of absolute methanol was added a cooled solution of 0.368 g. (16 m*M*) of sodium metal dissolved in 10 ml. of absolute methanol. The flask with this mixture was attached to a gas manifold to which another flask was connected containing 6.1 g. (10 m*M*) of frozen nitromethane-C^{14} of approximately 1 mC. radioactivity. The nitromethane was then allowed to distill into the Dry Ice-cooled erythrose mixture. When the distillation was completed, the flask with the reaction mixture was detached, stoppered and allowed to stand at room temperature for 20 hours. The flask with the contents was cooled in an ice-bath, and an equal volume of ether was added to the mixture. The precipitated nitropentitols were rapidly filtered, washed with ether and petroleum ether and dried in a vacuum desiccator. The yield of sodium nitropentitols was 3.2 g. (77% based on the amount of nitromethane-C^{14} used).

Pentose-1-C^{14}.—A quantity of 9.0 ml. of 18 *N* sulfuric acid was introduced into a 50-ml. wide-mouth flask equipped with a magnetic stirrer, and placed in an isopropyl alcohol-Dry Ice-bath maintained at −10 to −15°. The solid sodium nitroalcohols (3.2 g.) were dissolved in a minimum amount of ice-cooled water and the solution added dropwise with stirring to the cooled sulfuric acid. The mixture was then allowed to stand with stirring for 15 minutes, 100 ml. of ice-water was added and the solution immediately passed through Amberlite IR-100 and Duolite A-4 columns. Each column was washed until the radioactivity in the effluent approached background counts. After concentration of the solution by vacuum distillation, 2.2 g. of crude pentose sirup was obtained.

Isolation of L-Arabinose-1-C^{14}.—The crude pentose sirup was dissolved in a minimum amount of water and the solution placed on a powdered cellulose (Whatman No. 1, ashless pellets) column, 22.5 inches long and 0.75 inch in diameter.[9] This column was attached to a "Technicon" fractionator and the sirup was fractionated, using butanol saturated with water containing approximately 0.3% concentrated ammonia. The fractions were collected in 400 test-tubes, each tube containing 1.2 ml. of eluate. The locations of L-arabinose and L-ribose were determined by paper chromatography of every tenth test-tube, using aniline phthalate as a pentose spray reagent.[11] The arabinose containing fractions were combined and a sample was chromatographed in two dimensions on Whatman No. 1 paper, first with butanol–ethanol–water and then with phenol–water. The chromatogram showed that in addition to the L-arabinose-1-C^{14}, a small amount of L-ribose-1-C^{14}, some inactive glucose and traces of two unidentified radioactive compounds were present.

Purification of L-arabinose-1-C^{14} was accomplished by means of band chromatography on paper. Of the partially purified sirup, 29 mg. was dissolved in 0.6 ml. of water and 0.25 ml. was deposited in 0.01-ml. portions along a penciled line on two sheets of Whatman No. 1 paper (22 × 18 inches). Inactive L-arabinose, placed along the edges of the paper sheets, was used as a marker. The papers were chromatographed for 24 hours with phenol saturated with water by the descending unidimensional technique. The papers were then dried, and radioautographs were made on an X-ray film. The arabinose band was identified by spraying the markers after they had been cut from the paper. The L-arabinose-1-C^{14} bands were then cut from the papers using the radioautographs as a guide, and then eluted with water. The solutions were combined and concentrated to dryness in a vacuum oven at 40°. The residue was dissolved in 0.3 ml. of water and chromatographed again on one sheet of paper as previously described using butanol–ethanol–water (21:13:5). Subsequently, the single band of L-arabinose-1-C^{14} was cut out, eluted with water and concentrated under reduced pressure to dryness. The yield was 1.2 mg. of L-arabinose-1-C^{14} with a specific activity of 2.2 × 10^6 counts/minute mg., which is equivalent to 1.2 μc/mg. The total yield of the synthetic L-arabinose-1-C^{14} was 22.2 mg. (3%, based on nitromethane-C^{14} activity).

The crude L-ribose-1-C^{14} can be similarly purified by the paper chromatographic procedure.

D-Arabinophenylosazone.—In order to further establish the identity of the labeled pentose material, D-erythrose was combined with inactive nitromethane as previously described. Upon treatment of the sirupy product with phenylhydrazine hydrochloride and sodium acetate,[12] a phenylosazone was obtained which was identified as that of arabinose; m.p. 160°.

Anal. Calcd. for $C_5H_8O_3(N_2H\cdot C_6H_5)$: C, 62.2; H, 6.1; N, 17.1. Found: C, 61.8; H, 6.1; N, 16.9.

