1-METHYL(BENZYL)-2,5-DIMETHYL-4-N-[ARYL(ALKYL)AMINO]PIPERIDINES AND THEIR ACYL DERIVATIVES

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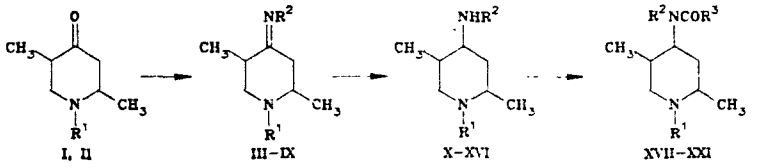
N-Substituted γ-aminopiperidines and their benz- and propioamides have been synthesized from γ-piperidones. The stereoisomeric amines and amides have been separated and identified.

Many derivatives within the 4-aminopiperidine class of compounds are known to exhibit a wide spectrum of pharmacological activity (analgesic, antihistamine activity, etc.); we have thus undertaken the synthesis of ring-substituted secondary 4-aminopiperidines and their N-acylated derivatives. 1,2,5-Trimethylpiperidin-4-one (I) [1] and 1-benzyl-2,5-dimethylpiperidin-4-one (II) [2] were used as the starting materials in these synthesis; they were converted first to Schiff bases, then to secondary amines, and, finally, to the N-acyl derivatives.

Azomethines III-IX were obtained in 50-70% yield by refluxing piperidones I and II with the corresponding primary amines in toluene or benzene solution in the presence of zinc chloride or a catalytic amount of acetic acid [3, 4]; compounds III-VI have been described previously by us [3, 5].



I, III—V, VII—XV, XVII—XX $R^1=CH_3$; II, VI, XVI, XXI $R^1=CH_2C_6H_5$; III, VI, X, XVI, XVII, XXI $R^2=C_6H_5$; IX, XI $R^2=C_6H_4OCH_3$-*p*; V, XII, XVIII, XIX $R^2=2$-C_5H_4N; VII, XIII, XX $R^2=CH_2C_6H_5$; VIII, XIV $R^2=CH_2CH_2OH$; IX, XV $R^2=CH_2CH_2CH_2OH$; XVII, XVIII, XXI $R^3=C_6H_5$; XIX, XX $R^3=C_2H_5$

Secondary amines X-XVI were prepared by sodium borohydride reduction of azomethines III-IX.

All of the secondary amines prepared in this way consisted of mixtures of isomers with different configurations of the methyl groups in the piperidine ring. The individual isomer components of these mixtures were separated chromatographically. The isomeric composition and purity of individual isomers, as well as their configuration determinations, were made on the basis of PMR spectral analysis (400 MHz) together with the necessary ^{13}C-NMR data. The details of these results will be reported separately. We have previously demonstrated [6] that reduction of N-(1,2,5-trimethylpiperidylidene-4)aniline (III) gives a mixture of isomeric 1,2,5-trimethylpiperidyl-4-phenylamines (X). Two isomers,* Xa and b, of the four theoretically possible geometric isomers for this compound, were isolated preparatively. Based on PMR (360 MHz) and ^{13}C-NMR spectral analysis, it was established [6] that one of these isomers was 1-methyl-2-cis-5-cis-dimehtyl-4-r-phenylaminopiperidine (Xa), which had been designated the "δ-isomer), and that of the other isomer was 1-methyl-2-cis-5-trans-dimentyl-4-r-phenylaminopiperidine (Xb), which was called the "δ-isomer). This experiment was repeated and we were able to detect the formation of a third isomer, Xc, which was identified as 1-methyl-2-trans-5-cis-4-r-phenylaminopiperidine based on its PMR spectrum.

*Correct IUPAC nomenclature is used herein, rather than the empirical designations which were used previously.

