GENERAL INTRODUCTION

Chromones and flavones, which are benzo-γ-pyrone derivatives, occur in a variety of plants either in combination with rhamnose and glucose or associated with tannins or in the uncombined state.

The structures of a large number of flavones have been elucidated and many of them have been synthesised. In recent years the interest in the study of these compounds has been enhanced as a result of the discovery of their interesting biochemical properties. Rutin (3-rhamnoglucoside of quercetin) shows vitamin P activity and is important in preventing capillary fragility (Couch and Krewson, U.S. Dept. Agr., Eastern Regional Research Lab., 1944, A.I.C.-52, 4 ; C.A., 1945, 39, 4326). Other flavones such as Quercitrin, Rhamnetin and 6,8-dihydroxyflavone are reported to reduce blood pressure (Highby, J. Amer. Pharm. Assoc., 1943, 32, 74) and to act as diuretics (Nakamura, et al., J. Pharm. Soc., Japan, 1936, 56, 68 ; C.A., 1938, 32, 5833). Further, Calycopterin and its 4'-methyl ether, Herbacetin, Gossypetin etc. act as fish poisons (Murti, Rao and Seshadri, Proc. Indian Acad. Sci., 1947, 25A, 22 ; 1948, 27A, 33 ; Seshadri and Vishwanadham, ibid, 1947, 25A, 337). The aminomethyl derivatives of chromones and flavones are reported to act as powerful central nervous system stimulants, especially on the brain stem and to have cardiokinetic and hypertensive action (Da Re et al., J. Org. Chem., 1960, 25, 1097).

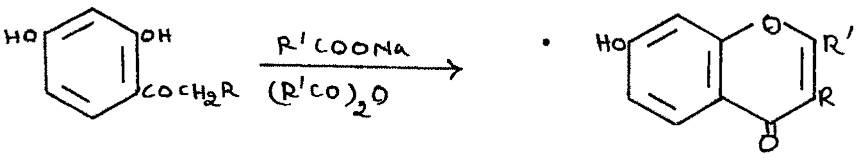
Further, the antioxidant properties of a large number of flavones and flavonols have been studied and Gossypetin and

Robinetin have been found to be of great potency (Simpson and Uri., Chem. and Ind., 1956, 956 ; Lea and Swoboda, ibid, 1956, 1426). Seshadri (Tetrahedron, 1959, 6, 169) has recently reviewed the recent developments in the Chemistry of Flavonoids.

Methods for the synthesis of chromones and flavones :

A number of methods are available for the synthesis of chromones and flavones. Of these, the Kostanecki Robinson reaction, which is utilised in the present work has been described here in detail and the other methods have been described briefly.

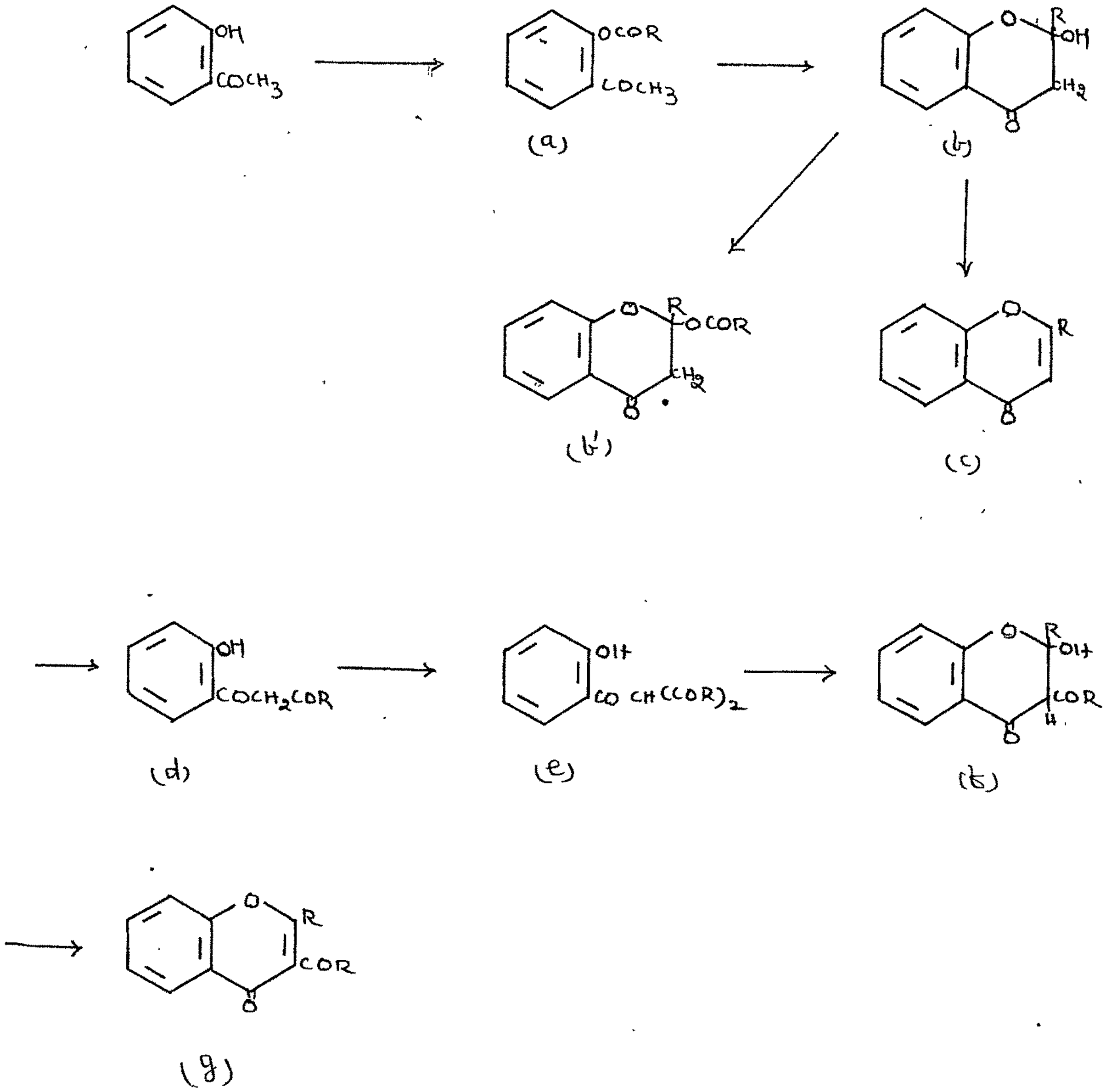
1. Kostanecki-Robinson Reaction :- Kostanecki and Rozycki (Ber., 1901, 34, 102) showed that a chromone derivative was formed when resacetophenone or peonol was heated with sodium acetate and acetic anhydride.



