

"SYNTHETICAL EXPERIMENTS IN THE
FLAVONE AND THE ISOFLAVONE GROUPS"

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By

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COMPUTERISED

"SYNTHETICAL EXPERIMENTS IN THE
FLAVONE AND THE ISOFLAVONE GROUPS"

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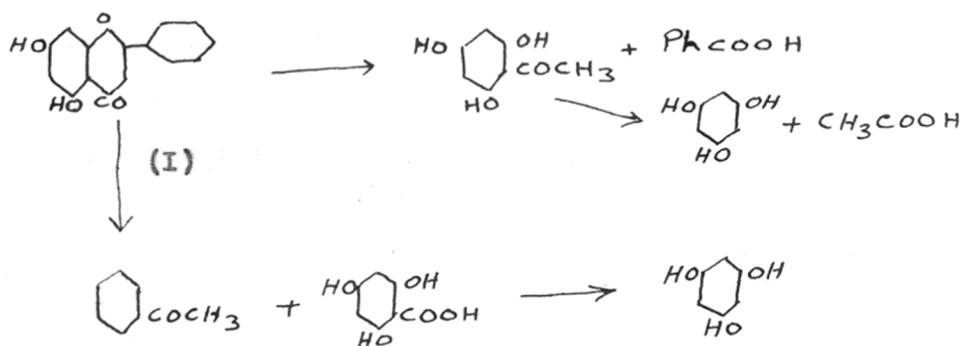
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HISTORICAL.

The study of the Benzo- γ -pyrone of the flavone group was originated by Piccard (Ber., 1873, 6, 884; 1874, 7, 888; 1877, 10, 176), who isolated a yellow pigment, chrysin, from the leaf buds of the poplar (Populus pyramidalis, Salisb., P. nigra, Linn., P. monilifera, Ait.), which contained chrysin to the extent of 0.5 per cent; crystallizing in colourless leaflets, m.p. 275°C. Analysis of chrysin and its derivatives led to the composition, $C_{15}H_{10}O_4$, for chrysin; and it was hence considered to be a homologue of alizarin, $C_{14}H_8O_4$. The suggestion was, however, soon abandoned, as no anthracene derivative was obtained on distilling chrysin with zinc dust in a stream of hydrogen. On digestion with boiling concentrated aqueous caustic potash it gave phloroglucinol, benzoic acid, acetic acid and in very small quantities acetophenone; and as a result Piccard indicated that chrysin was a derivative of phloroglucinol in which one hydroxyl group was benzoylated, another acetylated, and the third eliminated in some way as water. Acetophenone was regarded as a secondary product of the degradation.

V. Kostanecki (Ber., 1893, 26, 2901) observed that

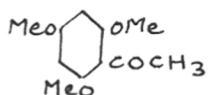
chrysin on acetylation gave a diacetyl derivative, $C_{15}H_8O_4$ $(C_2H_3O)_2$, colourless needles, m.p. 185° , but on methylation with methyl iodide in the usual manner gave a monomethyl ether, $C_{15}H_9O_3 \cdot OCH_3$, m.p. 163° . The latter yielded acetylchrysin monomethyl ether, $C_{15}H_8O_3(OCH_3)C_2H_3O$, colourless needles, m.p. 149° , and with alcoholic sodium hydroxide gave a bright yellow sodium salt which was decomposed by washing with water. Chrysin was, therefore, a dihydroxy compound and its properties and degradation products were best explained by a benzo- γ -pyrone structure. The constitution 5:7-dihydroxy-2-phenylbenzo- γ -pyrone (I) was thus assigned to chrysin; and its degradation into phloroglucinol, benzoic acid, acetic acid and acetophenone took place according to the following scheme.



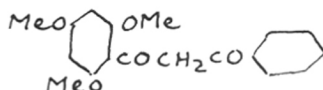
V. Kostanecki and his coworkers carried out the syntheses of chrysin by the following two methods and confirmed the constitution (I).

(1) By the condensation of phloracetophenone trimethyl ether (II) with ethyl benzoate in presence of metallic sodium, 2:4:6-trimethoxybenzoylacetophenone (III) was obtained and on digestion with hydriodic acid demethylation and ring closure occurred with the formation of chrysin (I) (Emilewicz, Kostanecki and Tambor, Ber., 1899, 32, 2448).

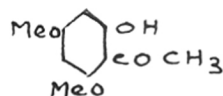
(2) Phloracetophenone dimethyl ether (IV) on condensation with benzaldehyde in presence of caustic potash resulted in 5:7-dimethoxyflavanone (V) which on bromination gave 3:6:8-tribromo-5:7-dimethoxyflavanone (VI). On boiling



(II)

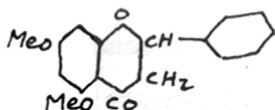


(III)

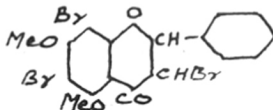


(IV)

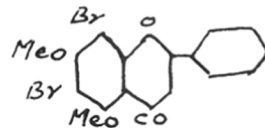
this with alcoholic potash 6:8-dibromo-5:7-dimethoxyflavone (VII) was obtained and on demethylation with hydriodic acid in the usual way gave chrysin (I) (Kostanecki and Lampe, Ber., 1904, 37, 3167).



(V)



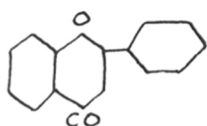
(VI)



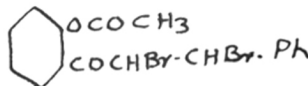
(VII)

2-Phenyl benzo-γ-pyrone or flavone (VIII) itself has been found in nature as the meal or farina which occurs

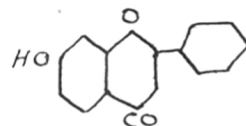
on the leaves, stalks and seed capsules of many varieties of Primula e.g. P.pulverulenta; P.Japonica (Muller, J.C.S., 1915, 107, 875). The synthesis of (VIII) had previously been accomplished by Feuerstein and Kostanecki (Ber., 1898, 31, 1757). O-Hydroxyacetophenone was condensed with benzaldehyde in presence of alkali to give 2-hydroxyphenyl styryl ketone, the acetyl derivative of which was brominated. Hydrolysis of the 2-acetoxyphenyl styryl ketone dibromide (IX) with alcoholic potash resulted in flavone (VIII).



(VIII)



(IX)



(X)

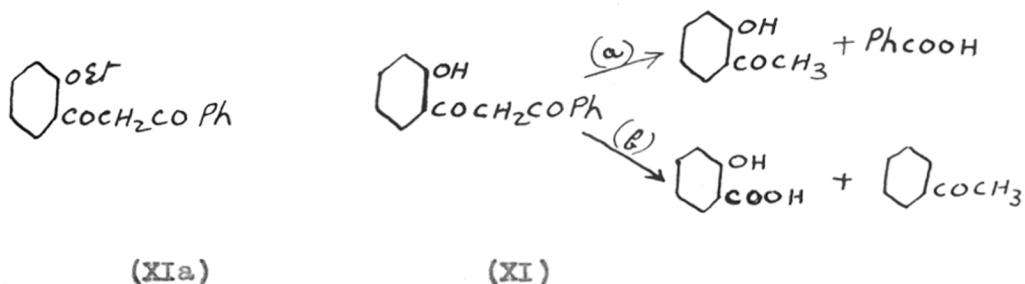
In an analogous manner Emilewicz, Kostanecki and Tambor (Ber., 1898, 31, 703) by using monomethylresacetophenone (instead of O-hydroxyacetophenone) prepared 7-methoxyflavone which on demethylation gave 7-hydroxyflavone (X).

This synthesis of flavones was not capable of extension, as on substituting veratraldehyde (Kostanecki and Rozycki, Ber., 1899, 32, 2257) or piperonal (Emilewicz and Kostanecki, ibid., 309) for benzaldehyde the products were not flavones but coumaranones.

By the action of alkalies flavone (VIII) and

hydroxyflavones suffer hydrolysis according to the following scheme:-

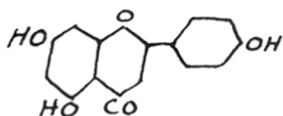
The first product of the reaction owing to the disruption of the pyrone ring (VIII) is the β -diketone (XI) which then decomposes in one of two ways according to the conditions of the experiment yielding (a) benzoic acid and o-hydroxyacetophenone or (b) salicylic acid and acetophenone.



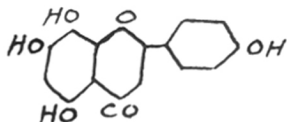
The reverse of both of these reactions was carried out by Kostanecki and Tambor (Ber., 1900, 33, 330); when (a) o-ethoxyacetophenone was condensed with ethyl benzoate and (b) ethyl o-ethoxybenzoate was condensed with acetophenone, in presence of metallic sodium, both resulted in o-ethoxybenzoylacetophenone (XIa) which on digestion with hydriodic acid gave flavone (VIII).

Although this method has been successfully utilised in synthesising a number of flavones, e.g. apigenin (XII) (Czajkowski, Kostanecki and Tambor, Ber., 1900, 33, 3410), and scutellarein (XIII) (Bargellini, Gazzetta, 1915, 45, 1,69); yet it suffers from several disadvantages, notably at the

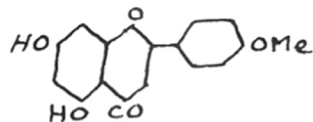
hydriodic acid treatment stage, where in certain cases it gives a very poor yield of the demethylated flavone or the final product is difficult to purify. The synthesis



(XII)

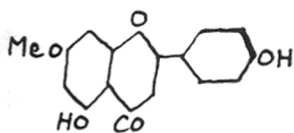


(XIII)

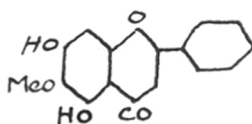


(XIV)

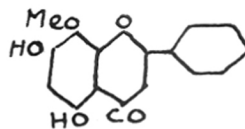
of partially methylated flavones like triclin (XXXVIII), wogonin (XVIa), diosmetin (XXXIX), acacetin (XIV), genkwanin (XV) and oroxylin (XVI) is obviously not possible by this method.



(XV)



(XVI)

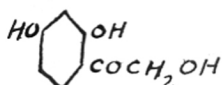


(XVIa)

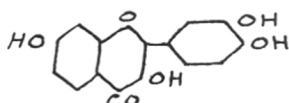
Having reviewed briefly the flavone group, 3-hydroxy-flavones or flavonols which form an important group in itself will be worthy of mention. Flavonols differ chiefly from flavones in that they dye deeper than flavones, but the shades given by the flavonols are not so fast as in the latter case. Flavonols are decomposed when air is blown through their alkaline solutions while flavones are unaffected by this treatment. Most of the flavonols yield well characterised crystalline compounds with mineral acids

by the simple process of adding mineral acids to the boiling solutions of the flavonols in glacial acetic acid (Perkin and Pate, J.C.S., 1895, 67, 647). The flavonols usually form yellow crystalline compounds with potassium acetate (Perkin, J.C.S., 1899, 75, 438; Perkin and Wilson, J.C.S., 1903, 83, 136).

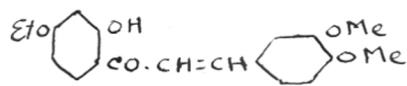
The first member of the flavonol group to be investigated was Fisetin, the colouring matter from the stem and branches of the *Rhus cotinus* (Linn.). Herzig (Monatsh., 1891, 12, 172) showed that fisetin had the molecular formula $C_{15}H_{10}O_6$, contained four hydroxyls and on passing air through an alkaline solution, fisetin was found to undergo degradation and yielded resorcinol and protocatechuic acid. Fisetin tetraethyl ether on hydrolysis with alcoholic potash gave fisetol diethyl ether which was shown to be identical with diethyl ether of ω -hydroxyresacetophenone (XVII), and based on these facts and the close similarity of fisetin to known flavones, Herzig assigned to it the constitution of a trihydroxyflavonol (XVIII). The correctness of this suggestion was proved by the synthesis of fisetin by Kostanecki, Lampe and Tambor (Ber., 1904, 37, 784). A mixture of 4-ethoxy-2-hydroxyacetophenone and veratraldehyde in presence of alkali gave 2-hydroxy-4-ethoxyphenyl 3:4-dimethoxystyryl ketone (XIX); this on boiling with mineral acids in alcoholic solution



(XVII)

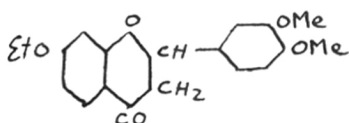


(XVIII)

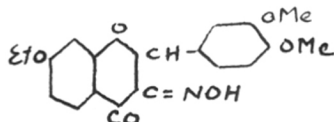


(XIX)

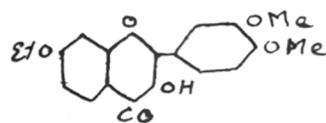
underwent isomeric ring closure to give 7-ethoxy-3':4'-dimethoxyflavanone (XX). The flavanone on treatment with amyl nitrite and hydrochloric acid gave the isonitroso derivative (XXI) which on boiling with glacial acetic acid containing 10 per cent sulphuric acid gave 7-ethoxy-3':4'-dimethoxyflavonol (XXII). Dealkylation with hydriodic acid then yielded fisetin (XVIII).



(XX)

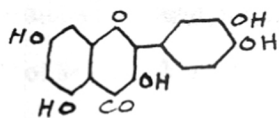


(XXI)

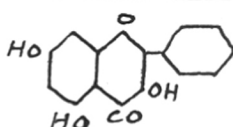


(XXII)

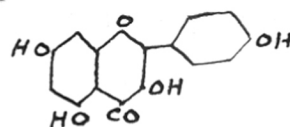
On similar lines quercetin (XXIII) (Kostanecki, Lampe and Tambor, Ber., 1904, 37, 1403), galangin (XXIV) (Kostanecki and Tambor, Ber., 1904, 37, 2803), kaempferol (XXV) (Kostanecki, Lampe and Tambor, ibid., 2096) and morin (XXVI) (Kostanecki, Lampe and Tambor, Ber., 1906, 39, 625) were synthesised without much difficulty.



(XXIII)

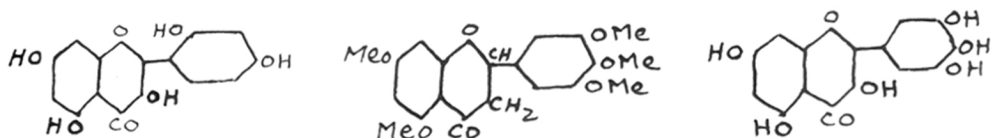


(XXIV)



(XXV)

Although the method appears to be quite simple and straightforward, yet in some cases difficulties arose, e.g. the flavanone (XXVII) did not form the isonitroso derivative and hence myricetin (XXVIII) could not be prepared by this method (Dean and Nierenstein, J.Amer.Chem.Soc., 1925, 47, 1676) and in others for instance morin (XXVI) and datiscetin (XXIX) the yields were extremely poor.



(XXVI)

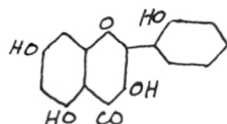
(XXVII)

(XXVIII)

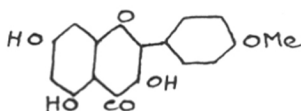
Tahara (Ber., 1892, 25, 1302) and also Nagai (ibid., 1287) observed that when resacetophenone was refluxed, for a long time, with sodium acetate and acetic anhydride it resulted in 2-methyl 3-acetyl-7-hydroxychromone. The observation remained unnoticed till 1924 when Robinson and his collaborators, in view of the various difficulties encountered in the Kostanecki's method for synthesising flavone and its derivatives, utilised this method for the syntheses of chromones and chromonols (Crabtree and Robinson, J.C.S., 1918, 113, 859; Allan and Robinson, J.C.S., 1924, 125, 2193). Similarly by heating an intimate mixture of ω -methoxyphloracetophenone, benzoic anhydride and sodium benzoate at 185° (oil-bath) for 8 hours and hydrolysing the product with alkali, Kalf and Robinson (J.C.S., 1925, 127, 181) prepared a

monomethyl ether of galangin (XXIV), a colouring matter isolated from galanga root (Testoni, Gazzetta, 1900, 30, ii, 327) and to which the constitution shown had been assigned by Perkin and Allison (J.C.S., 1902, 81, 472). Demethylation of the product gave them galangin identical with the specimen obtained from the natural source and with the synthetical product of Kostanecki and Tambor (loc. cit.). On similar lines myricetin (XXVIII) and datiscetin (XXIX) were also synthesised by using the appropriate ketone, acid anhydride and the sodium salt of the acid.

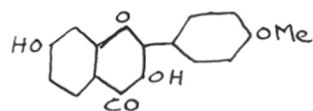
This method, however, presented another difficulty that the final product of reaction was obviously a 3-methyl ether of the flavonols, demethylation of which, of course, removed the alkyl group present on any other hydroxyls. This difficulty was partly overcome by using ω -benzoyloxy instead of ω -methoxy ketones (Heap and Robinson, J.C.S., 1926, 129, 2336), and the syntheses of kaempferide (XXX) and resokaempferide (XXXI) were thus accomplished.



(XXIX)



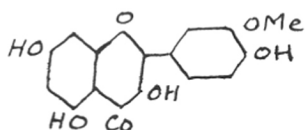
(XXX)



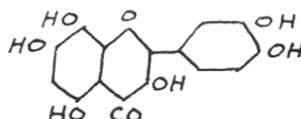
(XXXI)

Following this new method of making flavonols, a number of naturally occurring flavonol derivatives, e.g.

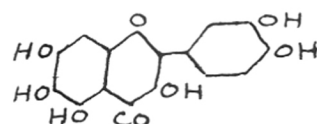
myricetin (XXVIII) (Kalff and Robinson, J.C.S., 1925, 181), galangin (XXIV) (Kalff and Robinson, loc. cit.; o.f. Chavan and Robinson, J.C.S., 1933, 368), fisetin (XVIII) and quercetin (XXIII) (Allan and Robinson, J.C.S., 1926, 2334), gossypetin (XXXIII) and quercetagetin (XXXIV) (Baker, Nodzu and Robinson, J.C.S., 1929, 74), robinetin (XXXV) (Charlesworth and Robinson, J.C.S., 1933, 268), Morin (XXVI) (Robinson and Venkataraman, J.C.S., 1929, 61), isorhamnetin (XXXII) (Heap and Robinson, J.C.S., 1926, 2336) and Kaempferol (XXV) (Robinson and Shinoda, J.C.S., 1925, 1973), have been synthesised.



