Alkenylidene Bisphenols, a New Class of Bisphenol Bactericide

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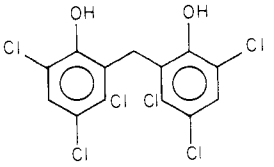
Alkenylidene bisphenols are prepared by condensation of an appropriate phenol with a haloacetaldehyde, followed by base-induced elimination, or by condensation of the corresponding aryl methyl ether, elimination, and deprotection of the phenol with boron tribromide. The resulting compounds may be further elaborated by reactions on the aromatic nucleus. A series of 13 such compounds showed activity against *Staphylococcus aureus*; the most active was 1,1-dichloro-2-(3-allyl-5-chloro-2-hydroxyphenyl)-2-(5-chloro-2-hydroxyphenyl)ethylene (**16**), MIC 0.16 μg/mL. 1,1-Dichloro-2,2-bis(5-chloro-2-hydroxyphenyl)ethylene (**6**) was similar in its activity and spectrum to hexachlorophene.

The bacteriostatic bisphenols have seen the apex of their development in the antistaphylococcal agent hexachlorophene (**1**).[2] Since the withdrawal from the consumer



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market of this drug, following findings of significant CNS disturbances in neonates bathed with soap preparations containing the compound, research on the class has languished. Virtually no new members of the class with significant antibacterial activity have been reported in a number of years.

In connection with other studies aimed at circumventing the problem of hexachlorophene's toxicity, we attempted the hydrolysis of the trichloroethylidene bisphenol **2** (R = H).[3] Rather than the anticipated[4] diphenylacetic acid (**3**), we recovered, in addition to ethers **4** and **5**,[5] the previously unreported compound **6** (see Scheme I). Although a few compounds of this type are known,[5,6] their potential as antiinfective agents has been overlooked. We report the results of exploratory studies on the in vitro activity of **6** and a number of its congeners.

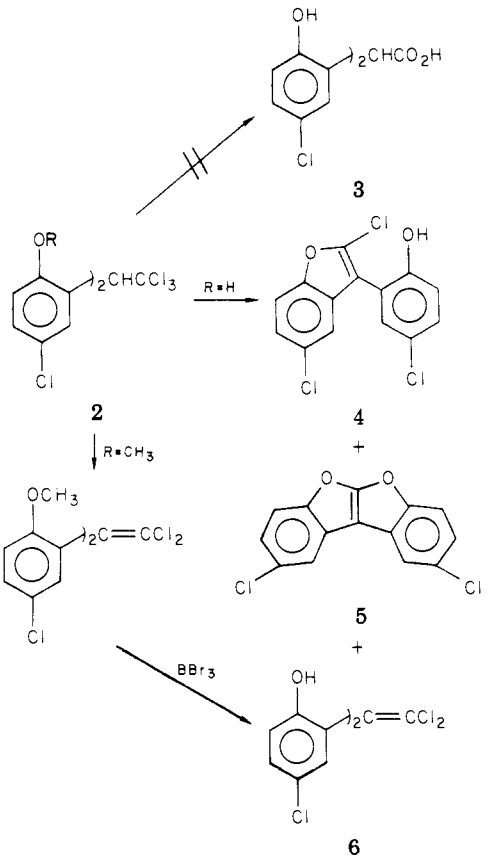
Results and Discussion

Chemistry. The alkenylidene bisphenols listed in Table I can be prepared by the methods shown in Scheme I for the preparation of **6**. The haloethylidene analogues to **2** were prepared by the method reported;[3] it was found convenient to use glacial acetic acid as a cosolvent for this reaction in some cases.

Dehydrohalogenation of **2** and its congeners is in competition with the displacement reactions which give rise to **4** and **5**. The relative amounts of ring-closed and simple elimination products are sensitive to substitution of both the halogen-bearing alkyl fragment and the aromatic residues. Unfortunately, ring closure is favored in the cases studied; dehydrohalogenation of the initial displacement products renders them stable to reversion. None of the products, **4**–**6**, are interconvertible with the others under the reaction conditions. The yields of the alkenylidene bisphenols by this route are poor, and some (e.g., **18**) are completely inaccessible.

