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Alkyl Mercury Derivatives

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Alkylmercuric hydroxides react with acids to give salts. Koten and Adams[1] have studied certain reactions of these compounds and have shown that ethylmercuric hydroxide would react with 2,4,6-trinitrobenzoic acid to give the corresponding salt. The present research was undertaken to study the products formed by the reaction of alkylmercuric hydroxides with phenolic compounds and to evaluate their bacteriological properties.

Waldo[2] has prepared some water-soluble mercury compounds by interaction of alkyl mercuric halides with thiophenols containing acid groups. These possessed marked bacteriological properties.[3] Some alkyl mercury compounds of phenols[4] have been described which are sufficiently water soluble to make them suitable for the study of antiseptic value. In the present work the properties of a number of such compounds have been investigated and the highest inhibiting dilutions for *Staphylococcus aureus* determined.

Alkylmercuric hydroxides are used because the halides do not react directly with phenols as they do with thiophenols. Alkylmercuric halides have been made by many methods.[5] From these the hydroxides can be obtained by treating with alcoholic sodium hydroxide[6] or moist silver oxide.[7]

A large number of phenols have been tried. Some amino compounds like anthranilic acid and sulfanilic acid were found to react similarly to phenols. Attempts were made to bring about reactions with aniline, *p*-chloro-*o*-aminoanisole, piperidine, chlorobenzene, benzene and benzoic acid, but no products were isolated.

Mercury compounds of phthaleins in which mercury is attached to carbon have been studied by various workers.[8] As no compounds of this type with mercury attached to oxygen have been described, a few representative ones were prepared and studied.

(1) Koten and Adams, THIS JOURNAL, **46**, 2764 (1924).
(2) Waldo, *ibid.*, **53**, 992 (1931).
(3) Waldo, Shonle and Powell, *J. Bact.*, **21**, 323 (1931).
(4) British Patent 329,987, Feb. 26, 1929.
(5) Whitmore, "Organic Compounds of Mercury," Chemical Catalog Co., New York, 1921.
(6) Slotta and Jacobi, *J. prakt. Chem.*, **120**, 249 (1929).
(7) (a) Sneed and Maynard, THIS JOURNAL, **44**, 2942 (1922); (b) Hinkel and Augel, *J. Chem. Soc.*, 1948 (1927).
(8) White, THIS JOURNAL, **42**, 2355 (1920); Dunning and Farinholt, *ibid.*, **51**, 804 (1929).

The analyses were carried out by decomposing with 30% hydrogen peroxide and sulfuric acid, and titrating with potassium thiocyanate as mentioned by Tabern and Shelberg.[9] Halogen containing compounds were analyzed by iodine titration for mercury, or by halogen determination.

In carrying out the bacteriological tests,[10] it was noted that few were actually bactericidal, but the bacteriostatic properties were quite high. The technique employed was the F. D. A. method with transfers at 37°. It was found important to make additional transfer tests since there often was no detectable growth in the forty-eight hour incubation period due to inhibition by the small quantity of antiseptic carried over in the original transplants. The second transfer tubes usually showed a growth indicating that the action was entirely bacteriostatic. The test organism used was *Staphylococcus aureus*. The highest inhibiting dilutions varied, but did not seem to depend on the structure of the phenol used nor on the length of the alkyl side chain.

Table I gives the analytical data and bacteriological results.

Experimental

Alkylmercuric Iodide.—Mercury dialkyl was made from alkyl iodide and sodium amalgam by the usual method.[5] It was not isolated, however, but added directly to a warm solution of alcohol containing the calculated quantity of mercuric iodide. After decanting from the metallic mercury and filtering hot, the solution was cooled and practically pure alkyl mercuric iodide precipitated.

Alkylmercuric Hydroxide.—Alkyl mercuric iodide in alcohol was treated with moist silver oxide by the method of Sneed and Maynard.[7a] The hydroxide was not isolated but used in concentrated alcoholic solution.

Ethylmercury Phenoxide.—A slight excess of a concentrated alcoholic solution of ethylmercuric hydroxide was filtered into a warm solution of phenol in a small volume of alcohol. On cooling, ethylmercury phenoxide precipitated. It was recrystallized from alcohol in white well-formed crystals.

The other compounds were prepared in the same manner. They were easily crystallized but most of them darkened on exposure to light for some time. They dissolved in practically all instances to give 0.1% aqueous

(9) Tabern and Shelberg, *Ind. Eng. Chem., Anal. Ed.*, **4**, 401 (1932).
(10) We are indebted to Dr. J. F. Norton, Bacteriological Laboratory, The Upjohn Company, for these results.

