CC.—*A Synthesis of Pyrylium Salts of Anthocyanidin Type. Part XV. The Synthesis of Cyanidin Chloride by Means of* O-*Benzoylphloroglucinaldehyde.*

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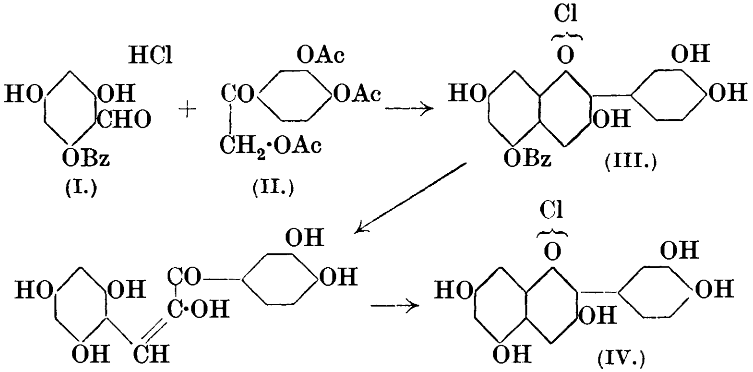
THE methods for the syntheses of the anthocyanidins by way of their methyl ethers, unless very carefully controlled, are apt to lead to impure products in the final stage of demethylation by means of hydriodic acid in the presence of phenol. Although this difficulty can be readily overcome, it is unlikely that workers without previous experience in the group would be successful in doing so at the first attempt, and we have for some time realised the desirability of devising, if possible, a synthetic method of preparation of the pure anthocyanidins that could be used, say, as a laboratory exercise by students. The processes developed in this and the two following communications are readily carried through and result in the production of homogeneous anthocyanidins.

Direct syntheses of pelargonidin and peonidin with the aid of *O*-triacetylphloroglucinaldehyde have been already described (Nolan, Pratt, and Robinson, J., 1926, 1968), but the yields were poor and the products difficult to purify. The synthesis of cyanidin by the same method has been attempted; it proceeds rather more smoothly but is still unsatisfactory. *O*-Benzoylphloroglucinaldehyde, on the other hand, gives good results on condensation with acetylated derivatives of substituted ω-hydroxyacetophenones by means of hydrogen chloride, and after comparative trials we selected ethyl acetate or ethyl acetate–alcohol as the most suitable solvent. It is remarkable that in all the cases examined the acetyl groups are removed by hydrolysis from the ketonic component either in the condensation or in the crystallisation of the product, but the benzoyloxy-group remains unaffected. The products are thus the benzoylated anthocyanidins and these exhibit the alkali-colour-reactions of the corresponding anthocyanins; *e.g.*, benzoylcyanidin, benzoylpelargonidin, benzoylpeonidin, and benzoylmalvidin resemble cyanin, pelargonin, peonin, and malvin, respectively. Since the benzoyl groups are in position 5, this evidence is in agreement with the view that the disaccharide units in the anthocyanins mentioned are also in position 5.

The benzoyloxy-groups are hydrolysed by means of aqueous alcoholic sodium hydroxide, a reagent which also ruptures the pyrylium ring, and finally by treatment with hydrochloric acid the anthocyanidin is produced. The case described in the present communication is represented below.



We are deeply indebted to Geheimrath Professor R. Willstätter for kindly sending us a specimen of cyanidin chloride of natural origin. After purification of this, the identity of the natural and the synthetic material was established.

EXPERIMENTAL.

ω : 3 : 4-Triacetoxyacetophenone (II) was prepared by a method based on that of Voswinckel (*Ber.*, 1909, **42**, 4651). A mixture of pure ω-chloro-3 : 4-dihydroxyacetophenone (Dreczgowski, *J. Russ. Phys. Chem. Soc.*, 1893, **25**, 154) (10 g.), potassium acetate (10 g.), and acetic anhydride (40 c.c.) was heated on the steam-bath for 3 hours and then refluxed for ½ hour. The cooled product was decomposed by water (200 c.c.). The ketone (yield, 14 g.) crystallised from carbon tetrachloride and then from methyl alcohol (charcoal) in colourless, rhombic plates, m. p. 95° (Found : C, 57·0; H, 5·0. Calc. for $C_{14}H_{14}O_7$: C, 57·1; H, 4·8%).

