SUMMARY

The present studies deal with (i) the synthesis of iodo-chromones and -flavones by direct iodination and by the Kostanecki-Robinson acetylation and benzoylation of iodo phenolic ketones ; (ii) synthesis of cyano-chromones and -flavones, by the Rosenmund-von Braun reaction on the iodo-chromones and-flavones synthesised and by the Kostanecki-Robinson acetylation and benzoylation of cyano phenolic ketones and a study of the hydrolysis of the cyano-chromones and -flavones with acids and alkali ; (iii) synthesis of bichromonyl and biflavonyl derivatives by the Ullmann reaction on iodochromones and flavones and (iv) chloromethylation of some chromones and flavones and the conversion of some of the chloromethyl derivatives into acetoxymethyl, methoxymethyl and cyanomethyl derivatives.

Part I : Synthesis of iodo-chromones and-flavones

Section (i) : The iodination of 2-methyl-, 5-hydroxy-2-methyl- and 7-hydroxy-2-methylchromone and 5-hydroxy-and 7-hydroxyflavone has been studied with three iodinating agents : (i) iodine and iodic acid, (ii) iodine and ammonia and (iii) iodine monochloride.

2-Methylchromone and flavone could not be iodinated by any of these three methods.

5-Hydroxy-2-methylchromone on iodination with theoretical amounts of iodine and iodic acid gave a mono iodo derivative which has been assigned the 8-iodo structure as on nitration it gave a product identical with the iodination product of 5-hydroxy-6-nitro-2-methylchromone. Further, its methyl ether on alkaline hydrolysis gave 2-hydroxy-3-iodo-6-methoxyacetophenone. With twice the amounts of iodine and iodic acid 5-hydroxy-2-methylchromone gave the 6,8-di-iodo derivative. Its methyl ether on hydrolysis gave 2-hydroxy-3,5-di-iodo-6-methoxyacetophenone. Similar results were obtained on iodinating 5-hydroxy-2-methylchromone with iodine and ammonia and iodine monochloride. 5-Methoxy-2-methylchromone could not be iodinated by any of the three methods.

5-Hydroxyflavone on iodination with iodine and iodic acid gave the 6,8-di-iodo derivative. The structure was assigned on the basis of the hydrolysis results.

7-Hydroxy-2-methylchromone on iodination with iodine and iodic acid in different proportions gave a mono-iodo and a di-iodo derivative. These were methylated and hydrolysed when the former gave a mixture of 2-hydroxy-3-iodo-4-methoxyacetophenone and 2-hydroxy-3-iodo-4-methoxybenzoic acid and the latter gave a mixture of 2-hydroxy-3,5-di-iodo-4-methoxyacetophenone and 2-hydroxy-3,5-di-iodo-4-methoxybenzoic acid. The structures of these were determined and on the basis of the results the iodo-chromones have been assigned the 8-iodo- and the 6,8-di-iodo structures. On iodination with iodine and ammonia or with iodine monochloride 7-hydroxy-2-methylchromone gave only the 8-iodo derivative. 7-Methoxy-2-methylchromone could not be iodinated by any of the three methods.

7-Hydroxyflavone on iodination with iodine and iodic acid gave the 8-iodo and the 6,8-di-iodo derivatives. With iodine and ammonia it gave the 8-iodo derivative in good yield. The structures have been assigned on the basis of the hydrolysis results.

No tri-iodo derivative could be obtained in any case even with excess of the iodinating reagents.

7-Hydroxy-6,8-di-iodo-2-methylchromone decomposed on heating with acetic acid. The iodine atom in the 8-position was eliminated leaving the 6-iodo derivative in almost pure condition. Its structure was determined on the basis of the products obtained on hydrolysis.

Section (ii) : The iodination of 2,4- and 2,6-dihydroxyacetophenone was then studied and 3-iodo-, 5-iodo- and 3,5-di-iodo-2,4-dihydroxyacetophenone and 3,5-di-iodo-2,6-dihydroxyacetophenone were synthesised.

3-Iodo-,5-iodo- and 3,5-di-iodo-2,4-dihydroxyacetophenone on Kostanecki-Robinson acetylation gave the 8-iodo-, 6-iodo- and 6,8-di-iodo-7-acetoxy-3-acetyl-2-methylchromone respectively which on de-esterification with cold sulphuric acid gave the corresponding 7-hydroxy compounds. The 8-iodo and 6,8-di-iodo derivatives were also obtained from 7-hydroxy-3-acetyl-2-methylchromone by iodination with iodine and iodic acid.