Use of the methyl ethers (Scheme I, R = CH_3) alleviates this problem, as well as avoiding the tedious chromatographic separation of the bisphenols and analogues of **4**. Boron tribromide was a satisfactory reagent for deprotection of the phenol, although both rate and yield of the reaction were highly variable. This circumstance was offset somewhat by the simplicity of the workup and purification. Usually a single crystallization sufficed to afford analytically pure products.

Scheme I



Compounds noted in Table I as being prepared by method C were derived from **6** by the usual electrophilic processes (**11**, **12**, and **15**) and/or elaboration of functionality of the aromatic ring (**13** and **14**). We encountered no evidence of instability of the olefinic unit to any of these modifications.

Antibacterial Activity. All of the bisphenols prepared were active when assayed against a liquid culture of *Staphylococcus aureus* (ATCC 6538-P), using an inoculum of 10^4 log phase organisms per milliliter. The MIC of **16** is noteworthy; this value is among the lowest reported for bisphenols. As is common for this class of drug, these materials suffer from sensitivity to extraneous proteins. In the presence of 3% bovine serum albumin, the MIC of **6** was increased from less than 1 to greater than 25 μg/mL.

Activity of the compounds was, as anticipated, largely restricted to the Gram-positive representative. Table II shows the result of testing vs. other microorganisms. All compounds not reported (except **15** and **16**, which were not tested) were inactive at 200 μg/mL, the highest concentration tested.

The toxicology of the alkenylidene bisphenols varies significantly from that of previously reported saturated

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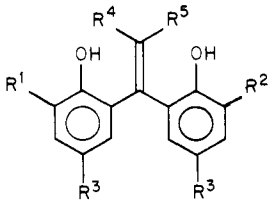
Table I. Physical Properties and Antistaphylococcal Activity of Alkenylidene Bisphenols



no.	R^1	R^2	R^3	R^4,R^5	method	mp, °C (recrystn solv)	formula	anal.	MIC,[a] μg/mL
6	H	H	Cl	Cl,Cl	A, B	172–174 (benzene)	$C_{14}H_8Cl_4O_2$	C, H, Cl	0.55
7	H	H	Br	Cl,Cl	A	180–182 (benzene–cyclohexane)	$C_{14}H_8Br_2Cl_2O_2$	C, H, Br; Cl[b]	3.12
8	H	H	CH_3	Cl,Cl	A	150–152 (hexane)	$C_{16}H_{14}Cl_2O_2$	C, H, Cl	50
9	H	H	*t*-Bu	Cl,Cl	B	169–170	$C_{22}H_{26}Cl_2O_2$	C, H, Cl	150
10	CH_3	CH_3	Cl	Cl,Cl	A	196–197 (benzene)	$C_{16}H_{12}Cl_4O_2$[c]	C, H, Cl	1.87
11	NO_2	NO_2	Cl	Cl,Cl	C	171–172 (hexane)	$C_{14}H_6Cl_4N_2O_6$	C, H, Cl, N	12.5
12	H	NO_2	Cl	Cl,Cl	C	88–94	$C_{14}H_7Cl_4NO_4$	N, H; C, Cl[d]	12.0
13	H	NH_2	Cl	Cl,Cl	C	188–189 (aq ethanol)	$C_{14}H_9Cl_4NO_2$	C, H, Cl, N	8.75
14	H	$NHCOC_5H_{11}$	Cl	Cl,Cl	C	80–82 (benzene–hexane)	$C_{20}H_{19}Cl_4NO_3$	C, H	6.13
15	H	Br	Cl	Cl,Cl	C	150–152 (benzene)	$C_{14}H_7BrCl_4O_2$	C, H, Br, Cl	0.78
16	H	allyl	Cl	Cl,Cl	C	159.5–161 (CCl_4)	$C_{17}H_{12}Cl_4O_2$	C, H, Cl	0.16
17	H	H	Cl	Br,Br	A	162.5–164 (benzene)	$C_{14}H_8Br_2Cl_2O_2$	C, H, Br, Cl	1.56
18	H	H	Cl	H,Cl	B	150–152	$C_{14}H_9Cl_3O_2$[e]	H, Cl; C[e]	1.56
1 (hexachlorophene)									1.56

[a] Twenty-four hour MIC vs. *Staphylococcus aureus* ATCC 6538-P. [b] Cl: calcd, 16.15; found, 14.32. [c] The compound crystallized and was analyzed with 0.33 mol of benzene as solvent of crystallization. [d] Calcd: C, 42.56; Cl, 35.90. Found: C, 43.67; Cl, 34.79. This compound, while homogeneous to TLC, has defied our attempts to purify it by either chromatography or crystallization. [e] Analyzed as the hemihydrate. C: calcd, 51.80; found, 52.31.

