SYNTHESIS AND STUDY OF ANTIINFLAMMATORY AND ANALGESIC ACTIVITY OF 1-HYDRAZINO-3,3-DIALKYL-3,4-DIHYDROISOQUINOLINE DERIVATIVES

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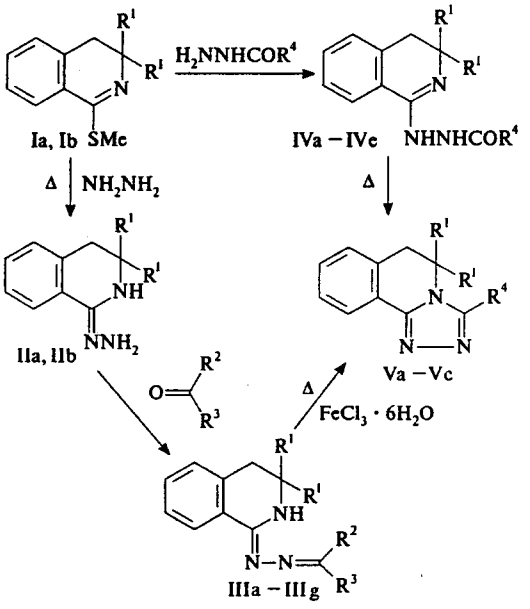
As is known, the class of 3,4-dihydroisoquinoline derivatives exhibits a broad spectrum of pharmacological activity [1 – 4], including compounds producing spasmolytic [5], antiarrhythmic and antiaggregative [6], and hypotensive effects [7]. Acid hydrazides and hydrazones of carbonyl compounds constitute another class of substances offering a broad spectrum of biological activity. Therefore, it would be of interest to study the compounds whose molecules include pharmacophore groups belonging to both classes.

For this study we have selected a previously described compound, 1-hydrazono-3,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (IIa) [8], and 1-hydrazono-3,3-tetramethylene-1,2,3,4-tetrahydroisoquinoline (IIb) synthesized by a similar procedure. According to [9], these compounds occur in the tautomer form of hydrazone. The conversions were carried out in accordance with the following scheme:



Ia, IIa: R^1 = Me;
Ib, IIb: $R^1 + R^1 = -(CH_2)_4-$;
IIIa: R^1 = Me, R^2 = Ph, R^3 = H;
IIIb: R^1 = Me, R^2 = 2-C_6H_4OH, R^3 = H;
IIIc: R^1 = Me, R^2 = 2-furyl, R^3 = H;
IIId: R^1 = Me, R^2 = 4-pyridyl, R^3 = H;
IIIe: R^1 = Me, R^2 = 3-methyl-5-oxo-1-phenylpyrazolin-4-yl, R^3 = H;
IIIf: R^1 = Me, $C(R^2,R^3)$ = 5-bromo-2-oxoindolin-3-ilidene;
IIIg: R^1 = Me, R^2 = 6-methyl-2,4-dioxo-3,4-dihydro-2H-pyran-3-yl, R^3 = Me;
IVa: R^1 = Me, R^4 = Et;
IVb: R^1 = Me, R^4 = Ph;
IVc: R^1 = Me, R^4 = 3,4,5-$C_6H_2(OMe)_3$;

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TABLE 1. Yields and Melting Temperatures of Compounds I – V

