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BACTERICIDAL PHENOLIC INVERT SOAPS[1]

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INTRODUCTION

In the capillary-active and water-soluble "invert soaps" containing a free phenolic hydroxyl group reported previously by Niederl and Abbruscato (1) and Bruson (2), the bactericidal action was reduced almost to the vanishing point. The decreased bactericidal activity (3) was believed due to the fact that the phenolic nucleus was attached directly to the quaternary ammonium nitrogen. Proceeding on this assumption, a new series of "phenolic invert soaps", having a halogenated, alkylated phenolic nucleus removed from the quaternary nitrogen by an aryloxy polyalkylene ether side chain was prepared. In the new series, it was believed that theoretically improved antibacterial activity should result, since the phenolic and quaternary ammonium functional groups would be separated sufficiently by the polyalkylene ether bridge to act more independently, and to effect an intramolecular synchronization of desirable properties.

The starting point for the synthesis of the new series of "phenolic invert soaps" was 4-($\alpha,\alpha,\gamma,\gamma$-tetramethyl)butyl-1,3-dihydroxybenzene, or 4-*tt*-octylresorcinol (I), described initially by J. B. Niederl and co-workers (4, 5). A number of derivatives of I, including nitro, benzoyl, and halo compounds, were prepared. One of the most important of these is 6-chloro-4-*tt*-octylresorcinol (II), which was obtained by chlorinating the initial compound I with sulfuryl chloride in carbon tetrachloride solution. This halogenated alkylresorcinol was found to be a powerful germicide (phenol coefficients, 625 against *Staph. aureus*, and 100 100 against *E. coli*). In addition compound II was found to possess low toxicity in spite of its potent antiseptic, bactericidal and fungicidal properties. 6-Chloro-4-*tt*-octylresorcinol was characterized further by the preparation of a number of derivatives, including the monobenzoyl (II a) and the methylene-bis (II b) derivatives.

Most outstanding of the derivatives of II are the ring-halogenated, phenolic, cationoidic capillary-active and highly bactericidal "invert soaps". These are prepared by treating II with β,β'-dichlorodiethyl ether in an aqueous alkaline medium according to the method of Bruson (6, 7) to form 6-chloro-4-($\alpha,\alpha,\gamma,\gamma$-tetramethyl)butyl-1-hydroxy-3-phenoxyethoxyethyl chloride (III). On treating the phenolic chloro ether (III) with various tertiary amines at 160–180°, the corresponding quaternary ammonium salts, N-3-[6-chloro-4-($\alpha,\alpha,\gamma,\gamma$-tetramethyl)butyl-1-hydroxy]phenoxyethoxyethyl ammonium salts are formed

