refluxed for 4 h and then washed with water and evaporated; **8d** was obtained in practically quantitative yield. ^{1}H NMR ($CDCl_3$): δ 9.58 (s, 2 H, H10, H20), 8.43 (dd, 2 H, H6), 8.00 (m, 4 H, H3, H4), 7.89 (ddd, 2 H, H5), 3.57 (m, CH_2), 2.39 (s, 12 H, CH_3), 1.67 (t, 12 H, ethyl CH_3); anthraquinone, see Table II.

5,15-Bis[2-[[[4-(dimethylamino)phenyl]sulfonyl]oxy]-phenyl]-2,8,12,18-tetraethyl-3,7,13,17-tetramethylporphyrin (8e). The porphyrin **8e** was prepared in the same way as **8c** from 1.22 g (4 mmol) of 2-[[[4-(dimethylamino)phenyl]sulfonyl]oxy]-benzaldehyde (dissolved in 25 mL of CH_2Cl_2 and 75 mL of CH_3OH) and 0.92 g of the dipyrrolylmethane (4 mmol). Yield: 49%. ^{1}H NMR ($CDCl_3$): δ 10.11 (s, 2 H, H10, H20), 8.01 (dd, 2 H, H6), 7.94 (dd, 2 H, H3), 7.87 (ddd, 2 H, H4), 7.68 (ddd, 2 H, H5), 3.98 (m, 8 H, CH_2), 2.52 (s, 12 H, CH_3), 1.81 (t, 12 H, ethyl CH_3), −2.93 (s, 2 H, NH); (dimethylamino)phenyl, see Table II.

Zinc Derivative 8f. The zinc derivative **8f** was obtained from **8e** in the way described above for **8d**. ^{1}H NMR ($CDCl_3$): δ 10.09 (s, 2 H, H10, H20), 8.11 (dd, 2 H, H6), 7.88 (m, 4 H, H3, H4), 7.72 (ddd, 2 H, H5), 4.01 (q, 8 H, CH_2), 2.54 (s, 12 H, CH_3), 1.81 (t, 12 H, ethyl CH_3); (dimethylamino)phenyl, see Table II.

5-[2-[(Anthraquinone-2-sulfonyl)oxy]phenyl]-15-[2-[[[4-(dimethylamino)phenyl]sulfonyl]oxy]phenyl]-2,8,12,18-tetraethyl-3,7,13,17-tetramethylporphyrin (8a). The porphyrin **8a** was prepared in the same way as described for **8c**, from 1.57 g (4 mmol) of 2-[(anthraquinone-2-sulfonyl)oxy]benzaldehyde and 1.22 g (4 mmol) of 2-[[[4-(dimethylamino)-phenyl]sulfonyl]oxy]benzaldehyde in 100 mL of CH_2Cl_2/CH_3OH, 3:2, with 1.84 g (8 mmol) (3,3′-diethyl-4,4′-dimethyl-2,2′-dipyrrolyl)methane under the catalytic influence of 0.4 g of *p*-toluenesulfonic acid. After the reaction, 1.3 g of a mixture of hexahydroporphyrins precipitated, consisting mainly of the dianthraquinone compound; by concentration of the mother liquor and subsequent addition of CH_3OH, another 2.05 g was obtained. After oxidation of this latter portion with DDQ, no precipitate was obtained. After evaporation of the solvent, the residue was dissolved in CH_2Cl_2; filtration of the solution and addition of $CH_3OH/N(C_2H_5)_3$, 3:1, gave a precipitate of a mixture of porphyrins. Repeated chromatography over silica gel (eluens CH_2Cl_2/diethyl ether, 98:2) gave pure **8a** in low yield (5–10%). ^{1}H NMR ($CDCl_3$): δ 9.92 (s, 2 H, H10, H20), 8.41 and 8.08 (dd, 2 H, H6), 7.89 (m, 6 H, H3, H4, H5), 4.00 (m, 4 H, CH_2), 3.78 and 3.68 (m, 4 H, CH_2), 2.59 and 2.44 (s, 12 H, CH_3), 1.88 and 1.77 (t, 12 H, ethyl CH_3), −3.41 and −3.64 (s, 2 H, NH); anthraquinone and (dimethylamino)phenyl, see Table II.

Zinc Derivative 8b. The zinc derivative was prepared in the same way as described for **8d**. ^{1}H NMR ($CDCl_3$): δ 9.82 (s, 2 H, H10, H20), 8.42 and 8.02 (dd, 2 H, H6), 7.98 (m, 6 H, H3, H4, H5), 3.92 and 3.63 (m, 4 H, CH_2), 3.78 (m, 4 H, CH_2), 2.46 and 2.43 (s, 12 H, methyl), 1.78 and 1.71 (t, 12 H, ethyl CH_3); anthraquinone and (dimethylamino)phenyl, see Table II.

(3,3′-Di-*n*-butyl-4,4′-dimethyl-2,2′-dipyrrolyl)methane. This compound was prepared in the same way as described for (3,3′-diethyl-4,4′-dimethyl-2,2′-dipyrrolyl)methane, with 3-*n*-butyl-2,4-pentanedione and diethylmalonate. Overall yield for five steps: 37%.

5-[2-[(Anthraquinone-2-sulfonyl)oxy]phenyl]-15-[2-[[[4-(dimethylamino)phenyl]sulfonyl]oxy]phenyl]-2,8,12,18-tetra-*n*-butyl-3,7,13,17-tetramethylporphyrin (8g). The porphyrin **8g** was prepared in the same way as described for **8c** from 0.98 g (2.5 mmol) of 2-[(anthraquinone-2-sulfonyl)-oxy]benzaldehyde and 1.22 g (2.5 mmol) 2-[[[4-(dimethyl-amino)phenyl]sulfonyl]oxy]benzaldehyde in 90 mL of CH_2Cl_2/CH_3OH, 4:5, with 1.43 g (5 mmol) of (3,3′-di-*n*-butyl-4,4′-dimethyl-2,2′-dipyrrolyl)methane and 0.25 g of *p*-toluenesulfonic acid. As the hexahydroporphyrins did not precipitate, the solvent was evaporated, the residue was oxidized with DDQ in THF, and the solvent was again evaporated. The residue was purified by repeated chromatography over silica gel (eluens $CHCl_3$); pure **8g** was obtained in low yield (5–10%). ^{1}H NMR ($CDCl_3$): δ 9.92 (s, 2 H, H10, H20), 8.41 and 8.08 (d, 2 H, H6), 7.90 (m, 6 H, H3, H4, H5), 3.95 (m, 4 H, CH_2), 3.73 and 3.63 (m, 4 H, CH_2), 2.27 and 2.14 (m, 8 H, CH_2), 1.83 (m, 8 H, CH_2), 1.21 and 1.16 (t, 12 H, butyl CH_3), 2.58 and 2.44 (s, 12 H, CH_3); anthraquinone and (dimethylamino)phenyl, see Table II.

