SYNTHESIS AND STERIC STRUCTURE OF 1-(2-ETHOXYETHYL)-3-METHYL-4-ANILINOPIPERDINES

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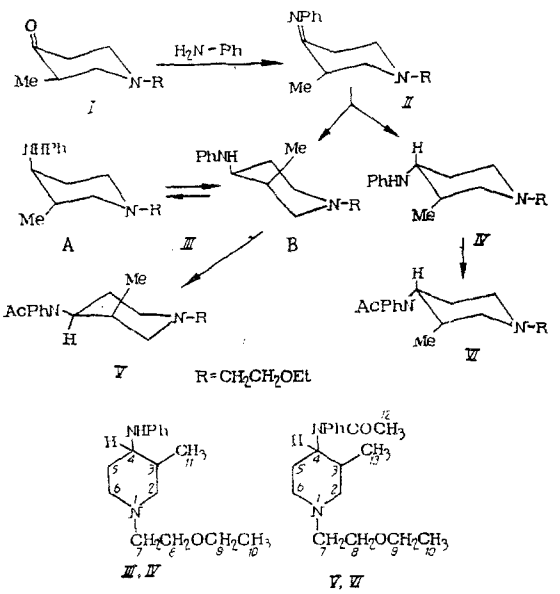
The search for new drug preparation possessing high activity and low toxicity combined with the simple technology of isolation remains an urgent problem. The comprehensive study of the interrelationship of the structure of the substance with its pharmacological action is necessary for the successful execution of the given search. The discovery of highly active analgesics — the 4-propionylanilidopiperidines (fentanyl, mefentanyl, and their analogs) [1, 3, 9-12] — provided the impetus for extensive synthetic and stereochemical investigations of 4-anilinopiperidiene derivatives [5, 7, 8].

In the continuation of these investigations, the present work describes the synthesis of stereoisomers of 1-(2-ethoxyethyl)-3-methyl-4-(N-phenylamino)piperidine and their N-acetyl derivatives, as well as the study of their steric structure.



The reaction of 1-(2-ethoxyethyl)-3-methyl-4-ketopiperidine (I) [4] with aniline in the presence of p-toluenesulfonic acid in abs. benzene leads to the formation of the imino derivative (II), which, after distillation in vacuo, was reduced by $NaBH_4$ in ethanol to the mixture of the 4-anilinopiperidine stereoisomers (III) and (IV). The separation of the mixture of (III) and (IV) into the individual forms was accomplished by column chromatography on Al_2O_3 of grade II activity; the elution was performed with the 2:1 mixture of ethyl ether—hexane. As a result of this, 62.1% of the total amount of the mixture was isolated for the stereoisomer (III) with the R_f 0.56, and 37.9% was isolated for the stereoisomer (IV) with the R_f 0.3.

The acetamides (V) and (VI) were synthesized by the action of AcCl on the individual 4-anilinopiperidine isomers (III) and (IV) in abs. benzene.

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TABLE 1. Data of the ^{13}C and ^{1}H NMR Spectra of the Synthesized Compounds, δ, ppm

Compound	^{13}C												^{1}H (80 MHz)				
	$C_{(2)}$	$C_{(3)}$	$C_{(4)}$	$C_{(5)}$	$C_{(6)}$	$C_{(7)}$	$C_{(8)}$	$C_{(9)}$	$C_{(10)}$	$C_{(11)}$	$C_{(12)}$	$C_{(13)}$	Ph	Ph	3-CH_3	CH_3 ethyl	CH_3 amide	4-Ha
III	57,9	32,4	58,2	28,6	51,7	57,9	68,7	65,8	15,1	13,3			q—147,9 m—113,6 o—128,8 n—116,9	6,7	1,27	0,89		
IV	61,3	37,6	56,3	32,2	53,3	57,6	68,6	65,8	15,1	16,5			q—147,7 m—112,9 o—128,8 n—116,6	6,74	1,34	0,87		
V	60,0	31,4	57,1	26,4	54,1	57,6	68,8	65,7	15,1	168,6	23,4	13,6	q—141,9 m—128,6 o—130,5 n—127,3	7,20	1,03	1,54	1,54	4,17 (20Hz)
VI	61,5	33,9	57,4	30,5	53,6	57,4	68,6	65,7	15,1	168,5	22,9	16,3	q—140,4 m—129,9 o—130,1 n—127,7	7,13	1,57	0,93	2,03	4,21 (25Hz)

