1,2,5-TRIMETHYL-4-ALLYL(PROPARGYL)-4-ARYL(HETARYL)AMINOPIPERIDINES

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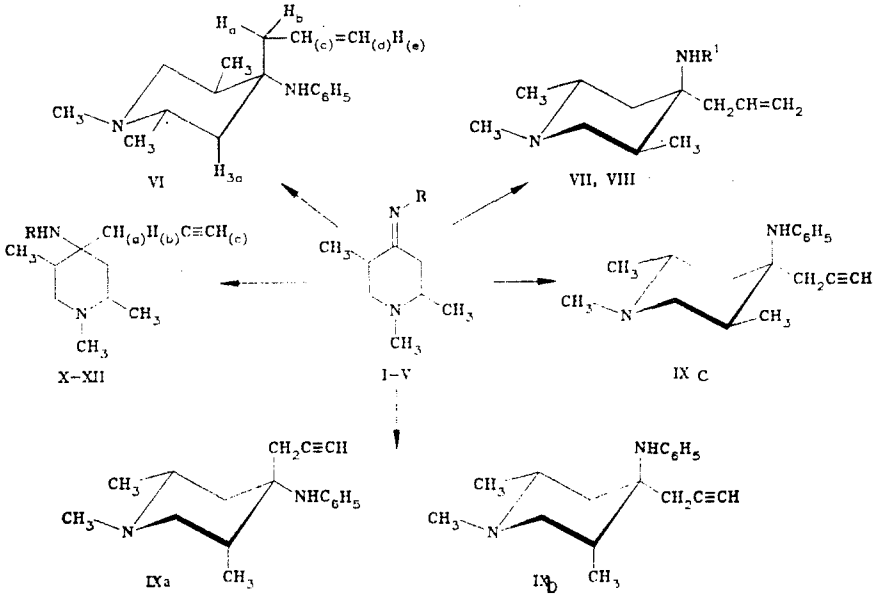
Individual geometrical isomers of some 1,2,5-trimethyl-4-allyl-4-aryl(hetaryl)aminopiperidines were isolated, and their structures were established. 1,2,5-Trimethyl-4-propargyl-4-aryl(aralkyl)aminopiperidines were obtained from 1,2,5-trimethyl-4-aryliminopiperidines and propargylmagnesium bromide.

The production of 1,2,5-trimethyl-4-allyl-4-arylaminopiperidines, which are used in syntheses of condensed heterocyclic compounds [2, 3], has been described [1]. γ-Aminopiperidine derivatives are also of interest as substances that have physiological activity [4]. In connection with the latter, it seemed important to isolate, establish the structures, and study the physiological activity of individual geometrical isomers of compounds of this series.

1,2,5-Trimethyl-4-allyl-4-phenyl[o-methoxyphenyl, p-methoxyphenyl, benzyl]aminopiperidines were previously obtained in the form of mixtures of geometrical isomers in the reaction of 1,2,5-trimethyl-4-phenyl (I)[o-methoxyphenyl (II), p-methoxyphenyl (III), benzyl (IV)]iminopiperidines with allylmagnesium bromide [1, 3]. 1,2,5-Trimethyl-4-(2-thiazolyl)iminopiperidine (V), obtained by reaction with allylmagnesium bromide, also gives a mixture of geometrical isomers of 1,2,5-trimethyl-4-allyl-4-(2-thiazolyl)aminopiperidine.



I R=C_6H_5; II, VIII, X R=R'=$C_6H_4OCH_3$-*o*; III, XI R=$C_6H_4OCH_3$-*p*; IV, XII R= =$C_6H_5CH_2$; V, VII R=2-thiazolyl

The formation of geometrical isomers of the indicated compounds occurs as a result of axial and equatorial attack by allylmagnesium bromide on the C=N bond of imines I, II, and V. 1,2e,5e-Trimethyl-4*a*-allyl-4e-phenylaminopiperidine (VI) and 1,2e,5e-trimethyl-4e-allyl-4*a*-(2-thiazolyl)aminopiperidine (VII) were isolated by means of column chromatography. 1,2e,5e-Trimethyl-4e-allyl-4*a*-(o-methoxyphenyl)aminopiperidine (VIII) was isolated by crystallization of the mixture of 1,2,5-trimethyl-4-allyl-4-(o-methoxyphenyl)aminopiperidine isomers.

