hydroxyl hydrogen in the 2-methyl-2-propanol by deuterium decreases the transfer constant by almost 50% at 100°, although no isotope effect was noted at 130°. The small apparent decrease in the transfer constant at the higher temperature is apparently not due to any isotope effect but to the slight acceleration in polymerization rate caused by the alcohol when prepared through the aluminum alkoxide.

In the case of the 2-propanol, however, it is also quite clear that replacement of the hydroxyl hydrogen by deuterium shows no rate effect but that replacement of the secondary hydrogen shows a definite effect. Hence it can be concluded that the chain transfer reaction involves the carbon–hydrogen bond in the secondary alcohol and the oxygen–hydrogen bond in the tertiary alcohol. The fact that the isotope effect involves only a factor of 2 instead of the usual 4 or more may suggest that other groups, *e.g.*, methyl hydrogen are also participating in chain transfer. However, there is enough indication that the above bonds are primarily involved in this reaction and that chain transfer with the methyl hydrogens would certainly not be a lower energy reaction.

The absolute values for the chain transfer rate constants listed in Table VIII can also be satisfactorily explained in the light of this information. Thus the activation energy for the rupture of the respective bonds would be expected to increase from the weakest sulfur–hydrogen bond of the thiol to the strongest oxygen–hydrogen bond of the tertiary alcohol. Furthermore the active hydrogen in the nitrile molecule would be activated to a greater extent than that of the secondary alcohol, since the nitrile group is much more polar than the hydroxyl. The relative uniformity in and low value of the frequency factor is also quite reasonable, since, in all of these compounds, the reactive hydrogen atom is shielded by three large substituent groups, *i.e.*, either three methyl groups or two methyl groups and a nitrile or hydroxyl group.

In view of the great differences found in the case of formation of these radicals, some semi-quantitative conclusions can be drawn about the relative activity in hydrogen abstraction of the four radicals corresponding to the four compounds studied. Thus the thiol radical can be safely assumed to have by far the lowest activity in abstracting hydrogen atoms, while the *t*-butoxy radical would be expected to be the most reactive. The isobutyronitrile and the hydroxy-isopropyl radicals can both be considered as carbon-headed free radicals and should be not too different in their reactivity toward hydrogen abstraction. Hence it might be concluded that an oxy radical, such as may be obtained from peroxides, may be only 5 or 10 times more active in hydrogen abstraction than a carbon-headed radical, such as forms the head of a growing radical chain. In view of the much greater predominance of growing chain radicals over initiator radicals during polymerization, it would, therefore, seem highly doubtful that the type of initiator used could seriously affect the degree of branching in the polymer chain.

AKRON 4, OHIO

[CONTRIBUTION FROM ABBOTT LABORATORIES]

Halogen Substituted Aryl Alkamine Ethers

BY M. VERNSTEN, H. B. WRIGHT AND M. B. MOORE

RECEIVED JUNE 18, 1956

A variety of halogenated phenols and naphthols has been used in the preparation of cyclic-aminoalkyl ethers for a study of their fungistatic activity.

The interest in this Laboratory in anesthetic aminoalkyl ethers[1] led to their testing for other types of biological activity. Nearly all proved to be fungistatic, and the members with halogen substituents exhibited greatly enhanced activity against fungi.

The aryl alkamine ethers here reported (Tables I–VI) were prepared for a study of the effects of position and kind of halogen, of more than one such substituent and of other substituents. Except for a few used for comparison, the amines of the aminoalkyl groups were cyclic.

Variations in .the cyclic amine usually exert much less effect upon the fungistatic activity than upon the animal toxicity. For this reason, the minimally toxic 4-morpholinyl derivatives are to be preferred. With respect to the aryl portion of the molecule, the fungistatic tests indicate superiority of the *p*-biphenylyl structure over other isomers. One halogen either on the same ring as the ether group or on the other ring of the biphenyl seems to confer maximum activity, no advantage being shown by two or three halogens. There appears to be little difference between chlorine and bromine derivatives. A second benzene ring (which may be condensed with the first) or a fairly large alkyl group is necessary for good antifungal activity.

(1) (a) H. B. Wright and M. B. Moore, THIS JOURNAL, **73**, 2281 (1951); (b) **73**, 5525 (1951); (c) **75**, 1770 (1953); (d) **76**, 4396 (1954).

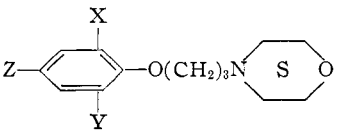
Experimental[2]

The ethers were prepared by one of three methods.

