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SYNTHESIS AND STRUCTURES OF METHYL-SUBSTITUTED 1,2,4,5-TETRAHYDRO-3H-SPIRO(BENZ-2-AZEPINE-3,4′-PIPERIDINES)

V. V. Kuznetsov, S. V. Lantsetov, A. É. Aliev, A. V. Varlamov, and N. S. Prostakov

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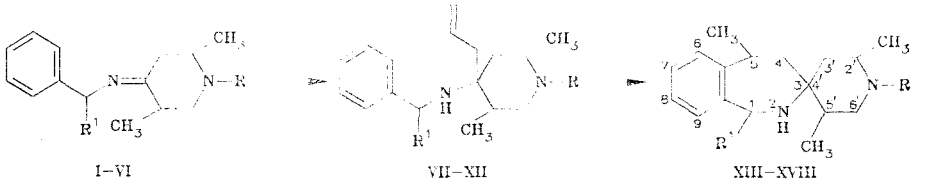
Methyl-substituted 1,2,4,5-tetrahydro-3H-spiro(benz-2-azepine-3,4′-piperidines) were obtained by the intramolecular cyclization of 4-allyl-4-N-benzyl(α-phenylethyl)aminopiperidines in an acidic medium. The individual isomers of 1′-benzyl-2′,5,5′-trimethyl-1,2,4,5-tetrahydro-3H-spiro(benz-2-azepine-3,4′-piperidine) were isolated, and their structures were established.

We have developed a preparative method for obtaining 1,2,3,4-tetrahydro-4-methylspiro(quinoline-2,1′-cycloalkanes) and -spiro(quinoline-2,4′-piperidines) by the intramolecular cyclization in an acidic medium of 1-N-arylaminocycloalkanes and 4-allyl-4-N-arylaminopiperidines, which were obtained from the corresponding Schiff bases and allylmagnesium bromide [1-3].

In the present research this method was used for the synthesis of compounds that are related to a new heterocyclic system — 1,2,4,5-tetrahydro-3H-spiro(benz-2-azepine-3,4′-piperidine).

The starting N-(1-methyl-, N-(1-n-propyl-, and N-(1-benzyl-2,5-dimethyl-4-piperidylidene)benzylamines (I, II, and III) and N-(1-methyl-, N-(1-n-propyl-, and N-(1-benzyl-2,5-dimethyl-4-piperidylidene)-α-phenylethylamines (IV, V, and VI) were obtained by condensation of the corresponding 4-piperidinones [4, 5] with benzyl- and α-phenylethylamines (see Table 1). Molecular-ion peaks corresponding to their empirical formulas are observed in the mass spectra of I-VI. The IR spectra contain an intense band of stretching vibrations of a C=N bond at 1669-1680 cm^{-1}.



I–VI VII–XII XIII–XVIII

I, IV, VII, X, XIII, XVI R=CH_3, II, V, VIII, XI, XIV, XVII R=$CH_2CH_2CH_3$, III, VI, IX, XII, XV, XVIII R=$CH_2C_6H_5$; I—III, VII—IX, XIII—XV R^1=H, IV—VI, X—XII, XVI—XVIII R^1=CH_3

1-Methyl-, 1-n-propyl-, and 1-benzyl-2,5-dimethyl-4-allyl-4-N-benzylaminopiperidines (VII, VIII, and IX) and 1-methyl-, 1-n-propyl-, and 1-benzyl-2,5-dimethyl-4-allyl-4-N-(α-phenylethyl)aminopiperidines (X, XI, and XII) were synthesized in 49-77% yields from Schiff bases I-VI and allylmagnesium bromide. Imine I and aminopiperidine VII were previously described in [2].

According to TLC data, aminopiperidines VII-XII are mixtures of stereoisomers. The molecular-ion peaks in the mass spectra of VII-XII correspond to their empirical formulas. The absorption bands in the IR spectra at 3310-3342 and 1620-1648 cm^{-1} confirm the presence of NH and CH=CH_2 groups.