Compound	Yield, %	M.p., °C	Empirical formula
Ib	76	*	$C_{14}H_{17}NS$
IIb	64	76 – 77	$C_{13}H_{17}N_3$
IIIa	72	229 – 230	$C_{18}H_{19}N_3 \cdot HCl$
IIIb	65	238 – 241	$C_{18}H_{19}N_3O \cdot HCl$
IIIc	85	220 – 222	$C_{16}H_{17}N_3O \cdot HCl$
IIId	64	178 – 180	$C_{17}H_{18}N_4$
IIIe	45	227 – 231	$C_{22}H_{23}N_5O \cdot HCl \cdot H_2O$
IIIf	31	287 – 288	$C_{19}H_{17}BrN_4O$
IIIg	81	204 – 207	$C_{19}H_{21}N_3O_3$
IVa	72	169 – 171	$C_{14}H_{19}N_3O$
IVb**	57	220 – 222	$C_{18}H_{19}N_3O$
IVc	78	204 – 206	$C_{21}H_{25}N_3O_4$
IVd	40	188 – 192	$C_{16}H_{16}BrN_3O_2$
IVe	72	199 – 201	$C_{18}H_{18}BrN_3O_2$
Va**	68	210 – 211	$C_{18}H_{17}N_3$
Vb	88	242 – 244	$C_{18}H_{17}N_3O$
Vc	92	169 – 171	$C_{18}H_{16}BrN_3O$

* B.p., 168 – 170°C (11 Torr).
** Described in [8].

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IVd: R^1 = Me, R^4 = 5-bromo-2-furil;
IVe: $R^1 + R^1 = -(CH_2)_4-$; R^4 = 5-bromo-2-furil;
Va: R^1 = Me, R^4 = Ph;
Vb: $R^1 + R^1 = -(CH_2)_4-$; R^4 = 2-furil;
Vc: $R^1 + R^1 = -(CH_2)_4-$; R^4 = 5-bromo-2-furil.

As expected, compounds IIa and IIb readily interact with carbonyl compounds on heating in 2-propanol. These reactions lead to the formation of mixed azines IIIa – IIIg that can be isolated both in the free state and in the form of hydrochloric acid salts. The ^{1}H NMR spectra of bases IIId – IIIf (in $CDCl_3$) contain a characteristic signal at 5.35 – 5.53 ppm attributed to NH protons of the ring, which is sharply displaced to weaker fields upon the salt formation (from 13.65 ppm for IIIb in DMSO-d_6 to 15.29 ppm for IIIc in $CDCl_3$). Note that signals from the second NH group are not observed in the 1H NMR spectra of salts because of a high proton exchange rate.

An interesting feature in chemical behavior of the above salts is their ability to form 1 : 1 crystallosolvates with isopropyl alcohol (compounds IIIa – IIIc, IIIe, IIIf). This property markedly facilitates the isolation and purification of these compounds. Subsequent crystallization from the mixture of acetone or ethyl acetate with chloroform (1 : 1) yields pure hydrochlorides. Data on the physicochemical properties of the synthesized compounds are presented in Table 1, and their spectroscopic parameters are listed in Table 2.

The reaction of hydrazine IIa with dehydracetic acid yields only a product formed as result of the nucleophilic attack at the exocyclic carbonyl group (IIIg). This result agrees with the previously described interaction of this acid with

