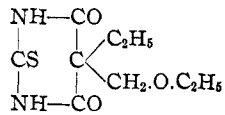
As a different method of approach to these barbituric acid derivatives, 5,5-ethyl-ethoxymethyl-2-thiobarbituric acid, III (No. 10, Table IV), was prepared by condensing ethyl ethyl-ethoxymethyl malonate with thio-urea, in manner similar to that of the urea condensations. The yield



III

was excellent. Attempts, however, to desulfurize this compound by digesting it in aqueous solution with 1.5 to 2 molecular proportions of chloroacetic acid resulted in failure. The thiobarbituric acid was either recovered unchanged by mild treatment, or decomposed by more drastic treatment with this reagent.

Summary

1. Ether-substituted derivatives of diethyl malonate, or of its monoalkylated products, may be prepared by interaction of the sodium salts of these substances and chloro-ethers of the general formula $ROCH_2Cl$. Nine of these esters have been synthesized.

2. These ether-substituted malonic esters condense normally with urea, in sodium ethylate solution, giving analogs of "Barbital" (di-ethyl barbituric acid), in which the 5 position of barbituric acid is occupied by one or two alkoxy-methyl groups.

3. Chloromethyl-benzyl ether and chloromethyl-*iso*butyl ether have been prepared.

NEW HAVEN, CONNECTICUT

[CONTRIBUTION FROM THE POLARIMETRY SECTION, BUREAU OF STANDARDS, UNITED STATES DEPARTMENT OF COMMERCE][1]

STUDIES ON SALICIN. I. EXCEPTIONAL ROTATIONS OF THE HALOGENO-TETRA-ACETYL DERIVATIVES OF SALICIN. A NEW SYNTHESIS OF SALICIN[2]

BY ALFONS KUNZ

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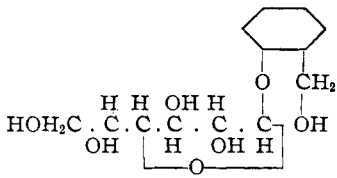
Salicin, the well known glucoside of the willow, is doubtless a beta derivative, since it yields β-glucose by enzymotic hydrolysis.[3] According to the results of Irvine and Rose,[4] it possesses the butylene oxide ring of methyl glucoside and has the structure I.

[1] Published by permission of the Director of the Bureau of Standards, U. S. Department of Commerce.

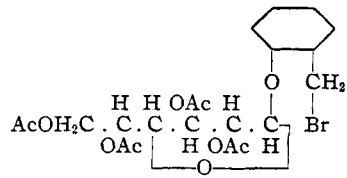
[2] Compare Michael, *Compt. rend.*, **89**, 355 (1879); *Ber.*, **12**, 2260 (1879).

[3] Hudson and Paine, THIS JOURNAL, **31**, 1242 (1909).

[4] Irvine and Rose, *Proc. Chem. Soc.*, **22**, 113 (1906); *J. Chem. Soc.*, **89**, 814 (1906).



I. Salicin

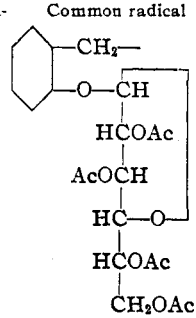


II. Tetra-acetyl-salicin bromide

Zemplén[5] has converted salicin to tetra-acetyl-salicin bromide (II) by acetylation followed by the action of hydrobromic acid in glacial acetic acid. This derivative is doubtless also a beta glucoside because of its preparation from salicin and, as will presently be shown, its re-conversion to salicin by reactions which would not be expected to change the glucosidic linkage. The bromine in this compound is reactive and may be readily exchanged to yield various salicin derivatives[6] possessing a common radical (see Table I) which contains the five asymmetric carbon atoms (1, 2, 3, 4 and 5) of glucose.

