

[CONTRIBUTION FROM THE KEDZIE CHEMICAL LABORATORY, MICHIGAN STATE COLLEGE]

**ACTION OF AROMATIC ALCOHOLS ON AROMATIC COMPOUNDS  
IN THE PRESENCE OF ALUMINUM CHLORIDE. V.  
BENZYLATION OF ORTHO-CRESOL**

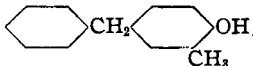
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In September, 1923, an investigation was started in this Laboratory on the condensation of benzyl alcohol and *o*-cresol in the presence of aluminum chloride. The main product of the reaction crystallized as hard flattened needles which melted at 49.5–50.5° and gave analytical results which indicated a formula of C<sub>14</sub>H<sub>14</sub>O.

Holleman's amplification of the Beilstein rule<sup>1</sup> would predict that the entering benzyl group would take a position ortho or para to the phenolic hydroxyl. In order definitely to prove this, the compound was heated in a closed tube with Zn(NH<sub>3</sub>)Cl<sub>2</sub>. The resulting amine was diazotized and reduced to the hydrocarbon, which was finally oxidized to *m*-benzoylbenzoic acid.

Our work with the condensation of primary and secondary aromatic alcohols with phenol,<sup>2</sup> as well as the work of Rennie,<sup>3</sup> Gattermann<sup>4</sup> and others with similar reactions, led us to assume that the product containing the benzyl group in the para position to the phenolic hydroxyl would predominate and we tentatively assigned the formula 

Final proof of this structure was found in the preparation of the isomeric 1-methyl-6-benzylphenol by the Claisen method, as described later in this article.

We were able to isolate from the petroleum ether mother liquor from which the 2-methyl-4-benzylphenol was crystallized a small amount of crystalline material which came down in bundles of very fine needles with a soft silky sheen. A melting point determination gave the rather surprising results of 49.5–50.5°.

A higher-boiling fraction of the reaction product came over after repeated fractionation at 225–227° (5 mm.) as a yellow oil from which we were unable to obtain crystals. Analysis gave results indicating a dibenzyl derivative of *o*-cresol, C<sub>21</sub>H<sub>20</sub>O. Because of the powerful directing influence of the phenolic hydroxyl and the behavior of the compound toward strong alkali, we have called it 2-methyl-4,6-dibenzylphenol.

<sup>1</sup> Holleman, *Chem. Rev.*, 1, 187 (1924).

<sup>2</sup> Huston, *THIS JOURNAL*, 46, 2775 (1924); 49, 1366 (1927).

<sup>3</sup> Rennie, *J. Chem. Soc.*, 41, 37 (1882).

<sup>4</sup> Gattermann, *Ber.*, 22, 1129 (1889); 23, 1199 (1890).

Upon application of the Claisen<sup>5</sup> method of benzylation to *o*-cresol, we obtained a good yield of a benzylated derivative which was identical in melting point, boiling point, solubility and crystal appearance with the compound which we obtained from the mother liquors of the main product of the aluminum chloride condensation. Besides the 2-methyl-6-benzylphenol, the Claisen process gave a smaller amount of 2-methylphenyl benzyl ether. The *o*-methyl group of the cresol precluded the formation of a di-*o*-dibenzyl derivative.

A short time after the experiment just described had been completed, Schorigin<sup>6</sup> published a description of the benzylation of *o*-cresol by the Claisen method. He stated that 2-methyl-6-benzylphenol melted at 51–52° and boiled at 182–188° (15 mm.).

A comparison of the physical properties of the two monobenzyl derivatives (both of which melt at 49.5–50.5°) brings out some rather striking differences, aside from the difference in appearance of the crystals.

2-Methyl-4-benzylphenol dissolves readily in the calculated amount of dilute potassium hydroxide (5%), is soluble in eighty-seven parts of petroleum ether (40–60°) at 20° and boils at 167–169° (5 mm.).

