SYNTHESIS OF GENTISIN, AND OTHER EXPERIMENTS IN THE PYRONE GROUP

A Thesis

submitted by

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for the degree

of

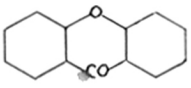
Ph. D

CONTENTS

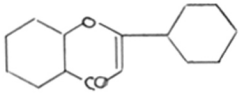
Part I

Synthesis of Gentisin, the yellow colouring matter of *Gentian* root.

Many of the naturally occurring yellow colouring matters belong to the xanthone (I) or flavone (II) group.



(I)



(II)

Euxanthone, gentisin, mangostin and ravenilin are the naturally occurring xanthones.

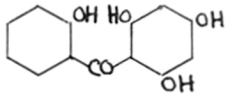
Xanthone was first synthesised by Kolbe and Lautermann[1] by the action of phosphorus oxychloride on sodium salicylate. Xanthones have since then been obtained from salicylic acid and its derivatives by employing various dehydrating agents. By distilling a mixture of acetic anhydride and salicylic acid,[2] xanthone is obtained in about 30% yield, a reaction in which it is supposed that phenol is first formed which reacts with salicylic acid to form the xanthone, and it has been shown that in this reaction the addition of one molecule of phenol increases the yield of the xanthone. This has been developed into a general method for the synthesis of xanthones; and various hydroxyxanthones, such as 2:5-dihydroxyxanthone,[3] gentisin,[4] and euxanthone[5] have been synthesised by the distillation of a mixture of o-hydroxycarboxylic acid,

and the appropriate phenol with acetic anhydride.

Xanthone can also be obtained by the thermal rearrangement of phenylsalicylate,[6,7] and by the action of warm sulphuric acid[8] on o-phenoxybenzoic acid. Fosse[9] obtained xanthones by warming phosphoric esters of phenols with potassium carbonate.

Diphenylether-o-carboxylic acids, which can be conveniently prepared by the interaction of sodium phenolates and o-chlorobenzoic acids in presence of copper powder,[10] can be cyclised to xanthones. This method has been very extensively used for the synthesis of various xanthones, such as 1- and 3-nitroxanthone,[11] euxanthone[12] and ravenilin.[13]

Nishikawa and Robinson[14] have described an elegant synthesis of xanthones. In an attempt to prepare an o:o'-dihydroxybenzophenone (III) by the Hoesch reaction between an o-hydroxybenzonitrile and phloroglucinol, they observed that the intermediate ketimine hydrochloride on treatment with dilute alkali gave the xanthone (IV)



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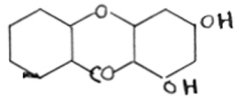
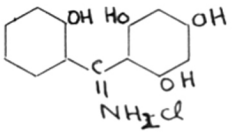


(IV)

in place of the expected benzophenone (III). The mechanism of the reaction is not yet clear, as to whether the

ketimine hydrochloride exists as the phlorobenzophenone derivative (V) or as the xanthene derivative (VI).



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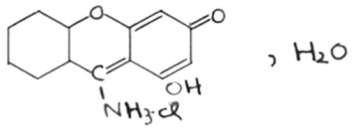
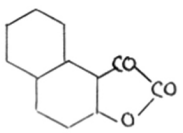


(VI)

Heilbron[15] has suggested that the latter is more probable, because 2:3:4:2'-tetrahydroxybenzophenone does not ring-close on treatment with water at 100°.

Schonberg and Moubasher[16] have obtained the xanthone (VIII) by heating the coumarandione (VII) at 200° in an



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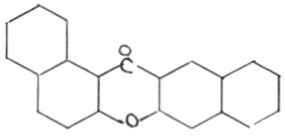
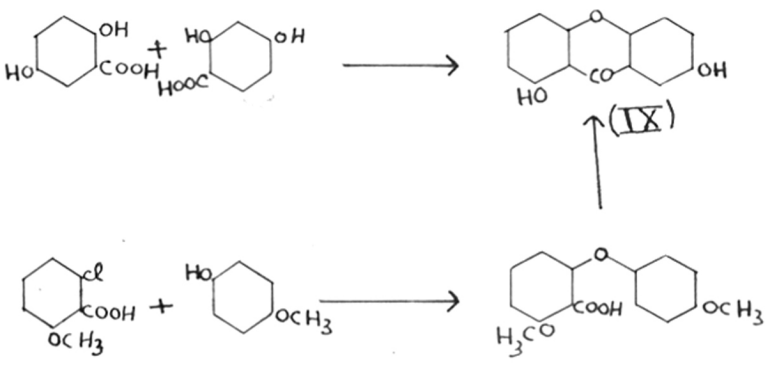


(VIII)

atmosphere of carbon dioxide. This method involves a large number of steps and the preparation of the intermediate (VII) is rather difficult.

Euxanthone, isolated from the urine of cattle fed on mango leaves, was shown by Baeyer[17] to be 1:7-dihydroxy-xanthone (IX). It has been synthesised by the distillation of a mixture of quinol carboxylic acid and β-resorcylic acid with acetic anhydride,[5] and also by an Ullmann's reaction between 2-chloro-6-methoxybenzoic acid[12] and hydroquinone monomethylether followed by ring closure and demethylation of the intermediate benzophenone.

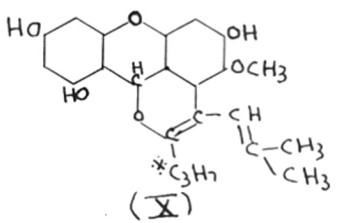
Mangostin has been isolated from the skin of the



fruit of Garcinia mangostina. From a study of the reactions of mangostin and its degradation products, Murakami[18] has suggested its constitution to be (X). The structure of the terminal alkyl group marked with an asterisk is still undetermined.

Ravenilin, isolated from the dried mycelium of Helminthosporium ravenilii, was shown by Robinson and collaborators[19] to be 3-methyl-1:4:8-trihydroxyxanthone (XI). It has been synthesised by Mull and Nord, by carrying out an Ullmann reaction between 3-bromo-2:5-dimethoxytoluene and 2-hydroxy-6-methoxybenzonitrile, followed by hydrolysis and ring closure of the intermediate benzophenone. The tetramethoxyxanthone thus obtained on demethylation gave ravenilin. Recently the study of metabolites of micro-organisms has led to the isolation of a few more xanthone pigments, e.g.

rubrofusarin and aurofusarin from Fusarium graminearium.



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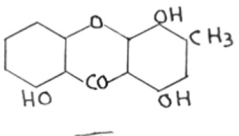
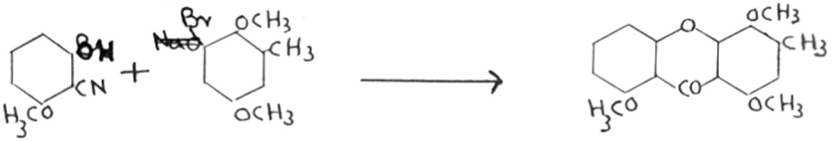


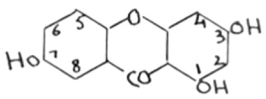
XI



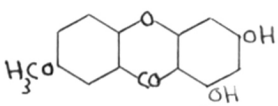
The constitution of the former has been suggested by a study of its absorption spectra to be either 2:8-dihydroxy-1-methoxy-7-methylxanthone or 2:1-dihydroxy-8-methoxy-7-methylxanthone.

Gentisin, the yellow colouring matter of Gentiana lutea (gentian root), was first isolated by Henry and Caventou,[20] and was shown by Baumert[21] to possess the formula $C_{14}H_{10}O_5$. Hlaiswetz and Habermann[22] demonstrated the presence of two hydroxyl groups and one methoxyl; but when fused with potassium hydroxide, it gave phloroglucinol and gentisic acid. Kostanecki[23] by demethylation of gentisin with hydriodic acid, showed it to be a monomethyl ether of gentisein, 1:3:7-trihydroxyxanthone (XII) which was synthesised by Kostanecki and Tambor[4] by the distillation of gentisic acid and phloroglucinol in presence of acetic anhydride. Gentisein on methylation

yielded gentisin, while gentisin on further methylation gave a monomethyl ether.[4] The methylation of gentisin to



(XII)



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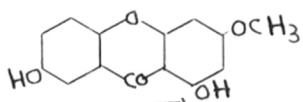


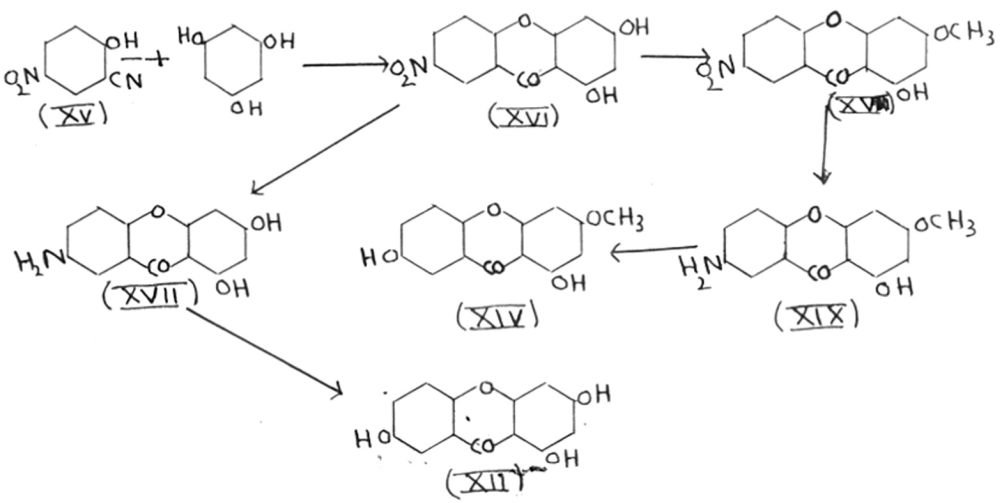
(XIV)

a monomethyl and not a dimethyl ether, indicated that the original methoxyl was not in the 1-position. Gentisin therefore had to be formulated as the 7-methyl ether (XIII) or the 3-methyl ether (XIV). In order to determine which of these two monomethyl ethers of gentisein was identical with gentisin, Kostanecki and Tambor[24] attempted to synthesise the 7-methyl ether by distilling a mixture of 2-hydroxy-5-methoxy benzoic acid, phloroglucinol and acetic anhydride, but they found that the product consisted of a mixture of gentisein, its dimethyl ether and a very small quantity of gentisin. This synthesis did not afford conclusive proof of the constitution of gentisin, as the possibility of its production from gentisein by methylation could not be excluded.

By a study of disazobenzene-gentisin, which formed a diacetyl derivative, Perkin[25] suggested that gentisin should be the 3-methyl ether (XIV). If (XIII) represented gentisin, the diazo coupling would have taken place in the 2:4-positions, and Perkin had found that such disazo

resorcinol derivatives did not undergo acetylation under the usual conditions. The constitution assigned by Perkin to gentisin has now been confirmed by an unambiguous synthesis. Shinoda[26] synthesised the 7-methyl ether (XIII) by a Hoesch reaction between 5-methoxysalicylonitrile and phloroglucinol, followed by cyclisation, and found that it was different from gentisin. We have synthesised the 3-methyl ether (XIV) by the following scheme, which has proved to be identical with natural gentisin.

2-Chloro-5-nitrobenzonitrile did not undergo Hoesch reaction with phloroglucinol to give 2-chloro-5-nitro-2':4':6'-trihydroxybenzophenone which could be ring-closed to



7-nitro-1:3-dihydroxyxanthone (XVI). Orito[28] has reported a similar steric hindering effect of the o-chloro group in benzonitriles in Hoesch reaction. Recourse was

therefore taken to the Hoesch reaction between 5-nitrosalicylonitrile (XV) and phloroglucinol, following the method of Nishikawa and Robinson[14] for 1:3-dihydroxyxanthone, which gave the required 7-nitro-1:3-dihydroxyxanthone (XVI), m.p. 295-296° (diacetate, m.p. 182-183°). Yumoto[28] who prepared (XVI), by a similar method quotes the m.p. 281-282° (diacetate, m.p. 162-163°). Reduction of (XVI) with alkaline hydrosulphite gave the 7-amino-1:3-dihydroxy xanthone (XVII), which on diazotisation and hydrolysis by 35% sulphuric acid yielded gentisein (XII). When (XVI) was methylated by means of dimethyl sulphate and alkali, the ether (XVIII) was always contaminated with a little of the dimethyl ether, and the pure monomethyl ether was not isolable even after repeated crystallisation. It could, however, be readily obtained by methylation with diazomethane (one mole) in ether solution. The nitro compound (XVIII) was then reduced to the amine (XIX) by iron and acetic acid. On diazotisation of the amine ( ) and hydrolysis with 40% sulphuric acid, 1:7-dihydroxy-3-methoxyxanthone (XIV), m.p. 266-267°, was obtained, identical in all its properties with natural gentisin.*

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* We are greatly indebted to Dr. A. T. Peter of the University of Leeds for a sample of natural gentisin, isolated by Professor A. G. Perkin.

E X P E R I M E N T A L

2-Chloro-5-nitrobenzonitrile. o-Chlorobenzonitrile was prepared by the method of Montagué[29] by subjecting diazotised o-chloroaniline to Sandmeyer reaction, with the difference that during the reaction, the reactants were covered with a layer of benzene, so that as the nitrile was formed, it was extracted into the benzene layer, otherwise some decomposition of the nitrile took place. 2-Chloro-5-nitrobenzonitrile,[30] m.p. 106°, was prepared by the nitration of o-chlorobenzonitrile by nitrating mixture at room temperature.

5-Nitrosalicylonitrile(XV)[32,33] 5-Nitrosalicylaldehyde (m.p. 126°) was prepared by the nitration of salicylaldehyde,[31] and the mixture of 3-nitro and 5-nitrosalicylaldehyde thus obtained was separated by fractional crystallisation of their sodium salts from water, in which the sodium salt of the former was more soluble. 5-Nitro-2-hydroxybenzaldoxime, prepared in the usual manner, crystallised from alcohol in stout, colourless needles, m.p. 219-20° (Found: N, 15.1. $C_7H_6N_2O_4$ requires N, 15.3%). 5-Nitrosalicylonitrile obtained on treatment of the oxime with boiling acetic anhydride for

2 hours and subsequent hydrolysis of the acetate (m.p. 55-56°) either by 5% warm sodium hydroxide solution or by heating with water on the water bath for 2-3 hours, crystallised from water in straw-yellow, long silky needles, m.p. 194-96° (Walker[32], m.p. 194-96°; Bone[33], 190°) (Found: N, 17.2. $C_7H_4N_2O_3$ requires N, 17.1%). The nitrile dissolves in sodium bicarbonate solution with effervescence, and gives a deep red colour with ferric chloride.

7-Nitro-1:3-dihydroxyxanthone (XVI): Through a cooled solution of 5-nitrosalicylonitrile (3.3g.) and phloroglucinol (2.5 g.) in dry ether (150 c.c.) containing 2 g. of freshly fused zinc chloride, a slow stream of dry hydrogen chloride was passed for 5 hours. The oil, which first separated in about an hour, gradually dissolved, giving a deep red solution. A deep orange oil again separated after 4 hours. The mixture was left in a refrigerator for 72 hours, the ether decanted off, the deep orange viscous oil washed twice with ether, and taken up in 10% aqueous caustic soda. On boiling for an hour, when no more ammonia was evolved, the deep brownish red solution was filtered from unreacted zinc hydroxide. The 7-nitro-1:3-dihydroxyxanthone, obtained by acidifying the filtrate, crystallised from alcohol in light yellow,

shining flat plates (1.7 g.), m.p. 295-96° (Found: N,5.3. $C_{13}H_7NO_6$ requires N, 5.1%). It gives a brownish violet colour with ferric chloride, and a deep red colouration when shaken with sodium amalgam in water.

Its diacetate prepared by refluxing with acetic anhydride and pyridine, crystallised from alcohol in colourless needles, m.p. 182-83° (Found: N, 4.1. $C_{17}H_{11}NO_8$ requires N, 3.9%).

