SCIENTIFIC SECTION

THE PREPARATION AND GERMICIDAL PROPERTIES OF SOME ALKYL DERIVATIVES OF HYDROXY DIPHENYLS.*

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The effect of an alkyl side chain on the bactericidal properties of phenols and other compounds has been the subject of several studies in recent years (1). It appears to be definitely established that the effect of a normal alkyl side chain is to augment greatly the bactericidal value of a phenol. The typhoid activity increases with the size of the alkyl group until a maximum is reached beyond which further increase in the size of the alkyl group results in progressively lowered activity; a maximum has not been found in tests on staphylococcus aureus, *i. e.*, each increase in the size of the alkyl group has been accompanied by a greater activity.

The present study covers the preparation and evaluation of a number of alkylated mono- and dihydroxy diphenyls. It was expected that the alkyl groups producing the greatest activity would be smaller than the groups present in the most active alkyl phenols, cresols and resorcinols, due to the presence of the additional phenyl nucleus, and it was thought probable that the *n*-propyl side chain would be most effective. This expectation was confirmed in the case of the 5-*n*-alkyl 2-hydroxy diphenyls; thus, the *staphylococcus aureus* activity of 2-hydroxy diphenyl is much greater than that of any other member of the series. For the germicidal tests the compounds were dissolved in a solvent consisting of alcohol (25 cc.), glycerin (35 cc.) and water (*q. s.* 100 cc.);[1] unless otherwise stated, the initial solution contained 0.25% of germicide. These solutions were diluted with water as necessary immediately prior to test. The results of these tests are contained in the following table:

TABLE I.

	Dilution at Which Bacteria Are Killed in 5 Minutes. Typhoid.	Staphylococcus.
A. 5-*n*-Alkyl 2-Hydroxy Diphenyls.		
2-hydroxy diphenyl	1–2000	1–800
5-ethyl 2-hydroxy diphenyl	1600	4000
5-*n*-propyl 2-hydroxy diphenyl	400 400	12000 20000
5-*n*-butyl 2-hydroxy diphenyl	400	2000
5-*n*-amyl 2-hydroxy diphenyl	400	1200
B. 3-*n*-Alkyl 2-Hydroxy Diphenyls.		
2-hydroxy diphenyl	1–2000	1–800
3-*n*-propyl 2-hydroxy diphenyl	400	400
3-*n*-butyl 2-hydroxy diphenyl	400	400
3-*n*-amyl 2-hydroxy diphenyl	400	400

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

[1] This liquid is not in itself germicidal.

C. Alkyl 3-Hydroxy Diphenyls.		
3-hydroxy diphenyl	1–800	1–4000
4-*n*-propyl 3-hydroxy diphenyl*	1000	3000
6-*n*-propyl 3-hydroxy diphenyl*	1000	<1000
D. Alkyl-Dihydroxy Diphenyls.		
2,5-dihydroxy diphenyl[1]	1–500	1–500
4-*n*-propyl 2,5-dihydroxy diphenyl*	<1000	10000
3,4-dihydroxy diphenyl	2000	1200
5-*n*-propyl 3,4-dihydroxy diphenyl[2]	2000	4000

* Initial concentration 1–1000.

[1] Initial concentration 1–250.

[2] Initial concentration 1–2000.

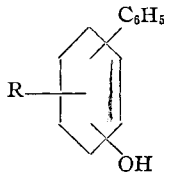
These results show:

(*a*) Alkylation of 2-hydroxy diphenyl in the 3- or 5-position decreases the typhoid activity.

(*b*) Alkylation of 2-hydroxy diphenyl in the 3-position decreases the *staphylococcus aureus* activity whereas alkylation in the 5-position increases it.

(*c*) In the 5-alkyl 2-hydroxy diphenyl series the maximum staphylococcus activity is obtained with the *n*-propyl compound.