(XXXII)



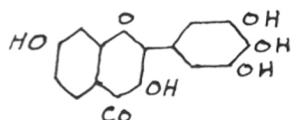
(XXXIII)



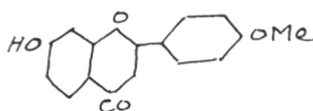
(XXXIV)

The new method of flavonol synthesis by direct acylation of derivatives of O-hydroxyacetophenone was further utilised by Allan and Robinson (J.C.S., 1924, 2192) in the synthesis of flavone and its derivatives unsubstituted in the 3-position. Robinson and Venkataraman (J.C.S., 1926, 2344), during the course of their study of conditions under which the best yields of flavone and its derivatives unsubstituted in the 3-position could be obtained by this method, found that more acid anhydride and longer heating were required than was the case with the earlier preparations of

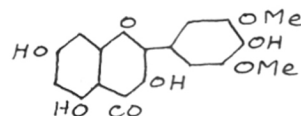
flavonol derivatives. Thus by condensing resacetophenone with benzoic anhydride, sodium benzoate and anisic anhydride and sodium anisate, 7-hydroxyflavone (X) and 7-hydroxy-4'-methoxyflavone (XXXVI) were obtained. Similarly by using phloracetophenone instead of resacetophenone in the above experiments chrysin (I) and acacetin (XIV) were also obtained by the same authors.



(XXXV)



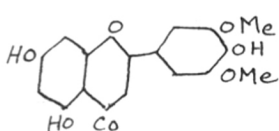
(XXXVI)



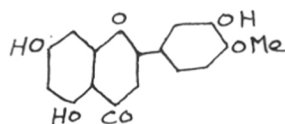
(XXXVII)

The following are a few more examples in which Robinson's new general method for synthesising flavone and flavonol derivatives has been successfully utilised:-

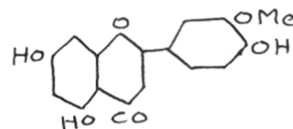
Syringetin (XXXVII) (Heap and Robinson, J.C.S., 1929, 67), Scutellarein (XIII) (Wesseley and Moser, Monatsh., 1930, 56, 97), acacetin (XIV) (Robinson and Venkataraman,



(XXXVIII)



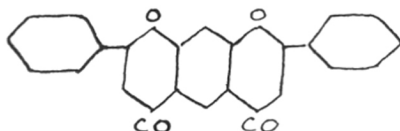
(XXXIX)



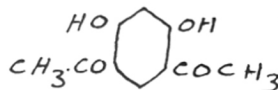
(XL)

J.C.S., 1926, 2344), tricetin (XXXVIII) (Gulati and Venkataraman, J.C.S., 1933, 942), diosmetin (XXXIX) and luteolin 3'-methyl ether (XL) (Lovecy, Robinson and Sugasawa, J.C.S., 1930, 817)

and genkwanin (XV) (Kwong-fong Tseng, J. Pharm. Soc. Japan, 1935, 55, 132).



(XLI)



(XLIa)

It will be interesting to note here that Rayon and others (Proc. Royal Irish Acad., 1915, 32, 167, 185, 193; 1930, 39, 425) found that the ester and chalkone methods of Kostanecki and others (loc. cit.) were not applicable to the synthesis of substituted diflavones; the former did not proceed and the latter led to the isomeric dicoumaranones but Gulati and Venkataraman (J.C.S., 1931, 2376) have prepared the diflavones of the general formula (XLI) by carrying on Robinson reaction on 4:6-diacetylresorcinol (XLIa) with different acid anhydride (see also; Wittig, Ber., 1926, 59, 116).

The discovery of numerous representatives of the flavone group from the roots, stems, barks, fruits, flowers, and leaves of various plants clearly indicates their wide occurrence in nature. As to their origin in plants it is not known with certainty; they may originate at the point of vegetation but are more frequently formed in the older tissue and their occurrence and definite localization in

plants often clearly indicates the relationship of plants in particular families, genera, and species (Klein and Werner, Z. Physiol. Chem., 1925, 143, 9-32). Their role in the plant cell too is not known with certainty but they are important in the process of assimilation in that they absorb oxygen and transport it away from the cell (Rouge, Bull. Soc. Bot. Geneve, 1921, 13, 18; Botan. Abstracts, 12, 866).

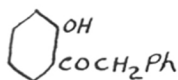
On account of the discovery, each year, of new benzo- γ -pyrone derivatives from natural sources and also due to their occurrence, as an active constituent, in some of the medicinal plants, e.g. calycopterin of *calycopteris floribunda* (Ratnagiriswaran, Sehra and Venkataraman, loc. cit.), it was considered that some of the flavone derivatives may prove of some medicinal value and the study of the methods of their preparation will be of importance. It will be of great interest to note that recently Rusznyak and Szent-Gyorgyi (Nature, July 1936, Vol. 138) from their various chemical and clinical observations have led them to assume that this great group of vegetable dyes, the flavones and flavonols, play an important role in animal life and that the dyes are of vitamin nature.

CHEMISTRY OF THE FLAVONE GROUP.

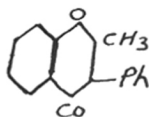
During the study of the possibility of the preparation of various types of substituted γ -pyrones by the Robinson reaction, several chromones have been prepared by this method, e.g. chromones derived from resacetophenone, phloracetophenone, ω -methoxyphloracetophenone, gallacetophenone, *o*-hydroxyacetophenone, 2:5-dihydroxyacetophenone, 2:4:5-trihydroxyacetophenone and *o*-hydroxyphenyl benzyl ketone of the benzene series (Robinson and Venkataraman (J.C.S., 1926, 129, 2344); Venkataraman (J.C.S., 1929, 2219); Badhwar, Kang and Venkataraman (J.C.S., 1932, 1107); Chadha and Venkataraman (J.C.S., 1933, 1073) and Chadha, Mahal and Venkataraman (J.C.S., 1933, 1459)) and others derived from 2-acetyl-1-naphthol, 1-acetyl-2-naphthol, 2-phenylacetyl-1-naphthol, 2- β -phenylpropionyl-1-naphthol and 1-phenylacetyl-2-naphthol of the naphthalene series have also been studied by Bhullar and Venkataraman (J.C.S., 1931, 1165); Menon and Venkataraman (J.C.S., 1931, 2591); Cheema and Venkataraman (J.C.S., 1932, 918) and Mahal, Chadha and Venkataraman (J.C.S., 1933, 1459).

In the present work I have observed (c.f. Cheema and Venkataraman, loc.cit.) that the Robinson reaction was more readily applicable to ω -substituted ketones; the reaction goes much more smoothly and the product requires scarcely any purification. Thus, when *o*-hydroxyphenyl

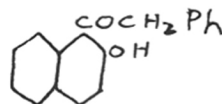
benzyl ketone (XLII) was heated with sodium acetate and acetic anhydride 2-methyl-3-phenyl chromone (XLIII) was obtained in good yields. Similarly 1-phenylacetyl-2-naphthol (XLIV) with sodium acetate or sodium phenylacetate and acetic anhydride gave the 3-methyl-2-phenyl-1:4- β -naphthapyrone (XLV), and ω -benzyl resacetophenone (XLVI) with sodium



(XLII)

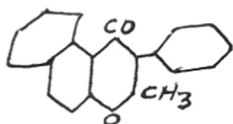


(XLIII)

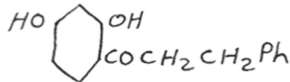


(XLIV)

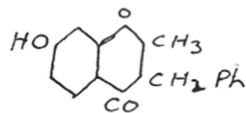
phenylacetate and acetic anhydride gave 2-methyl-3-benzyl-7-hydroxychromone (XLVII), although the methylene group in sodium phenylacetate is very reactive as indicated by the fact that when 2-hydroxyphenyl methyl ketone is heated with acetic anhydride and sodium phenylacetate (see, however, Heilbron, Hey and Lythgoe, J.C.S., 1934, 1581) it invariably gives coumarin. The ketone (XLIV) with sodium benzoate and benzoic anhydride gave the respective flavone (XLVIII). The action of sodium phenylacetate and acetic anhydride on ω -methoxy resacetophenone, however, gave the coumarin (XLIX) and not the chromone.



(XLV)

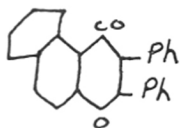


(XLVI)

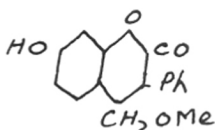


(XLVII)

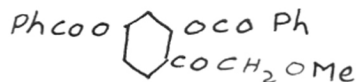
Another observation was made that when -methoxy resacetophenone dibenzoate (L) was distilled under high vacuum, a noncrystallisable material was obtained; its alcoholic solution gave a deep red colouration with aqueous ferric chloride and on treatment with sulphuric acid it gave the known 7-hydroxy-3-methoxyflavone (LI).



(XLVIII)

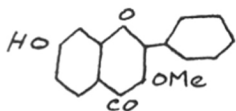


(XLIX)

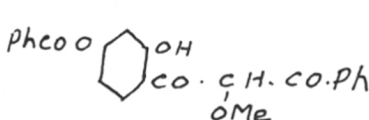


(L)

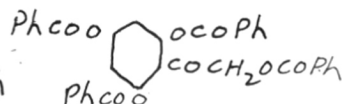
Nothing exactly can be said about the nature of the intermediate product; it may be the diketone (LIa), because it gave a colouration with ferric chloride and on treatment with sulphuric acid gave the flavone (LI) or a mixture of the diketone (LIa) and the flavone (LI), the formation of the latter being explained in the light of the observation of Chavan and Robinson, (J.C.S., 1933, 368) that on dehydration ω :2:4:6-tetrabenzoyloxy acetophenone (LIb) by means of potassium acetate in boiling alcoholic solution or by boiling acetic anhydride and sodium acetate and subsequent hydrolysis galangin is obtained. Similarly vacuum distillation of (L) may simply be a process of dehydration of (L) to form the flavone (LI).



(LI)



(LIa) KV



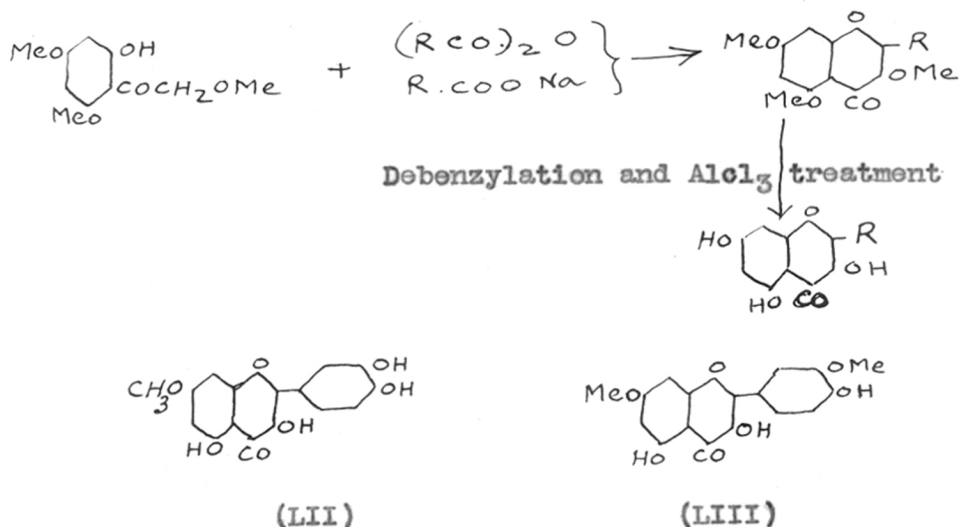
(LIb)

547.814.5(043)
MAH

The yield of the flavones by the Robinson reaction in certain cases is extremely poor, e.g. when o-hydroxyacetophenone was condensed with benzoic anhydride or trimethylgallie anhydride very poor yields of the respective flavones were obtained (Chadha and Venkataraman, loc.cit.; c.f. Bhullar and Venkataraman, loc.cit.) and in the case of gallacetophenone with anisic anhydride or veratric anhydride or trimethylgallie anhydride (Badhwar, Kang and Venkataraman, loc.cit.) the yields were so poor that the method had to be abandoned altogether.

Secondly the preparation of 3-hydroxyflavone derivatives usually involved demethylation by hydriodic acid hence synthesis of partially methylated flavonols was not possible by this method. This difficulty was partly overcome (Heap and Robinson, loc.cit.) by using ω -benzoyloxyacetophenone derivatives instead of ω -methoxyacetophenone derivatives, but the preparation of the former presented its own difficulties. I have observed now that demethylation of the 3-methoxyflavone can be effected by aluminium chloride (c.f. Gulati and Venkataraman, J.C.S., 1936, 267); this may prove a useful method for the synthesis of partially methylated flavonols. Thus the following scheme would be available for the synthesis of rhammetin

(LII) and rhamnazin (LIII) (Allison and Perkin, J.C.S., 1902, 469).

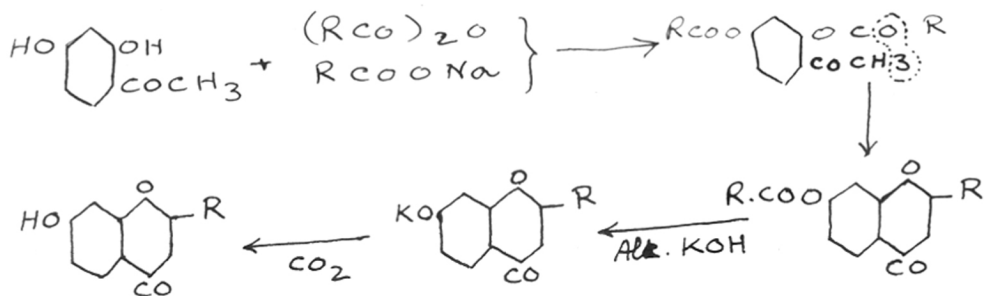


Lastly the synthesis of flavones by the Robinson reaction sometimes leads to 3-acylation. It was first observed by Allan and Robinson (J.C.S., 1924, 2192) that when resacetophenone was benzoylated it gave as a result 7-hydroxyflavone (X) and also a crystalline product m.p. 260° which they believed to be 7-hydroxy-3-benzoylflavone (LIV). Later Bhullar and Venkataraman (J.C.S., 1931, 1165) also recorded a similar observation when the reaction was carried out on 2-acetyl-1-naphthol with benzoic anhydride or anisic anhydride; the corresponding naphthaflavones along with their 3-acylated derivatives were obtained. The acyl group in the 3-acylated chromones has been easily removed by boiling them for one hour with 2-N caustic soda (Allan and Robinson, loc.cit.), but Bhullar and Venkataraman (loc.cit.) could not accomplish it with any of their above mentioned

3-acylated naphthapyrones; either their substance remained unaffected or with increased concentration of alkali and time of heating, the pyrone ring was broken down.

In view of some of these difficulties in carrying out the synthesis of certain flavones by the Robinson reaction, several attempts were made to devise a new method which would preclude 3-acylation and would yield pure products of unambiguous structure in good yields.

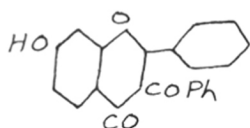
Ghadha and Venkataraman (J.C.S.,1933,1073), following the commonly assumed mechanism of the Robinson reaction (see also Wittig, Baugert and Richter,Annalen,1925,446,155), as shown in the following scheme, made many unsuccessful



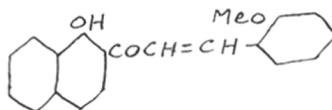
attempts to close round the ring by the elimination of a molecule of water in the acyl derivatives of α -naphthol ketones by using a variety of dehydrating agents such as phosphorous pentoxide, acetic anhydride, phosphorous oxychloride and zinc chloride and under varied experimental conditions. It thus ruled out the second stage of the

assumed mechanism and direct dehydration of an *o*-acyloxyphenyl methyl ketone to a flavone was extremely improbable (contrast Simonis, Z. Angew. Chem., 1926, 39, 1461).

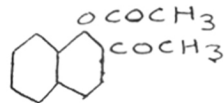
Desiring to complete the series of α -naphthylflavones by one of the older methods of Kostanecki which would preclude 3-acylation (Bhullar and Venkataraman, loc. cit.), 2-*o*-methoxycinnamoyl-1-naphthol (LV) was converted into the dibromide of its *o*-acetyl derivative. Treatment of the latter with alkali did not take either of the known courses, leading to a flavone or coumaranone. It was then considered desirable to continue the attempts made by Ghadha and Venkataraman (loc. cit.) to effect dehydration of 1-acyloxy-2-naphthyl methyl ketone (LVI) to 2-methyl-1:4- α -naphthopyrone (LVII). Since the reagents



(LIV)



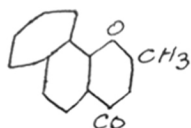
(LV)



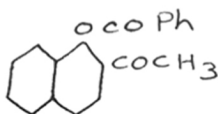
(LVI)

examined, so far, were of an acidic or kationoid type, attention in the present work was then directed to anionoid reagents and the observation was made that the action of sodamide on an ethereal solution of 2-acetyl-1-naphthyl benzoate (LVIII) at room temperature during 12 hours or more gave a bulky precipitate which, on treatment with

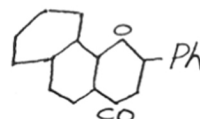
acetic acid led to a bright yellow compound whose analysis, intense colouration with ferric chloride and closure to α -naphthaflavone (LIX) by means of sulphuric acid readily revealed its structure as 2-benzoylacetyl-1-naphthol (LX). The reaction was repeated with the o-trimethylgalloyl



(LVII)

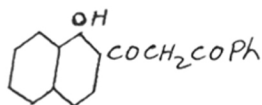


(LVIII)

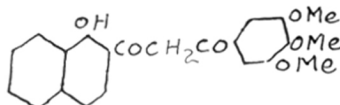


(LIX)

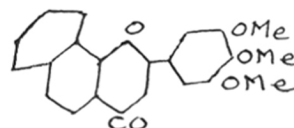
derivative of 2-acetyl-1-naphthol, the diketone (LXI) and the naphthaflavone (LXII) were readily obtained. In a third case, contact of the o-methoxybenzoate (LXIII) with sodamide led to the diketone (LXIV) dissolution of the



(LX)

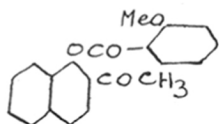


(LXI)

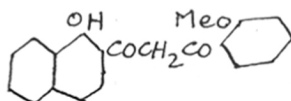


(LXII)

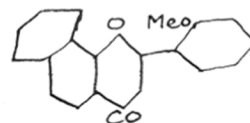
latter in sulphuric acid did not, however, give the expected naphthaflavone (LXV) but its sulphonic acid, probably (LXVI). The desired naphthaflavone was then prepared by treatment of



(LXIII)

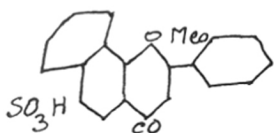


(LXIV)

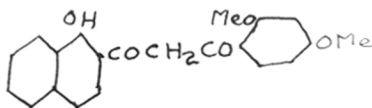


(LXV)

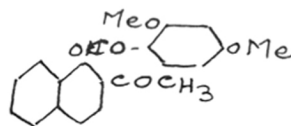
the diketone with alcoholic sulphuric acid and in traces by hydrolysis of (LXVI) with superheated steam. Alcoholic sulphuric acid was therefore employed in the conversion of the diketone (LXVII), obtained from the 2:4-dimethoxybenzoate (LXVIII), into the naphthaflavone (LXIX).



