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Studies on Local Anesthetics XVI*

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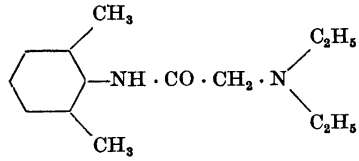
Twentyfour new compounds, closely related to xylocaine **, have been synthesized and studied pharmacologically, especially for their surface anesthetic action on the rabbit cornea. Some conclusions have been drawn as to the relation between corneal anesthetic activity and chemical constitution.

As an extension of previous works on local anesthetics by Löfgren *et al.* twentyfour new analogues of xylocaine



Xylocaine

have been synthesized and tested pharmacologically. The compounds are of the general type

$$\text{Ar-NH} \cdot \text{CO} \cdot \underset{\displaystyle \text{R}}{\text{CH}}\text{-Am}$$

in which Ar is phenyl, 2-methylphenyl, 2,6-dimethylphenyl, or 2,4,6-trimethylphenyl, R hydrogen or methyl, and Am alkylamino, dialkylamino, *cyclo*-hexylamino, pyrrolidino, piperidino, or 2-methylpiperidino. The combinations

* For paper XV of this series see Lindström [1].
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of the groups Ar, R, and Am are evident from Table 1 where the compounds (I—XXIV) are listed.

To synthesize these compounds, the arylamines ($Ar \cdot NH_2$) were first converted to the corresponding halogenoacylated compounds by reaction with a halogenoacyl halide (chloroacetyl chloride or α-bromopropionyl bromide) in an aqueous acetate buffer, the general directions of Löfgren [2] being followed. Thus the following N-(halogenoacyl) arylamines were prepared as intermediates for the synthesis of compounds I—XXIV, *viz.* for I: α-chloroacetanilide; II: α-chloro-2-methylacetanilide; III—V: α-chloro-2,6-dimethylacetanilide; VI—XI: α-bromo-2,6-dimethylpropionanilide; XII—XIX: α-chloro-2,4,6-trimethylacetanilide; XX—XXIV: α-bromo-2,4,6-trimethylpropionanilide. The halogeno derivatives produced were then heated with an excess of the necessary primary or secondary amine to give the products desired. In the reactions where primary amines were involved, a high excess of amine (5 moles of amine per mole of halogeno compound) was used to avoid the formation of compounds of the alkylimino-bis(N-acyl-arylamine) type:

$$\text{Alkyl-N}\begin{matrix}\diagup\ \text{acyl} \cdot \text{NH} \cdot \text{Ar} \\ \diagdown\ \text{acyl} \cdot \text{NH} \cdot \text{Ar}\end{matrix}$$

The compounds were tested for their local anesthetic action on the rabbit cornea and compared with xylocaine, the technique of Wiedling [3] being followed (*cf.* also Löfgren and Tegnér [4]). Xylocaine and all the other compounds were used as solutions of their hydrochlorides containing 0.85 % sodium chloride.

As a measure of the potency *relative activity* (RA) was used, *i.e.* the activity which is found by dividing the molarity of a standard xylocaine solution by the molar concentration of the actual compound at which the duration of anesthesia is the same as that of the xylocaine standard. The molarity of the latter was 0.0738 (= 2 % xylocaine · HCl solution). Before measuring the duration of anesthesia for the solution of the actual compound and that for xylocaine, both solutions were adjusted to the same pH, usually 6.0 *.

In the toxicity investigations the LD_{50} values were obtained from subcutaneous injections in white mice and calculated (a) as grams of the base per

* For a few compounds, test solutions of lower pH — but in no case lower than 5.3 — had to be prepared since the solubilities were too low at pH 6.0. These solutions were then compared with the 0.0738 M xylocaine solution adjusted to the same lower pH value. There is no reason to believe that the RA values originating from measurements of such solutions differ significantly from those which would have been obtained from a comparison of solutions of pH 6.0. Thus, for several of our compounds of which test solutions can be prepared at pH 6.0, solutions were made at various pH values between 5 and 6 and RA values were obtained by comparison with a 0.0738 M xylocaine solution of the same pH. No significant difference in the RA values could be found; *cf.* also Löfgren and Tegnér [4].

Table 1. Chemical data of xylocaine analogues I—XXIV. Melting points corrected unless ether of b.p. 40—60°; Dibut.eth., di-*n*-butyl ether; benz.,