7-Amino-1:3-dihydroxyxanthone (XVII): 7-Nitro-1:3-dihydroxyxanthone (0.2 g.) was dissolved in one per cent sodium hydroxide (20 c.c.), heated to 70°, and sodium hydrosulphite added till the reduction was complete, at which stage there was a marked change in the colour of the solution from orange to yellow. The amine, precipitated by acetic acid, crystallised as its hydrochloride from water containing hydrochloric acid in yellow needles (0.14 g.), m.p. 318-20° (with charring) (Found: N, 4.9. $C_{13}H_{10}ClNO_4$ requires N, 5%).

1:3:7-Trihydroxyxanthone (Gentisein) (XII): The amine hydrochloride (0.1 g.) was dissolved in a mixture of water (10 c.c.), acetic acid (2 c.c.) and concentrated hydrochloric acid (0.2 c.c.), cooled, and diazotised by sodium nitrite (0.03 g.). After keeping at 0-5° for 15

minutes, excess of nitrous acid was destroyed by urea, and the diazo solution slowly added in about 5 minutes to 30 c.c. of boiling 35% sulphuric acid. Boiling was continued for 5 minutes, when the diazo salt had completely decomposed, as tested by β-naphthol. On cooling the solution, the yellow product was ether extracted, and the ether removed. The pinkish yellow residue crystallised from dilute alcohol in thin yellow needles (0.05 g.), m.p. 314-15° (Kostanecki and Tambor[4], 315° in the material dried at 120° under vacuum (Found: C, 63.6; H, 3.5. $C_{13}H_8O_5$ requires C, 63.9; H, 3.3%). The substance dissolves in aqueous sodium hydroxide to form an orange sodium salt and a yellow solution; gives a brownish green colour with ferric chloride; and a blood-red colour when vigorously shaken with sodium amalgam in alkali.

1:3:7-Triacetoxyxanthone, obtained by refluxing (XII) with acetic anhydride and a drop of pyridine, crystallised from acetic acid in long, thin needles, m.p. 225-26° (Kostanecki,[34] m.p. 226°). (Found: C, 61.8; H, 3.9. $C_{19}H_{14}O_8$ requires C, 61.8; H, 3.8%).

7-Nitro-1-hydroxy-3-methoxyxanthone (XVIII): 7-Nitro 1:3-dihydroxyxanthone (0.27 g.) was dissolved in ether (150 c.c.), and diazomethane (0.04 g.; 1 mol.) in ether was added, and the mixture kept at the room temperature for one hour with occasional shaking, when a yellow

shining mass of crystals separated. After 12 hours in the refrigerator, the product was filtered (0.23 g.). It crystallised from acetic acid (if boiled for a long time, partial acetylation takes place) - or from benzene in light yellow, thin, rectangular plates, m.p. 249-50° (Found: N, 4.9. $C_{14}H_9NO_6$ requires N, 4.9%). The substance gives a reddish brown colour with ferric chloride. It does not dissolve in aqueous alkali, but in alcoholic sodium hydroxide it gives a sparingly soluble orange sodium salt.

The acetate obtained by refluxing with acetic anhydride and pyridine, crystallised from acetic acid in long, thin colourless needles, m.p. 263-64° (Found: N, 4.5. $C_{16}H_{11}NO_7$ requires N, 4.2%).

7-Amino-1-hydroxy-3-methoxyxanthone (XIX): The nitro compound (XVIII; 0.2 g.) was suspended in 30 c.c. of boiling alcohol containing acetic acid (3 c.c.), and iron powder (0.2 g.) was added to it in the course of an hour, when the nitro compound gradually dissolved, giving a brown solution. It was refluxed for a further 30 minutes, filtered from the unreacted iron, most of the alcohol boiled off, and 2 c.c. of concentrated hydrochloric acid added, when the amine hydrochloride

was precipitated. The amine crystallised as its hydrochloride from 150 c.c. of water containing hydrochloric acid, in bunches of short, thin, flat colourless needles (0.15 g.) which shrank at 270° and melted at 273-75° (with charring) (Found: N, 4.8. $C_{14}H_{12}ClNO_4$ requires N, 4.7%). The amine, liberated by neutralising the aqueous solution of the hydrochloride with sodium carbonate, crystallised from alcohol in long, thin, greenish yellow needles, m.p. 215-16° (Found: N, 5.2. $C_{14}H_{11}NO_4$ requires N, 5.4%). The alcoholic solution gives a brown colour with ferric chloride.

1:7-Dihydroxy-3-methoxyxanthone (Gentisin)(XIV): A cooled suspension of the hydrochloride (0.15 g.) in acetic acid (4 c.c.), water (2 c.c.), and hydrochloric acid (0.2 c.c.) was diazotised by means of sodium nitrite (50 mg.). The amine hydrochloride dissolved slowly, and after keeping for 15 minutes, excess of nitrous acid was destroyed by urea, and the diazo solution added slowly to boiling 40% sulphuric acid (30 c.c.), and boiling continued for 10 minutes, when the solution gave no test for a diazo salt. On cooling and dilution, a yellow product separated, which was collected, and crystallised from alcohol. The long, light yellow, shining needles (0.09 g.), softened slightly at 258-59° and melted at

266-67°, being identical in behaviour with a sample of natural gentisin. A mixture of the synthetic substance and gentisin gave the same m.p. (Found: C, 65.4; H, 4.2. $C_{14}H_{10}O_5$ requires C, 65.1; H, 3.9%). The substance exhibits all the properties described for natural gentisin It dissolves readily in alkali with a golden yellow colour, and gives an olive-green colour with ferric chloride. When heated and shaken with sodium amalgam in water, it gives a deep green solution, which on acidification gives a cherry red precipitate. In concentrated sulphuric acid it gives a yellow solution, which on standing develops a bright green fluorescence, which earlier workers have not recorded. We have found, however, that natural gentisin behaves similarly.

The diacetate, obtained in the usual manner by treatment with acetic anhydride and pyridine, crystallised from alcohol in long thin needles, m.p. 195-96°, not depressed when mixed with the diacetate prepared from natural gentisin (Hlaiswetz and Habermann[22], m.p. 195.5°) (Found: C, 63.6 ; H, 4.2 . $C_{18}H_{14}O_7$ requires C, 63.2; H, 4.1%).

The dibenzoate, obtained by shaking a solution of the compound in 10% sodium hydroxide with 6-8 mols. of benzoyl chloride, crystallised from alcohol in bunches of short thick needles, m.p. 192° (Kostanecki and Tambor,[4] m.p. 192°.).

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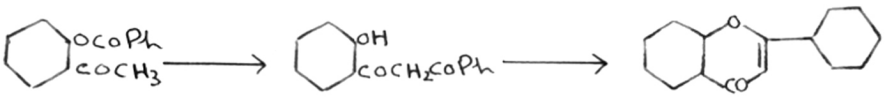
Part II

Synthesis of partially methylated polyhydroxyflavones and flavonols.

Polyhydroxy and partially methylated polyhydroxyflavones are widely distributed in plants. The synthesis of flavones with varying orientation of hydroxyl and methoxyl groups has been one of the major problems in synthetic flavone chemistry.

Amongst the older methods for the synthesis of flavones, the method of Kostanecki and Emilewiz,[1] by the treatment of o-acetoxychalkone dibromides with alcoholic alkali, and that of Kostanecki and Tambor,[2] by the action of hydriodic acid on o-ethoxydibenzoyl methanes obtained by the action of ethyl-o-ethoxybenzoate on acetophenone are the most important. These methods are limited in application and have been largely superseded by the more convenient and widely applicable methods of (1) Allan and Robinson,[3] which involves the condensation of the appropriate o-hydroxyacetophenone and the anhydride and alkali salt of the appropriate acid; and (2) that due to Baker,[4] and to Mahal and Venkataraman,[5] which starts with the O-benzoyl derivative of the o-hydroxyketone; these are converted under the influence of potassium carbonate or sodamide into the corresponding dibenzoylmethanes,

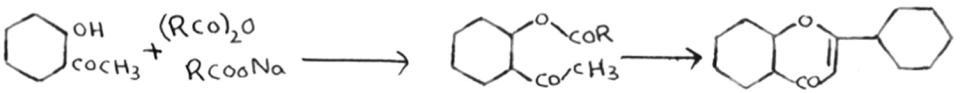
which are subsequently cyclized into the flavone by a suitable dehydrating agent. Wheeler and co-workers have



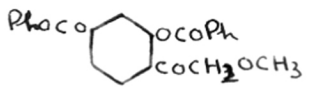
shown that sodium[6] in toluene and sodium ethoxide[7] can also bring about this transformation. It has been observed that, though these reagents are of general applicability, specific reagents have to be used in some cases for bringing about the rearrangement of the aroyl ester to the required diketone. In the present investigation, it was observed that with most of the nitro-aroyl esters, very good yields of the corresponding diketones were obtained by using potassium carbonate or metallic sodium in toluene, but in the case of 2-p-nitrobenzoyl-4:6-dimethoxyacetophenone (XVII), these reagents failed to bring about the rearrangement, only sodamide in toluene or benzene yielded the corresponding diketone (XVIII); while 4-nitro-2-acetφyl-1-naphthyl benzoate (VI) could not at all be rearranged to the corresponding diketone by any of these reagents. Similarly Baker et al[22] have reported that 2-benzoyloxy-3:5-dimethoxyacetophenone did not undergo rearrangement to to the corresponding diketone when treated with sodamide in toluene. In the case of 2-acetylresorcindibenzoate, Iyer working in this laboratory has found that only sodium ethoxide in alcohol gave the diketone, which on cyclisation gave 5-hydroxyflavone; sodamide in ether gave an inter-

mediate product which on ring-closure gave 3-benzoyl-5-hydroxyflavone, while potassium carbonate in toluene gave the 3-benzoyl-5-hydroxyflavone. Similarly in the case of O-benzoyl-1-aceto-2-naphthol, which is discussed later (Part III, p. 62), only sodium ethoxide in alcohol gave the corresponding diketone.[7] No general explanation has yet been found for the difference in the behaviour of these various reagents in different cases.*

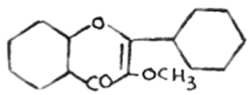
One of the earlier explanations given for the Robinson reaction was the intermediate formation of o-aroylacetophenone, which then dehydrate to give the flavone. Chavan and Robinson[8] observed that ω:2:4:6-



tetrahydroxyacetophenone on dehydration, by treatment with potassium acetate in boiling alcohol or better by sodium acetate and acetic anhydride, followed by hydrolysis yielded galangin. Mahal (Ph.D. Thesis, Punjab University) has shown that ω-methoxyresacetophenone-dibenzoate (I) on thermal rearrangement gave an inter-



(I)



(II)

mediate product, which on treatment with sulphuric acid,

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* See Appendix I

gave 3'-methoxy-7-hydroxyflavone (II). It has been observed that the ester (I) does not give the flavone (II), merely by treatment with cyclizing agents such as benzoyl chloride and a drop of concentrated sulphuric acid. However, by treating the ester (I) with potassium carbonate in toluene the flavanol ether (II) was obtained, which shows that the conversion of (I) into (II) is not merely a case of dehydration but one of rearrangement, followed by dehydration. When the ester (I) was treated with sodamide in ether, a colourless crystalline product m.p. 118-20°, was obtained from whose analytical data the constitution could not be deduced.

It has been definitely demonstrated by Baker[4] that the Robinson reaction involves the intermediate formation of a dibenzoylmethane.

Mahal, Rai and Venkataraman[9] have shown that chalkones and flavonones in general, when subjected to the action of selenium dioxide in amyl alcohol or xylene yield flavones. Hutchins and Wheeler[10] observed that chalkone dibromides give flavones, when they are either heated above their melting point, or treated with boiling alcoholic potassium cyanide.

Modifying the Robinson flavone synthesis by using

benzyloxy or benzoyloxy derivatives in the acetophenone or the acid anhydride reactant, to take advantage of the easier removal of O-benzoyl and benzyl groups in comparison with the O-methyl, partially methylated polyhydroxyflavones such as kaempferide,[12] isorhamnetin,[12] myricetin[13] diosmetin,[14], tricin,[15] and rhamnazin,[16] have been synthesised.

The observation[17], that by the action of aluminium chloride under specified conditions preferential demethylation in the 5-position takes place in methylated polyhydroxyflavones, has been utilised for the synthesis of 5:8-dihydroxyflavone,[18] and several partially methylated polyhydroxyflavones such as genkwanin,[19] Wogonin,[20] tectochrysin,[21] and primetin-8-methyl ether.[22] Hydrobromic acid in acetic acid[23] can also be used for the same purpose. It has been found that the 3-methoxyl is also susceptible to demethylation by aluminium chloride and by hydrobromic acid in acetic acid,[23] and this has been used by Seshadri and Venkateswarlu[24] for the synthesis of calycopterin and rhamnazin, It was observed[23] that hydrobromic acid in acetic acid at room temperature attacked the 5-methoxyl in preference to the 3-methoxyl

Potassium persulphate which is a well known reagent for the nuclear oxidation of hydroxy aromatic nuclei, has been used in a very ingenious way by Seshadri and co-workers[25] for the facile nuclear oxidation in the flavones, for the introduction of one more hydroxyl group in the fused benzene ring of the flavones para, and sometimes even ortho, to the existing hydroxyl group. In this way a number of flavones like gossypetrin, 8-hydroxygalangin, norwogonin, isonorwogonin, wogonin, primetin, calycopterin and nobilitin have been synthesised from the corresponding hydroxylflavones.

Perkin[26] obtained the disazo dyes from naturally occurring colouring matters derived from resorcinol and phloroglucinol, by coupling with diazo salts. Mahal and Venkataraman[27] prepared from 6-hydroxyflavone the 5-benzeneazo derivative, which has been reduced, diazotised and hydrolysed to the corresponding dihydroxy compound[28]. While this method has obvious possibilities for the synthesis of polyhydroxy and partially methylated poly-hydroxyflavones, our alternate route to the intermediate amines would be through the corresponding nitroflavones. The introduction of a hydroxyl group through the diazo coupling reaction has the limitation that the new group

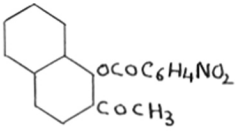
can only be located ortho or para to a hydroxyl group ~~en~~ originally present in the 2-phenyl or the fused benzene ring of the flavone molecule. Proceeding through a nitroflavone there will be a greater latitude regarding the position of the hydroxyl group to be introduced. The exploratory experiments described in this part show that the method may be utilised for synthesis in the flavone and iso-flavone series. Nitroflavone could be synthesised either by direct nitration of the flavones or by starting from the appropriate nitroaroyl chloride or nitroacetophenone. The latter method has the advantage of the certainty of the position of the nitro group, and thus of the hydroxyl group in the hydroxyflavone being synthesised, and we have mostly followed the latter method.

Bogert,[29] in a study of the nitration of flavones, nitrated α-naphthaflavone to a mixture of 2'-, 3'- and 4'-nitro-α-naphthaflavone, which were separated as their amines, the latter being characterised after diazotisation as their β-naphthol dyes. He also prepared 2'-hydroxy-α-naphthaflavone from the corresponding amine via the diazo salt. Sugasawa[30] prepared 5-amino-6-hydroxy flavone from the corresponding acetamido compound, but failed to hydrolyse it to the corresponding dihydroxy-

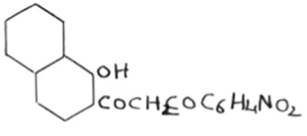
flavone. Virkar[31] in a study of the rearrangement of nitroaroyl esters prepared some nitroflavones, which were reduced to the corresponding amines.

4'-Hydroxy-α-naphthaflavone, ~~6-hydroxy-α-naphthaflavone~~, 7:4'-dihydroxyflavone, 4'-hydroxy-7-methoxyflavone (isopratol) and 5:4'-dihydroxy-7-methoxyflavone (genkwanin) have now been synthesised by hydrolysing the corresponding aminoflavones, through the diazo salts, the amines being obtained by the reduction of the nitroflavones. The nitroflavones were obtained by rearrangement of nitroaroyl acetophenones, through the intermediate diketones.