I. (**Compounds 36–47**).—An aryloxyalkyl halide was refluxed with a large excess (up to ten equivalents) of the appropriate cyclic amine for about two hours. Distillation of most of the excess amine was followed by solution of the residue in chloroform, and water extraction of the remaining excess amine from the chloroform solution. The residual oil obtained by distillation of the chloroform was dissolved in dry ether, decolorized with carbon, filtered and the solid hydrochloride precipitated and recrystallized from 2-propanol.

(2) All melting points are corrected.

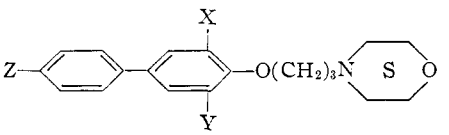
TABLE I



No.	X	Y	Z	B.p. or m.p. °C.	Mm.	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
1	Cl	H	OC_4H_9-*n*	204–205	3.2	54	$C_{17}H_{26}ClNO_3$	62.28	62.28	7.99	8.18
2	Cl	H	C_5H_{11}-*t*	196–197		72	$C_{18}H_{28}ClNO_2 \cdot HCl$	59.66	59.66	8.07	8.06
3	Cl	H	C_8H_{17}	190	1.4	64	$C_{21}H_{34}ClNO_2$	68.55	68.74	9.31	9.14
4	Cl	Cl	C_5H_{11}-*t*	188–189		90	$C_{18}H_{27}Cl_2NO_2 \cdot HCl$	54.48	54.73	7.11	7.13
								26.82[d]	26.48		
5	Cl	CH_3	C_5H_{11}-*n*	139–141		64	$C_{19}H_{30}ClNO_2 \cdot HCl$	60.60	61.37	8.30	8.48
6	Cl	C_6H_5	H	187–188		87	$C_{19}H_{22}ClNO_2 \cdot HCl$	61.96	61.98	6.29	6.54
7	C_6H_5	H	Cl	186–187		75	$C_{19}H_{22}ClNO_2 \cdot HCl$	61.96	61.87	6.29	6.18
8	Cl	C_6H_5	Cl	200–201		83	$C_{19}H_{21}Cl_2NO_2 \cdot HCl$	56.66	57.02	5.50	5.55
								26.41[d]	26.10		
9	Br	Br	H	156–158		70	$C_{13}H_{17}Br_2NO_2 \cdot HCl$	33.94	34.10	3.94	3.98
10	Br	H	C_5H_{11}-*t*	183–185		79	$C_{18}H_{28}Br_2NO_2 \cdot HCl$	53.14	53.06	7.19	7.24
11	Br	CH_3	Br	131–132		72	$C_{14}H_{19}Br_2NO_2 \cdot HCl$	39.14	39.44	4.69	4.86
12	Br	CH_3	C_5H_{11}-*t*	169–172		9	$C_{19}H_{30}BrNO_2 \cdot HBr$	49.04	47.83	6.72	6.73
								34.35[d]	32.87		
13	Br	CH_3	$CH(CH_3)C_3H_7$	153–155		65	$C_{19}H_{30}BrNO_2 \cdot HCl$	54.23	53.55	7.43	7.91
14	I	I	I	238–239		78	$C_{13}H_{16}I_3NO_2 \cdot HCl$	24.57	24.95	2.70	2.77
								59.92[e]	59.93		
15	H	H	*m*-$ClC_6H_4CH{=}CH$	71-72		29	$C_{21}H_{24}ClNO_2$	70.48	70.38	6.76	6.56
16	H	H	*p*-$ClC_6H_4CH{=}CH$	136–139		31	$C_{21}H_{24}ClNO_2$	70.48	69.91[a]	6.76	6.67[a]
17	H	H	*p*-$ClC_6H_4CH_2CH_2$	79–80		63	$C_{21}H_{26}ClNO_2$	70.08	70.25	7.28	7.21
18	H	H	*p*-$ClC_6H_4N{=}CH$	100–101		48	$C_{20}H_{23}ClN_2O_2$	66.93	66.74	6.46	6.25
19	C_6H_5	H	Cl[b]	181–186	1.1	44	$C_{19}H_{22}ClNO_2$	68.77	69.02[a]	6.68	6.63[a]
20	$CH(C_2H_5)_2$	5-CH_3	Cl	179–189	1.0	36	$C_{19}H_{30}ClNO_2$	67.15	66.15	8.90	8.29

[a] Average of two analyses. [b] Position uncertain. [c] Iodine. [d] Halogen, %.

