1003. *Vitexin. Part II.*[1] *The Synthesis of 3-Acetyl-2-hydroxy-4 : 6-dimethoxyphenylacetaldehyde Dimethyl Acetal.*

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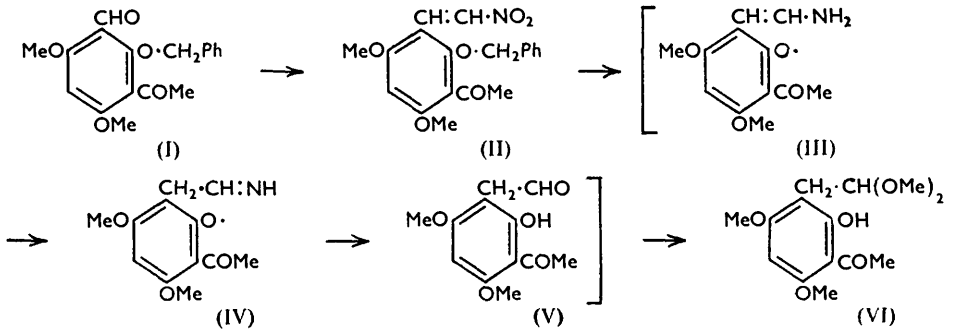
The structure of the degradation product of dehydrodi-*O*-methyl*secoapo*vitexin, believed to be 3-acetyl-2-hydroxy-4 : 6-dimethoxyphenylacetaldehyde dimethyl acetal,[1] has been confirmed by its synthesis from 2-benzyloxy-3-formyl-4 : 6-dimethoxyacetophenone by way of 3-acetyl-2-benzyloxy-4 : 6-dimethoxy-ω-nitrostyrene.

By the action of hot methanolic sulphuric acid dehydrodi-*O*-methyl*secoapo*vitexin [1] gave rise to pyruvaldehyde and an optically inactive compound $C_{10}H_8O_2(OMe)_4$ which from its properties was considered to be the dimethyl acetal (VI) of 3-acetyl-2-hydroxy-4 : 6-dimethylphenylacetaldehyde. This conclusion has been confirmed by a rational synthesis of the compound identical with the natural derivative.



Interaction of 2-benzyloxy-3-formyl-4 : 6-dimethoxyacetophenone (I) with nitromethane in pyridine containing a little piperidine gave 3-acetyl-2-benzyloxy-4 : 6-dimethoxy-ω-nitrostyrene (II) which on reduction with iron and acetic acid [2] in alcohol followed by heating of the resulting crude amine (III) with methanolic sulphuric acid, with simultaneous removal of the benzyl group, furnished the dimethyl acetal (VI) by way of the stages (IV) and (V).

In some exploratory experiments 3-acetyl-2-benzyloxy-4 : 6-dimethoxycinnamic acid was prepared but attempts to hydroxylate this gave only traces of an acidic substance. Reduction of 2-benzyloxy-ω : 4 : 6-trimethoxyacetophenone with lithium aluminium hydride, potassium borohydride, or aluminium amalgam furnished products inconsistent with the simple reduction of the carbonyl group.

Experimental

The infrared absorption spectra were determined in a Nujol mull with a Perkin-Elmer model 21 double-beam spectrophotometer.

2-Benzyloxy-3-formyl-4 : 6-dimethoxyacetophenone (I).—A mixture of 3-formyl-2-hydroxy-4 : 6-dimethoxyacetophenone [1] (1·27 g.), potassium carbonate (2·5 g.), benzyl bromide (5 ml.), a trace of potassium iodide, and acetone (50 ml.) was heated under reflux for 13 hr. On isolation the resulting *benzyl ether* solidified in contact with a little light petroleum (b. p. 40—60°) and then separated from acetone–light petroleum (b. p. 60—80°) in pale yellow needles (1·12 g.), m. p. 118—120°, with a negative ferric reaction and infrared max. at 1701 (aryl ketone), 1672 cm.$^{-1}$ (araldehyde) [Found: C, 68·7; H, 5·7; OMe, 19·5. $C_{16}H_{12}O_3(OMe)_2$ requires C, 68·7; H, 5·7; OMe, 19·7%]. The *monosemicarbazone* crystallised from 95% alcohol in needles, m. p.

[1] Part I, Evans, McGookin, Jurd, Robertson, and Williamson, *J.*, 1957, 3510.
[2] Beer, Clarke, Khorana, and Robertson, *J.*, 1948, 1605.

208—211° (Found: C, 61·5; H, 5·7; N, 11·4. $C_{19}H_{21}O_5N_3$ requires C, 61·4; H, 5·6; N, 11·3%), and the *mono*-2 : 4-*dinitrophenylhydrazone* from ethyl acetate in scarlet needles, m. p. 200° (Found: C, 58·2; H, 4·5; N, 11·3. $C_{24}H_{22}O_8N_4$ requires C, 58·3; H, 4·4; N, 11·3%).

