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 monoiodophloroglucinol. We expected these compounds to have been described long ago in the literature. A search in the literature revealed that monoiodophloroglucinol had not been described earlier and the published procedures for the preparation of 2- and 4-iodoresorcinols were confusing.[1-7] A recent paper describes the selective preparation of iodo(monohydroxy) aromatics.[8] It was therefore necessary to simplify and optimize the experimental conditions and to find selective routes to the compounds. The iodination of resorcylic 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*-dichlorourea in Lichoscherstow's iodination produce.[3] It was confirmed that iodine chloride in pyridine[6] gave 4-iodoresorcinol as the major product admixed with 2-iodoresorcinol and di- and tri-iodoresorcinols 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.[6] 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 hydrogencarbonate to an equimolar mixture of resorcinol and iodine in water caused a rapid discoloration 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.[2] 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.

Monoiodination 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 monoiodophloroglucinol (**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. Diiodophloroglucinol disproportionated into triiodophloroglucinol and monoiodophloroglucinol when heated in refluxing acetonitrile for a few minutes.

Iodination of 2,4-dihydroxybenzoic acid (resorcylic 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[9] in a yield of ca. 30 %. A better yield, ca. 70 %, was obtained by methylation with methanol and dry hydrogen chloride[10] in dioxane solution. When the previous iodination procedures were applied to **4a** mixtures of **4a–e** and probably also some 2,4,6-triiodo-5-methoxyresorcinol were obtained. It was eventually found that iodination of **4a** with the bulkier triiodide, I_3^- at pH ca. 9 predominantly led to **4b** together

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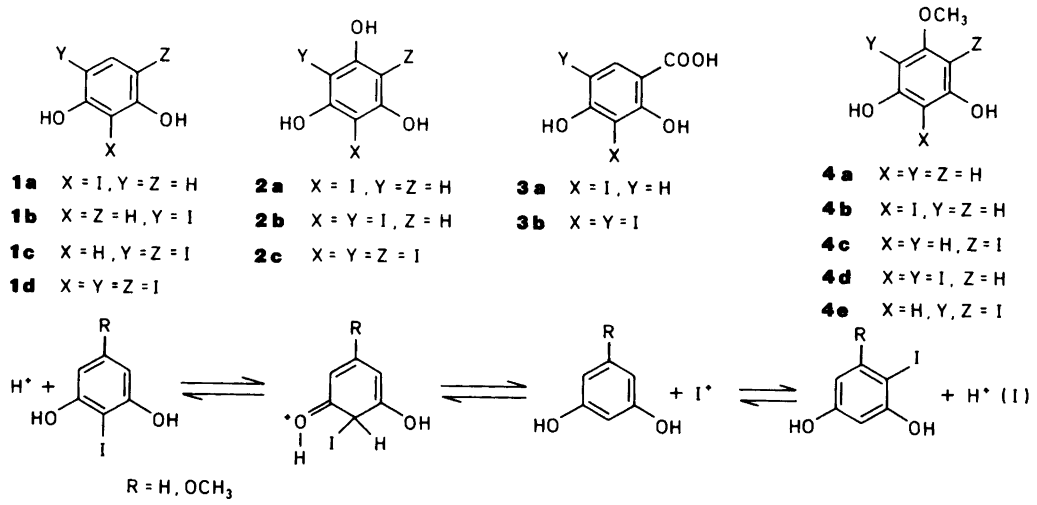

with minute amounts of **4a**, **4c** and **4d**. In acid solution **4c** was obtained as the main product. Compound **4b** underwent partial rearrangement in acid solution to **4c** according to eqn. (1). It was not possible to separate **4b–4d** by silica-gel chromatography. The iodides are not stable 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-Iodoresorcinol (**1a**). Iodine (6.7 g) and sodium hydrogencarbonate (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 $MgSO_4$ 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.[5] 105–108 °C). ^{1}H NMR ($CDCl_3$ + CD_3OD): δ 6.53 (2 H, d, *J* 8.0 Hz), 7.09 (1 H, t, *J* 8.0 Hz).

4-Iodoresorcinol (**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 $MgSO_4$. 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 (SiO_2, 150 g, $CHCl_3$: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 $CHCl_3$:CCl_4, 1:2 to give a white solid **1b**, ca. 10 g, 85 %, m.p. 67–70 °C, lit.[3] 63 °C. ^{1}H NMR ($CDCl_3$): 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-Iodoresorcinol **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 ^{1}H 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 $MgSO_4$ and evaporated. The ^{1}H NMR spectrum of the residue showed a molecular ratio **4b**:**4c** = 1:1.2. ^{1}H NMR ($CDCl_3$): **4c**, 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. ^{1}H NMR ($CDCl_3$): **4d**, δ 6.13 (1 H, s).

4,6-Diiodoresorcinol (**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 $MgSO_4$ 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.[2,5] 145 °C, 145–158 °C. ^{1}H NMR ($CDCl_3$): 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 hydrogencarbonate (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.[3] 154 °C.

Iodophloroglucinol (**2a**). To phloroglucinol · $2H_2O$ (4.86 g) in tetrahydrofuran (30 ml) and water (30 ml) was added a mixture of iodine (7.7 g) and sodium hydrogencarbonate (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 $MgSO_4$ 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 ^{1}H 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.) ^{1}H NMR ($CDCl_3$, CD_3OD): δ 5.90 (s). The crude product was used in subsequent reactions.

Diiodophloroglucinol (**2b**). To phloroglucinol · $2H_2O$ (1.62 g) in THF (10 ml) and water (10 ml) was added a mixture of iodine (5.08 g) and sodium hydrogencarbonate (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 $MgSO_4$ 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. ^{1}H NMR ($CDCl_3$, DMSO-d_6) δ 6.23 (s).

Triiodophloroglucinol (**2c**). To phloroglucinol · $2H_2O$ (0.81 g) and iodine (3.8 g) in water (20 ml) was added sodium hydrogencarbonate (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-iodobenzoic acid (**3a**) *and 2,4-Dihydroxy-3,5-diiodobenzoic acid* (**3b**). To 2,4-Dihydroxybenzoic acid (resorcylic 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-diiodobenzoic 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. ^{1}H NMR ($CDCl_3$, CD_3OD): δ 8.18 (C_6-H, 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-iodobenzoic acid (**3a**) was 0.7 g, 30 %, m.p. 197–200 °C. ^{1}H NMR ($CDCl_3$, CD_3OD): 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-iodobenzoic acid formed in competition with the 3-iodo derivative.

5-Methoxyresorcinol (**4a**): *method (a)*. **4a** was prepared by methylation of phloroglucinol with dimethyl sulphate in acetone.[9] The crude product was purified by column chromatography (SiO_2, CH_2Cl_2:$CH_3CO_2H_5$, 4:1) to give **4a** in a yield of ca. 30 %, m.p. 77–78 °C. ^{1}H NMR ($CDCl_3$): 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 %. ^{1}H NMR ($CDCl_3$): δ 3.70 (6 H, s), 6.01 (3 H, br s.).

Method (b).[10] Phloroglucinol · $2H_2O$ (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 (SiO_2, CCl_4: $CH_3CO_2C_2H_5$, 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 $MgSO_4$ 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. ^{1}H NMR ($CDCl_3$): δ 5.98 (2 H, s), 3.48 (3 H, s).

2,4-Diiodo-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

tetrachloride, m.p. 128–129 °C. ^{1}H NMR ($CDCl_3$): δ 3.81 (3 H, s) 6.22 (1 H, s).

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