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TABLE I

DERIVATIVES OF 4-*tt*-OCTYLRESORCINOL

NO.	COMPOUND	MP (°C.)	BP (°C.)	FORMULA	% CARBON		% HYDROGEN		% NITROGEN		% HALOGEN	
					Calc'd	Found	Calc'd	Found	Calc'd	Found	Calc'd	Found
I	4-*tt*-Octylresorcinol	107–108	215–220 20 mm.	$C_{14}H_{22}O_2$	75.62	75.57	9.98	10.11				
Ia	Monobenzoate (1-benzoyl)	170–171.5		$C_{21}H_{26}O_3$	77.27	77.33	8.03	8.24				
Ib	Dibenzoate	146–147.5		$C_{28}H_{30}O_4$	78.11	78.31	7.02	7.24				
Ic	Di-(*p*-nitrobenzoate)	154–155.5		$C_{28}H_{28}N_2O_8$	64.60	64.59	5.42	5.82	5.38	5.60		
Id	1-Benzoyl-6-nitro deriv.	202–203		$C_{21}H_{25}NO_5$	67.88	67.77	6.78	7.00	3.77	3.93		
Ie	1-Benzoyl-2,6-dinitro deriv.	124–125		$C_{21}H_{24}N_2O_7$	60.57	60.78	5.81	6.20	6.72	6.95		
If	1-Benzoyl-6-bromo deriv.	143–144.5		$C_{21}H_{25}BrO_3$	62.22	61.94	6.22	6.21			19.72	20.01
Ig	6-Nitro deriv.	142–143		$C_{14}H_{21}NO_4$	62.90	62.71	7.92	7.84	5.25	5.30		
II	6-Chloro deriv.	88–89		$C_{14}H_{21}ClO_2$	65.48	65.12	8.24	7.92			13.81	13.77
IIa	3-Benzoyl-6-chloro deriv.	147–148.5		$C_{21}H_{25}ClO_3$	69.89	69.93	6.98	7.04			9.83	9.54
IIb	Methylene-bis-6-chloro deriv. or [2,2′,6,6′-tetrahydroxy, 3,3′-dichloro-5,5′-di-(*tt*-octyl)diphenylmethane]	186–187.5		$C_{29}H_{42}Cl_2O_4$	66.27	66.64	8.06	8.15			13.49	13.90
III	1-Hydroxy-4-*tt*-octyl-6-chloro-3-phenoxyethoxyethyl chloride	87–88	175–205 3 mm.	$C_{18}H_{28}Cl_2O_3$	59.50	59.75	7.77	7.77			19.52	20.10
IV	N-(1-Hydroxy-4-*tt*-octyl-6-chloro-3-phenoxy-ethoxy ethyl)N,N-dimethyl-N-β-hydroxyethyl-ammonium chloride	120–122		$C_{22}H_{39}Cl_2NO_4$					3.10	3.35		
V	N-[1-Hydroxy-4-*tt*-octyl-6-chloro-3-phenoxyethoxyethyl]-N-methyl-morpholinium chloride	80–82		$C_{23}H_{39}Cl_2NO_4$					3.07	3.17		
VI	N-[1-Hydroxy-4-*tt*-octyl-6-chloro-3-phenoxyethoxyethyl]-N-ethyl morpholinium chloride	83–85		$C_{24}H_{41}Cl_2NO_4$					2.92	2.55		

