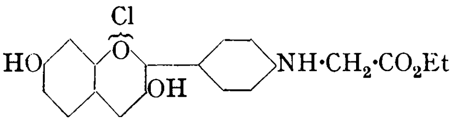
98. *Nitrogenous Anthocyanins. Part V. Synthesis of Substituted Aminoflavylium Salts.*

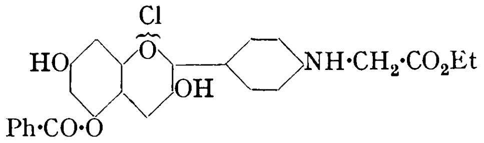
By A. D. AINLEY and ROBERT ROBINSON.

WHEN it became clear that the nitrogenous anthocyanins comprise a flavylium salt nucleus combined with an amino-acid residue, synthetical work directed to the preparation of typical substances of this kind was initiated. The problem proved to be a very difficult one, but some progress can be reported.

After a number of unsuccessful attempts in other directions, 4-amino-ω-acetoxyacetophenone (Robinson and Robinson, J., 1932, 1442) was converted into *4-carbethoxymethylamino-ω-acetoxyacetophenone*, $CO_2Et{\cdot}CH_2{\cdot}NH{\cdot}C_6H_4{\cdot}CO{\cdot}CH_2{\cdot}OAc$ (I) by treatment with ethyl bromoacetate in the presence of sodium iodide. On condensation with β-resorcylaldehyde in dioxan solution with the help of hydrogen chloride, *4'-carbethoxymethylamino-*3 : *7-dihydroxyflavylium chloride* (II) was obtained.

The ketone was also condensed with 2-*O*-benzoylphloroglucinaldehyde and hydrogen chloride in ethyl acetate solution with formation of *4'-carbethoxymethylamino-*3 : *7-dihydroxy-5-benzoyloxyflavylium chloride* (III).


(II.)


(III.)

These experiments appeared to clear the ground for an attempt to synthesise an isomeride of betanidin in which the nitrogen would be attached at position 4' or at some other position in the side-phenyl nucleus. We were, however, desirous of extending such preliminaries to derivatives of 5- and 7-aminoflavylium salts, and we have not yet been successful along the ordinary lines. Thus we have not been able to obtain a suitable derivative of 6-amino-2 : 4-dihydroxybenzaldehyde, although work in this direction is still in progress.

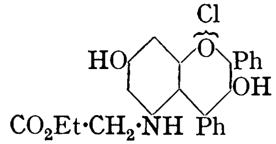
Phloroglucinol condensed with ethyl aminoacetate with formation of *ethyl* 3 : *5-dihydroxyphenylaminoacetate*, $C_6H_3(OH)_2{\cdot}NH{\cdot}CH_2{\cdot}CO_2Et$, but the attempt to introduce the formyl group failed.

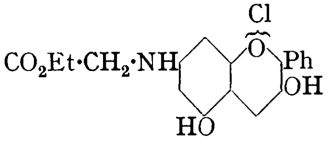
An indication of a method of attack has, however, been obtained by the synthesis of two flavylium salts of the required type by an adaptation of the new method of condensation of polyhydroxyphenols with unsaturated ketones in the presence of chloranil and hydrogen chloride (Robinson and Walker, J., 1934, 1435; 1935, 941). If such a substance as phenyl methyl diketone, $Ph{\cdot}CO{\cdot}CO{\cdot}CH_3$, reacted in the tautomeric form, $Ph{\cdot}CO{\cdot}C(OH){:}CH_2$, it would come within the scope of this synthetic method. The reaction has been found to take the anticipated course in two cases, and this interesting resource will be further explored.

Condensation of ethyl 3 : 5-dihydroxyphenylaminoacetate with phenyl benzyl diketone in alcoholic solution in the presence of chloranil and hydrogen chloride afforded 5(or 7)-*carbethoxymethylamino-*3 : 7(or 5)*-dihydroxy-4-phenylflavylium chloride* (IV), and phenyl methyl diketone, treated in the same way, gave rise to 7(or 5)*-carbethoxymethylamino-*

3 : 5(or 7)-*dihydroxyflavylium chloride* (V). The alternative constitutions are represented in (IV) and (V), and (V) might be constituted like (IV), or (IV) like (V).