TABLE I

ROTATIONS IN CHLOROFORM OF SOME ACETYLATED SALICIN DERIVATIVES

Substance, Tetra-acetyl-	Common radical	Attached group	M. p., °C.	Mol. wt.	$[\alpha]_D$	$[M]_D$
β-*o*-cresyl glucoside		—H	141	438.2	−25.4	−11,130
Salicin		—OH	126	454.2	−15.9	− 7,222
Penta-acetyl-salicin		—OOCCH$_3$	130	496.2	−18.5	− 9,180
Salicin chloride		—Cl	160	472.7	+11.5	+ 5,436
Salicin bromide		—Br	167	517.2	+43.3	+22,400
Salicin iodide		—I	158	564.2	+62.7	+35,370

The rotations of some of these salicin derivatives have unusual values. Although all of them are β-glucosides, the three halogeno-acetyl derivatives show dextrorotation in contrast with the levorotation of the other compounds. Also, the increase in dextrorotation with increasing halogen weight is exceptional since it has been noticed by Hudson[7] that α-glucosides

[5] Zemplén, *Ber.*, **53**, 996 (1920).

[6] (a) Zemplén and Kunz, *Ber.*, **55**, 979 (1922). (b) Zemplén and Hoffmann, *Ber.*, **55**, 992 (1922). (c) Zemplén and Braun, *Ber.*, **58**, 1405 (1925).

[7] Hudson, THIS JOURNAL, **46**, 468 (1924). D. H. Brauns [*ibid.*, **45**, 2383 (1923) and subsequent articles; *Physica*, **3**, 69–75 (1923)] has called attention to the progressive character of the rotation of the halogeno-acetyl sugars according to the increasing atomic weight of the halogen atom present. Hudson has shown in the cited reference that this progression is of a two-fold nature, being towards dextrorotation in the alpha series and towards levorotation in the beta, and has indicated that the direction of the progression may be used in allocating such substances to the alpha or beta series. The exceptional character of the halogeno-acetyl-salicin derivatives consists in their departing from the order that holds for the halogeno-acetyl sugars.

increase in dextrorotation with increasing weight of halogen, as shown in the series of the halogeno-acetyl-glucoses. It would, therefore, be expected that the present series of halogen derivatives of a β-glucoside would increase in the opposite direction, namely, in levorotation, with increasing halogen weight. But the reverse is the case.

It does not seem possible at the present time to account for the unusual rotations except by hypotheses that are only speculative because of the lack of experimental data by which they may be tested. Probably light can be thrown on the question by a knowledge of the rotations of the corresponding derivatives in the alpha series, but none of these compounds are now known. It is only by some new synthetic method that one can hope to obtain them, since the alpha form of salicin (saligenin α-glucoside) has not been found in nature. If a way could be devised to pass from β-*o*-cresyl glucoside to salicin (beta form) it would be expected to lead to the synthesis similarly of α-salicin, since it is probable that the unknown alpha form of *o*-cresyl glucoside can be synthesized by the reaction through which Fischer and Mechel[8] synthesized α-phenyl glucoside. These ideas have led to the attempt to pass from β-*o*-cresyl glucoside to ordinary salicin (saligenin β-glucoside) as a step towards the synthesis of the desired alpha compounds. It has indeed proved possible to synthesize ordinary salicin in good yield by this plan.

