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RESEARCH ARTICLES

Synthesis and Local Anesthetic Properties of Secondary Alkoxyalkylaminoacylanilides

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Abstract □ Nineteen secondary alkoxyalkylaminoacylanilides were prepared. They were weaker bases and were more hydrophilic than the corresponding analogs lacking the ether function. In 2% solution, these compounds blocked the rat sciatic nerve *in vivo* after relatively short onset times with good frequency of anesthesia. The duration of block was 0.4–1.5 times that of lidocaine. Their systemic toxicity was low, and their irritation liability in most instances was acceptable.

Keyphrases □ Alkoxyacylaminoacylanilides, various—synthesized, evaluated for local anesthetic activity in rats □ Anesthetic activity, local—various alkoxyacylaminoacylanilides evaluated in rats □ Structure-activity relationships—various alkoxyacylaminoacylanilides evaluated for local anesthetic activity in rats

A few alkoxyalkylaminoacetanilides related to lidocaine were described previously (1). This work has been extended, and 19 related secondary amines were prepared and studied as local anesthetics.

RESULTS AND DISCUSSION

Synthesis—The new compounds were synthesized using conventional methods according to the following two procedures.

1. Haloacylanilides (Table I) were refluxed with an alkoxyalkylamine in alcohol, benzene, or toluene, using excess amine as the proton acceptor.

2. Acrylanilides (Table II) were refluxed neat with an equimolar or excess amount of an alkoxyalkylamine.

The compounds obtained (Tables III and IV) were isolated and purified as described under *Experimental.*

The preparation of 3-haloacylanilides, using Löfgren's buffer method (2), was not always free of complications. Thus, the reaction between 2-ethylaniline and 3-bromobutyryl chloride resulted in a mixture of the expected compound, III (Table I), and the crotonyl compound, XI (Table II). Furthermore, the III yield was unacceptable. This tendency to eliminate also was observed in the reaction between 3-bromopropionyl chloride and 2-ethylaniline (3). In the latter case, only a small amount of 2′-ethylacrylanilide was formed, but the yield of the bromopropionanilide XLII was satisfactory.

When XIII was prepared from 2-ethylaniline and *trans*-2-methyl-2-butenoyl chloride (tiglyl chloride), experiments were performed using a molar excess of the aniline instead of sodium bicarbonate as a proton acceptor. This approach resulted in lower yields and inconvenient workup conditions and is, therefore, not recommended (*cf.*, Ref. 4). Attempts to distill the β-substituted amines XXII and XXIII resulted, as expected (5), in elimination of 2-methoxyethylamine and formation of the acryl (X) and crotonyl (XI) derivatives of 2-ethylaniline, respectively.

Significant amounts of 2-ethylaniline (39%) were formed in the preparation of the γ-substituted 4-(2-methoxyethylamino)-2′-ethylbutyranilide (XXV) from 4-chloro-2′-ethylbutyranilide (IV) and 2-methoxyethylamine by refluxing in anhydrous benzene for 4 hr. This phenomenon has never been observed in the synthesis of numerous α- and β-aminoacylanilides.

Two compounds could not be obtained with the aforementioned methods. Thus, 3-(2-methoxyethylamino)-2-methyl-2′-ethylbutyranilide could neither be prepared from the reaction between 2-methoxyethylamine and the bromo compound VIII nor obtained by addition of the alkoxyamine to the double bond of XIII. The 3-bromopivalyl derivative IX did not react with 2-methoxyethylamine to give 2,2-dimethyl-3-(2-methoxyethylamino)-2-ethylpropionanilide, which is not surprising in view of the similarity of Structure IX and neopentyl bromide.

Physicochemical Data—Determination of pKa values and partition coefficients (cod liver oil–water) (6) were made (Table IV). As expected, the introduction of an alkoxy group in the β-position to the amino nitrogen decreased the basicity. Löfgren (7) reported that the pKa values for 23 unsubstituted lidocaine homologs (α-aminoacylanilides) were in the 7.3–8.9 range, whereas the pKa values for the related α-alkoxyalkylaminoacylanilides, XIV–XXI and XXVI–XXXI, reported here ranged from 6.7 to 7.2. Compounds with a methyl on the amide nitrogen were the strongest bases in both series.

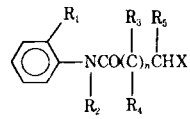
Lengthening of the acyl chain to β- and γ-substituted aminoacylanilides, XXII–XXV, increased the pKa values to 8.3–9.0, *i.e.*, to the higher part of the range for Löfgren's α-amines. Therefore, the influence of the β-alkoxy group was approximately compensated by the increased distance between the amine and amide groups.

The presence of the alkoxy group lowered the partition coefficient (decreased lipophilicity) and increased the water solubility of the bases considerably in comparison to unsubstituted analogs. Thus, the solubilities of the base form of the following compounds were: XV and XXIX, 6%; XXXI, 11%; and XVII, 39%.

