SYNTHESIS AND BIOLOGICAL ACTIVITY OF α-PHENYL-β-AMINO-(3-FLUORO-4-METHOXY)PROPIOPHENONE HYDROCHLORIDES AND THEIR REDUCTION PRODUCTS

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UDC 615.216.2:547.572.1].012.1

In continuing our search for biologically active compounds in the series of aminoketones and aminoalcohols [8], we have prepared α-phenyl-β-amino(3-fluoro-4-methoxy)propiophenones (IIa-d) by aminoethylation of 3-fluoro-4-methoxydeoxybenzoin with cyclic amines and paraform in ethanol. They were reduced with lithium aluminumhydride in absolute ether to the corresponding 1-(3-fluoro-4-methoxyphenyl)-2-phenyl-3-aminopropanols (IIIa-d).

$$4\text{-}(CH_3O)\text{-}3\text{-}F\text{-}C_6H_3COCH_2C_6H_5 + CH_2O + RNH \longrightarrow$$
$$\mathbf{I}$$
$$\longrightarrow 4\text{-}(CH_3O)\text{-}3\text{-}F\text{-}C_6H_3COCH(C_6H_5)CH_2NR \longrightarrow$$
$$\mathbf{II}^{a\text{-}d}$$
$$\longrightarrow 4\text{-}(CH_3O)\text{-}3\text{-}F\text{-}C_6H_3CH(OH)CH(C_6H_5)CH_2NR$$
$$\mathbf{III}^{a\text{-}d}$$

IIa, IIIa: R = —$(CH_2)_4$—; IIb, IIIb: R = —$(CH_2)_2O(CH_2)_2$—; IIc, IIIc: R = = —$(CH_2)_5$—; IId, IIId: R = —$(CH_2)_6$—.

Aminoketones IIa-d are crystalline compounds and aminoalcohols IIIa-d are viscous oils. The purity of the prepared compounds was confirmed by TLC and elemental analysis, and the structure by IR and PMR spectral data.

In the IR spectra of compounds IIa-d we find characteristic absorption bands of the carbonyl group (1680-1665 cm^{-1}) and in the IR spectra of compounds IIIa-d of the hydroxyl group (3420-3300 cm^{-1}).

In the PMR spectra of aminoketones IIa-d the protons of the methoxy group give a singlet at 3.63-3.90 ppm and the protons of the methine group give multiplets at 4.5-4.8 ppm.

The protons of the methoxy group of aminoalcohols IIa-d give singlets at 3.7-3.75 ppm and the proton of the CH-OH group gives a doublet at 4.5-5.0 ppm.

Compounds IIa-d and IIIa-d were converted to the hydrochlorides (IVa-d, Va-d).

EXPERIMENTAL CHEMICAL

TLC was performed on a fixed silica gel—gypsum layer. The eluent was n-butanol—ethanol—acetic acid—water 8:2:1:3 and the spots were visualized with iodine vapor and with an acidified solution of 2,4-dinitrophenylhydrazine. IR spectra were taken on a UR-20 (GDR) spectrophotometer in paraffin oil. PMR spectra were recorded on Varian T-60 (USA) and XL-200 (USA) spectrometers, operating at 60 MHz and 200 MHz, respectively, using tetramethylsilane as internal standard and CCl_4 as solvent.

3-Fluoro-4-methoxydeoxybenzoin (I) was prepared with a Friedel-Crafts reaction with some changes in described method [10] (instead of titanium tetrachloride and petroleum ether we used aluminum trichloride and carbon tetrachloride). Compound I had mp 108-110°C.

α-Phenyl-β-morpholino-(3-fluoro-4-methoxy)propiophenone (IIb). A mixture of 24.4 g (0.1 mole) of I, 8.7 g (0.1 mole) of morpholine, and 3.0 g (0.1 mole) of paraform in 150 ml of

A. L. Mndzhoyan Institute of Fine Organic Chemistry, Academy of Sciences of the Armenian SSR, Erevan. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 21, No. 4, pp. 419-425, April, 1987. Original article submitted December 10, 1985.

