Local Anesthetics: 2-*N*,*N*-Dialkylaminoacyl-2′-methyl (or 2′,6′-dimethyl)-4′-butylaminoanilides

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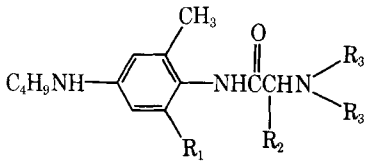
Received June 8, 1981, from the *Samuel M. Best Research Laboratory, Massachusetts College of Pharmacy and Allied Health Sciences, Boston, MA 02115;* and the **Astra Pharmaceutical Products, Inc., Worcester, MA 01606.* Accepted for publication September 29, 1981.

Abstract □ A series of tetracaine analogs based on the lidocaine structure, having a 2′-methyl-(or 2′,6′-dimethyl)-4′-butylaminoanilide moiety with α substitution on the dialkylaminoacyl function, has been synthesized. Local anesthetic activity was found with the *N*-butyl derivatives in both the 2′-methyl and 2′,6′-dimethyl series using both the method of rabbit cornea loss of reflex and spinal anesthesia in sheep. Duration of activity of the compounds was greater than that of lidocaine, but less than that of tetracaine, with comparable dosage levels.

Keyphrases □ Anesthetics—2-*N*,*N*- dialkylaminoacyl-2′-methyl (or 2′,6′-dimethyl)-4′-butylaminoanilides, local anesthetic, rabbits, sheep □ Tetracaine—synthesis of analogs from lidocaine structure □ Lidocaine—tetracaine synthesis

Tetracaine is employed as both an injectable and topical local anesthetic and remains in common use for spinal anesthesia (1). This compound, an ester, is fairly stable but suffers some loss of potency during autoclaving (2). To provide greater stability and possibly lower toxicity, a series of amide analogs based on the lidocaine structure has been synthesized. This series includes both 2-methyl and 2,6-dimethyl substituents in the aromatic ring, as well as alkyl groups on the α position of the aliphatic side chain, giving structures of Type 1:



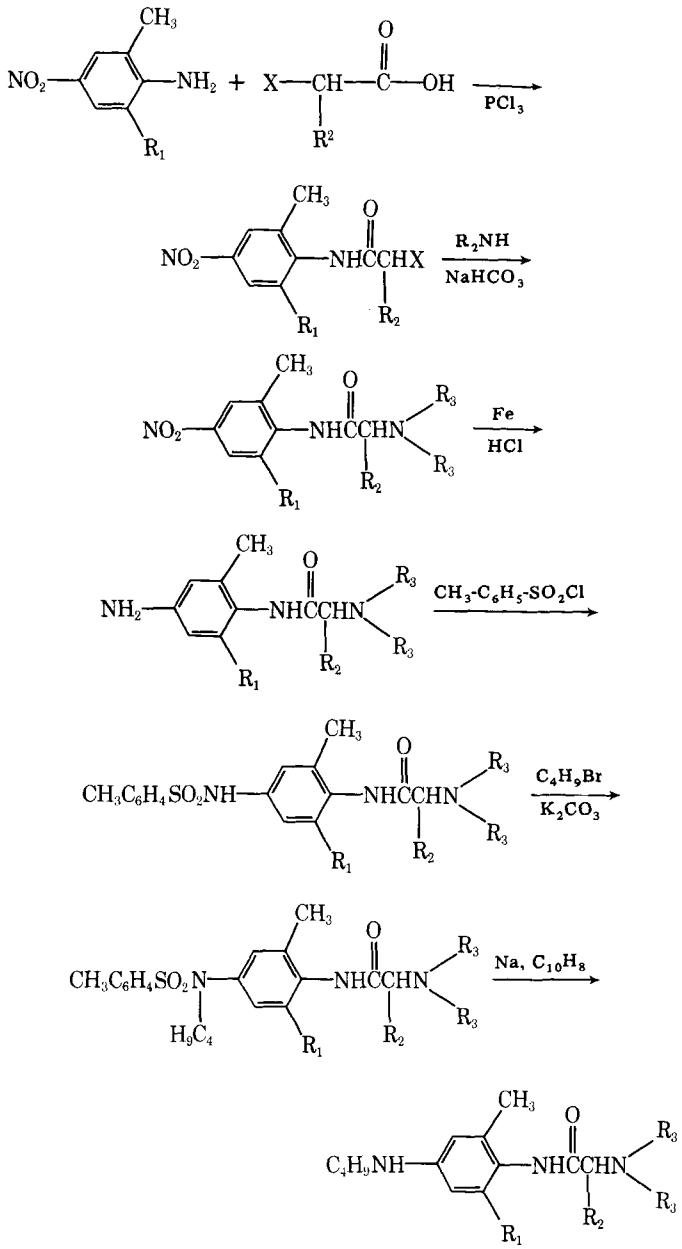
R_1 = H, CH_3
R_2 = H, CH_3, C_2H_5, C_3H_7, C_4H_9
R_3 = CH_3, C_2H_5

A few sterically hindered tetracaine analogs have been prepared previously: several 2-dialkylaminoethyl 4′-butylamino-2′,6′-dimethylbenzoates and two 2-*N*,*N*-dialkylaminoethyl-4′-butylamino-2′,6′-dimethylbenzamides (3). The latter compounds showed a long duration of activity but were appreciably toxic. No 2-*N*,*N*-dialkylaminoacyl-2′-methyl (or 2′,6′-dimethyl)-4′-butylaminoanilides, which comprise true lidocaine-type analogs of tetracaine, have been reported.

