latter, a compound, $C_3H_9O_5P$, was formed and its tribenzoyl derivative prepared. The action of ammonium chloride and calcium carbonate on tetrahydroxy-methylene-phosphonium chloride was studied and an insoluble curdy precipitate containing about 30% of phosphorus and 15% of nitrogen obtained.

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[CONTRIBUTION FROM THE DEPARTMENT OF PHARMACOLOGY, UNIVERSITY OF MINNESOTA.]

SOME DERIVATIVES OF SALIGENIN.[1]

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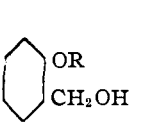
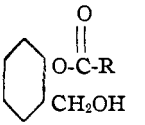
Since Hirschfelder, Lundholm and Norrgaard[2] have shown that saligenin (*o*-hydroxy-benzyl alcohol) possesses valuable properties as a local anesthetic it was thought that an investigation of some of the derivatives of saligenin might also prove valuable. In this study it is desired to vary the saligenin molecule in several different ways and to study pharmacologically the different properties of the derivatives.

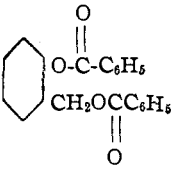
The saligenin molecule was first altered by varying the phenolic hydroxyl and simple ethers (Formula I) were synthesized. In this case ethers where R was both aliphatic and aromatic were prepared. The ethyl



(I).



(II).



(III).

propyl, *n*-butyl, *iso*-amyl, and the benzyl ethers of saligenin were made.

Other variations of the molecule were then prepared by making the esters of saligenin (Formula II) upon the phenolic hydroxyl. Representatives of this class of compounds were made by preparing the mono-acetate and the monobenzoate of saligenin. The mono-acetate was particularly desired because of its relation to acetyl salicylic acid (aspirin).

Also a derivative of saligenin, the dibenzoate, was prepared as a representative of the case where both the groups in the saligenin molecule were masked (Formula III).

The saligenin molecule was next modified by varying the nucleus. As the simplest and easiest way of doing this seemed through the introduction

[1] This work was done with the aid of funds granted by the United States Interdepartmental Board, for the investigation of the antiseptic and chemotherapeutic action of phenolic alcohols and their derivatives upon the gonococcus and the spirochaete.

[2] Hirschfelder, Lundholm and Norrgaard, *Science, N. S.*, **51**, 21 (1920); *J. Pharmacol.* **15**, 263 (1920).

of halogen into the nucleus, the monobromo and mono-iodo saligenin were prepared. It was necessary to produce these in fairly large quantities because they were used not only for pharmacological and clinical study, but they were found also to react slowly with mercuric acetate in dilute alcohol solution with the formation of mercury derivatives. It was desired to study these mercury derivatives both chemically and pharmacologically in comparison with the mercury derivative of saligenin.[3]

Of the ethers of saligenin (Formula I) we found that Cannizaro and Koerner[4] had prepared the methyl ether by treating molecular quantities of saligenin and potash in methyl alcohol with methyl iodide. Later this work was repeated by Pschorr, Wolfes and Buckow.[5] The methyl ether is an oil boiling at 240° with a pleasant ethereal odor.

Bötsch[6] prepared the ethyl ether of saligenin by heating an aqueous solution of saligenin with the theoretical amount of potassium hydroxide and ethyl iodide in a sealed vessel for 3 hours at 100°.

In this research the saligenin ethers were prepared by refluxing potassium saligenate with alkyl or aryl halides. The monosaligenin esters were made by the action of acid chlorides or acid anhydrides on potassium saligenate in ether or alcohol solutions. The dibenzoyl derivative may be prepared by the benzoylation of saligenin in pyridine solution in the presence of calcium carbonate.

The methods of preparing monobromo-saligenin were studied and that of Auwers and Büttner[7] was found to be the best. The mono-iodo-saligenin has been made by Seidel[8] by treating saligenin in alcohol with iodine in the presence of mercuric oxide. We found that a better method for the preparation of this compound was to treat saligenin in water solution with a potassium iodide solution of iodine.

Most of the above syntheses required the use of potassium saligenate. This had been made by R. Rivals[9] but his method was not suitable for the preparation of potassium saligenate in quantity. We found that by treating saligenin in acetone solution with alcoholic potash, we could obtain practically theoretical yields of potassium saligenate.

Experimental Part.

Preparation of Potassium Saligenate.—The saligenin used in these experiments was prepared according to the method given by us in a previous paper.