0091-150X/87/2104-0253$12.50

TABLE 1. Physicochemical Constants of Aminoketones IIa-d and Their Hydrochlorides

Compound No.	Yield, %	mp, °C	Found, %			Empirical formula	Calculated, %			R_f	Hydrochlorides			
			C	H	N		C	H	N		mp., °C	found % Cl	calculated, % Cl	R_f
II	50	103—6	73,50	6,65	4,75	$C_{20}H_{22}FNO_2$	73,38	6,72	4,28	0,75	171—3	10,1	9,74	0,71
II	50	88—9	70,40	6,06	4,59	$C_{20}H_{22}FNO_3$	69,95	6,46	4,07	0,79	157—8	10,13	9,33	0,87
II	67	110—2	73,60	7,58	4,28	$C_{21}H_{24}FNO_2$	73,87	7,08	4,10	0,69	144—5	8,70	9,38	0,72
II	40	84—5	74,70	7,70	3,80	$C_{22}H_{26}FNO_2$	74,34	7,37	3,94	0,71	138—9	10,07	9,04	0,76

TABLE 2. Physicochemical Constants of the Hydrochlorides of Aminoalcohols IIIa-d

Compound No.	Yield, %	mp., °C	Found, %				Empirical formula	Calculated, %				R_f
			C	H	N	Cl		C	H	N	Cl	
III	83	225—6	65,49	6,58	3,82	9,30	$C_{20}H_{24}FNO_2 \cdot HCl$	65,65	6,89	3,83	9,69	0,61
III	83	205—7	62,84	6,38	3,82	8,80	$C_{20}H_{24}FNO_3 \cdot HCl$	62,91	6,60	3,67	9,28	0,73
III	98	212—4	66,12	7,28	3,32	9,60	$C_{21}H_{26}FNO_2 \cdot HCl$	66,39	7,16	3,68	9,33	0,73
III	90	214—5	66,94	7,13	3,43	8,85	$C_{22}H_{28}FNO_2 \cdot HCl$	67,08	7,42	3,55	9,00	0,74

TABLE 3. Characteristic of the Local Anesthetic, Central, Toxic, and Local-irritating Action of the Hydrochlorides of Aminoketones and Aminoalcohols

Compound	Conduction anesthesia EC_{50}, %	Analgesia, mm Hg (M ± m)	LD_{50} intraperitoneally, mg/kg***	Local-irritating action**
Novocain	0,05 (0,029—0,078)	20±0,48	192 (176,6—208,7)	—
Trimecaine	0,022 (0,013—0,031)	22,5±2,1	187 (175,4—199,1)	—
Lidocaine	0,035 (0,026—0,048)	19±1,2	123 (108,6—142,2)	—
IIa*	0,165 (0,12—0,22)	15,5±0,5	122 (96,8±157)	++++
IIb*	—	18,3±2,2	460 (370,9—570,4)	++++
IIc*	0,43 (0,25—0,73)	16,5±0,3	187 (166,2—210,4)	++++
IId*	0,396 (0,24—0,653)	12,4±0,8	220 (172—281,6)	++++
IIIa*	0,45 (0,27—0,74)	12,5±1,7	221 (182,6—267,4)	—
IIIb*	0,056 (0,03—0,081)	11,5±2,6	560 (504,6—621,1)	+
IIIc*	0,048 (0,037—0,062)	12,8±2,4	245 (197,6—303,8)	++
IIId*	0,24 (0,155—0,283)	15,8±3,1	110 (91,6—132)	++

Notes. 1) Compounds marked with an asterisk were studied as the hydrochlorides. 2) LD_{50} on oral administration was: for novocain 50 (4.71-53.0) mg/kg; for trimecaine 48 (40.6-56.6) mg/kg; for lidocaine 35 (31.3-39-2) mg/kg; for the hydrochloride of IIIb 113 (100.9-126.6) mg/kg. 3) (−): No action; (+): weak reddening; (++): hyperemia; (++++): necrosis. 4) In parentheses the boundaries of the fluctuations are given.

