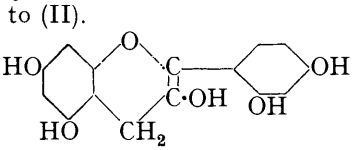
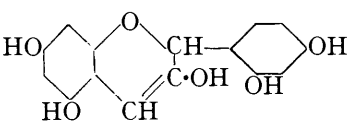
168. *The Constitution of Cyanomaclurin.*

By Herbert Appel and Robert Robinson.

Cyanomaclurin, isolated by A. G. Perkin and Cope (J., 1895, **67**, 939) from jackwood (*Artocarpus integrifolia*), was later more fully examined by Perkin (J., 1905, **87**, 715), who suggested the structure (I) (discussing also two other formulæ which may now be definitely ruled out) largely on the grounds of the general resemblance exhibited to catechin and the degradation of the substance, on fusion with potash, to phloroglucinol, β-resorcylic acid, and resorcinol. This view of the constitution of the substance was supported by the preparation of supposed penta-acetyl and pentabenzoyl derivatives, but it must be stated at once that we now regard these as tetra-acylcyanomaclurins.

Perkin's penta-acyl derivatives being assumed to be correctly so described, the optical activity of cyanomaclurin recorded in this communication would require the slight modification to (II).

(I.) 

 (II.)

Through the kindness of Professor A. G. Perkin, a small quantity of cyanomaclurin was available for investigation, and we first sought evidence of the fundamental correctness of (I) and (II) in respect of the carbon–oxygen skeleton. This could best be obtained by oxidation of cyanomaclurin to morin or to a morinidin salt and in the latter connection our experiments on the conversion of catechin into cyanidin chloride were instituted (this vol., p. 426). The action of bromine on cyanomaclurin in dioxan solution afforded pink solutions, but the morinidin bromide could not be isolated in this way.

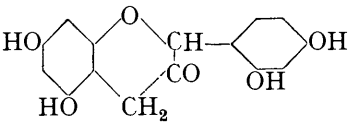
The very striking deep blue colour developed on gentle heating of alkaline solutions of cyanomaclurin (hence the name) was, however, very like that of a solution of morinidin in dilute aqueous sodium hydroxide, and similar changes occurred on heating, keeping, or acidifying the solutions.

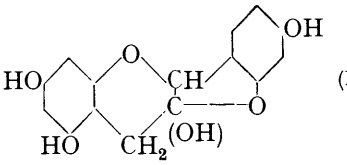
It seemed possible that cyanomaclurin is actually converted into the salt of morinidin-colour-base by the action of warm alkalis, possibly as the result of autoxidation (aeration)

* $C_{16}H_{14}O_6$ requires *M*, 302; $C_{24}H_{22}O_{10}$ requires *M*, 470.

or of a disproportionation of Cannizzaro-reaction type. Under special conditions we were able to show that the cyanomaclurin alkali-reaction is actually to be explained in this way, although we isolated only a few mg. of pure morinidin chloride after acidification of the solution. This was due in part to the very small amount of cyanomaclurin remaining at this stage and in part to difficulties in the purification similar to those encountered in the synthesis of morinidin chloride (Charlesworth, Chavan, and Robinson, J., **1933**, 370). Direct comparison with an authentic specimen established the identity of the morinidin salt to our satisfaction.

The skeleton having been recognised, we were in a better position to consider the actual detail of the alternative formulæ, which must embrace a ketone (III) and a semi-acetal (IV) in addition to (II).

(III.) 

 (IV.)

A re-examination of the acetyl derivative of cyanomaclurin showed that it is a tetra-acetyl compound (OAc estimations) and the same observation was made in regard to the tetrabenzoylcyanomaclurin (C and H estimation). Actually the theoretical values (C, H) for the tetra- and the penta-acetate are not very different. The choice seems then to lie between (III) and (IV), and we preferred the latter because it explained the failure of cyanomaclurin to be oxidised readily in acid solution with formation of morinidin salts. We considered that in neutral or acid solutions cyanomaclurin is (IV) and that in alkaline solution the ring might be broken with formation of (III), which then suffered oxidation to morinidin-colour-base. We were naturally well aware that the semi-acetal group is not *directly* hydrolysed by alkalis and the view we took was that the ring fission was a process consequent on salt-formation through the phenolic hydroxyls. In other words it might be the result of a change in stability due to the assumption of the anionic charge. The fact that cyanomaclurin does not exhibit mutarotation cannot be cited against (IV) so long as the possibility remains open that the modification (III), or its hydrate, represents an unfavoured configuration. Mutarotation would hardly be due to ring closure in *cis-cis* and *cis-trans* forms; one of these would doubtless preponderate or even be produced exclusively in the open-chain semi-acetal equilibria.

