ACTA CHEMICA SCANDINAVICA 12 (1958) 1830—1833

Synthesis of Compounds Related to Muscarufin

IV.* 2,5-Bis-(2-carbomethoxyphenyl)-veratraldehyde

MARTIN NILSSON

Organisk-kemiska Institutionen, Kungl. Tekniska Högskolan, Stockholm, Sweden

The preparation of the title compound (II) from 2,5-di-iodovanillin is reported.

Recently Bohlmann and Kritzler [1] described an approach to the synthesis of muscarufin starting with the preparation of 3-(4-carboxy-$\Delta^{1,3}$-butadienyl)-6-methoxybenzoquinone-(1,4) from *iso*vanillin. However, due to the poor solubility of the quinone they were unable to attach the 2-carboxyphenyl residues.

A somewhat similar approach has been investigated in this laboratory aimed at the preparation of a *p*-terphenylaldehyde, the aldehyde group of which could be the starting point for the attachment of a side chain by methods similar to those of Bohlmann and Kritzler.

The Ullmann reaction is often a convenient route to *p*-terphenyl derivatives [2,3] and as the aldehyde group might be difficult to introduce at a later stage a di-iodoaldehyde was chosen as the starting material. Aldehyde groups generally survive under the conditions of the Ullmann reaction (*cf.* review by Fanta [4]), but preliminary experiments on the reactions of 2-iodo- and 5-iodoveratraldehydes with copper indicated that some oxidation was likely to occur in the first case.

Acetalisation was therefore chosen for protection of the aldehyde group. No acetal of vanillin appears to be described in literature and early comments [5] indicate that *o*- and *p*-hydroxybenzaldehydes fail to give acetals under standard conditions.

Vanillin when treated with ethylene glycol and boron trifluoride at room temperature gave a blue solution, from which only starting material was recovered. 2,5-Di-iodovanillin [6] under the same treatment gave a colourless solution from which 2,5-di-iodovanillin ethylene acetal was obtained (30—40

* Part III. *Acta Chem. Scand.* **12** (1958) 537.

% yield); a faint pink coloration appeared at the very beginning but soon faded. Better yield (64 %) was obtained when the reaction was carried out at higher temperature with continuous removal of water.

The failure of vanillin to give an acetal may be ascribed to the stability of the "quinoid" vanillin-boron trifluoride complex. As judged from the faint colour the corresponding complex of 2,5-di-iodovanillin is not as stable and this is presumably due to steric interference of the iodine atom(s).

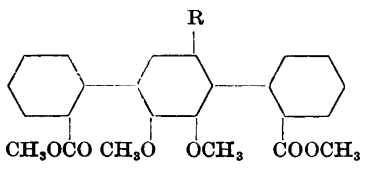
Treatment of 2,5-di-iodovanillin ethylene acetal with diazomethane gave 2,5-di-iodoveratraldehyde ethylene acetal in good yield. The alkaline methylation of 2,5-di-iodovanillin gave poor yields.

The Ullmann reaction with 2,5-di-iodoveratraldehyde ethylene acetal and methyl 2-bromobenzoate gave 2,5-bis-(2-carbomethoxyphenyl)-veratraldehyde ethylene acetal (I) in fair yield.

Mild acid hydrolysis of I gave 2,5-bis-(2-carbomethoxyphenyl)-veratraldehyde (II) which, however, did not give crystalline derivatives.

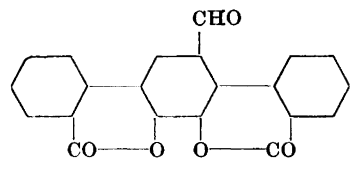
Demethylation of II (or I) with hydrobromic acid gave a high-melting, sparingly soluble product, which was difficult to purify and gave a poor analysis. Its resemblance to the stable dilactones described in previous communications [2,3] and infrared data indicate it to be the dilactone of 2,5-bis-(2-carboxyphenyl)-protocatechualdehyde (III).

Attempts to use the Reformatsky reaction with methyl γ-bromocrotonate [1,7], the Wittig reaction using the triphenylphosphonium salt from the same ester [7], and the acid-catalysed condensation with diethyl ethylidenemalonate [8] for the introduction of the muscarufin side-chain on 2,5-(2-carbomethoxyphenyl)-veratraldehyde (II) have so far been unsuccessful.



I R = —CH(O)(O)

II R = — CHO



III

EXPERIMENTAL

The melting points were determined on a Kofler block. The infrared spectra (potassium bromide discs) were recorded on a Perkin Elmer No. 21 instrument with a sodium chloride prism.

Ullmann coupling of iodoveratraldehydes. 2-Iodoveratraldehyde [6] (0.8 g) and copper bronze (2 g) were mixed in a test tube and heated to 250° for 15 min. The cooled mixture was extracted with chloroform, the opaque greenish solution was evaporated and the residue was distilled at 10 mm to give an oil (0.2 g, 45 %), which solidified and was recrystallised from methanol to give *5,5',6,6'-tetramethoxy-2,2'-diformyldiphenyl* as prisms, m. p. 136—137°. (Found: C 65.1; H 5.6. Calc. for $C_{18}H_{18}O_6$: C 65.4; H 5.5.)

5-Iodoveratraldehyde [9] by the same procedure gave *5,5',6,6'-tetramethoxy-3,3'-diformyldiphenyl* (65 %), m. p. 138–140°, undepressed by the product obtained by methylation of "dehydrodivanillin" [10] (*cf.* Ref.[9]). There were no obvious signs of oxidation in this experiment.

