Regiospecific 2,4-Diiodination of Resorcinol with Nascent Iodine

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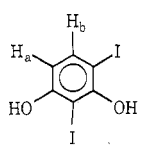
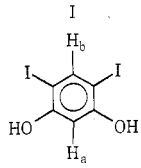
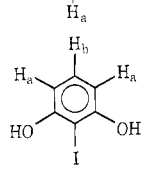
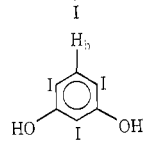
As part of a continuing effort to synthesize new x-ray contrast media, the iodination of hydroxyaryl precursors has achieved our attention. This note describes a new application of the $KIO_3/KI/HCl$ iodometric system[1] for iodination of the *m*-hydroxybenzenes, resorcinol and phloroglucinol.

A review of the literature dealing with the synthesis of mono-, di-, and trihalogenated resorcinols reveals the conspicuous absence of 2,4-diiodoresorcinol.[2,3] For example, diiodination of resorcinol with the interhalogen ICl (2 mol) in 20% aqueous HCl reportedly[4] provided the corresponding 4,6-diiodoresorcinol in 80% isolated yield. This experiment, repeated in our laboratory, gave crude 4,6-diiodoresorcinol which was isomerically pure as determined by NMR (Table I).

Table I. NMR Data (δ) for Iodinated Resorcinols

Compd	Structure	H_a	H_b
1		6.91,[a,b] d	7.63, d, J = 9 Hz, AB quartet
5		6.73, s	7.93, s
2		6.42,[b] d (unsym), 2 H J = 8 Hz	7.05, t (unsym), 1 H, J = 8 Hz
4		—	8.12, s

[a] NMR spectra (Me_2SO-d_6, D_2O, Me_4Si) were recorded on a Varian EM-360 spectrometer. D_2O was used to simplify the spectra by exchanging off the phenolic protons. [b] NMR data for these compounds also reported in ref 3.

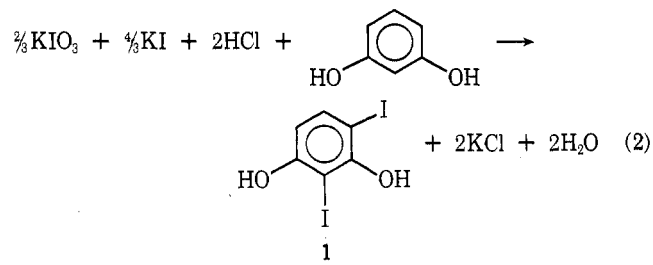
Moody and Thomas[5] detected the two-stage oxidation of iodide (eq 1) in aqueous HCl in the presence of iodate and

$$I^- \xrightarrow[HCl]{IO_3^-} \tfrac{1}{2}I_2 + e \xrightarrow[HCl]{IO_3^-} I^+ + e \qquad (1)$$

noted the "strong brown coloration" of the intermediate oxidation state, $\frac{1}{2}I_2$, i.e., nascent iodine. This work takes advantage of nascent iodine generated in situ as an iodinating species, (a) by using only stoichiometric amounts of all reagents, (b) by using reactive *m*-hydroxyaryls to rapidly react with the nascent iodine, and (c) by choosing the correct order of combination of reagents with substrate to preclude unwanted oxidations of both substrate and reagent.

Results and Discussion

Use of nascent iodine has resulted in the regiospecific 2,4-diiodination of resorcinol. In these experiments, stoichiometric amounts (eq 2) of aqueous KIO_3/KI were added



(2)

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dropwise to aqueous resorcinol/HCl vigorously stirred at room temperature. Alternatively, aqueous KIO_3/HCl can be added dropwise to resorcinol/KI. With each drop of reagent a brown color developed immediately but dissipated in approximately 1 s, thereby iodinating resorcinol in a rapid reaction. NMR spectra taken on crude diiodination mixtures revealed only two products, 2,4-diiodoresorcinol (56%, isolated) and 2,4,6-triiodoresorcinol (Table II).

