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SYNTHESIS AND ANALGESIC, ANTHELMINTIC, AND INSECTICIDAL ACTIVITY OF 3,3-DIALKYL-1-(2-PHENYLAMINO-2-THIOXOETHYL)-3,4-DIHYDROISOQUINOLINIUM CHLORIDES

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A series of 1,2,3,4-tetrahydroisoquinoline enaminothioamides were synthesized by reacting 1-methyl-3,3-dialkyl-3,4-dihydroisoquinolines with phenylisothiocyanate. Treatment of the obtained enamines with HCl gave 3,3-dialkyl-1-(2-phenylamino-2-thioxoethyl)-3,4-dihydroisoquinolinium chlorides. Benzo[*f*]isoquinoline derivatives were synthesized analogously. All hydrochlorides showed analgesic effects in the hot-plate test at the level of metamizole sodium. Isoquinolines with 6- and 7-alkoxy groups were most active. The hydrochloride of the thioamide containing benzo[*f*]isoquinoline and spirocyclopentane motifs had the greatest anthelmintic and insecticidal activities, which were similar to those of levamisole and diazinon.

Keywords: reaction of 1-methyl-3,3-dialkyl-3,4-dihydroisoquinolines with phenylisothiocyanate, 3,3-dialkyl-1-(2-phenylamino-2-thioxoethyl)-3,4-dihydroisoquinolinium chlorides, benzo[*f*]isoquinolines, analgesic effect at the level of metamizole sodium, anthelmintic and insecticidal activity close to levamisole and diazinon.

3-Alkyl- and 3,3-dialkylisoquinoline derivatives are known to exhibit analgesic [1 – 6] and anthelmintic and insecticidal activity [7 – 9]. Recently, a method for preparing a series of isoquinoline *N*-phenyl enaminothioamides that consisted of reacting 1,2,3,4-tetrahydroisoquinoline enamines with phenylisothiocyanate was developed by us [10]. It is noteworthy that the biological activity of S-containing isoquinoline derivatives is still little studied. Also, S-containing compounds include several with anthelmintic [11] and insecticidal activity [12]. The goals of the present work were to synthesize 3,3-dialkyl-1-(2-phenylamino-2-thioxoethyl)-3,4-dihydroisoquinolinium chlorides; to study their analgesic, anthelmintic, and insecticidal activity; and to establish a structure–activity relationship.

Thioamides IIa-j were synthesized by reacting 1-methyl-3,3-dialkyl-3,4-dihydroisoquinolines Ia-j with phenylisothiocyanate [10]. Benzo[*f*]isoquinolines IIIa and -b gave corresponding enamines IVa and -b if used as starting materials.

The hydrochlorides of IIa-j and IVa and -b were used for the pharmacological studies and were prepared by passing dry HCl through an EtOAc solution of the corresponding base. The obtained hydrochlorides [(IIa-j) · HCl and (IVa, b) · HCl] were yellow crystalline compounds that were difficultly soluble in H_2O (Table 1).

The structures of the obtained compounds were elucidated using PMR spectra. Spectra of IIa-j and IVa and -b bases differed from those of the corresponding hydrochlorides. They contained singlets for the olefinic proton at 5.5 – 6.1 ppm and the ring NH at 11 – 12 ppm [10]. This corresponded to the *Z*-configuration of the enaminothioamide, which was stabilized by a H-bond. Spectra of the hydrochlorides of these compounds had a 1-CH_2 singlet in the range 4.23 – 4.34 ppm (Table 2). This corresponded to the imino form with a β-protonated enamine [9, 10]. The spectra also contained resonances for alkyl protons in the isoquinoline 3-position, i.e., two alkyl or one methyl. In the latter instance (thioamides IIh-j), a CH quadruplet (2.86 – 2.93 ppm) and a

