[CONTRIBUTION FROM ABBOTT LABORATORIES]

Local Anesthetics. V. 4-Morpholinylalkyl Aryl Ether[1]

BY HOWARD B. WRIGHT AND M. B. MOORE

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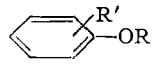
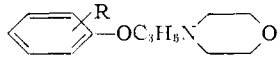
Sixty-four 4-morpholinylalkyl aryl ethers have been prepared and tested for local anesthetic activity. The method of synthesis has been described in previous papers. The compound 4-*n*-butoxyphenyl γ-4′-morpholinylpropyl ether seems to combine maximum anesthetic efficiency with minimum toxicity.

In previous papers,[2] we have reported some aryl alkamine ethers of the general formula 

R′ = alkyl, aryl or ether substituents
R = various alkamine residues

TABLE I

4-MORPHOLINYLALKYL ARYL ETHERS 

No.	R	Yield, %	B.p. or m.p. °C.	Mm.	Hydrochloride m.p., °C.	Formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
1	2-OCH_3	99	155–156	2.0		$C_{14}H_{21}NO_3$	66.90	8.42		66.79	8.16	
2	4-C_6H_{11}(cyclo)	53	90			$C_{19}H_{29}NO_2$	75.26	9.63	4.63	75.36	9.63	4.67
3	2-OC_2H_5, 5-$CH{=}CHCH_3$	58	195–196	2.5		$C_{18}H_{27}NO_3$	70.79	8.91	4.59	70.84	8.98	4.62
4	2-OC_2H_5, 5-$CH_2CH_2CH_3$[a]	100			149	$C_{18}H_{29}NO_3{\cdot}HCl$	62.86	8.79		62.83	8.88	
5	2-$OCH_2C_6H_5$	84	78–79			$C_{20}H_{25}NO_3$	73.37	7.70	4.28	73.72[b]	7.35	4.38
6	4-$OC_4H_9(n)$	45	196	6.0		$C_{17}H_{25}NO_3$	69.59	9.27		69.79	9.09	
7	2-OCH_3, 5-$CH{=}CHCH_3$	48	200–201	3.8		$C_{17}H_{25}NO_3$	70.07	8.65		69.92	8.45	
8	4-$O(CH_2)_3$N⟨O⟩	55	84–85			$C_{20}H_{32}N_2O_4$	65.91	8.85		65.87[b]	9.00	
9	4-C_6H_5	78	97–98			$C_{19}H_{23}NO_2$	76.74	7.79		76.75[b]	7.58	
10	2-[$(CH_3)CHCH_2CH_2CH_3$], 4-CH_3[c]	50	182–184	4.2		$C_{19}H_{31}NO_2$	74.71	10.23		74.34	10.32	
11	4-C_6H_{11}[d]	75			176	$C_{19}H_{35}NO_2{\cdot}HCl$	65.96	10.20		66.23	9.94	
12	2-OCH_3, 4-$CH_2CH{=}CH_2$	31	171–172	0.75		$C_{17}H_{25}NO_3$	70.07	8.65		70.03	8.50	
13	2-*t*-C_4H_9, 5-CH_3	23	165	1.4		$C_{18}H_{29}NO_2$	74.19	10.03		74.18	10.05	
14	2-OCH_3, 4-$CH{=}CHCH_3$	52.5	192	3.0		$C_{17}H_{25}NO_3$	70.07	8.65		70.21	8.38	
15	4-Cl	94			164–165	$C_{12}H_{15}ClNO_2{\cdot}HCl$[e]	53.62	6.23		53.88	6.40	
16	4-*t*-C_6H_{11}	51	177	1.4		$C_{18}H_{29}NO_2$	74.19	10.03		74.39	9.98	
17	4-$SO_2C_6H_4OC_3H_6$N⟨O⟩	72	90–91			$C_{26}H_{26}N_2O_6S$	61.88	7.19		61.95	7.22	
18	2-C_6H_5	100	200–201	2.8		$C_{19}H_{23}NO_2$	76.74	7.79		76.52	7.77	
19	2-Cl	51	170–172	2.5		$C_{12}H_{15}ClNO_2$	61.05	7.09		61.35	6.83	
