SYNTHESIS OF 4-ALLYL-4-ARYLAMINOPIPERIDINES AND THEIR TRANSFORMATIONS TO SPIRO[TETRAHYDROQUINOLINE-2,4'-PIPERIDINES]

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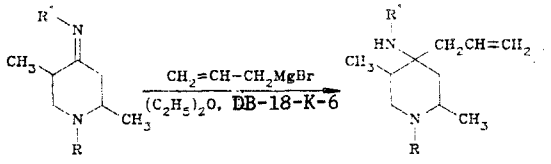
It was established that the yields of a 4-allyl-4-aryl-aminopiperidines in the reaction of 4-aryliminopiperidines with allylmagnesium bromide increase significantly if the reaction is carried out in the presence of a crown ether. A number of previously unknown spiro[tetrahydroquinoline-2,4'-piperidines] were obtained in the cyclization of 4-allyl-4-arylaminopiperidines in the presence of sulfuric acid.

γ-Aryliminopiperidines, obtained from γ-piperidones and arylamines by reaction with allylmagnesium bromide, are converted to γ-allyl-γ-arylaminopiperidines [1]. The conversion of 1,2,5-trimethyl-4-allyl-4-phenylaminopiperidine, obtained via this method, to 1',2',4,5'-tetramethyl-1,2,3,4-tetrahydrospiro[quinoline-2,4'-piperidine] was also described in [1]. Thus spiro[tetrahydroquinoline-2,4'-piperidines], information regarding which is not available, can be obtained from accessible γ-piperidones via this three-step method. This method is also of interest for obtaining 1,2,3,4-tetrahydroquinolines, accessible methods for the synthesis of which are restricted to the reduction of quinoline derivatives [2], the cyclization of cinnamanylids under the influence under the influence of polyphosphoric acid (PPA) [3], and the condensation of Schiff bases with unsaturated compounds [4].

1,2,5-Trimethyl- and 1-benzyl-2,5-dimethyl-4-allyl-4-phenylaminopiperidine (III and IV) were previously obtained in 80% and 33% yields, respectively, from 1,2,5-trimethyl- and 1-benzyl-2,5-dimethyl-4-phenyliminopiperidine (I and II) and allylmagnesium bromide when the reaction was carried out in ether [1]. According to [5], the yields of alcohols are, as a rule, 15-20% higher in the reaction of the ketones with Grignard reagents in the presence of crown ethers than under the conditions that are ordinarily used to carry out the reaction.

In the present research the reactions of imines I and II, as well as 1,2,5-trimethyl-4-(o-anisyl)(V)[(p-anisyl)(VI), benzyl(VII), α-naphthyl(VIII)]iminopiperidine and 2,5-dimethyl-4-phenyliminopiperidine (IX) with allylmagnesium bromide were carried out in the presence of catalytic amounts of dibenzo-18-crown-6 (DB-18-K-6).



I, II, V–IX III, IV, X–XIV

I, III, V—VIII, X—XIII R=CH_3, II, IV R=$CH_2C_6H_5$, IX, XIV R=H; I—IV, IX, XIV R^1=C_6H_5, V, X R^1=$C_6H_4OCH_3$-*o*, VI, XI R^1=$C_6H_4OCH_3$-*p* VII, XII R^1=$C_6H_5CH_2$, VIII, XIII R^1=α-$C_{10}H_7$ naphthyl)

Under these conditions the yields of diamines III, IV, and 1,2,5-trimethyl-4-allyl-4-(o-anisyl)(X)[(p-anisyl)(XI)]aminopiperidine are higher by a factor of 1.6 and the yield of 1,2,5-trimethyl-4-allyl-4-benzylaminopiperidine (XII) is higher by a factor of 1.1 than when the reaction is carried out without the crown ether. 1,2,5-Trimethyl-4-allyl-4-(α-naphthyl)- and 2,5-dimethyl-4-allyl-4-phenylaminopiperidine (XIII and XIV) were obtained in 55% and 30% yields, respectively.

