[CONTRIBUTION FROM THE PLAUT RESEARCH LABORATORY OF LEHN AND FINK, INC.]

THE PREPARATION OF SOME ALKYL AND ARYL DERIVATIVES OF PHLOROGLUCINOL

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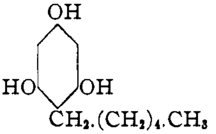
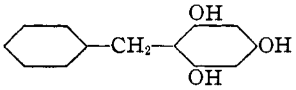
It appears from the investigations of Johnson and co-workers[1] and those of V. Leonard[2] that the introduction of alkyl groups into the nucleus of resorcinol is able to increase greatly the germicidal properties of the latter, the maximum being reached with hexylresorcinol. It has been shown in a previous paper having to do with oxyderivatives of diphenylmethane and diphenylethane[3] (E. Klarmann), that compounds of a considerable germicidal strength are obtained with aromatic substituents in the nucleus of resorcinol, namely, the benzyl and phenylethyl group.

In order to obtain more information regarding the nature of this phenomenon we studied the question of whether the introduction of the above-named groups into the nucleus of polyphenols, which do not originally possess any germicidal action, would result in the formation of compounds having germicidal properties.

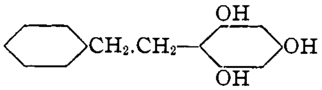
We chose phloroglucinol which, as is known,[4] does not possess germicidal properties, although it retards the process of putrefaction. We prepared the hitherto unknown compounds hexylphloroglucinol (I), 2,4,6-trihydroxydiphenylmethane (II) and 2,4,6-trihydroxydiphenylethane (III). The compounds thus obtained proved to possess strong antiseptic properties. Phenol coefficients were about 8. This phenomenon is comparable to that which occurs in the case of resorcinol derivatives.



I



II



III

The keto compounds from which the phloroglucinol derivatives in question are derived cannot be obtained by condensation of phloroglucinol with the respective acids, since the former does not permit heating with zinc chloride. We obtained them, however, using the method of Hoesch,[5] which had already been successfully applied by one of us in the preparation of resorcinol derivatives.[3] These keto compounds were treated with amalgamated zinc and dil. hydrochloric acid. Zinc dust and dil. acetic

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[1] Johnson and Lane, THIS JOURNAL, **43,** 348 (1921).

[2] Leonard, *J. Am. Med. Assoc.*, **85,** 1855 (1925); **83,** 2006 (1924).

[3] Klarmann, THIS JOURNAL, **48,** 791 (1926).

[4] S. Fränkel, "Arzneimittelsynthese," Springer, Berlin, **1921,** p. 54.

[5] Hoesch, *Ber.*, **48,** 1122 (1915).

acid were used where it was found that a resinification followed on heating with dil. hydrochloric acid.

The phenol coefficients were determined according to the method of the Hygienic Laboratory.

Experimental Part

Preparation of Hexylphloroglucinol.—This method of preparing the phlorophenones had already been applied by Karrer and Rosenfeld.[6] We, therefore, confine ourselves to mentioning the properties of *n*-phlorocaprophenone.

It crystallizes from water in shiny leaflets. The melting point of the air-dry substance is 95°. After it has dried in a vacuum at 100° in a micro vacuum desiccator, the melting point is 118°.

Anal. Subs., 19.302 mg.: CO_2, 45.806 mg.; H_2O, 13.340 mg. Calcd. for $C_{12}H_{16}O_4$: C, 64.25; H, 7.18. Found: C, 64.73; H, 7.73.

The reduction of this compound was carried out with amalgamated zinc and 5% hydrochloric acid by heating for 16 hours. Fresh acid was added occasionally. The mixture was shaken out with ether, the ethereal solution dried with potassium carbonate and the residue recrystallized from benzene forming small platelets; m. p., 108; yield, about 70% of the keto compound used.

Anal. Subs., 7.350 mg.: CO_2, 18.420 mg.; H_2O, 5.900 mg. Calcd. for $C_{12}H_{18}O_3$: C, 68.57; H, 8.62. Found: C, 68.34; H, 8.98.

Preparation of 2,4,6-Trihydroxydiphenylmethane.—The 2,4,6-trihydroxybenzophenone was prepared according to the method of Hoesch[5] and possesses the properties given by this author.

