SYNTHESIS OF 4-SUBSTITUTED 1-METHYL(BENZYL)-2,5-DIMETHYL-4-R-AMINOPIPERIDINES

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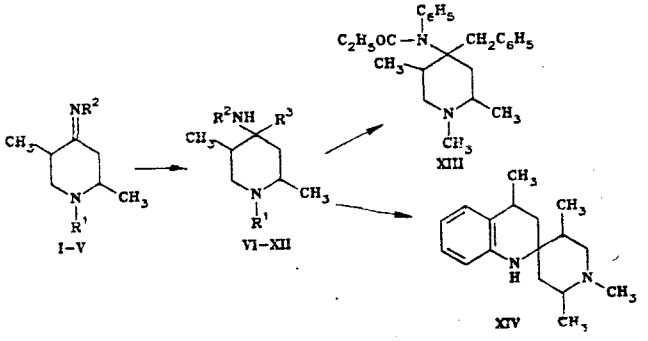
Schiff base derivatives of 1-methyl(benzyl)-2,5-dimethylpiperidin-4-ones with phenyl, α-pyridyl, benzyl, and β-hydroxyethyl substituents attached to the imine nitrogen atom react with organometallic compounds to give analogously substituted piperidine bases with methyl, allyl, phenyl, and benzyl substituents in the 4-position. Pure individual geometric isomers of these newly synthesized compounds have been isolated and their structures determined.

The reaction of Schiff bases with Grignard reagents has been known for more than 70 years [1]. This method has been applied to the synthesis of amines with physiological activities [2]. The most interesting compounds in this regard are azomethines prepared in quantitative yields from γ-piperidones. There have been only limited reports concerning the reactions of these types of derivatives with organometallic compounds [3].

As part of our continuing studies of the synthesis and three dimensional structures of γ-aminosubstituted piperidines, we have examined the preparation of potential biologically active γ-aminopiperidine derivatives from azomethines synthesized from 1-methyl(benzyl)-2,5-dimethylpiperidin-4-ones with the corresponding aromatic, aliphatic-aromatic, and aliphatic amines. 1,2,5-Trimethyl-4-N-phenyl(α-pyridyl, benzyl, β-hydroxyethyl)iminopiperidines (I-IV) and 1-benzyl-2,5-dimethyl-4-N-phenyliminopiperidine (V) [3, 4] were used as the starting materials for these syntheses. Special attention was paid in this study of their reactions with organometallic compounds to the possibility of the formation of geometric isomers, since the addition of organometallic compounds to the imine double bond results in the formation of products with three asymmetric centers. In several cases it was possible to determine using PMR spectroscopy the formation of several isomers and to show the structures of these isomers, which were isolated in pure form by chromatography.

Reaction of azomethine I with benzylmagnesium chloride (bromide) gave one of the isomers of 1,2,5-trimethyl-4-benzyl-4-N-phenylaminopiperidine (VI, mp 134-134.5°C).



I—IV, VI—XI $R^1=CH_3$; V, XII $R^1=CH_2C_6H_5$; I, V—VII, XII $R^2=C_6H_5$; II, VIII, IX $R^2=\alpha$-C_5H_5N; III, X $R^2=CH_2C_6H_5$; IV, XI $R^2=CH_2CH_2OH$; VI $R^3=CH_2C_6H_5$; VII, IX, XII $R^3=CH_2CH=CH_2$; VIII $R^3=CH_3$; X, XI $R^3=C_6H_5$

Based on its PMR spectral data, the isolated geometric isomer of compound VI is assigned the structure 1-methyl-2r,5c-dimethyl-4t-benzyl-4c-phenylaminopiperidine. The structure was confirmed by the values of the vicinal spin-spin coupling constants for the piperidine ring protons: $J_{3e4e} = 2.5$, $J_{3e4a} = 3.5$, $J_{2a3a} = 11.0$, and $J_{2a,3e} = 2.5$ Hz. The most probable axial orientation of the benzyl substituent is supported by the observation of a quite large

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nonequivalence for the methylene protons attached to the $C_{(4)}$ asymmetric carbon atom (3.32 ppm), $\Delta\nu_{AB}$ = 67, J_{AB} = 13.5 Hz. Based on this data, the isolated aminopiperidine isomer VI is assigned the structure 1-methyl-2e,5a-dimethyl-4a-benzyl-4e-phenylaminopiperidine.

Reaction of azomethine I with allylmagnesium bromide gave 1,2,5-trimethyl-4-allyl-4-N-phenylaminopiperidine (VII) in 80% yield. According to TLC, this product consits of a mixture of three geometric isomers. The PMR spectral data verify the structure of compound VII, and the presence of three signals due to the methyl groups attached to the nitrogen atom supports the conclusion that the mixture contains three of the four possible geometric isomers, differing in the positions of the substituents in the 2, 4, and 5-positions.

