CHAPTER I

INTRODUCTION

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General Introduction

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. Flavanones are the 2,3-dihydro derivatives of the flavones. They do not occur as widely as flavones in nature.

The structures of a large number of flavones and flavanones 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 (1). Other flavones such as Quercitrin, Rhamnetin and 6,8-dihydroxyflavone are reported to reduce blood pressure (2), and to act as diuretics (3). Further, Calycopterin and its 4'-methyl ether, Herbacetin, Gossypetin etc. act as fish poisons (4,5) and the aminomethyl derivatives of flavones are reported to act as powerful central nervous system stimulants, especially on the brain stem and to have cardiokinetic and hypertensive action (6).

Further, the antioxidant properties of a large number of flavones and flavanols have been

studied and Gossypetin and Robinetin have been found to be of great potency (7,8). Seshadri (9) reviewed in 1959 the developments in the Chemistry of Flavonoids.

A number of methods are available for the synthesis of flavones and flavanones and these have been reviewed in detail in standard works (10) and need not be enumerated here.

The flavones and flavanones have been subjected to many substitution reactions. As the present work deals with substitution in flavones and flavanones, the previous work on substitution in flavones and flavanones has been briefly reviewed here to illustrate the pattern of substitution in flavones and flavanones.

Substitution in flavones and flavanones

Halogenation :

As a part of the present work deals with the iodination of flavones and flavanones the work on the halogenation of flavones and flavanones is described here in some detail.

Chlorination :

Duncanson et al. (11) prepared 5,7-dihydroxy-8-chloro-4'-methoxyflavone by heating 5,7-dihydroxy-4'-methoxyflavone with sulphuryl chloride in acetic acid. Pendse and Patwardhan (12) chlorinated 4'-methoxyflavanone

and obtained 3-chloro derivative. A few chloroflavanones have been prepared by cyclisation of chlorochalcones (13 to 19).

Bromination :

Early attempts at the bromination of naturally occuring flavones yielded the bromo derivatives to which no definite structures were assigned (20 to 23). Limaye et al. (24) brominated flavone and obtained 3-bromoflavone, the position of the bromine atom being proved by its conversion to coumarone with alkali. Jadhav et al. (25) brominated 6-nitro-7-hydroxy-2'-methoxy-5'-bromoflavone and obtained the 3,8,5'-tribromo derivative. 6-Nitro-7-benzyloxy-4'-methoxyflavone and 6-methyl-8-nitro flavone on bromination gave the corresponding 3-bromo derivative. Wagh and Jadhav (26) brominated, by refluxing with bromine and acetic acid, 6-bromo-3',4'-dimethoxy-7,8-benzoflavone and obtained the corresponding 3-bromoflavone derivative. Naik (27) brominated 5-hydroxyflavone and obtained the 6,8-dibromo and the 3,6,8-tribromo derivative. He also brominated 7-hydroxyflavone and obtained the 8-bromo, the 6,8-dibromo- and the 3,6,8-tribromo derivative. Cusker, Philbin and Wheeler (28) brominated 5-hydroxyflavone and obtained the 8-bromo derivative. Marathey and Athavale (29) synthesised 3,8-dibromo-6-ethyl-7-hydroxy flavanone and 6-ethyl-7-hydroxy-8-bromo-4'methoxyflavone, by brominating the

corresponding flavanone derivative and treating the bromoflavanone with alcoholic sodium hydroxide solution.

Bognar and Rakosi (30) brominated simple flavanone and obtained 3-bromoflavanone. Limaye et al. (31) brominated 6-methyl-4'-methoxyflavanone and 6-benzoyl-4'-methoxyflavanone and obtained the 3-bromo derivative in each case. The bromo derivative was converted into the corresponding coumarone derivative. The same authors also brominated 4'-methoxyflavanone and obtained the 3-bromo and the 3,3'-dibromo derivatives. Zemplen et al. (32) brominated 5,7-dimethoxy-4',6-diacetoxyflavanone and obtained the 3-bromo derivative. Masamatsu Hoshino (33) studied the bromination of flavanone and obtained 6-bromo-flavanone with one mole of bromine in acetic anhydride whereas bromine in acetic acid gave 3-bromoflavanone. Two moles of bromine in acetic acid gave 3,3,6-tribromo-flavanone. Similarly 6-methylflavanone gave the 8-bromo derivative. Chandorkar, Phatak and Kulkarni (34) brominated 5,3',4'-trimethoxyflavanone and obtained the 3-bromo derivative. The same authors also prepared 5,7-3',4'-tetramethoxy-3-bromoflavanone. Merio Suzuki (35) brominated 7-acetoxy-3-methylflavanone, 7-hydroxy-3-methyl-flavanone and 7-acetoxyflavanone with bromine in dioxan and obtained the 3-bromo derivative in all cases. The bromo flavanones were converted into flavone derivatives by treatment with alkali. Chen and Chan (36) brominated

