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

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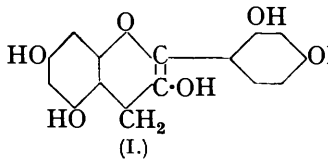
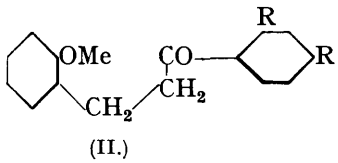
The formula (I) is one of the two constitutions suggested by Perkin (J., 1905, **87**, 721) for cyanomaclurin, and an attempt has now been made to confirm it by the synthesis of the substance or a near derivative.

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.


(I.)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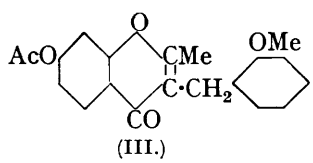
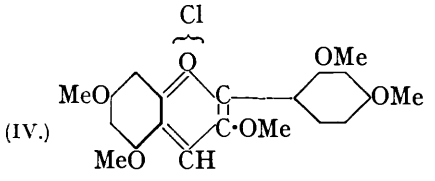
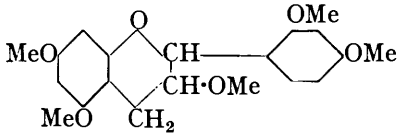

(III.)

Demethylation and ring closure of 2 : 4-*dihydroxy*-2′-*methoxy*- and 2 : 4 : 2′-*trimethoxy*-β-*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*-β-*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 β-resorcylaldehyde 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′-Pentamethoxyflavylium chloride (IV) (Pratt and Robinson, J., 1925, **127**, 1136) on catalytic reduction, gave 3 : 5 : 7 : 2′ : 4′-*pentamethoxyflavan* (V), the com-


(IV.)


(V.)

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*-β-*phenylpropiophenone* (II; R = OH).—A mixture of resorcinol (4 g.), β-*o*-methoxyphenylpropionic acid (6 g.), and $ZnCl_2$ (5 g.) was heated at 100—110° for 5 hr. in a current of dry H. The cooled mass was agitated with H_2O (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 Et_2O, C_6H_6–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. $C_{16}H_{16}O_4$ requires C, 70·6; H, 5·9; OMe, 11·4%). The *substance* gave a violet colour with $FeCl_3$. On being boiled with Ac_2O (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. $C_{20}H_{18}O_5$ requires C, 71·0; H, 5·3%), but if the acetylation was done with 2·25 mols. of Ac_2O 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*-β-*phenylpropiophenone* (II; R = OMe).—To a mixture of β-*o*-methoxyphenylpropionyl chloride (7 g.), dry CS_2 (30 c.c.), and resorcinol dimethyl ether (5 g.) at 0°, $AlCl_3$ (12 g.) was added during 1 hr. After 12 hr., the product was decomposed with ice and HCl aq. (4 c.c.), the CS_2 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. $C_{18}H_{20}O_4$ requires C, 72·0; H, 6·7%).

Chalkones and their Reduction Products.—2′-*Hydroxy*-β-*phenylpropiophenone*. A mixture of 2′-hydroxybenzylideneacetophenone (Perkin, Robinson, and Turner, J., 1908, **93**, 1108) (2 g.), EtOAc (100 c.c.), 1% $PdCl_2$ (5 c.c.), abs. EtOH (10 c.c.), and $BaSO_4$ (2 g.) was shaken in H. 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*-β-*phenylpropiophenone*. *o*-Hydroxybenzylideneresacetophenone

dimethyl ether (Perkin, Robinson, and Turner, *loc. cit.*) (2 g.) in abs. neutral EtOH (100 c.c.) was reduced with Pd–$BaSO_4$ 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 $FeCl_3$ reaction (Found : C, 71·4; H, 6·6. $C_{17}H_{18}O_4$ requires C, 71·7; H, 6·3%). When it (0·8 g.) was suspended in H_2O (50 c.c.) and reduced with Na–Hg (5 g. of 5%), it furnished *α-2 : 4-dimethoxyphenyl-γ-o-hydroxyphenyl-n-propyl alcohol*, m. p. 106—107° after crystn. from C_6H_6–ligroin (Found : C, 70·6; H, 7·0. $C_{17}H_{20}O_4$ requires C, 70·8; H, 6·9%).

2′-Hydroxy-2 : 4 : 4′-trimethoxybenzylideneacetophenone. 2-Hydroxy-4-methoxybenzaldehyde (prepared from 10 g. of resorcylaldehyde, 4 g. of KOH in 20 c.c. of H_2O, and 8·5 g. of Me_2SO_4 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. $C_{18}H_{18}O_5$ requires C, 68·8; H, 5·7%). This was reduced with Pd–$BaSO_4$ catalyst, and the product isolated, in the manner described above. Cryst. successively from hot dil. EtOH and C_7H_8, the product had m. p. 110°. It dissolved in hot dil. NaOH aq. or a cold conc. solution, developed in H_2SO_4 a reddish-yellow colour, which became yellowish on dilution, an orange ppt. forming, and did not lose H_2O in vac. at 100° (Found : C, 68·6; H, 6·5. $C_{18}H_{20}O_5$ 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. $C_{19}H_{20}O_6$ requires C, 66·3; H, 5·8%). On catalytic reduction it gave *2′-hydroxy-3 : 4 : 4′ : 6′-tetramethoxy-β-phenylpropiophenone*, m. p. 135° (Found : C, 65·9; H, 6·5. $C_{19}H_{22}O_6$ 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. $C_{19}H_{24}O_6$ 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. $C_{17}H_{14}O_4Cl_2$ 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–$BaSO_4$ (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 Et_2O, washed thrice with ice-cold 2% HCl aq. and once with H_2O, dried (Na_2SO_4), and recovered as a viscous solid, which, after being dried in vac. ($CaCl_2$) and washed with ligroin (2 × 10 c.c.), solidified when scratched. Cryst. from C_6H_6–ligroin, it formed slender needles, m. p. 42° (Found : C, 66·6; H, 7·0. $C_{20}H_{24}O_6$ 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 Et_2O (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. $C_{18}H_{17}O_6Cl,1·5H_2O$ requires C, 55·2; H, 5·2%). The H_2O 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 Et_2O and recryst. from AcOH, it had m. p. 153° (Found : C, 62·5; H, 4·9. $C_{18}H_{17}O_5Cl$ 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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