

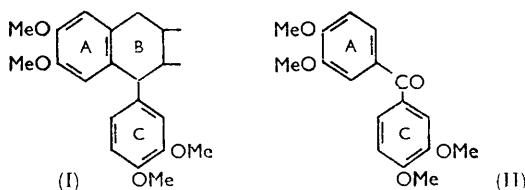
887. Lignans. Part I. Acylation in Polyphosphoric Acid as a Route to Intermediates.

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Phenols and their ethers with alkyloxybenzoic acids in polyphosphoric acid yield esters or benzophenones; the latter are intermediates in prospective syntheses of phenyltetrahydronaphthalene lignans.

Phosphorylation was found to affect the course of some reactions.

PODOPHYLLOTOXIN and some other lignans of its class have attracted attention because of their activity as cancer inhibitors;¹ their chemistry has been reviewed by Hartwell and Schrecker.² The lignan iso-olivil is inactive in therapy, but is readily available³ in high yield from olivil of the resin of *Olea europaea* and may prove a useful precursor for synthesis of active analogues. Iso-olivil dimethyl ether (I) undergoes oxidative degradation to 3,3',4,4'-tetramethoxybenzophenone (II), and lignan synthesis by elaboration of suitably substituted alkyloxybenzophenones of this type (II) has been explored⁴ and successfully concluded by Gensler *et al.* in their synthesis of picropodophyllin.⁵



Details of ring B substituents are omitted.

We find that phenolic ethers and alkyloxybenzoic acids in polyphosphoric acid give benzophenones, whereas phenols are esterified under similar conditions: Nakazawa and Kusuda⁶ noted that phenol itself is esterified, not acylated, in its reaction with benzoic acid.

Synthesis of benzophenones, as lignan precursors, is better effected in polyphosphoric acid than by the normal Friedel-Crafts reaction. For instance, Traverso has described a four-step synthesis of 4-hydroxy-3,3',4'-trimethoxybenzophenone, m. p. 50–60° (an intermediate in the synthesis of iso-olivil methyl ether), and we find that direct reaction between veratrole and vanillic acid in polyphosphoric acid is preferable, giving the ketone with m. p. 142–143°, in good yield: methylation of an alkaline solution of this compound precipitated 3,3',4,4'-tetramethoxybenzophenone,⁷ m. p. 144°, as reported by Traverso.⁸

¹ Kelly and Hartwell, *J. Nat. Cancer Inst.*, 1954, **14**, 967.

² Hartwell and Schrecker, "Progress in the Chemistry of Organic Natural Products," Springer, Vienna, 1958, Vol. XV, p. 83.

³ Koerner and Cernelutti, *Rend. R. Inst. Lomb. Sci.*, 1882, **15**, II, 654.

⁴ Walker, *J. Amer. Chem. Soc.*, 1953, **75**, 3390.

⁵ Gensler, Samour, Wang, and Johnson, *J. Amer. Chem. Soc.*, 1960, **82**, 1714.

⁶ Nakazawa and Kusuda, *J. Pharm. Soc. Japan*, 1955, **75**, 257.

⁷ Kostanecki and Tambor, *Ber.*, 1906, **39**, 4026; Perkin and Weizmann, *J.*, 1906, **89**, 1661.

⁸ Traverso, *Gazzetta*, 1957, **87**, 67.

Acylation of veratrole by trimethylgallic acid under similar conditions furnished 3,3',4,4',5'-pentamethoxybenzophenone⁷ (95% yield); this ketone is related to sikkimotoxin⁹ and has been derived from the partly characterised lignan acid, plicatic acid.¹⁰

A monofunctional ether, anisole, was readily acylated by vanillic acid to give 4-hydroxy-3,4'-dimethoxybenzophenone, obtained earlier in an impure condition by Traverso;⁸ methylation to the known 3,4,4'-trimethoxybenzophenone⁷ confirmed the orientation of the product. Reaction between the trimethyl ethers of pyrogallol and gallic acid afforded 2,3,3',4,4',5'-hexamethoxybenzophenone, a degradation product of lyoniresinol dimethyl ether.¹¹

