CCLX.—*A Synthesis of Pyrylium Salts of Anthocyanidin Type. Part X. Delphinidin Chloride 3-Methyl Ether.*

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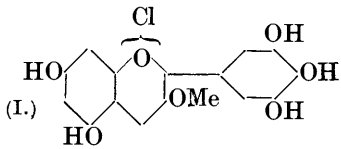
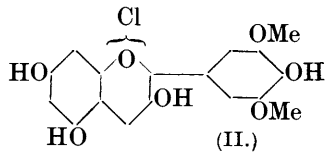
Among the naturally occurring methyl ethers of delphinidin a constitution can be unequivocally assigned to ampelopsidin alone. This is considered by Willstätter and Zollinger (*Annalen*, 1916, **412**, 216) to be the 4′-methyl ether on account of the weak ferric chloride reaction. Furthermore, since neither myrtillidin nor petunidin gives rise to a methylated phloroglucinol fragment even

on treatment with concentrated alkalis at relatively low temperatures, Willstätter and his collaborators concluded that each of these monomethyl ethers of delphinidin possessed free hydroxyl groups in positions 5, 7, and 4′. Apparently, therefore, one of these anthocyanidins should be delphinidin 3-methyl ether and the other the 3′-methyl ether. We have synthesised a flavylium salt which is regarded (see below) as delphinidin chloride 3-methyl ether (I), but it is quite different from myrtillidin chloride and from petunidin chloride. The new salt is, for example, very much more sparingly soluble in dilute hydrochloric acid than are the isomerides originating from natural sources.* Probably, therefore, one of the salts—myrtillidin chloride or petunidin chloride—is pure delphinidin chloride 3′-methyl ether and the other is either the same substance in a less pure condition,† or, after all, has a methoxyl group in position 5 or 7 in the phloroglucinol nucleus. And, further, since myrtillidin is derived from two distinct anthocyanins whilst definite evidence was obtained that petunidin has a methoxyl group outside the phloroglucinol nucleus, therefore, in connexion with the above alternatives, it would be petunidin which might be less pure myrtillidin or myrtillidin which has a methoxyl in the phloroglucinol nucleus.



(I.)



(II.)

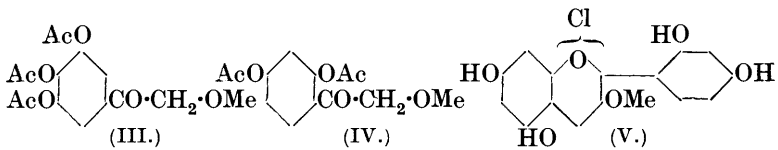
We take this opportunity of pointing out that the bearing of the evidence for the constitution of malvidin chloride is not free from ambiguity. Willstätter and Mieg (*Annalen*, 1915, **408**, 122) consider that one of the methoxyl groups is in the phloroglucinol nucleus, and this being so, the remaining methoxyl must be in position 4′, since the ferric chloride reaction is weak. But this leaves two of the three free phenolic hydroxyls of malvin in positions which do not contribute to strong alkali colour reaction, and yet malvin dissolves in aqueous sodium carbonate to a blue solution. It seems better to regard malvidin provisionally as delphinidin 3′ : 5′-dimethyl ether—a dimethoxypelargonidin (II)—and this formulation is the only one in harmony with the colour reactions. The methoxylated phenolic compound obtained on fusion with

* We are greatly indebted to Geheimrath Prof. R. Willstätter for a specimen of myrtillin chloride.

† Myrtillidin and petunidin have identical reactions but differ in crystalline form and in some solubility relations.

alkali would then be a pyrogallol derivative.* An attempt to synthesise delphinidin 3′ : 5′-dimethyl ether is in progress.

The course of the synthesis of delphinidin chloride 3-methyl ether did not run smoothly and it is necessary at this stage to consider carefully the evidence bearing on the constitution of the product. Triacetylgalloyl chloride was allowed to react with ethyl (or methyl) sodio-$\alpha\gamma$-dimethoxyacetoacetate in ethereal solution, and the product hydrolysed by means of dilute aqueous alcoholic potassium hydroxide on the steam-bath. After acidification the solution was extracted with ether and then with butyl alcohol. The product from the ether extract, on acetylation with acetyl chloride, afforded a crystalline substance, m. p. 132—133°, which gave results on analysis in close agreement with those required for a triacetoxy-ω-methoxyacetophenone (III). Since the methoxyl content and molecular weight were also found to be in harmony with this hypothesis, it is extremely difficult to suggest an alternative interpretation and we therefore designate the substance in accordance with this view. The anomaly arises from the circumstance that this crystalline compound exhibits no tendency to condense with 2 : 4 : 6-triacetoxybenzaldehyde, β-resorcylaldehyde or *o*-vanillin in formic acid solution in the presence of hydrogen chloride to give flavylium salts. For comparison we prepared 2 : 4-diacetoxy-ω-methoxyacetophenone (IV) by acetylation of ω-methoxyresacetophenone (Slater and Stephen, J., 1920, **117**, 312) and experienced little difficulty in condensing this substance with 2 : 4 : 6-triacetoxybenzaldehyde, ultimately obtaining *morinidin chloride* 3-*methyl ether* (V).