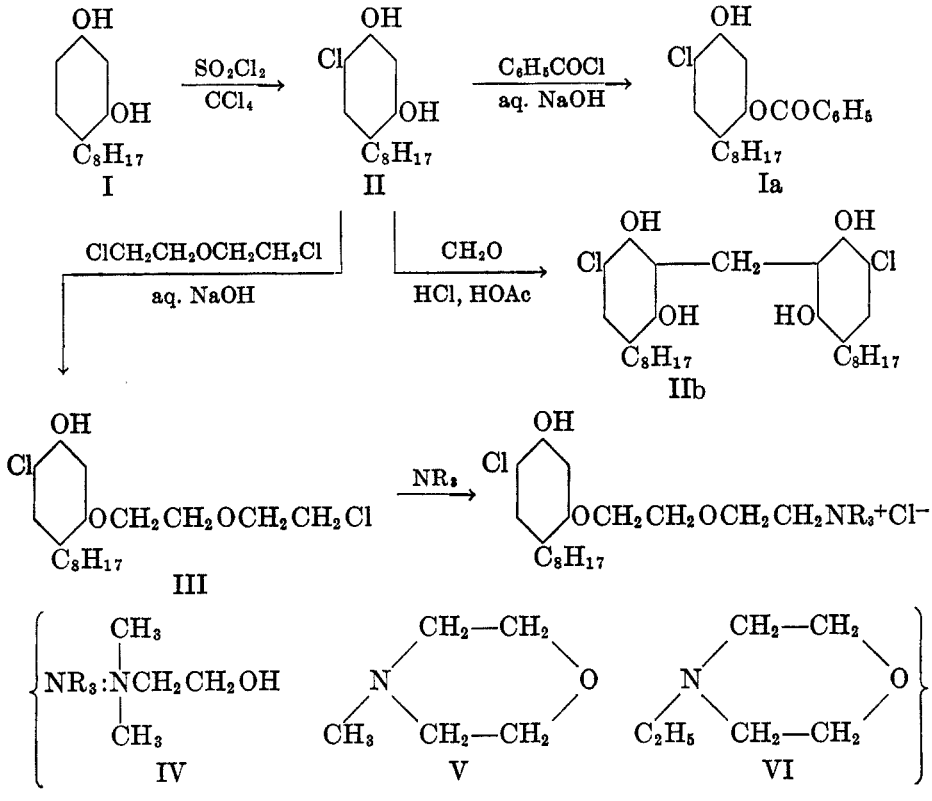
TABLE II

BACTERIOLOGICAL REPORTS

These tests were run according to the F.D.A. Method at 20°C.

NO.	COMPOUND	PHENOL COEFFICIENT	
		E. typhosa	Staph. aureus
I	4-*tt*-Octylresorcinol	31	500
Ig	6-Nitro-4-*tt*-octylresorcinol	20	67
II	6-Chloro-4-*tt*-octylresorcinol	100	625
IV	N-[3-(6-Chloro-4-*tt*-octyl-1-hydroxy)phenoxyethoxy-ethyl]-N,N-dimethyl-N-β-hydroxyethylammonium chloride	200	166
V	N-[3-(6-Chloro-4-*tt*-octyl-1-hydroxy)phenoxyethoxy-ethyl]-N-methylmorpholinium chloride	160	133
VI	N-[3-(6-Chloro-4-*tt*-octyl-1-hydroxy)phenoxyethoxy-ethyl]-N-ethylmorpholinium chloride	160	133

CHART A



N,N-Dimethylethanolamine, N-methylmorpholine, and N-ethylmorpholine were treated with III to produce the respective ammonium and morpholinium salts (IV, V, VI). The synthesis of the new "phenolic invert soaps" and some intermediates is represented schematically as in Chart A.

EXPERIMENTAL

4-tt-Octylresorcinol (I) (4, 5, 8). *A.* One mole (112 g.) of diisobutylene (b.p. 101–103°) was added to 50 cc. of glacial acetic acid and the resulting solution was cooled below 15°. With constant stirring, 98 g. of sulfuric acid diluted by 50 cc. of glacial acetic acid was added slowly to the first solution. The temperature was maintained below 15° during the process. The resulting cooled mixture was added, while stirring, to a solution of one mole (110 g.) of resorcinol in 110 cc. of glacial acetic acid, the temperature being maintained below 15°. After the addition, the stirring was continued for two hours. A pink solution resulted, which was allowed to come slowly to room temperature and then to stand for about 24 hours at room temperature. The reaction mixture was poured into 500 cc. of cold water, and 40 g. of sodium hydroxide was added under cooling. The lower, deeply colored layer was separated, washed with sodium carbonate solution, then water, and finally dried in ether solution with calcium chloride. The ether was evaporated, and the oily residue was fractionally distilled *in vacuo*. The fraction distilling 200° to 225° at a pressure of about 20–24 mm. was collected. The distillate appeared as a yellow oil which crystallized to a white solid on standing; crude yield about 40%. On repeated recrystallization of the product from petroleum ether, long white crystalline needles, melting 106–108°, were obtained (5).

Anal. Calc'd for $C_{14}H_{22}O_2$: C, 75.62; H, 9.98.
Found: C, 75.57; H, 10.11.

B. One mole (112 g.) of diisobutylene and one mole (110 g.) of resorcinol were well mixed with an efficient stirrer until a paste-like consistency was effected (4, 8). At this point, a few drops of concentrated sulfuric acid was added. The temperature rose spontaneously to about 70°, and the mixture became oily. An additional 3 g. of sulfuric acid was added and the mixture was stirred vigorously for about one to two hours, while the mixture cooled and set into a solid mass. After allowing the solid mass to stand for about 4 hours, it was broken up into small pieces, boiled and stirred with 1 liter of water to remove water-soluble impurities. The oily product was washed with hot water several times and then dried. On recrystallization from petroleum ether 4-*tt*-octylresorcinol was obtained in good yield (40 to 60%).