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TABLE 1. PMR Spectra of Individual Isomers of Piperidines VI-IX

Compound	Chemical shifts, δ, ppm ($CDCl_3$)*															
	piperidine ring protons						substituent protons									aryl (hetaryl)
	2*a*	3*a*	3*e*	5	6*a*	6*e*	N—CH_3	2-CH_3	5-CH_3	*a*-H	*b*-H	*c*-H	*d*-H	*e*-H	NH	
VI	2,16	1,84	1,63	2,56	2,27	2,74	2,27	1,05	0,90	2,60	2,14	5,91	5,22	5,20	—**	6,79 (*o*); 7,12 (m); 6,76 (n)
VII	2,17	1,48	2,53	2,07	2,20	2,61	2,25	1,06	0,94	2,94	2,39	5,77	5,10	5,07	4,96	7,11 (*f*-H); 6,49 (*g*-H)
VIII	2,15	1,43	2,21	2,07	2,33	2,59	2,24	1,01	0,99	2,71	2,38	5,81	5,04	5,07	4,39	6,67 ... 6,81; 3,86 (OCH_3)
IX a	2,04	1,63	1,81	2,21	2,36	2,66	2,23	1,12	1,25	2,71	2,80	1,94	—	—	—**	6,70 (*o*); 7,14 (m); 6,76 (p)
IX b	2,37	1,46	1,87	2,18	2,83	2,48	2,24	1,10	1,19	2,32	2,42	2,01	—	—	—**	6,83 (*o*); 7,18 (m); 6,84 (p)
IX c	2,24	1,76	2,18	2,49	2,26	2,65	2,27	1,05	0,98	2,80	2,45	2,04	—	—	3,38	6,72 (*o*); 7,16 (m); 6,78 (p)

*With tetramethylsilane (TMS) as the internal standard.
**Could not be assigned.

TABLE 2. Spin-Spin Coupling Constants (SSCC)

Compound	J_{HH}, Hz												
	2*a*3*a*	2*a*3*e*	3*a*3*e*	6*a*6*a*	5*a*6*e*	5*e*6*a*	5*e*6*e*	6*a*6*e*	2*a*, 2-CH_3	5,5-CH_3	3*a*,*b*	*a*,*b*	3*e*5*e*
VI	11,5	2,6	−13,6	11,5	4,2	—	—	−12,0	6,2	7,0	1,5	−14,4	—
VII	11,5	2,4	−14,3	11,7	3,8	—	—	−11,8	6,2	6,8	—*	−14,0	—
VIII	11,1	2,3	−14,0	11,8	4,0	—	—	−11,8	6,2	7,0	—*	−14,4	—
IX a	11,5	2,8	−13,1	—	—	3,4	2,3	−12,3	6,1	7,1	1,4	—	2,0
IX b	11,6	2,7	−14,4	—	—	3,3	2,2	−11,5	6,2	7,1	—*	—	2,2
IX c	11,5	2,4	−14,2	11,7	4,2	—	—	−11,7	6,2	7,0	—*	—	—

*Not observed.

TABLE 3. Physicochemical Characteristics of Piperidines IX-XII

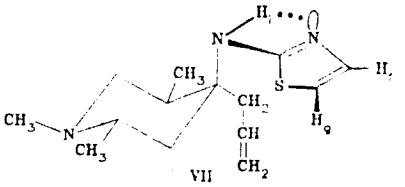
Compound	Empirical formula	bp, °C (mm)	n_D^{20}	IR spectrum, ν, cm⁻¹		m/z(I_{rel}, %)								Yield, %
				NH	≡CH	M⁺	(M−NHR)⁺	(M−NH₂R)⁺	(M−CH₂C≡CH)⁺	(M−NH₂R−CH₂C≡CH)⁺	(M−CH−CH₂C≡CH)⁺	CH₃ | (M−CH−CH₂C≡CH)⁺ | NHR	[(M−CH₃)−CH−CH₃]⁺ | CH≡CCH₂−C−NHR	
IX	$C_{17}H_{24}N_2$	169...171 (7)	1,5521	3420	3300	256 (21)	164 (19)	163 (26)	217 (38)	124 (100)	98 (15)	84 (26)	70 (60)	34
IXa+IXb	$C_{17}H_{24}N_2$	—*	—	3400	3300	256 (51)	164 (30)	163 (18)	217 (52)	124 (100)	98 (12)	84 (9)	70 (57)	23
IXc	$C_{17}H_{24}N_2$	—*	—	3415	3300	256 (38)	164 (12)	163 (16)	217 (36)	124 (100)	98 (6)	84 (10)	70 (50)	12
X	$C_{18}H_{26}N_2O$	165...170 (6)	1,5555	3418	3298	286 (15)	194 (4)	193 (6)	247 (25)	124 (91)	98 (9)	84 (15)	70 (100)	37
XI	$C_{18}H_{26}N_2O$	180...185 (10)	1,5565	3441...3386	3300	286 (18)	194 (5)	193 (8)	247 (32)	124 (64)	98 (8)	84 (16)	70 (100)	30
XII**	$C_{18}H_{26}N_2$	155...160 (15)	1,5415	3380	3300	270 (3)	178 (2)	177 (2)	231 (11)	124 (27)	98 (5)	84 (7)	70 (16)	29

*The R_f values [alufol, ethyl acetate—hexane (1:2)] for the mixture of IX and IXb and for IXc were 0.41 and 0.28, respectively.