20	2-NO_2	29.4	171–173	1.9		$C_{13}H_{18}N_2O_4$	58.63	6.81		58.63	6.62	
21	2-$NHCOCH_3$, 6-*n*-C_6H_7	46	67–68			$C_{18}H_{28}N_2O_3$	67.47	8.81		67.26	8.74	
22	4-COC_6H_5	38	226–227	0.9		$C_{20}H_{23}NO_3$	73.82	7.12		73.59	7.18	
23	3-$O(CH_2)_3$N⟨O⟩	22	217–218			$C_{20}H_{32}N_2O_4$	65.91	8.85		65.87	8.63	
24	2-OH	50	103–104			$C_{13}H_{19}NO_2$	65.80	8.07	5.90	66.04[b]	7.93	5.76
25	4-$(CH_2)_2OC_6H_4C_6H_5$		208–210	1.2		$C_{21}H_{27}NO_2$	73.87	7.97		73.80	8.08	
26	4-NHC_6H_5	50	238–240	3.7		$C_{19}H_{23}N_2O_2$	73.28	7.44		73.38	7.35	
27	4-H		134–135	3.3		$C_{13}H_{19}NO_2$	70.55	8.65		70.75	8.85	
28	4-NO_2	60	82–84			$C_{13}H_{18}N_2O_4$	58.63	6.81		58.68	6.59	
29	4-NH_2	33			213	$C_{13}H_{20}N_2O_2{\cdot}HCl$	57.23	7.76	10.27	57.41	7.64	10.13
30	4-$CH{=}NC_6H_5$	17	75–76			$C_{20}H_{24}N_2O_2$	74.27	7.17		74.52	7.18	
31	4-$CH_2NHC_6H_5$	72	88			$C_{20}H_{26}N_2O_2$	74.00	7.86	8.58	73.58	8.03	8.77
32	2-$OC_4H_9(n)$	43	193–194	4.3		$C_{17}H_{27}NO_3$	69.59	9.27		69.44	9.10	
33	3-NHC_6H_5	70.5	80–81			$C_{19}H_{24}N_2O_2$	73.04	7.74		73.33	7.50	
34	4-$N(CH_3)C_6H_5$	[f]	52–53			$C_{20}H_{26}N_2O_2$	73.58	8.03	8.58	73.46	7.75	8.96
35	3-$OC_4H_9(n)$	22	190–191	2.1		$C_{17}H_{27}NO_3$	69.59	9.27		69.87	9.22	
36	2-NHC_6H_5	35.2	255–257	5.0		$C_{19}H_{24}N_2O_2$	73.04	7.74		73.20	7.48	
37	4-$CH_2C_6H_5$	45	184–185	2.3		$C_{20}H_{25}NO_2$	77.13	8.09		77.06	8.05	
38	4-$C{=}(NOH)C_6H_5$	[f]	159–161			$C_{20}H_{24}N_2O_3$	70.56	7.11		70.77	6.84	
39	3-OCH_3, 4-$COOC_2H_5$	[f]			121–122	$C_{17}H_{25}NO_5{\cdot}HCl$	56.74	7.00		56.66	7.01	
40	4-C_8H_{17}	68	190	1.5		$C_{21}H_{35}NO_2$	75.63	10.55		75.57	10.45	
41	4-SCH_3	47	165	0.7		$C_{14}H_{21}NO_2S$	62.90	7.92		62.72	7.87	
42	[g]	[f]			214–215 (dec.)	$C_{17}H_{28}N_2O_2{\cdot}2HCl$	55.89	8.27		55.87	8.43	
43	4-$SC_4H_9(n)$	59	164–166	0.15		$C_{17}H_{27}NO_2S$	65.99	8.79		65.66	8.83	
44	[h]	58	219–221	3.2		$C_{17}H_{27}NO_2S$	65.99	8.80		65.89	8.87	
45	4-$NHC_{10}H_7$[i]	[f]	98–99			$C_{22}H_{26}N_2O_2$	76.21	7.23		76.07	7.31	

[a] Catalytic reduction of 3. [b] Average of two analyses. [c] 2-(1′-Methylbutyl)-4-methyl. [d] Catalytic reduction of 2 to give *p*-cyclohexylcyclohexyl alkamine ether. [e] Chlorine calcd. 24.35, found 24.09. [f] Obtained in low yield. [g] *n*-C_4H_9O⟨⟩NHC_3H_6N⟨O⟩ does not fit into the above general formula. [h] *n*-C_4H_9O⟨⟩SC_3H_6N⟨O⟩ does not fit into the above general formula. [i] β-Naphthylamino radical.

