[Contribution from the Chemical Laboratory of Northwestern University]

THE SYNTHESIS AND PROPERTIES OF SOME ALKYLIODOPHENOLS

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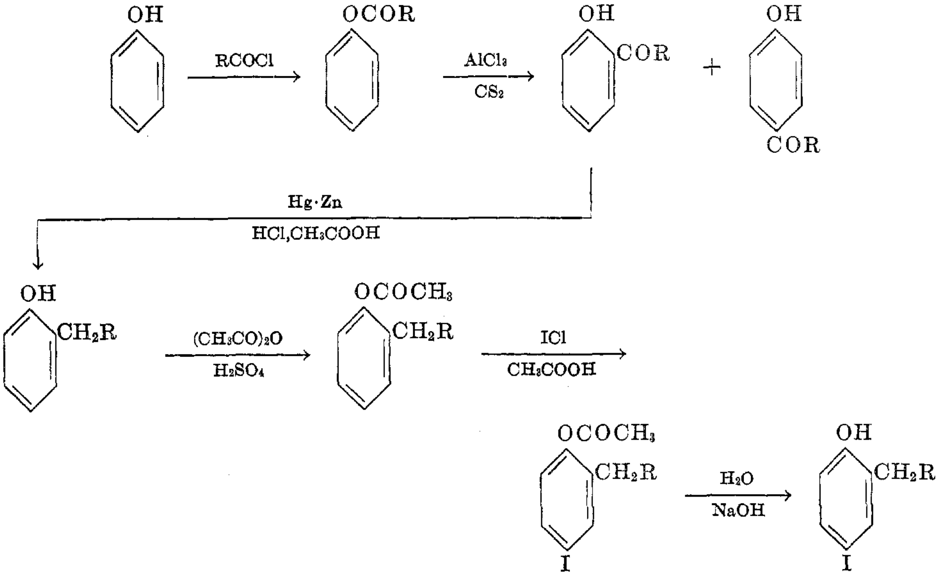
The synthesis and bactericidal properties of the fluoro- (1), chloro-, and bromoalkylphenols (2, 3) have been investigated whereas no information is available concerning the corresponding iodine derivatives. It was felt that the preparation of the alkyliodophenols would be of interest since a comparison and correlation of the chemical, physical, and antibacterial properties of these compounds with those of the known fluoro, chloro, and bromo derivatives might give some clue to the complex relationships between chemical constitution and bactericidal action.

The steps in the first method of syntheses studied for the alkyliodophenols are shown in the accompanying equations:



The essential data and properties of the intermediate 2-alkylphenyl acetates which have been prepared for the first time are shown in Table I. Only one of the phenols was obtained in the crystalline state. All attempts to isolate the pure 2-alkyl-4-iodophenyl acetates in the case of the ethyl, propyl, and *n*-butyl homologs by vacuum-distillation failed, yielding only mixtures of uniodinated, monoiodinated, and diiodinated products in small amounts. Another attempt to iso-

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late the 2-alkyl-4-iodophenols was made by first hydrolyzing the impure 2-alkyl-4-iodophenyl acetates followed by vacuum-distillation. This resulted in only small amounts of impure 2-alkyl-4-iodophenols. Thus iodine monochloride is a poor iodinating agent for the nuclear substitution of iodine in the 2-alkylphenyl acetates.

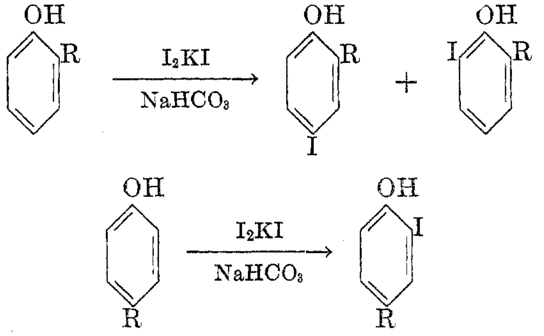
Since only small impure samples of the desired compounds were obtained with the exception of the first member of the series, a more satisfactory method for introducting iodine into the nucleus of the 2-alkylphenols was sought. The alkyliodophenols were then obtained in small yields by the direct iodination of the alkylphenols with iodine and potassium iodide in an aqueous sodium bicarbonate solution (4).