	Compound AR—NH · CO · CH(R)—Am			
	Name	Ar	R	Am
I	α-(2-Methyl-1-piperidyl)acetanilide	C_6H_5	H	2-CH_3 · C_5H_9N
II	α-(*n*-Amylamino)-2-methylacetanilide	2-CH_3 · C_6H_4	»	NH-*n*-C_5H_{11}
III	α-*Iso*amylamino-2,6-dimethylacetanilide	2,6-$(CH_3)_2$ · C_6H_3	»	NH-*i*-C_5H_{11}
IV	α-(1-Pyrrolidyl)-2,6-dimethylacetanilide	»	»	C_4H_8N
V	α-(2-Methyl-1-piperidyl)-2,6-dimethylacetanilide	»	»	2-CH_3 · C_5H_9N
VI	α-Ethylamino-2,6-dimethylpropionanilide	»	CH_3	NHC_2H_5
VII	α-(*n*-Propylamino)-2,6-dimethylpropionanilide	»	»	NH-*n*-C_3H_7
VIII	α-*Iso*propylamino-2,6-dimethylpropionanilide	»	»	NH-*i*-C_3H_7
IX	α-(*n*-Butylamino)-2,6-dimethylpropionanilide	»	»	NH-*n*-C_4H_9
X	α-*Iso*butylamino-2,6-dimethylpropionanilide	»	»	NH-*i*-C_4H_9
XI	α-Dimethylamino-2,6-dimethylpropionanilide	»	»	$N(CH_3)_2$
XII	α-(*n*-Propylamino)-2,4,6-trimethylacetanilide	2,4,6-$(CH_3)_3$ · C_6H_2	H	NH-*n*-C_3H_7
XIII	α-*Iso*propylamino-2,4,6-trimethylacetanilide	»	»	NH-*i*-C_3H_7
XIV	α-(*n*-Butylamino)-2,4,6-trimethylacetanilide	»	»	NH-*n*-C_4H_9
XV	α-*Iso*butylamino-2,4,6-trimethylacetanilide	»	»	NH-*i*-C_4H_9
XVI	α-*Iso*amylamino-2,4,6-trimethylacetanilide	»	»	NH-*i*-C_5H_{11}
XVII	α-*Cyclo*hexylamino-2,4,6-trimethylacetanilide	»	»	$C_6H_{11}NH$
XVIII	α-Dimethylamino-2,4,6-trimethylacetanilide	»	»	$N(CH_3)_2$
XIX	α-(1-Piperidyl)-2,4,6-trimethylacetanilide	»	»	$C_5H_{10}N$
XX	α-Ethylamino-2,4,6-trimethylpropionanilide	»	CH_3	NHC_2H_5
XXI	α-(*n*-Propylamino)-2,4,6-trimethylpropionanilide	»	»	NH-*n*-C_3H_7
XXII	α-*Iso*propylamino-2,4,6-trimethylpropionanilide	»	»	NH-*i*-C_3H_7
XXIII	α-(*n*-Butylamino)-2,4,6-trimethylpropionanilide	»	»	NH-*n*-C_4H_9
XXIV	α-*Iso*butylamino-2,4,6-trimethylpropionanilide	»	»	NH-*i*-C_4H_9

a) Uncorrected value.
b) Purified *via* the hydrochloride, see Table 2.
c) Titration of the base in 30 % ethanol with 0.1 N HCl; mixed indicator methylene blue — methyl red.

kilogram of body weight and (b) as moles per kilogram of body weight ("molar" LD_{50} value).

The ratio of the *molar* LD_{50} value for xylocaine to the corresponding value for one of the other compounds is called here the *relative toxicity* (RT) of the compound. For the quotient RA/RT we use the term *anesthetic index* (Q).

To determine the RA value of a compound, 10—30 animals were used. In general, the maximum error in the RA values is about 20 %. The error in the RT values is much less. The results of the pharmacological measurements are collected in Table 3. The material allows a study of the relationship between the chemical constitution and the pharmacological properties. Thus we

otherwise stated, boiling points uncorrected. Abbreviations for solvents: Pet., petroleum benzene; Xyl., xylene; Lgr., ligroin of b.p. 90—120°.

Empirical formula	Yield %	B.p., °C uncorr.	M.p., °C corr.	Solvent for recrystallization	Euqivalent weight c)		Analyses C		Analyses H	
					Calc.	Found	Calc.	Found	Calc.	Found
$_{14}H_{20}N_2O$	77	—	74—75	Pet.	232.3	230	72.4	72.1	8.68	8.55
$_{14}H_{22}N_2O$	90	162—163 0.3 mm	—	—	234.3	—	71.8	72.0	9.46	9.38
$_{15}H_{24}N_2O$	83	—	42—43	Dibut.eth.	248.4	250	72.5	72.5	9.74	9.58
$_{14}H_{20}N_2O$	73	—	82—83	Pet. — Dibut.eth.	232.3	—	72.4	72.1	8.68	8.55
$_{16}H_{24}N_2O$	90	—	118—120a)	Xyl.	260.4	262	73.8	73.7	9.29	9.11
$_{13}H_{20}N_2O$	90	—	86—88	Pet. — Dibut.eth.	220.3	221	—	—	—	—
$_{14}H_{22}N_2O$	89	—	76—77	Dibut.eth.	234.3	234	71.8	71.6	9.46	9.38
$_{14}H_{22}N_2O$	87	—	86—87	Dibut.eth.	234.3	—	71.8	71.8	9.46	9.35
$_{15}H_{24}N_2O$	80	—	40—42	Pet.	248.4	248	—	—	—	—
$_{15}H_{24}N_2O$	93	—	65—66	Dibut.eth.	248.4	—	72.5	72.6	9.74	9.70
$_{13}H_{20}N_2O$	93	—	70—72	Dibut.eth.	220.3	219	70.9	70.8	9.15	9.13
$_{14}H_{22}N_2O$	86	175 0.6 mm	60—61	Pet. — Dibut.eth.	234.3	234	71.8	71.6	9.46	9.33
$_{14}H_{22}N_2O$	65	163—164 0.4 mm	81—83	— b)	234.3	—	71.8	71.7	9.46	9.50
$_{15}H_{24}N_2O$	67	180—181 0.6 mm	59—60a)	Pet. — dibut.eth.	248.4	248	72.5	72.3	9.74	9.61
$_{15}H_{24}N_2O$	94	—	73—74	Dibut.eth.	248.4	—	72.5	72.4	9.74	9.53
$_{16}H_{26}N_2O$	87	—	58—60a)	Dibut.eth.	262.4	263	73.2	73.1	9.99	9.90
$_{17}H_{26}N_2O$	83	—	71—72	Dibut.eth.	274.4	276	74.4	74.7	9.55	9.52
$_{13}H_{20}N_2O$	77	—	73—74a)	Lgr.	220.3	222	70.9	70.6	9.15	9.03
$_{16}H_{24}N_2O$	72	—	111—114	Dibut.eth.	260.4	261	73.8	73.8	9.29	9.22
$_{14}H_{22}N_2O$	88	—	100—101	Dibut.eth.	234.3	236	71.8	71.8	9.46	9.34
$_{15}H_{24}N_2O$	93	—	67—70	Pet.	248.4	250	72.5	72.7	9.74	9.62
$_{15}H_{24}N_2O$	85	158—159 0.3 mm	92—94	Pet. — Benz.	248.4	248	72.5	72.1	9.74	9.62
$_{16}H_{26}N_2O$	88	—	67—69	— b)	262.4	—	73.2	73.3	9.99	9.94
$_{16}H_{26}N_2O$	78	—	65—67a)	— b)	262.4	261	—	—	—	—