(1) Paper presented before the Division of Medicinal Chemistry at the 125th Meeting of the American Chemical Society, Kansas City, Mo., March, 1954.

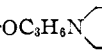
(2) (a) H. B. Wright and M. B. Moore, THIS JOURNAL, **73**, 2281 1951); (b) *ibid.*, **73**, 5525 (1951).

and some aryloxyalkyl alkamine ethers of general formula

$$ArOR'OR''NR_2$$

Ar = aryl or arylalkyl residue, R′ and R″ = bivalent alkylene radicals and NR_2 = a tertiary amine residue

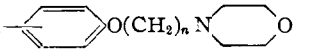
TABLE II

4-MORPHOLINYLALKYL ARYL ETHERS $ArOC_3H_6N$ 

No.	Ar	Yield, %	B.p. or m.p. °C.	Mm.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
46	$C_{10}H_7$[a]	52	193–194	1.2	$C_{17}H_{21}NO_2$	75.24	75.01	7.80	7.87
47	C_9H_6N[c]	23.2	64–66		$C_{16}H_{20}N_2O_2$	70.56	70.90[b]	7.40	7.22
48	C_9H_6N[d]	[e]	195–196	2.0	$C_{16}H_{20}N_2O_2$	70.56	69.83[b]	7.40	7.32
49	C_5H_9O[f]	18.3	135	1.8	$C_{12}H_{23}NO_3$	62.85	63.06	10.11	9.94
50	$C_{10}H_{11}$[g]	24	150–152	0.35	$C_{17}H_{25}NO_2$	74.14	74.25	9.15	9.02
51	$C_{10}H_{11}$[h]	32.7	147	0.2	$C_{17}H_{25}NO_2$	74.14	74.26	9.15	8.99

[a] α-Naphthyl radical. [b] Average of two analyses. [c] 8-Quinolinyl radical. [d] 1-Isoquinolinyl radical. [e] Obtained in low yield. [f] 2-Tetrahydropyranyl radical. [g] 5,6,7,8-Tetrahydronaphthyl-1 radical. [h] 1,2,3,4-Tetrahydronaphthyl-2 radical.

TABLE III

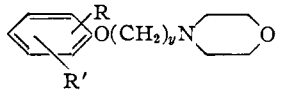
4-MORPHOLINYLALKYL ARYL ETHERS R— 

No.	R	n	Yield, %	B.p. or m.p. °C.	Mm.	Hydrochloride m.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
52	4-$OC_4H_9(n)$	2	57	201	9.0		$C_{16}H_{25}NO_3$	69.03	68.80	8.69	8.72
53	4-C_6H_5	4	[a]	60–61			$C_{20}H_{25}NO_2$	77.13	77.23	8.09	7.87
54	4-$OC_4H_9(n)$	5	[a]	39			$C_{19}H_{31}NO_3$	70.99	70.11	9.72	9.44
						164–166	$C_{19}H_{31}NO_3$·HCl	63.76	63.89	9.00	8.78
55	4-$OC_4H_9(sec.)$	3	60	166	0.8		$C_{17}H_{27}NO_3$	69.59	69.67	9.27	9.11
56	4-$OC_5H_{11}(n)$	3	69	188	1.7		$C_{18}H_{29}NO_3$	70.33	70.62	9.51	9.47
57	4-$OC_7H_{15}(n)$	3	63	200	0.7		$C_{20}H_{33}NO_3$	71.60	71.86	9.91	9.65
58	4-OCH_3	3	31	42–44			$C_{14}H_{21}NO_3$	66.90	66.94	8.42	8.27
59	4-$OC_3H_7(n)$	3	11	153	0.55		$C_{16}H_{25}NO_3$	68.78	69.18	9.02	8.96[b]
						165–166	$C_{16}H_{25}NO_3$·HCl	60.84	60.32	8.23	8.21[b]
60	4-$OC_2H_5(n)$	3	46	142	0.25		$C_{15}H_{23}NO_3$	67.90	67.81	8.74	8.77
61	4-$OC_8H_{17}(n)$	3	27.8			171–172	$C_{21}H_{35}NO_3$·HCl	65.35	65.24	9.40	9.47
62	4-$OC_4H_9(n)$	4	71.5	165	0.7		$C_{18}H_{29}NO_3$	70.33	70.60	9.51	9.21
63	4-$OC_{10}H_{21}(n)$	3	[a]	39–40			$C_{23}H_{39}NO_3$	73.17	72.88	10.41	10.41
64	4-OC_6H_{13}	3	46	188	1.1		$C_{19}H_{31}NO_3$	70.99	70.89	9.72	9.74