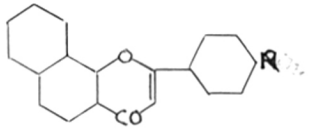
p-Nitrobenzoyl-2-acetyl-1-naphthol (III) was rearranged by potassium carbonate in toluene to the corresponding diketones (IV), which on cyclisation with cold concentrated sulphuric acid gave 4'-nitro-α-naphthaflavone



(III)



(IV)

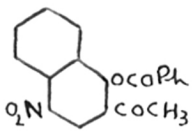


(V) R = NO_2, NH_2 or OH

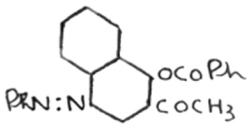
(V, R = NO_2). The nitroflavone on reduction with iron and acetic acid gave the corresponding aminoflavone (V, R = NH_2). The diazo salt of the aminoflavone could be hydrolysed very

readily and in a good yield to 4'-hydroxy- α-naphthaflavone (V, R = OH) only by boiling with 30% sulphuric acid, after the complete removal of free nitrous acid; if a higher concentration of the acid was used or there was some free nitrous acid bye-products were formed.

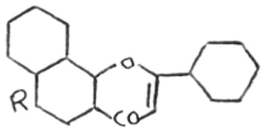
O-Benzoyl-4-nitro-2-acetyl-1-naphthol (VI) was



(VI)



(VII)

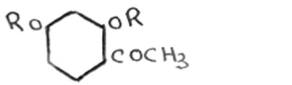


(IX) R = N:NPh or NH_2

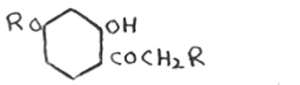
prepared by the benzoylation of 4-nitro-2-acetyl-1-naphthol. This did not undergo rearrangement, this showing that 4-nitro group in the acetophenone nucleus inhibits the rearrangement of aroyl esters to the corresponding diketone. Deliwala and Shah[32] have observed a similar inhibiting effect by the nitro group in the resacetophenone nucleus to the formation of coumarins by condensation with acetoacetic ester. 4-Benzeneazo-2-acetyl-1-naphthyl benzoate (VII, see part III, p. 59), however, smoothly rearranged to the corresponding diketone (VIII) with potassium carbonate in toluene. The diketone was ring-closed to the corresponding flavone

(IX, R = N:NPh), which on reduction with hydrogen under pressure in presence of Raney nickel gave 6-amino-α-naphthoflavone (IX, R = NH_2). During hydrolysis of the diazotized amine decomposition took place, and the required hydroxyflavone could not be obtained.

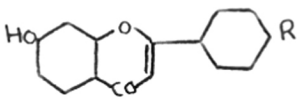
O-Di-p-nitrobenzoylresacetophenone (X) was rearranged by potassium carbonate and toluene to the diketone (XI), which on cyclisation gave 4'-nitro-7-hydroxyflavone (XII, R = NO_2). It was reduced to the amine (XII, R = NH_2), which on diazotisation and hydrolysis, as in the previous cases, gave 7:4'-dihydroxyflavone (XII, R = OH), 4'-Nitro-7-methoxyflavone (XIII, R = NO_2), prepared by methylation of the corresponding hydroxyflavone, was reduced to the amine (XIII, R = NH_2), which was diazotised and hydrolysed



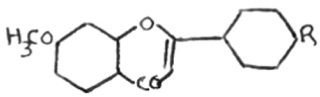
(X) R = $COC_6H_4NO_2$



(XI) R = $COC_6H_4NO_2$



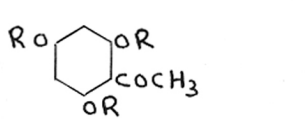
(XII) R = NO_2, NH_2 or OH



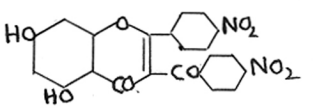
(XIII) R = NO_2, NH_2 or OH.

as in the previous case, to 4'-hydroxy-7-methoxyflavone (XIII, R = OH).

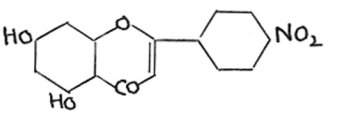
Genkwanin (XXII) was synthesised by Nakao and Tseng[19] by the Robinson reaction between phloracetophenone and alkali salt and anhydride of p-benzyloxybenzoic acid, followed by partial methylation and debenzylation; and by Mahal and Venkataraman[19] by the oxidation of 2-hydroxy-4:6-dimethoxy-4'-benzyloxystyrylketone by selenium dioxide to the corresponding flavone, followed by debenzylation and partial demethylation with aluminium chloride. Genkwanin (XXII) has now been synthesised from the corresponding nitroflavones through the aminoflavones. The tri-p-nitrobenzoyl ester of phloracetophenone (XIV), prepared by condensing p-nitrobenzoyl chloride and phloracetophenone in pyridine under specified conditions, gave on rearrangement with potassium carbonate in toluene and subsequent treatment with concentrated sulphuric acid in the cold, the ~~px~~ 3-p-nitrobenzoyl-4'-nitro-5:7-dihydroxyflavone (XV), which could not be hydrolysed to 4'-nitro-5:7-dihydroxyflavone



XIV R = $COC_6H_4NO_2$



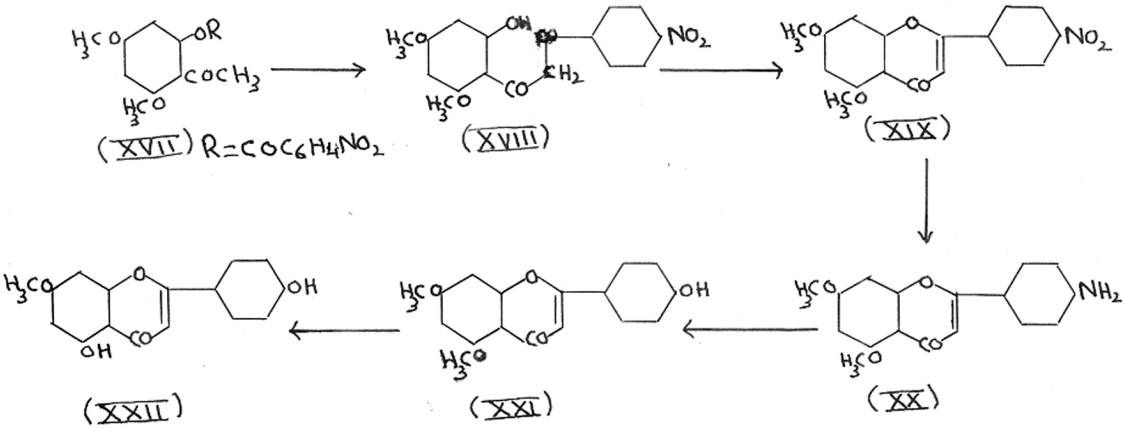
(XV)



(XVI)

(XVI). When the rearrangement was carried out with

sodium ethoxide in alcohol, the ester was merely hydrolysed. The p-nitrobenzoyl ester of 4:6-O-dimethylphloraceto phenone (XVII) was then prepared; it could not be rearranged to the diketone by means of potassium carbonate or metallic sodium in toluene, the ester remaining unaffected, but gave the diketone (XVIII) when treated

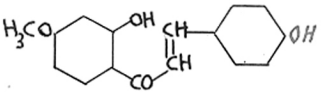


with sodamide in benzene or toluene. This on cyclisation gave 4'-nitro-5:7-dimethoxyflavone (XIX), which crystallised in two dimorphic form; on reduction both gave the same amine (XX). Diazotisation of the amine and hydrolysis gave the 5-monomethyl ether of Genkwanin (XXI), which on treatment with aluminium chloride in nitrobenzene gave Genkwanin.

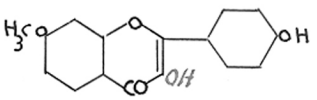
The probability that pruddumetin, isolated by Chakravarti and Ghosh[33] from the bark of Prunnus puddum,

is identical with Genkwanin, has been suggested by Venkataraman.[34] The identity has been confirmed by taking a mixed melting point of puddumetin* and genkwanin now synthesised.

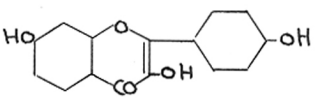
Algar and Flynn[11] have accomplished the synthesis of flavonols from chalkones by oxidation with alkaline hydrogen peroxide. Applying this reaction, the 7-methyl ether of 3:7:4'-trihydroxyflavone (XXV) has been synthesised in one step by the oxidation of the corresponding



(XXIII)



(XXIV)



(XXV)

chalkone (XXIII) which was prepared by the condensation of 4-methyl ether of resacetophenone and p-hydroxybenzaldehyde. This shows that in the oxidation of chalkones to flavonols a free hydroxyl group in the 4'-position does not interfere and this model experiment indicates a very simple route for the synthesis of flavonols with a free 4'-hydroxy group like rhamnazin,[16] rhamnetin[35] and rhamnocitrin[36], which commonly occur in nature.

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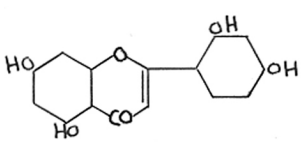
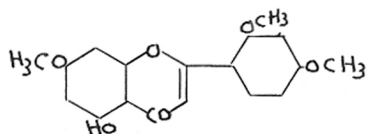
* We are thankful to Dr. D. K. Chakravarti of the Calcutta University for a sample of Puddumetin isolated by him.

Of the other two monomethyl ethers of 3:7:4'-trihydroxy flavone (XXV), the 4'-methyl ether was synthesised by Heap and Robinson[37] by Robinson reaction between ω-benzyloxyresacetophenone and sodium salt and anhydride of anisic acid, followed by debenzylation, and the 3'-methyl ether by Gulati (Ph.D. Thesis, Punjab University) by the Robinson reaction between ω-methoxyresacetophenone and sodium salt and anhydride of p-benzyloxybenzoic acid, followed by debenzylation.

Lotoflavin, the natural colouring matter of Lotus arabicus was shown by Dunstan and Henry[38] to be 5:7:2':4'-tetrahydroxyflavone. But the synthesis of 5:7:2':4'-tetrahydroxyflavone (XXVI) by Robinson and Venkataraman[39] and by Cullinane[40] et al indicated



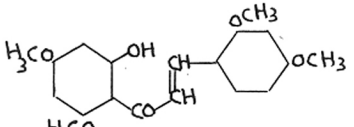
(XXVI)



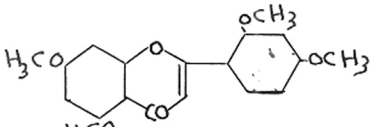
(XXVII)

its non-identity with lotoflavin. The properties of lotoflavin trimethyl ether[38], which crystallises in dimorphic forms with different melting points were, more characteristic than those of lotoflavin. It was therefore considered desirable to synthesise 5-hydroxy-7:2':4'-trimethoxyflavone (XXVII) for a comparison with lotoflavin

trimethyl ether. 2-Hydroxy-4:6:2':4'-tetramethoxy chalkone, m.p. 152° (XXVIII) was prepared by the condensation of β-resorcylaldehyde dimethyl ether with phloracetophenonedimethyl ether in alcoholic sodium hydroxide solution. This has been prepared in a similar manner by Kostanecki et al[41] who quote the m.p. 152°, and by Mitter and Guha[42], who quote the m.p. 124°. The chalkone was treated with selenium dioxide in amyl alcohol and the product obtained after removal of amyl alcohol was



(XXVIII)



(XXIX)

a mixture of the tetramethoxyflavone (XXIX) and the unconverted chalkone (XXVIII), which could not be separated by crystallisation. Chromatographing also failed to effect any separation. The mixture could only be separated by taking it up in benzene, extracting it repeatedly with 2% alcoholic sodium hydroxide containing 50% alcohol, which extracted only the unconverted chalkone. The benzene extract on evaporation and crystallisation from alcohol gave the tetramethoxyflavone (XXIX), m.p. 174°, in about 15% yield. This poor yield in the conversion of the chalkones to the flavone might

probably be due to the steric effect of the methoxyl group in the 2'-position. A ~~s~~similar difficulty in the conversion of the chalkone (XXVIII) to the corresponding flavanone has been reported by Kostenecki[41] et al (and Mitter & Guha[42]) who obtained the flavanone in a very poor yield ~~and~~ by any of the usual methods for the conversion of chalkones to flavanones. When the demethylation ~~of the~~ of the tetramethoxyflavone (XXIX) was tried with hydrobromic acid in acetic acid, it formed an insoluble red oxonium salt which decomposed to the tetramethoxyflavone (XXIX) on washing with water. Demethylation with aluminium chloride in nitrobenzene ultimately yielded the trimethyl ether which crystallised from alcohol in yellow needles, m.p. 163°. Its acetate crystallised from alcohol in colourless needles, m.p. 164-65°. Dunstan and Henry[38] have reported that lotoflavin trimethyl ether crystallised in dimorphic forms from methyl alcohol; the lesser soluble form crystallised in rosettes of bright yellow needles, m.p. 125°, and the more soluble form crystallised in old gold lustrous long silky needles, m.p. 175°. Both these gave the

same acetate, m.p. 147°. Thus lotoflavin trimethyl ether and acetyltrimethyl lotoflavin do not correspond with 5-hydroxy-7:2':4'-trimethoxyflavone and 5-acetoxy-7:2':4'-triemthoxyflavone.

EXPERIMENTAL

3-Methoxy-7-hydroxyflavone (II):

ω-Methoxyresacetophenonedibenzoate (I) was prepared by treating ω-methoxyresacetophenone with benzoyl chloride (2.2 moles) on the water bath for 30 minutes. It crystallised from alcohol in colourless needles, m.p. 76-77° (Mahal; m.p. 76-77°). ω-Methoxyresacetophenone dibenzoate (1 g.) in toluene (10 c.c.) and freshly ignited potassium carbonate (3 g.) were refluxed on the water bath for 8 hours, the solvent removed under vacuum and the residue stirred into dilute acetic acid. The precipitate was filtered and crystallised from alcohol in colourless needles (0.2 g.), m.p. 230°, not depressed when mixed with a sample prepared earlier by Mahal (Allan and Robinson, m.p. 227°).

Rearrangement of ω-methoxyresacetophenone dibenzoate with sodamide.

The ester (1 g.) in dry ether (20 c.c.) and sodamide (1 g.) was mechanically stirred at 0° for 8 hours and left overnight at the same temperature. The sodamide was

filtered, it did not yield any product on acidification. The ether filtrate on evaporation gave a semi sticky solid which on rubbing with alcohol became an amorphous powder. It crystallised from alcohol in small colourless plates, m.p. 118-120° (0.15 g.) (Found: C, 65.4; H, 4.3. The diketone $C_{23}H_{18}O_6$ requires C, 70.8; H, 4.6%. The flavone $C_{16}H_{12}O_4$ requires C, 71.6; H, 4.5%). It gives a red colour with ferric chloride in an alcoholic solution. It forms an insoluble yellow sodium salt with aqueous sodium hydroxide, and is unaffected by treatment with cold concentrated sulphuric acid.

4'-Nitro-α-naphthaflavone (V, R = NO_2):

2-Aceto-1-naphthol-p-nitrobenzoate (III), obtained by heating acetonaphthol (10 g.) in pyridine (40 c.c.) and p-nitrobenzoyl chloride (1 mole, 10 g.) for half an hour on the water bath, crystallised from alcohol or benzene in light yellow thick needles (16 g.), m.p. 151-152° (Found: N, 4.4. $C_{19}H_{13}O_5N$ requires N, 4.2%) (Virkar,[31] m.p. 151°). The ester (4 g.) in toluene (30 c.c.) and freshly ignited potassium carbonate (12 g.) was refluxed for 8 hours with mechanical stirring, toluene filtered off, the orange red mass washed with benzene, dried and stirred into dilute acetic acid, and

the diketone (IV) collected (3 g.). It crystallised from acetic acid in yellow thin long needles or from acetone in yellowish orange needles, m.p. 222° (Found: N, 4.0: $C_{19}H_{13}O_5N$ requires N, 4.2%) (Virkar,[31] m.p. 222°).