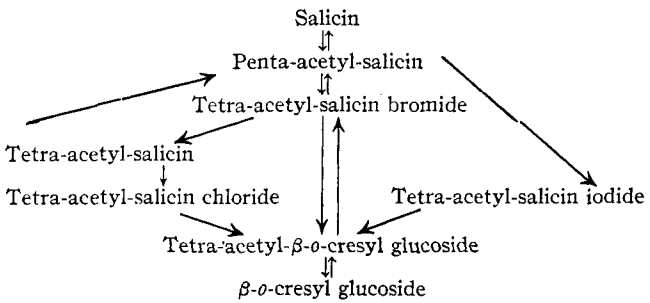
Ryan[9] has synthesized β-*o*-cresyl glucoside from chloro-acetyl-glucose and *o*-cresol. Tetra-acetyl-β-*o*-cresyl glucoside has now been obtained from this compound by acetylation. This acetate reacts with bromine in chloroform solution in sunlight yielding a crystalline mixture which is chiefly tetra-acetyl-salicin bromide. The rotation of the mixture in chloroform solution is about $[\alpha]_D^{25} = +25$. With silver nitrate the mixture yields an amount of silver bromide that corresponds to a content of about 12.5% of reactive bromine. These data indicate a content of about 75% of tetra-acetyl-salicin bromide. The impurities are not easily removed by recrystallization and therefore the isolation of pure tetra-acetyl-salicin bromide was not carried out. However, the mixture can well be used for a synthesis of salicin. The chloroform solution of the mixture is evaporated to dryness under reduced pressure. The residue is dissolved in aqueous acetone and treated with silver carbonate to replace the reactive bromine atom by the hydroxyl group, filtered and the acetone solution of impure tetra-acetyl-salicin is poured into hot water. The impurities, which are insoluble, remain as a yellow oil and the filtered aqueous solution contains the crude tetra-acetyl-salicin which readily crystallizes on cooling. This compound likewise need not be isolated but is merely extracted from aqueous solution with chloroform and the chloroform solution evaporated

[8] Fischer and Mechel, *Ber.*, **49**, 2813 (1916).

[9] Ryan, *J. Chem. Soc.*, **75**, 1056 (1899).

to dryness. The dry residue is acetylated and the resulting penta-acetyl-salicin is purified by three recrystallizations from alcohol. Penta-acetyl-salicin is easily de-acetylated to salicin and thus the synthesis from β-*o*-cresyl glucoside to salicin has been completed.

The following outline indicates the various reactions that have been carried out.



Penta-acetyl-salicin was obtained by Schiff[10] who described it as tetra-acetyl-salicin. Brauns[11] has lately shown that it is a penta-acetate and that Schiff's conclusion has resulted from an incorrect method of analysis. The present experiments show that the acetylation of salicin is practically quantitative and the yield is much larger than could be expected for a tetra-acetate but agrees well for a penta-acetate, confirming Brauns' proof. The real tetra-acetyl-salicin has now been obtained by treating tetra-acetyl-salicin bromide with silver carbonate in aqueous acetone solution. Its rotation and melting point are near the corresponding values of penta-acetyl-salicin but the tetra-acetate has a free hydroxyl group and reacts readily at room temperature with phosphorus pentachloride to yield crystalline tetra-acetyl-salicin chloride which cannot be obtained at room temperature in this way from penta-acetyl-salicin.[6c,12]

Tetra-acetyl-salicin iodide was prepared first by Zemplén from tetra-acetyl-salicin bromide. The compound has now been obtained from penta-acetyl-salicin with hydrogen iodide. The chloride, the bromide, and the iodide of tetra-acetyl-salicin have been reduced by zinc, and a crystalline substance which proves to be tetra-acetyl-β-*o*-cresyl glucoside has been obtained in each case. The reduction proceeds so well that its use furnishes an excellent preparative method for making β-*o*-cresyl glucoside tetra-acetate from salicin, the reactions giving an over-all yield of about 60%. The tetra-acetate can be de-acetylated to give a good yield of the glucoside. These reactions furnish the best method for preparing the glucoside.

[10] Schiff, *Ann.*, **154**, 9 (1870).

[11] Brauns, THIS JOURNAL, **47**, 1286 (1925).

[12] In this and all other papers mentioning tetra-acetyl-salicin previous to Brauns' paper of 1925, the substance, so designated in conformity with Schiff's older statement, was really penta- rather than tetra-acetyl-salicin.

The author wishes to take this occasion to express his sincere thanks to the International Education Board, whose support has made this investigation possible. Thanks are also expressed to Dr. C. S. Hudson for his valuable criticisms and helpful suggestions.