The formula (IV) is also favoured by the correspondence between catechin and cyanomaclurin in many reactions, including so-called phlobaphene formation. The natural flavanones are in general quite stable to hot dilute acids and, although the contrast with cyanomaclurin might be attributed, on the basis of (III), to the removal of the carbonyl group from direct attachment to the phloroglucinol nucleus, yet (IV) offers an even more natural explanation. The conclusive argument in favour of (IV) is derived from the preparation of an amorphous *trimethyl* ether of cyanomaclurin. This is insoluble in aqueous alkalis (a proof that, as suggested above, the semi-acetal group is not itself directly affected by alkalis) and it does not yield a semicarbazone. It forms a *monoacetyl* derivative, also amorphous. The poverty of our resources precluded a further examination of these derivatives.

Experimental.

Optical Activity of Cyanomaclurin.—In ethyl acetate (*c*, 1·0), $[\alpha]_D^{20°}$ + 215°; in water (*c*, 0·94), $[\alpha]_D^{20°}$ + 192°. No mutarotation was observed in either case; a drop of aqueous ammonia was added to the aqueous solution (0·5 c.c.) and the rotation was unchanged during 10 minutes; further observation was hindered by the development of a red coloration. As the asymmetric carbon atom is contiguous to a carbonyl group, or potential carbonyl group, it might be thought surprising that cyanomaclurin retains its optical activity during the process of isolation. Dr. A. Weissberger contributes, in this connection, a note which shows that even *d*-benzoin is racemised with difficulty in acid solution :

" *d*-Benzoin dissolved in *ca.* 0·3*N*-alcoholic (90%) hydrogen chloride showed no observable

change of rotatory power after keeping at room temperature for 18 hours. On boiling, the rotatory power was diminished by 20 per cent. of its value in the course of 1 hour."

Tetra-acetylcyanomaclurin.—Professor Perkin's specimen was examined (Found: MeCO, 38·2. $C_{23}H_{20}O_{10}$ requires C, 60·5; H, 4·4; 4MeCO, 37·7%. $C_{25}H_{22}O_{11}$, penta-acetate, requires C, 60·2; H, 4·5; 5MeCO, 43·2%). In ethyl acetate (*c*, 1·2), $[\alpha]_D^{19°}$ was found to be + 95°.

Tetrabenzoylcyanomaclurin.—Professor Perkin's sample (Found: C, 72·7; H, 4·1. $C_{43}H_{28}O_{10}$ requires C, 73·3; H, 4·0%. $C_{50}H_{32}O_{11}$, pentabenzoate, requires C, 74·2; H, 4·0%). The presence of a small proportion of the tribenzoyl derivative is indicated.

O-*Trimethylcyanomaclurin.*—Aqueous potassium hydroxide (2 c.c. of 50%) was added dropwise to a mixture of cyanomaclurin (0·2 g.), methyl sulphate (2 c.c.), and methyl alcohol (5 c.c.) cooled in running water. When the methyl sulphate was decomposed, water was added and the product (0·2 g.) was collected and purified by careful addition of water to its alcoholic solution. The colourless substance was amorphous or indefinitely crystalline, m. p. 73—85° (Found: MeO, 28·5. $C_{18}H_{18}O_6$ requires 3MeO, 28·2%). The derivative is certainly not a phenol, for it is insoluble in dilute aqueous sodium hydroxide and it exhibits no ferric reaction in alcoholic solution. It was recovered unchanged after heating for 75 minutes with an excess of semicarbazide acetate in alcoholic solution. Rather surprisingly there was no evidence of the formation of a morinidin derivative on heating with bromine in hot peroxide-containing dioxan.

The trimethyl ether (30 mg.) was heated with acetic anhydride (1 c.c.) and a drop of pyridine for 5 minutes at 100°. After keeping for 48 hours at the room temperature, the acetyl derivative was isolated, dissolved in a little alcohol, an equal volume of water added, and the mixture concentrated in a desiccator. The white amorphous solid that separated was washed with water and collected. It was similar to the initial material but more readily soluble in aqueous alcohol (Found: MeCO, 10·1. $C_{20}H_{20}O_7$ requires MeCO, 11·6%).