[a] Obtained in low yield. [b] Average of two analyses.

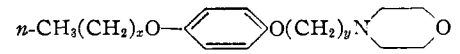
Compounds of these types displayed topical anesthetic action.

A few morpholinylalkyl aryl ethers were examined for local anesthetic effect. They were of sufficient interest to warrant the preparation of an entire series of compounds of the general formula



R = alkoxy, aryl, nitro, amino, acetamino, thioalkoxy, chloro, hydroxy or acetyl; R′ = hydrogen or alkene (y = 2–5)

One of the first compounds prepared, the *p*-cyclohexyl derivative, compound 2 (Table I), gave slight topical anesthesia. Compound 3, the 2-ethoxy-5-propenyl derivative, showed very good anesthetic effect. Hydrogenation of the side chain did not alter the activity or toxicity (compound 4). Replacement of the ethoxy group of compound 3 with methoxy in compound 7 reduced the anesthetic activity but did not change the toxicity. Shifting of the propenyl group from position five to four reduced activity practically to zero (compound 14). In compound 12, the propenyl group has been replaced with allyl and shifted to position four with no change in activity. The 4-phenyl derivative, 9, and the 4-butoxy derivative, 6, seemed to give maximum topical anesthetic activity and minimum toxicity. The compound 6 was selected by Dr. R. K. Richards and Dr. J. L. Schmidt, of the Pharmacology Laboratory, for complete pharmacological investigation.[3] It was compared with other members of the series



x = 0–10 (with the exception of 9), y = 2–5

The compounds in which x = 3–7, y = 2–5, all exhibit topical anesthetic activity. The 4-*n*-butoxyphenyl γ-4′-morpholinylpropyl ether seems to combine maximum anesthetic efficiency with minimum toxicity. This excellent efficiency of a compound containing a morpholinyl radical was surprising to us since morpholine derivatives usually show both low toxicity and low pharmacologic activity. However, in the case of compound 6, toxicity is low but local anesthetic activity is retained. The diethylamino analog of compound 6[4] was much more toxic and had a definitely lower therapeutic index.

The compounds reported in the tables were prepared by the reaction of γ-4-morpholinylpropyl chloride with the potassium salt of the phenolic compound, as previously reported.[2a] Compound 24 resulted from the incomplete alkylation of catechol, while 23 and 8 were formed by the dialkylation of resorcinol and hydroquinone, re-

(3) J. L. Schmidt, L. E. Blockus and R. K. Richards, *Anesthesia and Analgesia*, **32**, 418 (1953).

(4) Compound described as 9 in ref. 2a. Unpublished pharmacological data.

spectively. The intermediate, (4-hydroxybenzal)-aniline, was synthesized by an adaptation of a known method.[5] All of the monoalkoxyhydroquinones used were prepared by a modification of the method of Klarmann,[6] and the *m*-hydroxydiphenylamine and *o*-hydroxydiphenylamine intermediates by modification of a known method.[7]

Acknowledgments.—We are indebted to Dr. R. K. Richards and Dr. J. L. Schmidt for pharmacologic studies, to M. Freifelder and G. R. Stone for hydrogenation and pressure reactions and to E. F. Shelberg, Chief Microanalyst, and his staff for analytical data.

(5) H. Herzfeld, *Ber.*, **10**, 1271 (1877).

(6) E. Klarmann and L. Gatyas, U. S. Patent 1,883,952 (October 25, 1932).

(7) To be reported later by M. Freifelder and G. R. Stone.