are able to analyse the influence on RA, RT and Q of certain variations in the groups R_1, R_2 and R_3 in the structure shown in Table 4. The change in RA, RT and Q is indicated by factors f_A, f_T and f_Q, respectively. In this connection, it should be emphasized that, in the following, an increase or a decrease in RA, RT or Q always means a proportional, and not an absolute, increase or decrease. The results may be summarized as follows:

1. A straight lengthening of a *normal* alkyl group R_1 by a single carbon atom (*cf.* Table 4: A) increases the activity RA ($1.2<f_A<2.5$) as well as the toxicity RT ($1.7<f_T<4.6$) — the increase of the latter being, however, greater so that the anesthetic index Q changes unfavourably ($0.5<f_Q<0.9$). The

Table 2. Chemical data of salts prepared (hydrochlorides, methanesulphonates and perchlorates). Melting points corrected unless otherwise stated. Abbreviations for solvents: *n*-Prop., *n*-propanol; Me.et.ket., methyl ethyl ketone; Aq., water; Al., ethanol; Diox., dioxan; Dibut.eth., di-*n*-butyl ether; *i*-But., *isobutanol; *n*-But., *n*-butanol.

	Salt	Empirical formula	M.p., °C corr.	Solvent for recrystallization	Analyses					
					C		H		Cl	
					Calc.	Found	Calc.	Found	Calc.	Found
II	hydrochloride	$C_{14}H_{23}ClN_2O$	218—219[a]	*n*-Prop.	62.1	62.1	8.56	8.52	—	—
II	methanesulphonate	$C_{15}H_{28}N_2O_4S$	124—125	Me.et.ket.	54.5	54.7	7.93	7.82	—	—
III	hydrochloride	$C_{15}H_{25}ClN_2O$	211—213	Al. — Aq.	—	—	—	—	12.45	12.38
VI	»	$C_{13}H_{21}ClN_2O$	248—250	*n*-Prop.	60.8	60.7	8.24	8.13	—	—
VII	»	$C_{14}H_{23}ClN_2O$	200—201	Me.et.ket. — *n*-Prop.	62.1	61.8	8.56	8.50	—	—
IX	»	$C_{15}H_{25}ClN_2O$	153—157	Me.et.ket.	63.3	63.4	8.85	8.68	—	—
XI	»	$C_{13}H_{21}ClN_2O$	196—198	Diox. — *n*-Prop.	—	—	—	—	13.81	13.82
XII	»	$C_{14}H_{23}ClN_2O$	277—278[a]	Aq.	—	—	—	—	13.09	13.02
XIII	»	$C_{14}H_{23}ClN_2O$	218—220	Me.et.ket.	62.1	61.9	8.56	8.44	—	—
XIV	»	$C_{15}H_{25}ClN_2O$	237—238[a]	Aq.	—	—	—	—	12.45	12.39
XVI	»	$C_{16}H_{27}ClN_2O$	236—238	Al. — Aq.	—	—	—	—	11.87	11.86
XVII	»	$C_{17}H_{27}ClN_2O$	261—262	Dibut.eth. — Al.	—	—	—	—	11.41	11.49
XIX	»	$C_{16}H_{25}ClN_2O$	197—199	*n*-Prop. — Dibut.eth.	—	—	—	—	11.95	12.06
XX	»	$C_{14}H_{23}ClN_2O$	145—146	*n*-But.	—	—	—	—	13.09	13.13
XXI	»	$C_{15}H_{25}ClN_2O$	236—239 (decomp.)	*i*-But.	63.3	63.3	8.85	8.67	—	—
XXII	»	$C_{15}H_{25}ClN_2O$	212—214	Me.et.ket.	63.3	63.0	8.85	8.53	—	—
XXIII	»	$C_{16}H_{27}ClN_2O$	203—208	Diox.	63.3	63.3	8.85	8.84	—	—
XXIV	perchlorate	$C_{16}H_{27}ClN_2O_5$	212—213	Al.	53.0	53.3	7.52	7.62	—	—

a) Uncorrected value.

greatest increase in RA and also in RT is obtained by substituting a *n*-butyl group for the *n*-propyl group in XXI ($R_1 = n\text{-}C_3H_7$, $R_2 = R_3 = CH_3$), *i.e.* by transition from XXI to XXIII ($f_A = 2.5$, $f_T = 4.6$, $f_Q = 0.5$).

2. The introduction of a methyl group at the penultimate carbon atom of a *normal* alkyl group R_1, *i.e.* the transition from a *normal* alkyl group R_1 to the

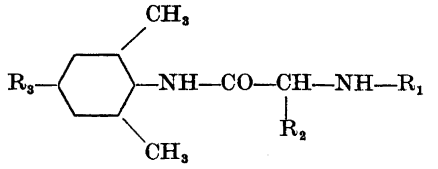
Table 3. Local anesthetic activity (rabbit cornea) and toxicity (white mouse) of compounds I—XXIV. For the terms relative anesthetic activity and relative toxicity, see p. 1725.