A difficulty in synthesis of methylenedioxybenzophenones, precursors of the podophyllotoxin group, has been the ready fission of the ether residue by the action of Lewis acids,¹² but a satisfactory acylation of methylenedioxybenzene was described recently.⁵ We tried to achieve this result by acylation in polyphosphoric acid, but failed because of rapid cleavage of the ether. The diphenylmethylenedioxy group has been used¹³ to protect phenolic hydroxyl groups in the partial esterification of gallic acid, but was not retained under the conditions we used in an attempted acylation of diphenylmethylenedioxybenzene, since an ester, identical with that formed from catechol, was obtained. Catechol formed monoesters in its reaction with syringic and trimethylgallic acid, and the monoester of the latter was also the product when boron trifluoride was tested as an acylation catalyst. The free hydroxyl group of the trimethylgallic ester was readily methylated, but it could not be further esterified in polyphosphoric acid by treatment with a second equivalent of trimethylgallic acid. The diester¹⁴ was, however, prepared by fusion of catechol and trimethylgalloyl chloride; its behaviour in the Fries reaction was similar to that reported¹⁵ for catechol dipropionate, since catechol and syringic acid were isolated.

Phosphorylation of free hydroxyl groups is known¹⁶ to occur in polyphosphoric acid, and quinol phosphate has been made recently¹⁷ in this way. In two instances we found that phosphorylation affected the course of reaction: pyrogallol trimethyl ether and gallic acid yielded 3',4',5'-trihydroxy-2,3,4-trimethoxybenzophenone, but the product was only extractable from the aqueous liquors after they had been acidified with hydrochloric acid and refluxed, behaviour which is consistent with phosphorylation of free phenolic hydroxyl groups before or after acylation. Further, a phosphorus-containing polymer was the product from guaiacol and vanillic acid; their recovery on alkaline hydrolysis indicated that they had become associated through phosphate ester linkages. It is possible that the hydroxyl group of catechol half-esters is blocked by phosphorylation; if so, hydrolysis of the phosphate must occur in the acid liquor obtained during working up; the acid-catalysed hydrolysis of salol phosphate¹⁸ provides a formal analogy with this postulated behaviour.

EXPERIMENTAL

Infrared absorption spectra were measured for Nujol mulls.

Polyphosphoric acid was prepared by mixing phosphorus pentoxide (8 parts by weight) with 90% orthophosphoric acid (*d* 1.75; 5 parts by volume) and was stirred at 85° for 30 min. before use.

4-Hydroxy-3,3',4'-trimethoxybenzophenone.—A mixture of vanillic acid (5.0 g., 0.03 mole) and veratrole (4.1 g., 0.034 mole) was stirred into polyphosphoric acid (from 50 g. of phosphorus

⁹ Chatterjee and Chakravarti, *J. Amer. Pharmaceut. Assoc. (Sci. Edn.)*, 1952, **41**, 415.

¹⁰ Gardner, MacDonald, and MacLean, *Canad. J. Chem.*, 1960, **38**, 2387.

¹¹ Yasue and Kato, *Chem. and Pharm. Bull. Japan*, 1960, **9**, 844.

¹² Gensler and Stouffer, *J. Org. Chem.*, 1958, **23**, 909 and refs. cited.

¹³ Haworth, Pedler Lecture, Jan. 1961, *Proc. Chem. Soc.*, in the press.

¹⁴ Pepe, *Anales Asoc. quim. argentina*, 1940, **28**, 34.

¹⁵ Awad, El-Newehy, and Selim, *J. Org. Chem.*, 1958, **23**, 1783.

¹⁶ Cherbuliez, Probst, and Rabinowitz, *Helv. Chim. Acta*, 1960, **43**, 464, and earlier papers in the series.

¹⁷ Wieland and Patterson, *Chem. Ber.*, 1959, **92**, 2917.

¹⁸ Chanley, *J. Amer. Chem. Soc.*, 1952, **74**, 4347.

pentoxide); the solution was kept at 80—83° for 30 min. and then poured into ice-water (250 ml.); the *ketone* (8.0 g., 96%) separated as a pink solid. After three recrystallisations from aqueous alcohol (1:1) white needles, m. p. 142—143°, were obtained (Found: C, 66.9; H, 5.6. $C_{16}H_{16}O_5$ requires C, 66.8; H, 5.6%), having ν_{\max} . 3300 (broad band, bonded OH) and 1669 cm^{-1} (C=O).

The ketone (1.0 g.) in 3% aqueous sodium hydroxide was shaken with dimethyl sulphate (1.0 g.) at room temperature for 15 min. The precipitated 3,3',4,4'-tetramethoxybenzophenone⁷ (0.81 g., 77%) formed rhombs, m. p. 144°, from ethanol (Found: C, 67.4; H, 5.9. Calc. for $C_{17}H_{18}O_5$: C, 67.5; H, 6.0%), ν_{\max} . 1635 cm^{-1} (C=O).