ethanol was refluxed for 6 h, 100 ml of ethanol was distilled off, the mixture was cooled, and the precipitate was filtered off and washed with 20 ml of cold ethanol. Yield 17.2 g (50.0%) of IIb, mp 88-89°C (ethanol). IR spectrum, ν, cm^{-1}: 1680 (C=O). PMR spectrum ($CDCl_3$, 200 MHz), δ, ppm: 2.8-3.4 [6H, m, $N(CH_2)_3$]; 3.8-4.3 [7H, m, OCH_3, $O(CH_2)_2$]; 3.9 (3H, s, OCH_3); 5.9-6.0 (1H, m, COCH); 6.8-8.0 (8H, m, C_6H_5, C_6H_3).

Compounds IIa,c,d were prepared in the same way; yields and some constants are listed in Table 1. Compounds IIa-d were converted to the hydrochlorides with an ethereal hydrogen chloride solution; they were purified by crystallization from ethanol (Table 1).

1-(3-Fluoro-4-methoxyphenyl)-2-phenyl-3-morpholinopropanol-1 (IIIb). To a suspension of 0.7 g (0.025 mole) of lithium aluminum hydride in 50 ml of dry ether was added dropwise with cooling a solution of 3.44 g (0.01 mole) of IIb, the mixture was refluxed for 2 h, and then 10 ml of ice-water was added dropwise with cooling. The ethereal solution was decanted, the residue was washed with ether, the ethereal extracts were combined, dried with waterfree sodium sulfate, and the ether was evaporated. Yield 2.86 g (83.0%) of IIIb. IR spectrum, ν, cm^{-1}: 3420-3320 (OH), 1610, 1600, 1580 (C-C, aromatic). PMR spectrum ($CDCl_3$, 60 MHz), δ, ppm: 2.30-3.01 [7H, m, CH and $N(CH_2)_3$]; 3.63 [4H, t, $O(CH_2)_2$]; 3.71 (3H, s, OCH_3); 4.90 (1H, d, CHOH); 6.33-7.30 (8H, m, C_6H_5, C_6H_3).

Aminopropanols IIIa,c, d were prepared in the same way (Table 2). The aminoalcohols were converted to the hydrochlorides with an ethereal solution of hydrochloric acid and were recrystallized from acetone (see Table 2).

EXPERIMENTAL PHARMACOLOGICAL

Pharmacological investigations of the prepared hydrochlorides of the α-phenyl-β-amino-(3-fluoro-4-methoxy)propiophenones and their reduction products were carried out with anesthesimetry and analgesimetry tests. We determined the antagonistic action to opoids, the acute toxicity, and the local irritating action. Investigations of the local anesthetic activity in conduction anesthesia were carried with isolated frog nerves [6]. The surface

TABLE 4. Duration of the Local Anesthetic Action of the Hydrochloride of Aminoalcohol IIIb in Case of Conduction Anesthesia (rats)

Compound	Average effective time, in minutes				
	1% solution	relative to novocain, %	3% solution	relative to novocain, %	1% solution + adrenaline (0.05%)
Novocain	27 (24,3—29,9)	100	40 (37,7—43,2)	100	41,1** (39,3—42,9)**
Lidocaine	42,5 (37,3—48,4)	157	70,5 (63,5—78,2)	176	64 (54,2—75,5)**
Trimecaine	46 (41,8—50,6)	170	76 (62,7—93,5)	190	69,3 (66,9—72,7)**
III b	39 (35,9—42,3)	144	62 (56,3—68,1)	155	56 (49,5—63,6)**

Notes. 1) Marked with one asterisk is the significance ($p = 0.05$) of the differences with the action of novocain, and with two asterisks with the activity of the compounds as a 1% solution together with adrenaline. 2) The experiments were carried out with 7 animals. 3) In parentheses the boundaries of the fluctuations are shown.

anesthetic activities of 1% solutions of the compounds were determined with rabbit corneas by Régnier's method [9].