RESULTS AND DISCUSSION

Synthesis—The synthetic procedure followed is outlined in Scheme I. The starting material for the synthesis of the 2,6-dimethylanilides, 2,6-dimethyl-4-nitroaniline, was prepared by the method of Wepster (4), which involved the nitration of the *N*-tosyl derivative of 2,6-dimethylaniline. Attempts to nitrate *N*-chloroacetyl-2,6-dimethylanilide failed.

The preparation of some of the *N*-chloroacyl-2′-methyl-4′-nitroanilides was carried out using the procedure of Löfgren (5), using the reaction of chloroacyl chlorides with 2-methyl-4-nitroaniline. When this reaction was applied to 2,6-dimethyl-4-nitroaniline, no amide resulted. For the preparation of the *N*-haloacyl-2′,6′-dimethyl-4′-nitroanilides, or 2′-methyl derivatives where the acid halide was not commercially available,



R_1 = H, CH_3
R_2 = H, CH_3, C_2H_5, C_3H_7, C_4H_9
R_3 = CH_3, C_2H_5

Scheme I

the method of Lemaire *et al.* (6) was successful. This involved the preparation of the acid chloride *in situ* with phosphorus trichloride.

The *N*,*N*-dialkylaminoacyl-2′-methyl (or 2′,6′-dimethyl)-4′-nitroanilides were obtained in conventional fashion from treatment of the α-haloacylanilides with dimethylamine hydrochloride in the presence of anhydrous sodium bicarbonate or from diethylamine. E_2 elimination was observed with the longer chain acyl functions. Physical constants of the haloacyl and dialkylaminoacyl derivatives are listed in Table I.

0022-3549/82/0600-0680$01.00/0
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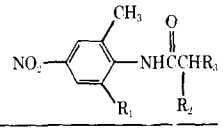
Table I—Physical Properties of 2-*N*,*N*-Dialkylaminoacyl-2′-methyl (or 2′,6′-dimethyl)-4′-nitroanilides



R_1	R_2	R_3	Yield, %	mp	Formula	IR, C=O cm^{-1}	Analysis, % Calc.	Found
H	H	Cl	74	121–122.5	$C_9H_9ClN_2O_3$	1675	C 47.28	47.28
							H 3.98	4.10
							N 12.25	12.20
							Cl 15.51	15.42
H	CH_3	Cl	70	115–116	$C_{10}H_{11}ClN_2O_3$	1670	C 49.50	49.67
							H 4.57	4.61
							N 11.54	11.49
							Cl 14.61	14.77
H	C_2H_5	Br	87	142–144	$C_{11}H_{13}BrN_2O_3$	1665	C 43.87	44.03
							H 4.35	4.49
							N 9.30	9.23
							Br 26.53	26.72
H	C_3H_7	Br	84	131.5–133	$C_{12}H_{15}BrN_2O_3$	1665	C 45.73	45.84
							H 4.80	4.96
							N 8.89	8.72
							Br 25.35	25.15
H	C_4H_9	Br	81	118–120	$C_{13}H_{17}BrN_2O_3$	1665	C 47.43	47.53
							H 5.21	5.28
							N 8.51	8.37
							Br 24.27	24.45
CH_3	H	Cl	77	234–236	$C_{10}H_{11}ClN_2O_3$	1660	C 49.50	49.60
							H 4.57	4.51
							N 11.54	11.44
							Cl 14.61	14.72
CH_3	CH_3	Cl	53	187–189	$C_{11}H_{13}ClN_2O_3$	1660	C 51.47	51.57
							H 5.10	5.18
							N 10.91	10.72
							Cl 13.81	14.01
CH_3	C_2H_5	Br	74	203–205	$C_{12}H_{15}BrN_2O_3$	1650	C 45.73	45.84
							H 4.80	5.09
							N 8.89	8.78
							Br 25.35	25.15
CH_3	C_3H_7	Br	73	181–183	$C_{13}H_{17}BrN_2O_3$	1650	C 47.43	47.57
							H 5.21	5.25
							N 8.51	8.35
							Br 24.27	24.35
CH_3	C_4H_9	Br	71	138–140	$C_{14}H_{19}BrN_2O_3$	1655	C 48.99	49.09
							H 5.58	5.67
							N 8.16	8.10
							Br 23.28	22.97
H	H	$N(CH_3)_2$	79	77–78	$C_{11}H_{15}N_3O_3$	1695	C 55.69	55.66
							H 6.37	6.38
							N 17.71	17.84
H	CH_3	$N(CH_3)_2$	87	81–82	$C_{12}H_{17}N_3O_3$	1700	C 57.36	57.43
							H 6.82	6.67
							N 16.72	16.84
H	C_2H_5	$N(CH_3)_2$	85	54.5–56	$C_{13}H_{19}N_3O_3$	1705	C 58.85	58.91
							H 7.22	7.25
							N 15.84	15.77
H	C_3H_7	$N(CH_3)_2$	86	85–86.5	$C_{14}H_{21}N_3O_3$	1700	C 60.20	60.22
							H 7.58	7.58
							N 15.04	14.99
H	C_4H_9	$N(CH_3)_2$	82	69–70	$C_{15}H_{23}N_3O_3$	1700	C 61.41	61.32
							H 7.90	7.72
							N 14.32	14.43
CH_3	H	$N(CH_3)_2$	87	91–93	$C_{12}H_{17}N_3O_3$	1670	C 57.36	57.36
							H 6.82	6.75
							N 16.72	16.67
CH_3	C_2H_5	$N(CH_3)_2$	80	125–127	$C_{14}H_{21}N_3O_3$	1655	C 60.20	60.18
							H 7.58	7.45
							N 15.04	15.01
CH_3	C_3H_7	$N(CH_3)_2$	82	106–108	$C_{15}H_{23}N_3O_3$	1650	C 61.41	61.60
							H 7.90	7.77
							N 14.32	14.27
CH_3	C_4H_9	$N(CH_3)_2$	75	95–96	$C_{16}H_{25}N_3O_3$	1650	C 62.52	62.25
							H 8.20	8.13
							N 13.67	13.56
H	H	$N(C_2H_5)_2$	93	73–74.5	$C_{13}H_{19}N_3O_3$	1700	C 58.85	58.93
							H 7.22	7.15
							N 15.84	15.90
H	CH_3	$N(C_2H_5)_2$	83	88–89	$C_{14}H_{21}N_3O_3$	1700	C 60.20	60.29
							H 7.58	7.49
							N 15.04	15.14
H	C_2H_5	$N(C_2H_5)_2$	80	69–70	$C_{15}H_{23}N_3O_3$	1710	C 61.41	61.42
							H 7.90	7.83
							N 14.32	14.18

