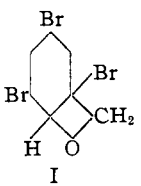
[FROM THE CHEMICAL RESEARCH LABORATORY, HYNSON, WESTCOTT & DUNNING, INC.]

Some Derivatives of Dibromohydroxybenzyl Bromide

BY WILTON C. HARDEN

A comprehensive study of the bromine derivatives of saligenin was made by Auwers and Buttner[1] in 1898, in connection with an investigation of the nature of pseudo phenols. Among the compounds prepared and described by these authors was dibromohydroxybenzyl bromide, dibromosaligenin bromide or dibromosaligenin bromohydrate. This compound, to which Auwers assigned the formula I, is a true pseudo phenol; *i. e.*, its phenolic properties are completely overshadowed by the greater reactivity of bromine in the side chain. Auwers and Buttner prepared many derivatives of this compound, among which were the monomethyl ether, the acetates, the anilide and the piperidine derivatives. In this connection, it should be noted that when the phenolic hydroxyl is replaced by methoxy or acetoxy the reactivity of the side chain halogen is greatly reduced.



I

The purpose of the present paper is to describe some additional derivatives of this compound. In view of the physiological activity and therapeutic usefulness of certain benzyl esters, it was thought that it would be interesting to prepare a series of dibromohydroxybenzyl esters by the reaction between the sodium salts of various acids and dibromosaligenin bromide. Dibromohydroxybenzyl esters of the following acids were hence prepared: benzoic, salicylic, *p*-hydroxybenzoic, *p*-nitrobenzoic, cinnamic, mandelic, succinic and phthalic. These compounds are listed in Table I. A preliminary investigation indicates that several of these esters have valuable physiological properties.

TABLE I

DIBROMOSALIGENIN BROMIDE CONDENSED WITH SODIUM SALTS OF ACIDS

Acids	Dibromohydroxy-	Empirical formula	Mol. wt.	M. p., °C.	Bromine, % Calcd.	Found
Benzoic	Benzyl benzoate	$C_{14}H_{10}O_3Br_2$	386	154	41.45	41.25
Cinnamic	Benzyl cinnamate	$C_{16}H_{12}O_3Br_2$	412	127	38.83	39.12
Mandelic	Benzyl mandelate	$C_{15}H_{12}O_4Br_2$	416	108	38.46	38.27
Succinic	Bis-(benzyl)-succinate	$C_{18}H_{14}O_6Br_4$	646	161	49.53	49.29
Phthalic	Benzyl acid phthalate	$C_{15}H_{10}O_5Br_2$	430	174	37.20	37.06
p-Hydroxybenzoic	Benzyl *p*-hydroxybenzoate	$C_{14}H_{10}O_4Br_2$	402	148	39.80	40.10
p-Nitrobenzoic	Benzyl *p*-nitrobenzoate	$C_{14}H_9O_5Br_2N$	431	153	37.12	36.83
Salicylic	Benzyl salicylate	$C_{14}H_{10}O_4Br_2$	402	156	39.80	40.00

Dibromohydroxybenzyl urea and dibromohydroxyphenylpropionic acid have also been prepared and are shown in Table II.

Since Paterno and Mazzara[2] prepared benzylphenol by the action of

(1) Auwers and Buttner, *Ann.*, **302**, 131 (1898).

(2) Paterno and Mazzara, *Gazz. chim. ital.*, **3**, 254 (1873).

TABLE II

	Dibromosaligenin bromide condensed with	Product, dibromohydroxy-	Mol. wt.	M. p., °C.
1	Urea	Benzyl-urea	324	207
2	Sodium acetoacetic ester	Phenylpropionic acid	324	117

	Empirical formula	Bromine, % Calcd.	Found	Nitrogen, % Calcd.	Found
1	$C_8H_8O_2Br_2N_2$	49.38	49.50	8.6	8.3
2	$C_9H_8O_3Br_2$	49.38	49.41	...	...

benzyl chloride on phenol in the presence of a small piece of zinc, it seemed worth while to prepare dibromohydroxybenzylphenol by the method of these authors. This compound as well as the corresponding ethers and their acetates and dibromo derivatives are shown in Table III. This reaction is at present being applied to various substituted phenols.

TABLE III

	Product, dibromohydroxy-	Mol. wt.	M. p., °C.	Empirical formula	Bromine, % Calcd.	Found
1	Benzylphenol	358	174	$C_{13}H_{10}O_2Br_2$	44.69	44.83
2	Benzylphenyl ether	358	119	$C_{13}H_{10}O_2Br_2$	44.69	44.90

		Acetate			Dibromo derivatives		
	Acetate derivatives	M. p., °C.	Bromine, % Calcd.	Found	M. p., °C.	Bromine, % Calcd.	Found
1	Diacetate	81	36.20	36.41	198	62.01	61.82
2	Monoacetate	73	40.00	40.10	105	62.01	61.50

Dibromohydroxybenzylphenol readily forms a soluble mono-sodium salt. Although in general the sodium salts of phenols are weak or totally ineffective germicides, a 1% solution of this compound was found to kill *Staphylococcus aureus* in a dilution of 1 to 9.

