but this may have been due entirely to the darkened solution; original α_D +4.05°; after treatment with alkali: α_D +4.10°, 4.15°, 4.12°; average, +4.12°.

Racemization.—An alcoholic 1% solution of the *l* compound was heated on the water-bath at 60–65° for four hours, alcohol being added to maintain the original volume. No evolution of gas was observed; original α_D −4.20°; after heating, α_D −3.72°, a decrease of about 12%. The compound is thus somewhat stable optically. Heating to boiling caused some decomposition to the ketazine.

Summary

A stable, optically active, crystalline aliphatic diazo compound, β-naphthol-phenyldiazomethane, melting at 120° and having a high specific rotation, $[\alpha]_D^{30}$ ±420°, has been prepared. The rotatory dispersion is rather high, approximately 1000° between the red and violet.

On decomposition by heat or acids it forms the ketazine melting at 182°.

This shows conclusively that a carbon atom attached to the diazo group may retain its asymmetry.

CINCINNATI, OHIO

[CONTRIBUTION FROM THE PLAUT RESEARCH LABORATORY OF LEHN & FINK, INC.]

BACTERICIDAL PROPERTIES OF MONOETHERS OF DIHYDRIC PHENOLS. II. THE MONOETHERS OF HYDROQUINONE

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RECEIVED AUGUST 13, 1931 PUBLISHED JANUARY 7, 1932

It has been shown in the preceding communication (Part I of this series) that among the monoethers of resorcinol there are a number of compounds which show very considerable bactericidal potency as determined with *B. typhosus* and *Staphylococcus aureus* as test organisms.[1] This bactericidal efficacy was found to depend particularly upon the length of the chain and the molecular weight of the substituting aliphatic or aromatic radical.

Continuing this series of investigations, we prepared several monoethers of hydroquinone in order to study the antibacterial effect of replacing the hydrogen atom of one hydroxyl group of this dihydric phenol by an organic radical.

Discussion

The number of hydroquinone monoethers described in the literature is comparatively small, and none appear to have been tested for their effect upon bacteria. Hydroquinone itself and some of its nucleus substituted derivatives were studied by several investigators with the aid of certain common pathogenic microbes. Thus Cooper and Woodhouse[2] found the phenol coefficient of hydroquinone to be 1.0 against *B. typhosus*, 1.1 against *Staphylococcus* and 0.96 against *B. coli*. Cooper and Forstner[3]

[1] E. Klarmann, L. W. Gatyas and V. A. Shternov, THIS JOURNAL, **53**, 3397 (1931).

[2] E. A. Cooper and D. L. Woodhouse, *Biochem. J.*, **17**, 600 (1923).

[3] E. A. Cooper and G. E. Forstner, *ibid.*, **18**, 940 (1924).

determined the growth-inhibiting concentrations of hydroquinone and some of its nucleus substituted homologs for *B. pyocyaneus* and *B. coli*. They found the growth of the former bacteria to be inhibited by the following dilutions: hydroquinone 1:2550, methylhydroquinone 1:1040, dimethylhydroquinone 1:1240 and thymohydroquinone 1:330. The corresponding bacteriostatic dilutions for *B. coli* were 1:710, 1:700, 1:1740 and 1:1100, respectively. Additional data on the antibacterial properties of hydroquinone may be found in the publications of Cooper,[4] Regenstein,[5] Morgan and Cooper,[6] Cooper and Haines[7] and others.

The compounds prepared and studied by us to date comprise the normal aliphatic saturated monoethers of hydroquinone up to the nonyl ether, some secondary ethers and a number of ethers obtained by substitution with aromatic groups. The bacteriological investigation was carried out with the aid of the two pathogenic bacteria used before, *viz.*, *B. typhosus* and *Staphylococcus aureus;* the reasons for their selection were given in our preceding paper. However, experiments with several other bacteria are under way at this time.