Table II. Iodination of Resorcinol with $KIO_3/KI/HCl$

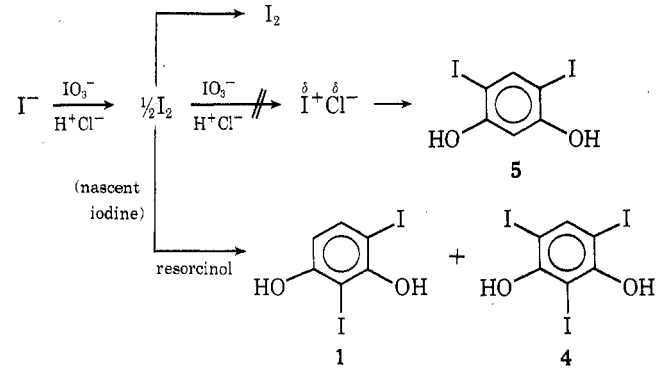
Stoichiometry[a] $KIO_3/KI/HCl$, mol	Product ratio[b,c] (1/4)	Yield, % (compd)
1/2/3	57/43	
$^2/_3/^4/_3/2$	89/11	56 (1)
$^1/_3/^2/_3/1$	*d*/0	32 (2)

[a] $IO_3^- + 5I^- + 6H^+ \rightarrow 3I_2 + 3H_2O$, see ref 1. The overall reaction stoichiometry is calculated for resorcinol iodination by I_2 and assuming HI as a product. [b] Crude product (EtOAc extracted) ratios determined by NMR integration of aromatic protons. [c] No evidence for 4,6-diiodoresorcinol observed in any crude products. [d] NMR of crude product mixture too complex to measure ratios and probably containing 4-iodo- and 2,4-diiodo- as well as 2-iodoresorcinol.

Monoiodination of resorcinol resulted in 2-iodoresorcinol (32%, isolated) but the crude mixture was too complex to determine products and ratios by NMR (Table II).

Triiodination of resorcinol gave primarily 2,4-diiodoresorcinol, the remainder being 2,4,6-triiodoresorcinol (Table II). This result suggests that for less reactive substrates such as diiodoresorcinol, dimerization (or deactivation) of nascent iodine to give molecular (or unreactive) iodine is a process in competition with iodination of the *m*-hydroxybenzene (Scheme I). However, the more reactive substrate phloroglucinol is triiodinated to 2,4,6-triiodophloroglucinol[6] (89%, isolated) in good yield.

Scheme I



By analogy to the action of ICl,[4] a source of "relatively positive" iodine, any I^+ (i.e., $I^{\delta+}Cl^{\delta-}$) formed in the redox reaction (eq 1, Scheme I) should have resulted in 4,6-diiodoresorcinol, but none was observed. Loss of nascent iodine to

give unreactive iodine results in decreased yields of iodination. It is anticipated that the KIO_3/KI/HCl system will complement the already used iodination methods opening the way to the synthesis of new iodoaryls.[7]

Experimental Section

General. Elemental analyses were performed by Chemalytics, Inc., Tempe, Ariz. Melting points are uncorrected and taken on a Thomas-Hoover apparatus. NMR spectra (Me_2SO-d_6, D_2O, Me_4Si) were recorded on a Varian EM 360. All evaporations were accomplished on a Buchi Rotovapor-RE at ≤45 °C. Resorcinol and phloroglucinol·$2H_2O$ were obtained from Aldrich Chemical Co., Milwaukee, Wis. ICl was obtained from Matheson Coleman and Bell.