Acknowledgment.—The authors wish to express their thanks to Mr. E. W. Putman for his assistance with the paper chromatographic work.

(11) S. M. Partridge, "Partition Chromatography," Biochemical Symposia No. 3, Cambridge University Press. 1950, p. 57.

(12) W. Z. Hassid and R. M. McCready, *Ind. Eng. Chem., Anal. Ed.*, **14**, 683 (1942).

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[CONTRIBUTION FROM ABBOTT LABORATORIES]

Local Anesthetics. II. Some Aryloxyalkyl Alkamine Ethers[1]

BY HOWARD B. WRIGHT AND M. B. MOORE

Paper I of this series reported the synthesis of various aryl alkamine ethers. The work is now extended to include related compounds in which the alkylene chain is interrupted by an oxygen, according to the general formula Ar–O–R′–O–R″–NR_2, in which Ar is an aryl or arylalkyl residue, R′ and R″ are bivalent alkylene radicals and NR_2 is the residue from a tertiary amine. The salts of these bases have been studied as local anesthetics.

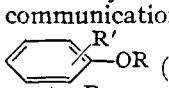
The aryl alkamine ethers reported in the previous communication[2] were of the general formula  (R′ = hydrocarbon or ether substituents, R = various alkamine residues) and were of sufficient pharmacological interest to indicate the desirability of studying other closely related compounds. Interruption of the alkylene chain by an oxygen seemed worthwhile and such compounds are reported in this paper. Some compounds of this type have been briefly described[3] but their therapeutic use was not suggested.

Table I lists the ethers synthesized, with pertinent physical and analytical data. Hydrochlorides of these compounds have been tested for local anesthetic activity by Dr. R. K. Richards and Miss Eunice Siewert, and all exhibited some degree of local anesthetic activity. Several of the salts, as those of the first two compounds in the table, resemble procaine in their local anesthetic action in wheals. Some, as in the case of the third compound in the table, produce good corneal anesthesia.

(1) Presented at the Division of Medicinal Chemistry, American Chemical Society, Cleveland, Ohio, April 8–12, 1951.

(2) H. B. Wright and M. B. Moore, THIS JOURNAL, **73**, 2281 (1951).

(3) H. A. Bruson, U. S. Patent 2,115,250, April 26, 1938.