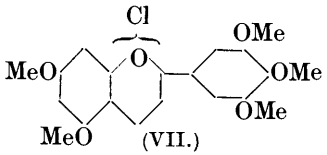


The butyl-alcoholic extract, to which reference has already been made, yielded no crystalline material, but the acetylated product condensed under the usual conditions with 2 : 4 : 6-triacetoxybenzaldehyde and after hydrolysis our delphinidin chloride 3-methyl ether (I) was obtained. The only explanation of these observations which has occurred to us is that the hydrolysis of the original condensation product, $(OAc)_3C_6H_2\cdot CO\cdot C(OMe)(CO_2Et)\cdot CO\cdot CH_2\cdot OMe$, was incomplete and that whilst ether extracted the trihydroxy-

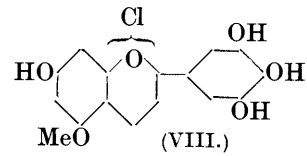
* This would be more readily produced from a *p*-hydroxybenzoic acid than from a *p*-methoxybenzoic acid, that is, more readily from malvidin than from oenidin on the suggested hypothesis.

ω-methoxyacetophenone, the triacetyl derivative of which is not reactive, butyl alcohol also extracted a compound containing the group $(HO)_3C_6H_2$·CO·CH(OMe)·COR. After acetylation, the latter substance reacted with the benzaldehyde derivative with simultaneous expulsion of the group –COR. Apart from the method of synthesis, the examination of the new delphinidin methyl ether, details of which will be found in the experimental section, leaves little room for doubt in regard to its constitution. The alkali colour reaction of the salt is much redder than that of delphinidin and the alteration is similar to that which occurs on passing from cyanidin to luteolinidin or from cyanin to mecocyanin.

For comparison, we wished to synthesise 5 : 7 : 3′ : 4′ : 5′-pentahydroxyflavylium chloride and accordingly condensed 2-hydroxy-4 : 6-dimethoxybenzaldehyde with 3 : 4 : 5-trimethoxyacetophenone to 3 : 4 : 5-*trimethoxyphenyl* 2-*hydroxy*-4 : 6-*dimethoxystyryl ketone*, $(MeO)_2C_6H_2(OH)$·CH:CH·CO·$C_6H_2(OMe)_3$ (VI), in the usual manner. This unsaturated ketone is converted by hydrochloric acid with great facility into 5 : 7 : 3′ : 4′ : 5′-*pentamethoxyflavylium chloride* (VII). On demethylating this and converting the product into the chloride a *tetrahydroxymethoxyflavylium chloride* was obtained which we consider to have the formula (VIII), although position 7 is an alternative situation for the methoxyl group.



(VII.)



(VIII.)

Since fisetinidin and butinidin exhibit almost the same alkali colour reactions as cyanidin and luteolinidin, respectively, (VIII) represents a salt which would doubtless closely resemble the parent pentahydroxy-derivative. It is therefore of interest that the reactions of our new tetrahydroxymethoxyflavylium chloride resemble those of the supposed delphinidin chloride 3-methyl ether. It appears to be a general rule in the series of flavylium salts containing free hydroxyl groups in positions 7, 3′, and 4′, and including cyanidin and delphinidin derivatives, that, if a violet solution of the salt in aqueous sodium carbonate becomes greenish-blue on the addition of sodium hydroxide, there is no free hydroxyl group in position 3.

Experimental.

Morinidin Chloride 3-Methyl Ether (V).—ω-Methoxyresacetophenone (Slater and Stephen, *loc. cit.*) often crystallises with water

of crystallisation and then melts unsharply at 85°. After drying over phosphoric anhydride, such specimens melt at 136—137°.