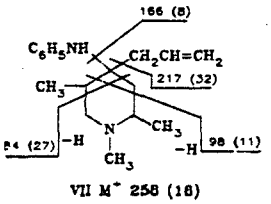
Reaction of azomethine II with methylmagnesium iodide or allylmagnesium gave 1,2,4,5-tetramethyl-4-N-(α-pyridyl)aminopiperidine (VIII) and 1,2,5-trimethyl-4-allyl-4-N-(α-pyridyl)-aminopiperidine (IX), respectively, as mixtures of geometric isomers, which were isolated via their corresponding picrates.

Reaction of azomethine III with phenyllithium gave a low yield of one of the possible isomers of 1,2,5-trimethyl-4-phenyl-4-N-benzylaminopiperidine (X). In a similar manner, a very small yield of 1,2,5-trimethyl-4-phenyl-4-N-(β-hydroxyethyl)aminopiperidine (XI) was obtained from the reaction of imine IV with phenyllithium. The low yields of compounds X and XI, which were isolated in the form of one of their isomers, can be attributed to the relative instabilities of the Schiff base starting materials, which decompose to their constituent components.

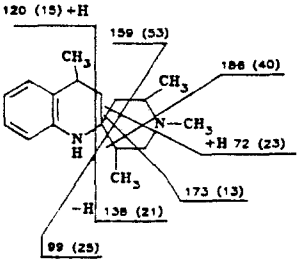
Reaction of the 1-benzylsubstituted azomethine V with allylmagnesium bromide gave 1-benzyl-2,5-dimethyl-4-allyl-4-N-phenylaminopiperidine (XII) as a mixture of isomers. N-(1, 2,5-trimethyl-4-benzylpiperidin-4-yl)propanilide (XIII) was prepared from amine VI and propionic anhydride in order to study its biological properties.

The γ-aminopiperidines studied herein are of interest as starting materials for the synthesis of novel heterocyclics. We have examined the possibility of carrying out the intramolecular cyclization of γ-allylcontaining γ-phenylaminopiperidine VII. 5a,6,7,12-tetrahydro-1,3,4,7-tetramethylspiro(quinoline-2,4-piperidine) (XIV) was obtained upon heating VII with sulfuric acid.

The spiro compound XIV was isolated as a glassy substance, which could be distilled under vacuum. The PMR spectrum of this compound did not contain any vinyl proton signals in the 4-6 ppm region, which are characteristic of the starting material VII, and the IR spectrum retained the band due to the secondary amino group.



VII M^+ 258 (18)



XIV M^+ 258 (100)

Amine VII and spirocompound XIV appear to be isomers based on their quantitative and qualitative compositions. In order to conform their structures, their mass spectra, as well as the mass spectra of their deuterated analogs, were investigated. The presence of molecular peaks at 258* correspond to the molecular formulas of compounds VII and XIV. However, the two compounds exhibit different mass spectra, which verifies the structural difference of these two compounds. The presence of a piperidine ring with three substituents in compound VII is supported by the appearance of ions at 84 and 98, which can be attributed to ring cleavage at the $C_{(3)}$—$C_{(4)}$, $C_{(5)}$—$C_{(6)}$, and $C_{(2)}$—$C_{(3)}$, $C_{(4)}$—$C_{(5)}$ bonds, respectively [5]. The presence of two substituents attached to the 4-position is indicated by the appearance of the following fragments, $[M - CH_2CH{=}CH_2]^+$ (217), $[M - NHC_6H_5]^+$ (166), $[M - NH_2C_6H_5]^+$ (165), and the maximum intensity ion peak for $[M - CH_2CH{=}CH_2, {-}NH_2C_6H_5]^+$ (124). In the mass spectrum of the deutero analog of VII, the 217 ion peak is shifted by 1 a.u. toward higher m/e values.

*The numbers given for the ions correspond to m/e values.

The presence of a piperidine ring in compound XIV is confirmed by the formation of characteristic decay fragments at 72, 99, 159, 173, and 186. The latter three peaks are shifted 1 a.u. toward higher m/e values in the mass spectrum of the deutero analog of XIV. The presence of a tetrahydroquinoline ring in spiro compound XIV is supported by the appearance of ions at 120 and 138, corresponding to retro-diene decomposition [6], with retention of charge at one or the other of the two rings. The formation pathway for the first of these ions is consistent with the observed 1 a.u. shift to higher m/e values in the mass spectrum of the deuteroanalog; the genetic relationship of these two ion peaks is demonstrated by the presence of a metastable ion peak mat m* = 73.8, corresponding to the transition $258^+ \rightarrow 138^+ + 120$.