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TABLE 1. Characteristics of Amines XI-XVI*

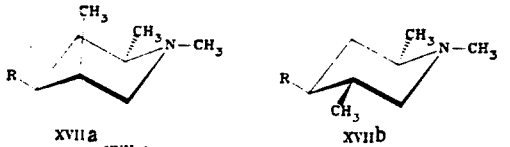
Compound	bp, °C (mm Hg) or mp, °C	n_D^{20}	R_f**	Found N, %	M	Molecular formula	Calc. N, %	M+	^{1}H-NMR (δ, ppm, $CDCl_3$, TMS)	
									N—CH_3	2-CH_3; 5-CH_3
XI	116—120 (5)	1,5459	0,50; 0,23	11,3	248	$C_{15}H_{24}N_2O$		248		
XIa			0,50	11,7			11,3		2,26	0,88—1,23
XIb+XIc			0,23	11,4					2,24	0,93—1,23
XII	120—125 (4)		0,58; 0,23; 0,16	18,1	219+ +18	$C_{13}H_{21}N_3 \cdot H_2O$	17,7	219		
XIIa			0,58	19,1	219	$C_{13}H_{21}N_3$	19,2	219	2,02	0,94; 1,00
XIIb			0,23	19,2					2,05	0,96; 0,88
XIIc	70—73		0,16	19,2					2,04	0,90; 0,80
XIII	131—134 (2)	1,5250	0,61; 0,44; 0,30	12,0	232	$C_{15}H_{24}N_2$	12,1	232	2,19; 2,23; 2,26	0,82—1,18
XIV	114—115 (2)	1,4882	0,42; 0,35; 0,20	15,4		$C_{10}H_{22}N_2O$	15,0	186	2,21; 2,25; 2,33	0,91—1,18
XV	130—131 (5)	1,4879	0,45; 0,40; 0,20	13,8	200	$C_{11}H_{24}N_2O$	14,0	200	2,20; 2,25; 2,27	0,89—1,18
XVIa	88—89		0,80	9,5	294	$C_{20}H_{26}N_2$		294	3,00; 4,07 (N—CH_2)	1,19; 0,93
XVIb+ +XVIc			0,62	9,6			9,5	294	3,00; 4,18	0,92—1,03

*The IR spectra of amines XI-XVI contain νN-H bands in the region 3200-3400 cm^{-1}.
**The following solvents were used: XI, ethyl acetate—heptane, 1:2; XII, ethyl acetate—heptane, 1:1; XIII, ether; XIV and XV, ethyl acetate—heptane, 2:1; and for XVI, ethyl acetate—heptane, 1:3.

Amines XI, XII, and XVI were separated chromatographically in an analogous manner. The following individual isomers, or mixtures of isomers, were isolated in this way: XIa, XIb + XIc, XIIa, XIIb, XIIc, XVIa, XVIb + XVIc. The remaining mixtures of amines XIb + XIc, XIII-XV, and XVIb + XVIc could not be separated into individual components due to the similarities in their chromatographic mobilities. The structures of the newly synthesized amines were confirmed based on their IR and PMR spectral data (Table 1). The homogeneity of the isolated stereoisomers of compounds X-XII and XVI was indicated by the presence of only a single signal for the N-CH_3 group in the range 2.20-2.30 ppm in their PMR spectra.

Propionic acid amide derivatives, in which the amide nitrogen atom contains an aryl or γ-piperidyl substituent [7], are currently receiving intensive study as potential analgesic agents. In a structural sense these compounds appear to be isomers of prodines and promedols [8], in analogy with the propionic esters of γ-piperidols. Benzoylation of the individual isomers of amine X (benzoyl chloride, 150°C) gave the corresponding configurational isomers of N-(1,2,5-trimethylpiperidin-4-yl)-N-phenylbenzamides (XVIIa-c).