This method was further developed by Allan and Robinson (J. Chem. Soc., 1924, 125, 2192) who found that when o-hydroxyacetophenones were heated with the sodium salt and the anhydride of an aromatic acid, a flavone derivative was obtained. This method, now known as the Kostanecki-Robinson reaction, has been extensively used for the synthesis of chromone and flavone derivatives.

Mechanism for the formation of chromones and 3-acylated chromones

Baker (J. Chem. Soc., 1933, 1384) ~~has~~ suggested the following mechanism for the production of chromones and 3-acylated chromones when an o-hydroxyacetophenone is heated with the anhydride and the sodium salt of a carboxylic acid. According to him the first step is the esterification



of the phenolic hydroxyl group (a) then ring closure to a 2-hydroxyflavanone (b) or possibly 2-acyloxyflavanone (b'). Loss of a molecule of water with the production of chromone (c). Alternately to (c) the ring of the 2-hydroxyflavanone may open to give the diketone (d) under the influence of the sodium salt of the acid. Then acylation of the methylene carbon atom to give a triacylmethane derivative (e), ring closure to the 2-hydroxy-3-acylflavanone (f) followed by dehydration to the 3-acylchromone (g).

Factors governing the nature of the product formed in the Kostanecki-Robinson reaction

It has been found that the Kostanecki-Robinson reaction does not give chromones in all cases. Coumarins or a mixture of coumarins and chromones may be formed in some cases.

Thus both 4-chloro-6-acetylphenol and o-hydroxy acetophenone on Kostanecki-Robinson acetylation yield a mixture of chromone and coumarin derivatives (Wittig, Ber., 1924, 57, 88 ; Wittig, Bangert and Richter, Ann. 1926, 446, ~~178~~ 144). It was further observed by Bargellini (Atti R. Accad. Lincei, 1925, 2, 178, 201) and by Baker and Eastwood (J. Chem. Soc., 1929, 2900) that the use of phenylacetic anhydride and sodium phenylacetate in the Kostanecki-Robinson reaction leads to coumarin and not chromone formation.

The nature of the product formed in Kostanecki-Robinson reaction depends on the nature of the *o*-hydroxy ketone, the acid anhydride and the salt used.

(1) Using sodium acetate and acetic anhydride the introduction of the higher alkyl substituent in the side chain of the hydroxyketone favours chromone formation e.g. resacetophenone gives chromone (Kostanecki and Rózycki loc.cit.), respropiophenone also gives chromone (Ganter, Curd, and Robertson J. Chem. Soc., 1931, 1263). Chadha, Mahal and Venkataraman (J. Chem. Soc., 1933, 1459) found that an ω - substituent in the o-hydroxy aryl methyl ketone leads to chromone formation and from the point of view of increase in yield and ease of purification the groups can be arranged in the order: methoxyl, methyl, benzyl and phenyl. They also found that the chromone formation took place as a rule more readily in the naphthalene than in the benzene series, and is often quantitative from derivatives of α-naphthol.

(2) Keeping the o-hydroxy ketone the same if the anhydride and sodium salts of higher acids like propionic and butyric acid are taken then there is a tendency towards coumarin formation.

(3) When benzoic anhydride and sodium benzoate or their derivatives are used the products formed are always flavone derivatives. With phenylacetic anhydride or acetic anhydride and sodium phenylacetate the products formed are mostly 3-phenylcoumarin derivatives.

Effect of the substitutents in the phenolic nucleus of the o-hydroxyketones on the Kostanecki-Robinson reaction

Considerable amount of work has been done on the effect of substituents like the alkyl groups, halogens and nitro groups in the phenolic ketones on the course of the Kostanecki-Robinson reaction. An alkyl substituent in the phenolic nucleus, while it may have some effect on the yield of the product formed does not appear to have any effect on the nature of the product formed.

In their studies on the Kostanecki-Robinson reaction on the halogenated phenolic ketones Wittig and his co-workers (Ber., 1924, 57B, 88 ; Ann., 1925, 446, 155) obtained a mixture of 2,7-dimethyl-6-chlorochromone and 4,7-dimethyl-6-chlorocoumarin by the Kostanecki-Robinson acylation of 4-chloro-6-acetyl-m-cresol. In the Kostanecki-Robinson acetylation, propionylation and chloro-acetylation of 2-propionyl-4-chlorophenol they obtained exclusively the chromones. The same authors (loc.cit.) obtained a mixture of coumarin and chromone by heating 4-chloro-2-acetylphenol with propionic anhydride and sodium propionate. In acetylation of 2-benzoyl-4-chlorophenol a coumarin derivative was formed. Similarly by heating 2-aceto-4-chloro-5-methylphenylacetate with propionic anhydride and sodium propionate 3,4,7-trimethyl-6-chlorocoumarin was formed ; on Kostanecki acetylation of 2-isobutyro-4-chlorophenol the same authors have reported the formation of 2-acetoxy-2,3, 3-trimethyl-6-chloro-8-acetochromanone.

Chakravarti and Bagchi (J. Indian Chem. Soc., 1936, 13, 689) subjected 4-chloro-2-aceto-1-naphthol and 4-chloro-2-propio-1-naphthol to Kostanecki-Robinson acylation.

With sodium acetate and acetic anhydride both aceto- and propionaphthols gave exclusively chromones. With sodium propionate and propionic anhydride however both the ketones gave coumarin derivatives. With phenylacetic anhydride and sodium phenylacetate 4-chloro-2-aceto-1-naphthol gave 3-phenylcoumarin derivative and with benzoic anhydride and sodium benzoate the 3-benzoylflavone derivative.

Chakravarti and Majumdar (J. Indian Chem. Soc., 1939, 16, 151) studied Kostanecki-Robinson reaction on the halogenated aceto-, propio-, and butyrophenones to find out whether the halogen atoms have any marked influence on the formation of γ-pyrones as in Simonis' reaction. 5-Chloro-3-methyl-2-hydroxyacetophenone, 3-chloro-5-methyl-2-hydroxyacetophenone, 5-chloro-3-methyl-2-hydroxypropiophenone-3-chloro-5-methyl-2-hydroxypropiophenone, 5-chloro-2-hydroxypropiophenone and 5-bromo-2-hydroxypropiophenone were subjected to the Kostanecki-Robinson acetylation, propionylation and butyrylation. 3-Acetylchromones were obtained in the acetylation of acetophenones but in the in propionylation coumarins were obtained which were identical with the coumarins obtained from the appropriate phenols and ethyl α-methyl-acetoacetate by the Pechmann reaction (Chakravarti and Banerjee, J. Indian Chem. Soc., 1936, 13, 619). The halogenated o-hydroxypropiophenones on acetylation gave exclusively chromones. Similarly the products obtained in the propionylation of o-hydroxypropiophenones were also chromones and no trace of a coumarin was detected by the Wittig's method (Ber., 1924, 57, 88) of separation of coumarins from chromones. The products obtained in the butyrylation of the halogenated *o*-hydroxypropiophenones were also chromones.