TABLE I

2-ALKYLPHENOL ACETATES

ALKYL GROUP[a]	B.P., °C./MM.	d_4^{25}	n_D^{25}	M_0		ANALYSES			
				Calc'd	Obs'd	Calc'd		Found	
						C	H	C	H
n-Propyl	77–78/3	1.0165	1.5040	50.640	51.958	74.16	7.83	74.39	8.39
n-Butyl	100–103/3	0.9881	1.4897	55.258	56.227	74.95	8.39	74.95	8.59
n-Amyl	104–106/3	0.9697	1.4888	59.876	59.949	75.68	8.72	75.70	9.04

[a] The 2-ethylphenyl acetate, b.p. 77–78°/4 mm., d_4^{25} 1.0334, n_D^{25} 1.5002, and the 2-hexylphenyl acetate, b.p. 113–116°/4 mm., d_4^{25} 0.9500, n_D^{25} 1.4973, were also prepared. They were not analyzed but were used directly in further work.



The important properties and data of the alkyliodophenols which are new and are here described for the first time are shown in Table II. The position of the iodine in the 2-methyl-4-iodophenol obtained from 2-methylphenyl acetate with iodine monochloride was established by treating the phenol with methyl sulfate which converted it into 2-methyl-4-iodoanisole. This has previously been reported by Dains, Magers, and Steiner (5) and also by Robinson (6). That one of the positions which iodine enters in the direct iodination of *o*-cresol with iodine and potassium iodide in alkaline solution is the 4-position, was again established by converting one of the phenols obtained to the known 2-methyl-4-iodoanisole. The structure of the other product isolated in this reaction was assumed to be the 6-iodo-2-methylphenol. For the higher homologs of the methyliodophenols the iodine was assumed to be in the 6- or 4-position when the alkyl group was in the 2-position, and in the 2-position when the alkyl group was in the 4-position as shown by the equations. The lower boiling points of the 6-iodo compounds are in accord with the assigned structures. Structures of the alkyliodophenols were further established by determination of their equivalent weight by the bromate-bromide method of analysis for phenols (7). The solubilities of the alkyliodophenols in water and in 20% ethyl alcohol were determined by titrating saturated solutions of the phenols using the bromate-bromide method.

TABLE II

ALKYLIODOPHENOLS

PHENOL	YIELD, %	M.P., °C.	B.P., °C./MM.	d_4^{25}	n_D^{25}	EQUIV. WGT.[a]		SOLUBILITY[b]	
						Calc'd	Found	H_2O	20% EtOH
2-Methyl-4-iodo	5.2	64–65	105–110/2			117.0	116.6	0.09	0.16
2-Methyl-6-iodo	4.2	15–16	70–75/2	1.661	1.6100	117.0	117.2	.17	.34
4-Methyl-2-iodo	12.4		96–98/3	1.684	1.5531	117.0	116.8	.08	.29
2-Ethyl-4-iodo	3.0	48–50	126–129/3			124.0	123.4	.21	.28
2-Ethyl-6-iodo	2.5		98–100/3	1.679	1.6017	124.0	123.6	.09	.086
4-Ethyl-2-iodo	26.2		98–100/4	1.670	1.5750	124.0	123.6	.31	.45
2-Propyl-4-iodo	1.5		119–120/2			131.0	130.8		
2-Propyl-6-iodo	1.8		94–95/2	1.681	1.5846	131.0	131.2		
4-Propyl-2-iodo	11.0		132–135/4	1.655	1.5568	131.0	130.9	.009	.014
4-Butyl-2-iodo	5.3		150–152/4	1.637	1.5895	138.0	138.0	.0000	.0000

[a] Equivalent weights are those of the alkyliodophenols in their quantitative reaction with bromate-bromide in acid solution to yield the monobromo derivative.[b] Grams per 100 grams at 25°.

EXPERIMENTAL

Materials. Some of the intermediates used were available in this laboratory, namely, 2-ethylphenol, 4-ethylphenol, 2-amylphenol, 2-hexylphenol, and a small crude sample of 2-methyl-4-iodophenyl acetate.

Phenyl esters. These were prepared according to procedures previously described (8, 9) employing the acid chloride and phenol.