1-Benzoyl-4-tt-octylresorcinol (Ia). The preparation of the monobenzoate involved the Schotten-Baumann reaction in an aqueous sodium hydroxide medium (9). The 4-*tt*-octylresorcinol (I) (22 g., 0.1 mole) was suspended in 100 cc. of 10% aqueous sodium hydroxide solution. To this mixture was added, in small portions, with constant stirring, 14 g. (0.1 mole) of benzoyl chloride. The reaction mixture was warmed gently, with stirring, on a steam-bath and was then permitted to stand for about 30 minutes. The reaction product separated initially as an oil, but solidified after being washed with water and standing. The benzoate was purified in an ethereal solution, where it was washed with 5% aqueous sodium carbonate solution and water and dried. After removing the ether by distillation *in vacuo*, the oily residue was dissolved in a benzene-petroleum ether mixture, from which fine, white crystalline platelets of the benzoate, m.p. 170–171.5° were obtained on recrystallization.

Anal. Calc'd for $C_{21}H_{26}O_3$: C, 77.27; H, 8.03.
Found: C, 77.33; H, 8.24.

4-tt-Octylresorcinol dibenzoate (Ib). By treating 4-*tt*-octylresorcinol (I) (22 g., 0.1 mole) with 2 molar equivalents (28 g.) of benzoyl chloride in anhydrous pyridine (100 cc.) the dibenzoate was found to be the principal product (10, 11). The reactants were mixed and refluxed for 30 minutes. The reaction mixture was cooled and poured into 250 cc. of 2% aqueous sulfuric acid. The product precipitated as a white oil which solidified on standing. It was purified by solution in ether, where it was washed with 5% sodium carbonate solution and water, and dried with calcium chloride. On evaporation of the ether, the residual oil was crystallized from 95% alcohol. On recrystallization of the white crystalline platelets from the same solvent, the dibenzoate Ib, m.p. 146–147.5°, was isolated. By dilution of the 95% alcoholic mother liquor with water, some of the monobenzoate Ia was also obtained.

Anal. Calc'd for $C_{28}H_{30}O_4$: C, 78.11; H, 7.02.
Found: C, 78.31; H, 7.24.

4-tt-Octylresorcinol di-(p-nitrobenzoate) (Ic). 4-*tt*-Octylresorcinol (5.0 g., 0.022 mole) and *p*-nitrobenzoyl chloride (8.2 g., 0.044 mole) were condensed in 15 cc. of anhydrous pyridine in a manner described in the previous preparation (Ib). The crude product was worked up as described above, and was recrystallized from a mixture of ether (3 parts) and ethanol (1 part). The purified di-(*p*-nitrobenzoate) Ic appeared in the form of very light, greenish white crystals, m.p. 154–155.5°.

Anal. Calc'd for $C_{28}H_{28}N_2O_8$: C, 64.60; H, 5.42; N, 5.38.
Found: C, 64.59; H, 5.82; N, 5.60.

1-Benzoyl-6-nitro-4-tt-octylresorcinol (Id). With gentle heating 33 g. (0.1 mole) of 4-*tt*-octylresorcinol monobenzoate (Ia) was dissolved in 500 cc. of glacial acetic acid. After cooling the solution to about 30°, 30 cc. of a nitration mixture consisting of 43% aqueous nitric acid (*d* 1.2) was slowly added, with constant stirring, so that the temperature did not rise above 38–40° (9). When all the nitrating agent was added, yellow crystals of the reaction product began to separate from the solution. The reaction mixture was allowed to stand for 30 minutds, was cooled and filtered. The crystals were washed with water, and recrystallized from an acetic acid-water mixture, and finally from a small volume of 95% alcohol in the form of colorless, crystalline platelets, m.p. 202–203°.

Anal. Calc'd for $C_{21}H_{25}NO_5$: C, 67.88; H, 6.78; N, 3.77.
Found: C, 67.77; H, 7.00; N, 3.93.