Compound	Relative anesthetic activity (RA) xylocaine = 1	Toxicity, LD_{50}		Relative toxicity (RT) xylocaine = 1	RA / RT
		g base/kg	moles/kg·10^3		
Xylocaine	1.0	0.34	1.4	1.0	1.0
I	~0.5	0.85	3.7	0.38	~1.3
II	<0.2	—	—	—	—
III	3.3	0.35	1.4	1.0	3.3
IV	~0.2	0.56	2.4	0.58	~0.3
V	~1.6	0.075	0.29	4.8	~0.3
VI	1.1	0.44	2.0	0.70	1.6
VII	1.7	0.27	1.2	1.2	1.4
VIII	0.9	0.26	1.1	1.3	0.69
IX	3.1	0.094	0.38	3.7	0.84
X	1.8	0.089	0.36	3.9	0.46
XI	~0.3	0.52	2.4	0.58	~0.5
XII	1.9	0.56	2.4	0.58	3.3
XIII	0.9	0.47	2.0	0.70	1.3
XIV	2.3	0.29	1.2	1.2	1.9
XV	1.7	0.35	1.4	1.0	1.7
XVI	4.8	0.42	1.6	0.87	5.5
XVII	16	0.11	0.40	3.5	4.6
XVIII	~0.1	0.52	2.4	0.58	~0.2
XIX	2.4	0.34	1.3	1.1	2.2
XX	1.9	0.54	2.3	0.61	3.1
XXI	2.6	0.26	1.0	1.4	1.9
XXII	1.7	0.50	2.0	0.70	2.4
XXIII	6.4	0.058	0.22	6.4	1.0
XXIV	3.5	0.20	0.76	1.8	1.9

next higher homologous *iso*alkyl group (*cf.* Table 4: B), sometimes increases and sometimes decreases the activity ($0.8<f_A<1.3$) — the change in no case being great — whereas the toxicity increases in all five cases ($1.1<f_T<3.25$), the increase being considerable in three of them ($1.7<f_T<3.25$). In these three cases the anesthetic index is altered very unfavourably ($0.3<f_Q<0.5$). In the other two, *i.e.* by replacing (a) the ethyl group in XX ($R_1 = C_2H_5$, $R_2 = R_3 = CH_3$) by an *i*-propyl group and (b) the *n*-propyl group in XXI ($R_1 = n\text{-}C_3H_7$, $R_2 = R_3 = CH_3$) by an *i*-butyl group, the anesthetic index remains approximately constant ($f_Q = 0.8$ and 1.0).

3. During the discussions in *1* and *2* we have at the same time obtained an idea of what would happen on replacing a *normal* alkyl group R_1 by an isomeric *iso*alkyl group. Direct information on this point is obtained by comparing the isomers available (comparison not tabulated), *i.e.* VII with VIII, IX with X, XII with XIII, XXI with XXII, and XXIII with XXIV. These comparisons show that the replacement of a *normal* alkyl group R_1 by an isomeric *iso*alkyl group in all five cases definitely decreases the activity ($0.5<f_A<0.7$). The toxicity increases slightly in three cases (VII→VIII, IX→X, XII→XIII; $1.05<f_T<1.2$), while in the other two, *i.e.* by replacing (a) the *n*-propyl group

Table 4. Change in relative anesthetic activity (RA), relative toxicity (RT) and anesthetic index (Q) when varying the groups R_1, R_2 and R_3 (*cf.* formula).



R_1 = {C_2H_5, *n*-C_3H_7, *i*-C_3H_7, *n*-C_4H_9, *i*-C_4H_9 or *i*-C_5H_{11}

R_2 or R_3 = H or CH_3

Factors f_A, f_T and f_Q indicate the change in RA, RT and Q, respectively; *cf.* also text on pp, 1725–1727.

Compound No.	R_1	R_2	R_3	RA	f_A	RT	f_T	$Q (=\frac{RA}{RT})$	f_Q
A. Introduction of a methyl group at the end of a *normal* alkyl group R_1 (straight lengthening of a *normal* alkyl group R_1 by a single carbon atom).									
VI	C_2H_5	CH_3	H	1.1	1.5	0.70	1.7	1.6	0.9
VII	*n*-C_3H_7	CH_3	H	1.7		1.2		1.4	
VII	*n*-C_3H_7	CH_3	H	1.7	1.8	1.2	3.1	1.4	0.6
IX	*n*-C_4H_9	CH_3	H	3.1		3.7		0.84	
XII	*n*-C_3H_7	H	CH_3	1.9	1.2	0.58	2.1	3.3	0.6
XIV	*n*-C_4H_9	H	CH_3	2.3		1.2		1.9	
XX	C_2H_5	CH_3	CH_3	1.9	1.4	0.61	2.3	3.1	0.6
XXI	*n*-C_3H_7	CH_3	CH_3	2.6		1.4		1.9	
XXI	*n*-C_3H_7	CH_3	CH_3	2.6	2.5	1.4	4.6	1.9	0.5
XXIII	*n*-C_4H_9	CH_3	CH_3	6.4		6.4		1.0	
B. Introduction of a methyl group at the penultimate carbon atom of a *normal* alkyl group R_1 (transformation of a *normal* alkyl group R_1 into the next higher homologous *iso*alkyl group).									
VI	C_2H_5	CH_3	H	1.1	0.8	0.70	1.9	1.6	0.4
VIII	*i*-C_3H_7	CH_3	H	0.9		1.3		0.69	
VII	*n*-C_3H_7	CH_3	H	1.7	1.1	1.2	3.25	1.4	0.3
X	*i*-C_4H_9	CH_3	H	1.8		3.9		0.46	
XII	*n*-C_3H_7	H	CH_3	1.9	0.9	0.58	1.7	3.3	0.5
XV	*i*-C_4H_9	H	CH_3	1.7		1.0		1.7	
XX	C_2H_5	CH_3	CH_3	1.9	0.9	0.61	1.1	3.1	0.8
XXII	*i*-C_3H_7	CH_3	CH_3	1.7		0.70		2.4	
XXI	*n*-C_3H_7	CH_3	CH_3	2.6	1.3	1.4	1.3	1.9	1.0
XXIV	*i*-C_4H_9	CH_3	CH_3	3.5		1.8		1.9	
C. Introduction of a methyl group at the *α* position of the amide chain (change of R_2 from H to CH_3).									
XII	*n*-C_3H_7	H	CH_3	1.9	1.4	0.58	2.4	3.3	0.6
XXI	*n*-C_3H_7	CH_3	CH_3	2.6		1.4		1.9	
XIV	*n*-C_4H_9	H	CH_3	2.3	2.8	1.2	5.3	1.9	0.5
XXIII	*n*-C_4H_9	CH_3	CH_3	6.4		6.4		1.0	
XIII	*i*-C_3H_7	H	CH_3	0.9	1.9	0.70	1.0	1.3	1.8
XXII	*i*-C_3H_7	CH_3	CH_3	1.7		0.70		2.4	
XV	*i*-C_4H_9	H	CH_3	1.7	2.1	1.0	1.8	1.7	1.1
XXIV	*i*-C_4H_9	CH_3	CH_3	3.5		1.8		1.9	