5-O-*Benzoylcyanidin Chloride* (III).—A solution of *O*-benzoylphloroglucinaldehyde (2·5 g.) (Part I, J., 1927, 1713) and ω : 3 : 4-triacetoxyacetophenone (3·5 g.) in a mixture of ethyl acetate (50 c.c.) and 98% alcohol (20 c.c.) was cooled and saturated with hydrogen chloride. After 3 days the crystalline product was collected (4·6 g.); very little oxonium salt remained in the mother-liquor. When dry ethyl acetate (70 c.c.) was used instead of the mixture with alcohol, the yield was 4·0 g. of a somewhat inferior product. The crude salt (7·5 g.) was purified by solution in the minimum quantity of 80% ethyl alcohol and passage of hydrogen chloride into the solution (which boils) for 5 minutes. On cooling, the *benzoylcyanidin chloride* separated in compact crystals having a dark green appearance (5 g.). Recrystallisation was effected by solution in a mixture of boiling ethyl alcohol and 0·5% hydrochloric acid (1 : 1) and addition of hot 10% hydrochloric acid until there were indications of the incipient separation of solid. The cooled solution deposited dark red, slender, prismatic needles which matted together on the filter and when dried had a purplish appearance in mass. The substance was dried in a high vacuum and was then too hygroscopic to weigh accurately; it was kept in the air until the weight was constant (Found : C, 57·8; H, 4·2. $C_{22}H_{15}O_7Cl,1{\cdot}5H_2O$ requires C, 58·3; H, 4·0%). Benzoylcyanidin chloride dissolves in ethyl alcohol to a bluish-red solution that becomes permanganate-coloured on dilution but never violet (distinction from benzoylpelargonidin, benzoylpeonidin and benzoylmalvidin); on the addition of water a pink solution is obtained and this is rapidly decolorised on heating. The restoration of colour by the addition of hydrochloric acid is immediate but not quite complete. The solution of the salt in aqueous sodium carbonate is pure blue, and becomes a little greener on the addition of alcohol. Ferric chloride added to an alcoholic solution gives an intense deep blue coloration; on dilution with water the solution becomes reddish-violet—the reaction is identical with that exhibited by cyanidin.

Cyanidin Chloride (IV).—Benzoylcyanidin chloride (5 g.) was added to cold 8% aqueous-alcoholic sodium hydroxide (65 c.c.; solvent was 3 vols. of alcohol mixed with 2 vols. of water), air being excluded from the apparatus by nitrogen. The mixture, which was frequently agitated, was at first deep blue and gradually became dull orange-brown; after 3 hours, concentrated hydrochloric acid (100 c.c.) was added, and the whole heated at 60° until no further increase in the intensity of the colour occurred. After being kept for 12 hours in the ice-chest, the solid was collected, washed with 5% hydrochloric acid and ether, and dried in the air (yield, 3 g.).

This product was almost pure, but was converted into the picrate, which crystallised from not too much aqueous-alcoholic picric acid in fibrous needles. The chloride regenerated in the usual manner, from a solution in methyl alcohol containing hydrogen chloride by the addition of ether, was a chocolate-brown, crystalline powder. The salt was recrystallised by solution in alcohol, addition of 10% hydrochloric acid, and distillation of the alcohol until crystals made their appearance in the liquid. On cooling, the cyanidin chloride separated almost completely in clusters of straight, thin, chocolate-brown needles (Found: C, 52·8; H, 3·9; Cl, 10·1. Calc. for $C_{15}H_{11}O_6Cl,H_2O$: C, 52·9; H, 3·8; Cl, 10·4%).

Under other conditions the salt usually crystallises in prismatic needles or elongated rhombic prisms. The specimen exhibited all the properties of cyanidin chloride; for example, the sparing solubility in dilute sulphuric acid, the colours of acid, neutral, and alkaline alcoholic and aqueous solutions, the mode of pseudo-base formation, the precipitation of the colour-base by the addition of water to an alcoholic solution, and the ferric chloride colour reaction were all found to be normal.

