**2-Hydroxy-3-allyl Benzoic Acid,** $C_6H_3(COOH)^1(OH)^2(C_3H_5)^3$.—This compound is obtained by the saponification of its methyl ester. 59 g. of the 2-hydroxy-3-allyl-methyl benzoate is dissolved in 300 cc. of absolute alcohol and refluxed for about two hours with 25 g. of potassium hydroxide. The solution is then diluted with water and the product precipitated by the addition of hydrochloric acid. After recrystallization from ether and petroleum ether it melts at 93°.

Upon treatment with acetic anhydride, this compound is recovered unchanged.

**2-Hydroxy-3-allyl-benzoic-acid Dibromide,** $C_6H_3(COOH)^1(OH)^2(C_3H_5Br_2)^3$.—24 g. of the 2-hydroxy-3-allyl-benzoic acid just described is dissolved in carbon disulfide and 21.8 g. of bromine gradually added, the temperature being held near 0°. The product crystallizes out and is filtered with suction. After recrystallization from ether and carbon disulfide, the product is in the form of white needles, m. p. 162.5–163.5°.

Subs., 0.3438: AgBr, 0.3838.
Calc. for $C_{10}H_{10}O_3Br_2$: Br, 47.35. Found: 47.40.

On refluxing this with alcoholic potash *o*-carboxy-$\alpha$-methylene coumarane results identical with the product obtained by the action of alcoholic potash on the 2-hydroxy-3-allyl-methyl benzoate.

## Summary.

1. *o*-Allyl phenols are converted readily to $\alpha$-methylene coumaranes by the following succession of reactions: (1) acylation, (2) bromination, (3) treatment with alcoholic potash.

2. Proof of the structure of $\alpha$-methylene coumarane obtained from *o*-allyl phenol was accomplished by step-wise decomposition of the acetyl-*o*-allyl-phenol dibromide and proof of the structure of the intermediate products. Additional proof resulted from the direct bromination of *o*-allyl phenol.

3. Bromination of $\alpha$-methylene coumarane yields $\alpha$-bromo-methylene coumarane.

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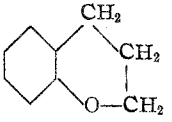
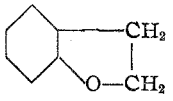
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS.]

# SYNTHESES OF CHROMANES AND COUMARANES.

BY R. E. RINDFUSZ.

Received January 8, 1919.

Although chromane  and coumarane  have been known for a number of years, there has never been a convenient method for their preparation, and only a very few of their derivatives

with substitutions in the benzene ring have been made. The present investigation was undertaken to furnish methods for their synthesis which should be both simple and general.

Chromane was first prepared by Von Braun and Steindorff.[1] During their studies on the splitting of nitrogen ring compounds, they treated tetrahydro-quinoline with benzoyl chloride and phosphorus pentachloride and obtained γ-chloro-*o*-propyl aniline, $C_6H_4(NH_2)(CH_2CH_2CH_2Cl)$. This they diazotized to replace the amino group by an hydroxyl and then closed the ring by means of alkali, giving chromane. The inconveniences of this method are obvious. The following year Semmler,[2] using his general method of converting lactones to glycols, reduced coumarin with sodium and alcohol to *o*-γ-hydroxy-propyl phenol, $C_6H_4C_3H_2O_2 \longrightarrow C_6H_4(OH)(CH_2CH_2CH_2OH)$. The dehydration to produce chromane was brought about by treatment with sulfuric acid or alcoholic hydrogen chloride in a bomb. These two are the only methods of preparation of chromane so far published. However, α-methyl chromane has twice been synthesized, each time through *o*-γ-hydroxyl-butyl phenol, $C_6H_4(OH)(CH_2.CH_2.CHOH.CH_3)$. Harries and Busse[3] condensed salicylic aldehyde with acetone and reduced the product with sodium amalgam to give the saturated ketonic phenol.