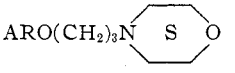
TABLE II



No.	X	Y	Z	B.p. or m.p., °C.	Mm.	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
21	Cl	H	H	56–57		58	$C_{19}H_{22}ClNO_2$	68.77	68.76	6.68	6.63
22	H	H	Cl	93–94		52	$C_{19}H_{22}ClNO_2$	68.77	68.89	6.68	6.80
23	Cl	Cl	H	206–208		74	$C_{19}H_{21}Cl_2NO_2 \cdot HCl$	56.66	57.52	5.50	5.59
								26.41[a]	25.55		
24	Br	H	H	208	0.9	35	$C_{19}H_{22}BrNO_2$	60.64	60.83	5.90	6.00
25	H	H	Br	251–253		67	$C_{19}H_{22}BrNO_2 \cdot HCl$	55.28	55.40	5.62	5.95
26	Br	Br	H	214–216	0.4	53	$C_{19}H_{21}Br_2NO_2$	35.11[a]	36.19		
				198–200			$C_{19}H_{21}Br_2NO_2 \cdot HBr$	42.56	43.78	4.14	4.19
								44.72[a]	44.38		
27	Br	H	Br	205–206		91	$C_{19}H_{21}Br_2NO_2 \cdot HBr$	44.72[a]	44.30		
28	Br	Br	Br	219–220		87	$C_{19}H_{20}Br_3NO_2 \cdot HBr$	51.98[a]	51.50		

[a] Halogen, %.

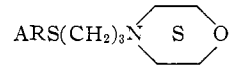
TABLE III



No.	AR	Salt m.p., °C.	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
29	2,3,4,5,6-Cl_5C_6	208–209	84	$C_{13}H_{14}Cl_5NO_2 \cdot HCl$	36.31	36.12	3.52	3.81
30	2,3,4,5,6-Br_5C_6	214–216	75	$C_{13}H_{14}Br_5NO_2 \cdot HCl$	23.94	23.67	2.32	2.55
					61.26[a]	61.41		
31	2,4-Cl_2-1-$C_{10}H_5$[b]	215–216	56	$C_{17}H_{19}Cl_2NO_2 \cdot HCl$	54.18	54.37	5.36	5.42
					28.24[c]	27.48		
32	1,3,6-Br_3-2-$C_{10}H_7$[b]	224–226	77	$C_{17}H_{18}Br_3NO_2 \cdot HBr$	37.49	37.66	3.52	3.54

[a] Bromine. [b] Naphthyl. [c] Halogen, %.

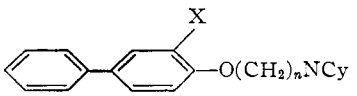
TABLE IV



No.	AR	M.p., °C.	Yield, %	Formula	Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found
33	4,2,6-Cl(CH$_3$)$_2$C$_6$H$_2$	174–176	96	$C_{15}H_{22}ClNOS\cdot HCl$	53.57	53.56	6.89	6.89
34	4,2-Cl(CH$_3$)C$_6$H$_3$	176–177	89	$C_{14}H_{20}ClNOS\cdot HCl$	52.17	52.44	6.57	6.70
35	2,3,4,5,6-Cl$_5$C$_6$	54–56	76	$C_{14}H_{14}Cl_5NOS$	43.24[a]	43.59[a]		

[a] Halogen, %.

TABLE V



No.	X	n	—NCy	Salt m.p., °C.	Yield, %	Formula	Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found
36	Cl	4	4-Morpholinyl	190–191	75	$C_{20}H_{24}ClNO_2\cdot HCl$	62.83	63.12	6.59	6.69
37	Cl	4	1-Piperidinyl	174–175	77	$C_{21}H_{26}ClNO\cdot HCl$	66.31	66.47	7.16	7.30
38	Cl	4	1-Methyl-4-piperazinyl	247–250	36	$C_{21}H_{27}ClN_2O\cdot 2HCl$	58.39	58.23	6.72	6.61
39	Cl	4	1-Pyrrolidinyl	179–180	68	$C_{20}H_{24}ClNO\cdot HCl$	65.55	65.75	6.88	6.78
40	Br	5	4-Morpholinyl	175–176	73	$C_{21}H_{26}BrNO_2\cdot HCl$	57.22	58.36[a]	6.17	6.60
41	Br	5	1-Piperidinyl	184–186	78	$C_{22}H_{28}BrNO\cdot HCl$	60.21	60.60[a]	6.66	6.72
42	Br	5	1-Methyl-4-piperazinyl	250–252	37	$C_{22}H_{29}BrN_2O\cdot 2HCl$	53.89	54.21[a]	6.37	6.63
43	Br	6	4-Morpholinyl	151–153	84	$C_{22}H_{28}BrNO_2\cdot HCl$	58.09	58.32	6.43	6.30
44	Br	6	1-Piperidinyl	165–167	75	$C_{23}H_{30}BrNO\cdot HCl$	61.00	61.27	6.90	6.73
45	Br	6	1-Pyrrolidinyl	138–140	60	$C_{22}H_{28}BrNO\cdot HCl$	60.21	60.24	6.66	6.49

[a] The starting ϵ-(2-bromo-4-phenylphenoxy)-hexyl bromide had lost bromine when distilled.