4'-Nitroflavone, obtained by diluting a solution of the diketone (1 g.) in concentrated sulphuric acid (20 c.c.) after having been kept overnight, crystallised from acetic acid in long thin light yellow plates, m.p. 293° (Found: N, 4.5. $C_{19}H_{11}O_4N$, requires N, 4.4%)(Virkar,[31] m.p. 293°).

4'-Amino-α-naphthaflavone (V, R = NH_2):

To a boiling solution of the nitroflavone (0.5 g.) in acetic acid (5 c.c.), iron powder (0.5 g.) was added in about one hour's time, refluxed for another half an hour, the unreacted iron filtered, the dark brown solution diluted, and the greenish yellow amine collected. It was crystallised as its hydrochloride from water containing hydrochloric acid in bunches of small orange needles (0.4 g.); when heated it discolours and melts at 250-251°. (Found: N, 4.4. $C_{19}H_{14}O_2NCl$ requires N, 4.3%). The amine, obtained by neutralising a solution of the hydrochloride with sodium carbonate, crystallised from dilute alcohol in long thin light yellow plates, m.p. 265°.

(Virkar,[31] m.p. 265°, non-crystalline). ~~The~~ yellow solutions in alcohol and in sulphuric acid exhibit a bright green fluorescence.

4'-Hydroxy-α-naphthaflavone (V, R = OH):

The amine (0.1 g.) was dissolved in water (50 c.c.) containing hydrochloric acid, cooled and diazotised by sodium nitrite (0.03 g.). After keeping at 0-5° for ten minutes, excess of nitrous acid was destroyed by urea, and the diazo solution slowly added to 30% boiling sulphuric acid (100 c.c.), when some frothing due to the evolution of nitrogen took place, and the diazo solution was almost immediately hydrolysed as shown by testing with alkaline β-naphthol. If a higher concentration of acid was used or there was free nitrous acid, only bye-products were formed. On cooling the solution, light yellow bunches of short needles separated, which were collected, washed free from acid and crystallised from alcohol and acetic acid mixture in small colourless needles (0.05 g.), m.p. 315-316° (Found: C, 78.8; H, 3.9. $C_{19}H_{12}O_3$ requires C, 79.2; H, 4.0%) (Kostanecki,[44] m.p. 315-316°). It does not give any colour with ferric chloride, and is turned yellow with concentrated sulphuric acid, giving an almost colourless solution with a bright

green fluorescence, as described by Kostanecki[44] for 4'-hydroxy- -naphthaflavone.

The acetate, prepared by refluxing with acetic anhydride and pyridine, crystallised from acetic acid in long thin colourless needles, m.p. 214° (Found: C, 76.8; H, 4.2. $C_{21}H_{14}O_4$ requires C, 76.4; H, 4.2%) (Kostanecki,[44] m.p. 215°) It shows the same behaviour as the hydroxyflavone towards concentrated sulphuric acid.

4-Nitro-2-acetyl-1-naphthylbenzoate (VI):

4-Nitro-2-acetyl-1-naphthol[45] (2.5 g.), prepared by the nitration of 2-acetyl-1-naphthol with 40% nitric acid at room temperature, pyridine (15 c.c.) and benzoyl chloride (1.5 c.c.) were heated on the water bath for 30 minutes and the solution poured over ice and hydrochloric acid. The semi-sticky solid which separated was taken up in ether, washed with dilute hydrochloric acid, water and cold sodium carbonate solution respectively, the ether extract dried and the solvent removed. The semi-sticky solid crystallised from alcohol in short colourless plates (1.5 g.), m.p. 126-127° (Found: N, 4.0. $C_{19}H_{13}O_5N$ requires N, 4.2%).

2-Hydroxy-4-(p-nitro)benzoyloxy-4'-nitrodibenzoylmethane (XI):

Resacetophenone-di-(p-nitro) benzoate (X), prepared as in the last case, from resacetophenone and p-nitrobenzoyl chloride, was obtained as an amorphous solid from benzene, alcohol or acetic acid, m.p. 151-152° (Found: N, 5.9.

$C_{22}H_{14}O_9N_2$ requires N, 6.2%). 2-Hydroxy-4-(p-nitro) benzoyloxy-4'-nitrodibenzoylmethane (14 g.) obtained by the rearrangement of the ester (20 g.), as in the last case, crystallised from acetone in yellow plates, m.p. 225-226°. (Found: N, 6.0. $C_{22}H_{14}O_9N_2$ requires N, 6.2%).

This on treatment with glacial acetic acid cyclised, 7-p-nitrobenzoyloxy-4'-nitroflavone thus obtained crystallised from acetic acid in bunches of colourless needles, m.p. 294-295° (Found: N, 6.3. $C_{22}H_{12}O_8N_2$ requires N, 6.4%).

4'-Nitro-7-hydroxyflavone (XII, R = NO_2)

The diketone (2 g.) was dissolved in concentrated sulphuric acid (20 c.c.) left overnight, poured over chipped ice, the flavone thus obtained was collected, washed with cold alcohol and crystallised from acetic acid in light yellow, long thin plates (1.0 g.), m.p. 310-311°. (Found: N, 5.1. $C_{15}H_9O_5N$ requires N, 4.9%). It gives a reddish brown colour with ferric chloride.

7:4'-Dihydroxyflavone (XII, R = OH):

7-Hydroxy-4'-aminoflavone (XII, R = NH_2), obtained by reduction of the nitro flavone (0.5 g.) with iron and acetic acid, as in the last case, crystallised from

dilute alcohol in bunches of light yellow curved needles (0.3 g.), m.p. 338-340°, after darkening at 310° (Found: N, 5.4. $C_{15}H_{11}O_3N$ requires N, 5.5%). Its alcoholic solution exhibits a blue fluorescence, and it dissolves in concentrated sulphuric acid, giving an almost colourless solution with a strong blue fluorescence.

7:4'-Dihydroxyflavone (XII, R = OH), obtained by diazotisation and hydrolysis of the amine (0.35 g.) with 30% boiling sulphuric acid, crystallised from alcohol in bunches of light yellow needles (0.2 g.), m.p. 315° (Kostanecki and Osius,[46] m.p. 315°) (Found: C, 70.7; H, 4.1. $C_{15}H_{10}O_4$ requires C, 70.9; H, 3.9%). It agrees with all its properties with those described for 7:4'-dihydroxyflavone by Kostanecki and Osius.[46]

The diacetate, obtained by refluxing with acetic anhydride and pyridine, crystallised from alcohol in colourless needles, m.p. 184° (Kostanecki and Osius,[46] m.p. 184°) Found: C, 67.4; H, 4.1. $C_{19}H_{14}O_6$ requires C, 67.4; H, 4.1%).

4'-Nitro-7-methoxyflavone (XIII, R = NO_2):

4'-Nitro-7-methoxyflavone, obtained by methylation of 4'-nitro-7-hydroxyflavone (1 g.) with alkali and dimethyl sulphate in the cold, crystallised from acetic

acid in light yellow needles (0.85 g.), m.p. 216-217° (Found: N, 5.0. $C_{16}H_{11}NO_5$ requires N, 4.7%).

4'-Hydroxy-7-methoxyflavone (Isopratol)(XIII, R = OH):

The amine (XIII, R = NH_2), obtained by reduction of the nitroflavone (0.7 g.) with acetic acid and iron powder, crystallised from dilute alcohol in thin light yellow needles (0.5 g.), m.p. 201-202° (Found: N, 5.5. $C_{16}H_{13}O_3N$ requires N, 5.3%). Its light yellow solution in alcohol exhibits a bluish fluorescence, and it dissolves in concentrated sulphuric acid giving an almost colourless solution with a blue fluorescence.

The amine (0.5 g.) dissolved in water (25 c.c.) containing hydrochloric acid, was diazotised and hydrolysed by adding to 30% boiling sulphuric acid in the usual manner. It crystallised from alcohol in light yellow needles (0.37 g.), m.p. 260°, not depressed by admixture with a sample which had been prepared by Mahal and Venkataraman[9] (Found: C, 71.8; H, 4.4. $C_{16}H_{12}O_4$ requires C, 71.6; H, 4.5%). The m.p. of the substance in Mahal and Venkataraman's paper[9] should read as 260°. The alcoholic solution gives brown colour with ferric chloride, and its light yellow solution in concentrated sulphuric acid exhibits a blue fluorescence. On

demethylation with hydriodic acid in acetic anhydride it gave 7:4'-dihydroxyflavone.

7:4'-Dimethoxyflavone, obtained by methylating with dimethyl sulphate in alkaline solution in the cold crystallised from alcohol in long thin colourless needles, m.p. 149-150° (Kostanecki and Osius,[46] m.p. 149°) (Found: C, 72.5; H, 5.2. $C_{17}H_{14}O_4$ requires C, 72.3; H, 4.9%).

7-Methoxy-4'-acetoxyflavone, obtained by refluxing with acetic anhydride and pyridine, crystallised from alcohol in colourless needles, m.p. 155° (Found: C, 69.8; H, 4.6. $C_{18}H_{14}O_5$ requires C, 69.7; H, 4.5%).

Tri-O-(p-nitro)-benzoyl phloracetophenone (XIV):

Phloracetophenone (3.4 g.) was dissolved in pyridine (40 c.c.) and p-nitrobenzoyl chloride (3 mole, 11.5 g.) was added in small quantities, with good shaking so that the temperature did not rise above 50°; it was then left overnight, when a yellow mass separated, which was poured on to crushed ice and hydrochloric acid. The product separated as a white amorphous solid from benzene (6 g.), m.p. 195-197° (Found: N, 6.9. $C_{29}H_{17}O_{13}N_3$ requires N, 6.8%).

3-p-Nitrobenzoyl-4'-nitro-5:7-dihydroxyflavone (XV):

The ester, on rearrangement with potassium carbonate (6 g.) and toluene, gave a cream coloured compound (4.5 g.) m.p. 272-273°, which was very insoluble in organic solvents and could not be crystallised. It was insoluble in aqueous alkali in the cold. On warming with 2% sodium hydroxide or by treatment with concentrated sulphuric acid in the cold, it gave 3-(p-nitro)benzoyl-4'-nitro-5:7-dihydroxyflavone, which crystallised from alcohol in light yellow needles, m.p. 279° (Found: N, 6.1. $C_{22}H_{12}O_9N_2$ requires N, 6.25%). Its alcoholic solution gives a violet colour with ferric chloride.

The 3-benzoyl group could not be removed; when treated with hydriodic acid in acetic anhydride, it remained unaffected; and when treated with 10%, alcoholic or 10% aqueous alkali, and acidified, an orange compound which did not melt was obtained.

2-p-Nitrobenzoyl-4:6-dimethylphloracetophenone (XVII):

Phloracetophenone-4:6-dimethyl ether was prepared by methylation of phloracetophenone in acetone solution with dimethyl sulphate (2 moles) in presence of anhydrous potassium carbonate. Phloracetophenone dimethyl ether

(2.5 g.), p-nitrobenzoyl chloride (2.5 g.) and pyridine (20 c.c.) were heated on the water bath for half an hour and the product worked up as usual. The ester crystallised from alcohol in colourless needles (3 g.), m.p. 152-153° (Found: N, 4.3. $C_{17}H_{15}O_7N$ requires N, 4.1%).

2-Hydroxy-4:6-dimethoxy-4'-nitrodibenzoylmethane (XVIII):

The ester (2 g.) was dissolved in benzene or toluene (30 c.c.), sodamide (2 g.) added, and refluxed for two hours. The deep red compound that separated was filtered, washed with benzene, and acidified with dilute acetic acid, the diketone collected and crystallised from acetic acid (40 c.c.) in bunches of small thin yellow needles (0.4 g.), m.p. 220-222° (Found: N, 4.2. $C_{17}H_{15}O_7N$ requires N, 4.1%).

4'-Nitro-5:7-dimethoxyflavone (XIX):

The flavone, obtained by treating the diketone (0.6 g.) with concentrated sulphuric acid in the cold crystallised from acetic acid in light yellow, long thin plates (0.4 g.), m.p. 262° (Found: N, 4.3. $C_{17}H_{13}O_6N$ requires N, 4.3%). Crystallised again from acetic acid, the first fraction had m.p. 235°, but on dilution the filtrate gave a light yellow crystalline precipitate, m.p. 262°. Both these

dimorphic forms on reduction gave the same amine.

4'-Hydroxy-5:7-dimethoxyflavone (XXI):

The amine (XX), obtained by the reduction of the nitroflavone (0.5 g.) with acetic acid and iron, crystallised from alcohol in shining yellow needles (0.30 g.), m.p. 212°. Its alcoholic solution exhibits a blue fluorescence (Found: N, 4.5. $C_{17}H_{17}O_4N$ requires N, 4.7%).

4'-Hydroxy-5:7-dimethoxyflavone, obtained by diazotisation and hydrolysis of the amine (0.3 g.) with boiling 30% sulphuric acid, crystallised from alcohol in long, light yellow needles (0.2 g.), m.p. 294-295° (Mahal and Venkataraman,[19] m.p. 298°)(Found: C, 68.2; H, 4.8. $C_{17}H_{14}O_5$ requires C, 68.4; H, 4.7%). Its alcoholic solution exhibits a very weak blue fluorescence.

The acetate, prepared by boiling with acetic anhydride and pyridine, crystallised from alcohol in colourless needles, m.p. 220° (Mahal and Venkataraman,[19] 220°) (Found: C, 67.4; H, 4.7. $C_{19}H_{16}O_6$ requires C, 67.1; H, 4.7%).

4:5-Dihydroxy-7-methoxyflavone (Genkwanin)(XXII):

The above methyl ether (0.2 g.), aluminium chloride (0.4 g.) and nitrobenzene (4 c.c.) were heated on the

water-bath for one hour, ice and hydrochloric acid added, and nitrobenzene steam-distilled; the yellow residue crystallised from alcohol in bright yellow needles (0.13 g. m.p. 284-285°, not depressed when admixed with a genuine sample of puddumetin (Tseng,[19] m.p. 285°; Mahal and Venkataraman,[19] 285-286°)(Found: C, 67.4; H, 4.2. $C_{16}H_{12}O_5$ requires C, 67.5; H, 4.2%). It gives a brownish violet colour with ferric chloride.

The diacetate obtained by refluxing with acetic anhydride and pyridine crystallised from alcohol in long thin colourless needles, m.p. 197-198° (Tseng[19] m.p. 196°; Mahal and Venkataraman,[19] 197-198°)(Found: C, 65.2; H, 4.3. $C_{20}H_{16}O_7$ requires C, 65.2; H, 4.3%).

2-Hydroxy-4-methoxyphenyl 4-~~4-Methoxy-2,4-di~~hydroxystyryl ketone (XXIII).

The 4-methyl ether of resacetophenone was prepared by methylation of resacetophenone in acetone solution with dimethyl sulphate (1 mole) in presence of anhydrous potassium carbonate. To a solution of resacetophenone monomethyl ether (~~0.55~~ 1.1 g.) in alcohol (~~5~~ 10 c.c.) and potassium hydroxide (~~10~~ 20 c.c.; ~~50~~%), ~~0.45~~ 0.9 g. of p.hydroxybenzaldehyde was added, ~~and~~ the mixture refluxed on the water bath for one hour, and left overnight. The deep

red solution was poured into crushed ice and acidified, the yellow precipitate that separated was filtered and crystallised from aqueous alcohol in orange yellow needles (0.7 g.), m.p. 162-163° (Found: C, 71.3; H, 5.2. $C_{16}H_{14}O_4$ requires C, 71.1; H, 5.1%).

7-methoxy 3:4'-Dihydroxyflavone (II).