Preparation of Other Compounds. The following compounds were prepared according to directions given in the literature: 4-fluorobenzenesulfonyl chloride,[35] 4-*tert*-butylbenzenesulfonyl chloride,[36] 4-cyclohexylbenzenesulfonyl chloride,[36] 4-methoxybenzenesulfonyl chloride,[37] 4-(dimethylamino)-benzenesulfonyl chloride,[38] 2,4,6-trimethylbenzenesulfonyl chloride,[36] 2,4,6-triisopropylbenzenesulfonyl chloride,[39] 4-methylbenzoyl chloride,[41] and 6-bromohexanol.[42] 3-Nitrobenzenesulfonyl chloride was prepared by refluxing the sodium salt of 3-nitrobenzenesulfonic acid with $POCl_3$, removal of excess $POCl_3$ in vacuo, pouring onto ice, extraction with $CHCl_3$, and purification.[40]

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Selectivity in the Iodination of Phenol in the Presence of β-Cyclodextrin[1]

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The ratio of products formed in the iodination of phenol and *o*-chlorophenol with I_2/I^- in water solution depends on the pH and buffer concentration. At high pH and high buffer concentration the para/ortho ratio increases. This ratio also increases in the presence of β-cyclodextrin (CD). The kinetics of the iodination reaction was measured for phenol, *o*-iodophenol, *o*-chlorophenol, and *p*-iodophenol, and in all cases the observed rate decreases with the addition of CD. The decrease in the overall rate is due to consumption of the active iodinating species through complexation of I_2, I^-, and I_3^- with CD. The iodination occurs in the bound substrates as well as in the free substrates. The equilibrium constants for the association of the phenols with CD were determined, and it is possible to conclude that the reaction of the bound substrates is faster than that of the free substrates not only for the para position but also for the ortho position. The catalysis is attributed mainly to a microsolvent effect which in the case of the ortho position is counterbalanced by a steric effect.

Cyclodextrins are doughnut-shaped molecules formed by six, seven, or eight glucose units, which are produced by enzymatic degradation of starch. During the last 10 years there has been a growing interest in several aspects

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Table I. Effect of pH, Buffer, and β-Cyclodextrin Concentration on the Iodination of Phenol, o-Chlorophenol, and Aniline[a]

no.	[PhZ],[b] mM	[I_2],[b] mM	[I^-],[b] mM	[CD],[b] mM	o-PhZ,[c] %	p-PhZ,[c] %	o/p[d]
				Phenol[e]			
1	5.28	0.579	15.4	5.13	47 ± 2	30.6 ± 0.8	1.5 ± 0.1 (2.1 ± 0.1)
2	5.00	0.500	15.0	10.0	44 ± 4	34 ± 4	1.3 ± 0.1 (2.1 ± 0.1)
3	5.00	0.500	15.0	15.0	45 ± 3	35 ± 3	1.3 ± 0.2 (2.1 ± 0.1)
4[f]	1.62	0.174	4.53	15.0	44 ± 3	15 ± 0.7	3.0 ± 0.2 (6.1 ± 0.5)
5	0.55	0.535	15.0	5.00	13.9 ± 0.1[g]	19.7 ± 0.7	1.75 ± 0.07 (2.5 ± 0.1)[h]
6[i]	0.44	0.080	1.80	15.0	10.2 ± 0.2	51 ± 3	0.20 ± 0.02 (1.0 ± 0.1)
7	0.36	0.062	1.84	15.0	32 ± 2	19 ± 0.4	1.7 ± 0.1 (3.1 ± 0.3)
				o-Chlorophenol			
8[f]	5.00	0.526	15.0		60 ± 1	40 ± 2	1.5 ± 0.1
9	5.00	0.526	15.0		34 ± 2	42.6 ± 0.6	0.83 ± 0.06
10	5.00	0.556	15.3	15.0	26 ± 2	51 ± 5	0.50 ± 0.01
11[j]	5.00	0.517	15.1		44 ± 2	56.3 ± 0.4	0.78 ± 0.04
12[k]	5.00	0.517	15.1		75 ± 9	25 ± 2	3.0 ± 0.5
13[l]	5.00	0.556	15.3		24 ± 2	68 ± 5	0.35 ± 0.05
				Aniline			
14[m]	4.00	0.400	12.0		13 ± 2	68 ± 6	0.20 ± 0.05
15	4.00	0.400	12.0	4.00	15 ± 2	70.2 ± 0.6	0.21 ± 0.03
16	1.50	0.170	4.55		11.7 ± 0.5	88 ± 2	0.13 ± 0.01
17	1.50	0.170	4.55	15.0	10 ± 1	90 ± 3	0.11 ± 0.01
18[n]	5.00	0.570	15.8		13 ± 3	70 ± 4	0.19 ± 0.05

[a] Room temperature; with buffer [KH_2PO_4] = 4.25 mM and [Na_2HPO_4] = 20.75 mM; pH 7.5 unless otherwise indicated. [b] Initial concentration of the reagents. PhZ = substrate. [c] The percent is based on the I_2 concentration; error limits are calculated from three or four chromatographic determinations. [d] Error limits are calculated considering the ratio of the maximum value of one of the products and the minimum of the other. [e] Numbers in parentheses are for a reaction carried out under exactly the same conditions but without CD. Data from ref 7. [f] The buffer is [KH_2PO_4] = 1.27 mM and [Na_2HPO_4] = 6.22 mM. [g] 21% of diiodophenol formed. [h] Calculed considering that all the diiodophenol comes from the o-iodophenol. [i] [NaHO] = 1 mM instead of buffer; pH 11. [j] The buffer is [KH_2PO_4] = 8.65 mM and [Na_2HPO_4] = 41.3 mM. [k] The buffer is [KH_2PO_4] = 21.7 mM and [Na_2HPO_4] = 3.3 mM; pH 6.1. [l] [NaHO] = 100 mM instead of buffer; pH 13. [m] The buffer is [KH_2PO_4] = 3.4 mM and [Na_2HPO_4] = 16.6 mM. [n] The buffer is [KH_2PO_4] = 6.52 mM and [Na_2HPO_4] = 0.98 mM; pH 6.1.