(LXVI)

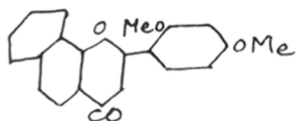


(LXVII)

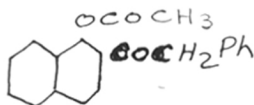


(LXVIII)

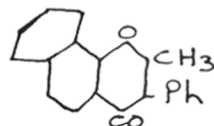
In line with my previous observation that an ω -substituent in an *o*-hydroxyaryl methyl ketone is an aid to chromone formation, 2-phenylacetyl-1-naphthyl acetate (LXX) led directly to 3-phenyl-2-methyl-1:4- α -naphtha-pyrone (LXXI).



(LXIX)



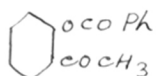
(LXX)



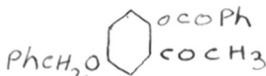
(LXXI)

To further study the scope of the new reaction Bhalla, Mahal and Venkataraman (J.C.S., 1935, 868) have prepared the diketones from *o*-benzoyloxyacetophenone (LXXII), 2-benzoyloxy-5-benzyloxyacetophenone (LXXIII), 2-acetyl-1-naphthyl cinnamate (LXXIV), and 2-acetyl-1-naphthyl-*p*-methoxycinnamate (LXXV); all the diketones

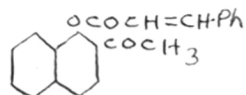
were smoothly convertible into the respective chromones by treatment with sulphuric acid. The production of the diketones in the last two cases (LXXIV and LXXV) is noteworthy, since the unsaturated diketones cannot be prepared



(LXXII)

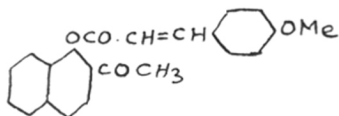


(LXXIII)

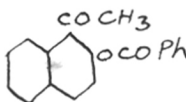


(LXXIV)

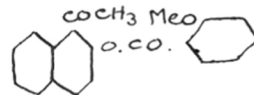
by a Claisen condensation between 2-acetyl-1-naphthol and ethyl cinnamate (Cheema, Gulati and Venkataraman, J.C.S., 1932, 926). 1-acetyl-2-naphthyl benzoate (LXXVI) and *o*-methoxybenzoate (LXXVII) and (LXXV) provided an example of partial direct conversion into the pyrone.



(LXXV)



(LXXVI)

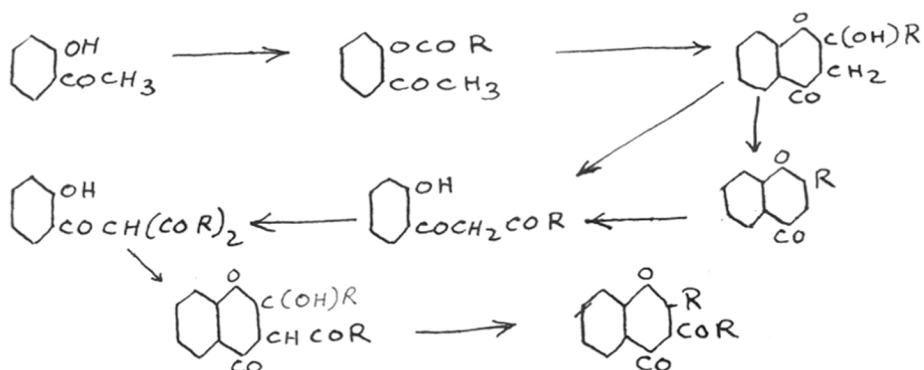


(LXXVII)

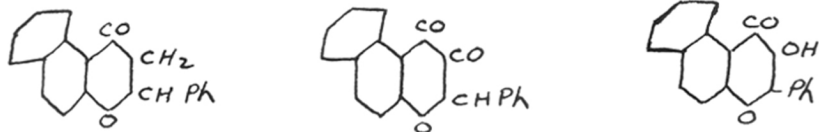
Since the syntheses of a number of flavones and naphthaflavones have been carried out at room temperature by this new method, it is of phytochemical significance and it may prove useful for the syntheses of naturally occurring flavones and flavone glucosides.

While this work was still in its initial stages Baker (J.C.S., 1933, 143, 1381) achieved the transformation

of o-acyloxyacetophenones to the dibenzoylmethanes by means of potassium carbonate in toluene at the temperature of the steam bath during a few hours and advanced a complete theory of the mechanism of the Robinson reaction which, without doubt, is essentially correct and offers a feasible explanation of the formation of 3-acylated flavones (c.f. Schneider and Kunau, Ber., 1921, 52, 2302; also Wittig, Annalen, 1925, 446, 159).

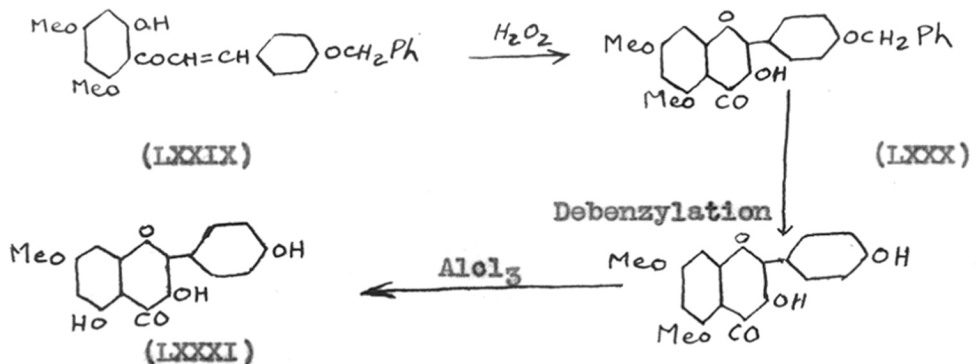


Selenium dioxide is a specific oxidising agent for the conversion of $-\text{CH}_2-$ to $-\text{CO}-$ (Muller, Ber., 1935, 66, 1668; Evans, Ridgion and Simonsen, J.C.S., 1934, 137; Chakravarti and Swaminathan, J.Indian Chem.Soc., 1934, 9, 715), but I observed that when 2:3-dihydro- α -naphthaflavone (LXXVIII) was heated in xylene solution with selenium dioxide, it gave α -naphthaflavone and not the α -naphthaflavonol as was expected thus:-

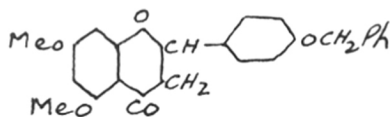


(LXXVIII)

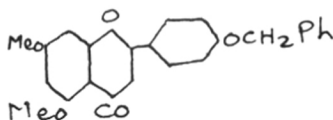
Similarly o-hydroxy chalcones themselves were smoothly converted into flavones by means of selenium dioxide. All attempts so far to isolate any flavonol formed during the oxidation have met with no success. Algar and Flynn (Proc. Royal Irish Acad., 1934, Ser. B., 42, separate issue; also Gyamada, J. Chem. Soc. Japan, 1934, 55, 1256) have shown that flavonols are produced by the oxidation of 2-hydroxy chalcones with alkaline hydrogen peroxide. It will be of interest to note here that I have attempted the oxidation of 2-hydroxy-4:6-dimethoxyphenyl 4-benzyloxystyryl ketone (LXXIX) with alkaline hydrogen peroxide under a variety of conditions with the hopes of getting the flavonol (LXXX) which on debenzylation and partial demethylation by the



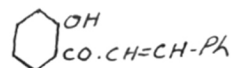
aluminium chloride method (Gulati and Venkataraman, loc.cit.) would give 3:5:4'-trihydroxy-7-methoxyflavone (LXXXI) which I consider to be the probable structure of rhamnocitrin (Oesch and Perkin, J.C.S., 1914, 105, 2332). The pale yellow crystalline substance, m.p.198°, gave, however, no colouration with ferric chloride; it was coloured red on treatment with sulphuric acid and the light brown solution exhibited no fluorescence. The analytical results indicated the flavanone (LXXXII); the mixed m.p.with 4'-benzyloxy-5:7-dimethoxyflavone (LXXXIII) was very much depressed.



(LXXXII)

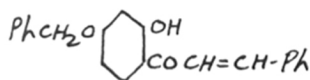


(LXXXIII)

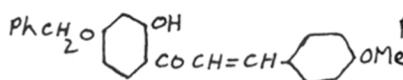


(LXXXIV)

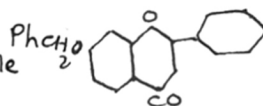
O-Hydroxyphenyl styryl ketone (LXXXIV), 2-hydroxy-4-benzyloxyphenyl styryl ketone (LXXXV) and 2-hydroxy-4-benzyloxyphenyl 4-methoxystyryl ketone (LXXXVI) in amyl alcohol were smoothly oxidised to the respective flavones (VIII), (LXXXVIII) and (LXXXIX). The two benzyl ethers



(LXXXV)



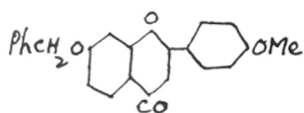
(LXXXVI)



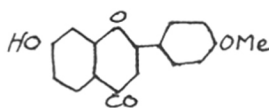
(LXXXVIII)

were unaffected by hydrochloric acid in acetic acid; hydrobromic acid effected debenylation, but the product

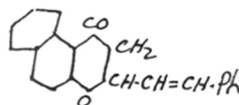
from the latter ether was 7:4'-dihydroxyflavone, not pratol (LXXXVII). The interaction of 1-acetyl-2-naphthol with cinnamaldehyde and alkali produced 3-styryl-2:3-dihydro-1:4- β -naphthapyrone (XC), which on treatment with selenium dioxide gave 3-styryl-1:4- β -naphthapyrone (XCI) identical with the substance prepared by the method of Heilbron, Barnes and Morton (J.C.S., 1923, 123, 2565; see Cheema, Gulati and



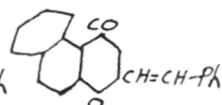
(LXXXIX)



(LXXXVII)



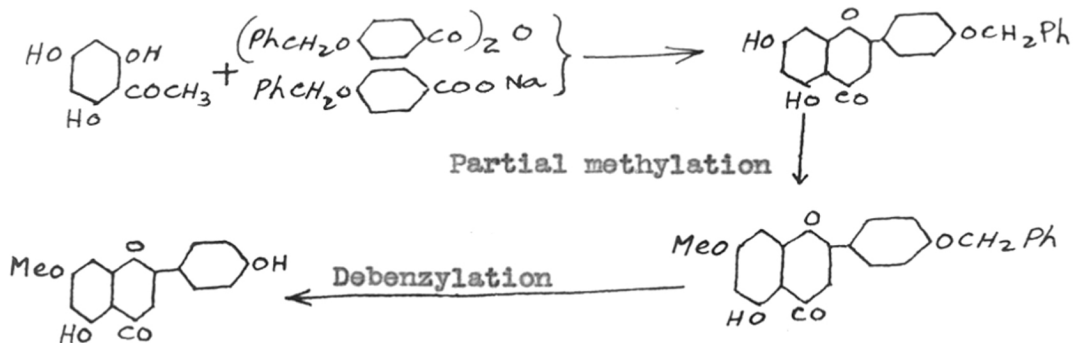
(XC)



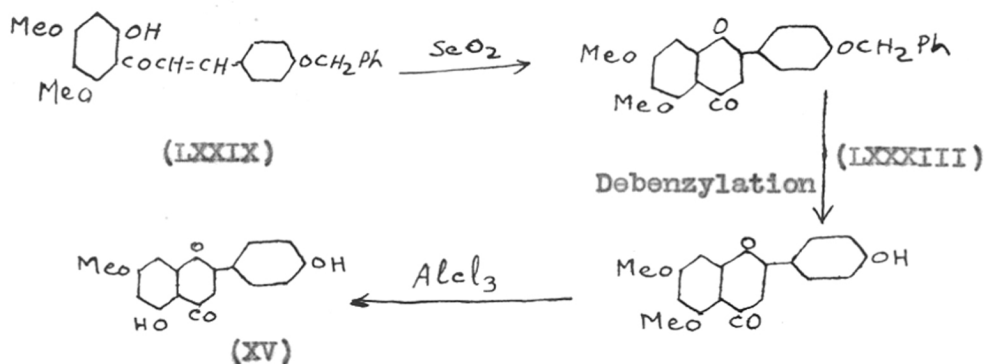
(XCI)

Venkataraman, J.C.S., 1932, 926).

Nakao and Tseng (J.Pharm.Soc.Japan, 1932, No. 602, 343; 1933, No. 608, 905) isolated apigenin and a new methoxy-dihydroxyflavone, Genkwanin, from the Chinese drug 'Yuen-hua' reputed to have diuretic and anthelmintic properties. Since it was found to be an apigenin methyl ether, different from acacetin (XIV), the 4'-methyl ether, and leading only to a monomethyl ether, Nakao and Tseng concluded that genkwanin had the structure (XV) confirmed by Tseng (J.Pharm.Soc. Japan, 1935, No. 636, 30) during the progress of my work by synthesis from phloracetophenone and p-benzyloxybenzoic anhydride followed by partial methylation and debenylation according to the scheme shown below.

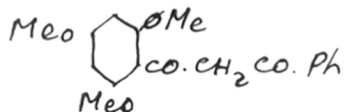


I have synthesised it according to the following scheme. The chalcone (LXXIX) was oxidised to the flavone (LXXXIII) by means of selenium dioxide; debenzylation and subsequent partial demethylation with aluminium chloride (Gulati and Venkataraman (loc.cit.) gave genkwanin.

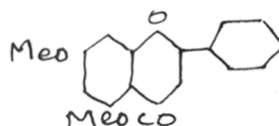


Although 2:4:6-trimethoxybenzoylacetophenone (XCII) could be demethylated in the 2-position and cyclisation to chrysin dimethyl ether (XCIII) effected in one operation by aluminium chloride in nitrobenzene, a similar reaction on the 4'-benzyloxy analogue gave the flavone (LXXXIII) in very poor yield.

Interaction with alcoholic caustic potash of the dibromide of the o-acetyl derivative of the chalcone (LXXIX) resulted in the corresponding coumaranone as indicated by the colour reactions and not in the flavone.



(XCII)

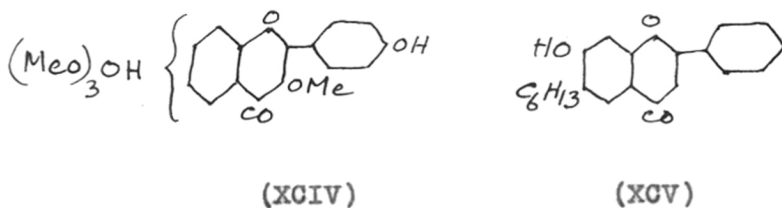


(XCIII)

Since the conversion of a flavanone to the flavone is a process of dehydrogenation of a hydroaromatic to an aromatic system, it appeared likely that selenium dioxide might be of use in the preparation of naphthalenes from tetrahydronaphthalenes, the latter being an intermediate stage in the synthesis of naphthalenes by the usual succinic anhydride method.

Heating tetrahydronaphthalene with selenium dioxide without a solvent at 160° in an oil bath, resulted in a 25% yield of naphthalene. This new method will have the advantage over the older method of converting tetrahydronaphthalene derivatives to naphthalene derivatives by heating with sulphur or selenium that the selenium dioxide oxidation is carried out at a much lower temperature and the purification of the product will

probably not involve a vacuum distillation.



Ratnagiriswaran, Sehra and Venkataraman (Biochem. J. 1934, Vol. XXVIII, No.6, 1964) isolated a bright yellow crystalline substance from the leaves of *calycopteris floribunda* Lamk., which is reputed to have laxative and anthelmintic properties (Nadkarni, Indian Materia Medica, p.238). The preliminary examination of the substance readily revealed to them its nature as a colouring matter of the flavone group and they proposed to name the substance calycopterin. It was identified as the active constituent of the leaves (Dr.K.Venkatachalam, Pharmacology Research Officer, Medical College, Madras, private communication), who observed that it is toxic to round worms (*Ascaris lumbricoides*) suspended in a mixture of bile with aqueous sodium carbonate approximating to the composition of the intestinal fluid in which the worms reside.

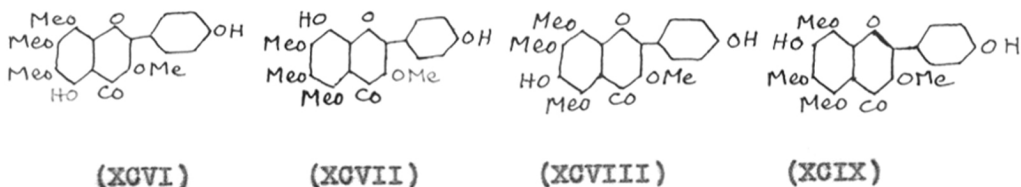
Calycopterin had the molecular formula, $\text{C}_{19}\text{H}_{18}\text{O}_8$, and contained two hydroxyl and four methoxyl groups; fusion with alkali gave p-hydroxybenzoic acid and a water-soluble phenol of undetermined constitution; and the stability of

calycopterin in alkali solution to aerial oxidation led the authors to believe that it is a 4'-hydroxy-3-methoxy flavone derivative having three methoxyls and one hydroxyl in the fused benzene ring (XCIV). This has been further confirmed by Karrer (Helv.Chim.Acta, 1934, 17, 1560) who has recognised it as a constituent of Digitalis thapsi.

This being the first example of a flavone with anthelmintic properties, further elucidation of the constitution of calycopterin was undertaken in the present work and certain flavones genkwanin (XV), chrysin (I), 7-hydroxyflavone (X) and 6-hexyl-7-hydroxyflavone (XCV) were synthesised and their anthelmintic and antiseptic properties have been studied.

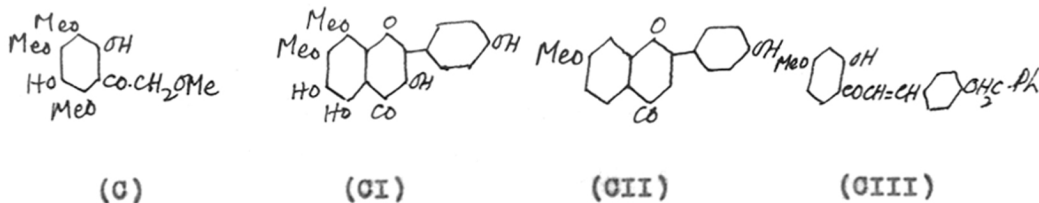
Having formulated calycopterin as (XCIV) (Ratnagiriswaran, Sehra and Venkataraman, loc.cit.) four possibilities (XCVI, XCVII, XCVIII and XCIX) remained to be considered. The ease with which calycopterin gave a dimethyl ether, the latter being obtained also by the action of methyl iodide and caustic potash in methyl alcohol precluded a 5-hydroxyl (XCVI), and this was confirmed by the preparation of a dibenzyl ether whose alcoholic solution did not exhibit a colouration with ferric chloride (c.f. Gulati and Venkataraman, J.C.S., 1936, 267). From the alkaline hydrolysis of calycopterin was isolated a small amount of a ketone, assumed to be (C) which did

not behave like a catechol derivative, thus excluding structure (XCVII) for calycopterin. The choice lying between (XCVIII and XCIX), a study of the action of aluminium chloride on calycopterin was made in the light of the observation that methoxyl in the 3- and 5- positions are preferentially attacked (c.f. Gulati and Venkataraman, loc.cit.). Calycopterin has thus given rise to a new flavone, demethylcalycopterin, to which the structure (CI) has been assigned on the basis of the analysis and the characteristic catechol



colour reactions. It would then follow that calycopterin is 6:4'-dihydroxy 3:5:7:8-tetramethoxyflavone (XCVIII).

