SYNTHESIS AND LOCAL ANESTHETIC ACTIVITY OF ENAMIDES AND AMIDES OF 3-[ALKYL(ARYL)AMINO]TROPANE

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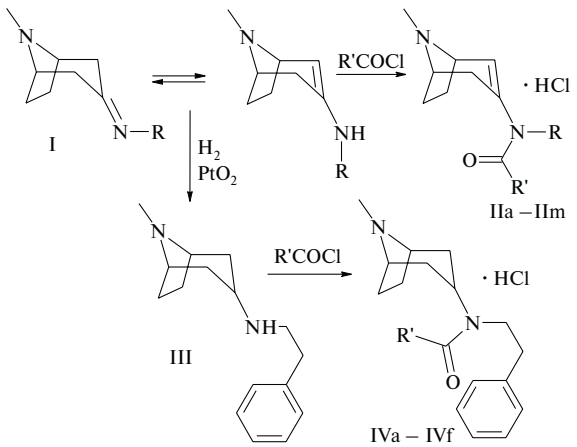
Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 34, No. 12, pp. 8 – 10, December, 2000.

Original article submitted December 2, 1999.

We know that local anesthetic activity of acetomesidides containing a tropane moiety depends on the presence of a double bond in their structure [1].

We showed earlier that the enamine form of tropane Schiff's bases (I) reacts with acid chlorides to form enamides (II) [2]. In order to determine the effect of the double bond, i.e., to compare the local anesthetic activity of enamides and amides, in the preceding paper we synthesized and studied enamides and amides of 3-butylaminotropane. We have shown that the enamides are the most active in infiltration anesthesia, while tropane amides are more active in conduction and surface anesthesia [3]. In continuing work searching for effective local anesthetic compounds among the enamides and amides of 3-[alkyl(aryl)amino]tropanes, we synthesized the enamides IIa – IIm and the amides IVa – IVf, obtained by acylation of respectively the Schiff's base I and phenylethylaminotropane (III) under conditions similar to those used in the preceding paper [3]:



IIa – IIf: R=$(CH_2)_2C_6H_5$; a, R′ = C_6H_5; b, R′ = *p*-F–C_6H_4;
c, R′ = *p*-Cl– C_6H_4; d, R′ = 3,4,5-$(CH_3O)_3C_6H_2$; e, R′ = 3,5-$(CH_3)_2C_6H_3$;
f, R′ = C_6H_4-C_6H_5-*p*;
II g: R = C_6H_5, R′ = C_6H_5; IIh – IIk: R = *p*-CH_3O–C_6H_4; h, R′=C_6H_5;
i, R′ = *p*-F–C_6H_4; j, R′=p-Cl-C_6H_4; k, R′=$Cu(OH)_2$=$Cu(OH)_2$–C_6H_5;
II l: R = 3,4-$(CH_3O)_2C_6H_3$, R′ = *p*-Cl–C_6H_4; II m: R = p-$CH_3OC_6H_4$,
R′ = $Cu(OH)_2$ = $Cu(OH)_2$–C_6H_3-3,4-$(CH_3O)_2$;
IV: a, R′ = C_6H_5; b, R′ = *p*-F–C_6H_4; c, R′ = *p*-Cl–C_6H_4;
d, R′ = 3,4,5-$(CH_3O)_3C_6H_2$; e, R′ = 3,5-$(CH_3)_2C_6H_3$; f, R′ = C_6H_4–C_6H_5-*p*.

The final compounds were obtained in good yields, but an attempt to increase the yield of the starting imines I (where R = C_6H_5 and 3,4-$(CH_3O)_2C_6H_3$) using *p*-toluenesulfonic acid or HCl as the catalyst is not successful (in the case of *p*-toluenesulfonic acid) or leads to even more tar formation and a decrease in yield (in the HCl case).

Hydrogenation of phenylethyliminotropane to 3-(β-phenylethylamino)tropane (III) was conducted under the conditions suggested in [4, 5]: room temperature, PtO_2 catalyst.

All the amides and enamides were obtained in the form of the hydrochlorides as a result of binding of the HCl liberated from the reaction by the tertiary amino group of the tropane ring. The experimental results and the spectral characteristics of compounds IIa – IIm and IVa – IVf are given in Table 1; their structure is supported by the presence of a signal from the methine proton (δ 5.4 – 5.8 ppm) in the PMR spectra of the enamides II and the lack of such a signal in the spectra of the amides IV.

