

Synthesis of Substituted 2,3-Dihydro-4H-1,3-benzoxazin-4-ones and Their Biological Activities

JACOB FINKELSTEIN AND ELLIOT CHIANG

Chemical Research Department, Hoffmann-La Roche Inc., Nutley, New Jersey 07110

Received May 8, 1968

A series of substituted benzoxazinones was synthesized and evaluated for pharmacological and chemotherapeutic activities. The compounds were prepared by the reaction of a substituted salicylamide with an aldehyde under varying acidic conditions. The biological testing revealed that certain compounds possess analgetic, antitumor, and antiviral activities.

Salicylic acid, acetylsalicylic acid, salicylamide, and salicylanilide comprise a family of analgetics that has constantly grown in popularity. Numerous derivatives of these drugs have been prepared, involving alkylation of the phenolic group as well as the introduction of various substituents on the benzene nucleus without conferring any advantages on the parent drugs. Nevertheless, the search for new analgetic agents in this area continues. In 1950, Horrom and Zaugg¹ investigated the related cyclic compounds, 2,3-dihydro-4H-1,3-benzoxazin-4-ones, and claimed that the 2-phenyl derivative exhibited analgetic activity in the dog equal to that of salicylamide. Later, Thomae² described the synthesis of 2- β -chloroethyl-2,3-dihydro-4H-1,3-benzoxazin-4-one which had been shown by Kadatz³ to a more potent analgetic than the 2-phenyl derivative. It also possesses antipyretic and antiphlogistic properties, low toxicity, and proved to be superior to acetylsalicylic acid in most of the tests studied. Baoli and coworkers⁴ expanded this study and synthesized 6-substituted (OH, Cl, NH₂) derivatives. Based upon their studies on various types of experimental inflammations, they reported the 6-amino hydrochloride to possess the highest antiphlogistic activity. This paper describes the preparation and biological screening results of a series of 3-substituted 2,3-dihydro-4H-1,3-benzoxazin-4-ones. These N-substituted compounds, listed in Table I, may be viewed as heterocyclic derivatives of salicylamides and salicylanilides.

Chemistry.—Keane and Nicholls⁵ and Titherley⁶ simultaneously and independently discovered that the reaction between salicylamide and benzaldehyde produced 2-phenyl-2,3-dihydro-4H-1,3-benzoxazin-4-one. Later, Hicks⁷ reported the synthesis of the corresponding 2-methyl derivative as the reaction product from salicylamide and paraldehyde in the presence of HCl as a catalyst. Since then, and including the work of Horrom and Zaugg,¹ this reaction has been extended to include aromatic aldehydes, several aliphatic aldehydes, ketones, and cyclic ketones.⁸ The latter workers reported that the reaction with formaldehyde gave a polymer, and others^{9,10} reported on a general lack of

reactivity between monoacylated primary amines of the type RCONHR' with formaldehyde in aqueous or alcoholic hydrochloric acid.

In this communication, we describe experimental procedures for the successful reactions of salicylanilide and a number of its derivatives with paraldehyde, trioxane, acrolein, and *p*-ethoxybenzaldehyde to yield the corresponding N-substituted 2,3-dihydro-4H-1,3-benzoxazin-4-ones. According to the anilides and aldehydes employed, it was necessary to develop five procedures to obtain the desired compounds. These procedures are described in the Experimental Section, and the one found suitable for each product is indicated in Table I. The chemical structure of each compound prepared was confirmed by elemental analyses, ir, uv, and nmr spectra.

A satisfactory synthesis for 6-nitro-3-(*p*-nitrophenyl)-2,3-dihydro-4H-1,3-benzoxazin-4-one (**14**) could not be developed from the reaction of 2-hydroxy-5-nitro-4'-nitrobenzanilide with trioxane by any of the described methods. This difficulty was overcome by the nitration of **2** to give **14**. The structure of **14** was established by the usual parameters and by hydrolysis to 5-nitrosalicylic acid and 4-nitroaniline which were identical with respective authentic samples. This dinitro compound **14** was reduced to the corresponding diamine **15**.

In a similar manner, **19** was nitrated to give **20**, whose structure was also confirmed by hydrolysis to 5-nitrosalicylic acid. When **20** was reduced in the presence of Raney nickel, the corresponding amine **21** was obtained. The reduction of **20** in the presence of formalin produced the corresponding dimethylamino derivative **22**.

