EXPERIMENTS IN THE BRAZILANE SERIES—I THE PREPARATION OF 2-PHENYL-5',6',7-TRIMETHOXYBRAZILANE

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Abstract—Superposition of flavan on brazilane would afford 2-phenyl-brazilane. Although this structure has not yet been isolated, biogenetically it is feasible. The synthesis of 2-phenyl-5',6',7-trimethoxy-brazilane is described.

INTEREST in this work lay in the observation that whereas derivatives of chromans and flavans are well known in nature and have been prepared in the laboratory, the only compounds known to have the brazilane structure (I) are brazilin (II, R = H) and haematoxylin¹ (II, R = OH). Apart from earlier attempts² which culminated in the total synthesis of brazilin and haematoxylin,³ very little work has been done on compounds having the brazilane skeleton (I). In this communication the preparation of 2-phenyl-5',6',7-trimethoxybrazilane (III) is described.

In a review on the biogenesis of flavonoid compounds,⁴ the authors stated that brazilin and haematoxylin possess structures which appear from their hydroxylation patterns, to be related to flavonoid substances. They also suggest that brazilin (II, R = H) and haematoxylin (II, R = OH) may be regarded as examples of $C_6-C_3-C_6$ compounds in which the added C atom constitutes a bridge between the A- and the B-rings and the C_3 -chain (IV) or in which the added C atom forms a bridge between the C_6B - and the C_3 -chain (V). Of the two precursors IV and V, the authors favour the latter.

Robinson⁵ mentioned that the simple flavan like system (VI) had not yet been recognized among products, but brazilin (II, R = H) isolated from *Caesalpinia spp.* and haematoxylin (II, R = OH) a related pyrogallol derivative isolated from *Haematoxylon campechian* contains this skeleton and an addition C atom linking position 3 to the phenyl ring. However, a 4-phenylcoumarin derivative has been isolated from degradation studies of calophyllolide.⁶

* The nomenclature is according to that adopted by Grabtree and Robinson.¹³







Superposition of flavan on brazilane (I) affords 2-phenylbrazilane (VII), a diphenylated chroman with an additional C atom. Such a compound contains the $C_6-C_3-C_6$ structure common to all flavonoid compounds found abundantly in nature. The $C_6-C_3-C_6$ unit could be formed in three possible ways as illustrated, $C_6A-C_3-C_6B$ (VIII), $C_6A-C_3-C_6C$ (IX) or $C_6B-C_3-C_6C$ (X).

The state of oxidation of the C_3 chain may be assumed to be in the most favoured condition so that the additional ring to complete the required structure can be added through condensation with a benzaldehyde derivative or its equivalent. It may be of interest that a diphenylated chromene system has been proposed for the structures of santalin and santarubin, both colouring matters from commercial camwood and barwood.⁷

Resacetophenone⁸ condensed readily with benzaldehyde. In all experiments, a mixture of the chalcone (XI) and flavanone (XII, R = H) were obtained which could be separated by careful fractional crystallization. It was found advantageous to treat the mixture of chalcone (XI) and flavanone (XII, R = H) directly with dilute sodium hydroxide⁹ in order to obtain the flavanone (XII, R = H) in better yields. The 7-OH group of XII was methylated. Condensation of XII (R = Me) with veratraldehyde proceeded smoothly to yield 3-veratrylidene-7-methoxyflavanone (XIII) in good yields.

In the experiments on the synthesis of brazilin, the reduction of derivatives of 3-veratrylidene-4-chromanone gave either the 3-homoveratrylchromanone or the 3-homoveratrylchroman depending on the conditions of the reduction.^{10, 2c} Similarly, the reduction of 3-veratrylidene-7-methoxyflavanone (XIII) with palladium on strontium carbonate (2%) did not give a homogeneous product but instead a mixture of three products which could be separated by chromatography. The main product was the required 3-homoveratryl-7-methoxyflavanone (XIV; IR peak at 60 μ).

One of the other two products (obtained in small yields), based on IR measurements (peak at 29 μ ; 60 μ band missing) and C and H analyses was considered to be the 3-homoveratryl-7-methoxyflavanone (XV). Reduction of the flavanone (XIV) with potassium borohydride gave an isomeric flavanol (XV) which differed from the one obtained by the reduction of XIV with palladium on strontium carbonate. These isomers have identical IR spectra (peak at 29 μ) and could be the two forms of the flavanol XV. Both forms of 4-hydroxyflavan together with traces of a pinacol are claimed to have been obtained by reduction of flavanone with titanium trichloride, while reduction with aluminium amalgam gave only one form.¹¹ The third product isolated was isomeric with the starting material but the amount obtained was too small for further investigation.

