

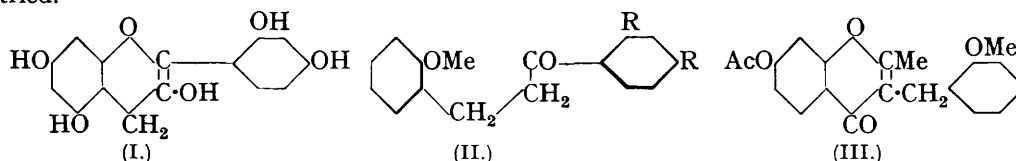
80. *Experiments on the Synthesis of Cyanomaclurin and its Derivatives. Part I. 3 : 5 : 7 : 2' : 4' -Pentamethoxyflavan.*

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THE formula (I) is one of the two constitutions suggested by Perkin (J., 1905, **87**, 721) for cyanomaclurin, and an attempt has now been made to confirm it by the synthesis of the substance or a near derivative.

The methods of Harris and Busse (*Ber.*, 1896, **29**, 380) and Feuerstein and Musculus

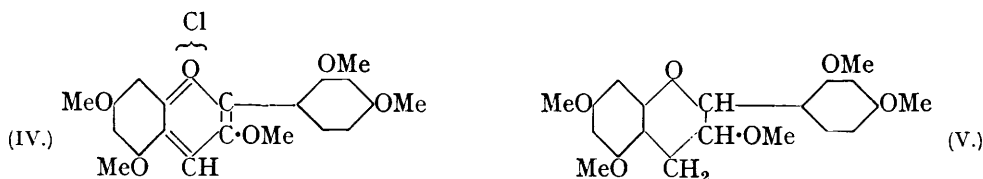
(Ber., 1901, **34**, 411) for the preparation of flavans being impracticable, other means were tried.



Demethylation and ring closure of 2 : 4-dihydroxy-2'-methoxy- and 2 : 4 : 2'-trimethoxy-beta-phenylpropiophenone (II; R = OH and OMe respectively) could not be satisfactorily accomplished, dark amorphous products being obtained after treatment with hot acids (cf. cyanomaclurin; Perkin and Cope, J., 1895, **67**, 94 : deoxytrimethylbrazilin; Perkin, Rây, and Robinson, J., 1928, 1512). On acetylation, the substance (II; R = OH) furnished a *chromone* (III).

2'-Hydroxy- and 2'-hydroxy-2 : 4-dimethoxy-beta-phenylpropiophenone also gave only amorphous products during attempts to close the ring, and the *carbinol* obtained by reduction of the latter ketone was not convertible into a flavan. A chalkone could not be prepared from either beta-resorcyraldehyde or 2-hydroxy-4 : 6-dimethoxybenzaldehyde and resacetophenone dimethyl ether, but 2-hydroxy-4-methoxybenzaldehyde readily reacted with it. 2-Hydroxy-4 : 6-dimethoxybenzaldehyde, however, condensed with acetoveratrone to give the corresponding chalkone.

3 : 5 : 7 : 2' : 4'-Pentamethoxyflavylum chloride (IV) (Pratt and Robinson, J., 1925, **127**, 1136) on catalytic reduction, gave 3 : 5 : 7 : 2' : 4'-pentamethoxyflavan (V), the com-



parison of which with the catalytic reduction product of cyanomaclurin pentamethyl ether will be made as soon as possible.

EXPERIMENTAL.

2 : 4-Dihydroxy-2'-methoxy-beta-phenylpropiophenone (II; R = OH).—A mixture of resorcinol (4 g.), beta-o-methoxyphenylpropionic acid (6 g.), and ZnCl₂ (5 g.) was heated at 100–110° for 5 hr. in a current of dry H₂. The cooled mass was agitated with H₂O (50 c.c.) and conc. HCl (2 c.c.) and heated on the steam-bath for a few min. The solid cake deposited after 12 hr. was crystallised in turn from Et₂O, C₆H₆–light petroleum, and hot dil. MeOH and furnished plates (2.5 g.), m. p. 138° (Found : C, 70.3; H, 5.9; OMe, 12.0. C₁₆H₁₆O₄ requires C, 70.6; H, 5.9; OMe, 11.4%). The substance gave a violet colour with FeCl₃. On being boiled with Ac₂O (10 mols.) it gave 7-acetoxy-2'-methoxy-3-benzyl-2-methylchromone (III), m. p. 141–142° after crystn. from EtOH (Found : C, 71.15; H, 5.7. C₂₀H₁₈O₅ requires C, 71.0; H, 5.3%), but if the acetylation was done with 2.25 mols. of Ac₂O and the heating continued for not more than 30 min. the diacetyl derivative (II; R = OAc), m. p. 81–82°, was formed.

