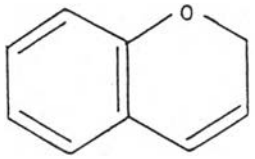
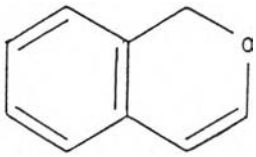
CHAPTER II

HISTORY OF CHROMONES

Compounds with fused benzene and pyran ring are called benzopyran. The two classes of benzopyran are shown as 1-benzopyran and 2-benzopyran . The double bond in the pyran ring of 1-benzopyran may also be in the 2,3 position.

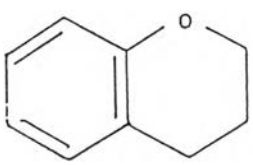


1-benzopyran

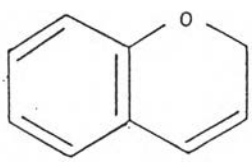


2-benzopyran

The 1-benzopyrans had various levels of saturation, reduction and oxidation states, namely, derivatives of chroman(XII), 2H-chromene(XIII), 4H-chramene (XIV), 4-chromanone(XV), 2,4-chromandione (XVI) and chromone (XVII). These compounds are important because many of them occur in plants and they have been considered to be biological actives (Ellis, 1977).



XII



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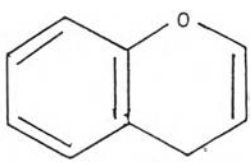
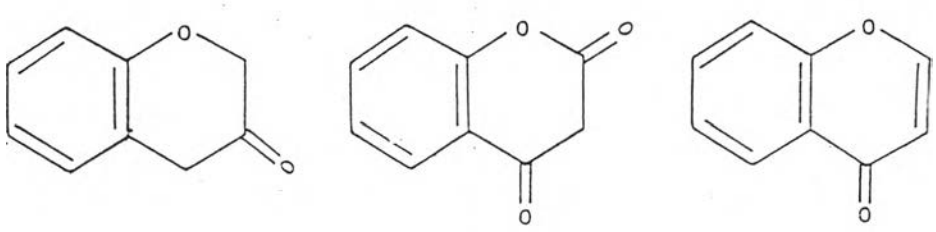
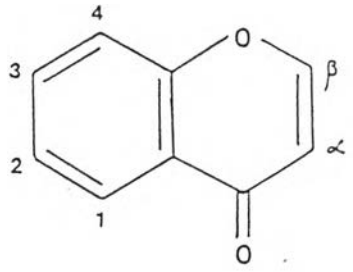


XIV

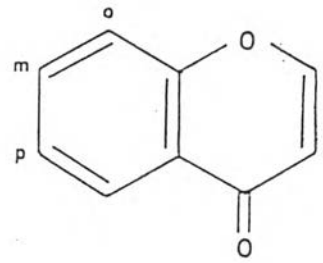


XV XVI XVII

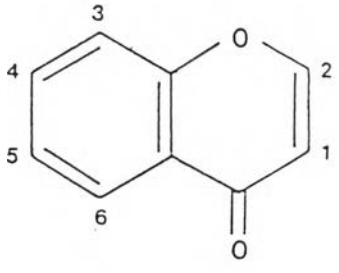
After the discovery of 1-benzopyrans in the late nineteenth century, the nomenclature of chromones were as shown in the derivatives XVIII-XX . However, in modern practice in formular, XXI has been utilized.