TABLE I

BACTERICIDAL ACTION OF MONOETHERS OF HYDROQUINONE

	B. typhosus Bactericidal concentrations				*Staph. aureus* Bactericidal concentrations			
	5 min.	10 min.	15 min.	Phenol coeff.	5 min.	10 min.	15 min.	Phenol coeff.
Hydroquinone	1:1500	<1:2000	<1:2000	>12	1:30	1:35	1:45	0.44
Alkyl ethers								
Methyl	1:130	1:140	1:150	1.0	1:60	1:70	1:70	0.8
Ethyl	1:200	1:225	1:225	1.5	1:100	1:100	1:100	1.5
n-Propyl	1:700	1:750	1:750	5.4	1:275	1:300	1:325	4.1
Isopropyl	1:450	1:500	1:500	3.6	1:150	1:180	1:200	2.3
n-Butyl	1:1800	1:2000	1:2250	14	1:700	1:800	1:800	9.3
n-Amyl	1:3500	1:4000	1:4000	29	1:2250	1:2500	1:2500	30
sec.-Amyl	1:2500	1:2750	1:2750	19	1:2000	1:2000	1:2250	26
n-Hexyl	1:2500	1:2750	1:3250	18	1:7500	1:7500	1:7500	100
n-Heptyl	1:2250	1:2500	1:2500	17	1:13000	1:16000	1:20000	200
n-Octyl					1:30000	1:32500	1:32500	360
Aromatic ethers								
Phenyl	1:5500	1:6000	1:7000	41	1:1800	1:2000	1:2000	28
Benzyl	1:2500	1:2750	1:3000	21	1:1000	1:1100	1:1200	14
Phenylethyl	1:3500	1:3500	1:3750	25	1:2250	1:2250	1:2500	29
Phenylpropyl	1:1400	1:1500	1:1500	10	1:1200	1:1400	1:1500	13
Control								
Phenol (average)	1:130	1:140	1:160	1	1:70	1:80	1:90	1

The bactericidal effectiveness of the monoethers of hydroquinone appears from Table I and the two graphs. The minimum bactericidal concentrations were determined for periods of exposure of five, ten and fifteen

[4] E. A. Cooper, *British Medical J.*, I, 1234, 1293, 1359 (1912).

[5] H. Regenstein, *Zentr. Bakteriologie I*, Orig., **63**, 281 (1912).

[6] G. T. Morgan and E. A. Cooper, *Biochem. J.*, **15**, 587 (1921).

[7] E. A. Cooper and R. B. Haines, *J. Hygiene*, **28**, 163 (1928).

minutes at 37° and the phenol coefficients were calculated from these data. As in the case of the resorcinol monoethers the series of compounds shows a different general behavior toward the two test organisms (incidentally of different Gram reaction). Thus the germ killing effect upon *B. typhosus* of the aliphatic derivatives increases from the methyl ether to the *n*-amyl ether, and then decreases again down to the *n*-heptyl derivative. In the case of *Staphylococcus aureus* a continuous rise is observed, the maximum being reached apparently with the *n*-octyl ether. No tests could be carried

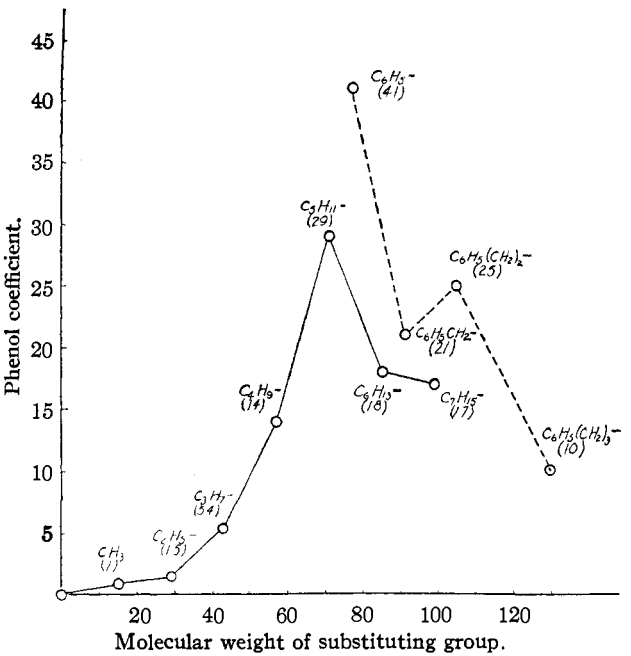


Fig. 1.—The effect of the substituting radical upon the bactericidal action of monoethers of hydroquinone; test organism, *B. typhosus:* full line ——— alkyl derivatives; dash line – – – aromatic derivatives.

