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SYNTHESIS AND BIOLOGICAL ACTIVITY OF 1,2-DIMETHYL-4-(N-ACYL)-ANILINOHEXAHYDROPYRIDAZINES

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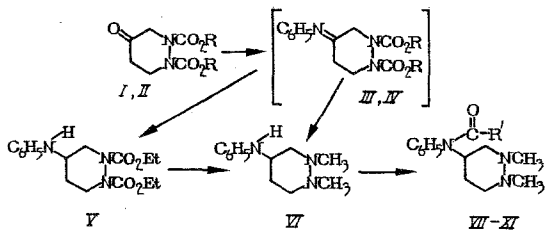
Earlier we showed that 1- and 2-phenylethyl-4-aminopiperidines [1] have local anesthetic activity. In this work we have attempted to assess the role and effect of 1,2,4-substituents on the biological activity of 4-anilinopiperidazines.

For a more detailed study of the relationship between chemical structure and biological activity in the series of hexahydropyridazine compounds it seemed of interest to prepare 1,2-dimethyl-4-(N-acyl)anilinohexahydropyridazines (VII-XI).

As starting compounds for the synthesis of compounds VII-XI we used 1,2-di(alkoxycarbonyl)hexahydropyridazine-4-pones I and II [2]. The synthesis of 1,2-dimethyl-4-(N-acyl)hexahydropyridazines was carried out according to the scheme:



R=C_2H_5(I, III, V), CH_3(II, IV); R'=CH_3(VII), CH_2CH_3(VIII), C_6H_5(IX); $CH_2C_6H_5$(X); C_4H_3O(XI).

By reaction of ketones I and II with aniline according to [3] we prepared Shiff bases III and IV. Hydrogenation of the latter with lithium aluminum hydride according to [5] leads to 1,2-dimethyl-4-anilinohexahydropyridazine (VI). We have also realized consecutive reduction of the imino and urethane groups with intermediate formation of V according to [4]. By reacting compound VI with acid chlorides according to [6] we have prepared a series of 1,2-dimethyl-4-(N-acyl)anilinohexahydropyridazines (VII-XII).

EXPERIMENTAL (CHEMICAL)

IR spectra were taken on a UR-20 spectrometer in paraffin oil. PMR spectra were recorded on a Varian T-60 spectrometer in $CDCl_3$ with TMS as internal standard. TLC was carried out on Silufol UV-254 plates in the system hexane–acetone, 1:1. Data of elemental analyses for C, H, and N corresponded with calculated values.

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TABLE 1. Physicochemical Properties of Compounds VI-XI

Compound	Yield %	Bp, °C/mm Hg	R_f	Empirical formula	IR spectrum, ν_{max}, cm^{-1}	PMR spectrum, δ, ppm
VI	64	140—142/2	0,42	$C_{12}H_{19}N_3$	1630 (C_6H_5)	7,20—6,58 (5H, m, C_6H_5), 3,95—3,86 (1H, br, s, N—H), 3,68—3,55 (1H, m, CH), 3,00—2,60 (4H, m, $2CH_2$), 2,45 (6H, d, $2N—CH_3$), 1,95—1,55 (2H, m, CH_2)
VII	55	160—165/1	0,52	$C_{14}H_{21}N_3O$	1715 (C=O)	7,68—7,04 (5H, m, C_6H_5), 4,40—3,90 (16, m, CH), 3,21—1,40 (6H, m, $C^3—H_2$, $C^5—H_2$, $C^6—H_2$), 2,44 (3H, s, $N^2—CH_3$), 2,24 (3H, s, $N^1—CH_3$), 1,66 (3H, s, CH_3)
VIII	41	175—180/1	0,43	$C_{15}H_{23}N_3O$	1718 (C=O)	7,50—6,80 (5H, m, C_6H_5), 4,98—4,40 (1H, m, CH), 3,00—1,39 (8H, m, $4CH_2$), 2,36 (3H, s, $N^2—CH_3$), 2,18 (3H, s, $N^1—CH_3$), 1,10—0,84 (3H, t, $CH_2—CH_3$)
IX	74	200—205/1	0,49	$C_{19}H_{25}N_3O$	1710 (C=O)	7,46—6,80 (10H, m, $2C_6H_5$), 5,20—4,66 (1H, m, CH), 3,20—1,40 (6H, m, $3CH_2$), 2,42 (3H, s, $N^2—CH_3$), 2,32 (3H, s, $N^1—CH_3$)
X	68	205—215/1	0,43	$C_{20}H_{25}N_3O$	1710 (C=O)	7,42—6,80 (10H, m, $2C_6H_5$), 5,08—4,40 (1H, m, CH), 3,31 (2H, s, CH_2), 2,90—1,20 (6H, m, $3CH_2$), 2,41 (3H, s, $N^2—CH_3$), 2,24 (3H, s, $N^1—CH_3$)
XI	65	197—201/1	0,41	$C_{17}H_{21}N_3O_2$	1715 (C=O)	7,35—6,92 (5H, m, C_6H_5), 6,50—5,70 (3H, m, C_4H_3O), 4,95—4,40 (1H, s, CH), 2,80—1,20 (6H, m, $3CH_2$), 2,36 (3H, s, $N^2—CH_3$), 2,20 (3H, s, $N^1—CH_3$)