TABLE I

RHgOH	Compound with RHgOH	M. p., °C.	Yield, %	Hg analyses, % Calcd.	Found	Inhibiting dilution to *Staph. aureus* in 5 min.
Ethyl	Salicylic acid	75–76	77	54.6	54.3	1–20,000[c]
Ethyl	*p*-Hydroxybenzoic acid	177–178	77	54.6	54.7	1–20,000
Ethyl	Phenol	115–116	62	62.1	62.0	1–10,000
Ethyl	α-Naphthol	78–79	68	53.7	53.5	1–10,000
Ethyl	*m*-Cresol	54.5–55.5	60	59.5	59.8	1–20,000
Ethyl	Resorcinol	191–192[a]	70	70.6	70.3	1–10,000
Ethyl	Resorcinol monomethyl ether	72–73	55	56.7	56.9	1–10,000
Ethyl	*p*-Hydroxydiphenyl	139–140	54	50.3	50.3	1–20,000
Ethyl	*p,p'*-Dihydroxydiphenyl	201–203	69	62.3	61.7	1–20,000
Ethyl	*p*-Hydroxymethyl benzoate	85.5–86.5	60	52.6	52.2	1–10,000
Ethyl	Triiodophenol	169–170	92	28.5	28.2	.....
Ethyl	Tribromophenol	107	62	35.7	34.3	1–5,000
Ethyl	Trichlorophenol	60–61	86	47.0	46.9	1–10,000
Ethyl	*o*-Bromophenol	98–99	93	49.8	50.0	1–5,000
Ethyl	*p*-Bromophenol	98–99[b]	87	49.8	49.4	1–10,000
Ethyl	Chlorocyclohexylphenol	79.5–80.5	42	45.6	45.0	1–10,000
Ethyl	4-Chloro-2-phenylphenol	101–102	66	46.2	46.9	1–5,000
Ethyl	Vanillin	100–101	84	52.7	52.2	1–10,000
Ethyl	4-Hydroxy-3-nitrotoluene	89–90	68	52.4	52.4	1–10,000
Ethyl	*o*-Nitrophenol	76–77	75	54.4	54.8	1–10,000
Ethyl	*p*-Nitrophenol	122–123	75	54.4	53.9	1–10,000
Ethyl	Chlorothymol	81–82	51	48.0	47.1	1–10,000
Ethyl	Anthranilic acid	81–82	..	54.8	54.5	1–10,000
Ethyl	Sulfanilic acid	.....	..	49.8	49.4	1–10,000
Ethyl	2-Chloro-5-hydroxytoluene	77.5–78.5	71	Cl 9.6	Cl 9.9	1–10,000
Ethyl	*p*-Chlorophenol	108	85	Cl 9.9	Cl 9.0	1–10,000
Ethyl	*o*-Chlorophenol	83–84	71	Cl 9.9	Cl 9.2	1–10,000
Methyl	Resorcinol	.....	..	74.3	73.9	1–20,000
Methyl	Salicylic acid	119–120	..	56.8	56.7	1–15,000
Methyl	*m*-Cresol	84–86	21	62.1	61.7	1–15,000
Propyl	Resorcinol	161–162	65	67.3	67.0	1–10,000
Propyl	Salicylic acid	75	94	52.6	52.7	1–10,000
Propyl	*m*-Cresol	61–62	60	55.5	55.0	1–20,000
Butyl	Resorcinol	148	45	64.3	63.7	1–20,000
Butyl	Salicylic acid	51–52	61	50.7	50.5	1–20,000
Butyl	*m*-Cresol	.....	..	53.4	53.9	1–10,000
Amyl	Resorcinol	132.5–133.5	53	61.5	61.0	1–10,000
Amyl	Salicylic acid	46–47	48	49.0	48.5	1–15,000
Hexyl	Resorcinol	128–129	57	58.9	58.2	1–5,000
Ethyl	Phenolphthalein	198–199	96	50.1	50.6	1–10,000
Ethyl	*o*-Cresolsulfonephthalein	128–131	80	47.7	47.7	1–10,000
Ethyl	Phenolsulfonephthalein	118–121	87	49.4	49.6	1–10,000
Ethyl	Thymolsulfonephthalein	145–155	78	43.4	43.4	1–10,000

[a] The same compound was obtained with resorcinol monoacetate.

[b] A mixed melting point with the *o*-bromophenol derivative was depressed to 66.5°.

[c] For comparison, phenol is bactericidal 1–80.

solutions for bacteriological examination. The more insoluble ones were used in 25% alcohol solutions. Acid and alkalies brought about hydrolysis. Ferric chloride produced the same color as the original phenols. The water solutions, however, are not hydrolyzed as most of the compounds may be crystallized from water. The phthalein compounds did not crystallize from alcohol, but were obtained pure for analysis by distilling the alcohol from a diluted alcoholic solution. The products settled out as solids as the solutions became more concentrated. They appeared as reddish powders on drying.

Summary

A number of phenolic mercury compounds have been prepared and studied in which mercury is linked to oxygen.

With the R—Hg—O—R′ structure, variations in the R and R′ have a very limited influence on the bacteriostatic properties of the resulting compounds.

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