ether, the crystalline product melted at 115–116.2°, undepressed by mixture with pure starting material.

B. **Acid Present.**—The above experiment was repeated except that a small amount of aniline hydrochloride was added (10^{-3} mole per mole of reactants). The recovered formamidine was recrystallized ten times from isopropyl alcohol–petroleum ether; N,N′-di-*o*-chlorophenylformamidine, m.p. 138–140°, was obtained.

***o*-Toluidine and Ethyl N-Phenylformimidate. A. Acid-Free.**—A mixture of 0.03 mole of the amine and 0.01 mole of the imidic ester was heated as before. The crude crystalline product was washed with petroleum ether; m.p. 111–112°. Four recrystallizations raised the m.p. to 113.1–113.5°. This product was also prepared from aniline and ethyl N-*o*-tolylformimidate; it was recrystallized from isopropyl alcohol–petroleum ether. The analytical sample melted at 114.4–114.9°.

Anal. Calcd. for $C_{14}H_{14}N_2$: C, 79.96; H, 6.71. Found: C, 80.07; H, 6.98.

B. **Acid Present.**—*o*-Toluidine (0.03 mole), ethyl N-phenylformimidate (0.1 mole) and *o*-toluidine hydrochloride (10^{-5} mole) were heated as before. The crude petroleum ether-washed product melted at 125–138°. Seven recrystallizations from isopropyl alcohol–petroleum ether raised the m.p. to 147–150°, undepressed by mixture with N,N′-di-*o*-tolylformamidine (m.p., 151–152°).

Aniline and N-Phenyl-N′-*p*-chlorophenylformamidine.—A mixture of 0.005 mole of each reactant plus a trace of sulfuric acid was heated for three hours at 100°. The crude product was recrystallized three times from petroleum ether and isopropyl alcohol–petroleum ether, giving crystals, m.p. 110–120°; after three more recrystallizations, 120–125°; after two more recrystallizations, 122–126°. Purification by recrystallization was abandoned at this point due to the small amount of material remaining; apparently extensive disproportionation took place. Previous experiments (see ref. 1, p. 3607) have shown that a symmetrical formamidine may readily be recovered unchanged after heating with ethanol and *p*-toluenesulfonic acid for two hours, so the likelihood of decomposition by means other than disproportionation under these conditions appears negligible.

***p*-Toluidine and N-*m*-Chlorophenyl-N′-*p*-tolylformamidine.**—The new unsymmetrical formamidine was prepared from *m*-chloroaniline and ethyl N-*p*-tolylformimidate with the proper precautions against acid and was recrystallized from isopropyl alcohol–petroleum ether. The pure substance melted at 130–131°.

Anal. Calcd. for $C_{14}H_{13}N_2Cl$: C, 68.71; H, 5.35; mol. wt., 245. Found: C, 68.73; H, 5.20; mol. wt. (Rast), 248.

A picrate was prepared by mixing isopropyl alcohol solutions of the formamidine and picric acid and was recrystallized from the same solvent; m.p. 187–188°.

Anal. Calcd. for $C_{20}H_{16}O_7N_5Cl$: C, 50.69; H, 3.40. Found: C, 51.05; H, 3.42.

A 0.92-g. (0.0038 mole) sample of the formamidine and 0.39 g. (0.0037 mole) of *p*-toluidine were heated at 100° for three hours. No acid was added since the *p*-toluidine used had not been redistilled for several weeks. Petroleum ether was added to the warm reaction mixture, and the fine white needles which separated on cooling to room temperature were collected; m.p. 107–109°. Two recrystallizations from isopropyl alcohol–petroleum ether raised the m.p. to 109–110.5°, and four subsequent recrystallizations from the same solvent pair did not change the m.p. This product was dissolved in the minimum amount of isopropyl alcohol at room temperature and the solution was added to an equal volume of a saturated solution of picric acid in the same solvent. A yellow precipitate separated immediately; it was collected and washed with isopropyl alcohol; m.p. 170–175°. This product was recrystallized seven times from isopropyl alcohol; the m.p. was then 218–222°, undepressed by mixture with N,N′-di-*p*-tolylformamidine picrate (m.p., 220–225°), depressed to 190–205° by mixture with N,N′-di-*m*-chlorophenylformamidine picrate (m.p., 240° dec.).

The molecular weight of the product melting at 109–110.5° was determined by the Rast procedure: Calcd. for N,N′-di-*m*-chlorophenylformamidine, 265; for N-*m*-chlorophenyl-N′-*p*-tolylformamidine, 245; for N,N′-di-*p*-tolylformamidine, 224; found, 233.