TABLE 2. Spectral Characteristics of Compounds I – V

Compound	IR spectrum: ν, cm^{-1}						^{1}H NMR spectrum: δ, ppm			
	C=N	C=O	N–H	R^1	4-H_2	8-H	5,6,7-H isoquinoline	Other H_{arom}	N–H	Other protons
Ib	1620	–	–	1.62 m (8H)	2.67 s	7.20 m	7.08 – 7.14 m	–	–	2.33 s (SCH_3)
IIb	1630	–	3185, 3275, 3345	1.77 m (8H)	2.90 s	7.89 m	6.99 – 7.36 m	–	3.72 bs (2H, NH_2), 5.01 bs (1H, 2-NH)	–
IIIa · HCl	1620	–	3180, 3350	1.43 s (6H)	2.92 s	9.00 m	7.21 – 7.76 m (8H)		15.37 bs	9.54 s (CH=)
IIIb · HCl	1630	–	3270, 3170	1.36 s (6H)	3.00 s	9.20 m	6.65 – 7.75 m, (5H, 5.6.7.3',5'-H)	8.05 d (4'-H), 8.50 m (6'-H)	13.65 bs	9.40 s (CH=), 10.50 bs (OH)
IIIc · HCl	1630	–	3250	1.40 s (6H)	2.98 s	9.08 m	7.49 – 7.60 m (4H, 5.6.7.5'-H)	6.48 dd (4'-H), 6.90 d (3'-H)	15.29 bs	9.59 s (CH=)
IIId	1630	–	3260	1.28 s (6H)	2.85 s	8.17 m	7.05 – 7.39 m	7.55 dd (2H, 3',5'-H), 8.57 dd (2',6'-H)	6.62 bs	8.41 s (CH=)
IIId · HCl	1610	1630	3240	1.40 s (6H)	2.95 s	7.00 – 7.56 m (9H)			15.19 bs	9.65 s (CH=), 2.45 s (CH_3), 5.53 s (CH)
IIIf	1655	1690	3200 (bs)	1.29 s (6H)	2.96 s	7.85 m	7.20 – 7.60 m (4H, 5.6.7.6'-H)	6.75 dd (7'-H), 8.10 s (4'-H)	7.60 bs (2-NH), 10.69 s ((NH isatin))	–
IIIg	1640	1670	3300 (bs)	1.36 s (6H)	2.83 s	8.07 m	7.30 – 7.40 m	–	5.35 bs	2.82 s (6'-CH_3), 2.08 s (CH_3C=N), 5.66 s (CH=), 16.61 bs (1H, OH enol)
IVa	1630	1650	3200 – 3270	1.14 s (6H)	2.72 s	7.93 m	6.98 – 7.31 m	–	6.36 bs (β-NH), 9.61 bs (β-NH)	1.01 t (CH_3), 2.13 k (CH_2CO)
IVc	1605	1630	3170 (bs)	1.21 s (6H)	2.83 s	7.32 – 7.50 m (4H, 5.6.7.8-H)		7.20 d (2H, 2',6'–H)	5.83 s (b-NH), 7.20 s (α-NH)	3.81 s (9H, OCH_3)
IVd	1605	1640	3235 – 3320	1.17 s (6H)	2.76 s	7.01 – 7.39 m (4H, 5.6.7.8-H)		6.56 – 6.75 m (2H, 3',4'-H)	7.91 s (β-NH), 9.60 s (α-NH)	–
IVe	1620	1665	3375 (bs)	1.39 – 1.76 m (8H)	2.83 s	7.05 – 7.39 m (4H, 5.6.7.8-H)		6.60 – 6.83 m (3',4'-H)	7.88 s (β-NH), 10.13 s (α-NH)	–
Vb	1585	–	–	1.45 – 1.98 m (8H)	3.00 s	8.02 – 8.20 m	7.29 – 7.38 m	6.50 m (4'-H), 6.81 m (3'-H), 7.52 m (5'-H)	–	–
Vc	1600	–	–	1.57 – 2.05 m (8H)	3.03 s	8.08 – 8.19 m	7.23 – 7.39 m	6.44 d (4'-H), 6.82 d (3'-H)	–	–

* The ^{1}H NMR spectra of IIIb, IIIf, IVa, IVd, and IVe were measured in DMSO-d_6 and the other spectra, in $CDCl_3$.

amines [10] or 4-hydrazinoquinazoline [11], although the presence of a signal characteristic of the enolic hydroxy group (δ = 16.61 ppm) in the ^{1}H NMR spectrum suggests that compound IIIg may exist in a form (different from that observed for the 4-hydrazinoquinazoline) containing enolized carbonyl at C-4'. Apparently, this may be related to an energy gain achieved at the expense of increasing conjugation chain.

The reactions of thiolactim esters Ia and Ib with carboxylic acid hydrazides proceed both at room temperature (taking 1 – 3 days) and on boiling in methanol (0.5 h), leading to the formation of compounds IVa – IVe. Heating these compounds in *o*-dichlorobenzene or DMF for 1 – 2 h yields substituted triazolo[3, 4-a]isoquinolines Va – Vc [8]. In the case of compound Vb, the intermediate hydrazide exhibit spontaneous cyclization even at room temperature (1 – 3 days).