Biological Results.—In the pharmacological screening tests for blood pressure and analgetic and antiinflammatory effects, none of the compounds showed any significant activity. Compound **15** showed an analgetic effectiveness in the hot plate test¹¹ with mice (ED₅₀ 16 mg/kg *po*) and in the writhing¹² test with mice (ED₅₀ 64 mg/kg *po*).

Compounds **9** and **13** showed slight activity against Sarcoma 180.¹³ Moderate activity against Herpes virus¹⁴ (CD 138 mg/kg ip) and slight activity against Col SK virus¹⁴ (40% protection at 250 mg/kg ip) was shown by **3**. Otherwise, none showed any significant activity against local and systemic infections with

(1) B. W. Horrom and H. E. Zaugg, *J. Amer. Chem. Soc.*, **72**, 721 (1950).

(2) K. Thomae, British Patent 806,729 (1958); *Chem. Abstr.*, **53**, 14127h (1959).

(3) R. Kadatz, *Arzneim.-Forsch.*, **7**, 651 (1957).

(4) F. Baoli, A. Bottazzi, W. Ferrari, A. Garzia, I. Trabucchi, and L. Vargiu, *ibid.*, **13**, 884 (1963).

(5) C. A. Keane and W. S. Nicholls, *J. Chem. Soc.*, 264 (1907).

(6) A. W. Titherley, *ibid.*, 1425 (1907).

(7) W. L. Hicks, *ibid.*, 1032 (1910).

(8) See ref 1 for literature citations.

(9) R. D. Haworth, D. H. Peacock, W. R. Smith, and R. Mac Gillwray, *J. Chem. Soc.*, 2972 (1952).

(10) A. Einhorn and G. Schupp, *Ann. Chem.*, **313**, 252 (1905).

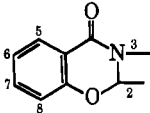
(11) N. B. Eddy, C. F. Touchbeny, and J. E. Lieberman, *J. Pharmacol. Exptl. Therap.*, **90**, 121 (1950).

(12) E. Sigmund, R. Cadmus, and G. Lu, *Proc. Soc. Exptl. Biol. Med.*, **95**, 729 (1957).

(13) E. Grunberg, H. N. Prince, E. Tittsworth, G. Beskid, and M. D. Tendler, *Chemotherapy*, **11**, 240 (1966).

(14) R. J. Schnitzer, M. Buck, and N. Steiger, *Proc. Soc. Exptl. Biol. Med.*, **77**, 182 (1951).

