SYNTHESIS OF 2-(3,3-DIMETHYL-3,4-DIHYDROISOQUINOL-1-YL)PROPANOIC ACID AMIDES AND THEIR INFLUENCE ON BLOOD COAGULATION

E. S. Limanskii,[1] N. N. Polygalova,[1] B. Ya. Syropyatov,[1] A. G. Mikhailovskii,[1] and M. I. Vakhrin[1]

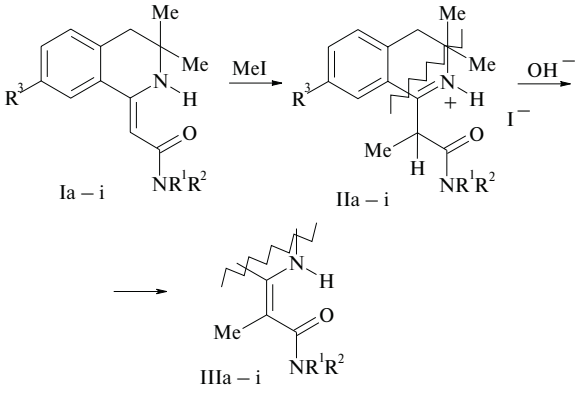
Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 43, No. 2, pp. 20 – 22, February, 2009.

Original article submitted November 1, 2007.

A series of new 2-(3,3-dimethyl-3,4-dihydroisoquinol-1-yl)propanoic acid amides have been synthesized using the reaction of methyliodide with 2-(3,3-dimethyl-1,2,3,4-tetrahydroisoquinolin-1-idene)ethanamides that proceeds on the β-atom of the enamine fragment to form iodides of 2-(isoquinol-1-yl)propanoic acid derivatives. Investigation of the influence of the synthesized compounds on blood coagulation showed that all of them are hemostatics. The most active compounds possess radicals such as morpholine and 2-(3,4-dimethoxyphenyl)ethylamine, are not substituted at the amide fragment, and decrease the blood coagulation time by 14 – 16%.

Key words: 2-(3,3-dimethyl-1,2,3,4-tetrahydroisoquinolin-1-idene)ethanamides, iodomethylation, 2-(3,3-dimethyl-3,4-dihydroisoquinol-1-yl)propanoic acid amides, influence on blood coagulation, hemostatics, acceleration of blood coagulation time by 14 – 16%

Amides of 1-isoquinolylcarboxylic acids have previously been prepared and studied for anti-aggregation activity with respect to thrombocytes [1 – 4]. The direct effect of these compounds on blood coagulation has not yet been investigated. The goal of our work was to find the relationship between the structure and direct effect on blood coagulation in a series of 2-(3,3-dimethyl-3,4-dihydroisoquinol-1-yl)propanoic acid amides.



Isoquinoline derivatives **IIa-i** were synthesized by iodomethylation of the corresponding enaminoamides **Ia-i** [5]. The studies showed that methylation occurs at the β-C atom of the enamine group. The reaction is carried out by refluxing in isopropanol. Analogous data were obtained earier for the corresponding enaminoesters [6].

Salts **IIa-i** were converted to bases **IIIa-i**, which had the enamine structure, by treatment with base solution.

The iodide salts **IIa-i** are yellow crystalline compounds (Table 1).

Use of ethyliodide and propyliodide as the alkylating agents gave the starting materials.

The structures of the products were confirmed by PMR spectra (Table 2). Spectra of hydroiodides **IIa-i** contained a doublet for the methyl at 4.95 – 6.03 ppm, which indicated that the alkylation occurred at the β-enamine C atom. A comparison of the chemical shifts of the CH quadruplets of various amides showed that they depended on the nature of the substituents on the amide N atom. The largest shift (4.95 – 5.28 ppm) was observed in spectra of *N*,*N*-dialkylated amides (**IIa**, **-c**, **-i**). This reflects the donor effect of the alkyl groups. The singlet for the proton of the salt form of the N atom was located at 10.82 – 12.75 ppm. Spectra of bases **IIIa-i** that were prepared by treatment of the iodides

[1] Perm State Pharmaceutical Academy, Perm, Russia.

