ACTA CHEMICA SCANDINAVICA 16 (1962) 1397–1400

Studies on Local Anesthetics XXI *

BJÖRN LÜNING

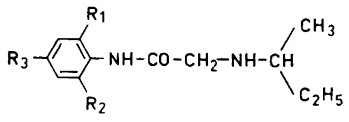
Institution of Organic Chemistry and Biochemistry, University of Stockholm, Stockholm, Sweden

Three *sec*-butylaminoacetanilides related to Xylocaine® have been synthesized. Their local anesthetic action on rabbit cornea and their subcutaneous toxicity in white mice were determined and compared with those of some of their homologues.

In the preceding investigations of alkylaminoacyl anilides related to Xylocaine®, no compounds containing a *sec*-butylaminoacyl group have been synthesized or tested for their local anesthetic properties. Thus, three *sec*-butylaminoacetanilides (for their structures see Table 1) have been prepared and their durations of anesthesia measured on rabbit cornea. To synthesize the compounds, the appropriate arylamine was condensed with chloroacetyl chloride to give the corresponding α-chloroacetanilide according to the general method of Löfgren [2]. *sec*-Butylamine and the suitable chloroacetanilide were then allowed to react in benzene to form the desired *sec*-butylaminoacetanilide.

The anesthetic potency of the compounds is given as RA ("relative activity") which is obtained by dividing the molarity of a standard Xylocaine solution by that molar concentration of the actual compound which gives the same duration of anesthesia as the Xylocaine standard. Further details regarding the testing of compounds are presented by Löfgren *et al.*[3] LD50 values were obtained by subcutaneous injections in white mice and calculated as (*a*) grams of the base per kilogram of body weight and (*b*) moles per kilogram of body

Table 1. Synthesized compounds.



Compound	R_1	R_2	R_3
I	CH_3	H	H
II	CH_3	CH_3	H
III	CH_3	CH_3	CH_3

* For paper XX of this series see Löfgren and Tegnér [1].

Table 2. Local anesthetic activity (rabbit cornea) and subcutaneous toxicity (white mouse) of compounds I—III and four compounds (A—D) synthesized by Löfgren *et al.*[3,4,a].

Compound	Relative anesthetic activity (RA) xylocaine = 1	Toxicity, LD50		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	0.3	~1.7	~9.1	~0.16	~1.9
II	2.0	0.27	1.2	1.3	1.6
III	1.9	0.30	1.2	1.2	1.6
α-(Propylamino)-2,6-dimethylacetanilide (A)[a]	1.0	0.52	2.4	0.61	1.6
α-(Propylamino)-2,4,6-trimethylacetanilide (B)[a]	1.9	0.56	2.4	0.58	3.3
α-(Isopropylamino)-2,6-dimethylacetanilide (C)[a]	0.8	0.48	2.2	0.67	1.2
α-(Isopropylamino)-2,4,6-trimethylacetanilide (D)[a]	0.9	0.47	2.0	0.70	1.3

[a] The pharmacological properties of B and D are found in Löfgren *et al.* [3] For A and C the relative anesthetic activity and the toxicity were obtained by private communication with Dr. S. Wiedling, A.B. Astra, Södertälje, Sweden.

weight ("molar" LD50 value). The term RT ("relative toxicity") is the ratio of the molar LD50 value of Xylocaine and that of the actual compound. The change in RA and RT is indicated by *factors* f_A and f_T; respectively.

The pharmacological data of the compounds are found in Table 2. In Table 2 are also included the pharmacological data of four compounds (A—D) synthesized by Löfgren *et al.*[3,4] *. The material allows a brief study on the relationship between chemical constitution and pharmacological properties:

(1) The introduction of a methyl group into the alkylamino group (R_4NH; *cf.* Table 3: A) at the carbon atom next to the nitrogen atom is in one case (A → II) accompanied by a rise in RA ($f_A = 2.0$), whereas in another case (B → III) RA is not changed ($f_A = 1.0$) **. In both cases the toxicity increases strongly ($f_T = 2.0$) **.

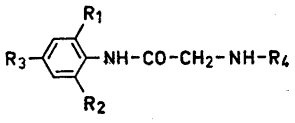
(2) When an isopropylamino group (R_4NH; *cf.* Table 3: B) is replaced by a *sec*-butylamino group, a strong increase in RA ($2.1 < f_A < 2.5$) as well as in RT ($1.7 < f_T < 1.9$) is observed.

(3) The effect on the pharmacological properties of changes in situation and number of methyl groups attached to the benzene nucleus offers some interesting features. The introduction of a methyl group *para* to the amide nitrogen has very little influence on the pharmacological properties, which is

* As regards the pharmacological data of compounds A—D, ses footnote to Table 2.

** The changes in the pharmacological properties which are connected with the same structural change, *i.e.* the introduction of a methyl group at the carbon atom next to the nitrogen atom in the alkylamino group R_4NH (*cf.* Table 3: A), have been studied by Löfgren *et al.* [3] by comparing compounds containing an ethylamino group with those containing an isopropylamino group; see Löfgren *et al.* [3], Table 4:B.

Table 3. Change in relative anesthetic activity (RA) and relative toxicity (RT) when varying the group R_4 (*cf.* formula).



R_1, R_2 or R_3 = H or CH_3
R_4 = *n*-C_3H_7, *i*-C_3H_7 or *sec*-C_4H_9.

Factors f_A and f_T indicate the changes in RA and RT, respectively; *cf.* also text.