5-methoxyflavanone with N-bromosuccinimide and obtained the 3-bromo, the 8-bromo and the 3,8-dibromo derivative. The same authors also brominated 5,7-dimethoxyflavanone and obtained the 8-bromoflavanone. Keogh, Philbin, Ushioda and Wheeler (37) brominated 5,7,3',4'-tetramethoxyflavanone and obtained the 8-bromo derivative. Several bromoflavanones have been obtained by isomerisation of the bromochalkones to bromoflavanones (38 to 42).

Iodination :

Piccard (43) iodinated 5,7-dihydroxyflavone with iodine and iodic acid and obtained a di-iodo derivative to which he did not assign any structure. Shah and Sethna (55) studied the iodination of 5-hydroxy- and 7-hydroxyflavone. The former gave 6,8-di-iodo derivative and the latter gave the 8-iodo and the 6,8-di-iodo derivatives. Wheeler et al. (37) iodinatdd 5-hydroxy-7,3',4'-trimethoxyflavanone and obtained the 3,6-(or 8) di-iodo derivative. Nakazawa and Ito (44) iodinated 5,7,4'-tribenzoyloxyflavanone with iodine and nitric acid and obtained the 8-iodo derivative. Several iodo-flavanones have been obtained by isomerisation of the iodochalkones (14,17,39,45).

Fluorination :

No direct fluorination of flavones and flavanones is attempted so far but fluoroflavones and flavanones have been synthesised indirectly by Whalley (46)

Chen and Shu (47), Chang,Chen,Chen,Hsu and Hung (17), Chen,Chen and Ueng (48) and Joshi and Jauhar (49).

The results obtained in the application of a few other substitution reactions on flavones and flavanones may now be briefly described.

Nitration :

Early attempts at nitration of the naturally occurring flavones yielded nitro products to which definite structures were not assigned (43,50,51). Bogert and Marcus (52) nitrated flavone but failed to isolate any pure nitroflavone. After reduction 2'-amino-,3'-amino and 4'-aminoflavone were isolated. Shah et al. (53) nitrated 7-hydroxy-and 5-hydroxyflavone and their methyl ethers,and degraded the nitroflavones obtained to the known nitroacetophenones. 5-Hydroxy-,7-hydroxy-and 7-methoxy-flavone gave the 8-nitro and the 6,8-dinitro derivatives. Further, 7-hydroxyflavone and its methyl ether gave the 6,8-4'-trinitro derivative. 6-Nitro- and 8-nitro-5-hydroxy-flavone gave the same 6,8-dinitro derivative. 5-Methoxy-flavone gave a dinitro derivative the structure of which was not established. Wheeler et al. (37) nitrated 5-hydroxyflavone and obtained the 8-nitro derivative. Fujise, Suzuki, Shinoda and Hoshino (54) nitrated flavanone and obtained the 8-nitro-and the 6-nitro isomers. Masamatsu. Hoshino ((33)) nitrated 6-methylflavanone and obtained 6-methyl-8-nitroflavanone. He also nitrated

4'-hydroxyflavanone and obtained the 3-nitro derivative.

Some other nitroflavanones have also been prepared by the isomerisation of the nitrochalkones (56 to 59).

Sulphonation :

Benedikt and Hazura (60), Herzig (61), Watson and Sen (62) sulphonated a number of naturally occurring flavones but the structures were not assigned to the sulphonated products. Shah et al. (63) sulphonated 7-hydroxy and 5-hydroxyflavone and obtained the 8-sulphonic acids and the 6,8-disulphonic acids. They also obtained the 6,8,2'-trisulphonic acid derivative. The structures were assigned from the results of nitration on the assumption that the sulphonic acid group was replaced by the nitro group.

No work on the sulphonation of flavanones has been carried out.