Continued on next page

Table I—*Continued*

R_1	R_2	R_3	Yield, %	mp	Formula	IR, C=O cm^{-1}	Analysis, % Calc.	Found
H	C_3H_7	$N(C_2H_5)_2$	82	56–58	$C_{16}H_{25}N_3O_3$	1710	C 62.52	62.73
							H 8.20	8.05
							N 13.67	13.51
H	C_4H_9	$N(C_2H_5)_2$	79	52–53	$C_{17}H_{27}N_3O_3$	1705	C 63.53	63.61
							H 8.47	8.38
							N 13.07	13.13
CH_3	H	$N(C_2H_5)_2$	90	100–101	$C_{14}H_{21}N_3O_3$	1700	C 60.20	60.34
							H 7.58	7.80
							N 15.04	14.86
CH_3	C_2H_5	$N(C_2H_5)_2$	47	84–86	$C_{16}H_{25}N_3O_3$	1650	C 62.52	62.35
							H 8.20	8.15
							N 13.67	13.73
CH_3	C_3H_7	$N(C_2H_5)_2$	43	94–96	$C_{17}H_{27}N_3O_3$	1650	C 63.53	63.39
							H 8.47	8.41
							N 13.07	12.92
CH_3	C_4H_9	$N(C_2H_5)_2$	41	73–75	$C_{18}H_{29}N_3O_3$	1650	C 64.64	64.52
							H 8.71	8.68
							N 12.53	12.44

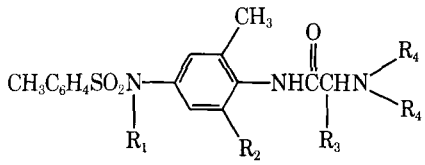


Table II—Physical Properties of 2-*N,N*-Dialkylaminoacyl-2′-methyl (or 2,′6′-Dimethyl-4′-(*p*-toluenesulfonamido)anilides

R_1	R_2	R_3	R_4	Yield, %	mp	Formula	IR, C=O cm^{-1}	Analysis, % Calc.	Found
H	H	H	CH_3	90	138–139	$C_{18}H_{23}N_3O_3S$	1660	C 59.81	59.76
								H 6.41	6.47
								N 11.62	11.50
								S 8.87	9.02
H	H	H	C_2H_5	95	119–121	$C_{20}H_{27}N_3O_3S$	1660	C 61.67	61.81
								H 6.99	7.06
								N 10.79	10.65
								S 8.23	8.31
H	H	CH_3	C_2H_5	85	67–68.5	$C_{21}H_{29}N_3O_3S$	1670	C 62.50	63.07
								H 7.24	7.44
								N 10.41	10.02
								S 7.95	7.70
H	H	C_2H_5	CH_3	82	128–130	$C_{20}H_{27}N_3O_3S$	1660	C 61.67	61.36
								H 6.99	6.96
								N 10.79	10.60
								S 8.23	8.37
H	H	C_2H_5	C_2H_5	78	54–57	$C_{22}H_{31}N_3O_3S$	1665	C 63.28	63.30
								H 7.48	7.61
								N 10.06	9.85
								S 7.68	7.64
H	H	C_3H_7	CH_3	87	81–84	$C_{21}H_{29}N_3O_3S$	1665	C 67.28	67.41
								H 7.27	7.32
								N 8.72	8.82
								S 6.65	6.68
H	H	C_4H_9	CH_3	69	80–84	$C_{22}H_{31}N_3O_3S$	1670	C 67.80	67.42
								H 7.47	7.62
								N 8.48	8.54
								S 6.45	6.47
H	CH_3	*H*	CH_3	79	195–197	$C_{19}H_{25}N_3O_3S$	1650	C 60.78	61.19
								H 6.71	6.61
								N 11.19	11.01
								S 8.54	8.20
H	CH_3	H	C_2H_5	64	160–162	$C_{21}H_{29}N_3O_3S$	1655	C 62.50	62.65
								H 7.24	7.18
								N 10.41	10.26
								S 7.95	7.95
H	CH_3	C_2H_5	CH_3	73	182–184	$C_{21}H_{29}N_3O_3S$	1655	C 62.50	62.28
								H 7.24	7.30
								N 10.41	10.00
								S 7.95	7.77
H	CH_3	C_2H_5	C_2H_5	81	174–177	$C_{23}H_{33}N_3O_3S$	1665	C 64.01	64.07
								H 7.71	7.60
								N 9.74	9.71
								S 7.43	7.39
H	CH_3	C_3H_7	CH_3	62	171–173	$C_{22}H_{31}N_3O_3S$	1650	C 63.28	63.16
								H 7.48	7.38
								N 10.06	9.95
								S 7.68	7.80