TABLE I
 2,3-DIHYDRO-4H-1,3-BENZOXAZIN-4-ONES. SYNTHETIC CONDITIONS, PHYSICAL PROPERTIES, AND ANALYTICAL DATA



Starting substance	Product no.	Product	Prepn method	Yield, % ^a	Mp, °C	Crystn solvent	Formula
Salicylanilide ^c	1	2-Methyl-3-phenyl-	A	41.2	78-80	EtOH	C ₁₆ H ₁₃ NO ₂
Salicylanilide ^c	2	3-Phenyl-	B	40.7	90-92	C ₆ H ₆ ^d	C ₁₄ H ₁₁ NO ₂
N- <i>p</i> -Chlorophenylsalicylanilide ^e	3	2-Methyl-3-(<i>p</i> -chlorophenyl)-	A	49.3	95-96	EtOH	C ₁₆ H ₁₃ ClNO ₂
N- <i>p</i> -Chlorophenylsalicylanilide ^e	4	3-(<i>p</i> -Chlorophenyl)-	B	73.6	134-135	C ₆ H ₆ ^d	C ₁₄ H ₁₀ ClNO ₂
N-(<i>p</i> -Ethoxyphenyl)salicylanilide ^f	5	3-(<i>p</i> -Ethoxyphenyl)-2-methyl-	B	78.0	135-137	EtOH	C ₁₇ H ₁₇ NO ₂
N-(<i>p</i> -Ethoxyphenyl)salicylanilide ^f	6	3-(<i>p</i> -Ethoxyphenyl)-	B	85.0	133-135.5	EtOH	C ₁₆ H ₁₅ NO ₂
5-Nitrosalicylanilide ^g	7	6-Nitro-3-phenyl-	C	60.8	168.5-171	EtOH-EtOAc	C ₁₄ H ₁₀ N ₂ O ₄
<i>p</i> -Ethoxybenzaldehyde ^h	8	2-(<i>p</i> -Ethoxyphenyl)-3-phenyl-	D	10.8	140-141	EtOH	C ₂₀ H ₁₉ NO ₂
5-Chlorosalicylanilide ^c	9	6-Chloro-2-methyl-3-phenyl-	C	58.1	94-95.5	<i>i</i> -PrOH	C ₁₆ H ₁₃ ClNO ₂
5-Methoxysalicylanilide ⁱ	10	6-Methoxy-3-phenyl-	B	67.1	102-104	<i>i</i> -PrOH	C ₁₆ H ₁₅ NO ₂
5-Chloro-2-hydroxy-4'-chlorobenzanilide ⁱ	11	6-Chloro-3-(<i>p</i> -chlorophenyl)-	C	54.4	172-173	EtOH	C ₁₆ H ₉ Cl ₂ NO ₂
2-Hydroxy-N-(3,4-dichlorophenyl)benzamide ^j	12	3-(3,4-Dichlorophenyl)-	E	44.5	175-177	<i>n</i> -BuOH	C ₁₄ H ₉ Cl ₂ NO ₂
4'-Nitrosalicylanilide ^f	13	3-(<i>p</i> -Nitrophenyl)-	C	27.9	187-189	C ₆ H ₆	C ₁₄ H ₁₀ N ₂ O ₄
Compound 2	14	6-Nitro-3-(<i>p</i> -nitrophenyl)-	X ^k	42.8	206.5-207.5	<i>n</i> -C ₅ H ₁₁ OH	C ₁₄ H ₉ N ₃ O ₆
Compound 14	15	6-Amino-3-(<i>p</i> -aminophenyl)-	X ^k	88.2	173.5-175	EtOH	C ₁₄ H ₁₃ N ₃ O ₂
3,5-Dichlorosalicylanilide ⁱ	16	6,8-Dichloro-3-phenyl-	C	59.9	197-199	EtOAc	C ₁₄ H ₉ Cl ₂ NO ₂
N-(β-Diethylaminoethyl)salicylamide ^k	17	3-(β-Diethylaminoethyl)-	C	50.4	147-149 ^l		C ₁₆ H ₂₆ N ₂ O ₂
Salicylanilide ^c acrolein ^c	18	2-(β-Chloroethyl)-3-phenyl-	B	18.9	115-117	EtOH	C ₁₆ H ₁₄ ClNO ₂
<i>n</i> -N-Propylsalicylamide ^m	19	3- <i>n</i> -Propyl-	B	78.6	112-113 ^l		C ₁₇ H ₁₉ NO ₂
Compound 19	20	6-Nitro-3- <i>n</i> -propyl-	X ^k	55.4	142.5-144.5	EtOH	C ₁₆ H ₁₅ N ₂ O ₄
Compound 20	21	6-Amino-3- <i>n</i> -propyl-	X ^k	46.5	119.5-121 ⁿ	EtOAc	C ₁₅ H ₁₅ N ₂ O ₂ ⁿ
Compound 21	22	6-Dimethylamino-3- <i>n</i> -propyl	X ^k	46.3	108-110 ⁿ	<i>n</i> -C ₅ H ₁₁ OH	C ₁₇ H ₂₅ N ₂ O ₂ ⁿ

^a Bases on one or two preparations and not optimized. ^b All compounds showed satisfactory C, H, N analyses, and their structures were confirmed by means of ir, uv, and nmr spectra. ^c Eastman Organic Chemicals, Distillation Products Industries, Rochester, N. Y. 14603. ^d After chromatographing over alumina. ^e G. Speroni, *Chim. Ind. (Milan)*, **34**, 391 (1952); *Chem. Abstr.*, **47**, 2924e (1953). ^f G. Cohn, *J. Prakt. Chem.*, [2] **61**, 547 (1900). ^g G. V. Jadhav and P. G. Neslekar, *J. Univ. Bombay, A*, **20** (Pt. 3, *Science No.* **30**), 93 (1951); *Chem. Abstr.*, **47**, 2734d (1953). ^h St. V. Kostenechi and M. Schneider, *Chem. Ber.*, **29**, 1892 (1896). ⁱ See Experimental Section. ^j T. Syrowatka, B. Jonezyk, M. Brzezicka, and T. Taskowska, *Rocz. Chem.*, **11**, 571 (1960); *Chem. Abstr.*, **55**, 13776b (1961); mp 212-213°. ^k Knoll A.-G. Chemische Fabriken, British Patent 874,206 (1961); *Chem. Abstr.*, **57**, 7180f (1962). ^l Boiling point at 1 mm. ^m Aldrich Chemical Co., Milwaukee, Wis. 53210. ⁿ Maleate.

representative gram-positive and gram-negative bacteria, *Mycobacterium tuberculosis*, *Candida albicans*, *Histoplasma capsulatum*, *Trichomonas vaginalis*, *Trichomonas foetus*, *Entamoeba histolytica*, and Ehrlich solid tumor.

