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# THE SYNTHESIS OF COUMARANE DERIVATIVES FROM SALICYLIC ACID

BY

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THESIS

For The Degree of

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THIS IS TO CERTIFY THAT THE THESIS PREPARED UNDER MY SUPERVISION BY

ROSCOE H. GERKE

ENTITLED THE SYNTHESIS OF COUMARANE DERIVATIVES FROM SALICYLIC ACID

IS APPROVED BY ME AS FULFILLING THIS PART OF THE REQUIREMENTS FOR THE

DEGREE OF BACHELOR OF SCIENCE IN CHEMICAL ENGINEERING

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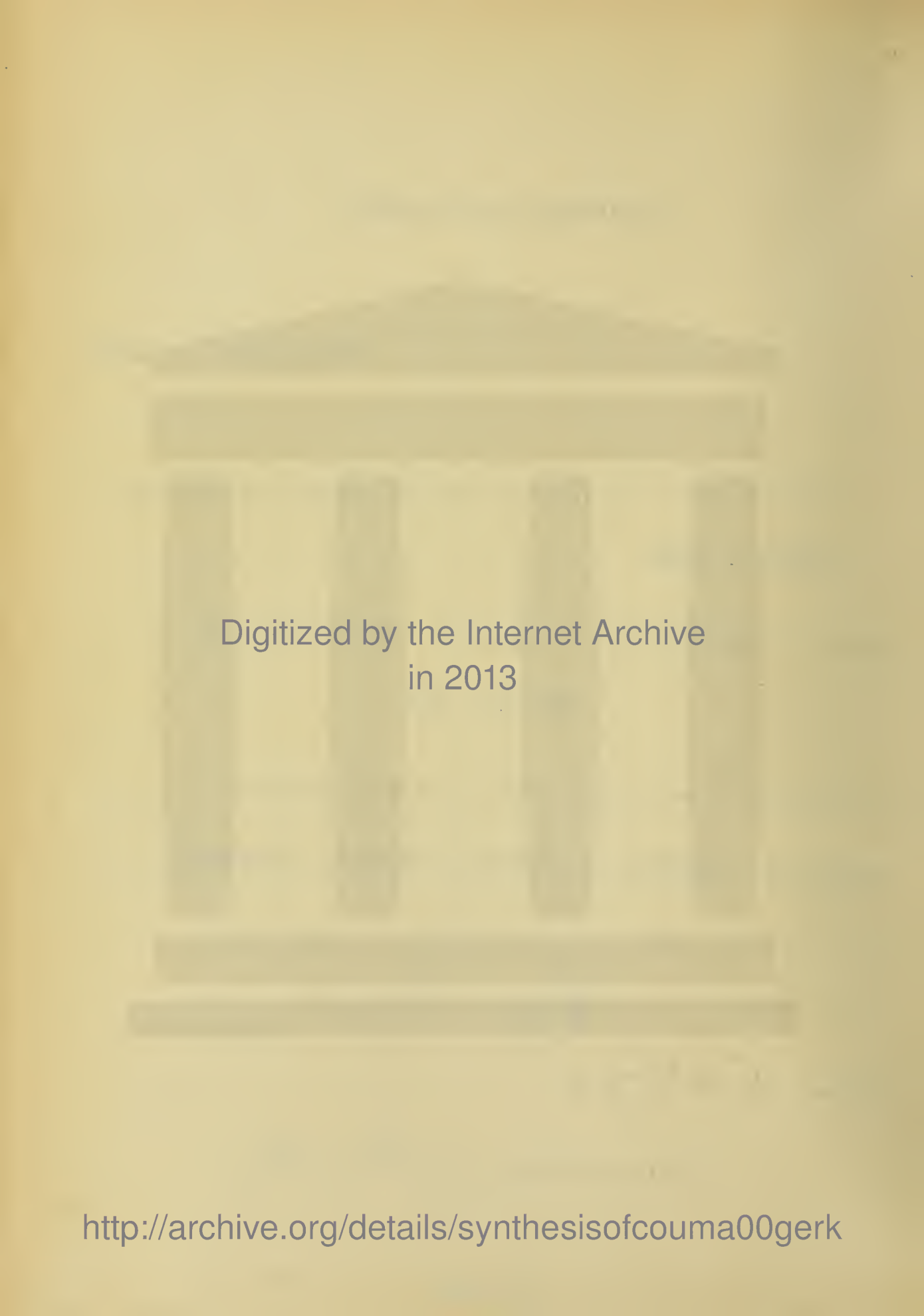