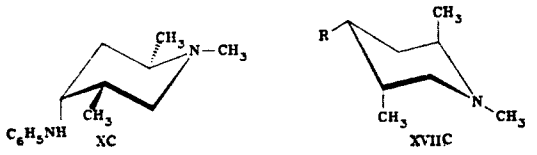
The configurations of the substituents in these amides, as in the corresponding amines, were established based on their PMR spectra. PMR analysis revealed that the 2-cis-5-cis-4-r-isomer of XVIIa exists predominantly in the 2e,4e,5a-conformation, and that the 2-cis-5-trans-4-r- isomer XVIIb consists entirely of the 2e,4e,5e-conformer, just as was true for the corresponding Xa, b amine isomers [6]:



XVIIa XVIIb

XVII a-c R=N(C_6H_5)COC_6H_5

PMR analysis also indicated that isomer XVIIc exists predominantly in a conformation with a diaxial orientation of the 2- and 5-methyl groups, in contrast to the situation with the corresponding amine derivative Xc, where the 2e,4a,5e-conformer predominates:



XC XVIIC

Benzoylation of compound XII also gave a mixture of three stereoisomers. It was possible to separate in this case three crystalline pure benzamides XVIIIa-c by column chromatography of the mixture; these isomers possessed the same configurations as the corresponding isomers of XVII.

Treatment of amine XII with sodium amide, followed by excess propionyl chloride, resulted in the isolation of only one pure isomer of propionamide XIXb, whose structure was confirmed by PMR spectroscopy. The other two isomers of this amide, namely XIXa and XIXc, were contaminated with very small amounts of amine XII impurity, as revealed by the presence of stretching vibrational bands for NH groups at 3200-3400 cm^{-1}, in addition to the intense C=O bands at 1665-1670 cm^{-1}, in their IR spectra. Three stereoisomeric N-benzylpropionamides XX were obtained upon treatment of the mixture of isomers of compound XIII with propionic anhydride. Benzoylation of the pure amine isomer XVIa gave 1-benzyl-2-cis-5-cis-dimethyl-4-(N-benzoylanilido)piperidine (XXI) in 64% yield.

In this way, we have demonstrated for the first time the synthesis of three of the four theoretically possible stereoisomers of 1,2,4,5-tetrasubstituted piperidines.

EXPERIMENTAL

IR spectra were recorded on a Specord IR-75 (using thin films on KBr plates) or a UR-20 spectrophotometer (for KBr pellets). PMR spectra were measured on a Bruker WP-80 spectrometer at 80 MHz. Mass spectra were obtained on an MX-1303 spectrometer with direct sample introduction to the ion stream at an ionizing voltage of 70 eV. Thin layer and column chromatography were carried out on activity II grade alumina.

N-(1,2,5-Trimethylpiperidylidene-4-)benzylamine (VII) [β-hydroxyethylamine (VIII), γ-hydroxypropylamine (IX)]. These were prepared in 76.5, 35, and 72% yields, respectively. Azomethine VII, bp 133-138°C (2 mm Hg); n_D^{17} 1.5380. IR spectrum: (thin film): 1675 cm^{-1} (C=N). . Picrate, mp 186°C (dec., from alcohol). Found: N 15.2%. $C_{15}H_{22}N_2 \cdot C_6H_3N_3O_7$. Calculated: N 15.3%. Azomethine VII, bp 95-98°C (2 mm Hg); n_D^{18} 1.4867. IR spectrum (thin film): 3400 (br, OH) and 1670 (C=N). Picrate, mp 155-158°C (from alcohol). Found: N 17.3%. $C_{10}H_{20}N_2O \cdot C_6H_3N_3O_7$. Calculated: N 16.9%. Azomethine IX, bp 118-120°C (2 mm Hg); n_D^{21} 1.4930. IR spectrum (thin film): 3400 (br, OH), 1670 cm^{-1} (C=N). Picrate, mp 162-164°C (from alcohol). Found: N 16.6%. $C_{11}H_{22}N_2O \cdot C_6H_3N_3O_7$. Calculated: N 16.4%.

N-(Piperidin-4-yl)-N-aryl(alkyl)amines (X-XVI). An alcohol solution of sodium borohydride (5-10 mmole) was treated gradually with 1 mmole of freshly distilled azomethine III-IX in alcohol solution. The mixture was refluxed ca. 10 h, 150 ml water was added, and the mixture was heated again until no more hydrogen was evolved. The alcohol and some of the water was removed by distillation. The reaction products were extracted into ether and dried over magnesium sulfate. Compounds X-XV were isolated by distillation of the residues of these extracts. Compound XVIa was obtained by crystallization of the residue from petroleum ether. The physical chemical characteristics of amines X-XVI are summarized in Table 1.