2-Methyl-6-benzylphenol is insoluble even in a large excess of dilute potassium hydroxide (5%). It dissolves when warmed in the equivalent amount of strong potassium hydroxide (50%), but separates out when an equal volume of water is added. It is soluble in 18.2 parts of petroleum ether at 20°. Its boiling point is seventeen degrees lower than that of its isomer.

The monobromo derivatives of the two monobenzyl cresols were prepared by treating them in chloroform solutions with the calculated amounts of bromine. In the case of 2-methyl-4-benzylphenol we assumed that the bromine entered the phenolic ring in the only available ortho or para position with the formation of 6-bromo-2-methyl-4-benzylphenol.

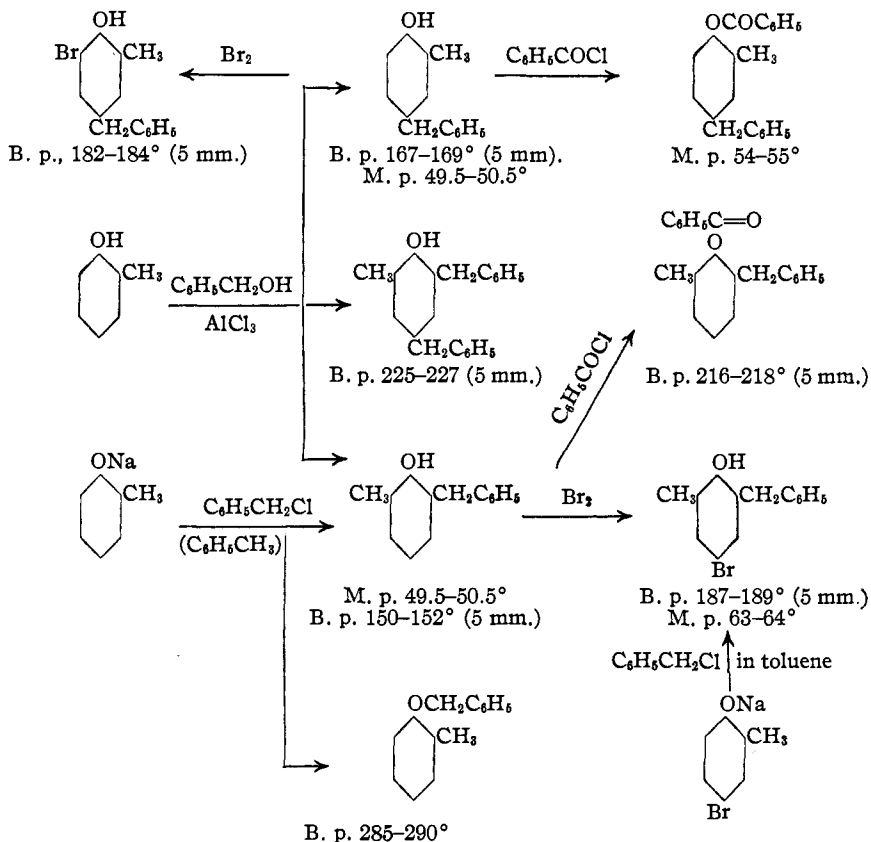
Making the same assumption, 2-methyl-6-benzylphenol would give 4-bromo-2-methyl-6-benzylphenol. In this last case we were able to prove the validity of the assumption by benzylating 2-methyl-4-bromophenol by the Claisen method to obtain the same product that was formed by the bromination of 2-methyl-6-benzylphenol. This gives additional proof of the structure of the last-named compound.

The two monobenzyl derivatives were further characterized by the preparation of their benzoyl derivatives. It is worthy of note that the 2-methyl-6-benzylphenol in which both ortho positions are occupied reacted much less readily under the Schotten-Baumann treatment than did the isomeric 2-methyl-4-benzylphenol.

The following is a graphic outline of the field covered.

