

Reactions of Salicylamides with Thionyl Chloride

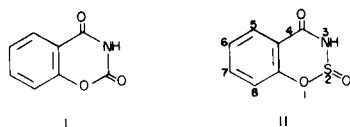
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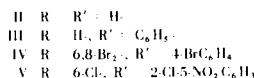
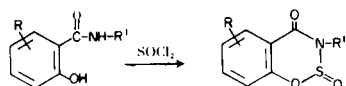
Received September 13, 1974

A series of compounds having the 1,2,3-benzoxathiazin-4(3H)one 2-oxide structure have been synthesized by the interaction of thionyl chloride with the appropriate salicylamide. Some properties of these compounds as well as some by-products are described.

Numerous references (1) describe the synthesis of 2H-1,3-benzoxazine-2,4(3H)dione (I) and its derivatives. Analogous compounds should be possible containing sulfur in the heterocyclic ring, i.e., 1,2,3-benzoxathiazin-4(3H)one 2-oxide (II). However, only one citation to derivatives of this structure is known, this to the 3-(4-chlorobenzylideneamino)-1,2,3-benzoxathiazin-4(3H)one 2-oxide prepared by Katz and Schroeder (2), with nitrogen substitution at the 3-position.



During a study of salicylamide reactions, several derivatives of II as well as the parent heterocycle have been characterized, each prepared by reaction of the appropriate salicylamide with thionyl chloride.



These compounds have been found to be reasonably stable solids, with discrete melting points, varying from pale yellow to colorless. With the exception of IV, where side-reactions predominated, yields of 63-90% were obtained. As expected, these cyclic sulfites were readily hydrolyzed by acid or base to give the parent salicylamide as the primary product. Indeed, storage without precaution against moisture produced a sulfur dioxide odor in most samples.

As a major side-reaction in the preparation of IV, and to a lesser extent in some of the other derivatives, a mixed product lacking the elements of sulfur dioxide was isolated. Elemental and mass spectroscopic analyses

indicated this was principally the cyclic dimer and trimer corresponding to condensation polymers of an anthranilic acid. However, purification and rigorous structure proof of this by-product were not pursued.

As a general procedure for the synthesis of compounds III-V, one equivalent each of the corresponding salicylamide and thionyl chloride were heated with two equivalents of triethylamine in refluxing dichloromethane for one hour. After water washes to remove salts and concentration to remove solvent, recrystallizations from isopropanol or benzene-isopropanol mixtures gave the benzoxathiazinone oxides described in Table I.

When the above procedure was applied to the parent unsubstituted salicylamide, the predominant reaction was formation of *o*-hydroxybenzotrile, presumably by dehydration of the amide. It was found, however, that good yields of II were obtained simply by refluxing equivalent amounts of salicylamide and thionyl chloride in benzene without added amine. This latter procedure was found ineffective for preparing IV, with no detectable product being formed under similar conditions.

EXPERIMENTAL

Dichloromethane, thionyl chloride, triethylamine, salicylamide, salicylanilide, and 3,4',5-tribromosalicylanilide were all commercially available products. The dichloronitrosalicylanilide was obtained by the procedure of Szabo, *et al.* (3). Microanalyses and mass spectroscopy were performed by the Analytical Laboratory, The Dow Chemical Company. Melting points are uncorrected. Reaction of Salicylamide with Thionyl Chloride. (Method A).

A mixture of 6.86 g. (0.05 mole) of salicylamide, 6.55 g. (0.0555 mole) of thionyl chloride and 75 ml. of benzene was heated to reflux for two hours, then cooled, filtered, and the cake washed once with benzene. After drying, there was obtained 7.5 g. (0.04 mole) of 1,2,3-benzoxathiazin-4(3H)one 2-oxide (II). Further washing with benzene and drying gave an analytical sample of II, m.p. 183-185°, with the analyses as listed in Table I. Ir analysis (nujol mull) showed absorption at 1685, 1330, 1180, and 1125 cm⁻¹, similar to that observed with the other derivatives of this series.

Table I
Analysis and Properties of Some 1,2,3-Benzoxathiazin-4(3H)one 2-Oxides

Compound	Substitution	M.p. (°C)	Yield (%, Crude)	Elemental Analyses (%)						
				C	H	Br	Cl	N	S	
II	None	183-185	80	Found	46.2	2.9			7.7	16.8
				Calcd.	45.9	2.8			7.6	17.5
III	3-Phenyl	114-115.5	90	Found	60.6	3.6			5.3	12.0
				Calcd.	60.2	3.5			5.4	12.4
IV	6,8-Dibromo-3-(4-bromophenyl)	193.5-194.5	20	Found	31.4	1.2	48.6		2.7	6.6
				Calcd.	31.5	1.2	48.3		2.8	6.5
V	6-Chloro-3-(2-chloro-5-nitrophenyl)	209.5-211	63	Found	42.0	1.6		18.9	7.5	8.7
				Calcd.	41.8	1.6		19.0	7.5	8.6

Using similar conditions to the above, 3,4',5-tribromosalicylanilide was recovered unchanged in 99% yield.