7-Hydroxy-6,8-di-iodo-3-acetyl-2-methylchromone on heating with acetic acid underwent decomposition giving the 6-iodo derivative.

2,4-Dihydroxy-3-iodo-acetophenone on Kostanecki-Robinson benzoylation and subsequent treatment with sulphuric acid gave 7-hydroxy-8-iodo-3-benzoylflavone which was also obtained from 7-hydroxy-3-benzoylflavone by iodination with iodine and iodic acid or iodine and ammonia. Both 5-iodo- and 3,5-di-iodo-2,4-dihydroxyacetophenone on benzoylation and subsequent treatment with sulphuric acid gave 7-hydroxy-6-iodo-3-benzoylflavone. The 6,8-di-iodoflavone was however obtained by the iodination of 7-hydroxy-3-benzoylflavone.

2,6-Dihydroxy-3,5-di-iodo-acetophenone on Kostanecki-Robinson acetylation and benzoylation gave 5-acetoxy-6,8-di-iodo-3-acetyl-2-methylchromone and 5-benzoyloxy-6,8-di-iodo-3-benzoylflavone respectively. These were de-esterified with cold sulphuric acid. The hydroxy-di-iodo-chromone and -flavone were found to be identical with the di-iodo derivatives obtained from 5-hydroxy-3-acetyl-2-methylchromone and 5-hydroxy-3-benzoylflavone respectively.

The alkaline hydrolysis of the 3-acyl-iodo-chromones and -flavones has been studied.

Part II :- <u>Synthesis of cyano-chromones and -flavones</u>

Section (i) : 7-Methoxy-8-iodo- and 7-methoxy-6-iodo-2-methylchromone and 7-methoxy-8-iodoflavone on Rosenmund-von Braun reaction gave the corresponding cyano derivatives. These were demethylated to the corresponding hydroxycyano compounds and hydrolysed with sulphuric acid to the corresponding hydroxy carboxylic acids. The 8-cyano-7-methoxy derivatives on hydrolysis with 70 % sulphuric acid gave 7-hydroxy-2-methylchromone and 7-hydroxyflavone. With 50 % sulphuric acid the cyanomethoxyflavone gave a mixture of the 8-carbamoyl and 8-carboxylic acid derivatives. 7-Methoxy-6-cyano-2-methylchromone with 50 %

sulphuric acid gave 7-methoxy-2-methylchromone-6-carboxylic acid whereas with 70 % sulphuric acid it gave the demethylated acid. On alkaline hydrolysis depending on the cyanochromone a mixture of 3-cyano-or 5-cyano-2-hydroxy-4-methoxyacetophenone and 3-cyano-or 5-cyano-2-hydroxy-4-methoxybenzoic acid was obtained. 7-Methoxy-8-cyanoflavone gave a mixture of 2-hydroxy-3-cyano-4-methoxybenzoic acid and 2-hydroxy-3-cyano-4-methoxydibenzoylmethane as seen by direct comparison with the product synthesised by the Baker-Venkataramann transformation of 2-benzoyloxy-3-cyano-4-methoxyacetophenone. The cyano compounds could not be reduced either with sodium and alcohol or lithium aluminium hydride. Attempted synthesis of an aldehyde by Stephen reaction also failed.

5-Hydroxy-8-iodo-2-methylchromone on heating with cuprous cyanide gave the corresponding 8-cyano derivative in a very poor yield.

3-Cyano- and 5-cyano-2-hydroxy-4-methoxyacetophenone were synthesised by partial demethylation of the cyano ketones obtained by the Rosenmund-von Braun reaction on 3-iodo- and 5-iodo-2,4-dimethoxyacetophenone.

