Remove the drug from the percolator and expose it to air until dry and the odor of benzin is no longer noticeable. Extract this defatted drug by percolation, using a mixture of 4 volumes of alcohol and 1 volume of water as the menstruum, after macerating three days and then percolating slowly. Collect 920 cc. of percolate, add to this the glacial acetic acid and then dissolve the anhydrous sodium acetate in the mixture. Assay a portion of this liquid and dilute the remainder with sufficient of a solution composed of 80 cc. of alcohol, 20 cc. of water, 1 cc. of glacial acetic acid and 6 Gm. of anhydrous sodium acetate to conform to the above biological standard.

RESEARCH LABORATORIES OF PARKE, DAVIS & CO.,
DETROIT, MICH.

THE GERMICIDAL ACTION OF 2-CHLORO-4-*n*-ALKYLPHENOLS.*

BY F. F. BLICKE AND R. P. G. STOCKHAUS.[1,2]

During the last few years a considerable number of new phenolic germicides have been introduced as therapeutic agents—compounds in which the antiseptic value of the phenolic nucleus has been augmented by the introduction of nuclear halogen or alkyl groups or by both types of substituents; for example, hexylresorcinol, *n*-amyl-*m*-cresol, chlorothymol and chlorocarvacrol.

It seemed to us that a very effective manner in which the germicidal power of phenol itself could be increased would be through the introduction of halogen and a long, straight side chain. Consequently, a homologous series of 2-chloro-4-*n*-

TABLE I.—2-CHLORO-4-*n*-ALKYLPHENOLS AND CORRESPONDING α-NAPHTHOATES.

Alkyl Group	B. P., ° C.	Phenols, Formulas.	Analyses, % Cl.		α-Naphthoates,[b]	Analyses, % Cl.	
			Calc'd.	Found.	M. P., ° C.	Calc'd.	Found.
Methyl[a]	197–198, 738 mm.	C_7H_7OCl	24.88	25.14	108–110	11.95	12.03
Ethyl	216–217, 742 mm.	C_8H_9OCl	22.64	22.51	70–72	11.41	11.44
Propyl	226–227, 741 mm.	$C_9H_{11}OCl$	20.78	20.34	71–73	10.92	10.78
Butyl	243–244, 735 mm.	$C_{10}H_{13}OCl$	19.21	18.87	44–46	10.47	10.28
Amyl	259–260, 740 mm.	$C_{11}H_{15}OCl$	17.85	17.38	63–65	10.05	10.03
Hexyl	275–276, 740 mm.	$C_{12}H_{17}OCl$	16.67	16.00	43–45	9.67	9.71
Heptyl	290–291, 738 mm.	$C_{13}H_{19}OCl$	15.64	15.53	45–47	9.31	9.12

[a] This compound was first prepared by Schall and Dralle (*Ber.*, 17 (1884), 2528, and then by Zincke (*Ann.*, 328 (1903), 277). The last-mentioned investigator recorded the boiling point as 194–196°. [b] The α-naphthoate of *p*-cresol melts at 61–63°, the diphenyl-*p*-carboxylate at 122–124°. The benzoate of 2-chloro-4-methylphenol melts at 67–68°, the *p*-nitrobenzoate at 88–90°, the diphenyl-*p*-carboxylate at 111–113°. The benzoate of 2-chloro-4-ethylphenol melts at 44–46°.

All of the naphthoates listed in the above table were recrystallized from absolute alcohol; other esters which were found to be too soluble in alcohol were recrystallized from petroleum ether (30–60°). In a few instances the crude naphthoates were somewhat oily, hence they were cooled with ice and thoroughly triturated several times with small amounts of absolute alcohol prior to recrystallization.

---

* Scientific Section, A. PH. A., Madison meeting, 1933.

[1] This paper represents the first part of a dissertation to be submitted to the Graduate School by Mr. Stockhaus in partial fulfilment of the requirements for the degree of Doctor of Philosophy in the University of Michigan.

Mr. Stockhaus is the present Frederick Stearns and Company Fellow.

[2] College of Pharmacy, University of Michigan, Ann Arbor, Michigan.

alkylphenols was prepared and it was found that the phenol coefficients of the compounds increased progressively from the methyl- to the heptylphenol, inclusive. The highest members of the series, the hexyl- and heptylchlorophenols, possess unusually high phenol coefficients.

Special emphasis was placed on the preparation of very pure samples for bacteriological tests. The chlorophenols which we prepared are oils and, consequently, it is almost impossible to purify small quantities of them by distillation. We purified each phenol in the following manner: fractionation of the crude product; conversion of a fraction which boiled over not more than one degree range into the crystalline α-naphthoate; careful purification of the latter by recrystallization; hydrolysis of the naphthoate; distillation of the recovered phenol. The purity of the material used for bacteriological tests was established by analysis (Table I).

The chloroalkylphenols were prepared in four stages according to the following general method: (*a*) preparation of the phenyl ester from the aliphatic acid chloride and phenol; (*b*) rearrangement of the ester by means of aluminum chloride into the 4-hydroxyphenylalkyl ketone; (*c*) reduction of the ketone to the 4-alkylphenol; (*d*) chlorination of the latter with sulphuryl chloride.