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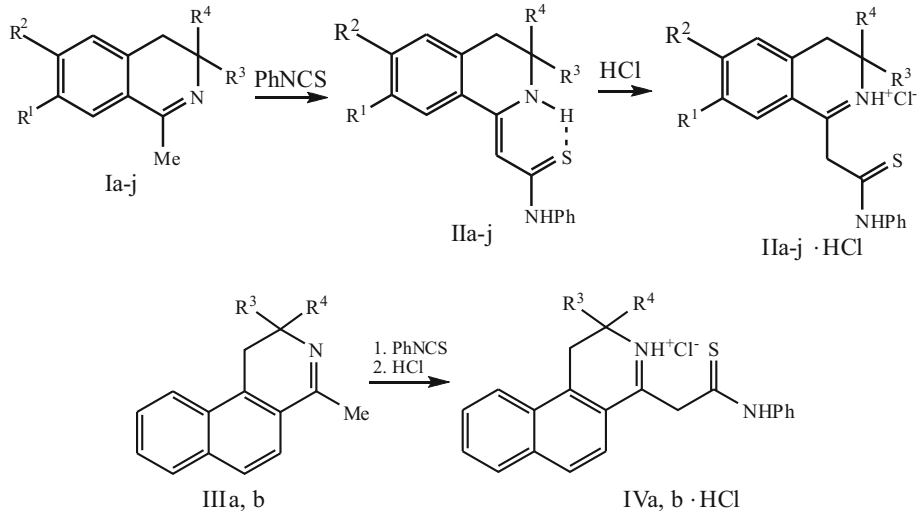

CH_3 doublet with diastereotopic splitting of the 4-CH_2 protons (4.28 – 4.33 ppm) were observed. The thioamide NH proton gave a singlet at weaker field than for the corresponding amides [9]. This reflected its more acidic nature because of the large polarizability of S as compared to O.

IR spectra of the synthesized compounds were more informative for the bases than for the hydrochlorides. The spectra contained a band for thioamide NH stretching vibrations at 3310 – 3320 cm^{-1} and a broad band for the H-bonded isoquinoline NH at 3100 – 3150 cm^{-1}.

EXPERIMENTAL CHEMICAL PART

IR spectra were taken from KBr pellets on a Specord M-80 spectrometer. PMR spectra were recorded in DMSO-d_6 with HMDS internal standard (0.05 ppm vs. TMS) on a Bruker AMX 300 instrument (300 MHz).

Compounds were recrystallized from *i*-PrOH. Elemental analyses (C, H, N, Cl) agreed with those calculated. The purity of products was monitored using TLC and $CHCl_3$–Me_2CO (9:1) with detection by I_2 vapor.

Starting 1-methyl-3,4-dihydroisoquinolines Ia-g [13, 14], Ih-j [6 – 8], and benzo[*f*]isoquinolines IIIa and -b [15] were synthesized as before. Pure bases for recording spectra were prepared by treating the hydrochlorides with NaOH solution (10%).

7-R^1-6-R^2-3-R^3-3-R^4-1-(2-Phenylamino-2-thioxoethyl)-3,4-dihydroisoquinolinium chlorides (IIa-j · HCl) and 2-R^1-2-R^2-4-(2-phenylamino-2-thioxoethyl)-1,2-dihydrobenzo[*f*]isoquinolinium chlorides (IVa, b · HCl). A mixture of base (I, 10 mmol) and phenylisothiocyanate (1.43 mL, 12 mmol) in anhydrous C_6H_6 (50 mL) was refluxed for 15 min and evaporated at reduced pressure. The resulting precipitate was filtered off, dried, and dissolved in EtOAc (200 mL). The corresponding hydrochloride was prepared by

TABLE 1. Characteristics of Synthesized Compounds

Compound	R^1, R^2, R^3 + R^4	Empirical formula	mp, °C	Yield, %
IIa · HCl	H, H, Me + Me	$C_{19}H_{20}N_2S$ · HCl	188 – 190	66
IIb · HCl	H, H, Me + Et	$C_{20}H_{22}N_2S$ · HCl	179 – 181	64
IIc · HCl	H, H, $(CH_2)_4$	$C_{21}H_{22}N_2S$ · HCl	199 – 201	59
IId · HCl	H, H, $(CH_2)_5$	$C_{22}H_{24}N_2S$ · HCl	187 – 189	70
IIe · HCl	MeO, MeO, Me + Me	$C_{21}H_{24}N_2O_2S$ · HCl	193 – 195	63
IIf · HCl	MeO, MeO, Et + Et	$C_{23}H_{28}N_2O_2S$ · HCl	190 – 192	57
IIg · HCl	MeO, MeO, *n*-Pr + n-Pr	$C_{25}H_{32}N_2O_2S$ · HCl	211 – 213	67
IIh · HCl	EtO, MeO, H, Me	$C_{21}H_{24}N_2O_2S$ · HCl	185 – 187	63
IIi · HCl	*n*-PrO, MeO, H, Me	$C_{22}H_{26}N_2O_2S$ · HCl	187 – 189	61
IIj · HCl	*n*-BuO, MeO, H, Me	$C_{23}H_{28}N_2O_2S$ · HCl	186 – 188	63
IVa · HCl	$(CH_2)_4$	$C_{25}H_{24}N_2S$ · HCl	224 – 226	70
IVb · HCl	Me + Me	$C_{23}H_{22}N_2S$ · HCl	171 – 173	62

passage of dry HCl and was filtered off, dried, and recrystallized.

