## 151. *Anthoxanthins. Part XV. Experiments on the Synthesis of Garcinin.*

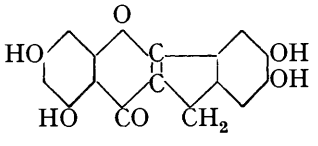
By Robert Robinson and R. C. Shah.

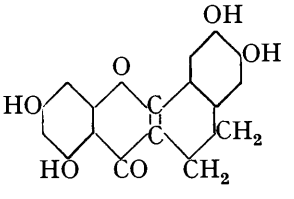
According to Shinoda (*J. Pharm. Soc. Japan*, 1927, **541**, 35) the Japanese dye "fukugi" (from the bark of *Garcinia spicata* or *Xanthocymus ovalifolia*) contains garcinin, $C_{16}H_{10}O_6$ (or $C_{16}H_{12}O_6$), as well as the better known fukugetin, $C_{17}H_{12}O_6$.*

A. G. Perkin and Phipps (J., 1904, **85**, 56) showed that fukugetin gives phloroglucinol and protocatechuic acid on fusion with potash, so the possibility that the substance is tetrahydroxy-2-styrylchromone was contemplated until synthetical experiments (Robinson and Shinoda, J., 1925, **127**, 1973) showed that the properties of styryl analogues of flavonols were such as to throw considerable doubt on the validity of the hypothesis.

The alternatives have been discussed by Shinoda (*loc. cit.*), who showed that 3-ethyl- and 3-methyl-substituted luteolins are not identical with fukugetin and garcinin respectively. It is apparent that these colouring matters may contain a ring structure as in (I) for garcinin and (II) for fukugetin, but there is very little direct evidence for these suggestions and hence synthetical experiments were instituted. The present communication contains an account of some preliminary attempts, which have now been superseded by a more promising line of attack to be described in due course.

(I.)



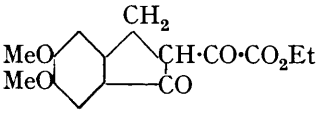

(II.)

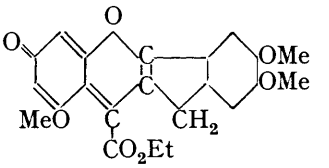
Bülow and Wagner (*Ber.*, 1903, **36**, 1941) found that 7-hydroxy-4-carboxyflavylium-betaine could be oxidised to 7-hydroxyflavone, and Robinson and Schwarzenbach (J., 1930, 822) confirmed this observation and improved the yield but could not apply the reaction in analogous cases. Unfortunately an attempt to apply it to the synthesis of a substance of the formula (I) also failed.

5 : 6-Dimethoxyhydrindone (Perkin and Robinson, J., 1907, **91**, 1081) was condensed with ethyl oxalate in alcoholic solution in the presence of sodium ethoxide, and the resulting *ethyl* 5 : 6-*dimethoxy*-1-*hydrindone*-2-*glyoxylate* (III) condensed with phloroglucinol dimethyl ether by means of hydrogen chloride to a pyrylium salt, most easily purified in the form of the related quinonoid *colour-base* (IV).

* Murakami (*Proc. Imp. Acad. Japan*, 1932, **8**, 500) has indicated that fukugetin and garcinin are isomerides of the formula $C_{22}H_{10}O_8$. They both appear to be *C*-*p*-hydroxybenzylquercetins.

The acid corresponding to the ester (IV) possesses the usual properties of a pyrylium-betaine; it furnished no γ-pyrone derivative on oxidation.

(III.) 

 (IV.)

We have also to record the breakdown of the standard flavone synthesis of von Kostanecki in this series. The preparation of methyl 2 : 4 : 6-trimethoxybenzoate (Herzig, Wenzel, and Tölk, *Monatsh.*, 1902, **23**, 90) has been greatly improved, but this ester could not be condensed with 5 : 6-dimethoxyhydrindone even by means of sodium in boiling xylene. This is doubtless the result of hindrance by the *o*-situated methoxyl groups and it may be recalled that Mauthner (*J. pr. Chem.*, 1930, **124**, 319) was unable to bring methyl 2 : 6-dimethoxybenzoate and ethyl acetate into reaction in the presence of sodium, even during 8 hours at 100°.