1,2-Di(ethoxycarbonyl)-4-anilinohexahydropyridazine (V). A mixture of 24.4 g (0.1 mole) of 1,2-di(ethoxycarbonyl)hexahydropyridazin-4-one (I), 18.6 g (0.2 mole) of aniline, 1 ml of acetic acid, and 300 ml of toluene is refluxed at a Dean-Stark adaptor till the separation of water stops [3]. The solution is evaporated to yield 32 g of compound III (yield of crude product 100%). Then crude Shiff base III is dissolved in 400 ml of methanol and with stirring 3.8 g (0.1 mole) of sodium borohydride is added in small portions [4]. Stirring is continued for 6 h, methanol is evaporated, 80 ml of water is added, and the mixture is stirred till complete disintegration of the complex. The precipitated crystals are recrystallized from ethyl acetate. Yield 25 g (77.9%) of V, mp 101-105°C, R_f 0.62. IR spectrum, ν, cm^{-1}: 1620 (C_6H_5), 1725 (C=O ester). PMR spectrum, δ, ppm: 7.60-7.14 (5H, m C_6H_5), 4.80-3.19 (12H, m, CH, NH, $3CH_2$, $2OCH_2$), 1.18-1.02 (6H, t, $2CH_3$, I=6).

1,2-Dimethyl-4-anilinohexahydropyridazine (VI). In much the same way, 24.4 g (0.1 mole) of compound I, 18.6 g (0.2 mole) of compound I, 18.6 g (0.02 mole) of aniline, and 1 ml of acetic acid in 300 ml of toluene is refluxed at a Dean-Stark separator for 3 h. Toluene is evaporated and to Shiff base III obtained is added 300 ml of absolute ether. The obtained solution is added dropwise to a stirred suspension of 7.4 g (0.3 mole) of lithium aluminum hydride in 200 ml of absolute ether [5]. The mixture is stirred for 6 h and with cooling the complex is decomposed with 7.5 ml of 15% sodium hydroxide and 22.5 ml of water. The precipitate is filtered off, washed with ether, the ether is evaporated, and the residue is distilled. Yield 13.0 (63%) of VI.

In much the same way, from 21.6 g (0.1 mole) of 1,2-di(methoxycarbonyl)hexahydropyridazin-4-one II, 18.6 g (0.2 mole) of aniline, and 1 ml of acetic acid is prepared 14.5 g of VI.

Further, by the method described above, 25 g (0.08 mole) of V is hydrogenated with 5.9 g (0.19 mole) of lithium aluminum hydride in 500 ml of absolute ether. Yield 10.5 g (64%) of VI.

General Method for the Preparation of 1,2-dimethyl-4-(N-acyl)anilinohexahydropyridazines (VII-XI). To a mixture of 10.25 g (0.05 mole) of VI and 5 g (0.05 mole) of triethylamine in 200 ml of benzene is added 0.05 mole of the appropriate acid chloride. The mixture is refluxed for 0.5 h [6], cooled, filtered, extracted twice with 20 ml of 3% sodium carbonate solution, and once with water (20 ml). The extract is dried over sodium sulfate, benzene is evaporated, and the residue is distilled.

Constants of compounds IV-XI are listed in Table 1.

EXPERIMENTAL (PHARMACOLOGICAL)

A first selection of the prepared compounds was made by tests for anesthetic and analgetic activities. We have studied the antagonistic effect with regard to opioids, local irritating and anticonvulsive properties, and acute toxicity.

TABLE 2. Pharmacological Properties of the Compounds

Compound	LD_{50}, mg/kg	Conduction anesthesia, EK_{50}, %	Antagonism to morphine, %	Local irritating activity
VIIa	1300 and more	0,245 (0,11—0,52)	20	+++
VIIIa	960 (750—1229)	0,32 (0,2—0,49)	0	++++
IXa	395 (227—687)	0,12 (0,068—0,21)	0	—
Xa	580 (508—661)	0,23 (0,1—0,46)	22	—
XIa	690 (627—759)	0,43 (0,3—0,63)	0	++++
VIIb	800 (655—976)	0,62 (0,5—0,91)	0	++++
VIIIb	640 (576—710)	0,48 (0,2—0,93)	0	++++
IXb	275 (153—360)	0,14 (0,09—0,2)	9	++++
Xb	380 (352—410)	0,047 (0,03—0,07)	75,1	++++
XIb	550 (404—748)	0,51 (0,3—0,08)	24,8	+
Novocain	192 (176—208,7)	0,05 (0,029—0,078)	0	—

*a) citrate; b) hydrochoride of compounds VII-XI.