2,4-Diiodoresorcinol (1). To 11.0 g (0.10 mol) of resorcinol in 250 ml of H_2O was added 16.7 ml (0.20 mol) of concentrated HCl. To this stirred solution was added at a drop rate over a 1-h period a second solution prepared from 14.3 g (0.067 mol) of KIO_3, 22.1 g (0.13 mol) of KI, and 500 ml of H_2O. (Note that nascent iodine color formed in situ after each drop dissipates in about 1 s.) Stirring was continued an additional 1.5 h before extracting the (essentially iodine free) reaction mixture with EtOAc (4 × 100 ml). Evaporation of the EtOAc layer gave an oil which was dissolved in boiling CCl_4, filtered while hot to clarify, then cooled to obtain 20.3 g (56%) of white solid title compound, mp 87–89 °C.[3]

Anal. Calcd for $C_6H_4I_2O_2$: C, 19.91; H, 1.11; I, 69.99. Found: C, 19.63; H, 1.02; I, 70.13.

2-Iodoresorcinol (2). Using the same procedure as for **1**, 11.0 g (0.10 mol) of resorcinol and 8.3 ml (0.10 mol) of concentrated HCl in 250 ml of H_2O was combined with 7.1 g (0.033 mol) of KIO_3 and 11.1 g (0.067 mol) of KI in 250 ml of H_2O. Thus was obtained an oil which was dissolved in $CHCl_3$ adjusted to turbidity with petroleum ether and placed in the freezer for several days to obtain tan solid. Twice recrystallized from benzene this material gave 7.6 g (32%) of white, crystalline **2**, mp 105–108 °C (lit.[2,3] 100 °C).

2,4,6-Triiodophloroglucinol (3).[6] To 10.0 g of phloroglucinol·$2H_2O$ (0.062 mol) slurried in 250 ml of H_2O with 15.1 ml (0.18 mol) of concentrated HCl was added at a drop rate, in 2 h, a solution of 13.2 g (0.062 mol) of KIO_3 and 20.5 g (0.12 mol) of KI in 400 ml of H_2O. The reaction slurry was stirred overnight and then the crude product collected by filtration, washed with H_2O, and dried in vacuo to obtain a pink powder, mp 160 °C dec. Recrystallization from boiling $CHCl_3$ gave 27.8 g (89%) of white, crystalline **3**, mp 171–172 °C dec. Anal. Calcd for $C_6H_3I_3O_3$: C, 14,30; H, 0.60; I, 75.57. Found: C, 14.56; H, 0.81; I, 75.51.

2,4,6-Triiodoresorcinol (4). A. Using the same procedure as for **1**, 5.5 g (0.050 mol) of resorcinol and 12.5 ml (0.15 mol) of concentrated HCl in 100 ml of H_2O was combined with 10.7 g (0.050 mol) of KIO_3 and 16.6 g (0.10 mol) of KI in 350 ml of H_2O. After stirring for an additional 2 h, Na_2SO_3 was added to decolorize (I_2) the reaction mixture, then EtOAc (4 × 100 ml) was used to extract all products. Evaporation of the organic layer gave tan solid dried in vacuo over P_2O_5 to give 19.3 g (79% of expected weight) of tan solid. NMR showed this material to consist of a 43/57 mixture of 2,4,6-triiodo- and 2,4-diiodorescorcinol, respectively.

B. Solid resorcinol (22.0 g, 0.20 mol) was added at once to a stirred solution of 875 ml of 0.8 N ICl in 1.6 N HCl and held at 50 °C for 1 h. Next Na_2SO_3 was added to decolorize (I_2) the mixture, and product was collected by filtration and recrystallized from boiling $CHCl_3$ to obtain 49.5 g (51%) of tan, crystalline **4**, mp 154–157 °C (lit.[2] 154 °C).

4,6-Diiodoresorcinol (5). Using the exact procedure of Nicolet and Sampey,[4] 5.0 g (30%) of crude white solid **5** was obtained, mp 145–158 °C (lit. 145 °C). NMR showed this compound to be isomerically pure (Table I).

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Registry No.—**1**, 41046-69-9; **2**, 41046-67-7; **3**, 57730-42-4; **4**, 19403-92-0; **5**, 19514-91-1; KIO_3, 7758-05-6; KI, 7681-11-0; resorcinol, 108-46-3; phloroglucinol, 108-73-6.