7-methoxy-4'-hydroxyflavone (CII) has been synthesised from 2-hydroxy-4-methoxy phenyl 4'-benzyloxystyryl ketone (CIII) by means of selenium dioxide, followed by debenylation, and it is different from a hydroxymethoxyflavone isolated from a species of Digitalis (Adrian and



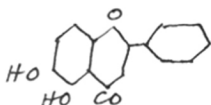
Trillat, comp. rend., 1899, 129, 889) which did not give catechol or phloroglucinol by alkali treatment.

The first observation was made by Shibata and Kimotsuki (J. Tokyo Chem. Soc. 1918, 39, 771-808; Acta Phytochim. 1923, 1, 91-104) that aqueous or preferably alcoholic solutions of flavone and its derivatives showed two absorption bands in the violet region in 0.0001 Mol. solution. The introduction of a hydroxyl group into the fused benzene ring as well as in the 3-position had a bathochrome effect on the first band $\lambda = 3000$ in flavone, which was also effected hyperchromatically by the number of hydroxyl and methoxyl groups in the benzene ring. The second band at 4000 was exhibited by all the compounds and was supposed to be due to the pyrone ring. The flavone itself had two bands at frequencies 3500 and 4050. The position of these two bands was affected by the number and orientation of the hydroxyl groups. The position of the second band was scarcely influenced by hydroxyl groups, but the first is shifted towards the red by hydroxyl groups in the benzopyrone nucleus and in the opposite direction by hydroxyl in the side phenyl group. Moreover, the depth of this band increased with the number of hydroxyl groups as in the series kaempferol (XXV), quercetin (XXIII), and myricetin (XXVIII) containing, respectively, one, two and three hydroxyls in the side phenyl group.

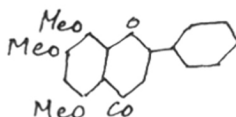
Tasaki (Acta Phytochim., 1925, 2, 119-128; ibid., 129) and Hattori (Acta Phytochim. (Japan) 1928, 4, No.1, 41-61; 1930, 5, 99-116; 1932, 6, 131-154) following on Shibata and Kimotsuki's lines (loc.cit.) showed that the auxochrome action of the hydroxyl groups was not affected by methylation or in general by alkylation, but was annulled by acetylation or acylation. Thus diacetyl chrysin and pentacetyl quercetin had exactly the same absorption spectrum as that of flavone; similarly chrysin and chrysin dimethyl ether showed almost identical spectra and the methylenedioxy group behaved like two adjacent hydroxyl or methoxyl groups. In the flavonols methylation of the hydroxyls resulted in marked displacement of the first band towards blue, the second band remaining, usually, unaltered in position while becoming less deep. It was also suggested that the bathochromic effect of introduction of hydroxyl into the pyrone ring of flavones was due to the possibility of tautomerism in the flavonols, whereby an α -diketone or o-quinonoid form was produced stabilization of hydroxyl groups by methylation reversed this effect, so that the methylated flavonols again became more nearly like the corresponding flavones. Hydroxyl substitution in position 8, 2' or 3' had no effect on the absorption spectra of flavones; hydroxyl in the 7-position influenced only the first band and in position 5- only the second. 5-Hydroxy-7-methylflavone showed only one absorption band, while

5:4'-dihydroxy-7-methylflavone showed two. The effect of 4':7-disubstitution on the first absorption band was additive. 6:4'-Dihydroxyflavone showed one band and 5:7:8-trihydroxyflavone showed the additive effect of 7,8 and 5-substitution.

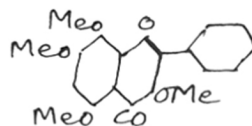
Following the results of some of these fundamental experiments on the absorption spectra of flavones Shibata and Kimotsuki (loc.cit.) confirmed the position of the hydroxyls in the molecule of primetin (CIV) found in Primula farinosa L. (Yukiwariso) and Hattori (loc.cit.) confirmed the constitution of wogonin (XVIa) by comparison of the absorption spectra of acetyl wogonin with that of 8-hydroxy and 8-methoxyflavones.



(CIV)



(CV)



(CVI)

In passing it may be mentioned that in flavone and flavonol glucosides (Tasaki, loc.cit.) the character of the absorption spectra was determined by the position of the sugar residue in the molecule and not by the individual sugar or sugars present in the glucoside.

In the light of these experiments on the constitution of flavones and absorption spectra it is hoped that

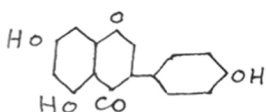
the comparison of absorption spectra of diacetyl calycopterin with 5:7:8-trimethoxy (CV) or trihydroxy and 3:5:7:8-tetramethoxy (CVI) or tetrahydroxyflavones will further confirm the constitution of calycopterin as (XCVIII). The preparation of these compounds and the study of their absorption spectra have now been undertaken.

HISTORY AND CHEMISTRY OF THE ISOFLAVONE GROUP.

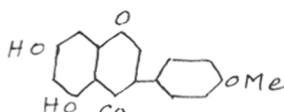
The derivatives of 2-phenylchromone or flavone have been widely studied since 1873, while the derivatives of 3-phenylchromone or isoflavone remained unnoticed till very recent times.

The first member of the series to be isolated from natural sources was prunetin, $C_{16}H_{12}O_5$, which was obtained by the hydrolysis of the glucoside prunetrin of prunus bark. Finemore (Pharm.J., 1910, 31, 1761), on fusing prunetin with alkali, recognised p-methoxyphenylacetic acid as one of the products of hydrolysis, on the basis of which he put forward the suggestion that prunetin may be a monomethyl ether of a trihydroxyisoflavone. Perkin and his pupils (J.C.S., 1899, 75, 830; 1900, 77, 1310) observed that prunetin on demethylation gave a product, prunetol, which was identical with genistein (GVII), the colouring matter of dyer's broom. The correctness of this observation was later demonstrated by Baker and Robinson (J.C.S., 1926, 127, 2713); prunetin was thus assigned the constitution (GVIII).

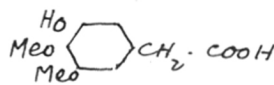
The second member of the series to be recognised as an isoflavone was irigenin, $C_{18}H_{16}O_8$, which was obtained by the hydrolysis of the glucoside, iridin, contained in the dried rhizomes of Iris florentina. Irigenin on degradation with alkali gave iridic acid (3-hydroxy-4:5-dimethoxyphenylacetic acid) (CIX), iretol (methoxyphloroglucinol) (CX)



(CVII)



(CVIII)

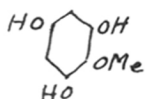


(CIX)

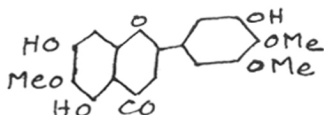
and formic acid (Laire and Tiemann, Ber., 1893, 26, 2010); on the basis of these results Baker (J.C.S., 1928, 1022) interpreted the degradation experiments correctly and assigned to irigenin the structure of an isoflavone (CXI).

ψ -Baptigenin was the third member of the group to be obtained (Spath and Schmidt, Monatsh., 1929, 54, 454) by hydrolysis of the glucoside ψ -baptisin, a constituent of Baptista tinctoria.

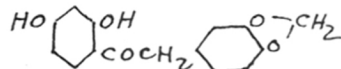
ψ -Baptigenin, $C_{15}H_{10}O_5$, on treatment with alkali gave a ketone ψ -baptigenitin and formic acid. The constitution of the ketone was shown to be 2:4-dihydroxyphenyl 3:4-methylenedioxybenzyl ketone (CXII) by comparison with the synthetic product obtained by a Hoesch reaction on



(CX)



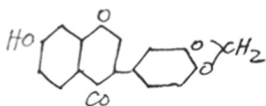
(CXI)



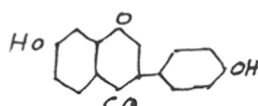
(CXII)

resorcinol and 3:4-methylenedioxybenzyl cyanide and subsequent hydrolysis. ψ -Baptigenin was, therefore, considered to be an isoflavone and Spath and Lederer (Ber., 1930, 63, 743) succeeded in demonstrating the constitution (CXIII) of ψ -baptigenin by its synthesis.

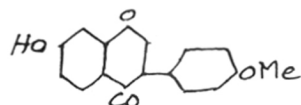
A little later Walz (Ann. 1931, 489, 118) showed that daidzein, the aglucone of one of the constituents of Soja hispida, was a colouring matter of the isoflavone group and had the constitution (CXIV). Almost simultaneously Wessely



(CXIII)



(CXIV)



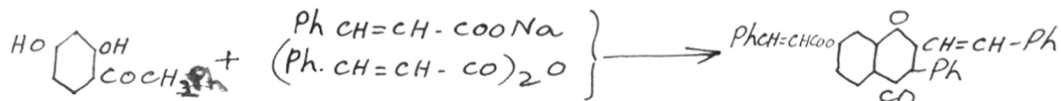
(CXV)

and Lehner (Monatsh., 1931, 57, 395) elucidated the constitution (CXV) of formononetin, the aglucone (Hemmelmayr, Monatsh., 1902, 23, 133) of one of the constituents, ononin, of ononis spinosa.

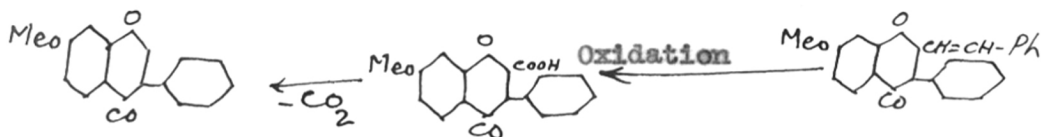
A fairly wide occurrence of isoflavones, a closely

related group to flavones, in nature being thus revealed, their synthesis became of interest.

The first method for the synthesis of isoflavones was developed by Baker and Robinson (J.C.S., 1925, 127, 1981) and was carried out according to the scheme indicated below:-

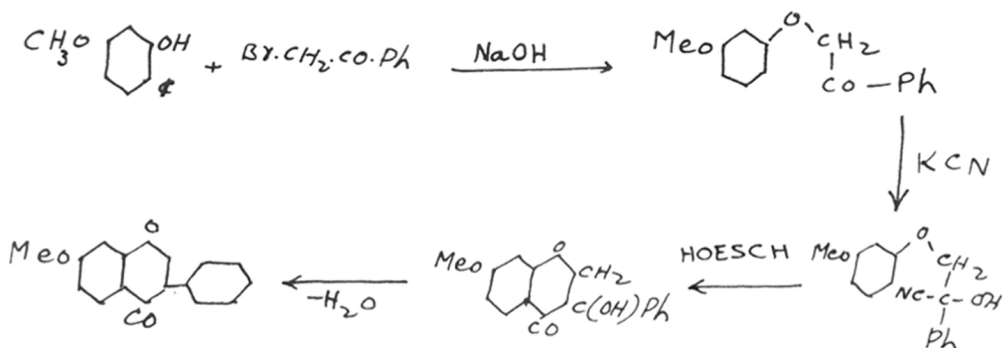


Hydrolysis and methylation

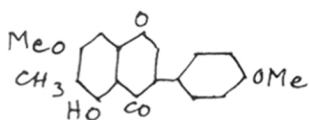


Although Baker and Robinson (J.C.S., 1926, 129, 2713; 1928, 133, 3115) and Baker, Robinson and Simpson (J.C.S., 1933, 143, 274) utilised this method for the syntheses of 6-methylgenistein-7:4'-dimethyl ether (GXVI), genistein (GVII) and daidzein (GXIV) yet it broke down in the case of irigenol (GXVII), the oxidation of the 2-styryl derivative of the hexamethyl ether to the 2-carboxylic acid proving impracticable (Baker and Robinson, J.C.S., 1929, 135, 152).

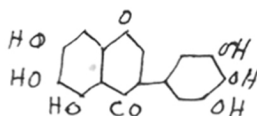
Baker, Pollard and Robinson (J.C.S., 1929, 135, 1468) then developed a second method for the synthesis of isoflavones according to the following scheme:-



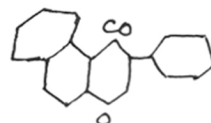
The method has been successfully employed for the syntheses of ψ -baptigenin (CXIII) (Spath and Lederer, Ber., 1930, 63, 743) and β -naphthaisoflavone (CXVIII) (Badhwar and



(CXVI)



(CXVII)

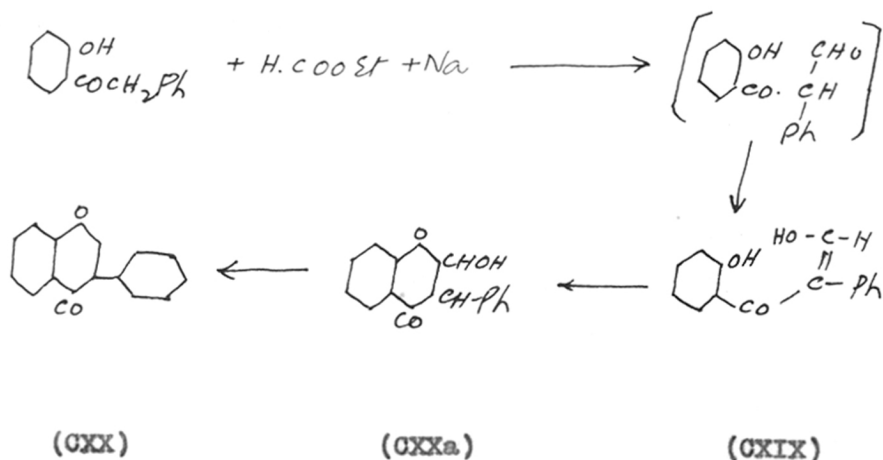


(CXVIII)

Venkataraman, J.C.S., 1932, 141, 2420). It must, however, be pointed out that this method too, is of limited application. Baker, Morgans and Robinson (J.C.S., 1933, 143, 374) pointed out that the method failed in the synthesis of certain isoflavones; either the cyanhydrin could not be obtained or ring closure was not affected by the Hoesch reaction to the corresponding isoflavone.

Spath and Lederer, in view of these difficulties in synthesising isoflavones by the known methods, developed

another method which in its essentials was carried out by heating derivatives of 2-hydroxyphenyl benzyl ketone with ethyl formate and sodium in a sealed tube, followed by the treatment of the reaction mixture with boiling alcohol and fuming hydrochloric acid in order to effect closure of the oxymethylene compound (CXIX), assumed to be an intermediate product, to the γ -pyrone (CXX) as given in the following scheme:-



The isoflavones so formed were purified by sublimation under high vacuum. Following this method Spath and Lederer (Ber., 1930, 63, 745) synthesised γ -baptigenin (CXIII) and Wessely, Kornfeld and Lechner (Ber., 1933, 66, 685) synthesised daidzein (CXIV) and formononetin (CXV) although the yields were extremely poor.

More recently Joshi and Venkataraman (J.C.S., 1934, 513) observed that the action of sodium on an ice cooled

In the present work the synthesis of ψ -baptigenin (CXIII) has been described. The action of benzyl chloride on ψ -baptigenetin (CXII) led exclusively to the 4-benzyl ether (CXXIII) from which ψ -baptigenin 4-benzyl ether (CXXIV) was prepared by the new method in 90% yield; debenylation in the usual way gave ψ -baptigenin.

PHARMACOLOGY OF CERTAIN FLAVONES.

A systematic study of the pharmacological action of flavones was first made by Koike (Folia Pharmacol. Japon., 1931, 12, No.1, 89, Breviaria, 6) who observed that myricetin, morin and campherol showed diuresis in normal rabbits and the diuretic action was greater with the flavones having greater number of hydroxyls. Fukuda (Arch. Exptl. Path. Pharmacol., 1932, 164, 685) also studied the pharmacological action of camphor oil, morin, quercitrin, rutin, myricetin and myricitrin and confirmed the previous observation of Koike (loc. cit.) that these naturally occurring group of dyes have a diuretic action; they are also cardiac stimulants, vasoconstrictors and increase the blood pressure. They are absorbed from the intestinal canal and from the subcutaneous tissue and are excreted unchanged in the urine.

It having been shown recently that calycopterin, the active constituent of Calycopteris floribunda known to have anthelmintic action, belonged to the flavone group

(Ratnagiriswaran, Sehra and Venkataraman, loc. cit.), the study of the pharmacological action particularly the anthelmintic action of chrysin (I), genkwanin (XV), 7-hydroxyflavone (X) 6-hexyl-7-hydroxyflavone (XCV) and 4-methylumbelliferon (CXXV) was undertaken in the present work.

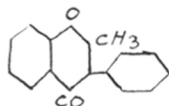
The anthelmintic action of the compounds was studied in vitro (a) by directly immersing round-worms (*Ascaris lumbricoides*), tape-worms (*Taenia serrata*) and leeches (*Hirudo medicinalis*) in different concentrations of the solution of the substances, (b) by the application of the Dale and Laidlaw's method (J. Pharm. Exper. Therap., 1912, Vol.4, p.75) and it was observed that the substances did not have any action on the parasites. The compounds were insufficient to be tried invivo only 4-methylumbelliferon which could be prepared in quantity and cheaply too, was tried on fowls and dogs. It showed a general constipative effect on the animals and most of the substance got absorbed in their system and could be traced out in their urine even on the fourth day after the administration. Although no definite conclusions can be drawn from these few experiments on the substance (CXXV) yet it will be worthwhile pointing it out here that its high absorption from the gastro intestinal tract will be an important point against its possibility of being an ideal anthelmintic.

These compounds inhibited the movements of the isolated rabbits gut and uterus in concentrations of about 1-140,000; they caused depression in the blood pressure in doses of 20 mg. per Kg. weight in dogs increased the movements of respiration and caused contraction in the uterus and in concentrations varying from 1-500,000 - 2,000,000 inhibited the beats of an isolated frog's heart.

To determine the antiseptic properties of these compounds their effect on the growth of B.coli was studied. It was found that chrysin and genkwanin had no action on the bacilli, but (CXXV), however, inhibited the growth of the bacilli in 1-1,000 concentration while in concentration 1-10,000 only slight inhibition was observed.