Compound Va (previously described in [8]) was obtained in this work by oxidation of compound IIIa in the presence of a five-fold excess of iron(III) chloride in boiling ethanol (see the experimental part below)

EXPERIMENTAL CHEMICAL PART

The IR spectra were measured on an UR-20 spectrophotometer (Germany) using samples prepared as nujol mulls. The ^{1}H NMR spectra were recorded on a Tesla BS-587A spectrometer (Czech Republic) operated at a working frequency of 80 MHz. The measurements were performed at 25°C using $CDCl_3$ or DMSO-d_6 as solvents and HMDS as an internal standard. The mass spectrum of compound IIIg was obtained using a Hitachi M-80 spectrometer (Japan) with direct introduction of the samples into the ion source operated at an electron impact energy of 70 eV. The course of the reactions was monitored and the purity of the synthesized compounds was checked by TLC on Silufol plates eluted with chloroform – acetone (9 : 1) mixture; the spots were developed by a 3% chloranyl solution in toluene.

TABLE 3. Antiinflammatory and Analgesic activity and Acute Toxicity Compounds V – XXVIII

Compound	Edema inhibition relative to control, %	Maximum defensive reflex duration, sec
IIIb	–	20.0*
IIIc	9.5	22.2*
IIId	12.3	25.0*
IIIe	11.5	22.8*
IIIf	17.5	21.0*
IIIg	14.5	21.2*
IVa	15.7	14.4
IVb	2.3	18.8
IVc	18.3	19.2*
IVd	26.5	16.0
IVe	49.2*	15.0
Vb	29.1	25.0*
Vc	–9.5	21.4*
Voltaren	64.1*	26.2*
Control (2% starch jelly, 1 ml / 100 g)		11.2

* Difference from control reliable for $p \leq 0.05$.

1-hydrazono-3,3-tetramethylene-1,2,3,4-tetrahydroisoquinoline (IIb) was synthesized using a modification of the method described in [8]. According to this modified procedure, a mixture of 2.31 g (10 mmole) of compound Ib and 1.5 g (30 mmole) of hydrazine hydrate in 30 ml of methanol was boiled for 3 h, after which methanol was distilled off. To the residue was added 20 ml of water and 20 ml of an ether – hexane (1 : 1) mixture. Upon shaking, the organic layer was separated and dried over $MgSO_4$. Finally, the solvents were distilled off and residue recrystallized from 25 ml hexane to obtain 1.37 g (64%) of compound IIb.

Mixed 3,3-dimethyl-3,4-dihydroisocarbostyryl and salicylaldehyde azine hydrochloride (IIIb). A mixture of 1.0 g (5.3 mmole) hydrazone IIa and 0.65 g (0.55 ml, 5.3 mmole) salicylaldehyde in 15 ml of 2-propanol was boiled for 1 h. Upon cooling, to this mixture was added 1.5 ml of concentrated HCl. The precipitated crystals of a IIIb · HCl · *i*-PrOH adduct were separated, dried, and recrystallized from ethyl acetate with chloroform addition. Yield of compound IIIb, 1.13 g (65%). Similar procedures were used to obtain hydrochlorides of compounds IIIa and IIIc. In the synthesis of IIIe, the primary adduct with 2-propanol precipitated from aqueous 2-propanol in the form of hydrate. At 25°C, bases IIIa – IIIc and IIIe have the form of oily substances.

Mixed 3,3-dimethyl-3,4-dihydroisocarbostyryl and pyridine-4-carbaldehyde azine (IIId). A mixture of 1.0 g (5.3 mmole) hydrazone IIa and 0.48 g (5.3 mmole) pyridine-4-carbaldehyde in 10 ml of 2-propanol was stirred for 1 h at 20°C. The precipitate was separated and recrystallized from 12 ml of 2-propanol. Yield of compound IIId, 0.93 g (64%).

