Short Communication

Iodination of Resorcinol, 5-Methoxyresorcinol, Phloroglucinol and Resorcyclic Acid

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In connection with other work we wished to prepare 2-iodo- and 4-iodo-resorcinol and monooiodophloroglucinol. We expected these compounds to have been described long ago in the literature. A search in the literature revealed that monooiodophloroglucinol had not been described earlier and the published procedures for the preparation of 2- and 4-iodoresorcinols were confusing. A recent paper describes the selective preparation of iodo(mono)hydroxy aromatics. It was therefore necessary to simplify and optimize the experimental conditions and to find selective routes to the compounds. The iodination of resorcyclic acid (2,4-dihydroxybenzoic acid), 5-methoxyresorcinol and catechol have also been investigated.

It was soon realized that the preparation of these simple compounds was not as straightforward as one might expect. Slight changes in the preparative conditions gave different results. A complex mixture of iodinated products was obtained from resorcinol when N-chlorosuccinimide, NCS, was substituted for N,N-dichloroarrea in Lichoscherstow’s iodination produce. It was confirmed that iodine chloride in pyridine gave 4-iodoresorcinol as the major product admixed with 2-iodoresorcinol and di- and tri-iodoresorcins but it was difficult to separate the mixture. An improved yield of 4-iodoresorcinol was obtained when the iodination was carried out in refluxing ether. Iodination of resorcinol with elementary iodine under slightly acidic conditions was very slow. An excess of iodine in aqueous solution gave, after 1–2 days, a mixture of 2- and 4-iodoresorcinol. However, addition of sodium hydrogen carbonate to an equimolar mixture of resorcinol and iodine in water caused a rapid disoloration and precipitation of 2,4,6-triiodoresorcinol. Work-up of the filtrate unexpectedly gave 2-iodoresorcinol (1a) in good yield, contaminated only with minute amounts of 2,4,6-triiodoresorcinol (1d), 2,4- and 4,6-diiodoresorcinol (1c) and 4-iodoresorcinol (1b). Pure 1a was obtained by recrystallization from water.

It had been noted earlier that phenolic iodo compounds were deiodinated by hot aqueous hydrochloric acid. We found that a slurry of 2-iodoresorcinol in 6 M hydrochloric acid rapidly rearranged predominantly to 4,6-diiodoresorcinol (1c), 4-iodoresorcinol (1b) and resorcinol. When the rearrangement was carried out in conc. hydrochloric acid: dioxane, 1:1, 1b was the main product and 1a, c, d were minor components in the reaction mixture; 1a:1b = 2:5. The reaction is explained as a reversible electrophilic iodination as formulated in eqn. (1). Sulfuric acid also catalyzed the rearrangement but less 4-iodoresorcinol 1b was formed. The formation of 1a in slightly basic solution is apparently kinetically controlled. In acid solution the more stable 1b was formed. We found that 1b could be selectively obtained in excellent yield by reacting resorcinol with iodine chloride in ether at 0°C.

Monooiodination of phloroglucinol has not been described previously. The only characterized derivative was triiodophloroglucinol. Previous procedures gave mixtures of starting material, mono-, di- and tri-iodophloroglucinol. A fair yield of monooiodophloroglucinol (2a) was obtained by use of a procedure similar to that described for 1a. With two moles of iodine diiodophloroglucinol (2b) was obtained as the principal product. Diodophloroglucinol disproportionate into triiodophloroglucinol and monooiodophloroglucinol when heated in refluxing acetonitrile for a few minutes.

Iodination of 2,4-dihydroxybenzoic acid (resorcyclic acid) at pH 9–10 gave 2,4-dihydroxy-3-iodobenzoic acid (3a). Thus, in slightly basic solution the iodination took place at the sterically more hindered position between the meta-hydroxy groups, which apparently has the highest electron density.