2 : 4 : 2'-Trimethoxy-beta-phenylpropiophenone (II; R = OMe).—To a mixture of beta-o-methoxyphenylpropionyl chloride (7 g.), dry CS₂ (30 c.c.), and resorcinol dimethyl ether (5 g.) at 0°, AlCl₃ (12 g.) was added during 1 hr. After 12 hr., the product was decomposed with ice and HCl aq. (4 c.c.), the CS₂ removed, and the gummy solid separated and dissolved in MeOH. The solution, freed from a gummy material which first separated, furnished a brownish-white cryst. deposit after 24 hr. Recryst. (charcoal) from MeOH, this formed colourless needles, m. p. 78° (Found : C, 71.7; H, 6.9. C₁₈H₂₀O₄ requires C, 72.0; H, 6.7%).

Chalkones and their Reduction Products.—2'-Hydroxy-beta-phenylpropiophenone. A mixture of 2'-hydroxybenzylideneacetophenone (Perkin, Robinson, and Turner, J., 1908, **93**, 1108) (2 g.), EtOAc (100 c.c.), 1% PdCl₂ (5 c.c.), abs. EtOH (10 c.c.), and BaSO₄ (2 g.) was shaken in H₂. The filtered solution, on concn. in vac., gave a solid, which was crystallised from EtOH; m. p. 91° (Kostanecki, Ber., 1898, **31**, 718, gives m. p. 91–92°).

2'-Hydroxy-2 : 4-dimethoxy-beta-phenylpropiophenone. o-Hydroxybenzylideneresacetophenone

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dimethyl ether (Perkin, Robinson, and Turner, *loc. cit.*) (2 g.) in abs. neutral EtOH (100 c.c.) was reduced with Pd-BaSO₄ catalyst (1 g.), and the filtered solution freed from solvent in vac. The residue crystallised from 80% EtOH in slender needles (1.5 g.), m. p. 95°. The substance produced a sodium salt from 5% NaOH aq. solution, developed with AcCl a yellowish colour, rapidly changing to brown (in the cold) and then red (after 2 hr.), but gave no FeCl₃ reaction (Found: C, 71.4; H, 6.6. C₁₇H₁₈O₄ requires C, 71.7; H, 6.3%). When it (0.8 g.) was suspended in H₂O (50 c.c.) and reduced with Na-Hg (5 g. of 5%), it furnished α -2:4-di-methoxyphenyl- γ -o-hydroxyphenyl-n-propyl alcohol, m. p. 106–107° after crystn. from C₆H₆-ligroin (Found: C, 70.6; H, 7.0. C₁₇H₂₀O₄ requires C, 70.8; H, 6.9%).

2'-Hydroxy-2:4:4'-trimethoxybenzylideneacetophenone. 2-Hydroxy-4-methoxybenzaldehyde (prepared from 10 g. of resorcyaldehyde, 4 g. of KOH in 20 c.c. of H₂O, and 8.5 g. of Me₂SO₄ at 70–80° and isolated by steam distillation; yield, 6 g.) condensed with resacetophenone dimethyl ether in aq.-methyl alc. KOH to give the *chalkone*, which formed greenish-yellow, fine needles, m. p. 156°, from hot dil. acetone (Found: C, 68.5; H, 5.7. C₁₈H₁₈O₅ requires C, 68.8; H, 5.7%). This was reduced with Pd-BaSO₄ catalyst, and the product isolated, in the manner described above. Cryst. successively from hot dil. EtOH and C₇H₈, the product had m. p. 110°. It dissolved in hot dil. NaOH aq. or a cold conc. solution, developed in H₂SO₄ a reddish-yellow colour, which became yellowish on dilution, an orange ppt. forming, and did not lose H₂O in vac. at 100° (Found: C, 68.6; H, 6.5. C₁₈H₂₀O₅ requires C, 68.4; H, 6.3%).