The effect of the nitro group on the course of the Kostanecki-Robinson reaction has also been studied. Wittig, Bangert and Richter (loc.cit.) obtained 2,6-dimethyl-3-acetyl-8-nitrochromone in the Kostanecki-Robinson acetylation of 2-acetyl-4-methyl-6-nitrophenol. Baker (J. Chem. Soc., 1930, 261) synthesised 7-hydroxy-3-phenyl-2-(*o*-nitrophenyl) chromone by heating *o*-nitrobenzoic anhydride and sodium *o*-nitrobenzoate with 2,4-dihydroxyphenylbenz~~o~~yl ketone.

Naik and Thakor (Proc. Indian Acad. Sci., 1953, *37A*, 774) studied the Kostanecki-Robinson reaction on various nitro *o*-hydroxyacetophenones. 2,6-Dihydroxy-3-nitroacetophenone on Kostanecki-Robinson acetylation gave 5-hydroxy-2-methyl-6-nitrochromone and 5-hydroxy-2-methyl-3-acetyl-6-nitrochromone and on benzoylation gave 5-hydroxy-6-nitroflavone and 5-hydroxy-3-benzoyl-6-nitroflavone. 2-Hydroxy-3-nitro-6-methoxyacetophenone gave 5-hydroxy-2-methyl-8-nitrochromone. 2,4-Dihydroxy-5-nitro-acetophenone on a similar acetylation and benzoylation gave 7-hydroxy-2-methyl-3-acetyl-6-nitrochromone and 7-hydroxy-3-benzoyl-6-nitroflavone respectively. The Kostanecki-Robinson acetylation and benzoylation of 2,4-dihydroxy-3-nitro-acetophenone gave a dark unworkable mass.

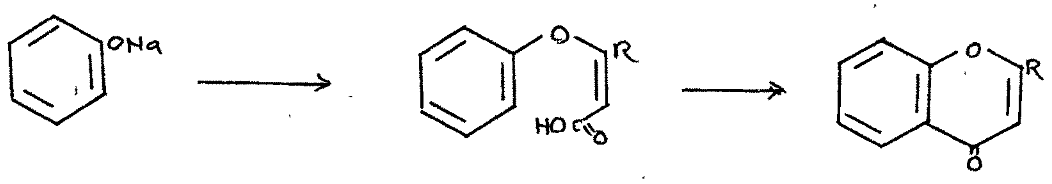
The effect of the carboxy and carbomethoxy groups on the course of the Kostanecki-Robinson reaction has also been investigated.

Desai and Desai (J. Sci. Ind. Research, India, 1954, 13B, 249) subjected methyl 2,4-dihydroxy-3-bromo-5-acetylbenzoate to Kostanecki-Robinson acetylation and obtained methyl 7-hydroxy-8-bromo-3-acetyl-2-methylchromone-6-carboxylate . Joshi and Shah (J. Indian Chem. Soc., 1954, 223) studied the acetylation of 1-acetyl-2-hydroxy-3-naphthoic acid and its ester and obtained 2'-methyl-3'-acetyl-1,4-β-naphtho-γ-pyrone-3-carboxylic acid and its ester respectively. Desai et al. (J. Indian. Chem. Soc., 1960, 37, 491) subjected 5-butyryl and 5-propionyl derivatives of methyl 2,4-dihydroxybenzoate to Kostanecki-Robinson acetylation and obtained a mixture of the corresponding carbomethoxy and carboxy derivatives of chromones. Further, 3-acetyl- and 3-propionyl derivatives of methyl 2,4-dihydroxybenzoate on a similar acetylation gave a mixture of 5-hydroxy-3-acyl-2-methylchromone-6-carboxylic acid, its methyl ester and 5-hydroxy-3-acyl-2-methylchromone.

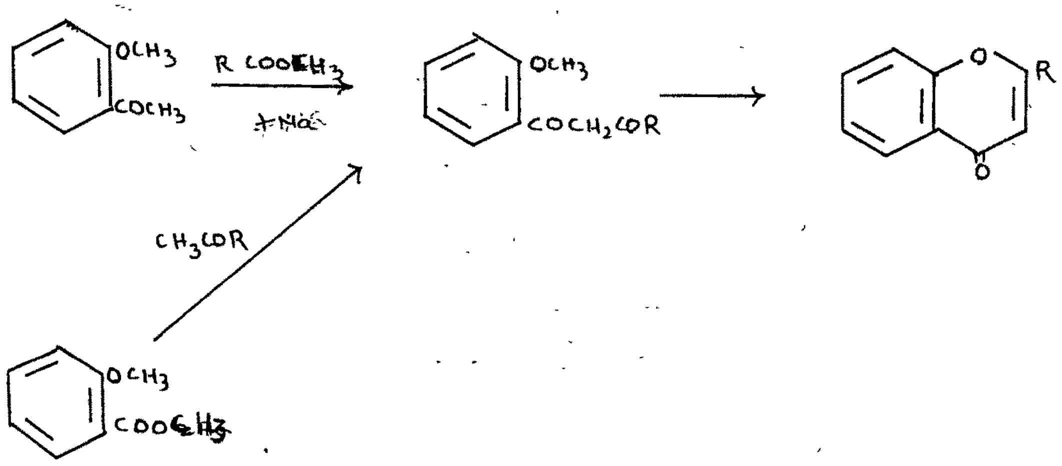
Thus both the nitro and the carboxy or carbomethoxy groups have no specific effect on the course of the Kostanecki-Robinson reaction.

2. Cyclisation of β-phenoxy acrylic acids : When sodium phenolates are condensed with ethyl chlorofumarate, ethyl phenylpropiolate and ethyl-β-chloro~~carbonate~~crotonate are obtained which can be cyclised with concentrated sulphuric acid, phosphorous pentachloride or aluminium chloride to chromones (Ruhemann et al. J. Chem. Soc., 1900, 77, 1185 etc. ; Ber., 1913, 46

2188 ; 1920, 53, 285).