10 g. of pure saligenin was dissolved in 150 mils of acetone. To this was added 35 mils of a 25% solution of potassium hydroxide. A voluminous white precipitate

[3] Hart and Hirschfelder, THIS JOURNAL, **42**, 2678 (1920).
[4] Cannizaro and Koerner, *Gazz. chim. ital.*, **2**, 65–68 (1872).
[5] Pschorr, Wolfes and Buckow, *Ber.*, **33**, 165 (1900).
[6] Bötsch, *Monatsh.* **1**, 621 (1880).
[7] Auwers and Büttner, *Ann.*, **301-302**, 131 (1898).
[8] Seidel, *J. prakt. Chem.*, **59**, 105 (1899).
[9] R. Rivals, *Ann. chim., phys.*, **12**, 556 (1897).

was formed and the mixture was allowed to stand in the cold for several hours. It was then filtered on a Büchner funnel and washed with a little acetone. 12.6 g. or 96% was obtained.

The potassium saligenate formed white microscopic plate-like crystals. It was insoluble in ether and acetone, sparingly soluble in alcohol, and extremely soluble in water.

It was dissolved in a little water and acidified with acetic acid. The acid solution on extraction with ether and the crystallization of the ether residue from benzene gave pure saligenin, melting at 86°.

We found that the formation of the potassium saligenate was the quickest and the best method so far developed for the purification of crude saligenin. In this method the crude saligenin obtained after the evaporation of the ether from the extraction of the aqueous reduction products of the salicyl amide, was taken up in acetone and the potassium saligenate formed by the addition of the 25% alcoholic potash. By this method we obtained directly the potassium saligenate which could either be used in the preparation of derivatives of saligenin or treated with dil. acetic acid, extracted with ether, and crystallized from benzene, giving pure saligenin. By this method of the purification of saligenin we were able to obtain from salicyl-amid 50 to 55% of the theoretical yield very quickly and with a minimum of trouble.

Preparation and Properties of the Ethers of Saligenin.—Potassium saligenate was dissolved in an excess of the alkyl or aryl halide and refluxed on the steam-bath for several hours. The solution was then filtered and the precipitate of potassium halide washed with a little of the organic halide. The filtrate was then distilled at atmospheric pressure to a temperature high enough to remove most of the excess of organic halide. The residue was then fractionally distilled under reduced pressure.

The aliphatic saligenin ethers were pleasant, ethereal smelling oils. The benzyl ether was a crystalline solid melting at 37°. In general these ethers had the same solubilities, being very soluble in the usual organic solvents with the exception of petroleum ether in which they were sparingly soluble. They were insoluble in water. They gave no coloration with ferric chloride and with conc. sulfuric acid they gave the typical red saligenin resin.

From 80 g. of potassium saligenate in 150 mils of ethyl iodide, 47 g. (62.6% yield) of the ethyl ether of saligenin boiling at 149–150° under 28 mm. pressure was obtained. This was a clear colorless oil when freshly distilled and, like the ethyl ether prepared by Bötsch[6], slowly turned yellow on exposure to the air. It was redistilled at atmospheric pressure and boiled at 264°, practically the same as the ether described by Bötsch (b. p. 265°). The yellow color was probably due to an iodine compound, as the color disappeared on redistillation and could be removed by sodium thiosulfate.

From 70 g. of potassium saligenate in 100 g. of propyl iodide, 28 g. (39% yield) of the propyl ether of saligenin boiling at 155–157° under 24 mm. pressure was obtained. This was a clear colorless oil that turned slightly yellow on standing.

From 95 g. of potassium saligenate in 100 mils of *n*-butyl bromide, 54 g. (51.2% yield) of the *n*-butyl ether of saligenin boiling at 160–162° under 25 mm. pressure was obtained. This was a clear colorless oil.

From 40 g. of potassium saligenate in 100 g. of *iso*-amyl bromide, 22 g. (45.9% yield) of the *iso*-amyl ether of saligenin boiling at 176° under 27 mm. pressure was obtained. This was a clear colorless oil.

From 50 g. of potassium saligenate in 100 mils of benzyl chloride, 29 g. (43.9% yield) of the benzyl ether of saligenin boiling at 221–222° under 25 mm. pressure was obtained. This was a clear colorless oil that hardened to a crystalline solid (long slender needles) melting at 37°. This was dried on a clay plate and analyzed.

Analysis. Subs. 0.1910: H_2O, 0.1116; CO_2, 0.5510. Calc. for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59. Found: C, 78.69; H, 6.53.