1-Benzoyl-2,6-dinitro-4-tt-octylresorcinol(Ie). After filtering the mononitro compound Id from the reaction mixture in the above preparation, the clear filtrate was poured into a mixture of ice and water, which caused an orange oil to precipitate. The oil was dissolved in ether, where it was washed with water, dried with calcium chloride, and treated with Norit. On evaporation of the ether, a yellow crystalline compound was obtained by recrystallization of the residue from petroleum ether. The product (Ie) gave the correct analysis for the dinitro compound, m.p. 124–125°.

Anal. Calc'd for $C_{21}H_{24}N_2O_7$: C, 60.57; H, 5.81; N, 6.72.
Found: C, 60.78; H, 6.20; N, 6.95.

1-Benzoyl-6-bromo-4-tt-octylresorcinol (If). To a solution of 6.4 g. (0.02 mole) of 4-*tt*-octylresorcinol monobenzoate (Ia) in 50 cc. of glacial acetic acid was added 2 cc. of bromine diluted with 25 cc. of glacial acetic acid in small portions (9). The reaction mixture finally assumed a permanent red-orange color and was permitted to stand for 30 minutes after all of the brominating agent was added. It was poured into 10 times its volume of a dilute aqueous sodium bisulfite solution. The bromo compound separated as a white solid, and was filtered, washed with water, and dried. The dry material was recrystallized from a mixture of benzene (small volume) and petroleum ether (excess). The purified bromo compound (If) appeared in the form of white crystalline needles, m.p. 143–144.5°.

Anal. Calc'd for $C_{21}H_{25}BrO_3$: C, 62.22; H, 6.22; Br, 19.72.
Found: C, 61.94; H, 6.21; Br, 20.01.

6-Nitro-4-tt-octylresorcinol (Ig). Was prepared by the hydrolysis of 6-nitro-4-tt-octylresorcinol monobenzoate (Id). Ten grams (0.03 mole) of Id was dissolved in 250 cc. of 10% alcoholic potassium hydroxide solution and the resulting solution was refluxed for 2 hours. The alkaline solution was acidified with 10% hydrochloric acid solution and extracted with ether. The ethereal extracts were combined and washed with water, and dried with calcium chloride. On evaporation of the ether, the residual oil solidified on standing, and was recrystallized from petroleum ether in the form of a pale yellow-green crystalline powder, m.p. 142–143°.

Anal. Calc'd for $C_{14}H_{21}NO_4$: C, 62.90; H, 7.92; N, 5.25.
Found: C, 62.71; H, 7.84; N, 5.30.

6-Chloro-4-tt-octylresorcinol (II). One mole (222 g.) of 4-*tt*-octylresorcinol (I) was dissolved in 1 liter of carbon tetrachloride and chlorinated with a chlorinating agent, consisting of 142 g. (1 mole + 5% excess) of sulfuryl chloride plus about 1.5 g. of sulfur chloride as a catalyst (12, 13, 14, 15). The chlorinating agent was added dropwise slowly to the carbon tetrachloride solution of I at an oil-bath temperature of 100–120°, after five grams of

aluminum chloride was added to the reaction mixture as an additional chlorine carrier. When all of the chlorinating agent was added, the time requiring about 1 hour, the reaction mixture was allowed to reflux an additional 2 hours. On cooling to room temperature, the reaction mixture was washed with water to remove all water soluble impurities. The carbon tetrachloride layer was separated, and to it was added an excess of ether. The resultant solution was dried with calcium chloride. The solvent was removed by distillation *in vacuo* and the residual, dark brown, oily product was purified by distillation at 2 to 4 mm. The fraction distilling at 140–160° (bath temperature, 190–210°) was collected. The distillate, a light yellow oil, solidified on standing to a white crystalline mass, yield about 50%. It was recrystallized from petroleum ether as white crystalline needles of 6-chloro-4-*tt*-octylresorcinol, m.p. 88–89°.

