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The Photo-Fries Rearrangement of Bis(methoxymethoxy)-phenyl Cinnamates

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Synopsis. The irradiation of bis(methoxymethoxy)-phenyl cinnamates in benzene solution gave 2′-hydroxy-bis-(methoxymethoxy)chalcones in 5.4—7.6% yields and 2′,3′,4′-, 2′,3′,5′-, and 2′,4′,6′-trihydroxychalcone were obtained by the hydrolysis of the resulting chalcones.

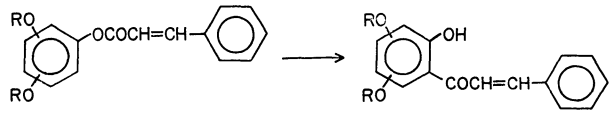
In previous papers,[1,2] we have reported the formation of hydroxychalcones by the photo-Fries rearrangement of phenyl cinnamate and hydroxyphenyl cinnamate. Further, we have attempted the photo-irradiation of 2,3- and 3,5-dihydroxyphenyl cinnamate (I and III); however, the isolation of the corresponding trihydroxy-chalcones (X and XII) was very difficult.[3]

In this note we wish to report the photo-Fries rearrangement of dihydroxyphenyl cinnamates protected their hydroxyl groups with methoxymethyl groups.

2,3-,[3] 2,4-, and 3,5-[3] Dihydroxyphenyl cinnamate (I, II, and III) were isolated from the reaction mixture obtained by the acylation of pyrogallol, 1,2,4-trihydroxybenzene, and phloroglucinol with cinnamoyl chloride in pyridine.

The structure of II was confirmed by a comparison of the melting points of the 2,4-dimethoxyphenol obtained by the hydrolysis of the dimethylether of II and its benzoate with those of authentic samples.[4,5]

2,3-, 2,4-, and 3,5-Bis(methoxymethoxy)phenyl cinnamate (IV, V, and VI) were obtained from the corresponding dihydroxyphenyl cinnamate by treatment with sodium amide, followed by that of chloromethyl ether in a tetrahydrofuran–benzene solution; these bis(methoxymethoxy)phenyl cinnamates were then purified by means of silica gel column chromatography.



I, IV (2,3-) VII, X (3′,4′-)
II, V (2,4-) VIII, XI (3′,5′-)
III, VI (3,5-) IX, XII (4′,6′-)

I ~ III I ~ XII : R=H IV ~ IX : R=CH_3OCH_2

The irradiation was carried out in a benzene solution under a nitrogen atmosphere and at room temperature using a high-pressure 100 W mercury arc. After irradiation, the benzene was evaporated *in vacuo*, and the residue was chromatographed on a column of silica gel. By the irradiation of IV and VI, 2′-hydroxy-3′,4′- and 2′-hydroxy-4′,6′-bis(methoxymethoxy)chalcones (VII and IX) were obtained, in 7.6 and 6.0% yields; they were converted into 2′,3′,4′- and 2′,4′,6′-trihydroxy-chalcones respectively (X and XII) by heating with methanolic hydrochloric acid. The structures of X and XII were identified by comparing their melting points and IR spectra with those of authentic samples.[6,7]

Similarly, 2′-hydroxy-3′,5′-bis(methoxymethoxy)-chalcone (VIII) was obtained in a 6% yield by the irradiation of V; it was then converted into 2′,3′,5′-trihydroxychalcone (XI) (mp 174—175 °C). The structure of this new chalcone was identified by the elemental analysis and by a study of its UV and IR spectra.

From these results, it may be thought that the protection of the hydroxyl groups of dihydroxyphenyl cinnamate with methoxymethyl group can be used in obtaining trihydroxychalcones by photo-Fries rearrangement.

Experimental

All the melting points are uncorrected.