$$C_6H_4(OH)CH{:}CH.CO.CH_3 \longrightarrow C_6H_4(OH)^1(CH_2.CH_2.CO.CH_3).^2$$

Further reduction with zinc and hydrochloric acid changed the group to an alcohol which at once reacted to form methyl chromane

$$C_6H_4(OH)^1(CH_2.CH_2.CO.CH_3)^2 \longrightarrow C_6H_4(OH)^1(CH_2.CH_2CHOH.CH_3)^2 \longrightarrow C_6H_4\underbrace{CH_2.CH_2.CH(CH_3)\text{—}O}.$$

Stoermer[4] prepared and isolated this intermediate alcohol phenol by reducing α-acetyl coumarone and then closed the ring by means of alcoholic hydrogen chloride.

The work on coumaranes has been as meager as that on chromanes. Stoermer and Gohl[5] synthesized the parent substance by treating *o*-bromo-sodium phenolate with one molecule of ethylene bromide and then adding sodium. $C_6H_4(Br)^1(OCH_2CH_2Br)^2 + 2Na = 2NaBr + C_6H_4\underbrace{CH_2CH_2O}$. They also prepared the derivatives with one and with two methyl groups in the benzene ring. Alexander[6] had previously

[1] *Ber.*, **38**, 855 (1905).
[2] *Ibid.*, **39**, 2856 (1906).
[3] *Ibid.*, **28**, 501 (1895).
[4] *Ber.*, **36**, 2870 (1903).
[5] *Ibid.*, **36**, 2873 (1903).
[6] *Ibid.*, **25**, 2409 (1892). For explanation of the reaction see Stoermer, *Ibid.*, **34**, 1806 (1901).

obtained the same substance together with *o*-ethyl phenol by the reduction of coumarone,

$$C_6H_4CH = CH - O \longrightarrow C_6H_4.CH_2.CH_2O.$$

In addition to these two methods for the synthesis of coumarane, there are recorded two instances where derivatives of the parent substance were produced. Claisen[1] heated *o*-allyl phenol with pyridine hydrochloride and so prepared $\alpha$-methyl coumarane, while Fries and Moskopp[2] by treating *o*-1,2-dibromo-ethyl phenol with sodium acetate and acetic acid obtained a $\beta$-acetyl derivative. A number of methylene coumaranes have recently been reported by Adams and Rindfusz.[3]

In the present investigation, three successful methods have been found for the synthesis of either chromane or coumarane.

I. Trimethylene-glycol-monophenyl ether or ethylene-glycol-monophenyl ether, which are easily prepared from the corresponding chlorohydrine and sodium phenolate, is heated with zinc chloride.

$$C_6H_5O.CH_2.CH_2.CH_2OH \longrightarrow C_6H_4CH_2CH_2CH_2O.$$

$$C_6H_5OCH_2.CH_2OH \longrightarrow C_6H_4CH_2CH_2O.$$

II. $\beta$-bromo-ethyl-phenyl ether and $\gamma$-bromo-propyl-phenyl ether are converted into cyclic ethers by the action of zinc chloride.

$$C_6H_5O.CH_2.CH_2.CH_2Br \longrightarrow C_6H_4.CH_2.CH_2.CH_2O.$$

$$C_6H_5OCH_2.CH_2Br \longrightarrow C_6H_4CH_2.CH_2O.$$

III. Free phenol when heated with ethylene or trimethylene chlorohydrine and zinc chloride gives coumarane or chromane as the case may be. The third method gives but poor yields, while those from I are 30–35% and from II, 50–65% of the theoretical amount. Preliminary tests on the substitution of aluminum chloride for the zinc salt seem to indicate that it is not as satisfactory.

The mechanism which naturally suggests itself as an explanation of the formation of cyclic ethers from glycol-phenol ethers is a simple dehydration. There is, however, some reason for questioning this. Such eliminations of water between an alcoholic group of a side chain and a hydrogen of the benzene ring, if known at all outside of the enolic forms of aldehydes and ketones, are certainly not common; and a dehydration to form an ethylene compound might be expected to take place more easily. From the products obtained, there was no evidence that any part of the reaction went in this direction.

[1] *D. R. P.* 279,864; *Chem. Zentr.*, [2] 1914, p. 1213.