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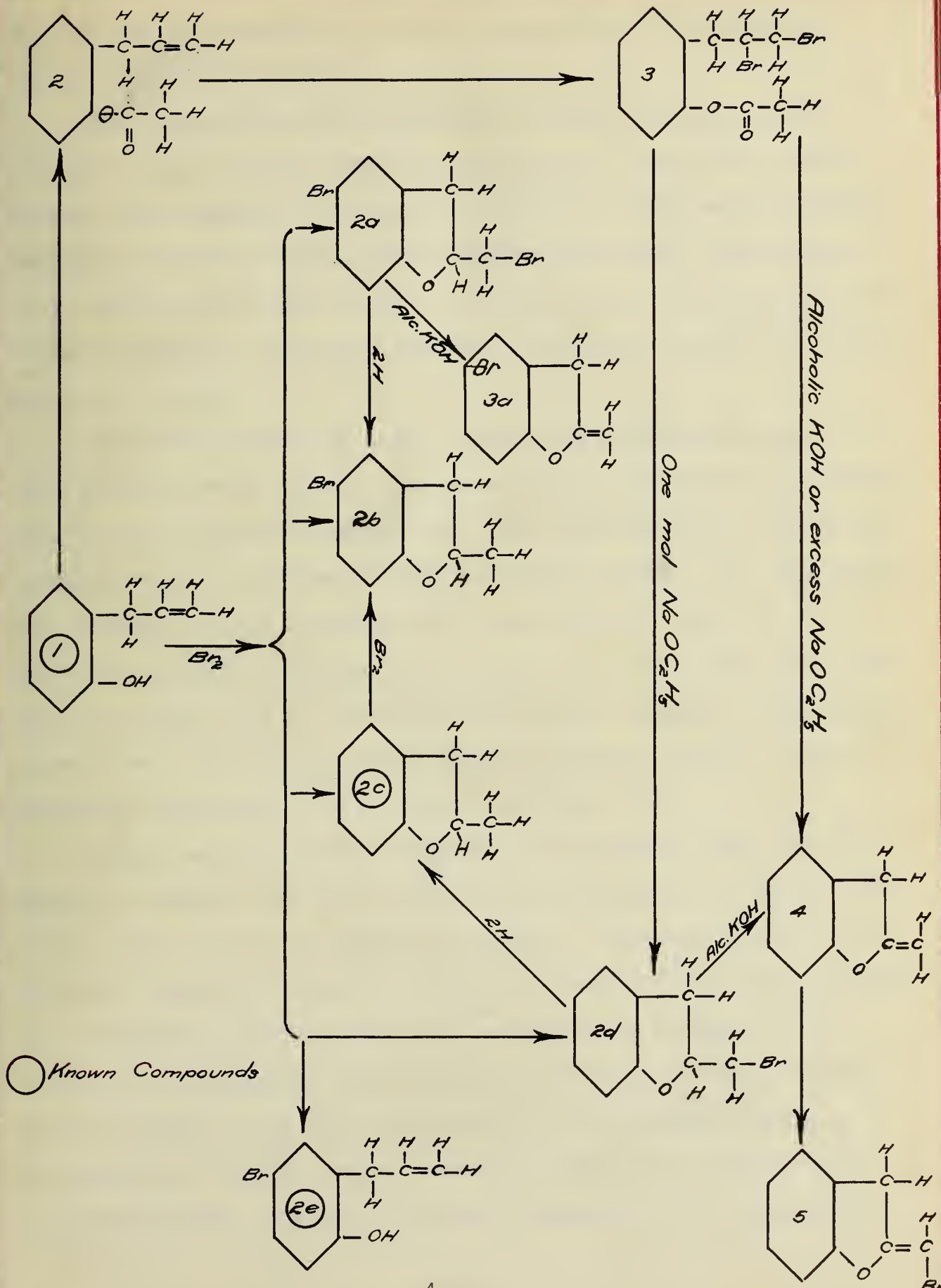
## THEORETICAL DISCUSSION

### GENERAL

Under the direction of Dr. Roger Adams, a new method for the synthesis of the alpha methylene derivatives of a class of compounds called coumaranes has been developed. These compounds have a five membered side ring containing one oxygen atom and are formed by the treatment of the acetyl derivative of b, r, dibrom ortho allyl phenols with alcoholic potash. The experimental work was commenced by Mr. Hubert Moor and Mr. Louis Krug. It was continued by Mr. R. E. Rindfusz, who established the mechanism of the reaction and the proof of structure, an exhaustive account of which is included in his thesis.