Table II—*Continued*

R_1	R_2	R_3	R_4	Yield, %	mp	Formula	IR, C=O cm^{-1}	Analysis, % Calc.	Found
H	CH_3	C_3H_7	C_2H_5	72	169–171	$C_{24}H_{35}N_3O_3S$	1660	C 64.69	64.71
								H 7.92	7.82
								N 9.43	9.26
								S 7.20	7.30
H	CH_3	C_4H_9	CH_3	81	70–75	$C_{23}H_{33}N_3O_3S$	1660	C 64.01	64.12
								H 7.71	7.73
								N 9.74	9.58
								S 7.43	7.16
H	CH_3	C_4H_9	C_2H_5	62	131–133	$C_{25}H_{37}N_3O_3S$	1660	C 65.33	65.41
								H 8.11	7.98
								N 9.14	9.12
								S 6.98	7.08
C_4H_9	H	H	CH_3	79	102–103	$C_{22}H_{31}N_3O_3S$	1690	C 63.28	63.33
								H 7.48	7.54
								N 10.06	10.02
								S 7.68	7.63
C_4H_9	H	H	C_2H_5	73	77–79	$C_{24}H_{35}N_3O_3S$	1700	C 64.69	64.85
								H 7.92	7.80
								N 9.43	9.28
								S 7.20	7.34
C_4H_9	H	CH_3	C_2H_5	63	110–111	$C_{25}H_{37}N_3O_3S$	1700	C 65.33	65.43
								H 8.11	8.06
								N 9.14	9.26
								S 6.98	7.09
C_4H_9	H	C_2H_5	CH_3	78	74–75	$C_{24}H_{35}N_3O_3S$	1695	C 64.69	64.58
								H 7.92	7.88
								N 9.43	9.32
								S 7.20	7.37
C_4H_9	H	C_2H_5	C_2H_5	80	62–68	$C_{26}H_{39}N_3O_3S$	1695	C 65.93	66.36
								H 8.30	8.42
								N 8.87	8.60
								S 6.77	6.68
C_4H_9	H	C_3H_7	CH_3	78	68–70	$C_{25}H_{37}N_3O_3S$	1695	C 65.33	65.30
								H 8.11	7.98
								N 9.14	9.07
								S 6.98	7.16
C_4H_9	H	C_4H_9	CH_3	75	55–57	$C_{26}H_{39}N_3O_3S$	1695	C 65.93	65.89
								H 8.30	8.44
								N 8.87	8.86
								S 6.77	6.74
C_4H_9	CH_3	H	C_2H_5	74	74–76	$C_{25}H_{37}N_3O_3S$	1690	C 65.33	65.34
								H 8.11	8.06
								N 9.14	9.00
								S 6.98	7.15
C_4H_9	CH_3	C_2H_5	C_2H_5	72	117.5–120	$C_{27}H_{41}N_3O_3S$	1650	C 66.49	66.65
								H 8.47	8.39
								N 8.62	8.56
								S 6.57	6.49
C_4H_9	CH_3	C_3H_7	CH_3	73	139–141	$C_{26}H_{39}N_3O_3S$	1650	C 65.93	65.89
								H 8.30	8.36
								N 8.87	8.88
								S 6.77	6.71
C_4H_9	CH_3	C_3H_7	C_2H_5	79	97–99	$C_{28}H_{43}N_3O_3S$	1650	C 67.03	67.02
								H 8.64	8.66
								N 8.37	8.28
								S 6.39	6.40
C_4H_9	CH_3	C_4H_9	CH_3	71	124–125	$C_{27}H_{41}N_3O_3S$	1650	C 66.49	66.42
								H 8.47	8.41
								N 8.62	8.58
								S 6.57	6.68