The 2,3-dihydroxyphenyl cinnamate (I, mp 172—174 °C) and the 3,5-dihydroxyphenyl cinnamate (III, mp 188—189 °C) were prepared according to the method of a previous report.[3]

2,4-Dihydroxyphenyl Cinnamate (II). To a stirred solution of 2.2 g of 1,2,4-trihydroxybenzene in 20 ml of pyridine, there was slowly added 5.2 g of cinnamoyl chloride at 8—12 °C; then the mixture was stirred at 45 °C over a period of about 1 hr. The reaction mixture was then poured into 150 ml of cold 3 M hydrochloric acid and extracted with ethyl acetate; the ethyl acetate layer was washed with water. The ethyl acetate solution was evaporated *in vacuo*, and the residue was chromatographed with benzene–ether (2:1) on a column of silica gel.

From the last elution, II was obtained as light yellow crystals. Yield, 1.2 g (26%); mp 144—145 °C (from benzene). IR (KBr): 3430, 3240 (ν OH) and 1700 cm^{-1} (ν CO). UV: λ_{max}^{EtOH} 283 mμ(log ε=4.44). Found: C, 70.42; H, 4.94%. Calcd for $C_{15}H_{12}O_4$: C, 70.30; H, 4.72%. Dimethyl ether, mp 104—105 °C (colorless prisms from ethanol). NMR ($CDCl_3$): δ 3.80 (-OMe), 6.61, 7.84 (-CH=CH-, J=16.0 Hz). Found: C, 71.66; H, 5.75%. Calcd for $C_{17}H_{16}O_4$: C, 71.82; H, 5.67%.

The hydrolysis of this dimethylether with an aqueous sodium hydroxide solution gave 2,4-dimethoxyphenol (mp 25—27 °C) (lit, mp 28 °C,[4] benzoate, mp 88—89 °C (lit, mp 89 °C[5])).

2,3-Bis(methoxymethoxy)phenyl Cinnamate (IV). To a solution of 1.0 g of I in 10 ml of dry tetrahydrofuran and 30 ml of dry benzene, there was added 2.0 g of sodium amide; after the mixture had then been stirred for 30 min, 3.2 g of monochloromethyl ether was added to the reaction mixture, drop by drop, over a period of about 30 min at room temperature. The reaction mixture was then poured into a cold, dilute, aqueous sodium carbonate solution and extracted with ether. The ether layer was washed with water and dried over anhydrous sodium sulfate. The ether was evapolated

in vacuo, and the resulting crude oil was chromatographed on a column of silica gel. 2,3-Bis(methoxymethoxy)phenyl cinnamate (IV) was obtained as colorless crystals from the second elution with benzene–ether (20: 1). Yield, 0.50 g (37%); mp 75—77 °C (from petroleum ether). IR (KBr): 1730 cm^{-1} (ν CO). NMR ($CDCl_3$): δ 3.49, 3.52 (–OMe), 5.18, 5.12 ($-CH_2-$), 6.67, 7.89 (–CH=CH–, J=16.0 Hz).

3,5-Bis(methoxymethoxy)phenyl Cinnamate (VI). This compound was prepared from III by the method described above. The crude VI was purified by silica-gel-column chromatography with benzene–ethyl acetate (5: 1). Yield, 35%; pale yellow oil. IR ($CHCl_3$): 1725 cm^{-1} (ν CO). NMR ($CDCl_3$): δ 3.44 (–OMe), 5.11 ($-CH_2-$), 6.56, 7.80 (–CH=CH–, J=16.0 Hz).

2,4-Bis(methoxymethoxy)phenyl Cinnamate (V). This compound was prepared from II by the method described above. The crude V was purified by silica-gel-column chromatography with benzene–ethyl acetate (20: 1). Yield, 31%; pale yellow oil. IR (neat): 1730 cm^{-1} (ν CO). NMR ($CDCl_3$): δ 3.44 (–OMe), 5.12 ($-CH_2-$), 7.81, 6.56 (–CH=CH–, J=16.0 Hz).

