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INTRAMOLECULAR OXIDATIVE COUPLING OF BROMINATED 2,4'-DIHYDROXYDIARYLMETHANES. A BIOGENETIC SYNTHESIS OF THELEPIN AND ITS ANALOGS

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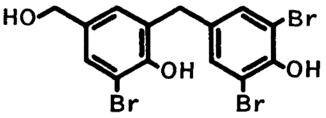
Oxidation of brominated 2,4'-dihydroxydiarylmethanes with aqueous $NaOCl$ under phase-transfer catalysis or $NaOCl$ on Celite afforded new spiro-p-quinol ethers. Thelepin, which was isolated from the marine annelid *Thelepus setosus*, was first synthesized from thelephenol by these methods.

Many bromophenols and their related compounds have been isolated from marine organisms.1) From the marine annelid *Thelepus setosus* Higa and Scheuer2) have isolated five bromophenol-related compounds including 2,4'-dihydroxy-5-hydroxymethyl-3,3',5'-tribromodiphenylmethane (1) (designated as thelephenol) and spiro-p-quinol ether (2) (designated as thelepin). Thelepin 2 is very interesting because of sharing structural similarity and antifungal activity2) with the antimycotic agent griseofulvin (3).3)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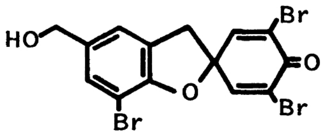
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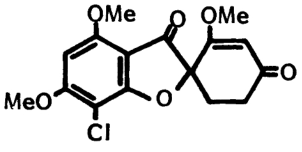
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Oxidative phenol coupling has received considerable attention owing both to its utility as a synthetic reaction and its proposed involvement in the biosyntheses of a number of classes of natural products.4) To date, various oxidizing reagents have been investigated but with limited success. A biogenetic-type oxidative coupling of thelephenol 1 should form thelepin 2, but its transformation with ferricyanide or lead dioxide was unsuccessful.2) Moreover, the investigation of intramolecular oxidative coupling of dihydroxydiarylmethane series has not been extended beyond that of t-butyl-substituted 2,2'-dihydroxydiarylmethanes.5) Thus, we were interested in studying intramolecular oxidative coupling of brominated 2,4'-dihydroxydiarylmethanes in connection with the synthesis of thelepin 2.

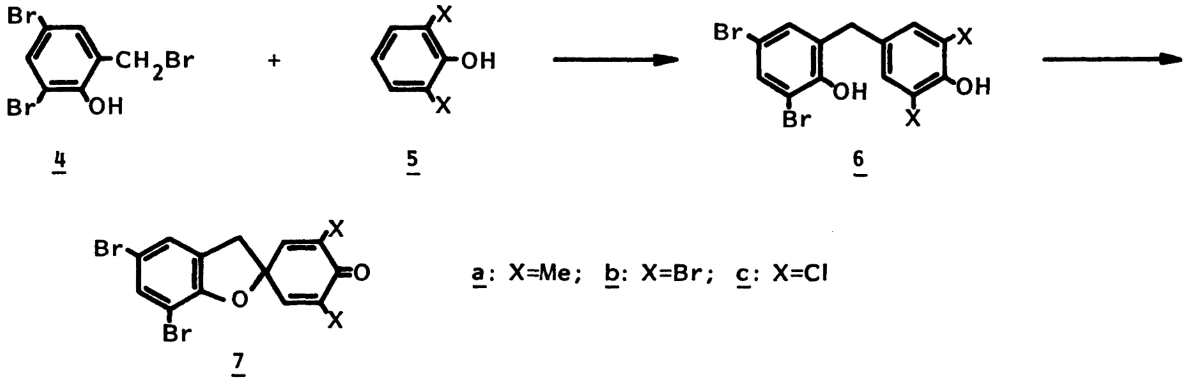
In this communication we wish to report a new approach that shows considerable promise for the synthesis of thelepin 2 and its analogs.