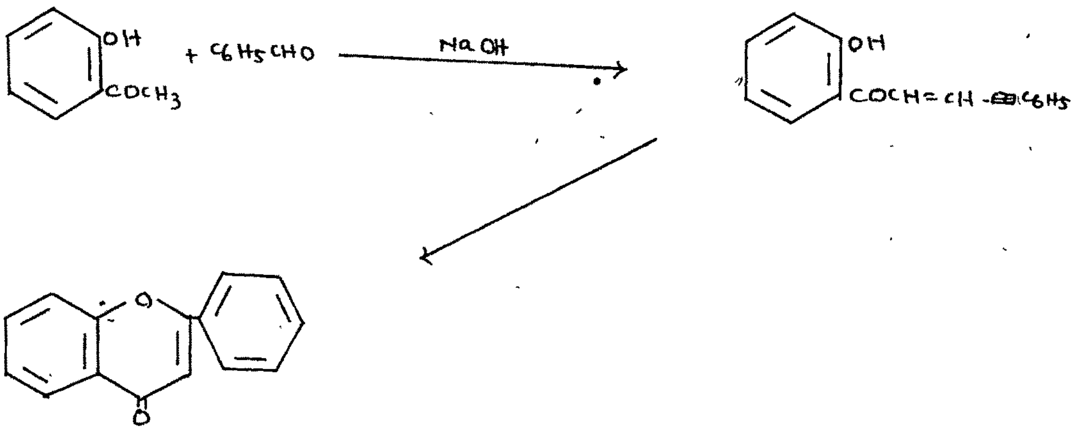


3. Cyclisation of β-diketones : When esters of aliphatic or aromatic acids are condensed with o-methoxyacetophenones, β-diketones are formed which can be cyclised to chromones or flavones by heating with hydriodic acid (Kostanecki, Ber., 1900, 33, 330, 471 etc.). Alternately esters of o-methoxybenzoic acids can be condensed with ketones and the β-diketones formed cyclised with hydriodic acid (Kostanecki, Ber., 1900, 33, 32, 1998) to the corresponding chromones or flavones.



4. Cyclisation of chalkones : o-Hydroxyacetophenones on condensation with aromatic aldehydes in presence of aqueous alkali or sodium ethylate yield chalkones (Kostanecki, Ber., 1898, 31, 696). These can be converted directly into flavones by heating with selenium dioxide (Mahal et al. J. Chem. Soc., 1935, 866) ~~170]~~ or cyclised first to flavanones by heating with a mineral acid and then subjected to phosphorous pentachloride or selenium dioxide treatment (Kostanecki and Szabranski, Ber., 1904, 37, 2634 ; Lowenbein, Ber., 1924, 57, 1515 ; Mahal et al. J. Chem. Soc., 1935, 866). ~~loc.cit. ; Venkataraman et al., J. Chem. Soc., 1935, 866)~~.

The chalkones could be converted into the chalkone dibromides and then heated with alkali to get the flavones (Kostanecki loc.cit. ; Wheeler et al., J. Chem. Soc., 1937, 1798).

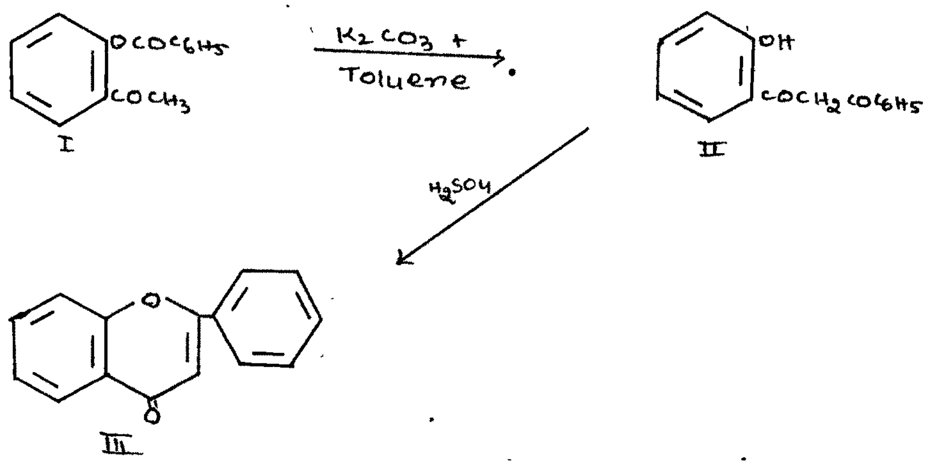


5. Simonis Reaction : When phenols are condensed with β-ketonic esters in presence of phosphorous pentoxide coumarins are obtained if the phenols are reactive but chromones are obtained if they are not reactive (Simonis et al., Ber.,1913, 46,2014 ; 1914,47,692,2229 ; Chakravarti, J. Indian Chem. Soc.,

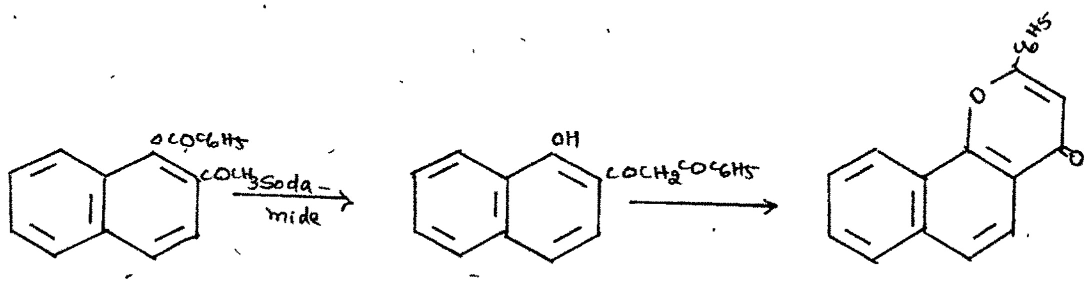
1931, 8, 31, 407). Thus resorcinol, phloroglucinol, α-naphthol etc give coumarins when condensed with β-ketonic esters but phenol, β-naphthol, β-anthrol etc. give chromones.

6. Molecular rearrangement of o-acyloxy-aceto-arones (Baker- Venkataraman transformation) :

Baker (J. Chem. Soc., 1933, 1386) observed that o-benzoyloxyaceto-arones or their derivatives (I) rearrange to o-hydroxydibenzoylmethanes (II) when treated with anhydrous potassium carbonate in presence of dry benzene or dry toluene which can be cyclised to the corresponding flavones (III) by treatment with suitable dehydrating agents such as sulphuric acid or boiling acetic acid and sodium acetate.



At about the same time Mahal and Venkataraman (Current Sci., 1933, 2, 214 ; J. Chem. Soc., 1934, 1767) while attempting to convert 2-acetyl-1-naphthylbenzoate (IV) to α-naphthylflavone (VI) by direct ring closure observed that the action of sodamide on 2-acetyl-1-naphthybenzoate (IV) in dry ether solution gave ω-benzoyl-2-acetyl-1-naphthol (V) which with sulphuric acid underwent cyclisation to yield flavone (VI)



IV V VI

Many other reagents are also used to bring about this transformation viz. sodium metal (effective in bringing about the migration of esters of both aliphatic and aromatic acids) (~~Heilbron et al~~. ~~J. Chem. Soc., 1934, 1311 ;~~ Virkar and Wheeler, J. Chem. Soc., 1939, 1679), potassium carbonate (Baker, loc. cit). and sodiun ethoxide (Ullal, Shah and Wheeler, J. Chem. Soc., 1940, 1499 ; J. Univ. Bombay, 1941, X(3), 118).