<sup>5</sup> Claisen, *Ann.*, **442**, 221 (1924).

<sup>6</sup> Schorigin, *Ber.*, **58B**, 2033 (1925).



### Experimental

**Benzyl Alcohol and *o*-Cresol with Aluminum Chloride.**—A mixture of 100 g. of *o*-cresol, 100 g. of benzyl alcohol and 200 g. of petroleum ether (40–60°) was placed in a tall vessel, surrounded by water and stirred mechanically while 65 g. of anhydrous aluminum chloride was added in small portions over a period of an hour. The temperature was maintained at 30–35°. At times troublesome frothing occurred which was controlled by the addition of further portions of cold petroleum ether. When the evolution of hydrogen chloride had nearly ceased, the mixture was allowed to stand overnight. The brown semi-solid intermediate product was decomposed with ice and a little hydrochloric acid and extracted with ether. The ether extract was dried over potassium carbonate, the ether distilled off and the residue fractionated under reduced pressure.

#### Fifth fractionation (5 mm.)

90–150°	12.2 g.
150–170°	51.5 g.
170–215°	3.3 g.
215–235°	26.2 g.
Residue	13.5 g.

The first fraction was crude *o*-cresol.

The second fraction (150–170°) crystallized. The crystals were pressed between filter papers and recrystallized repeatedly from petroleum ether. The purified compound melted at 49.5–50.5° and boiled at 167–169° (5 mm.). It crystallized in clusters or rosetts of fine brittle needles. Two 50-cc. portions of a solution of purified crystals in petroleum ether (40–60°) at 20° gave on evaporation 0.5715 g. and 0.5743 g. of residue.

*Anal.* Subs., 0.523: CO<sub>2</sub>, 0.4746; H<sub>2</sub>O, 0.0971. Calcd. for C<sub>14</sub>H<sub>14</sub>O: C, 84.8; H, 7.12. Found: C, 84.99; H, 7.19.

The filter papers which were used to remove the oily impurity from these crystals were extracted with ether and the ether extract was distilled. Two and one-half grams came over at 150–155° (5 mm.). This crystallized when seeded with 2-methyl-6-benzylphenol (see p. 4488) and was further identified by bromination and by its benzoyl derivative.

The 215–235° fraction was repeatedly distilled until most of it came over at 225–227° (5 mm.). All attempts to induce this oil to solidify failed. It is insoluble in dilute potassium hydroxide. In hot 50% potassium hydroxide it changed to a blue, gummy mass, but did not dissolve. Its ready solution in Claisen's alcoholic potassium hydroxide proved it to be a phenol. Its failure to absorb bromine readily when dissolved in chloroform indicated that all positions ortho and para to the phenolic hydroxyl were occupied and justified the assignment of the structure 2-methyl-4,6-dibenzylphenol.

*Anal.* Subs., 0.2147: CO<sub>2</sub>, 0.6861; H<sub>2</sub>O, 0.1343. Calcd. for C<sub>20</sub>H<sub>21</sub>O: C, 87.45; H, 7.00. Found: C, 87.62; H, 7.01.

**4-Amino-3-methyl-diphenylmethane.**—The phenol which formed the bulk of the 150 to 170° fraction (b. p. 167–169°) was mixed thoroughly in a mortar with twice its weight of zinc ammonia chloride and one-fifth its weight of ammonium chloride. The mixture was sealed in Carius tubes (care being taken not to fill each tube more than one-quarter full) and heated in a bomb furnace for twenty hours at 330°.

The reaction product was thoroughly shaken with hydrochloric acid (1:1), allowed to stand overnight and extracted with ether to remove the unchanged phenol. The acid solution was just neutralized with ammonium hydroxide and then treated with dilute sodium hydroxide to precipitate the amine. This came down as very fine light brown plates and was not further purified. Five grams was obtained from 50 g. of phenol.

