Journal of Chromatography, 590 (1992) 369–372
Elsevier Science Publishers B.V., Amsterdam

CHROM. 23 801

Short Communication

Separation and preparative isolation of phenolic dialdehydes by on-line overpressured layer chromatography☆

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(First received April 15th, 1991; revised manuscript received October 14th, 1991)

ABSTRACT

The Reimer–Tiemann reaction carried out in a heterogeneous solid–liquid medium was found to give the isomeric dialdehydes 2-hydroxy-1,3-benzenedicarboxaldehyde and 4-hydroxy-1,3-benzenedicarboxaldehyde. The PRISMA model was employed to optimize the eluent mixture, and with careful choice of silica gel high-performance thin-layer chromatographic plates, the two isomers could be isolated and purified by on-line overpressured layer chromatography.

INTRODUCTION

The Reimer–Tiemann [1] reaction, involving condensation of phenol with chloroform in a basic medium, gives rise to salicylaldehyde (**2**) and *p*-hydroxybenzaldehyde (**3**). In the presence of a solid alkali metal hydroxide in chloroform–methanol–water, this reaction leads to the mono- and diformylation of phenol [2]. Apart from compounds **2** and **3**, 2-hydroxy-1,3-benzenedicarboxaldehyde (**4**) and 4-hydroxy-1,3-benzenedicarboxaldehyde (**5**) are also formed (Fig. 1).

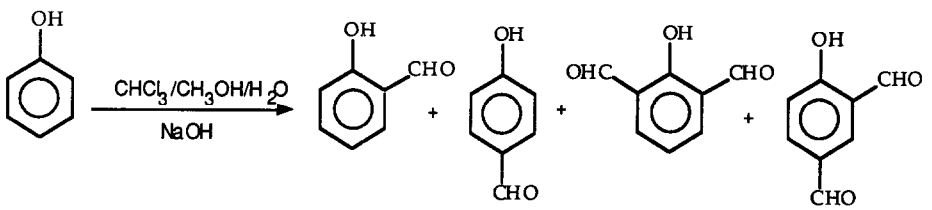

Fig. 1. Reimer–Tiemann reaction. Percentages represent yields with respect to a phenol conversion of 53%.

☆ Presented at the 18th International Symposium on Chromatography, Amsterdam, September 23–28, 1990.

0021-9673/92/$05.00

Although compounds **2** and **3** are readily separated by gas chromatography with a packed column [3], the complex mixture of dialdehydes cannot be separated by this method. We report here the use of on-line overpressured layer chromatography (OPLC) according to Tyihák *et al.* [4] for the rapid and efficient separation and purification of the phenolic dialdehydes. The advantages of this technique are the small amounts of eluent required, a short time for development, which is carried out in a closed chamber avoiding interaction with air, and the fact that detection and separation are carried out simultaneously.

EXPERIMENTAL

The ^1H NMR spectra of the dialdehydes were recorded on a Bruker WN 250-MHz NMR spectrometer using [$^2H_6$]acetone as solvent and tetramethylsilane (TMS) as internal reference. The IR spectra were recorded on a Perkin-Elmer Model 1710 spectrometer with samples in KBr potassium bromide disks.

The mass spectra of the two isomers were recorded using electron impact ionization on a Nermag R15-10 spectrometer (Delsi, Paris, France) coupled to a gas chromatograph equipped with a CP-Sil 5 quartz capillary column (25 m × 0.25 mm I.D., film thickness 0.2 mm) (Chrompack, Paris, France) under the following conditions: carrier gas, helium; temperature initally 100°C, then increased at 5°C/min to 220°C; input pressure, 0.25 bar.

High-performance liquid chromatographic (HPLC) separations were carried out on a Milton-Roy instrument with a LiChrosorb RP-18 (5-μm) column (25 cm × 0.46 cm I.D.) (Merck, Paris, France) using water–acetonitrile–acetic acid (8:2:0.02) as the mobile phase with a UV detector set at 254 nm (LDC Analytical, Roissy, France).