7. Condensation of β-ketonic esters with phenol without the use of any condensing agent

Mentzer et al. (Bull. Soc. Chem., France, 1953, 538) found that if a phenol was heated with β-ketonic esters at a high temperature (about 250°) without any condensing agent, chromones were produced instead of the coumarins. Desai, Trivedi and Sethna (J. M.S.University of Baroda 1955, IV, No. 2 , 1) found that the reaction was more rapid and better products were obtained if diphenyl ether was used as a solvent and the reaction mixture refluxed with a short condenser to remove the water formed.

Substitution in chromones and flavones

The chromones and flavones have been subjected to many substitution reactions. As a part of the present work deals with the iodination of chromones and flavones the work on the halogenatio of chromones and flavones is described here in detail. In addition a few other reactions such as nitration, sulphonation, formylation, Fries and Claisen rearrangements, coupling and Mannich reactions of some chromones and flavones, though not directly connected with the present work, have been described to illustrate the general pattern of substitution in simple and substituted chromones and flavones.

(A) Fluorination :

No direct fluorination of chromones and flavones is attempted so far but fluorochromones and flavones have been synthesised indirectly (Whalley, J. Chem. Soc., 1951, 3229 ; Chen and Shu, J. Taiwan Pharm. Assoc., 1953, 5, 49 ; C.A. 1955, 49, 6929).

(B) Chlorination :

Offe (Ber., 1938, 71B, 1837) claimed to have obtained 2-chloromethylchromone by refluxing 2-methylchromone with manganese dioxide and hydrochloric acid in acetic acid solution. 2-Trichloromethylchromone was obtained in the same way by using three moles of manganese dioxide. The structures were assigned on the assumption that chromone derivatives halogenated at the double bond between carbon atoms 2 and 3 are very unstable and yield simple salicyclic acids on alkaline hydrolysis. Wittig et al. (Liebig's Ann., 1925, 446, 155) chlorinated 6-chloro-2-methylchromone using manganese dioxide and hydrochloric acid and obtained 3,6-dichloro derivative

derivative identical with the product obtained on Kostanecki-Robinson acetylation of ω,5-dichloro-o-hydroxyacetophenone.

Duncanson et al. (J. Chem. Soc., 1957, 3555) prepared 5,7-dihydroxy-8-chloro-4'-methoxyflavone by heating 5,7-dihydroxy-4'-methoxyflavone with sulphuryl chloride in acetic acid. Gowan et al. (Tetrahedron, 1958, 2, 116) isolated 7-chloroflavone by heating 7-hydroxyflavone with phosphorous oxychloride.

Bromination :

Simonis and Herovici (Ber., 1917, 50, 646) studied the bromination of 2,3-dimethylchromone and obtained a dibromo product. They stated that the compound merely absorbed bromine at the ethylene linkage and that bromine atoms were given up when the product was dried. They observed that under drastic conditions methyl groups were affected and benzene nucleus was only affected in extreme cases. This was proved by the fact that simpler bromo derivatives yielded unsubstituted salicylic acids on hydrolysis. Thus ω-bromo- and ω,ω-dibromo-2,3-dimethylchromone could be obtained. Bromination in carbon disulphide with a little iodine gave tribromo- and tetrabromo- derivatives to which they did not assign any definite structures. Arndt et al. (Ber., 1925, 58B, 1612) brominated chromone with bromine in carbon disulphide and obtained a colourless dibromide which on heating with alcohol or other solvents yielded a monobromo derivative to which they assigned 3-bromochromone structure. Later Colonge and Guyot (Bull. Soc. Chim., France, 1958, 325) in their studies on bromination of chromones and chromanones obtained 2,3-dibromochromanone which on treatment with piperidine in ether yielded 3-bromochromone m.p. 93° different from Arndt's 3-bromochromone m.p. 65°. Thus Arndt's bromochromone must have some other structure. They also brominated 6-methylchromone and 7-methylchromone and obtained 2,3-dibromochromanone derivatives which on similar treatment with piperidine gave 6-methyl-3-bromo and 7-methyl-3-bromochromone. 8-Methylchromone on bromination and subsequent treatment with piperidine gave 3-bromo-8-methylchromone. Desai et al. (Rasayanam, 1938, <u>1</u>, 155 ; J. Indian Chem. Soc., 1952, <u>29</u>, 447) brominated 2',3'-dimethyl-1,2-naphtho-γ-pyrone and its 4-bromo-and 4-nitro derivatives as well as 2'-methyl-3'-ethyl,1,2-naphtho-γ-pyrone with bromine in chloroform and found that in each case a perbromide was obtained and this was assumed to be formed by addition of two bromine atoms to the pyrone oxygen. These bromine atoms were removed on treatment with sulphurous acid with the regeneration of the original pyrones. They also observed that chromones with hydroxyl groups react with bromine in chloroform to yield substituted pyrones. Baker and Robinson (J. Chem. Soc., 1925, 1424) brominated 7-methoxy-3-hromopiperonyl-2-methylchromone and obtained the dibromide which on boiling in water gave 7-methoxy-3-(6-bromohomopiperonyl-)-2-methylchromone. Offe (loc.cit.) brominated 2-methylchromone by refluxing its acetic acid solution with bromine and manganese dioxide and obtained a bromo derivative to which he assigned 2-bromomethylchromone structure as it was stable and gave salicyclic acid on alkaline hydrolysis. Bromination with bromine in acetic acid (with or without sodium acetate) gave the di- and tri-bromo derivatives to which no definite structures were assigned. Winter and Hamilton (J. Amer. Chem. Soc., 1952,74,3999) for the first time used N-bromosuccinimide for bromination of chromones. They obtained the same monobromo-2-methylchromone from 2-methylchromone as reported by Offe with either N-bromosuccinimide in carbon tetrachloride or bromine in acetic acid. They assigned 3-bromo-2-methylchromone structure. In assigning the structure particular emphasis was laid on the low reactivity of the bromine atom which is characteristic of α-bromo-α,β-unsaturated carbonyl compounds. This was confirmed by an iodine release study which gave negative results characteristic of such a system. But they found that it reacted with piperidine to yield 3-piperidino derivative and this was explained as due to initial 1,4-addition and subsequent removal of hydrobromic acid with simultaneous rearrangement. Wiley (J. Amer. Chem. Soc., 1952, 74, 4326 ; 4329) brominated 7-methoxy-2-methylchromone and 6-methoxy-2-methylchromone with N-bromosuccinimide and obtained the monobromo derivatives in both the cases, which were considered to be 2-bromomethylchromones. In support of these structures he converted the 6-methoxy compound into dimethylaminomethyl derivative which was different from the Mannich reaction product of 6-methoxy-2-methylchromone, on reaction with formaldehyde and dimethylamine hydrochloride. The Mannich reaction was considered to take place in 3-position and hence the product obtained in the initial bromination was considered to be substituted in 2-position. Seshadri and co-workers (J. Sci. Ind. Research, India, 1954, 13B, 160) brominated 7-methoxy-2-methylchromone with N-bromosuccinimide using benzoyl peroxide as a catalyst and with bromine in acetic acid and obtained the same bromo compound as reported by Wiley (loc. cit.). They directly synthesised 7-methoxy-2-bromomethylchromone by treating 2-ethoxymethyl-7-methoxychromone with hydrobromic acid. This was different from the above bromochromone derivative. Therefore they assigned 7-methoxy-3-bromo-2-methylchromone structure to Wiley's bromo compound. 7-Acetoxy-2-methylchromone on bromination with N-bromosuccinimide in presence of benzoyl peroxide gave 7-acetoxy-3-bromo-2-methylchromone.

