Summary

1. Ethyl 2-ethylmercapto-6-chloropyrimidine-5-acetate interacts with potassium thiocyanate to form first a normal thiocyanate. The latter easily undergoes a normal molecular rearrangement to give ethyl 2-ethylmercapto-6-isothiocyanopyrimidine-5-acetate.

2. Several derivatives of this isothiocyanate have been prepared by the action of amines and ethyl alcohol.

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The Alkyl Derivatives of Halogen Phenols and their Bactericidal Action. II. Bromophenols

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Introduction

Continuing the investigation of the bactericidal properties of the alkyl derivatives of halogen phenols[1] we prepared and studied a number of bromophenol homologs. A complete series of normal *o*-alkyl derivatives of *p*-bromophenol was synthesized comprising the compounds up to and including the 2-*n*-hexyl-4-bromophenol. We directed our attention primarily to the derivatives of *p*-bromophenol, since the exhaustive investigation of the two homologous series of *o*- and *p*-chlorophenol derivatives disclosed an antibacterial superiority of the *p*-chloro series over the *o*-chloro series in almost all instances. It was logical to assume that similar conditions would obtain in the group of bromophenol derivatives, and this opinion was borne out in certain individual test cases.

We were interested in determining the germicidal action of this series of compounds upon a number of representative resistant pathogenic microorganisms belonging to different bacteriological groups. On the basis of the previously observed group parallelism in the susceptibility of different microörganisms to the action of compounds of several homologous series of phenol derivatives,[2] the following test organisms were selected for the bacteriological evaluation of the bromophenol derivatives: the Gram-negative *Eberthella typhi*, the Gram-positive *Staphylococcus pyogenes aureus*, the acid-fast *Mycobacterium tuberculosis* (*hominis*) and the fungus *Monilia albicans*. The method of cultivating the microörganisms and of performing the tests will be described elsewhere.

(1) Klarmann, Shternov and Gates, THIS JOURNAL, **55**, 2576 (1933).

(2) Klarmann, "The Antibacterial Action of Certain Classes of Phenol Derivatives and Its Quasi-specific Character," paper presented before the section of Medicinal Chemistry of the American Chemical Society, Washington, March, 1933.

Bactericidal Action of Alkyl Bromophenol Derivatives.—Table I and Fig. 1 illustrate the relation between the chemical constitution of the compounds of this class and their germicidal action (expressed in terms of minimum germicidal concentrations effective in ten minutes at 37°, and of the "phenol coefficients" calculated therefrom). One observes at first an increase of germicidal power with the increasing weight of the substituting normal alkyl radical, a phenomenon common to different classes of homologous phenol and polyphenol derivatives. One encounters here, too, the "quasi-specific" effect of the higher homologs referred to in our preceding paper on chlorophenol derivatives. With respect to *Eberthella typhi*, the germicidal efficacy reaches its maximum with the *n*-butyl derivative, and declines thereafter with the *n*-amyl compound; it continues to rise with respect to the other three test organisms to considerable heights without the evidence of a maximum being reached in the case of the 2-*n*-hexyl-4-bromophenol, except perhaps with regard to *Monilia albicans*. If it is permitted to conclude by analogy with the conditions encountered among the alkyl chlorophenol derivatives, the rise of the curve for *Staphylococcus aureus* and *Mycobacterium tuberculosis* probably continues beyond the *n*-hexyl abscissa.