out beyond the *n*-heptyl ether with *B. typhosus* and the *n*-octyl ether with *Staphylococcus aureus*, owing to the insolubility of the compounds and the resulting impossibility of preparing solutions of the required concentrations. Generally the bactericidal action of the aliphatic monoethers of hydroquinone is found to be less than that of the resorcinol monoethers, although some derivatives appear to be very potent bactericides, particularly for *Staphylococcus aureus*. As in the case of resorcinol derivatives, the monoethers of hydroquinone obtained by substitution with a secondary radical are less effective than the corresponding straight chain derivatives.

Introduction of aromatic groups also leads to strongly bactericidal com-

pounds. The potency of some of them compares favorably with that of the corresponding resorcinol monoethers. In both cases there is a drop in efficacy from the phenyl to the benzyl ether derivatives, then a rise with further increase of the molecular weight of the phenylalkyl group to the phenylethyl ether; but unlike the case of resorcinol, there is another decline of bactericidal potency in the hydroquinone phenylpropyl ether.

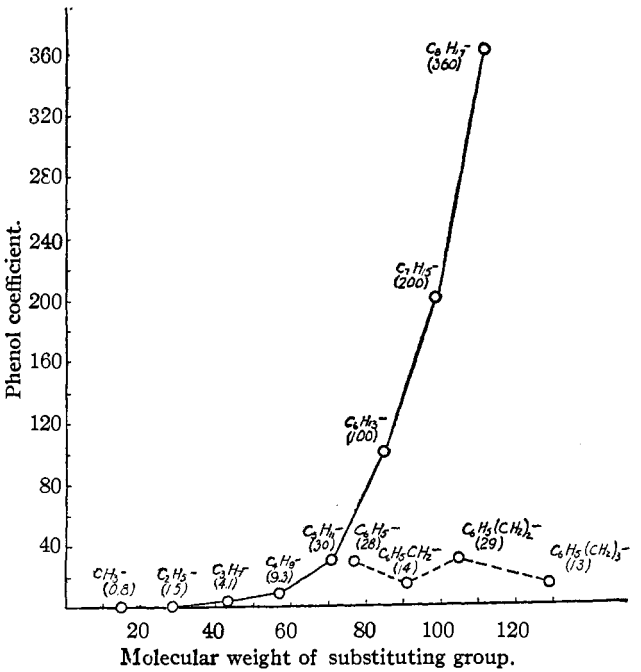


Fig. 2.—The effect of the substituting radical upon the bactericidal action of monoethers of hydroquinone; test organism, *Staph. aureus:* full line ——— alkyl derivatives; dash line – – – aromatic derivatives.

In contrast to resorcinol, the parent compound hydroquinone appears to be a more potent germicide for *B. typhosus* than some of its monoether derivatives. Undoubtedly this is due to the capacity of hydroquinone to act in certain cases not only as a phenol, but also as a powerful reducing agent, because of its ease of oxidation to benzoquinone. Besides, it is possible that the benzoquinone formed further acts on bacteria; Morgan and Cooper[6] attribute considerable germicidal potency to this compound. In contrast to this, the structural configuration of the monoethers of hydroquinone precludes the easy oxidation to benzoquinone derivatives: the ethers, therefore, may be expected to act upon bacteria as phenol derivatives, without any collateral action. This contention is also borne out by the consideration of the temperature coefficients

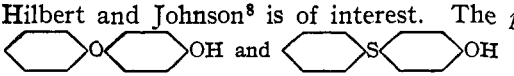
$$\left(\frac{\text{average min. bacteric. concn. at } 20°}{\text{average min. bacteric. concn. at } 37°}\right)$$

of the bactericidal action upon *B. typhosus* of hydroquinone on one hand, and of its ethers on the other, as shown in Table II.

