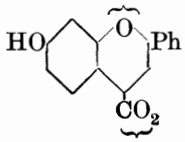
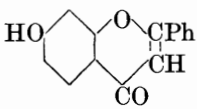
CIX.—*Anthoxanthins. Part XII. Transition from a Flavylium Salt to a Flavone, illustrated by a New Synthesis of Scutellarein Tetramethyl Ether.*

By Robert Robinson and Gerold Schwarzenbach.

Although the pyrones stand in the relation to the pyrylium salts that the pyridones bear to the alkylpyridinium salts, and although the latter can be very readily changed to the pyridones by oxidation, yet there are surprisingly few recorded examples of the production of pyrones by direct or indirect processes from members of the pyrylium group.

Bülow and Wagner (*Ber.*, 1903, **36**, 1941) found an isolated example in the oxidation of 7-hydroxy-4-carboxyflavylium betaine

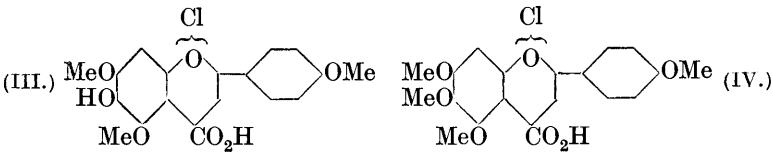
(I.) 



(II.)

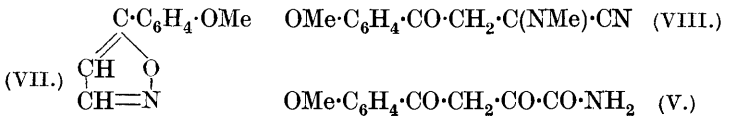
(I) (formulated previously as a pyranol) to 7-hydroxyflavone (II) by means of chromic acid in acetic acid solution. This we have confirmed, but, although the conditions have been somewhat improved, the yield of the flavone remains highly unsatisfactory.

Moreover, the reaction is not a general one, and proposed applications to the synthesis of scutellarein failed. *Anisoylpyruvic acid*, $MeO{\cdot}C_6H_4{\cdot}CO{\cdot}CH_2{\cdot}CO{\cdot}CO_2H$, obtained by the usual method, has been condensed with 2 : 6-dimethoxyquinol and with antiarol in the presence of hydrogen chloride, furnishing the flavylium salts (III) and (IV), respectively.



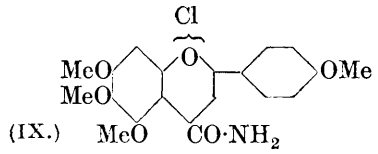
In spite of various attempts, neither these salts nor the related *betaines* could be oxidised to scutellarein derivatives. It was, however, possible to achieve our object indirectly by applying the Hofmann reaction to the amide of the acid (IV). The chief difficulty was the preparation of the required *anisoylpyruvamide* (V). If a convenient method of preparation of compounds of this type could be devised, the new flavone synthesis now to be described might acquire considerable importance, since it is applicable to certain types of structure not readily built up by hitherto known processes. Some of the more obvious routes to the aroylpyruvamides have been tested without success, and we were forced back upon an interesting but indirect series of reactions due to Mumm and Münchmeyer (*Ber.*, 1910, **43**, 3335), who obtained benzoylpyruvamide. The stages in the present case were the following :

Anisoylacetaldehyde (Pratt, Robinson, and Williams, J., 1924, **125**, 202) was converted into its *oxime*, $MeO{\cdot}C_6H_4{\cdot}CO{\cdot}CH_2{\cdot}CH{:}NOH$ (VI), and this was dehydrated by the action of acetyl chloride, giving 5-*anisyl*isooxazole (VII). The *methosulphate* of this base reacted with potassium cyanide in aqueous solution with formation of α-*methylimino*-β-*anisoylpropionitrile* (VIII), which was hydrolysed to anisoylpyruvamide (V) by means of dilute hydrochloric acid.



