, 70.32; H, 5.81; N, 5.63.

N-Furfurylsalicylamide.—A mixture of furfurylamine (9.7 g, 0.1 mole) and phenyl salicylate (21.4 g, 0.1 mole) was shaken for 10 min at room temperature. An exothermic reaction occurred. The mixture was then heated on the steam bath for 15 min and poured into water. Acidification with HCl gave the product, 21.0 g (97%), mp 110–111°.

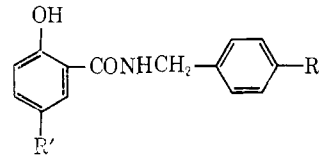
Anal. Calcd for $C_{12}H_{11}NO_3$: C, 66.34; H, 5.11; N, 6.45. Found: C, 66.19; H, 5.14; N, 6.80.

N-Furfuryl-2-mercaptobenzamide.—Reaction of phenyl thiosalicylate[7] (10 g, 0.06 mole) and furfurylamine (4.9 g, 0.05 mole) by the above method gave the product which melted at 182–183° after one crystallization from ethanol; yield 5.0 g (43%).

Anal. Calcd for $C_{12}H_{11}NO_2S$: C, 61.76; H, 4.75; N, 6.00; S, 13.75. Found: C, 61.86; H, 4.61; N, 6.18; S, 13.99.

TABLE I

SUBSTITUTED BENZYLSALICYLAMIDES



R	R′	Method used	Yield, %	Mp, °C	Formula	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found	Nitrogen, % Calcd	Nitrogen, % Found	Chlorine, % Calcd	Chlorine, % Found
H	Br	A	73	154–156[a]	$C_{14}H_{12}BrNO_2$[b]	54.91	55.01	3.95	4.02	4.58	4.76		
H	Cl	A	74	145–146[a]	$C_{14}H_{12}ClNO_2$	64.27	64.57	4.62	4.70	5.34	5.18	13.54	13.29
H	I	A	54	134–135[a]	$C_{14}H_{12}INO_2$[c]	47.61	47.65	3.43	3.30	3.98	4.16		
H	NO_2	A	87	221–223[d]	$C_{14}H_{12}N_2O_4$	61.75	61.62	4.44	4.45	10.30	10.14		
4-Cl	Br	A	35	158–159[a]	$C_{14}H_{11}BrClNO_2$[e]	49.36	49.20	3.26	3.26	4.11	4.07	10.41	10.38
4-Cl	Cl	B	63	156–158[a]	$C_{14}H_{11}Cl_2NO_2$	56.78	57.00	3.74	3.79	4.73	4.84	23.94	24.24
4-Cl	H	B	86	133–134[a]	$C_{14}H_{12}ClNO_2$	64.27	64.41	4.62	4.42	5.34	5.18	13.54	13.53
4-Cl	I	A	70	161–162[a]	$C_{14}H_{11}ClINO_2$[f]	43.40	43.60	2.85	2.78	3.62	3.51	9.15	9.33
3,4-Cl_2	Br	A	67	160–161[a]	$C_{14}H_{10}BrCl_2NO_2$[g]	44.83	44.83	2.71	2.68	3.74	3.71	18.91	18.96
3,4-Cl_2	Cl	A	73	154–156[a]	$C_{14}H_{10}Cl_3NO_2$	50.86	50.83	3.05	3.20	4.24	4.30	32.19	32.63
3,4-Cl_2	H	A	62	136–137[a]	$C_{14}H_{11}Cl_2NO_2$	56.78	56.50	3.74	3.46	4.73	4.71	23.94	23.92
3,4-Cl_2	I	A	50	174–175[a]	$C_{14}H_{10}Cl_2INO_2$[h]	39.84	40.07	2.39	2.56	3.32	3.44	16.80	16.95

[a] Recrystallized from aqueous ethanol. [b] *Anal.* Calcd: Br, 26.11. Found: Br, 26.29. [c] *Anal.* Calcd: I, 35.93. Found: I, 35.79. [d] Recrystallized from acetone–water. [e] *Anal.* Calcd: Br, 23.76. Found: Br, 23.81. [f] *Anal.* Calcd: I, 32.74. Found: I, 32.51. [g] *Anal.* Calcd: Br, 21.31. Found: Br, 21.59. [h] *Anal.* Calcd: I, 30.07. Found: I, 29.61.

N-3,4-Dichlorobenzyl-2-mercaptobenzamide.— Thiosalicyloyl chloride[8] (14.3 g, 0.08 mole) was dissolved in 150 ml of benzene and 3,4-dichlorobenzylamine (35.2 g, 0.2 mole) was added. The exothermic reaction was moderated by cooling and then allowed to stand overnight at room temperature. The solid formed was filtered, washed with ethanol, and triturated with hot water; yield 22.8 g (73.0%), mp 218–220°. One crystallization from methyl ethyl ketone raised the melting point to 224–225°.

Anal. Calcd for $C_{14}H_{11}Cl_2NOS$: C, 53.86; H, 3.55; Cl, 22.72; N, 4.47; S, 10.26. Found: C, 54.12; H, 3.74; Cl, 23.01; N, 4.35; S, 10.54.

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Synthesis of Analogs of Bacterial Cell Wall Glycopeptides

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The enzymatic synthesis of the glycopeptides involved in bacterial cell wall formation by the stepwise addition of amino acids to uridine-5′-diphospho-N-acetylmuramic acid[1] offers a