Section (ii) : 3-Cyano- and 5-cyano-2-hydroxy-4-methoxyacetophenone on Kostanecki-Robinson acetylation gave 8-cyano- and 6-cyano-7-methoxy-3-acetyl-2-methylchromone respectively. On benzoylation they gave 8-cyano- and 6-cyano-7-methoxy-3-benzoylflavone respectively. These were identical with the products obtained by the Rosenmund-von Braun reaction on the 8-iodo- and 6-iodo derivatives of 7-methoxy-3-acetyl-2-

methylchromone and 7-methoxy-3-benzoylflavone. On hydrolysis with 70 % sulphuric acid 7-hydroxy-2-methylchromone and -flavone were obtained in the case of the 8-cyano derivatives. In the case of the 6-cyano-chromone and -flavone the corresponding hydroxy carboxylic acids were obtained. On alkaline hydrolysis the 8-cyano chromone gave a mixture of 2-hydroxy-3-cyano-4-methoxyacetophenone and 2-hydroxy-3-cyano-4-methoxybenzoic acid. The 6-cyanochromone on similar hydrolysis gave a mixture of 2-hydroxy-4-methoxy-5-cyanoacetophenone and 2-hydroxy-4-methoxy-5-cyanobenzoic acid. The 8-cyanoflavone derivative on alkali treatment gave 2-hydroxy-3-cyano-4-methoxybenzoic acid and 2-hydroxy-3-cyano-4-methoxydibenxoylmethane. The 6-cyanoflavone on a similar hydrolysis gave a mixture of 2-hydroxy-4-methoxy-5-cyanobenzoic acid and 2-hydroxy-4-methoxy-5-cyanodibenzoylmethane, identical with that obtained by the Baker-Venkataraman transformation of 2-benzoyloxy-4-methoxy-5-cyano-acetophenone. It cyclised with sulphuric acid to give 7-methoxy-6-cyanoflavone which on hydrolysis with 70 % sulphuric acid gave the hydroxy carboxylic acid.

The above chromone and flavone carboxylic acids have been decarboxylated to the known chromones and flavones.

Part III :- Synthesis of some bichromonyls, biflavonyls and 8-phenyl-chromone and -flavone derivatives

7-Methoxy-8-iodo-2-methylchromone and 7-methoxy-8-iodo-flavone on Ullmann reaction gave 7,7'-dimethoxy-2,2'-dimethyl-8,8'-bichromonyl and 7,7'-dimethoxy-8,8'-biflavonyl respectively.

7-Methoxy-6-iodo-2-methylchromone on a similar reaction gave 7,7'-dimethoxy-2,2'-dimethyl-6,6'-bichromonyl. As 7-methoxy-6-iodo-3-benzoylflavone could not be debenzoylated to 7-methoxy-6-iodoflavone it was directly subjected to the Ullmann reaction when it gave 7,7'-dimethoxy-3,3'-dibenzoyl-6,6'-biflavonyl.

On crossed Ullmann reaction with iodobenzene 7-methoxy-8-iodo-2-methylchromone and 7-methoxy-8-iodoflavone gave the corresponding 8-phenyl derivatives.

The bichromonyl, biflavonyl and 8-phenyl derivatives were demethylated to the corresponding hydroxy compounds except 7,7'-dimethoxy-3,3'-dibenzoyl-6,6'-biflavonyl ~~which~~ however did not give a pure demethylation product.

Part IV :-Chloromethylation of some chromones and flavones

2-Methylchromone and simple flavone on chloromethylation gave the 3-chloromethyl derivatives. These on reduction gave the 3-methyl derivatives identical with the products obtained from o-hydroxypropiophenone through the Kostanecki-Robinson acetylation and benzoylation respectively. 7-Methoxy-2-methylchromone and 7-methoxyflavone on chloromethylation gave the 8-chloromethyl derivatives which on reduction gave products identical with 7-methoxy-2,8-dimethylchromone and 7-methoxy-8-methylflavone synthesised by refluxing 2-methylresorcinol with ethyl acetoacetate and ethyl benzoylacetate respectively in diphenyl ether and subsequent methylation. The 8-chloromethyl derivatives on further chloromethylation gave the 3,8-dichloromethyl derivatives. These on reduction gave products which were identical with 7-methoxy-2,3,8-trimethylchromone and 7-methoxy-3,8-dimethylflavone obtained by the reduction of 7-methoxy-8-chloromethyl-2,3-dimethylchromone and 7-methoxy-8-chloromethyl-3-methylflavone synthesised according to Da Re and Verlicchi (Ann. Chim., Rome, 1956, 46, 904). The reduction products on alkaline hydrolysis gave the known 2-hydroxy-3-methyl-4-methoxybenzoic acid.

Some of the above chloromethyl derivatives have been converted into the corresponding acetoxymethyl, methoxymethyl and cyanomethyl derivatives.