Irradiation of 2,3-Bis(methoxymethoxy)phenyl Cinnamate (IV). A solution of 500 mg of IV in 300 ml of dry benzene was irradiated under a nitrogen atmosphere at room temperature by means of a high-pressure 100 W mercury arc for 20 hr. After irradiation, the benzene was evapolated *in vacuo*, and the resulting crude mixture was chromatographed on a column of silica gel. 2′-Hydroxy-3′,4′-bis(methoxymethoxy)-chalcone (VII) was obtained as yellow needles from the second elution with petroleum ether–ether (2: 1). Yield, 38 mg (7.6%); mp 95—96 °C (from ligroin). Found: C, 66.26; H, 5.64%. Calcd for $C_{19}H_{20}O_6$: C, 66.27; H, 5.85%. UV: λ_{max}^{EtOH} 336 mμ(log ε=4.47). NMR ($CDCl_3$): δ 3.15, 3.66 (–OMe), 5.22, 5.29 ($-CH_2-$), 7.52, 7.89 (–CH=CH–, J= 16.0 Hz), 13.24 (–OH). A solution of 40 mg of VII in 1.5 ml of methanol containing 0.3 ml of 6 M hydrochloric acid was refluxed for 5 min. After cooling, 2′,3′,4′-trihydroxychalcone (X) was obtained as yellow needles. Yield, 20 mg (67%); mp 164—165 °C (lit, mp 166 °C[6]). The structure of this trihydroxychalcone was identified by comparison with that of an authentic sample.[6]

Irradiation of 3′,5′-Bis(methoxymethoxy)phenyl Cinnamate (VI). A solution of 600 mg of VI in 400 ml of dry benzene was irradiated for 20 hr as has been described above. Subsequent elution with petroleum ether–ether (2: 1) gave 2′-hydroxy-4′,6′-bis(methoxymethoxy)chalcone (IX) as yellow prisms. Yield, 36 mg (6.0%); mp 89—92 °C (from ligroin). Found: C, 66.32; H, 6.01%. Calcd for $C_{19}H_{20}O_6$: C, 66.27; H, 5.85%. NMR ($CDCl_3$): δ 3.49, 3.53 (–OMe), 5.18, 5.29 ($-CH_2-$), 7.76, 7.90 (–CH=CH–, J=16.0 Hz), 13.74 (–OH). The hydrolysis of IX gave 2′,4′,6′-trihydroxychalcone (XII) as yellow needles; mp 176—178 °C (from benzene). The structure of XII was identified by a comparison of its IR spectrum with that of an authentic sample.[7]

Irradiation of 2,4-Bis(methoxymethoxy)phenyl Cinnamate (V). A solution of 820 mg of V in 400 ml of dry benzene was irradiated for 42 hr as has been described above. 2′-Hydroxy-3′,5′-bis(methoxymethoxy)chalcone (VIII) was obtained as orange red crystals from the third elution with benzene–ethyl acetate (20: 1). Yield, 44 mg (5.4%); mp 122—124 °C (from ligroin). Found: C, 66.13; H, 5.98%. Calcd for $C_{19}H_{20}O_6$: C, 66.27; H, 5.85%. UV: λ_{max}^{EtOH} 328 mμ(log ε= 4.40). NMR ($CDCl_3$): δ 3.50, 3.53 (–OMe), 5.12, 5.22 ($-CH_2-$), 7.52, 7.89 (–CH=CH–, J=16.0 Hz), 13.78 (–OH).

2′,3′,5′-Trihydroxychalcone (XI). To a solution of 20 mg of VIII in 0.5 ml of methanol, there was added 0.1 ml of 6 M hydrochloric acid, after which the mixture was boiled for 5—6 min. After cooling, 2 ml of a saturated aqueous sodium chloride solution was added to the mixture, and then the mixture was extracted with ether. The ether layer was dried over anhydrous sodium sulfate, and the ether was evaporated *in vacuo*. The resulting residue was crystalized by the addition of petroleum ether to give 2′,3′,5′-trihydroxychalcone (XI). Yield, 10 mg (65%); mp 174—176 °C (from benzene). Found: C, 70.00; H, 4.68%. Calcd for $C_{15}H_{12}O_4$: C, 70.30; H, 4.72%. UV: λ_{max}^{EtOH} 330 and 440 mμ(log ε= 4.44 and 3.43).

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