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Studies on Local Anesthetics XX *

Synthesis of Some α-Monoalkylamino-2-methylpropionanilides. A New Useful Local Anesthetic

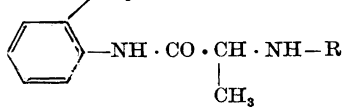
NILS LÖFGREN and CLAËS TEGNÉR

Institute of Organic Chemistry and Biochemistry, University of Stockholm, Stockholm, and Research Laboratories, AB Astra, Södertälje, Sweden

Five new α-monoalkylamino-2-methylpropionanilides in which the alkyl group is an ethyl, *n*-propyl, *iso*propyl, *n*-butyl or *iso*butyl group have been synthesised. All five compounds possess local anesthetic activity and one of them, the *n*-propylamino compound ("L 67"), had such valuable properties that it was subjected to clinical tests. These showed the new compound to be an effective injection anesthetic.

A review of the chemistry of local anesthetics has recently been published by Killian [2] in which the aminoacylanilides are discussed as well as other groups of anesthetics. A number of papers on the synthesis of local anesthetics of this type have been published from this institute, one of which describes the preparation of α-diethylamino-2,6-dimethylacetanilide [3] (Xylocaine®). Since its introduction into clinical use it has become the most important injection anesthetic. This paper presents a new local anesthetic, α-n-*propylamino-2-methylpropionanilide*, which in its pharmacological properties is similar to Xylocaine.

A series of compounds of the general formula



in which R is an ethyl (I), *n*-propyl (II), *iso*propyl (III), *n*-butyl (IV), or *iso*butyl (V) group were synthesised and tested pharmacologically. The inter-

* For paper XIX of this series, see Lüning [1].

mediate α-bromo-2-methylpropionanilide was prepared by reacting α-bromopropionyl bromide with *o*-toluidine in an aqueous acetate buffer [4]. One mole of the α-bromo-2-methylpropionanilide was then heated with an excess of the appropriate monoalkylamine in benzene solution.

Compounds I—V were tested for local anesthetic activity on rabbit cornea, using the technique of Wiedling [5] and the lethal doses (LD50) of each compound was determined by subcutaneous injection in white mice. The activity and toxicity values presented here are relative values referring to Xylocaine as a standard, *i.e.* the activity and toxicity of Xylocaine are both, by definition, taken as unity. Thus, a compound is characterised by its *relative anesthetic activity*, RA (for Xylocaine: RA = 1) and its *relative toxicity*, RT (for Xylocaine: RT = 1)*. For the quotient RA/RT the term *anesthetic index*, Q, is used (for Xylocaine: Q = 1). The results of the pharmacological measurements are compiled in Table 1. As can be seen from the table, compound I has the lowest activity (RA $\sim$ 0.3) being approximately 70 % lower than that of Xylocaine. Compound I has also, compared with Xylocaine, a low toxicity (RT = 0.41) and therefore its anesthetic index (Q $\sim$ 0.7) is only about 30 % lower than that of Xylocaine. Compound IV possesses the highest activity (RA = 2.2). It also has the highest toxicity (RT = 0.91), equal to or slightly less than that of Xylocaine. Since however RA is considerably higher than RT, the Q value is high (2.4). The RA values of II, III and V are 0.9, 0.7 and 0.8 respectively and since their relative toxicities are all < 0.7, they have Q values higher than that of Xylocaine. When tested for irritant properties by injection in the rabbit ear ** (aqueous solutions of the hydrochlorides), IV gave a moderate and V a strong irritant action but the other three compounds (I, II and III) did not appreciably irritate the skin. Among the three nonirritant compounds, II and III have rather good RA values (especially II) and very favourable Q values and they were therefore subjected to clinical tests.

Table 1. Local anesthetic activity (rabbit cornea) and toxicity (white mouse) of compounds I—V. For the terms relative anesthetic activity and relative toxicity, see above.

Compound	Relative anesthetic activity (RA)	Toxicity, LD50		Relative toxicity (RT)	$Q\left(=\frac{RA}{RT}\right)$
		g base/kg	moles/kg × 10^3		
Xylocaine	1.0	0.34	1.45	1.0	1.0
I	0.30	0.72	3.5	0.41	0.7
II	0.86	0.71	3.2	0.45	1.9
III	0.68	0.73	3.3	0.44	1.5
IV	2.2	0.38	1.6	0.91	2.4
V	0.82	0.55	2.3	0.63	1.3

* For further information on the meaning of the terms RA and RT, see Löfgren, Tegnér and Takman [6].