The crude natural cyanidin chloride supplied by Professor Willstätter was purified through the picrate and crystallised in the manner described above for the synthetic material. A careful comparison disclosed no differences existing between the two specimens. The appearance and habit of crystallisation were identical and the solubility in 0·1% hydrochloric acid was also the same (colorimetric determination). A filtered saturated solution of the synthetic material in 0·1% hydrochloric acid dissolved no trace of the natural, and *vice versa*; the solutions were only weakly coloured.

The natural specimen (5·08 mg.) and the synthetic (5·07 mg.) were separately dissolved in 50 c.c. of ethyl alcohol. The following description applies to both solutions, no shade of divergence being noted at any stage. The solution was dark red, bluish-red in thin layers (10 c.c. treated with 1 c.c. of dilute aqueous ferric chloride became deep blue and then rapidly changed to green and greenish-yellow; on long standing, yellowish-brown), and 40 c.c. made up to 100 c.c. with alcohol had a more bluish-red colour (colorimetric comparison). 50 C.c. of this solution were mixed with 10 c.c. of aqueous copper acetate, giving a bright blue solution which soon became greenish-blue, bluish-green, and green, successively, and the colour faded; after 12 hours, the green solutions became turbid, but if at once heated there was a colourless precipitate and a brown film formed on the sides of the vessel. The remainder of the cyanidin solution was diluted to 100 c.c. with alcohol, giving a very bluish-red solution (colorimetric comparison) (50 c.c. treated with potassium acetate gave a violet solution and then, on the addition of hydrochloric acid, a red solution). Dilution of the remainder of the cyanidin solution to 250 c.c. with water gave a reddish-violet solution (colorimetric comparison), which became pink on acidification (colorimetric comparison); when a portion (not acidified) was heated, it became colourless, and on strong acidification with hydrochloric acid scarcely any colour-salt was regenerated. On boiling, a part of the colour was restored (comparison of rate of pseudo-base formation and extent and rate of regeneration of colour-salt). A similar quantitative comparison was made in connexion with the alkali-colour-reactions in aqueous and alcoholic solutions and again no differences could be detected.

The manuscript of this paper was prepared in March and we must now append some preliminary comments on a memoir which appeared on April 11th, in which it is alleged that cyanidin chloride is not 3 : 5 : 7 : 3′ : 4′-pentahydroxyflavylium chloride.

The evidence on which Malkin and Nierenstein (*Ber.*, 1928, **61**, 797) base this claim is, however, wholly inadequate to sustain their view, as may be seen from a brief analysis of their argument, which runs as follows :

(1) A specimen, X, considered to be 3 : 5 : 7 : 3′ : 4′-pentahydroxyflavylium chloride, was obtained by the demethylation of its trimethyl ether (Pratt and Robinson). This had certain definite properties; *e.g.*, it gave a pure blue coloration in aqueous solutions having p_H 11·57.

(2) The specimen X differed in many respects from pure cyanidin chloride (Y) derived from cyanin chloride. Malkin and Nierenstein establish this by comparisons described with much circumstantial detail; but here they are forcing an open door, since it is agreed that X and Y as prepared by these authors might exhibit somewhat divergent properties.

(3) Our statement (J., 1927, 1711) that the results of the earlier anthocyanidin syntheses are subject to unexplained variations (hence the necessity for the present communication) was noticed by Malkin and Nierenstein, but they nevertheless considered X to be perfectly homogeneous, chiefly because it was found to be identical with a specimen (Z) synthesised from *O*-triacetylphloroglucinaldehyde and ω : 3 : 4-triacetoxyacetophenone.

This section of the argument is of vital importance, since our view is that X was not a specimen of a pure pentahydroxyflavylium chloride.

The method of preparation of Z given by Malkin and Nierenstein is based on the process previously used by Nolan, Pratt, and Robinson (J., 1926, 1968) for the syntheses of pelargonidin and peonidin and in the original paper on the latter topics the difficulties experienced in the isolation of the pure salts were emphasised. As stated above, we have tested this synthesis of cyanidin and abandoned it as unsatisfactory. Its use as a method of preparation of a standard is unquestionably an inversion of correct procedure.