Compound					RA	f_A	RT	f_T	RA/RT
No.	R_1	R_2	R_3	R_4					
A. Introduction of a methyl group at the carbon atom next to the nitrogen atom in an alkylamino group R_4NH.									
A	CH_3	CH_3	H	*n*-C_3H_4	1.0	2.0	0.61	2.0	1.6
II	CH_3	CH_3	H	*sec*-C_4H_9	2.0		1.3		1.6
B	CH_3	CH_3	CH_3	*n*-C_3H_7	1.9	1.0	0.58	2.0	3.3
III	CH_3	CH_3	CH_3	*sec*-C_4H_9	1.9		1.2		1.6
B. Introduction of a methyl group at one of the methyl groups of an isopropylamino group R_4NH.									
C	CH_3	CH_3	H	*i*-C_3H_7	0.8	2.5	0.67	1.9	1.2
II	CH_3	CH_3	H	*sec*-C_4H_9	2.0		1.3		1.6
D	CH_3	CH_3	CH_3	*i*-C_3H_7	0.9	2.1	0.70	1.7	1.3
III	CH_3	CH_3	CH_3	*sec*-C_4H_9	1.9		1.2		1.6

demonstrated by the fact that II and III have almost identical RA and RT values. In comparing, I and II, which differ from each other by one *ortho* methyl group, it is found that the local anesthetic activity as well as the toxicity are noticably higher in II than in I ($f_A = 6.7$; $f_T = 8.0$).

EXPERIMENTAL *

α-Chloro-2-methylacetanilide, *α-chloro-2,6-dimethylacetanilide*, and *α-chloro-2,4,6-trimethylacetanilide* were prepared by condensing the suitable arylamine with chloroacetyl chloride in an aqueous sodium acetate buffer, following the general method of Löfgren [2].

α-(sec-Butylamino)-2-methylacetanilide (I). A mixture of 9.2 g (0.050 mole) of α-chloro-2-methylacetanilide, 18 g (0.25 mole) of *sec*-butylamine ** and 40 ml of dry benzene was boiled under reflux for 5 h. The benzene was removed *in vacuo* and the

* The equivalent weights of the bases were determined by titrating them in 30 % ethanol with 0.1 N HCl; mixed indicator methylene blue-methyl red.

** Before use, the *sec*-butylamine was dried over NaOH and distilled.

residue dissolved in 25 ml of concentrated hydrochloric acid. To the solution thus formed, 60 ml of water were added. The slightly soluble α-(*sec*-butylamino)-2-methylacetanilide hydrochloride, which soon deposited, was filtered off and recrystallized twice from isopropanol; yield 8.5 g (0.033 mole, 66 %), m.p. 152° (corr.). (Found: Cl 13.8. Calc. for $C_{13}H_{21}ClN_2O$: Cl 13.9.) The base was liberated from the hydrochloride by addition of dilute aqueous sodium hydroxide, taken up in ether and distilled; b.p. 140°—142°/0.2 mm, n_D^{25} 1.5312. (Found: equiv. wt. 222. Calc. for $C_{13}H_{20}N_2O$: equiv. wt. 220.)

α-(sec-Butylamino)-2,6-dimethylacetanilide (II). α-Chloro-2,6-dimethylacetanilide (9.9 g, 0.050 mole) and *sec*-butylamine (18 g, 0.25 mole) were allowed to react in the same manner as is described under compound I (*cf.* above). The resulting α-(*sec*-butylamino)-2,6-dimethylacetanilide hydrochloride was recrystallized twice from isopropanol; yield 7.4 g (0.027 mole, 55 %), m.p. 180° (corr.). (Found: Cl 12.9. Calc. for $C_{14}H_{23}ClN_2O$: Cl 13.1.) The base was liberated by treatment with dilute aqueous sodium hydroxide and distilled; b.p. 147°—148°/0.2 mm, n_D^{25}1.5206 *. (Found: equiv. wt. 235. Calc. for $C_{14}H_{22}N_2O$: equiv. wt. 234.) The base soon solidified to a crystalline mass; m.p. 46°—47° (corr.).

α-(sec-Butylamino)-2,4,6-trimethylacetanilide (III). α-Chloro-2,4,6-trimethylacetanilide (10.6 g, 0.050 mole) and *sec*-butylamine (18 g, 0.25 mole) were condensed according to the method described under compound I. The α-(*sec*-butylamino)-2,4,6-trimethylacetanilide hydrochloride obtained in the synthesis was recrystallized from isopropanol; yield 8.7 g (0.031 mole, 61 %), m.p. 180° (corr.). (Found: Cl 12.4. Calc. for $C_{15}H_{25}ClN_2O$: Cl 12.4.) The base was liberated from the hydrochloride and distilled; b.p. 152°—154°/0.2 mm. The oily distillate soon solidified to a crystalline mass; m.p. 55°—56° (corr.). (Found: equiv. wt. 247. Calc. for $C_{15}H_{24}N_2O$: equiv. wt. 248.)

Great thanks are due to Dr. S. Wiedling, A.B. Astra, Södertälje, Sweden, for performing the pharmacological tests.

REFERENCES

1. Löfgren, N. and Tegnér, C. *Acta Chem. Scand.* **14** (1960) 486.
2. Löfgren, N. *Studies on Local Anesthetics. Xylocaine, a New Synthetic Drug.* Dissertation, Stockholm 1948.
3. Löfgren, N., Tegnér, C. and Takman, B. *Acta Chem. Scand.* **11** (1957) 1724.
4. Löfgren, N. and Widmark, G. *Svensk Kem. Tidskr.* **58** (1946) 323.

Received December 31, 1961.

* Supercooled.