Anal. Calc'd for $C_{14}H_{21}ClO_2$: C, 65.48; H, 8.24; Cl, 13.81.
Found: C, 65.12; H, 7.92; Cl, 13.77.

3-Benzoyl-6-chloro-4-tt-octylresorcinol (IIa). 6-Chloro-4-*tt*-octylresorcinol monobenzoate (IIa) was prepared by treating 26 g. (0.1 mole) of 6-chloro-4-*tt*-octylresorcinol with 14 g. (0.1 mole) of benzoyl chloride in a 10% aqueous sodium hydroxide solution, as in the preparation of 4-*tt*-octylresorcinol monobenzoate (Ia). The purified material was recrystallized from a small volume of benzene plus an excess of petroleum ether. A white crystalline powder, m.p. 147–148.5°, was obtained.

Anal. Calc'd for $C_{21}H_{25}ClO_3$: C, 69.89; H, 6.98; Cl, 9.83.
Found: C, 69.93; H, 7.04; Cl, 9.54.

Methylene bis-(6-chloro-4-tt-octylresorcinol), or (2,2',6,6'-tetrahydroxy-3,3'-dichloro-5,5'-di-tt-octyldiphenylmethane) (IIb). Twenty-six grams (0.1 mole) of 6-chloro-4-*tt*-octylresorcinol (II) was dissolved in 50 cc. of glacial acetic acid. To this solution was added 5 g. (0.05 mole + 5% excess) of formaldehyde solution (37%). To the resulting mixture was added 25 cc. of 15% aqueous hydrochloric acid. The reaction mixture was heated to a low boil for about 15 minutes and then allowed to cool. On pouring the mixture into water and ice, a red oil precipitated. The oil was dissolved in ether, washed with water, dried with calcium chloride, treated with Norit, and recrystallized from petroleum ether after evaporation of the ether. A white crystalline powder, melting 186–187.5°, was obtained. Microanalyses proved it to be the methylene bis derivative (IIb) of II.

Anal. Calc'd for $C_{29}H_{42}Cl_2O_4$: C, 66.27; H, 8.06; Cl, 13.49.
Found: C, 66.64; H, 8.15; Cl, 13.90.

6-Chloro-4-tt-octyl-1-hydroxy-3-phenoxyethoxyethyl chloride (III). One mole (257 g.) of 6-chloro-4-*tt*-octylresorcinol, four moles (562 g.) of β,β'-dichlorodiethyl ether, and one mole (42 g.) of 97% sodium hydroxide in 500 cc. of water, were placed in a large flask and heated under reflux at 100–120° for about 16 hours, under efficient stirring (6). At the end of the reaction period, the lower layer was separated, acidified and dissolved in ether. The ethereal solution was washed with water and dried with calcium chloride. On evaporation of the ether, the residual oily product was distilled at 4–5 mm. The main fraction distilled between 175–205°. The distillate appeared as a viscous, light yellow-orange oil, which produced crystals from petroleum ether. On recrystallization of the product from the same solvent, a white, crystalline powder, m.p. 87–88°, was isolated.

Anal. Calc'd for $C_{18}H_{28}Cl_2O_3$: C, 59.50; H, 7.77; Cl, 19.52.
Found: C, 59.75; H, 7.77; Cl, 20.10.

N-[3-(6-Chloro-4-tt-octyl-1-hydroxy)phenoxyethoxyethyl]-N,N-dimethyl-N-β-hydroxyethyl ammonium chloride (IV). A mixture of 36 g. (0.1 mole) of 6-chloro-4-*tt*-octyl-1-hydroxy-3-phenoxyethoxyethyl chloride (III) and 9 g. (0.1 mole) of dimethylethanolamine were heated under reflux in an oil-bath at 160–180° for 6 hours (7). On cooling, the reaction mixture set into a stiff, purple-colored, water-soluble mass. The crude product was dissolved in absolute ethanol and treated with Norit several times. Upon removal of the solvent by distillation *in vacuo*, a viscous, light brown oil was obtained. The oily product was extremely soluble in water and its aqueous solution exhibited excellent surface active properties. Further purification of the product was effected by dissolving it in dry acetone

and precipitating it with an excess of petroleum ether. The solution and reprecipitation treatment was repeated several times. The supernatant liquid was decanted, and the oil was triturated with petroleum ether until it became a waxy solid. A small portion of the waxy solid was recrystallized from a mixture of dry acetone and petroleum ether on long standing. Long crystalline needles of the dimethylethanolamine salt (IV) were isolated and dried on a porous plate in a vacuum desiccator; m.p. 120–122°.