A mixture of the ketone (5 g.) and acetyl chloride (25 c.c.) was kept for 20 minutes and then gently warmed until a clear solution resulted. This was kept in a vacuum for a long time, and the oil obtained together with 2 : 4 : 6-triacetoxybenzaldehyde (5·2 g.) was dissolved in formic acid (30 c.c.) and the solution saturated with hydrogen chloride during 4 hours. On the following day the product was precipitated by the addition of ether (500 c.c.) and dissolved, after the liquid had been decanted, in ethyl alcohol (100 c.c.). Concentrated hydrochloric acid (20 c.c.) having been added, the solution was refluxed for 35 minutes; most of the alcohol was then distilled off, water (50 c.c.) added, the precipitate isolated, and extracted with boiling 0·5% hydrochloric acid (300 c.c.). The concentration of acid in the filtered extract was increased to 5%; crimson, microscopic needles (3 g.) then separated on cooling. These were recrystallised by the slow evaporation of an alcoholic solution to which so much concentrated hydrochloric acid had been added that the concentration of hydrogen chloride was 5%. The bright red needles thus obtained were dried to constant weight in a vacuum over sulphuric acid (Found: C, 56·8, 56·8; H, 3·9, 4·0; MeO, 9·1. $C_{16}H_{13}O_6Cl$ requires C, 57·1; H, 3·9; MeO, 9·2%).

The dry salt is hygroscopic; it darkens above 200°, but does not melt at 290°. On treatment with water pseudo-base formation was slow, and the colour was completely restored by the addition of hydrochloric acid (distinction from morinidin). The substance is very sparingly soluble in boiling 10% hydrochloric acid. The alcoholic solution has a deep red colour a shade yellower than that of morinidin chloride and distinctly bluer than the aqueous acid solutions. Sodium carbonate added to the latter gives a violet-red coloration, whilst sodium hydroxide produces a very unstable violet. The characteristic behaviour of morinidin on reduction is not exhibited by this monomethyl ether of the substance. On demethylation in the usual manner morinidin iodide and then morinidin chloride were obtained; these were recognised by comparison with authentic specimens. The demethylated salt gave an ether-soluble reduction product which developed an intense blue colour on solution in cold aqueous sodium hydroxide.

3 : 4 : 5-*Trimethoxyphenyl* 2-*Hydroxy*-4 : 6-*dimethoxystyryl Ketone* (VI).—3 : 4 : 5-Trimethoxyacetophenone prepared by Mauthner's method (*J. pr. Chem.*, 1910, **82**, 278) crystallised from light petroleum in needles, m. p. 76—77° (Mauthner gives m. p. 72°). The *p*-nitrophenylhydrazone, m. p. 194—195°, crystallises in bright

yellow needles (Mauthner; reddish-brown needles). The orange-red solution obtained on adding aqueous sodium hydroxide (9 g. in 13 c.c.) to a mixture of 2-hydroxy-4 : 6-dimethoxybenzaldehyde (5 g.), 3 : 4 : 5-trimethoxyacetophenone (6 g.), and methyl alcohol (25 c.c.) was kept at about 60° for 2 days, then cooled, acidified with dilute acetic acid, and the yellow solid resulting from the slow crystallisation of the viscous mass was collected, washed, and dried (yield, 10 g.). The substance crystallised from ethyl alcohol in bright yellow, blunt prisms, m. p. 151—152°, to a dark red liquid (Found : C, 64·1; H, 5·9. $C_{20}H_{22}O_7$ requires C, 64·2; H, 5·9%). The potassium salt is sparingly soluble in dilute aqueous potassium hydroxide and crystallises from the orange-yellow solution in glistening, orange needles.

5 : 7 : 3′ : 4′ : 5′-*Pentamethoxyflavylium Chloride* (VII).—The chalkone is very sensitive to acids and is changed to the flavylium salt with great facility. Actually a hot mixture of acetic acid and concentrated hydrochloric acid was employed and, on cooling, the *chloride* separated in woolly, red needles, m. p. 150°, to a beetle-green liquid. A specimen was crystallised from a mixture of methyl alcohol and hydrochloric acid and dried in a vacuum over sodium hydroxide [Found : MeO (by Pregl–Zeisel method), 31·5. $C_{15}H_6O(OMe)_5Cl$ requires 4MeO, 31·6%]. This salt is moderately readily soluble in water to a brownish-orange solution and is sparingly soluble in dilute hydrochloric acid. The corresponding base is a relatively strong one and the acetate and hydrogen carbonate are stable in cold aqueous solution. In order to prepare solutions of these salts the mauve pseudo-base, obtained by the addition of an excess of sodium carbonate to the flavylium chloride, was dissolved as far as possible in ether, and the extract shaken with dilute acetic acid or treated with water and carbon dioxide. When perchloric acid is added to an aqueous solution of the chloride a gelatinous precipitate is obtained and, on boiling, this very sparingly soluble, brick red *perchlorate* becomes crystalline in the form of microscopic, fibrous needles. The *ferrichloride* crystallises from acetic acid in slender, silky, crimson needles, m. p. 199—201° (Found : C, 43·1; H, 3·8. $C_{20}H_{21}O_6Cl_4Fe$ requires C, 43·3; H, 3·8%). The *mercurichloride* is insoluble in boiling dilute hydrochloric acid containing mercuric chloride.

