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2-Alkylmercurithiopyridine-5-Carboxylic Acids*,†

Preparation of, and Stability of Their Solutions

By Lewis A. Walter and Russel J. Fosbinder

INTRODUCTION

In 1922 Kharasch (1) and Vieth (2) described some mercury compounds prepared by reacting a mercurial of the type R Hg X with a mercapto acid of the type R′ S H where R′ is a group containing an alkyl or aryl carboxylic or sulfonic acid. The resulting compounds, having the general formula R Hg S R′ Ac could be dissolved in solutions of sodium bicarbonate or alkali metal hydroxides. Later Kharasch (3) applied the same general method to the preparation of alkylmercurithio compounds more stable in character and suitable for medicinal application.

The preparation, antiseptic efficiency and toxicity of a series of alkyl derivatives were reported by Waldo (4) in 1931. One derivative, ethylmercurithiosalicylate, has since found widespread use as an external antiseptic.

Alkylmercurimercapto compounds, in general, when dissolved in aqueous solutions in the form of their alkali metal salts acquire medicinally undesirable properties, presumably as a result of the splitting-off of the alkylmercuri radical at the sulfur linkage, due to the oxidation of the mercapto compound or residue to the disulfide form. Although oxidation proceeds slowly at room temperature, in the presence of minute concentrations of certain metal ions, such as copper, iron and manganese acting as metallic catalysts, the normal oxidation is accelerated, resulting in marked deterioration over a period of several days. Kharasch (5) was able to stabilize aqueous solutions of these compounds by the addition of small amounts of aliphatic amines and diamines, the latter type of compound being most effective.

This paper describes alkylmercuri derivatives of 2-mercaptopyridine-5-carboxylic acid. Stability tests carried out at room temperature and at 60° C. on aqueous solutions of sodium 2-ethylmercurithiopyridine-5-carboxylate indicate that compounds of this type are substantially resistant to oxidation, even in the presence of metal ion catalysts.

EXPERIMENTAL

PREPARATION OF 2-ALKYLMERCURITHIOPYRIDINE-5-CARBOXYLIC ACIDS

An excess of alkylmercuric chloride, prepared by the Grignard reaction (6), was added to an alkaline alcoholic solution of 2-thiopyridine-5-carboxylic acid. After refluxing for 1 hour the solution was concentrated to one-half volume, diluted with water and filtered. The mercury compound was then precipitated with acetic acid and recrystallized from alcohol.

The compounds were analyzed for mercury by oxidizing with fuming nitric and sulfuric acids, then with permanganate, and titrating with potassium thiocyanate.

STABILITY OF SOLUTIONS

Oxidation Tests.—Stock solutions of the mercury compounds were prepared by dissolving 2 Gm. of the alkylmercurithiopyridine carboxylic acid in the theoretical quantity of 1% sodium hydroxide solu-

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† From the Research Laboratories of The Maltbie Chemical Company.

Table I.—Melting Points and Mercury Contents of Alkylmercuri Derivatives of 2-Mercaptopyridine-5-Carboxylic Acid

Derivative	M. P., ° C.	Formula	Per Cent Mercury Calcd.	Found
2-Ethylmercuri	250 decomp.	$C_8H_9O_2NSHg$	52.22	52.14
2-*n*-Propylmercuri	210 decomp.	$C_9H_{11}O_2NSHg$	50.45	50.28
2-*n*-Butylmercuri	190 decomp.	$C_{10}H_{13}O_2NSHg$	48.69	48.42

tion and diluting to 1 liter. Unless otherwise noted, a solution of this concentration was always employed in making up the test solution, the final concentration of the mercury compound being 1 Gm. in 1000 cc. Double distilled water prepared by a method similar to that described in the N. F. VI (7) was employed as the solvent.

Aliquot portions of the test solution were sealed in clean ampuls and either heated at 60° C. or permitted to stand at room temperature (ca. 25°) for the observation period. At the proper time the ampuls were opened and appropriate samples, generally 5 cc., withdrawn for analysis. Initially a series of experiments was carried out in which oxygen was bubbled through the solutions contained in the ampuls, but no appreciable acceleration of deterioration was observed as compared to those ampuls containing air above the liquid. Consequently all of the data reported in this paper were obtained on solutions having an atmosphere of air above them during the test period.