1,2,5-trimethyl-4-N-(benzoylanilido)piperidines (XVIIa-c). A. Amine Xa (1.5 g, 6.8 mmole) was treated with 1.8 g (13 mmole) of benzoyl chloride and the mixture was heated at 150°C for 15 min. The experiment was carried out under an argon stream. Water (50 ml) was added and the solution was saturated with KOH. The mixture was extracted with ether. The residue remaining after evaporation of the ether (2.1 g) was crystallized from hexane. Yield 0.5 g (23%) of amide XVIIa as colorless prisms, mp 121-122°C, R_f 0.42 (ethyl acetate–hexane, 1:2). IR spectrum (KBr): 1670 cm^{-1} (C=O). Found: C 78.5, H 7.8, N 8.6%. M^+ 322. $C_{21}H_{26}N_2O$. Calculated: C 78.6, H 8.0, N 8.6%. M 322. The mother liquor was also evaporated and the residue (1.5 g) chromatographed (h = 60 cm, d = 2.5 cm ethyl acetate–hexane, 1:10). Isolated: 0.5 g of starting amine Xa and 0.7 g of amide XVIIa were isolated. Total yield of the latter, 55%.

B. Amine Xb (0.17 g, 0.8 mmole) and 0.2 g (1.1 mmole) of benzoyl chloride were used. The experiment was carried out in an analogous manner to that described above. Isolated yield 0.13 g (52%) of amide XVIIb, mp 78-80°C (from heptane), R_f 0.57 (ethyl acetate–heptane, 2:1). IR spectrum (KBr): 1660 cm^{-1} (C=O). Found: N 8.4%. M^+ 322. $C_{21}H_{26}N_2O$. Calculated: N 8.6%. M 322.

C. In an analogous manner, 2.4 g (11 mmole) of a mixture of amines Xb and c and 3.6 g (20 mmole) of benzoyl chloride gave 0.7 g (30%) of amide XVIIc, as needle-shaped crystals, mp 118-120°C (from hexane), R_f 0.27 (ethyl acetate–hexane, 1:1). IR spectrum (KBr): 1653 cm^{-1} (C=O). Found: C 78.4, H 8.0, N 8.5%. M^+ 322. $C_{21}H_{26}N_2O$. Calculated: C 78.6, H 8.0, N 8.6%.

M 322. The mother liquor was concentrated and the residue (1.55 g) chromatographed under the same conditions as in part A. Yield 0.65 g of a mixture of compounds with R_f values 0.3 and 0.28, as well as 0.75 g of amide XVIIc (total yield, 58%).

N-(1,2,5-Trimethylpiperidin-4-yl)-N-(pyridyl-2)benzamide (XVIII). A mixture of 1.4 g (4 mmole) of amine XII and 2.16 g (15 mmole) benzoyl chloride was heated 30 min under a stream of nitrogen. After conventional workup as above, 1.9 g (91%) of benzamide XVIII was obtained. The mixture (1.3 g) of isomers of compound XVIII was chromatographed (h = 48 cm, d = 2.5 cm). The column was eluted successively with heptane, mixtures of ethyl acetate and heptane, in ratios from 1:20 to 1:5, and finally with ethyl acetate, collecting 15 ml fractions. The isomers of compound XVIII were separated successively. Isomer XVIIIa, 0.22 g (17%), mp 131-132°C (from heptane), R_f 0.63 (ethyl acetate–hexane, 2:1). IR spectrum (KBr): 1655 cm^{-1} (C=O). Found: C 74.1, H 7.8, N 13.0%. M^+ 323. $C_{20}H_{25}N_3O$. Calculated: C 74.3, H 7.7, N 13.0%. M 323. Isomer XVIIIb, 0.24 g (18.5%), mp 74-76°C (from heptane), R_f 0.41. IR spectrum (KBr): 1680 cm^{-1} (C=O). Found: N 12.7%. M^+ 323. $C_{20}H_{25}N_3O$. Calculated: N 13.0%. M 323. Isomer XVIIIc, 0.34 g (26%), mp 126-129°C (from heptane), R_f 0.13. IR spectrum (KBr): 1665 cm^{-1} (C=O). Found: C 74.1, H 7.7, N 13.0%. M^+ 323. $C_{20}H_{25}N_3O$. Calculated: C 74.3, H 7.7, N 13.0%. M 323.