To determine whether or not the reaction was general for this type of compounds, it was decided to synthesize methylene coumarane of salicylic acid. This particular compound was chosen, to determine the effect of the carboxyl and ester group, respectively, on the reaction; furthermore it was to be expected that these derivatives of salicylic acid, if not of its methyl ester, would be solids, which would admit of easier and simpler methods of purification than the liquids obtained as derivatives from phenol.

Before discussing the coumarane resulting from salicylic acid and its methyl ester, it may be well to briefly discuss the method by which Dr. Roger Adams and Dr. R. E. Rindfusz proved the structure of the methylene coumarane resulting from phenol.


2
3
2a
Alc. KOH
2H
3a
2b
Br2
One mol NaOC2H5
Alcoholic KOH or excess NaOC2H5
1
OH
2c
2H
Alc. KOH
4
2d
Known Compounds
2e
OH
5
Br

The diagram of compounds shows the mechanism of the reactions and the proof of structure.

The preparation and properties of allyl ether of phenol and ortho allyl phenol have been described. [I] The ortho allyl phenol was converted to the acetyl derivative (by means of acetic anhydride) which on bromination yielded the acetyl derivative of b, r, dibrom ortho allyl phenol. Upon treating this compound with alcoholic potash, the final compound, methylene coumarane of benzene was formed.

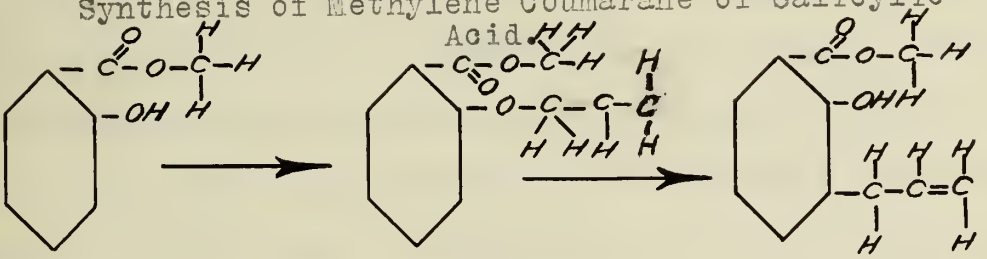
When the free ortho allyl phenol was brominated a series of side products were formed. The monobrom ring substituted compounds, (2a, 2b, 2c, 2d, see diagram) were both reduced with zinc and hydrochloric acid and treated with alcoholic potash. In both cases the residues of the compounds with substituted bromine in the benzene ring were obtained, but it was also found that those that did not reduce, did not react with alcoholic potash. These residues were, respectively alpha methyl coumarane and the alpha methylene coumarane of brom benzene, (2c and 3a).

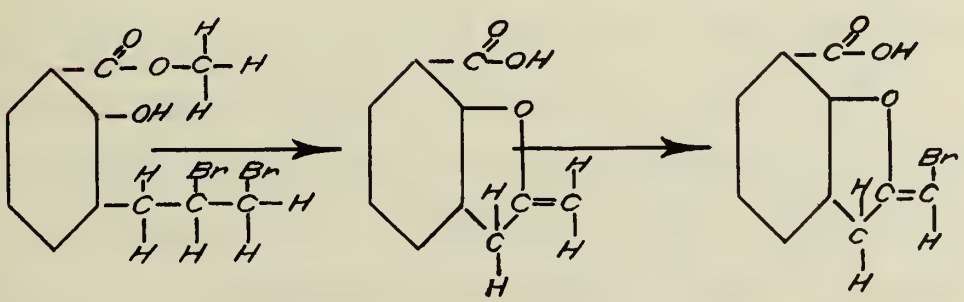
Alpha monobrom methyl coumarane of benzene, (2d), was prepared by treating one mol of the acetyl derivative of dibrom allyl phenol with one mol of sodium alcoholate. This was reduced with zinc and hydrochloric acid, yielding saturated alpha methyl coumarane of benzene, whose properties are in entire agreement with those of the compounds containing a five membered ring with one atom of oxygen [V] and not with those of the compounds having a six membered ring [VI]. This monobrom compound was treated with alcoholic potash or with more sodium alcoholate and alpha meth-