Experimental Part

Acetylation of Salicin. Penta-acetyl-salicin.—About 5 g. of salicin (5.0227 g.) was dissolved in 30 cc. of acetic anhydride and 15 cc. of pyridine. After being heated at 100° for one hour the reaction mixture was cooled to room temperature, poured into ice water and a crystalline precipitate immediately formed. It was thoroughly washed with cold water and dried in a vacuum desiccator over phosphorus pentoxide to constant weight. The yield was 8.8833 g. The calculated yield for penta-acetyl-salicin is 8.7074 g.; for tetra-acetyl-salicin, 7.9722 g.

A chloroform solution containing 1.0120 g. of crude penta-acetyl-salicin, made up to 100 cc. with chloroform, rotated 1.10 circular degrees to the left, in a 600mm. tube, using sodium light, at 25°; hence $[\alpha]_D^{25} = -18.1$; m. p., 125°. After two recrystallizations from alcohol the pure penta-acetyl-salicin melted at 130° and showed $[\alpha]_D^{23.5} = -18.5$ (1.0356 g. of substance, 100 cc. of chloroform solution, 1.15 circular degrees to the left, 600mm. tube) which agree with Brauns' recent measurements.

De-acetylation of Penta-acetyl-salicin.—Ten g. of pure penta-acetyl-salicin was dissolved in 25 cc. of absolute methyl alcohol in which 0.25 g. of metallic sodium had been dissolved. Then 25 cc. of water was added and after half an hour the reaction mixture was made slightly acid with a few drops of acetic acid. The solution was evaporated under reduced pressure to a volume of about 20 cc. During the concentration the salicin separated. It was redissolved by warming, and on cooling pure salicin crystallized in needles; yield, 3.3 g.; m. p., 201°.

Tetra-acetyl-salicin Bromide.—A slight modification of Zemplén's method of preparation follows. Fifty g. of crude penta-acetyl-salicin was dissolved in 150 cc. of chloroform, and 100 cc. of 40% hydrobromic acid solution in glacial acetic acid was added. After the reaction mixture had stood for half an hour at room temperature it was washed thrice with ice water and dried with calcium chloride. On the addition of ether to the chloroform solution the tetra-acetyl-salicin bromide crystallized readily; yield, 43 g., or 82%.

A chloroform solution containing 1.0603 g. of tetra-acetyl-salicin bromide, made up to 100 cc. with chloroform, rotated 2.75 circular degrees to the right in a 600mm. tube, using sodium light, at 21.5°; hence, $[\alpha]_D^{21.5} = +43.2$. After one recrystallization from chloroform and ether, $[\alpha]_D^{21.5} = +43.3$. After a second recrystallization from chloroform and ether, $[\alpha]_D^{24.5} = +42.7$ (0.9717 g. of substance, 100 cc. of chloroform solution, 2.49 circular degrees to the right, 600mm. tube). A sample prepared in the way described by Zemplén showed $[\alpha]_D^{23.5} = +42.2$ (0.5674 g. of substance, 50 cc. of chloroform solution, 2.87 circular degrees to the right, 600mm. tube).

Tetra-acetyl-salicin.—Thirty g. of tetra-acetyl-salicin bromide was dissolved in 250 cc. of aqueous acetone, and 12 g. of freshly prepared silver carbonate added to the solution which was then kept at 50° for two hours, filtered and poured into 10 liters of hot water. From the filtered aqueous solution the tetra-acetyl-salicin crystallized in long needles; m. p., 120°; $[\alpha]_D^{25} = -14.1$ in chloroform; yield, 18.75 g., or 71%. This first product is not quite pure but can be used satisfactorily for the preparation of tetra-acetyl-salicin chloride. After one recrystallization from water the substance is quite pure; m. p., 126°; $[\alpha]_D^{25} = -15.9$ (0.9949 g. of pure tetra-acetyl-salicin, 100 cc. of chloroform solution, 0.95 circular degrees to the left, 600mm. tube). The substance is soluble

in alcohol, acetone, ethyl acetate and chloroform, slightly soluble in ether, but insoluble in petroleum ether.