TABLE 1. Properties of Synthesized Compounds

Compound	*NR^1R^2	Empirical formula	mp, °C	Yield, %
IIa	pyrrolidin-1-yl-	$C_{18}H_{24}N_2O \cdot HI$	142 – 143	63
IIb	4-methylphenylamino-	$C_{21}H_{24}N_2O \cdot HI$	92 – 94	70
IIc	morpholin-4-yl-	$C_{18}H_{24}N_2O_2 \cdot HI$	102 – 104	47
IId	methylamino-	$C_{15}H_{20}N_2O \cdot HI$	172 – 173	89
IIe	2,4-dimethylphenyl-	$C_{22}H_{26}N_2O \cdot HI$	122 – 124	43
IIf	2-(3,4-dimethoxyphenyl)ethylamino-	$C_{24}H_{30}N_2O_3 \cdot HI$	102 – 104	93
IIg	NH_2	$C_{14}H_{18}N_2O \cdot HI$	92 – 94	89
IIh	2,4,6-trimethylphenyl-	$C_{23}H_{28}N_2O \cdot HI$	120 – 122	57
IIi	azepan-1-yl-	$C_{21}H_{30}N_2O \cdot HI$	180 – 182	56

* R_3 = Me (**IIi**); H (all others).

TABLE 2. PMR Spectra of Synthesized Compounds

Compound	$(Me)_2$, s	4-CH_2, s	Ar, m	$C\underline{H}_3$-CH, d	CH_3-$C\underline{H}$, q	NR_1R_2 protons etc.	NH^+, c
IIa	1.57	3.08	7.10 – 7.56 (4H)	1.64	5.05	1.81 – 1.95 m (4H, $2CH_2$-C),, 3.53 – 3.84 m (4H, $2CH_2$-N)	12.40
IIb	1.58	3.07	6.99 – 7.69 (8H)	1.69	5.82	2.30 s (CH_3-Ar), 8.55 c (NH)	10.62
IIc	1.50	3.10	7.42 – 7.88 (4H)	1.57	4.95	7.42 – 7.88 m (8H, $4CH_2$)	12.27
IId	1.41	3.07	7.01 – 7.71 (4H)	1.63	5.78	5.10 s (NH), 2.85 d (3H, $NHC\underline{H}_3$)	12.31
IIe	1.58	3.03	6.91 – 7.60 (7H)	1.71	6.03	8.32 s (NH), 2.30 c (6H, $2CH_3$-Ar)	10.82
IIf	1.56	3.07	6.62 – 7.90 (7H)	1.65	5.30	9.0 s (NH), 3.10 m ($CC\underline{H}_2CH_2N$),, 3.35 m ($CCH_2C\underline{H}_2N$), 3.74 c, 3.78 s (2MeO)	12.57
IIg	1.65	3.10	7.19 – 7.67 (4H)	1.73	5.85	8.03 s (NH_2)	12.75
IIh	1.54	3.09	7.0 – 7.74(6H)	1.80	6.01	8.6 s (NH), 2.40 c (9H, $3CH_3$-Ar)	12.53
IIi	1.53	3.08	7.08 – 7.36 (3H)	1.81	5.28	1.82 – 1.97 m (4H, $3CH_2$-C), 3.54 – 3.87 m (4H, $2CH_2$-N), 2.40 c (3H, 7-CH_3)	12.53

with ammonia solution (25%) corresponded to the enamine structure. They contained singlets for the methyl at about 2.5 ppm and a singlet for the chelated proton of the ring NH at 10.5 – 11.2 ppm. This corresponded to the *Z*-configuration of an enaminoamide involved in an intramolecular H-bond (IMHB).

IR spectra of iodides **IIa-i** in mineral oil contained absorption bands for C=O groups (1690 – 1700 cm^{-1}). Spectra of the bases of these compounds in $CHCl_3$ solution (0.01 M) showed absorption bands for chelated C=O (1620 cm^{-1}) and NH (3100 – 3120) groups. This proved the structure of the enaminoamide.

Thus, amides **IIa-i** exist in the imino (azomethine) form. The bases of these compounds have the enaminoamide structure, for which the *Z*-configuration stabilized by an IMHB is typical.

EXPERIMENTAL CHEMICAL PART

IR spectra were recorded on a Specord M-80 spectrometer; PMR spectra in DMSO-d_6 (amides **IIc**, **-f**, **-i**) and $CDCl_3$ (all others), on a Tesla BS-567A (100 MHz) instrument with HMDS internal standard (0.05 ppm vs. TMS).