We have established that compounds IIa – IIm and to a lesser degree compounds IVa – IVf have local anesthetic action (Table 2 – 4).

Compounds IIa and IIc proved to be most active for different types of anesthesia. Compound IIa induces a more prolonged conduction and infiltration anesthesia than Trimecaine; this compound is twice as active as cocaine for surface anesthesia.

The strength of compound IIc for surface anesthesia is comparable with the strength of compound IIa, and for conduction anesthesia it is comparable with Trimecaine. This compound is 1.6 times more active than Novocain for infiltration anesthesia.

The other compounds in this series are less active. The efficacy of compounds IIb, IIe, IIf and IVb, c for surface anesthesia is close to that of cocaine. For infiltration anesthesia,

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TABLE 1. Physicochemical Properties of Compounds IIa – IIm and IVa – IVf

Compound	Empirical formula	m.p., °C	Chemical shifts, δ, ppm					Yield, %
			$N–CH_3$	CH_2	CH (1H, 5H)	=CH	Ar	
IIa	$C_{23}H_{26}N_2O \cdot Cl$	251 – 253	2.7 s	1.3 – 3.9 m	3.9 – 4.0 m	5.4 – 5.7 m	7.2 – 7.5 m	93
IIb	$C_{23}H_{25}N_2OF \cdot HCl$	232 – 234	2.75 s	1.35 – 3.9 m	3.9 – 4.05 m	5.4 – 5.75 m	7.1 – 7.55 m	53
IIc	$C_{23}H_{25}N_2OCl \cdot HCl$	226 – 227	2.75 s	1.35 – 3.9 m	3.9 – 4.05 m	5.4 – 5.7 m	7.2 – 7.5 m	65
IId	$C_{26}H_{32}N_2O_4 \cdot HCl \cdot 0.25H_2O$	187 – 189	2.7 s	1.35 – 3.8 m	3.8 – 4.0 m	5.4 – 5.7 m	7.2 – 7.5 m	45
IIe	$C_{25}H_{30}N_2O \cdot HCl$	216	2.7 s	1.3 – 3.8 m	3.9 – 4.05 m	5.5 – 5.75 m	7.2 – 7.55 m	61
IIf	$C_{29}H_{30}N_2O \cdot HCl \cdot H_2O$	134 – 136	2.75 s	1.4 – 3.9 m	3.8 – 4.0 m	5.4 – 5.7 m	7.1 – 7.5 m	53
IIg	$C_{21}H_{22}N_2O \cdot HCl$	232 – 234 subl.	2.5 s	1.5 – 3.0 m	3.75 m	5.5 – 5.75 m	7.0 – 7.4 m	40
IIh	$C_{22}H_{24}N_2O_2 \cdot HCl$	213 – 214.5	2.55 s	1.5 – 3.5 m	3.7 m	5.5 – 5.75 m	7.1 – 7.5 m	60
IIi	$C_{22}H_{23}N_2O_2F \cdot HCl$	202 – 203	2.5 s	1.5 – 3.5 m	3.7 m	5.4 – 5.75 m	7.2 – 7.5 m	68
IIj	$C_{22}H_{23}N_2O_2Cl \cdot HCl$	208 – 209	2.55 s	1.5 – 3.0 m	3.75 m	5.45 – 5.7 m	7.0 – 7.5 m	63
IIk	$C_{24}H_{26}N_2O_2 \cdot HCl$	188 – 189	2.55 s	1.45 – 3.5 m	3.75 m	5.5 – 5.7 m	7.2 – 7.5 m	50
IIl	$C_{23}H_{25}N_2O_3Cl \cdot HCl$	230 subl.	2.5 s	1.5 – 3.0 m	3.75 m	5.4 – 5.75 m	7.1 – 7.5 m	52
IIm	$C_{26}H_{30}N_2O_4 \cdot HCl$	204 – 206	2.6 s	1.55 – 3.0 m	3.75 – 4.0 m	5.4 – 5.65 m	6.6 – 7.1 m	56
IVa	$C_{23}H_{28}N_2O \cdot HCl \cdot 0.5H_2O$	168 – 171	2.7 s	1.8 – 3.0 m	3.95 m	–	7.0 – 7.4 m	43
IVb	$C_{23}H_{27}N_2OF \cdot HCl$	175 – 177	2.75 s	1.9 – 3.6 m	3.9 m	–	6.9 – 7.5 m	73
IVc	$C_{23}H_{27}N_2OCl \cdot HCl \cdot H_2O$	184 – 186	2.75 s	1.9 – 3.6 m	3.95 m	–	6.9 – 7.55 m	61
IVd	$C_{26}H_{34}N_2O_4 \cdot HCl \cdot 0.5H_2O$	147 – 149	2.7 s	1.8 – 3.0 m	3.7 – 4.0 m	–	6.5 – 7.4 m	64
IVe	$C_{25}H_{32}N_2O \cdot HCl$	205 – 207	2.75 s	1.9 – 3.6 m	3.9 m	–	7.0 – 7.5 m	50
IVf	$C_{29}H_{32}N_2O \cdot HCl$	237	2.7 s	1.8 – 3.6 m	3.95 m	–	7.1 – 7.5 m	64