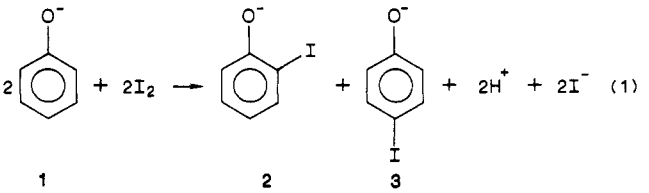
of the chemistry of this type of compounds. Their ability to influence reactivity is being studied from a fundamental point of view as a model for enzyme-catalyzed reactions as well as for practical reasons.[2]

One property of these compounds, which is of our current interest, is that they can change the selectivity of organic reactions. In this respect it has been reported that the influence of α- or β-cyclodextrin in reactions that form more than one type of compound, for instance, in the chlorination of anisole by hypochlorous acid,[3] the addition of α-cyclodextrin changes the para/ortho ratio from 1.48 to 21.6 when the percentage of bound anisole changes from zero to 72%. A very high selectivity for the para position of phenol was observed in its carboxilation[4] and formilation[5] reactions.

We undertake a study of the iodination of phenol and aniline in the presence of β-cyclodextrin (CD) in order to determine whether the increase in selectivity observed in previously reported reactions is mainly due to the interaction of the substrate or to the electrophile with the host. We also report here results concerning the influence of CD on the rate of iodination of phenol **1**, o-iodophenol **2**, p-iodophenol **3**, and o-chlorophenol **4**, which help to interpret the results obtained in the product studies.

Results

Product Distribution Studies. Effect of Buffer and pH. The kinetics of the iodination of aromatic compounds with I_2 in water has been extensively studied with the aim of determining the nature of the halogenating species.[6] However, there have not been studies in regard to the determination of isomers when more than one can be formed. We recently reported that the ratio of ortho and para products formed in the iodination of phenol (eq 1)



depends on the pH and on the buffer concentration.[7] The ortho/para ratio changes from 6.1 to 1.5 when the total buffer concentration ($PO_4H_2^-/PO_4H^{2-}$) increases from 7.5 to 50 mM. Besides, the ortho/para ratio changes from 8.2 to 2.1 when the pH increases from 6.1 to 7.5 at constant buffer concentration.

We have now determined the product distribution in the iodination of o-chlorophenol (**4**) and aniline (**5**) at different pH and buffer concentrations. The results are summarized in Table I, and as it can be seen, the ratio of 2-chloro-4-iodophenol and 2-chloro-6-iodophenol formed from **4** depends on pH and buffer concentration in a similar way as that observed with **1** as substrate. Runs 8, 9, and 11 (Table I) show that the increase in buffer concentration induces an increase in the para product relative to the ortho product, and this effect is even more important for an increase in pH (compare runs 12 and 13, Table I). On the other hand, p-iodoaniline is the predominant product of the iodination of **5** under all conditions, and the change in products due to changes in pH or buffer concentration is barely outside experimental error. (Table I, runs 14–18). These results confirm our suggestion that the change in

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Table II. Association Constants of Phenol and Substituted Phenol with β-Cyclodextrin in Water Solution[a]

substrate	λ_{max},[b] nm	λ_p,[c] nm	K_S, M^{-1}
1	279.7	260	70 ± 15
2	288.4	265	150 ± 40
3	294.5		600 ± 200
4[d]	283.6	270	250 ± 40
5	293.4	270	40 ± 10

[a] T = 25 °C; [substrate]$_0$ = 1 × 10^{-3} M unless otherwise noted. [b] Wavelength maximum of the difference spectrum. [c] Wavelength of the isosbestic point. [d] [Substrate]$_0$ = 6 × 10^{-4} M.

the ortho/para ratio is not due to a change in the iodinating species.[7]

The reactions were carried out in water solution with $H_2PO_4^-/HPO_4^{2-}$ buffer or NaHO. The substrate concentration (PhOH or $PhNH_2$) was in all cases 5–10 times higher than the I_2 concentration because when lower substrate/I_2 ratios were used a high proportion of diiodination products were formed.

Effect of β-Cyclodextrin. At constant pH and buffer concentration, the addition of CD produces an increment in the para isomer relative to the ortho isomer in the iodination of phenol and *o*-chlorophenol. This effect is more significant at low buffer concentration and at high pH (compare, for instance, runs 3, 4, and 6 in Table I). There is not a significant change in the reactions of aniline (Table I).

Inclusion Complex Formation. The addition of CD to a water solution of the substrates 1–4 at neutral pH produces a batochromic shift in the spectrum, indicating that an inclusion complex is being formed. There is a good isosbestic point for all the substrates except for 3. The difference spectrum was done, and the change in optical density (ΔOD) was measured at the wavelength that shows maximum value. The ΔOD values at different CD concentration were used together with eq 2, which is derived

$$\frac{[CD][S]_o}{\Delta OD} = \frac{1}{K_s\Delta\epsilon} + \frac{1}{\Delta\epsilon}[CD] \qquad (2)$$

for a simple 1:1 interaction between the substrate and CD (eq 1, Apendix), to determine the equilibrium constants for the association K_s (Table II). In all cases the plots (not shown) of the left-hand side of eq 2 vs CD concentration are linear, even for 3, which does not show an isosbestic point, indicating that more than one type of interaction must be taking place (see Appendix).

Kinetics. The rate of iodination was measured by following the decrease in absorbance at the λ_{max} of I_3^-, and then the concentration of this species was adjusted to give an initial absorption below 1. The concentration of I^- used was that required to have a rate of iodination in a range suitable for the measurement since the observed rate constant is inversely dependent on the square of the iodide ion concentration.[8] The data are collected in Table III. In all cases the addition of CD decreases the observed reaction rate, and there is a curvilinear dependence of the observed rate on the CD concentration (Figure 1 is representative).