All salts were recrystallized from isopropanol. Elemental analyses (C, H, N) agreed with those calculated.

2-(3,3-Dimethyl-7-R^3-3,4-dihydroisoquinol-1-yl)propanoic acid amides (IIa-i). A mixture of the appropriate amide (0.01 mol, **Ia-i**) and methyliodide (0.92 mL, 0.015 mol) in isopropanol (20 mL) was refluxed for 2 h and cooled to 20°C. The precipitated iodide was filtered off, dried, and recrystallized.

EXPERIMENTAL PHARMACOLOGICAL PART

Pharmacological studies were performed using a Minilab 701 coagulometer. The studies used citrated (3.8%) canine blood (9:1). The influence of the compounds on blood coagulation was studied at a single concentration (1 mg/mL of blood). The standards of anticoagulant activity were solutions of heparin (1 U/mL) and papaverine hydrochloride (1 mg/mL); the standard of procoagulant activity,

TABLE 3. Influence of **IIa-i** on Blood Coagulation

Compound	NR^1R^2	Coagulation time, s		% change of coagulation	*P*
		control	experimental		
IIa	pyrrolidine	47.3 ± 1.89	37.9 ± 2.10	– 0.2	> 0.05
IIb	*p*-toluidine	40.1 ± 1.89	37.9 ± 2.10	+5.5	> 0.05
IIc	morpholine	40.3 ± 1.49	33.8 ± 1.36	+16.1	< 0.05
IId	methylamine	47.0 ± 2.57	43.5 ± 1.19	+7.4	> 0.05
IIe	2,4-xylidine	47.2 ± 1.91	47.3 ± 2.74	– 0.2	> 0.05
IIf	2-(3,4-dimethoxyphenyl)ethylamine	50.6 ± 2.33	43.5 ± 1.64	+14.0	< 0.01
IIg	NH_2	44.0 ± 2.30	37.3 ± 1.40	+15.2	< 0.001
IIh	2,4,6-trimethylaniline	51.8 ± 3.29	48.5 ± 2.83	+6.4	> 0.02
IIi	hexamethylenimine	48.7 ± 2.27	47.0 ± 1.54	+3.5	> 0.05
Heparin	–	29.9 ± 0.48	36.6 ± 1.82	– 22.4	< 0.01
Papaverine	–	40.9 ± 3.12	47.8 ± 3.17	– 16.8	< 0.05
Ethamsylate	–	28.9 ± 1.11	24.5 ± 0.94	+15.2	< 0.01

ethamsylate (1 mg/mL). Each compound was tested seven times.

Results were processed statistically using the Student t-criterion. Results were considered reliable for $p < 0.05$.

TABLE 3 shows that most of the studied compounds (except **IIa** and **-e**) exhibited procoagulant activity. The most active compounds were **IIc**, **-f**, and **-g** with influences comparable to that of ethamsylate.

REFERENCES

1. A. G. Mikhailovskii, B. Ya. Syropyatov, V. S. Shklyaev, et al., *Khim.-farm. Zh.*, **32**(8), 21 – 23 (1998).
2. A. G. Mikhailovskii, A. V. Dolzhenko, B. Ya. Syropyatov, et al., *Khim.-farm. Zh.*, **36**(6), 8 – 10 (2002).
3. A. G. Mikhailovskii, B. Ya. Syropyatov, A. V. Dolzhenko, and M. I. Vakhrin, *Nitrogen-containing Heterocycles and Alkaloids*, Iridium Press, Moscow (2001), Vol. 1, pp. 393 – 397.
4. N. N. Polygalova, A. G. Mikhailovskii, E. S. Limanskii, et al., *Chemistry and Biological Activity of Synthetic and Natural Compounds: Nitrogen-containing Heterocycles*, ICSPF, Moscow (2006), Vol. 2, p. 199.
5. V. S. Shklyaev, B. B. Aleksandrov, A. G. Mikhailovskii, and M. I. Vakhrin, *Khim. Geterotsikl. Soedin.*, 9, 1239 – 1242 (1989).
6. B. B. Aleksandrov, M. S. Gavrilov, M. I. Vakhrin, and V. S. Shklyaev, *Khim. Geterotsikl. Soedin.*, 6, 794 – 797 (1985).