(IV.)





(V.)

EXPERIMENTAL.

Ethyl 4-*Carbethoxyphenylaminoacetate.*—Dry hydrogen chloride was passed into a suspension of 4-carboxyphenylglycine (10 g.) in alcohol (150 c.c.) until complete solution was effected. After a few hours the liquid was added to water (1 l.), stirred, and kept until separation of solid was complete. The *product* crystallised from light petroleum (b. p. 40—60°) in stout, very pale yellow prisms (6·0 g.), m. p. 63—63·5° (Found : C, 61·9; H, 6·9; N, 5·7. $C_{13}H_{17}O_4N$ requires C, 62·1; H, 6·8; N, 5·6%). No use could be made of this compound in directions which it is unnecessary to describe in detail; neither could the acid chloride of ethyl *N*-4-carboxyphenyl-*N*-methylaminoacetate be obtained. We were unable to introduce the chloroacetyl group in the *p*-position to nitrogen in ethyl *N*-phenyl-*N*-methylaminoacetate or ethyl *N*-acetyl-*N*-phenylaminoacetate, although several methods were tried in each case.

ω-*Chloro*-4-p-*toluenesulphonamidoacetophenone.*—A solution of ω-chloro-*p*-aminoacetophenone (4·1 g.) and *p*-toluenesulphonyl chloride (5·0 g.) in pyridine (50 c.c.) was stirred at 0° for 30 minutes. The mixture was added to dilute hydrochloric acid; the paste that separated gradually solidified. The *substance* crystallised from alcohol (charcoal) in pale yellow prisms (6·0 g.), m. p. 184° (Found : N, 4·6. $C_{14}H_{14}O_3NClS$ requires N, 4·5%).

4-p-*Toluenesulphonamido-ω-acetoxyacetophenone.*—A mixture of 4-amino-ω-acetoxyacetophenone (1 g.) and *p*-toluenesulphonyl chloride (1·2 g.) was shaken for 5 minutes with a little pyridine, and the reaction completed by heating for 5 minutes on the steam-bath. The *product* crystallised from aqueous alcohol in long, thin, rectangular plates (1·5 g.), m. p. 179—179·5° (Found : C, 58·7; H, 4·9; N, 4·1; S, 9·2. $C_{17}H_{17}O_5NS$ requires C, 58·8; H, 5·0; N, 4·0; S, 9·0%).

4-p-*Toluenesulphonamido-ω-hydroxyacetophenone.*—Ethyl bromoacetate (0·5 g.) and ether (1—2 c.c.) were added gradually to a stirred solution of 4-*p*-toluenesulphonamido-ω-acetoxyacetophenone (1 g.) in aqueous sodium hydroxide (10 c.c. of 8%). After 30 minutes' stirring, the mixture was added to 7% hydrochloric acid (25 c.c.), and the solid collected (0·9 g.); it crystallised from alcohol in very pale yellow, long, thin plates, m. p. 202—204° (decomp.) (Found : C, 58·8; H, 4·9; N, 4·8; S, 10·6. $C_{15}H_{15}O_4NS$ requires C, 59·0; H, 4·9; N, 4·6; S, 10·5%). The *substance* could not be employed for the desired purpose.

4-*Carbethoxymethylamino-ω-acetoxyacetophenone* (I).—Ethyl bromoacetate (8·5 g.) was added to a solution of sodium iodide (8·5 g.) in acetone (70 c.c.) and when the reaction was complete 4-amino-ω-acetoxyacetophenone (10 g.) was added to the filtered liquid, which was then refluxed for 15 hours. The product was added to water (100 c.c.), the mixture boiled, and filtered, and the residue extracted four times with boiling water–alcohol (5 : 1). The solid (2 g.) that separated on cooling crystallised from alcohol in pale yellow needles, m. p. 113° (Found : C, 60·5; H, 6·2; N, 5·0. $C_{14}H_{17}O_5N$ requires C, 60·2; H, 6·1; N, 5·0%).