Discussion

In the iodination of phenol, the active species was suggested to be the phenoxide ion.[8] We confirmed this suggestion since anisole, which should react at a similar rate

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Table III. Effect of β-Cyclodextrin on the Iodination of Phenols 1–4[a]

k_2^{obsd} × 10^{-3},[b] min^{-1} M^{-1}	$[CD]_o$[c] × 10^3, M	$[CD]_f$[d] × 10^3, M	f_P[e]	f_I[f]
		Phenol		
7.3 ± 0.7			1.00	0.200
8.1 ± 0.9	0.507	0.432	0.971	0.0624
3.9 ± 0.1	1.03	0.868	0.943	0.0378
4.9 ± 0.1	1.03	0.879	0.942	0.0374
2.1 ± 0.4	1.54	1.33	0.915	0.0266
2.1 ± 0.2	2.25	2.02	0.876	0.0186
2.1 ± 0.4	3.04	2.71	0.841	0.0143
1.84 ± 0.03	5.04	4.59	0.756	0.00888
1.22 ± 0.07	7.54	6.92	0.674	0.00612
1.1 ± 0.1	10.0	9.22	0.607	0.00472
		o-Iodophenol		
11.7 ± 0.1			1.00	0.200
11.0 ± 0.6	0.507	0.416	0.941	0.0640
7.1 ± 0.5	1.03	0.852	0.887	0.0382
5 ± 1	1.54	1.30	0.836	0.0272
3.95 ± 0.09	2.25	1.96	0.773	0.0191
2.21 ± 0.09	5.04	4.50	0.597	0.00904
2.00 ± 0.08	7.54	6.82	0.493	0.00620
1.46 ± 0.02	10.0	9.12	0.422	0.00476
		p-Iodophenol		
1.4 ± 0.1			1.00	0.200
1.30 ± 0.06	0.507	0.354	0.825	0.0706
0.7 ± 0.1	1.03	0.756	0.687	0.0420
0.55 ± 0.02	1.54	1.18	0.587	0.0296
0.50 ± 0.06	2.25	1.80	0.480	0.0206
0.396 ± 0.008	3.04	2.50	0.400	0.0154
0.253 ± 0.007	5.04	4.32	0.279	0.00938
0.174 ± 0.001	7.54	6.65	0.201	0.00634
0.108 ± 0.004	10.0	8.97	0.157	0.00484
		o-Chlorophenol		
6.7 ± 0.2			1.00	0.200
1.6 ± 0.1	0.500	0.391	0.911	0.0665
1.3 ± 0.1	1.00	0.810	0.832	0.0398
1.2 ± 0.05	1.50	1.23	0.763	0.0282
0.94 ± 0.01	2.25	1.90	0.678	0.0196
0.9 ± 0.1	3.00	2.57	0.609	0.0150
0.58 ± 0.03	5.00	4.39	0.477	0.00930
0.42 ± 0.03	7.50	6.70	0.374	0.00630

[a] T = 25 °C; pH 7.5; [KH_2PO_4] = 4.25 × 10^{-3} M and [Na_2HPO_4] = 2.75 × 10^{-2} M as buffer; [KI] = 6 × 10^{-3} M; [I_2] = 5 × 10^{-5} M; [substrate]$_0$ = 5 × 10^{-4} M. [b] Observed pseudo-first-order rate constant divided by the initial concentration of substrate. Rate constants are the average of three or four determinations, and the error limits represent the maximum deviation from the mean value. [c] Initial concentration of CD. [d] Free concentration of CD calculated as indicated in ref 19. [e] Fraction of free phenol. [f] Fraction of free iodine.

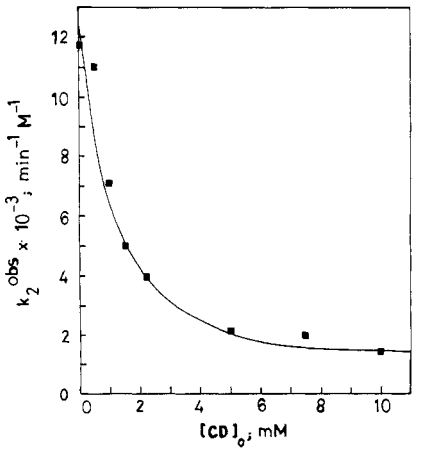
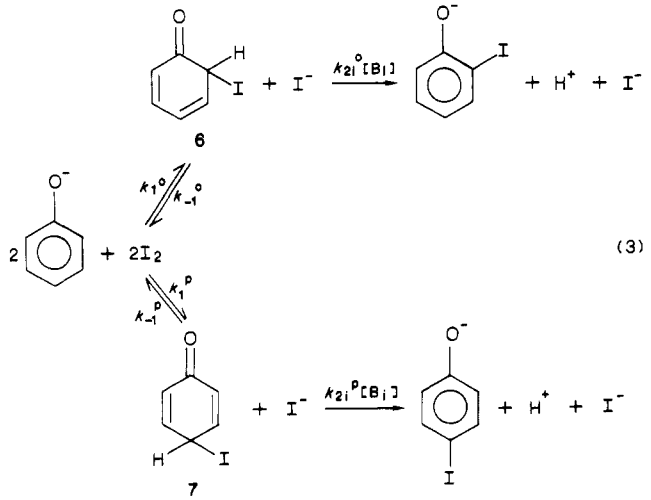


Figure 1. Effect of β-cyclodextrin on the second-order rate constant, k_2^{obsd}, for the iodination of *o*-iodophenol. $[2]_o$ = 5 × 10^{-4} M; pH 7.5; buffer, KH_2PO_4 = 4.25 × 10^{-3} M/Na_2HPO_4 = 2.075 × 10^{-2} M; T = 25 °C; $[I_2]_o$ = 5 × 10^{-5} M; $[I^-]_o$ = 6 × 10^{-3}.

as phenol, does not react in 48 h under the conditions of run 9 in Table I.

The mechanism of iodination of phenol may be described as in eq 3.[7]



The ratio of the ortho/para products is given by eq 4, where k_2^o and k_2^p are the solvent-catalyzed rate constants and k_{2i}^o and k_{2i}^p are the rate constants for proton transfer for all the bases present in the solution.

$$\frac{[2]}{[3]} = 2\,\frac{k_1^o k_{-1}^p}{k_{-1}^o k_1^p}\left[\frac{k_2^o + \sum k_{2i}^o[B_i]}{k_2^p + \sum k_{2i}^p[B_i]}\right] \qquad (4)$$

The fact that the **2**/**3** ratio of products of iodination of phenol decreases when the buffer concentration or the pH increases was attributed to different rates of proton transfer from the ortho **6** and para **7** quinoide intermediates. The observed rate constant for the iodination of phenol is given by eq 5.[9]

$$k_2^{obsd}\ (M^{-1}\ min^{-1}) = 2(k_o^o + k_o^p) + (2k_B^o + k_B^p)[HPO_4^{2-}] = 3 \times 10^3 + (2.08 \times 10^5)[HPO_4^{2-}] \qquad (5)$$

