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The Syntheses of 5,5′-, 6,6′-, and 5,6′-Diformyl-2,2′,3,3′-tetramethoxybiphenyls

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Very recently Chapman and Swan[1] have reported the syntheses of biphenyls and related compounds, which are possible intermediates in the melanogenesis of 3,4-dihydroxyphenylalanine (DOPA). They have synthesized three DOPA dimers, one of which had already been reported by us.[2] In relation to the DOPA dimers, three kinds of veratrumaldehyde dimers, 5,5′-, 6,6′-, and 5,6′-diformyl-2,2′,3,3′-tetramethoxybiphenyl (I, II, and III), are of interest.

Among these, I and II are known. The dimer I was obtained by the oxidative coupling of vanillin with ferric chloride,[3] or by that of sodium persulfate catalyzed by ferrous sulfate,[4] followed by methylation. The dimer II was obtained by an Ullmann reaction on 2-iodo-3,4-dimethoxybenzaldehyde.[5] Chapman and Swan,[1] however, found it more convenient to use the 2-bromo-compound, which is easier to prepare. They prepared I and II, but did not give any spectral data.

Now we wish to report on the synthesis of the unknown head-to-tail dimer (III), and present the spectra of I, II, and III. The dimer III was obtained by the Ullmann reaction of 2- and 5-iodo-veratraldehyde. The molecular models of these dimers suggest that two benzene rings

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[1] R. F. Chapman and G. A. Swan, *J. Chem. Soc., C*, **1970**, 865.

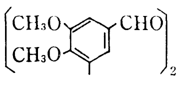
[2] a) Y. Omote, Y. Fujinuma, and N. Sugiyama, *Chem. Commun.* **1968**, 190; This Bulletin, **42**, 1752 (1969); b) Y. Omote, Y. Fujinuma, and N. Sugiyama, *Nippon Kagaku Zasshi*, **89**, 94 (1968).

[3] F. Tiemann, *Ber.*, **18**, 3493 (1885).

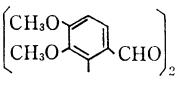
[4] K. Elbs and H. Lerch, *J. Prakt. Chem.*, **93**, 1(1916).

[5] M. Nilsson, *Acta Chem. Scand.*, **12**, 1830 (1958).

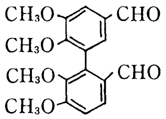
of each dimer are perpendicular to each other. The UV data support this suggestion, because the spectra of the dimers roughly coincide with that of veratraldehyde.



I



II



III

Experimental

Attempted Synthesis of the Dimer I by an Ullmann Reaction. It was examined if 5-bromoacetylvanillin gives its dimer by an Ullmann reaction.[6] Reactions at fusion or in various solvents, such as nitrobenzene, dimethylformamide, or methyl benzoate, were tested. In spite of many attempts under various conditions, the dimer was not obtained.

Attempted Synthesis of II by an Oxidative Coupling. The dimerization of isovanillin in the presence of sodium persulfate or ferric chloride was examined, but the formation only of black, intractable materials was observed. This result is consistent with the consideration that isovanillin can behave as a bifunctional compound to give polymeric pigments.

2-Iodo-and 5-Iodo-veratraldehyde. The former was prepared from vanillin by the route of acetylation, nitration, reduction, halogenation, and methylation,[7] while the latter was prepared by the same route except for acetylation. We found that 2-nitrovanillin was reduced smoothly to 2-aminovanillin with ferrous sulfate, but not with stannous chloride,[8] while 5-nitrovanillin was reduced only with stannous chloride.[7]

5,5′-Diformyl-2,2′,3,3′-tetramethoxybiphenyl (I). By the oxidative coupling of vanillin with sodium persulfate, followed by methylation with dimethyl sulfate, I was obtained nearly quantitatively. Colorless needles; mp 136°C, IR (KBr) cm^{-1} 2930(CH), 2840(CH), 1685(CHO), 1575(aromatic), 1450 (CH), 1388(CH), 1265(COC), and 1135(COC); UV $\lambda_{\max}^{\mathrm{EtOH}}$ nm (ε) 228(34900), 275(18600), and 313(12000); NMR($CDCl_3$) δ 9.92(2H, s, CHO), 7.51(2H, d, J=2.5Hz, 6,6′-H), 7.32 (2H, d, J=2.5 Hz, 4,4′-H), 4.00(6H, s, 3,3′-OCH_3), and 3.80 (6H, s, 2,2′-OCH_3).