NORTH CHICAGO, ILLINOIS

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF WAYNE UNIVERSITY]

Nitrogen Analogs of Ketenes. II. Dehydrochlorination of Imino Chlorides[1,2]

BY CALVIN L. STEVENS AND JAMES C. FRENCH[3]

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A method for the preparation of nitrogen analogs of ketenes (*cf.* Table III) has been developed which involved dehydrochlorination of the corresponding imino chlorides.

The purpose of this investigation was the preparation of representative examples of nitrogen analogs of ketenes as a prelude to the study of the chemical and physical properties of these compounds.

The results indicated that certain ketenimines could not be conveniently prepared by the recently discovered method of dechlorination of α-chloroimino chlorides[2] using sodium iodide. Subsequently, another new method for the preparation of nitrogen analogs of ketenes was developed which involved the facile dehydrochlorination of imino chlorides bearing a single α-hydrogen atom.[4] Although previous work with imino chlorides which contained an α-hydrogen indicated that these compounds were unstable,[5] useful imino chloride intermediates of this type were prepared in this work. Each α-hydrogen imino chloride could be dehydrochlorinated with triethylamine to give the corresponding ketenimine.

A preliminary survey of the scope of the recently discovered method for the preparation of ketenimines[2] indicated that the method failed for the preparation of examples such as dimethylketene *p*-tolylimine (II). The corresponding α-chloroimino chloride VIII was readily prepared in 87% yield from the *p*-toluidide of isobutyric acid (VI) and the structure was shown by hydrolysis to the *p*-toluidide of α-chloroisobutyric acid (X). Treatment of VIII with excess sodium iodide in acetone for three hours at room temperature caused the precipitation of 86% of one equivalent of sodium chloride, accompanied by only a small evolution of iodine. That the intermediate product was the α-chloroimino iodide IX was shown by hydrolysis of the reaction mixture at this stage to give an 86% yield of the α-chloroamide X. After nine days at room temperature, 89% of the iodine had been liberated; the presence of a ketenimine was indicated by hydrolysis at this stage to afford a 60% yield of α-hydrogen amide VI. However, using the isolation procedure previously described,[2] no ketenimine could be obtained.

In contrast to the above procedure, dimethylketene *p*-tolylimine (II) could be prepared conveniently and rapidly in 66% yield by dehydrochlorination of the corresponding imino chloride VII. This imino chloride was prepared from the known amide and phosphorus pentachloride in 87% yield. In contrast to the report of v. Braun[5] which indicated that imino chlorides of the type $R_2CH—CCl{=}NR$ were unstable and could not, as a rule, be isolated, VII could be obtained analytically pure by distillation. The structure of VII was proved by hydrolysis to the amide VI in 94% yield.

The ketenimine II was a yellow liquid which was stable for several weeks at −80° but which was converted to a deep yellow, viscous oil when stored for two days at room temperature. The ketenimine structure was confirmed by rapid hydrolysis to the corresponding α-hydrogen amide VI and by the characteristic infrared absorption band at 4.95 μ.

The preparation of ethylbutylketene *n*-butylimine (I) in 57% over-all yield from the N-butyl amide XI of α-ethylcaproic acid represented a rapid and convenient synthesis of a ketenimine completely substituted with aliphatic groups. The structures of the intermediate imino chloride XII and the ketenimine I were both confirmed by hydrolysis to the starting amide. The ketenimine and the imino chloride in this series proved to be unusually stable. Whereas the ketenimines which have aromatic substituents on the carbon or nitrogen are yellow in color, I is colorless. The infrared absorption band corresponding to the twinned double bond appeared at 4.89 μ and the ultraviolet spectrum showed a maximum at 294 mμ (log ε 2.06). This ketenimine, as well as the others, had a distinctive odor.

Initially, the preparation of diphenylketene

(1) Presented before the Organic Division at the 125th meeting of the American Chemical Society in Kansas City, March, 1954.

(2) The previous paper in this series was: C. L. Stevens and J. C. French, THIS JOURNAL, **75**, 657 (1953).

(3) Public Health Service Research Fellow of the National Institutes of Health, 1952–1953.

(4) *Cf.* the dehydrochlorination of acid chlorides with the formation of ketenes as summarized by W. E. Hanford and J. C. Sauer in "Organic Reactions," Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1946, p. 124.

(5) For leading references, see J. v. Braun and W. Rudolph, *Ber.*, **67**, 1762 (1934).