5-Methoxyresorcinol (4a) was prepared by methylation of phloroglucinol with dimethyl sulfate in acetone in a yield of ca. 30 %. A better yield, ca. 70 %, was obtained by methylation with methanol and dry hydrogen chloride in dioxane solution. When the previous iodination procedures were applied to 4a mixtures of 4a-e and probably also some 2,4,6-triido-5-methoxyresorcinol were obtained. It was eventually found that iodination of 4a with the bulkier triiodide, I₃⁻ at pH ca. 9 predominantly led to 4b together.

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with minute amounts of 4a, 4c and 4d. In acid solution 4c was obtained as the main product. Compound 4b underwent partial rearrangement in acid solution to 4c according to eqn. (1). It was not possible to separate 4b-4d by silica-gel chromatography. The iodides are not stable on that support.

Catechol gave intractable dark-coloured products with iodine in slightly basic water:dioxane solution. This reaction was not investigated further.

**Experimental**

2-Iodosorescinol (1a). Iodine (6.7 g) and sodium hydrogen carbonate (2.3 g) were added in one portion to resorcinol (2.75 g) dissolved in ice-water (20 ml) with stirring. Any precipitate was rinsed down from the glass walls with water. The solution was stirred at room temperature for a further 30 min. The precipitate was filtered off and the filtrate was extracted twice with diethyl ether. The combined organic phases were dried over MgSO₄ and evaporated in vacuo. The crude product, consisting predominantly of 1a, was triturated with chloroform (20 ml) at −10°C for a few hours and filtered to give practically pure 1a, 77%, 4.6 g, which could be recrystallized from water. M.p. 107-109°C (lit. 7 105-108°C). 1H NMR (CDCl₃ + CD₂OD): δ 6.53 (2 H, d, J 8.0 Hz), 7.09 (1 H, t, J 8.0 Hz).

4-Iodosorescinol (1b). To resorcinol (5.5 g) in dry diethyl ether (50 ml) was slowly added ICl (8.2 g) in diethyl ether (100 ml) over ca. 30 min at 0°C. After ca. 1 h at 25°C water (100 ml) and sodium sulfite (1.0 g) were added. The ether phase was separated and the water phase extracted once with ether. The combined ether phases were dried with MgSO₄. Silica gel (20 g, 70-230 mesh) was added and the mixture was evaporated in vacuo at 25°C. The product was chromatographed on silica (SiO₂, 150 g, CHCl₃:HOAc, 9:1) and the chromatogram was followed by analytical TLC. The first eluate contained some 1c and then followed a large middle fraction consisting of nearly pure 1b. The last fractions were contaminated with resorcinol. The solvent was removed by evaporation in vacuo. Small quantities of remaining acetic acid were removed by trituration with cold CHCl₃:CCl₄, 1:2 to give a white solid 1b, ca. 10 g, 85%, m.p. 67-70°C, lit. 7 63°C. 1H NMR (CDCl₃): 7.31 (1H, d, J 8 Hz), 6.42 (1 H, d, J 2.5 Hz) 6.12 (1 H, dd, J 8 and 2.5 Hz).

Acid-catalysed rearrangement of 1a into 1b, 1c and resorcinol. 2-Iodosorescinol 1a (0.23 g) in dioxane (3 ml) and conc. hydrochloric acid (1 ml) was heated to 60°C for 1 h. Ice and water were added and the mixture was extracted with ether which was separated, dried and evaporated in vacuo. The 1H NMR spectrum of the crude residue showed that the molecular ratio of 1b:1a:1c:resorcinol was 5:2:1:3.

Acid-catalysed rearrangement of 4b. A crude iodination product (50 mg) consisting of 4b:4c = 1:2.1 was treated with hydrochloric acid (1 ml, 4 M) at 25°C for 1.5 h. The reaction mixture was extracted with ether and the ether solution was dried with MgSO₄ and evaporated. The 1H NMR spectrum of the residue showed a molecular ratio 4b:4c = 1:1.2. 1H NMR (CDCl₃): 4e, δ 5.88 (1 H, d, J 2 Hz), 6.09 (1 H, d, J 2 Hz). Small amounts of 4a and 4d were also formed. 1H NMR (CDCl₃): 4d, δ 6.13 (1 H, s).