The mixed m. p. of the synthetic products gave a marked depression (115–135°).

2,5-Di-iodovanillin ethylene acetal. 2,5-Di-iodovanillin (45 g) prepared in 35 % overall yield from vanillin [6], ethylene glycol (40 ml) and boron trifluoride-ether complex (47 %, 10 ml) were heated in trichloroethylene (250 ml) under reflux with continuous removal of water from the condensate for 16 h. After cooling the glycol phase was separated and extracted with trichloroethylene. The combined trichloroethylene solution was washed quickly with water and sodium hydrogen carbonate solution and dried over sodium sulphate. Evaporation of the solvent gave a solid (32 g, 64 %, m. p. 110–125°), which was recrystallised from dry methyl *cyclo*hexane to give 2,5-di-iodovanillin ethylene acetal as elongated plates, m. p. 127–128°, occasionally resolidifying and finally melting at 135–137°. (Found: C 27.1; H 2.1; I 56.4. Calc. for $C_{10}H_{10}I_2O_4$: C 26.8; H 2.3; I 56.7.) The acetal was rather sensitive to water; recrystallisation from ethanol-water mixtures and even from moist light petroleum caused extensive hydrolysis.

2,5-Di-iodoveratraldehyde ethylene acetal. Crude 2,5-di-iodovanillin ethylene acetal was suspended in ether and treated with a moderate excess of diazomethane. After 1 h the nitrogen evolution ceased, the solvent was removed and the solid product was recrystallised from small volumes of methanol, m. p. 80–81° (70 % yield). (Found: C 28.2; H 2.6; 55.1. Calc. for $C_{11}H_{12}I_2O_4$: C 28.6; H 2.6; I 54.9.)

2,5-Bis-(2-carbomethoxyphenyl)-veratraldehyde ethylene acetal (I). 2,5-Di-iodoveratraldehyde ethylene acetal (4.3 g, 0.009 mole), methyl 2-bromobenzoate (17 g, 0.08 mole) and copper bronze (50 g) were allowed to react at 250°. The oil obtained by extraction with chloroform was distilled giving methyl benzoate, dimethyl diphenate and a fraction, b. p. 240–260°, 1 mm (2.5 g, yellow oil), which was dissolved in benzene and passed through a column of alumina. The solvent was removed and the residue was dissolved in a small volume of methanol and after keeping in the refrigerator gave I as compact prisms, m. p. 124–126° (1.0 g). (Found: C 67.9; H 5.8. Calc. for $C_{27}H_{26}O_8$: C 67.8; H 5.5.)

The infrared spectrum showed an ester carbonyl band at 1 730 cm^{-1}.

Mild acid hydrolysis of the material in the mother liquors gave a further quantity of crystalline material (II, 0.5 g, m. p. 135–137°; see below) bringing the total yield for the Ullmann coupling to 35 %.

2,5-Bis-(2-carbomethoxyphenyl)-veratraldehyde (II). The acetal I was heated on the water bath for 0.5 h in aqueous acetic acid containing a trace of *p*-toluenesulphonic acid. On cooling the aldehyde II separated in quantitative yield and was recrystallised from methanol to give prisms, m. p. 140–141°. (Found: C 68.8; H 5.3. Calc. for $C_{25}H_{22}O_7$: C 69.1; H 5.1.)

The infrared spectrum showed ester carbonyl (1 730 cm^{-1}), aldehyde carbonyl (1 695 cm^{-1}) and aldehyde C–H stretching band (2 760 cm^{-1}).

Attempts to prepare the 2,4-dinitrophenylhydrazone and the semicarbazone gave only amorphous material.

Demethylation. The aldehyde II (0.20 g), hydrobromic acid (*d* 1.48, 1 ml) and acetic acid (2 ml) were heated under reflux for 0.5 h. After cooling the precipitate was collected and was recrystallised from large volumes of acetic acid to give small needles, which were always somewhat brownish, m. p. *ca.* 360° (decomp.). (Found: C 72.8; H 2.9. Calc. for $C_{21}H_{10}O_5$: C 73.7; H 2.9.)

The infrared spectrum showed a very strong band at 1 755 cm^{-1}, which may be ascribed to a six-membered ring lactone, and bands due to an aldehyde group (1 695 and 2 760 cm^{-1}). The dilactone of 2,5-dihydroxy-1,4-bis-(2-carboxyphenyl)-benzene [2] gave a very strong band at 1 750 cm^{-1}.

The author is indebted to *Statens Tekniska Forskningsråd* for a fellowship and to Dr. B. R. Thomas for linguistic criticism.

REFERENCES

1. Bohlmann, F. and Kritzler, H. *Chem. Ber.* **90** (1957) 1512.
2. Erdtman, H. and Nilsson, M. *Acta Chem. Scand.* **10** (1956) 735.
3. Nilsson, M. *Acta Chem. Scand.* **10** (1956) 1377.
4. Fanta, P. *Chem. Revs.* **38** (1946) 139.
5. Fischer, E. and Giebe, G. *Ber.* **30** (1897) 3053.
6. Raiford, L. C. and Wells, E. H. *J. Am. Chem. Soc.* **57** (1935) 2500.
7. Bohlmann, F. *Chem. Ber.* **90** (1957) 1519.
8. Higginbotham, L. and Lapworth, A. *J. Chem. Soc.* **121** (1922) 2823.
9. Erdtman, H. *Svensk Kem. Tidskr.* **47** (1935) 223.
10. Elbs, K. and Lerch, H. *J. prakt. Chem.* [2] **93** (1916) 2.

Received June 28, 1958.