4′-*Carbethoxymethylamino*-3 : 7-*dihydroxyflavylium Chloride* (II).—A solution of carbethoxymethylaminoacetoxyacetophenone (0·5 g.) and β-resorcylaldehyde (0·25 g.) in dry dioxan (15 c.c.) was saturated with hydrogen chloride at 0° for 3½ hours, kept at 0° for 13 days, filtered, and poured into ether (250 c.c.). The dark bluish-red flocculent precipitate (0·45 g.) crystallised from alcohol–ethyl acetate (1 : 3) in compact clusters of very slender needles (Found : loss at 110° in a high vacuum, 10·2. Found in dried material : C, 60·9; H, 4·6; N, 3·9; Cl, 9·6. $C_{19}H_{18}O_5NCl,2{\cdot}5H_2O$ requires H_2O, 10·6%. $C_{19}H_{18}O_5NCl$ requires C, 60·7; H, 4·8; N, 3·7; Cl, 9·3%).

4′-*Carbethoxymethylamino*-3 : 7-*dihydroxy*-5-*benzoyloxyflavylium Chloride* (III).—Hydrogen chloride was passed into a solution of carboxymethylaminoacetoxyacetophenone (1 g.) and 2-*O*-benzoylphloroglucinaldehyde (1 g.) in ethyl acetate (80 c.c.) at 0° until saturated and the mixture was kept for 12 hours at 0°, again saturated with hydrogen chloride, and kept at 0° for 12 days. After filtration from a light-coloured precipitate the deep bluish-violet solution was added to ether, and the purplish-black, deliquescent precipitate (0·58 g.) collected. A solution in alcohol–ethyl acetate (1 : 2) gradually deposited crystals when kept at 0° for 2 days. The clusters of very dark purple, slender needles had a green reflex (Found : loss at 110° in a high vacuum, 6·9, 7·0. Found in dried material : C, 63·0 ; H, 4·7 ; N, 3·0 ; Cl, 7·7. $C_{26}H_{22}O_7NCl,2H_2O$ requires H_2O, 6·8%. $C_{26}H_{22}O_7NCl$ requires C, 63·0 ; H, 4·4 ; N, 2·8 ; Cl, 7·2%).

By using *o*-vanillin as the aldehyde component, an analogous salt was obtained (dioxan–ethyl acetate as solvent) ; it crystallised from acetic acid, containing a trace of hydrogen chloride, in small plates, brown-red by transmitted light and exhibiting a blue metallic reflex (Found : N, 3·8. Calc. : N, 3·6%).

2-O-p-*Toluenesulphonylphloroglucinaldehyde.*—Several methods for the preparation of this substance were tried ; some failed altogether and none gave good results. It will suffice to say that phloroglucinaldehyde (2 g.) was treated with *p*-toluenesulphonyl chloride and 10% aqueous potassium hydroxide in acetone solution at — 2° to + 2°. The product was dissolved in chloroform, and the solution mixed with ether and extracted with aqueous sodium carbonate. The extract was acidified, and the product taken up in ether and eventually crystallised from chloroform–light petroleum and from benzene ; it formed slightly brownish, thick prisms (0·2 g.), m. p. 130° (Found : C, 54·5 ; H, 3·9 ; S, 10·4. $C_{14}H_{12}O_6S$ requires C, 54·5 ; H, 3·9 ; S, 10·4%). This *substance* was prepared in order to attempt the direct introduction of substituted ammonia residues by replacement of the *p*-toluenesulphonoxy-group. In view of the difficulty of the preparation, the project was not pursued.

Ethyl 3 : 5-*Dihydroxyphenylaminoacetate.*—This substance could not be obtained from phloramine by interaction with ethyl iodoacetate. A solution of anhydrous phloroglucinol (10 g.) and ethyl aminoacetate (8 c.c.) in alcohol (24 c.c.) was kept under nitrogen for 3 days and then concentrated under diminished pressure over sulphuric acid. The magma of almost colourless prisms was washed with water and dried (10·8 g., m. p. 150—154°). The *substance* was readily soluble in ethyl alcohol, moderately readily soluble in ether and hot water, and sparingly soluble in cold water. It crystallised from water in short thick prisms, m. p. 153·5—154° (Found : C, 56·7 ; H, 6·3 ; N, 6·9. $C_{10}H_{13}O_4N$ requires C, 56·9 ; H, 6·3 ; N, 6·6%). The reaction can also be carried out in aqueous solution with about the same results.