EXPERIMENTAL PHARMACOLOGICAL PART

Analgesic activity was assessed using laboratory white mice (male, 20 ± 2 g) and thermal paw irritation in the hot-plate test [16]. The studied compounds were injected i.p. at a dose of 50 mg/kg as suspensions in starch paste (2%) 30 min before placing the animals on a metal plate heated to 53.5°C.

The maximum duration of the latent period (cut-off period) was set at 40 sec because placing an animal on the plate for longer times could burn the paw and cause physical suffering. The parameter for analgesic activity was the residence time (in seconds) of the animal on the hot plate before manifestation of a defensive reflex, i.e., licking the hind paws, shaking them, or attempting to jump. Effects were assessed 0.5, 1, 1.5, and 2 h after injecting the compounds. Animals with an initial time for manifestation of a defensive reflex of <15 sec were used in the tests. Each compound was tested in six animals.

TABLE 2. PMR Spectra of Synthesized Compounds, δ, ppm (*J*, Hz)

Compound	R^1	R^2, CH_3O, c, 3H	$R^3 - R^4$	4-CH_2, c	1-CH_2	Aromatic protons	Thioamide NH, s	NH^+, c
IIa · HCl	-	-	1.23 (s, 6H, $2CH_3$)	2.94 s	4.23	7.22 – 8.12 (m, 9H)	10.34	11.46
IIb · HCl	-	-	1.25 (s, 3H, CH_3), 1.18 (t, 3H, $C\underline{H}_3CH_2$, 7.3), 1.90 (q, 2H, $CH_3C\underline{H}_2$, 7.3)	2.97 s	4.26	7.27 – 8.24 (m, 9H)	10.28	11.52
IIc · HCl	-	-	1.21 – 1.57 (m, 8H, $4CH_2$)	3.02 s	4.28	7.21 – 8.26 (m, 9H)	10.25	11.54
IId · HCl	-	-	1.22 – 1.63 (m, 10H, $5CH_2$)	3.01 s	4.32	7.23 – 8.27 (m, 9H)	10.27	11.61
IIe · HCl	3.88 (s, 3H, $2CH_3$Î)	3.86	1.20 (s, 6H, $2CH_3$)	2.98 s	4.28	7.05 (s, 1H, 6-H), 7.22 – 8.32 (m, 6H)	10.30	11.58
IIf · HCl	3.83 (s, 3H, $2CH_3$Î)	3.86	1.20 (t, 6H, $2C\underline{H}_3CH_2$, 7.1), 1.88 (q, 4H, $2CH_3C\underline{H}_2$, 7.1)	3.02 s	4.31	7.07 (s, 1H, 6-H), 7.17 – 8.43 (m, 6H)	10.32	11.60
IIg · HCl	3.86 (s, 3H, $2CH_3$Î)	3.87	0.96 (t, 6H, $2C\underline{H}_3CH_2CH_2$), 1.34 – 1.52 (m, 4H, $2CH_3C\underline{H}_2CH_2$), 1.68 – 1.92 (t, 4H, $2CH_3CH_2C\underline{H}_2$)	3.03 s	4.33	7.08 (s, 1H, 6-H), 7.15 – 8.39 (m, 6H)	10.29	11.56
IIh · HCl	1.03(t, 3H, $C\underline{H}_3CH_2O$), 4.20 (q, 2H, CH_3CH_2O)	3.83	1.30 (d, 3H, CH_3, 8.1), 2.86 (q, 1H, CH_3, 8.1)	2.99 dd	4.29	7.07 (s, 1H, 6-H), 7.18 – 8.32 (m, 6H)	10.27	11.64
IIi · HCl	1.06(t,3H, $C\underline{H}_3CH_2CH_2O$), 1.06(m,3H, $CH_3C\underline{H}_2CH_2O$), 4.08(q, 3H, $CH_3CH_2C\underline{H}_2O$)	3.87	1.29 (d, 3H, CH_3, 8.2), 2.92 (q, 1H, CH_3, 8.2)	3.04 dd	4.32	7.08 (s, 1H, 6-H), 7.16 – 8.42 (m, 6H)	10.35	11.67
IIq · HCl	1.17(t,3H, $C\underline{H}_3(CH_2)_2CH_2O$), 1.40 – 1.63 (m, 4H, $CH_3(CH_2)_2CH_2O$ 4.10 (m, 2H, $CH_3(CH_2)_2C\underline{H}_2O$)	3.86	1.31 (d, 3H, CH_3, 8.1), 2.93 (q, 1H, CH_3, 8.1)	3.01 dd	4.28	7.09 (s, 1H, 6-H), 7.23 – 8.48 (m, 6H)	10.37	11.62
IVa · HCl	-	-	0.98 – 1.26 (m, 8H, $4CH_2$)	3.12 s	4.34	7.15 – 8.41 (m, 11H)	10.36	11.64
IVb · HCl	-	-	1.12 (s, 6H, $2CH_3$)	3.08 s	4.33	7.17 – 8.52 (m, 11H)	10.42	11.63