The 2-benzoylation of hydrindone could be effected in the normal way or by the action of benzoyl chloride on the sodium derivative.

## Experimental.

*Ethyl* 5 : 6-*Dimethoxy*-1-*hydrindone*-2-*glyoxylate* (III).—The difficulty experienced in dehydrating β-3 : 4-veratrylpropionic acid (Perkin and Robinson, *loc. cit.*) by means of $P_2O_5$ in $C_6H_6$ was traced to the use of carefully dried reagents. When the $C_6H_6$ was first shaken with $H_2O$, uniform satisfactory yields were obtained (7·8 g. of ketone from 10 g. of acid). Dimethoxyhydrindone crystallises from $CCl_4$ in yellow prisms, m. p. 116—118°.

A solution of dimethoxyhydrindone (25 g.) and ethyl oxalate (30 g.) in EtOH (50 c.c.) was added, with cooling, to one of NaOEt (2·9 g. Na) in EtOH (50 c.c.). Next day the reddish-yellow sodium salt was collected after addition of $Et_2O$ to complete pptn., washed with $Et_2O$, and decomposed by dil. HCl in ice-cold aq. solution; the *product* (30 g.) crystallised from $C_6H_6$ or aq. acetone in yellow prismatic needles, m. p. 158—159° (Found : C, 61·9; H, 5·5. $C_{15}H_{16}O_6$ requires C, 61·6; H, 5·5%). The related *acid*, best obtained by hydrolysis of the ester (1 g.) in a mixture of conc. HCl (10 c.c.) and AcOH (10 c.c.) at 70—80° for 30 min., crystallised from AcOH in yellow prisms, m. p. 245—247° (Found : C, 58·3; H, 4·8. $C_{13}H_{12}O_6$ requires C, 59·1; H, 4·5%). The analysis indicates about 0·2 mol. of $H_2O$, and this seems to be difficult to remove.

*Colour-base* * *of* 7-*Hydroxy*-5 : 5′ : 6′-*trimethoxy*-4-*carbethoxy*-2 : 3(3′ : 2′)-*indenobenzopyrylium Chloride* (IV).—A solution of phloroglucinol dimethyl ether (8 g.) and ethyl dimethoxyhydrindoneglyoxylate (15 g.) in AcOH (120 c.c.) was saturated with HCl at 60—70° for 10 hr. After 12 hr. at room temp. the solid was collected (4 g.) and recrystallised from hot AcOH containing HCl; it separated in deep orange prismatic needles with green reflex, gradual decomp. above 300°. The analysis (Found : C, 60·2; H, 4·7; Cl, 8·0; MeO, 26·8. $C_{22}H_{21}O_7Cl$ requires C, 61·0; H, 4·9; Cl, 8·2; 4MeO,† 28·7%) indicates partial demethylation and, fortunately, complete purification of the colour-base proved feasible. The ferrichloride crystallised from AcOH in reddish-violet prisms.

The 4-carboxy-derivative was prepared by refluxing the ester with AcOH–conc. HCl for many hours. The salt gradually separated in deep red crystals. This substance could not be obtained directly by employing dimethoxyhydrindoneglyoxylic acid in the original condensation.

The betaine was obtained from the carboxy-chloride by the action of NaOAc as a microcryst., deep red powder, decomp. above 300°. Its constitution follows from the method of prepn., analogies, and from its reconversion into a pyrylium salt.

The original ester-chloride (2 g.) was dissolved in hot MeOH, and excess of NaOAc in hot

* Substances of this class have formerly been described as anhydro-benzopyranols, but it does not seem desirable to perpetuate superseded conceptions of reaction mechanism in the nomenclature and hence a change is now suggested. There can be little doubt that the formation of quinonoid colour-bases from kations of hydroxylated pyrylium salts (as also in analogous series) and vice versa is the result of the direct removal or attachment of protons and does not proceed *via* a pyranol stage.

† 3MeO,1EtO.

MeOH added, quickly followed by AcOH. The *colour-base*, which was pptd. in micro-crystals, was collected, washed with MeOH, and recrystallised from $CHCl_3$, forming small, dark brown-crimson prisms, m. p. 240—245° after softening at 220—225° (Found: C, 64·0; H, 5·1; MeO, 29·1. $C_{22}H_{22}O_8$ requires C, 63·8; H, 5·3; 4MeO, 29·2%). The $CHCl_3$ solution of this quinone is deep violet; it is readily changed by mineral acids to the orange-red pyrylium salts.