Reaction of Salicylanilide with Thionyl Chloride. (Method B).

To a mixture of 21.3 g. (0.1 mole) of salicylanilide in 100 ml. of dichloromethane, 20.8 g. (0.206 mole) of triethylamine was added over five minutes at 25°. Then 12.5 g. (0.105 mole) of thionyl chloride was added over seven minutes, the temperature rising to 24°. Reflux was then maintained for one hour, giving a slurry that was cooled, washed twice with 150 ml. portions of 5% hydrochloric acid, once in water, and then dried over anhydrous sodium sulfate. Removal of solvent at 55°/20 mm. for one hour gave 23.4 g. (0.09 mole) of crude III as a brown liquid which slowly solidified. Recrystallization of 11.7 g. of this product from isopropanol gave 5.7 g. of 3-phenyl-1,2,3-benzoxathiazin-4(3H)one 2-oxide (III), m.p. 114-115°, further described in Table I.

In a similar manner, each of the other substituted salicylamides was treated with thionyl chloride and triethylamine to give the products IV-V as summarized in Table I, with recrystallization from dioxane-water, 2-propanol, or mixtures of 2-propanol and benzene as necessary.

Reaction of 3,4',5-Tribromosalicylanilide with Thionyl Chloride.

Using Method B, a reaction of 45.0 g. (0.1 mole) of 3,4',5-tribromosalicylanilide, 20.8 g. (0.206 mole) of triethylamine and 12.5 g. (0.105 mole) of thionyl chloride gave a slurry that was washed twice with cold water. Solids which separated from the dichloromethane solution were filtered and dried, giving 10.0 g. (0.02 mole) of crude IV, m.p. 189-190°. Recrystallization from a dioxane-water solvent gave 5.6 g. of pure IV, m.p. 193.5-194.5°, as listed in Table I. From the dichloromethane-soluble mother liquors, concentration gave 22.5 g. of solid, m.p. 209-213°.

Anal. Calcd. for C₁₃H₆Br₃NO₂: C, 34.8; H, 1.3; N, 3.1; Br, 53.6. Found: C, 36.2; H, 1.6; N, 2.8; Br, 53.7; S, 0.9.

Attempts to purify this product by recrystallization from various solvents did not readily give material with uniform melting

behavior or constant ir spectra. A typical ir spectrum (sample m.p. 208-213.5°) showed peaks at 1635, 1330, 1245, 1220, 1190, 1100, 975, 945, 870, and 735 cm⁻¹. A small variable peak at 1700-1690 cm⁻¹ (doublet) appeared in some samples. No significant absorption above 3000 cm⁻¹ was noted. Mass spectrometric analysis using a direct probe procedure at 175° showed a m/e ratio of 858 containing the proper isotope ratios for six bromine atoms. Further heating to 220° gave a m/e ratio of 1278, consistent with the presence of nine bromines. These data are indicative of the product containing 2,4,8,10-tetrabromo-5,11-bis(4-bromophenyl)dibenzo[*b,f*][1,5]diazocine-6,12(5*H*, 11*H*)-dione and 2,4,8,10,14,16-hexabromo-5,11,17-tris(4-bromophenyl)-tribenzo[*b,f,j*][1,5,9]triazacyclododecine-6,12,18-(5*H*, 11*H*, 17*H*)-trione.

Hydrolyses of 1,2,3-Benzoxathiazin-4(3H)one 2-Oxide (II).

Acid Hydrolysis.

A mixture of 1.0 g. of II in 2.5 ml. of ethanol and 2.5 ml. of concentrated hydrochloric acid was refluxed fifteen minutes, cooled, and diluted with 15 ml. of water. Precipitated solids were filtered and dried, giving 0.7 g. of salicylamide, identified by an ir spectrum identical with that of known material.

Basic Hydrolysis.

A mixture of 1.0 g. of II in 2.5 ml. of ethanol and 2.5 ml. of 10% aqueous sodium hydroxide was refluxed fifteen minutes, cooled, and neutralized with dilute hydrochloric acid. Filtration and drying gave 0.7 g. of salicylamide identified by ir.

REFERENCES

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- (3) Z. Szabo, *et al.*, Hung. Patent 151,691; *Chem. Abstr.*, **62**, 7698b (1965).