Anal. Calc'd for $C_{22}H_{39}Cl_2NO_4$: N, 3.10. Found: N, 3.35.

N-[3-(6-Chloro-4-tt-octyl-1-hydroxy)phenoxyethoxyethyl]-N-methylmorpholinium chloride (V). A mixture of 36 g. (0.1 mole) of 6-chloro-4-*tt*-octyl-1-hydroxy-3-phenoxyethoxyethyl chloride and 10 g. (0.1 mole) of N-methylmorpholine was refluxed in an oil-bath at 160–180° for 6 hours (7). The reaction product was cleaned by dissolving it in anhydrous alcohol and treating the resultant solution with Norit several times. The solvent was removed by distillation *in vacuo*. The residual, light brown, oily product was found to be very water-soluble and to exhibit excellent surface active properties in aqueous solutions. Further purification was achieved by dissolving the oil in dry acetone and precipitating it with an excess of petroleum ether. The solution and reprecipitation procedure was repeated several times. The purified oil was then dried in a high vacuum oven at 60°. A crystalline mass melting around 80–82° was obtained.

Anal. Calc'd for $C_{23}H_{39}Cl_2NO_4$: N, 3.07. Found: N, 3.17.

N-[3-(6-Chloro-4-tt-octyl-1-hydroxy)phenoxyethoxyethyl]-N-ethylmorpholinium chloride (VI). A mixture of 36 g. (0.1 mole) of 6-chloro-4-*tt*-octyl-1-hydroxy-3-phenoxyethoxyethyl chloride and 12 g. (0.1 mole) of N-ethylmorpholine was treated and worked up as described in the previous preparation. A crystalline mass melting around 83–85° was formed.

Anal. Calc'd for $C_{24}H_{41}Cl_2NO_4$: N, 2.92. Found: N, 2.55.

PHARMACOLOGICAL

Preliminary tests indicate that 4-*tt*-octylresorcinol and 6-chloro-4-*tt*-octylresorcinol are relatively non-toxic. Doses up to 1.0 gram of the drug were administered to dogs weighing 10 to 20 pounds without any noticeable gross toxic disturbances. Cows, weighing about 1200 pounds, were given doses as high as 30 grams a day for four days (120 grams) without any gross toxic symptoms being noted.

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SUMMARY

New phenolic compounds derived from 4-($\alpha,\alpha,\gamma,\gamma$-tetramethyl)butyl-1,3-dihydroxybenzene, or 4-*tt*-octylresorcinol have been synthesized and characterized; these include, among others, 6-chloro-, 6-bromo-, 6-nitro, 2,6-dinitro-, mono- and di-benzoyl-4-*tt*-octylresorcinols. One of the most outstanding of these compounds is the highly bactericidal and relatively non-toxic 6-chloro-4-*tt*-octylresorcinol, which was characterized with monobenzoyl and methylene-bis derivatives. A very significant fact was the discovery that the highly desirable antibacterial properties of the halogenated alkylresorcinol were found to be

carried over into a new series of ring-halogenated, phenolic, cationoidic, capillary-active and bactericidal quaternary ammonium salts derivatives, namely, 3-[6-chloro-4-(α,α,γ,γ-tetramethyl) butyl-1-hydroxy] phenoxyethoxyethyl substituted ammonium and morpholinium salts, where an intramolecular synchronization of desirable properties is effected. Bacteriological tests have shown these compounds to possess high phenol coefficients (100 to 200) against both gram-positive and gram-negative organisms.

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