6,6-Diformyl-2,2′,3,3′-tetramethyoxybiphenyl (II). A mixture of 1 g of 2-iodo-3,4-dimethoxybenzaldehyde and 7 g of copper powder was heated in a pressure tube at 180—190°C for 1 hr. The reaction mixture was then extracted with chloroform. After the removal of the solvent, the residue was extracted with ether. The extract was evaporated to dryness and recrystallized from ethanol to afford 0.25 g (37.6%) of II as colorless prisms; mp 134—135°C; sublimed at 130—140°C/10^{-3}—10^{-4} Torr. When the reaction period was extended to 4 hr, the yield was 9.4%; when it was shortened to 30 min at 170—185°C, the yield was 63.4%. IR(KBr) cm^{-1} 2930, 2840, 1675, 1585, 1450, 1386, 1250, and 1135; UV $\lambda_{\max}^{\mathrm{EtOH}}$ nm(ε) 232(28200) and 287(21500); NMR($CDCl_3$) δ 9.56 (2H, s, CHO), 7.82(2H, d, J=8.4Hz, 5,5′-H), 7.11(2H, d, J= 8.4Hz, 4,4′-H), 4.00(6H, s, 3,3′-OCH_3 and 3.61(6H, s, 2,2′-OCH_3).

5,6-Diformyl-2,2′,3,3′-tetramethoxybiphenyl (III). From a solution of 5 g of 2-iodo-3,4-dimethoxybenzaldehyde and 5 g of 5-iodo-3,4-dimethoxybenzaldehyde in benzene, the solvent was evaporated. The residual mixture was heated with 50 g of copper powder in a pressure tube at 180—187°C for 30 min. The reaction mixture was then worked up as has been described above to give 4.5 g of the product, which was chromatographed on silica gel with benzene-ethyl acetate (20:1 v/v). Each dimer, I, II, and III, was eluted, in that order. The yields of the dimers in a pure form were 27.8, 20.4, and 18.6% respectively. We attempted to improve the yield of III by changing the ratio of the 2-iodo- and 5-iodo-compounds. When a mixture of 2 g of coper powder was heated under the above conditions, the yields of I, II, and III, were 15.3, 37.1, and 13.5% respectively. The dimer III; colorless prisms from ethanol; mp 126—127°C. (Found: C, 65.22; H, 5.67%. Calcd for $C_{18}H_{18}O_6$; C, 65.44; H, 5.49%.; IR (KBr) cm^{-1} 2930, 2840, 1685, 1580, 1455, 1385, 1250, and 1135; UV $\lambda_{\max}^{\mathrm{EtOH}}$ nm(ε) 229(31800) and 280(19100); NMR($CDCl_3$) δ 9.92(1H, s, 5-CHO), 9.61 (1H, s, 6′-CHO), 7.82(1H, d, J=8.4Hz, 5′-H), 7.55(1H, d, J=2.5Hz, 6-H), 7.35(1H, d, J=2.5Hz, 4-H), 7.11(1H, d, J=8.4Hz, 4′-H), 4.01(6H, s, 3,3′-OCH_3), 3.76(3H, s, 2-OCH_3), and 3.66(3H, s, 2′-OCH_3).

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6) a) P. H. Gore and G. H. Hughes, *J. Chem. Soc.*, **1959**, 1615; b) W. Davey and R. W. Latter, *ibid.*, **1948**, 264; c) N. Kornblum and D. L. Kendall, *J. Amer. Chem. Soc.*, **74**, 5782 (1952); d) S. Kobayashi, M. Azekawa, and H. Morita, *Chem. Pharm. Bull.* (Tokyo), **17**, 89 (1969).

7) L. C. Raiford and E. H. Wells, *J. Amer. Chem. Soc.*, **57**, 2500 (1935).

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