Separation by TLC was carried out on silica gel 60 F_{254} plates (5 × 7.5 cm, 0.2 mm thick layer) (Merck). A 0.5-μl volume of a solution containing a mixture (5%, w/w) of the compounds to be separated was placed 0.5 cm from the end of the plates, which were then placed in a closed glass tank (10 × 6 cm) previously saturated with vapour of the optimized eluent (diethyl ether–hexane–chloroform, 3:2:0.25). The plates were removed when the solvent front was 1 cm from the top of the plate. The plates were dried and the spots revealed under UV light (254 nm). Diethyl ether–hexane–chloroform (3:2:0.25) was found to give the best ΔR_F between compounds **4** and **5** (R_F = 0.41 and 0.29, respectively). TLC was employed to optimize the eluent mixture, which was subsequently employed for on-line OPLC.

TLC under pressure was carried out using a Chrompres 25 system (Factory of Laboratory Instruments, Budapest, Hungary) equipped with an automatic injector, fraction collector (Eurosas, Toulouse, France) and refractometer (LDC Analytical). Experiments were carried out using 20 × 20 cm silica gel 60 F_{254} HPTLC plates (Merck) (thickness 0.2 mm) on either 20 × 20 cm polyamide 11 F_{254} (Merck) (thickness 0.15 mm) or 20 × 20 cm alumina 150 F_{254} (Merck) (thickness 0.25 mm) sorbents. For the analytical separations, a standard mixture containing 47% of **1**, 21% of **2**, 16% of **3**, 7% of **4** and 9% of **5** was prepared in chloroform and 10-μl volumes of this mixture were injected. Prior to each separation, the plate was preconditioned with hexane at 1.5 ml/min for 15 min to eliminate air in the adsorbent layers. A flow-rate of 0.65 ml/min was used for all the analytical OPLC separations. The cushion pressure was kept at 16–18 bar during all separations. The mixture of **4** and **5** was separated by the systems illustrated in Fig. 2.

Phenol, methanol, chloroform and sodium hydroxide were obtained from Merck and were used as received. The solvents for HPLC and OPLC were

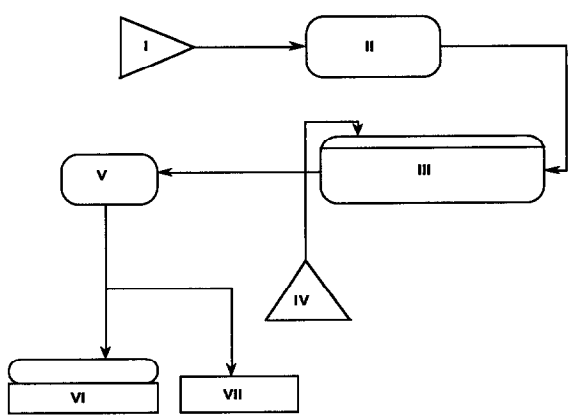

Fig. 2. Schematic diagram of analytical and preparative on-line OPLC system. I = Eluent micropump; II = automatic injector; III = Chrompres 25; IV = water micropump; V = refractometer; VI = fraction collector; VII = integrator.

of chromatographic grade (Merck). Water for HPLC was doubly distilled.

Synthesis

A 0.1-mol amount of phenol (9.41 g), 100 ml of chloroform, 25 ml of methanol and 20 ml of water were placed in a 250-ml flask fitted with a cooling system, thermometer and mechanical stirrer. The mixture was heated to 55–56°C and sodium hydroxide (1 mol; 40 g) was added in portions. The reaction was stopped 1 h after the final addition of sodium hydroxide. After acidification of the reaction mixture to pH 2–3, the reaction products were extracted by steam distillation and were obtained in analytical purity after separation by on-line OPLC. We only present here the spectral characteristics of the phenolic dialdehydes **4** and **5** as those of the monoaldehydes are known. The conversion of the starting phenol was 53%.