Experimental

All of the esters shown in Table I were prepared in a similar manner. The preparation of the benzoate will, therefore, serve as a typical example.

One-twentieth mole (7.2 g.) of sodium benzoate was suspended in 50 cc. of dry benzene in a 500-cc. round-bottomed three-necked flask, fitted with stirrer, reflux condenser and dropping funnel; 17.2 g. ($^1/_{20}$ mole) dibromosaligenin bromide, dissolved in 250 cc. of warm benzene, was added drop by drop while the solution was stirred and heated to boiling on the water-bath. After three hours boiling, the sodium bromide was filtered from the hot solution and the filtrate cooled. The ester crystallized at once and was recrystallized from benzene.

Preparation of Dibromohydroxyphenylpropionic Acid.—12.8 g. of acetoacetic ester was dissolved in 100 cc. of dry toluene, stirred mechanically, and 2.3 g. of sodium, cut in small pieces, was added. After formation of the sodium salt of the acetoacetic ester, the solution was cooled to room temperature and 34.4 g. of dibromosaligenin bromide in 100 cc. of dry toluene was added drop by drop. After completion of the reaction, the sodium bromide was removed by filtration and the filtrate concentrated *in vacuo* to remove the solvent. The resulting product was a clear yellow oil of characteristic odor. This was dissolved in alcohol and added to a hot 20% alcoholic solution of potassium hydroxide and finally boiled for three hours. The solution was then cooled, poured into water and made acid. A heavy tar separated, and on standing overnight in the ice-box hardened to a semi-crystalline mass. This was repeatedly recrystallized from water.

Preparation of Dibromohydroxybenzylphenol.—17.2 g. of dibromosaligenin bromide was dissolved in 250 cc. of hot toluene in a 500-cc. round-bottomed, three-necked flask, fitted with mechanical stirrer, reflux condenser, and dropping funnel. A small piece of mossy zinc, previously cleaned by hydrochloric acid, was added, followed by 7.0 g. of phenol in 50 cc. of toluene. The mixture was then heated to boiling until the evolution of hydrogen bromide had practically ceased (about three hours). The toluene solution was then washed with water to remove hydrogen bromide, dried with anhydrous sodium sulfate and concentrated *in vacuo*. The solution was then diluted with one-half its volume of ligroin and cooled in the ice-box. The crystals thus obtained were recrystallized from toluene.

Preparation of Dibromohydroxybenzyldibromophenol.—5.0 g. of dibromohydroxybenzylphenol, prepared as described above, was dissolved in 50 cc. of warm glacial acetic acid and 5 g. of bromine added drop by drop. The solution was allowed to stand at room temperature for several hours and finally cooled in ice. The resulting white crystals were recrystallized from acetic acid.

Preparation of Dibromohydroxybenzyl Phenyl Ether.—The filtrate from the preparation of dibromohydroxybenzylphenol was steam distilled to remove the toluene and ligroin. The resulting heavy oil was crystallized repeatedly from dilute alcohol. After refluxing for three hours with acetic anhydride in the presence of anhydrous sodium acetate, this compound yielded only a mono-acetate, indicating the formula assigned it.

The author wishes to acknowledge the valuable assistance of Mr. Grant Spurrier, who performed many of the analyses.

Summary

1. A number of derivatives of dibromosaligenin bromide have been prepared.

2. A preliminary investigation indicates that certain of these derivatives possess valuable pharmacological properties.

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The Occurrence of a New Case of Isomerism in the Fluorenone Carboxylic Acid Series: Isomeric Products from the Action of Sulfuric Acid upon 3,3′-Dichlorodiphenic Acid

BY ERNEST H. HUNTRESS, IVAN S. CLIFF AND EDWARD R. ATKINSON

The Effect of Acetic Anhydride and of Concentrated Sulfuric Acid upon 3,3′-Dichlorodiphenic Acid.—In the course of some work upon 3,3′-dichlorodiphenic acid[1] we had occasion to examine its behavior with acetic anhydride and with concentrated sulfuric acid. With the former it readily yielded a monomolecular anhydride which has been reported in the earlier paper. Upon turning to the action of sulfuric acid, however, we found that two distinct but isomeric products were formed according to the temperature employed. One of these substances (formed at 125°) appears to be

(1) Huntress and Cliff, THIS JOURNAL, **55**, 2559–2567 (1933).