Table 4, contd.

D. Introduction of a methyl group at the position of the nucleus which is *para* to the amide nitrogen (change of R_3 from H to CH_3).

III	i-C_5H_{11}	H	H	3.3	1.5	1.0	0.9	5.3	1.7
XVI	i-C_5H_{11}	H	CH_3	4.8		0.87		5.5	
VI	C_2H_5	CH_3	H	1.1	1.7	0.70	0.9	1.6	1.9
XX	C_2H_5	CH_3	CH_3	1.9		0.61		3.1	
VII	n-C_3H_7	CH_3	H	1.7	1.5	1.2	1.2	1.4	1.4
XXI	n-C_3H_7	CH_3	CH_3	2.6		1.4		1.9	
VIII	i-C_3H_7	CH_3	H	0.9	1.9	1.3	0.5	0.69	3.5
XXII	i-C_3H_7	CH_3	CH_3	1.7		0.70		2.4	
IX	n-C_4H_9	CH_3	H	3.1	2.1	3.7	1.7	0.84	1.2
XXIII	n-C_4H_9	CH_3	CH_3	6.4		6.4		1.0	
X	i-C_4H_9	CH_3	H	1.8	1.9	3.9	0.5	0.46	4.1
XXIV	i-C_4H_9	CH_3	CH_3	3.5		1.8		1.9	

in XXI ($R_1 = n$-C_3H_7, $R_2 = R_3 = CH_3$) by an i-propyl group and (b) the n-butyl group in XXIII ($R_1 = n$-C_4H_9, $R_2 = R_3 = CH_3$) by an i-butyl group, the toxicity is decreased more ($f_T = 0.5$ and 0.3) than the activity ($f_A = 0.7$ and 0.5), *i.e.* the anesthetic index is altered unfavourably in three cases ($0.4 < f_Q < 0.5$) and favourably in two ($f_Q = 1.3$ and 1.9).

4. By introducing a methyl group at the α-position of the amide-chain (*cf.* Table 4: C) the activity increases in all four available cases ($1.4 < f_A < 2.8$). In the first two of these (see Table), the toxicity increases more than the activity and, therefore, the anesthetic index is altered unfavourably ($f_Q = 0.6$ and 0.5). Introduction of the methyl group into XIII ($R_1 = i$-C_3H_7, $R_2 = H$, $R_3 = CH_3$), *i.e.* the third case, does not alter the toxicity and, since the increase in activity is considerable, the anesthetic index is changed favourably ($f_Q = 1.8$). In the fourth case, *i.e.* introduction of the methyl group in XV ($R_1 = i$-C_4H_9, $R_2 = H$, $R_3 = CH_3$), the toxicity increases ($f_T = 1.8$) approximately in the same ratio as the activity ($f_A = 2.1$) so that the anesthetic index remains practically unchanged ($f_Q = 1.1$). It should be emphasized that, due to the limited material at present available, the above examination includes only the introduction of a methyl at the α-position in such molecules that have their nuclear position *para* to the amide nitrogen occupied by a methyl group ($R_3 = CH_3$).

5. The introduction of a methyl group *para* to the amide nitrogen * (*cf.* Table 4: D) is in all six cases accompanied by an increased activity ($1.5 < f_A < 2.1$). The toxicity may increase, decrease or remain practically unchanged ($0.5 < f_T < 1.7$) and, since the increase is in no case greater than the corresponding increase in activity, the anesthetic index is in all cases improved ($1.2 < f_Q < 4.1$). In two cases, *i.e.* introduction of the methyl group in VIII ($R_1 = i$-C_3H_7, $R_2 = CH_3$, $R_3 = H$) and X ($R_1 = i$-C_4H_9, $R_2 = CH_3$, $R_3 = H$), the activity is increased to about double its value whereas the toxicity is decreased to about half its value so that the anesthetic index is increased greatly, *viz.* approximately four times.

* In the following this position is called the *p* position.