The lower members of the series are characterized by a strong cresol-like odor while the higher members are practically odorless.

EXPERIMENTAL PART.

The phenyl esters were prepared in the following manner. Equivalent amounts of phenol and the required acid chloride were heated at 140° for three hours. The esters were washed with sodium hydroxide solution and then purified by distillation. The yields varied from 75–86%. The boiling points of compounds not described hitherto are as follows: phenyl valerate, 116–120° (16 mm.); phenyl caproate, 134–136° (19 mm.); 255–257° (738 mm.); phenyl heptanoate, 155–157° (23 mm.).

Rearrangement of the esters to the 4-hydroxyphenylalkyl ketones was effected as follows. To one mole of the phenyl ester, dissolved in 400 cc. of nitrobenzene, there was added 1.5 moles of aluminum chloride. After four days the mixture was poured on ice and, after removal of the nitrobenzene by steam distillation, the ketone was purified by distillation under reduced pressure and then by recrystallization from benzene or xylene. The yields of pure products varied from 50–60%. The physical constants found agreed with those published in the literature.

In order to obtain the 4-*n*-alkylphenols a mixture prepared from one mole of the ketone, 1250 Gm. of amalgamated zinc, 750 cc. of water and 750 cc. of hydrochloric acid, was refluxed for four to seven days. During the course of each day an additional 100 cc. of hydrochloric acid was added. The boiling points found for the alkylphenols were practically the same as those recorded in the literature. The yields varied from 50–75%.

Finally, the 2-chloro-4-*n*-alkylphenols were obtained by the following general process. The alkylphenol was mixed with 1.1 molecular equivalents of sulphuryl chloride and after five days the product was washed free from halogen compounds with sodium carbonate solution and then purified by distillation. The distilled material was converted into the α-naphthoate in the following manner. Equimolecular amounts of the phenol and α-naphthoyl chloride were mixed and shaken vigorously while one molecular equivalent of pyridine was added slowly. After several hours the solid reaction mixture was triturated with ice water which contained one equivalent of hydrochloric acid. The solid product was filtered, washed with sodium carbonate solution, dried and recrystallized from alcohol. The ester was then hydrolyzed with one molecular equivalent of sodium hydroxide in 75% alcohol, the alcohol removed and the mixture neutralized with hydrochloric acid. After the addition of excess sodium carbonate the material was subjected to steam distillation. The phenol was extracted from the distillate with ether and purified by distillation.

The phenol coefficients (Table II, Column 1) were determined by Dr. W. L. Mallmann and carefully checked at a later date. 2-Chloro-4-*n*-heptylphenol was tested, independently, by Dr. C. W. Geiter who, likewise, found that this compound possesses the relatively high phenol coefficient of 666. Bacteriological data on 2-chloro-4-*n*-alkylphenols have been presented recently by Klarmann, Shternov and Gates (1); their results are reproduced in Table II, Column 2. Striking discrepancies between the values in Columns 1 and 2 are to be noticed in connection with the hexyl- and heptylphenols.

TABLE II.—PHENOL COEFFICIENTS.

(Reddish Method.)

	Test Organism, *Staph. aureus.* (37° C.)	
Phenol.	1.	2.
2-Chloro-4-methyl	9	7.5
2-Chloro-4-ethyl	18	15.7
2-Chloro-4-*n*-propyl	31	32.1
2-Chloro-4-*n*-butyl	115	93.8
2-Chloro-4-*n*-amyl	333	286.0
2-Chloro-4-*n*-hexyl	444	714.0
2-Chloro-4-*n*-heptyl	666	375.0
2-Chloro-4-tert.-amyl[a]	150	125.0
4-*n*-Capronyl[b]	40	...
2-Chloro-4-*n*-capronyl[c]	40	...
2,6-Dichloro-4-*n*-hexyl[d]	50[e]	...

---

[a] B. p. 247–248°. [b] M. p. 61–62° after recrystallization from absolute alcohol. [c] M. p. 79–81° after recrystallization from absolute alcohol; Anal. calcd. for $C_{12}H_{15}O_2Cl$: Cl, 15.65. Found: Cl, 15.50. [d] B. p. 308–310° under 745 mm. pressure; Anal. calcd. for $C_{12}H_{16}OCl_2$: Cl, 28.70. Found: Cl, 28.90. [e] This value was obtained by Dr. Geiter.

SUMMARY AND CONCLUSIONS.

A homologous series of 2-chloro-4-*n*-alkylphenols has been prepared in which the alkyl groups range from methyl to heptyl, inclusive.

The phenol coefficients of highly purified samples of these compounds increased progressively from the methyl- to the heptylphenol and for the latter substance the relatively high value of 666 was obtained.

REFERENCE.

(1) Emil Klarmann, V. A. Shternov and L. W. Gates, *J. Am. Chem. Soc.*, 55 (1933), 2580. Except for a few confirmatory bacteriological tests our investigation had been completed about six months prior to the publication of the article by Klarmann and coworkers.