(*d*) Propylation of 3-hydroxy diphenyl has little effect on the typhoid activity but decreases the staphylococcus activity. The 6-*n*-propyl 3-hydroxy diphenyl in which the propyl group is para to the hydroxyl group is definitely less active than the 4-*n*-propyl isomer in which the alkyl and hydroxyl groups are ortho to each other. This result is the opposite of that found in the 2-hydroxy diphenyl series; in the latter the compound containing the propyl group para to the hydroxyl group is definitely more active than the ortho isomer. The activity of an alkyl hydroxy diphenyl is therefore dependent upon the relative positions of the alkyl, hydroxyl and phenyl nuclei:



(*e*) Propylation of 2,5- and 3,4-dihydroxy diphenyls has little effect on the typhoid activity but does increase the staphylococcus activity.

The initial concentration of the germicide in the alcohol: glycerin: water solution affects the results of the germicidal test at least in the case of 5-*n*-propyl 2-hydroxy diphenyl (Table II).

TABLE II.

Initial Concentration of 5-*n*-Propyl 2-Hydroxy Diphenyl.	Dilution at Which Bacteria Are Killed in 5 Minutes. Typhoid.	Staphylococcus.
0.25%	1–400	1–12000
	1–400	1–20000
0.10%	1–1000	1–30000
	1–1000	1–20000

The solubility of propylhydroxydiphenyl in water is low and the difference between the germicidal results obtained with 0.25% and 0.1% solutions may be due

to the fact that the larger ratio of alcohol to germicide in the latter case permits greater dilution without throwing the germicide out of true solution. Thus, when 25% alcohol solutions containing 0.25 and 0.1% germicide are diluted so that the concentration of germicide is 1–30,000 (0.0033%) the alcohol concentrations would be 0.33% (with the 0.25% solution) and 0.83% (with the 0.1% solution). The results given in Table I were obtained mainly with 0.25% solutions; a similar series of tests made with 0.1% solutions might give higher activities for some of the compounds. These additional tests would make the work more complete but it is doubtful whether they would alter the conclusions drawn from the data now available.

The presence of sodium hydroxide affects the activity of these phenols; Table III contains a comparison of the results obtained in the absence and presence of alkali. The alkaline solutions contained 0.25% germicide, 10–30% alcohol[1] and sufficient NaOH to yield a clear solution; this varied from 3.8 to 4.6 moles.

TABLE III.

	Dilution at Which Bacteria Are Killed in 5 Minutes.			
	Without NaOH.		With NaOH in Original Solution.	
	Typhoid.	Staphylococcus.	Typhoid.	Staphylococcus.
2-hydroxy diphenyl	1–2000	1–800	1–2000	1–400
5-ethyl-2-hydroxy diphenyl	1–1600	1–4000	1–2800	<1–400
5-*n*-propyl 2-hydroxy diphenyl	1–400	1–12000	1–2800	<1–400
5-*n*-butyl 2-hydroxy diphenyl	1–400	1–2000	1–2000	1–10000
5-*n*-amyl 2-hydroxy diphenyl	1–400	1–1200	1–400	1–2000

The addition of alkali:

(*a*) Decreases the staphylococcus activity of the lower members of the series.
(*b*) Increases the staphylococcus activity of the high members of the series.
(*c*) Increases the typhoid activity of the lower members of the series.
(*d*) Does not increase the typhoid activity of the highest member of the series.

Although these phenolic substances are more readily soluble as the sodium salts, at high dilution these salts frequently hydrolyze to such an extent that the free phenol may begin to crystallize out. Then, too, it is probable that the acidic nature of the phenol diminishes as the size of the alkyl group increases, for it is known that introduction of certain groups into phenols may depress the acidity to such an extent that the compound will not form salts, and becomes insoluble in aqueous alkali.

Thus it is conceivable that the Gm.-negative typhoid bacillus is attacked more readily by the sodium salt of the phenol, and that increased action ceases when the substituted phenol is not materially converted to the salt. In similar manner the Gm.-positive organism staphylococcus appears to be much less vigorously attacked by the sodium salt than by the free phenol. The reversal of relative activity here occurs earlier in the series of progressively heavier substituents, and is much more pronounced.