Various attempts to introduce the formyl group were made and in one case, using the triacetyl derivative with hydrogen cyanide and aluminium chloride, a product yielding a *p*-nitrophenylhydrazone was isolated, but the yield was so small that the work was abandoned.

5(or 7)-*Carbethoxymethylamino*-3 : 7(or 5)-*dihydroxy*-4-*phenylflavylium Chloride* (IV or like V).—A well-shaken mixture of ethyl 3 : 5-dihydroxyphenylaminoacetate (2·1 g.), phenyl benzyl diketone (2·2 g.), chloranil (2·5 g.), and ethyl-alcoholic hydrogen chloride (40 c.c. of 12%) became dark mauve after 3 hours and the chloranil passed into solution. After 2 days the dark brown liquid was filtered into ether and the product (2·05 g.) was collected and washed with anisole (15 c.c.) containing a trace of hydrogen chloride. The crude product (1 g.) was dissolved in ethyl-alcoholic hydrogen chloride (24 c.c. of 2%) and slowly diluted with ether, by means of the vapour, a very dark purple, almost black, powder consisting of microscopic plates (0·8 g.) being obtained (Found : C, 60·1 ; H, 5·2 ; N, 3·0. $C_{25}H_{22}O_5NCl,2{\cdot}5H_2O$ requires C, 60·4 ; H, 5·4 ; N, 2·8%). The *substance* showed the general character of an aminoflavylium salt. The alcoholic solution is reddish-mauve and on dilution becomes nearly colourless ; addition of hydrochloric acid causes partial regeneration of the violet colour. On addition of sodium carbonate to an alcoholic solution the colour becomes browner and duller ; sodium hydroxide gives a reddish-brown solution. The salt is insoluble in water and very sparingly soluble in hot dilute 1% hydrochloric acid to a faintly violet solution.

7(or 5)-*Carbethoxymethylamino*-3 : 5(or 7)-*dihydroxyflavylium Chloride* (V or like IV).—The foregoing preparation was repeated, phenyl methyl diketone (1·5 g.) being substituted for the phenyl benzyl diketone. During 5 days the mixture became dark purple ; the liquid was filtered and mixed with ether, giving 1·4 g. of a purplish-black precipitate. This, treated as in the foregoing example, was obtained as a black powder of microscopic thin prisms, which were dark brownish-purple by transmitted light (Found : C, 53·3 ; H, 5·3 ; N, 3·4.* $C_{19}H_{18}O_5NCl,3H_2O$ requires C, 53·1 ; H, 5·6 ; N, 3·3%). The *salt* showed the general character of its class.

The reddish-violet solution in hot 1% hydrochloric acid is not completely extracted on shaking with *iso*amyl alcohol. The violet solution in alcohol is partly decolorised on dilution and the colour is regenerated on the addition of hydrochloric acid. The solution in sodium carbonate is brownish-mauve ; that in aqueous sodium hydroxide is reddish-brown and remains so on boiling.

p-*Acetoxypropiophenone.*—This *substance* was prepared in order to attempt its conversion into an α-diketone. A mixture of *p*-hydroxypropiophenone (10 g.) and acetic anhydride (50 c.c.)

---

* A specimen recrystallised by slow evaporation of a solution in 6% alcoholic hydrogen chloride.

was refluxed for 4 hours; the product, isolated in the known manner, formed long needles, m. p. 59°, from aqueous alcohol (Found: C, 68·8; H, 6·2. $C_{11}H_{12}O_3$ requires C, 68·8; H, 6·3%).

The authors thank the Department of Scientific and Industrial Research for a Senior Research award (A. D. A.) and are also grateful for research grants made by Imperial Chemical Industries Ltd. and by the Government Grants Committee of the Royal Society. The same acknowledgments apply to Part III of this series.

DYSON PERRINS LABORATORY, OXFORD UNIVERSITY.

[*Received, January* 14*th*, 1937.]