EXPERIMENTAL.

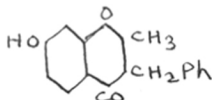
2-Methylisoflavone:- (Chadha, Mahal and Venkataraman,



J.C.S., 1933, 1459). A mixture of phenol (10 g.) and phenylacetyl chloride (20 g.) was heated at 150° (oil-bath) for 8 hours, and poured

into water. The ester extracted by benzene distilled at 174°/3 mm. (20 g.). The ester (20 g.) was heated with aluminium chloride (20 g.) and carbon disulphide (40 c.c.) for one hour on a water-bath and for 4 hours at 120° (oil-bath). The product crystallised from petroleum ether in large, colourless hexagonal plates (2 g.), m.p. 60°. The ketone (2 g.), sodium acetate (2 g.) and acetic anhydride (10 g.) were heated in an oil-bath at 170-80°. After 8 hours the reaction mixture was poured into water and the oil that separated which solidified on stirring was collected and crystallised from dilute alcohol in colourless needles (0.4 g.), m.p. 140° (Found: C, 81.1; H, 5.0. C₁₆H₁₂O₂ requires C, 81.4; H, 5.1%). It was unaffected by boiling with 50% hydrochloric acid; the colourless solution in sulphuric acid exhibited a weak blue fluorescence.

7-Hydroxy-3-benzyl-2-methylchromone:- Fused zinc

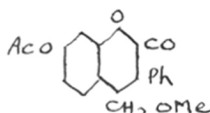


chloride (5.5 g.) was dissolved in β -phenylpropionic acid (14 g.) at 145-150°, resorcinol (3 g.) was then added and the mixture kept at

145° for one hour. The deep red solution was poured into water

and after two hours the precipitate was collected, powdered, and shaken with sodium bicarbonate solution. The residue was crystallised from 50% acetic acid in very pale cream-coloured needles (3.5 g.), m.p. 88°. The ketone (3 g.), sodium phenylacetate (2 g.) and acetic anhydride (20 g.) were refluxed on a sand-bath for 30 hours. The reaction mixture was then poured into water; the oil that separated did not solidify even on placing it in contact with solvents like alcohol, benzene and petroleum ether. It was then refluxed with 50% hydrochloric acid (100 c.c.) the semi-solid mass that separated was crystallised twice from glacial acetic acid in colourless needles (1 g.), m.p. 284° (Found: C, 76.6; H, 5.3. Calculated for $C_{17}H_{14}O_3$: C, 76.6; H, 5.3%). The acetyl derivative was prepared by means of acetic anhydride and a drop of pyridine; crystallised from alcohol, the colourless needles had m.p. 126° (Found: C, 74.4; H, 5.3. Calculated $C_{19}H_{16}O_4$: C, 74.0; H, 5.2%).

7-Acetoxy-5-phenyl-4-methoxymethylcoumarin:- A mixture of resorcinol (13 g.), methoxyacetonitrile

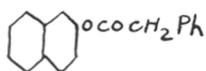


(10 g.) and fused zinc chloride (2 g.) in dry ether (50 c.c.) after the Hoesch condensation

and hydrolysis of the ketimide hydrochloride gave ω -methoxyresacetophenone, recrystallised from hot water (12 g.), m.p. 134° (Slater and Stephen, J.C.S., 1920, 117, 309). The ketone (4 g.), sodium phenylacetate (3.75 g.) and acetic

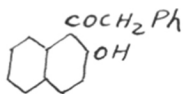
anhydride (40 c.c.) were refluxed on a sand-bath for 30 hours. After the reaction was over it was poured into water the oil that was obtained was taken up in ether and the slow evaporation of the solvent gave some solid which was recrystallised twice from alcohol in colourless needles, m.p. 163° (Found: C, 70.2; H, 5.0. $C_{19}H_{16}O_5$ requires C, 70.4; H, 4.9%). Hydrolysis with hydrochloric acid and crystallisation from 30% alcohol gave very pale yellow needles, m.p. 213° (Found: C, 72.3; H, 5.2. $C_{17}H_{14}O_4$ requires C, 72.4; H, 5.0%). 7-acetoxy- and 7-hydroxy-3-methoxy-2-methyl chromone melt respectively at 113° and 214° (Allan and Robinson, J.C.S., 1924, 125, 2192).

β-Naphthyl phenylacetate:- A mixture of phenyl-



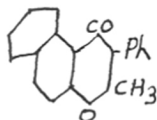
acetic acid (100 g.) and thionyl chloride (300 c.c.) was refluxed for 5 hours on the water-bath. The excess of thionyl chloride was first distilled off under vacuum (water pump) and finally the acid chloride distilled over at 102°/6 mm. Yield, 103 g. β-Naphthol (38 g.) and phenylacetyl chloride (60 g.) were heated at 150° for 6 hours. The brown precipitate obtained when the product was poured into water was washed with sodium bicarbonate solution, dried and crystallised twice from light petroleum (b.p. 50-60°), forming stout colourless plates, m.p. 87° (Found: C, 82.2; H, 5.4. $C_{18}H_{14}O_2$ requires C, 82.4; H, 5.3%).

1-Phenylacetyl-2-naphthol:- (1) β -Naphthyl phenyl-



acetate (5 g.), aluminium chloride (4 g.), and carbon disulphide (10 c.c.) were heated on the water-bath for 1 hour, the solvent removed, and the residue heated at 130° for 4 hours. Ice was added, the product dissolved in hot 10% aqueous sodium hydroxide, and the filtered solution acidified. Two crystallisations from dilute acetic acid gave pale yellow needles (0.5 g.) m.p. 101° (Found: C, 82.1; H, 5.5. $C_{18}H_{14}O_2$ requires C, 82.4; H, 5.3%). An alcoholic solution gave a dark reddish-brown colouration with ferric chloride. (2) To a mixture of β -naphthol (20 g.), aluminium chloride (40 g.), and carbon disulphide (100 c.c.), cooled in ice and salt, phenylacetyl chloride (30 g.) was added during one hour. After 12 hours, ice and hydrochloric acid were added, the mixture was extracted with ether, and the extract shaken with 5% sodium hydroxide solution. Acidification of the alkaline solution gave a semi-solid substance, which was treated with boiling water to remove β -naphthol and crystallised from dilute acetic acid (charcoal), giving colourless needles (10 g.), m.p. 101° .

3-Phenyl-2-methyl-1:4- $\beta\alpha$ -naphthapyrone:-

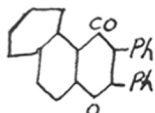


(1) 1-Phenylacetyl-2-naphthol (2 g.) sodium acetate (2 g.) and acetic anhydride (15 c.c.) were refluxed on a sand-bath for 8 hours and

poured into water. The oil that separated which rapidly solidified on shaking was collected and crystallised from alcohol in long, cream-coloured needles (0.7 g.), m.p. 161° (Found: C, 83.6; H, 5.0. $C_{20}H_{14}O_2$ requires C, 83.9; H, 4.9%).

(2) A mixture of 1-phenylacetyl-2-naphthol (2 g.), sodium phenylacetate (3 g.) and acetic anhydride (15 c.c.) was refluxed on a sand-bath for 30 hours and poured into water. The substance crystallised from alcohol in long, cream-coloured needles (0.3 g.), m.p. and mixed m.p. with the product obtained in the previous experiment was 161°.

2:3-Diphenyl-1:4- $\beta\alpha$ -naphthapyrone:- 1-phenyl

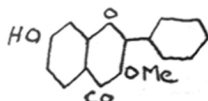


acetyl-2-naphthol (2.5 g.), benzoic anhydride (12 g.) and sodium benzoate

(2 g.) were heated together at 185°, in

an oil bath, for 8 hours. The product was then hydrolysed with caustic potash (2.9 g.) (in 10% alcoholic solution) for 0.5 hour, poured into water, filtered and the residue crystallised from alcohol in long colourless needles, m.p. 188° (Found: C, 85.9; H, 4.3. $C_{25}H_{16}O_2$ requires C, 86.2; H, 4.6%).

3-Methoxy-7-hydroxyflavone:- ω -Methoxy-

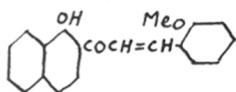


-resacetophenone (5 g.) was heated with benzoyl chloride (6.5 g.) and pyridine (13 g.) for 20 minutes on the water-bath

and the product shaken vigorously with dilute hydrochloric acid. The semi-solid mass was crystallised from alcohol in colourless needles (3.7 g.), m.p. 76° - 77° (Found: C, 70.7; H, 4.7. $C_{23}H_{18}O_6$ requires C, 70.7; H, 4.6%). ω -Methoxy resacetophenone dibenzoate thus obtained (3 g.) was distilled under a reduced pressure of 3 mm. The light brown oily distillate, forming a sticky solid mass on cooling, which distilled between 230° - 280° was collected. The sticky solid mass solidified to a white amorphous powder (0.9 g.) on placing in contact with light petroleum, but showed no tendency to crystallise from any of the ordinary organic solvents. The crude product melted at 100° - 110° and an alcoholic solution of the substance gave a deep reddish brown colouration with aqueous ferric chloride; on treatment with concentrated sulphuric acid for 15 minutes and pouring on to crushed ice, the precipitate was collected and crystallised from alcohol in colourless needles (0.4 g.) m.p. 230° . The alcoholic solution of the substance gave no colouration with aqueous ferric chloride. The crystalline substance (0.2 g.) was refluxed with 10% alcoholic caustic potash for 30 minutes and most of the alcohol removed on the water-bath. The residue was poured into water and saturated with carbon dioxide. The solid that separated was collected and crystallised from Alcohol in colourless needles, m.p. 230° ; the mixed m.p. with the untreated substance was also 230° (Allan and Robinson, J.C.S., 1924, 125,

2192, 227^o). (Found* : C, 71.5; H, 4.6. Calculated for C₁₆H₁₂O₄; C, 71.6; H, 4.4%).

2-o-Methoxycinnamoyl-1-naphthol:- 2-Acetyl-1-

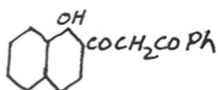


-naphthol was prepared as follows:-

Powdered fused zinc chloride (48 g.) was first dissolved in glacial acetic acid (55 g.) at 145^o-48^o in an oil-bath. To the clear solution acetic anhydride (71 g.) and then α -naphthol (100 g.) were added quickly. The mixture was heated in the oil-bath for 1 hour at 150^o, poured into water, filtered, washed with cold alcohol and crystallised from alcohol in light green crystals (90 g.), m.p.98^o (c.f. Witt, Ber., 1888, 21, 321). Salicylaldehyde (50 g.) was methylated as usual with caustic potash (50 g. in 100 c.c. water) and dimethyl sulphate (100 g.). The o-methoxy benzaldehyde distilled at 242^o-245^o; Yield 10 g. To the boiling solution of 2-acetyl-1-naphthol (7.5 g.) and o-methoxybenzaldehyde (6.3 g.) in alcohol (50 c.c.) was added 50% caustic potash (17.5 g.) and the mixture was refluxed for 1 hour. It was then poured into water and the orange oil that separated soon solidified. It was filtered off and repeatedly crystallised from glacial acetic acid in orange-yellow, woolly needles, m.p.155^o (Found: C, 78.8; H, 5.4. C₂₀H₁₆O₃ requires C, 78.9; H, 5.3%). The acetyl derivative crystallised from alcohol in pale yellow plates, m.p.83^o (Found: C,76.1;H,5.4. C₂₂H₁₈O₄ requires

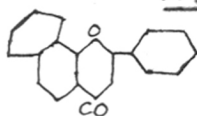
C, 76.3; H, 5.2%). The dibromide, prepared in carbon disulphide solution, crystallised from alcohol-benzene in colourless prisms, m.p. 157° (Found: Br, 31.9. $C_{22}H_{18}O_4Br_2$ requires Br, 31.6%). The orange-red mixture, produced by adding caustic potash (2.2 g. in 6 c.c. of water) to a suspension of the dibromide (6.4 g.) in alcohol (30 c.c.), deposited after some hours a yellow solid (2.2 g.), which did not consist of a single substance. Many crystallisations from alcohol gave stout, brownish yellow needles (0.2 g.), m.p. 252° (decomp.) (Found: C, 79.4; 4.5. $C_{20}H_{14}O_3$ requires C, 79.5; H, 4.6%). The substance was not identical with 2'-methoxynaphthoflavone (see later). Addition of water to the alcoholic mother liquors precipitated a low melting product, which contained O-methoxybenzylidene naphthofuranone, since it gave a deep red colour with sulphuric acid and readily decolourised permanganate.

1-Hydroxy-2-naphthoyl benzoyl methane:- Benzoyl



chloride (5 g.) was heated with 2-acetyl-1-naphthol (5 g.) and pyridine (10 c.c.) for 20 minutes on the water-bath, dilute hydrochloric acid was then added, the solid that separated was filtered off and crystallised from alcohol in pale yellow needles (3.5 g.) m.p. 133°. A mixture of the 2-acetyl-1-naphthyl benzoate (5 g.), powdered sodamide (5 g.) and dry ether (66 c.c.) in a stout glass-stoppered bottle was

shaken mechanically for 5 hours and let stand over night at room temperature (maximum temperature 22°). The bulky, yellowish green precipitate, which darkened rapidly in air, was collected, washed with ether and stirred immediately into aqueous acetic acid; crystallisation of the orange product from acetone gave bright orange-yellow needles (1.5 g.), m.p. 147° (Found: C, 78.6; H, 5.0. $C_{19}H_{14}O_3$ requires C, 78.6; H, 4.8%). The substance was coloured orange by sulphuric acid and the yellow solution exhibited a bright green fluorescence. The alcoholic solution gave dark olive-green colour with ferric chloride.



1-Naphthaflavone:- A solution of the above ketone

(0.5 g.) in concentrated sulphuric acid

(10 c.c.) was let stand for 10 minutes and

poured on to crushed ice. The nearly

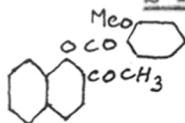
colourless precipitate crystallised from alcohol in long,

pale cream-coloured needles (0.4 g.), m.p. 157° . The m.p.

was not depressed by admixture with the substance prepared

by the Robinson reaction (Bhullar and Venkataraman, J.C.S.,

1931, 1165) pale yellow plates, m.p. 155° .



2-Acetyl-1-naphthyl o-methoxybenzoate:- o-methoxy-

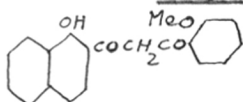
benzoic acid was obtained in 80% yield by

methylating salicylic acid under the condi-

tions described for 2:4-dimethoxybenzoic

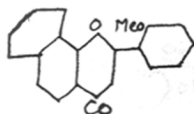
acid (Robinson and Venkataraman, J.C.S., 1929, 62). The chloride (5 g.), obtained by means of thionyl chloride, was heated with 2-acetyl-1-naphthol (5 g.) and pyridine (10 c.c.) for 20 minutes on the water-bath shaken vigorously with dilute hydrochloric acid, the semi-solid mass was crystallised from alcohol. The stout, colourless needles melted at 115° (Found: C, 75.1; H, 5.0. $C_{20}H_{16}O_4$ requires C, 75.0; H, 5.0%).

1-Hydroxy-2-naphthoyl-o-methoxybenzoyl methane:-



Contact of the ester (6 g.) with sodamide (12 g.) and ether (50 c.c.) during 12 hours (maximum temperature 23°), followed by 6 hours on a mechanical shaker, resulted in a dark green gel, which was collected, washed with ether and decomposed with ice and acetic acid. The orange product crystallised from acetone in glistening golden-yellow needles (1.5 g.), m.p. 113° (Found: C, 75.0; H, 4.9. $C_{20}H_{16}O_4$ requires C, 75.0; H, 5.0%). The colour reactions were similar to those of the previous diketone. The preparation was also repeated with toluene as solvent but there was no difference in behaviour and resulted in the same product as in the first experiment when ether was used.

2'-Methoxy- α -naphthaflavone:- On boiling the dike-

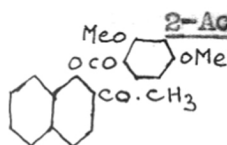


tone (0.9 g.) with absolute alcohol (100 c.c.) and sulphuric acid (d. 1.84; 10 c.c.) for 90 minutes, the solution changed from deep brown

to pale yellow. Dilution with water gave a colourless precipitate, which crystallised from alcohol in long, colourless, silky, needles (0.7 g.), m.p. 164° (Found: C, 79.4; H, 4.8. $C_{20}H_{14}O_3$ requires C, 79.5; H, 4.6%).

Demethylation in the usual way with hydriodic acid and acetic anhydride or phenol did not lead to homogeneous alkali-soluble substance. The difficulty in smooth demethylation is doubtless associated with the 2'-methoxy group (compare 5:7-dihydroxy-3:2':4'-trimethoxyflavone, Robinson and Venkataraman, J.C.S., 1929, 61).

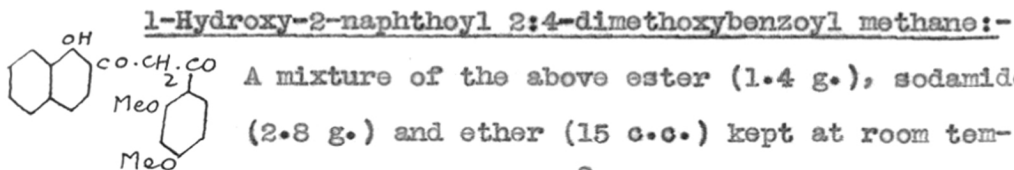
Dissolution of the diketone in concentrated sulphuric acid and addition to crushed ice gave a yellow substance, which was insoluble in the common organic solvents. A clear solution was obtained when the substance was suspended in boiling glacial acetic acid and treated with an equal volume of water. On cooling, bright yellow needles separated, which melted and decomposed at 326° (Found: S, 8.1; by titration with standard caustic soda solution, SO_3H , 21.0. $C_{20}H_{14}O_6S$ requires S, 8.2; SO_3H , 21.2%).



2-Acetyl-1-naphthyl 2:4-dimethoxybenzoate:-

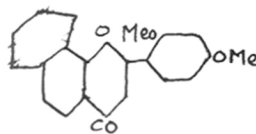
Prepared as in the case of the o-methoxybenzoate, from 2-acetyl-1-naphthol (2.5 g.), 2:4-dimethoxybenzoyl chloride (2.7 g.) and

pyridine (8 g.) and after 2 crystallisations from alcohol, the substance was obtained in colourless rectangular plates (2.0 g.) m.p.126° (Found: C, 72.2; H, 4.8. C₂₁H₁₈O₅ requires C, 72.0; H, 5.1%).