EXPERIMENTAL.

During the early part of the study the 5-alkyl derivatives were synthesized by condensing the appropriate acid chloride or anhydride with 2-methoxy diphenyl by the Friedel and Craft

[1] Ten per cent in the cases of the ethyl and propyl compounds, 20% in that of the butyl and 30% in that of the amyl.

method. The resulting ketones were reduced by the method of Clemmenson and subsequently demethylated. Considerable losses were experienced during the demethylation and this led to the adoption of an alternative method with notably smoother results. This consisted of rearrangement of fatty acid esters of 2-hydroxy diphenyl by means of aluminum chloride to a mixture of 3- and 5-acyl 2-hydroxy diphenyls. These ketones were separated and reduced to the corresponding alkyl compounds as before, no demethylation being required.

The esters were prepared by the action of the fatty acid on 2-hydroxy diphenyl in the presence of $POCL_3$ at 135° C. Excellent yields were obtained of viscous, colorless liquids which we were not able to obtain in crystalline form; an exception to this was the acetate which was obtained as white needles from dilute alcohol, m. p. 64° C. In spite of repeated fractionation or cooling to low temperatures, no other ester would crystallize.

The rearrangement of the esters was accomplished by heating to 160° C. with anhydrous aluminum chloride for half an hour. This gave the aluminum chloride compound of the mixed ketones in the form of a hard glassy mass which was decomposed in the usual way with dilute HCl. The separation was conveniently brought about by extracting the mixture with petroleum ether in which the 3-acyl compounds were readily soluble. The insoluble 5-acyl compounds which gave no red color with $FeCl_3$ were filtered off and recrystallized from a mixture of ether or benzol and petroleum ether. The 3-acyl compounds were obtained by evaporating the solvent and distilling the residue. These gave a deep red color with $FeCl_3$.

It was observed that the length of the side chain had a marked effect on the products of rearrangement, the 5-acyl compound being the predominant product with shorter chains and a larger proportion of the 3-acyl compound being obtained when the *n*-butyric and *n*-valeric esters were rearranged.

In spite of carefully standardized conditions, very variable yields of the alkyl derivatives were obtained on reducing these ketones. The lost material was always encountered as a resin-like distillation residue from which all attempts to isolate crystalline products failed. It is conceivable that these compounds are condensation products of the pinacone type. A single detailed example of each typical reaction is given.

2-HYDROXY DIPHENYL PROPIONATE (2-PHENYL-PHENYLPROPIONATE).

One mol. of 2-hydroxy diphenyl was dissolved in one mol. of propionic acid and the mixture heated to 135° C. under reflux with mechanical agitation. 0.5 mol. $POCl_3$(or PCl_3) was then added slowly and the mixture maintained at 135° C. till HCl was no longer evolved. The ester was then decanted from the phosphorous acid, washed with water and dissolved in ether. After being dried over $CaCl_2$, the ether was evaporated and the residue distilled; b. p., 151–152° C. at 4 mm. Yield, 90%.

REARRANGEMENT OF 2-HYDROXY DIPHENYL PROPIONATE.

1.1 mols. of powdered anhydrous aluminum chloride were added in small portions to one mol. of 2-hydroxy diphenyl propionate. Considerable heat developed and HCl was evolved. The mixture was then heated in an oil-bath at 160° C. for 30–45 minutes. The glassy reaction product was cooled, powdered and decomposed by adding gradually to well-stirred 5% HCl. The decomposition was completed by warming on the steam-bath for a short time. The mixture of 3- and 5-propionyl 2-hydroxy diphenyl was filtered off, washed with dilute HCl and water and dried. The dried product was extracted with a large volume of boiling petroleum ether, b. p. 40–60° C., and the undissolved 5-propionyl 2-hydroxy diphenyl filtered off. After recrystallization from a mixture of ether and petroleum ether, 5-propionyl 2-hydroxy diphenyl was obtained as a white powder, m. p. 151–152° C. (2).