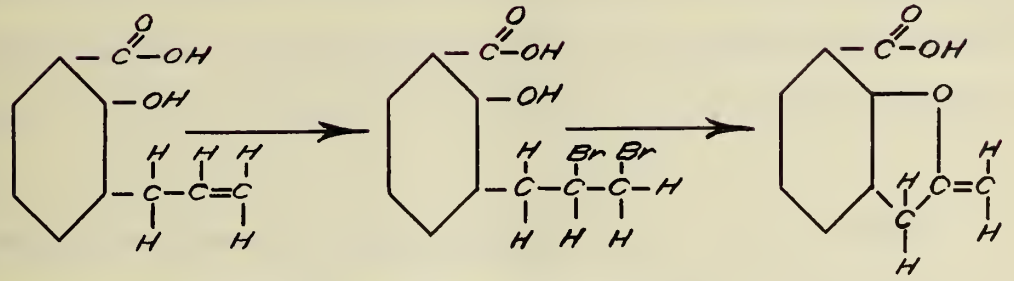
ylene coumarane of benzene, which had been synthesized directly from the acetyl derivative of dibrom ortho allyl phenol, was obtained.

It was expected that the application of this reaction to a derivative of salicylic acid would involve some changes in the nature of the reaction. One would predict that the preparation of the acetyl derivative ortho allyl salicylic acid or its methyl ester would be more difficult due to steric hindrance; and that the bromination should be much cleaner and smoother because the same phenomenon prevents the reaction from proceeding in the usual manner in the case of phenols, i. e. that of the bromine reacting with the phenolic group and then shifting into the para position in the benzene ring.

Synthesis of Methylene Coumarane of Salicylic Acid







Meta allyl salicylic acid methyl ester was prepared according to L. Claissen [I]. The acid was made by saponifying its ester. (Salicylic acid could not be used as a starting point since its ortho allyl ether rearranged to ortho allyl phenol with the loss of the carboxyl group instead of forming the meta allyl salicylic acid). The acetyl derivatives of both the allyl acid and its methyl ester were not formed by long and vigorous action of acetic anhydride. This confirms the predictions and forms a very interesting illustration of the phenomenon of steric hindrance.

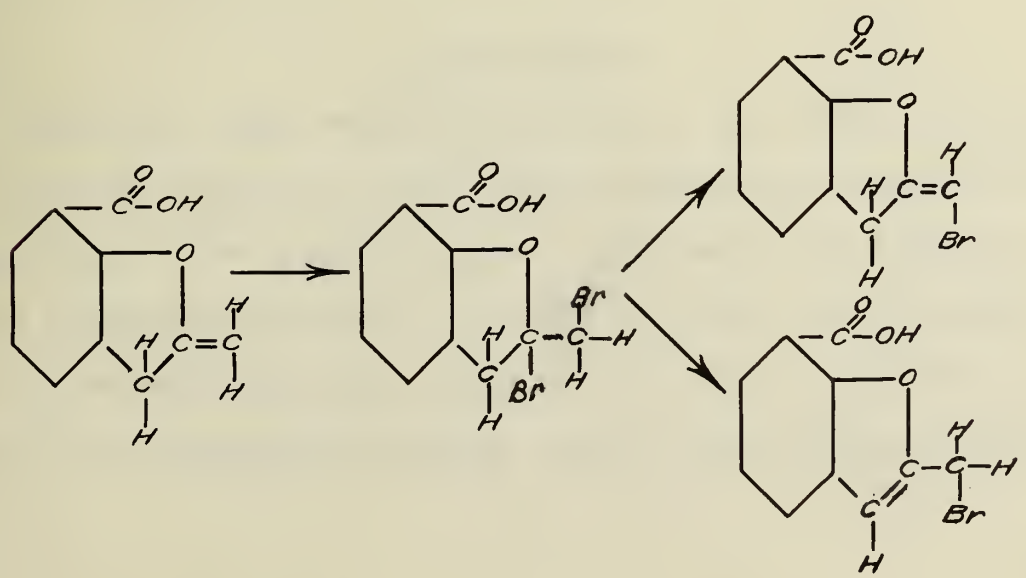
The meta allyl salicylic acid and its methyl ester were brominated in an ice bath. Such conditions are not favorable for bromine substitution in the benzene ring, and in fact, only a mild evolution of hydrobromic acid was noticed in the case of the ester and practically none with the acid. That the product of bromination did not contain substituted bromine in the benzene ring was proven by the fact that, upon treatment with alcoholic potash, the residue gave no test for halogen. This is another case of steric hindrance, the carboxyl as well as the ester group