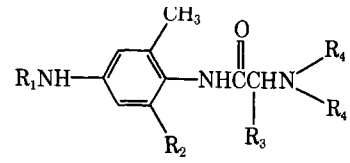
The reduction of the nitro group was done with iron and hydrochloric acid, according to the method of Clinton *et al.* (7), giving 85–95% yields of amine. The butylation of the 4-amino group was attempted by several procedures. Both direct alkylation with butyl bromide and reductive alkylation procedures using propionaldehyde and reducing agents gave mixtures of mono- and dibutylamino compounds. Monobutylation succeeded by using a modification of the method of Hendrickson and Bergeron (8), in which the amino group is first tosylated and then alkylated with butyl bromide. The alkylations generally required 5–10 days at room temperature. The regeneration of the amine from the *N*-butylsulfonamide was achieved in excellent yield by treatment with sodium naphthalene anion radical in 1,2-dimethoxyethane. The mechanism for this procedure is assumed to be the same as that proposed previously (9) for the sodium–liquid ammonia cleavage of toluenesulfonamides.

Physical constants of the 4′-*N*-tosyl intermediates prepared are listed in Table II, and of the 4′-amino and 4′-butylamino compounds are recorded in Table III.

Local Anesthetic Evaluation—Primary local anesthetic activity was measured by determining loss of reflex of the rabbit cornea (10), using lidocaine for comparison. With this method, both time of onset and duration of action may be determined; testing data are recorded in Table IV. Of the 4′-amino compounds which were not *N*-butylated, none showed significant activity by this procedure. Of the *N*-butyl derivatives, the 2′,6′-dimethyl compounds generally had a longer duration of action than the 2′-methyl substituted compounds. One 2′-methyl derivative, the α-butyl compound, had a comparable time for duration of activity, indicating that a greater extent of alkylation gave greater duration times. This was also the case among the 2′,6′-dimethyl derivatives, where the α-propyl and α-butyl compounds had the longest duration times. Times of onset of action were comparable in both series and were somewhat less than that of lidocaine. Duration times in both series were significantly greater than that for lidocaine.

Determination of the degree of spinal anesthesia in sheep, using the method of Lebeaux (11), was also done with four of the 2′,6′-dimethyl series, including one non-*N*-butyl derivative. Times of onset of activity as well as duration of anal block, digital block, and motor block were

Table III—Physical Properties of 2-*N,N*-Dialkylaminoacyl-2′-methyl (or 2,6′-Dimethyl)-4′-aminoanilides



	R_1	R_2	R_3	R_4	%, Yield	mp	Formula	IR, C=O cm^{-1}	pKa	Analysis, % Calc.	Found
1	H	H	H	CH_3	95	100.5–102	$C_{11}H_{17}N_3O$	1650	7.39	C 63.74	63.77
										H 8.27	8.15
										N 20.27	20.29
2	H	H	H	C_2H_5	90	53–54	$C_{13}H_{21}N_3O$	1670	7.85	C 66.35	66.37
										H 8.99	8.89
										N 17.86	17.88
3	H	H	CH_3	CH_3	82	76–78	$C_{12}H_{19}N_3O$	1635	7.30	C 65.13	65.20
										H 8.65	8.61
										N 18.99	19.05
4	H	H	CH_3	C_2H_5	81	77–78	$C_{14}H_{23}N_3O$	1670	8.01	C 67.44	67.32
										H 9.30	9.31
										N 16.85	17.04
5	H	H	C_2H_5	CH_3	75	76–77	$C_{13}H_{21}N_3O$	1650	7.23	C 66.35	66.09
										H 8.99	8.81
										N 17.86	18.07
6	H	H	C_2H_5	C_2H_5	89	78–80	$C_{15}H_{25}N_3O$	1650	8.12	C 68.40	68.32
										H 9.57	9.58
										N 15.95	16.13
7	H	H	C_3H_7	CH_3	79	99–100	$C_{14}H_{23}N_3O$	1655	7.18	C 67.44	67.47
										H 9.30	9.36
										N 16.85	17.02
8	H	H	C_3H_7	C_2H_5	72	52–53	$C_{16}H_{27}N_3O$	1675	7.92	C 69.28	69.50
										H 9.81	9.83
										N 15.15	15.24
9	H	H	C_4H_9	CH_3	90	120–121	$C_{15}H_{25}N_3O$	1650	7.15	C 68.40	68.63
										H 9.57	9.63
										N 15.95	16.10
10	H	CH_3	H	CH_3	85	129–130	$C_{12}H_{19}N_3O$	1660	7.27	C 65.13	65.20
										H 8.65	8.55
										N 18.99	19.11
11	H	CH_3	H	C_2H_5	80	101–103	$C_{14}H_{23}N_3O$	1660	7.80	C 67.44	67.60
										H 9.30	9.39
										N 16.85	16.88
12	H	CH_3	C_2H_5	CH_3	69	139–141	$C_{14}H_{23}N_3O$	1650	7.15	C 67.44	67.15
										H 9.30	9.39
										N 16.85	16.54
13	H	CH_3	C_2H_5	C_2H_5	82	97–99	$C_{16}H_{27}N_3O$	1650	8.05	C 69.28	69.01
										H 9.81	9.84
										N 15.15	15.20
14	H	CH_3	C_3H_7	CH_3	70	179–181	$C_{15}H_{25}N_3O$	1650	7.20	C 68.40	68.28
										H 9.57	9.63
										N 15.95	15.97
15	H	CH_3	C_3H_7	C_2H_5	69	83–85	$C_{17}H_{29}N_3O$	1650	7.85	C 70.06	70.18
										H 10.03	10.10
										N 14.42	14.53
16	H	CH_3	C_4H_9	CH_3	82	183–185	$C_{16}H_{27}N_3O$	1650	7.01	C 69.28	69.29
										H 9.81	9.93
										N 15.15	15.23
17	H	CH_3	C_4H_9	C_2H_5	65	90–92	$C_{18}H_{31}N_3O$	1650	7.85	C 70.78	70.90
										H 10.23	10.24
										N 13.76	13.91
18	C_4H_9	H	H	CH_3	89	50–51	$C_{15}H_{25}N_3O$	1675	7.21	C 68.40	68.40
										H 9.57	9.47
										N 15.95	16.14
19	C_4H_9	H	H	C_2H_5	93	41–41.5	$C_{17}H_{29}N_3O$	1675	7.67	C 70.06	69.63
										H 10.03	9.99
										N 14.42	14.51
20	C_4H_9	H	CH_3	C_2H_5	79	134–136	$C_{18}H_{31}N_3O{\cdot}2HCl{\cdot}H_2O$	1690	8.20	C 54.49	54.41
										H 8.89	9.27
										N 10.59	9.98
										Cl 17.87	17.77
21	C_4H_9	H	C_2H_5	CH_3	84	55.5–57	$C_{17}H_{29}N_3O$	1660	7.25	C 70.06	69.88
										H 10.03	9.91
										N 14.42	14.31
22	C_4H_9	H	C_2H_5	C_2H_5	80	63–65	$C_{19}H_{33}N_3O$	1660	8.02	C 71.43	71.40
										H 10.41	10.47
										N 13.15	13.20
23	C_4H_9	H	C_3H_7	CH_3	85	48–49	$C_{18}H_{31}N_3O$	1665	7.25	C 70.78	70.83
										H 10.23	10.31
										N 13.76	13.81