Investigation of the analgetic and the antagonistic action to opioids of the compounds at a dose of 10 mg/kg (e.g., suppression of the analgetic action of morphine at a dose of 5 mg/kg) was carried out with the method of mechanical irritation of rat tails [13].

The acute toxicity of the compounds was determined with male white mice on intraperitoneal and oral administration. Statistical processing (here and hereinafter) was carried out according to Litchfield and Wilcoxon [4]. The local toxicity was studied in guinea pigs [16] with regard to the sensitive zone of the animal's back [2]. The compounds were tested as 0.1, 0.25, 0.5, 1, and 2% solutions prepared with a 0.9% sodium chloride solution.

For a more through study the active compounds were subjected to further investigation with anesthesimetry and physico-chemical analyses. Studies of the duration of the local anesthetic action of the compounds on conduction anesthesia were performed with intact rats. The compound under investigation was administered as 1 and 3% solutions to one of the hind legs at the plantar side in the region of termination of the distal branches of the tibial and fibular nerves [7]. Infiltration anesthesia was studied in guinea pigs [12, 16] using 0.2 and 0.5% solutions of the compounds (pH 7.1). Spinal anesthesia was studied in rabbits [15, 17]. The compounds were studied as 1 and 3% solutions; first the pH and specific gravity of these solutions were determined [5]. Statistical processing was carried out with Student's test. The effect of the active reaction medium on the local anesthetic activity of the compounds was established with isolated frog nerves at pH 3.0, 7.0, and 9.0. Ionization constants of the compounds were measured by means of the potentiometric approximation method [3]. The surface activity of the local anesthetic compounds was determined with the method of maximal pressure in the vesicles or in a drop on a Rebinder apparatus [1] at the boundaries anesthetic—air and anesthetic—benzene.

RESULTS AND DISCUSSION

The data obtained show that the compounds investigated have local anesthetic activity in case of conduction anesthesia. The efficacy of the analgetic action of the aminoalcohols was found to be higher than that of the corresponding aminoketones. The hydrochlorides of IIIc and IIIb, having in the amine moiety piperidine and morpholine, correspond in activity with novocain, but are inferior to trimecaine and lidocaine (Table 3). Morpholine-containing aminoalcohol IIIb is also favorably distinguished by much lower toxicity. The advantage of the fluoro-containing aminoalcohols lies also in the fact that the corresponding β-aminoketones display strong local-irritating action (occurrence of a necrosis zone with a diameter of 10-12 mm was observed), while the aminoalcohols either do not display such an action or

TABLE 5. Duration of the Local Anesthetic Action of the Hydrochloride of Aminoalcohol IIIb in Case of Infiltration Anesthesia (guinea pigs)

Compound	Average effective time, in minutes			
	0,2 % solution	relative to novocain, %	0,5 % solution	relative to novocain, %
Novocaine	10 (8,0—12,6)	100	42 (33,6—51,8)	100
Lidocaine	59,5 (49,5—71,4)	595	98 (81,1—107,8)	233
Trimecaine	35 (29,0—42,2)	350	102 (82,1—125,8)	243
IIIb	38 (30,9—46,7)	380	86 (72,3—102,3)*	205

Note. The significant difference with the action of novocain is marked with an asterisk. The action of the compound at each concentration was tested with 2 animals in 6 areas.

only hyperemia is observed. Weak surface anesthesia is shown by the hydrochlorides of aminoketones IId and IIb (32 and 55.8 Régnier units, respectively). Investigations of the analgetic and the antagonistic action to opioids showed that the compounds investigated do not have these properties.