which cover the phenol radical ortho to the allyl group, prevented, to a large extent, the bromination in the benzene ring and the formation of side products as described in the case of the free phenol.

Methylene coumarane of salicylic acid was prepared in two ways, by refluxing the dibrom allyl salicylic acid and its methyl ester, respectively, with alcoholic potash. This compound gave no test for halogen and no longer responded to the ferric chloride test for the phenol radical.

The analysis checked the theoretical. It is true that one other possibility, namely, a compound having a six membered ring containing an oxygen atom, would possess the same composition but that it is not formed is demonstrated by the mechanism of the reaction and proof of structure of methylene coumarane of benzene.

Furthermore, upon bromination of the methylene coumarane of salicylic acid, a monobrom product was formed which did not react with alcoholic potash or alcoholic silver nitrate.

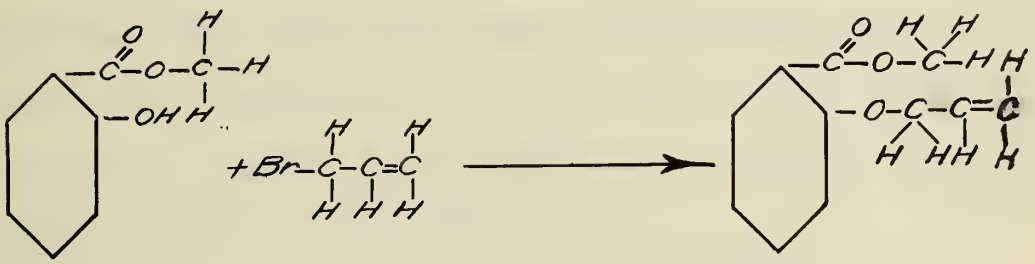


Since our bromine atom added and hydrobromic acid did not split out when the monobrom compound was treated with alcoholic potash, the evidence is conclusive that the bromine atom is attached to the double bonded methylene carbon atom.

## EXPERIMENTAL

### Ortho-Allyl Ether of Salicylic Acid Methyl Ester.

Molar weights of methyl salicylate and allyl bromide, with an excess of anhydrous potassium carbonate and a small quantity of acetone were refluxed on a steam bath for five or six hours gave the ortho-allyl ether of salicylic acid. I



### Purification

Water and ethyl ether were added to the flask containing the reaction products. The potassium salts were separated by siphonation of the aqueous layer. More water was added and 10% sodium hydroxide solution was gradually added from beneath the ether layer with continual shaking, in order to prevent the formation of the tenacious emulsion, which readily forms upon the

addition of concentrated alkali solutions. (The length of time required for the emulsion, if formed, to break, causes a loss in the yield due to saponification of the ester).

When the concentration of the alkali has reached approximately 8 - 10%, a portion of the ether layer was tested with alcohol and ferric chloride for the presence of any phenolic compounds. If none were present, the NaOH liquors were siphoned off and were then replaced by distilled water, and finally washed by siphonation with water till the alkali was removed, when tested with litmus paper.

The ether extract is separated from the water layer in a separatory funnel and dried for a couple of hours over anhydrous calcium chloride. The ether was driven off the ortho-allyl ether on the steam bath. The properties of the ortho-allyl ether of the methyl ester of salicylic acid have been described. [I] B. P. 130°, 10 m.m. Ref. Ind. 1.520, 20°C.

Meta-Allyl Salicylic Methyl Ester

The ortho allyl ether was placed in a flask with an air reflux condenser, attached by a ground glass connection. A thermometer was allowed to dip into the ortho-allyl ether. Heat was gradually applied. (Vapors of allyl bromide were driven off if the product had not been previously distilled). When the temperature reaches 240°C., an exothermic reaction commences and the temperature rises to 270°C and remains constant from four to five minutes. The temperature then begins to fall and the liquid boils

constantly at 260°C. Ref. Ind. 1.538 - 20°C.