Pharmacology—The following tests were performed according to methods described under *Experimental.*

1. Conduction anesthesia: Observations were made on the frequency of successful block of the sciatic nerve in the rat (8), the onset time, and the duration (Table V). In some cases, the effect of the addition of epinephrine to the local anesthetic solutions was studied.

Table I—Haloacylanilides



Compound	R_1	R_2	R_3	R_4	R_5	n	X	Yield, %	Recrystallization Solvent	Melting Point	Formula	Analysis, % Calc.	Found
I[a]	CH_3	CH_3	—	—	CH_3	0	Br	92	—	—	$C_{11}H_{14}BrNO$	C 51.6	51.6
												H 5.51	5.50
II	C_2H_5	H	—	—	C_2H_5	0	Br	84	95% ethanol	113.5–114.5°	$C_{12}H_{16}BrNO$	C 53.3	53.9
												H 5.97	6.03
III[b]	C_2H_5	H	H	H	CH_3	1	Br	92	Benzene–cyclohexane	113–114.5°	$C_{12}H_{16}BrNO$	C 53.3	53.7
												H 5.97	5.98
												Br 29.6	29.3
IV	C_2H_5	H	H	H	H	2	Cl	72	Benzene–petroleum ether	61.5–62°	$C_{12}H_{16}ClNO$	N 5.18	5.17
												C 63.9	63.9
												H 7.15	7.42
V[c]	$C(CH_3)=CH_2$	H	—	—	CH_3	0	Br	90	—	—	$C_{12}H_{14}BrNO$	C 53.7	53.5
												H 5.26	5.38
												Br 29.8	30.2
VI	$CH(CH_3)_2$	H	—	—	CH_3	0	Br	92	Cyclohexane	96–97°	$C_{12}H_{16}BrNO$	C 53.5	53.5
												H 5.97	5.96
												Br 29.6	29.7
VII	$C(CH_3)_3$	H	—	—	CH_3	0	Br	73	Cyclohexane	133.5–134°	$C_{13}H_{18}BrNO$	C 54.9	54.7
												H 6.38	6.34
												Br 28.1	28.1
VIII	C_2H_5	H	CH_3	H	CH_3	1	Br	43	2-Propanol	149–150°	$C_{13}H_{18}BrNO$	C 54.9	55.1
												H 6.38	6.45
												Br 28.1	28.0
IX	C_2H_5	H	CH_3	CH_3	H	1	Br	83	Acetone–petroleum ether	132–133°	$C_{13}H_{18}BrNO$	C 54.9	55.2
												H 6.38	6.63
												Br 28.1	28.3

[a] Boiling point 143–144°; n_D^{25} 1.5519. [b] Molecular weight: calc., 270; found, 267. [c] Analysis done on a small sample distilled under high vacuum.

2. Systemic toxicity (8): Estimates of the acute systemic toxicity (LD_{50}) were made following intraperitoneal and intravenous administrations in female albino mice (Table VI).

3. Irritation liability (9): The intradermal wheal technique in the rabbit back was used to compare the local irritation of most compounds (Table VI).

Local Anesthetic Properties (Table V)—The onset times of all new compounds were somewhat longer (generally 3–4 min) than that of lidocaine (1–2 min). Compound XXV was much slower in onset (8–11 min) than the others.

The frequency of anesthesia was good for all compounds except XXV, which only produced block in two-thirds of the injected animals, even in the experiments with 4% solutions. Compound XXV deviates structurally from the rest by being the only γ-aminoacylanilide.

Among the ester-type local anesthetics, *i.e.*, agents related to amylocaine (stovaine) and procaine, an increase in the distance between the aromatic ring and the (aliphatic) amino nitrogen from $COOCH_2CH_2$ (*e.g.*, procaine) to $COOCH_2CH_2CH_2$ does not influence the local anesthetic effects in a remarkably detrimental manner (10). Usually, the higher homolog is not too different from the lower one, and sometimes an advantageous change in the parameters is observed (*e.g.*, piperocaine) (11).

If, however, the similar change is made in aminoacylanilide local anesthetics, *i.e.*, a change from $NHCOCH_2CH_2$ to $NHCOCH_2CH_2CH_2$, a distinctly degenerative effect in local anesthetic properties can result.

The 1% solutions of the new compounds, except XXIII, produced a shorter duration of block than lidocaine; XXIII was about as effective as the reference compound. At the 2% level, XXIII blocked significantly longer than lidocaine ($p < 0.01$), whereas the other agents gave durations shorter or equal to that of the standard. However, XXII–XXV gave the most long-lasting blocks, and the distance between the amino nitrogen and the benzene ring is larger in these compounds than in the others.

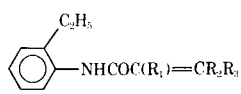
The addition of epinephrine prolonged the duration of anesthesia of the new agents. Compound XVIII is a representative example of the series in this respect. The dose–duration curve (Fig. 1) for solutions containing epinephrine in a concentration of 1:100,000 (w/v) is significantly separated from the curve for plain anesthetic solutions. The prolongation of duration by epinephrine is further illustrated in Fig. 2, where the effects of increasing amounts of epinephrine on the duration are shown for three different concentration levels of XVIII.