3,3',4,4',5-Pentamethoxybenzophenone.—Trimethylgallic acid (4.6 g., 0.023 mole) and veratrole (3.0 g., 0.025 mole) were treated in polyphosphoric acid (from 35 g. of phosphorus pentoxide) as described above. The product⁷ (6.9 g., 95%) crystallised from ethanol as needles, m. p. 118—119° (Found: C, 65.1; H, 6.1. Calc. for $C_{18}H_{20}O_6$: C, 65.1; H, 6.1%), ν_{\max} . 1630 cm^{-1} (C=O).

4-Hydroxy-3,4'-dimethoxybenzophenone.—This *ketone* was obtained as a syrup (8 g., 84%) which rapidly solidified, when vanillic acid (5 g.) and anisole (3.2 g.) were treated in polyphosphoric acid (from 50 g. of phosphorus pentoxide) as before. Recrystallisation from ethanol furnished needles, m. p. 109—110° (Found: C, 69.8; H, 5.5. $C_{15}H_{14}O_4$ requires C, 69.8; H, 5.5%), ν_{\max} . 3300b and 1635 cm^{-1} .

The ketone (1.0 g.) was methylated with dimethyl sulphate (0.8 g.) as above, reaction being completed on a water-bath (30 min.). The product⁷ (0.80 g., 73%) crystallised from aqueous alcohol (1:1) as needles, m. p. 98—99° (Found: C, 70.8; H, 6.0. Calc. for $C_{16}H_{16}O_4$: C, 70.6; H, 5.9%), ν_{\max} . 1636 cm^{-1} .

2,3,3',4,4',5'-Hexamethoxybenzophenone.⁷—Trimethylgallic acid (10.6 g.) and pyrogallol trimethyl ether (8.4 g.) were treated as above in polyphosphoric acid (from 88 g. of phosphorus pentoxide). The material (16.3 g., 87%) which separated on dilution recrystallised from aqueous ethanol with m. p. 121°, as reported by Perkin and Weizmann⁷ (Found: C, 62.9; H, 6.2. Calc. for $C_{19}H_{22}O_7$: C, 62.9; H, 6.1%). It had ν_{\max} . 1650 cm^{-1} .

Reactions of Catechol and its Cyclic Ethers in Polyphosphoric Acid.—(a) Methyleneedioxybenzene (0.50 g.) dissolved in the acid with a red colour which deepened during 2 hr. of stirring at 20—22°. After dilution in water two polymeric products were separated, one (0.26 g.) by ether-extraction and the other (0.11 g.) by subsequent extraction with benzene. None of the starting material was recovered.

(b) A mixture of catechol (13.0 g.) and trimethylgallic acid (25.0 g.) was stirred into polyphosphoric acid (from 200 g. of phosphorus pentoxide) to give a solution initially yellow and deepening to red in 30 min. at 85°. After 40 minutes' heating, the solution was poured into ice-water (400 ml.). The *monoester* (33 g., 91%) separated and crystallised from aqueous ethanol (1:1) with m. p. 178—179° (Found: C, 63.1; H, 5.2. $C_{16}H_{16}O_6$ requires C, 63.2; H, 5.3%) and ν_{\max} . 3450b and 1736 cm^{-1} (ester C=O).

When the experiment was repeated with catechol (11.0 g.) and trimethylgallic acid (42.4 g., 2 equiv.) and the product (35 g.) washed with sodium hydrogen carbonate solution, the product (30 g., 97%) was recrystallised from aqueous alcohol and identified as the *monoester* obtained previously.

(c) Catechol and syringic acid were converted into the *monoester* by method (b) on a 0.05-mole scale, a yield of 75% being obtained. The product had m. p. 212° after recrystallisation from 1:1 aqueous ethanol (Found: C, 62.0; H, 4.8. $C_{15}H_{14}O_6$ requires C, 62.1; H, 4.9%), ν_{\max} . 3350b and 1725 cm^{-1} (ester C=O).

(d) Diphenylmethylenedioxybenzene¹⁹ (3.0 g.) and trimethylgallic acid (2.32 g.) were stirred into polyphosphoric acid (from 25 g. of phosphorus pentoxide); the temperature of the solution was kept at 85° for 35 min. and pouring into water gave material (4.9 g.) that, recrystallised from aqueous ethanol (1:4), had m. p. [and mixed m. p. with the *monoester* from (b)] 176—177° (3 g., 90%) yield; the infrared spectra of the two products were identical.