Acetylation of Tetra-acetyl-salicin to Penta-acetyl-salicin.—Two g. of tetra-acetyl-salicin was acetylated with 6 cc. of acetic anhydride and 3 cc. of pyridine in a manner similar to that described for salicin; yield, 2.2 g. After recrystallization from 15 cc. of alcohol, the product was pure penta-acetyl-salicin; m. p., 130°; $[\alpha]_D^{22} = -18.2$.

Tetra-acetyl-salicin Chloride.—Nine g. of tetra-acetyl-salicin and 4.2 g. of phosphorus pentachloride were allowed to react in 50 cc. of absolute chloroform in a flask closed with a calcium chloride tube. The reaction proceeded at room temperature and was complete in 40 minutes. The chloroform solution was washed thrice with ice water and dried with calcium chloride. When ether was added to the filtered chloroform solution tetra-acetyl-salicin chloride crystallized in long needles; yield, 7 g., or 74%; m. p., 160°; $[\alpha]_D^{23.5} = +11.5$ (1.0014 g. of substance, 100 cc. of chloroform solution, 0.69 circular degree to the right, 600mm. tube). The chlorine percentage was found to be 7.1 in comparison with 7.5 calculated for tetra-acetyl-salicin chloride (0.3314 g. of substance yielded 0.0951 g. of AgCl). It is soluble in chloroform, acetone, ethyl acetate and hot alcohol, slightly soluble in ether, but insoluble in water and in petroleum ether.

Tetra-acetyl-salicin Iodide.—Ten g. of crude penta-acetyl-salicin was dissolved in 30 cc. of chloroform, 20 cc. of a 30% solution of hydrogen iodide in glacial acetic acid was added and the solution was kept at room temperature (20–25°) for 45 minutes. Then it was washed with ice water, with dil. sodium thiosulfate solution, which decolorized it, and again with ice water. It was dried with calcium chloride. Crystallization took place immediately upon the addition of ether; yield, 7.5 g., or 66%. After two recrystallizations from chloroform and ether, the melting point was 158° and $[\alpha]_D^{24} = +62.7$ (1.0131 g. of substance, 100 cc. of chloroform solution, 3.81 circular degrees to the right, 600mm. tube). A sample prepared by Zemplén's method[13] showed $[\alpha]_D^{24.5} = +63.1$, and after one recrystallization from chloroform and ether $[\alpha]_D^{25} = +62.6$ (1.0203 g. of substance, 100 cc. of chloroform solution, 3.83 circular degrees to the right, 600mm. tube).

Tetra-acetyl-β-*o*-cresyl Glucoside.—Forty-three g. of tetra-acetyl-salicin bromide and 43 g. of zinc dust were heated for one hour at about 90° in 1 liter of 50% acetic acid. Then the solution was poured off and diluted with 1 liter of water. The tetra-acetyl-β-*o*-cresyl glucoside crystallized readily and contained no bromine; yield, 28 g. or 76%.

A chloroform solution containing 0.9839 g. of tetra-acetyl-β-*o*-cresyl glucoside, made up to 100 cc. with chloroform, rotated 1.52 circular degrees to the left in a 600mm. tube, using sodium light; hence, $[\alpha]_D^{25} = -25.7$. After recrystallization from alcohol $[\alpha]_D^{25} = -25.4$; m. p., 141°. It is soluble in chloroform, acetone, ethyl acetate, benzene and hot alcohol, slightly soluble in ether, but insoluble in petroleum ether. It crystallizes from alcohol in long, shining prisms. With concd. sulfuric acid it gradually gives a yellow color reaction, and a strong odor of cresol becomes noticeable.

Tetra-acetyl-salicin chloride was reduced in a similar manner and the yield obtained was about the same. The product without recrystallization had the rotation, $[\alpha]_D^{24} = -26.5$. A sample obtained from tetra-acetyl-salicin iodide in a similar manner showed $[\alpha]_D^{24} = -26.4$.