A proof of the identify of X and Z is stated to be found in the fact that Z, like X, gives a pure blue coloration at p_H 11·57. We admire the delicacy of perception that enables the p_H of a solution to be determined to one part in a thousand by observation of a change of colour from violet-blue to pure blue. Even if the specimens X and Z were identical, that would not prove that they consisted of pure pentahydroxyflavylium chloride; it would certainly suggest that the impurities have nothing to do with the demethylation and would point to the common factor, namely, the use of *O*-triacetylphloroglucinaldehyde as the starting point (Malkin and Nierenstein state that triacetylphloroglucinaldehyde has m. p. 157°, instead of 151° as recorded by Pratt and Robinson, but they have overlooked the fact that this correction had already been made by the present authors, *loc. cit.*, p. 1713).

The divergences noted as existing between X and Y are not inconsistent with the view that X was an impure specimen of Y except in the one particular that Y gave a good yield of an oxidation product, no trace of which was obtainable from X under the same conditions. This is the only experiment mentioned by Malkin and Nierenstein which has in our opinion a real bearing on the question of the constitution of cyanidin and in this case the details were not disclosed.

After our study of the paper of Malkin and Nierenstein we performed the following experiment. A specimen of cyanidin chloride was prepared from mecocyanin chloride, for the provision of which we are greatly indebted to Professor Willstätter. This was quantitatively compared with our newly synthesised salt (above) and differences, such as those noted by Malkin and Nierenstein as existing between X and Y, could not be detected. The natural and the synthetic specimens gave the same colorations with solutions of definite p_H (6·0, 7·0, 8·0, 9·0, and 10·0) made from the universal buffer solution supplied by the British Drug Houses, Limited. 2 C.c. of a 0·005% alcoholic solution were added to 50 c.c. of the various solutions. As a check, very dilute hydrochloric acid was added to very dilute aqueous sodium carbonate containing thymolphthalein until the solution became colourless. The p_H should then be 9·0—9·3, and both salts dissolved in this medium to a pure blue solution.

The test with copper sulphate in very dilute solution was repeated under the conditions prescribed by Malkin and Nierenstein with the result that the cyanidin chloride from mecocyanin and our synthetical salt showed an identical behaviour, and it should be observed that this behaviour was similar to that which Malkin and Nierenstein state to be characteristic of natural cyanidin chloride and differed from that of the supposed synthetic pentahydroxyflavylium chloride of these authors.

A sample of cyanidin chloride synthesised by the first method of Pratt and Robinson (J., 1924, **125**, 172) was also examined; it was not quite pure, but its behaviour was so close to that of the cyanidin chloride from mecocyanin that there could be no doubt in regard to the fundamental identity of the substances. Furthermore the description of the salt prepared from trimethylcyanidin by Malkin and Nierenstein does not apply to the material obtained in this manner by Pratt and Robinson (J., 1925, **127**, 1189).

Finally, we note that Malkin and Nierenstein have prepared ω-chloro-3 : 4-diacetoxyacetophenone by the interaction of diacetoxybenzoyl chloride and diazomethane. They state that the yellow substance has m. p. 94—95° and have apparently overlooked the already known and convenient method of preparation of this colourless chloro-ketone, which actually melts at 110° * (Voswinckel, *loc. cit.*). It has recently been observed in this laboratory that the interaction of acid chlorides and diazomethane yields the diazoketones, and the case of 3 : 4-diacetoxybenzoyl chloride is no exception. Drs. W. Bradley and G. Schwarzenbach have found that the primary product in this case is ω-diazo-3 : 4-diacetoxyacetophenone, yellow crystals, m. p. 77°, and the details will be published in due course.

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* Dreczgowski (*J. Russ. Phys. Chem. Soc.*, 1893, **25**, 157) gave the m. p. 95° for this substance, but this was corrected by Voswinckel and we have confirmed the m. p. 110° on several occasions. The m. p. of ω : 3 : 4-triacetoxyacetophenone is 95°.