precaution which we have found necessary is to wrap the filter with asbestos paper if it is to be heated to a high temperature in a vacuum. This protection should also be used to provide slow cooling for a hot filter.

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SOME NEW WATER-SOLUBLE ORGANO-MERCURY COMPOUNDS[1]

BY JOHN H. WALDO

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Introduction

The application of organo-metallic compounds in the therapeutic field too often has been limited by their insolubility in water. Organic mercury compounds having the mercury attached to a carbon atom have had considerable use in therapy, especially as germicidal agents, although the introduction of the —HgX group into an organic molecule tends to make the resulting compound insoluble in water. When mercury compounds are rendered soluble in water or dilute alkali solutions through the introduction of a sulfonic or carboxylic acid group, they generally become less toxic but undergo a marked reduction in their germicidal activity. However, if nitrogen-containing groups are introduced to give the desired solubility, the germicidal activity is retained, but they are many times more toxic than the group which contains an acid radical.

In 1922, Kharasch[2] developed a method whereby organo-metallic compounds can be made water soluble by condensing them with mercapto-carboxylic or sulfonic acids.

When mercurials of the type RHgX, where X is an inorganic radical, react with a mercapto acid, HSR′, where R′ is a group containing an alkyl or aryl carboxylic or sulfonic acid, a double decomposition occurs

$$RHgX + HSR' = RHgSR' + HX$$

The new compound RHgSR′ is soluble in sodium bicarbonate solution and forms with the alkali metals soluble salts whose solutions are in general stable and do not give an immediate precipitate of mercuric sulfide with ammonium sulfide.

[1] A portion of this paper was presented before the division of Medicinal Products at the Detroit meeting of the American Chemical Society, September, 1927, by M. S. Kharasch, H. A. Shonle, and John H. Waldo.

[2] M. S. Kharasch, U. S. Patent 1,589,599, reissue 16,921.

Kharasch and Chalkley[3] showed that variations in the degree of electronegativity of the organic radical will produce a marked effect on the degree of ionization of mercury as evidenced by the readiness with which mercuric sulfide is formed when compounds are treated with hydrogen sulfide or ammonium sulfide. It should therefore be possible to prepare predetermined mercuri-carbon compounds possessing various degrees of lability of the mercury.

The stability of these new compounds depends upon two factors, first, the stability of the R—Hg linkage and second, the S—R′ linkage. In regard to the former it could be predicted from the work of Kharasch and Marker,[4] that the higher homologs in the alkyl series would be more stable than the lower members and that aryl groups would be less stable than alkyl or alkaryl groups. Such a prediction proved to be true in this instance. The sulfur atom is quite strongly electronegative and it would therefore be predicted that an electronegative group, such as an aromatic nucleus, attached to it, would tend to produce a greater stability than less electronegative groups, such as those of the straight-chain aliphatic series. Experimental work confirmed this hypothesis.

Experimental Part

Preparation of Organo Mercury Halides.—The various alkyl and aryl mercury halides used in this investigation were prepared by the Grignard reaction. In carrying out these reactions, two reflux systems were used, designed to filter the Grignard reagent without contact with air. The flask containing mercuric chloride in ether was connected by a glass tube extending to the bottom of the Grignard reaction flask. At the completion of the original reaction the Grignard reagent was forced into the second flask by compressed air. The end of the connecting tube was covered with 200-mesh silk bolting cloth to act as a filter.

Preparation of Mercapto Acids.—All of the mercapto acids used in this investigation have been described previously in the literature. Two general methods were used, the first according to Schacht and of Duvillier,[5] which consisted in treating the desired aliphatic halogen substituted acids with potassium hydrogen sulfide in alcohol solution; and the second as outlined by Leuchart,[6] which involves the formation of the xanthogen ester, by treating the desired diazonium salt with potassium ethyl xanthate. This hydrolyzed to the mercapto acid in about 60–70% yield. If, however, the initial precipitate of the crude acid is dissolved in excess alkali and reduced by boiling with zinc dust, the yield is frequently increased to 90%.

Preparation of the Salts of Organo Mercuri-mercapto Acids.—As

[3] M. S. Kharasch and L. Chalkley, Jr., THIS JOURNAL, **46**, 1211 (1924).

[4] M. S. Kharasch and R. Marker, *ibid.*, **48**, 3130 (1926).

[5] C. Schacht, *Ann.*, 129, 1 (1864); E. Duvillier, *Bull. soc. chim.*, 30, 507 (1878).