It was reduced by heating under a reflux condenser for ten hours with zinc dust and acetic acid diluted with water and alcohol. The mixture was poured into water and the cloudy suspension shaken out with ether. After the evaporation of the latter a dark oil remained which could not be crystallized on account of the small amount at our disposal. The analysis was carried out after drying the substance in the micro-desiccator at 65°; yield, 50%.

Anal. Subs., 7.990 mg.: CO_2, 21.250 mg.; H_2O, 4.397 mg. Calcd. for $C_{13}H_{12}O_3$: C, 72.18; H, 5.6. Found: C, 72.53; H, 6.16.

Preparation of 2,4,6-Trihydroxydiphenylethane.—The condensation leading to the 2′,4′,6′-trihydroxydesoxybenzoin was carried out in the same way as that described for the foregoing compound.

It has been obtained before by E. Chapman and E. Stephen.[7] It formed long, shiny plates from water; m. p., 163–164°. With ferric chloride in dilute alcohol it gave a dark red coloration.

Anal. Subs., 5.055 mg.: CO_2, 12.725 mg.; H_2O, 2.346 mg. Calcd. for $C_{14}H_{12}O_4$: C, 68.82; H, 4.96. Found: C, 68.68; H, 5.19.

The reduction was carried out with amalgamated zinc and 5% hydrochloric acid. The product was separated with ether and recrystallized from benzene; yield, about 65%. It formed small crystallized aggregates, m. p. 159–160°, and gave a pink precipitate with ferric chloride.

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[6] Karrer and Rosenfeld, *Helv. Chim. Acta*, **4**, 707 (1921).

[7] Chapman and Stephen, *J. Chem. Soc.*, **123**, 404 (1923).

Anal. Subs., 8.682 mg.: CO_2, 23.140 mg.; H_2O, 5.013 mg. Calcd. for $C_{14}H_{14}O_3$: C, 73.01; H, 6.13. Found: C, 72.70; H, 6.46.

Acetylation of the 2,4,6-Trihydroxydiphenylethane.—This was carried out in order to establish that the number of hydroxyl groups of the phloroglucinol was not affected by the reactions involved in the preparation of these compounds. The process leads to a mixture of the di- and tri-acetyl derivatives.

We effected it by warming the trihydroxydiphenylethane with an excess of acetyl chloride on the water-bath. The excess of the acid chloride was evaporated in a vacuum at room temperature and alcohol was added to the oil. After standing, a compound crystallized in needles which were soluble in alkali and gave a brown precipitate with ferric chloride in alcoholic solution; m. p., 135–136°, after drying in a vacuum.

The results of analysis agree with the calculated formula of a diacetyl derivative, $C_6H_5.CH_2.CH_2.C_6H_2(OH)(O.C_2H_3O)_2$.

Anal. Subs., 4.375 mg.: CO_2, 11.025 mg.; H_2O, 2.447 mg. Calcd. for $C_{18}H_{18}O_5$: C, 68.78; H, 5.76. Found: C, 68.75; H, 6.26.

Another portion was diluted with alcohol, treated with potassium hydroxide and the mixture shaken with ether. We obtained a heavy oil, insoluble in alkali, giving no coloration with ferric chloride.

This behavior and the analysis indicate the presence of the triacetyl derivative, $C_6H_5.CH_2.CH_2.C_6H_2(O.C_2H_3O)_3$.

Anal. Subs., 3.200 mg.: CO_2, 7.870 mg.; H_2O, 1.737 mg. Calcd. for $C_{20}H_{20}O_6$: C, 67.37; H, 5.67. Found: C, 67.07; H, 6.07.

Our thanks are due to Dr. V. Ross who carried out the determinations of the phenol coefficients.

Summary

The preparation of several new derivatives of phloroglucinol has been described, namely, hexylphloroglucinol, 2,4,6-trihydroxydiphenylmethane and 2,4,6-thiohydroxydiphenylethane. Substituents that increase the germicidal action of resorcinol show the same behavior with phloroglucinol, rendering an originally inactive compound highly germicidal to *B. typhosus*. The phenol coefficients are about 8.

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