Toxicity (Table VI)—None of the compounds was significantly more toxic systemically than lidocaine after intravenous and intraperitoneal administration.

The degree of irritation at the site of injection increased with increasing lipid partitioning (*cf.*, Table IV). This tendency is clear and in line with observations on many other series and depends obviously on the close relationship between compound solubility at tissue pH and lipophilicity. The good correlation between decreasing solubility at physiological pH and increasing irritation liability was convincingly demonstrated by Koelzer and Wehr (12).

The thioether analogs of XVIII and XXXI were reported previously (3). The significant biological difference observed between the oxygen

Table II—Acrylanilides



Compound	R_1	R_2	R_3	Yield, %	Melting Point	Recrystallization Solvent	Formula	Analysis, % Calc.	Found
X	H	H	H	66	107–108°	Aqueous ethanol	$C_{11}H_{13}NO$	C 75.4	75.5
								H 7.48	7.63
XI	H	H	CH_3	85	140.5–141°	Petroleum ether (bp 60–110°)	$C_{12}H_{15}NO$	C 76.2	76.3
								H 7.99	7.99
								N 7.40	7.37
XII	H	CH_3	CH_3	70	81.5–82.5°	2-Propanol–water	$C_{13}H_{17}NO$	C 76.8	77.1
								H 8.43	8.53
XIII[a]	CH_3	H	CH_3	71	71.5–72°	Petroleum ether (bp 30–60°)	$C_{13}H_{17}NO$	C 76.8	77.0
								H 8.43	8.37

[a] *trans*-Configuration.

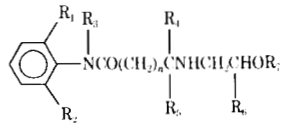


Table III—Alkoxyalkylaminoacylanilides

Compound	R_1	R_2	R_3	n	R_4	R_5	R_6	R_7	Form	Yield, %	Melting Point	Boiling Point (mm Hg)	n_D^{25}	Recrystallization Solvent
XIV	H	H	H	0	CH_3	H	H	CH_3	Base	76	61–62°	—	—	Petroleum ether (bp 60–110°)
XV	CH_3	H	H	0	CH_3	H	H	CH_3	Base	54	42.5–44°	135–137° (0.15)	—	Petroleum ether (bp 60–110°)
XVI	CH_3	H	H	0	CH_3	H	H	C_2H_5	Base	90	—	134–137° (0.11)	1.5224	—
XVII	CH_3	H	CH_3	0	CH_3	H	H	CH_3	Base	87	—	125°(0.08)	1.5159	—
XVIII	C_2H_5	H	H	0	CH_3	H	H	CH_3	Base	87	—	134–138° (0.11)	1.5260	—
XIX	C_2H_5	H	H	0	CH_3	H	H	C_2H_5	Base	89	—	145–147° (0.10)	1.5199	—
XX[a]	C_2H_5	H	H	0	CH_3	H	CH_3	CH_3	Hydrochloride	52	135–140°	—	—	2-Propanol–ether
XXI	C_2H_5	H	H	0	C_2H_5	H	H	CH_3	Base	85	—	133–135° (0.12)	1.5232	—
XXII	C_2H_5	H	H	1	H	H	H	CH_3	Hydrochloride	92	170.5–171°	—	—	2-Propanol
XXIII	C_2H_5	H	H	1	CH_3	H	H	CH_3	Hydrochloride	85	84–85°	—	—	Ethanol–ether
XXIV	C_2H_5	H	H	1	CH_3	CH_3	H	CH_3	Hexamate	63	112–112.5°	—	—	2-Propanol or acetone–ether
XXV	C_2H_5	H	H	2	H	H	H	CH_3	Hydrochloride	20	141–142°	—	—	Absolute ethanol
XXVI	CCH_3 ‖ CH_2	H	H	0	CH_3	H	H	CH_3	Oxalate	55	145–146°	—	—	Acetonitrile
XXVII	$CH(CH_3)_2$	H	H	0	CH_3	H	H	CH_3	Hydrochloride	95	138–140°	—	—	Ethanol–ether
XXVIII	$C(CH_3)_3$	H	H	0	CH_3	H	H	CH_3	Methanesulfonate	91	179–180°	—	—	Ethanol–ether
XXIX	CH_3	CH_3	H	0	H	H	H	C_2H_5	Base	58	50–51°	154–155° (0.15)	—	—
XXIX*a*									Hydrochloride		198.5–199°	—	—	Absolute ethanol–ether
XXX	CH_3	CH_3	H	0	H	H	CH_3	CH_3	Hydrochloride	53	136–140°	—	—	Ethanol–ether or ethyl acetate
XXXI	CH_3	CH_3	H	0	CH_3	H	H	CH_3	Base	71	56–57°	—	—	Cyclohexane–petroleum ether (bp 30–70°)
XXXII[a]	CH_3	CH_3	H	0	CH_3	H	CH_3	CH_3	Perchlorate	71	184–186°	—	—	2-Propanol

[a] Diastereomeric mixture.

and sulfur analogs is the much lower irritation liability of the oxygen ethers. This result is the expected consequence of the greater water solubility of the base form of the oxygen analogs.