Reaction of Catechol with Trimethylgallic Acid Catalysed by Boron Trifluoride.—The reagents (0.02 mole) were refluxed for 5 hr. in diethyl ether (40 ml. containing 45% of boron trifluoride), a deep red colour developing. The cold ethereal solution was treated with water (100 ml.), the ether was distilled off, and the hot liquor decanted from an insoluble oil (2 g., 35%) which, crystallised from aqueous alcohol (1:1), had m. p. 179°; the mixed m. p. and the infrared

¹⁹ Mason, *J. Amer. Chem. Soc.*, 1944, **66**, 1157.

spectrum showed that this material was the monoester obtained previously. Methylation of the product (1.0 g.), under the conditions used in preparation of 3,3',4,4'-tetramethoxybenzophenone, afforded *guaiacol trimethylgallate* (0.70 g.), m. p. 113° (from ethanol) (Found: C, 64.2; H, 5.7. $C_{17}H_{18}O_6$ requires C, 64.1; H, 5.7%). An identical product was obtained on methylation of the monoester prepared as in (b) above.

Catechol Bistrimethylgallate: Attempted Fries Rearrangement.—A mixture of catechol (2.5 g.) and trimethylgalloyl chloride (10.5 g.) was kept molten for 2 hr. Evolution of hydrogen chloride having ceased, the melt was cooled and the solid product washed with sodium hydrogen carbonate solution, to yield the diester¹⁴ (11.4 g., 97%) which, recrystallised from benzene-light petroleum (1:1; b. p. 60–80°), had m. p. 154° (Found: C, 62.7; H, 5.4. Calc. for $C_{26}H_{26}O_{10}$: C, 62.7; H, 5.3%).

The diester (4.0 g., 0.008) was heated in nitrobenzene (70 ml.) on a steam-bath for 4 hr. with aluminium trichloride (3.5 g.): on cooling, the mixture was acidified with 5N-hydrochloric acid (20 ml.) and steam-distilled. Syringic acid (1.5 g.), m. p. 203°, separated from the aqueous residue and a further quantity (1.3 g., bulk yield 85%) was obtained by ether extraction of the water-insoluble residue. A test with ferric chloride showed that catechol was present in the steam-distillate.

3',4',5'-Trihydroxy-2,3,4-trimethoxybenzophenone.—A mixture of gallic acid (4.0 g.) and pyrogallol trimethyl ether (3.95 g.) was stirred into polyphosphoric acid (from 48 g. of phosphorus pentoxide) and the solution kept at 90° for 1 hr., then poured into ice-water (100 ml.). Solid (0.5 g.) separated, a further quantity (2.2 g.) being extracted with ether. These fractions were found to be a mixture of starting materials, in which pyrogallol trimethyl ether predominated. The aqueous liquor was refluxed with 2N-hydrochloric acid (200 ml.) for 2 hr. and extracted with ether (4 × 100 ml.), then evaporation of the dried ($MgSO_4$) extracts afforded the *ketone* (2.7 g., 39%) that crystallised from aqueous ethanol (1:1) as needles, m. p. 181–182° (Found: C, 60.1; H, 5.0. $C_{16}H_{16}O_7$, requires C, 60.0; H, 5.0%), ν_{max} . 3300b and 1663 cm^{-1} (ketone C=O).

The ketone (0.34 g.) in sodium hydroxide solution (0.18 g. in 15 ml. of water) was heated with dimethyl sulphate (0.5 ml.) on a steam-bath for 30 min. A sample of the precipitate (0.16 g., 83%) crystallised from methanol with m. p. 121–122°, and was identified as 2,3,3',4,4',5'-hexamethoxybenzophenone by mixed m. p. and comparison of infrared spectra.

Reaction between Guaiacol and Vanillic Acid.—A mixture of the reagents (0.03 mole) was heated in polyphosphoric acid (from 50 g. of phosphorus pentoxide) for 30 min. at 80°, then poured into ice-water (250 g.). A yellow solid A (3.7 g.) separated, which contained phosphorus and was insoluble in the common organic solvents. Two other fractions were obtained: B (1.45 g.) by ether extraction of the mother liquor; and C (2.3 g.) by ether extraction of the same liquor after 3 hours' heating with 4N-hydrochloric acid on a steam-bath. The three fractions were worked up as follows: (A) Treatment with 2N-sodium hydroxide solution (50 ml.) for 4 hr. on a steam-bath, and extraction with ether, yielded a solid (2.8 g.) which was separated into vanillic acid (1.5 g.) and guaiacol (1.0 g.) by crystallisation from benzene containing 5% of ethanol. Fractions (B) and (C) by crystallisation as above gave vanillic acid (2.2 g.) and guaiacol (1.3 g.). The total recovery of vanillic acid was 74% and of guaiacol 60%; no ketone was detected.

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