2- and 4-Acylphenols. The phenyl esters were isomerized at 135° with anhydrous aluminum chloride following the method used by Miller and Hartung (10).

2- and 4-Alkylphenols. These compounds were prepared by the Clemmensen reduction employing the procedure of Mikeska, Smith, and Lieber (11) with the exception that glacial acetic acid instead of hydrocarbon solvents was used as a solvent for the acylphenols.

2-Alkylphenyl acetates. To 100 g. (0.910 mole) of 2-ethylphenol containing 0.1 ml. of conc'd sulfuric acid was added with a dropping-funnel 58 g. (0.560 mole, a 25% excess) of acetic anhydride also containing 0.1 ml. of conc'd sulfuric acid. Good stirring was maintained during the three hours required to add the acetic anhydride. Distillation in a 50-cm. Vigreux column gave 112 g. (81%) of 2-ethylphenyl acetate, b.p. 77–78° at 4 mm. Using the same procedure the 2-alkylphenyl esters shown in Table I were prepared.

2-Methyl-4-iodophenyl acetate. A small impure quantity of this material had been prepared by Mr. Sandborn of this laboratory from 2-methylphenyl acetate and iodine monochloride. This black oily material, washed with 20 ml. of 10% sodium thiosulfate solution, yielded a light brown oil that solidified on standing. Recrystallization from ligroin gave a white solid, m.p. 55–56°.

Anal. Calc'd for $C_9H_9IO_2$: I, 45.99. Found: I, 46.45.

2-Methyl-4-iodophenol. The 2-methyl-4-iodophenyl acetate was hydrolyzed with 10% sodium hydroxide on a steam-bath in ten minutes. On acidification with dilute hydrochloric acid the 2-methyl-4-iodophenol crystallized. It was recrystallized from ligroin, m.p. 64–65°.

Anal. Calc'd for C_7H_7IO: Equiv. wt., 117.0. Found: Equiv. wt., 116.6.

The alkyliodophenols were all analyzed by titration with potassium bromate-bromide in acetic acid solution according to the general directions of Francis and Hill (7).

2-Methyl-4-iodoanisole. This compound was prepared from 2-methyl-4-iodophenol by adding 0.81 g. (0.0193 mole) of methyl sulfate from a dropping-funnel over 30 min. to 5% sodium hydroxide containing 3.0 g. (0.0128 mole) of 2-methyl-4-iodophenol kept at 30° in a water-bath. Heating on a steam-bath was continued for another half-hour to complete the reaction. A white solid was obtained which crystallized from glacial acetic acid, m.p. 75–76° (9).

2-Alkyl-4-iodo-, 2-alkyl-6-iodo-, and 4-alkyl-2-iodo-phenol. The method used for the synthesis of these compounds is illustrated by the preparation of 4-methyl-2-iodophenol. To 75 g. (0.693 mole) of *p*-cresol in a 5-l. round-bottom flask was added 400 ml. of water, 120 g. (1.430 moles) of sodium bicarbonate, and 400 ml. of water containing 150 g. (0.590 mole) of iodine and 98.5 g. (0.590 mole) of potassium iodide. The flask was stoppered and placed on a power shaker for three hours. The clear upper liquid was decanted off and the oil remaining was extracted with ether. The ether extract was washed with water, then with 100 ml. of 5% sodium thiosulfate, dried over magnesium sulfate, and the ether removed on a water-bath. Distillation under reduced pressure through a 50-cm. Vigreux column gave 20 g. of 4-methyl-2-iodophenol, b.p. 96–98° at 3 mm. (12.4% yield based on *p*-cresol). The essential data for this and other alkyliodophenols similarly prepared are given in Table II.

SUMMARY

1. The 2-alkyl-6-iodophenols from methyl to propyl, 2-alkyl-4-iodophenols from methyl to propyl, and 4-alkyl-2-iodophenols from methyl to butyl have been prepared for the first time and some of their properties investigated.

2. The 2-alkylphenyl acetates from ethyl to *n*-hexyl have been prepared and characterized for the first time.

3. The solubilities of several of the lower members of the alkyliodophenols in water and 20% alcohol solutions were determined at room temperature.

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