Morinidin Chloride from Cyanomaclurin.—Cyanomaclurin (0·15 g.), dissolved in water (30 c.c.), was added to a solution of sodium carbonate (12·5 g.) in water (500 c.c.) previously heated to 95°. The mixture was shaken and immediately poured on crushed ice. The deep blue solution exhibited the characteristic dichroism (blue and red) of alkaline morinidin solutions; it was acidified with hydrochloric acid, and the oxonium salt extracted by *iso*amyl alcohol (120 c.c.). The extract was shaken with 7% hydrochloric acid, separated, filtered, and mixed with 7% hydrochloric acid (30 c.c.) and light petroleum (1000 c.c.). The morinidin chloride that separated was collected and dissolved in a little alcohol and after the addition of 7% hydrochloric acid (6 c.c.) the solution was concentrated under diminished pressure. A few mg. of pure morinidin chloride were obtained; the greater part of the salt remained in the aqueous hydrochloric acid solution and could not be isolated therefrom in a pure condition. The experiment was twice repeated with the same results. The morinidin chloride so obtained was compared with a specimen prepared according to the method (B) (Charlesworth, Chavan, and Robinson, *loc. cit.*, p. 373) and the two products behaved in identical fashion in so far as the colour reactions and other properties already described were concerned; the material made from cyanomaclurin was, however, more densely aggregated and dissolved the more slowly in hot dilute hydrochloric acid on that account. Continued boiling of a solution in *N*/10-hydrochloric acid caused decolorisation and the colour was not restored on the addition of hydrochloric acid; the two specimens showed the same behaviour in this respect. In order to obtain solutions for comparison of the distribution ratios the following procedure was adopted in order to avoid inequalities in the formation of the colourless transformation product. The synthetic specimen (10·01 mg.) was dissolved in ethyl alcohol (25 c.c.) with the gradual addition of *N*-hydrochloric acid (25 c.c.) and water (225 c.c.). The specimen from cyanomaclurin (4·23 mg.) was made up to a solution in approximately *N*/10-hydrochloric acid in the same way, the proportionate volume of alcohol being used. The solution from the cyanomaclurin specimen was a little the weaker and the comparison solution was therefore diluted with a mixture of alcohol and nine times its volume of *N*/10-hydrochloric acid until the concentrations were identical; only a few c.c. were required. The properties of these solutions were identical in every respect. They were orange-red, and salmon-red in thin layers; the alkali-colour reactions were again observed and tallied with previous descriptions. Comparisons of the coloured zones made by floating the solutions on saturated sodium acetate and saturated sodium carbonate solutions were made. The behaviour on addition of zinc dust was also noted. Morinidin chloride shows characteristic distribution between dilute hydrochloric acid and mixtures of toluene and *cyclo*hexanol; in comparison with cyanidin chloride, less of the *cyclo*hexanol needs to be added in order to produce solubility in the mixed organic solvent. The two solutions behaved again in the same way and the organic layers made as described were colorimetrically identical. Equal volumes of the

prepared morinidin solutions and the *cyclo*hexanol–toluene mixtures were shaken together. *cyclo*Hexanol (1 vol.) and toluene (3 vols.) (CT3) dissolved the whole of the pigment to a reddish-violet solution. CT6 gave a distribution, a slightly bluer-violet organic layer and a pale salmon aqueous layer. The graded series CT7—CT12 was examined, the organic layer in the last case being pale violet.

The following report of an examination of *O*-tetra-acetylcyanomaclurin is submitted by Miss D. Crowfoot.

The crystals are monoclinic needles, elongated along *b* and slightly flattened on (100). Birefringence negative. Plane of the optic axes (010). γ slightly inclined to (100).

X-*Ray data*: $a = 15{\cdot}1\ \alpha$, $b = 6{\cdot}5\ \beta$, $c = 23{\cdot}7\ \gamma$; $\beta = 74°$. $0k0$ halved when k is odd. Space group $P2_1$. Number of molecules in unit cell = 4, if $\rho = 1{\cdot}27$, *i.e.*, number in asymmetric unit = 2.

The fact that there are two molecules in the asymmetric unit makes it difficult to limit the crystallographic possibilities of the arrangement of the molecules sufficiently to distinguish with any certainty the chemical differences. There is, however, a general weakening of the intensities of the planes ($h0l$) when l is odd, which suggests that these two molecules are crystallographically related by an approximate *c* glide plane of symmetry. On the basis of these results it is difficult to make a decision between the ketonic and the cyclic ketose acetate formula, both of which can accommodate the data.

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