Results were assessed from the increased time for manifestation of a defensive reflex as compared with the starting values. Control animals received starch paste (2%). The reference standards were metamizole sodium at a dose of 93 mg/kg, which corresponded to ED_{50} [17, 18] and orthophen and ibuprofen at a dose of 50 mg/kg. The dose of 50 mg/kg for the tested compounds and reference drugs was chosen based on existing data for the activity and toxicity of isoquinoline derivatives of related structure [2 – 6]. Those studies were performed using a dose of 50 mg/kg i.p. Therefore, it was advisable to use the same dose in order to compare the activities with those of previously studied compounds. The dose also corresponded to that in a handbook [19].

Experimental results were processed statistically using the Student coefficient. An effect was considered statistically significant for $p < 0.05$ vs the control and reference drugs [20].

Anthelmintic activity was studied using earthworms and the literature method [21]. Earthworms were placed into aqueous solutions (0.5%) of the studied compounds. Their lifespans were measured. The lifespan of control worms was 1 d.

The reference standards were pyrantel and levamisole, which had different mechanisms of action (the former blocks signal transduction in nerve and muscle fibers; the latter, disrupts metabolism) [11].

Insecticidal activity was studied using *Chironomidae* larvae [7 – 9]. Larvae were placed into solutions (0.1%) of the studied compounds. The time of death was recorded. The reference standards were imidacloprid (Tanrek), which is

TABLE 3. Analgesic Effects of Synthesized Compounds in the Hot-plate Model

Compound	R^1, R^2, R^3-R^4	Latent period of defensive reflex, min
IIa · HCl	H, H, Me + Me	23.20 ± 0.64*
IIb · HCl	H, H, Me + Et	19.92 ± 0.82*
IIc · HCl	H, H, $(CH_2)_4$	21.16 ± 0.76*
IId · HCl	H, H, $(CH_2)_5$	20.42 ± 0.68*
IIe · HCl	MeO, MeO, Me + Me	26.88 ± 1.26*
IIf · HCl	MeO, MeO, Et + Et	24.62 ± 1.48
IIg · HCl	MeO, MeO, *n*-Pr + *n*-Pr	20.52 ± 0.64*
IIh · HCl	EtO, MeO, H, Me	19.30 ± 0.82*
IIi · HCl	*n*-PrO, MeO, H, Me	24.00 ± 0.72*
IIj · HCl	*n*-BuO, MeO, H, Me	20.22 ± 0.54*
IVa · HCl	$(CH_2)_4$	19.86 ± 0.44*
IVb · HCl	Me + Me	20.10 ± 0.26*
Control, 2% starch paste	-	11.1 ± 0.9
Metamizole sodium	-	16.33 ± 1.2 $p < 0.1$
Orthophen	-	29.88 ± 1.68 $p < 0.01$
Ibuprofen	-	23.50 ± 1.12 $p < 0.05$