1,2,4,5-Tetrahydro-1′,2′,5,5′-tetramethyl-, -2′,5,5′-trimethyl-1′-n-propyl-, -2′,5,5′-trimethyl-1′-benzyl-, -1,1′,2′,5,5′-pentamethyl-,-1,2′,5,5′-tetramethyl-1′-n-propyl-,and-1,2′,5,5′-tetramethyl-1′-benzyl-3H-spiro(benz-2-azepine-3,4′-piperidines) (XIII-XVIII), respectively, are formed in 29-52% yields from aminopiperidines VII-XII by the action of sulfuric acid as a result of intramolecular cyclization. Spiro compounds XIII-XVIII are complex mixtures of isomers. This is due to the fact that starting N-substituted allylaminopiperidines VII-XII are mixtures of isomers with respect to the location of the methyl groups in the $C_{(2')}$ and $C_{(5')}$ positions of the piperidine ring, as indicated by the presence of two signals from the protons of the N—CH_3 group in the PMR spectra of X, XIII,

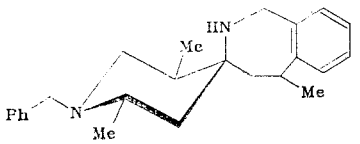
Patrice Lumumba International-Friendship University, Moscow 117198. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1528-1532, November, 1991. Original article submitted July 17, 1990.

TABLE 1. Physicochemical Characteristics of Imines II-VI

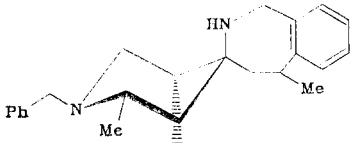
Compound	Empirical formula	bp (mm)	n_D^{20}	M^+	Yield, %
II	$C_{17}H_{26}N_2$	162...166 (5)	1,5341	258	54
III	$C_{21}H_{26}N_2$	204...207 (5)	1,5663	306	77
IV	$C_{16}H_{24}N_2$	124...128 (2)	1,5273	244	49
V	$C_{18}H_{28}N_2$	152...156 (6)	1,5256	272	49
VI	$C_{22}H_{28}N_2$	175...178 (3)	1,5685	320	65

and XVI (see Table 2). Spiro compounds XVI-XVIII are also isomers with respect to the mutual orientation of the methyl groups in the tetrahydrobenzazepine fragment. Because of this, the complete assignment of the signals in the PMR spectra of XIII-XVIII is difficult. The PMR spectra of XIII-XVIII (Table 1) are characterized by the presence at 1.27-1.34 ppm of a doublet from the protons of a methyl group attached to the $C_{(5)}$ atom and, in addition to this, for spirans XVI-XVIII, by the presence of a doublet signal at 1.45-1.52 ppm from the protons of a 1-CH_3 group. Molecular-ion peaks corresponding to their empirical formulas are observed in the mass spectra of XIII-XVIII. The IR spectra contain a band of stretching vibrations of an N—H group at 3329-3351 cm^{-1}.

By crystallization from hexane spiro compound XV was separated into individual isomers — isomer XVa (colorless crystals with mp 135.5-136.5°C) and isomer XVb (a pale-yellow oil). The configurations of the substituents in these stereoisomers were established by means of high-resolution PMR spectroscopy (see Table 3).



XVa



XV b

The vicinal $^3J_{23a}$, $^3J_{56a}$, and $^3J_{4a5a}$ spin-spin coupling constants (SSCC) indicate a diequatorial orientation of the methyl groups attached to the $C_{(2')}$ and $C_{(5')}$ atoms of the piperidine ring and a pseudoequatorial orientation of the methyl group attached to the $C_{(5)}$ atom for isomer XVa. The values of the same constants constitute evidence for an equatorial orientation of the methyl group attached to the $C_{(2')}$ atom, an axial orientation of the methyl group attached to the $C_{(5')}$ atom, and a pseudoequatorial orientation for the methyl group attached to the $C_{(5)}$ atom for isomer XVb. An axial orientation of the NH fragment in the 4′ position of the piperidine ring was assigned for isomers XVa and XVb on the basis of the conformational energies of alkyl and aminoalkyl substituents [6].

EXPERIMENTAL

The IR spectra of films of the compounds were recorded with a Specord IR-75 spectrometer. The PMR spectra of solutions of the compounds in $CDCl_3$ were recorded with Bruker WP-80 (80 MHz) and WM-400 (400 MHz) spectrometers with tetramethylsilane (TMS) as the internal standard. Plates with a fixed layer of Alufol aluminum oxide and a heptane—ethyl acetate (3:1) solvent system were used for TLC. The results of experimental analysis for C, H, and N were in agreement with the calculated values. The physicochemical characteristics of the compounds are presented in Tables 1 and 2.

N-(1-n-Propyl- and N-(1-Benzyl-2,5-dimethyl-4-piperidylidene)benzylamines (II and III) and N-(1-Methyl-, N-(1-n-Propyl-, and N-(1-Benzyl-2,5-dimethyl-4-piperidylidene)-α-phenylethylamines (IV-VII). These compounds were obtained by refluxing equimolar amounts of benzylamine or (α-phenylethyl)amine and the corresponding 4-piperidinones in toluene with removal of the water by azeotropic distillation [7, 8]. The residue after removal of the toluene by distillation was fractionated in vacuo.