Naik and Sethna (J. Indian Chem. Soc., 1952, 29, 493) ~~were the first~~ ~~to~~ systematically investigated the reactivity of hydroxychromones in bromination. They brominated 7-hydroxy-2-methylchromone and 5-hydroxy-2-methylchromone with bromine in acetic acid. Monobromination of these chromones furnished the 8-bromo derivatives and the dibromination products were the 6,8-dibromo derivatives. Structures were assigned by degradation to the known bromo-acetophenones. Further bromination with liquid bromine yielded tribromo derivatives to which the tentative structures of 3,6,8-tribromo derivatives were assigned. They also brominated 5-hydroxy-8-

nitro-2-methylchromone and obtained the 6-bromo derivative. Desai and Desai (J. Sci. Ind. Research, India, 1954, 13B, 249) brominated 7-hydroxy-6-ethyl- and 7-hydroxy-6-propyl-2-methylchromone with bromine in acetic acid and assumed the formation of the 8-bromo derivatives. Desai et al. (J. Indian Chem. Soc., 1954, 145) brominated 7-hydroxy-2,3-dimethylchromone and 7-hydroxy-2-methyl-3-ethylchromone and obtained the 8-bromo and the 6,8-dibromo derivatives. Structures were assigned by hydrolysis to the known resorcinol derivatives. 6-Hydroxy-2-methylchromone on bromination gave the 8-bromo and the 5,8-dibromo derivatives (Desai et al. J. Sci. Ind. Research, India, 1954, 13B, 328). The structures were assigned from the results of their hydrolysis to the known bromoquinacetophenones. Schonberg et al. (J. Amer. Chem. Soc., 1953, 75, 4992) found that the action of bromine in chloroform on 5-methoxy-7-hydroxy-6-formyl-2-methylchromone resulted in the 8-bromo derivative.

Early attempts at the bromination of naturally occuring flavones yielded the bromo derivatives to which no definite structures were assigned (Piccard, Ber., 1878, 6, 884 ; Jahns, Ber., 1881, 14, 2389, 2809 ; Perkin et al., J. Chem. Soc., 1896, 69, 209, 1897, 71, 807 ; 1902, 81, 58 Fainberg and Kostanecki, Ber., 1904, 37, 2626). Limaye et al. (Rasayanam, 1956, 2, 121) brominated flavone and obtained 3-bromoflavone, the position of the bromine atom being proved by its conversion to coumarone with alkali. Jadhav and co-workers (J. Uni. Bombay, 1957, 25, 1) brominated

6-nitro-7-hydroxy-2'-methoxy-5'-bromoflavone and obtained 3,8,5'-tribromo-6-nitro-7-hydroxy-2'-methoxyflavone. 6-Nitro-7-benzyloxy-4'-methoxyflavone and 6-methyl-8-nitroflavone on bromination gave the corresponding 3-bromoflavone derivatives in both the cases. Gowan et al. (loc. cit.) isolated 7-bromoflavone on fusion of 7-hydroxyflavone with phosphorous pentabromide and sodium chloride. Wagh and Jadhav (J. Uni. Bombay, 1958, 26, 28) brominated by refluxing with bromine and acetic acid 6-bromo-3',4'-dimethoxy-7,8-benzoflavone and 6-bromo-3',4'-methylenedioxy-7,8-benzoflavone and obtained the corresponding 3-bromoflavone derivatives.

Iodination :

Piccard (Ber., 1873, 6, 887) iodinated 5,7-dihydroxyflavone with iodine and iodic acid and obtained a di-iodo derivative to which he did not assign any structure. Offe (loc. cit.) iodinated 2-methylchromone with iodine and manganese dioxide by refluxing its chloroform solution and obtained a monoiodo derivative to which he assigned the 2-iodomethylchromone structure as it could be converted into a phenyl ether by heating with phenol. No other work on the iodination of chromones and flavones appears to have been reported.

The results obtained in the application of a few other substitution reactions ~~on~~ to chromones and flavones may now be briefly described to indicate the range of the work done and the pattern of substitution.

Nitration :

Simonis and co-workers (Ber., 1913, 46, 2014 ; 1917, 50, 790) obtained the 6-nitro derivatives from 2,3-dimethyl- and 2,3,5,7-tetramethylchromone on nitration. They established the structures on the basis of the nitrosalicylic acid derivatives obtained on oxidation. Shah and co-workers (Proc. Indian Acad. Sci., 1949, 29A, 314 ; 1953, 38A, 31) nitrated 7-hydroxy- and 5-hydroxy-2-methylchromone and their methyl ethers and obtained the 8-nitro and the 6,8-dinitro derivatives. Demethylation occurred in the dinitration of 5-methoxy-2-methylchromone. The structures were assigned from their hydrolysis to the known nitro-acetophenones. Naik and Sethna (J. Indian Chem. Soc., 1952, 29, 493) obtained the 6-nitro derivative in the nitration of 5-hydroxy-8-bromo-2-methylchromone. The corresponding 6,8-dibromochromone on nitration at room temperature gave the 6-nitro-8-bromochromone and at 100° it gave the 6,8-dinitro derivative, both the bromine atoms being replaced by the nitro groups. Schonberg et al. (J. Amer. Chem. Soc., 1953, 75, 4992) found that 5,7-dihydroxy-6-formyl-2-methylchromone and its 5-O-methyl derivative gave the 8-nitro derivatives. Desai et al. (J. Indian. Chem. Soc., 1954, 31, 145) nitrated 7-hydroxy-2,3-dimethyl- and 7-hydroxy-2-methyl-3-ethylchromone and obtained the 8-nitro compounds. Nitration under more drastic conditions yielded 3,5-dinitroresorcylic acid. Da Re (Farmaco (Pavia) Ed. Sci., 1956, 11, 662)nitrated chromone, 3-methyl- and 3-

ethylchromone and obtained the 8-nitrochromones but in the nitration of 2-methyl-, 2-ethyl- and 2,3-dimethylchromone the 6-nitrochromone derivatives were obtained. Joshi et al. (J. Indian Chem. Soc., 1959, 36, 59) obtained the 8-nitrochromone derivatives from 7-hydroxy-, 5-methoxy- and 7-methoxychromone and the 5-nitro derivative in the case of 6-chlorochromone.