The product boils within a range of two to three degrees, with the exception of a small residue which is not collected, it colors ferric chloride deep violet and a yield of 63% of the theoretical, computed from the quantity of methyl ester of salicylic acid used, is obtained. (The rearrangement goes almost quantitatively.)

Treatment of Meta-Allyl Salicylic Acid Methyl Ester with Acetic Anhydride.

One mol, 191 grams, of M-allyl calicylic methyl ester was refluxed for several hours with an excess of acetic anhydride. The excess acetic anhydride and acetic acid, if formed, were distilled off under diminished pressure. 190 grams of product were covered, B. P. 160°- 33 mm. Ref. Ind. 1.538 - 20°C. The experiment has been repeated with the same results. The acetyl derivation had not been formed.

Meta-b,r Dibrom Allyl-Ortho Hydroxy-Methyl Carboxy Benzene.

A molar weight of bromine was gradually added to a mol of m-allyl salicylic acid methyl ester, dissolved in carbon disulfid, with constant shaking. The reaction was cooled by an ice bath.

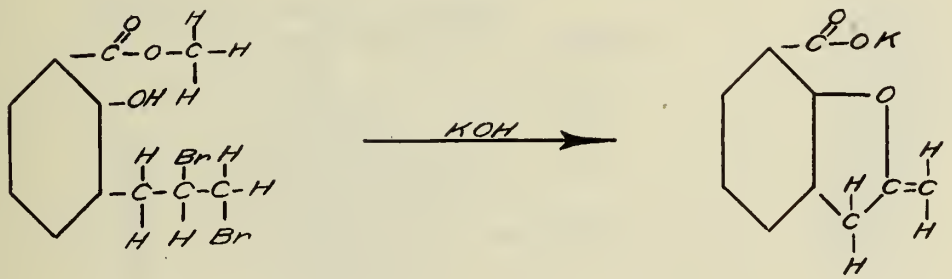
Hydrobromic acid was evolved in small quantities during the addition of the bromine. The carbon disulfid was evaporated off and upon cooling and vigorous stirring, the oily mass solidified and was sucked dry on a funnel. The product crystallized from alcohol. M.P.72.0-72.5°C. white granular crystals.

Analysis.

| Wt. Sample Grams | Wt. Ag.Br. Grams | % Bromine |
|---|---|---|
| 0.1986 | 0.2121 | 45.5 |
| Theoretical | | 45.6 |

(Product could possibly have been ring brominated, but upon treatment with alcoholic potash, gave no test for halogen.)

Methylene Coumarane of Salicylic Acid.




M-dibrom allyl salicylic acid methyl ester was refluxed with an excess potassium hydroxide dissolved in absolute alcohol for three or four hours. The reaction products were diluted with water and the resulting acid was precipitated with hydrocloric acid. M.P. of impure product 144 - 6°C.

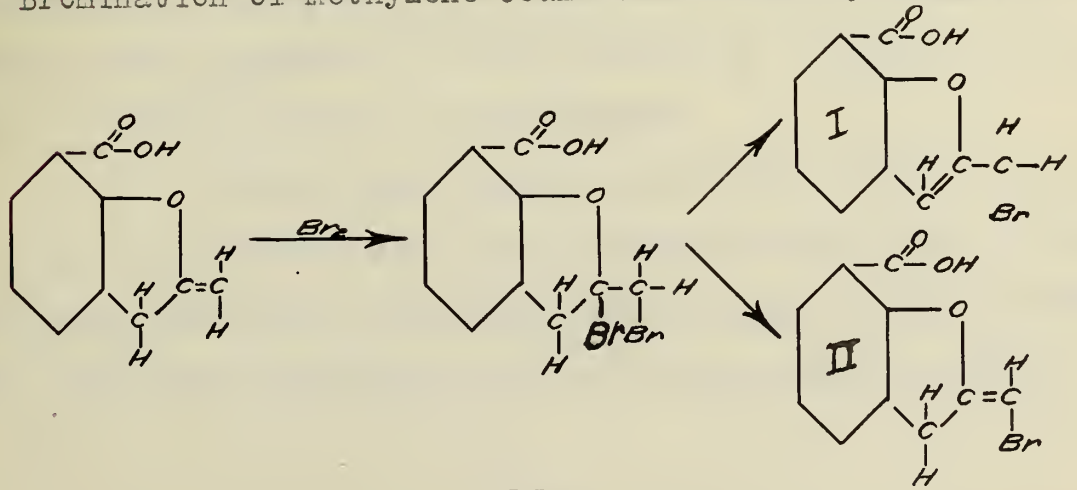
A small portion of the product was dissolved in ether and