6. The discussions in *4* and *5* suggest that a transfer of a methyl group from the α position to the p position would lead to an improved anesthetic index. Direct information on this point can be obtained by comparing the isomers available (comparison not tabulated), *i.e.* VII with XII, VIII with XIII, IX with XIV, and X with XV. An examination shows that the said transfer in three of the four cases (VII→XII, VIII→XIII, X→XV) causes no appreciable change in the activity ($0.9<f_A<1.1$) and in one case (IX→XIV) decreases it slightly ($f_A = 0.7$). The toxicity decreases in all cases considerably ($0.3<f_T<0.5$). Accordingly, the anesthetic index changes favourably in all cases and calculation shows that the improvement throughout is considerable ($1.9<f_Q<3.7$).

In addition to what has been said under *1—6*, it should be emphasized that a certain structural change in one of the groups R_1, R_2 and R_3 is followed by an alteration in activity and/or toxicity which, as expected, is sometimes greatly dependent on the nature of the two other groups remaining unchanged. Thus, for instance, if in VII (R_1 = *n*-C_3H_7, R_2 = CH_3, R_3 = H), XII (R_1 = *n*-C_3H_7, R_2 = H, R_3 = CH_3) and XXI (R_1 = *n*-C_3H_7, $R_2 = R_3$ = CH_3) the *n*-propyl group is replaced by a *n*-butyl group (*cf.* Table 4:A) an increase in activity as well as toxicity will occur which in the last case is much greater than in the other two cases. In other words, if the α and p positions are *both* occupied by methyl groups and if a *n*-propyl group at the amino-end of the molecule is replaced by a *n*-butyl group, then this change is accompanied by an accentuated increase in activity and toxicity. Other examples: If the structure is changed in such a way that the resulting molecule is furnished with an *iso*alkyl group R_1 at the amino-end and with a methyl group in the α position as well as in the p position, *i.e.* a change which involves (a) the transformation of a *normal* alkyl group R_1 into the next higher homologous *iso*alkyl group (α and p positions with $R_2 = R_3 = CH_3$ kept unchanged; *cf.* Table 4:B) or (b) isomerization of R_1 from a *normal* alkyl group into an *iso*alkyl group (α and p positions with $R_2 = R_3 = CH_3$ kept unchanged; available examples: XXI → XXII and XXIII → XXIV; *cf.* also section *3*, p. 1729) or (c) introduction of a methyl group at the α position (p position occupied by a methyl group, R_1 being an *iso*alkyl group; *cf.* Table 4:C) or (d) introduction of a methyl group at the p position (α position occupied by a methyl group, R_1 being an *iso*alkyl group; *cf.* Table 4:D), then it is seen from the eight cases available that such a change is never accompanied by a marked decrease in anesthetic index. Thus, there is only one case of transformation (XX→XXII) which is associated with a slight decrease in the index ($f_Q = 0.8$) whereas, in the other seven cases, the index remains unchanged or is increased. In four of the cases (XIII→XXII, XXIII→XXIV, VIII→XXII, X→XXIV) the increase is very pronounced ($1.8<f_Q<4.1$).

The following comparison which does not fall within the above types of examination can also be made:

7. Replacement of the ethylamino group in VI (α-ethylamino-2,6-dimethylpropionanilide) by the isomeric dimethylamino group, *i.e.* the transformation of VI into XI, results in a considerable decrease in activity ($f_A \sim 0.3$) and a moderate decrease in toxicity ($f_T = 0.8$).

8. By cyclization of the diethylamino group in xylocaine to the pyrrolidino group, *i.e.* by transformation of xylocaine into IV, the activity is strongly decreased ($f_A \sim 0.2$). The toxicity is also decreased, though less ($f_T = 0.6$).

It should be realised that what has been said under *1—8* concerning the chemical structure and the pharmacological properties must be regarded as limited to the material treated here and great care chould be taken when trying to extend the results to other structures — even those which are closely related to the ones considered here.

Judged by the results hitherto obtained, fourteen of the compounds were considered worthy of a further study in subcutaneous anesthesia on man. These tests were undertaken merely from a clinical point of view and were thus restricted to the usual clinical technique, *i.e.* solutions of the same percentage concentration were made and, after injection of equal volumes, the duration was measured. The comparison with xylocaine was made in the presence as well as in the absence of epinephrine.

Solutions containing 0.5 % of the hydrochloride and a physiological NaCl content (0.85 %) * were prepared. From these solutions another series was made up by adding epinephrine to a strength of 1 : 100 000. The pH of the solutions was in both series adjusted to 4.0 **. Together with xylocaine, 3 or 4 compounds were compared at the same time on each individual in a group of twelve persons. The individuals in this group varied from time to time. The amount injected was always 0.5 ml and the injections were made on the volar side of the forearm, each compound being applied to the right as well as to the left arm. Thus, for each of the 3 or 4 compounds, two average values (presence or absence of epinephrine) were obtained, which were comparable with the corresponding values for xylocaine.

The following compounds were tested: III, VI, VII, XII—XVII, XIX—XXII and XXIV. With the exception of VI and XIII, each of these fourteen compounds has a RA value which is significantly larger than the corresponding value for xylocaine, most of the compounds having very high activities compared with xylocaine (*cf.* Table 3). Compounds VI and XIII have values (1.1 and 0.9, respectively) which are approximately equal to that of xylocaine (= 1.0). All fourteen compounds have Q values which are greater than the corresponding value for xylocaine.

Because of the RA values of these fourteen compounds, one could expect that all of them, with the exception of XIII and possibly VI, would, when injected under the above conditions, give greater durations than that of xylo-

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* When preparing the solution of XVII glucose (5.5 %) was added instead of NaCl. The hydrochloride of this compound is so slightly soluble in water that the presence of NaCl lowered its solubility to such a degree that a 0.5 % solution could not be prepared.