To a cooled solution of the chalkone (I) (0.5 g.) in aqueous sodium hydroxide (25 c.c.; 2%), hydrogen peroxide (1.3 c.c.; 30%) was added, and the solution left in the refrigerator overnight. The deep yellowish orange solution was acidified with acetic acid, the yellow precipitate filtered, it crystallised from alcohol in yellow spindle shaped rods, m.p. 262-263° (Found: C, 67.9; H, 4.4. $C_{16}H_{12}O_5$ requires C, 67.6; H, 4.2%). The substance gives a dark brownish colour with ferric chloride, and a yellow solution, with a bright green fluorescence in concentrated sulphuric acid. The

diacetate, prepared by heating with acetic anhydride and pyridine, crystallised from alcohol in long, flat, colourless plates, m.p. 203-204° (Found: C, 65.6; H, 4.6. $C_{20}H_{16}O_7$ requires C, 65.2; H, 4.3%).]

2-Hydroxy-4:6:2':4'-tetramethoxystyryl ketone (XXVIII):

β-Resorcylic aldehyde was prepared by passing dry hydrogen chloride through a solution of resorcinol in ether, containing zinc cyanide. Its dimethyl ether was obtained by methylation with excess of dimethyl sulphate in acetone solution, in presence of anhydrous potassium carbonate. Phloracetophenone dimethyl ether (0.65 g.), prepared as given before, was dissolved in alcohol (5 c.c.) and 50% sodium hydroxide (1 c.c.), β-resorcyl aldehyde (0.55 g.) added. The mixture was left at room temperature for 24 hours and shaken occasionally. The deep red solution was poured over ice, acidified, the yellow product that separated was filtered and crystallised from alcohol in shining yellow needles, (0.75 g.), m.p. 152° (Kostanecki et al[41] m.p. 152°; Mitter and Guha,[42] m.p. 124° (Found: C, 66.4; H, 5.6. $C_{19}H_{20}O_6$ requires C, 66.3; H, 5.8%). It gives a reddish brown colour with ferric chloride.

5:7:2':4'-Tetramethoxyflavone (XXIX):

The phenyl styryl ketone (XXVIII) (1.0 g.), amyl alcohol (20 c.c.) and selenium dioxide (1.0 g.) ~~was~~ were refluxed in an oil bath with occasional shaking at 140° for 18 hours, till there was no further diminution of

ferric chloride colour. The reduced selenium metal was filtered off, the filtrate steam-distilled, and the yellow sticky residue taken up in benzene. The benzene solution was extracted with 2% sodium hydroxide solution containing 50% alcohol, until no more was extracted. The aqueous alcoholic alkaline extract on acidification, and crystallisation of the product thus separated, gave the unreacted phenyl styryl ketone. The benzene layer was dried, the solvent removed and the residue crystallised from alcohol in small yellow needles (0.15 g.), m.p. 174° (Found: C, 66.9; H, 5.4; OCH_3, 36.0. $C_{19}H_{18}O_6$ requires, C, 66.7; H, 5.4; OCH_3, 34.4%). Its light orange solution in concentrated sulphuric acid exhibits a weak green flourescence.

5-Hydroxy-7:2':4'-trimethoxyflavone ~~(XXVII)~~:

A soln of the tetramethoxyflavone (XXVIII) (0.25 g.) ~~was dissolved~~ in nitrobenzene (2 ~~c.c.~~ ml.) was heated with aluminium chloride (0.3 g.) ~~added, heated~~ on the water-bath for one hour, acidified with hydrochloric acid, and nitrobenzene steam-distilled. The green ~~coloured~~ residue was filtered and treated with 2% aqueous sodium hydroxide, when a ~~little~~ minor part of the product dissolved; the filtrate on acidification gave a ~~small~~ minute quantity of a yellow ~~product~~ substance which was ~~too little to be worked up~~ not identified. The insoluble residue (0.13 g.) crystallised from ~~methyl and ethyl alcohol~~ or methanol in ~~yellow r~~

(Gupta & Seshadri, m.p. 163-164°)

yellow rhombohedral plates, m.p. 163° (Found: C, 66.0; H, 5.1 . $C_{18}H_{16}O_6$ requires C, 65.8; H, 4.9%). The substance It gives a reddish brown colour with ferric chloride, and ~~is not soluble in aqueous sodium hydroxide, but~~ dissolves in alcoholic sodium hydroxide ~~giving a yellow solution.~~ The

~~It's~~ acetate, ~~obtained by treatment with acetic anhydride and pyridine,~~ crystallised from alcohol in long thin colourless needles, m.p. 164-5°, ~~mixed m.p. with (XXVII) 140-145°~~ (Found: C, 64.7; H, 4.9 . $C_{20}H_{18}O_7$ requires C, 64.9; H, 4.8%).

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Part III

Coupling behaviour of 2-benzoylacetyl-1-naphthol.

The members of the Naphtol AS series derived from 2-hydroxy-3-naphthoic acid and similar o-hydroxycarboxylic acids yield orange, red and deeper colours. The attachment of an arylazo group to a carbon atom in an aliphatic group being one method for preparing yellow dyes, the I.G. in 1921 introduced Naphtol AS-G, which is bisacetoacet-o-tolidide, as a "naphthol" for the production of yellow shades; coupled on the fibre with diazotised chloranilines lemon-yellow shades could be obtained. The poor substantivity and the moderate light fastness of the Naphtol AS-G shades then led to the introduction of Naphtol AS-LG, L_3G and L_4G, the constitution of which has been elucidated by Desai and Mehta.[1] The first two are arylides of terephthaloyl diacetic acid and the last is 2-acetoacetamido-6-ethoxybenzthiazole. With specified diazonium salts the bright yellow shades from Naphtol AS-L_4G possess very high light fastness. It is to be noted, however, that on

account of its adequacy for general purposes Naphtol AS-G continues to be widely used for dyeing yellow azoic shades.

The present work is an investigation of the utility, as azoic coupling components, of diketones, which are intermediates in the synthesis of flavones, prepared by the action of sodamide,[2] potassium carbonate[3] or sodium ethoxide[4] on o-benzoyloxyaryl methyl ketones. A substance such as 2-benzoylacetyl-1-naphthol (I) has two coupling positions, and the comparative reactivity of these sites for diazonium couplings is of interest. Further, the introduction of a 1:3-diketone group in a dye or a 2-hydroxy-3-naphthanilide type of coupling component might offer a useful method for modifying shades.

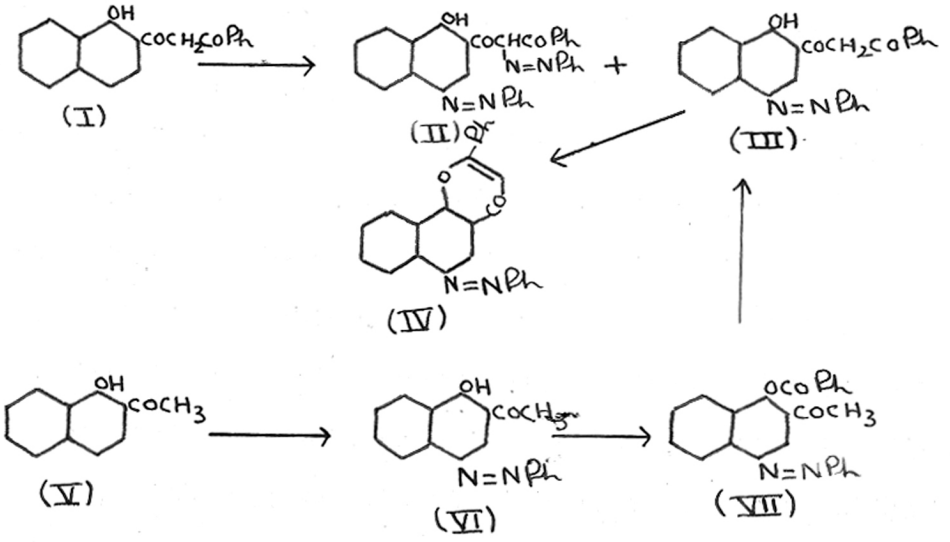
2-Benzoylacetyl-1-naphthol (I) was obtained by the action of anhydrous potassium carbonate in toluene on 2-acetyl-1-naphthyl benzoate in very good yield.[2] The diketone (I) gave weak dyeings when used as a "naphthol" and coupled with diazotised Fast Red Base B (5-nitro-o-anisidine) and Scarlet Base GG (2:5-dichloroaniline); the shades lacked fastness to soaping and

light. Treatment of the dyeings with potassium dichromate and copper sulphate did not improve the fastness.

The diketone (I), when coupled in substance with one or more moles of diazotised aniline in alcoholic sodium hydroxide solution, yielded the disazo dye (II). Coupling in alcoholic sodium carbonate or pyridine solution with diazotised aniline (1 mole) yielded a mixture of the disazo dye (II) and a monoazo dye (III), which were separated by careful fractional crystallisation from acetic acid, the latter being less soluble. It was observed that boiling the monoazo dye (III) with acetic acid for a long time during crystallisation yielded a third product, which was ultimately found to be the corresponding flavone (IV). The monoazo dye (III), when dyed as a "naphthol", and developed with diazotised Fast Red Base B, gave brown shades which bled considerably during soaping.

The disazo dye was unaffected by treatment with concentrated sulphuric acid in the cold, while the monoazo dye, either by treatment with concentrated sulphuric acid in the cold or by refluxing with glacial acetic

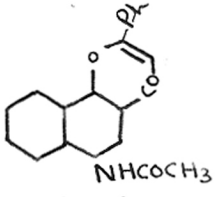
acid gave the flavone (IV) by cyclisation. In view of the ring closure taking place only in the case of the monoazo dye, it is evident that the coupling must have taken place in the 4-position. However, to confirm the constitution of the monoazo dye as (III), it was also prepared by an unambiguous method. 2-Acetyl-1-naphthol (V) was coupled with diazotised aniline to obtain 4-benzeneazo-2-acetyl-1-naphthol (VI). Condensation of (VI) with ethyl benzoate in presence of sodium, sodium ethoxide or sodamide was not successful. The benzoate (VII), prepared under the conditions specified, readily underwent rearrangement with



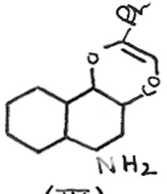
potassium carbonate in toluene, and gave 4-benzeneazo-

2-benzoylacetyl-1-naphthol (III), identical with the monoazo dye obtained by coupling (I) with diazotised aniline.

The benzeneazonaphthaflavone (IV) on reduction with acetic acid and zinc dust, gave the acetamido derivative (VIII). Even when the reduction was carried out in a large volume of alcohol with the addition of 1-2 moles



(VIII)



(IX)

of acetic acid, the acetamido derivative (VIII), and not the amine (IX), was obtained. Reduction with iron and hydrochloric acid in alcoholic solution gave amorphous red products. The deacetylation of (VIII) proved difficult since it remained unaffected when treated either with 30% hydrochloric acid or 10% sodium hydroxide solution. The aminoflavone (IX) could however be very readily obtained by reduction of (IV) by hydrogen

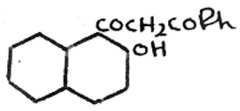
under pressure in presence of Raney nickel. When the diketone (III) was reduced under these conditions, the corresponding amine could not be isolated since it was very unstable. However, when (III) was reduced with sodium hydrosulphite in alcoholic alkali, the amino-flavone (IX) was obtained, reduction of the azo group and cyclisation of the diketone taking place simultaneously.

When the diketone (I) was coupled with diazotised 2:5-dichloroaniline (1 mole) in pyridine or alcoholic sodium hydroxide solution, it gave the disazodye (II; $C_6H_3Cl_2$ instead of Ph). However, coupling in alcoholic sodium carbonate solution with diazotised 2:5-dichloro-aniline (1 mole) gave the disazo dye (II; $C_6H_3Cl_2$ instead of Ph), together with about 5% of the monoazo dye (III; $C_6H_3Cl_2$ instead of Ph), which was isolated as the flavone (IV; $C_6H_3Cl_2$ instead of Ph). The same monoazo dye was also obtained by the rearrangement of (VII; $C_6H_3Cl_2$ instead of Ph) with potassium carbonate in toluene.

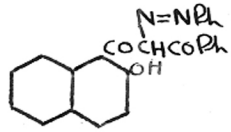
In order to prepare a diketone which does not have a nuclear site for coupling as in (I), ω-benzoyl-1-

acetyl-2-naphthol (X) was prepared by the rearrangement of 1-acetyl-2-naphthyl benzoate with sodium ethoxide.[4] Bhalla et al,[5] who carried out the transformation of 1-acetyl-2-naphthyl benzoate with sodamide in ether, obtained, instead of the diketone (X), a semi-sticky solid of undetermined constitution, which on treatment with cold concentrated sulphuric acid gave β-naphthaflavone. The diketone (X), when coupled in sodium hydroxide solution with diazotised aniline, gave a red substance, which appeared to be a mixture of the desired azo dye (XI) and 1-benzeneazo-2-naphthol. 1-Acetyl-2-naphthol undergoes a similar displacement on treatment with diazonium salts.[6] Application of (X) in azoic dyeing by the normal process of impregnation from an aqueous alkaline solution was therefore not possible. The diketone (X) coupled readily in alcohol-sodium acetate solution and gave ω-benzoyl-ω-benzeneazo-1-acetyl-2-naphthol (XI); but on account of the influence of alcohol in lowering the substantivity of the diketone towards cellulose, a very weak yellow shade, loose to soaping was obtained when (X) was

applied to cotton yarn from an alcoholic sodium



(X)



(XI)

acetate solution and developed with diazotised 2:5-dichloroaniline.

EXPERIMENTAL

2-Benzoyl-1-acetyl-1-naphthol (I).

2-Acetyl-1-naphthyl benzoate (15 g.), toluene (75 c.c.) and freshly ignited potassium carbonate (45 g.) were refluxed under stirring for 8 hours. The deep orange potassium salt was filtered and treated with dilute acetic acid. The diketone (12 g.) crystallised from acetone in bright orange needles, m.p. 147° (Mahal and Venkataraman,[2] 147°).

Coupling of the diketone (I) with diazotised aniline:

The diketone (1.5 g.) was pasted with 10% sodium hydroxide solution (10 c.c.) and dissolved in alcohol (50 c.c.). The solution was diluted with water (10-15 c.c.) and after adding sodium acetate (4 g.), cooled to 0° and coupled with aniline (1.5 g., 3 mols.) in hydrochloric acid (4.5 c.c.) diazotised with sodium nitrite (1.2 g.). The bright red dye which separated (2.1 g.), crystallised from acetic acid in thin, elongated plates, m.p. 168-70° (Found: N, 11.2. $C_{31}H_{22}O_3N_4$ requires N, 11.2%). A little more of the

disazo dye was obtained from the filtrate by acidification. The substance also crystallises from the same solvent in a second form with m.p. 204-205°. It gives a brown colour with ferric chloride and a deep cherry red colour with concentrated sulphuric acid. The dye was recovered unchanged from its solution in concentrated sulphuric acid, no cyclization to a flavone taking place under the usual conditions.

When the diketone was coupled under similar conditions using one mole of diazotised aniline, the dye that separated out proved to be (II). The filtrate on acidification gave a sticky substance, which dissolved in concentrated sulphuric acid with a bright green fluorescence, indicating the presence of unreacted diketone.

When the diketone (I) (0.5 g.) in 10% sodium carbonate solution (10 c.c.), alcohol (100 c.c.) and sodium acetate (1 g.), was coupled with diazotised aniline (1 mole) and stirred for one hour, a deep red solution was obtained which was acidified with dilute hydrochloric acid and the orange red dye collected (0.6 g.). The dye was taken up in acetic acid (20 c.c.), heated

to about 110° and the resulting mixture was filtered immediately. The residue (0.2 g.) crystallised from alcohol-acetic acid mixture in thin short orange rods, m.p. 201-202° (Found: N, 7.3. $C_{25}H_{18}O_3N_2$ requires N, 7.2%). The monoazo dye gives a brown colour with ferric chloride and a cherry red colour with concentrated sulphuric acid. From the acetic acid mother-liquors, the disazo dye (II), m.p. 168-170°, was recovered.