**The following ion peaks [m/z (I_{rel}, %)] are also present in the mass spectrum: 91 (95) and 149 (100).

The structures of these compounds were established by PMR spectroscopy. The orientations of the methyl groups in the $C_{(2)}$ and $C_{(5)}$ positions of the piperidine ring were determined on the basis of the trans spin-spin coupling constants (SSCC) $^3J_{5,6}$ taking into account the Karplus dependence [5] (Tables 1 and 2). To establish the orientations of the substituents attached to the $C_{(4)}$ atom we propose a method that is based on the use of the $^4J_{HH}$ constant of spin-spin coupling (SSC) of the 3*a*-H proton of the piperidine ring with one of the protons of the methylene group of the allyl substituent (designated as b-H). A W configuration of the 3*a*-H and b-H protons, which leads to an increase in the $^4J_{HH}$ SSCC, is realized in the case of an axial orientation of the allyl substituent in one of the possible rotamers with respect to the $C_{(4)}-C_{(3')}$ bond [6].

This sort of W configuration is not realized in the case of an equatorial orientation of the allyl substituent, and the corresponding $^4J_{HH}$ SSCC for the 3*a*-H proton is not observed. On the basis of this criterion we were able to establish that the allyl substituent has an axial orientation only in the case of VI ($^4J_{3ab}$ = 1.5 Hz). An axil orientation of the 2-thiazolylamino substituent for aminopiperidine VII was also confirmed by the two-dimensional NOESY spectrum, in which cross peaks from the *a*-3*a*, b-3*a*, *a*-5*a*, and b-5*a* proton pairs. The $^5J_{g\text{-}H,NH}$ SSCC value of 0.8 Hz constitutes evidence for a W configuration of these protons, which is possible when an N···H intramolecular hydrogen bond is present.



VII

The geometry of the VII molecule was optimized by molecular mechanics [7]. The equilibrium $H_i\cdots N$ distance in the VII molecule is 2.38 Å, while the dihedral angle between these atoms $\theta_{H_i-N-C-N}$ = 2°. The calculated distance is less than the sum of the van der Waals radii of the proton and the nitrogen atom (2.75 Å), which additionally confirms the existence of the intramolecular hydrogen bond indicated above.

The condensation of imines I-IV with propargylmagnesium bromide was carried out in the presence of mercury(II) chloride and a crown ether (DB-18-K-6). 1,2,5-Trimethyl-4-propargyl-4-phenyl(IX)[o-methoxyphenyl (X), p-methoxyphenyl (XI), benzyl (XII)]aminopiperidines – oily substances that were fractionated in vacuo – were obtained in moderate yields. The structures of these compounds were established on the basis of IR and mass-spectral data (Table 3). A peculiarity of the fragmentation of IX-XII under electron impact is the formation of $[M - NHR]^+$, $[M - NH_2R]^+$, $[M - CH_2C\equiv CH]^+$, and $[M - NH_2R - CH_2C\equiv CH]^+$ fragments, the appearance of which is due to the presence in the $C_{(4)}$ position of N-arylamino and propargyl substituents. The scanning PMR spectra of γ-propargyl-γ-arylaminopiperidines IX-XII also confirm their structures. However, the detailed interpretation of these spectra is difficult in view of their complexity because of the existence of mixtures of stereoisomers.

Chromatography of the mixture of isomers of IX yielded two substances – a mixture of 1,2e,5*a*-trimethyl-4*a*-propargyl-4e-propargyl-4e-phenylaminopiperidine and 1,2e,5*a*-trimethyl-4e-propargyl-4*a*-phenylaminopiperidine isomers (IXa and IXb) (in a ratio of 2.4:1), as well as 1,2e,5e-trimethyl-4e-propargyl-4*a*-phenylaminopiperidine (IXc). The structures of these compounds were established on the basis of the $^4J_{HH}$ SSCC used in the determination of the structures of individual isomers of γ-allyl-γ-arylaminopiperidines VI-VIII (see Tables 1 and 2).