TABLE 2. Chemical Shifts of the Protons of the Stereoisomers (III) and (IV), δ, ppm

Isomer	2Ha	2He	3Ha	3He	4Ha	5Ha	5He	6Ha	6He	$3CH_3$	NH	Ph	$-CH_2-CH_2-O-CH_2-CH_3$			
III	1.82	2.38	—	2.59	3.65	1.77	2.18	2.31	2.5	0.98	3.69	6.93	2.56	3.56	3.52	1.23
IV	1.87	2.9	1.7	—	3.0	1.4	2.15	2.11	2.98	1.0	3.37	6.92	2.6	3.58	3.52	1.23

TABLE 3. Spin—Spin Coupling Constants (I), Hz

Isomer	2Ha	2He	3Ha	3He	4Ha	5Ha	5He	6Ha	6He
III	2a2e 11.8 2a3e 7.0	2e2a 11.8 2e3a 7.0		3e3CH_3 7.0 3e2a 7.0 3e2e 7.0	4a5a 13.5 4a3e 7.0 4a5e 7.0	5a5e 13.5 5a4a 13.5 5a6a 13.5 5a6e 4.2	5e5a 13.5 5e4a 7.0 5e6a 3.7 5e6e 3.7	6a6e 13.5 6a5a 13.5 6a5e 3.7	6e6a 13.5 6e5a 4.2 6e5e 3.7
IV	2a2e 11.0 2a3a 11.0	2e2a 11.0 2e3a 3.5	3a2a 11.0 3a4a 11.0 3a3CH_3 7.0 3a2e 3.5		4a3a 11.0 4a5a 10.0 4a5e 5.0	5a5e 14.0 5a4a 10.0 5a6a 14.0 5a6e 3.0	5e5a 14.0 5e4a 5.0 5e6a 2.5 5e6e 2.5	6a6e 14.0 6a5a 14.0 6a5e 2.5	6e6a 14.0 6e5a 3.0 6e5e 2.5

The IR spectra of the diamines (III) and (IV) have the absorption band in the region of 3433 and 3417 cm^{-1} correspondingly; this is characteristic of the N—H bond of the anilino group. The intense absorption band of the C=O amide bond is observed for the acetamides (V) and (VI) at 1659 cm^{-1} (V) and 1663 cm^{-1} (VI).

The analysis of the ^{13}C NMR spectra with broad-band uncoupling from the protons shows that the 4-anilinopiperidine stereoisomers (III) and (IV) and their acetyl derivatives (V) and (VI) only differ from each other in the orientation of the methyl group at C_3 of the piperidine ring, whereby, according to a known rule [2], this group is axially disposed in the stereoisomers (III) and (V) (δ = 32.4 and 31.4 ppm correspondingly), and equatorially disposed in their epimers [the signals of the C_3 atom are displaced to low field by comparison with the corresponding signals of (III) and (V): δ = 37.6 and 33.9 ppm] (Table 1).

The signals of the carbon atoms of the methyl group at C_3 of the piperidine ring in the compounds (IV) and (VI) occur at lower field [16.5 and 16.3 ppm correspondingly) relative to the signals of the isomers (III) and (V) (13.3 and 13.6 ppm); this is explained by the deshielding influence of the electronegative nitrogen atom at C_4 in the compounds (IV) and (VI) on the methyl group.

The steric position assigned to the methyl group is also confirmed by the values of the width of the separate components of the quartets of the methyl carbon atom of the diamines (III) and (IV). The width for the stereoisomer (III) comprises 17 Hz (the 3-CH_3 is axial), [6], and the width for (IV) is 11 Hz (the 3-CH_3 is equatorial).

In the PMR spectra (80 MHz) of the acetamides (V) and (VI), the signal of the 4-H proton was found to be shifted to low field [4.17 ppm in (V), and 4.21 ppm in (VI)] in consequence of the deshielding influence of the N-phenylacetamide group, although the multiplets remained unresolved. The width of the signal of the 4-H proton in the acetamide (VI) equals 25 Hz, and the width in (V) equals 20 Hz; this indicates the presence of two axial—axial interactions of the 4-H proton in (VI). Therefore, the proton at C_3 (3-H) is disposed axially, consequently the 3-CH_3 is disposed equatorially. In the amide (V), the analogous methyl group has the opposite orientation. The chemical shifts of the protons of the phenyl and methyl groups and the 4-H of the compounds (III)-(VI) are presented in Table 1.