AUSTIN, TEXAS RECEIVED NOVEMBER 13, 1950

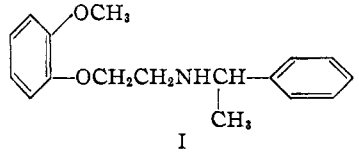
[CONTRIBUTION FROM THE RESEARCH DEPARTMENT OF ABBOTT LABORATORIES]

Local Anesthetics. I. Some Aryl Alkamine Ethers

BY HOWARD B. WRIGHT AND M. B. MOORE

Thirty-one alkamine aryl ethers have been synthesized and examined for local anesthetic effect. None proved more promising than β-(α-methylbenzylamino)-ethyl *o*-anisyl ether, which is approximately twice as active as procaine.

Numerous alkamine ethers of phenols[1] and arylalkanols[2] have been reported in the literature. β-(α-Methylbenzylamino)-ethyl *o*-anisyl ether (I) was prepared in this Laboratory and submitted for testing as a local anesthetic. Its interesting pharmacological properties led us to synthesize a series of alkamine aryl ethers, most of which are new. One arylalkanol ether was included in the study for comparative purposes. Preparative methods are given in the Experimental part, and all of the compounds with the exception of I were made by method B. They are listed in the tables with their physical constants and analytical data.



I

The hydrochlorides of the compounds reported have been studied pharmacologically by Dr. R. K. Richards and his staff, especially with regard to their local anesthetic value. Nearly all exhibit some degree of local anesthetic effect, exceptions being compounds 6 and 26 of Table I. However, none showed particular advantage over compound 1, which is approximately twice as effective as procaine.

Experimental[3]

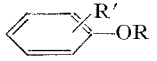
Method A. β-(α-Methylbenzylamino)-ethyl *o*-Anisyl Ether.—β-(2-Methoxyphenoxy)-ethyl bromide, 1.15 g.

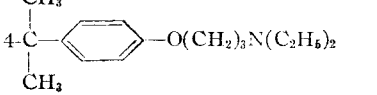
(1) (a) A. Einhorn and L. Rothlauf, *Ann.*, **382**, 254 (1911); (b) D. Bovet and A. M. Staub, *Compt. rend. soc. biol.*, **124**, 547 (1937); (c) D. Bovet and P. Maderni, *ibid.*, **114**, 980 (1933); (d) J. Trefouel, H. Strickler and D. Bovet, *ibid.*, **130**, 27, 29 (1939); (e) E. Fourneau and J. Matti, *Bull. soc. chim.*, **7**, 615 (1940); (f) D. E. Jackson, *J. Pharmacol.*, **39**, 254 (1930); (g) D. J. Drain, D. A. Peak and F. F. Whitmont, *J. Chem. Soc.*, 2680 (1949); (h) S. Gabriel and R. Stelzner, *Ber.*, **29**, 2381 (1896); (i) J. von Braun, *ibid.*, **42**, 2040 (1909); (j) H. C. Brill, THIS JOURNAL, **47**, 1134 (1925).

(2) (a) W. B. Wheatley, L. C. Cheney and S. B. Binkley, *ibid.*, **71**, 3795 (1949); (b) L. C. Cheney, R. R. Smith and S. B. Binkley, *ibid.*, **71**, 60 (1949); (c) W. B. Wheatley, L. C. Cheney and S. B. Binkley, *ibid.*, **71**, 64 (1949).

(3) All melting points are uncorrected.