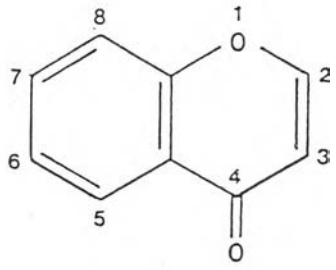
XVIII



XIX



XX



XXI

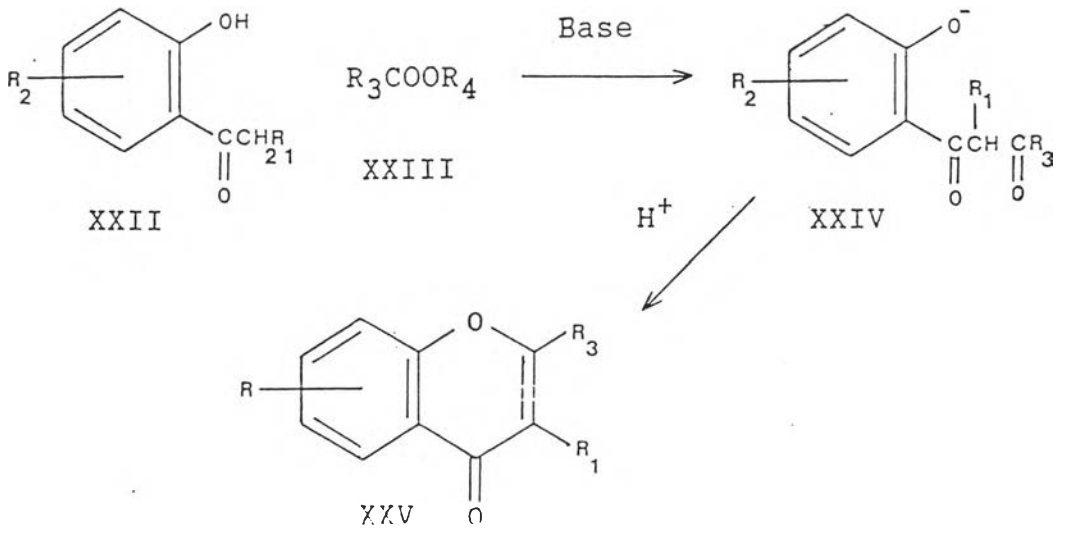
General Methods for The Preparation of Chromone Moiety.

The preparation methods, which resulted in the formation of chromone moiety, were the ring closure process of o-hydroxyaryl alkyl ketones. There were at least five methods as follows :

a. Claisen Condensation with carboxylic esters.
b. The Baker-Venkataraman Rearrangement.
c. Condensation under acidic condition.
d. Condensation with formaldehyde, formic acid or their derivatives.
e. Kostanecki-Robinson Reaction.

a. Claisen Condensation with carboxylic esters.

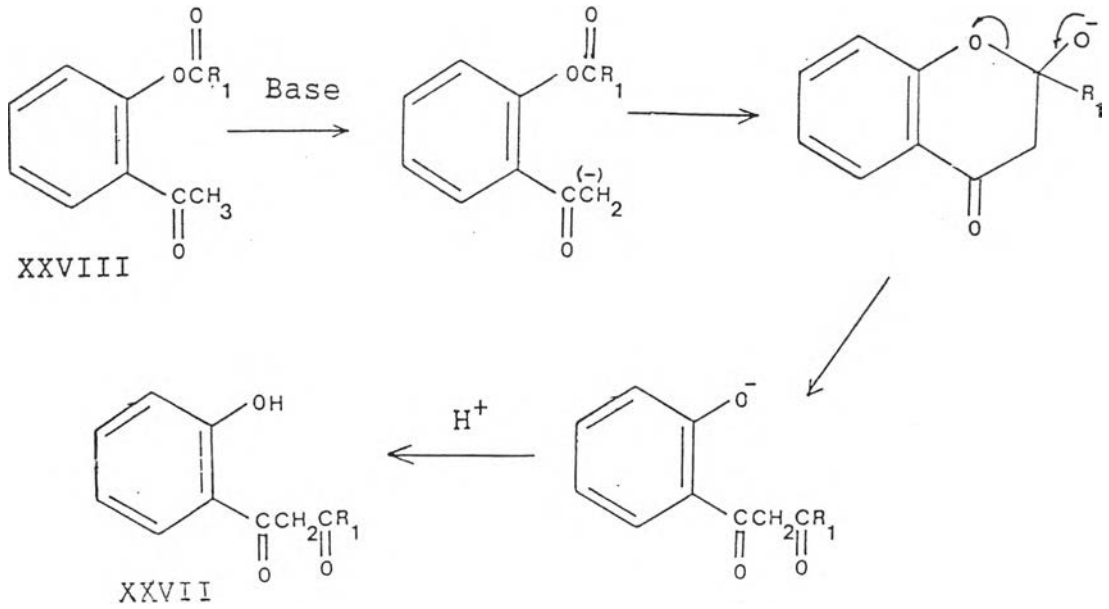
One of most frequently used to prepare chromones was the Claisen Condensation of o-hydroxyaryl alkyl ketone (XXII) with carboxylic esters (XXIII) in the presence of strong base . The dioxophenol intermediate(XXIV), thus formed, was cyclized by heating in an acidic medium to give the chromone(XXV).