2'-Hydroxy-3:4:4':6'-tetramethoxybenzylideneacetophenone, prepared in good yield from 2-hydroxy-4:6-dimethoxybenzaldehyde and acetoveratrone, formed pale yellow needles, m. p. 165–166°, from hot dil. acetone (Found: C, 66.1; H, 5.85. C₁₉H₂₀O₆ requires C, 66.3; H, 5.8%). On catalytic reduction it gave 2'-hydroxy-3:4:4':6'-tetramethoxy- β -phenylpropio-phenone, m. p. 135° (Found: C, 65.9; H, 6.5. C₁₉H₂₂O₆ requires C, 65.9; H, 6.4%), which was reduced by Na-Hg (5%) to α -3:4-dimethoxyphenyl- γ -2-hydroxy-4:6-dimethoxyphenyl-n-propyl alcohol, m. p. 118–119° (Found: C, 65.75; H, 7.1. C₁₉H₂₄O₆ requires C, 65.5; H, 6.9%).

3-Chloro-2'-hydroxy-7:4'-dimethoxyflavylium Chloride.—This was prepared from ω -chloro-2-hydroxy-4-methoxyacetophenone (1 g.) and 2-hydroxy-4-methoxybenzaldehyde (0.8 g.) in dry EtOAc (10 c.c.) at 0° by means of HCl. After 12 hr., the deposit was collected and recrystallised from EtOH containing a little HCl; it formed deep red needles, not molten at 250° (Found in material dried at 100° in vac.: C, 57.7; H, 3.9. C₁₇H₁₄O₄Cl₂ requires C, 57.8; H, 4.0%). This chloride could not be satisfactorily reduced catalytically.

3:5:7:2':4'-Pentamethoxyflavan (V).—3:5:7:2':4'-Pentamethoxyflavylium chloride (Pratt and Robinson, *loc. cit.*) (0.4 g.), dissolved in abs. EtOH (50 c.c.), was reduced with Pd-BaSO₄ (0.2 g.) in H. When the solution had only a faint pale rose tint (*ca.* 4 hr.), it was filtered, and the solvent removed, in H. The residue was dissolved in Et₂O, washed thrice with ice-cold 2% HCl aq. and once with H₂O, dried (Na₂SO₄), and recovered as a viscous solid, which, after being dried in vac. (CaCl₂) and washed with ligroin (2 \times 10 c.c.), solidified when scratched. Cryst. from C₆H₆-ligroin, it formed slender needles, m. p. 42° (Found: C, 66.6; H, 7.0. C₂₀H₂₄O₆ requires C, 66.7; H, 6.7%).

Morinidin 3:5:7-Trimethyl Ether.—HCl was passed into 2-hydroxy-4:6-dimethoxybenzaldehyde (0.5 g.) and ω -methoxyresacetophenone (0.5 g.) in dry Et₂O (15 c.c.) till the colour of the solution changed to claret. The mixture was left for 12 hr. at 0°, and the solvent then removed in vac. The residue was dissolved in NaOH aq., and the solution acidified with AcOH (a flocculent red ppt. formed), boiled, and filtered. To the hot filtrate, enough HCl aq. was added to give a 2% HCl solution. The ppt. of the *flavylium chloride* was recrystallised from hot dil. HCl aq.; m. p. 160° (Found: C, 55.4; H, 5.4. C₁₈H₁₇O₆Cl_{1.5}H₂O requires C, 55.2; H, 5.2%). The H₂O of crystn. was given off at 100° in high vac., but could not be estimated because of partial decomp. This substance, unlike morinidin chloride pentamethyl ether, is very difficultly reduced and no satisfactory product could be isolated.

3-Chloro-7:3':4'-trimethoxyflavanone was similarly prepared in EtOAc (30 c.c.) from ω -chloro-2-hydroxy-4-methoxyacetophenone (1.0 g.) and veratraldehyde (0.8 g.). The clear dark solution was poured over ice after 12 hr. The EtOAc layer gave a semi-solid mass, which crystallised in contact with EtOH. Washed with Et₂O and recryst. from AcOH, it had m. p. 153° (Found: C, 62.5; H, 4.9. C₁₈H₁₇O₅Cl requires C, 61.9; H, 4.9%). The substance could not be reduced by Clemmensen's method after replacement of Cl by OH.

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