The diketone (I) (0.5 g.) was then dissolved in pyridine (20 c.c.) and coupled with one mole of diazotised aniline. The dark red solution, on dilution and acidification with hydrochloric acid, gave an orange red dye, which could be separated into mono- (III) and disazo dye (II) as in the previous cases; about 0.12 g. of the pure monoazo and 0.1 g. of the disazo dye were obtained.

4-Benzeneazo-2-acetyl-1-naphthol (VI):

The bright red dye, prepared in the usual manner from acetonaphthol (V) and diazobenzene chloride, crystallised from acetic acid or chlorobenzene in reddish

orange needles, m.p. 143° (Found: N, 9.8. $C_{18}H_{14}O_2N_2$ requires N, 9.7%). It gives a deep brown colour with ferric chloride and a violet colour with concentrated sulphuric acid.

4-Benzeneazo-2-acetyl-1-naphthyl benzoate (VII):

The dye (VI) (2 g.), pyridine (10 c.c.) and benzoyl chloride (1.5 g.) were refluxed for six hours in the oil bath at 140°. The solution was poured over crushed ice and hydrochloric acid. The dark red sticky product was taken up in ether, washed with ice-cold dilute hydrochloric acid, water and finally with ice cold sodium carbonate solution. Removal of the solvent and crystallisation from alcohol gave orange prismatic needles (1.7 g.), m.p. 153° (Found: N, 7.1, $C_{25}H_{18}O_3N_2$ requires N, 7.2%).

4-Benzeneazo-2-benzoylacetyl-1-naphthol (III):

A mixture of the benzoate (VII) (1 g.), toluene (20 c.c.) and potassium carbonate (4 g.) was refluxed for 8 hours. The dark red potassium salt was filtered, washed with benzene and decomposed with dilute acetic acid. The brownish red diketone (0.65 g.) crystallised

from acetic acid or alcohol-acetic acid in short orange rods, m.p. 201-202° (Found: N, 7.4. $C_{25}H_{18}O_3N_2$ requires N, 7.2%). A mixed m.p. point with the monoazo dye (III), obtained by direct coupling of the diketone, showed no depression.

6-Benzeneazo-7:8-benzeflavone (IV):

4-Benzeneazo-2-benzoylacetyl-1-naphthol (III) (0.2 g.) was refluxed with glacial acetic acid for 30 minutes, and cooled. The flavone (IV) crystallised in shining yellow needles, m.p. 271° (Found: N, 7.2. $C_{25}H_{16}O_2N_2$ requires N, 7.4%). The substance does not give a ferric chloride colour and is insoluble in aqueous or alcoholic alkali.

Treatment of the dye (III) with cold concentrated sulphuric acid also yielded the same flavone (IV).

6-Acetamido-7:8-benzoflavone (VIII) was obtained by reduction of the flavone (IV) with zinc dust in acetic acid solution. It crystallised from acetic acid in small lustrous, yellow needles, which melted with darkening in colour at 306-307° (Found: N, 4.3. $C_{21}H_{15}O_3N$ requires N, 4.2%).

6-Amino-7:8-benzoflavone (IX):

(i) The benzeneazoflavone (IV) (0.5 g.) was suspended in alcohol (30 c.c.), Raney nickel catalyst added and shaken with hydrogen under pressure (40 lbs.) for two hours when the flavone slowly went into solution. The catalyst was filtered off and the yellow filtrate diluted with water, the product which separated (0.25 g.) crystallised from alcohol in long, shining yellow needles, m.p. 220° (Found: N, 4.6. $C_{19}H_{13}O_2N$ requires N, 4.8%). It dissolves in concentrated sulphuric acid giving a colourless solution with a bright bluish violet fluorescence.

(ii) The dye (III) (0.1 g.), dissolved in alcohol (20 c.c.) and 10% sodium hydroxide solution (1 c.c.) was warmed to about 70°, and reduced by sodium hydrosulphite till the colour of the solution changed from deep red to yellowish red. After heating for a few minutes, the solution was acidified with dilute acetic acid, concentrated and cooled. The aminoflavone (X) crystallised from alcohol in long, shining yellow needles.

Coupling of the diketone (I) with diazotised 2:5-dichloroaniline:

The diketone (I) (0.5 g.), dissolved in pyridine (20 c.c.), was coupled in the usual manner with one molϕ of diazotised 2:5-dichloroaniline. The dye precipitated by dilution and acidification with hydrochloric acid, crystallised from acetic acid in fluffy aggregates of red needles (0.2 g.) m.p. 215-16° (Found: N, 8.9. $C_{31}H_{18}Cl_4O_3N_4$ requires N, 8.9%). The disazo dye (II; $C_6H_3Cl_2$ instead of Ph) gives a light brown colour with ferric chloride. The filtrate, after separation of the disazo dye, on dilution and crystallisation, gave the unreacted diketone (I) (0.2 g.).

The diketone (I)(0.5 g.) dissolved in alcoholic sodium carbonate solution was then coupled with one molϕ of diazotised 2:5-dichloroaniline. The dye was boiled in acetic acid (50 c.c.) and a small quantity of a yellowish orange solid which separated was immediately filtered ~~off~~. It crystallised from a large volume of acetic acid, in thin small yellow rods (30 mgm.), m.p. 295-96° (Found: N, 6.4. $C_{25}H_{14}Cl_2O_2N_2$ requires N, 6.2%). It does not give any ferric chloride colour and is not

soluble in aqueous or alcoholic alkali. Analysis and its properties indicated that it was the flavone (IV; $C_6H_3Cl_2$ instead of Ph). From the acetic acid mother liquor, the disazo dye (II; $C_6H_3Cl_2$ instead of Ph) (0.2 g.) was obtained.

4-(2':5'-Dichloro)-benzeneazo-2-acetyl-1-naphthol (VI; $C_6H_3Cl_2$ instead of Ph):

Acetonaphthol was coupled with diazotised 2:5-dichloroaniline, and the red dye crystallised from chlorobenzene in long needles, m.p. 229-30° (Found: N, 8.1. $C_{18}H_{12}Cl_2O_2N_2$ requires N, 7.8%).

4-(2':5'-Dichloro)-benzeneazo-2-acetyl-1-naphthyl benzoate (VII; $C_6H_3Cl_2$ instead of Ph):

The dye (VI, $C_6H_3Cl_2$ instead of Ph) was benzoylated by refluxing with benzoyl chloride in pyridine. The benzoate crystallised from alcohol in yellowish orange needles, m.p. 184-85° (Found: N, 6.1. $C_{25}H_{16}Cl_2O_3N_2$ requires N, 6.0%).

6-(2':5'-Dichloro)-benzeneazo-7:8-benzoflavone (IV; $C_6H_3Cl_2$ instead of Ph):

The benzoate on treatment with potassium carbonate in toluene rearranged to the yellowish red diketone

(III; $C_6H_3Cl_2$ instead of Ph), m.p. 238-240°, which was converted into the corresponding flavone (IV; $C_6H_3Cl_2$ instead of Ph) by treatment with boiling glacial acetic acid, when it crystallised in thin small yellow rods, m.p. 295-96° (Found: N, 6.3. $C_{25}H_{14}Cl_2O_2N_2$ requires N, 6.2%), identical with the corresponding flavone, obtained by direct coupling of the diketone with diazotised 2:5-dichloroaniline, followed by treatment with acetic acid.

ω-Benzeneazo-ω-benzoyl-1-acetyl-2-naphthol (XI):

The diketone (X) (0.3 g.), prepared by the rearrangement of 1-acetyl-2-naphthyl benzoate with sodium ethoxide,[4] was dissolved in alcohol (20 c.c.) and sodium acetate (1 g.) added, when the solution became greenish in colour. The solution was cooled and coupled with one mol. of diazotised aniline. The orange dye was filtered (0.3 g.), which crystallised from alcohol in small orange plates, m.p. 162° (Found: N, 7.2. $C_{25}H_{18}O_3N_2$ requires N, 7.2%). It gives a deep brown colour with ferric chloride.

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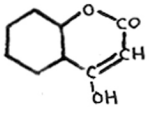
2. Mahal and Venkataraman, J. Chem. Soc., 1934, 1767; Curr. Sci., 1933, 2, 214.
3. Baker, J. Chem. Soc., 1933, 1381.
4. Ullal, Shah and Wheeler, ibid., 1940, 1499.
5. Bhalla, Mahal and Venkataraman, ibid., 1935, 870.
6. Fries, Ber., 1921, 54, 712.

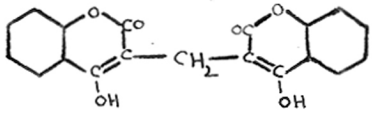
Part IV

A new synthesis of 4-hydroxycoumarins.

Roderick[1] and Schofield[2] noticed a hemorrhagic disease in cattle and showed that it was due to badly cured hay made from sweet clover. Campbell and Link[3] isolated this anticoagulant factor from spoiled sweet clover hay, and determined its structure to be 3:3'-methylene-bis-4-hydroxycoumarin (II) by alkaline degradation and cleavage with phenylhydrazine. The constitution has been confirmed by its synthesis from



(I)



(II)

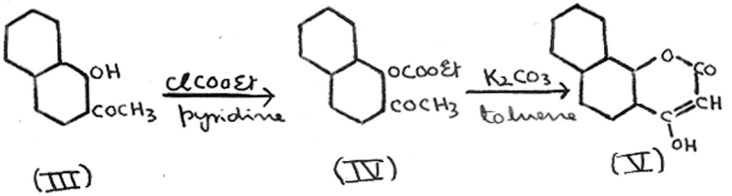
4-hydroxycoumarin (I) and formaldehyde.[4] In view of the anticoagulant properties of 3-substituted-4-hydroxycoumarins,[5] methods for the synthesis of 4-hydroxycoumarins (I) have assumed importance.

Three general methods for the synthesis of 4-hydroxycoumarins have so far been described:
(1): o-Acetoxybenzoyl chlorides are condensed with malonic ester, cyanacetic ester or acetoacetic ester in presence of sodium, when the corresponding 3-substituted-4-hydroxycoumarins are formed, which are then hydrolysed

to 4-hydroxycoumarins.[6] (2): Cyanacetic ester is condensed with phenols[7] according to the method of Hoesch, which is limited to the use of m-dihydric phenols. In some cases, the hydrolysis of the intermediate ketimine hydrochloride is difficult. (3): The cyclisation of the O-acetyl derivative of an ester of salicylic acid by means of sodium at high temperatures[8] which gives low yields of 4-hydroxycoumarins.

Earlier work carried out by one of us and others on the transformation of o-benzoyloxyacetophenone to dibenzoylmethanes by means of sodamide,[9] potassium carbonate[10] or sodium in toluene,[11] indicate that an application of this reaction to the O-carbethoxy derivatives of o-hydroxyacetophenones might lead to a new general method for the synthesis of 4-hydroxycoumarins. We have now examined the scope of this reaction by model experiments on the behaviour of the O-carbethoxy derivative (IV) of the readily available 2-acetyl-1-naphthol (III) towards sodamide,[9] anhydrous potassium carbonate,[10] metallic sodium and sodium ethoxide[11] in appropriate solvents. When the ester (IV) was treated with potassium carbonate in toluene, 4-hydroxynaphtho-

coumarin (V) was obtained in an optimum yield of 45%



(III) (IV) (V)

but the reaction did not proceed solely in the desired direction.

The preparation of the ester (IV), which proved difficult initially due to its instability resulting in hydrolysis to (III), had to be carried out under closely defined conditions. When ethyl chlorocarbonate was added to (III) in pyridine solution in the cold, an instantaneous reaction took place, and by working up the product immediately a quantitative yield of (IV) was obtained. Treatment of (IV) with potassium carbonate in toluene gave a mixture of products (A) and (B), which could be easily separated either by taking advantage of the insolubility of (A) and of the ready solubility of (B) in chloroform, or by extracting with sodium bicarbonate solution in which (A) alone was soluble. The product (A) when obtained in this manner was almost

pure, while (B) could only be purified by chromatographic adsorption or by crystallisation from acetic acid. Comparatively lower yields of the products (A) and (B) were obtained when the transformation was carried out with metallic sodium in toluene.

The product (A) crystallised from alcohol or dioxane in small, colourless needles, m.p. 279-80° (Decomp.). 4-Hydroxynaphthocoumarin (V) has been prepared by Anschutz[12] by the condensation of 1-hydroxy-2-naphthoyl chloride with sodiomalonic ester, followed by hydrolysis of the 3-carbethoxy-4-hydroxynaphthocoumarin. He has described this as greyish white crystals, m.p. 256-258°. On repeating Anschutz's work we obtained the intermediate 3-carbethoxy-derivative as yellow needles, m.p. 179° (Anschutz, m.p. 179°). This on hydrolysis gave 4-hydroxynaphthocoumarin as colourless needles, m.p. 279-80°, identical with (A) in all respects. A similar discrepancy in the melting point has been noticed in the case of 3:3'-methylene-bis-4-hydroxycoumarin (II), which was first synthesised by Anschutz, who gave the m.p. 260°, and later by Stahmann et al,[4] who gave the m.p. 288-89°; natural dicoumarin has m.p. 288-89°.

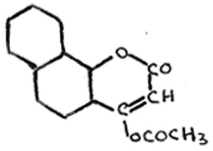
When the intramolecular condensation of the ester (IV) was carried out with sodamide in ether, substance (B) and acetonaphthol (III) were the only products isolated. In a few of the experiments while the product after the sodamide reaction was being worked up, it turned violet on exposure to air; and from the mixture a small quantity of (B), (III) and a violet compound (C) could be isolated by chromatography. The exact conditions for this transformation could however not be ascertained. The condensation of the ester with sodium methoxide in ether gave a 5% yield of product (B), the rest of the ester being hydrolysed to (III). When sodium ethoxide in alcohol was used, the ester merely underwent hydrolysis to (III).

While this work was in progress Boyd and Robertson[13] described a one-step synthesis of 4-hydroxycoumarins in excellent yields from o-hydroxyacetophenones by treatment with ethyl carbonate in presence of metallic sodium. By carrying out the same reaction on (III), a nearly quantitative yield of 4-hydroxynaphthocoumarin (V) could be obtained. For the preparation of 4-hydroxycoumarins, Boyd and Robertson's method is therefore superior to our method via the carbethoxy derivatives

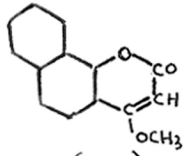
of o-hydroxyacetophenones.

4-Hydroxynaphthocoumarin (V) dissolves in sodium bicarbonate solution with effervescence, and on acidification the hydroxycoumarin is precipitated unchanged. It could be titrated with alkalis using phenolphthalein as indicator (Found: M.W. 2250. $C_{13}H_8O_3$ requires M.W. 212). The possibility of the opening of the ring during titration to form 1-hydroxy-2-naphthoyl acetic acid ($C_{13}H_{10}O_4$ requires M.W. 230) which again cyclises on acidification, cannot be ruled out. After boiling for 2 to 3 hours with 10% aqueous or alcoholic alkali, 4-hydroxynaphthocoumarin could be recovered unchanged by acidification. On fusion with caustic potash, it gave a quantitative yield of 1-hydroxy-2-naphthoic acid. It remained unaffected by treatment with cold concentrated sulphuric acid. When heated above its melting point, a mixture of products was obtained, from which 2-acetyl-1-naphthol (III) and an unidentified product (D), m.p. 306-307°, were isolated by chromatography. The hydroxycoumarin (V) gave an acetyl derivative (VI) by long boiling with acetic anhydride, and a methyl ether (VII) by treating its solution

in acetone with excess of diazomethane in ether. Coupled with diazotised p-nitraniline in aqueous alkaline solution or in alcohol in presence of sodium acetate, (V) gave a yellowish orange dye, 3-p-nitrobenzeneazo-4-

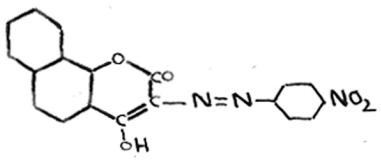


(VI)



(VII)

hydroxynaphthocoumarin (VIII). Huebner and Link[14] have shown that 4-hydroxycoumarin (I) couples with diazonium salts to give 3-azoderivatives. On treatment of a hot alcoholic solution of (V) with excess of formaldehyde 3:3'-methylene-bis-4-hydroxynaphthocoumarin (IX) was



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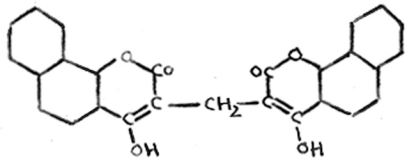
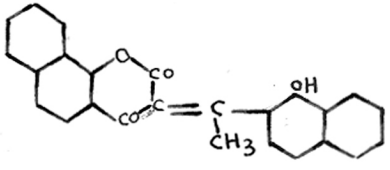


(IX)

obtained. 4-Hydroxynaphthocoumarin (V) could not be converted into product (B) by treatment with potassium carbonate in toluene.