[6] R. Leuchart, *J. prakt. Chem.*, [II] **41**, 179 (1890).

indicated above, the condensation of organo mercury salts with the mercapto acids proceeds very quickly and smoothly in a dilute alcoholic sodium hydroxide solution.

In carrying out the synthesis it was more convenient to use two moles of alkali instead of one, thus initially obtaining the water-soluble sodium salt. The water-insoluble acids are precipitated by acidification and purified by crystallization from alcohol or acetone.

Methyl Mercurithiosalicylic Acid, (o-$CH_3HgSC_6H_4COOH$).—Forty grams of methyl mercuric iodide (0.12 mole) is moistened with 20–30 cc. of 95% ethyl alcohol and to this is added 96 cc. of 10% sodium hydroxide solution (0.24 mole). This solution is then added to a 95% ethyl alcohol solution of 18 g. of thiosalicylic acid (0.12 mole). The solution is filtered, and methylmercurithiosalicylic acid precipitates by acidification with 10% sulfuric acid. Crystallization from 50 cc. of 95% ethyl alcohol gives an 80–85% yield. It is a white crystalline compound melting at 174°,[7] soluble in alcohol, ether and acetone, but insoluble in water and acid.

Anal. Subs., 0.2237: CO_2, 0.2135; H_2O, 0.0408. Calcd. for $C_8H_8O_2SHg$: C, 26.09; H, 2.17. Found: C, 26.01; H, 2.03. Subs., 0.2500: 13.2 cc. of $N/10$ KSCN. Calcd.: Hg, 54.34. Found: Hg, 52.95.

Ethyl Mercurithiosalicylic Acid, (o-$C_2H_5HgSC_6H_4COOH$).—Ethyl mercuric chloride and thiosalicylic acid are combined by an identical method, giving a white crystalline solid melting at 111°.

Anal. Subs., 0.2950: CO_2, 0.3077; H_2O, 0.0714. Calcd. for $C_9H_{10}O_2SHg$: C, 28.27; H, 2.63. Found: C, 28.40; H, 2.68. Subs., 0.2000: 10.45 cc. of $N/10$ KSCN. Calcd.: Hg, 52.41. Found: Hg, 52.40.

p-Ethyl Mercuri-mercaptobenzoic Acid, (p-$C_2H_5HgSC_6H_4COOH$).—Ethylmercuric chloride and p-mercaptobenzoic acid are combined by an identical method giving a white crystalline solid which does not melt up to 250°.

Anal. Subs., 0.2570: CO_2, 0.2718; H_2O, 0.0575. Calcd. for $C_9H_{10}O_2SHg$: C, 28.27; H, 2.63. Found: C, 28.84: H, 2.49. Subs., 0.3000: 15.6, 15.8 cc. of $N/10$ KSCN. Calcd.: Hg, 52.41. Found: Hg, 52.14, 52.82.

Isoamyl Mercurithiosalicylic Acid, (o-iso-$C_5H_{11}HgSC_6H_4COOH$).—Isoamyl mercuric chloride and thiosalicylic acid are combined by an identical method giving a white crystalline solid melting at 78°.

Anal. Subs., 0.2720: CO_2, 0.3321; H_2O, 0.0883. Calcd. for $C_{12}H_{16}O_2SHg$: C, 33.95; H, 3.77. Found C, 33.30; H, 3.60. Subs., 0.3000: 14.25 cc. of $N/10$ KSCN. Calcd.: Hg, 47.19. Found: Hg, 47.63.

Several additional products were made, but due to small amounts of reagents low yields were obtained. It seemed more desirable to ascertain their germicidal value and sacrifice a complete chemical analysis. There-

[7] All melting points taken with a standardized thermometer and corrected for stem exposure.

fore, only mercury assays were made. In view of the fact, however, that identical methods were used and that they were purified by crystallization to constant melting points, it is reasonable to assume the structure of all is the same.