EXPERIMENTAL[1]

Chemistry—2-Isopropenylaniline (XXXIII) (13) and 2-*tert*-butylaniline (XXXIV) (14) were prepared as described previously. 2-Isopropylaniline (XXXV) was prepared, following a literature method (15) for 3-bromoisopropylbenzene, by hydrogenation of 2-isopropenylaniline in ethyl acetate over 5% palladium-on-charcoal at the initial pressure of 3 atm; the yield was 95%.

Haloacylanilides—2-Chloro-2′,6′-acetoxylidide (XXXVI) (16), 2-bromo-2′,6′-acetoxylidide (XXXVII) (17), 2-bromopropionanilide (XXXVIII) (18), 2-bromo-2′-propionotoluidide (XXXIX) (18), 2-bromo-2′,6′-propionoxylidide (XL) (19), 2-bromo-2′-ethylpropionanilide (XLI) (3), and 3-bromo-2′-ethylpropionanilide (XLII) (3) were obtained by Löfgren's acetate buffer method (2) as described for II.

2-Bromo-*N*-methyl-2′-propionotoluidide (I)—A solution of 2-bromopropionyl bromide (91.5 g, 0.424 mole) in dry ether (50 ml) was added slowly, with stirring and cooling (5°), to a solution of *N*-methyl-2-toluidine (46.1 g, 0.380 mole) and dry pyridine (30.1 g, 0.380 mole) in anhydrous ether (200 ml). The mixture was left overnight, and the precipitated pyridinium bromide was filtered off and washed. The ether solution and washings were evaporated *in vacuo*, and the residual oil was distilled.

2-Bromo-2′-ethylbutyranilide (II)—2-Ethylaniline (46.1 g, 0.380 mole) was dissolved in 320 ml of acetic acid and cooled to 5–10°. 2-Bromobutyryl bromide (98.7 g, 0.429 mole) was added, and the solution was mixed; then, immediately, a cold solution of sodium acetate trihydrate (125 g, 0.922 mole) in 525 ml of water was added. After shaking for 30 min, the precipitate was filtered, washed with water, and recrystallized.

The following intermediates were prepared in the same manner as II: IV, from 4-chlorobutyryl chloride and 2-ethylaniline; VI, from 2-bromopropionyl bromide and XXXV; and VII, from 2-bromopropionyl bromide and XXXIV.

3-Bromo-2′-ethylbutyranilide (III)—To a solution of 2-ethylaniline (12.1 g, 0.0998 mole) in benzene (50 ml) was added, with stirring, 3-bromobutyryl chloride (20) (9.25 g, 0.0499 mole) dissolved in benzene (100 ml). Stirring was continued for 2 hr, and the resulting 2-ethylanilinium chloride was filtered and washed with benzene. From the evaporated benzene solution and washings was obtained a crystalline material, which was further purified by recrystallization.

2-Bromo-2′-isopropenylpropionanilide (V)—Compound V was prepared in the same way as III from 2-bromopropionyl bromide and XXXIII, using ether as a solvent. The nonsolidifying product could be used without further purification or be distilled *in vacuo*.

3-Bromo-2,2-dimethyl-2′-ethylpropionanilide (IX)—Hydroxypivaldehyde was converted into hydroxypivalic acid (21), from which bromopivalic acid (22) was obtained. This acid was transformed into bromopivalyl chloride (23), which was allowed to react with 2-ethylaniline

[1] Melting points (uncorrected) were obtained with a Thomas-Hoover capillary melting-point apparatus. IR spectra were recorded on a Perkin-Elmer Infracord 137 spectrophotometer and were as expected. The elemental analyses were provided by Schwarzkopf Microanalytical Laboratory, Woodside, N.Y.