The acute toxicity (LD₅₀) in 72 hr determined in mice intraperitoneally and orally for each compound was approximately 500 mg/kg.

Experimental Section

The ir spectra were determined on a Beckman IR-5 double-beam spectrophotometer with NaCl optics in CHCl₃ or as KBr pellets. The nmr spectra were obtained with a Varian A-60 spectrophotometer with TMS as internal standard. Uv spectra were determined on a Cary spectrophotometer (Model 14M). Melting points are corrected and were taken on a Uni-Melt Thomas-Hoover capillary melting point apparatus. Woelm grade I neutral alumina was used wherever the absorbent name was mentioned and usually as a column 40 × 150 mm.

Substituted Benzoxazinones (Table I). Method A, 1.—A mixture of 9.75 g (0.046 mole) of salicylanilide and 6.6 g (0.05 mole) of paraldehyde in 75 ml of CHCl₃ was saturated with dry HCl without external cooling and a complete solution was obtained. The solution was then refluxed for 1 hr and the solvent was evaporated *in vacuo*. The gummy residue was triturated with 50 ml of aqueous 1 N NaOH. The insoluble product was extracted with ether which was washed free from alkali with H₂O, dried, and evaporated, and a white crystalline substance, mp 78-80°, was obtained.

Method B, 2.—A mixture of 10.6 g (0.05 mole) of salicylanilide, 2.5 g (0.03 mole) of trioxane in 75 ml of CHCl₃, and 5 ml of AcOH was saturated with dry HCl at 10-15°. After remaining at room temperature for several days, the small amount of immiscible liquid was separated and the solution was concentrated *in vacuo* to a small volume; the material solidified when triturated with 100 ml of cold H₂O. The recrystallized product (from EtOH) was solvated. It was suspended in 500 ml of C₆H₆ and

heated until pure C₆H₆ distilled. The benzene solution was passed through a column of alumina, and the eluate was evaporated to deposit a pure white solid, mp 90-92°.

Method C, 9.—A mixture of 12.3 g (0.05 mole) of 5-chlorosalicylanilide, 6.6 g (0.05 mole) of paraldehyde, and 150 ml of trifluoroacetic acid was heated in a shaking autoclave for 12 hr at 50-60° under 70.3 kg/cm² pressure of N₂. The excess solvent was distilled *in vacuo* and the residue was triturated with portion-wise additions of an aqueous 4 N NaOH solution until alkaline. The insoluble product was extracted with CHCl₃, washed free from alkali with H₂O, and passed through a column of alumina. The yellowish eluate was concentrated *in vacuo*, and the oily residue crystallized on standing. It was recrystallized from *i*-PrOH; mp 94-95.5°.

Method D, 8.—A mixture of 21.3 g (0.1 mole) of salicylanilide, 10 g (0.07 mole) of *p*-ethoxybenzaldehyde in 300 ml of CH₂Cl₂, and 1.5 ml of concentrated H₂SO₄ was refluxed for 10 hr as the returned reflux passed through a thimble containing anhydrous CaCl₂ to remove the H₂O formed from the refluxing azeotrope. After the reaction mixture was cooled and filtered, the filtrate was washed with H₂O, dried, and evaporated *in vacuo* to leave a red viscous oil which was stirred with 100 ml of aqueous 1 N NaOH solution and extracted with ether from which a crystalline product was obtained and recrystallized from EtOH.