** For this technique, see Wiedling [7].

At present we are able to present briefly the clinical results for compound II, in clinical tests known as *L 67* or *Astra 1512* *. This compound, *i.e.* α-n-*-propylamino-2-methylpropionanilide*, did not produce any sign of irritation when tested for infiltration anesthesia in man **. No side effects were observed. The efficiency of the compound was studied in practically all forms of injection anesthesia (subcutaneous anesthesia of the skin, terminal anesthesia of the teeth, various forms of block anesthesia, *e.g.* sacral and mandibular anesthesia, *etc.*). From these tests it is evident that compound II has a similar action to that of Xylocaine. The two compounds produce approximately the same incidence, onset, extent and duration of anesthesia. In dental use, compound II gives a shorter anesthesia of the soft tissues than Xylocaine, *i.e.* in this respect compound II is more favourable than Xylocaine. Furthermore, as shown in Table 1, the toxicity of compound II is about 50 % lower than that of Xylocaine ***. It is thus a very promising injection anesthetic for clinical use.

EXPERIMENTAL †

α-Bromo-2-methylpropionanilide was prepared from α-bromopropionyl bromide and *o*-toluidine by the aqueous acetate buffer method given by Löfgren [4]. Colourless needles were obtained from benzene, m. p. 132—133°, yield 81 %. The melting point agrees with that observed by Tigerstedt [10] who synthesised the compound from α-bromopropionyl bromide and *o*-toluidine in a dry organic solvent.

α-Ethylamino-2-methylpropionanilide (I). A mixture of α-bromo-2-methylpropionanilide (24 g, 0.10 mole), ethylamine (12 g, 0.27 mole) and benzene (50 ml) was heated in a steel autoclave at 80° for 8 h. The reaction mixture was then diluted with absolute ether and filtered to remove the amine hydrobromide formed. After evaporation of the solvent the residue was distilled under reduced pressure and the fraction b. p. 145—147°/0.9 mm was collected as a colourless oil (16.5 g, 80 %). The oil soon solidified and was recrystallised from petroleum ether (b. p. 40—60°). Colourless crystals, solidifying point 36—37°. (Found: C 69.7; H 8.92. Calc. for $C_{12}H_{18}N_2O$ (206.3): C 69.9; H 8.79.)

α-n-*Propylamino-2-methylpropionanilide* (II). A solution of α-bromo-2-methylpropionanilide (24 g, 0.10 mole) and *n*-propylamine (16 g, 0.27 mole) in benzene (100 ml) was refluxed for 8 h. The reaction mixture was treated as described under compound I and the base was isolated as colourless needles, m. p. 37—38°, b. p. 159—162°/1 mm, n_D^{20} 1.5298†† (19 g, 87 %). (Found: C 71.0; H 8.95. Calc. for $C_{13}H_{20}N_2O$ (220.3): C 70.9; H 9.15.)

Salts of this compound were prepared by dissolving the base in dry ether and adding an ether solution or an ether-ethanol solution of the acid. The precipitated salts were recrystallised from ethanol — *iso*propyl ether. To prepare the sulphamate a different technique had to be used (see below). The following salts were prepared:

Hydrochloride. M. p. 167—168°. (Found: C 60.8; H 8.21; N 10.73. Calc. for $C_{13}H_{21}ClN_2O$ (256.8): C 60.8; H 8.24; N 10.91.)

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* A paper on clinical results with the compound has already appeared [8]. Further results of the pharmacological and the clinical investigations will be published shortly.

** Aqueous solutions of the hydrochloride, with or without the addition of epinephrine, were used for the clinical tests.

*** In experiments carried out by Wiedling [9] both the intravenous and the intraperitoneal toxicities (white mouse) were 60—65 % of those of Xylocaine.

† All melting points are corrected.

†† supercooled liquid.

Hydrogen sulphate. M. p. 175—176°. (Found: C 49.7; H 6.95; N 8.66. Calc. for $C_{13}H_{22}N_2O_5S$ (318.4): C 49.0; H 6.97; N 8.80.)