4,6-Diiodorescinol (1c). To resorcinol (2.75 g) in dry ether (25 ml) was slowly added ICl (8.2 g, ca. 20% excess) in dry ether (50 ml) at 0°C. After ca. 1 h at 25°C, water (50 ml) and sodium sulfite (1.5 g) were added whereupon a light yellow solution was obtained. The ether phase was separated, dried with MgSO₄ and evaporated in vacuo. The crystalline residue was triturated with water (50 ml) for 30 min, filtered, washed once with water and dried in a desiccator. The yield of 1c was 8.1 g, 90%, m.p. 156-160°C, (decomp.) lit. 7 145°C, 145-158°C. 1H NMR (CDCl₃): 7.63 (s), 6.46 (s).
2,4,6-Triiodoresorcinol (1d). To resorcinol (0.55 g) and iodine (3.8 g) suspended in water (20 ml) was added sodium hydrogen carbonate (1.3 g) in portions at 25 °C with stirring. After 20 h the precipitate was filtered and dried. The product was extracted with hot chloroform (6 ml), filtered and the filtrate evaporated in vacuo to give practically pure triiodoresorcinol, 1.4 g, 57 %, m.p. 156–159 °C, lit.1 154 °C.

Iodophloroglucinol (2a). To phloroglucinol· 2H₂O (4.86 g) in tetrahydrofuran (30 ml) and water (30 ml) was added a mixture of iodine (7.7 g) and sodium hydrogen carbonate (2.7 g) with stirring in one portion. The iodination proceeded with strong evolution of carbon dioxide. Solids on the glass wall were rinsed down with water. The iodination was complete within ca. 15 min. The solution was diluted with water and extracted twice with ether. The combined ether phases were dried over MgSO₄ and evaporated to dryness. The residue was dissolved in acetone (5 ml) and chloroform (40 ml) was added. Phloroglucinol precipitated when the solution was cooled in the freezer at −10 °C for 3 h. It was filtered off and the filtrate was evaporated in vacuo to give a yellow solid, 6.6 g, ca. 87 %. According to the 1H NMR spectrum it contained minor amounts of 2b, δ 6.09 (s) and phloroglucinol, δ 5.73 (s). 2a crystallized from nitromethane (moderate heating) as light yellow crystals, m.p. 162–164 °C (decomp.) 1H NMR (CDCl₃, CD₃OD): δ 5.90 (s). The crude product was used in subsequent reactions.

Diiodophloroglucinol (2b). To phloroglucinol· 2H₂O (1.62 g) in THF (10 ml) and water (10 ml) was added a mixture of iodine (5.08 g) and sodium hydrogen carbonate (1.73 g) in one portion with stirring. A few drops of ether reduced the foaming. The iodination was complete within ca. 15 min. The solution was diluted with water (50 ml) and extracted twice with ether. The combined ether phases were dried over MgSO₄ and evaporated in vacuo. Acetone (1.5 ml) and chloroform (15 ml) were added and the mixture was stirred for 15 min, filtered and evaporated in vacuo to give crude 2b, 2.3 g, ca. 56 %. It contained traces of 2c and ca. 7 % of 2a. A small amount was recrystallized from nitromethane, m.p. 150–155 °C. 1H NMR (CDCl₃, DMSO-d₆) δ 6.23 (s).

Triiodophloroglucinol (2c). To phloroglucinol· 2H₂O (0.81 g) and iodine (3.8 g) in water (20 ml) was added sodium hydrogen carbonate (1.3 g) in portions with stirring. After 30 min the triiodide was filtered off and recrystallized from acetonitrile, 2.0 g, 80 %, m.p. 173–174 °C, lit.5 171–172 °C.