allowed to crystalize on a watch glass. Two compounds could be distinguished by their different crystal forms; one which was more soluble in ether than the other. The product was subjected to fractional crystalization. Six crops were obtained from a mixture of ether and petroleum ether. The crystals from the second and third crops melted most sharply, 152-4°C. These two crops were recrystalized from ether and petroleum ether. These white fine crystals melted at 151 - 2°C: and when again recrystallized from ether and petroleum ether melted sharply at 152°C. The product recrystallized from alcohol and water and readily sublimed. (The residue or last crop from the fractional crystallization were yellow crystals of mercaptan or garlic like odor).

Analysis.

| | | |
|---|---|---|
| Weight of sample grams | | 0.2878 |
| " " | $CO_2$ absorbed, grams | 0.7131 |
| " " | $H_2O$ " " | 0.1272 |
| " " | Carbon " | 0.1945 |
| " " | Hydrogen " | 0.0142 |
| % | Carbon found | 67.8 |
| % | Hydrogen " | 4.95 |
| % | Carbon theoretical | 68.2 |
| % | Hydrogen " | 4.55 |

Bromination of Methylene Coumarane of Salicylic Acid.



To 1.5 grams of methylene coumarane of salicylic acid dissolved in ether were gradually added 1.6 g. bromine. The temperature of the reaction was kept at about 0°C. by an ice bath. Such small amounts were used that no hydrobromic acid vapors were noticed. The ether was partly evaporated off and crystals separated out. The crude crystals melted with decomposition at 216°C.

The product recrystallized from ether and petroleum ether. White needle like crystals melted with some decomposition, at 218-220°C. Crystallizing again, compound melted without decomposition at 222-3°C.

Analysis.

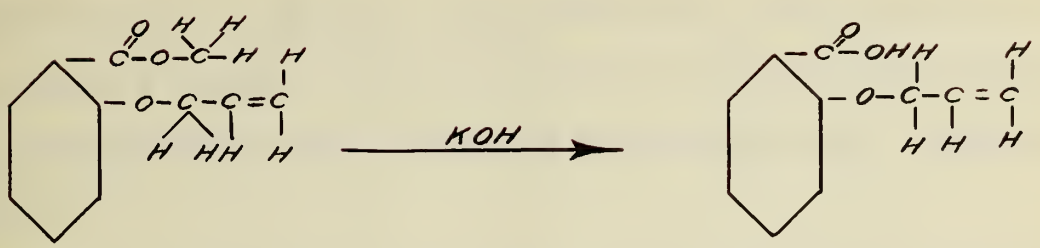
| Wt. Sample grams | Wt. AgBr grams | % Bromine |
|---|---|---|
| 0.1630 | 0.1261 | 32.9 |
| Theoretical | | 31.4 |

Properties.

The brominated product of methylene coumarane of salicylic acid was treated with alcoholic potash, no KBr separated out; it was also treated with alcoholic silver nitrate, and the reaction by no means was complete for, if any, only traces of AgBr were precipitated. Since HBr is so difficult to split out, it is very probable that compound II is the one formed, because of the difficulty to form a tripple bonded carbon.

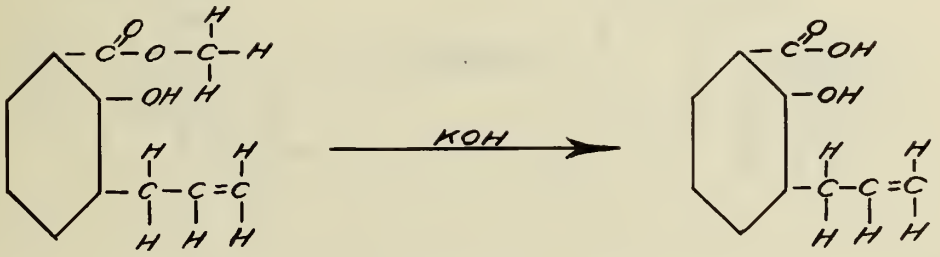
Ortho allyl ether of Salicylic Acid.