1-n-Propyl- and 1-Benzyl-2,5-dimethyl-4-allyl-4-N-benzylaminopiperidines (VIII and IX) and 1-Methyl-, 1-n-Propyl-, and 1-Benzyl-2,5-dimethyl-4-allyl-4-N-(α-phenylethyl)aminopiperidines (X-XII). A solution of 8.3 g (0.03 mole) of Schiff base II-VI in 50 ml of absolute ether was added to allylmagnesium bromide, obtained from 5.2 g (0.22 mole) of magnesium and 13.1 g (0.11 mole) of allyl bromide in 100 ml of absolute ether, and the mixture was refluxed for 4 h. It was then decomposed with saturated ammonium chloride solution and extracted with ether. The extract was dried with magnesium sulfate, the ether was removed by distillation, and the residue was fractionated in vacuo.

1,2,4,5-Tetrahydro-1′,2′,5,5′-tetramethyl-, -2′,5,5′-trimethyl-1′-n-propyl-, -2,5,5′-trimethyl-1′-benzyl-, -1,1′,2′,5,5′-pentamethyl-, -1,2′,5,5′-tetramethyl-1-n-propyl-, and -1,2′,5,5′-tetramethyl-1′-benzyl-3H-spiro(benz-2-azepine-3,4′-piperidines) (XIII-XVIII). A 0.006-mole sample of VII-XII was heated in 5 ml of concentrated

TABLE 2. Physicochemical Characteristics of Aminopiperidines VIII-XII and Spiro(benz-2-azepine-3,4′-piperidines) XIII-XVIII

Compound	Empirical formula	bp (mm)	n_D^{20}	R_f	Mol.	PMR spectrum, δ, ppm δ, m.d.						other protons	Yield, %
						1-CH_3 (d, 3H)	5-CH_3 (d, 3H)	2-and 5-CH_3 (m, 6H)	CH_2 = (m, 2H)	-CH= (m, 1H)	H_{arom}, (m)		
VIII	$C_{20}H_{32}N_2$	161...166 (5)	1,5304	0,53; 0,76	300	—	—	0,77...1,10	4,95...5,22	5,52...6,02	7,27	3,65 (2H, br.d, —CH_2NH—)	46
IX	$C_{24}H_{32}N_2$	168...174 (4)	1,5539	0,68; 0,80	348	—	—	0,72...1,10	4,92...5,25	5,57...6,05	7,25	3,65 (2H, br.d, —CH_2NH—); 3,97 and 4,15 (1H each, dd —CH_2N—)	68
X	$C_{19}H_{30}N_2$	139...142 (2)	1,5234	0,45; 0,59	286	—	—	0,82...1,12	4,77...5,20	5,65...5,87	7,22	1,27 (3H, d CH_3CH—); 2,17 and 2,27 (each 3H, s, N—CH_3)	65
XI	$C_{21}H_{34}N_2$	168...172 (5)	1,5193	0,65; 0,77	314	—	—	0,82...1,05	4,92...5,25	5,37...5,87	7,27	1,27 (3H, d, CH_3CH—)	47
XII	$C_{25}H_{34}N_2$	206...210 (2)	1,5533	0,53; 0,76	362	—	—	0,70...1,12	4,88...5,17	5,40...6,02	7,25	1,27 (3H, d, CH_3CH—); 3,72 & 4,07 (each 1H, dd., —CH_2N—)	72
XIII	$C_{18}H_{28}N_2$	—	1,5427	0,36; 0,48	272	—	1,34	0,67...1,14	—	—	7,11...7,20	2,25 (6H, s, N—CH_3); 3,30 (1H, m, 5-H); 3,64 & 4,07 (each 1H, m, 1-H)	34
XIV	$C_{20}H_{32}N_2$	—	1,5273	0,57; 0,79	300	—	1,34	0,90...1,15	—	—	7,05...7,40	3,52 & 4,07 (each 1H, m, 1-H)	25
XV	$C_{24}H_{32}N_2$	210...215 (5)	1,5639	0,40; 0,63	348	—	1,30	0,92...1,10	—	—	7,01...7,35	3,07...3,37 (1H, m, 5-H); 3,65 and 4,10 (each 1H, m, 1-H)	29
XVI	$C_{19}H_{30}N_2$	163...165 (4)	1,5380	0,29; 0,42	286	1,47	1,35	0,60...1,14	—	—	7,14...7,30	2,29 (6H, s, N—CH_3); 3,24...3,40 (1H, m, 5-H); 4,05...4,22 (1H, m 1-H)	30
XVII	$C_{21}H_{34}N_2$	—	1,5323	0,28; 0,54	314	1,52	1,35	0,87...1,11	—	—	7,10...7,36	3,26...3,42 (1H, m, 5-H); 4,11...4,22 (1H, m. 1-H)	30
XVIII	$C_{25}H_{34}N_2$	—	1,5547	0,67; 0,81	362	1,45	1,27	0,77...1,10	—	—	7,07...7,37	3,08...3,20 (1H, m, 5-H); 4,05...4,30 (1H, m, 1-H)	52

