

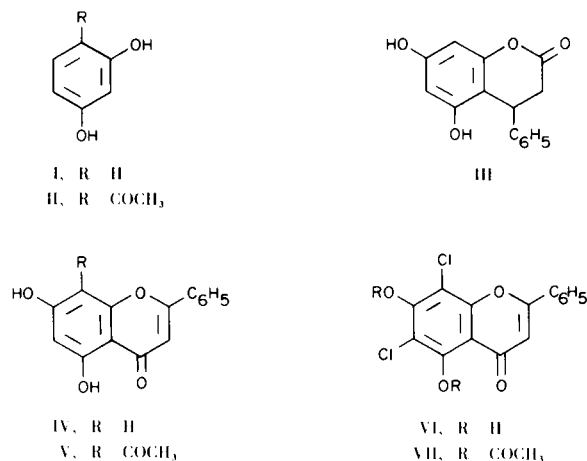
## Chlorination of 5,7-Dihydroxyflavone in the Hoesch Reaction

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Received September 4, 1970

The Hoesch reaction (1) involves the condensation of a phenol and a nitrile in the presence of anhydrous zinc chloride, followed by the hydrolysis of the resulting ketimine to afford a phenolic ketone (Example, I  $\rightarrow$  II). In the abnormal Hoesch reaction with an  $\alpha,\beta$ -unsaturated nitrile and phenol, the phenol adds on to the olefinic double bond (Example, phloroglucin and cinnammonitrile  $\rightarrow$  III).



In our attempts to synthesize an acetyl compound by the Hoesch reaction of 5,7-dihydroxyflavone (IV) and acetonitrile, we have been unable to obtain V, but found that the anomalous chlorination of IV under the condition of the Hoesch reaction occurred. The fact that the product contains chlorine was indicated by the nmr spectrum which lacks two doublet peaks at  $\delta$  6.25 and 6.55 corresponding to 6-H and 8-H in the starting material IV, confirming the position of chlorine on the 5- and 7-carbon atoms. Other spectral data and elemental analysis also supported the structure VI for this chlorinated product as well as both spectral and elemental analyses of the diacetyl derivative of VI (VII).

It is of interest that chlorination, which is an oxidative reaction, occurs in the Hoesch reaction which is considered to take place under non-oxidative conditions. Although the chlorination by hydrogen chloride has been reported,

the reactions are carried out under the influence of light irradiation (2) or high temperature (3). In order to clarify the essential factors of this reaction we have varied the reaction conditions as shown in Table I. It is obvious that both hydrogen chloride and zinc chloride as well as atmospheric oxygen are essential. Some natural (4) or synthetic (5) chloroflavones have been reported and this reaction might be useful for the direct chlorination of a hydroxyflavone. The addition and elimination mechanism of this reaction is tentatively suggested as shown in Scheme I.

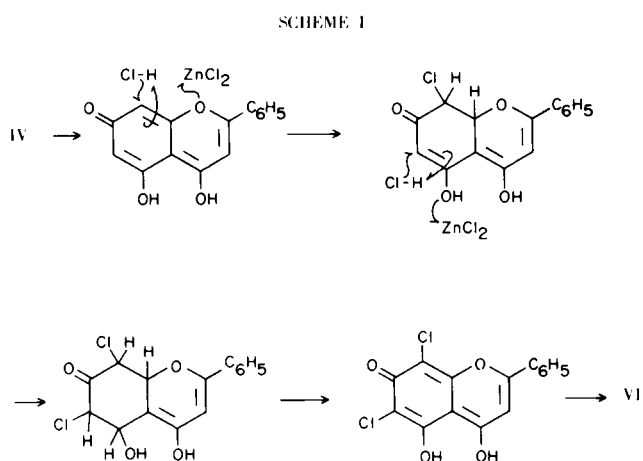


TABLE I

Exp. No.	Atmosphere, Reagents and Solvents	Product
1	air CH <sub>3</sub> CN, ZnCl <sub>2</sub> , HCl, THF	VI
2	N <sub>2</sub> CH <sub>3</sub> CN, ZnCl <sub>2</sub> , HCl, THF	none
3	air - , - , HCl, THF	trace
4	air - , ZnCl <sub>2</sub> , - , THF	VI
5	air - , ZnCl <sub>2</sub> , - , THF	none
6	air - , - , Cl <sub>2</sub> , THF	others