References and Notes

(1) I. M. Kolthoff and E. B. Sandell, "Textbook of Quantitative Inorganic Analysis", 3d ed, Macmillan, New York, N.Y., 1952, p 594.
(2) S. Coffee, Ed., "Chemistry of Carbon Compounds", Vol. 34, American Elsevier, New York, N.Y., 1971, p 398.
(3) Compound **1** was claimed, but no melting point or analysis given: V. Machacek, V. Sterba, and K. Valter, *Collect. Czech. Chem. Commun.*, **37**, 3073–3080 (1972).
(4) B. H. Nicolet and J. R. Sampey, *J. Am. Chem. Soc.*, **49**, 1796–1801 (1927).
(5) G. J. Moody and J. D. R. Thomas, *J. Inorg. Nucl. Chem.*, **25**, 221–226 (1963).
(6) First prepared in our laboratory, using this method, J. Lang and B. Nahlovsky, 1973, unpublished; for analogous synthesis of tribromophloroglucinol, see A. W. Francis and A. J. Hill, *J. Am. Chem. Soc.*, **96**, 2503 (1924).
(7) Attempted iodinations of catechol and hydroquinone using the same procedure as for resorcinol resulted in copious quantities of finely divided I_2. It was noted that the brown color of nascent iodine was not dissipated even after the first several drops; rather the reaction mixture became progressively darker and I_2 vapors progressively more apparent.

Stereochemistry and Conformation of Biogenetic Precursors of Indole Alkaloids[1]

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The biosynthetic pathway of indole alkaloids found in several plant genera, notably in the Apocynaceae family, commences with tryptophan and mevalonic acid.[3] Upon transformation of the latter into loganin (**1a**) and secologanin (**2a**) the metabolic substances meet in the form of vincoside (**3a**). It appears currently that **3a** or, in at least one instance, isovincoside (**3b**)[4] is a biogenetic precursor of many, structurally diverse indole alkaloids.[3,5] In order to facilitate investigations of the chemistry and metabolism of loganin (**1a**), secologanin (**2a**), the vincosides (**3a** and **3b**), and their lactams (**4a** and **4b**), provide NMR spectral parameters for the vincosides and the lactams, and reinforce and extend the ORD-based determination of the C(3) configuration of these substances,[6] a ^{13}C NMR analysis of **1a** and derivatives **1b**, **2b**, **3c–e**, and **4c,d** was undertaken.

The ^{13}C NMR analysis was initiated on the natural glucoside loganin (**1a**). The carbon shifts of the β-glucosyl unit were assigned on the basis of known literature values,[7] while all but the methine shifts were recognized by the characteristic field position and/or multiplicity of the signals of the unique aglycone carbon centers.[8] Carbon 19 was distinguished from the two other methines by its shift perturbation on acetylation of the neighboring 3-hydroxy group (vide infra). The differentiation of the remaining methines, C(15) and C(20), was founded on the shift difference of related carbons in dihydropyran and the expected strong deshielding of the homoallylic vs. allylic carbon by the neighboring methyl and glucosyloxy groups.

The ^{13}C NMR spectra of loganin pentaacetate (**1b**) revealed expected deshielding of C(3) and shielding of C(14) and C(19) as well as a shift pattern for the sugar moiety reminiscent of methyl tetraacetyl-β-D-glucopyranoside.[9] Rupturing the five-membered ring, i.e., loganin pentaacetate (**1b**) → secologanin tetraacetate (**2b**), caused no shift changes in the glucose unit, but induced ca. 2–5 ppm shift alterations for the characteristic dihydropyran ring carbons. The shift assignment for C(15) and C(20) of the secologanin derivative **2b** was confirmed by a correlation of the H(15) and H(20) shifts with the carbon resonances.[10,11] All δ values of compounds **1a**, **1b**, and **2b** are listed in Table I.