Table II—*Continued*

	R_1	R_2	R_3	R_4	%, Yield	mp	Formula	IR, C=O cm^{-1}	pKa	Analysis, % Calc.	Found
24	C_4H_9	H	C_4H_9	CH_3	86	163–165	$C_{19}H_{33}N_3O$·HCl	1670	7.12	C 64.11	63.65
										H 9.63	9.66
										N 11.80	11.64
										Cl 9.96	10.11
25	C_4H_9	CH_3	H	C_2H_5	81	39–40	$C_{18}H_{31}N_3O$	1670	7.82	C 70.78	70.92
										H 10.23	10.14
										N 13.76	13.82
26	C_4H_9	CH_3	C_2H_5	C_2H_5	72	155–158	$C_{20}H_{35}N_3O$·2HCl·H_2O	1690	8.05	C 56.59	56.54
										H 9.26	9.62
										N 9.90	9.58
										Cl 16.70	16.45
27	C_4H_9	CH_3	C_3H_7	CH_3	90	45–47	$C_{19}H_{33}N_3O$	1660	7.18	C 71.43	71.51
										H 10.41	10.54
										N 13.15	13.20
28	C_4H_9	CH_3	C_3H_7	C_2H_5	71	176–178	$C_{21}H_{37}N_3O$·2HCl·0.7H_2O	1690	7.77	C 58.74	58.67
										H 9.46	9.32
										N 9.79	9.41
										Cl 15.69	15.82
29	C_4H_9	CH_3	C_4H_9	CH_3	79	204–206	$C_{20}H_{35}N_3O$·2HCl·0.5H_2O	1695	7.22	C 58.33	58.50
										H 9.28	9.05
										N 10.20	9.71
										Cl 16.36	16.15

measured and are listed in Table V. With this determination, the non-*N*-butyl derivative tested (number 13) showed activity somewhat greater in duration than that of lidocaine. The three *N*-butyl compounds tested showed greater duration of activity than 13, but were significantly less than that of tetracaine. It is concluded that this series of compounds has local anesthetic potency intermediate between that of lidocaine and tetracaine.

Ionization constants are listed in Table III for the 4′-amino derivatives. No correlation is evident between local anesthetic potency and pKa values. A previous attempt to find a correlation between ionization constants, oil–water partition coefficients, and local anesthetic activity failed to give statistically significant results (12), although some general trends were noted. Also, IR absorption frequencies for carbonyl absorption are listed in Table III. A previous study (13) revealed an optimum absorption frequency range for good anesthetic potency, but no optimum range for carbonyl absorption is evident for the durations of activity reported here. However, a definite effect of the α-substituent on increasing the wavelength at which carbonyl absorption occurs is apparent.

EXPERIMENTAL

Melting points were taken[1] and are uncorrected[2]. Infrared spectra were recorded on a spectrophotometer[3] using KBr pellets. TLC was carried out using silica gel plates, and the products were detected by exposure to iodine vapor or UV light. Organic reagents were supplied[4–6].