## EXPERIMENTAL

## 6,8-Dichloro-5,7-dihydroxyflavone (VI) (Exp. No. 1).

In a 100 ml. flask, fitted with a calcium chloride tube, was placed 0.5 g. of 5,7-dihydroxyflavone (IV), 1.0 g. of anhydrous acetonitrile, 40 ml. of anhydrous tetrahydrofuran and 1.5 g. of finely powdered, fused zinc chloride. The flask was cooled in an ice-salt mixture and shaken occasionally, while a rapid stream of dry hydrogen chloride was passed through the solution for three hours. When the flask was allowed to stand in a refrigerator overnight, a yellow precipitate separated, 200 mg. of which were purified by silica gel column chromatography (benzene-pyridine, 8:1), m.p. above 250° dec.; nmr (deuteriochloroform)  $\delta$  7.03 (s, 1, 3-H), 7.4-7.6 (m, 3, 3'-H, 4'-H, 5'-H) and 8.0-8.15 (m, 2, 2'-H, 6'-H); ir (potassium bromide)  $\nu$  1640, 1600, 1570, 1400, 1380 and 1200  $\text{cm}^{-1}$ .

*Anal.* Calcd. for  $\text{C}_{15}\text{H}_8\text{Cl}_2\text{O}_4$ : C, 55.75; H, 2.49; Cl, 21.98. Found: C, 56.04; H, 2.61; Cl, 21.75.

## 6,8-Dichloro-5,7-diacetoxyflavone (VII).

A mixture of 110 mg. of VI, 2 ml. of acetic anhydride and three drops of pyridine was heated on the steam bath for one hour. The solution was poured into water and the precipitate was recrystallized from methanol-ethyl acetate (9:1) to give 90 mg. of a white powder, m.p. 213-214°; positive Beilstein test; nmr (deuteriochloroform)  $\delta$  2.5 (s, 6,  $\text{OCOCH}_3$ ), 6.70 (s, 1, 3-H), 7.4-7.6 (m, 3, 3'-H, 4'-H, 5'-H) and 7.8-8.0 (m, 2, 2'-H, 6'-H); ir (potassium bromide) 1775, 1650, 1620, 1600, 1350, 1180 and 1080  $\text{cm}^{-1}$ .

*Anal.* Calcd. for  $\text{C}_{19}\text{H}_{12}\text{Cl}_2\text{O}_6$ : C, 56.04; H, 2.96; Cl, 17.42. Found: C, 56.24; H, 3.09; Cl, 17.69.

## 6,8-Dichloro-5,7-dihydroxyflavone from 5,7-Dihydroxyflavone, Hydrogen Chloride and Zinc Chloride (Exp. No. 4).

The flask, containing 0.4 g. of IV, 30 ml. of tetrahydrofuran

and 1.5 g. of zinc chloride was cooled and a rapid stream of hydrogen chloride was passed through the solution for two hours. By the same procedure as in Exp. No. 1, VI was obtained in 70% yield.

## Hoesch Reaction of 5,7-Dihydroxyflavone under a Nitrogen Atmosphere.

The reaction was carried out in the same way as in Exp. No. 1 except that nitrogen was passed into the reaction mixture prior to the passing of hydrogen chloride. No precipitate appeared and IV was recovered unchanged.

## Attempted Chlorination of 5,7-Dihydroxyflavone by Chlorine (Exp. No. 6).

The flask, containing 0.4 g. of IV and 40 ml. of tetrahydrofuran, was cooled and a stream of dry chlorine was passed through the mixture for 3 hours. After evaporating the solution, the residue was chromatographed on silica gel to give 2-chlorotetrahydrofuran, ms,  $m/e$   $M^+$  107; ir (film) 2800, 1430, 1100, 1000 and 920  $\text{cm}^{-1}$ . No flavone derivatives were identified.

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