Anisoylpyruvamide and antiarol with the help of hydrogen chloride yielded a product containing 4-carbamyl-5 : 6 : 7 : 4′-tetramethoxyflavylium chloride (IX), and this, on treatment with potassium

hypochlorite and potassium hydroxide in methyl-alcoholic solution, reacting doubtless as the pseudo-base, gave another pseudo-base



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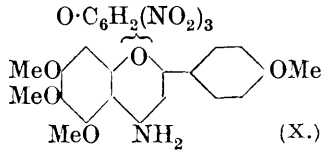
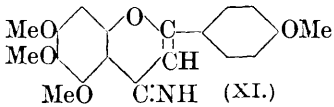
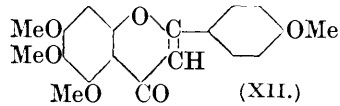


(X.)

which could be transformed into 4-*amino*-5 : 6 : 7 : 4′-*tetramethoxyflavylium picrate* (X). The corresponding base is, doubtless, the flavone-imine (XI), and the tetramethoxyflavone (XII) resulted when the imine was treated with boiling dilute aqueous sodium hydroxide. The existence of the flavone-imine recalls that of a xanthone-imine obtained by the condensation of phloroglucinol with salicylonitrile under the conditions of the Hoesch reaction (Nishikawa and Robinson, J., 1922, **121**, 839); the resistance to hydrolysis by acids and



(XI.)

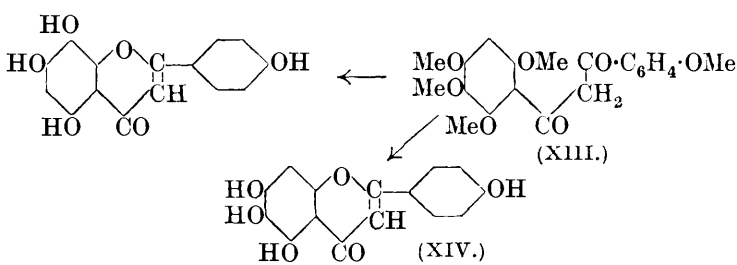


(XII.)

other properties are parallel in the two series.

The substance (XII) had the melting point and other properties of scutellarein tetramethyl ether (Molisch and Goldschmiedt, *Monatsh.*, 1910, **31**, 439), and we were able to establish the identity by direct comparison with a specimen prepared from scutellarein. For providing the latter, we are greatly indebted to Professor E. Späth and Dr. F. Wessely.

Scutellarein has been previously synthesised by Bargellini (*Gazzetta*, 1915, **45**, 69), who submitted pentamethoxydibenzoylmethane (XIII) to the action of hydriodic acid; the reaction might have



proceeded in the two directions indicated. Actually, scutellarein (XIV) was produced and the reaction was correctly interpreted in the light of certain analogies. The present unambiguous synthesis confirms these deductions and supplies a proof of the constitution of scutellarein.

EXPERIMENTAL.

7-Hydroxy-4-carboxyflavylium Derivatives.—Bülow and Wagner (*loc. cit.*) did not crystallise the chlorides obtained by the condensation of resorcinol, benzoylpyruvic acid or its ester, and hydrogen chloride, so the following data may be recorded.

7-Hydroxy-4-carboxyflavylium betaine (I) decomposes at 248°, the corresponding picrate decomposes at 226°; on solution in ethyl-alcoholic hydrogen chloride and gradual addition of ether, *7-hydroxy-4-carboxyflavylium chloride* (decomp. 250°) crystallised in orange-red leaflets (Found: Cl, 11·6. $C_{16}H_{11}O_4Cl$ requires Cl, 11·7%).

7-Hydroxy-4-carbethoxyflavylium picrate decomposes at 225° and similarly yields *7-hydroxy-4-carbethoxyflavylium chloride*, orange leaflets decomposing at 198° (Found: Cl, 10·2. $C_{18}H_{15}O_4Cl$ requires Cl, 10·5%).

The oxidation of the betaine to 7-hydroxyflavone does not proceed satisfactorily; a slight improvement followed on the adoption of the following conditions:

A solution of chromic anhydride (0·7 g.) in water (10 c.c.) was added to one of 7-hydroxy-4-carboxyflavylium betaine (0·7 g.) in hot 25% sulphuric acid (30 c.c.); carbon dioxide was then briskly evolved and an orange precipitate (0·45 g.) was formed. After crystallisation, 7-hydroxyflavone (0·15 g., m. p. 240°) was obtained.

Our further experience has shown that this is a special case, and the reaction is by no means a general one. It fails in the scutellarein series described below.

Anisoylpyruvic Acid and its Ethyl Ester.—A mixture of *p*-methoxyacetophenone (79 g.) and ethyl oxalate (77 g.) was added to a solution of sodium ethoxide (25 g. of sodium) in alcohol (400 c.c.), the whole refluxed for ½ hour, and the alcohol evaporated. An aqueous solution of the residue was saturated with carbon dioxide and filtered, and the crude *acid* (64 g.) precipitated by the addition of hydrochloric acid. This substance crystallised from alcohol in pale brown needles or irregular prisms, decomp. at 162·5° (Found: C, 54·9; H, 5·0; loss at 110° in a vacuum, 7·6. $C_{11}H_{10}O_5,H_2O$ requires C, 55·0; H, 5·0; H_2O, 7·5%). The yield can be improved by carrying out the condensation in the cold and subsequently hydrolysing the ester, but this is hardly worth doing.