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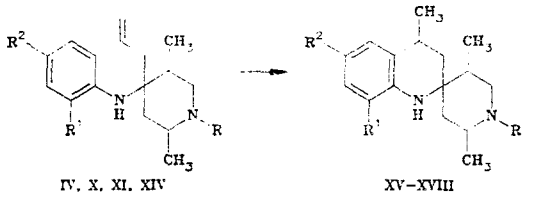
TABLE 1. Data from the PMR Spectra of the Synthesized Compounds

Compound	Chemical shifts, δ, ppm (in $CDCl_3$, TMS)					
				vinyl protons		protons of other groups
	N—CH_3 (s, 3H)	2-CH_3, 5-CH (m, 6H)	4-CH_3 (d, 3H)	—CH= (m, 1H)	=CH- (m, 2H)	
X	2,11; 2,12; 2,13	0,90 ... 1,20		5.4 ... 5.7	4,9 ... 5.05	3,80; 3,81; 3.85 (CH_3O, s 3H each)
XI	2,25; 2,30	0,89 ... 1,12		5,61 ... 5.83	4,8 ... 5,3	3,75; 3,80 (CH_3O, s 3H each)
XII	2,40; 2,50	0,80 ... 1.20		5,53 ... 6,0	4,84 ... 5.33	3,58; 3,65 (N—$CH_2C_6H_5$, m, 4H)
XIII	2,15; 2,20; 2,21	0,92 ... 1,30		5,45 ... 6,08	4,75 ... 5,20	—
XIV	—	0,80 ... 1,10		5,38 ... 6,03	4,75 ... 5,20	—
XV*	—	0,63 ... 1,51		—	—	—
XVI	2,03; 2,05; 2,10	0,60 ... 1,25		—	—	3,58; 3,67 (CH_3O, s, 3H each)
XVII	2,18; 2,25	0,83 ... 1,28		—	—	3,61; 3,68 (CH_3O, s, 3H each)
XVIII		0,67 ... 1,17		—	—	—
XIX	2,30; 2,35	0,87 ... 1,47		—	—	—
XX	—	—		5,40 ... 6,18	4,70 ... 5,11	1,30 ... 2,00 (CH_2-cyclohexane, m, 10H)
XXI	—	—		5,45 ... 6,15	4,70 ... 5,15	1,76 (CH_2-cyclopentane, s 8H)
XXII	—		1,28	—	—	
XXIII	—		1,20	—	—	
XXIV	—	—		—	—	1.16 ... 2,40 (CH_2-cyclohexane, pyrrolidine, m, 14H), 3,23 ... 3,50 (α-CH_2 pyrrolidine, m, 2H)

*3.85-4.10 ppm (N—$CH_2C_6H_5$, m, 4H).

The cyclization of γ-allyl-γ-arylaminopiperidines with the formation of spiro[tetrahydroquinolinepiperidines] occurs when they are heated with concentrated H_2SO_4. 2',4,5'-Trimethyl-1'-benzyl-1,2,3,4-tetrahydrospiro[quinoline-2,4'-piperidine] (XV) was obtained in 55% yield from IV. 1',2',4,5'-Tetramethyl-1,2,3,4-tetrahydro-8-methoxy(XVI)[6-methoxy-(XVII)]spiro[quinoline-2,4'-piperidines] are formed from X and XI in considerably lower yields; this is evidently due to the presence of an electron-donor methoxy group in the aryl radical. Spiro compound XVIII with a secondary amino group in the piperidine ring was obtained from XIV.

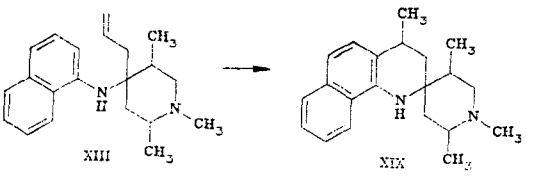


IV, X, XI, XIV XV–XVIII

XV R=$CH_2C_6H_5$, R^1=R^2=H; XVI R=CH_3, R^1=OCH_3, R^2=H; XVII R=CH_3, R^1=H, R^2=OCH_3; XVIII R=R^1=R^2=H

The structures of spiro compounds XV-XVIII are confirmed by data from the PMR spectra (Table 1), in which signals of olefin protons that are characteristic for the starting amines are absent. A band of stretching vibrations of an NH bond at 3350-3450 cm^{-1} is retained in the IR spectra of the spiro compounds.