Treatment of the flavanone (XIV) with phosphorus pentoxide in boiling benzene¹⁰ afforded 2-phenylanhydrotrimethylbrazilin (XVI). It gave a deep red solution with concentrated sulphuric acid, similar in behaviour to the brazilin and haematoxylin compounds which readily form benzopyrylium salts with mineral acids.^{12, 2a, 2b} Thus XVI on treatment with ferric chloride in acetic acid solution gave 2-phenyl-5',6'7-trimethoxybrazilium ferrichloride (XVII)* while hydrogenation with palladium gave the required 2-phenyl-5',6'7-trimethoxybrazilane (III).

^{*} These salts are pyrylium derivatives and Micovic and Robinson¹ have suggested that they be termed brazylium, similar to the flavylium salts derived from flavans.

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EXPERIMENTAL

2,4-Dihydroxyphenyl styryl ketone (XI). A mixture of resacetophenone (20 g; prepared according to Organic Synthesis⁸), benzaldehyde (14 g), alcohol (80 ml) and KOH aq (40 g in 40 ml water) was kept at 65° for $2\frac{1}{2}$ hr in an atmosphere of N₂, after which it was allowed to stand overnight at room temp. Unchanged benzaldehyde was removed by extraction with ether, and on acidification with dil HCl, an oil separated which solidified in the refrigerator after 2 days. This consisted of a mixture of 2,4-dihydroxyphenyl styryl ketone and 7-hydroxyflavanone. To obtain the required product, the solid was suspended in water containing EtOH (15–20%). On gentle warming, most of the solid dissolved except for a dark reddish oil. The aqueous soln was decanted and on standing light yellow needlelike crystals separated. It was recrystallized twice from aqueous alcohol yielding. 4-5 g, m.p. 149–150° as reported by Wheeler.¹³

7-Hydroxyflavanone (XII, R = H). In order to obtain a better yield, the oil which solidified in the above experiment was dissolved in alcohol (200 ml), kept in an atmosphere of N₂, and treated with 2% NaOH aq (700 ml). The mixture was then kept at room temp for 2 days. The dark soln was poured into water, acidified with dil HCl, and the ppt taken up in ether. The ethereal soln was washed with water, dried over MgSO₄ and concentrated, affording a dark viscous oil which crystallized readily from toluene. Two more recrystallizations from the same solvent gave almost colourless short needles m.p. 188–189° (110 g). Wheeler reported m.p. 189–190°.¹³

7-methoxyflavanone (XII, R = Me). The mixture of 7-hydroxyflavanone (5 g), dry acetone (125 ml), MeI (5 g) and K₂CO₃ (7·5 g) was refluxed for 24 hr. The cooled yellow soln was filtered from the K₂CO₃ and the acetone removed. The oil crystallized readily from EtOH in yellow needles m.p. 85–86° (3·6 g), raised to 87–88° after 4 recrystallizations from the same solvent. (Found: C, 75·53; H, 5·65. Calc. for C₁₆H₁₄O₃: C, 75·60; H, 5·55%). The literature reported m.p. 91°.¹⁵

The 2,4-dinitrophenylhydrazine derivative separated in orange hair-like needles from AcOH m.p. 255°. (Found: C, 60.52; H, 4.21. $C_{22}H_{18}O_6N_4$ requires: C, 60.80; H, 4.17%).

3-Veratrylidene-7-methoxyflavanone (XIII). A rapid stream of dry HCl was passed for approximately 1 hr through a soln of XII ($\mathbf{R} = \mathbf{Me}$; 3 g) and veratraldehyde (2 g) in absolute alcohol (70 ml) kept at 5-10°. The passage of HCl was stopped when the soln assumed a dark red colour. The next day, the dark crstyalline solid was isolated and recrystallized from a large volume of EtOH, from which it separated in light yellow needles, m.p. 171-172° (4·2 g), raised to 173° after 3 further recrystallizations from the same solvent. (Found : C, 74·88; H, 5·68. C_{2.5}H_{2.2}O₅ requires: C, 74·61; H, 5·51%). With conc H₂SO₄ a dark red soln was obtained.