***N*-Haloacyl-2′-methyl (or 2′,6′-dimethyl)-4′-nitroanilides**—*Method 1*—Chloroacetyl chloride (14.91 g, 0.132 mole) was added rapidly to a solution of 18.26 g (0.12 mole) of 2-methyl-4-nitroaniline in 100 ml of glacial acetic acid at 15°. A solution of 45.2 g of sodium acetate trihydrate in 200 ml of water at 10° was added quickly. The mixture was shaken for 35 min, and the product was filtered, washed with 50% hydrochloric acid and water and dried. Recrystallization was generally done with ethanol and charcoal.

Method 2—A mixture of 15.22 g (0.1 mole) of 2-methyl-4-nitroaniline, 7 ml (0.084 mole) of phosphorus trichloride, and 0.105 mole of 2-bromocarboxylic acid in 250 ml of dry benzene was refluxed for 3 hr and filtered. The filtrate was evaporated, and the crude product was washed with 50% hydrochloric acid and water and dried. Recrystallization was done with aqueous ethanol and charcoal. Refluxing time for acylation of 2,6-dimethyl-4-nitroaniline was 24–48 hr.

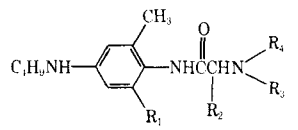
Method 3—2,6-Dimethyl-4-nitroaniline (4) (15.0 g, 0.09 mole) and redistilled triethylamine (10.0 g, 0.1 mole) in 200 ml of anhydrous ether was cooled to 0–5°, and 14.12 g (0.125 mole) of chloroacetyl chloride was added dropwise with vigorous stirring and ice cooling for 1 hr. The mixture was shaken for 6 hr at room temperature and the ether was evaporated under reduced pressure. The crude product was washed with 50% hydrochloric acid and water, dried, and recrystallized from ethanol and charcoal.

2-*N,N*-Dimethylaminoacyl-2′-methyl (or 2′,6′-dimethyl)-4′-nitroanilides—Dimethylamine hydrochloride (16.15 g, 0.198 mole) and anhydrous sodium bicarbonate (16.63 g, 0.198 mole) in 300 ml of anhydrous benzene was stirred for 30 min, and chloroacetyl-2′-methyl-4′-nitroanilide (13.8 g, 0.066 mole) was added. The mixture was refluxed for 30 hr, cooled, and filtered. The benzene filtrate was extracted with four 80-ml portions of 1 *N* HCl, and the combined extracts were brought to pH 10 with 7 *N* NaOH solution. The precipitate was recrystallized from aqueous ethanol. When this method was applied to α-haloacyl 2,6-dimethyl-4-nitroanilines, the refluxing required 4–6 days.

For preparation of the *N,N*-diethyl derivatives, redistilled diethylamine was used.

2-*N,N*-Dialkylaminoacyl-2′-methyl (or 2′,6′-dimethyl)-4′-aminoanilides—To a stirred, boiling mixture of powdered iron (10.35 g, 0.185 mole), ethanol (85 ml), water (25 ml), and concentrated hydrochloric acid (1 ml) was added in 7.0-g portions (0.026 mole) of *N,N*-diethylaminoacetyl-2′-methyl-4′-nitroanilide. The heat source was removed during the addition. The mixture was stirred and boiled gently for 35 min, cautiously treated with 10.0 g of powdered sodium bicarbonate, stirred at boiling for 10 min, and filtered hot. The filter cake was washed with hot alcohol, and the alcohol was removed *in vacuo*. The residue was added to 15 ml of water and extracted three times with ethyl acetate. The extract was

Table IV—Local Anesthetic Activity: Method of Loss of Reflex by the Rabbit Cornea



Number[a]	R_1	R_2	R_3	Onset, sec	Duration, min
18	H	H	CH_3	45	40
19	H	H	C_2H_5	25	65
20	H	CH_3	C_2H_5	40	50
21	H	C_2H_5	CH_3	30	35
22	H	C_2H_5	C_2H_5	55	40
23	H	C_3H_7	CH_3	15	55
24	H	C_4H_9	CH_3	30	90
25	CH_3	H	C_2H_5	30	65
26	CH_3	C_2H_5	C_2H_5	25	75
27	CH_3	C_3H_7	CH_3	35	100
28	CH_3	C_3H_7	C_2H_5	20	120
29	CH_3	C_4H_9	C_2H_5	65	105
Lidocaine				90–120	20–25

[a] 1% solutions, pH ~6.7, were tested.

[1] Mel-Temp apparatus.
[2] Microanalyses were done by Dr. F. B. Strauss, Oxford, England.
[3] Perkin-Elmer spectrophotometer Model 457A.
[4] Aldrich Chemical Co.
[5] Fisher Scientific Co.
[6] J. T. Baker Chemical Co.