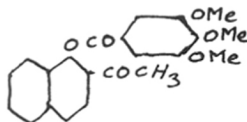
A mixture of the above ester (1.4 g.), sodamide (2.8 g.) and ether (15 c.c.) kept at room temperature (maximum 39°) became yellow in colour in 20 minutes. After 8 days, during which it was shaken up occasionally, the mixture had turned greenish yellow and was then worked up in the usual manner. The diketone separated from alcohol in long, shining, orange-yellow needles (0.4 g.), m.p.133° (Found: C, 72.2; H, 4.7. C₂₁H₁₈O₅ requires C, 72.0; H, 5.1%). The substance fluoresced a brilliant green in sulphuric acid.

2':4'-dimethoxy-~~O~~-naphthoflavone:- On boiling the



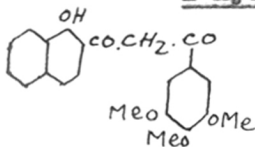
diketone (0.19 g.) with alcohol (12 c.c.) and concentrated sulphuric acid (1.5 c.c.) for one hour and pouring into water, the product crystallised from alcohol in long, lustrous, colourless, silky needles (0.13 g.), m.p.214° (Found: C, 76.2; H, 4.5. C₂₁H₁₆O₄ requires C, 75.9; H, 4.8%). The colourless solution in sulphuric acid exhibited a bright green fluorescence.

2-Acetyl-1-naphthyl trimethylgallate:- Trimethyl



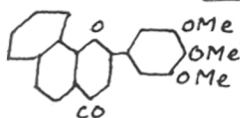
gallie acid (Organic Synthesis, 6, 96) was obtained in better yields when the process was modified slightly, being carried out in a current of hydrogen and the mixture being mechanically stirred. Gallic acid (50 g.) gave the trimethyl ether (50 g.), m.p. 167°. A mixture of the acid (50 g.) and thionyl chloride (100 c.c.) gave in the usual way the trimethylgalloyl chloride, crystallised from benzene-petroleum ether (36 g.), m.p. 76°. The product, obtained by heating 2-acetyl-1-naphthol (5 g.), trimethylgalloyl chloride (6.5 g.) and pyridine (13 g.) on the water-bath for half an hour and pouring into water, was washed with dilute hydrochloric acid, ice-cold aqueous caustic soda and then with water. Crystallised from alcohol until free from ferric chloride colouration, the colourless needles (8 g.), melted at 143° (Found: C, 69.3; H, 5.4. $C_{22}H_{20}O_6$ requires C, 69.4; H, 5.2%).

1-Hydroxy-2-naphthoyl 3:4:5-trimethoxybenzoyl methane:-



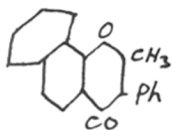
A clear solution of the ester (3 g.) in toluene (50 c.c.) was mechanically shaken with sodamide (7 g.) for 30 hours and let stand at room temperature (maximum 19°) for a week. The mixture had set to a viscous yellow gel, which was filtered with difficulty on the pump; washed with toluene, the sticky solid was triturated with ice cold aqueous acetic acid. The orange-yellow product

crystallised from alcohol in deep yellow needles (1.2 g.), m.p. 142° (Found: C, 69.2; H, 5.3. $C_{22}H_{20}O_6$ requires C, 69.4; H, 5.2%). The crystals are coloured orange by sulphuric acid; unlike the previous diketone, the solution exhibited only a faint green fluorescence. The colouration with ferric chloride was dark green as in the other cases.



3':4':5'-trimethoxy- α -naphthaflavone:- The above

diketone (1 g.) dissolved in sulphuric acid (10 c.c.) and, after 90 minutes, added to powdered ice, the diketone (0.7 g.) gave the naphthaflavone (0.6 g.), which crystallised from alcohol-acetic acid in lustrous, pale yellow needles, m.p. 224° (Found: C, 72.8; H, 4.9. $C_{22}H_{18}O_5$ requires C, 72.9; H, 5.0%).

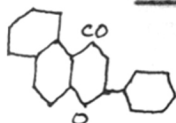


3-phenyl-2-methyl-1:4- α -naphthapyrone:- A solution

of zinc chloride (13 g.) in phenylacetic acid (30 g.) on treatment with phenylacetic anhydride (48 g.) and α -naphthol (25 g.) gave the 2-phenylacetyl-1-naphthol, crystallised from alcohol (23 g.), m.p. 96°; the alcoholic solution gave a dirty green colouration with ferric chloride; the acetyl derivative was prepared by heating the ketone with twice its weight of acetic anhydride and a drop of pyridine; colourless shining needles from alcohol, m.p. 109° (Gheema and Venkataraman, J.C.S., 1932, 218). A mixture of the above

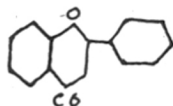
ester (1.5 g.), sodamide (3 g.) and ether (20 c.c.) kept at room temperature (maximum 39°) became yellow in colour in 5 minutes. The colour had become deep yellow in two days, during which it was shaken occasionally. It was then filtered off and washed the residue (A) with ether on the pump. Removal of ether from the filtrate and two crystallisations from aqueous alcohol gave the pyrone m.p. 203-4° (c.f. Cheema and Venkataraman loc.cit.). Treatment of (A) with acetic acid and crystallisation of the semi-solid orange mass gave more of the pyrone.

Selenium dioxide:- Pure selenium metal (Kahlbaum's, 25 g.) was thinly spread in the combustion tube of a combustion furnace and all the burners underneath it were lighted. After the tube had become red hot a rapid stream of oxygen from an oxygen cylinder was passed through. The metal burnt in the tube with a blue flame and the selenium dioxide so formed was carried away by the rapid stream of oxygen into the receiver attached to the other end of the combustion tube. Selenium dioxide condensed in the receiver in the form of a fine grey powder, which was collected at the end when all the selenium in the combustion tube had combusted and kept in a glass-stoppered bottle.



β -Naphthylflavone:- Fries reaction on β -naphthol acetate (50 g.) in carbon disulphide (100 c.c.) carried on the water-bath for the first 1 hour

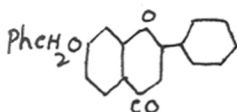
and then for 4 hours at 120° (oil-bath) gave 1-acetyl+2-naphthol in pale yellow needles from petroleum ether (10 g.), m.p. 64° (Fries, Ber., 1921, 54, 809). The ketone (6 g.), benzaldehyde (5.8 g.), 50% caustic soda solution (12 g.) and lime distilled alcohol (60 c.c.) were mixed, thoroughly shaken and left over night. The deep red solution was then poured into ice-cold water and allowed to stand for 2 hours. The substance crystallised out in colourless plates, m.p. 118°C . The 2:3-dihydro- β -naphthoflavone obtained above (0.5 g.), selenium dioxide (0.7 g.), and xylene (5 c.c.) were heated at 140° - 150° (oil-bath) for 5 hours. Selenium dioxide was filtered off and washed with ether. The ether-xylene was extracted with 10% caustic soda solution; acidification of the alkaline layer gave no precipitate. Removal of the ether-xylene and crystallisation of the residue from alcohol gave β -naphthoflavone, m.p. 163° , undepressed by admixture with an authentic specimen (Menon and Venkataraman, J.C.S., 1931, 2592).



Flavone:- Phenyl acetate (100 g.) was heated with aluminium chloride (200 g.) at 120° (oil-bath) for 5 hours, after decomposition and superheated steam-distillation the impure o-hydroxyacetophenone that distilled over was ether extracted, dried (magnesium sulphate anhydrous) in ether, removed the ether and the residue distilled under vacuum and the fraction

distilling at $98^{\circ}/18$ mm. was collected. Yield, 38 g. The ketone (5 g.) and benzaldehyde (5 g.) were dissolved in alcohol (40 c.c.); 50% caustic soda solution (10 g.) was added; the mixture was let stand over night when the whole set to a solid mass. Crushed ice and hydrochloric acid were then added and the product collected and crystallised from alcohol in bright yellow needles (6 g.) m.p. 90° . The chalcone (3 g.), selenium dioxide (3 g.) and amyl alcohol (30 c.c.) were heated (oil-bath at 150°) under reflux for 12 hours. After removal of the selenium and its washing with ether, the ether-amyl alcohol was extracted with 10% aqueous caustic soda; nothing was obtained by acidification of the alkaline layer. Ether and amyl alcohol were removed by steam-distillation; the pale brown, oily residue crystallised from petroleum (b.p. $50^{\circ}-60^{\circ}$) in long colourless needles (1.3 g.) of flavone, m.p. 99° .

7-benzyloxyflavone:—A mixture of zinc chloride

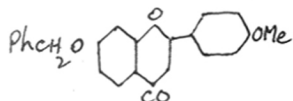


(50 g.) in acetic acid (50 c.c.) and resorcinol (50 g.) gave resacetophenone (50 g.), m.p. 146° (Robinson and Shah,

J.C.S., 1934, 1494). For benzylation the ketone (30 g.), anhydrous potassium carbonate (54 g.), benzyl chloride (98 g.) and acetone (200 c.c.) were refluxed for 8 hours. Most of the acetone was distilled off and the excess of benzyl chloride steam-distilled. The residue crystallised

from alcohol in glistening colourless leaflets (30 g.), m.p. 100° (Gulati, Seth and Venkataraman, J.C.S., 1934), 1765). The resacetophenone-4-benzyl ether (3 g.), benzaldehyde (3 g.) and 50% aqueous caustic soda in the usual way yielded 2-hydroxy-4-benzyloxyphenyl styryl ketone; crystallised from a mixture of alcohol and acetic acid in bright yellow leaflets (2.9 g.), m.p. 135° (Mahal, Rai and Venkataraman, J.C.S., 1935, 866). The chalcone (2 g.) was oxidised as in the previous case, the selenium filtered off, and amyl alcohol removed by steam-distillation. The residual solid crystallised from aqueous acetic acid in long colourless needles (0.7 g.), m.p. 187° (Found: C, 80.3; H, 4.6. $C_{22}H_{16}O_3$ requires C, 80.5; H, 4.9%). For debenylation (Gulati, Seth and Venkataraman, loc.cit. the flavone (0.5 g.), glacial acetic acid (30 c.c.) and hydrobromic acid saturated at 0° (5 c.c.) were heated on the water-bath for 1 hour then on a sand-bath for 2 minutes. The reaction mixture on dilution with equal volume of water was let stand over night; 7-hydroxyflavone crystallised out in colourless needles (0.2 g.), m.p. 240° (Found: C, 75.6; H, 4.4. Calculated for $C_{15}H_{10}O_3$: C, 75.6; H, 4.2%).

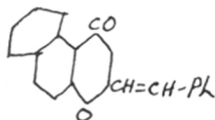
7-benzyloxy-4'-methoxyflavone:- Resacetophenone-4-



-benzyl ether (3 g.), anisaldehyde (3 g.) and 50% aqueous caustic soda (6 g.) in alcohol yielded 2-hydroxy-4-benzyloxyphenyl-4-

-methoxystyryl ketone, crystallised from a mixture of alcohol and acetic acid in glistening orange-yellow needles (3 g.), m.p. 132-133° (Mahal, Rai and Venkataraman, loc.cit.). The chalkone (2.5 g.) was oxidised as in the previous case, the selenium filtered off and amyl alcohol removed by steam-distillation. The residual solid on two crystallisations from alcohol gave yellow needles, m.p. 137° (Found: C, 76.9; H, 5.0. $C_{23}H_{18}O_4$ requires C, 77.1; H, 5.0%). Treatment with hydrobromic acid in acetic acid and addition of water gave a gelatinous precipitate, which was collected and crystallised from 50% acetic acid. The pale yellow needles obtained melted at 310°-311° (Kostanecki and Osius, Ber., 1899, 32, 321 give m.p. 315°) (Found: C, 70.6; H, 3.7. Calculated for $C_{15}H_{10}O_4$: C, 70.9; H, 3.9%). The other properties of the product were similar to those described by Kostanecki and Osius for 7:4'-dihydroxyflavone; pratol (Robinson and Venkataraman, J.C.S., 1926, 2346) melts at 262°.

3-Styryl-1:4- $\beta\alpha$ -naphthapyrone:- (1) 1-acetyl-2-



naphthol (1.5 g.), sodium acetate (2.5 g.) and acetic anhydride (5 c.c.) were heated together for 5 hours at 170° (oil-bath),

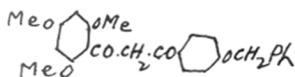
worked as usual; the 2-acetyl-3-methyl-1:4- $\beta\alpha$ -naphthapyrone crystallised from alcohol in pale yellow needles (1 g.), m.p. 157° (Menon and Venkataraman, J.C.S., 1931, 2591).

Hydrolysis of the 2-acetyl naphthapyrone was most conveniently carried out by boiling with 5% sodium carbonate solution for 2 hours. The 3-methyl-1:4- $\beta\alpha$ -naphthapyrone obtained condensed with benzaldehyde in presence of alcoholic sodium ethoxide to give the 3-styryl compound, very pale yellow, woolly needles from alcohol, m.p. 200° (Found: C, 84.4; H, 4.5.

$C_{21}H_{14}O_2$ requires C, 84.5; H, 4.7%). The substance was coloured deep yellow by sulphuric acid and the yellow solution exhibited a bright green fluorescence.

(2) 3-Styryl-2:3-dihydro-1:4- $\beta\alpha$ -naphthapyrone was prepared by keeping a mixture of 1-acetyl-2-naphthol (1 g.), cinnamaldehyde (0.8 g.), alcohol (10 c.c.) and 50% aqueous caustic soda (2 g.) at ordinary temperature for 48 hours and then pouring it into water. The precipitate was collected, washed with water and crystallised from alcohol in colourless lustrous needles (4.2 g.), m.p. 144° (Found: C, 84.1; H, 5.1. $C_{21}H_{16}O_2$ requires C, 84.0; H, 5.3%). It developed no colouration with alcoholic ferric chloride. Oxidation of 3-styryl-2:3-dihydro-1:4- $\beta\alpha$ -naphthapyrone (0.3 g.) with selenium dioxide was effected in xylene solution, the method of isolation following the instance of β -naphthaflavone. On crystallisation from alcohol-acetic acid gave very pale yellow needles (0.1 g.), m.p. 200°, undepressed by admixture with the previous specimen.

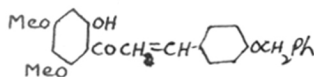
2:4:6-Trimethoxy-4-benzyloxydibenzoylmethane:-



To a solution of methyl p-hydroxybenzoate (126 g.) and benzyl chloride (100 g.) in methyl alcohol (200 c.c.) was added potassium hydroxide (45 g.) in methyl alcohol (400 c.c.). The mixture was refluxed on a water bath for 5 hours. The still hot solution was filtered rapidly and the filtrate on cooling deposited elongated prismatic crystals (65 g.) of methyl p-benzyloxybenzoate, m.p. 98° (Cohen and Dudley, J.C.S., 1910, 97, 1764, 99°). (Found*: C, 74.6; H, 5.9. C₁₅H₁₄O₃ requires C, 74.4; H, 5.7%). An improved yield of phloroglucinol trimethylether (Mauthner, J.pr. [2] 87, 408) was obtained by boiling phloroglucinol (39 g. dried at 180° for 4 hours) for 8 hours on a water-bath with methyl alcohol (125 g.) and concentrated sulphuric acid (50 g.). Water (250 c.c.) was then added and most of the methyl alcohol removed on the water-bath; the oil that separated was extracted with ether. The residue that was left on removing ether from the ether layer was taken up in 40% caustic potash (250 g.) and methylated by dropwise addition of dimethyl sulphate (150 g.). Finally the trimethyl ether was steam-distilled, the solid collected from the distillate and crystallised from petroleum ether (b.p. 50°-60°) in colourless needles (30 g.), m.p. 52°. The trimethyl ether (30 g.) and acetyl chloride (75 c.c.) were placed in a flask fitted

with a calcium chloride tube. The mixture was placed in a bath of freezing mixture at a temperature of -10° . Finely powdered aluminium chloride (30 g.) was then added in the course of an hour. The reaction flask was then left at the same temperature for 3 hours after which the contents were treated with crushed ice. The crude phloracetophenone trimethyl ether was collected and crystallised from dilute alcohol in the form of fine white needles (28 g.), m.p. 101° (Friedlander and Schnell, Ber., 1897, 30, 2152). A mixture of the trimethylether (3 g.), methyl p-benzyloxybenzoate (7.2 g.) and sodium dust (0.5 g.) was heated in an oil-bath at 120° for 3 hours. On treatment with ice-water the mixture was filtered and the clear filtrate saturated with carbon dioxide. The pale yellow precipitate of the diketone crystallised from alcohol in yellow needles (1.1 g.), m.p. 101° - 102° , the alcoholic solution giving a dark red colour with ferric chloride (Found*: C, 71.5; H, 5.8. $C_{25}H_{24}O_6$ requires C, 71.4; H, 5.7%).

2-Hydroxy-4:6-dimethoxyphenyl 4-benzyloxystyryl



ketone:- Phloracetophenone trimethylether

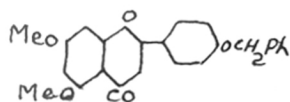
(25 g.) and powdered aluminium chloride

(25 g.) were heated together in an oil-

bath at 114° for 30 minutes. The mass was then treated with crushed ice and hydrochloric acid. The dirty brown semi-solid mass that separated was mixed with fine, washed

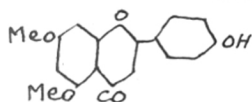
sand and extracted in a soxhlet apparatus with petroleum ether (b.p. 50°-60°). On removing the solvent, the petroleum ether extract gave beautiful small white needles of 2-hydroxy-4:6-dimethoxyacetophenone (19 g.), m.p. 82°-3° (Friedlander and Schnell, loc. cit.). p-Benzoyloxybenzaldehyde was prepared in the usual way by benzylation with benzyl chloride and potassium carbonate of p-hydroxybenzaldehyde (20 g.) in acetone solution and yielded benzyl ether, crystallised from alcohol (25 g.), m.p. 75°-76°. 2-Hydroxy-4:6-dimethoxyacetophenone (7 g.) and p-benzoyloxybenzaldehyde (9 g.) gave by treatment with alcoholic caustic soda and isolation in the known manner the chalcone which crystallised from glacial acetic acid in golden yellow needles (7 g.), m.p. 159°. (Found*: C, 73.6; H, 5.7. $C_{24}H_{22}O_5$ requires C, 73.8; H, 5.6%). The alcoholic solution gave a deep red colour with ferric chloride. The acetyl derivative, stout colourless needles from alcohol, melted at 105° (Found: C, 72.0; H, 5.7. $C_{26}H_{24}O_6$ requires C, 72.2; H, 5.6%).