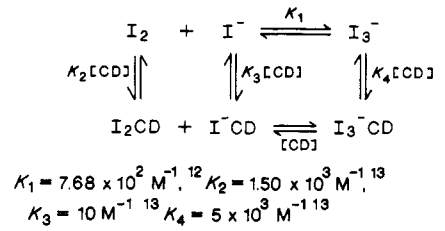
From the values of the observed **2**/**3** ratio at different concentrations of HPO_4^{2-} we can calculate $k_B^p/k_B^o = 2.4$ and $k_o^p/k_o^o \sim 0.1$, which confirms that the rate of proton transfer to the base HPO_4^{2-} is faster for **7** than for **6**. On the other hand, the uncatalyzed rates show the opposite behavior. We carried out similar calculations for the iodination of aniline with the ratio of products for runs 13 and 15 in Table I and the observed rate constant, which is given by eq 6.[10] Thus we determined that $k_o^p/k_o^o \sim 10$ and $k_B^p/k_B^o \sim 13$.

$$k_2^{obsd}\ (M^{-1}\ min^{-1}) = 1.77 \times 10^{-3} + 0.417[HPO_4^{2-}] \qquad (6)$$

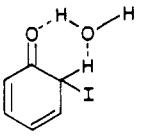
Although the numbers itself have large errors because they are obtained from small differences in prouct ratio, it is important to note that in this case both proton-transfer rates, the catalyzed and the uncatalyzed, are higher for the *p*-quinoide intermediate than for the *o*-quinoide intermediate.

The uncatalyzed rate of proton transfer probably involves transfer of the proton to the solvent, thus hydrogen bonding to the oxygen in the transition state **8** may be an important factor which makes $k_o^o > k_o^p$ for the reaction of phenoxide ion. Similar contribution is not expected in the aniline reactions since in this case the nitrogen bears a formal positive charge.

Scheme I



$K_1 = 7.68 \times 10^2\ M^{-1}$,[12] $K_2 = 1.50 \times 10^3\ M^{-1}$,[13]
$K_3 = 10\ M^{-1}$[13] $K_4 = 5 \times 10^3\ M^{-1}$[13]



With the individual rate constants (k_o^o, k_o^p, k_B^o, k_B^p, and k_B^p) estimated for the aniline reaction, we can go back to eq 4 and calculate the change in the product ratio expected under our reaction conditions. These values are 0.13 and 0.20, which are very difficult to distinguish from experimental error.

The difference in selectivity for the ortho and para position in the reactions of aniline and phenoxide ion is consistent with the difference in electron density as estimated from frontier molecular orbital calculation, namely ortho > para for phenoxide ion and para > ortho for aniline.[11]

The β-Cyclodextrin Effect. The main species present in solutions of I_2 and I^- at neutral pH in the presence of CD are represented in Scheme I where the values of the various equilibrium constants are given.

At a given I_2/I^- concentration, the presence of CD drives the equilibrium toward the right, thus the amount of the active iodinating species, $I_2 + I_2CD$, decreases as the CD increases.

The observed decrease in reaction rate may be attributed to this effect; however, this is not the only reason why the same decrease in rate should be observed in all the reactions independently of the substrate, and this is not what is found.

All the phenols studied form inclusion compounds with CD, and the equilibrium constants for the association are given in Table II. It should be noted that the equilibrium constant that we report here for phenol is about one order of magnitude smaller than one value reported in the literature, namely 600 M^{-1},[14] but similar to others, that is, 37 M^{-1}.[15] We noted that very often different values are reported from different laboratories.[16] We think that the reason is that the nature of the interaction of cyclodextrins with the guest is more complex than generally supposed; however, for the sake of simplicity we will assume a simple 1:1 interaction in the discussion that follows.

The observed pseudo-first-order rate constant for the

(9) Berliner, E. *J. Am. Chem. Soc.* **1951**, *73*, 4307.
(10) Berliner, E. *J. Am. Chem. Soc.* **1950**, *72*, 4003.
(11) Ogata, Y.; Katoh, H.; Takagi, T.; Kimura, M.; Konda, Y.; Chen, F. C.; Hsin, S. C.; Woo, W. I. Seventh IUPAC Conference on Physical Organic Chemistry, Auckland, New Zealand, 1984.
(12) Bell, R. P.; Galles, E. *J. Chem. Soc.* **1951**, 2734.
(13) Diard, J. P.; Saint-Aman, E.; Serve, D. *J. Electroanal. Chem.* **1985**, *189*, 113.
(14) Shiraiahi, S.; Komiyama, M.; Hirai, H. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 507.
(15) Komiyama, M.; Siura, I.; Hirai, H. *J. Mol. Catal.* **1986**, *36*, 271.
(16) See for instance note 13 in Barra, M.; de Rossi, R. H., de Vargas, E. B. *J. Org. Chem.* **1987**, *52*, 5004 and Tables I and II in ref 13.

Table IV. Rate Constants for the Reactions of Phenols with Iodine in the Presence and Absence of β-Cyclodextrin

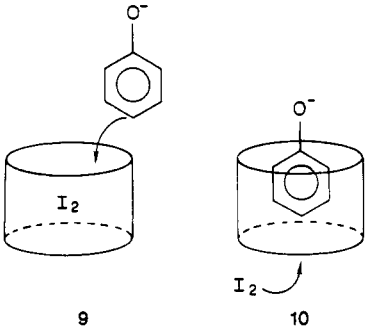
substrate	$k_2 \times 10^{-4}$,[a] M^{-1} min^{-1}	slope $\times 10^{-7}$,[b] M^{-2} min^{-1}	k_2'/k_2[c]
1	3.6 ± 0.4 (8 ± 2)	3.3 ± 0.4	13
2	5.85 ± 0.05 (13 ± 4)	6.9 ± 0.9	8
3	0.70 ± 0.10 (1.8 ± 0.9)	1.6 ± 0.2	4
4	3.40 ± 0.10 (2.7 ± 0.8)	2.3 ± 0.2	2.7

[a] $k_2^{obsd}/f_P f_I$ in the absence of CD. Rate constants are the average of three or four determinations, and the error limits represent the deviation from the mean value. Values in parentheses are the intercept of plots according to eq 14. [b] Slope of plots according to eq 14. [c] Ratio of the rate constants for the reaction of bound phenol k_2' to the reaction of free phenol k_2.