Table II. Antibacterial Spectrum of Alkenylidene Bisphenols

no.	MIC, μg/mL: *E. coli* (ATCC 10536)	*Ps. aeruginosa* (ATCC 23619-2)	*Candida albicans* (ATCC 10231)
6	16	200	25
13	~200	>200	>200
15	100	>200	>200
17	88	>200	>200
1 (hexachlorophene)	100	~200	

systems in that olefinic series retains activity with a wide range of substituents. While it is attractive to sieze upon the possible conjugation of the two phenol rings or of the styryl system to explain these differences, this speculation is not borne out by either ultraviolet spectrometry or chemical reactivity evidence.

The ultraviolet spectrum of 2,2′-methylenebis(4-chlorophenol) (dichlorophene) shows λ_{max} 293 nm, a value to be expected if the two phenol rings are essentially insulated from one another; 4-chloro-*o*-cresol has λ_{max} 292 nm. The spectrum of **6** shows only a small bathochromic shift, λ_{max} 298 nm, a value appreciably smaller than anticipated if conjugation were important in stabilizing a conformation of the molecule. Whether conjugation of one ring with the vinyl group is appreciable is uncertain, due to the unknown effect of the vinylic chlorines on the position of the absorption maximum.

Comparison of the chemical reactivity of dichlorophene and **6** further militates against conjugation of the phenol rings. Under comparable conditions (see Experimental Section), the two compounds give the same ratio of mono- to dinitration (*o*,*o*′) products.[7] One would anticipate that, if conjugation were substantial in **6**, introduction of the first nitro group would deactivate both rings sufficiently to alter this ratio to favor the mononitration product.

Experimental Section

General. Reagents and solvents were of reagent grade and were used without further purification. Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Ultraviolet spectra were determined in ethanol solution using a Perkin-Elmer Model 124 spectrophotometer. Infrared spectra were recorded from KBr pellets on a Perkin-Elmer Model 21 spectrometer; spectra for all new compounds were consistent with the assigned structures. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.; analyses reported in Table I were within 0.4% of theory, except as noted.

Alkenylidene Bisphenols. Method A. 1,1-Dichloro-2,2-bis(5-chloro-2-hydroxyphenyl)ethylene (6). 1,1,1-Trichloroethylidenebis(4-chlorophenol) (**2**) was prepared as described.[3] To 300 mL of a 1 M solution of sodium hydroxide in methanol was added 19.25 g (50 mmol) of **2**, and the mixture was refluxed for 2 h. The cooled solution was concentrated at reduced pressure and was poured into 600 mL of water. After stirring for several hours, the mixture was filtered, and the filtrate was recovered and acidified to pH 1. The solid which precipitated was collected and was dried. This mixture of **5** and **6** was purified by chromatography on silica. Elution with dichloromethane afforded the crude **6**; crystallization of the product afforded 6.5 g (37%) of a colorless powder, mp 172–174 °C.

1,1-Dichloro-2,2-bis(5-bromo-2-hydroxyphenyl)ethylene (7). The compound was prepared by the above method. Condensation of 4-bromophenol and chloral gave 1,1,1-trichloroethylidenebis(4-bromophenol), mp 158–161 °C (benzene), in 69% yield. Dehydrochlorination as described afforded **7** in 10% yield, mp 180–182 °C (benzene–hexane).

1,1-Dichloro-2,2-bis(2-hydroxy-5-methylphenyl)ethylene (8). The compound was prepared by the above method. Condensation of *p*-cresol and chloral gave 1,1,1-trichloroethylidenebis(4-methylphenol), mp 147–150 °C (benzene–hexane), in 17% yield. Dehydrochlorination as described afforded 6% of **8**, mp 150–152 °C (hexane).

1,1-Dichloro-2,2-bis(5-chloro-2-hydroxy-3-methylphenyl)ethylene (10). The compound was prepared by the above method. Condensation of 4-chloro-2-methylphenol and chloral gave 1,1,1-trichloroethylidenebis(4-chloro-2-methylphenol), mp

180–182.5 °C (benzene–hexane), in 46% yield. Dehydrochlorination as described afforded 40% of **10**, mp 196–197 °C (benzene). The material crystallized with 0.33 mol of benzene.