The Mono-acetate of Saligenin.—50 g. of potassium saligenate was refluxed with an excess of acetic anhydride (80 mils). The mixture was then boiled up to 150° to remove most of the excess of acetic anhydride, and the residue taken up in ether and filtered to remove potassium acetate. The residue from the dried ether filtrate was fractionally distilled under reduced pressure. From 50 g. of the potassium saligenate we obtained 33.5 g. (65.4% yield) of the mono-acetate of saligenin, boiling at 167–168° under 29 mm. pressure.

This compound is also formed by treating potassium saligenate with molecular quantities of acetic anhydride in the presence of ether. From 80 g. of potassium saligenate, 33 g. (40.2% yield) of the mono-acetate of saligenin boiling at 168–169° at 30 mm. pressure was obtained.

This compound was a clear, colorless oil and extremely soluble in the usual organic solvents. It was insoluble in water. It gave no coloration with ferric chloride and gave the typical red saligenin resin with conc. sulfuric acid. On standing it was slowly hydrolyzed with the formation of acetic acid, and was more quickly hydrolyzed in the presence of water.

Analysis.—A small sample was heated under a reflux condenser for 8 hours with 25 mils of 1.6% alcoholic potash solution, then diluted with 100 mils of water and extracted twice with ether. The aqueous solution was titrated with 0.1 *N* hydrochloric acid with phenolphthalein as an indicator. Two blanks of the alcoholic potash were treated in an identical manner. Subs., 1.1146: 0.1*N* KOH, 66.84 mils. Calc. for $(C_7H_7O)OCO.CH_3$: $HC_2H_3O_2$, 36.14. Found: 36.00.

The Monobenzoate of Saligenin.—40 g. of potassium saligenate was suspended in 250 mils of alcohol to which 27 mils of benzoyl chloride was slowly added. Potassium chloride was formed. Most of the alcohol was distilled on the water-bath and the residue taken up in 300 mils of ether. This was extracted thrice with 10% sodium carbonate solution. The first extract removed a trace of benzoic acid but the later extracts were free from this substance. The ether was then washed thrice with water and dried over anhydrous calcium chloride. The ether was removed and the resulting oil was dried in a vacuum at 100° to remove any traces of alcohol or ether. A yield of 52 g. was obtained.

This was a clear, colorless oil and was free from benzoic acid as was shown by taking it up in ether and extracting it with sodium carbonate solution. On hydrolysis with alcoholic potash it gave benzoic acid melting at 122°. It decomposed on trying distillation under reduced pressure, giving benzoic acid.

This compound was extremely soluble in the usual organic solvents. It was sparingly soluble in petroleum ether and glycerine. It was insoluble in water. It gave the typical red saligenin resin with conc. sulfuric acid, but gave no coloration with ferric chloride.

Analysis.—This was carried out in the same way as the analysis given above for the mono-acetate of saligenin. Subs., 1.1995: 0.1 *N* KOH, 52.40 mils. Calc. for $(C_7H_7O)OCOC_6H_5$: C_6H_5COOH, 53.51. Found: 53.33.

The Dibenzoate of Saligenin.—Ten g. of saligenin was dissolved in 35 mils of pyridine. Ten g. of calcium carbonate was added and then 27 mils of benzoyl chloride was added slowly. The mixture was kept cooled by means of a bath of cold water. After two hours the mixture was taken up in 400 mils of ether and filtered to remove the calcium carbonate. The ether solution was then washed 4 times with 10% sodium carbonate solution. The first extract removed a slight amount of benzoic acid and the succeeding 3 extracts were free from this. It was then well washed with water. The

dried ether was then evaporated by a current of air. A white crystalline solid was obtained. The crystals were fine needles. This material was dried on a clay plate after having been extracted with a little petroleum ether. 18 g. (67.2% yield) was obtained. The melting point was 51°.

This substance was crystallized from 70% alcohol by taking it up in the alcohol at 50° and then cooling in a vacuum desiccator. When crystallized in this manner the dibenzoate came down as white feathery clusters of needle-like crystals. The melting point, 51°, was not raised by further crystallization.

This compound was very soluble in the usual organic solvents, very sparingly soluble in petroleum ether, and insoluble in water and glycerine. It gave no coloration with ferric chloride. On hydrolysis with alcoholic potash it gave benzoic acid, melting at 122°.

Analysis of the Dibenzoate of Saligenin.—The material from the crystallization from the dilute alcohol was dried to constant weight in a vacuum. A small sample was dissolved in 20 mils of 3% alcoholic potash and heated under a reflux condenser for 2 hours. Ten mils of water was added during the process of heating. At the end of this time the solution was diluted with 100 mils of water and extracted with ether. The alkaline solution was then made acid and extracted with ether thrice. The ether extracts were evaporated by a current of air and the residue dissolved in neutral alcohol and titrated with 0.1 *N* sodium hydroxide solution.