A quantitative measure of the deterioration, due to oxidation, of the mercapto compounds was obtained by titrating samples, acidified with hydrochloric acid, with *N*/200 iodine. In preliminary experiments it was found that exactly one equivalent of iodine was necessary to oxidize one molecule of alkylmercurithiopyridine compound to the disulfide acid.

Results.—The observations reported in Tables II and III show the apparent stability of sodium 2-ethylmercurithiopyridine-5-carboxylate in aqueous solution, and in the presence of metal ion catalysts usually effective in promoting the oxidation of mercapto compounds.

From the extent of deterioration of the mercuri compound in the absence of a catalyst and in the presence of ethylene diamine which was added as an additional stabilizer it seems justifiable to assume that a large part of the small loss is due to some factor other than catalytic oxidation. It is to be noted from Table III that the concentration of copper ion was increased to 1:50,000. This concentration of Cu ion was employed in order to obtain a maximal effect for copper. From the observations of Elliott (8) on the catalytic oxidation of cysteine and thioglycolic acid it may be assumed, however, that in so far as copper is concerned a 1:1,000,000 concentration is sufficient for a catalytic maximum.

For the purpose of comparing the stability of 2-ethylmercurithiopyridine-5-carboxylic acid with a related compound, ethylmercurithiosalicylate was prepared according to the procedure described by Waldo (4). A solution of the sodium ethylmercurithiosalicylate was made up by dissolving 1 Gm. of the free acid in the calculated amount of 1% sodium hydroxide solution, adding 1.4 Gm. of sodium borate, 1.0 Gm. of sodium chloride, sufficient copper sulfate to yield a copper ion concentration of 1:1,000,000 and diluting to 1 liter. Aliquot parts of the solution were sealed in glass ampuls, one sample allowed to stand at room temperature for 163 hours, a second sample heated at 60° C. for a period of 237 hours, while a third sample, to which 1% of ethylene diamine had been added, was similarly treated. On titrating the test solutions at the end of the experiment the extent of oxidation was found to be 51, 96 and 0.0 per cent, respectively. From Table I it is seen that the thiopyridine salt, under

Table II.—Stability of a 1:1000 Solution of 2-Ethylmercurithiopyridine-5-Carboxylic Acid (in Form of Sodium Salt) at 60° C.

Buffered solutions contain: sodium borate 0.14%; sodium chloride 0.10%

Solution	Catalyst	Per Cent Oxidized after Heating 237 Hours	405 Hours	573 Hours
Unbuffered p_H 11.0	None	3.82	6.88	7.63
Buffered p_H 8.8	None	4.96	6.88	6.50
Buffered p_H 8.8	Mn 1×10^{-6}	2.67	5.35	3.43
Buffered p_H 8.8	Fe 1×10^{-6}	0.00	2.29	0.00
Buffered p_H 8.8	Cu 1×10^{-6}	4.96	9.92	12.20
Buffered p_H 8.8 1% $C_2H_4(NH_2)_2$	Cu 1×10^{-6}	4.58	8.41	9.94

Table III.—Stability of a 1:1000 Solution of 2-Ethylmercurithiopyridine-5-Carboxylic Acid (Sodium Salt) at Room Temperature

Solution	Catalyst	Per Cent Oxidized After— 13 Weeks	39 Weeks	70 Weeks	96 Weeks
Unbuffered p_H 11.0	None	0.37	1.88	3.39	3.01
*Unbuffered p_H 11.0	None	0.00	1.56	3.84	5.76
Unbuffered p_H 11.0	Cu 1:50,000	0.00	3.76	11.65	9.77
Buffered p_H 8.8	None	0.00	1.50	3.75	0.37
Tincture	None	0.73	0.00	1.84	2.95

* Stored in an amber glass bottle.

the same experimental conditions, deteriorated only 4.9% as compared to 96% for the thiosalicylate compound.