5:7-Dimethoxy-4'-benzyloxyflavone:- After refluxing



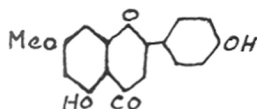
a mixture of the above chalcone (7 g.), selenium dioxide (7 g.) and amyl alcohol (100 c.c.) for 12 hours, the selenium was filtered off and washed with ether. On extracting the ether-amyl alcohol solution with 20% aqueous caustic soda, the solid that was thrown out of solution was collected (3.5 g.) and crystallised

from alcohol. Removal of the solvents from the ether-amylic alcohol layer by warming on the water-bath followed by steam distillation gave more (1.5 g.) of the same substance. Two crystallisations of the combined product from alcohol led to orange-yellow needles m.p. 178°, exhibiting no ferric chloride reaction (Found*: C, 74.3; H, 5.4. $C_{24}H_{20}O_5$ requires C, 74.2; H, 5.1%).



5:7-Dimethoxy-4'-hydroxyflavone:- The debenzylated

substance obtained from 3.5 g. of the benzyl ether by hydrochloric acid in acetic acid crystallised from alcohol in pale yellow needles (1.6 g.), m.p. 298° (Found*: C, 68.2; H, 4.9. $C_{17}H_{14}O_5$ requires C, 68.4; H, 4.7%). The ferric chloride colouration was pale brown. The acetyl derivative crystallised from alcohol in colourless needles, m.p. 220° (Found: C, 66.6; H, 4.5. $C_{19}H_{16}O_6$ requires C, 67.0; H, 4.7%).

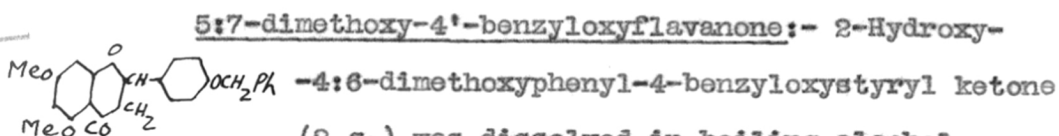


5:4'-Dihydroxy-7-methoxyflavone:- The above di-

methyl ether (0.5 g.), aluminium chloride (0.6 g.) and nitrobenzene (3 c.c.) were heated on a boiling water-bath for 1 hour. Crushed ice and hydrochloric acid were then added, the nitrobenzene removed with steam and the residue acetylated by means of acetic anhydride and pyridine. The fine colourless needles (0.2 g.) from alcohol melted at 197°-198° undepressed by admixture with the acetate of natural

genkwanin (Found*: C, 64.9; H, 4.2. $C_{20}H_{16}O_7$ requires C, 65.2; H, 4.3%). I am deeply indebted to Dr. Kwong-fong Tseng for specimens of genkwanin and diacetylgenkwanin.

Hydrolysis of the acetate by warming with 50% hydrochloric acid on the water-bath for a few minutes and crystallisation from aqueous acetone gave bright yellow needles, m.p. and mixed m.p. with natural genkwanin 285° - 286° (Found*: C, 67.9; H, 4.6. $C_{16}H_{12}O_5$ requires C, 67.6; H, 4.2%). The colour reactions were also identical.



(2 g.) was dissolved in boiling alcohol (30 c.c.) and to the hot solution was added N-alcoholic caustic potash (14 c.c.) followed by 30% hydrogen peroxide (2 c.c.). The mixture was shaken while hot for 10 minutes, when 30% hydrogen peroxide (1 c.c.) was added and the solution was shaken for a further 10 minutes with gentle warming. (c.f. Algar and Flynn, Proc. Roy. Irish Acad., 1934, B 42, 1). The colour of the solution had changed from deep orange to bright yellow at the end of the reaction. It was then cooled, diluted with water, and acidified with dilute sulphuric acid. The bright yellow solid that separated was collected and crystallised from 50% alcoholic acetic acid mixture in pale yellow microscopic needles (1.1 g.), m.p. 198°

3 (Found* : C, 73.7; H, 5.6. $C_{24}H_{22}O_5$ requires C, 73.8; H, 5.6%).

The alcoholic solution of the substance gave no colouration with aqueous ferric chloride; the substance was insoluble in alcoholic caustic potash and was coloured red on treatment with sulphuric acid and the light brown solution exhibited no fluorescence. The mixed m.p. of the substance with 5:7-dimethoxy-4'-benzyloxyflavone was 165° - 75° .

A few other experiments with increasing amounts of hydrogen peroxide and allowing the reaction to take place for a longer time resulted only in the same substance, m.p. 198° , as in the first experiment.

In one experiment the oxidation was carried out under the conditions described by Taichiro Gyamada (J. Chem. Soc. Japan, 1934, 55, 1256). The chalcone (1.5 g.) was dissolved in boiling methyl alcohol (30 c.c.); 16% caustic soda (10 c.c.) followed by 15% hydrogen peroxide (4 c.c.) were then added and the reaction mixture allowed to stand over night. Next day it was diluted with water, acidified with dilute sulphuric acid and filtered. The bright yellow residue was crystallised from alcohol-acetic acid mixture and was found to be identical with the flavanone described above.

Naphthalene:- Tetrahydronaphthalene (5 g.) and selenium dioxide (5 g.) were heated together (oil-bath at

160°) for 24 hours. On cooling, the mixture was filtered on the pump to remove oily unconverted tetrahydronaphthalene, and the solid residue of naphthalene and selenium dioxide taken up in boiling alcohol. After removal of the selenium dioxide, the alcoholic filtrate was treated with Norit charcoal, refiltered and diluted with twice the volume of water. Colourless leaflets of naphthalene (1.3 g.) were thus obtained.

The oily drops from the reaction mixture appeared to consist of a mixture of naphthalene and tetrahydronaphthalene; the picrate melted over a long range, 110°-120°. Tetrahydronaphthalene picrate crystallises from alcohol in long, bright yellow needles, m.p. 151°.

The oxidation of tetrahydronaphthalene to naphthalene by means of selenium dioxide was carried out under various other conditions given below but the best yield of the pure naphthalene was only obtained when the above mentioned conditions were followed.

(1) Tetrahydronaphthalene (5 g.) and selenium dioxide (3 g.) refluxed for 24 hours at 160° gave naphthalene (0.9 g.).

(2) Tetrahydronaphthalene (5 g.) and selenium dioxide (8 g.) under similar conditions as in (1) gave

naphthalene (1.2 g.).

(3) Tetrahydronaphthalene (5 g.), selenium dioxide (5 g.) and absolute alcohol (distilled over sodium, 5 c.c.) were heated on the water-bath. After 48 hours selenium was filtered off, the filtrate diluted with water (10 c.c.); first some dark oil had separated which was removed and the turbid mother liquor on keeping in the refrigerator over night gave only impure naphthalene (0.2 g.).

(4) Tetrahydronaphthalene (5 g.), selenium dioxide (5 g.) and amyl alcohol (5 c.c.) were heated for 24 hours at 160° (oil-bath) but instead of isolating the naphthalene from the reaction mixture, direct picrate formation was tried and it gave dirty brown needles (0.15 g.), m.p. 110°-120°.

(5) Instead of amyl alcohol in (4) xylene was used and gave a dirty brown picrate (0.2 g.), m.p. 110°-120°.

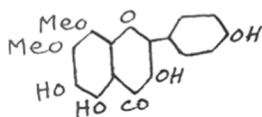
Preparation of Calycopterin:-

Air dried leaves (700 g.) of Calycopteris flori-
bunda were packed in a 5-l round bottom flask and refluxed with 3.5 liters of acetone on the water bath. After 2 hours the hot acetone extract was quickly decanted off into a bottle and the once extracted leaves were treated with a fresh lot of 3.5 liters of acetone and again refluxed on the water bath. After 2 hours the second acetone extract was also

decanted off. The first and the second acetone extracts were mixed and practically the whole of the acetone was distilled off from the combined acetone extracts. The removal of the final few hundred c.c. of the acetone from the extract was carried out under reduced pressure. The thin syrupy dark-green resinous mass that was left, after the recovery of the solvent, was immediately transferred to a beaker and left in the refrigerator over night. Next day it was repeatedly washed with petroleum ether (b.p. 50°-60°) and the petroleum ether layer separated each time from the aqueous layer by decantation. Finally the aqueous layer, which was partly filled with crystals of calycopterin, was treated with 5% aqueous caustic soda (200 c.c.) and filtered. The alkaline filtrate, on saturating with carbon dioxide, gave a precipitate of a dirty brown solid which on one crystallisation from alcohol gave bright yellow needles (1.65 g.) m.p. 225-26°. It gave 0.23 g. of calycopterin from 100 g. of air dried leaves, while a 0.12% yield had been obtained previously.

Calycopterin dibenzyl ether:- Benzylation of calycopterin (1 g.) with benzyl chloride (20 g.), potassium carbonate (16 g.) and acetone (150 c.c.) during 32 hours gave the dibenzyl ether, which crystallised from alcohol-acetic acid in pale yellow needles (1.25 g.), m.p. 185° (Found*: C, 71.0; H, 5.6. $C_{33}H_{30}O_8$ requires C, 71.4; H, 5.4%).

Demethylcalycopterin:- Addition of calycopterin



(2 g.) to a clear solution of aluminium chloride (2 g.) in nitrobenzene (10 c.c.)

immediately produced a colour change to deep orange. On heating the mixture on the water-bath for one hour, the viscous, deep orange product was treated with ice and hydrochloric acid, the nitrobenzene steam-distilled and the aqueous solution filtered hot. Bright yellow crystalline material (0.7 g.) separated over night, recrystallisation from sulphurous acid yielding bright yellow needles, m.p. 268-272° (Found * in material dried over phosphorous pentoxide in a desiccator, when the colour changed to a dull grey; C, 52.6; H, 4.4. $C_{17}H_{14}O_8$, $2H_2O$ requires C, 53.4; H, 4.7%. Loss of weight on heating at 120° for 4 hours: 9.6. $C_{17}H_{14}O_8$, $2H_2O$ requires H_2O , 9.4%). The hydroxyl content was determined by the acetic anhydride-pyridine method (Marks and Morrell, Analyst, 1931, 56, 428; Ratnagiriswaran, Sehra and Venkataraman, Biochem.J., 1934, 28, 1964), although only 0.1 g. of the dried material was available for the purpose and minimal amounts of 0.5 g. are required for accurate results (Found: OH, 13.3. $C_{17}H_{10}O_4$ (OH)₄ requires OH, 19.7%). The substance is coloured brownish orange by sulphuric acid and the pale orange solution exhibits a weak green fluorescence. The aqueous solution reduces ammoniacal silver nitrate in the cold, as well as

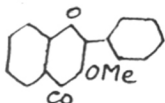
boiling Fehling's solution. Lead acetate gives an orange-brown precipitate, the mixture rapidly darkening and changing in colour to olive green. The solution in dilute caustic soda is first a greenish yellow, then leaf green, orange and finally brown. Addition of a few drops of very dilute ammonia to the aqueous solution of demethylcalycopterin produces a series of colour changes as in the case of calycopterin, myricetin, gossypetin and robinetin; pale green pale bluish green deep turquoise blue dark blue dull olive green; the orange and magenta observed with calycopterin were absent. The pale brown solution in alcohol has a weak green fluorescence; with magnesium and hydrochloric acid the solution first turns yellow, then yellowish orange and finally deep reddish orange; the ferric chloride colouration is an intense olive green (with separation of a blue-green precipitate), which changes with ammonia to a dark brown. The characteristic catechol reaction with ammonium molybdate and acetic acid (Quastel, Analyst, 1931, 56, 311) was clearly observed; carrying out the test with 2 c.c. of a dilute aqueous solution of the substance to which was added 0.5 c.c. of glacial acetic acid and 1 c.c. of 14% ammonium molybdate solution, it was found that while catechol and demethylcalycopterin gave a reddish brown colouration, a solution of the ketone (vide infra) obtained by alkaline hydrolysis of calycopterin

showed no colour change. Calycopterin, resacetophenone, 2-hydroxy-4-methoxyacetophenone, 2:6-dihydroxyacetophenone and 1-acetyl-2-naphthol gave a negative test.

Degradation of calycopterin:- Hydrolysis with 50% aqueous caustic potash was effected as previously described (Ranagiriswaran, Sehra and Venkataraman, loc.cit.), but on cooling the deep red solution it was saturated with carbon dioxide. The precipitate (A) was collected and the filtrate thoroughly extracted with ether. Removal of the solvent gave a pale brown sticky substance (B). Potassium carbonate was the main constituent of (A); extraction with acetone led on evaporation to a semi-solid product. The crystalline material obtained by treatment with water proved to be unchanged calycopterin. The aqueous filtrate was allowed to evaporate slowly in a desiccator and the residue, whose properties were similar to those of (B), was mixed with (B). The substance dissolved in aqueous alkali to form a pale yellow solution, and formed a 2:4-dinitro-phenylhydrazone, dark red needles, m.p. 230°. The alcoholic solution of the substance gave a deep red colour with ferric chloride. By separation of the substance into a more sparingly soluble in water and crystallising it by slow evaporation of the aqueous solution in vacuo, a minute amount of material crystallising in well-defined needles

has been obtained and is under examination.

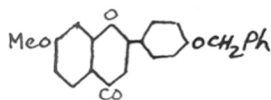
Demethylation of 3-methoxyflavone:- 2-Hydroxy



chalkone (2 g.) was dissolved in boiling alcohol (30 c.c.) and to the hot solution was added N-alcoholic caustic potash.

(14 c.c.) followed by 30% hydrogen peroxide (3 c.c.) in two equal lots during the interval of 10 minutes and worked as previously described. The substances crystallised from alcohol in colourless needles (1.2 g.), m.p. 171-72° (Algar and Flynn, loc.cit.). The flavonol (1 g.) on methylation with dimethyl sulphate and alkali gave the 3-methyl ether (0.5 g.), m.p. 117°. On heating the substance (0.4 g.) with aluminium chloride in nitrobenzene and isolating the product as described for demethylcalycopterin, on one crystallisation from alcohol gave colourless needles (0.1 g.), m.p. and mixed m.p. with flavonol, 171°-172°.

7-Methoxy-4'-benzyloxyflavone:- Resacetophenone

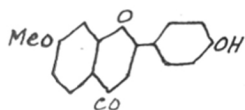


(100 g.) was methylated with dimethyl sulphate and caustic soda solution. Resacetophenone monomethyl ether (27 g.) distilled

at 270°-80°/4 mm. and solidified on cooling to a mass of transparent crystals m.p. 50°. (Adams, J. Amer. Chem. Soc., 1819, 41, 260). The ketone (5 g.), p-benzyloxybenzaldehyde (6.4 g.)

alcohol (50 c.c.) and caustic soda 50% solution (10 g.) were mixed and left overnight. Next morning treated with crushed ice and hydrochloric acid. The precipitate was collected and crystallised from alcohol-acetic acid in orange-yellow needles (6 g.), m.p.125-26° (Mahal,Rai and Venkataraman, J.C.S., 1934, 886). Oxidation of the 2-hydroxy-4-methoxyphenyl 4-benzyloxystyryl ketone (6 g.) with selenium dioxide (6 g.) in amyl alcohol (60 c.c.) two crystallisations from alcohol-acetic acid and a third from acetone gave tiny pale yellow needles (1.2 g.), m.p.195° (Found*: C, 76.7; H, 5.3. $C_{23}H_{18}O_4$ requires C,77.1; H, 5.0%).

7-Methoxy-4'-hydroxyflavone:- A mixture of the



4'-benzyl ether (1 g.), acetic acid (500 c.c.) and hydrochloric acid (10 c.c.) was heated in the water bath for 1 hour and then on the sand-bath for 2 minutes; dilution with equal volume of water gave a solid which on two crystallisations from alcohol gave pale yellow needles (0.4 g.), m.p.258°. (Found*: C, 71.4; H, 4.8. $C_{16}H_{12}O_4$ requires C, 71.6; H,4.5%). The substance dissolves in aqueous caustic soda with a yellow colouration; the colouring matter of Digitalis lutea had m.p. 217°-18° and gave "a beautiful red in alkalies". The acetyl derivative of 7-methoxy-4'-hydroxyflavone, colourless needles, melted at 156° (Found*: C, 70.0; H, 4.8. $C_{18}H_{14}O_5$ requires C, 69.7; H, 4.5%).

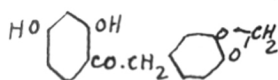
3:4-Methylenedioxyphenylpyruvic acid:- Finely powdered hippuric acid (216 g.) and sodium acetate fused (72 g.) were mixed with piperonal (100 g.) and heated with acetic anhydride (192 c.c.) for 10 minutes when the yellow crystalline precipitate just dissolved. Alcohol (96 c.c.) was added to the cold mixture. The azlactone was collected and washed with rectified spirit and hot water, yield (180 g.).

The azlactone (180 g.) was boiled with a solution of caustic soda (70 g.) in water (400 c.c.) for 1 hour. 560 c.c. of water were added and the solution saturated with sulphur dioxide and after 3 hours the benzoic acid filtered off. The filtrate was boiled with excess of hydrochloric acid for one hour 3:4-methylenedioxyphenylpyruvic acid was collected and crystallised successively from alcohol and glacial acetic acid (40 g.), m.p. 215° C.

3:4-methylenedioxyphenylacetonitrile:- To a solution of 3:4-methylenedioxyphenylpyruvic acid (40 g.) in 10% caustic soda solution (400 c.c.) was added a solution of hydroxylamine hydrochloride (40 g.) in caustic soda (40 g., dissolved in the minimum quantity of water), and the mixture left at room temperature. After 3 days the oxime was precipitated by the addition of hydrochloric acid. The solid that separated was filtered, washed with water and dried in a vacuum desiccator over phosphorous pentoxide; 41 g; m.p. 170-71°.

The dry oxime (41 g.) was heated with acetic anhydride (70 g.) for 3-5 minutes on a water-bath. When the vigorous reaction had subsided water (300 c.c.) was added and the mixture cooled. The oil was ether extracted and the ether extract washed (first with water and then with 5% sodium bicarbonate solution) till the ether layer was no more acidic, dried over anhydrous magnesium sulphate, and the ether removed. The nitrile distilled over at 153-56°/10 m.m. The yield was 18 g.

2:4-dihydroxyphenyl 3:4-methylenedioxybenzyl ketone



(ψ -Baptigenetin, Spath and Schmidt, Monatsh.,

1929, 53, 454):- A rapid stream of dry hydro-

gen chloride was passed through a mixture of

resorcinol (12 g.), the above nitrile (18 g.), fused powdered

zinc chloride (5 g.) and dry ether (30 c.c.), while the mix-

ture was strongly cooled in ice and salt. After passing

hydrogen chloride for 4 hours the mixture was allowed to

stand for 48 hours. The light brown semi solid mass that

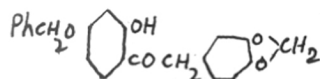
had separated was collected and washed with dry ether and

boiled with water (400 c.c.) for 2 hours. After cooling the

reaction mixture, the water was separated from the oily mass

and the oil crystallised out from alcohol; m.p.149°;Yield 18 g.