EXPERIMENTAL

The mass spectra were obtained with an MKh-1303 spectrometer. The IR spectra were recorded with Specord IR-75 (films) and UR-20 (KBr pellets) spectrometers. The PMR spectra of solutions in $CDCl_3$ were recorded with Bruker WP-80 and Bruker VM-400 spectrometers with tetramethylsilane (TMS) as the internal standard. Chromatography was carried out on activity II Al_2O_3.

The results of elementary analysis for N were in agreement with the calculated values.

1,2,5-Trimethyl-4-(2-thiazolyl)iminopiperidine(V, $C_{11}H_{17}N_3S$). This compound was obtained by the method in [8] from 21.3 g (0.15 mole) of 1,2,5-trimethyl-4-piperidinone and 10 g (0.10 mole) of 2-aminothiazole in 100 ml of absolute toluene by heating in the presence of p-toluenesulfonic acid. Workup gave 10.1 g (30%) of V in the form of a vitreous yellowish mass with bp 125-130°C (3 mm) and n_D^{20} 1.5630. IR spectrum (film): 1650 cm^{-1} ($\nu_{C=N}$).

1,2e,5e-Trimethyl-4*a*-allyl-4e-phenylaminopiperidine(VI,$C_{17}H_{23}N_2$). A 0.9-g sample of a mixture of 1,2,5-trimethyl-4-allyl-4-phenylaminopiperidine isomers [1] was chromatographed [H = 50 cm, d = 2.5 cm, elution with ethyl acetate–hexane (1:20)] to give 0.1 g (11.1%) of VI in the form of an oily pale-yellow liquid with R_f 0.37 [alufol, ethyl acetate–hexane (1:2)]. IR spectrum (film): 3410 cm^{-1} (ν_{NH}). Mass spectrum: M^+ 258. Also eluted was 0.6 g (66%) of a substance with R_f 0.60 and 0.81, which, according to the PMR spectral data, was a mixture of isomers – analogs of VI.

1,2e,5e-Trimethyl-4e-allyl-4*a*-(2-thiazolyl)aminopiperidine(VII, $C_{14}H_{23}N_3S$). This compound was obtained by the method in [3] from 4.1 g (0.02 mole) of imine V and allylmagnesium bromide prepared from 2.6 g (0.11 mole) of magnesium and 6.53 g (0.054 mole) of allyl bromide in 50 ml of ether. Workup gave 1.6 g (33%) of the product in the form of a mixture of isomers; the vitreous mass had bp 145-150°C (5 mm) and R_f 0.45, 0.40, and 0.18 [alufol, ethyl acetate–hexane (3:1)]. IR spectrum (film): 3201 cm^{-1} (ν_{NH}). Mass spectrum: M^+ 265. Chromatography of 0.5 g of this mixture (H = 30 cm, d = 1 cm, elution with ethyl acetate) gave 0.1 g (25%) of VII in the form of colorless crystals with mp 55-56°C (from hexane) and R_f 0.18 (with the same system). Mass spectrum: M^+ 265.

1,2e,5e-Trimethyl-4e-allyl-4*a*-(o-methoxyphenyl)aminopiperidine(VIII,$C_{18}H_{28}N_2O$). A 0.3-g sample of the mixture of 1,2,5-trimethyl-4-allyl-4-(o-methoxyphenyl)aminopiperidine isomers [3] was crystallized in hexane. This procedure gave 0.05 g (16%) of VIII in the form of colorless crystals with mp 78-80°C and R_f 0.21 [alufol, ethyl acetate–hexane (1:2)]. IR spectrum (KBr): 3405 cm^{-1} (ν_{NH}).

1,2,5-Trimethyl-4-propargyl-4-phenyl(IX)[o-methoxyphenyl(X), p-methoxyphenyl(XI), benzyl(XII)]aminopiperidines. A solution of 0.2 mole of propargyl bromide in 20 ml of ether was added gradually with gentle refluxing of the ether to a mixture of 0.4 mole of finely cut magnesium and 0.25 g of mercuric chloride in 100 ml of absolute ether, after which the mixture was refluxed for 30 min. A 0.03-g sample of a crown ether (DB-18-K-6) was then added at 20°C, after which a solution of 0.07 mole of imine I-IV in 30 ml of absolute ether was added dropwise, and the mixture was refluxed for 30 min. The unchanged magnesium was separated by filtration, and the solution was treated with a saturated solution of ammonium chloride. The ether layer was separated, and the aqueous layer was extracted with ether (3 × 100 ml). The extract was dried with magnesium sulfate, and the residue from the ether extract was fractionated in vacuo.

Chromatography of the mixture of IX isomers with a column [H = 40 cm, d = 1.5 cm, elution with ethyl acetate–hexane (1:15)] yielded a mixture of isomers IX and IXb and individual isomer IXc.

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