2,4-Dihydroxy-3-idothenzoic acid (3a) and 2,4-Dihydroxy-3,5-idothenzoic acid (3b). To 2,4-Dihydroxybenzoic acid (1.54 g) and iodine (2.5 g) in tetrahydrofuran:water (10 ml, 1:1) was added sodium hydrogencarbonate (1.8 g) in portions. After ca. 2 h, the solution was acidified with conc. hydrochloric acid (1 ml) and extracted twice with ether. Evaporation of the solvent gave a crude product (3.0 g), which was dissolved in methanol (6 ml). Addition of water (7 ml) at 25 °C gave a precipitate consisting of 2,4-dihydroxy-3,5-diidothenzoic acid, 3b (0.93 g), admixed with minor amounts of 3a. This fraction was recrystallized from acetonitrile to give 3b, 23 %, m.p. 236–238 °C, lit.2 193–196 °C. 1H NMR (CDCl₃, CD₃OD): δ 8.18 (C₆H, s). The aqueous methanol filtrate was evaporated in vacuo to ca. 5–6 ml, water (12 ml) was added and the solution was kept in the refrigerator for 24 h. The precipitate was filtered and recrystallized from a small amount of water. The yield of 2,4-dihydroxy-3-idothenzoic acid (3a) was 0.7 g, 30 %, m.p. 197–200 °C. 1H NMR (CDCl₃, CD₃OD): δ 6.32 (1 H, d, J 9 Hz), 7.58 (1 H, d, J 9 Hz). In the NMR spectra of the crude fractions there was observed singlets at δ 6.4 and 8.0, which could originate from minute amounts of 2,4-dihydroxy-5-idothenzoic acid formed in competition with the 3-ido derivative.

5-Methoxyresorcinol (4a): method (a). 4a was prepared by methylation of phloroglucinol with dimethyl sulphate in acetone. The crude product was purified by column chromatography (SiO₂, CH₂Cl₂:CH₃CO₂H: 4:1) to give 4a in a yield of ca. 30 %, m.p. 77–78 °C. 1H NMR (CDCl₃): δ 3.47 (3 H, s), 5.80 (2 H, d, J 2 Hz), 5.88 (1 H, t, J 2 Hz). The chromatography was followed by TLC. The first fraction consisted of 3,5-dimethoxyphenol, ca. 9 %. 1H NMR (CDCl₃): δ 3.70 (6 H, s), 6.01 (3 H, br s).

Method (b). Phloroglucinol· 2H₂O (0.40 g) in dioxane (1 ml) and methanol (4 ml, saturated with dry HCl at 0 °C) was kept at 70 °C for 3 h in a sealed-pressure glass bottle. Evaporation of the solvent and separation of the residue on a preparative TLC plate (SiO₂, CCl₄: CH₃CO₂C₂H₅: 7:3) gave 4a, (0.24 g, 71 %) and 3,5-dimethoxyphenol (0.06 g, 15 %).

2-Iodo-5-methoxyresorcinol (4b). Solid 4a (0.28 g) and sodium hydrogencarbonate (0.25 g) were added in one portion to a solution of iodine (0.58 g) and potassium iodide (1.2 g) in water (3 ml) and ice (3 g) with stirring. The iodination was complete in ca. 5 min at 0 °C. The colour changed from dark brown to yellow and a precipitate was formed. The reaction mixture was extracted with ether (2×10 ml). Drying of the solution with MgSO₄ and evaporation gave a crude, solid product (0.55 g), which was triturated with chloroform (5 ml) to dissolve small amounts of 4d and left in the freezer at −10 °C for 20 h. Filtration gave pure 4b, 0.40 g, 75 %, m.p. 119–123 °C. A sample was recrystallized from chloroform, m.p. 122–124 °C. 1H NMR (CDCl₃): δ 5.98 (2 H, s), 3.48 (3 H, s).

2,4-Diido-5-methoxyresorcinol (4d). Iodine (1.02 g) and sodium hydrogencarbonate (0.40 g) were added in one portion to 4a (0.28 g) in ice–water (6 ml). The mixture was stirred at 0 °C for 2 h and filtered and the precipitate was washed with water and dried to give pure 4d (0.69 g, 88 %) m.p. 126–128 °C. A sample was recrystallized from carbon.
tetracloride, m.p. 128–129°C. $^1$H NMR (CDCl$_3$): $\delta$ 3.81 (3 H, s) 6.22 (1 H, s).

References


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