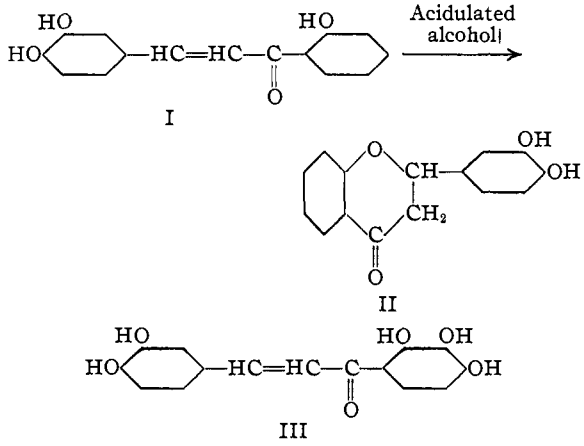
[CONTRIBUTION FROM THE INSTITUTE OF PAPER CHEMISTRY]

# The Preparation of the Polyhydroxychalcones

BY ERVIN F. KURTH

A direct synthesis of the polyhydroxychalcones through the condensation of hydroxyacetophenones and aromatic aldehydes with strong alkali in the cold appears to have been given little attention. The more general practice has been to use methoxy compounds with condensations carried out in hot alkaline solutions and acetylated or benzoylated derivatives where condensation is effected with hydrogen chloride. Since the reaction of the ketone with the aldehyde to form the chalcone is reversible in hot alkaline solutions,[1] it is doubtful that a complete conversion to the chalcone is obtained when equimolecular portions are employed. Although carefully performed, the dealkylation of the chalcone is accompanied with a further reversal to ketone and aldehyde and also with the formation of other secondary products.

In the present procedure, both *o*-hydroxyacetophenone and gallacetophenone have been successfully condensed with protocatechuic aldehyde in a cold solution of potassium hydroxide to give 2′,3,4-trihydroxychalcone (I) and 2′,3′,4′,3,4-pentahydroxychalcone (III). The latter compound has been prepared previously from gallacetophenone tribenzoate and protocatechuic aldehyde dibenzoate by Russell and Todd.[2]




## Experimental Work

**2′,3,4-Trihydroxychalcone** (I).—To a mixture of 11 g. of protocatechuic aldehyde, 11 g. of *o*-hydroxyacetophenone, and 25 cc. of alcohol in an ice-bath was slowly added 190 g. of cold 60% potassium hydroxide. The flask was tightly stoppered to exclude air, shaken to break up the yellow precipitate, allowed to reach room temperature, and after three days its contents was poured into cold dilute hydrochloric acid. A crystalline precipitate separated which, after recrystallizing from dilute alcohol, was obtained as bright yellow microscopic needles melting at 185–186°. The yield was 8.5 g. or 46%.

The slightly acid mother liquor from the chalcone separation contained some additional chalcone and the uncondensed ketone and aldehyde. These were recovered by saturating the liquor with sodium chloride and extracting with ethyl acetate. After first removing the solvent by evaporation and repeating the condensation with potassium hydroxide as above, additional chalcone was obtained.

*Anal.* Calcd. for $C_{15}H_{12}O_4$: C, 70.3; H, 4.7. Found: C, 70.3, 70.2; H, 4.8, 4.9.

2′,3,4-Trihydroxychalcone gives a clear red color with alkalies and a bright green color with ferric chloride solution.

**2′,3,4-Triacetyloxychalcone.**—The acetate was prepared by refluxing 0.5 g. of the above chalcone and 0.5 g. of anhydrous sodium acetate dissolved in 5 cc. of acetic anhydride for one-half hour. On pouring into water the acetate separated as a light yellow oil. Extraction with ether, evaporation of the solvent and crystallization of the residue from 50% alcohol gave white needles melting at 112–113°.

*Anal.* Calcd. for $C_{21}H_{18}O_7$: C, 66.0; H, 4.7. Found: C, 66.0, 66.1; H, 4.7, 4.7.

**3′,4′-Dihydroxyflavanone** (II).—Attempts at securing ring closure by recrystallizing the pure chalcone from hot 70% acetic acid or by refluxing with 2.5% sodium hydroxide for four hours were unsuccessful. With the former, 2′,3,4-trihydroxychalcone was recovered unchanged as yellow crystals melting at 185°; with the latter, only dark-colored amorphous degradation products were obtained.

The flavanone was finally prepared by refluxing for twenty-four hours in a hot water-bath a mixture of 1 g. of 2′,3,4-trihydroxychalcone, 60 cc. of 50% alcohol, and 2 cc. of concentrated sulfuric acid. Upon cooling and diluting with water, the flavanone separated as light yellow crystals. These contained some chalcone as an impurity and after fractional crystallization from 50% alcohol, the flavanone was obtained as white prisms melting at 188°. It gave a clear red color with alkaline solutions.

*Anal.* Calcd. for $C_{15}H_{12}O_4$: C, 70.3; H, 4.7. Found: C, 70.2, 70.2; H, 4.7, 4.6.