A mixture of *p*-methoxyacetophenone (13·5 g.), ethyl oxalate (13 g.), sodium ethoxide (from 2 g. of sodium) and alcohol (35 c.c.) was kept for 12 hours at 0° and then added to ether. The cake of sodium derivative was collected and decomposed at 0° in aqueous solution with carbon dioxide (yield, 16 g.).

Ethyl anisoylpyruvate crystallised from alcohol in colourless

prisms, m. p. 54° (Found : C, 62·3; H, 5·7. $C_{13}H_{14}O_5$ requires C, 62·3; H, 5·6%).

6-*Hydroxy*-5 : 7 : 4′-*trimethoxy*-4-*carboxyflavylium Derivatives* (Chloride, III).—A solution of 2 : 6-dimethoxyquinol (4·25 g.) and anisoylpyruvic acid (5·6 g.) in acetic acid (50 c.c.) was saturated with hydrogen chloride at 90—100° for 1 hour, then cooled to 0°, and ether (150 c.c.) added without interrupting the passage of hydrogen chloride. The dark red solid was collected (5·8 g.), and a portion converted into the *picrate* in hot alcoholic solution by the addition of picric acid; the derivative crystallised immediately in dark red leaflets which decomposed at 224° (Found : C, 49·6; H, 3·8; N, 7·2. $C_{25}H_{19}O_{14}N_3,H_2O$ requires C, 49·7; H, 3·5; N, 6·9%). This picrate was suspended in pure methyl alcohol and hydrogen chloride introduced until it dissolved; on the addition of ether, the chloride crystallised in dark red needles, decomposing at 170—180° and readily soluble in water and alcohol.

Another portion of the crude chloride was dissolved in hot aqueous sodium acetate, and the filtered solution acidified with acetic acid. The *betaine* separated in red needles, and the substance could be recrystallised from alcohol, forming very small, green prisms, decomp. 182° (Found : C, 59·6; H, 5·0. $C_{19}H_{16}O_7,1\frac{1}{2}H_2O$ requires C, 59·6; H, 5·0%), sparingly soluble in water and giving a bright orange solution in sulphuric acid.

5 : 6 : 7 : 4′-*Tetramethoxy*-4-*carboxyflavylium Derivatives* (Chloride, IV).—A solution of antiarol (9·2 g.) and anisoylpyruvic acid (11·6 g.) in acetic acid (60 c.c.) was saturated with hydrogen chloride at 100° for 3 hours, cooled, and dry ether (200 c.c.) added, hydrogen chloride being passed meanwhile. After being kept at 0° for 12 hours, the solid was collected (21 g., air-dried) and this chloride was converted into the *betaine* by solution in aqueous sodium acetate and acidification with acetic acid. The orange needles obtained were readily soluble in water and could be recrystallised from alcohol in a similar form, m. p. 127—130° (Found : C, 59·8; H, 5·6. Found in material dried at 100° in a vacuum : C, 65·1; H, 5·2. $C_{20}H_{18}O_7,1\frac{1}{2}H_2O$ requires C, 60·4; H, 5·3%. $C_{20}H_{18}O_7$ requires C, 64·9; H, 4·9%).

The related *picrate* crystallised from alcohol in deep orange needles, decomp. 204—205° (Found : C, 50·4; H, 4·1; N, 7·1. $C_{26}H_{21}O_{14}N_3,H_2O$ requires C, 50·6; H, 3·7; N, 6·8%).

The oxidising agents tested with the object of preparing *O*-tetramethylscutellarein were chromic acid in acetic acid and dilute sulphuric acid solutions, persulphate in dilute sulphuric acid, lead peroxide and acetic acid, manganese dioxide and dilute sulphuric acid and hydrogen peroxide in acetic acid, and finally potassium

ferricyanide in neutral and in alkaline solution; in all cases, the results were negative.

The action of phosphorus pentachloride on the betaine appeared to proceed normally, giving the acid chloride flavylium chloride, but the action of ammonia or hydrazine on this derivative did not give the anticipated results.

