[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF NEW YORK UNIVERSITY]

Basis for the Physiological Activity of -Onium Compounds. XII. Aryl Ethers of Choline[1,2,3]

BY R. R. RENSHAW AND C. Y. HOPKINS

In a previous paper, the physiological activity[4] of the phenyl ether of choline has been described. The marked stimulating action of this substance on the respiration, and its effect upon the blood pressure, suggested to Hunt that it might have an antidotal action to narcotic poisons, particularly if the molecule could be so altered as to bring about an augmentation of certain effects. We have thought it desirable, therefore, to prepare a number of substituted phenyl ethers of choline by introducing various polar and water soluble groups in the aryl nucleus. It was thought that these groups would modify the orientation of the molecule at the adsorbing membrane and thus bring about a change in the intensity or duration of the stimulating actions. We have, therefore, prepared compounds in which a nuclear hydrogen atom has been replaced by hydroxyl, ether, ester, amino and acetamino groups. Hunt[4] has found that these groups markedly diminished the stimulating nicotine action and, in certain cases (the *p*-methoxy derivative), the activity was but little more than 5% of the activity of unsubstituted phenyl ether of choline, and that the acetamino group further greatly reduced or abolished this action.

In the preparation of these choline ethers, β-bromoethyl phenyl ethers were condensed with trimethylamine. The bromo ethers were prepared by condensing ethylene bromide with the corresponding phenol in the presence of potassium hydroxide. With the unsubstituted phenols, the method of Marvel,[5] in which the phenol is condensed by using aqueous alkali, gives excellent results, but with substituted phenols the yields are lower and the use of alcoholic alkali seems to be superior. In the case of polyphenols, there seems to be no record of the production of a monobromoethyl ether, although the interaction of the polyphenols with dihalogen alkanes has been studied by several workers. Vorländer,[6] in treating hydroquinone with sodium ethylate and varying quantities of ethylene bromide, succeeded in getting only the bis-ether and, at times, a small quantity of alkali insoluble, bromine free product. On repeating the experiment with aqueous potassium hydroxide, he reported getting an "inextricable mixture of substances." With catechol, he isolated only the ethylene ether,

(1) This problem is being carried out in coöperation with Dr. Reid Hunt of the Harvard Medical School. The physiological data are the basis of another series of papers published elsewhere by him.

(2) This is the second paper constructed from a thesis presented by C. Y. Hopkins, June, 1929, for the degree of Doctor of Philosophy at New York University.

(3) The authors wish to express their appreciation to Parke, Davis & Co. for a Fellowship which has made this work possible.

(4) Hunt and Renshaw, *J. Pharmacol.*, **37**, 193 (1929).

(5) Marvel and Tanenbaum, THIS JOURNAL, **44**, 2647 (1922).

(6) Vorländer, *Ann.*, **280**, 203 (1894).

and with resorcinol he obtained a mixture from which nothing could be isolated.

We have found it possible, with hydroquinone, to get a yield of from 14 to 16% of the mono β-bromoethyl ether by using a methyl alcohol solution of potassium hydroxide, whereas the best yield, using aqueous potassium hydroxide, was 10%. In all cases investigated with the polyhydroxyphenol, large quantities of the diether and bis compound were formed.

$$C_6H_4(OH)_2 + C_2H_4Br_2 \longrightarrow BrC_2H_4OC_6H_4OH + (BrC_2H_4O)_2C_6H_4 + (HOC_6H_4OCH_2—)_2$$

Less thorough investigation failed to yield a mono ether of resorcinol. Attempts to obtain the desired product through the monobenzoyl derivative of hydroquinone also failed because of the easy hydrolysis of the latter substance.

Experimental Part

β-Bromoethyl Aryl Ethers

Hydroquinone Mono β-Bromoethyl Ether, $BrC_2H_4OC_6H_4OH$.—A mixture of 22 g. of hydroquinone (0.2 mole) and 45 g. of ethylene dibromide (0.25 mole) was dissolved in a solution of 11.2 g. of potassium hydroxide (0.2 mole) in 150 cc. of methyl alcohol. The mixture was stirred and refluxed for five hours. The potassium bromide was removed, most of the alcohol distilled off and the residue poured into 500 cc. of water. The precipitate was stirred vigorously with cold benzene (150 cc.), which dissolved the mono- and dibromoethyl ethers but not the unchanged hydroquinone nor the bis-ether. (The bis compound, previously prepared by Vorländer,[6] was isolated from the residue.) The benzene solution was washed thoroughly with 8% aqueous sodium hydroxide (100 cc.) in order to separate the mono-ether from the di-ether. The aqueous layer was partly neutralized with hydrochloric acid, filtered with charcoal and acidified. The precipitate (7.0 g.) was purified by recrystallizing from a mixture of benzene and ligroin, from which it separated as faintly yellow, glistening plates, m. p. 107° (corr.). It is soluble in alcohol, ether, acetone, chloroform, benzene, acetic acid and *n*-butyl alcohol, moderately soluble in methyl alcohol and carbon tetrachloride and slightly soluble in petroleum ether and water.