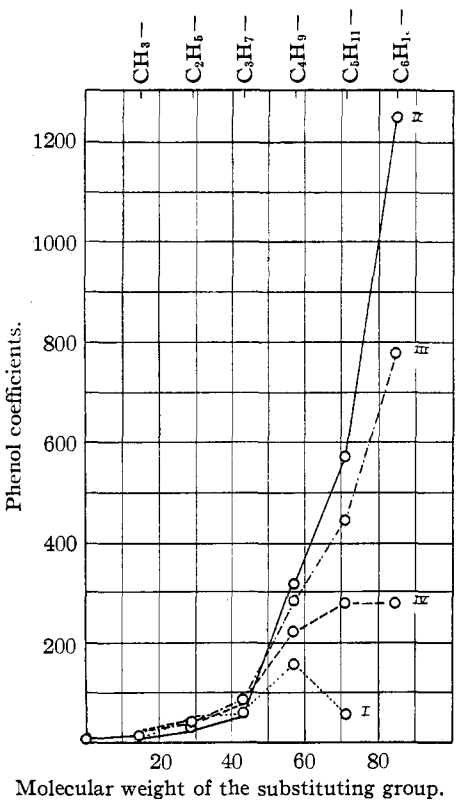

Fig. 1.—The germicidal action of *o*-alkyl derivatives of *p*-bromophenol. Test organisms: I....*Eberthella typhi;* II——*Staphylococcus pyog. aureus;* III·— — ·*Mycobacterium tuberculosis (hom.);* IV – – –*Monilia albicans.*

Considered *per se*, there are among the normal alkyl derivatives of *p*-bromophenol some highly effective agents whose bactericidal potency in the majority of cases compares favorably with or exceeds that of the corresponding chloro derivatives described in the preceding papers. Thus with respect to *Eberthella typhi*, the 2-*n*-butyl-4-bromophenol shows the greatest efficacy of the series. It surpasses that of 2-*n*-butyl-4-chlorophenol and approaches that of 2-*n*-amyl-4-chlorophenol. Against *Staphy-*

TABLE I

GERMICIDAL ACTION OF HOMOLOGOUS DERIVATIVES OF BROMOPHENOL

Minimum Concentrations Effective in 10 Min. (I) and Phenol Coefficients (II)

2-Alkyl derivatives of 4-bromophenol	*Eberthella typhi*		*Staphylococcus pyog. aureus*		*Mycobacterium tuberculosis (hom.)*		*Monilia albicans*	
	I	II	I	II	I	II	I	II
p-Bromophenol	1: 900	6.0	1: 400	5.0	1: 500	5.6	1: 500	6.3
Alkyl radicals								
Methyl	1: 2,000	12.5	1: 900	11.3	1: 1,200	13.3	1: 1,200	13.3
Ethyl	1: 5,000	31.3	1: 2,000	25.0	1: 2,500	27.8	1: 2,500	27.8
n-Propyl	1:10,000	62.5	1: 5,000	62.5	1: 7,000	77.8	1: 7,000	77.8
n-Butyl	1:25,000	156	1: 25,000	313	1:25,000	278	1:20,000	222
n-Amyl	1:10,000	625	1: 40,000	571	1:40,000	444	1:25,000	278
sec-Amyl	<1: 5,000	> 33	1: 12,000	150	1:14,000	156	1:12,000	150
n-Hexyl	....	...	1:100,000	1250	1:70,000	778	1:25,000	278
Cyclohexyl	<1: 3,500	> 23	1: 30,000	429	1:25,000	278	1:20,000	222
Alkyl derivatives of 2-bromophenol								
o-Bromophenol	1: 500	3.3	1: 250	3.1	1: 350	3.9	1: 300	3.8
Alkyl radicals								
4-*tert*-Amyl-	1: 5,000	33.3	1: 12,000	150	1:10,000	100	1: 7,000	77.8
4-*n*-Hexyl-	<1: 3,000	> 20	1: 50,000	625	1:50,000	556	1:20,000	222
4-*n*-Propyl-3,5-dimethyl-	indef.	indef.	1: 25,000	357	1:20,000	222	1:11,000	138
Phenol (control)	1:140–160	1	1: 70–80	1	1:90–100	1	1: 80–90	1

lococcus aureus, the *n*-butyl and *n*-amyl derivatives of *p*-bromophenol are more effective than those of *p*-chlorophenol, while the *p*-chloro and *p*-bromo derivatives of *o*-*n*-hexylphenol show practically the same efficacy. With respect to *Mycobacterium tuberculosis*, the entire series of *n*-alkyl-*p*-bromophenol derivatives surpasses the corresponding *p*-chlorophenol series.[2] As to *Monilia albicans*, the same is true of the members of the series up to and including the *n*-butyl derivative, while the opposite is true of the higher normal homologs studied.[2]

The effect of *o*-cyclohexyl-*p*-bromophenol upon *Staphylococcus aureus* and *Mycobacterium tuberculosis* is comparable to that of the corresponding chlorophenol derivative; it is lower with regard to *Monilia albicans*.