Table V—Local Anesthetic Activity: Spinal Anesthesia in the Sheep

Number	%, Concentration	pH	Number of Animals	Onset (Anal), Min	Duration, min			Complete Recovery, Min
					Anal Block	Digital Block	Motor Block	
11	2.0	6.5	2	1–2	73	78	73[a]	178
25	0.25	6.0	2	3–5	25	18[a]	20[b]	60
	1.0	6.0	2	1.5	100	100	80	158
26	1.0	5.9	3	1	169	129	88[c]	320
27	1.0	5.3	2	1	180	142	36	>360[d]
Lidocaine	1.5	6.7	6	1	61 ± 16	51 ± 9	24 ± 7	95 ± 21
Tetracaine	0.5	6.25	6	1–1.5	302 ± 66	285 ± 46	208 ± 77	>360[d]
Glucose	5.0	6.2	4	—	0	0	0	—

[a] Frequency 75%. [b] Frequency 50%. [c] Frequency 67%. [d] Less than 24 hr.

dried ($MgSO_4$) and concentrated to a small volume. The syrupy residue was recrystallized from benzene–commercial hexane[7].

2-*N*,*N*-Dialkylaminoacyl-2′-methyl (or 2′,6′-dimethyl)-4′-(*p*-toluenesulfonamido)anilides—2-Dimethylaminoacetyl-2′-methyl-4′-aminoanilide (4.2 g, 0.021 mole) and redistilled pyridine (1.5 ml) in 40 ml of methylene chloride was cooled to 0°, and 4.46 g (0.023 mole) of *p*-toluenesulfonyl chloride was added slowly with stirring and ice-cooling during 30 min. The mixture was stirred for several hr at 0–5°, methylene chloride was removed *in vacuo*, and the residue was added to 80 ml of water. The pH was adjusted to 10 with dilute sodium hydroxide solution, the solution was extracted with ethyl acetate, and the extract was dried ($MgSO_4$). It was concentrated to a small volume, and the residue was recrystallized from benzene–commercial hexane[7].

2-*N*,*N*-Dialkylaminoacyl-2′-methyl (or 2′,6′-dimethyl)-4′-(*N*′-butyl-*p*-toluenesulfonamido)anilides—2-Dimethylaminoacetyl-2′-methyl-4′-(*p*-toluenesulfonamido)anilide (2.8 g, 0.0078 mole), anhydrous potassium carbonate (4.31 g, 0.031 mole), and redistilled *n*-butyl bromide (9.62 g, 0.0702 mole) in 70 ml of dry acetone was stirred at room temperature for 7 days. The mixture was filtered, and acetone was removed in a rotary evaporator. The residual syrup was crystallized from benzene–or ether–commercial hexane[7].

2-*N*,*N*-Dialkylaminoacyl-2′-methyl (or 2′,6′-dimethyl)-4′-butylaminoanilides—Naphthalene (4.64 g, 0.036 mole) in 30 ml of 1,2-dimethoxyethane was kept under nitrogen, and 0.83 g (0.036 mole) of sodium was added. After 5 min, 2.49 g (0.006 mole) of 2-dimethylaminoacetyl-2′-methyl-4′-(*N*′-butyl-*p*-toluenesulfonamido) anilide in 10 ml of 1,2-dimethoxyethane was added, and the solution was kept at room temperature under nitrogen for 80 min. Water was added to quench the reaction, and the solvent was removed in a rotary evaporator. The residue was added to 50 ml of water, the pH was brought to ~2, and the solution was extracted three times with ether. The aqueous solution was adjusted to pH 10 and extracted with ethyl acetate. The extract was dried ($MgSO_4$) and concentrated, and the residual syrup was crystallized from hexane.

Local Anesthetic Evaluation—Primary local anesthetic testing was done by measuring loss of reflex of the rabbit cornea according to Rose (10). Each compound was tested in sterile 1% aqueous solution, pH 6.7, using 1% lidocaine solution, containing no epinephrine, as standard. The test solution (3–4 drops) was applied to one eye of the rabbit, the other eye being treated with control solution, pH 6.7, containing no anesthetic. Using a soft cotton filament rolled to a fine point, the time at which loss of reflex on touching with the filament was recorded to indicate onset of action. The procedure was continued, and the time at which reflex activity returned was recorded for duration of action.

The extent of spinal anesthesia in the sheep was determined according to the procedure of Lebeaux (11). Sterile solutions (2 ml) of the test compounds at the concentrations indicated in Table V and containing glucose (50 mg/ml) were injected intrathecally between the L6 and S1 vertebra. Onset and duration times for sensory blocks from the anal and digital (hind limb) areas were recorded, and for motor block when the animals were able to stand. Frequency of block was 100% except where indicated. Lidocaine (1.5%) and tetracaine (0.5%) solutions were used as standards and glucose (5.0%) solution as control.

Ionization Constants—Determination of ionization constants was done according to the procedure of Albert and Serjeant (14) using a pH meter[8] with glass and calomel electrodes. Titrations of 0.001 *M* aqueous solutions of the compounds were made with 0.01 *N* KOH in 0.5-ml portions. Each titration yielded 10 pH values, giving 10 values for the pKa's, which were averaged. If pH values fell outside the 5–9 range, corrections were made for hydrogen or hydroxide ion concentrations.

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ACKNOWLEDGMENTS

Abstracted from a thesis submitted by C.-M. Jan to the Massachusetts College of Pharmacy and Allied Health Sciences in partial fulfillment of Doctor of Philosophy degree requirements.

Supported by funds from the John R. and Marie K. Sawyer Memorial Fund, Massachusetts College of Pharmacy and Allied Health Sciences.

[7] Skellysolve B.

[8] Beckman Research pH Meter.