TABLE 4. Anthelmintic and Insecticidal Activities of Synthesized Compounds

Compound	Anthelmintic activity, worm lifespan, min	*p* vs. pyrantel	Insecticidal activity, larva lifespan, min	*p* vs.		
				pirimiphos	imidacloprid	diazinon
IIa · HCl	58.4 ± 5, 87	< 0.001	> 200	-	-	-
IIb · HCl	43.2 ± 5, 38	< 0.001	> 200	-	-	-
IIc · HCl	> 200	-	70.4 ± 17.44	-	> 0.05	-
IId · HCl	> 200	-	> 200	-	-	-
IIe · HCl	50.8 ± 4.71	< 0.001	> 200	-	-	-
IIf · HCl	> 200	-	> 200	-	-	-
IIg · HCl	> 200	-	> 200	-	-	-
IIh · HCl	43.6 ± 1, 69	< 0.001	> 200	-	-	-
IIi · HCl	> 200	-	> 200	-	-	-
IIj · HCl	77.8 ± 11, 48	< 0.001	> 200	-	-	-
IVa · HCl	33.8 ± 2, 60	< 0.001	18.6 ± 3, 50	> 0.05	< 0.001	> 0.05
IVb · HCl	> 200	-	> 200	-	-	-
Pyrantel	215.0 ± 0, 37	-	-	-	-	-
Levamisole	20.2 ± 2.08	-	-	-	-	-
Imidacloprid	-	-	43.5 ± 3.39	-	-	-
Diazinon	-	-	17.0 ± 1, 87	-	-	-
Pirimiphos	-	-	24.5 ± 1.69	-	-	-

currently widely used for disinfection, diazinon, and pirimiphos [7].

Pyrantel tablets (Polfa, Poland); decaris (levamisole, Gedeon Richter, Hungary); imidacloprid (Tanrek, August Co., Russia); diazinon (Fox and Co., Russia); and pirimiphos (Syngenta Ltd., Russia) were used in the tests.

Test results were processed statistically using the Student coefficient and were considered statistically significant for $p < 0.05$. Anthelmintic activity was determined using 6 tests; insecticidal activity, 10. A compound was considered unpromising for further development if an anthelmintic effect did not appear in 200 min. The maximum observation time was also 200 min for insecticidal activity.

The test results showed that all 12 compounds at a dose of 50 mg/kg surpassed metamizole sodium with respect to analgesic activity and were comparable to orthophen and ibuprofen (Table 3). Thioamides (IIe, f,i · HCl) were most active and had times for defensive reflexes that were about 1.5 times longer than for metamizole sodium.

Anthelmintic activity was found for 6 of 12 compounds (Table 4). They all were statistically significantly better than pyrantel and decreased the lifespan of worms by 2.76 – 6.36 times as compared to it. Benzo[*f*]isoquinoline IVa · HCl with a spirocyclopentane ring in its structure was most active. This compound killed the worms in 33.8 min, which was close to levamisole and 6.36 times faster than pyrantel.

Insecticidal activity was found for only two compounds, IIc · HCl and IVa · HCl (Table 4). The latter killed larvae in 18.6 min, i.e., practically at the level of diazinon (17 min). The efficacy did not differ statistically significantly from those of diazinon and pirimiphos. However, the tested compound was statistically significantly more active than pirimiphos (24.5 min).

An analysis of the structure–activity relationship indicated that the analgesic effect was more pronounced for isoquinolines with alkoxy groups in the 6- and 7-positions. A compound exhibiting simultaneously high anthelmintic and insecticidal activity contained benzo[*f*]isoquinoline and spirocyclopentane motifs. Uncondensed isoquinolines (IIc, d) · HCl, which also had a spirocyclopentane and spirocyclohexane in their structures, were inactive. This indicated that benzo[*f*]annellation played a role for these types of activity.

The results led to the conclusion that future searches for analgesics among 3,3-dialkyl-1-(2-phenylamino-2-thioxoethyl)-3,4-dihydroisoquinolinium chlorides and other isoquinolines should focus on 6,7-dialkoxy derivatives. Two types of activity, e.g., analgesic and anthelmintic, could fortuitously be combined in a single compound because helminthiasis is often associated with painful symptoms.

The pharmacological target for the analgesic activity of the studied compounds would logically be proposed to be nerve endings because central deactivating action (side position etc.) was not observed in the animal behavior. The effect was clearly peripheral in nature. The same effect on the target was indicated for the anthelmintic activity. Increased muscle contraction transitioning into spastic paralysis was observed. Therefore, nerve and muscle tissues are the targets. The same could be said of the insecticidal effect because the caterpillar is a worm-like lepidopteran larva.

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