*Methyl* 2 : 4 : 6-*Trimethoxybenzoate*.—(a) Phloroglucinol trimethyl ether was condensed with methyl chloroformate in the presence of $AlCl_3$ (Herzig, Wenzel, and Tölk, *loc. cit.*); after separation from demethylated by-products the yield was 10%. Use of $CS_2$ as diluent reduced the yield (4%); use of $FeCl_3$ gave an amorphous product, m. p. 100—160°, and this could not be purified.

(b) The carboxylation of phloroglucinol dimethyl ether by means of $KHCO_3$ in glycerol solution succeeded, but the yield was inferior (0·2—0·5 g. from 5 g.) and this route was abandoned.

(c) Phloroglucinolcarboxylic acid was prepared by Skraup's method (*Monatsh.*, 1889, **10**, 724), but the purification of the crude acid was found to be most easily carried out by solution in hot MeOH and addition of $H_2O$ to incipient crystn. Methylation by $CH_2N_2$ in *dry* $Et_2O$, following Herzig, Wenzel, and Tölk (*loc. cit.*), afforded methyl 6-hydroxy-2 : 4-dimethoxybenzoate (1·5 g. from 1·7 g. of the acid) and in the further methylation by means of MeI and KOH in MeOH the ester (2 g.) gave fully methylated ester (1·5 g.).

(d) The complete methylation of phloroglucinolcarboxylic acid by means of $CH_2N_2$ succeeds in *moist* $Et_2O$ and this is by far the most convenient method of prepn.

An $Et_2O$ solution of $CH_2N_2$ (from 30 c.c. of NO·NMe·$CO_2Et$) was distilled into a suspension of phloroglucinolcarboxylic acid (5·1 g.) in $Et_2O$ (25 c.c., dried over $CaCl_2$) and next day the excess of $CH_2N_2$ was destroyed by AcOH. On working up, incompletely methylated products (0·4 g.) were separated from the tetramethyl derivative (5 g.), which, best cryst. from $CS_2$, formed colourless prisms, m. p. 67—69°. This ester could not be brought into reaction with 5 : 6-dimethoxyhydrindone in the presence of metallic Na: the failure cannot be attributed to the dimethoxyhydrindone, which condenses normally with ethyl oxalate (above) and was also found in preliminary trials to condense with ethyl benzoate to a characteristic β-diketone (copper salt and deep brown $FeCl_3$ reaction).

2-*Benzoyl*-1-*hydrindone*.—(a) 1-Hydrindone (2·6 g.) was added to a suspension of granulated Na (0·75 g.) in dry toluene, a vigorous reaction ensuing. BzOEt (6 g.) was gradually introduced, and the mixture refluxed for 3 hr. The solid was collected, shaken with dil. HCl and $Et_2O$, and the $Et_2O$ solution separated and shaken with $Cu(OAc)_2$ aq. The copper derivative (0·5 g.) was decomposed by means of dil. $H_2SO_4$ in the presence of $Et_2O$; the resulting *diketone* crystallised from EtOH in almost colourless needles, m. p. 104° (Found: C, 81·2; H, 5·2. $C_{16}H_{12}O_2$ requires C, 81·2; H, 5·2%). The alc. solution is coloured deep brown on the addition of $FeCl_3$.

(b) Powdered $NaNH_2$ (2 g.) was gradually added to 1-hydrindone (7 g.) in dry $Et_2O$ (50 c.c.) and after the reaction had subsided $NH_3$ was removed below 10° in a stream of N. PhCOCl (3·5 g.) was added, and the mixture occasionally shaken for 24 hr. It was possible to isolate the copper derivative (1·5 g.) of the diketone from this reaction product, and the benzoyl-hydrindone crystallised from EtOH in faintly yellow needles, m. p. 104°.

UNIVERSITY OF LONDON, UNIVERSITY COLLEGE.
THE DYSON PERRINS LABORATORY, UNIVERSITY OF OXFORD. [*Received, April 6th*, 1933.]