TABLE II

	Temp., °C.	*B. typhosus* Bactericidal concentrations 5 min.	10 min.	15 min.	Phenol coeff.	Temp. coeff. for 17° C.	*Staph. aureus* Bactericidal concentrations 5 min.	10 min.	15 min.	Phenol coeff.	Temp. coeff. for 17°C.
Hydroquinone	20	1:100	1:100	1:200	1.4		1:20	1:20	1:25	0.34	
	37	1:1500	<1:2000	<1:2000	>12	>15	1:30	1:35	1:45	.44	1.7
Hydroquinone methyl ether	20	1:80	1:90	1:90	1.0						
	37	1:130	1:140	1:150	1.0	1.6					
Hydroquinone propyl ether	20	1:450	1:550	1:600	6.1		1:225	1:150	1:250	4.4	
	37	1:700	1:750	1:750	5.4	1.3	1:275	1:300	1:325	4.1	1.2

Thus at 20° the germicidal action of hydroquinone upon *B. typhosus* hardly exceeds that of phenol at the same temperature, while at 37° it is more than fifteen times greater than at 20° and more than twelve times greater than that of phenol at 37°. In contrast to this, an increase of temperature of 17° raises the bactericidal effect of the hydroquinone ethers studied to a much lesser extent. All of this indicates that in the case of the unsubstituted hydroquinone a rise in temperature not only increases what might be termed its antibacterial "phenol reactivity" against *B. typhosus* but even more so, intensifies another, collateral effect. *Staphylococcus aureus* apparently is not susceptible to this "collateral" action, and in this case the unsubstituted hydroquinone manifests a weaker antibacterial potency than its lowest monoether. Also a consideration of the temperature coefficient discloses nothing unusual here. Future experiments will have to show whether there is a relation between this phenomenon and the Gram reaction.

Since the monophenyl ethers of the dihydric phenols may also be regarded as hydroxydiphenyl oxides, a comparison with the hydroxydiphenyl sulfides studied by Hilbert and Johnson[8] is of interest. The *p*-derivatives in question are  and

A strict comparison is not feasible owing to differences in bacteriological testing methods, but the *p*-hydroxydiphenyl sulfide (with a *B. typhosus* phenol coefficient of 115) appears to be almost three times as potent as the corresponding oxide; the *m*-hydroxydiphenyl sulfide, however, is only somewhat over 50% more effective than the corresponding resorcinol phenyl ether.

The antibacterial superiority of the hydroxydiphenyl sulfides over the corresponding oxides is probably due to a better "lipoid" solubility of the former.

[8] G. E. Hilbert and T. B. Johnson. THIS JOURNAL, 51, 1526 (1929).

Experimental Part

(a) **Chemical.**—The compounds of this series were prepared by a number of different methods. Most of them were obtained by condensation of hydroquinone with an organic halide. This condensation was carried out either directly, or in the presence of potassium hydroxide or carbonate. The hydroquinone monophenyl ether (*p*-hydroxydiphenyl oxide) was prepared by condensation of *p*-bromophenol with phenol in the presence of potassium hydroxide since the bromine atom in bromobenzene is too firmly attached to the nucleus to react with hydroquinone directly.

The analytical properties of the hydroquinone monoethers prepared are given in Table III.

TABLE III

ANALYTICAL DATA OF MONOETHERS OF HYDROQUINONE

Alkyl Ethers	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	M. p., °C.	B. p., °C.	mm.
Ethyl[a]	$C_8H_{10}O_2$	69.54	69.39	7.30	7.44	65–66		
n-Propyl	$C_9H_{12}O_2$	71.01	71.28	7.95	7.91	56–57		
Isopropyl	$C_9H_{12}O_2$	71.01	71.70	7.95	8.15		117	4
n-Butyl	$C_{10}H_{14}O_2$	72.26	72.31	8.49	8.75	64–65		
n-Amyl	$C_{11}H_{16}O_2$	73.31	73.75	8.95	9.07	49–50		
Sec.-amyl	$C_{11}H_{16}O_2$	73.31	73.77	8.95	8.87	48–49		
n-Hexyl	$C_{12}H_{18}O_2$	74.20	74.02	9.34	9.36	48		
n-Heptyl	$C_{13}H_{20}O_2$	74.98	75.57	9.68	10.20	60		
n-Octyl	$C_{14}H_{22}O_2$	75.65	75.47	9.98	9.83	60–61		
n-Nonyl	$C_{15}H_{24}O_2$	76.22	76.25	10.24	10.14	68.5		
Aromatic ethers								
Phenyl[b]	$C_{12}H_{10}O_2$	77.43	73.32	5.42	5.31	83		
Benzyl[c]	$C_{13}H_{12}O_2$	78.01	77.91	6.05	6.32	121		
Phenylethyl	$C_{14}H_{14}O_2$	78.48	77.90	6.59	6.72		183	4
Phenylpropyl	$C_{15}H_{16}O_2$	78.92	78.24	7.07	7.10	75–76		