TABLE I

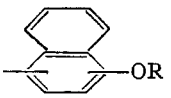
PHENYL ALKAMINE ETHERS AND HYDROCHLORIDES 

	R	R	Yield, %	B.p. °C.	B.p. Mm.	M.p., °C. hydrochloride	Formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
1	2-OCH_3	$-CH_2CH_2NHCH(CH_3)C_6H_5$	30			114–115	$C_{17}H_{21}NO_2 \cdot HCl$	66.33	7.21	4.55	66.46	6.98	4.86
2	2-OCH_3	$-CH_2CH_2NC_5H_{10}$[a]	Small			104–105	$C_{14}H_{21}NO_2 \cdot HCl$	61.87	8.16	5.15	61.97	7.91	5.25
3	2-OCH_3	$-CH_2CH_2CH_2N(C_2H_5)_2$	23	154–155	15		$C_{14}H_{23}NO_2$			5.9		6.2,	6.3
4	4-OCH_3	$-CH_2CH_2CH_2N(C_2H_5)_2$	42			95–96	$C_{14}H_{23}NO_2 \cdot HCl$	61.41	8.83	5.12	60.99	8.68	5.17
5	2-OCH_3	$-CH_2CH_2N(C_2H_5)_2$[c]	23	126–127	2	114–115	$C_{13}H_{21}NO_2$			6.27			6.20
6	4-$COCH_3$	$-CH_2CH_2CH_2N(C_2H_5)_2$	71	167–168	4.1		$C_{15}H_{23}NO_2$			5.62			5.37
							$C_{15}H_{23}NO_2 \cdot HCl$			4.90		4.71,	4.73
7	2-OCH_3	$-CH_2CH_2N(CH_3)CH_2C_6H_5$	44	111	3	142–143	$C_{17}H_{21}NO_2$			5.16			5.07
8	4-C_6H_{11}[g]	$-CH_2CH_2CH_2N(C_2H_5)_2$	59	171–172	3.4		$C_{19}H_{31}NO$	79.12	10.48	4.86	79.31	10.48	4.62
													4.61
9	4-$O(CH_2)_3CH_3$	$-CH_2CH_2CH_2N(C_2H_5)_2$	57.5	156–157	3.2	108–109	$C_{17}H_{29}NO_2$			5.01			5.05
10	2-OC_2H_5, 5-$CH{=}CHCH_3$	$-CH_2CH_2CH_2N(C_2H_5)_2$	56.5	164–166	3.1	116–117	$C_{18}H_{29}NO_2 \cdot HCl$	65.92	9.22	4.27	66.01	9.24	4.15
11	2-OC_2H_5, 5-C_7H_7-*n*	$-CH_2CH_2CH_2N(C_2H_5)_2$[d]	Small			103–104	$C_{18}H_{31}NO_2$	65.52	9.77		65.30	9.65	
12	2-OCH_3	$-CH_2CH(CH_3)N(C_2H_5)_2$[b]	44	117	3		$C_{14}H_{23}NO_2$			5.90		5.85,	5.90
13	2-$OCH_2C_6H_5$	$-CH_2CH_2N(C_2H_5)_2$	Small	184–185	6	88	$C_{19}H_{25}NO_2$			4.68		4.91,	4.84
14	4-$OCH_2C_6H_5$	$-CH_2CH_2N(C_2H_5)_2$	29	176	21	161	$C_{19}H_{25}NO_2$			4.68		4.21,	4.34
							$C_{19}H_{25}NO_2 \cdot HCl$	67.94	7.80		67.97	7.79	
15	3-OCH_3	$-CH_2CH_2N(C_2H_5)_2$	Small	139–140	10	132–133	$C_{13}H_{21}NO_2$			6.27		6.38,	6.42
16	4-OC_2H_5	$-CH_2CH_2CH_2N(C_2H_5)_2$	56	148	4.1	119–120	$C_{15}H_{25}NO_2$			5.57		5.65,	5.56
17	2-OC_2H_5, 5-$CH{=}CHCH_3$	$-CH_2CH_2N(C_2H_5)_2$	37.2	152–154	4.1	116–117	$C_{17}H_{27}NO_2$			4.84			5.09
18	2-$CH(CH_3)CH_2CH_2CH_3$, 4-CH_3	$-CH_2CH_2N(C_2H_5)_2$	9	123–126	1.5		$C_{18}H_{31}NO$			5.05			5.26
19	4-$CH_2O(CH_2)_3N(C_2H_5)_2$	$-CH_3$	Small	116–120	1.3		$C_{15}H_{25}NO_2$			5.57			5.71
20	4-$CH_2CH_2CH_3$	$-CH_2CH_2N(C_2H_5)_2$	60			141–142	$C_{15}H_{25}NO \cdot HCl$	66.28	9.64	5.15	66.23	9.39	5.78
21	4-$OCH_2CH_2CH_3$	$-CH_2CH_2CH_2N(C_2H_5)_2$	34	160–162	6	105–107	$C_{16}H_{27}NO_2$			5.28			5.41
22	3-OC_2H_5	$-CH_2CH_2CH_2N(C_2H_5)_2$	46	145–146	3.5	114–115	$C_{15}H_{25}NO_2$			5.57			5.52
23	4- 	$-(CH_2)_3N(C_2H_5)_2$[f]	33			195–197	$C_{29}H_{46}N_2O_2 \cdot HCl$			5.31			5.30
24	2-OCH_3, 6-OCH_3	$-CH_2CH_2CH_2N(C_2H_5)_2$	54	160–161	4.2	88–89	$C_{15}H_{25}NO_2$			5.24			5.31
25	2-$CH_2CH_2CH_3$	$-CH_2CH_2CH_2N(C_2H_5)_2$	32	139	4.2		$C_{16}H_{27}NO$	77.06	10.91		77.61	10.55	
						115–117	$C_{16}H_{27}NO \cdot HCl$	67.23	9.52		66.98	9.32	
26	4-$O(CH_2)_3N(C_2H_5)_2$	$-CH_2CH_2CH_2N(C_2H_5)_2$	28	185–186	1.5		$C_{20}H_{36}N_2O_2$	71.38	10.79		71.40	10.58	
27	2-C_6H_5	$-CH_2CH_2N(C_2H_5)_2$[e]	76	138–139	0.3		$C_{18}H_{23}NO$	80.25	8.61		80.39	8.48	
28	2-C_6H_5	$-CH_2CH_2CH_2N(C_2H_5)_2$	41.5	167	2.8		$C_{19}H_{25}NO$	80.52	8.89		80.67	9.01	