Method E, 12.—A mixture of 5.6 g (0.02 mole) of 2-hydroxy-N-(3,4-dichlorophenyl)benzamide, 200 ml of AcOH, 250 ml of CHCl₃, and 1.2 g (0.013 mole) of trioxane was stirred at 10-15° while 10 ml of concentrated H₂SO₄ was added. The solution was stirred for 2 additional hr and kept at room temperature overnight. The small amount of immiscible matter was separated, and the solution was concentrated *in vacuo* to 50 ml. Upon the addition of 250 ml of cold H₂O, a white semisolid precipitate formed. It was extracted with ether, washed until neutral, and evaporated to dryness. The solid was dissolved in C₆H₆ and the solution passed through a column of alumina. The eluate was evaporated and the product was recrystallized from *n*-BuOH; mp 175-177°.

6-Nitro-3-(*p*-nitrophenyl)-2,3-dihydro-4H-1,3-benzoxazin-4-one (14).—A solution of 2.5 ml of fuming HNO₃ in 30 ml of concentrated H₂SO₄ at 5-10° was slowly added to a solution of

7.9 g (0.034 mole) of **2** dissolved in 30 ml of AcOH and 4 ml of concentrated H_2SO_4 at 0 to 5° . Stirring was continued for 1 hr and the reaction was permitted to reach room temperature. It was poured onto 500 g of chipped ice and the yellow solid was filtered, washed with H_2O , and recrystallized from MeCN; mp $206.5\text{--}207.5^\circ$. Upon repeating the preparation with 20 g of starting material, 12 g of product was obtained.

Proof of Structure of 14.—A solution of 600 mg (2 mmole) of **14** in 25 ml of 6 *N* HCl was refluxed for 18 hr, cooled, and filtered. The precipitate was stirred with 10 ml of 1 *N* NaOH and filtered from a small amount of starting material, and the filtrate was acidified to give 5-nitrosalicylic acid which was identical with an authentic sample.¹⁵ The hydrolytic acid filtrate was made alkaline with aqueous NaOH, extracted with ether, dried, and evaporated to give a yellow solid identical in all respects with *p*-nitroaniline.¹⁶

3-(*p*-Aminophenyl)-6-amino-2,3-dihydro-4H-1,3-benzoxazin-4-one (15).—A solution of 3.1 g (0.01 mole) of **14** in 250 ml of THF was reduced under 3 atm pressure of H_2 in the presence of Raney Ni. The solvent was evaporated and the gummy product was recrystallized from EtOH; mp $173.5\text{--}175^\circ$.

3-*n*-Propyl-6-nitro-2,3-dihydro-4H-1,3-benzoxazin-4-one (20).—A suspension of 1.9 g (0.1 mole) of **19** in 10 ml of AcOH and 2 ml of concentrated H_2SO_4 at $10\text{--}15^\circ$ was nitrated with a solution of 2.5 ml of fuming HNO_3 and concentrated H_2SO_4 cooled to 5° . After stirring for 1 hr after the addition, the solution was poured onto 400 g of chipped ice and the white precipitate was filtered and recrystallized from EtOH; mp $142.5\text{--}144.5^\circ$.

Proof of Structure of 20.—A solution of 2 g (8.5 mmole) of **20** in 100 ml of 6 *N* HCl was refluxed for 19 hr and cooled. The crystalline product obtained was filtered, washed with H_2O , and dried. The compound was 5-nitrosalicylic acid, identical in all respects with an authentic sample.¹⁶

6-Amino-3-*n*-propyl-2,3-dihydro-4H-1,3-benzoxazin-4-one Maleate (21).—A solution of 7.08 g (0.033 mole) of **20** in 250 ml of absolute EtOH was reduced under 3 atm pressure of H_2 in the presence of Raney Ni. The filtered solution was concentrated *in vacuo*, and the residue was dissolved in ether and added to an ethereal solution of maleic acid. The crystalline salt obtained was recrystallized from EtOAc; mp $119.5\text{--}121^\circ$.

6-Dimethylamino-3-*n*-propyl-2,3-dihydro-4H-1,3-benzoxazin-4-one Maleate (22).—A solution of 11.8 g (0.05 mole) of **20** in 190 ml of absolute EtOH containing 10 ml of 37% formalin was reduced at 3 atm pressure of H_2 in the presence of Raney Ni. Upon evaporation of the solvent, the oily residue was dissolved in ether and mixed with an ethereal solution of maleic acid to form the maleate which was recrystallized from *n*-AmOH; mp $108\text{--}110^\circ$.