The data shown in Table 3 allow one to conclude that the hydrochlorides of aminoalcohols IIIb and IIIc causing conduction anesthesia corresponding with that of novocain, have a relatively low toxicity, and do not cause necrosis. The hydrochloride of aminoalcohol IIIb, being the most active and least toxic, was selected for further investigations.

A major factor of the characteristics of analgetics with peripheral action is the duration of the local anesthetic action (Table 4). The results obtained show that the hydrochloride of aminoalcohol IIIb surpasses novocain in this respect but is inferior to trimecain and lidocaine; using it as a 1% solution together with a 0.05% solution of adrenaline prolongs the local anesthetic action 1.4 times.

The results of the experiments that were obtained in case of infiltration anesthesia (Table 5) give evidence that compound IIIb as 0.2 and 0.5% solutions of its hydrochloride with respect to the duration of the anesthetic action surpass novocain by 3.8 and 2.05 times, respectively, and as 0.2% solution is not inferior to trimecaine.

On determining the specific gravity of 1 and 3% solutions of the hydrochloride of IIIb and of the control preparations, we have noted much lower values compared with the specific gravity of the cerebrospinal fluid of the rabbit; to compensate these, the local anesthetic agents were prepared with a 5% glucose solution.

The results obtained in studying the cerebrospinal anesthesia are evidence that compound IIIb as a 3% solution induces a local anesthetic effect more rapidly than trimecaine and novocain. With respect to duration and intensity of the action it does not surpass the preparations mentioned.

According to the data obtained with isolated frog nerves it must be noted that the change in the active reaction of the agent has an effect on both the speed of onset of the local anesthesia and on its strength. The blocking effects of compound IIIb and the well-known preparations selected for comparison increase with increasing pH of the medium. Thus, if at pH 3.0 their activity in the 25th minute is 20-30%, then at pH 7.0 and 9.0 the activity increases to 85-100% at the same time. Probably advantageous conditions are thereby created for passing of the compounds through memebranes, which governs their local anesthetic action. The effect of the compounds depends on the degree of their ionization. Compound IIIb has a pK_α of 7.21; for novocain, trimecaine, and lidocaine the pK_α values are 8.79, 8.29, and 8.15, respectively. The opinion prevails that pharmacological agents with a high pK_α value are the least diffusing at normal pH and have the least degree of solubility in lipids and of binding with plasma proteins, which explaines the short duration of their action [14, 15, 18].

A characteristic property of biologically active compounds having membranotropic activity is their ability to be absorbed on the cell membrane and to penetrate into the membrane. The results of our experiments show that compound IIIb, just as the preparations taken for comparison, have surface activity at the interfaces of the phases anesthetic-air and anesthetic-benzene. We have found that the surface activity of compound IIIb ($27.9 \cdot 10^{-3}$ N/m at pH 5.0 and $24.5 \cdot 10^{-3}$ N/m at pH 7.0 at a concentration of 0.2 mole/liter) corresponds with the values for novocain ($26.2 \cdot 10^{-3}$ N/m at pH 5.0 and $22.7 \cdot 10^{-3}$ N/m at pH 7.0 at a concentration of 0.2 mole/liter), which points to a relationship of this preparation and the biological activity of them.

Thus, the results of our experiments points to the capacity of the compounds investigated to evoke local anesthesia in case of conduction anesthesia. The hydrochloride of aminoalcohol IIIb is not inferior to novocain with respect to its local anesthetic effectiveness, but is less active than the other widely used preparations, trimecaine and lidocaine. It is known that the majority of aminoketones with a halogen atom at the para position of the aromatic fragment display local-irritating activity as a side effect [11]. Comparative investigation of this effect in the compounds studied showed that there is a relationship between the expression of the local-irritating activity and the chemical structure of the compound. Thus, reduction of the aminoketones to the corresponding aminoalcohols decreases the local toxicity and does not lower the local anesthetic activity of these compounds. This creates a prerequisite for directed search for effective agents with peripheric anesthetic action among halogen-containing aminoalcohols.

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