Anal. Calcd. for $C_8H_9O_2Br$: Br, 36.83. Found: Br, 37.01, 36.64.

Hydroquinone Di-β-bromoethyl Ether, p-$(BrC_2H_4O)_2C_6H_4$.—The benzene solution obtained in the foregoing, from which the mono ether had been extracted with sodium hydroxide, was dried over sodium sulfate and evaporated to dryness. The residue (2.5 g.) was recrystallized from benzene containing a little ligroin from which it separated as slightly yellow, shiny plates, m. p. 115° (corr.), This di-ether is soluble in alcohol, benzene, acetone, chloroform and insoluble in water.

Anal. Calcd. for $C_{10}H_{12}O_2Br_2$: Br, 49.35. Found: Br, 49.33, 49.27.

Ethylene Glycol Bis-(*m*-hydroxyphenyl) Ether $(HOC_6H_4OCH_2-)_2$.—To a solution of 11.2 g. of potassium hydroxide (0.2 mole) in 150 cc. of water was added 22 g. of resorcinol (0.2 mole) and 60 g. of ethylene dibromide (0.33 mole). The mixture was boiled under reflux with stirring for five hours. The heavy brown oil which formed was separated and treated twice with 50-cc. portions of 5% sodium hydroxide, whereupon most of it dissolved. The alkaline solution was filtered with charcoal and the filtrate made just acid to Congo red, thereby precipitating an oil and a white solid. After drying, the oil was dissolved by boiling with chloroform and the dry crystals were purified by two recrystallizations from 50% alcohol. The substance crystallizes in white, glistening

flakes, m. p. 165° (corr.). It is soluble in alcohol, ether and acetone, but insoluble in benzene, chloroform, water and ligroin.

Anal. Calcd. for $C_{14}H_{14}O_4$: C, 68.3; H, 5.7. Found: C, 68.8; H, 5.5.

The oil obtained by chloroform extraction of the crude bis-ether decomposed when subjected to a vacuum distillation.

The ethers described in Table I were prepared in a similar manner by the use of methyl alcoholic potassium hydroxide.

TABLE I

	M. p. (corr.), °C.	Halogen, Calcd.	Found I	Found II
p-$BrC_2H_4OC_6H_4OOCCH_3$	[a] 76.5–77	30.86	30.92	30.94
p-$BrC_2H_4OC_6H_4OOCC_6H_5$	[b] 119	24.90	24.79	24.90
p-$BrCH_2CH_2OC_6H_4OCH_3$	[c] 49–50	34.59	34.79	34.59
$BrCH_2CH_2OC_6H_3$-2-OCH_3-4-$CH{=}CHCH_3$	[d] B. p. 190° (12 mm.)	29.48	29.43	29.32
$BrCH_2CH_2OC_6H_3$-2-OCH_3-4-$CH_2CH{=}CH_2$	[e] 23° (uncorr.) B. p. 182° (13 mm.)	Characterized by trimethylamine addition product. See Table II		
$(p\text{-}CH_3OC_6H_4CH_2\text{-})_2$	[f] 147.5°	Calcd.: C, 70.0; H, 6.6 Found: C, 69.6; H, 6.8		

[a] Diamond-shaped plates from butyl alcohol. [b] Fine needles from 95% alcohol. [c] The product was freed from the bis compound by dissolving in cold acetone and from the phenol by repeated washing of its benzene solution with aqueous sodium hydroxide. It separated from 80% alcohol in shiny plates having an odor suggestive of licorice. Yield of purified product, 20%. [d] The oil has a peculiar sweetish odor. [e] Colorless oil obtained in 22% yield having a slight odor resembling eugenol. [f] The residue from the cold acetone extraction in (*c*) was purified by recrystallizing from hot acetone. It separates as white plates, which are soluble in alcohol, acetic acid, hot water, hot acetone and nearly insoluble in benzene.

Aryl Choline Ethers.—These choline ethers were prepared by condensing the β-bromoethyl aryl ethers with trimethylamine, usually in toluene. The rate at which this condensation took place varied considerably with the particular compound. Where there was a tendency for the elimination of the hydrohalide with a formation of trimethylammonium halide, it was found that this secondary reaction could be diminished and sometimes prevented by carrying out the condensation at ordinary temperatures. At this lower temperature, however, the reaction is frequently very slow, requiring a number of days. In work with these materials, as one of us has already found with a number of other halogen derivatives, the first material crystallizing out sometimes contained a greater amount of the products of the secondary reaction, in these cases, trimethylammonium halide. It was found, therefore, desirable in certain instances to cool the reaction mixture to 0° after the reaction had been allowed to go on for a time, and then decant from the crystals formed into another pressure bottle and allow the reaction to proceed. It seems worth while to call attention to this phenomenon since it has happened frequently when definite tests had been