** When a local anesthetic is used for infiltration anesthesia, the pH of its solution may be varied within wide limits without affecting the duration. This has been demonstrated by various investigators (*cf.* Adriani [5], Tainter, Throndson and Moose [6], Björn and Huldt [7], Huldt [8]). Investigations just on 0.5 % xylocaine · HCl solutions have been made by Löfgren and Lundqvist [9]. In a fairly large number of subcutaneous wheal experiments, the durations of 0.5 % xylocaine· HCl solutions (NaCl concn. = 0.85 %, epinephrine concn. = 1 : 100 000), adjusted to different pH values between 4 and 7, were measured and no significant differences between the values could be found.

caine *. The results from the measurements do not, however, support such a conclusion.

In the test series where no epinephrine had been added, only three of the fourteen compounds gave durations which were greater than that of xylocaine, the order of magnitude being as follows: XXI>XIII ≅ XXII>xylocaine ≅ III, VI, VII, XV, XVI and XXIV>XII ≅ XVII and XX>XIV>XIX. The most active compound in this series, *i.e.* XXI, has a duration approximately 60 % larger than that of xylocaine whereas the compound with the lowest action, *i.e.* XIX, has a duration about 70 % smaller. It is particularly notable that compound XIII, which one might expect to have the lowest duration, is one of those three which have durations higher than that of xylocaine and that XVII, which has the highest relative activity on the cornea, *viz.* no less than 14 (= the RA value 16 multiplied by a conversion factor (0.87); *cf.* above), is inferior to xylocaine.

In the test series where epinephrine was added, none of the fourteen compounds showed a duration significantly greater than that of xylocaine. The order of magnitude was: Xylocaine ≅ VII, XIII, XV, XX and XXI>III ≅ XXII and XXIV>VI ≅ XIV and XVII>XII ≅ XVI and XIX. The least active compounds in this series, *i.e.* XII, XVI and XIX, all show durations about 45 % less than that for xylocaine. It should be emphasized that, also in this series, XIII belongs to the most active of the compounds — here it has approximately the same duration as xylocaine — and that XVII belongs to those which are inferior to xylocaine.

There is therefore a great discrepancy between the durations which were found by the topical application to the rabbit cornea and those which were found by subcutaneous injection in man. This kind of discrepancy has been noticed previously [4,10].

In a special series of subcutaneous injections in man, the fourteen compounds were investigated as to their irritant action **. Here, the above-described solutions containing epinephrine were used. On each of 12 persons, 2 or 3 of the compounds together with xylocaine were tested at the same time by subcutaneous injection of 2 ml of their solutions on the *dorsum*. The reaction of the skin was observed after 16 h. To judge from these screening tests, VII, XVI, XVII, XX, XXII and XXIV did not seem to differ very much from xylocaine, *i.e.* they were considered harmless to the tissues, whereas the other compounds gave evidence of more or less irritating properties. However, XX was later tried topically as an anesthetic in bronchoscopy and it was then found that this compound can produce severe tissue reactions.

* Consideration has here been given to the facts that (a) the RA values — valid for surface anesthetic potency — refer to a quotient of *molarities* with equal durations (= the duration of a 0.0738 M xylocaine solution) and (b) in the subcutaneous anesthesia, the evaluated durations refer to the same amount by weight of the *hydrochlorides* (= 0.5 ml of 0.5 % hydrochloride solutions). To make the RA values valid for a mutual comparison on the gram scale of the hydrochlorides, we thus have to multiply each RA value by a factor equal to the quotient of the molecular weight of xylocaine hydrochloride and the molecular weight of the hydrochloride of the compound.

** In the subcutaneous tests which were performed for the evaluation of anesthesia durations (*cf.* above), the injected amount was so small that only very limited information about the irritant action was obtained.

From what has been discovered about these fourteen compounds selected for studies in infiltration anesthesia, it can be stated that two of them, *viz.* VII and XXII, should be regarded as possible competitors to xylocaine. For this reason, a summary of the observed characteristic features of VII and XXII together with some additional experiments made in order to obtain a clearer picture of their possible clinical value in infiltration anesthesia is given:

By LD_{50} measurements on white mice (*cf.* Table 3) it was found that VII is about 25 % more toxic and XXII approximately 30 % less toxic than xylocaine *. The subcutaneous tests in man showed that xylocaine, VII and XXII do not differ greatly as to their durations. This was found to be the case in the presence as well as in the absence of epinephrine. Concerning irritant properties the screening tests described above were negative and the present authors could not find any irritant action when these two compounds and xylocaine were later compared in block anesthesia of the fingers. In these experiments all three compounds were used in form of their 1 % hydrochloride solutions containing epinephrine (1 : 100 000) and the physiological amount of sodium chloride. From a considerable number of such block anesthesias, it was found that, in comparison with xylocaine, both compounds were somewhat inferior in duration, the value for both being approximately 20 % lower than that of xylocaine. The latency time of VII was about 100 % greater than that of xylocaine whereas XXII gave approximately the same rapid onset as xylocaine.

Since VII has a higher toxicity and a much greater latency time than xylocaine, the compound was not considered to merit clinical trials in infiltration anesthesia. Compound XXII, in view of its properties, was submitted to clinical tests in dental anesthesia (therminal anesthesia, mandibular block)**. These experiments were made in the presence of epinephrine (1 : 80 000). As compared with xylocaine, XXII gave a somewhat shorter duration and the incidence of anesthesia was somewhat lower.