The local anesthetic activity in the case of conduction anesthesia in vitro was studied with isolated frog nerves [7]. The central anesthetic activity of the compounds was studied by the "hot plate" test at an intraperitoneal dose of 80 mg/kg [8]. The antagonistic effect with regard to opioids of the compounds (suppression of the analgetic effect of morphine at a dose of 5 mg/kg) was determined with the model of mechanical irritation of rat tails at a subcutaneous dose of 10 mg/kg [9]. The local irritating activity was studied in guinea pigs with regard to the sensitivity zone of the animal [10]. Anticonvulsive properties of the compounds were investigated in white mice of both sexes weighing 18-24 g, using the following models: maximum electroshock, corazol and nicotine convulsions, and arecoline tremors [8, 12-14]. The acute toxicity of the compounds was determined in white mice weighting 20-22 g on intraperitoneal administration. Statistical processing of the results was carried out by the Litchfield-Wilcoxon method [11].

The results of the investigations, which are summarized in Table 2, show that all the compounds under investigation have some local anesthetic activity. The highest activity is found in compound Xb, which in effectivity corresponds with novocain. However, that compound has also local irritating activity. Compounds IXa and Xa do not have local irritating activity.

Compounds VIIa, Xa, and XIb weakly suppress the analgetic effect of morphine, compound Xb by 75%. The compounds under investigation do not evoke a central anesthetic effect. All tested compounds are less toxic than novocain.

With regard to preventing the tonic phase of maximum electroshock only compound VIIIa shows activity, ED_{50} 170 (121-238) mg/kg at $p = 0.05$. The tested compounds do not have anticorazol and central H- and M-cholinolytic properties.

As a result of the investigations it has been found that two factors have influence on the biological activity of 1,2,4-substituted hexahydropyridazines.

I: introduction of a second nitrogen atom at the piperidine ring leads to emergence of local anesthetic activity, in contrast to 1-phenylethyl-4-anilinopiperidines, which show clearly expressed analgetic activity [15].

II: the nature of the substituent at position 4 predetermines the distinctness of local anesthesia of compounds VII-XI, which for nonaromatic substituents is increased on changing from N-acetyl to N-propionyl, and for an aromatic ring from N-benzoyl to N-phenylethyl.

Thus, all salts of 1,2-dimethyl-4-(N-acyl)anilinohexahydropyridazines have some local anesthetic activity and some of them show antagonism to morphine. One compound has anticonvulsive activity. The obtained data are promising for further study of hexahydropyridazine systems.

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SYNTHESIS AND CYTOSTATIC ACTIVITY OF ACETYLFORMAMIDOXIME DERIVATIVES CONTAINING PIPERAZINE, HEXAHYDRODIAZEPINE, AND DISPIROTRIPIPERAZINIUM RESIDUES

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It was found previously that N-arylacetylformamidoxime derivatives exhibit antitumor activity [3, 5]. In the present study we have synthesized some acetylformamidoxime derivatives in order to investigate novel antitumor compounds and establish the relationship between their structure and biological activity. These derivatives contain piperazine, hexahydrodiazepine, and dispirotripiperazinium residues, which form part of the structure of the antitumor drugs prospidin, spirobromin, and pipobroman [4, 7, 11, 12]. The starting materials used were α-chloro-α-isonitrosoacetone (Ia), its oxime (Ib), and semicarbazone (Ic). Reaction of dispirotripiperazinium dichloride with Ia and Ic in aqueous alcohol in the presence of Et_3N gave N,N'''-bis(1-hydroxyimino-2-oxopropyl)-N',N''-dispirotripiperazinium dichloride (IIa) and its semicarbazone (IIc). The latter was isolated from the aqueous alcoholic solution as its tetrahydrate, which was then dried at 70°C for 6 h to give the monohydrate. Reaction of Ia with anhydrous piperazine in the presence of Et_3N and in ether gave N,N'-bis(1-hydroxyimino-2-oxopropyl)piperazine (IIIa) in 51% yield. Reaction of Ia with piperazine hexahydrate gave IIIa (18%) and N-acetyl-N'-(1-hydroxyimino-2-oxopropyl)piperazine (V) (10.2%). The latter is formed because in this case electrophilic attack on the second nitrogen atom of the piperazine ring by the nitrile oxide generated from chloroisonitrosoacetone Ia occurs more slowly, and a proportion of the nitrile oxide is dimerized to diacetylfuroxan, which acts as an acetylating agent [1].

Reaction of anhydrous piperazine with Ib and of piperazine hexahydrate with Ic yields the oxime (IIIb) and semicarbazome (IIIc) in 92.5 and 74% yield respectively. On treatment of a suspension of these compounds in alcohol with an ethereal solution of HCl it is possible to obtain their hydrochlorides, which are rapidly hydrolyzed in water to the corresponding bases. Treatment of IIIa with hydrazine hydrate gives the hydrazone (IIId) (Scheme 1).

The derivatives IVb and IVc are synthesized in a similar manner by reaction of hexahydrodiazepine dihydrobromide with compounds Ib and Ic. The structure of the resulting compounds is supported by the presence of absorption bands due to C=N groups at 1590-1630 cm^{-1} and from N–OH at 950-985 cm^{-1} that are characteristic of amidoximes in the IR spectra of IIa, IIc, and IIIa-d. For V the bands are typical of acetylformamidoximes– CO at 1690 cm^{-1} and C=N

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