7(or 5) : 3′ : 4′ : 5′-*Tetrahydroxy*-5(or 7)-*methoxyflavylium Chloride* (VIII or alternative).—A mixture of the pentamethoxyflavylium chloride (2 g.), phenol (10 g.), and hydriodic acid (100 c.c.; *d* 1·7) was boiled in an atmosphere of carbon dioxide for 30 minutes. The iodide crystallised, on cooling, in reddish-brown needles with a greenish-golden reflex (2 g.). The salt was placed in a silvered

flask along with hot alcohol (40 c.c.), concentrated hydrochloric acid (15 drops), and an excess of precipitated silver chloride. A considerable amount of the *chloride* crystallised from the hot solution and the substance (1 g.) was separated from the silver salt by extraction with boiling alcohol and addition of hydrochloric acid to the filtrates. The substance was recrystallised, by slow evaporation of an aqueous methyl-alcoholic hydrochloric acid solution, in short, flat, red needles or plates which blackened above 200° without melting (Found in material dried in a vacuum over sodium hydroxide: C, 54·2; H, 4·4. $C_{16}H_{13}O_6Cl,H_2O$ requires C, 54·3; H, 4·3%). The presence of a methoxyl group in this substance was qualitatively demonstrated by means of the Pregl–Zeisel apparatus, with a mixture of hydriodic acid, phenol and acetic anhydride as reagent. The salt is very sparingly soluble in dilute hydrochloric acid and moderately readily soluble in alcohol to a red solution which becomes blue on the addition of ferric chloride. The colorations developed in aqueous sodium carbonate and sodium hydroxide solutions are rich violet and blue, respectively.

3 : 4 : 5-*Triacetoxy-ω-methoxyacetophenone* (III).—A suspension and solution of 3 : 4 : 5-triacetoxybenzoyl chloride (30 g.; Fischer, Bergmann, and Lipschutz, *Ber.*, 1918, **51**, 45) in dry ether was gradually added to the product of the action of granulated sodium (2·2 g.) on an ethereal solution of methyl αγ-dimethoxyacetoacetate (18 g.; Pratt and Robinson, J., 1925, **127**, 168). The mixture was boiled for 2 hours, kept over-night, and again boiled for 2 hours. After removal of the ether by distillation, the residue was quickly added to a mixture of alcohol (500 c.c.) and aqueous potassium hydroxide (1000 c.c. of 2·5%) through which hydrogen had been led, and agitation by means of a stream of the gas was continued for several hours. After 12 hours the solution was refluxed in an atmosphere of hydrogen for 4 hours, then cooled, acidified with dilute hydrochloric acid, and concentrated to a small volume under diminished pressure. The liquid was twice extracted with ether and then with warm butyl alcohol. The material left after removal of the solvent from the dried (sodium sulphate) ethereal extract partly solidified (2·8 g.) and was acetylated by heating it for 15 minutes with acetyl chloride. The excess of the reagent was distilled away in a vacuum, and the solution of the crude product in acetone shaken with precipitated barium carbonate and filtered. On concentration, crystals separated, and these, after being washed with ether, crystallised from alcohol (yield, 2·2 g.) in colourless, rhombic tablets, m. p. 132—133° (Found: C, 55·4, 55·4; H, 4·7, 4·8; MeO, 9·6; *M*, cryoscopic in camphor, 327. $C_{14}H_{13}O_7{\cdot}OMe$ requires C, 55·5; H, 5·0; MeO, 9·6%; *M*, 324). The sharp

analytical results in conjunction with the method of preparation appear to require that this substance should be regarded as 3 : 4 : 5-triacetoxy-ω-methoxyacetophenone. It is insoluble in cold dilute aqueous sodium hydroxide and gives no coloration with ferric chloride in alcoholic solution. On hydrolysis a pyrogallol derivative was produced and recognised by colour reactions.