Early attempts at nitration of the naturally occurring flavones yielded nitro products of which the structures were not established (Piccard, Ber., 1873, 6, 888 ; Perkin, J. Chem. Soc., 1900, 77, 417 ; Watson, J. Chem. Soc., 1914, 105, 306 ; 314 ; 1915, 107, 207). Bogert and Marcus (J. Amer. Chem. Soc., 1919, 41, 83) nitrated flavone but failed to isolate any pure nitroflavone. After reduction 2'-amino-, 3'-amino- and 4'-aminoflavone were isolated. Shah and co-workers (loc. cit.) nitrated 7-hydroxy- and 5-hydroxyflavone and their methyl ethers and degraded the nitroflavones obtained to the known nitro-acetophenones. 5-Hydroxy-, 7-hydroxy- and 7-methoxyflavone gave the 8-nitro and the 6,8-dinitro derivatives. Further, 7-hydroxyflavone and its methyl ether gave the 6,8,4'-trinitro derivatives. 6-nitro- or 8-nitro-5-hydroxyflavone gave the same 6,8-dinitro derivative. 5-Methoxyflavone gave a dinitro derivative the structure of which was not established.

Sulphonation :

Early attempts at sulphonation consisted only in sulphonating a number of naturally occurring flavones but the structures were not assigned to the sulphonated products. (Benedikt and Hazura, Monatsh, 1884, <u>5</u>, 667 ; Herzig, Monatsh, 1896, <u>17</u>, 421 ; Watson and Sen, J. Chem. Soc., 1914, <u>105</u>, 393).

Kruger (Ber., 1923, <u>56B</u>, 487) did not succeed in the sulphonation of chromone but obtained a monosulphonic acid in the sulphonation of 2,3-dimethylchromone with sulphuric acid of 50 % anhydride content to which he arbitrarily assigned the 6-sulphonic acid structure. This was confirmed by Shah and co-workers (J. Org. Chem., 1956, <u>21</u>, 1104) who further found that in the sulphonation of 7-hydroxy-2-methylchromone and its methyl ether the 8-sulphonic acids were formed. On further sulphonation both gave the 6,8-disulphonic acids. In the case of 5-hydroxy-2-methylchromone and its methyl ether only monosulphonic acids were obtained to which no definite structures were assigned. 7-Hydroxy- and 5-hydroxyflavone on sulphonation yielded the 8-sulphonic acids and the 6,8-disulphonic acids. They also obtained the 6,8,2'-trisulphonic acid derivatives. The structures were assigned from the results of nitration on the assumption that the sulphonic acid group was replaced by the nitro group.

<u>Formylation</u> :

8-Formyl derivatives were obtained from 7-hydroxy-3-methoxy- and 7-hydroxy-3-methoxy-2-methylchromone on heating with hexamin. 5-Hydroxy-2-methyl-7-(carbethoxymethoxy) chromone gave the 6-formyl derivative on similar treatment.

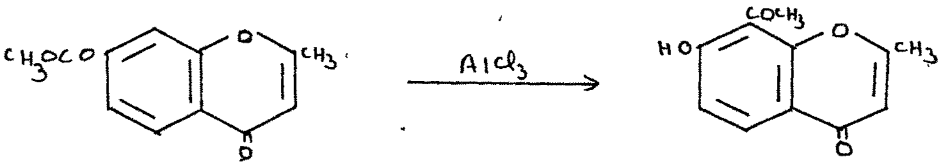
On hexamin treatment 6-hydroxyflavone yielded the 5-formyl derivative and 7-hydroxy- and 5-hydroxyflavone the 8-formyl derivatives. 5,7-Dihydroxy-8-methylflavone gave the 6-formyl derivative on a similar treatment. 5,7,8-Trihydroxyflavone and 5,7,8-trihydroxy-2-methylchromone however did not give any formyl derivative on hexamin treatment but - on Gattermann reaction the 6-formyl derivatives were obtained. Their 8-methyl ethers however gave the 6-formyl derivatives on hexamin treatment. (Seshadri and co-workers, Proc. Indian Acad. Sci., 1939, 9A, 7 ; 1949, 30A, 107 ; 1951, 33A, 148 , 168 ; 1950, 32A, 250 ; 1952, 36A, 217 ; 1959, 50A, 192).

Seshadri and co-workers (J. Sci. Ind. Research, India, 1954, 13B, 539 ; Australian J. Chem., 1955, 8, 409 ; J. Chem. Soc., 1955, 3908) obtained 8-formyl derivatives from 5,7-dihydroxy-3,3',4'-trimethoxyflavone and 5,7-dihydroxy-2,8-dimethylchromone and the 5-formyl derivatives from 6-hydroxy-3,7-dimethoxyflavone, 6-hydroxy-3,4',7-trimethoxyflavone and 6-hydroxy-3,3',4',7-tetramethoxyflavone on reaction with hexamin.

Seshadri and co-workers (Proc. Indian Acad. Sci., 1950, 31A, 31) reported the synthesis of 6-formyl derivative from 5-hydroxy-8-methoxyflavone by hexamin treatment but Wheeler et al. (Tetrahedron, 1958, 2, 120) obtained mainly di(5-hydroxy-8-methoxyflavon-6-yl)- methane from this reaction. The structures of the formyl derivatives have been generally proved by Dakin Oxidation of the formyl derivatives to the corresponding hydroxy derivatives.