Monohydrogen citrate. On treating 1 mole of the base with 1 mole of citric acid the dibasic citrate separated, m. p. 140—142° decomp. (Found: C 60.7; H 7.55; N 9.10. Calc. for $C_{32}H_{48}N_4O_9$ (632.8): C 60.7; H 7.65; N 8.85.)

Lactate. M. p. 133—134°. (Found: C 61.7; H 8.45; N 9.18. Calc. for $C_{16}H_{26}N_2O_4$ (310.4): C 61.9; H 8.44; N 9.03.)

Methanesulphonate. M. p. 169—171°. (Found: C 53.2; H 7.63; N 8.50. Calc. for $C_{14}H_{24}N_2O_4S$ (316.4): C 53.1; H 7.65; N 8.86.)

Sulphamate. The sulphamate of compound II was prepared in the following way:

A mixture of the base (22 g, 0.10 mole) and sulphamic acid (9.7 g, 0.10 mole) in absolute ethanol (40 ml) was boiled under reflux (condenser with calcium chloride tube) until dissolved. Dry acetone (30 ml) and then absolute ether (30 ml) were added to this clear solution through the condenser. After cooling the crystals that separated were sucked off and washed with a mixture of equal volumes of dry acetone and dry ether. Yield 24 g, 75 %. The salt thus obtained is of high purity but, if desired, it can be recrystallised from absolute ethanol-*iso*propyl ether. M. p. 130—131°. (Found: C 49.1; H 7.42; N 12.9. Calc. for $C_{13}H_{23}N_3O_4S$ (317.4): C 49.2; H 7.30; N 13.2.)

If in the procedure described above aqueous alcohol is used instead of absolute alcohol the sulphamate may be obtained in a hydrated form. However, a closer characterisation has not yet been carried out.

All the salts, described here, are readily soluble in water.

*α-Iso**propylamino-2-methylpropionanilide hydrochloride* (III). A mixture of α-bromo-2-methylpropionanilide (24 g, 0.10 mole), *iso*propylamine (16 g, 0.27 mole) and benzene (100 ml) was heated in a steel autoclave at 80° for 8 h. The reaction mixture was then diluted with dry ether and filtered to remove precipitated *iso*propylammonium bromide. The addition of a dry ethereal solution of hydrogen chloride precipitated the hydrochlorides of III and the remaining *iso*propylamine. The salts were filtered off, washed with ether and then dissolved in hot water to which had been added some activated carbon. From the filtered solution the hydrochloride of III separated as colourless crystals, m. p. 236—237° decomp. (16.5 g, 64 %). (Found: C 61.3; H 8.30; Cl (Mohr) 13.8. Calc. for $C_{13}H_{21}ClN_2O$ (256.8): C 60.8; H 8.24; Cl 13.8.)

α-n-Butylamino-2-methylpropionanilide hydrochloride (IV). α-Bromo-2-methylpropionanilide (24 g, 0.10 mole), *n*-butylamine (20 g, 0.27 mole) and benzene (100 ml) were boiled under reflux for 8 h. After dilution with dry ether the *n*-butylammonium bromide was filtered off and the filtrate evaporated to dryness. The residue was dissolved in ether and ethereal hydrogen chloride was added until no more precipitate was formed. This was filtered off and then recrystallised from absolute ethanol giving colourless crystals, m. p. 175—177° (19 g, 71 %). (Found: C 61.9; H 8.39; Cl (Mohr) 13.1. Calc. for $C_{14}H_{23}ClN_2O$ (270.8): C 62.1; H 8.56; Cl 13.1.)

*α-Iso**butylamino-2-methylpropionanilide hydrochloride* (V). The compound was obtained from α-bromo-2-methylpropionanilide and *iso*butylamine. The procedure described under compound III was followed, but instead of heating the reaction mixture in an autoclave it was boiled under reflux for 8 h. The hydrochloride was obtained from water as colourless crystals (*cf.* under compound III) and was recrystallised from the same solvent, m. p. 221—223° decomp., yield 63 %. (Found: C 61.9; H 8.29; Cl (Mohr) 13.1. Calc. for $C_{14}H_{23}ClN_2O$ (270.8): C 62.1; H 8.56; Cl 13.1.)

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