[2] *Ann.*, **372**, 197 (1910).

[3] THIS JOURNAL, 41, 648 (1919).

A possible alternative which might be considered is that the action takes place in two steps: First, due to the effect of zinc chloride, the alcoholic group is replaced by chlorine. Second, a reaction similar to that of Friedel and Crafts takes place giving the final product. This explanation is suggested by the second method of preparation of the cyclic ethers, where the γ-bromo-propyl-phenyl ether is treated with zinc chloride. Since there is only one step in this process, the halogen already being in place, better yields would be expected and are really obtained than from the glycol-phenyl ether. The objection to this hypothesis is that there appears to be no evidence that a halogen compound can be prepared from an alcohol by treatment with zinc chloride.

The third method of preparation is explained by assuming that under the influence of the zinc chloride an ether is formed by the phenol and the chlorohydrine, the action then proceeding as above. As would be expected, the yield by this method is less than that by either of the other two.

The advantages of the present syntheses are obvious. The materials used are all quite common and easily obtained; the reactions are simple and quickly carried out. By the older methods almost no substituted chromanes or coumaranes were prepared because of the complexity of the necessary substances. This difficulty does not apply to the present processes, so by using different phenols it should be possible to prepare a large number of such compounds. Work on these is now being carried on and will be reported in a later paper. These reactions are also being applied to the preparation of other types of cyclic ethers.

## Experimental.

**γ-Hydroxy-propyl-phenyl Ether,** $C_6H_5O.CH_2.CH_2.CH_2OH$.—This compound has previously been prepared by Lohmann[1] by treating the corresponding amino ether with nitrous acid. It is, however, very easily prepared as follows: 23 g. of sodium is dissolved in absolute alcohol and a mole of phenol added. This is then treated with a mole of trimethylene chlorohydrine and refluxed for three hours on the steam bath. Most of the alcohol is then distilled off, water is added and the product extracted with ether. This extract is then washed with 10% sodium hydroxide solution and with water, dried over potassium carbonate and distilled. The product is a clear oil boiling at 158–160° at 25 mm. $[n]_D^{20}$ 1.491. Yield, 75%.

**Chromane from γ-Hydroxy-propyl-phenyl Ether.**—The ether just obtained is heated under a reflux with $^1/_{10}$ its weight of fused zinc chloride. When the temperature reaches 210–215°, a vigorous reaction begins and the temperature drops rather quickly to 185–190°. It is heated for 20 to 30 minutes longer allowed to cool and then fractionally distilled. How-

[1] *Ber.*, 24, 2635 (1891).

ever, during the reaction there is often a considerable amount of tar formed, in which case it is best to take the mixture up in ether, wash with sodium hydroxide solution and with water, dry over calcium chloride and distil. After fractionating from unchanged γ-hydroxy-propyl-phenyl ether, the chromane is obtained in 30 to 35% yields as a clear oil boiling at 98–99° at 18 mm., 214° at 742 mm., $[n]_D^{20}$ 1.544, $d_{20}$ 1.0610. The constants given by Semmler[1] are b. p. 93.5° at 8 mm., $d_{22}$ 1.0587, $[n]_D$ 1.544, while von Braun and Steindorf[2] give 214–215° as the boiling point.

Aluminum chloride was substituted for zinc chloride in two runs. The product was obtained, but the reaction did not seem to go as well and its use was discontinued.

**Chromane from γ-Bromo-propyl-phenyl Ether.**—The γ-bromo-propyl-phenyl ether is prepared by treating sodium phenolate with an excess of trimethylene bromide after the method of Salonina.[3] This is then heated under a reflux with $^1/_{10}$ its weight of fused zinc chloride. A vigorous action starts at about 200° and volumes of acid fumes are evolved. The heating is continued until these fumes have practically ceased. The product is then taken up in ether, washed with sodium hydroxide and water, dried and distilled. Yield, 65%. The properties agree with those given above and the product is more easily purified.