**Preparation of 3-Methyldiphenylmethane and *m*-Benzoylbenzoic Acid.**—Five grams of 4-amino-3-methyldiphenylmethane was dissolved in 15 g. of hydrochloric acid (sp. gr. 1.2) and diluted with 30 cc. of water. Sodium nitrite was added (in 10% solution) until a positive test for nitrous acid was obtained with starch-iodide paper. The solution of diazonium chloride was added slowly to a well-cooled solution of 10 g. of sodium hydroxide in 30 cc. of water and reduced in the cold with sodium stannite (prepared from 20 g. of stannous chloride). Extraction with ether gave 0.6 g. of 3-methyldiphenylmethane boiling at 274–276°. <sup>7</sup> This was oxidized by means of potassium dichromate and sulfuric acid to *m*-benzoylbenzoic acid melting at 142–144°. <sup>8</sup>

**Benylation of *o*-Cresol by the Claisen Method.**—Twelve grams of sodium was melted under 130 cc. of toluene and shaken to produce "bird-shot" sodium. After cooling to room temperature, this was treated with 54 g. of *o*-cresol. The reaction appeared to be complete at the end of two hours, but the mixture was gently heated for another hour under a reflux condenser. The flask was again cooled and 64 g. of benzyl chloride was added. After standing overnight, the mixture was refluxed on an oil-bath for five hours at 150–160°. When cool, the sodium chloride was removed by washing

<sup>7</sup> Ador and Rilliet, *Ber.*, 12, 2300 (1879).

<sup>8</sup> Senff, *Ann.*, 220, 237 (1883).

twice with water and the toluene was removed by distilling until the temperature reached 125°.

The residue was dissolved in 250 cc. of Claisen's alcoholic potash<sup>9</sup> and shaken out with 200 cc. of petroleum ether (40–60°) in 50-cc. portions. Distillation of the petroleum ether extract gave 16 g. of 2-methylphenylbenzyl ether boiling at 285–290°.<sup>10</sup>

The alcoholic solution left after extraction with petroleum ether was made distinctly acid with hydrochloric acid (1:1), diluted until the potassium chloride first formed was redissolved, and extracted three times with ether. Distillation of the ether left a reddish-brown oil, which was fractionated three times at 5 mm. Seventy-one grams came over at 140–160°, and solidified in the receiver. Repeated recrystallization from petroleum ether gave long white needles or fibers with a soft silky sheen which showed a tendency to form in bundles or a felted mass. The pure compound melted at 49.5–50.5° and boiled at 150–152° (5 mm.) or at 187–189° (15 mm.). This melting point differs from that recorded by Schorigin<sup>11</sup> for 2-methyl-6-benzylphenol by 1.5°. Two 50-cc. portions of a solution of the purified crystals in petroleum ether saturated at 20° gave on evaporation 2.7210 g. and 2.7392 g. of residue.

*Anal.* Subs., 0.1443; CO<sub>2</sub>, 0.4473; H<sub>2</sub>O, 0.0915. Calcd. for C<sub>14</sub>H<sub>14</sub>O: C, 84.8; H, 7.2. Found: C, 84.5; H, 7.07.

We were unable to isolate a constant-boiling fraction from the higher-boiling residue.

### Bromine Derivatives

6-Bromo-2-methyl-4-benzylphenol was prepared by treating 2-methyl-4-benzylphenol in chloroform solution with a molecular equivalent of bromine at 0°. Evaporation of the chloroform left an oil which distilled at 180–182° (5 mm.). The assignment of structure is based upon the assumption (which has been proved in many cases) that the bromine enters the phenolic ring and upon the directive influence of the hydroxyl group.

*Anal.* Subs., 0.2582, 0.2071; AgBr, 0.1763, 0.1426. Calcd. for C<sub>14</sub>H<sub>13</sub>OBr: Br, 28.48. Found: Br, 28.68, 28.87.