**3′,4′-Diacetyloxyflavanone.**—The flavanone readily was acetylated by heating 0.3 g. with 0.3 g. anhydrous sodium acetate and 4 cc. of acetic anhydride in a hot water-bath for thirty minutes. The reaction mixture was diluted with water and extracted with ether. After removing the solvent and crystallizing the residue from 70% alcohol, the acetate was obtained as white prisms melting at 139°.

(1) A. V. Wacek and E. David, *Ber.*, **70B**, 190 (1937).

(2) Alfred Russell and John Todd, *J. Chem. Soc.*, 1506 (1934).

**2',3',4',3,4-Pentahydroxychalcone (III).**—Five and four-hundredths grams of gallacetophenone and 4.2 g. of protocatechuic aldehyde in 10 cc. of alcohol, condensed with 85 g. of 60% potassium hydroxide, gave 3.2 g. (39% yield) of pure 2',3',4',3,4-pentahydroxychalcone. The chalcone separated from 50% alcohol as yellow microscopic crystals, melting at 249°. Russell and Todd[2] obtained this chalcone as a deep orange-red microcrystalline solid melting at 233° by saponification of 2',3',4',3,4-pentabenzoyloxychalcone.

From the acid mother liquor saturated with sodium chloride, the unchanged gallacetophenone and protocatechuic aldehyde were recovered by extraction with ethyl acetate.

**2',3',4',3,4-Pentabenzoyloxychalcone** was prepared by dissolving 0.5 g. of the chalcone in 10 cc. of a 50–50 benzoyl chloride–pyridine mixture and heating in a hot water-bath for two hours. After diluting the reaction mixture with water and extracting with ether, followed by washing the ether extract with cold alcohol, the pentabenzoate separated from hot alcohol as a white powder melting at 85°, as given by Russell and Todd.

## Summary

The preparation of the polyhydroxychalcones by a direct condensation of the appropriate hydroxyacetophenone and aromatic aldehyde is described. 2',3,4-Trihydroxychalcone and 2',3',4',3,4-pentahydroxychalcone have been obtained in yields of 46 and 39%, respectively. Ring closure was effected with the former by refluxing with acidulated alcohol to give 3',4'-dihydroxyflavanone.

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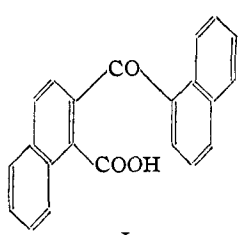
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

# 9-Methyl-1,2,5,6-dibenzanthracene

BY LOUIS F. FIESER AND GLEN W. KILMER

In view of the marked cancer-producing properties of 10-methyl-1,2-benzanthracene and the moderate activity displayed by 9-methyl-1,2-benzanthracene[1] it seemed of interest to synthesize for comparison the *meso*-methyl derivative of 1,2,5,6-dibenzanthracene. All previously studied homologs of this moderately powerful carcinogen, including the 9,10-dimethyl derivative, are less active than the parent hydrocarbon, whereas the introduction of a methyl group into either or both *meso*-positions of the inactive 1,2-benzanthracene favors the development of carcinogenic potency.[1,2]

As starting material for the synthesis of 9-methyl-1,2,5,6-dibenzanthracene we employed 2-($\alpha$-naphthoyl)-1-naphthoic acid, I. This was obtained as the chief product of the reaction between 1,2-naphthalic anhydride and $\alpha$-naphthylmagnesium bromide. A reaction product isolated in smaller amounts corresponded in melting point and in the melting point of the lactol acetate with the isomeric 1-($\alpha$-naphthoyl)-2-naphthoic acid synthesized in a different manner by Cook,[3] and the structure of the new acid follows from the observation that it is an isomer of this substance.

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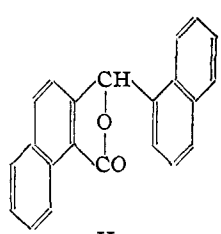


II

Since both *meso*-positions of the desired hydrocarbon are equivalent, two routes were open for the introduction of the methyl group starting with keto acid I. The reduction of the acid was investigated with the idea of proceeding through the anthranyl acetate and the anthrone,[4] but the results were unpromising. Treatment with zinc and alkali led only to resins. High pressure hydrogenation over copper chromite catalyst at temperatures at which the naphthalene rings were not attacked to an appreciable extent gave as a principal crystalline product the lactone II. A very small amount of the fully reduced 2-($\alpha$-naphthylmethyl)-1-naphthoic acid was isolated from the acidic fraction, and small amounts of the same substance were obtained from the lactone II by Clemmensen reduction and by reduction with zinc and alkali following Newman's[5] procedure. The yields, however, were too low to be practical.

(1) For a summary of the literature and biological tests see Fieser, *Am. J. Cancer*, **34**, 37 (1938).

(2) Additional data on the carcinogenic action of 9,10-dimethyl-1,2-benzanthracene are given by W. E. Bachmann, E. L. Kennaway and N. M. Kennaway, *Yale J. Biol. Med.*, **11**, 97 (1938).

(3) Cook, *J. Chem. Soc.*, 1472 (1932).

(4) Fieser and Hershberg, THIS JOURNAL, **59**, 1028 (1937).

(5) Newman, *ibid.*, **60**, 1368 (1938).