TABLE I

COMPOUNDS, CONSTANTS AND ANALYTICAL DATA

Acid, ( ) = mercuri	M. p., °C.	Formula	Mercury analyses, % Calcd.	Found
Phenyl ()-thiosalicylic	228.5 (dec.)	$C_{13}H_{10}O_2SHg$	46.57	46.63 46.79
Benzyl ()-thiosalicylic	144.5 (dec.)	$C_{14}H_{12}O_2SHg$	45.04	45.12 44.95
α-Ethyl ()-mercaptobutyric	76	$C_6H_{12}O_2SHg$	57.47	56.66
p-Ethyl ()-mercaptophenylacetic	116.7	$C_{10}H_{12}O_2SHg$	50.50	50.30 50.39
p-Ethyl ()-mercaptobenzenesulfonic	Above 300	$C_8H_{10}O_3S_2Hg$	47.84	46.67

All compounds are white crystalline solids. Mercury analyses by the potassium thiocyanate method.

p-Ethyl Mercuri-mercaptobenzenesulfonic Acid, (p-$C_2H_5HgSC_6H_4SO_3H$.—Five grams of ethyl mercuric chloride dissolved in 20–30 cc. of warm 95% ethyl alcohol is added to 3.6 g. of p-mercaptobenzenesulfonic acid in an equal volume of alcohol. A precipitate starts forming in a few minutes. After standing for two to three hours at room temperature, the precipitate is recovered and dried.

Discussion

It is not the purpose of this paper to outline any bacteriological test. However, some indication of the change in toxicity and germicidal effect may be obtained from an examination of the values for the sodium salts of the above compounds. Disregarding other factors, the best germicide in any series should combine the lowest toxicity with the highest bactericidal value. A therapeutic index may be obtained by the product of these values, and if sodium ethyl mercurithiosalicylate be given the value one, a representative ratio of indices is given. The germicidal values were obtained by a slight modification of the technique outlined by Reddish,[8] by using undiluted horse serum for the diluent. The data and therapeutic index are given in Table II.

The table indicates that the alkaryl mercuri derivatives are less toxic than the aryl, that salts of carboxylic acids are less toxic than sulfonic acids, that some decrease in the index is produced by a change from the ortho to the para position on the benzene ring,[9] and by alkyl instead of alkaryl derivatives. Further, it has been observed that alkyl compounds are decidedly less stable, either in solution or dry than alkaryl products.

The benzyl mercurithiosalicylic acid described above was not obtained in sufficient quantity to obtain authentic figures on toxicity, but its germi-

[8] G. F. Reddish, *Am. J. Pub. Health*, **17**, 320–329 (1927).

[9] The meta derivative, which has been prepared in about 94% purity, gives data in agreement with this conclusion.

TABLE II

THERAPEUTIC INDICES

Compounds	Toxicity to rats, M. L. D. in mg. per kg.	Bactericidal dilutions *B. typhosus*	Bactericidal dilutions *Staph. Aureus*	Index *B. Typhosus*	Index *Staph. Aureus*
o-$CH_3HgSC_6H_4COONa$	40	1–2000	1–4000	0.533	0.80
o-$C_2H_5HgSC_6H_4COONa$	50	1–3000	1–4000	1.0	1.0
o-$C_5H_{11}HgSC_6H_4COONa$	60	1–2000	1–3000	0.80	0.90
o-$C_6H_5HgSC_6H_4COONa$	15	1–1000	1–1000	.10	.075
p-$C_2H_5HgSC_6H_4COONa$	100	1–1000	1–1000	.667	.50
p-$C_2H_5HgSC_6H_4CH_2COONa$	100	1–1000	1–2000	.667	1.0
$C_2H_5HgSCH(COONa)CH_2CH_3$	80	1–1000	1–1000	.533	0.40
p-$C_2H_5HgSC_6H_4SO_3Na$	25	1–1000	1–1000	.167	.125

cidal values were sufficiently low to indicate the influence of the aryl group on toxicity and its probable low index.

The writer is indebted to Dr. G. H. A. Clowes and H. A. Shonle for many suggestions connected with the preparation of these compounds and to R. M. Lingle for the mercury assays.

Summary

1. Nine new organo-mercury compounds have been prepared.
2. In water solution their sodium salts are desirable germicides.
3. A therapeutic index indicates that an alkaryl combination is the most stable and germicidal type.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF PURDUE UNIVERSITY]

ACYL DERIVATIVES OF ORTHO-AMINOPHENOL. VI

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When diacyl derivatives of *o*-aminophenol were prepared in the past by the usual methods, it was found in most cases that the order of introduction of the two different acyl groups has no influence upon the formation of the diacyl, identical products being isolated from the two acylations. The position of the acyl groups of the molecule can be determined by removing the group attached to the oxygen by saponification with dilute alkali, and determining from the physical constants of the remaining monoacylated product the group attached to the nitrogen. The identical diacyls mentioned above were found to saponify to yield identical products, as would be expected.

The formation of identical rather than isomeric products on reversing the order of acylation indicates that during acylation a rearrangement must have occurred in one of the two cases. It has been found that certain