Recently, the use of the phase-transfer technique in oxidations with hypochlorite has been shown to provide good results in the conversion of hydroquinones and catechols into p- and o-benzoquinones$^{6)}$ or alcohols into carboxylic acids.$^{7)}$ We have first applied this method to the oxidative coupling of 3,5-dibromo-2,4'-dihydroxydiarylmethanes, 6a-6c, which were easily prepared from 3,5-dibromo-2-hydroxybenzyl bromide 4 and 2,6-disubstituted phenols 5a-5c.$^{8)}$ This method has been found to be superior to those using other oxidizing reagents$^{9)}$ in terms of simple procedure and yields.

The following example is a representative. A 2.5% aqueous sodium hypochlorite solution (14.2 mL, 5.7 mmol as NaOCl) containing t-butylammonium hydrogensulfate (14 mg) was adjusted to pH 8 with hydrochloric acid. The above solution was vigorously stirred with a solution of 3,5-dibromo-3',5'-dimethyl-2,4'-dihydroxydiphenylmethane (6a) (0.5 g, 1.3 mmol) in ethyl acetate (50 mL) at room temperature for 1h. After quenching with an aqueous sodium hydrogensulfite solution, a usual work up of the organic layer gave 369 mg (74%) of spiro-p-quinol ether 7a, mp 152-154 °C, as colorless prisms.

The spiro-p-quinol ethers 7b, mp 222-224 °C (decomp), and 7c, mp 214-216 °C (decomp), both as pale yellow prisms were obtained from the oxidative coupling of the corresponding diarylmethanes, 6b and 6c, under similar conditions. The reaction conditions and yields of 7 are given in Table 1.

Structural elucidation of all the spiro-p-quinol ethers 7 was accomplished on the basis of spectral data.$^{10)}$



a: X=Me; b: X=Br; c: X=Cl

The application of the above phase-transfer technique resulted in a drastic increase in the yields of 7 (see Ref. 9); nevertheless, the yields of 7b and 7c were still not satisfactory.

The use of reagents adsorbed on or intercalated in an insoluble inorganic support has also been developed in the field of organic syntheses. It is known that silver carbonate adsorbed on Celite developed by Fétizon et al.$^{11)}$ is a remarkably useful reagent for oxidation.$^{12)}$ The reagent, however, was found to be ineffective for the oxidative coupling of 6. We have eventually found a satisfactory reagent, sodium hypochlorite supported on Celite (NaOCl on Celite), for our intramolecular oxidative coupling.

A typical run is as follows. A mixture of the dihydroxydiarylmethane 6a (0.1 g, 0.26 mmol) and NaOCl on Celite (0.52 mmol NaOCl on 1.0 g Celite)$^{13)}$ in ethyl acetate (100 mL) was stirred at room temperature for 20 min. The solid was

Table 1. Intramolecular Oxidative Coupling of 2,4'-Dihydroxydiarylmethanes 6

Diarylmethane 6	X	Method[a)]	6/NaOCl (mol/mol)	Temp °C	Time min	Spiro-p-quinol ether 7	Yield, %
6a	Me	A	1/4.4	r.t.	60	7a	74
		B	1/2.0	r.t.	20		83
6b	Br	A	1/2.2	-5 — -10	30	7b	21.5[b)]
		B	1/1.5	r.t.	20		70
6c	Cl	A	1/4.4	-5 — -10	120	7c	15[b)]
		B	1/2.0	r.t.	20		32[b)]

a) A: NaOCl under phase-transfer catalysis. B: NaOCl on Celite.

b) Polymers were formed.

filtered and washed with ethyl acetate. The combined filtrate was evaporated in vacuo, and the resultant residue was chromatographed (alumina, benzene) to give 83 mg (83%) of the spiro-p-quinol ether 7a.

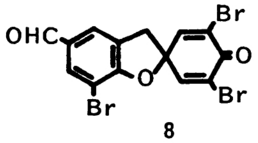
The diarylmethanes, 6b and 6c, gave the corresponding spiro-p-quinol ethers, 7b and 7c, by the oxidative coupling under similar conditions. The reaction conditions and yields are also shown in Table 1.

Finally, we have investigated the oxidative coupling of thelephenol 1 by the above two methods, and succeeded in synthesis of thelepin 2. Both methods gave 2, together with the formyl derivative 8.[14)] The results are shown below.