EXPERIMENTAL

Preparation of N-(halogenoacyl)arylamines. Of these derivatives prepared as intermediates in the synthesis of compounds I—XXIV, α-chloro-2-methylacetanilide, α-chloro-2,6-dimethylacetanilide and α-chloro-2,4,6-trimethylacetanilide were made as described previously by Löfgren [2] and α-bromo-2,6-dimethylpropionanilide as described by Löfgren and Lundquist [11], *i.e.* all these compounds were prepared by coupling a halogenoacyl halide (chloroacetyl chloride or α-bromopropionyl bromide) with an arylamine in an aqueous sodium acetate buffer according to the general method described by Löfgren [2]. The same method was used for the preparation of α-chloroacetanilide and α-bromo-2,4,6-trimethylpropionanilide (*cf.* below).

α-Chloroacetanilide. Prepared from chloroacetyl chloride and aniline in accordance with the method mentioned above. The yield of white microcrystalline powder was 86 %. On recrystallization from ligroin the compound was obtained as needles. M.p. 134 – 135° (uncorr.), in agreement with the value given by Meyer [12] who previously synthesized the compound by reacting aniline and chloroacetyl chloride in dry ether.

* In the subcutaneous experiments, the durations refer to the amount of hydrochloride used (0.5 ml of 0.5 % hydrochloride solution). Therefore, in this comparison of the toxicities of VII, XXII and xylocaine, the LD_{50} values of their *hydrochlorides* are considered. (In Table 3 the LD_{50} values are those of the bases.)

** Experiments performed by S. Ekmanner.

α-Bromo-2,4,6-trimethylpropionanilide. Prepared from α-bromopropionyl bromide and mesidine (*cf.* above). Yield of white microcrystalline powder 88 %. Needles from di-*n*-butyl ether. M.p. 188–190° (uncorr.). (Found: C 53.5; H 5.99. Calc. for $C_{12}H_{16}BrNO$ (270.2): C 53.3; H 5.97.)

Preparation of compounds I–XXIV (*cf.* Table 1). For the synthesis of I, IV, V, XI, XVIII and XIX, which are all *tertiary* bases, a mixture of 0.10 mole of the appropriate N-(halogenoacyl)arylamine (*cf.* p. 1725), 0.26 mole of the secondary amine (*cf.* Table 1) and 70 ml of dry benzene was boiled under reflux for 5 h (for I, IV, V and XIX) or heated for 5 h at a temperature of 80° in an autoclave (for XI and XVIII). When cool the mixture, including a possible water-soluble precipitate of the hydrochloride of the starting amine, was extracted in a separating funnel twice with 4 N hydrochloric acid, first with 75 ml and then with 40 ml. The combined aqueous extracts were washed with ether and then made alkaline with concentrated ammonia. The liberated base was extracted with ether and the solution thus obtained was dried over anhydrous sodium sulphate. The ether and the residual amount of starting amine were removed by distillation, first at atmospheric pressure, and then at water pump *vacuum* with a bath temperature of 100°. From the residue the desired base was purified either by recrystallization or by distillation under reduced pressure (*cf.* Table 1).

To synthesize II, III, VI–X, XII–XVII, and XX–XXIV, which are all *secondary* bases, a mixture of 0.10 mole of the appropriate N-(halogenoacyl)arylamine (*cf.* p. 1725), 0.50 mole of the primary amine (*cf.* Table 1) and 100 ml of absolute alcohol was refluxed for 5 h (for II, III, IX, XIV–XVII, XXIII, and XXIV) or heated for 5 h at a temperature of 100° in a pressure bottle or an atuoclave (for VI–VIII, X, XII, XIII, and XX–XXII). From the mixture obtained, the alcohol and the excess starting amine were distilled off, first at atmospheric pressure and then at water pump *vacuum* with a bath temperature of 100°. To the residue, 125 ml of 4 N hydrochloric acid was added. The resulting mixture was kept at 50° for half an hour under mechanical stirring and then allowed to cool. If the mixture contained a solid, *i.e.* a hydrochloride which may be contaminated with a small quantity of a halogenoacylarylamine, then it was filtered off by suction. The solid was dried and washed with benzene. The acid filtrate was purified by extracting twice with ether. The solid hydrochloride was combined with the acid filtrate. The base was liberated from this mixture with a sufficient amount of 5 N sodium hydroxide solution, mechanical stirring being applied for half an hour. The alkaline mixture was extracted sufficiently with chloroform and the solution dried over anhydrous sodium sulphate. (If no hydrochloride had appeared after the addition of hydrochloric acid (*cf.* above), the mixture was filtered. The filtrate was extracted twice with ether and from the aqueous solution the base was liberated and treated as described above.) The chloroform was distilled off and the base was isolated from the residue by either recrystallization or distillation.

The bases thus produced were analysed by determining the equivalent weight * or by usual elementary analyses or by both methods. Further analytical characterization was obtained from elementary analyses of the salts prepared (*cf.* below).

Yields, melting and boiling points, solvents for recrystallization, and analytical data are shown in Table 1.

Preparation of salts. Hydrochlorides of all the compounds, except I, IV, V, VIII, X, XV, XVIII and XXIV, were made. The methanesulphonate of II and the perchlorate of XXIV were also prepared. The salts were made by dissolving the compound in dry ether and adding the required amount of dry acid dissolved in dry ether **. The colourless microcrystalline precipitate was then recrystallized from a suitable solvent.

Melting points, solvents for recrystallization, and analytical data are shown in Table 2.

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* Titration of the base in 30 % ethanol with 0.1 N HCl; mixed indicator methylene blue — methyl red.

** When perchloric acid was used, the commercial 73 % acid was dissolved in absolute ether.

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