The 1,3-dioxophenol (XXVI) often partially separated out of solution as its yellow or orange sodium salt during the first stage of the reaction, but it was not usually necessary to isolate or purify at this stage . Addition of excess mineral acid followed by a short period under reflux, or a longer period of standing at room temperature gave in chromone(Ellis, 1974).

b. The Baker-Venkataraman Rearrangement.

1,3-Dioxophenols (XXVII) that are formed in the Claisen Condensation may also be prepared from o-acyloxy-acylbenzenes (XXVIII) by a transformation which is called the Baker-Venkataraman Rearrangement (Hauser, Swamer, Adams, 1954). The scope and mechanism are demonstrated in figure 4 . The formation of chromones by heating phenyl acetates with sodium are also relevant. It has been suggested that sodium derivatives and the keto esters may be the intermediates.



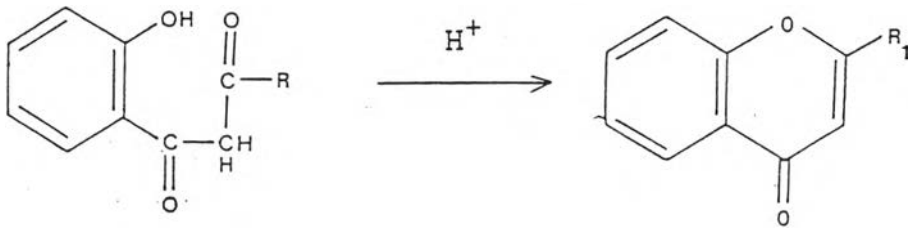
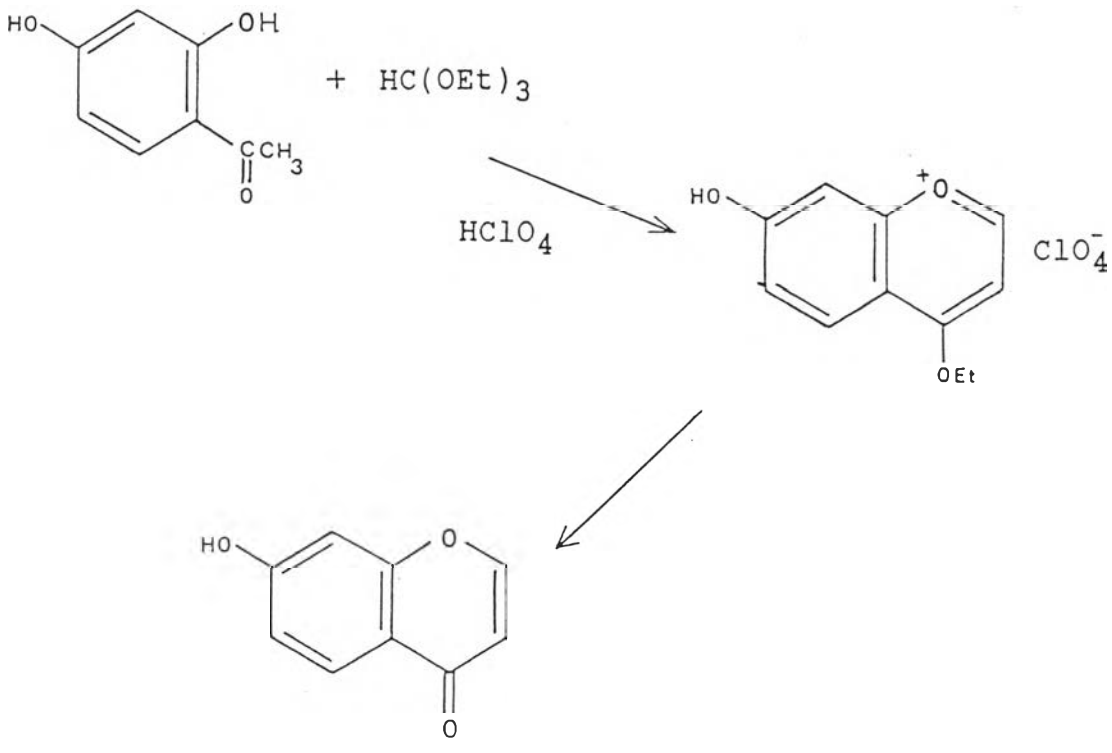