[a] Piperidine. Previously prepared by E. Fourneau. [b] E. M. Schultz and J. M. Sprague, THIS JOURNAL, 70, 48 (1948), indicate that 1-chloro-2-dimethylaminopropane rearranges on heating to give the 2-chloro-1-dimethylaminopropane. Thus it is possible that the methyl group in our compound could be in the α- or β-position. This position was not determined. [c] Reference 1a gives b.p. 148–150° (10 mm.). [d] Prepared by low pressure reduction of compound 10 in alcohol with PtO_2. [e] Prepared by condensing β-chloroethyl *o*-phenylphenyl ether with an excess of diethylamine in an autoclave at 150°. [f] The phenol, 2,2-bis-(4-hydroxyphenyl)-propane, was made according to U. S. Patent 2,468,982 in excellent yield. [g] Cyclohexyl.

TABLE II

NAPHTHYL ALKAMINE ETHERS



	R′	R	Yield, %	B.p., °C.	Mm.	M.p., °C. hydrochloride	Formula	Calcd. C	Calcd. H	Analyses, % Found N	Found C	Found H	Found N
1	H	1-$CH_2CH_2CH_2N(C_2H_5)_2$	57.5	174–175	3.8		$C_{17}H_{23}NO$			5.44			5.55
2	H	2-$CH_2CH_2CH_2N(C_2H_5)_2$[a]	32	172	3.2	114–115	$C_{17}H_{23}NO$			5.42			5.52
							$C_{17}H_{23}NO\cdot HCl$	69.49	8.23		68.76	8.26	
3	4-OCH_3	1-$CH_2CH_2CH_2N(C_2H_5)_2$	31.4	203	4.4	167–170	$C_{18}H_{25}NO_2$	75.23	8.77		75.45	8.52	
4	H	1-$CH_2CHN(C_2H_5)_2$ (CH$_3$)	54	155–156	1.8		$C_{17}H_{23}NO$	79.34	9.01		79.60 79.48	8.67 8.73	

[a] Reference 1a b.p. 202° (18 mm.). [b] Reference *b*, Table I.

(0.005 mole), was dissolved in 25 ml. of dry xylene and stirred, while α-methylbenzylamine, 1.2 g. (0.01 mole), dissolved in dry xylene, was added dropwise. The solution was stirred and refluxed for 16 hours, the clear solution was washed with water and the xylene was dried. The addition of ethereal hydrogen chloride yielded a small amount of pasty material. Fresh dry ether was added three times and decanted. The paste slowly crystallized and the crude product melted at *ca.* 110°. A small portion was dissolved in a minimum amount of isopropyl alcohol and diluted with several volumes of dry ether. After standing four days at about 5°, the product crystallized. This material was recrystallized again and dried *in vacuo* at 56°; m.p. 114–115°.

Method B.—γ-Diethylaminopropyl 4-methoxynaphthyl ether: five and six-tenths grams of potassium hydroxide (0.1 mole) was dissolved in 150 ml. of ethyl alcohol by refluxing and 17.4 g. (0.1 mole) of 4-methoxy-1-naphthol[4] was added to the boiling solution. The solution became dark red almost at once and 14.9 g. (0.1 mole) of γ-diethylaminopropyl chloride (dissolved in a little alcohol) was dropped in rapidly. The mixture was then refluxed for 48 hours, cooled and filtered to remove the potassium chloride. The alcohol was removed under vacuum on the steam-bath and the residue was dissolved in dilute hydrochloric acid with cooling. The aqueous acid was then shaken once with ether and the layers were separated. The aqueous layer was made strongly basic with 40% sodium hydroxide and the oil which separated was extracted into ether and/or benzene. The organic layer was dried, the solvent removed under vacuum and the product was distilled. The red product boiled at 203° (4.4 mm.); $n^{24.5}D$ 1.5624.