**Chromane from Phenol and Trimethylene Chlorohydrine.**—50 g. of phenol is heated for about 2.5 hours with an equal weight of trimethylene chlorohydrine and 12 g. of zinc chloride. The mass is then taken up in ether, washed with sodium hydroxide and with water, dried and distilled. The yield is 15–22 g. of a somewhat impure product.

**Coumarane from β-Hydroxy-ethyl-phenyl Ether,** $C_6H_5O.CH_2CH_2OH$.—This ether is prepared in 50% yields from sodium phenolate and ethylene chlorohydrine as described by Bentley, Haworth, and Perkin.[4] It is a colorless liquid boiling at 134–5° at 18 mm., $[n]_D^{20}$ 1.534, $d_{22}$ 1.102.

50 g. of this ether is heated for 5 hours with 5 g. of zinc chloride. The temperature goes at first to 225° and then slowly drops to 190°. The product may be distilled directly and boils at 88–90° at 18 mm. Yield 25%, $d_{24}$ 1.0576, $[n]_D^{20}$ 1.543. The constants given by Stoermer and Göhl[5] are b. 188–189°, $[n]_D^{19}$ 1.542, $d_{19}$ 1.0571.

**Coumarane from Phenol and Ethylene Chlorohydrine.**—One-third of a mole each of phenol and of ethylene chlorohydrine are refluxed for 4 hours with 8 g. of zinc chloride. The product is taken up in ether, washed with sodium hydroxide and with water, dried and distilled. Yield, 5 g.

[1] *Ber.*, 39, 2856 (1906).
[2] *Ibid.*, 38, 855 (1905).
[3] *Ibid.*, 26, 2987 (1893).
[4] *J. Chem. Soc.*, 69, 164 (1896).
[5] *Ber.*, 36, 2873 (1903).

**Coumarane from β-Bromo-ethyl-phenyl Ether.**—The β-bromo-ethyl phenyl ether is prepared by treating sodium phenolate with an excess of ethylene bromide, following the method of Weddige.[1] On treating this with $^1/_{10}$ of its weight of zinc chloride, the reaction is not so vigorous as in the analogous formation of chromane and two hours' heating is necessary. The product may then be distilled directly in 30–40% yields.

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[CONTRIBUTION FROM THE CHEMICAL RESEARCH LABORATORY, THE UPJOHN COMPANY.]

## THE PROTEIN EXTRACT OF RAGWEED POLLEN.

BY FREDERICK W. HEYL.

Received January 16, 1919.

In a previous communication[2] from this laboratory the proximate analysis of ragweed pollen was reported. The distribution of the nitrogen was particularly sought in order to have more precise information concerning the proper quantitative composition of pollen antigen, as required for immunization work. It became apparent at once that a very considerable quantity of nonprotein nitrogen was present, and in view of the possibility of an active base being present the investigation was extended for the purpose of isolating not only the proteins but also these bases.

The presence of agmantin which was found may have some bearing on the hay fever problem because of the possibility of a similarity which it may possess with β-iminazolylethylamine. The latter is known to produce asphyxia in guinea pigs with anaphylactic shock. This similarity is quite doubtful however, and the nature of the hexone bases isolated does not cause the protein fraction to appear less incriminated in the production of hay fever. The preparation of protein antigen as usually conducted appears entirely rational. In the opinion of the writer it remains for some large hay fever clinic to test out the various proteins, especially the proteose, and determine which of them may be responsible for hay fever. This proteose is unstable and becomes insoluble on preserving so that a very close coöperation must exist between the clinicians and those doing the chemical work. The writer intends to analyse by the Van Slyke method the preparations herein described, and regrets the insurmountable difficulties which have prevented the satisfactory clinical study of the products obtained.

Kamman[3] holds the view that the substance (toxin) which produces the peculiar pollen reaction, *e. g.*, the ophthalmic reaction, is not due to the albumin itself, but to a closely associated substance. This is paral-

[1] *J. prakt. Chem.*, [2] **24**, 242 (1881).

[2] THIS JOURNAL, **39**, 1470 (1917).

[3] *Biochem. Z.*, **46**, 151 (1912).