Anisoylacetaldoxime (VI).—The sodium salt of ω-hydroxymethylene-*p*-methoxyacetophenone (45 g.) (Pratt, Robinson, and Williams, *loc. cit.*) was dissolved in ice-water (600 c.c.), and hydroxylamine hydrochloride (25 g.) in water (50 c.c.) added; separation of the *oxime* began immediately. The substance (yield, 25 g.) crystallised from benzene in colourless microscopic needles, m. p. 120° (Found: C, 62·4; H, 5·7; N, 7·4. $C_{10}H_{11}O_3N$ requires C, 62·3; H, 5·7; N, 7·3%). It retained benzene tenaciously, and the determination of nitrogen was carried out with a specimen giving C, 63·3; H, 5·6%, and probably containing a trace of the solvent.

5-*Anisyl*isooxazole (VII).—Claisen (*Ber.*, 1891, **24**, 132) has shown that the dehydration of the oxime of benzoylacetaldehyde with acetyl chloride yields phenyl*iso*oxazole, whereas the use of acetic anhydride leads to the formation of ω-cyanoacetophenone, which is also obtained by the action of alkalis on phenyl*iso*oxazole.

Finely powdered anisoylacetaldoxime (10 g.) was added to acetyl chloride (10 g.) with cooling; a vigorous reaction and brisk evolution of hydrogen chloride ensued. The excess of the reagent was removed by evaporation and the oily residue was mixed with 3% sodium hydroxide solution (150 c.c.); the oil then quickly solidified. The product crystallised from 80% alcohol (100 c.c.) in almost colourless, flat prisms, m. p. 63° (yield, 7·5 g.) (Found: C, 68·7; H, 5·1; N, 8·0. $C_{10}H_9O_2N$ requires C, 68·7; H, 5·1; N, 8·0%). On boiling for 5 minutes with alcoholic sodium hydroxide, 5-*anisyl*isooxazole was transformed into the isomeric ω-cyano-*p*-methoxyacetophenone, which crystallised from alcohol in colourless needles, m. p. 131° (Found: C, 68·9; H, 5·2; N, 8·1%) in good agreement with the statement of Bargellini (*Gazzetta*, 1911, **41**, 748), who prepared the compound in another way.

The *methosulphate* was obtained by heating a mixture of anisyl*iso*oxazole (8·9 g.) and pure methyl sulphate (5·3 g.) on the steam-bath. Reaction occurred at about 90° and soon afterwards the whole crystallised with evolution of heat. The salt was washed with acetone and separated on the addition of ether to its alcoholic solution in bright yellow crystals, m. p. 142·5° (Found: N, 4·5; S, 10·4. $C_{12}H_{15}O_6NS$ requires N, 4·7; S, 10·6%). The golden-yellow picrate has m. p. 147·5°.

α-*Methylimino*-β-*anisoylpropionitrile* (VIII).—Potassium cyanide

(5 g.) in water (50 c.c.) was very gradually added to a solution of anisyl*iso*oxazole methosulphate (6·5 g.) in ice-cold water (50 c.c.). The precipitate obtained (4·5 g.) consisted of the pure *nitrile*, m. p. 109° (not raised by crystallisation); it separated from alcohol in pale yellow needles or well-shaped prisms (Found: C, 66·6; H, 5·6; N, 13·0. $C_{12}H_{12}O_2N_2$ requires C, 66·8; H, 5·6; N, 13·0%). The solution in sulphuric acid had a dark purple colour. Experiments on the condensation of this substance with antiarol had no definite outcome.

Anisoylpyruvamide (V).—Anisoylpyruvic acid could not be directly converted into its amide either by way of the chloride or through the ester by means of ammonia. Nor could the amide be obtained by the condensation of ethyl oxamate and *p*-methoxyacetophenone.

Methyliminoanisoylpropionitrile (23 g.) was powdered and agitated with *N*-hydrochloric acid (500 c.c.) for 36 hours, and the product isolated (19 g.). The *amide* was sparingly soluble in hot ethyl alcohol and crystallised from *iso*amyl alcohol in colourless microscopic needles, decomp. 192° (Found: C, 59·8; H, 5·2; N, 6·0. $C_{11}H_{11}O_4N$ requires C, 59·7; H, 5·0; N, 6·3%). The solution in sulphuric acid was reddish-brown. The substance, when boiled with concentrated hydrochloric acid, was hydrolysed to anisoylpyruvic acid.

The acid mother-liquor from the preparation described above contained 10% more than the theoretical amount of volatile bases, so it might be advantageous to interrupt the process at an earlier stage. There was also a considerable loss on crystallisation of the crude product.