Mixed 5-bromoisatin and pyridine-3,4-carbaldehyde azine (IIIf). A mixture of 1.00 g (5.3 mmole) hydrazone IIa and 1.20 g (5.3 mmole) 5-bromoisatin in a mixture of 20 ml 2-propanol and 20 ml DMF was boiled for 2 h. The precipitate was separated and recrystallized from 120 ml of toluene to obtain 0.65 g (31%) of compound IIIf in the form of an orange curdled precipitate; R_f 0.17 ($CHCl_3$ – acetone, 9 > 1, Silufol).

Mixed 3,3-dimethyl-3,4-dihydroisocarbostyryl and 3-acetyl-6-methyl-2,4-dioxo-1,2,3,4-tetrahydropyran (dehydracetic acid) azine (IIIg). A mixture of 1.89 g (10 mmole) hydrazone IIa and 1.85 g (11 mmole) dehydracetic acid in 20 ml of 2-propanol was boiled for 2 h. Upon cooling, the precipitate was separated and recrystallized from a 2-propanol – dioxane mixture to obtain 2.89 g (81%) of compound IIIg. Mass spectrum, m/z (I_{rel}, %): M^+ 339 (30), 282 (56), 255 (45), 198 (14), 166 (15), 158 (47), 144 (48), 125 (32), 116 (100), 102 (32). The most intense peak at m/z = 116 is due to the $C_9H_8^+$ ion formed from the isoquinoline part of the molecule.

β-(3,3-Dialkyl-3,4-dihydro-1-isoquinolyl)carboxylic acid hydrazides (IVa – IVe). To 11 mmole of 1-methylthio-

3,3-disubstituted 3,4-dihydroisoquinoline (Ia and Ib) in 25 ml methanol was added 10 mmole of the corresponding acid hydrazide. The mixture was boiled for 0.5 h and allowed to stand for 24 h. The precipitate was filtered, washed with methanol, and dried.

5,5-Dimethyl-3-phenyl-5,6-dihydro-1,2,4-triazolo[3,4-a]-isoquinoline (Va). To a solution of 0.5 g (1.6 mmole) of hydrochloride IIIa · HCl in 20 ml methanol was added 2.14 g (8 mmole) of $FeCl_3 \cdot 6H_2O$ and the mixture was boiled for 3 h. Upon cooling, 30 ml water was added and the mixture was alkalized with 5% NaOH to pH 8 and extracted with ether. The ether was distilled off and the residue recrystallized from ethanol to obtain 0.35 g (80%) of compound Va. Compound Va can be also obtained as described in [8] at a yield of 68%.

Compounds Vb and Vc were obtained from the corresponding hydrazides IV by boiling in *o*-dichlorobenzene as described in [8].

EXPERIMENTAL PHARMACOLOGICAL PART

The antiinflammatory activity of the synthesized compounds was studied on white rats weighing 150 – 170 g using a model of acute inflammatory edema initiated by 0.1-ml subplantar injections of 1% carrageenan solution into the hind paws of animals. The edema volume dynamics was monitored by oncometric techniques [12, 13].

The analgesic activity was studied on a group of white mongrel mice weighing 18 – 20 g using the "hot plate" test [14]. The compounds tested were introduced perorally at a dose of 50 mg / kg as suspensions in a 2% starch jelly [15]. The reference drug voltaren was introduced at a dose of 8 mg / kg. The results of our biological tests, processed by statistical methods, and the corresponding reliability parameters are listed in Table 3.

It was found that hydrazides IVa – IVc, containing the residues of an aliphatic or a substituted aromatic acid, possess no antiinflammatory properties. At the same time, the attachment of a 5-bromofuroyl radical (IVd, IVe) gives rise to certain antiinflammatory effect.

The cyclization of IVe with the formation of a triazolo[3, 4-a]isoquinoline (Vc) gives rise to moderate analgesic activity, but eliminates the antiinflammatory action.

Azines IIIa – IIIg possess no antiinflammatory activity, but produce a weak analgesic effect comparable to that of triazolo[3, 4-a]isoquinolines Vb and Vc.

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