Analysis. Subs., 0.5153: 0.1 *N* NaOH, 30.84 mils. Calc. for C_6H_4 ($OCOC_6H_5$) ($CH_2OCOC_6H_5$): C_6H_5COOH, 73.49. Found: 73.07.

Monobromo-saligenin (2-hydroxy-5-bromo-benzyl alcohol).—This was prepared by the method of Auwers and Büttner.[7] Several other methods were tried for the preparation of this compound but the above gave the best results.

Potassium Salt of Monobromo-saligenin.—One g. of monobromo-saligenin was dissolved in 15 mils of acetone, and 2 mils of 25% alcoholic potash was added. A heavy white precipitate of the potassium salt of the monobromo-saligenin was obtained. It crystallized in fine white microscopic plates. It is extremely soluble in water, is soluble in alcohol, and is sparingly soluble in ether, petroleum ether, and acetone. On acidifying an aqueous solution of it crystalline microscopic plates of the monobromo-saligenin melting at 110° are obtained.

This potassium salt of monobromo-saligenin is also formed when monobromo-saligenin acetate (2-hydroxy-5-bromo-benzyl acetate) is treated in acetone solution with alcoholic potash.

Mono-iodo-saligenin (2-hydroxy-5-iodo-benzyl alcohol).—As Seidel[8] from 8.5 g. of saligenin obtained only 1 g. of the mono-iodo compound, it was quite necessary to find a method that would give greater yields. We found that a better method for the preparation of this compound was to treat saligenin in aqueous solution with a solution of iodine in 40% potassium iodide solution. 10 g. of saligenin was dissolved in 500 mils of water and to this was added a solution of 20 g. of iodine in 100 mils of 40% potassium iodide solution. This was allowed to stand for a week as much as possible in the sunlight. At the end of this time the solution was treated with solid sodium hydrogen carbonate until it turned light yellow. A pinkish white precipitate slowly formed and was filtered off. This precipitate was crystallized from hot water. Several extractions were necessary, the later yielding the purer product. The various crops obtained by this method melted from 128 to 130° in the case of the first, to 134 to 136° in the case of the last. Another crystallization from water was sufficient to give pure mono-iodo-saligenin melting at 138°. From 40 g. of saligenin, 12 g. of the pure mono-iodo-saligenin was obtained. This was in the form of white silky needles, melting at 138°.

Potassium Salt of Iodo-saligenin.—This was formed in a similar manner to that of the potassium salt of monobromo-saligenin. It consisted of fine white crystalline plates,

very soluble in water, soluble in alcohol, and sparingly soluble in acetone and petroleum ether. On treating an aqueous solution of it with acetic acid, crystals of the mono-iodo-saligenin, melting at 138° are obtained.

Summary.

1. A method has been developed of treating saligenin in acetone solution with alcoholic potash by which practically theoretical yields of the potassium saligenate were obtained. This method was also used successfully in the preparation of the potassium salts of monobromo- and monoiodo-saligenin.

By the reaction of potassium saligenate on ethyl iodide, the ethyl ether of saligenin identical with ethyl ether of saligenin prepared by Bötsch was prepared. In an analogous manner the propyl, *n*-butyl, *iso*-amyl, and benzyl ethers of saligenin were made.

3. The mono-acetate and the monobenzoate of saligenin were prepared from potassium saligenate and acetic anhydride and benzoyl chloride, respectively. The dibenzoate of saligenin was made by the benzoylation of saligenin in pyridine in the presence of calcium carbonate and with a slight excess of the benzoyl chloride.

4. The method of Auwers and Büttner for preparation of monobromo-saligenin by the bromination of saligenin in aqueous solution was found to give the best results.

5. For the preparation of mono-iodo-saligenin the best method found was the treatment of saligenin dissolved in water with an aqueous potassium iodide solution of iodine.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY, No. 359.]

SOME ERRORS IN THE STUDY OF INVERTASE ACTION.

BY WARREN C. VOSBURGH.[1]

Received April 28, 1921.

It was pointed out by Nelson and Vosburgh[2] that a source of error about which little was known existed in the measurement of the velocity of hydrolysis of sucrose by invertase. The trouble was thought to consist in a change in activity which took place when invertase solutions were diluted, and the magnitude of the resulting error was found to vary with different invertase preparations. In some recent experiments an invertase preparation particularly subject to this error was used and as considerable accuracy in the experimental work was necessary for the purpose in view the results were of little value. An investigation was therefore undertaken of

[1] National Research Fellow.

[2] Nelson and Vosburgh, THIS JOURNAL, 39, 807 (1917).