Table IV—Alkoxyalkylaminoacylanilides: pKa, Partition Coefficients, and Analysis

Compound	pKa[a]	Partition[a,b] Coefficient	Formula	Analysis, % Calc.	Found
XIV	7.0	1.4	$C_{12}H_{18}N_2O_2$	C 64.8	64.6
				H 8.16	8.27
XV	6.9	1.0	$C_{13}H_{20}N_2O_2$	C 66.1	65.8
				H 8.53	8.58
XVI	6.8	4.5	$C_{14}H_{22}N_2O_2$	C 67.2	67.2
				H 8.86	8.88
XVII	7.2	1.0	$C_{14}H_{22}N_2O_2$	C 67.2	66.9
				H 8.86	8.91
XVIII	6.9	4.5	$C_{14}H_{22}N_2O_2$	C 67.2	66.8
				H 8.86	9.03
XIX	6.9	12	$C_{15}H_{24}N_2O_2$	C 68.1	67.8
				H 9.15	9.17
XX[c]	—	—	$C_{15}H_{25}ClN_2O_2$	C 59.9	59.8
				H 8.38	7.96
				Cl 11.8	11.7
XXI	6.7	13	$C_{15}H_{24}N_2O_2$	C 68.1	67.4
				H 9.15	9.09
XXII	8.3	—[d]	$C_{14}H_{23}ClN_2O_2$	C 58.6	58.1
				H 8.08	8.21
XXIII	8.3	1.9	$C_{15}H_{25}ClN_2O_2$	C 59.9	59.9
				H 8.38	8.58
				Cl 11.8	11.6
XXIV	8.8[e]	4.2	$C_{22}H_{39}N_3O_5S$	C 57.7	58.0
				H 8.59	8.62
XXV	>9.0[e]	0.84	$C_{15}H_{25}ClN_2O_2$	C 59.9	59.8
				H 8.38	8.12
				Cl 11.8	11.8
XXVI	6.8	24	$C_{17}H_{24}N_2O_6$	C 57.9	57.2
				H 6.87	6.92
XXVII	6.9	7.4	$C_{15}H_{25}ClN_2O_2$	C 59.9	59.4
				H 8.38	8.48
XXVIII	6.9	20	$C_{17}H_{30}N_2O_5S$	C 54.5	54.5
				H 8.07	8.39
				O 21.4	21.5
XXIX[f]	6.9	—[d]	$C_{14}H_{23}ClN_2O_2$	C 58.6	58.7
				H 8.08	8.08
XXX	7.1	0.9	$C_{14}H_{23}ClN_2O_2$	C 58.6	58.6
				H 8.08	8.31
XXXI	6.8	—[d]	$C_{14}H_{22}N_2O_2$	C 67.2	66.9
				H 8.86	9.06
XXXII[c]	—	—	$C_{15}H_{25}ClN_2O_6$	C 49.4	49.6
				H 6.91	6.57
				Cl 9.72	9.75
Lidocaine	7.9	36	—	—	

[a] A. Brändström, AB Hässle, Mölndal, Sweden, personal communication. [b] System: cod liver oil (Oleum Jecoris aselli, Pharmacop. Nord.)–water (6). [c] Diastereomeric mixture. [d] Partition coefficient low (0.6). [e] Approximate value. [f] Analysis performed on the hydrochloride.

in the same way as described for III, except that the reaction mixture was heated to 75° for 1 hr.

3-Bromo-2′-ethyl-2-methylbutyranilide (VIII)—At 0°, hydrobromic acid (30.4 g, 0.376 mole) was dissolved in ether (300 ml). Then XIII (16.5 g, 0.0812 mole) was added, and the homogeneous mixture was left for 2 weeks at room temperature. After several days at −20°, the separated solid material was filtered and recrystallized.

Acrylanilides (Table II)—These compounds were prepared by a literature method (24).

2′-Ethylacrylanilide (X)—Sodium hydroxide (97 ml, 1.25 *M*), 2-ethylaniline (12.1 g, 0.100 mole), and acryloyl chloride (10 g, 0.11 mole) were mixed and shaken vigorously for 5 min. After cooling, the precipitate was filtered, washed with water, and recrystallized.

2′-Ethylcrotonanilide (XI)—To a mixture of 2-ethylaniline (26.6 g, 0.220 mole), sodium bicarbonate (25.2 g, 0.300 mole), and dry acetone (250 ml) in a Morton flask equipped with a stirrer and reflux condenser was added a solution of crotonyl chloride (26.6 g, 0.254 mole) in dry acetone (100 ml) at such a rate that a moderate reflux was obtained. Refluxing was continued for 1 hr, and the reaction mixture was filtered hot. The separated inorganic salts were washed with acetone. The acetone solution was concentrated to 100 ml and diluted with 1 *M* HCl. The precipitated solid was filtered, washed with cold water, dried, and recrystallized.

2′-Ethyltiglanilide (XIII)—Compound XIII was prepared from 2-ethylaniline and tiglyl chloride (25) according to the procedure for XI; the mixture was refluxed for 2 hr.

2′-Ethylsenecioanilide (XII)—A solution of senecioyl chloride (25) (59.1 g, 0.498 mole) in toluene (150 ml) was added, with vigorous stirring,

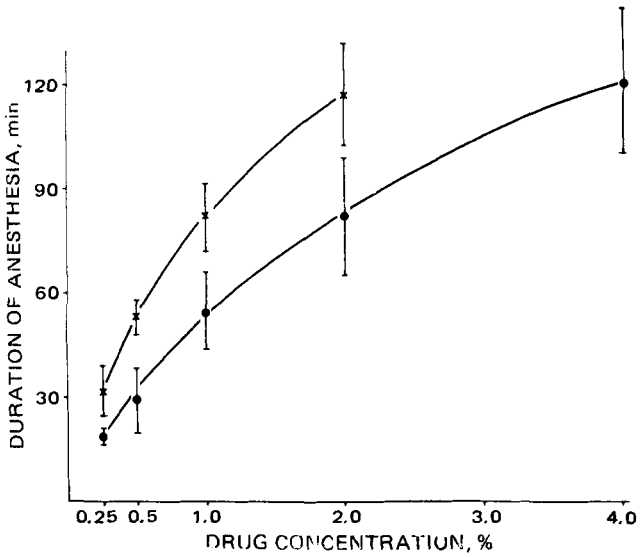


Figure 1—*Sciatic nerve block in the rat with XVIII. Key:* ●, *XVIII alone; and* ×, *XVIII with epinephrine, 1:100,000. Standard deviations are indicated by bars.*