4-Bromo-2-methyl-6-benzylphenol was prepared in two ways: (a) by the bromination of 2-methyl-6-benzylphenol in chloroform at 0° and (b) by the benzylation of 4-bromo-2-methylphenol (m. p. 64°) by the Claisen method. It recrystallized from petroleum ether in characteristic rosetts. It melted at practically the same temperature as the unbenzylated phenol 63–64°, and boiled at 187–189° (5 mm.).

*Anal.* Subs., 0.2259, 0.2867; AgBr, 0.1550, 0.1961. Calcd. for C<sub>14</sub>H<sub>13</sub>OBr: Br, 28.48. Found: Br, 28.82, 28.65.

### Benzoyl Derivatives

The benzoyl derivative of 2-methyl-4-benzylphenol was readily prepared by the Schotten-Baumann reaction. It crystallized from petroleum ether or alcohol (75%) in small colorless rhombic crystals melting at 54–55°.

The benzoyl derivative of 2-methyl-6-benzylphenol could not be prepared by the Schotten-Baumann reaction because of the insolubility of the phenol in dilute potassium hydroxide. When the latter compound was warmed with an equivalent amount of 50% potassium hydroxide it formed a solution which solidified on cooling. The crude potassium salt was warmed with an equivalent amount of benzoyl chloride. The reaction product was washed with water and distilled. It came over as a very viscous

<sup>9</sup> Claisen, *Ann.*, 442, 224 (1924).

<sup>10</sup> Staedel, *ibid.*, 217, 45 (1883).

<sup>11</sup> Schorigin, *Ber.*, 58B, 2033 (1925).

light yellow oil at 216–218° (5 mm.). This ester was more readily prepared from the phenol and benzoyl chloride by the pyridine method.

### Summary

1. *o*-Cresol was benzylated by means of benzyl alcohol in the presence of aluminum chloride. The main product was 2-methyl-4-benzylphenol. Smaller amounts of 2-methyl-6-benzylphenol and 2-methyl-4,6-dibenzylphenol were formed.

2. Benzylation by the Claisen method gave an excellent yield of 2-methyl-6-benzylphenol.

3. The monobromo derivatives and benzoyl derivatives of the two monobenzylcresols were prepared.

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## RESEARCHES ON PYRIMIDINES. CXVII. A METHOD FOR THE SYNTHESIS OF NUCLEOSIDES

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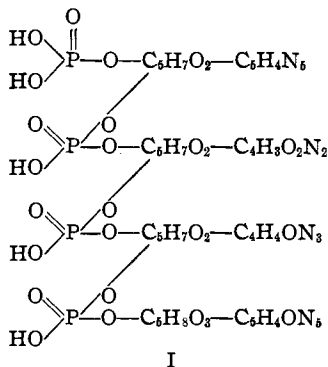
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The present generally accepted structure of a nucleic acid molecule is based chiefly on the results of experimental work by Levene and his co-workers. They represent it as being a tetranucleotide construction, in which the individual nucleotides are combined through phosphoric acid ester linkages as expressed in the formula of yeast nucleic acid I. In this acid the functioning sugar is *d*-ribose.

The approach to a synthesis of a nucleic acid molecule calls first for methods of preparation of the pyrimidine and purine nucleosides, which may be considered as the glucosidic constructions characterizing the structure of nucleosides. If one accepts Levene's conception of the constitution of pyrimidine-nucleosides, in support of which he has contributed considerable indirect experimental evidence, the problem of nucleoside synthesis resolves itself into one of finding a practical method of coupling a sugar with a pyrimidine (uracil, thymine or cytosine) at the 3-position of the ring. The purpose of this paper is to describe a method of synthesis which has made it possible to obtain such a glucoside.

A comprehensive study of the behavior of 2,6-dioxy- and 2-thio- or 2-alkyl mercapto-6-oxypyrimidines toward different alkyl halides in alkaline



<sup>1</sup> Sterling Research Fellow in Chemistry, 1928–1930.