TABLE II

CHOLINE ETHER BROMIDES

Formulas		M. p. (corr.) °C.	Solubility alcohol	Solvent	Crystal form	Halogen, % Calcd.	Found	
p-$HOC_6H_4OC_2H_4N(CH_3)_3Br$	[a]	254	S. sol.	Abs. alc.	Needles	28.94	28.89	28.77
p-$CH_3OC_6H_4OC_2H_4N(CH_3)_3Br$	[b]	144	V. sol.	Hot acet.	Plates	27.55	27.52	27.57
o-$CH_3OC_6H_4OC_2H_4N(CH_3)_3Br$	[c]	139	V. sol.	Acet.	Short needles	27.55	27.72	27.65
p-$C_6H_5COOC_6H_4OC_2H_4N(CH_3)_3Br$	[d]	208–209	Sol.	Alc. eth.	....	21.02	21.16	21.14
p-$CH_3COOC_6H_4OC_2H_4N(CH_3)_3Br$	[e]	152	Sol.	.....	....	25.13	25.17	25.23
p-$H_2NC_6H_4OC_2H_4N(CH_3)_3Br$	[f]	195	Sol.	n-Butyl alc.	Triangular needles	29.05	28.96	28.90
p-$CH_3CONHC_6H_4OC_2H_4N(CH_3)_3Br$	[g]	248	S. sol. abs. alc.	Methyl.-ethyl alc.	Fine needles	25.20	25.15	25.23
2-CH_3O-4-CH_2=$CHCH_2C_6H_3OC_2H_4N(CH_3)_3Br$		147	Sol.	Alc. eth.	Leaflets	24.21	24.27	24.34
2-CH_3O-4-CH_3CH=$CHC_6H_4OC_2H_4N(CH_3)_3Br$		158	Sol.	Alc. eth.	Fine needles	24.21	24.41	24.29

[a] This condensation was brought about at room temperature during several weeks. [b] This reaction required two weeks at room temperature for completion. [c] The reaction required several days for completion at room temperature. The crystals began to form after two hours. They were impure and the product formed after twelve hours was removed and the reactants returned to the pressure bottle. The product formed subsequently was substantially pure. [d] This reaction was substantially complete after three hours of heating at 70°. [e] The reaction was substantially complete after ten days at room temperature. [f] This condensation seemed to be complete after two days at ordinary temperatures. Due to the strong colorations of solutions of this compound with iron salts, the Volhard method could not be used. It was analyzed by the Robertson procedure. The hydrochloride was obtained as feather-like crystals, m. p. 265° (corr.). [g] This reaction was complete in about a week at ordinary temperatures.

made to prove the absence of free halogen acids in the sample of halogen compound used. These substances were all soluble in water and insoluble in benzene, ligroin and ether. Their solubility in acetone and chloroform varied considerably.

Summary

Several aryl substituted β-bromoethyl phenyl ethers have been prepared including the mono derivative of hydroquinone. These halogen compounds have been converted into substituted phenyl ethers of choline. All of them were less active than the unsubstituted phenyl ether in stimulating respiration and blood pressure.

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The Dehydration and Rearrangement of Certain Pinacolyl Alcohols and Related Compounds

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The dehydration and rearrangement of pinacolyl alcohols have been studied in only four cases in which all the groups involved are aliphatic, namely, pinacolyl alcohol itself (*tert*-butylmethylcarbinol),[2] *tert*-butylethylcarbinol,[3,4] *tert*-amylmethylcarbinol[4] and *tert*-butylisopropylcarbinol.[5] With only the first of these substances has anything approaching a complete study been made. The present investigation was undertaken in connection with theoretical studies on the mechanism of rearrangements.[6] The pinacolyl alcohols selected were 6,6-dimethyldecanol-5 (I) and 3-methyl-3-butylheptanol-2 (II) because of their availability and the variety of courses which their rearrangements might follow. These were prepared by reducing the pinacolones obtained by Meerwein[7] from the rearrangement of the glycol made from butylmagnesium bromide and ethyl α-hydroxyisobutyrate. In order to conserve the pinacolones, the methods of reducing ketones, of dehydrating secondary alcohols and of ozonizing

(1) Presented in partial fulfilment of the requirements for the Ph.D. degree. Part of this work was done under a Grant-in-Aid from the National Research Council.

(2) Couturier, *Ann. chim. phys.*, [6] **26**, 433–501 (1892); Zelinsky and Zelikow, *Ber.*, **34**, 3250 (1901); Delacre, *Mem. acad. roy. Belg.*, 296 (1904); *Bull. soc. chim.*, [4] **1**, 575, 978 (1907); Nybergh, Hyllningsskrift tillagnad Ossian Aschan, 98–102 (1920); Van Risseghem, *Bull. soc. chim. Belg.*, **30**, 8 (1921); Fomin and Sochanski, *Ber.*, **46**, 244 (1913); H. S. Rothrock and P. L. Meunier, unpublished results from this Laboratory.

(3) Faworsky and Alexejewa, *J. Russ. Phys.-Chem. Soc.*, **50**, 557–70 (1918).

(4) Edgar, Calingaert and Marker, THIS JOURNAL, **51**, 1483 (1929).

(5) Whitmore and Houk, *ibid.*, **54**, 3714 (1932).

(6) Whitmore, *ibid.*, **54**, 3274 (1932).

(7) Meerwein, *Ann.*, **419**, 121–75 (1919).