EXPERIMENTAL

PMR spectra were measured on a Bruker WP-80 (80 MHz) spectrometer for $CDCl_3$ solutions. IR spectra were recorded on a Specord IR-75 spectrophotometer using thin films between KBr plates, and on a UR-20 spectrophotometer for KBr pellets. Mass spectra were obtained on an MS-1303 spectrometer at an ionizing voltage of 70 eV. Thin layer and column chromatography were carried out on activity II grade alumina.

1,2,5-Trimethyl-4-benzyl-4-N-phenylaminopiperidine (VI). Benzylmagnesium chloride, prepared from 7.6 g (0.06 mole) benzyl chloride and 4.0 g (0.16 mole) magnesium in 250 ml absolute ether, was treated dropwise over a 2 h period with a solution of 5.2 g (0.024 mole) freshly distilled azomethine I in 50 ml ether. The mixture was reflexed for 8 h. A 100 ml-volume of water was added, and the mixture was worked up with hydrochloric acid. The neutral products were extracted into ether. The aqueous solution was then treated with sodium carbonate, and the mixture was extracted with ether and dried over magnesium sulfate. The residue from the ethereal extract was distilled to give 2.86 g of a mixture of aniline and 1,2,5-trimethylpiperidin-4-one (82-83°C) (17 hPa). The pot residue was crystallized from petroleum ether. Yield 1.1 g (46% based on reacted azomethine) of compound VI, as crystalline plates, mp 134-134.5°C (from hexane). R_f 0.7 (ethyl acetate–hexane, 1:2). IR spectrum (KBr): 3435 cm^{-1} (NH). Found: C 81.9, H 9.2, N 8.9%. M^+ 308. $C_{21}H_{28}N_2$. Calculated: C 81.8, H 9.1, N 9.1%. M 308.

1,2,5-Trimethyl-4-allyl-4-N-phenylaminopiperidine (VII). Allylmagnesium bromide, prepared from 12.0 g (0.1 mole) allyl bromide and 9.0 g (0.38 mole) magnesium in 200 ml ether, was treated dropwise with a solution of 10.0 g (0.05 mole) azomethine I in 50 ml ether. The mixture was refluxed for 6 h and then 50 ml of water was added, followed by 20 ml of hydrochloric acid. The mixture was extracted with chloroform. The acidic solution was saturated with sodium carbonate, extracted with chloroform, and dried over sodium sulfate. Chloroform was evaporated and the residue (10.2 g) was distilled to give 9.15 g (80%) of compound VII as a light yellow liquid, bp 114-115°C (1.3 hPa), n_D^{20} 1.5490, R_f 0.60, 0.55, and 0.40 (ethyl acetate–hexane, 1:3). IR spectrum (thin film): 3425 cm^{-1} (NH). PMR spectrum: 0.88-1.22 (2-CH_3, 5-CH_3), 2.20, 2.21, 2.24 (N–CH_3); 5.0-6.25 ppm (–CH=CH_2). Found: C 79.0, H 10.3, N 11.2%. M^+ 258. $C_{17}H_{26}N_2$. Calculated: C 79.1, H 10.1, N 10.8%. M 258.

1,2,4,5-Tetramethyl-4-N-(α-pyridyl)aminopiperidine (VIII). Methylmagnesium iodide (from 5.2 g methyl iodide and 3.0 g magnesium in 125 ml ether) and 2.15 g (9.9 mmole) of azomethine II gave, in an analogous manner, 1.78 g (79%) of compound VIII as a mixture of geometric isomers. This in turn gave 4.2 g (80%) of a dipicrate of compound VIII, mp 173°C (from alcohol, dec.). Found: N 18.5%. $C_{14}H_{23}N_3 \cdot 2C_6H_3N_3O_7$. Calculated: N 18.2%. The dipicarate decomposes on alumina upon elution with chloroform. Isolated yield 1.57 g (70%) of compound VIII as a mixture of isomers, R_f 0.43, 0.29, and 0.14 (ethyl acetate–heptane, 2:1). IR spectrum (thin film): 3200 cm^{-1} (NH). Found: N 18.3%. M^+ 233. $C_{14}H_{23}N_3$. Calculated: N 18.0% M 233.

1,2,5-Trimethyl-4-allyl-4-N-(α-pyridyl)aminopiperidine (IX). In an analogous manner, reaction of imine II with allylmagnesium bromide gave the dipicrate of compound IX in 70% yield, mp 162-165°C (from alcohol). Found: N 17.5%. $C_{16}H_{25}N_3 \cdot 2C_6H_3N_3O_7$. Calculated: N 17.6%. Decomposition of the picrate gave compound IX as a mixture of geometric isomers as an oily substance, R_f 0.75, 0.54, 0.31 (ethyl acetate–heptane, 2:1). IR spectrum (thin film): 3405 cm^{-1} (NH). Found: N 16.4%. M^+ 259. $C_{16}H_{25}N_3$. Calculated: N 16.3%. M 259.