Physico-chemical characteristics of the phenolic dialdehydes

*2-Hydroxy-1,3-benzenedicarboxaldehyde (**4**).* Yield = 13%. M.p. = 119–120°C. IR: ν(OH) 3071 cm^{-1}, ν(C=O) 1680 cm^{-1}. ^1H NMR: δ (ppm), 11.9 (s, 1H, O*H*), 10.4 (s, 2H, C*H*O), 8.2 (d, 2H, J = 7 Hz, H^{-4}, H^{-6}) 7.3 (dd, 1H, J = 7 Hz, H^{-5}). Mass spectrum: *m/z* (%), 150 (M^+, 47), 149 (4.5), 122 (100), 121 (43), 93 (10.4). Analysis: calculated for $C_8H_6O_3$, C 64, H 4.03; found, C 64.04, H 4.06%.

*4-Hydroxy-1,3-benzenedicarboxaldehyde (**5**).* Yield = 17%. M.p. = 95–96°C. IR: ν(OH) 3080 cm^{-1}, ν(C = O) 1689, 1665 cm^{-1}. ^1H NMR: δ (ppm), 11.7 (s, 1H, O*H*), 10,3 (s, 1H, *p*-C*H*O), 10.1 (s, 1H, *o*-C*H*O), 8.5 (s, 1H, H^{-2}) 8.2 (d, 1H, J = *10 Hz, H^{-6}*), 7.3 (d, 1H, J = 10 Hz, H^{-5}). Mass spectrum: m/z (%), 150 (M^+, 98), 149 (100), 121 (16), 93 (24). Analysis: calculated for $C_8H_6O_3$, C 64, H 4.03; found, C 63.94, H 4.09%.

RESULTS AND DISCUSSION

Fig. 3 shows the OPLC of a standard mixture of the reaction medium of composition 47% phenol, 21% salicylaldehyde, 16% *p*-hydroxybenzaldehyde, 7% 2-hydroxy-1,3-benzenedicarboxaldehyde and 9% 4-hydroxy-1,3-benzenedicarboxaldehyde. The mixture was then separated in a two-stage process. First, compounds **1** and **2** were eliminated in a rotary evaporator. The dialdehydes **4** and **5** were recovered by steam distillation. Compound **3** remaining in the distillation flask was isolated by crystallization and recrystallization from toluene. Unsuccessful attempts were made to separate the dialdehydes by on-line OPLC on both polyamide or alumina sorbent layers. Better results were obtained with the silica gel HPTLC plates, which could be used three or four times before recycling. The composition of the eluent diethyl ether–hexane–chloroform (3:2:0.25) was optimized using the PRISMA model [5]. Sample and eluent injection and fraction recovery were automatic, and a refractometer was employed as a detector, placed between the Chrompres 25 and the fraction collector.

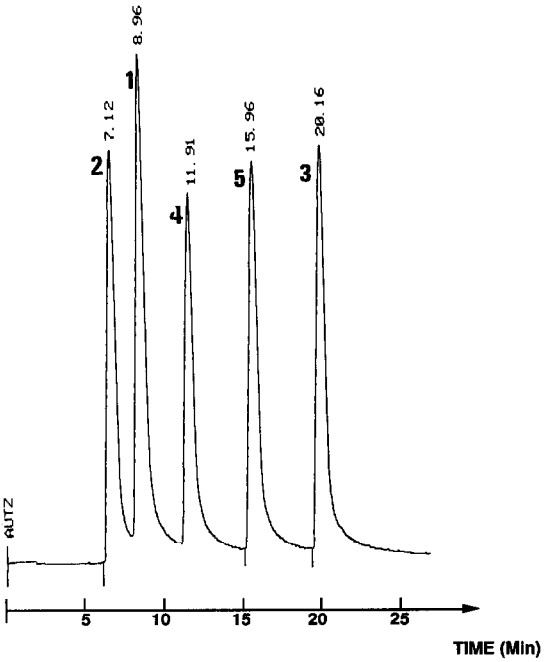

Fig. 3. Separation of a standard mixture on an HPTLC plate by on-line OPLC: 47% of **1**, 21% of **2**, 16% of **3**, 7% of **4** and 9% of **5**. Eluent flow-rate, 0.65 ml/min. for other conditions, see Experimental.