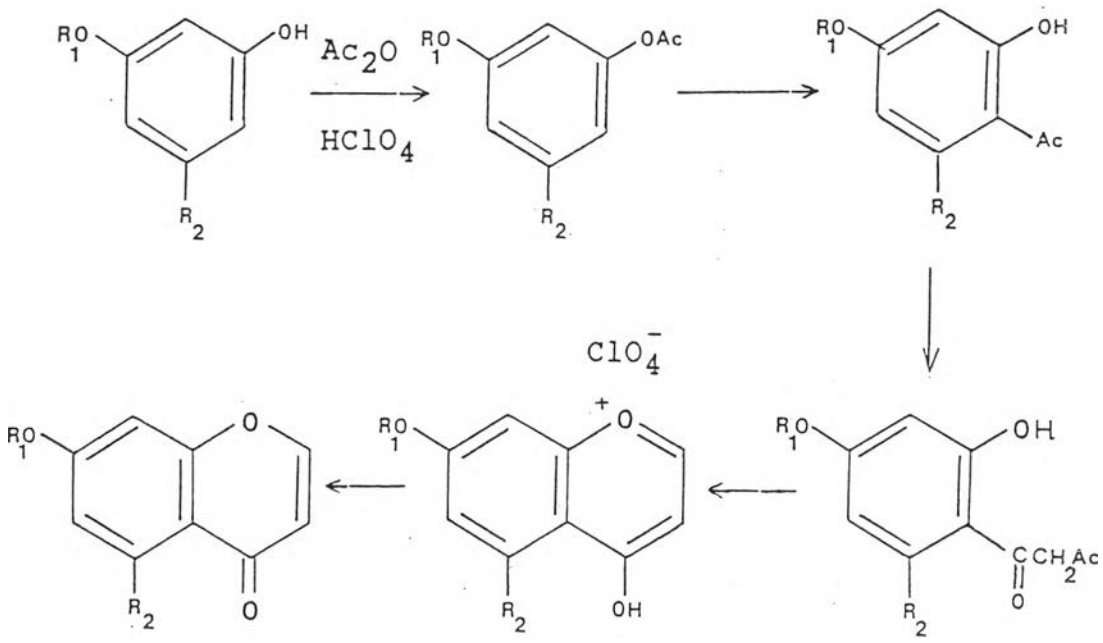
Figure 4 The mechanism of the Baker-Venkataraman Rearrangement

c. Condensation under acidic condition.

2-Hydroxyacetophenones that do not carry other electron-attracting substituents have been converted into C-2 unsubstituted benzopyrylium salts by treating under mild conditions with triethyl orthoformate and strong acid. The yield of benzopyrylium salts are usually good and also the conversion of their salts into the chromone by warming with water. Perchloric was the first acid catalyst to be used for this reaction.



It had been reported that when some phenol were heated with acetic anhydride and perchloric acid, the sucessive O-acylation, Fries Rearrangement, C-acylation, and cyclization to the benzopyrylium salt occured. For example, heating phloroglucinol or 3-phenoxyphenol with acetic anhydride and perchloric acid for about 45 minutes yielded the benzopyrylium salt in about 50% (Ellis, 1977).



d. Condensation with formaldehyde, formic Acid, or their derivatives.

This method was designed for 2-unsubstituted chromones preparation. Both dimethylformamide and its dimethyl acetal provided the C-2 atom and very good yield were obtained. N,N-Dimethylformamide condensed with hydroxyphenyl ketone in the presence of phosphorous

oxychloride to give a good yield in one step . The role of the catalyst was probably to form a complex with the ketone and created the methylene group at position 2 (Nohara, Umetani and Sanno, 1974).