to 2-ethylaniline (121 g, 0.999 mole) dissolved in toluene (1100 ml) over 15 min. Then the mixture was heated to 65° for 2 hr, the solvent was evaporated, and the oily residue was poured into 2 *M* HCl (400 ml). The solid was filtered, washed with dilute sodium bicarbonate solution and water, dried, and subsequently recrystallized.

Alkoxyalkylamines—2-Methoxyethylamine (XLIII) and 2-ethoxyethylamine (XLIV) were commercial products.

2-Methoxypropylamine (XLV) (26) and Bis(2-methoxypropyl)amine (XLVI)—Gaseous ammonia (51 g, 3.0 moles) was dissolved in cold methanol (300 ml) in an autoclave, and 1-bromo-2-methoxypropane (26) (45 g, 0.29 mole) was added. After heating at 50° for 48 hr, solvent and excess ammonia were evaporated. The residue was dissolved in 2 *M* HCl, washed with ether, made alkaline with 12.5 *M* NaOH, and extracted with ether. Then the extract was dried (sodium sulfate) and fractionated. The fraction boiling at 80–100° (XLV) was collected; the yield was 17 g (65%). Residues of several batches were distilled *in vacuo*, yielding XLVI, bp 84–90°/0.20–0.25 mm Hg. Equivalent weight ($C_8H_{19}NO_2$): calc., 161; found, 162.

Alkoxyalkylaminoacylanilides: 2-(2-Methoxyethylamino)propionanilide (XIV)—A solution of XXXVIII (1 mole) and XLIII (3.6 moles) in 700 ml of 95% ethanol was refluxed for 8 hr. The solvent and excess amine were evaporated under reduced pressure. The residue was dissolved in excess 6 *M* HCl, and the solution was washed with ether and made alkaline to pH 8–9 with 7 *M* NaOH. Then the base was taken up in ether. This solution was dried (sodium sulfate), the solvent was evaporated, and the solidifying residue was recrystallized.

The following compounds were prepared in a similar manner, except that the reaction product in certain instances was purified by distillation or by recrystallization of a suitable salt (Table III): XV, from XXXIX

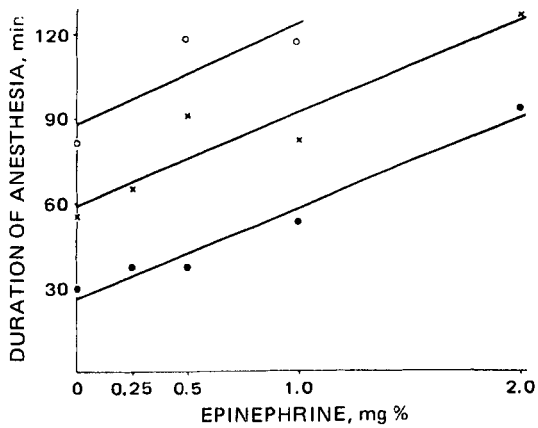


Figure 2—*Sciatic nerve block in the rat with XVIII. Key:* ●, *0.5% XVIII;* ×, *1% XVIII; and* ○, *2% XVIII.*

Table V—Local Anesthetic Activity: Sciatic Nerve Block in the Rat

Compound	pH of Solution	1% Onset, min	1% Duration[a], min	1% Frequency, %	2% Onset, min	2% Duration[a], min	2% Frequency, %	4% Onset, min	4% Duration[a], min	4% Frequency, %
XIV	6.7	—	—	—	3	41 ± 11	92	—	—	—
XV	6.4	3	28 ± 9	92	3	63 ± 13	89	3	67 ± 13	100
XVI	6.4	3	60 ± 42	67	3	84 ± 23	100	3	115 ± 8	100
XVII	6.8	—	—	—	3	50 ± 13	100	3	106 ± 17	100
XVIII	6.5	3	55 ± 11	92	3	82 ± 17	100	3	120 ± 22	100
XIX	6.2	—	—	—	3	67 ± 5	100	3	98 ± 8	100
XX	6–7	3–5	36 ± 6	92	3–5	56 ± 9	100	3	101 ± 10	100
XXI	6.3	3	66 ± 8	100	3	93 ± 7	100	3	>160[b]	100
XXII	6.3	4	69 ± 11	100	4	123 ± 19	83	—	—	—
XXIII	6.6	4	84 ± 15	100	4	151 ± 10	100	—	—	—
XXIV	6.0	3	58 ± 3	67	2	109 ± 16	100	—	—	—
XXV	6.7	—	0	0	8–11	118 ± 22	67	8–10	118 ± 26	67
XXVI	6.0	3	35 ± 5	100	3	72 ± 7	100	—	—	—
XXVII	6.0	3	29 ± 10	100	3	56 ± 8	100	—	—	—
XXVIII	6.0	—	—	—	3	58 ± 14	100	3	80 ± 17	100
XXIX	6.4	—	—	—	3	85 ± 18	100	—	—	—
XXX	6.0	—	—	—	3	55 ± 12	100	—	—	—
XXXI	6.3	3	51 ± 10	92	3	95 ± 18	96	—	—	—
XXXII	5.5–6.5	—	—	—	5	47 ± 12	100	—	—	—
Lidocaine	6.2	2	96 ± 10	100	1–2	115 ± 16	100	—	—	—