(4) Prepared by M. Freifelder and G. R. Stone according to German Patent 234,411. The melting point of the purple compound was 123°. (The patent value is 131°.)

Acknowledgment.—The high pressure reactions were carried out by Morris Freifelder and G. R. Stone. All microanalyses were performed by E. F. Shelberg, Chief Microanalyst, and his staff.

NORTH CHICAGO, ILL. RECEIVED NOVEMBER 27, 1950

[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

Epimeric 20-Hydroxypregnene Derivatives[1]

BY RICHARD B. TURNER AND DOROTHY M. VOITLE

Catalytic hydrogenation of *i*-pregnenolone methyl ether followed by benzoylation and treatment with zinc acetate and acetic acid furnishes a mixture of 3β-acetoxy-20α- and 20β-benzoyloxy-Δ⁵-pregnene. Separation of the pure epimers can be accomplished by chromatography. These substances, on partial hydrolysis, afford the corresponding 3β-hydroxy derivatives, which yield the benzoates of Δ⁴-pregnene-20α-ol-3-one and Δ⁴-pregnene-20β-ol-3-one when subjected to Oppenauer oxidation. Lithium aluminum hydride reduction of Δ⁵-pregnene-3β-ol-20-one likewise yields a mixture of epimers, but separation of the products as the free diols or as the diacetates is impracticable. Earlier work of Marker on the conversion of pregnane-3α-ol-20-one into pregnane-20β-ol-3-one has been repeated and the intermediates have been isolated.

Syntheses of Δ⁴-pregnene-20α-ol-3-one[2,3] and of the corresponding 20β-hydroxy derivative from 3β-hydroxy-Δ⁵-norcholene-22-one and from 3β-hydroxy-Δ⁵-20-iso-norcholene-22-one, respectively, have recently been reported by Wieland and Miescher.[4] We have also had occasion to prepare these substances, as well as certain related pairs of C.20 epimers, and have employed a somewhat different procedure, for which Δ⁵-pregnene-3β-ol-20-one served as starting material. The results of this investigation are described in the present communication.

Δ⁵-Pregnene-3β-ol-20-one was first converted into *i*-pregnenolone methyl ether[5] (I), which was then hydrogenated over Raney nickel in alcohol solution. The resulting oily product was benzoylated directly and, after treatment with acetic acid and zinc acetate, furnished a mixture of 3β-acetoxy-20α-benzoyloxy-Δ⁵-pregnene (IIa) and 3β-acetoxy-20β-benzoyloxy-Δ⁵-pregnene (IIb), which could be readily separated by chromatography on alumina. The two C.20 epimers (IIa and IIb) were obtained from *i*-pregnenolone methyl ether in a combined yield of 80%, the ratio of IIb to IIa being about 3:2.

Configurations assigned to these substances are based on the following evidence. Saponification of the lower melting isomer (IIa) gave Δ⁵-pregnenediol-3β,20α (m.p. 182–183.5°), whereas hydrolysis of the higher melting derivative (IIb) yielded Δ⁵-pregnenediol-3β,20β (m.p. 211–211.5°).[4] The corresponding diacetates melted at 145.5–146° and at 138.5–140°,[6] respectively. Hydrogenation of the diacetate (m.p. 146°) derived from

(1) This work was supported by funds provided by the American Cancer Society on the recommendation of the Committee on Growth of the National Research Council.

(2) A. Butenandt and J. Schmidt, *Ber.*, **67**, 2092 (1934).

(3) The designations 20α and 20β are used in the sense discussed by L. F. Fieser and M. Fieser, *Experientia*, **4**, 285 (1948); see also L. H. Sarett, THIS JOURNAL, **71**, 1165, 1169, 1175 (1949), and W. Klyne and D. H. R. Barton, *ibid.*, **71**, 1500 (1949).

(4) P. Wieland and K. Miescher, *Helv. Chim. Acta*, **32**, 1922 (1949).

(5) A. Butenandt and W. Grosse, *Ber.*, **70**, 1446 (1937).

(6) Wieland and Miescher (ref. 4) report a melting point of 125–126° for this compound.