Structural elucidation of 2 and 8 was accomplished on the basis of spectral data.[15)]

Thelephenol $\longrightarrow$ **Thelepin** +

1 **2**



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Method A	1/NaOCl (1/3.0)	-5 — -10 °C, 1 h	2	4%	8	0.5%
Method B	1/NaOCl (1/2.5)	r.t., 20 min	2	32%	8	2%

The spiro-p-quinol ethers, 7b and 7c, exhibit antifungal activity at a level comparable with thelepin 2: Details on the antifungal tests will be reported elsewhere.

Further application of the oxidizing reagent NaOCl on Celite is now under progress.

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8) Diarylmethanes 6a,[16] 6b,[17] and 6c[17] were prepared by the reported methods.

9) The results of oxidations of 6 by other reagents were as follows. $K_3Fe(CN)_6$ in aq. K_2CO_3 solution (-5 — -10 °C, 3.5 h): 7a (5%), 7b (2%). Freshly prepared PbO_2 in CCl_4 (r.t., 2 h): 7b (2%), 7c (2.5%). Polymers were formed in all cases. No 7b was formed in the treatment of 6b with $PdCl_2$ and SeO_2.

10) All new compounds reported herein gave satisfactory elemental analyses. 7a: IR (KBr) 1630 cm^{-1} (C=O); ^1H-NMR ($CDCl_3$) δ 1.90 (6H, s), 3.33 (2H, s, $C\underline{H}_2$), 6.65 (2H, s, =C$\underline{H}$), 7.21, 7.42 (each 1H, m); ^{13}C-NMR ($CDCl_3$) δ 15.8 (q), 40.6 (t), 83.1 (s), 185.9 ($\underline{C}$=O); MS m/z 386, 384, 382 (M^+). 7b: IR (KBr) 1680 cm^{-1} (C=O); ^1H-NMR (DMSO-d_6) δ 3.62 (2H, s, $C\underline{H}_2$), 7.47, 7.56 (each 1H, m), 7.80 (2H, s, =C$\underline{H}$); MS m/z 518, 516, 514, 512, 510 (M^+). 7c: IR (KBr) 1690 cm^{-1} (C=O); ^1H-NMR (DMSO-d_6) δ 3.62 (2H, s, $C\underline{H}_2$), 7.45, 7.55 (each 1H, m), 7.57 (2H, s, =C$\underline{H}$); MS m/z 428, 426, 424, 422 (M^+).

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13) Purified Celite[11] (1.0 g) was stirred with a 10% aqueous NaOCl solution (0.34 mL, 0.55 mmol as NaOCl) in distilled water (25 mL) at room temperature for 30 min. The water was evaporated in a rotary evaporator in vacuo (26 mmHg, 40 °C, 1 h and then 4 mmHg, r.t., 1 h). The reagent system thus prepared contained about 0.52 mmol of NaOCl as determined by iodometric titration.

14) Oxidation of 1 with reagents shown in Ref. 9 did not give 2. On oxidation with large excess $VOCl_3$ in ether (30 mol equiv., r.t., 3 h), however, 8 was obtained in 11% yield.

15) 2: pale yellow prisms; mp 200-202 °C (mp 202-203 °C (decomp)[2]); IR (KBr) 3395 (OH), 1685 cm^{-1} (C=O); ^1H-NMR (acetone-d_6) δ 2.78 (1H, bs, O$\underline{H}$), 3.69 (2H, m), 4.53 (2H, s), 7.17, 7.30 (each 1H, m), 7.69 (2H, s, =C$\underline{H}$); MS m/z 468, 466, 464, 462 (M^+). Acetate of 2: mp 187-188 °C (mp 190 °C[2]). 8: colorless prisms; mp 240-242 °C (decomp); IR (KBr) 1695, 1677 cm^{-1} (C=O); ^1H-NMR (DMSO-d_6) δ 3.68 (2H, s), 7.75 (1H, m), 7.83 (2H, s, =C$\underline{H}$), 7.94 (1H, m), 9.75 (1H, s, C$\underline{H}$O); MS m/z 466, 464, 462, 460 (M^+).

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