To be absolutely sure that the ortho allyl ether of salicylic acid methyl ester had rearranged to meta allyl salicylic methyl ester, both were saponified and their melting points taken.




½ mol .48 grams of ortho allyl salicylic acid methyl ester, Ref. Ind. 1.520, was refluxed with 20 grams of KOH and sufficient 95% alcohol to hold reaction mixture in solution. The product was precipitated from the reaction products by the addition of hydrochloric acid and recrystallized by cooling a hot solution of alcohol and water which was saturated in respect to the ether acid. The ortho allyl salicylic acid crystals are shiny flakes which melt at 64°C. Schichilone, gives the melting point as 113°C. [II] The melting point is given by Cohen and Dudley, also L. Claissen.[III]

Meta-Allyl Salicylic Acid.




59 grams of m-allyl salicylic acid methyl ester, Ref. Ind. - 1.355, dissolved in 300 cc. of absolute alcohol, were refluxed with 25 grams of potassium hydroxide. After a couple of hours, the

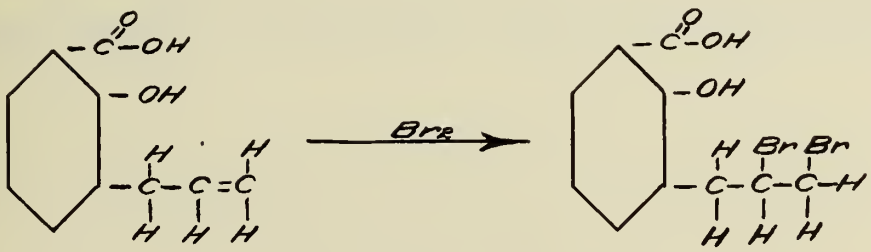
saponification was complete. The product was precipitated by diluting the alcohol solution with water and by adding hydrocloric acid. It was recrystallized from ether and petroleum ether: melted at 93°C. IV

Treatment of Meta-Allyl Salicylic Acid with Acetic Anhydrid.

102 grams of m-allyl salicylic acid were refluxed with 25 grams acetic anhydrid for five hours. The excess acetic anhydrid and acetic acid, if formed, were distilled off at a pressure of 25 m.m. The oily residue was washed with water four or five times which, upon standing, solidified.

The product was crystallized from water and melted at 93°C. Sublimed product melted at 94°C. Colored ferric chloride solution violet. The acetyl derivitative of m-allyl salicylic acid was not formed.

Meta b,r, Dibrom Allyl Salicylic Acid.




24 grams of m-allyl salicylic acid were dissolved in carbon disulfid. 21.6 grams of bromine were gradually added, with shaking, at the temperature of an ice bath. The bromination was smooth and

hardly any hydrobromic acid given off. At first the product crystallized out in the carbon disulfid to such an extent, so that it was necessary to add some ether to hold the reaction mixture in solution. About one-half of the carbon disulfid and ether was evaporated off and product was precipitated and then sucked dry on a filter. Crude product M.P. 160-161°C. crystallized from ether and carbon disulfid M.P. 162-64°C. and white needle like crystals, which also crystallize from alcohol and water were recrystallized from ether and carbon disulfid M.P. 162.5 - 163.5°C.

Analysis.

| Wt. of sample grams | Wt. of AgBr grams | % Bromine |
|---|---|---|
| 0.3438 | 0.3838 | 47.4 |
| Theoretical | | 47.35 |

Methylene Coumarane Salicylic Acid from meta b,r, Dibrom Allyl Salicylic Acid.

10 grams Dibrom allyl salicylic acid dissolved in absolute alcohol was refluxed with potassium hydroxide for four hours. The product was purified as described before M.P. 151 Mixed M.P. 152°.

The writer wishes to acknowledge his indebtedness to Dr. Roger Adams and Mr. R. E. Rindfusz for the interest shown and the helpful suggestions made during the progress of this investigation.

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# B I B L I O G R A P H Y


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II. Schichilone Gazzetta Chimica Italiana 12, 449

III. Cohen and Dudley. Journal of the Chemical Society 97, 1745

L. Claissen, Berichte der Deutschen Chemischen Gesellschaft. 1912, 45, 3165.

IV. L. Claissen. Ibid

V. Chemisches Central-blatt 1914, IV, 1213.

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