The petroleum-ether extract was evaporated and the residue distilled, yielding 3-propionyl 2-hydroxy diphenyl, b. p. 183–185° C./3.5 mm.

5-*n*-PROPYL 2-HYDROXY DIPHENYL.

One part by weight of 5-propionyl 2-hydroxy diphenyl was refluxed during 10–12 hours with 4 parts amalgamated mossy zinc and 15 parts 20% HCl. Brisk mechanical agitation during the reduction greatly reduced the time necessary for complete reduction. The oily product formed was separated from the acid liquor and washed with hot water. After drying with anhydrous

Na_2SO_4 in ether solution the ether was removed and the residue distilled; b. p. 171–172° C./9 mm.; yield, 90%.

TABLE IV.

2-Hydroxy Diphenyl Derivatives.	B. P. or M. P.	Yield, %.	Found. C.	Found. H.	Calculated. C.	Calculated. H.
Propionate	151–152°/4	85–90	79.6	6.32	79.6	6.2
n-butyrate	154/3.5	90	80.5	6.7	80.0	6.7
n-valerate	162–167°/4	80	80.8	7.2	80.3	7.1
3-propionyl	183–185/3.5	8	79.7	6.3	79.6	6.2
5-propionyl	M. p., 151–152	*				
3-*n*-butyryl	185–190/3.5	15	80.0	6.7	80.0	6.7
5-*n*-butyryl	M. p., 116–117	40	79.3	6.7	80.0	6.7
3-*n*-valeryl	200–210°/5	20	79.8	6.34	80.3	7.09
5-*n*-valeryl	M. p., 104	40	79.8	7.13	80.3	7.09
5-ethyl	152/5	10[1]	84.6	7.2	84.8	7.10
3-*n*-propyl	155–160/8	90	84.7	7.46	84.9	7.55
5-*n*-propyl	171–172/9	90	84.5	7.9	84.9	7.55
3-*n*-butyl	160–167/4	50	84.6	7.93	84.9	7.96
5-*n*-butyl	173–175/6	75	84.4	8.08	84.9	7.96
3-*n*-amyl	166–171/5	50	84.7	8.32	85.0	8.33
5-*n*-amyl	181–183/6	65	85.5	8.41	85.0	8.33
2-Methoxy Diphenyl Derivatives.						
5-acetyl	M. p., 90–90.5	46	79.8	6.31	79.7	6.2
5-propionyl	M. p., 93–94	50	79.3	6.54	80.0	6.7
5-*n*-valeryl	202–204/4	40	80.1	7.45	80.6	7.1
5-ethyl	163–166/7	70	85.2	7.6	84.9	7.6
5-*n*-propyl	171–172/9	90	85.5	7.9	85.0	8.0
5-*n*-amyl	178–182/5	61	84.3	8.4	85.0	8.7
3-Hydroxy Diphenyl Derivatives.						
Propionate	160–165/2	84.5	79.0	6.06	79.6	6.19
4-propionyl	M. p., 109	71.0	79.6	6.23	79.6	6.19
4-*n*-propyl	162–3/3 M. p., 56–56.5	62.0	85.0	7.48	84.9	7.55
3-methoxy	140/5	90.0	85.0	6.45	84.8	6.52
6-propionyl 3-methoxy	M. p., 72	75.0	79.6	6.40	80.0	6.67
6-*n*-propyl 3-methoxy	153–170/3	70.0	84.4	7.99	85.0	7.97
6-*n*-propyl 3-hydroxy	M. p., 140–141	1.0	Mol. wt. in C_6H_6. Found, 219; calcd., 212.			
Dihydroxy Diphenyl Derivatives.						
3,4-dimethoxy	153/4 M. p., 70	90	78.7	6.56	78.5	6.54
5-propionyl 3,4-dimethoxy	228–30/3 M. p., 113	10	75.0	7.16	75.6	6.67
5-*n*-propyl 3,4-dimethoxy	195–210/7	90	80.1	7.61	79.7	7.81
5-*n*-propyl 3,4-dihydroxy	Not determined	2	80.5	7.07	79.0	7.02
2,5-dimethoxy diphenyl	147–149/4	85	77.9	6.38	78.5	6.54
4-propionyl 2,5-dihydroxy	220–230/6 M. p., 138–139	15	74.5	6.07	74.4	5.78
4-*n*-propyl 2,5-dihydroxy	195/9	90	78.7	7.38	79.0	7.02