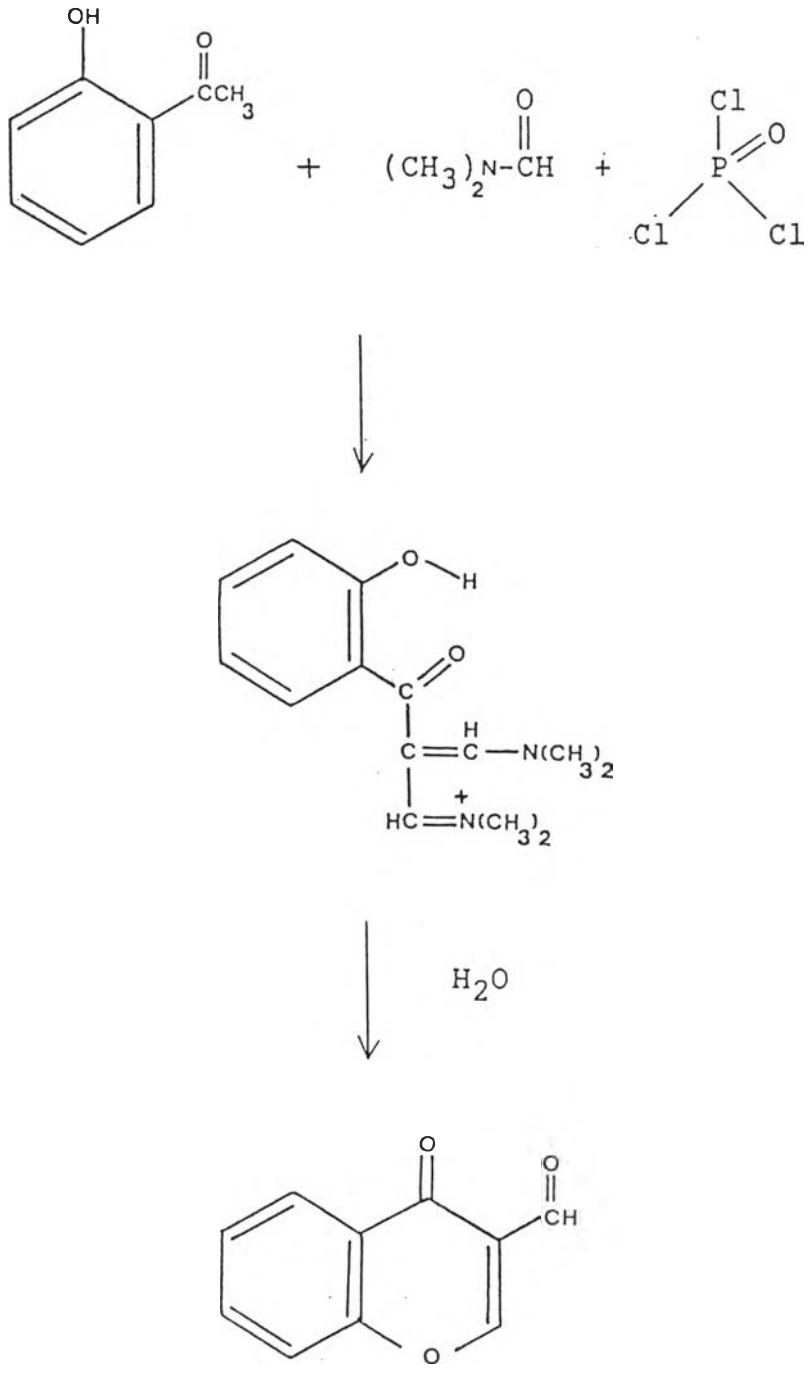


Figure 5 The method for preparing 2-unsubstituted chromone derivatives

Triethyl orthoformate in boiling acetic anhydride could cyclized phenolic 1,3 diketone to 2-unsubstituted chromones under rather drastic conditions, but this reaction had not been widely applied because the yield was rather low (Jones, MacKenizie, Robertson, Whalley, 1949)

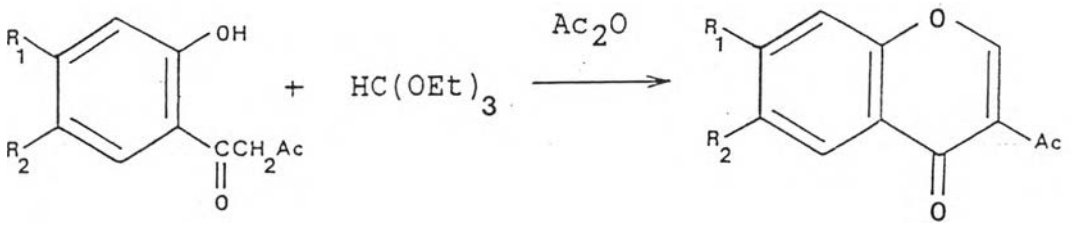


Figure 6 The method for preparing 3-acetylchromone derivatives

e. Kostanecki-Robinson Reaction.