[a] Previously prepared by Wichelhaus, *Ber.*, **12**, 1501 (1879); Hantzsch, *J. prakt. Chem.*, [II] **22**, 462 (1880). [b] Previously prepared by Häussermann and Bauer, *Ber.*, **29**, 2085 (1896); Mueller, *ibid.*, **34**, 1070 (1901). [c] Previously prepared by Schiff and Pelizzari, *Ann.*, **221**, 369 (1883).

The methods applied in the preparation of the hydroquinone monoethers are illustrated in the following examples.

Direct Condensation. Preparation of *p*-Hydroxyphenyl Benzyl Ether.—To a boiling solution of 45.5 g. (10% excess) of hydroquinone in 200 cc. of xylene, 47.5 g. of benzyl chloride was added drop by drop in the course of six hours. Hydrogen chloride fumes escaped during the process. The mixture was allowed to cool. It was diluted with ether and washed with water, then shaken repeatedly with a 10% solution of potassium hydroxide. The combined alkaline extracts were washed with ether and acidified with dilute hydrochloric acid. A crystalline precipitate of *p*-hydroxyphenyl benzyl oxide formed. It was filtered off and purified by crystallization from water.

The same compound was also obtained by condensation in acetone solution in the presence of potassium carbonate.

The hydroquinone dibenzyl ether which forms at the same time was isolated from

the ether solution after extraction with alkali, and purified by crystallization from alcohol. It melts at 127–128° (uncorr.).

Anal. Calcd. for $C_{20}H_{18}O_2$: C, 82.76; H, 6.21. Found: C, 82.54; H, 6.39.

Condensation in the Presence of Potassium Hydroxide. Preparation of *p*-Hydroxyphenyl Monoisopropyl Ether.—Hydroquinone (37 g.) was dissolved in 40 cc. of alcohol. To this solution 56.7 g. of isopropyl iodide was added. A solution of 20 g. of potassium hydroxide in 60 cc. of water was added under reflux drop by drop in the course of one hour, and boiling continued for another three hours. An excess of alkali was added and the resulting mixture was steam distilled in order to remove the unconverted isopropyl iodide and the di-isopropyl ether of hydroquinone. The solution was acidified with hydrochloric acid and the steam distillation continued whereby the desired hydroquinone monoisopropyl ether was driven out. It was isolated from the distillate by extraction with ether, and after evaporation of the ether it was purified by repeated distillation in a vacuum.

The isolation of monoethers by distilling with ordinary steam cannot be applied conveniently in the case of the ethers containing a substituting group with more than four carbon atoms. Therefore, in the case of the butyl and higher ethers, the separation of the di-ether from the mono-ether was accomplished with the aid of alkali in the manner described under the preparation of the benzyl ether.

The lower aliphatic ethers which are solid at room temperature were crystallized from water, the higher ones (from the amyl ether upward) from ligroin (boiling range 60–70°).

Hydroquinone monophenylethyl ether was prepared by the condensation of hydroquinone with phenylethyl bromide in the presence of dilute potassium hydroxide as described above. After isolation by the alkali method it was purified by repeated vacuum distillation.