* Reference (2).

[1] By demethylation of 2-methoxy 5-ethyl diphenyl.

5-ACETYL 2-METHOXY DIPHENYL (3).

78 Gm. (2 mols.) 2-methoxy diphenyl were dissolved in 150 cc. dry carbon disulphide and 112 Gm. anhydrous aluminum chloride were added slowly with external cooling. The mixture was well stirred and refluxed gently on the water-bath while 31 Gm. acetic anhydride (2 mols.) were added during about one hour. The refluxing and stirring was continued for a further period of one hour and the carbon disulphide distilled off. The residue was decomposed with ice and HCl and the ketone extracted with ether. The extract was washed with water, dilute NaOH and again with water, and then dried with $CaCl_2$. After distilling off the ether, the residue was distilled, b. p. 194–204° C./6 mm. The reddish distillate solidified on cooling and after recrystallization from petroleum ether had a melting point of 90–90.5° C.; yield, 46%.

ALKYL 3-HYDROXY DIPHENYLS.

(*a*) *4-n-Propyl 3-Hydroxy Diphenyl.*—This was prepared by the rearrangement of 3-phenyl phenyl propionate and reductions of the resulting ketone as described under the preparation of 5-alkyl 2-hydroxy diphenyls. The intermediate ketone gave a deep red color with ferric chloride solution and was therefore assumed to be the 4-acyl derivative. The introduction of the acyl group into the 2-position is considered unlikely, owing to the stoic hindrance of the phenyl group.

(*b*) *6-n-Propyl 3-Hydroxy Diphenyl.*—Since the entire product of the ester rearrangement was the 4-acyl compound, the preparation of the 6-acyl 3-hydroxy diphenyl was necessarily carried out by the Friedel and Craft method on 3-methoxy diphenyl. The reaction conditions for the acylation of 3-methoxy diphenyl were exactly those described under 5-acetyl 2-methoxy diphenyl and reference (3). The resulting ketone, which gave no color with ferric chloride was reduced in the manner previously described for 5-*n*-propyl 2-hydroxy diphenyl.

On attempting to demethylate the 6-*n*-propyl 3-methoxy diphenyl by heating with hydriodic acid in glacial acetic acid much decomposition took place, only a small quantity of the desired 3-hydroxy 6-*n*-propyl diphenyl being obtained.

DIHYDROXY DIPHENYL DERIVATIVES.

The rearrangement of mono-propionic esters of 3,4-dihydroxy diphenyl and 2,5-dihydroxy diphenyl gave tarry products from which no definite compounds could be isolated. Direct introduction of acyl groups into the dimethyl ethers gave very poor yields, most of the ethers being recovered unchanged. In the case of 3,4-dimethoxy diphenyl a 10% yield of 5-propionyl 3,4-dimethoxy diphenyl was obtained while in the case of 2,5-dimethoxy diphenyl demethylation took place at the same time, giving a 15% yield of 6-propionyl 2,5-dihydroxy diphenyl. Various reaction-conditions were tried with little success. The above results were obtained when the methods described in reference (3) were followed. Both of the dihydroxy propionyl diphenyls gave a deep red color with $FeCl_3$.