The product (B) crystallised from acetone or acetic acid as greenish yellow, thin elongated plates, m.p. 244-45°. It was phenolic in character and gave a light olive colouration with ferric chloride. It gave a p-nitrobenzoate; and an acetate on treatment with either acetic anhydride and pyridine or ~~with~~ acetic acid in presence of hydrochloric acid. It did not form a dinitrophenylhydrazone under the usual conditions. Its yellowish orange alcoholic alkaline solution turned deep red on standing in the cold, and a deep violet compound was isolated by acidification, identical with the product (C) obtained earlier. Treatment with hot alcoholic alkali completely decomposed (B). Fusion of (B) with potassium hydroxide yielded 1-hydroxy-2-naphthoic acid, and a small quantity of a reddish-violet phenolic compound. A deep red dye was obtained by coupling (B) with diazotised aniline; and a yellow crystalline product (E), m.p. 345-50°, was obtained on treatment of product (B) with cold concentrated sulphuric acid. Attempts to convert (B) into (III) were unsuccessful. The analytical data for (B) and its derivatives correspond with the molecular formula $C_{25}H_{16}O_4$. A compound (X)

of the same molecular formula could be obtained by the condensation of 2-acetyl-1-naphthol, with 4-hydroxy-naphthocoumarin. The condensation of 2-acetyl-1-



(X)

naphthol and 4-dihydroxynaphthocoumarin has been tried under various conditions, such as by sodamide in ether, potassium carbonate in toluene, pyridine containing piperidine, but in every case only the original products were recovered unchanged. Further work to find out the constitution of this product is in progress.

EXPERIMENTAL

O-Carbethoxy-2-acetyl-1-naphthol (IV):

To a cooled solution of 2-acetyl-1-naphthol (10 g.) in pyridine (30 c.c.), ethyl chlorocarbonate (15 c.c.) was added drop by drop with shaking, when an instantaneous reaction took place. The reaction mixture was immediately stirred into crushed ice and hydrochloric acid. The precipitate crystallised from alcohol in thin colourless flakes (11 g.), m.p. 76° (Found: C, 70.1; H, 5.7. $C_{15}H_{14}O_4$ requires C, 69.8; H, 5.4%).

4-Hydroxynaphthocoumarin (V) and product (B):

(i): The compound (IV) (2 g.), toluene (20 c.c.) and freshly ignited potassium carbonate (6 g.) were refluxed under stirring for 12 hours. The potassium salt was filtered from the deep violet coloured toluene solution, which on treatment with norit for a long time gave some unconverted (IV). The greyish green potassium salt was decomposed with dilute acetic acid, filtered and treated thrice with hot chloroform, when a part went into solution. The residue (0.8 g.), which was 4-hydroxynaphthocoumarin (V), crystallised from alcohol or dioxane in small colourless needles, m.p. 279-80° (Found: C, 73.1;

H, 4.0. $C_{13}H_8O_3$ requires C, 73.5; H, 3.9).

The chloroform extract on concentration and chro graphy through a column of alumina gave product (B), crystallised from acetic acid in greenish yellow long plates (0.2 g.), m.p. 244-45° (Found: C, 78.5; H, 4.3. $C_{25}H_{16}O_4$ requires C, 78.9; H, 4.2%).

The separation of 4-hydroxynaphthocoumarin (V) a product (B) could also be very readily effected by mac ing the product, obtained after decomposing the potass salt with acetic acid, with sodium bicarbonate solutio when (V) could be obtained from the soluble part by ac dification, while (B) was obtained as the residue.

(ii): 3-Carbethoxy-4-hydroxynaphthocoumarin obta by treating 1-acetoxy-2-naphthoyl chloride in benzene sodio-malonic ester in benzene for 8 hours at room temperature and for two hours on the water-bath, cryst lised from alcohol in yellow needles, m.p. 179° (Ansch m.p. 179°). It gave a red colour with ferric chloride was soluble in aqueous sodium bicarbonate. 4-Hydroxy- naphthocoumarin (V) was obtained by hydrolysis of the 3-carbethoxy derivative by refluxing with excess of 1. potassium hydroxide solution for 12 hours, as colourle

needles from alcohol, m.p. 279-80° (Anschutz, greyish white needles, m.p. 256-58°), identical with the product obtained by the action of potassium carbonate on (IV).

(iii): 2-Acetyl-1-naphthol (III) (1.5 g.), ethyl carbonate (40 c.c.) and metallic sodium (2.5 g.) were heated on water bath for 30 minutes, excess of sodium destroyed by means of methyl alcohol, excess of ether added, and the sodium salt extracted with water. The aqueous solution was acidified, and the light cream coloured precipitate filtered (1.4 g.). It crystallised from alcohol in thin colourless needles, m.p. 279-80°, identical with 4-hydroxynaphthocoumarin (V).

4-Hydroxynaphthocoumarin (V) gives a light orange colour with ferric chloride. It is very sparingly soluble in chloroform, benzene or toluene. It dissolves in concentrated sulphuric acid with a brownish orange colour, having a light green fluorescence.

Decarboxylation of 4-hydroxynaphthocoumarin:

When (V) (0.2 g.) was heated at 285° for two minutes, it melted with the evolution of carbon dioxide.

The brownish red melt was taken up in chloroform, and the chloroform solution chromatographed through alumina, when it separated into two definite bands. The lesser absorbed yellow band on elution with chloroform gave a phenolic product, which crystallised from alcohol in yellow needles, m.p. 98°, and was identified by mixed m.p. to be 2-acetyl-1-naphthol (III). The column of alumina containing the second band on treatment with hot alcohol gave a non-phenolic product, which crystallised from alcohol in small yellow plates, m.p. 306-7° (with darkening in colour). Product (D) (Found: C 74·4; H, 3·9%). It was too little to be worked up further.

Fusion of (V) with potassium hydroxide:

Potassium hydroxide (2 g.) and water (0.5 c.c.) were heated in a nickel crucible till a clear solution was obtained, and (V) (0.5 g.) added. The substance began to go into solution at 240° and gave a clear yellow solution at 280°, at which temperature it was maintained for 15 minutes. On cooling, the yellow product was dissolved in water (20 c.c.) and carbon dioxide passed through the solution till it was no longer alkaline to phenolphthalein. A light brown shining crystalline

precipitate separated, which was filtered (0.4 g.) and proved to be a potassium salt. It was dissolved in the minimum quantity of alcohol and precipitated with dilute hydrochloric acid. Crystallised from alcohol, it had m.p. 190-91° (Found: C, 70.3; H, 4.4. $C_{11}H_8O_3$ requires C, 70.2; H, 4.2%). It was identified as 1-hydroxy-2-naphthoic acid. The filtrate after the separation of the potassium salt, on acidification and ether extraction ~~of the~~ yielded a small quantity of a phenolic, light brown crystalline substance, m.p. 89-93°; the alcoholic solution gave a green colour with ferric chloride.

4-Acetoxynaphthocoumarin (VI), obtained by refluxing (V) with acetic anhydride for 2 hours, crystallised from benzene in light yellow shining plates, m.p. 134-35° (Found: C, 70.4; H, 3.9; Acetyl 17.1. $C_{15}H_{10}O_4$ requires C, 70.8; H, 3.9; Acetyl 16.9%). It is insoluble in cold sodium bicarbonate solution, but can be readily hydrolysed by warming with alkalis, or even by hot water or alcohol to the parent 4-hydroxynaphthocoumarin.

4-Methoxynaphthocoumarin (VII), obtained by treating a solution of (V) (0.2 g.) in dry acetone (20 c.c.) with diazomethane in ether, crystallised from alcohol in thin colourless needles, m.p. 218° (Found: C, 74.4; H, 4.6. $C_{14}H_{10}O_3$ requires C, 74.3; O. 4.4%).

3-p-Nitrobenzeneazo-4-hydroxynaphthocoumarin(VIII):

A diazotised solution ~~from~~ of p-nitraniline (0.3 g.) was added to a solution of (V) (0.2 g.) in sodium hydroxide, and the mixture stirred for one hour, keeping the coupling bath alkaline throughout. The dye, obtained by acidifying the wine-red solution, crystallised from nitrobenzene in yellowish orange needles or from acetic acid in small red shining plates, m.p. 318° (Found: N, 11.5. $C_{19}H_{11}O_5N_3$ requires N, 11.6%). The same dye was also obtained when the coupling was done in alcohol in presence of sodium acetate.

3:3'-Methylene-bis-4-hydroxynaphthocoumarin (IX):

To a hot alcoholic solution of (V) (0.15 g.) in alcohol (4 c.c.), formaldehyde (40%; 1 c.c.) was added, and the mixture heated, when a white crystalline precipitate separated immediately. It was filtered while

hot (0.14 g) and crystallised from trichlorobenzene in fine thin needles ~~(0.14 g.)~~ melting with decomposition above 300° (Found: C, 73.7; H, 4.0. $C_{27}H_{16}O_6$ requires C, 74.3; H, 3.7%). The substance is insoluble in benzene, toluene, dioxane and chloroform.

Transformation of (IV) with sodamide:

The ester (IV) (2 g.), ether (10 c.c.) and powdered sodamide (2 g.) were shaken at room temperature for 8 hours, and allowed to stand overnight. The yellowish orange coloured solid that separated was filtered and stirred into acetic acid, and the dirty green sticky product thus obtained solidified after keeping in the refrigerator. It was taken up in hot acetone (Norit) and cooled, and the crystalline product that separated was recrystallised from acetic acid. The greenish yellow plates (0.4 g.), m.p. 244-45° were identical with Product (B). The acetone ~~filtrate~~ mother liquors on evaporation gave 2-acetyl-1-naphthol (III).

Product (B) is very sparingly soluble in alcohol. It gives light olive colour with ferric chloride. It is insoluble in cold sodium carbonate solution and sparingly soluble in cold sodium hydroxide solution,

but very soluble in alcoholic alkali giving a reddish yellow solution. It dissolves in concentrated sulphuric acid giving a deep red solution, which when poured over chipped ice gave a bright yellow product (E) crystallising from alcohol in yellow needles, m.p. 345-50° (with decomp.)(Found: C, 57.1; H, 5.7%). The substance (E) is soluble in warm sodium carbonate solution and cold caustic soda solution and gives an olive green colouration with ferric chloride. Product (B) on fusion with potassium hydroxide as in the case of (V), gave 1-hydroxy-2-naphthoic acid and a deep violet product which is being examined.

The acetate of product (B) obtained by refluxing with acetic anhydride and a drop of pyridine, crystallised from acetic acid in small light yellow plates, m.p. 234-35° (Found: C, 76.2; H, 4.6; Acetyl, 11.0. $C_{27}H_{18}O_5$ requires C, 76.5; H, 4.3; Acetyl, 10.0%).

The p-nitrobenzoate of (B), prepared by treatment with p-nitrobenzoyl chloride in pyridine on the water bath for 30 minutes, crystallised from acetic acid in small light yellowish brown plates, shrinks at 255°, m.p. 258-60° (Found: N, 2.6. $C_{32}H_{19}O_7N$ requires N,2.6%).

When product (B)(0.2 g.), dissolved in 2% alcoholic alkali, was coupled with diazotised aniline, stirred for 2 hours, a deep red solution was obtained, which on acidification gave a deep red dye. It could not be crystallised, but was purified by precipitation from a benzene solution by light petroleum (60-80°), when it was obtained as an amorphous powder which decomposed above 180° (Found: N, 5.7. $C_{31}H_{20}O_4N_2$ requires N, 5.4%).

Decomposition of product (B) with alcoholic alkali:

Product (B) (0.5 g.) was dissolved in 2% alcoholic caustic soda solution and the yellowish red solution kept overnight at room temperature. Carbon dioxide was passed through the solution, which had become deep red; but only sodium carbonate was precipitated and the colour of the solution became violet. The violet coloured filtrate was acidified, and the deep violet precipitate collected. The filtrate on evaporation gave a sticky violet-coloured product which could not be crystallised. The precipitate on purification by chromatography through alumina using benzene as solvent, gave a violet-coloured compound which

crystallised from benzene in greyish violet laminary plates (Product C) (0.2 g.), decomposing at 174-76° (Found: C, 82.9; H, 4.8%). The substance is not soluble in aqueous cold sodium carbonate or sodium hydroxide solution but dissolves in hot 10% aqueous sodium hydroxide. It dissolves in hot alcoholic alkali to give a brownish red solution, and ~~dissolves~~ in alcohol to give a violet coloured solution, which gives with ferric chloride a cherry red colouration, and with a drop of hydrochloric acid a reddish brown colour. It gives a brownish orange solution in concentrated solphuric acid, exhibiting a bright green fluorescence. It cannot be reduced with hydrosulphite and alkali or by tin and hydrochloric acid.

Referances

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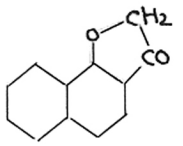
Part V

6:7-Benzocoumaranone.

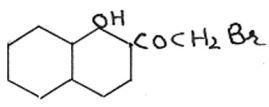
Part V

6:7-Benzocoumaranone

In the course of a study of the action of alkaline condensing agents on ethyl 2-acetyl-1-naphthyl carbonate,[1] it appeared that a possible product was 6:7-benzocoumaranone (I) and the substance had to be prepared for a direct comparison. It was first described by Ullmann,[2] who prepared it by the cyclisation of 2-bromacetyl-1-naphthol (II) and recorded the m.p. 91-92°.

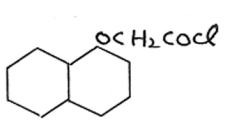


(I)

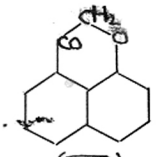


(II)

Fries,[4] quoting van Paul Lanz,[3] has stated that a benzocoumaranone constituted as (I) and melting at 116°, is obtained by the intramolecular acylation of α-naphthoxyacetyl chloride (III); the m.p. was slightly higher



(III)



(IV)

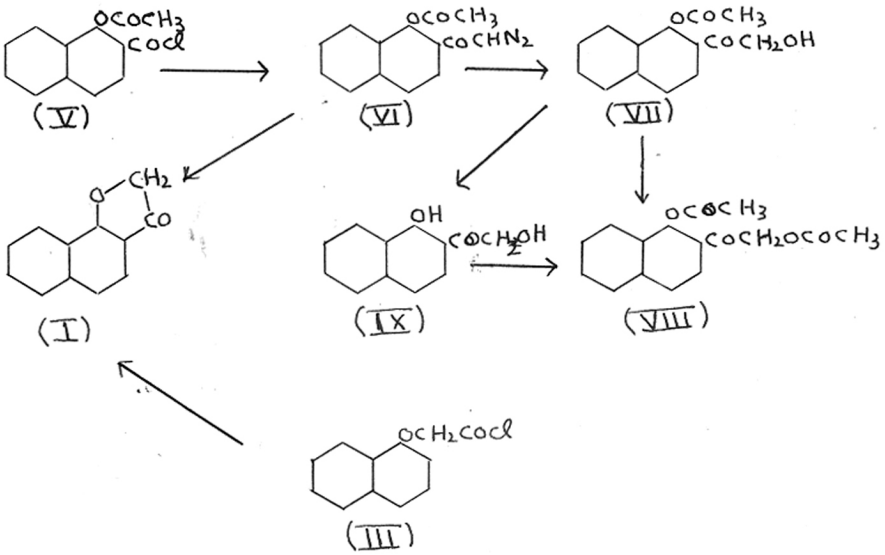
(119°), when the corresponding bromide was used. Ingham

Stephen and Timpe,[5] who have not referred to the work of Fries and Lanz, carried out the intramolecular acylation of α-naphthoxyacetyl chloride (III) with aluminium chloride in benzene, and obtained a product, m.p. 119°, which they considered to be the perinaphthopyrone (IV), rather than the coumaranone (I), since it condensed with benzaldehyde to form the benzylidene derivative, which could not be converted through its dibromide into the corresponding flavonol. Another argument advanced in favour of (IV) was the non-identity of its melting point with that of 6:7-benzocoumaranone (I), reported to have been synthesised by Ullmann[1] by an unambiguous method from 2-bromacetyl-1-naphthol (II) in which the 1:2-position is already fixed. Several similar instances of peri-ring closure are known, such as the condensation of α-naphthylacetyl chloride to give acenaphthenone, and the formation of benzanthrone from α-benzoylnaphthalene in presence of aluminium chloride.