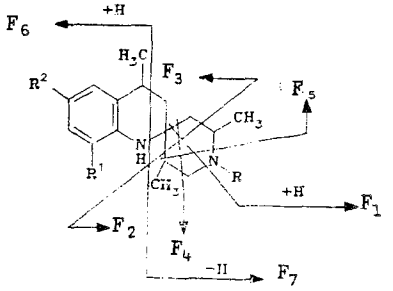
1',2',4,5'-Tetramethyl-1,2,3,4-tetrahydrospiro[benz(f)-quinoline-2,4'-piperidine] (XIX) was obtained in 15% yield in the cyclization of γ-allyl-γ-(α-napththylamino)piperidine XIII; its IR and PMR spectra are similar to the spectra of spiro compounds XV-XVIII.



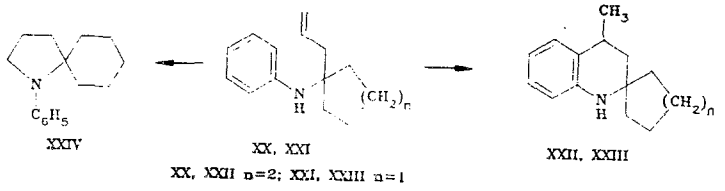
XIII XIX

The mass spectra confirm the structures of 4-allyl-4-arylaminopiperidines III, IV, and X-XIV. The dissociative ionization of the molecular ions (M^+) proceeds via several parallel pathways. The presence of arylamino and allyl radicals in the γ position of the ring is responsible for the appearance of peaks of $[M - CH_2CH{=}CH_2]^+$, $[M - R^1NH_2]^+$, and $[M - CH_2CH{-}CH_2, -R^1NH_2]^+$ fragments. The elimination of the α-methyl substituent leads to the formation of the $[M - CH_3]^+$ ion, which then undergoes fragmentation via the retrodiene fragmentation mechanism [6]. The resulting fragments with m/z 146 (IV), 70 (III, X-XIII), and 56 (XIV) convey information regarding the nature of the substituent attached to the ring nitrogen atom.

The mass spectra of spiro compounds XV-XIX, the M^+ ions of which have the same elementary compositions as the starting γ-aminopiperidines, differ substantially. The fragmentation of XV-XIX is due to intensive cleavage of the piperidine ring with the formation of F_1-F_5 ions. The retrodiene fragmentation of the tetrahydroquinoline ring [7], which is accompanied by migration of hydrogen atoms, leads to the development of the characteristic F_6 and F_7 ions (Table 2).



The cyclization of 1-allyl-1-phenylaminocyclohexane (XX) and 1-allyl-1-phenylaminocyclopentane (XXI), which were obtained in the present research in 48% and 58% yields from N-cyclohexylidene(cyclopentylidene)aniline and allylmagnesium bromide in the presence of DB-18-K-6, led to the formation of 4-methyl-1,2,3,4-tetrahydrospiro[quinoline-2-cyclohexane] (XXII) and 4-methyl-1,2,3,4-tetrahydrospiro[quinoline-2-cyclopentane] (XXIII) in 69% and 55% yields, respectively.



1-Phenylspiro[pyrrolidine-2-cyclohexane] (XXIV), which was isolated by chromatography from the complex mixture of reaction products in 23% yield, was obtained from amine XX under the conditions of the hydroxymercuration–demercuration reaction [8]. A band of stretching vibrations of an NH group is absent in the IR spectrum of XXIV. An M^+ peak with m/z 215 (60%), the principal pathways of the fragmentation of which are associated with cleavage of the cyclohexane ring with the formation of $[M - C_3H_7]^+$ 172 (I 100%; determined m = 172.1128 ($C_{12}H_{14}N$); calculated m = 172.1123) and $[M - C_4H_8]^+$ 159 (20%; determined m = 159.1048 ($C_{11}H_{13}N$); calculated m = 159.1045) fragments, is present in the mass spectrum.