[a] Mean ± *SD*. [b] A third of the animals were still blocked after 12 hr.

and XLIII; XVI, from XXXIX and XLIV; XVII, from I and XLIII; XVIII, from XLI and XLIII; XIX, from XLI and XLIV; XXI, from II and XLIII; and XXII, from XLII and XLIII.

Compound XXII could not be distilled *in vacuo*. Elimination took place with the formation of X, identified by comparison to an authentic sample.

Compounds XX (from XLI and XLV), XXX (from XXXVII and XLV), and XXXII (from XL and XLV) were prepared as described for XIV, except that the reflux time was increased to 18–19 hr. The diastereomers of XX and XXXII were not separated.

Compounds XXVI (from V and XLIII), XVII (from VI and XLIII), and XXVIII (from VII and XLIII) were prepared by analogy to XIV with the following modification in procedure. After the ethanol had been evaporated from the reaction mixture, the residue was dissolved in chloroform. This solution was extracted exhaustively with 1 *M* HCl. The acid extract was washed with ether, whereafter the amine was liberated from the acid solution with 7 *M* NaOH and treated as described.

Compounds XXIX (from XXXVI and XLIV) and XXXI (from XL and XLIII) were prepared as described for XIV with the following difference. The treatment of the reaction residue with 6 *M* HCl left an undissolved solid (hydrochloride), which was filtered off and washed with ether. After an ether wash of the acid filtrate, the acid filtrate was again combined with the solid, and the mixture was made alkaline with 7 *M* NaOH and treated as described.

2′-Ethyl-4-(2-methoxyethyl)butyranilide (XXV)—Dry benzene (70 ml), IV (27.7 g, 0.123 mole), and dry XLIII (25.4 g, 0.338 mole) were refluxed for 4 hr. The volatiles were evaporated *in vacuo*. The residue was dissolved in 1 *M* HCl, and the solution was washed with ether, made alkaline to pH 10 with concentrated ammonia, and extracted with ether. After evaporation of the ether, the residue was subjected to a simplified countercurrent extraction in a four-funnel operation (27, 28) between phases of 400 ml of 0.067 *M* phosphate buffer (pH 7.0) and 200 ml of ether. From the ether fraction, an oil (5.8 g, 0.0479 mole, 39%), identified by its IR spectrum as 2-ethylaniline, was obtained. From the buffer fraction, a solid base (XXV) (6.4 g, 0.0242 mole, 20%) was obtained by extraction into ether at pH 10 and evaporation of the ether.

2′-Ethyl-3-(2-methoxyethylamino)butyranilide (XXIII)—*Method A*—A mixture of III (9.00 g, 0.0333 mole), dry XLIII (9.91 g, 0.132 mole), and anhydrous toluene (50 ml) was refluxed for 26.5 hr. The solvent was evaporated, and the residue was dissolved in 100 ml of 1 *M* HCl and washed with ether. The acid solution was made alkaline to pH 8.5 (7 *M* NaOH) and extracted with ether. After drying over anhydrous sodium sulfate, the solvent was evaporated, and the hydrochloride was prepared from the oily residue. The yield was 85%. On vacuum distillation of a part of the base residue, it decomposed into a solid neutral compound and a volatile amine. The solid was identical to XI (IR and mixed melting point).

Method B—A mixture of XI (3.40 g, 0.0180 mole) and XLIII (22.5 g, 0.299 mole) was refluxed for 8.5 hr. After evaporation *in vacuo* of excess aminoether, the residue was worked up as in Method A. The yield was 59%. Prolonged reaction times reduced the yield to 52% (17 hr) and 35% (20 hr).

2′ - Ethyl - 3 - (2-methoxyethylamino) - 3 - methylbutyranilide (XXIV)—A mixture of XII (14.0 g, 0.0689 mole) and XLIII (51.6 g, 0.687 mole) was refluxed for 40 hr. The unreacted aminoether was evaporated *in vacuo*, and the residue was taken up in 2 *M* HCl and extracted with ether to separate 4.50 g (32%) of unreacted XII. The acid solution was made alkaline (7 *M* NaOH) and extracted with ether. After drying over anhydrous sodium sulfate and evaporation of the ether, the residue was dissolved in absolute alcohol and an alcoholic solution of hexamic acid was added. The salt precipitated slowly and was filtered off after 2 hr.