5-Chloro-2-hydroxy-4'-chlorobenzanilide.¹⁶—A mixture of 34.4 g (0.2 mole) of 5-chlorosalicylic acid, 25.4 g (0.2 mole) of *p*-chloroaniline, and 18 g (0.13 mole) of PCl_5 was heated in a bath at

170° and stirred for 0.5 hr. After cooling, the hard mass was broken up in 600 ml of EtOH and treated with an aqueous saturated solution of NaHCO_3 to pH 7. The yellow precipitate was filtered, washed with H_2O , dissolved in THF, and passed through a column of alumina. The eluate was evaporated to deposit the yellow crystalline product, mp $225\text{--}230^\circ$ (EtOH), yield 20 g (55.3%). *Anal.* ($\text{C}_{13}\text{H}_9\text{Cl}_2\text{NO}_2$) C, H, N.

3,5-Dichlorosalicylanilide.¹⁷—A mixture of 51.8 g (0.23 mole) of 3,5-dichlorosalicylic acid and 25.5 g (0.27 mole) of aniline in 250 ml of dry toluene was stirred and heated at $60\text{--}70^\circ$ while 7 g (0.05 mole) of PCl_5 was added. After refluxing 4 hr, the reaction mixture was cooled to 60° and 300 ml of H_2O was added followed by 120 ml of 30% aqueous NaOH solution. The solution was clarified by filtration, and the aqueous filtrate was adjusted to pH 3 with acid to precipitate the product which was recrystallized from AcOH and dried at 110° *in vacuo*; mp $135\text{--}136.5^\circ$, yield 42 g (65%). *Anal.* ($\text{C}_{13}\text{H}_9\text{Cl}_2\text{NO}_2$) C, H, N.

4'-Nitrosalicylanilide.—As above, 27.6 g (0.2 mole) of salicylic acid, 27.6 g (0.2 mole) of 4-nitroaniline, and 8 g (0.058 mole) of PCl_5 were allowed to react in 250 ml of dry toluene; yield 40 g (77.5%) (EtOH), mp $231\text{--}232.5^\circ$. *Anal.* ($\text{C}_{13}\text{H}_9\text{N}_2\text{O}_4$) C, H, N.

5-Methoxysalicylanilide.—To a solution of 5.04 g (0.033 mole) of 5-methoxysalicylic acid¹⁸ in 100 ml of dry C_6H_6 , 3.9 g (0.033 mole) of SOCl_2 and 1 drop of dry pyridine were added. On stirring at room temperature a solution was obtained, which was then heated at 50° for 0.5 hr and evaporated *in vacuo* at 30° . The residue was treated with dry C_6H_6 and again evaporated *in vacuo*. This operation was repeated three times. The residual acid chloride was then dissolved in 100 ml of dry C_6H_6 and added dropwise to 6 g (0.07 mole) of aniline in 25 ml of dry C_6H_6 with good stirring. After stirring and refluxing for 3 hr, the white solid was filtered and washed with water to remove the aniline hydrochloride, and the water-insoluble product was dissolved in ether and dried. After the ether was evaporated, the product was recrystallized from EtOH; yield 4.3 g, mp $160\text{--}161^\circ$. *Anal.* ($\text{C}_{14}\text{H}_{13}\text{NO}_3$) C, H.

Acknowledgment.—We wish to thank Dr. A. Brossi for his interest, helpful discussions, and suggestions during this investigation. We are indebted to Dr. Al Steyermark and his associates for the microanalyses, to Drs. F. M. Vane and T. Williams for the nmr spectra, to Dr. V. Toome for the ultraviolet spectra, and to Mr. S. Traiman for the infrared spectra. The chemotherapeutic testing was performed under the direction of Dr. E. Grunberg, Director of the Department of Chemotherapy. The pharmacological data was obtained under the direction of Dr. L. O. Randall, Director of the Pharmacological Laboratories.

(15) Eastman Organic Chemicals, Distillation Products Industries, Rochester, N. Y. 14603.

(16) N. W. Hirvi, G. V. Jadhav, and D. R. Sukhtankar, *J. Indian Chem. Soc.*, **16**, 281 (1939); **34**, 1640^a (1940), prepared this substance by treating the two compounds with SO_2Cl_2 ; mp $203\text{--}204^\circ$.

(17) R. Anschutz, *Ann. Chem.*, **346**, 305 (1906), prepared this compound by treating 3,5-dichlorosalicyloyl chloride with aniline.

(18) Prepared by the methylation of gentisic acid according to D. N. Chandbury, H. I. King, and A. Robertson, *J. Chem. Soc.*, 2220 (1948).