TABLE 3. PMR Parameters of Stereoisomers XVa and XVb

Isomer	δ, ppm													
	1*a*/1*e*	4*a*/4*e*	5	5-CH_3	6 and 9	7 and 8	2′*a*	3′*a*/3′*e*	5′	6′*a*/6′*e*	2′-CH_3	5′-CH_3	$CH_2C_6H_5$	$CH_2C_6H_5$
XVa	3,66/4,10	1,20/1,37	3,33	1,34	7,21	7,11	2,70	1,68/2,50	1,58	2,14/2,35	1,26	0,57	3,09; 4,14	7,30 . . . 7,36
XVb	3,72/4,11	1,24/1,64	3,25	1,37	7,22	7,10	2,65	1,44/2,13	1,36	2,63/2,25	1,20	1,00	3,01; 4,15	7,30 . . . 7,36

TABLE 4. Spin-Spin Coupling Constants of Stereoisomers XVa and XVb

Isomer	J_{HH}, Hz												
	1*a*,1*e*	4*a*,4*e*	4*a*,5*a*	4*e*,5*a*	5*a*, 5-CH_3	2′, 3′*a*	2′, 3′*e*	3′*a*, 3′*e*	5′, 6′*a*	5′, 6′*e*	6′*a*, 6′*e*	2′, 2′-CH_3	5′, 5′-CH_3
XVa	−15,4	−13,9	10,4	1,1	7,0	11,0	2,6	−14,0	11,6	4,1	−11,4	6,1	6,9
XVb*	−15,5	−13,9	10,4	1,1	7,0	11,3	2,6	−14,0	3,1	2,4	−11,3	6,1	6,9

*$\overline{{}^4J_{3'e5'e}} = 2.0$ Hz.

H_2SO_4 for 5-10 h at 70-80°C [2], after which the mixture was neutralized with ammonium hydroxide and extracted with ether. The extract was dried with magnesium sulfate, the ether was removed by distillation, and the residue was fractionated in vacuo (spirans XV and XVI) or chromatographed on activity II Al_2O_3 by elution with ether (spirans XIII, XIV, XVII, and XVIII).

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4-HYDROXY-2-QUINOLONES.

1. EFFICIENT METHOD FOR OBTAINING 3-ALKYL-4-HYDROXY-2-QUINOLONES

P. A. Bezuglyi, I. V. Ukrainets, V. I. Treskach, and A. V. Turov

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3-Alkyl-4-hydroxy-2-quinolones were obtained in high yields via the Dieckmann intramolecular condensation of substituted malonic acid ethyl ester 2-carbalkoxyanilides.

It is known that 4-hydroxy-2-quinolone and its derivatives with alkyl substituents in the 3 position of the quinolone ring are intermediates in the biosynthesis of furoquinoline, acridone, and some other alkaloids [1], while the synthetic method for obtaining the alkaloids lunacridine and lunacrine that is based on refluxing substituted malonic esters with aromatic amines in diphenyl oxide leads to 3-alkyl-4-hydroxy-2-quinolones in rather low yields (up to 27%) and is accompanied by the formation of symmetrical dianilides of substituted malonic acids.

We have developed an efficient method for obtaining 3-alkyl-4-hydroxy-2-quinolones that makes it possible to synthesize these compounds preparatively in high yields.

For this, methyl (ethyl) anthranilate I was acylated with substituted malonic acid monoethyl ester chlorides II, obtained by a previously developed method [3], or with substituted malonic acid monoethyl esters III in the presence of dicyclohexylcarbodiimide. The resulting substituted malonic acid ethyl ester 2-carbalkoxyanilides IV were subjected, without isolation, to Dieckmann intramolecular condensation. Subsequent acidification of the reaction mixtures made it possible to isolate the corresponding 3-alkyl-4-hydroxy-2-quinolones VII in high yields.

It is interesting that The Dieckmann condensation of esters IV is accompanied by the elimination of the carbethoxy grouping of the malonic acid residue, probably in the form of carbonic acid esters.

Kharkov Pharmaceutical Institute, Kharkov 310002.

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