The comparison of the unsubstituted *p*-bromophenol with *o*-bromophenol discloses a bactericidal superiority of the former.[3] As might have been expected from the comparison of the bacteriological effects of the compounds of the *o*-alkyl-*p*-chloro series with those of the *p*-alkyl-*o*-chloro series,[1] which indicates a greater germicidal potency of the former, the 2-*n*-hexyl-4-bromophenol is a more potent germicide than the 4-*n*-hexyl-2-bromophenol.

4-*tert*-Amyl-2-bromophenol appears to be generally more effective than the corresponding chlorophenol derivative.

Finally, if it is remembered that the phenolic hydroxyl group is most likely to be concerned primarily in bringing about the germicidal effect, and that therefore one would be justified in placing the quantitative

(3) Klarmann, Shternov and Von Wowern, *J. Bacteriol.*, **17**, 427 (1929).

consideration of the relationship between chemical constitution and germicidal action upon a basis of molecular equivalents rather than upon one of simple weight relations, the conclusion is justified (disregarding some exceptions) that the introduction of one bromine atom into the nucleus of phenol and its homologs leads to more potent germicides than the entrance of a chlorine atom.

Note.—The comments expressed in our preceding paper as to a potential usefulness of some of the compounds described therein, in the chemotherapy of certain infections, seem to apply to the several substituted bromophenols as well.

The pharmacological investigation of the homologous bromophenol series is in progress at this time.

By way of advance published information, enough experimental material has been obtained by us to show that the "quasi-specific" germicidal effect of substituted chloro and bromophenols of higher molecular weight is not an isolated characteristic of the two series of compounds under consideration, but, rather that, it appears to be a general phenomenon, common to certain members of different classes of phenol and polyphenol derivatives.

Notes on the Preparation of the Substituted Bromophenols.—The methods employed in the preparation of the bromophenol derivatives correspond closely to those described in the preceding paper for the chloro compounds; *i. e.*, all *o*-*n*-alkyl derivatives (with the exception of the methyl compound) were prepared by the reduction of the corresponding bromohydroxyphenyl alkyl ketones, the latter having been obtained by intramolecular rearrangement of the corresponding bromophenyl esters.

The secondary amyl derivative was made by direct condensation of *p*-bromophenol with *n*-amyl alcohol in the presence of zinc chloride.

The *o*-methyl and *o*-cyclohexyl derivatives of *p*-bromophenol were prepared by direct bromination.

The same method was applied in introducing bromine in the *o*-position of the following alkyl phenol derivatives: 4-*tert*-amyl-, 4-*n*-propyl-3,5-dimethyl- and 4-*n*-hexylphenol.

Preparation of *o*-*n*-Alkyl Derivatives of *p*-Bromophenol. Example: Preparation of 2-*n*-Hexyl-4-bromophenol.—Caproyl chloride (47.8 g.) was added to 58 g. of *p*-bromophenol and the mixture allowed to stand overnight. It was treated with warm water, dried and distilled *in vacuo*. The pure *p*-bromophenyl caproate distilled at 139–140° at 2 mm.

This ester was rearranged to the corresponding 5-bromo-2-hydroxycaprophenone by means of anhydrous aluminum chloride; 75 g. of the ester and 36.3 g. of the aluminum chloride were heated in an oil-bath at 150–160° for thirty minutes. The mixture thus obtained was treated with cold water and dilute hydrochloric acid. The suspended precipitate was taken up in ether and the ether solution washed repeatedly with water. After evaporation of the solvent, the residue was recrystallized from isopropyl alcohol.