Reviewing Ulmann's work[2] on the ω-bromination of 2-acetyl-1-naphthol, it was found that conflicting results have been recorded for this bromination. Ullmann obtained 2-bromacetyl-1-naphthol (II) (m.p. 124.5°) by brominating acetonaphthol or its acetyl derivative in carbon tetrachloride solution, while Torrey and Brewster[6] obtained 4-bromo-2-acetyl-1-naphthol m.p. 127° under the same conditions. Fries[7] also failed to get (II), and it has now been found that even bromination with N-bromosuccinimide, which normally leads to ω-bromination, yields 4-bromo-2-acetyl-1-naphthol. Bromination in acetic acid with two molecules of bromine gave a quantitative yield of the ω:4-dibromo derivative.

6:7-Benzocoumaranone (I) has now been synthesised by an unambiguous route starting from 1-hydroxy-2-naphthoic acid, through the intermediate diazoketone, by the following scheme. The acid chloride (V) of the acetate of 1-hydroxy-2-naphthoic acid, on treatment with an etherial solution of diazomethane, gave the diazoketone (VI). This on treatment with dilute sulphuric acid in dioxane gave the carbinol (VII) which on acetylation gave the corresponding acetate (VIII). Eistert[8]

has shown that the corresponding diazoketone from



2-hydroxy-3-naphthoic acid gives the benzocoumaranone on treatment with alcohol and dilute sulphuric acid, but the diazoketone (VI) when treated under similar conditions gave the carbinol (VII). Eistert[8] further found that the corresponding carbinol from 2-hydroxy-3-naphthoic acid on longer treatment with alcohol and sulphuric acid, also gave the benzocoumaranone. It was found, however, that the carbinol (VII) under similar conditions gave merely the deacetylated compound (IX), which was also obtained by treatment of the carbinol (VII) with sodium hydroxide.

This gives the same diacetate (VIII) as that obtained from the carbinol (VII). However, the diazoketone (VI) on treatment with concentrated sulphuric acid in the cold gave a compound, m.p. 119°, which from its properties and those of its derivatives proved to be 6:7-benzocoumaranone (I). The carbinol (VII) or (IX) did not give the 6:7-benzocoumaranone under the same conditions. As the 6:7-benzocoumaranone had the same melting point and properties as those described by Ingham[5] et al for their product, obtained by the intramolecular acylation of α-naphthoxyacetyl chloride, it was considered desirable to repeat their work.

The acid chloride, prepared by the action of phosphorus pentachloride on α-naphthoxyacetic acid, gave on treatment with aluminium chloride in benzene a substance m.p. 119°, identical in all respects with 6:7-benzocoumaranone. Thus cyclization of α-naphthoxyacetyl chloride takes place in the 2-position and not in the peri position. The acid chloride did not cyclize when treated with stannic chloride in benzene.

E X P E R I M E N T A L

1-Acetoxy-2-naphthyl diazomethyl ketone (VI):

1-Hydroxy-2-naphthoic acid (5 g.) was refluxed for 3 hours, with a mixture of acetic anhydride (10 c.c.) and acetic acid (10 c.c.), and chilled. The product that separated was filtered, washed with cold benzene and dried (4 g.). The acetate thus obtained was sufficiently pure for conversion to the acid chloride. It crystallised from benzene in colourless needles, m.p. 156°. The acetate was unstable to long keeping, and to the action of hot water or even hot alcohol. The acid chloride, m.p. 114° (Eistert, m.p. 114°) was obtained by treatment with thionyl chloride in petroleum ether (60-80°), for 2 hours on the water bath.

The finely powdered acid chloride (5 g.), dissolved in ether (100 c.c.), was added dropwise in the course of one hour to an agitated, ice-cold solution of diazomethane in ether, prepared from nitrosomethylurea (12 g.), 40% potassium hydroxide (30 c.c.) and ether (100 c.c.), and kept in the refrigerator for 24 hours. The diazoketone which separated as a light yellow crystalline precipitate was filtered (3 g.) and the filtrate on concentration gave

more of the diazoketone. The substance crystallised from benzene in small shining plates (3.2 g.), m.p. 131° (decomp.) (Found: N, 11.2. $C_{14}H_{10}O_3N_2$ requires N, 11.02%). It decomposes on long standing. It dissolves in concentrated sulphuric acid with decomposition giving a deep orange solution, with a bright green fluorescence.

1-Acetoxy-2-naphthoylcarbinol (VII): To a solution of the diazoketone (VI) (0.5 g.) in dioxane (10 c.c.), 2N sulphuric acid (2 c.c.) was added with shaking, and ~~the~~ solution allowed to stand at room temperature for two hours. The diazoketone slowly gave off nitrogen, and the solution became slightly deeper in colour. On dilution with water, the crystalline precipitate was collected and crystallised from alcohol. The shining yellow flat plates (0.35 g.) had m.p. 121°. (Found: C, 69.1; H, 4.9. $C_{14}H_{12}O_4$ requires C, 68.8; H, 4.9%). The substance gives a deep green colour with ferric chloride, and an orange solution in concentrated sulphuric acid, and dissolves in cold 1% ~~caustic soda~~ aqueous sodium hydroxide solution from which it can be reprecipitated unchanged. Because of its ferric chloride colouration and its solubility in ice-cold aqueous ~~caustic soda~~ sodium hydroxide, the possibility of the carbinol

(VIII) being 1-hydroxy-2-naphthoylacetyl carbinol cannot be ruled out. The product is being studied further to finally decide the position of the acetyl group.

The diacetate, prepared by refluxing (VII) with acetic anhydride and pyridine, crystallised from alcohol in long colourless needles, m.p. 119° (Found: C, 67.4; H, 5.1. $C_{16}H_{14}O_5$ requires C, 67.12; H, 4.9%).

The method used by Eistert[8] for converting a diazoketone of the type of (VI) to the coumaranone was then studied, and instead of the coumaranone (I), the carbinol (VII) was obtained.

The diazoketone (0.2 g) was suspended in alcohol (2 c.c.), 2N sulphuric acid (0.2 c.c.) added, and the mixture warmed on the water bath, when a brisk evolution of nitrogen took place. When nitrogen was no longer evolved, the solution was heated on the water bath for about 5 minutes (Norit), filtered and cooled, when light brown crystals separated (0.1 g.). The product crystallised from alcohol in light yellow plates, m.p. 121°, identical with (VII).

1-Hydroxy-2-naphthoylcarbinol (IX): To a solution of (VII) (0.1 g.) in alcohol (2 c.c.), four drops of concentrated sulphuric acid were added and the solution refluxed on the water bath for 30 minutes (Norit),

filtered and cooled. The yellow crystalline mass, which separated, crystallised from alcohol or benzene in small yellow plates, m.p. 151°, with darkening in colour. (Found: C, 71.3; H, 5.2. $C_{12}H_{10}O_3$ requires C, 71.3; H, 4.9%). The substance was also obtained by warming a dilute alkaline solution of the acetylated carbinol on the water bath for 2 minutes, and acidifying. It gives a green colour with ferric chloride and an orange solution in concentrated sulphuric acid.

Acetylation gave the same diacetate (VII) described earlier.

6:7-Benzocoumaranone (I):

(A) The diazoketone (VI) (0.2 g.) was added slowly with stirring to ice-cold concentrated sulphuric acid (2 c.c.); nitrogen was evolved and the substance slowly went into solution. The brownish orange solution, which had a strong green fluorescence was kept in the refrigerator for one hour, poured over crushed ice, and ether extracted. The ether extract was washed with ice-cold sodium hydroxide solution, which removed a trace of a colouring matter. The ether layer was washed and dried, and on removal of the ether the residue crystallised from dilute alcohol in shining colourless plates, m.p. 119°. (Ullmann, 91-2°; Lanz, 116°; Fries and Ingham et al, 119°)

(Found: C, 78.1; H, 4.5. $C_{12}H_8O_2$ requires C, 78.3; H, 4.3%). The substance does not give a colour with ferric chloride, and is not soluble in cold aqueous sodium hydroxide; but when slightly warmed it goes into solution with a deep red colour; deep reddish violet flakes then separate (cf. Ullmann[2]). It reduces Fehling's solution, and the brownish orange solution in concentrated sulphuric acid shows a bright green fluorescence.

The acetate prepared by refluxing with acetic anhydride and pyridine, crystallised from alcohol in light brown needles, m.p. 88°, (Ingham and co-workers, 85°) (Found: C, 74.7; H, 4.7. $C_{14}H_{10}O_3$ requires C, 74.3; H, 4.4%).

(B) α-Naphthoxyacetic acid was prepared by condensing chloracetic acid and α-naphthol in alkaline solution. The acid chloride, obtained by treatment of the acid (5 g.) with phosphorus pentachloride (5 g.) in benzene, followed by removal of the benzene and phosphorus oxychloride under vacuum on the water-bath, was taken up in benzene (25 c.c.). Aluminium chloride (4 g.) was then slowly added, when the colour of the solution changed from brownish red to green. After heating on the water-bath for 6 hours, the solution which had now become coppery red was poured on to ice and

hydrochloric acid, and steam-distilled. The white crystalline mass that separated in the distillate was taken up in ether, and the ether removed. The residue (1.2 g.) crystallised from dilute alcohol in colourless shining plates, m.p. 119°, not depressed by admixture with 6:7-benzocoumaranone, prepared earlier. The residue in the distillation flask was a deep red resinous mass and could not be crystallised.

References

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6. Torrey and Brewster, J. Am. Chem. Soc., 1909, 31, 1323.

7. Fries, Ber., 1921, 57, 270.

8. Eistert, ibid., 1936, 69, 1076.

Summary

Gentisin, the yellow colouring matter of *Gentiana lutea*, was shown by demethylation to be a monomethyl ether of gentisein, 1:3:7-trihydroxyxanthone. The methylation of gentisin to a monomethyl, and not a dimethyl ether, indicated that the original methoxyl was not in the 1-position. Gentisin could therefore be either the 7-methyl ether or the 3-methyl ether. The 7-methyl ether was synthesised by Shimoda and shown to be different from gentisin. The 3-methyl ether has now been synthesised and shown to be identical with natural gentisin. 7-Nitro-1:3-dihydroxyxanthone, obtained by a Hoesch reaction between 5-nitrosalicylonitrile and phloroglucinol, followed by hydrolysis and cyclisation, was methylated by diazomethane to its 3-methyl ether. This on reduction, diazotisation and hydrolysis with sulphuric acid gave 3-methoxy-1:7-dihydroxyxanthone (gentisin). 7-Nitro-1:3-dihydroxyxanthone on reduction, diazotisation and hydrolysis gave gentisein, 1:3:7-trihydroxyxanthone.

Hydroxyflavones have been prepared from nitroflavones

by reduction, diazotisation and hydrolysis. The utility of this general procedure has been shown by the synthesis of 4'-hydroxy-α-naphthaflavone, 7:4'-dihydroxyflavone, 4'-hydroxy-7-methoxyflavone and 5:4'-dihydroxy-7-methoxyflavone (genkwanin).

3:4'-Dihydroxy-7-methoxyflavone has been synthesised by the oxidation of the corresponding chalkone with alkaline hydrogen peroxide, thus showing that a free 4'-hydroxyl group does not interfere in this oxidation.

Lotoflavin, the natural colouring matter of Lotus arabicus was shown by Dunstan and Henry to be 5:7:2':4'-tetrahydroxyflavone. But the synthesis of 5:7:2':4'-tetrahydroxyflavone by Cullinane et al, and Robinson and Venkataraman indicated its non-identity with lotoflavin. The properties of lotoflavin trimethyl ether, which crystallises in dimorphic forms, are more characteristic than those of lotoflavin. 5-Hydroxy-7:2':4' tetramethoxyflavone has been synthesised by controlled demethylation of 5:7:2':4'-tetramethoxyflavone, and it has proved to be different from lotoflavin trimethyl

ether, thus finally confirming that lotoflavin is not 5:7:2':4'-tetrahydroxyflavone. 5:7:2':4'-Tetramethoxyflavone was obtained by oxidation of the corresponding chalkone by selenium dioxide in amyl alcohol.

The utility, as azoic coupling components, of o-hydroxydibenzoylmethanes, which are intermediates in the synthesis of flavones, has been investigated. 2-Benzoylacetyl-1-naphthol gives weak dyeings when used as a "naphthol" for impregnation of cotton and development with diazonium salts. The shades lacked fastness to soaping and light. On coupling the diketone in substance with diazonium salts, mono- and disazo dyes were obtained, the constitution of the former, which could have two possible structures, has been proved to be 4-benzeneazo-2-benzoylacetyl-1-naphthol by an unambiguous synthesis from 4-benzeneazo-2-acetyl-1-naphthol through the corresponding benzoate. The monoazo dye from 1-benzoylacetyl-2-naphthol has been prepared.

o-Benzoyloxyacetophenones can be readily transformed to dibenzoylmethanes by means of sodamide, potassium carbonate and similar reagents. This indicated that an application of this reaction to the O-carbethoxy-

derivatives of o-hydroxyacetophenone might lead to a new method for the synthesis of 4-hydroxycoumarins. The scope of the reaction has been shown by the synthesis of 4-hydroxynaphthocoumarin from o-carbethoxy-2-acetyl-1-naphthol by treatment with potassium carbonate in toluene. The behaviour of 4-hydroxynaphthocoumarin has been studied, and its derivatives, including the corresponding dicoumarin have been prepared. By the action of potassium carbonate or sodamide on the carbethoxy ester of 2-acetyl-1-naphthol a second product (B) was obtained.

One of the possible structures initially considered for product B was 6:7-benzocoumaranone. A reference to the literature showed that there existed an ambiguity about the constitution and the melting point of 6:7-benzocoumaranone. It was first synthesised by Ullmann, who prepared it by the cyclization of 2-bromoacetyl-1-naphthol and recorded the m.p. 91-92°. Fries prepared it later by the intramolecular acylation of α-naphthoxyacetyl bromide and recorded the m.p. 119°. A compound of the same m.p. prepared similarly from α-naphthoxyacetyl chloride has been considered by Ingham et al to be perinaphthapyrone. It was therefore

considered desirable to synthesise the benzocoumaranone for direct comparison by an ambiguous route. Starting from 1-hydroxy-2-naphthoic acid, 6:7-benzocoumaranone, m.p. 119°, has been obtained, through the intermediate diazo ketone and it has been shown that the product obtained by Ingham et al was also 6:7-benzocoumaranone.

The analytical data for Product (B) and its derivatives corresponds with the molecular formula $C_{23}H_{16}O_4$ for product (B). Its derivatives indicate the presence of one hydroxyl group. Further work is being done on product (B) to elucidate its constitution.

Appendix I

In a very recent publication Wheeler *et al* (*Sci. Proc. Roy. Dublin Soc.*, 1948, **24**, 29) have tried to explain the difference in behaviour of various condensing agents and the solvents used as dependent on the strength of the basic atmosphere provided by them, considering the reaction to be one involving a base-catalysed intramolecular condensation of the Claisen type.

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