The butyl-alcoholic extract mentioned above was dried with sodium sulphate and the solvent removed by distillation in a vacuum, leaving a dark oil (12 g.) from which no crystalline product could be isolated. This material was acetylated exactly like the product from the ethereal extract, and treatment with barium carbonate in acetone solution was again practised. The acetylated product was a dark oil (A) and did not crystallise.

5 : 7 : 3′ : 4′ : 5′-*Pentahydroxy*-3-*methoxyflavylium Chloride* (I).—A stream of hydrogen chloride was passed through a solution of 2 : 4 : 6-triacetoxybenzaldehyde (5 g.) and the oil (A) (10 g.) in anhydrous formic acid (30 c.c.) for 4 hours. After 12 hours, the solid precipitated by the addition of ether was hydrolysed, as in similar cases (compare Pratt and Robinson, J., 1925, **127**, 1182), by boiling aqueous-alcoholic hydrochloric acid. Most of the alcohol was removed by distillation and on the addition of water a dark reddish-brown precipitate was obtained. This was extracted several times with boiling 0·5% hydrochloric acid, the salt being recovered from the combined filtrates by the addition of concentrated hydrochloric acid. The material (1·1 g.) had a golden reflex, but was not definitely crystalline. It dissolved in hot methyl alcohol, but quickly separated again in dark brown needles and these were recrystallised by solution in boiling 0·05% hydrochloric acid and addition of a few drops of concentrated hydrochloric acid to the filtrate. Under the microscope, the crystals are seen to be very short, slender, opaque needles which usually form highly characteristic, stellate clusters. In mass the substance is deep chocolate-brown with a green reflex, especially when rubbed on paper (Found in air-dried material : C, 49·5, 49·6; H, 4·6, 4·5; Cl, 9·1, 9·0; MeO,* 7·8. $C_{15}H_{10}O_6Cl{\cdot}OMe,2H_2O$ requires C, 49·4; H, 4·4; Cl, 9·1; MeO, 8·0%).

The most striking property of this salt is its sparing solubility

* In the Pregl–Herzig–Meyer apparatus—earlier determinations by means of the Pregl–Zeisel apparatus and method gave low results (*e.g.*, MeO, 5·2% even in presence of phenol and acetic anhydride and on boiling for 1·5 hours). Similar results were obtained in the cases of other methoxylated pyrylium salts. Thus 7-methoxy-2 : 4-diphenylbenzopyrylium ferrichloride gave negative or very low results by the Pregl–Zeisel method and approximately correct results when the Pregl–Herzig–Meyer apparatus was employed. This behaviour is, however, exceptional.

in aqueous hydrochloric acid. It is practically insoluble in cold 0·1% hydrochloric acid and very sparingly soluble in boiling 1% acid. The solution in hot 0·05% hydrochloric acid is more brownish-red than that of delphinidin. The salt is soluble in alcohol to a rich bluish-crimson solution and on the addition of ferric chloride this becomes pure blue. The solution in aqueous sodium carbonate is bluish-violet and becomes pure blue on the addition of sodium hydroxide. (The colorations are more or less rapidly destroyed as the result of aërial oxidation.) The formation of a colourless pseudo-base and of a deep violet colour-base was observed under the usual conditions and the salt is completely extracted from aqueous solutions by *iso*amyl alcohol. Owing to the insolubility of the iodide, great difficulty was experienced in the demethylation of the salt. A mixture of the chloride (2 g.), phenol (35 g.), and hydriodic acid (65 c.c.; *d* 1·7) was boiled in an atmosphere of carbon dioxide for 3 hours, but a clear solution was not produced at any stage. Unchanged iodide (0·91 g.) was collected on a sintered-glass filter, and crude delphinidin iodide (0·45 g.) separated from the mother-liquor on standing. The recovered unchanged iodide (0·91 g.) was boiled with phenol (50 g.) and hydriodic acid (50 c.c.) for 1 hour, but again 0·56 g. was recovered and the delphinidin iodide obtained amounted to 0·08 g. A further quantity of the original chloride was dissolved in phenol on the steam-bath, and hydriodic acid (*d* 1·96) gradually added to the solution boiling in an atmosphere of carbon dioxide. Even in this case the iodide of the methoxylated base separated. The delphinidin iodide was recrystallised from phenol–hydriodic acid and then converted in the usual manner into the crystallised chloride. This material had the properties of delphinidin chloride and dissolved in aqueous sodium carbonate to a pure blue solution. No differences from delphinidin chloride could be detected, but the small amount available precluded a detailed examination of the characteristic hydrates.

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