3-*Acetyl*-2-*benzyloxy*-4 : 6-*dimethoxy*-ω-*nitrostyrene* (II).—The foregoing benzyl ether (1 g.) was heated with nitromethane (0·2 ml.) in pyridine (4 ml.) containing piperidine (4 drops) at 100° for 1 hr., the cooled mixture was poured into 2N-hydrochloric acid (40 ml.), and the solution extracted with benzene–ether. Evaporation of the dried extracts left a gum which on crystallisation from dilute alcohol gave 3-*acetyl*-2-*benzyloxy*-4 : 6-*dimethoxy*-ω-*nitrostyrene* in yellow needles (0·45 g.), m. p. 121—122°, infrared max. at 1701 (aryl ketone), 1616 (aryl conjugated double bond), 1567 (aromatic and nitro), and 1299 cm.$^{-1}$ (nitro) (Found: C, 63·7; H, 5·3; N, 4·0. $C_{19}H_{19}O_6N$ requires C, 63·9; H, 5·4; N, 3·9%).

When a mixture of the same benzyl ether (0·15 g.), excess of nitromethane (0·2 ml.), methanol (1 ml.), and piperidine (2 drops) was kept overnight and then diluted with water α-(3-*acetyl*-2-*benzyloxy*-4 : 6-*dimethoxyphenyl*)-β-*nitro*-α-(*nitromethyl*)*ethane* (0·1 g.) was obtained in needles, m. p. 143—145° after purification from dilute alcohol, infrared max. at 1704 (aryl ketone), 1560, 1548 (nitro), and 1351 cm.^{1} (nitro) (Found: C, 57·3; H, 5·3; N, 6·6. $C_{20}H_{22}O_8N_2$ requires C, 57·4; H, 5·3; H, 6·7%).

3-*Acetyl*-2-*hydroxy*-4 : 6-*dimethoxyphenylacetaldehyde Dimethyl Acetal* (VI).—A mixture of 3-acetyl-2-benzyloxy-4 : 6-dimethoxy-ω-nitrostyrene (70 mg.), iron filings (0·2 g.), alcohol (2·4 ml.), and acetic acid (0·4 ml.) was gently warmed for 11 min., filtered (residue washed with alcohol), and poured into water (40 ml.). The liquor was neutralised with sodium hydrogen carbonate and extracted with ether (20 ml. × 5), and the residual oil left on evaporation of the dried extract was boiled with methanol (20 ml.) containing concentrated sulphuric acid (0·1 ml.) for 1 hr., cooled, treated with barium carbonate (2 g.), filtered, and evaporated. The residue was triturated with water and extracted with ether, giving a dark gum which was chromatographed from benzene on silica powder. Crystallised from methanol, the product left on evaporation of the benzene eluate gave the dimethyl acetal of 3-acetyl-2-hydroxy-4 : 6-dimethoxyphenylacetaldehyde in pale yellow needles (*ca.* 10 mg.), m. p. and mixed m. p. 114—116°, having an infrared absorption spectrum identical with that of the natural specimen.

3-*Acetyl*-2-*benzyloxy*-4 : 6-*dimethoxycinnamic Acid*.—Interaction of 2-benzyloxy-3-formyl-4 : 6-dimethoxyacetophenone (0·86 g.) with malonic acid (1·16 g.) in pyridine (2 ml.) and piperidine (0·2 ml.) at 100° for 3 hr. followed by dilution of the cooled mixture with water (10 ml.) and alcohol (2 ml.) gave 3-*acetyl*-2-*benzyloxy*-4 : 6-*dimethoxycinnamic acid* as a yellow solid (0·3 g.), m. p. 180—186°, which on purification from 50% acetic acid formed yellow needles (0·25 g.), m. p. 185—187° [Found: OMe, 17·8%; equiv., 352. $C_{18}H_{14}O_4(OMe)_2$ requires OMe, 17·4%; equiv., 356]. Crystallised from benzene containing a little acetone the acid formed yellow rhombs (0·25 g.), m. p. 185·5—187°, with infrared max. at 1704 (aryl ketone), and 1675 cm.$^{-1}$ (acid carbonyl), which retained solvent of crystallisation [Found: C, 69·7; H, 5·6; OMe, 16·0. $C_{18}H_{14}O_4(OMe)_2,0{\cdot}5C_6H_6$ requires C, 69·8; H, 5·8; OMe, 15·4%]. On being boiled with methanol (30 ml.) containing concentrated sulphuric acid (1 ml.) for 6¼ hr. the compound (50 mg.) underwent esterification and simultaneous debenzylation, giving *methyl* 3-*acetyl*-2-*hydroxy*-4 : 6-*dimethoxycinnamate* which separated from ethyl acetate in pale yellow needles (20 mg.), m. p. 210°, with a dark green ferric reaction in alcohol [Found: C, 59·9; H, 6·0; OMe, 33·5. $C_{11}H_7O_3(OMe)_3$ requires C, 60·0; H, 5·7; OMe, 33·2%].

2-*Benzyloxy*-ω : 4 : 6-*trimethoxyacetophenone* was prepared by heating 2-hydroxy-ω : 4 : 6-trimethoxyacetophenone [3] (45·2 g.) with benzyl bromide (24 ml.) and potassium carbonate (28 g.) in boiling acetone (500 ml.) for 7·5 hr. Crystallised from 95% alcohol, the compound formed needles (39·2 g.), m. p. 74—76°, having a negative ferric reaction and a purple 3 : 5-dinitrobenzoic acid–aqueous sodium hydroxide reaction [Found: C, 68·5; H, 6·4; OMe, 29·8. $C_{15}H_{11}O_2(OMe)_3$ requires C, 68·3; H, 6·3; OMe, 29·4%].

The analyses were performed by Mr. A. S. Inglis, M.Sc., and his associates of this Department.

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[3] Row and Seshadri, *Proc. Indian Acad. Sci.*, 1946, **23**, *A*, 23.