1,1-Dibromo-2,2-bis(5-chloro-2-hydroxyphenyl)ethylene (17). The compound was prepared by the above method. Condensation of 4-chlorophenol with tribromoacetaldehyde gave 10% of 1,1,1-tribromoethylidenebis(4-chlorophenol), mp 162–165.5 °C (benzene–hexane). The compound was dehydrobrominated by the method described in 52% yield to give **17**, mp 162.5–164 °C (benzene).

Method B. 1,1-Dichloro-2,2-bis(5-*tert*-butyl-2-hydroxyphenyl)ethylene (9). Using the procedure of Miville,[3] 3.0 g (18 mmol) of 4-*tert*-butylanisole was condensed with 0.89 mL (9 mmol) of chloral. The reaction was quenched with methanol, and this solution was poured into ice–water. The mixture was extracted with ether. The ether solution was dried ($MgSO_4$), and the solvent was removed. There was obtained 1.74 g (42%) of colorless solid, mp 142–145 °C.

The above product (1.0 g, 2.2 mmol) was refluxed for 16 h with 20 mL of 3 N methanolic potassium hydroxide. The reaction was quenched with water, and the solid product was collected and dried. There was obtained 0.88 g (96%) of a colorless, chromatographically homogeneous solid, which was used immediately.

The solid obtained above was dissolved in 10 mL of CCl_4. The solution was chilled to −20 °C and was treated with boron tribromide (0.55 mL, 6.2 mmol). When the addition was complete, the mixture was warmed to room temperature and was stirred until TLC showed that the starting material had been consumed. The solution was quenched with 1 N HCl, and the product was isolated in dichloromethane. The solvent was removed and the residue was purified by chromatography on silica. Elution with dichloromethane afforded 0.13 g (15%, based on the condensation product) of **9**, mp 169–170 °C.

1-Chloro-2,2-bis(5-chloro-2-hydroxyphenyl)ethylene (18). The compound was prepared by the above method. Condensation of *p*-chloroanisole with dichloroacetaldehyde acetal gave the adduct, mp 171.5–173.5 (lit.[5] mp 172–174 °C) in 82% yield. Dehydrochlorination proceeded in 83% yield to give the bisanisylethylene, mp 113.5–114.5 °C. The phenol was regenerated in 30% yield, mp 150–152 °C.

1,1-Dichloro-2,2-bis(5-chloro-2-hydroxy-3-nitrophenyl)ethylene (11) and 1,1-dichloro-2-(5-chloro-2-hydroxyphenyl)-2-(5-chloro-2-hydroxy-3-nitrophenyl)ethylene (12). A solution of 10.0 g (28.6 mmol) of **6** in 175 mL of benzene and 175 mL of glacial acetic acid was heated to 45 °C. To the stirred solution was added dropwise 6.9 g (28.5 mmol) of cupric nitrate trihydrate in 70 mL of acetic acid. When the addition was complete, the solution was stirred an additional several hours and then poured into 300 mL of water, and the layers were separated. The organic layer and two benzene extracts of the aqueous layer were washed with water, and the solvent was removed. The residual orange oil was purified by chromatography on silica. Elution with dichloromethane afforded 1.7 g (14%) of **11**, mp 171–172 °C (hexane). Continued elution afforded 5.0 g (45%) of **12**, an amorphous solid, mp 88–94 °C.

1,1-Dichloro-2-(5-chloro-2-hydroxyphenyl)-2-(3-amino-5-chloro-2-hydroxyphenyl)ethylene (13). To a solution of stannous chloride dihydrate (2.62 g, 11.6 mmol), ethanol (40 mL), and concentrated hydrochloric acid (10 mL) was added 1.0 g (2.5 mmol) of **12**. The mixture was refluxed for 16 h, and the solvent was removed in vacuo. The residue was dissolved in boiling ethanol and was filtered with charcoal. The product was precipitated with water and was collected. There was obtained 0.33 g (36%) of **13**, mp 188–189 °C.