3-Homoveratryl-7-methoxyflavanone (XIV). Pd on SrCO₃ (2%) was added to XIII (2 g) suspended in abs EtOH (200 ml) and the mixture hydrogenated at room temp and press. Absorption was slow and after 3 hr slightly more than the theoretical quantity of H₂ was taken up. The colourless soln was filtered from the catalyst, concentrated, and on standing in EtOH, crystals slowly separated out m.p. 120–125° (1·3 g). Chromatographic separation on a column of alumina (20 × 2 cm; 45 g) gave three products. Elution with benzene-light petroleum (30:70) afforded the required product in colourless prisms from benzene-light petroleum m.p. 142° (0·9 g). (Found: C, 74·17; H, 6·13. C₂₅H₂₄O₅ requires: C, 74·24; H, 5·98%); IR peak at 6·0 μ . Further elution with benzene-light petroleum (70:30) gave a higher melting product in colourless prisms from benzene-light petroleum m.p. 168–169° (0·1 g). (Found: C, 74·66; H, 5·57. C₂₅H₂₂O₅ requires: C, 74·61; H, 5·51%); IR peak at 2·9 μ ; 6·0 μ band missing. Elution with 100% benzene gave a third product which crystallized in colourless hair-like needles from benzene-light petroleum m.p. 131° (0·07 g). (Found: C, 73·67; H, 6·41). C₂₅H₂₆O₅ requires: C, 73·85; H, 6·44%); IR peak at 2·9 μ ; 6·0 μ band missing. C and H analyses and IR measurements indicated the flavanol XV. With conc H₂SO₄, all three products gave a pale yellow soln.

3-Homoveratryl-7-methoxyflavanol (XV). The flavanone XIV (0.3 g) was dissolved in boiling MeOH (20 ml) and KBH₄ (0.3 g) was added in small lots. After all the reagent had been added, the soln was boiled for a further 10 min. On concentration, and the addition of a little water, a crystalline solid separated. The analytical sample was recrystallized 4 times from benzene-light petroleum from which it separated as an amorphous solid m.p. 155–157° (0.2 g). (Found : C, 73.70; H, 6.63. $C_{25}H_{26}O_5$ requires: C, 73.85; H, 6.44%); IR peak at 2.9 μ ; 6.0 μ band missing.

2-Phenylanhydrotrimethylbrazilin (XVI). P_2O_5 (15 g) was added in 4 lots at $\frac{1}{2}$ hr intervals to XIV (1 g) dissolved in benzene and heated under reflux. The red mixture was then heated for a further $2\frac{1}{2}$ hr.

The benzene layer was poured off and the red complex broken up with ice. The aqueous soln was extracted with ether (centrifuge) and the soln washed with water, dried and concentrated affording a yellow viscous oil which crystallized from EtOH in light yellow prismatic needles m.p. 170–173° (0.2 g), raised to 173–175° after 4 recrystallizations. (Found: C, 77.49; H, 5.80. $C_{25}H_{22}O_4$ requires: C, 77.70; H, 5.74%). With conc

 H_2SO_4 a dark red soln was obtained and on dilution with water an orange red ppt of the pyrylium sulphate salt separated. This behaviour is similar to brazilin and haematoxylin compounds.^{15, 2a}

2-Phenyl-5',6'-7-trimethoxybrazylium ferrichloride (XVII). The anhydrotrimethylbrazilin XVI (0.1 g) was dissolved in warm AcOH (8 ml) and anhyd FeCl₃ added in portions. The soln turned dark red and with scratching a red crystalline solid separated. More FeCl₃ was added until no more dissolved. After 3 hr the solid was isolated and recrystallized from AcOH, m.p. above 200° with dec. (Found: C, 51.12; H, 3.71; Cl, 24.5. $C_{25}H_{21}O_4FeCl_4$ requires: C, 51.47; H, 3.63; Cl, 24.3%). It dissolved readily in water, EtOH and AcOH giving a bright yellowish green fluorescence in all three solvents. It also dissolved in benzene affording a pinkish red soln without fluorescence.

2-Phenyl-5',6'7-trimethoxybrazilane (III). Pd on SrCO₃ catalyst (2%) was added to XVII (0·1 g) dissolved in EtOAc (15 ml) and the soln hydrogenated at room temp and press. Absorption was slow, but after 3 hr no more absorption occured. The soln was then filtered from the catalyst and concentrated. The product crystallized slowly from EtOH, and after 4 recrystallizations from the same solvent yielded colourless hairlike needles m.p. 145–146°. (Found: C, 77·57; H, 6·48. C₂₅H₂₄O₄ requires: C, 77·30; H, 6·23%). With conc H₂SO₄, a pale yellow soln was obtained and on dilution with water no pyrylium salt separated. This behaviour is similar to brazilin and haematoxylin compounds.

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