Given the migration time for each constituent of the mixture, the injection of the samples and the recovery of the dialdehydes could be readily programmed. For a load capacity of the HPTLC plates ranging from 20 to 30 mg, the phenolic dialdehydes **4** and **5** were isolated after 12 and 16 min, respectively (Fig. 4). It can be seen that on-line OPLC was

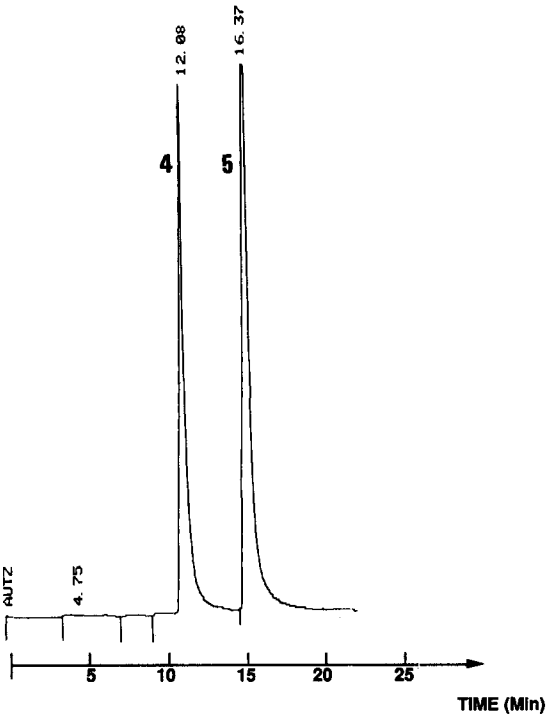

Fig. 4. Separation of dialdehydes **4** and **5** on an HPTLC plate by on-line OPLC. Eluent flow-rate, 0.65 ml/min. For other conditions, see Experimental.

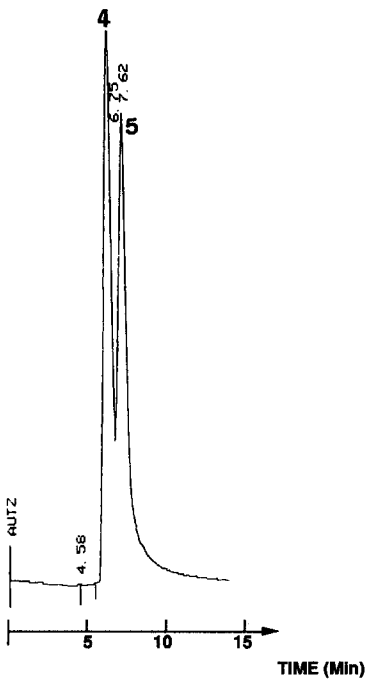

Fig. 5. Separation of dialdehydes **4** and **5** by HPLC. Eluent flow-rate, 0.8 ml/min. For other conditions, see Experimental.

a particularly efficient method for the separation and isolation of such a complex mixture, appearing much superior to HPLC (*cf.*, Fig. 5).

The physico-chemical characteristics of compounds **4** and **5** were determined by IR, ^{1}H NMR and mass spectrometry. pK_a values were determined by UV spectrophotometry. The two phenolic derivatives had similar pK_a values [6] (8.8 and 9, respectively), which accounts for the difficulty in separating them on an anion-exchange resin (Amberlite IRA 402) column.

Compounds **4** and **5** have been found to have marked antifungal activity toward *Candida albicans* and *Aspergillus* [7] and this activity is currently under investigation.

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