O-Hydroxy ketone (XXIX, with or without other substituents in the benzene ring) when heated with acid anhydride in the presence of sodium or potassium salts of the corresponding acids produced chromones. The most probable course of their transformation, called Kostanecki Reaction, was shown as follows : acylation of the phenolic hydroxyl group to form the ester (XXX) , rearrange to the diketone (XXXI) and cyclization of diketone (XXXIII). The Kostanecki Reaction had been conducted sucessfully with esters of the general structure (XXX). The rearrangement of an ester like XXX to a β-diketone like XXXI was an acylation of ketonic

proton of the molecule by the ester portion and was analogous to the rearrangement in the presence of potassium carbonate, sodium ethoxide, sodium, or sodium amide (Charles, et al, 1954).

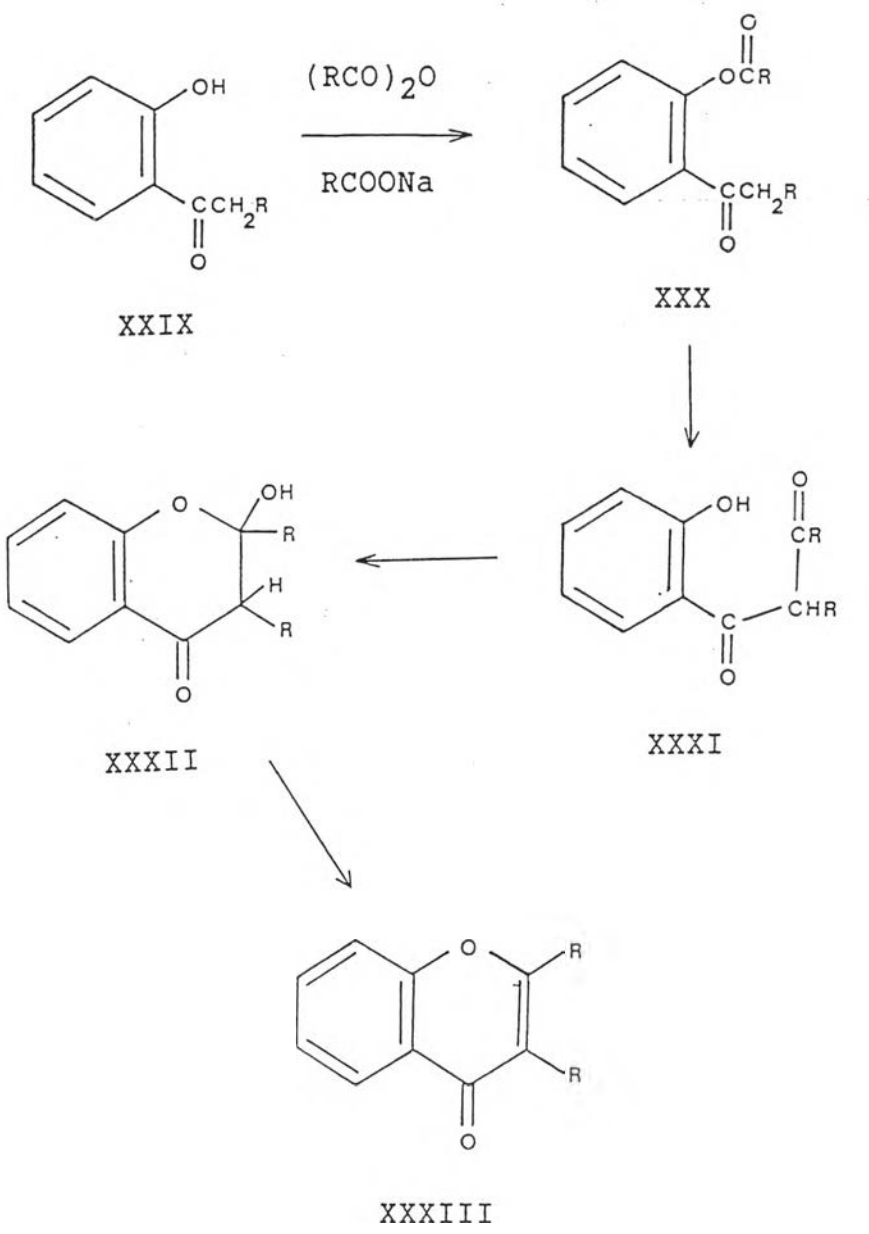
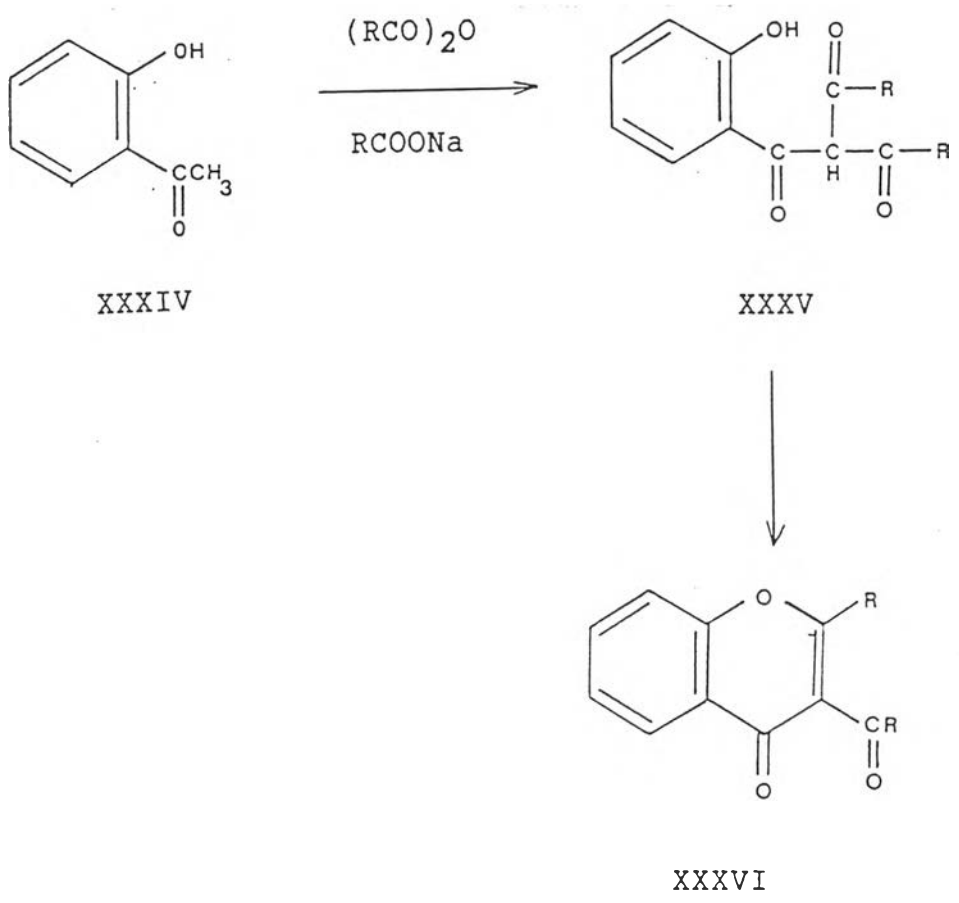


Figure 7 The mechanism of Kostanecki-Robinson Reaction

When the o-hydroxy ketone was an acetophenone derivative (XXXIV, R=H), the β-diketone (XXXI) was probably acylated by the anhydride before cyclization. This would furnish a triketone (XXXV) , which could undergo cyclization to yield the acyl derivative of a chromone, XXXVI (Charles, et al, 1954; Chakravarti, Majundar, 1939; Chakravarti, Bagchi,1936).



XXXIV XXXV XXXVI

Figure 8 The method for preparing 2-unsubstituted-3-acetylchromone derivatives