iodination of phenol at neutral pH is given by eq 7, where K_{PhOH} represents the ionization constant of phenol.

$$k_1^{obsd} = k[PhO^-] = k[PhOH]_o \frac{K_{PhOH}}{[H^+]} = k_2^{obsd}[PhOH]_o \quad (7)$$

Since I_2 as well as phenoxide ions form inclusion complexes with CD, and the ratio of ortho/para products depends on the concentration of CD, it is possible that complexed iodine reacts with free phenoxide ion **9** and/or complexed phenoxide ion reacts with free iodine 10. If



9 10

both pathways, which are kinetically undistinguishable, take place, the observed second-order rate constant is given by eq 8 where f_I and f_P are the fractions of free iodine and free phenol, and k_2, k_2' and k_2'' represent the reactions of free phenol with free iodine, free iodine with complexed phenol, and free phenol with complexed iodine, respectively.[17]

$$k_2^{obsd} = k_2 f_P f_I + k_2'(1 - f_P)f_I + k_2''(1 - f_I)f_P \quad (8)$$

Equation 8 can be rearranged to eq 9 where K_s and K_2 are the association equilibrium constants for the phenol and I_2 with CD, and $[CD]_f$ is the free CD concentration. This value was calculated by solving the system of simultaneous equations for each initial concentration of CD, I_2, I^-, and phenol.[18]

$$\frac{k_2^{obsd}}{f_P f_I} = k_2 + (k_2'K_s + k_2''K_2)[CD]_f \quad (9)$$

(17) It should be noted that the k_2 values in eq 8 are composite quantities, namely $k_2 = (k_1^o/k_{-1}^o)(k_{2i}^o[B_i]) + (k_1^P/k_{-1}^P)k_{2i}^P[B_i]$ (see ref 6).

(18) The following system of simultaneous equations were used for these calculations:

$$[CD]_o = [CD] + K_s[CD][PhOH] + K_2[CD][I_2] + K_3[CD][I^-] + K_4K_1[CD][I_2][I^-]$$

$$[I^-]_o = [I^-] + K_1[I_2][I^-] + K_3[CD][I^-] + K_4K_1[CD][I_2][I^-]$$

$$[I_2]_o = [I_2] + K_1[I_2][I^-] + K_2[CD][I_2] + K_4K_1[CD][I_2][I^-]$$

$$[PhOH]_o = [PhOH] + K_s[CD][PhOH]$$

The calculations were done on a Vax 11 computer by using a program for solving a system of nonlinear equations from the IMSL Library (Routin name ZSCNT).

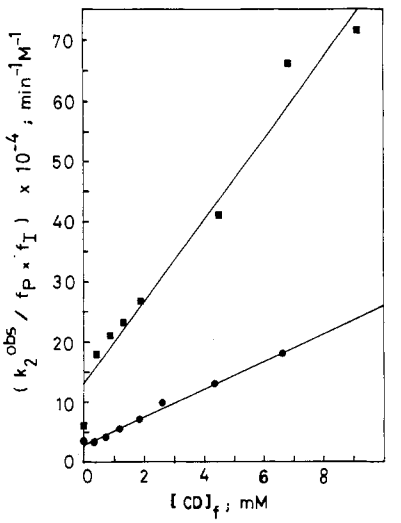


Figure 2. Effect of the concentration of free β-cyclodextrin, $[CD]_f$, on the observed second-order rate constant, k_2^{obsd}, corrected by the fraction of free phenol, f_P, and free iodine, f_I, for the iodination of **2** (■) and **4** (●).

The plots of the left hand side of eq 9 vs $[CD]_f$ are reasonably linear, although there is some scattering in the points (Figure 2 is representative). The values of the slopes and intercepts of these plots are given in Table IV.

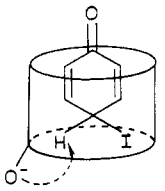
If we consider that only the k_2' pathway takes place, the ratio of the slopes and intercepts of the plots of Figure 2 represents $k_2'K_s/k_2$, and from the values of K_s for the phenols we can calculate the ratio of rates for the bound and free phenol k_2'/k_2, which are shown in Table IV. It can be seen that in all cases the phenol reacts faster in the complexed form. This means that the reactions of the ortho as well as that of the para position are catalyzed, since in the case of **3** there are only ortho positions available for the reaction. From the knowledge of the value of the observed rate constant in the absence of CD and the product ratio at different CD concentrations, it is possible to calculate for phenol the ratio of rate constants for the formation of **2** and **3** from bound and free phenol as 3.5 and 7, respectively. These values confirm the results described above, which indicate that CD catalyzes the reaction at both positions of the phenols, ortho and para; however, the catalysis is more important for the para position, and this leads to an increase in the para/ortho ratio with the addition of CD. This behavior contrasts with that found in the chlorination of anisole where the reaction of the electrophile with the ortho position in the anisole bound to α- and β-cyclodextrins is completely repressed[19] and with the bromination of *p*-methylanisole in the presence of α-cyclodextrine where only the free substrate reacts.[20] On the other hand, in the reaction of *p*-cresol with HClO, the ratio of k_{bound}/k_{free} is 2.4,[19] similar to the ratio found for *p*-iodophenol with iodine (Table IV). Besides, recently it was determined that the rate of bromination of several 4-substituted phenols is strongly catalyzed by α-cyclodextrin,[21] and these compounds have only ortho positions available for reaction. The structure of the complex of phenoxide ion with β-cyclodextrin was determined by NMR, and it was shown that the depth of penetration in the cavity for the ring carbons is para > meta > ortho[5] with the consequence that the ortho position is not sterically hindered for the reaction.

(19) Breslow, R.; Campbell, P. *Biorg. Chem.* **1971**, *1*, 140.
(20) Tee, O. S.; Bennett, J. M. *Can. J. Chem.* **1984**, *62*, 1585.
(21) Tee, O. S.; Bennett, J. M. *J. Am. Chem. Soc.* **1988**, *110*, 269.

If we assume that the reaction is between complexed iodine and free phenol, the ratio between k_2''/k_2 is calculated as 0.61, 0.79, 1.57, and 0.44 for phenol, *o*-iodo-, *p*-iodo-, and *o*-chlorophenol, respectively, which would indicate that the reactions at the ortho position are catalyzed whereas those at the para position are inhibited by CD. This is inconsistent with our product studies. We can not, however discard the possibility that both reactions take place simultaneously. There are evidences that in the bromination of phenol in the presence of α-cyclodextrin, the reaction occurs mainly between the complexed bromine and the free substrate.[21,22] There is yet another possibility, which is the formation of a ternary complex CD–phenol–I_2 with a lifetime longer than a normal encounter, but evaluation of this model is difficult since we have not an estimate of the equilibrium constant for the formation of this complex.