N-(1,2,5-Trimethylpiperidin-4-yl)-N-(2-pyridyl)propionamide (XIX). To 0.88 g (20 mmole) of sodium amide in 40 ml absolute ether was added 4.3 g (19 mmole) amine XII. The mixture was stirred 3 h under nitrogen. Propionyl chloride (6.0 g, 60 mmole) was then added dropwise at 0°C. The mixture was stirred 3 h at 20°C and 4 h in refluxing ether. The mixture was worked up with water and KOH, and extracted with ether. Yield 5.13 g (95%) of a mixture of impure isomers of propionamide XIX. The mixture (1.5 g) was chromatographed under the same conditions as above. Yield 0.26 g (17%) of amide XIXa, as a yellow oil, R_f 0.52 (ethyl acetate–hexane, 2:1). IR spectrum (thin film): 1675 (C=O), 3380 cm^{-1} (NH). Found: N 15.6%, M^+ 219, 275. $C_{16}H_{25}N_3O$. Calculated: N 15.3%. M 275. This was followed by 0.22 g (14.5%) of isomer XIXb, mp 76-78°C (from heptane), R_f 0.39. IR spectrum (KBr): 1667 cm^{-1} (C=O). Found: C 69.8, H 9.0, N 15.4%. M^+ 275. $C_{16}H_{25}N_3O$. Calculated: C 69.8, H 9.1, N 15.3%. M 275. Finally, 0.36 g (23.7%) of amide XIXc was separated by chromatography as an oil, R_f 0.19. IR spectrum (thin film): 1665 (C=O) and 3280 cm^{-1} (NH). Found: N 16.0%. M^+ 219 and 275. $C_{16}H_{25}N_3O$. Calculated: N 15.3%. M 275. A mixture of compounds (0.4 g) was also isolated.

N-(1,2,5-Trimethylpiperidin-4-yl)-N-benzylpropionamide (XX). A mixture of 2.11 g (9.1 mmole) of isomeric amines XIII and 4.0 g (30 mmole) propionic anhydride was refluxed for 12 h. The reaction mixture was worked up with 50 ml water and sodium carbonate to a pH of 8-9. The mixture was extracted with ether, and the extract was dried over magnesium sulfate. After solvent evaporation, 1.9 g (73%) of a mixture of isomers of amide XX was obtained, R_f 0.69, 0.36, and 0.18 (ether). IR spectrum (thin film): 1655 cm^{-1} (C=O). Found: N 9.3%. M^+ 288. $C_{18}H_{28}N_2O$. Calculated: N 9.7%. M 288.

1-Benzyl-2,5-dimethyl-4-N-(benzoylanilido)piperidine (XXI). To 0.2 g (0.68 mmole) of amine XVIa was added 0.15 g (1.06 mmole) benzoyl chloride and the mixture was heated at 150°C for 20 min. Twenty ml of water were added and the mixture was saturated with KOH. The mixture was extracted with ether and dried over magnesium sulfate. The residue (0.2 g) after solvent evaporation was crystallized from hexane. Yield 0.16 g (64%) of amide XXIa as crystalline needles, mp 132-133°C, R_f 0.61 (ethyl acetate–heptane, 1:3). IR spectrum (KBr): 1655 cm^{-1} (C=O). Found: N 6.4%. M^+ 398. $C_{27}H_{30}N_2O$. Calculated: N 6.7%. M 398.

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