4-*Carbamyl*-5 : 6 : 7 : 4′-*tetramethoxyflavylium Chloride* (IX).—Owing to the very great ease with which the amide group in this salt is hydrolysed, we have not obtained a pure specimen of the substance, but a product which must consist of it to a large extent was prepared in the following manner.

Hydrogen chloride was led into a solution of antiarol (7·0 g.) and anisoylpyruvamide (8·0 g.) in purified acetic acid at 70° for 1½ hours; ammonium chloride separated. The mixture was cooled and kept saturated with hydrogen chloride for 24 hours, then diluted with ether and kept in the ice-chest for 4 hours. The product was washed with ether and dried at 100° in a vacuum, giving a dark brownish-red mass with a green reflex (9·5 g.). Attempts to isolate the picrate of the amide gave only the already described tetramethoxycarboxyflavylium picrate, which crystallised from acetic acid in an anhydrous condition (Found: C, 52·1; H, 3·9; N, 7·1. $C_{26}H_{21}O_{14}N_3$ requires C, 52·1; H, 3·5; N, 7·0%). The identity of this picrate with the substance previously obtained was proved by a comparison

of colour reactions and decomposition points, and the related chloride was prepared and found to be free from nitrogen.

4-Amino-5 : 6 : 7 : 4′-tetramethoxyflavylium Picrate (X).—The crude chloride (9·5 g.) obtained as described in the last section was dissolved in methyl alcohol (75 g.) and cooled to 0°, a cooled solution of potassium hypochlorite (33 c.c. from 1·77 g. of chlorine, 4·82 g. of potassium hydroxide, and water) added, and the mixture heated on the steam-bath for ½ hour. Acetic acid (50 c.c.) and a solution of picric acid (12 g.) in acetic acid (100 c.c.) were successively introduced; a yellow *picrate* crystallised on cooling, and this was collected and washed with acetic acid and ether (yield, 4·8 g. in this experiment, but much less when more alkali was employed). The salt crystallised from acetic acid in flat golden-yellow prisms (3·0 g.), very sparingly soluble in all solvents and decomposing at 281° (Found : C, 52·6; H, 4·0; N, 9·7. $C_{25}H_{22}O_{12}N_4$ requires C, 52·6; H, 4·1; N, 9·8%). The corresponding chloride was obtained in pale pink needles by passing hydrogen chloride into a suspension of the picrate in acetic acid and adding ether. The base obtained on treatment with aqueous sodium hydroxide was a sticky, very pale yellow precipitate.

5 : 6 : 7 : 4′-Tetramethoxyflavone (*Scutellarein Tetramethyl Ether*) (XII).—4-Amino-5 : 6 : 7 : 4′-tetramethoxyflavylium chloride (0·7 g.) was refluxed with 10% sodium hydroxide solution (7 c.c.) for 45 minutes, ammonia being evolved and the substance becoming a dark brown oil. When this was washed with very dilute hydrochloric acid, it became solid and bright yellow; the substance crystallised from alcohol (charcoal) in thick colourless prisms (S), m. p. 161° (Found : C, 66·9; H, 5·6. Calc. for $C_{19}H_{18}O_6$: C, 66·6; H, 5·3%).

The crude scutellarein kindly supplied by Professor Späth was methylated by means of an excess of methyl sulphate and 15% sodium hydroxide solution in presence of acetone; the impurities formed as a result of oxidation were insoluble in ether, and, when the washed and dried extract was concentrated to a small bulk, scutellarein tetramethyl ether crystallised in colourless prisms. After one crystallisation from alcohol, the specimen (N) had m. p. 161°, undepressed by admixture with an equal amount of (S).

The two specimens had identical properties and gave indistinguishable yellow to orange solutions in mineral acids of various concentrations. Very characteristic is the fact that the ether is partly extracted from ethereal solution even by 2% hydrochloric acid, and that it dissolves in hot 10% hydrochloric acid to a yellow solution, from which the hydrochloride separates as a mass of woolly yellow needles on cooling. On addition of mercuric chloride to the hot solution of the hydrochloride, there is an immediate pre-

cipitation of the very sparingly soluble, pale yellow mercurichloride. The microscopic appearance of the crystals of (S) and (N) and of their hydrochlorides was the same, and the solubility properties also were compared.

The methoxyl content of *O*-tetramethylscutellarein should be 36·25%, but a Zeisel–Pregl estimation gave MeO, 34·22%, and even a Herzig–Meyer–Pregl estimation gave only MeO, 34·7%. Apparently, a fraction of the methyl attached to oxygen is transferred to carbon in the course of the demethylation process.

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