De-acetylation of Tetra-acetyl-β-*o*-cresyl Glucoside to β-*o*-Cresyl Glucoside.—Four g. of tetra-acetyl-β-*o*-cresyl glucoside was dissolved in 25 cc. of absolute methyl alcohol in which 0.25 g. of metallic sodium had been dissolved. Then the solution was diluted with 25 cc. of water. After half an hour the solution was made slightly acid with a few drops of acetic acid and evaporated under reduced pressure to a sirup.

[13] Abderhalden, "Biochem. Handlexikon," vol. **10**, p. 851.

The sirup was dissolved in acetone and the precipitated sodium acetate filtered off. Then the solution was again evaporated under reduced pressure to dryness. The residue crystallized readily from water; yield, about 1 g. After one recrystallization from water its melting point was 163–165°, as given by Ryan.

Acetylation of β-*o*-Cresyl Glucoside.—β-*o*-Cresyl glucoside (0.4 g.) was acetylated with 3 cc. of acetic anhydride and 2 cc. of pyridine, as described for salicin. The crude product was crystallized from alcohol; yield, 0.5 g.; m. p., 141°.

Conversion of Tetra-acetyl-β-*o*-cresyl Glucoside to Penta-acetyl-salicin.—A solution of 5.67 g. of tetra-acetyl-β-*o*-cresyl glucoside in 150 cc. of absolute chloroform and one of 2.068 g. of pure bromine in 100 cc. of absolute chloroform were prepared, cooled to —20°, mixed, and the flask was stoppered and exposed to strong sunlight. It is important that the chloroform used be washed several times with water, then dried with calcium chloride and distilled from phosphorus pentoxide. The solution was cooled by an ice-salt mixture during the exposure, which lasted for one hour, the solution being then almost colorless. It was washed with ice water containing a little sodium thiosulfate, which made it colorless, and was then washed twice with ice water, dried with calcium chloride and evaporated under reduced pressure to dryness. The residue was dissolved in 100 cc. of aqueous acetone and the solution was heated at 50° with 6 g. of freshly prepared silver carbonate for two hours to convert the tetra-acetyl-salicin bromide, formed in the sunlight, to tetra-acetyl-salicin. The silver bromide was filtered off and the filtrate poured into 1.5 liters of hot water (80°). The aqueous solution was filtered, cooled to room temperature, extracted thrice with 100cc. portions of chloroform, and the united extracts were evaporated under reduced pressure to dryness. This residue was acetylated with 30 cc. of acetic anhydride and 15 cc. of pyridine by heating for one hour on the steam-bath. On pouring the solution into ice-water crude crystalline penta-acetyl-salicin separated; yield, 3.7 g.; m. p., 115°. After three recrystallizations from 15–20 cc. of alcohol, 2.1 g. of pure penta-acetyl-salicin was obtained; m. p., 130°; mixed m. p., 130°; yield, 32%; $[\alpha]_D^{26} = -18.55$ in chloroform (0.4628 g. of substance, 50 cc. of solution in chloroform, rotation 1.03° to the left in a 600mm. tube).

Summary

The tetra-acetyl-salicin halides, which are β-glucosides, show exceptional rotations. They are dextrorotatory and there is an increase in dextrorotation with increasing halogen weight, which is the behavior that would be expected for α- rather than for β-glucosides. Probably the explanation of these unusual rotations may be obtained from a knowledge of the rotations of the corresponding derivatives in the alpha series, now unknown. As a step towards their synthesis a new synthesis of salicin, which starts from β-*o*-cresyl glucoside, has been carried out with a good yield. It is expected, therefore, that the desired α-salicin can be synthesized similarly in case it is possible to prepare the now unknown α-*o*-cresyl glucoside by Fischer and Mechel's method for preparing α-phenyl glucoside.

Two new compounds are described, namely, tetra-acetyl-salicin and tetra-acetyl-β-*o*-cresyl glucoside.

WASHINGTON, D. C.