In order to demonstrate the steric structure of the stereoisomeric 4-(N-phenylamino)piperidines (III) and (IV), the PMR spectra were also recorded at the working frequency of the instrument of 250 MHz (Table 2). Judging from the values of the vicinal constants of the protons of the piperidine ring and the chemical shifts of the axial protons displaced to high field by comparison with the equatorial protons, the diamines (III) and (IV) occur in the preferred chair conformation. The change in the orientation of the methyl group in the transition from the isomer (III) to the isomer (IV) is followed especially well from the values of the geminal and vicinal SSCCs of the 2-Ha, 3-H, and 4-Ha. The signal of the 2-Ha proton in the stereoisomer (IV) is a triplet with the constant of 11 Hz; the signal of the 4-Ha proton is an octet with the vicinal constants of 11, 10, and 5 Hz. In the isomer (III), the 2-Ha is a doublet of doublets with the SSCCs of 11.8 and 7 Hz; the 4-Ha is a doublet of triplets with $^3J_{4Ha3H}$ = 7 Hz, $^3J_{4Ha5Ha}$ = 13.5 Hz, and $^3J_{4Ha5He}$ = 7 Hz. Consequently, the 3-H proton in the isomer (IV) does not have one significant constant (3-He), whereas there are two of them in (III) (3-Ha). The shift of the signal of the 3-H proton is also characteristic in the transition 3-He—3-Ha; it is 0.89 ppm to high field.

Therefore, the reduction of the Schiff base (II) by $NaBH_4$ results in the formation of the mixture of two stereoisomers (III) and (IV) with the chair-type conformation of the piperidine ring and the equatorial orientation of the substituents at the positions 1 and 4. These stereoisomers are the epimers at C_3: the cis isomer — 1-(2-

ethoxyethyl)-3a-methyl-4e-(N-phenylamino)piperidine (III) (the 3a4e-conformation), and the trans isomer — 1-(2-ethoxyethyl)-3e-methyl-4e-(N-phenylamino)piperidine (IV) (the 3e4e-conformation).

The difference in the orientation of the methyl at the C_3 center of the diamines (III) and (IV) is explained by the fact that the stereoisomer (III), which is produced in the A form under the influence of the axial phenylamine substituent, undergoes inversion to the B form.

The pharmacological properties of the synthesized compounds will be described in the following communication.

EXPERIMENTAL (CHEMICAL)

The course of the reaction and the uniformity of the compounds were monitored by the method of TLC on alumina of the II grade of activity; development was performed with iodine vapor. The IR spectra were taken on the UR-20 spectrometer (GDR). The PMR spectra were obtained on the BS-487B spectrometer of the firm "Tesla" with the working frequency of 80 MHz for 10% solutions in $CDCl_3$ at room temperature. The ^{13}C NMR spectra were obtained using the WP-80 instrument of the firm "Bruker" at the temperature of 310 K; the internal standard was HMDS. The dihydrochlorides were obtained by the treatment of anilinopiperidines in ether with an alcoholic solution of HCl, and the subsequent crystallization of the resulting oily product. The values found for the elemental analyses correspond with the calculated values.

1-(2-Ethoxyethyl)-3-methyl-4-(phenylimino)piperidine (II). Into a flask equipped with a Dean-Stark attachment and a stirrer are placed 50 g (0.27 mole) of (I), 32.68 g (0.35 mole) of aniline, and 2.5 g of p-toluenesulfonic acid in 300 ml of abs. benzene. The mixture is heated with stirring on a boiling water bath in the course of 40 h. By this means, 2.7 ml of water are separated. The solvent is evaporated; the residue is distilled in vacuo prior to the isolation of 38.92 g (55.36%) of (II) with the bp 158-162°C (1 mm of Hg stem). The (II) is utilized without identification for the following stage.