TABLE I

ALKAMINE ETHERS Ar–O–R′–O–R″–NR_2

Ar	R′	R″	R_2	Reacn. time, hr.	Method	Yield, %	B.p., °C.	B.p., Mm.	Hydrochloride, m.p., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
C_6H_5	$(CH_2)_2$	$(CH_2)_2$	$(C_2H_5)_2$[a]	120	A	79	175	18	.....	$C_{14}H_{23}NO_2$	70.85	70.72	9.77	9.68
4-$CH_3C_6H_4$	$(CH_2)_2$	$(CH_2)_2$	C_4H_8O[b]	24	A	100	.....	...	144–145	$C_{15}H_{23}NO_3\cdot HCl$	59.69	59.43	7.68	7.84
4-$CH_3C_6H_4$	$(CH_2)_2$	$(CH_2)_2$	$(CH_3)CH_2C_6H_5$[c]	24	A	51	184–186	4.9	.....	$C_{19}H_{25}NO_2$	76.22	76.08	8.42	8.12
4-$C_6H_5C_6H_4$	$(CH_2)_2$	$CHCH_2$ | CH_3	$(C_2H_5)_2$	4	B	Small	190–192	1.7	.....	$C_{21}H_{29}NO_2$	77.02	77.14	8.93	8.67
4-$C_6H_5C_6H_4$	$(CH_2)_2$	$(CH_2)_3$	C_4H_8O	3	B	Small	208–210	1.2	.....	$C_{21}H_{27}NO_2$	73.87	73.80	7.97	8.08
$C_6H_5CH_2$	$(CH_2)_2$	$(CH_2)_2$	C_4H_8O	14	A	38.5	160	1.7	.....	$C_{15}H_{23}NO_3$	67.90	67.88[d]	8.74	8.50[d]
4-$CH_3C_6H_4$	$(CH_2)_2$	$(CH_2)_2$	$C_6H_{12}O$[e]	72	A	35	177–179	4.3	.....	$C_{17}H_{27}NO_3$	69.59	69.73	9.27	9.18
4-n-$C_3H_7C_6H_4$	$(CH_2)_2$	$(CH_2)_2$	C_4H_8O	24	A	49	187–188	3.5	116–117	$C_{17}H_{27}NO_3$	69.59	69.39	9.27	9.23
2-$C_6H_5C_6H_4$	$(CH_2)_2$	$(CH_2)_2$	C_4H_8O	6	B	32.7	208–209	2.7	122–123	$C_{20}H_{25}NO_2$	73.36	73.16	7.70	7.59
C_6H_5	$(CH_2)_2$	$(CH_2)_3$	C_4H_8O	5	B	42.5	169–171	3.4	.....	$C_{15}H_{23}NO_3$	67.90	68.13	8.74	8.80
C_6H_5	$(CH_2)_2$	$(CH_2)_2$	C_4H_8O	7	A	24	161–162	3.6	.....	$C_{14}H_{21}NO_2$	66.91	66.40	8.42	8.57
4-t-$C_4H_9C_6H_4$	CH_2CH | CH_3	$(CH_2)_3$	C_4H_8O	5	B	Small	178–179	2.7	.....	$C_{20}H_{33}NO_2$	71.60	72.23	9.92	9.50
C_6H_5	$(CH_2)_2$	$(CH_2)_2$	$(CH_2)CH_6CH_5$[c]	24	A	44.5	193–194	3.7	.....	$C_{18}H_{23}NO_2$	75.76	76.04	8.12	7.87
4-$CH_3C_6H_4$	$(CH_2)_2$	$(CH_2)_2$	$(H)CH_2C_6H_5$[g]	24	A	29.6	.....	..	120–122	$C_{18}H_{23}NO_2H\cdot Cl$	67.17	66.88	7.52	7.78
4-$CH_3(CH_2)_2C_6H_4$	$(CH_2)_2$	$(CH_2)_2$	$(CH_3)CH_2C_6H_5$[c]	24	A	31	186–187	1.5	.....	$C_{21}H_{29}NO_2$	77.02	77.29[d]	8.93	8.73[d]
4-$CH_3C_6H_4$	$CH_2CH{=}CHCH_2$		$(CH_3)CH_2C_6H_5$[c,i]	24	A	Small	177–178	1.7	.....	$C_{19}H_{22}NO$	81.39	81.39	7.91	8.00
4-$CH_3C_6H_4$	$(CH_2)_2$	$(CH_2)_2$	$(H)CH(CH_3)C_6H_5$[h]	24	A	38.5	184	4.5	108–109	$C_{19}H_{25}NO_2$	76.22	75.92	8.42	8.33
[f]				7	B	27	189	3.5	.....	$C_{19}H_{31}NO_3$	70.99	70.63[d]	9.72	9.46[d]

[a] Also prepared by G. R. Stone by heating 0.04 mole of β-phenoxyethoxyethyl bromide with 4 equivalents of diethylamine and 25 ml. of alcohol in an autoclave at 125° for 12 hr. [b] 4-Morpholinyl radical. [c] Radical from N-methylbenzylamine. [d] Average of 2 analyses. [e] 2,6-Dimethyl-4-morpholinyl radical. [f] $C_6H_5CH\begin{cases}CH_2OC_4H_9(n)\\O(CH_2)_2NC_4H_8O\end{cases}$, does not fit into the above general formula. [g] Radical from benzylamine. [h] Radical from α-methylbenzylamine. [i] This compound differs from the general formula in that the alkylene chain is interrupted by a double bond.

However, in many cases this activity was accompanied by irritation.

Experimental[4]

Method A. β-(4-*n*-Propylphenoxy) β′-Morpholinylethyl Ether.—Seven and two-tenths grams (0.03 mole) of β-(4-*n*-propylphenoxy)-ethoxyethyl chloride and 5.2 g. (0.06 mole) of morpholine were refluxed in dry xylene for 24 hours. After cooling, the solution was filtered and the precipitate was washed with dry ether. The filtrate was extracted with 40 ml. of 10% hydrochloric acid in portions. The aqueous layer was made basic and extracted with ether. The solution was dried, the solvent was removed under vacuum and the product was distilled; b.p. 187–188° (3.5 mm.); $n^{25}D$ 1.5110.

Method B. β-Phenoxyethyl γ-4-Morpholinylpropyl Ether.—β-Phenoxyethanol, 6.9 g. (0.05 mole), was stirred into 100 ml. of dry xylene containing 1.2 g. (0.05 mole) of sodium sand prepared in the usual way. After the sodium had reacted, γ-4-morpholinylpropyl chloride, 8.3 g. (0.05 mole), dissolved in a small amount of xylene was added rapidly. The solution was stirred and refluxed for 5 hours. After cooling and filtering, the product was worked up as in Method A. It distilled at 169–171° (3.4 mm.); $n^{25}D$ 1.5120.

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(4) All melting points are uncorrected. All microanalyses were carried out by E. F. Shelberg, Chief Microanalyst, and his staff.