TABLE 2. Activity of Compounds IIa, IIc, IId, IIe, IIf and IVa, IVb, IVc, IVe, IVf in Conduction Anesthesia According to the Tailflick Test

Compound	"Depth" of anesthesia (in %)[1,2] after:			
	5 min	15 min	30 min	60 min
IIa	100.0	100.0	100.0	100.0
IVa	42.0	50.0	43.0	42.0
IVb	27.0	27.0	30.0	44.0
IIc	30.0	100.0	100.0	27.0
IVd	28.0	44.0	46.0	46.0
IIe	51.0	54.0	60.0	49.0
IVe	27.0	32.0	48.0	30.0
IIf	40.0	55.0	45.0	44.0
IVf	25.0	50.0	50.0	33.5
IId	59.7	42.0	67.0	46.0
Novocain	28.0	30.0	30.0	24.0
Trimecaine	100.0	100.0	100.0	30.0

Note: [1] averaged data from 6 trials for 2% solution; [2] increase in threshold by a factor of four is taken as 100%.

TABLE 3. Activity of Compounds IIa, IIc,IId, IIe,IIf and IVa, IVb, IVc, IVe, IVf for Infiltration Anesthesia According to the Tailflick Test in Mice

Compound	"Depth" of anesthesia (in %)[1,2] after:			
	5 min	15 min	30 min	60 min
IIa	100.0	100.0	100.0	100.0
IVa	67.0	61.0	100.0	50.0
IVb	27.0	27.0	29.0	45.0
IIc	50.0	61.0	52.0	25.0
IVc	29.0	44.0	48.0	45.0
IIe	56.0	53.0	63.0	48.0
IVe	25.0	44.0	51.0	30.0
IIf	40.0	50.0	46.0	46.0
IVf	25.0	47.5	50.0	32.5
IId	60.0,	64.0	57.0	42.0
Novocain	35.0	34.5	32.0	29.0
Trimecaine	72.5	100.0	87.2	40.0

Note: [1] averaged data from 6 trials for 2% solution; [2] increase in threshold by a factor of four is taken as 100%.

compounds IId, e, f and IVa, c, e, f are somewhat more active than Novocain.

The activity of compounds IIg – IIm (difficultly soluble in water) is no different than the activity of Novocain for conduction and infiltration anesthesia; only compounds IIj and IIk are active for surface anesthesia (IIj approaches the effect of cocaine; IIk is somewhat more active).

Compounds IIb and IVd were not studied in the above-indicated tests (conduction and infiltration anesthesia), since in the test concentrations compound IIb induces convulsions in the animals, while compound IVd precipitates.

Among the studied compounds (1% and 2% solutions) compounds IVa, b, d and IIe have a weak local irritant effect when instilled into the conjunctival sacs of rabbits.