In order to explain the nature of the catalysis, we must consider the factors that might accelerate the first and second steps of the mechanism (eq 3). Catalysis may be due to an increase in the rate of addition of the electrophile to the aromatic ring (k_1^o and k_1^p), to a decrease in the reversion of the intermediate (k_{-1}^o and k_{-1}^p), to an increase in the proton transfer rate (k_{2i}^o and k_{2i}^p) or to a combination of them. In the first step of the reaction, a neutral intermediate is formed from a charged substrate, thus a decrease in solvent polarity should increase the rate of reaction. Since the cavity of the cyclodextrin is relatively unpolar compared to water,[23] the increase in the rates of substitution in the bound substrates might be attributed to a microsolvent effect as was observed in other reactions.[24]

The rate of proton transfer could increase due to the participation of one of the OH groups of CD as general base as shown in 11. This effect could be responsible for the increased formation of the para product at high pH, since a significant fraction of CD is ionized (pK_a of CD = 12.2)[25] but at the pH of our studies, 7.5, it would be difficult to justify why the OH groups of CD should be a better catalyst than the solvent itself.



11

Another way to explain the observed catalysis and change in product ratio could be to assume the formation of an iodinated cyclodextrin, which would be the agent that transfers the iodine atom to the bound substrate, similarly as was suggested for the chlorination of anisole.[19] However, we do not favor this mechanism because there are several studies of the interaction of iodine with CD,[13] and in none of them are there evidences for the formation of such a compound.

Conclusions

The iodination of phenol, and substituted phenols in water solution, proceeds with rate-determining decomposition of the intermediate σ-complex, and the rate of general base catalyzed reaction is faster for the *p*-quinoide than for the *o*-quinoide intermediate. The addition of CD causes an effective decrease in the overall rate of iodination, which is due to the complexation of this agent with I_2, I^-, and I_3^-. This interaction decreases the effective iodine concentration, which is the iodinating agent. In all cases the rate of iodination of the bound substrate is faster than that of the free substrate not only for the para position but for the ortho position as well, although in this case the catalysis is less significant, and so the ortho/para ratio of products decreases in the presence of CD. These results contrast with those found previously in the chlorination of anisole in the presence of α- or β-cyclodextrin where it is reported that in the bound anisole the ortho chlorination is completely suppressed. The different behavior of these two reactions indicate different mechanisms, and for the reactions reported in this study we suggest that the major effect is a microsolvent effect, which increases the overall rate of reaction of the bound substrate and to some steric effect for the attack of the iodine at the ortho position of the bound substrates. We suggest that at high pH the ionizated CD acts as general base, favoring the formation of the para substituted product. The fact that the reaction is totally inhibited at the ortho position in reactions of anisole but not in those of phenol and substituted phenols is attributed to differences in deepness of penetration of the two types of substrates into the cavity of CD.

Experimental Section

The water used was obtained from a Millipore apparatus. Dioxane was purified as before.[26] Inorganic compounds of analytical grade were used without further purification. Phenol was purified by distillation, bp 178 °C (lit.[27a] bp 181.7 °C). *o*-Iodophenol (Eastman) pf 39–40 °C (lit.[27b] of 43 °C) was used without further purification. *p*-Iodophenol was synthesized from *p*-aminophenol (Mallinckrodt) or from *p*-iodoaniline and was recrystallized from pentane mp 89–91 °C (lit.[27c] mp 93–94 °C). *p*-Iodoaniline was a sample existent in the laboratory and was recrystallized from petroleum ether, mp 61–62 °C (lit.[27d] mp 67–68 °C). Aniline (Merck) was distilled from Zn dust, bp 180 °C (lit.[27e] bp 184 °C). 2-Chloro-4-iodophenol was synthetized from *p*-iodophenol and Cl_2 in Cl_4C. The Cl_2 was generated from the reaction of $KMnO_4$ with HCl. It was recrystallized from pentane, mp 49–51 °C (lit.[28] 54 °C).

Product Studies. A solution of the substrate in water (~20 mL) was added to an aqueous solution containing the required amount of all the inorganic reagents and CD (~180 mL), with magnetic stirring, at room temperature and in the dark. When the color of the I_3^- disappeared, or in basic solutions after 10 min, some $NaHSO_3$ and HCl were added to destroy any remaining I_2 and lower the pH down to 2. The solutions were then extracted three times with 30 mL of ethyl ether. The combined ether extracts were dried with anhydrous Na_2SO_4 and were concentrated. The product analysis was done by gas chromatography with a Varian 1400 or a Shimadzu GC 8A instrument equipped with a Shimadzu CR 1A processor. A 1.5 m × $^1/_8$ in. 3% OV 101 on Chromosorb GHP column was used for the analysis of 1 and 5 and their iodinated derivatives; 1-bromonaphthalene (Fluka) was used as internal standard. For the analysis of 4 and their iodinated derivatives as 1.5 m × $^1/_8$ in. OV 17 5% on Chromosorb HP column was used (α-naphtol (Merck) as internal standard).

Kinetics Procedures. Reactions were initiated by adding 25 μL of the substrate dissolved in dioxane to 3 mL of a solution

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(23) Hamai, S. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 2721.
(24) De Rossi, R. H.; Barra, M.; de Vargas, E. B. *J. Org. Chem.* **1986**, *51*, 2157 and references cited therein.
(25) Van Etten, R. L.; Clowes, G. A.; Sebastian, J. E.; Bender, M. L. *J. Am. Chem. Soc.* **1967**, *89*, 3253.
(26) De Rossi, R. H.; de Vargas, E. B. *J. Am. Chem. Soc.* **1981**, *103*, 1533.
(27) *Handbook of Chemistry and Physics*, 61st ed. 1980-1981, Weast, R. C., Ed.; CRC: Boca Raton, FL, 1980–1981; (a) C-472; (b) C-479; (c) C-95; (d) C-90; (e) C-474.
(28) Brazier, S. A.; Mc Combic, H. *Proc. Chem. Soc.* **1913**, *28*, 127; *J. Chem. Soc.* 968; *Chem. Abstr.* **1913**, *7*, 67.

containing all the other constituents. The reactions were run at 25 °C in a thermostated cell of a Beckman 24 spectrophotometer by following the decrease in the absorption at the λ_{max} of I_3^- (358 nm). All reactions were carried out with the substrate at more than 10 times the concentration of that of I_3^- and the decrease in absorbance was recorded up to 80–90% conversion. In all cases good pseudo-first-order behavior was observed.