This 5-bromo-2-hydroxycaprophenone was reduced to the corresponding 2-*n*-hexyl-4-bromophenol by means of amalgamated zinc and 15% hydrochloric acid. The

product was purified by vacuum distillation. It solidified on standing and was recrystallized from heptane.

Preparation of Alkyl Derivatives of *o*-Bromophenol. Example: Preparation of 4-*tert*-Amyl-2-bromophenol.—*p*-*tert*-Amylphenol (41 g.) was dissolved in 100 cc. of carbon tetrachloride. To this a solution of 40.8 g. of bromine in 25 cc. of carbon tetrachloride was added drop by drop. The reaction mixture was allowed to stand overnight and was warmed gently the next morning. The solvent was removed by steam distillation, the residue was diluted with ether, washed with water and a solution of sodium bicarbonate, dried with sodium sulfate and, after removal of the ether, distilled in a vacuum.

Preparation of *o*-Isoalkyl Derivatives of *p*-Bromophenol. Example: Preparation of 2-*sec*-Amyl-4-bromophenol.—*p*-Bromophenol (86.5 g.), 83 g. of zinc chloride, 15 g. of concentrated hydrochloric acid and 31 g. of *n*-amyl alcohol were heated to mild boiling under reflux for two hours, whereupon a mixture of 62 g. of *n*-amyl alcohol and 5 g. of concentrated hydrochloric acid was allowed to flow in drop by drop. After gentle refluxing for another six hours the mixture was poured into ice-cold water. After addition

TABLE II

PHYSICAL AND ANALYTICAL DATA OF THE SUBSTITUTED BROMOPHENOLS AND THEIR INTERMEDIATES

2-Alkyl derivatives of 4-bromophenol	Formula	B. p., °C.	Mm.	M. p., °C.	Bromine, % Calcd.	Found
Methyl-[a]	$CH_3(2)Br(4)C_6H_3OH$	118–123	7	63.5		
Ethyl-	$C_2H_5(2)Br(4)C_6H_3OH$	110	3		39.76	40.17
n-Propyl-	n-$C_3H_7(2)Br(4)C_6H_3OH$	113–117	3	42.0	37.17	37.14
n-Butyl-	n-$C_4H_9(2)Br(4)C_6H_3OH$	125–127	2	43.5	34.89	34.41
n-Amyl-	n-$C_5H_{11}(2)Br(4)C_6H_3OH$	143–145	3	36	32.88	33.16
sec-Amyl-	*sec*-$C_5H_{11}(2)Br(4)C_6H_3OH$	134–138	4		32.88	32.69
n-Hexyl-	n-$C_6H_{13}(2)Br(4)C_6H_3OH$	150–152	4	53.6	31.09	31.36
Cyclohexyl-	cyclo-$C_6H_{11}(2)Br(4)C_6H_3OH$	167	5	43.8	31.34	31.39
Alkyl derivatives of 2-bromophenol						
4-*tert*-Amyl-	*tert*-$C_5H_{11}(4)Br(2)C_6H_3OH$	122	4		32.88	32.76
4-*n*-Propyl-3,5-dimethyl-	n-$C_3H_7(4)(CH_3)_2(3,5)Br(2)C_6HOH$			91.3	32.88	32.39
4-*n*-Hexyl-	n-$C_6H_{13}(4)Br(2)C_6H_3OH$	148	7		31.09	31.59
Ketones (intermediates) 5-bromo-2-hydroxy-						
Acetophenone[b]	$CH_3{\cdot}CO{\cdot}C_6H_3Br(5)OH(2)$			57.3	37.17	37.26
Propiophenone	$C_2H_5{\cdot}CO{\cdot}C_6H_3Br(5)OH(2)$			76.0	34.90	34.70
Butyrophenone	n-$C_3H_7{\cdot}CO{\cdot}C_6H_3Br(5)OH(2)$	127–132	3	53.6	32.89	32.61
Valerophenone	n-$C_4H_9{\cdot}CO{\cdot}C_6H_3Br(5)OH(2)$	127–136	2		31.10	31.56
Caprophenone	n-$C_5H_{11}{\cdot}CO{\cdot}C_6H_3Br(5)OH(2)$			60.5	29.49	29.38
Esters (intermediates), 4-bromophenyl-						
Acetate[c]	$CH_3CO_2{\cdot}C_6H_4Br(4)$	100	2		37.17	37.32
Propionate	$C_2H_5CO_2{\cdot}C_6H_4Br(4)$	113	3		34.90	35.41
Butyrate	n-$C_3H_7CO_2{\cdot}C_6H_4Br(4)$	112	2		32.89	33.98
Valerate	n-$C_4H_9CO_2{\cdot}C_6H_4Br(4)$	134–138	4		31.10	31.54
Caproate	n-$C_5H_{11}CO_2{\cdot}C_6H_4Br(4)$	139–140	2		29.49	29.93