TABLE 4. Activity in Surface Anesthesia in Rabbits and Acute Toxicity in Mice for Compounds IIa – IVf and IVa – IVf

Compound	Regnier index	LD_{50} (mg/kg intraperitoneally)
IIa	1185.5 ± 29.5	70.0 ± 2.6
IVa	16.0 ± 2.9	140.0 ± 6.6
IIb	426.5 ± 13.1	85.6 ± 4.4
IVb	511.0 ± 9.1	280.0 ± 10.1
IIc	1024.3 ± 4.8	90.0 ± 2.7
IVc	407.5 ± 10.1	200.7 ± 2.6
IId	13.0 ± 0.0	246.0 ± 3.0
IVd	13.0 ± 0.0	375.0 ± 11.4
IIe	415.5 ± 14.5	80.7 ± 3.2
IVe	13.0 ± 0.0	180.0 ± 8.2
IIf	598.5 ± 2.2	120.7 ± 2.6
IVf	13.0 ± 0.0	180.9 ± 3.5
Dicain	1300.0 ± 0.0	26.0 ± 2.2
Pyromecaine	1300.0 ± 0.0	190.0 ± 8.4
Cocaine	590.0 ± 16.0	80.0 ± 5.3

Note: averaged data for 8 trials with standard error of the mean for 1% solutions.

In experiments on mice, we established that compounds IIa-m and IVa – IVf display weak analgesic activity compared with the action of morphine (3 mg/kg subcutaneously). They are able to temporarily increase the pain sensitivity threshold of the animals by only 20 – 60%.

Thus the results obtained allow us to conclude that compounds IIa – IIm and IVa-f have local anesthetic activity. Compounds IIa – IIm, containing a double bond in the tropane ring, have higher activity than analogs with a single bond (compounds IVa – IVf) and also previously synthesized acetomesidides [1] and tropane 3-N-butyleneamides [3].

EXPERIMENTAL CHEMICAL PART

The PMR spectra were taken on a Bruker A-250 spectrometer, solvent CD_3OD, internal standard HMDS. The IR spectra of the compounds were recorded on a Perkin-Elmer 580 in KBr. GLC analysis of all the products was performed on a Tsvet-152 chromatograph (column of length 0.7 m, diameter 3 mm, liquid phase SE-30/5% on Chromaton N-AW 0.16 – 0.20 mm), carrier gas nitrogen, temperature programming 75 – 300°C/20°C per minute. The melting point was determined on a Boetius hot stage.

3-(β-Phenylethylamino)tropane (III).

1.5 g PtO_2 was added to a solution of 25 g phenylethyliminotropane in 100 ml ethanol and this was hydrogenated at atmospheric pressure. After distillation, we obtained 21.5 g III, yield 85.3%, b.p. 142 – 143°C/1 mm.

3-(3,4-Dimethoxyphenylimino)tropane [I, R = 3,4-$(MeO)_2C_6H_3$].

2.5 g (0.016 mole) 3,4-dimethoxyaniline was added to 11.4 g (0.08 mole) tropinone in 100 ml toluene. The reaction mixture was boiled for 3 days. After distillation, we obtained 3.45 g product, yield 15.3%, b.p. 190 – 194°C/2 mm.

The remaining tropanone Schiff's bases were obtained earlier in [2].

The calculated elemental analysis data correspond to the found values for all the compounds obtained.

EXPERIMENTAL PHARMACOLOGICAL PART

We determined the capacity of the compounds to induce surface anesthesia by the Regnier method on the cornea of rabbits' eyes (1% solution), and we determined their capacity to induce infiltration and conduction anesthesia on mice using the "tailflick" test (2% solution) [6]. The compounds were injected in a volume of 0.05 ml subcutaneously into the tail of the mice using a microinjector. We recorded the tailflick latency period upon thermal stimulation directly at the site of injection of the compounds (to assess the level of infiltration anesthesia) or at a site below injection of the compounds, at the tip of the tail (to assess the level of conduction anesthesia).

We studied the analgesic action on mice (in a dose that was 1/10 of LD_{50}) using the following tests: tailflick test on the Analgesia Test device (Kern, FRG); hot-plate test (55°C) [7] and tail pressure test (Randell Selitto) on an Ugo Basile (Italy) analgesimeter [8].

The acute toxicity was determined in mice by Behren's method; the local irritant effect was determined on rabbits by the Setnicar method (1% and 2% solutions) [6].

As the reference drugs, we used cocaine, Dicain, and Pyromecaine for surface anesthesia; Novocain and Trimecaine for conduction and infiltration anesthesia; and morphine for studying the analgesic activity.

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