1,1-Dichloro-2-(5-chloro-2-hydroxyphenyl)-2-[5-chloro-3-(hexanoylamino)-2-hydroxyphenyl]ethylene (14). Compound **13** (0.5 g, 1.26 mmol) was suspended in 100 mL of 0.5 N sodium bicarbonate, and the pH was adjusted to 9.5 with normal sodium hydroxide. With vigorous stirring, hexanoyl chloride (1.76 mL) was added. Stirring was continued, and the pH was maintained at 10 by addition of sodium hydroxide. After stirring overnight, the mixture was acidified and was extracted with several portions of ether. The combined ether extracts were washed with sodium bicarbonate and dried, and the solvent was removed. The residue was taken up in 0.05 N sodium hydroxide, and the mixture was stirred and heated until solution was complete. The cooled mixture was acidified and the solid product was collected. Recrystallization from benzene–hexane afforded 0.08 g (13%) of **14**, mp 80–82 °C.

1,1-Dichloro-2-(5-chloro-2-hydroxyphenyl)-2-(3-bromo-5-chloro-2-hydroxyphenyl)ethylene (15). To a solution of **6** (1.4 g, 4 mmol) and 20 mL of glacial acetic acid was added portionwise 0.22 mL (4.2 mmol) of bromine over a period of 1 h. The solution was stirred overnight and was then quenched with water containing a small amount of sodium bisulfite. The white precipitate was collected, washed with water, and dried. Recrystallization from benzene afforded 1.5 g (87%) of **15**, mp 150–152 °C.

1,1-Dichloro-2-(5-chloro-2-hydroxyphenyl)-2-(3-allyl-5-chloro-2-hydroxyphenyl)ethylene (16). A mixture of **6** (3.7 g, 10.6 mmol), potassium carbonate (1.6 g, 11.6 mmol), and 50 mL of acetone was treated with 1.0 mL (11.6 mmol) of allyl bromide. The solution was refluxed briefly and then stirred at room temperature for 40 h. The mixture was diluted with dichloromethane and washed with dilute sodium hydroxide solution. The organic layer was dried ($MgSO_4$), and the solvent was removed to give an oil. Chromatography on silica (4:1 hexane–ether) gave 3.5 g of the substantially pure allyl ether of **6**.

The ether obtained above was dissolved in 60 mL of *N,N*-dimethylaniline, and the solution was refluxed for 20 h. The cooled solution was poured into 6 N HCl and was extracted into dichloromethane. The organic solution was extracted with sodium hydroxide, and the aqueous layer was acidified. The acid solution was extracted with dichloromethane, the organic layer was dried, and the solvent was removed. Chromatography of the residue on silica gave the product, mp 156–158.5 °C. Recrystallization of this material from carbon tetrachloride gave 390 mg (9.5%, based on **6**) of **16**, mp 159.5–161 °C.

Antibacterial Assay. The compounds were pulverized in a ball mill (Vibramill, Beckman Instruments) and stock suspensions were prepared by ultrasonically dispersing 2.00 mg of the powder in 5.00 mL of sterile, normal saline. Twofold serial dilutions were prepared in saline, with additional sonication where indicated to maintain even suspension of the drug. Incubation flasks (250 mL) were charged with 9.0 mL of sterile growth medium 1[8] and 0.5 mL of drug suspension, to give a test series with drug concentrations ranging from 200 μg/mL downward to a level appropriate for the determination. All drugs appeared to be in solution at the concentrations tested, as judged by a lack of turbidity in the broth, except for **9**. The flasks were then inoculated with 0.5 mL of a 10^4 dilution of an overnight culture of *Staphylococcus aureus* ATCC 6538-P, which had been diluted and regrown to 90 units on a Klett–Summerson photometer. This inoculum is approximately 10^4 organisms per milliliter in the assay broth.

The flasks were incubated under ambient air at 32 °C with rocking for 24 h. The MIC was taken as the concentration at which no growth was apparent to the eye. The test was repeated at least three times; replicate determinations were usually within a factor of 2 of the others.

The same protocol was used with the organisms listed in Table II, with appropriate modifications in medium and growth conditions as recommended.[8] The culture dilution was also modified to assure inocula of 10^4 organisms per milliliter in all cases.

References and Notes

(1) Address correspondence to this author: Department of Chemistry, Tougaloo College, Tougaloo, Miss. 39174.
(2) For a review of bisphenol toxicology, see W. S. Gump and G. R. Walter in "Disinfection, Sterilization, and Preservation", C. A. Lawrence and S. S. Block, Eds., Lea and Febiger, Philadelphia, 1968, pp 257–277.
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