TABLE VI

MISCELLANEOUS HALOARYL ALKAMINE ETHERS

No.	Structural formula	B.p. or m.p., °C.	Mm.	Yield, %	Formula	Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found
46	2,4,6-Cl$_3$C$_6$H$_2$OCH$_2$CH$_2$OCH$_2$CH$_2$NC$_4$H$_8$O[a]	188–189		52	$C_{14}H_{18}Cl_3NO_3\cdot HCl$	42.99	43.22	4.90	5.19
47	2,4,6-Cl$_3$(C$_6$H$_5$)C$_6$H$_2$OCH$_2$CH$_2$NC$_4$H$_8$O[a]	185–187		14	$C_{18}H_{19}Cl_3NO_2\cdot HCl$	55.61	55.61	5.19	5.13
48	2,4-Cl(C$_6$H$_5$)C$_6$H$_3$O(CH$_2$)$_3$N(C$_2$H$_5$)$_2$	185–187	0.9	49	$C_{19}H_{24}ClNO$	71.80	71.69[b]	7.61	7.27[b]
49	2,4,6-Br(CH$_3$)(2-C$_5$H$_{11}$)C$_6$H$_2$OCH$_2$CH$_2$N(CH$_3$)$_2$	155–156	2.7	47	$C_{16}H_{26}BrNO$	58.52	58.49	7.92	8.00
50	[3,5,2-Cl$_2$(OCH$_2$CH$_2$CH$_2$NC$_4$H$_8$O[a])C$_6$H$_2$]$_2$S	197–198		82	$C_{26}H_{32}Cl_4N_2O_4S\cdot 2HCl$	45.70	45.47	5.02	5.26

[a] 4-Morpholinyl. [b] Average of two analyses.

The starting aryloxyalkyl halides for compounds 36–45 were prepared by the method of Marvel and Tannenbaum.[3] They were not obtained in analytically pure form but were satisfactory for the reactions reported here. Many of the phenols and naphthols were purchased or obtained as gifts, and some were synthesized here by halogenation. The halobiphenylphenols were prepared by published methods[4] except for 4-bromo-4′-hydroxybiphenyl. After bromination by the method of Hazlet[4c] had failed in our hands, correspondence with Dr. Hazlet led to the following procedure. The benzenesulfonate ester of *p*-phenylphenol in carbon tetrachloride was treated with 1.1 equivalents of bromine at 120° using traces of iron powder and iodine as catalysts. After heating for a total of one hour, the cooled solution was washed with water, 10% sodium bicarbonate solution, water, and was then dried by anhydrous sodium sulfate. Evaporation of the solvent left a crystalline residue (yield 79%) which was recrystallized from methanol, m.p. 80.5–81.5°. The desired phenol was recovered by hydrolysis of this ester.[4c]

(3) C. S. Marvel and A. L. Tannenbaum, "Organic Syntheses," Coll. Vol. I, John Wiley & Sons, Inc., New York, N. Y., 1941, p. 435.

(4) (a) F. Bell and P. H. Robinson, *J. Chem. Soc.*, **130**, 1127 (1927); (b) J. C. Colbert, W. Meigs and B. Mackin, THIS JOURNAL, **56**, 202 (1934); (c) S. E. Hazlet, *ibid.*, **59**, 1087 (1937); (d) S. E. Hazlet, G. Alliger and R. Tiede, *ibid.*, **61**, 1447 (1939); (e) C. M. S. Savoy and J. L. Abernethy, *ibid.*, **64**, 2219 (1942).

II. (**Compounds 2, 4, 8–14, 23 and 25–31**).—The appropriate phenol was added to a solution of an equivalent amount of sodium or potassium in 2-propanol. The salt so formed was treated with γ-4-morpholinylpropyl chloride and the mixture stirred and refluxed for 16–22 hours. The filtered reaction mixture was concentrated to dryness and the residue dissolved in dilute acid. After extracting any unreacted phenol with ether, the aqueous solution was made alkaline and the basic product extracted with ether or chloroform. The dried filtered extract, when treated with ethereal HCl, gave the salt which could be recrystallized from 2-propanol.

III.—The other ethers were prepared by heating an equivalent amount of phenol (or thiol) and potassium hydroxide in 2-propanol or ethanol with the appropriate alkamine halide. The product was worked up as in method II, or the free base was obtained by distillation.

Acknowledgments.—We are indebted to Professor G. L. Goerner, Michigan State College, for a gift of some of the intermediate halogenated phenols. Many others were supplied by Dow Chemical Company. The fungistatic tests were carried out by Dr. W. E. Grundy and the staff of the Microbiological Laboratories, and the microanalytical determinations by Mr. E. F. Shelberg and his staff.

NORTH CHICAGO, ILLINOIS