Formylation :

Seshadri et al. (64,65) studied the formylation of 6-hydroxyflavone with hexamine and obtained the 5-formyl derivative. 7-Hydroxy and 5-hydroxyflavone gave the 8-formyl derivatives. 5,7-Dihydroxy-8-methylflavone gave the 6-formyl derivative on a similar treatment. The 8-formyl derivative was obtained from 5,7-dihydroxy-3,3',4'-trimethoxyflavone and the 5-formyl derivatives from 6-hydroxy-3,7-dimethoxyflavone, 6-hydroxy-3,4',7-trimethoxy-

flavone and 6-hydroxy-3,3',4',7-tetramethoxyflavone on reaction with hexamine.

Seshadri et al. (66) reported the synthesis of 6-formyl derivative from 5-hydroxy-8-methoxyflavone by hexamine treatment but Wheeler et al. (67) obtained mainly di(5-hydroxy-8-methoxyflavone-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.

No formylation has been studied on flavanone derivatives.

Fries migration :

Baker (68) obtained the 6-acetyl derivative from 5-acetoxyflavone on Fries migration but 6-acetoxyflavone did not undergo the Fries migration, only 6-hydroxyflavone was obtained. Venkataraman et al.(69) observed that in the Fries rearrangement of 7-benzyloxy flavone only the unchanged 7-hydroxyflavone was obtained.

Row and Seshadri (70) found that the Fries migration of 7-chloroacetoxy-3-methoxyflavone and 7-chloroacetoxyflavone gave 3-hydroxyflavino-7,8-β-furanone and flavino-7,8-β-furanone respectively, showing that the cyclisation had also occurred.

No work on the Fries migration of flavanone derivatives appears to have been reported.

Claisen Rearrangement :

Seshadri and Rangaswami (71) obtained almost a quantitative yield of the 8-allyl derivative on rearrangement of 7-allyloxyflavone. 7-Allyloxy-8-allylflavone underwent further migration to yield 7-hydroxy-6,8-diallylflavone.

No work on the Claisen rearrangement of flavanone derivatives appears to have been reported in the literature.

Coupling Reaction :

Perkin (72) obtained bis-azo derivatives from apigenin, chrysin and morin by reaction with diazobenzene. No structures were assigned to these products. Rangaswami and Seshadri (73) found that 7-hydroxy-8-allylflavone, 7-hydroxy-8-methylflavone and 7-hydroxy-8-methyl-3-methoxyflavone yielded highly coloured dyes when coupled in alkaline solution with diazotised p-nitraniline. The same authors (74) examined the behaviour of 7-hydroxyflavone with regard to the formation of azo dyes. In the case of 7-hydroxyflavone they observed that the mono-azo dye was obtained pure with one molecular proportion of diazonium salt while with a large excess of the diazonium salt only a small quantity of a bis-azo dye was produced along with a large amount of a mono-azo compound, which was still the main component. Venkataraman et al. (75,76) observed the formation of only the 5-phenyl azo dye in the

case of 6-hydroxyflavone. Iyer and Venkatraman (76) 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.

No coupling reaction appears to have been carried out on flavanone derivatives.

Mannich Reaction :

Da Re et al. (77) 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.

Present work :

The present work forms a part of the systematic study of the chemistry of flavones and flavanones which has been going on in this laboratory for the past few years. Five aspects of the chemistry of flavones and flavanones have been studied in the course of the present work.

Chapter II deals with the iodination of flavones and flavanones which has been carried out by using either (1) iodine and iodic acid or (2) iodine and ammonia or (3) iodine monochloride as iodinating agent. The structures of the iodo derivatives obtained have been established by hydrolysis to the corresponding known phenolic iodo ketones and acids.

In chapter III, the chloromethylation of some flavones and flavanones has been described. The

chloromethyl derivatives have been converted into acetoxymethyl and formyl derivatives and into Mannich bases.

Chapter IV deals with the synthesis of biflavonyls from the mono iodo derivatives of flavones described in Chapter II by the Ullmann reaction. Some crossed Ullmann reactions between iodoflavones and iodobenzene have also been carried out.

Chapter V deals with the synthesis of cyano-flavones from the mono iodoflavones described in Chapter II by the Rosenmund-von Braun reaction. The hydrolysis of the cyano derivatives with sulphuric acid and potassium hydroxide has been studied.

Chapter VI deals with the Beckmann rearrangement of the oximes of some acetyl derivatives of flavones. The structure of the amino-flavones obtained have been proved by comparing them with the aminoflavones obtained from the corresponding nitroflavones of known orientation. Beckmann rearrangement of the oximes of some formyl flavones gave the corresponding cyano derivatives.

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