2-Hydroxy-4-benzyloxyphenyl 3:4-methylenedioxybenzyl



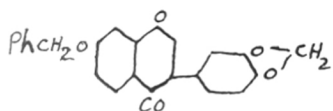
ketone:- ψ -Baptigenetin (12 g.), benzyl

chloride (40 g.); fused potassium carbonate

(22 g.), and acetone (120 c.c.) were heated

on the water-bath for 8 hours, the acetone recovered, and the residue steam-distilled to remove benzyl chloride. One crystallisation of the product from alcohol gave colourless leaflets (7 g.), m.p. 94° after sintering at 86° (Found: C, 72.5; H, 4.9. $C_{22}H_{18}O_5$ requires C, 72.9; H, 4.9%), which developed a deep red colour with alcoholic ferric chloride.

O-Benzyl-ψ-baptigenin:- The above ketone (3 g.)

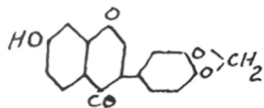


in ethyl formate (50 c.c.), cooled in ice and salt, was treated with sodium dust (1.5 g.) after 12 hours, the pasty mass was added to

ice. The yellow amorphous solid (2.9 g.) obtained after ice treatment was washed with water and crystallised from alcohol-acetic acid and from alcohol, giving colourless prismatic needles, m.p. 168° (Found: C, 74.0; H, 3.9.

$C_{23}H_{16}O_5$ requires C, 74.1; H, 4.3%). The crystals were coloured deep brown by sulphuric acid and the pale brown solution exhibited a weak violet fluorescence.

ψ-Baptigenin:- Debenzylation of the benzyl ether



(1.6 g.) and two crystallisations of the product from alcohol gave colourless

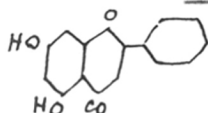
microscopic needles (0.8 g.), m.p. 292-293°

(Spath and Lederer; 298-299° in a vacuum) (Found: C, 68.0;

H, 3.4. Calc. for $C_{16}H_{10}O_5$: C, 68.1; H, 3.5%). Further

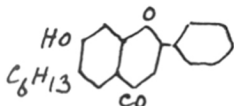
crystallisation did not raise the m.p. The substance darkened rapidly above 288° and melted to a dark red

liquid. Gorter (Arch. Pharm., 1897, 235, 494) cites 303-304° as the m.p. of ψ -baptigenin from ψ -baptisin of Baptisia tinctoria. The crystals were coloured green by sulphuric acid and the pale yellow solution did not fluoresce. Ferric chloride imparted no colour to the alcoholic solution. The acetyl derivative crystallised from alcohol in small curved needles, m.p. 176° (Gorter, loc. cit., gives 173°) (Found: C, 66.7; H, 3.9. Calc. for $C_{18}H_{12}O_6$: C, 66.6; H, 3.7%).



Chrysin: (Robinson and Venkataraman J.C.S., 1926,

2344) A mixture of Phloracetophenone (10 g.), benzoic anhydride (100 g.) and sodium benzoate (13 g.) was heated at 185° in an oil-bath for 6 hours. At the end of the reaction the product was hydrolysed with alcoholic caustic potash for 0.5 hour; most of the alcohol was then recovered under reduced pressure, the residue dissolved in water, saturated with carbon dioxide and filtered. The residue was crystallised from methanol in yellow prisms (3.5 g.) m.p. 275°.

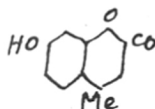


6-Hexyl-7-hydroxyflavone: - 5-Hexylresacetophenone

(Dhingra, Uppal and Venkataraman, Proc. Ind. Acad. of Sciences, 1936, Vol. III, No. 3, 206) was prepared by Hoesch's reaction on hexyl-resorcinol and acetonitrile in presence of anhydrous zinc chloride. After the hydrolysis of the ketimide hydrochloride with water the oil that separated was taken up in ether, the

ether extract dried over anhydrous magnesium sulphate and the residue on removal of ether was directly crystallised from petroleum ether (b.p.50-60°) without any previous purification by distillation under reduced pressure as recorded in the paper, in colourless plates, m.p.85°. The ketone (11 g.), benzoic anhydride (100 g.) and sodium benzoate (11 g.) were thoroughly mixed and heated at 185° in an oil bath. After 6 hours the product was hydrolysed for 30 minutes with 10% alcoholic potash (440 c.c.). The greater part of the alcohol was distilled off under reduced pressure, the residue dissolved in water and the solution filtered. The clear solution, on saturating with carbon dioxide, yielded a precipitate which was collected and crystallised from alcohol in colourless needles (4 g.), m.p.192° and mixed m.p. with the specimen previously prepared (Dhingra, Uppal and Venkataraman, loc. cit.) was not depressed.

4-Methylumbelliferon:- (Pechmann and Hanke, Ber.,



1901, 34, 338). A mixture of resorcinol (22 g.) and ethyl acetoacetate (26 g.) was

gradually poured into concentrated sulphuric acid (250 g.) keeping the temperature of the reaction mixture below 30°C. Next day it was diluted with water, filtered, the residue washed with water, redissolved in 5% caustic soda, again filtered and the alkaline filtrate acidified.

The analyses marked * were carried out by Dr. Ing. A. Schoeller.

The precipitate was filtered, washed and dried (12 g.), m.p. 185°. The product was quite pure therefore further crystallisation of it was not necessary for my work.

The anthelmintic action of the compounds chrysin (I), genkwanin (XV), 7-hydroxyflavone (X) and 4-methylumbelliferon (CXXV) was tried, in vitro, on tape-worms (*Taenia serrata*), round worms (*Arcaris lumbricoides*) and leeches (*Hirudo medicinalis*) as follows:-

The compounds being insoluble in water, they were dissolved in equivalent amounts of cold N/10 aqueous caustic soda and the stock solutions so obtained were further diluted to the required concentrations by adding the requisite amounts of water, saline or Locke's solution depending upon whether the compounds were to be tried in water, saline or Locke's solution. 10 c.c. of each solution of different concentrations was placed in different watch glasses and 2-5 segments of tape-worms previously washed with saline were placed in each. Their activity was constantly watched and when they had completely stopped showing any physical movements they were removed from the watch glasses, washed with saline and put into fresh Locke's solution to see if they could recover their activity. Leeches and round worms, for the test, were dipped into the solution in a test tube and plugged loosely with cotton so that they could not come out of the solution. The results so obtained in a series of experiments are tabulated below:-

(III) 7-hydroxyflavone:-

| Cons. | 1-1,000 | 1-5,000 | 1-10,000 | 1-50,000 | 1-100,000 | Control in distilled water. |
|-------------|----------|---------|----------|----------|-----------|-----------------------------------|
| Leeches | 30,45,+. | +,+,+. | +,+,+. | +,+,+. | +,+,+. | quite active even after 24 hours. |
| Round-worms | +,+,+. | +,+,+. | +,+,+. | +,+,+. | +,+,+. | Do. |
| Tape-worms | +,+,+. | +,+,+. | +,+,+. | +,+,+. | +,+,+. | Active for 45-60 mts. |

(IV) 4-Methylumbelliferon :-

| Cons. | 1-1,000 | 1-5,000 | 1-10,000 | 1-50,000 | 1-100,000 | Control in distilled water. |
|-------------|---|---------|----------|----------|-----------|-----------------------------------|
| Leeches | +,+,+. | +,+,+. | +,+,+. | +,+,+. | +,+,+. | quite active even after 24 hours. |
| Round-worms | +,+,+. | +,+,+. | +,+,+. | +,+,+. | +,+,+. | Do. |
| Tape-worms | 2 ⁺ ,+,+5°. 3 ⁺ ,+,+11°. 10 ⁺ ,+,+15°. 15 ⁺ ,+,+15°. 20 ⁺ ,+,+30°. | | | | | Active for 45-60 mts. |

The anthelmintic action of 6-hexyl-7-hydroxy-flavone (XCV) could not be tried in vitro as it does not dissolve even in boiling caustic soda solution.

Round worms and tape-worms used in the experiments were taken from the guts of dogs, cats and fowls; the animals were anaesthetized with ether, the guts removed and opened by a longitudinal incision. The worms after removal from the opened guts were immediately placed in Locke's solution and kept at room temperature (30-31°C.)

The figures in the respective columns show the number of minutes taken by the parasites to die in the particular solution; figures marked * show that they stopped their activity during that time and recovered again within 5 minutes when placed in fresh Locke's solution; positive signs (+) show that they were as active in the test solution as in the control experiment or apparently there was no effect of the compounds on the parasites.

The results in the above tables I,II,III and IV are given when the stock solutions were diluted to the required concentrations with distilled water but when the dilutions were made with saline or Locke's solution the compounds showed absolutely no effect on the parasites.

The second method that was followed for testing

the anthelmintic action of the compounds on tape-worms was an application of Dale and Laidlaw's method (J. Pharm. Exper. Therap., 1912, Vol. 4, p. 75) of estimating the strength of Pituitary extract on the guinea-pig uterus.

The apparatus that was used is shown here in the diagram (A). The tape-worm 'W' on one end was fixed to the tube 'U' and on the other to the lever 'L' by means of a fine thread and pinch clip as shown in the diagram. The pointer 'P' attached to the lever 'L' recorded the contraction and relaxation of the worm on the smoked paper 'S' which was kept rotating mechanically at a very slow speed of about 2 cm. per minute on "Sherrington-Starling recording drum with extended arm". The bath 'B' of a capacity of about 150 c.c. was maintained at 36-37°C. by the outer bath 'O' which was kept warm to the required temperature by the carbon-filament lamp 'C'.

To carry out the experiment 100 c.c. of Locke's solution previously warmed to 37°C, was put into the bath 'B'. In order to maintain the temperature of the Locke's solution constant throughout and also to keep it aerated, air from an aspirator was bubbled through it. When the movements of the tape-worm, as recorded on 'S', had become fairly constant an amount of chrysin solution representing 2.5 mg. of chrysin was then added to 'B'. The movements of

the worm suddenly came to a stop; the solution from 'B' was taken out through its bottom opening 'E' and afresh Locke's solution, previously warmed to 37° as before, was put into it but the worm did not recover its original movements (See Fig.4). Similarly in other experiments with fresh tape worms each time, different amounts of chrysin ranging from 0.5 mg. to 20 mg. were used. In a number of experiments that were carried out, most inconsistent results were obtained. It was observed that in some experiments the action of even 5 mg. chrysin was slower than when 2.5 mg. of it was used and the worms also regained their original movements when fresh Locke's solution was replaced in the bath 'B' (See Fig.2); in others 5 mg. of chrysin on the contrary activated the worm and 20 mg. of it was necessary to stop the movements (Fig.3); while in still others even 20 mg. of the drug did not produce any effect (Fig.1).

Similarly genkwanin, 7-hydroxyflavone and 4-methylumbelliferon were tried but showed no effect on the movements of the worms.

A few experiments were tried on animals with 4-methylumbelliferon while extremely high cost of production of I, X, XV and (XCV) in sufficient quantities prohibited me from carrying on their pharmacological tests in vivo.

Experiment I.

(CXXV) (1 g.) was emulsified in gum tragacanth mucilage and administered to a dog (Wt. 6.3 Kg.) orally in the evening at 5-30 P.M. It passed no stools till 11 A.M. next morning when a dose of magnesium sulphate (10 g.) was followed. In the evening it had a motion but passed no worms. Next day its faeces on examination showed that it had passed 2 small pieces of tape-worms but the subsequent motions did not show the presence of any tape-worms or round worms. The substance, it seemed, was highly absorbed in the alimentary track and it could be detected in the urine even on the fourth day while it had disappeared from the faeces after the second day of its administration. The dog was killed on the fifth day after the administration of the drug neither tape-worms nor round worms could be found in its gut.

For the detection of (CXXV) in the faeces and urine its characteristic blue fluorescence in alkaline solution was relied upon and it was found that (CXXV) in 1 in 10,000,000 parts of water could be easily detected in this way.

Experiment II.

An emulsion of (CXXV) (3 g.) in gum tragacanth was administered to a dog (Wt. 8 Kg.) orally at 12-30 P.M.;

it passed no stools till next day when a dose of magnesium sulphate (10 g.) was followed as in the previous experiment. It passed some hard, consolidated faeces by the next morning, the examination of which showed complete absence of tape-worms or round worms. Then at 11-30 A.M. it was given another dose of magnesium sulphate (12 g.). The loose faeces that it passed in the evening contained only 2 small bits of tape-worms. The faeces of the succeeding days were examined but neither any more tape-worms nor any round worms were passed. The dog was killed on the 5th day after the administration of the drug and the gut on examination showed complete absence of tape-worms and round worms. The drug could be detected in its urine even on the 4th day after its administration but had completely disappeared from its faeces after the second day.

Experiment III.

Two lots of (CXXV) (0.9 g. and 1.4 g.) were emulsified in gum tragacanth mucilage and administered respectively to two fowls (Wt. 1.072 Kg. and 1.52 Kg.) orally. They also showed usual constipative effects and did not pass any stools for two days; magnesium sulphate (1.2 g. and 1.8 g.) was then administered to each fowl respectively. The stools on examination for the succeeding two days did not show the presence of any tape-worms or round worms but the presence of medicine was quite

marked till the fourth day. The fowls were killed after ten days no tape-worms were present in their guts but round worms which were harbouring there in plenty in both the cases were quite unaffected by the medicine.

The effect of 7-hydroxyflavone, genkwanin and 4-methyl-umbelliferon on rabbit's isolated gut and uterine movements:-

The effect of these compounds was studied in Dale and Laidlaw's apparatus already described. It was found that concentration 1-140,000 of the compounds stopped the movements of the gut and that of the uterus (See Fig. 5,6 and 7) while lesser concentrations produced correspondingly less effect on their movements.

The effect of genkwanin and 7-hydroxyflavone on blood pressure and uterine movements of a dog:-

A female pregnant dog (Wt. 10 Kg.) was anaesthetized with morphia-urethane. The left carotid artery was exposed and a cannula was inserted in it. It was filled with anti-coagulant solution (sodium citrate half-saturated solution in water) and connected to a 'U' tube mercury manometer by an ordinary rubber tubing also filled with the same solution in such a way that there was no air left between the mercury level of the manometer and the carotid artery connection to the cannula. The other end of the mercury

manometer was attached to a simple mechanism to record fluctuations in the blood pressure on a smoked paper kept rotating on a drum. Similarly right femoral vein was attached to a burette containing normal saline through a small cannula; the trachea was connected to another cannula to allow free breathing to the animal. At the same time abdomen of the dog was opened and its uterus was connected by a fine thread to a lever arrangement to record its movements side by side with the blood pressure experiment. Then a concentrated solution of genkwanin dissolved in minimum quantity of 10% aqueous caustic soda was injected into the animal through the right femoral vein. It was noticed that 100 mg. of genkwanin clearly produced depression in the blood pressure and contraction in the uterus (See Fig.8) and the effect was proportional to the amount injected. Similar results were recorded with 7-hydroxyflavone (Fig.9).

The effect of chrysin, genkwanin and 4-methyl-umbelliferon on blood pressure and respiration of a dog:-

The dog was prepared as in the previous experiment but the tracheal cannula in this experiment was connected to a tambour to record the movements of respiration. Different amounts of the substance were injected and their effect recorded. It was found that 200 mg. of each,

chrysin and 4-methylumbelliferon, produced depression in the blood pressure and increase in the movements of respiration (See figs. 10 and 12) but in the latter case certain amount of depression in the respiration was also noticed which soon recovered to normal; while 100 mg. of genkwanin raised the blood pressure for a very short time, again coming to its normal, and an increase in the respiration movements was clearly noticeable (See Fig.11).

The effect of 7-hydroxyflavone, chrysin and genkwanin on the beats of an isolated frog's heart:-

A frog was pithed and the chest exposed by removing the sternum plate. The pericardium was then carefully removed from the heart and two cannulae were inserted, one in the inferior vena cava(A) and the other in the aorta (B). All the other arteries and veins leading from and coming to the heart were ligatured and the heart isolated from the body. To maintain beating of the heart and the circulation, measured quantity of Ringer's solution was put into the cannula (A) and the cannula (B) was led into (A) by means of a small piece of rubber tubing. The whole preparation was fixed on a stand in position, a pinch clip was attached to the apex of the heart and was tied to a heart lever by means of a fine thread and heart beats were thus recorded on a smoked paper. The Ringers solution from the circulation was pipetted out as far as possible and the solutions of the

substances in Ringer's solution were then tried at different concentrations at a time and it was observed that 7-hydroxy-flavone, chrysin and genkwanin in concentrations 1-2,000,000; 1-100,000; and 500,000 respectively inhibited the action of the heart (See Figs. 13, 14 and 15). A control experiment was also carried out with the maximum amount of caustic soda solution used to dissolve the substances in the above experiments (See Fig.16). The control showed practically no effect on the beats of the heart.

The antiseptic properties of genkwanin, chrysin and 4-methylumbelliferon were tried as follows:-

To three different sets of 4 test tubes each, containing broth culture, was added genkwanin, chrysin and 4-methylumbelliferon so that each one of these compounds had a concentration of 1-1,000; 1-10,000; 1-100,00; and 1-1,000,000 in the 4 different test tubes of each set. The tubes were inoculated with a few days old B.coli culture and incubated at 37°C. for 48 hours; a control was also carried out along with it by inoculating B.coli to pure broth culture. It was found that genkwanin and chrysin had no action on the bacilli, the growth in all the tubes being as profuse as in the control tube. In the case of umbelliferon, however, there was no growth in 1-1,000 concentration and a slight inhibition of growth in 1-10,000 concentration.

List of Publications:-

1. Some 4-styrylcoumarins.
H.S.Mahal and K.Venkataraman. Journal of the Chemical Society, 1933,616.
2. Coumarin and Chromone formation.
T.C.Chadha,H.S.Mahal and K. Venkataraman. Journal of the Chemical Society, 1933, 1459.
3. Synthesis of flavones at room temperature.
H.S.Mahal and K. Venkataraman. Current Science,1933,2,214.
4. Synthesis of 7-hydroxy iso-flavene and of α - and β -naphthaisoflavones.
H.S.Mahal, H.S.Rai, and K. Venkataraman. Journal of the Chemical Society,1934,1120.
5. The action of sodamide on 1-acyloxy-2-acetonaphthones.
H.S.Mahal and K.Venkataraman. Journal of the Chemical Society, 1934,1767.
6. A synthesis of Formononetin, Daidzein and ψ -baptigenin.
H.S.Mahal,H.S.Rai, and K. Venkataraman. Journal of the Chemical Society,1934,1769.
7. Chalkones and Flavanones and their oxidation to flavones by means of SeO_2 .
H.S.Mahal,H.S.Rai and K. Venkataraman. Journal of the Chemical Society,1935,866.
8. Further studies in the sodamide method of flavone synthesis.
D.C.Bhalla,H.S.Mahal and K. Venkataraman. Journal of the Chemical Society,1935,868.
9. The constitution of calycopterin.
H.S.Mahal and K.Venkataraman. Current Science,1935, Vol.IV,No.5,311.
10. Synthesis of Genkwanin,
H.S.Mahal and K.Venkataraman. Journal of the Chemical Society,1936, 569.

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