Inhibition of Catalytic Oxidation by 2-Ethylmercurithiopyridine-5-Carboxylic Acid.—Since 2-ethylmercurithiopyridine-5-carboxylic acid resisted substantial catalytic oxidation for long periods of time at room and elevated temperatures it might be assumed that this compound forms a coördination complex, catalytically inert in character, with copper. If a catalytically inactive complex is formed between copper salts or ions and the mercapto pyridine compound then the latter should inhibit the catalytic oxidation of a mercapto compound susceptible to such action. To test this hypothesis a series of solutions, the compositions of which are indicated below, was prepared, placed in vials and heated at 60° C. At hourly intervals 5-cc. samples were withdrawn, chilled immediately and titrated with *N*/200 iodine solution.

Solution *A*—100 cc. contain:

Sodium ethylmercurithiosalicylate	0.05 Gm.
Sodium borate	0.14 Gm.
Sodium chloride	0.10 Gm.
Cu	0.10 mg.

Solution *B*—100 cc. contain:

Sodium ethylmercurithiosalicylate	0.05 Gm.
Sodium 2-ethylmercurithiopyridine-5-carboxylate	0.05 Gm.
Cu	0.10 mg.
Sodium borate	0.14 Gm.
Sodium chloride	0.10 Gm.

Solution *C*—100 cc. contain:

Sodium ethylmercurithiosalicylate	0.05 Gm.
Sodium 2-ethylmercurithiopyridine-5-carboxylate	0.05 Gm.
Sodium borate	0.14 Gm.
Sodium chloride	0.10 Gm.

Table IV.—Inhibition of Oxidation of Sodium Ethylmercurithiosalicylate by Sodium 2-Ethylmercurithiopyridine-5-Carboxylate. $t = 60°$ C.

Hours Heated	Per Cent Oxidation—Solution *A*	Solution *B*	Solution *C*
1	28.7	2.1	0.6
2	33.4	0.0	0.0
3	41.6	0.0	0.0
4	46.7	0.9	0.0
5	51.4	4.8	0.0

From the results it is seen, at least for the interval of time indicated, that 2-ethylmercurithiopyridine-5-carboxylic acid effectively prevented the catalytic oxidation of ethylmercurithiosalicylate, and therefore the copper ions must have been bound by complex formation with the thiopyridine compound. It should be observed that the complex formed in this instance is not of the type formed by other sulfhydryl compounds such as cysteine (9), glutathione, etc., with metal ion oxidation catalysts.

Sodium 2-thiopyridine-5-carboxylate does not form a catalytically inactive complex with metal ion catalysts for in the presence of Cu 1:1,000,000 a 1:1000 solution of this salt, heated at 60° C. for 1 hour, was oxidized 20%, and when heated at 60° C. for 237 hours over 96% was oxidized. In the absence of added copper this compound, similarly treated for 237 hours, deteriorated 85% and was therefore susceptible to autocatalytic action in the presence of atmospheric oxygen.

The addition of a number of pyridine compounds to solutions of sodium ethylmercurithiosalicylate containing Cu 1:1,000,000 exerted no action in inhibiting the oxidation of the compound. In these experiments pyridine, 2-aminopyridine, 2-pyridone and 2-mercaptopyridine were studied.

SUMMARY

1. The preparation of some new organic mercurials has been described.

2. Oxidation tests carried out on one of the compounds indicate that they are substantially resistant to catalytic oxidation.

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Note on the U. S. P. XI (Supplement II) Monograph on Cyclopropane*

By G. H. W. Lucas and V. E. Henderson

This Department has been studying the standards of purity for Cyclopropane for a year or more but did not make rapid progress until the Research Division of the Ohio Chemical Company kindly provided us with small cylinders of a specially purified cyclopropane, of methyl acetylene, propylene and allene. Our thanks are due to them for making this study possible.

In the preparation of cyclopropane several unsaturated gases might be formed, and indeed in various commercial samples as much as 2% or over of unsaturated com-

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