Fries migration :

Wittig et al (Ann. 1925, 446, 105 ; Ber., 1926, 59B, 116) obtained the 8-acyl derivatives on heating 7-acetoxy- and 7-propionyloxy-2-methylchromone with aluminium



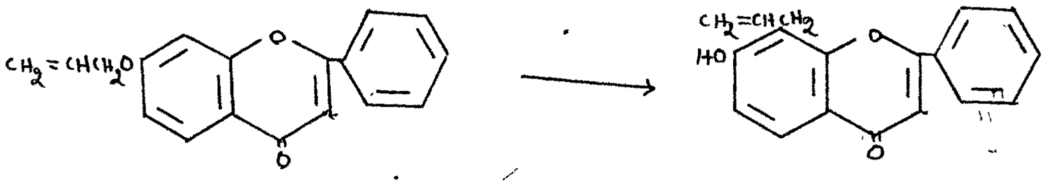
chloride. Kelkar and Limaye (Rasayanam, 1936, 1, 60) observed that in the case of 5-acetoxy- and 7-acetoxy-3-acetyl-2-methylchromone only 5-hydroxy- and 7-hydroxy-3-acetyl-2-methylchromone were obtained. No 8-acetyl derivatives of 5-hydroxy- and 7-hydroxy-2-methylchromone were obtained as reported by Baker (J. Chem. Soc., 1934, 71). The same authors (Rasayanam, 1939, 1, 183) also failed in the Fries migration of 7-benzoyloxy-3-acetyl-2-methylchromone. However, they obtained the 8-acyl derivatives from 7-benzoyloxy-2-methylchromone and 7-acetoxy- and 7-propionyloxy-

2,3-dimethylchromone. Baker (J. Chem. Soc., 1934, 1953) obtained the 6-acetyl derivative from 5-acetoxyflavone but 6-acetoxyflavone did not undergo the Fries migration, only 6-hydroxyflavone being obtained. Venkataraman and co-workers (Proc. Indian Acad. Sci., 1936, 3A, 206) observed that in the Fries rearrangement of 7-benzyloxyflavone only the ~~unchanged~~ 7-hydroxyflavone was obtained.

Row and Seshadri (Proc. Indian Acad. Sci., 1940, 11A, 206) in their attempted Fries migration of 7-chloroacetoxy-3-methyoxyflavone and 7-chloroacetoxyflavone obtained 3-hydroxyflavino-7,8-β-furanone and flavino-7,8-β-furanone, showing that the cyclisation had also occurred.

Claisen Rearrangement :

Seshadri and Rangaswami (Proc. Indian Acad. Sci., 1939, 9A, 1) obtained almost a quantitative yield of 8-allyl derivative on rearrangement of 7-allyloxyflavone.



7-Allyloxy-8-allylflavone underwent further migration to yield 7-hydroxy-6,8-diallylflavone.

8-Allyl derivatives were obtained from 7-allyloxy-2-methylchromone, 7-allyloxy-3-methoxy-2-methylchromone, 7-allyloxy-3-methoxyflavone, 5-hydroxy-7-allyloxy-3-methoxy-2-methylchromone (Davis and Norris, J. Chem. Soc., 1949, 3080 ;

Seshadri and co-workers, Proc. Indian Acad. Sci., 1941, <u>14A</u>, 289 ; J. Sci. and Ind. Research, India., 1953, <u>12B</u>, 283).

<u>Coupling Reaction</u> :

Perkin (J. Chem. Soc., 1898, <u>73</u>, 666) obtained bis-azo derivatives, from apigenin, chrysin and morin by reaction with diazobenzene to which no structures were assigned. Rangaswami and Seshadri (Proc. Indian Acad. Sci., 1939, <u>9A</u>, 1) found that 7-hydroxy-8-allylflavone, 7-hydroxy-8-methylflavone, 7-hydroxy-8-methyl-3-methoxyflavone, 7-hydroxy-8-allyl-2-methyl-3-methoxychromone yielded highly coloured dyes when coupled in alkaline solution with diazotised p-nitraniline, indicating the reactivity of the 6-position in compounds which are already substituted in the 8-position. The same authors (Proc. Indian Acad. Sci., 1939, <u>9A</u>, 526) examined the behaviour of 7-hydroxy-2-methyl-3-methoxychromone and 7-hydroxyflavone with regard to the formation of azo dyes in order to study the extent of rigidity of the ~~fixation of~~ double bonds. In the case of the former they observed a considerable formation of bis-azo dye even when a molecular proportion of diazonium salt was employed. With more than two molecular proportions the formation of bis-azo dye was complete. On the other hand in the case of 7-hydroxyflavone the mono-azo dye was obtained pure with one molecular proportion while with a large excess of the diazonium salt only a small quantity of bis-azo dye was produced along with a large amount of the mono-azo compound, which was still the main component. ~~Mahal and~~

Venkataraman and co-workers (Current Sci., 1938, 6, 450 ; Proc. Indian Acad, Sci., 1946, 23A, 278) observed the formation of only 5-phenyl azo dye in the case of 6-hydroxyflavone in accordance with the fixation of double bonds. Iyer and Venkataraman (Proc. Indian Acad. Sci., 1953, 37A, 629) condensed 5-hydroxyflavone with diazotised aniline and obtained the 8-phenyl azo dye. They also obtained 8-phenyl azo dyes from 5-hydroxy-3-benzoylflavone, tectochrysin and 5-hydroxy-6-methoxyflavone.

Mannich Reaction :

Wiley (J. Amer. Chem. Soc., 1952, 74, 4326) carried out the Mannich reaction on chromone with formaldehyde and dimethylamine and assigned the 3-dimethylaminomethylchromone structure to the product obtained. 3-Piperidinomethyl- and 3-morpholinomethylchromone were also prepared. Similar reactions on 6-methoxychromone, 7-methoxychromone, 6-methylchromone and 6-chlorochromone gave 3-substituted derivatives. 2-Methylchromone failed to condense with any base in this reaction. Structures have been assigned arbitrarily in all the cases. Da Re et al. (J. Org. Chem., 1960, 25, 1097) studied the Mannich reaction on 7-hydroxy-2,3-dimethyl and 7-hydroxy-3-methylflavone with formaldehyde and a number of bases and obtained the 8-substituted derivatives. In the case of 2,3-dimethyl-7-hydroxychromone with two moles of piperidine and formaldehyde they obtained the 6,8-dipiperidinomethyl derivative. The structures were assigned from a consideration of the reactivity of different positions and conversion to the 8-formyl derivatives in a few cases.

PRESENT WORK

A survey of the literature shows that iodination of chromones and flavones has not been systematically studied.

It was thought of interest to study the iodination of chromones and flavones to find out the pattern of substitution and compare it with similar bromination studies made by others. Further, the iodo compounds are substances of synthetical value and can be converted into the cyano compounds by the Rosenmund-von Braun reaction and into the bichromonyls and biflavonyls by the Ullmann reaction.

Part I deals with the synthesis of iodo chromones and flavones. In section (i) of this part the iodination of chromones and flavones using three different iodinating agents viz. (1) iodine and iodic acid, (2) iodine and ammonia and (3) iodine monochloride has been described. The structures of the iodo derivatives obtained have been established by hydrolysis to the corresponding iodo phenolic ketones, the structures of which have been proved.

Section (ii) of this part deals with the synthesis of the iodochromones and flavones by the Kostanecki-Robinson acetylation and benzoylation respectively of iodo derivatives from 2,4- and 2,6-dihydroxyacetophenones. Though the effect of the presence of various groups in the phenolic ketones on the course of the Kostanecki-Robinson reaction has been studied, no observations so far were available regarding the behaviour of the iodo compounds in the Kostanecki-Robinson reaction.