1-(2-Ethoxyethyl)-3-methyl-4-(phenylamino)piperidine (III) and (IV). To 39.72 g (1.05 mole) of $NaBH_4$ in 200 ml of abs. ethanol are added, dropwise, 38.92 g (0.15 mole) of (II) in 50 ml of ethanol. Insignificant warming up and frothing are thereby observed. The mixture is stirred for 11 h at room temperature; it is treated with 150 ml of distilled water and then approximately 250 ml of HCl (1:1) to the pH 4 for the complete decomposition of the excess $NaBH_4$. The solution is made alkaline with a saturated solution of NaOH to the pH 9-10 and extracted repeatedly with benzene. The extract is dried with $MgSO_4$, and the solvent is evaporated prior to the isolation of 38 g (96.5%) of the yellow oil, which is the mixture of the two isomers (III) and (IV) with the R_f 0.56 and 0.3; the eluent is the 1:2 mixture of ethyl ether—hexane.

Chromatographic Separation of the Stereoisomeric Mixture of the Amines (III) and (IV) into the Individual Forms. The stereoisomeric mixture (38 g) of (III) and (IV) is applied to a column of height 107 cm and diameter 3.4 cm, containing 1000 g of Al_2O_3 for chromatography. The 1:2 mixture of ethyl ether—hexane serves as the solvent for the washing out of the stereoisomers (III) and (IV). Samples are removed in portions of 15-20 ml. After the separation and the distillation of the solvent, 23.35 g (62.1% of the total amount of the mixture) of the oil-forming isomer (III) are obtained; it has the R_f 0.56. $C_{16}H_{26}N_2O$. The dihydrochloride (III) has the mp 208-209°C (from ethanol). $C_{16}H_{28}N_2OCl_2$. The yield of (IV) is 14.25 g (37.9% of the total amount of the mixture); it is an oil having the R_f 0.3. $C_{16}H_{26}N_2O$. The dihydrochloride (IV) has the mp 186-187°C (from ethanol). $C_{16}H_{28}N_2OCl_2$.

1-(2-Ethoxyethyl)-3-methyl-4-(N-phenylacetamido)piperidine (V) and (VI) Hydrochlorides. To the solution of 1.31 g (0.005 mole) of (III) or (IV) in 30 ml of abs. benzene are added 1.185 g (0.015 mole) of AcCl. The warming up of the mixture is thereby observed. The mixture is left at room temperature for 24 h. The solvent is then evaporated; the residue is recrystallized from ethanol and ethyl acetate correspondingly prior to the isolation of the hydrochlorides of the acetamides (V) and (VI) in the yield of 98.5 and 80.4%. The hydrochloride (V) is an oily liquid. $C_{18}H_{29}N_2O_2Cl$. The hydrochloride (VI) has the mp 143-144°C. $C_{18}H_{29}N_2O_2Cl$.

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SYNTHESIS AND PHARMACOLOGICAL ACTIVITY OF DERIVATIVES OF 1-[2-ETHOXYETHYL]-3-METHYL-4-ANILINOPIPERIDINE

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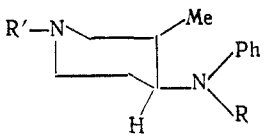
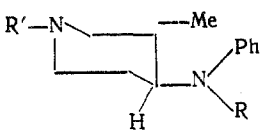
The discovery of fentanyl, a powerful neuroleptanalgesic, induced extensive investigations into the search for new highly effective analgesics in the series of derivatives of 4-phenylaminopiperidine and the study of the pharmacological properties of compounds of that series in dependence of the nature of the substituents. In the preceding publication [5] we have described the synthesis and spatial structure of the stereoisomers of 1-(2-ethoxyethyl)-3-methyl-4-phenylaminopiperidines (I, II) and their N-acetyl derivatives (III, IV).

This article describes the preparation of the stereoisomers of the propionylamides (V, VI) and the benzoylamides (VII, VIII), and the study of the pharmacological properties of compounds I-VIII.



I, III, V, VII



II, IV, VI, VII

R = H (I, II), Ac (III, IV), COEt (V, VI), COPh (VII, VIII); R' = $(CH_2)_2OEt$

Propionyl- and benzoylamides V-VIII were prepared by reacting the pure isomers of 4-anilinopiperidine I, II with propionyl and benzoyl chloride in absolute benzene. The purity and structure of the prepared compounds was confirmed by TLC, elemental analyses, and IR and NMR spectral data.

The results of the investigations that were carried out showed that the LD_{50} of the prepared compounds range from 195-680 mg/kg (Table 1). It should be noted that N-phenylamino derivatives I and II are less toxic than the N-phenylacetamido, N-phenylpropionylamido, and N-phenylbenzoylamido substituted piperidines. The compounds have

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