A number of aliphatic di-ethers which formed simultaneously in the course of the processes aiming at the preparation of the monoethers, were prepared in a pure state (by crystallization from alcohol). They are: hydroquinone diethyl ether, m. p. 70–71°. Calcd. for $C_{10}H_{14}O_2$: C, 72.29; H, 8.43. Found: C, 72.46; H, 8.54. Hydroquinone dibutyl ether, m. p. 45–46°. Calcd. for $C_{14}H_{22}O_2$: C, 75.67; H, 9.91. Found: C, 75.82; H, 9.95. Hydroquinone di-isoamyl ether, m. p. 58–59°. Calcd. for $C_{16}H_{26}O_2$: C, 76.80; H, 10.40. Found: C, 76.74; H, 10.56.

Preparation of *p*-Hydroxydiphenyl Oxide.—While this compound has been obtained previously by diazotization of the *p*-aminodiphenyl ether we secured it by a direct condensation of *p*-bromophenol with phenol in the presence of alkali and copper.

Phenol (47 g., *i. e.*, 100% excess) and potassium hydroxide (15 g.) were placed in a round-bottomed flask and heated in an oil-bath until the water was driven off. The mixture was allowed to cool and 43.5 g. of *p*-bromophenol and 0.2 g. of freshly precipitated copper were added. The flask was connected with a reflux condenser and an inlet tube for hydrogen. While a continuous current of hydrogen was allowed to pass through the apparatus the temperature of the oil-bath was raised gradually to 130° and maintained for two hours. After cooling, the reaction mixture was diluted with water, acidified and distilled with steam in order to remove the unconverted bromobenzene and phenol. The solution was shaken with ether and after evaporation of the latter the residue was crystallized from a mixture of equal volumes of benzene and ligroin.

(b) **Bacteriological.**—The bacteriological testing technique was the same as outlined in the preceding publication of this series, except for the experiments carried out at the lower temperature.

Because of the difficult solubility, particularly of the higher ethers,

alcohol had to be used to facilitate solution. In most cases, however, not more than 10% of alcohol was present in the bactericidal dilutions given in Table I. Only with the heptyl and octyl ethers of hydroquinone were we compelled to have 15% of alcohol present, while the benzyl ether required 20% in the test with *Staphylococcus aureus*.

Summary

The second report in the series of investigations on the bactericidal properties of monoethers of dihydric phenols, deals with the derivatives of hydroquinone. The compounds studied have been obtained by introduction of the following aliphatic and aromatic radicals: methyl, ethyl, *n*- and isopropyl, *n*-butyl, *n*- and *sec.*-amyl, *n*-hexyl, *n*-heptyl, *n*-octyl, *n*-nonyl; phenyl, benzyl, phenylethyl and phenylpropyl.

As in the case of the resorcinol monoethers, described in the preceding paper, a number of compounds of considerable germicidal potency are also found in the hydroquinone series; here, too, the molecular weight and the structure of the substituting radicals play a determining role. The two test microörganisms used in this investigation, *viz.*, *B. typhosus* and *Staphylococcus aureus*, show a different behavior toward these compounds, similar to that observed in the case of the resorcinol ethers. Thus in experiments with *B. typhosus* the bactericidal potency of the aliphatic monoethers increases with increasing molecular weight of the substituting group, reaching the maximum with the *n*-amyl ether and decreasing thereafter. In contrast to this the maximum effect upon *Staphylococcus aureus* is not reached with the *n*-octyl ether; an extension beyond this point was not feasible, for the time being, because of the insufficient solubility of the higher ethers.

In the case of the resorcinol monoethers the maximum of germicidal potency was shown by the hexyl ether, with *B. typhosus* as test organism while the effect upon *Staphylococcus aureus* did not reach a definite maximum with the nonyl ether.

The normal alkyl derivatives are more potent germicides than those containing secondary alkyl groups.

The monoethers of hydroquinone obtained by the introduction of aromatic groups are also powerful germicides. The phenyl ether (*p*-hydroxydiphenyl oxide) is most effective against *B. typhosus*, the phenylethyl ether against *Staphylococcus aureus*. The antibacterial action drops with the benzyl ethers, rises again with the phenylethyl ether, and decreases with the phenylpropyl ether. While the corresponding resorcinol monoethers were generally more effective, a similar behavior was observed except that the bactericidal action of the phenylpropyl ether upon *Staphylococcus aureus* surpassed that of the phenylethyl derivative.

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