[a] Previously prepared by Claus and Jackson, *J. prakt. Chem.*, [2] **38**, 324 (1888); Zincke and Hedenstroem, *Ann.*, **350**, 273 (1906); Goldschmidt, Schulz and Bernhard, *ibid.*, **478**, 1 (1930); Raiford and Couture, THIS JOURNAL, **44**, 1793 (1922).

[b] Previously prepared by Claus, German Patent 96,659 (1897); v. Kostanecki and Ludwig, *Ber.*, **31**, 2953 (1898); Feuerstein and Kostanecki, *ibid.*, **31**, 716 (1898).

[c] Previously prepared by Wohlleben, *ibid.*, **42**, 4374 (1909); Autenrieth and Muehlinghaus, *ibid.*, **40**, 746 (1907).

of ether the aqueous portion was discarded and the ethereal layer treated as in the preceding example.

Hydrochloric acid in zinc chloride condensation has been used by R. R. Read.[4]

In the bacteriological part of this work we were assisted by Mr. A. Grawehr of our laboratory staff, whose efficient collaboration is herewith gratefully acknowledged.

Summary

The investigation of the antibacterial properties of homologous halogen phenol derivatives is being continued. A number of alkylbromophenol derivatives were prepared and tested bacteriologically. Among them are a complete series of *o*-*n*-alkyl compounds of *p*-bromophenol up to the *n*-hexyl compound, the *o*-*sec*-amyl and the *o*-cyclohexyl derivatives of *p*-bromophenol and several para substituted *o*-bromophenol compounds, such as the *p*-*tert*-amyl-, *p*-*n*-hexyl- and *p*-*n*-propyl-*m*-dimethyl-derivatives of *o*-bromophenol.

Four pathogenic microörganisms were used in the bacteriological experiments, *viz.*, *Eberthella typhi*, *Staphylococcus pyogenes aureus*, *Mycobacterium tuberculosis* (*hom.*) and *Monilia albicans*. This selection of four representative test organisms was based on the observation of a "group-parallelism" in the susceptibility of a larger number of microörganisms to the action of the substituted halogen phenol derivatives; it implies a qualitative and quantitative similarity in the germicidal effect of the compounds in question upon the members of various groups of microörganisms such as the typhoid-colon group, the group of pathogenic cocci, the group of acid fast bacteria and the group of pathogenic fungi.

When tested with the aid of these microörganisms the substituted bromophenol derivatives were found to be strongly germicidal and to compare favorably in this respect with the chloro derivatives studied previously. As in the latter case the constitution of the molecule and the weight of the substituents not only influence the intensity of the germicidal action, but also determine the point at which the "quasi-specific" effect becomes apparent, *i. e.*, where the germicidal action of a given compound with respect to the Gram-negative *Eberthella typhi* (and also other organisms of the colon-typhoid group) declines or practically disappears while at the same time reaching very considerable heights with regard to pathogenic cocci (as represented by *Staphylococcus aureus*), acid-fast bacteria (represented by *Mycobacterium tuberculosis*) and pathogenic fungi (represented by *Monilia albicans*).

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(4) Read, U. S. Patent 1,887,662, Nov. 15, 1932.