Synthesis of Ethyl 3-Bromo-2-ethoxy-2-(4-hydroxybenzoyloxy)propionate and Attempts at Cyclisation (A Correction)

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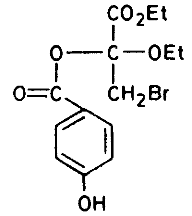
The title compound (1) has been synthesised by a new, easily reproducible route. Attempts to cyclise (1) to the dienone (2) were not successful. Some products of these experiments were identified.

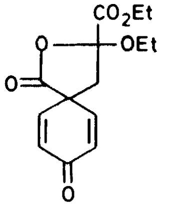
SOME time ago one of us[1] described a synthesis of the title compound (1) and its cyclisation to the dienone (2) as a route to prephenate. We know today that (2) is in fact the crucial intermediate in two independent syntheses of prephenate.[2,3] However, we also know that the synthesis of (1) and (2) described in the previous paper[1] cannot be correct, since we were never able to reproduce these results.[4a] The preparation of the dienone (3), also described in this paper could be reproduced after some improvements[4a] had been made to the original procedure[5] (published[4b]).

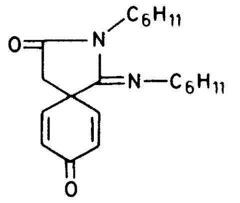
We have now found a simple and well reproducible synthesis for the title compound (1) from the sodium salt of 4-hydroxybenzoic acid and ethyl 2,3-dibromo-2-ethoxypropionate, prepared by bromination of ethyl 2-ethoxyacrylate and used without purification.

RESULTS AND DISCUSSION

The constitution of (1) follows from the spectral data, analysis, and its reactions. Treatment with dinitrophenylhydrazine leads to the dinitrophenylhydrazone of ethyl bromopyruvate. The bromine in (1) reacts rather slowly with alkali as is known for α-bromoacetals.

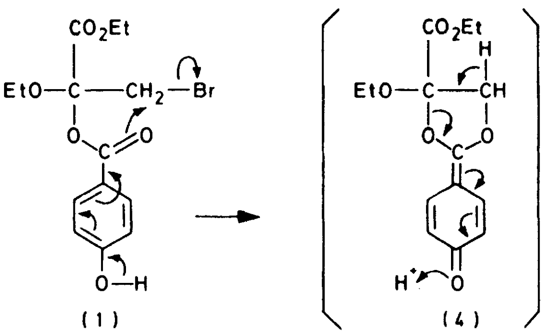

(1)

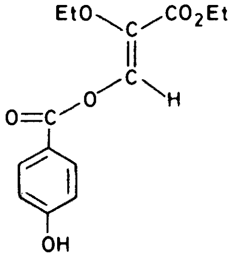

(2)

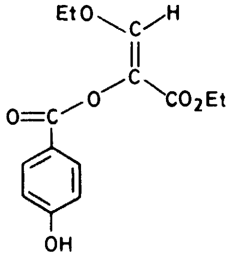

(3)

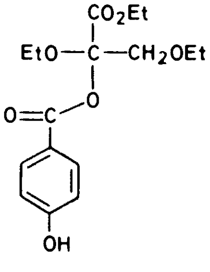
With potassium t-butoxide at 20 °C only the potassium phenolate of (1) is formed. After refluxing (1) with potassium t-butoxide in t-butyl alcohol, ethyl 4-hydroxybenzoate was isolated. The same ester is formed by the reaction of (1) with lithium ethoxide.

With ethylmagnesium iodide in refluxing acetonitrile a compound is formed which must be either the ester (5) or (6), or a stereoisomer thereof. Calculations of the chemical shifts of the vinylic protons of the possible four isomers using respective increments[6] indicate with high probability the structure (5). Only for this ester or its stereoisomer, can a reasonable reaction mechanism *via* intermediate (4) be formulated. Recent experiments[7] with a simple model compound indeed confirm an intermediate of type (4).


(1) (4)


(5)


(6)


(7)

Reaction of (1) with silver tetrafluoroborate in refluxing benzene–ethanol in the presence of lithium ethoxide leads to ester (7). Here, the dioxolan (4) could be an intermediate.

These negative cyclisation experiments show that ' Ar_1-participation '[8,9] seems not to be possible with derivatives of 4-hydroxybenzoic acid esters because of the participation of the ester carbonyl group which is activated by the mesomeric influence of the phenolic OH group, or even more by the phenolate anion.

EXPERIMENTAL

I.r. spectra were obtained on a Perkin-Elmer spectrometer, u.v. spectra on a Leitz-Unicam spectrophotometer S.P. 800, and ^1H n.m.r. spectra on a Variant A-60 spectrometer (tetramethylsilane as internal standard).

Ethyl 3-Bromo-2-ethoxy-2-(4-hydroxybenzoyloxy)propionate (1).—To ethyl 2-ethoxyacrylate[10] (14.4 g, 0.1 mol) dry bromine (16 g, 0.1 mol) was added dropwise with stirring at 0 °C. After dilution with acetonitrile (100 ml), sodium 4-hydroxybenzoate (15 g, 0.1 mol) (dried in an oven at 100 °C *in vacuo*) was added in small amounts. The mixture was stirred for 12 h at 20 °C, the sodium bromide removed by filtration, and the solvent evaporated *in vacuo*. The oily residue showed 5 spots on t.l.c. [ether–light petroleum (1 : 1)]. The following chromatographic procedure yielded the best separation:

In a 1-l round bottom flask, silica gel (500 g) (Merck; 0.05—0.2 mm) was thoroughly mixed with dry ether (150 ml). The mixture was then quickly introduced into a polyamide tube (130-cm length × 5-cm diameter, closed at one end by welding) and compacted under pressure. Then the oil (10 g) was mixed with some silica gel and the paste deposited at the top of the column. After adding a mixture of dry ether–light petroleum (1 : 1) the chromatography was started by perforating the foot of the column with a needle; chromatography was stopped when the solvent had reached the foot of the column. The column was then cut into pieces of 10-cm length and the silica gel from each segment extracted with ethyl acetate. The extracts were investigated by t.l.c. The fractions containing only the spot 3 were combined and evaporated down to 50 ml. On standing at 0 °C *ethyl 3-bromo-2-ethoxy-2-(4-hydroxybenzoyloxy)propionate* (10 g, 27%) crystallized out slowly, m.p. 116—118 °C (from CCl_4); $\nu_{max.}$ (KBr) 1 755 and 1 735 (ester carbonyl); $\lambda_{max.}$ (ethanol) 263 (qualitative) shifted by sodium hydroxide to 307 nm; δ(60 MHz, $CDCl_3$) 1.25—1.3 (6 H, 2 t, $\mathrm{CH_2}Me$), 3.97 (2 H, m, $\mathrm{C}H_2\mathrm{Me}$), 4.1 (2 H, d, CH_2Br), 4.4 (2 H, q, $\mathrm{C}H_2\mathrm{Me}$), and 6.9 and 7.9 (d, 2 H, AA′BB′ pattern, Ar-H) (Found: C, 46.5; H, 4.8; Br, 23.1. $C_{14}H_{17}O_6Br$ requires C, 46.5; H, 4.8; Br, 22.2%).

Dinitrophenylhydrazone of Ethyl Bromopyruvate.—To a few mg of (1) in a little ethanol dinitrophenylhydrazine in 1N-HCl was added. After a short time a yellow precipitate was formed, which by t.l.c. [silica gel, ether–light petroleum (1 : 1)] was shown to be identical with an authentic sample.

Reaction of (1) *with Potassium t-Butoxide.*—A solution of (1) (3.8 g, 8.3 mmol) and potassium t-butoxide (1.2 g, 10 mmol) in t-butyl alcohol (50 ml) was refluxed under nitrogen for 3 h. After evaporation of the solvent *in vacuo* the residue was extracted with ether. The mixture was separated by preparative t.l.c. on silica gel. The zone running behind the starting material was extracted with ethyl acetate and evaporated *in vacuo*. The crystalline residue was identified by its i.r. spectrum, m.p., and mixed m.p. with an authentic sample, as ethyl 4-hydroxybenzoate.

Reaction of (1) *with Ethylmagnesium Iodide.*—Compound (1) (3.61 g, 10 mmol) in dry ether (50 ml) was reacted quickly, with good stirring and exclusion of moisture, with ethylmagnesium iodide (10 mmol) in dry ether (50 ml). Evolution of gas was observed and a yellow product precipitated, which after evaporation of the solvent, was dissolved in dry acetonitrile (250 ml). The red mixture was then refluxed under nitrogen for 15 h and the solvent evaporated *in vacuo*. The oily residue was separated by preparative t.l.c. on silica gel [ether–light petroleum (1 : 1)]. The second zone was separated and extracted with ethyl acetate. Evaporation of the solvent *in vacuo* yielded *ethyl 2-ethoxy-3-(4-hydroxybenzoyloxy)acrylate* (5) (300 mg, 10.7%), m.p. 113—115 °C (CCl_4); $\nu_{max.}$ 1 735, 1 690 (ester carbonyl), and 1 660 (C=C); $\lambda_{max.}$ (ethanol) 282 (qualitative), shifted by NaOH to 322 nm; δ(60 MHz, $CDCl_3$) 1.3—1.32 (6 H, 2 t, $\mathrm{CH_2}Me$), 4.15—4.20 (4 H, 2 q, $\mathrm{C}H_2\mathrm{Me}$), 6.95 and 8.0 (4 H, AA′BB′ pattern, Ar-H), 7.45 (1 H, br s, OH), and 8.30 (1 H, s, vinyl-H) (calculated[6] 7.36) (Found: C, 59.9; H, 5.8; OEt, 31.6%; *M* (osmometric), 290; $C_{14}H_{15}O_5$ requires C, 59.9; H, 5.8; OEt, 32.1%; *M*, 280.3].

Ethyl 2,3-Diethoxy-2-(4-hydroxybenzoyloxy)propionate (7).—To a solution of (1) (1.08 g, 3 mmol) and silver tetrafluoroborate (585 mg, 3 mmol) in dry ethanol (50 ml) was added a solution of lithium (2 mg, 3 mg-atom) in dry ethanol (10 ml) and dry benzene (30 ml). After refluxing for 30 min a dark precipitate was deposited (0.56 mg AgBr, 94%). After evaporation of the solvent *in vacuo*, the residue was dissolved in ether–water. The ethereal phase was separated, washed with water, dried, and the solvent removed *in vacuo*. The residual oil crystallized on scratching; it was purified by preparative t.l.c. [silica gel, ether–light petroleum (1 : 1)] (650 mg, 66.5%) to give *crystals*, m.p. 102—103 °C (ether–light petroleum); δ(60 MHz, $CDCl_3$) 1.29 (9 H, m, $\mathrm{CH_2}Me$), 3.65 (4 H, m) and 4.37 (2 H, q, $\mathrm{C}H_2\mathrm{Me}$), 4.6 (2 H, s, $\mathrm{C}H_2\mathrm{OEt}$), 6.98 and 7.92 (4 H, AA′BB′ pattern, Ar-H) (Found: C, 59.1; H, 7.1; OEt, 41.5; $C_{16}H_{22}O_7$ requires C, 58.9; H, 6.8; OEt, 41.4%).

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