1,2,5-Trimethyl-4-phenyl-4-N-benzylaminopiperidine (X). The reaction was carried out with 7.0 g (30 mmole) of azomethine III and a twofold molar ratio of phenyllithium. The experiment was conducted in a manner similar to the preparation of compound VI. Chromatography of the pot residue of the basic reaction products (3.0 g, h = 62 cm, d = 3.5 cm, mixture of

ethyl acetate–heptane, 1:20) resulted in the isolation of 0.9 g (10% based on imine conversion) of compound X, mp 81.5-83°C (from heptane), R_f 0.45 (ethyl acetate–hexane, 1:1). IR spectrum (CCl_4): 3450, 3360 cm^{-1} (NH). PMR spectrum: 0.40 and 0.98 (5-CH_3 and 2-CH_3), 2.26 ppm (N-CH_3). Found: C 81.6, H 9.2, N 9.2%. M^+ 308. $C_{21}H_{28}N_2$. Calculated: C 81.8, H 9.1, N 9.1%. M 308.

1,2,5-Trimethyl-4-phenyl-4-N-(β-hydroxyethyl)aminopiperidine (XI). Phenyllithium was prepared from 0.3 g (42 mmole) lithium and 6.45 g (40 mmole) bromobenzene in 100 ml ether. A solution of 4.0 g (20 mmole) imine IV in 20 ml ether was added gradually to it. After an analogous workup of the residue (2.15 g) of the basic reaction products, 1.5 g of a mixture of 1,2,5-trimethylpiperidin-4-one and ethanolamine were isolated [46-50°C (1 mm Hg)], while the pot residue yielded 0.3 g (11%) of compound XI, mp 98.5-100°C (from hexane), R_f 0.42 (ethyl acetate). IR spectrum (KBr): 3380 (OH assoc.), 3170 cm^{-1} (NH). PMR spectrum: 0.59 and 1.14 (2-CH_3 and 5-CH_3), 2.33 ppm (N–CH_3). Found: N 10.8%. M^+ 262. $C_{16}H_{26}N_2O$. Calculated: N 10.7%. M 262.

1-Benzyl-2,5-dimethyl-4-allyl-4-N-phenylaminopiperidine (XII). Imine V and allylmagnesium bromide gave piperidine XII in a manner similar to that used for the preparation of compound VI. The reaction product was isolated chromatographically in the form of an oil (33.5%), R_f 0.80 (ethyl acetate–heptane, 1:4). IR spectrum (thin film): 3410 cm^{-1} (NH). PMR spectrum: 0.75-1.23 (2-CH_3 and 5-CH_3); 4.01 and 4.18 ppm (N–$CH_2C_6H_5$). Found: C 82.4, H 9.3, N 8.5%. M^+ 334. $C_{23}H_{30}N_2$. Calculated: C 82.6, H 9.0, N 8.4%. M 334.

N-(1,2,5-Trimethyl-4-benzylpiperidin-4-yl)propanilide (XIII). A mixture of 0.5 g (1.6 mmole) amine VI and 5.0 g (40 mmole) propionic anhydride was refluxed for 12 h. Water (30 ml) was added, and the mixture was treated with sodium carbonate, extracted with ether, and dried over magnesium sulfate. The residue remaining after ether evaporation (0.6 g) was crystallized from heptane. Yield 0.23 g (38%) of compound XIII as colorless crystals, mp 153-155°C, R_f 0.52 (ethyl acetate–heptane, 2:5). IR spectrum (KBr): 1665 cm^{-1} (CO). Found: C 79.4, H 8.8, N 7.6%. M^+ 364. $C_{24}H_{32}N_2O$. Calculated: C 79.1, H 8.8, N 7.7%. M 364.

5a,6,7,12-Tetrahydro-1,3,5,7-tetramethylspiro(quinoline-2,4'-piperidine) (XIV). A mixture of 0.7 g (2.7 mmole) of isomeric amines VII and 5 ml concentrated H_2SO_4 was heated at 80-85°C for 1 h and 30 min. After cooling (50 g ice) the mixture was neutralized with 25 ml of a 25% solution of ammonia. The mixture was extracted with ether and dried over magnesium sulfate. The residue gave, after distillation, 0.46 g (65.7%) of compound XIV as a glassy yellow mass, bp 149-151°C (1.3 hPa), R_f 0.77 and 0.50 (ether). IR spectrum (thin film): 3407 cm^{-1} (NH). PMR spectrum: 0.83-1.37 (methyl groups); 2.25 and 2.30 ppm (N–CH_3). Found: C 79.3, H 10.1, N 10.8%. M^+ 258. $C_{17}H_{26}N_2$. Calculated: C 79.1, H 10.1, N 10.8%. M 258.

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