Pharmacology and Toxicology—*Rat Sciatic Nerve Block* (*8*)—Solutions containing 10, 20, or 40 mg/ml of the hydrochlorides were prepared in isotonic saline; if another salt was used, an amount equivalent to the corresponding hydrochloride was employed. If epinephrine was desired as a constituent of the test solution, an appropriate amount of 0.1% stock solution of the vasoconstrictor was added before the solutions were brought to final volume. If necessary, the pH of the solution was adjusted with either dilute hydrochloric acid or sodium hydroxide. A volume of 0.20 ml was administered to female Wistar rats around the sciatic nerve at the midpoint of the femur (Table V).

Systemic Toxicity (*8*)—Isotonic saline solutions of the hydrochlorides, or other pharmaceutically acceptable salts in amounts equivalent to the

Table VI—Toxicity

Compound	LD_{50} (Mouse) iv, mg/kg	LD_{50} (Mouse) ip, mg/kg	Local Irritation[a] (Rabbit) 2% Solution	Local Irritation[a] (Rabbit) 4% Solution
XIV	70	275	—	—
XV	50	275	(+)	+
XVI	38	275	—	(+)
XVII	—	250	—	—
XVIII	38	250	—	0
XIX	36[b]	250	+++	+++
XX	45	300	(+)[c]	+[c]
XXI	26[b]	150	—	+++
XXII	65	250	(+)	+
XXIII	40	225	(+)	+
XXIV	22[b]	125	+	++
XXV	80[b]	400	(+)	+
XXVI	55[b]	350	++(+)	+++
XXVII	65[b]	450	(+)	(+)
XXVIII	115[d]	450	+	+
XXIX	35	130	(+)	(+)
XXX	35[b]	150	0	0
XXXI	40	120	0	0
XXXII	22	100	(+)	(+)
Lidocaine	25	130	—	—

[a] 0 = no irritation; + = some irritation; ++ = pronounced irritation; +++ = serious irritation, necrosis; parentheses indicate intermediate stages; and — = no determination. [b] One percent solution. [c] On addition of epinephrine (1:100,000), necrosis developed at both concentration levels. [d] Four percent solution.

corresponding hydrochloride, were prepared in concentrations of 10, 20, and 40 mg/ml. Acute intravenous or intraperitoneal toxicities were determined in female albino mice (Charles River CD random-bred). The results are estimates and should only be regarded as approximate LD_{50} values (Table VI).

Local Tissue Irritation (9)—Solutions were prepared containing 20 and 40 mg of the hydrochloride/ml (or equivalent amounts of other salts) in isotonic saline. Injections were made intradermally in female New Zealand White rabbits, and the effects were estimated from gross examination of the sites 24 hr after injection (Table VI).

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Syntheses and Pharmacological Activity of *N*-Acyl-substituted Imidazolidinethiones and Thioimidazolines

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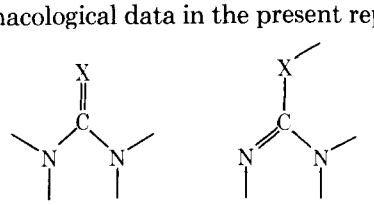
Abstract □ A series of imidazolidinethiones and thioimidazolines was synthesized and tested for their effects on both forced and spontaneous motor activities as well as their ability to raise the convulsion threshold. The *N*-acyl-substituted 2-*p*-fluorobenzylthioimidazolines were the most active compounds, producing protection against maximal electroshock seizures and tonic convulsions induced by pentylenetetrazol. Both compounds had high LD_{50} values and safety indexes.

Keyphrases □ Imidazolidinethiones, substituted—synthesized, evaluated for CNS depressant and anticonvulsant activity □ Thioimidazolines, various—synthesized, evaluated for CNS depressant and anticonvulsant activity □ CNS depressant activity—evaluated in substituted imidazolidinethiones and various thioimidazolines □ Anticonvulsant activity—evaluated in substituted imidazolidinethiones and various thioimidazolines □ Structure–activity relationships—substituted imidazolidinethiones and various thioimidazolines evaluated for CNS depressant and anticonvulsant activity

An increasingly larger number of medicinal agents containing either the ureido (I) or the isoureido (II) moiety as part of their molecular framework have been developed recently (1–3). The syntheses and CNS depressant and anticonvulsant properties of a series of isomeric acyl-substituted imidazolidinethiones and thioimidazolines were described previously (4). Based on a limited number of compounds, the thioimidazolines examined all significantly prolonged the time for the onset of convulsions induced by maximal electroshock in male Swiss-Webster mice when compared to the isomeric imidazolidinethiones. To provide additional insight into the pharmacological properties of these two types of compounds, the thioimidazolines III–VI (5) and the imidazolidinethione VII were synthesized. In general, these compounds contain substituents that are more lipophilic in nature than those previously investigated (4).

The pharmacological data in the present report indicate



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