The biological tests on compounds reported herein were made in the Biological Research Laboratories of E. R. Squibb & Sons and we gratefully acknowledge their assistance.

SUMMARY.

A number of 3-alkyl and 5-alkyl 2-hydroxy diphenyls and propyl derivatives of 3-hydroxy diphenyl and of two dihydroxy diphenyls have been prepared and tested for germicidal activity. The 5-alkyl 2-hydroxy diphenyls were obtained by (*a*) the Friedel and Craft reaction on 2-methoxy diphenyl, and (*b*) rearrangement of the fatty acid ester of 2-hydroxy diphenyl. The rearrangement method gave the 3-alkyl compounds as by-products.

Bactericidal tests showed that the 3-alkyl compounds are comparatively inactive and that the 5-alkyl compounds have a markedly specific activity; the potency against *Staphylococcus aureus* being high compared with that against *B. Typhosus*. Of the 5-alkyl 2-hydroxy diphenyls, the 5-*n*-propyl was by far the most active.

LITERATURE REFERENCES.

(1) (*a*) Schaffer and Tilley, *J. Bact.*, 14 (1927), 259.
(*b*) Johnson and Lane, *J. A. C. S.*, 43 (1921), 348.
(*c*) Dohme, Cox and Miller, *Ibid.*, 48 (1926), 1688.
(*d*) Coulthard, Marshal and Pyman, *J. Chem. Soc.* (1930), 280.
(*e*) Klarmann, *J. A. C. S.*, 53 (1931), 3397.
(*f*) Black, Stein and Walker, *J. Chem. Soc.* (1931), 277.
(2) Auers and Wittig, *J. prakt. Chem.*, 108 (1924), 99.
(3) "Organic Synthesis," Vol. V, page 7, Wiley and Sons, N. Y., 1925.

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ISOMERIC NITRO-CRESOLS.*

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In the preparation of a series of mercurials, it was necessary first to obtain the ten isomeric nitro-cresols. Most of the research on these compounds is found in the earlier literature, very little having been done in recent years. The methods vary and are in many cases indefinite and the results obtained by their use do not always lead to the conclusions described, either in yield or quality of the material.

We believe that a condensed comparison of the known methods coupled with a reference to the preparation of each isomer in the best obtainable yields and purity would be of service to the organic chemist. In those cases where we have improved the methods, a detailed description of the compound is given. We present, moreover, methods which involve the least expense in starting material and complication in process.

The nitro-cresols are prepared either by direct nitration of the cresol, resulting in single derivatives or mixtures, or by diazotization and subsequent replacement of the corresponding nitro-toluidine. The nitro-toluidines are prepared by direct nitration of the toluidines. In a few instances the nitro-cresols can also be prepared by simultaneous diazotization and nitration of the toluidines. The 5-nitro-2-hydroxy-toluene is also prepared by oxidation of the 5-nitroso derivative.

However, in the case of two isomers, the 6-nitro-2-hydroxy-toluene and 5-nitro-3-hydroxy-toluene, it is unavoidable to employ roundabout procedures inasmuch as the nitro group cannot be introduced, in the desired position, directly into the nucleus either of the cresol or the corresponding toluidine. In fact, we have as yet been unsuccessful in isolating any definite quantity of the former according to the described methods, but we are still working on what may prove a successful attempt.

DISCUSSION AND EXPERIMENTAL PART—NITRO-ORTHO-CRESOLS.

3-Nitro-2-Hydroxy-1-Methyl-Benzene.—This was prepared by Wohl (1) using a mixture of meta-nitro-toluene and powdered alkali, keeping the temperature below 40° C. The material had to be mixed thoroughly for 24 hours and the unchanged nitro-toluene, of which there was a considerable quantity, separated from the sodium salt of the nitro-cresol.

Noelting and Wild (2) diazotized ortho-toluidine in dilute H_2SO_4 and after adding dilute HNO_3 heated the mixture until no further evolution of nitrogen took place. The nitro-cresol was

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