Equilibrium Constant Determinations. The equilibrium constants were determined by measuring the optical density of a solution containing the substrate at constant concentration [(0.6–1.0) × 10^{-3} M] and CD in variable concentration in the range (0–15) × 10^{-3} M. The wavelength for measurement was that where the difference spectrum shows a maximum. These values are shown in Table IV. All determinations were carried out in the thermostated cell of a Shimadzu spectrophotometer UV 260 with a solution of CD in water at the same concentration in the blank cell to substract any contribution to the observed absorption due to CD.

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Appendix

The interaction between CD and the substrate **3** may be described as in eq 1–3, where S represents the guest. The lack of an isosbestic point in solutions containing **3** and variable concentrations of CD indicate that more than one type of complex is being formed. These type of complexes may result from a 2:1 or 1:2 interaction between the guest S and the host CD (eq 2 and 3).

$$S + CD \rightleftharpoons \underset{\mathbf{1}}{SCD} \quad K_s \tag{1}$$

$$SCD + S \rightleftharpoons \underset{\mathbf{2}}{(S)_2CD} \quad K_{2s} \tag{2}$$

$$SCD + CD \rightleftharpoons \underset{\mathbf{3}}{S(CD)_2} \quad K_{2c} \tag{3}$$

Both types of complexes 2:1 and 1:2 (guest:cyclodextrin) have been observed with other substrates.[29,30] The expression for ΔOD as a function of the equilibrium constant for the case that eq 1 and 2 hold, is given by eq 4, where [S] represents the free substrate concentration.

$$\Delta OD = \frac{\{(\epsilon_1 - \epsilon_s) + (\epsilon_2 - 2\epsilon_s)K_{2s}[S]\}\, K_s[CD][S]_o}{1 + K_s[CD](1 + 2K_{2s}[S])} \tag{4}$$

A linear dependence of $(\Delta OD)^{-1}$ vs $[CD]^{-1}$ is expected if $K_{2s}[S] < 1$ and $\epsilon_1 \approx \epsilon_2 \approx \epsilon$ since in this case eq 4 can be simplified and trasformed into an equation of the form of eq 2 (Results). Interaction of cyclodextrins with substrates in stoichiometry different to 1:1 are known in the literature, and in general the equilibrium constant for the interactions are of similar order of magnitude.[29,30] The substrate concentration used in our experiments was 10^{-3} M and K_s and K_{2s} are expected to be of the same order of magnitude of the equilibrium constants reported in Table II for the other phenols. It follows that $K_{2s}[S] < 1$. Thus from the value of the slope and intercept of plots of $(\Delta OD)^{-1}$ vs $[CD]^{-1}$, K_s can be determined and this value is reported in Table II.

On the other hand, if eq 1 and 3 hold, the expression of ΔOD as a function of CD concentration is given by eq 5, which can be transformed into an equation of the form of eq 2 (Results) only if $K_{2c}[CD] < 1$. This would imply that $K_{2c} \ll K_s$, a relationship difficult to justify. We conclude that the main two types of interactions between **3** and CD are represented by eq 1 and 2.

$$\Delta OD = \frac{(\epsilon - \epsilon_s)K_s[CD][S]_o(1 + K_{2c}[CD])}{1 + K_1[CD](1 + K_{2c}[CD])} \tag{5}$$

Registry No. **1**, 108-95-2; **1**·CD, 73621-01-9; **2**, 533-58-4; **2**·CD, 104015-41-0; **3**, 540-38-5; **3**·CD, 104015-42-1; **4**, 95-57-8; **4**·CD, 70763-75-6; **5**, 62-53-3; **5**·CD, 73621-02-0; 2-chloro-4-iodophenol, 116130-33-7; 2-chloro-6-iodophenol, 28177-52-8; *p*-iodoaniline, 540-37-4; β-cyclodextrin, 7585-39-9; *o*-iodoaniline, 615-43-0.

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Azepino[1,2-*a*]indole Synthesis from a 1,2,3,4-Tetrahydro-9(10*H*)-acridinone and Sodium Dichloroisocyanurate[1] or Singlet Oxygen

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Sodium dichloroisocyanurate (**4**) acts on 7-methyl-1,2,3,4-tetrahydro-9(10*H*)-acridinone (**1**) to give principally either *cis*-1,2-diol **2** or azepino[1,2-*a*]indole **3**, by suitable choice of reactant proportions. 2,3,6-Trimethyl-4-(1*H*)-quinolinone (**6**) yields a novel, methylene-bridged, oxygenated dimer **9**, while with excess **4** the chief product is the 1,2-dihydro-3*H*-indol-3-one **7**. 6-Methyl-2-phenyl-4(1*H*)-quinolinone (**12**) initially gives the 3-chloro derivative **14**, which then reacts further with **4**, yielding chlorine-free 6-methyl-2-phenyl-4*H*-3,1-benzoxazin-4-one (**16**). The sensitized photooxidation of acridinone **1** furnishes azepinoindole **3** en route to dicarboxylic acid **5**; upon similar treatment, quinolinone **6** provides the analogous indolone **7**. Reaction pathways to account for the results are presented. *N*-Halo imide **4** offers advantages over the more conventional NaOCl in synthesis as illustrated also with a "one-pot" Hofmann degradation of 4-chlorobenzamide.

Recently,[2,3] we described the oxidation of 7-methyl-1,2,3,4-tetrahydro-9(10*H*)-acridinone (**1**) with sodium hypochlorite to give, initially, *cis*-4a,9a-dihydroxy-1,2,3,4,4a,9a-hexahydro-7-methyl-9(10*H*)-acridinone (**2**)

(1) Chemical Abstracts name for sodium dichloroisocyanurate: 1,3-dichloro-1,3,5-triazine-2,4,6(1*H*,3*H*,5*H*)-trione, sodium salt. That for trichloroisocyanuric acid is 1,3,5-trichloro-1,3,5-triazine-2,4,6-(1*H*,3*H*,5*H*)-trione.

(2) Boeyens, J. C. A.; Denner, L.; Marais, J. L. C.; Staskun, B. *S. Afr. J. Chem.* **1986**, *39*, 221.
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