TABLE 2. Mass Spectra of Spiro[tetrahydroquinoline-2,4'-piperidines] XV-XIX

Compound	Mass spectrum, m/z (I, %)							
	$M^{+\cdot}$	F_1	F_2	F_3	F_4	F_5	F_6	F_7
XV*	334 (54)	148 (15)	175 (10)	159 (27)	173 (15)	186 (25)	120 (16)	214 (13)
XVI	288 (30)	72 (16)	99 (38)	189 (100)	203 (25)	216 (28)	150 (15)	138 (19)
XVII	288 (15)	72 (10)	99 (35)	189 (100)	203 (24)	216 (13)	150 (14)	138 (20)
XVIII	244 (71)	58 (18)	85 (71)	159 (100)	173 (25)	186 (40)	120 (15)	124 (51)
XIX	308 (19)	72 (14)	99 (27)	209 (100)	223 (29)	237 (15)	170 (25)	138 (28)

*In addition, ion peaks with m/z 243 (35) $[M - CH_2C_6H_5]^+$ and 91 (100) $[CH_2C_6H_5]^+$ are present.

TABLE 3. 4-Allyl-4-arylaminopiperidines III, IV, and X-XIV and 1-Allyl-1-phenylaminocyclohexane(cyclopentane) XX and XXI

Compound	Empirical formula	bp, (mm)	M	ν_{NH}, cm^{-1}	Yield, %	
					without DB-18-K-6	with DB-18-K-6
III	$C_{17}H_{26}N_2$	144...146(2)	258	3425	80	95
IV	$C_{23}H_{30}N_2$	212...216(2)	314	3410	33	58
X	$C_{18}H_{28}N_2O$	160...163(2)	288	3410	44	70
XI	$C_{18}H_{28}N_2O$	176...179(2)	288	3400	45	58
XII	$C_{18}H_{26}N_2$	164...168(4)	272	3350	66	75
XIII	$C_{21}H_{28}N_2$	202...204(2)	308	3460	—	55
XIV	$C_{16}H_{24}N_2$	160...164(2)	244	3420...3290		30
XX	$C_{15}H_{21}N$	125...128(2)	215	3400	—	48
XXI	$C_{14}H_{19}N$	114...116(2)	201	3405	—	58

TABLE 4. Spiro Compounds XV-XIX and XXII-XXIV

Compound	Empirical formula	bp (mm), mp, °C	ν_{NH}, cm^{-1}	Yield, %
XV	$C_{23}H_{30}N_2$	218...222(3)	3412	55
XVI	$C_{18}H_{28}N_2O$	178...181(3)	3421	34
XVII	$C_{18}H_{28}N_2O$	190...193	3420	10
XVIII	$C_{16}H_{24}N_2$	174...177(4)	3410...3300	40
XIX	$C_{21}H_{28}N_2$	246...250	3400	15
XXII	$C_{15}H_{21}N$	135...138(1)	3400	69
XXIII	$C_{14}H_{19}N$	128...130(2)	3395	55
XXIV	$C_{15}H_{21}N$	140...141(2)	—	23

Spiro compound XXIV is evidently formed in the dehydrocyclization of 1-(γ-hydroxypropyl)-1-phenylaminocyclohexane. It is known that products of addition in accordance with the Markownikoff rule are obtained almost exclusively from mono-, di-, tri-, and tetraalkyl-substituted olefins in the case of hydroxymercuration with subsequent demercuration. In this connection in carrying out this reaction one might have expected the formation of 1-phenyl-4-methylspiro[azetidine-2-cyclohexane], in the mass spectrum of which one should record the intense signal of an $[M - CH_3]^+$ fragment, formed as a result of α fragmentation [9] associated with the elimination of a 4-CH_3 group. However, this peak is absent in the mass spectrum of XXIV. It follows from an examination of a model of the possible transition state of the reaction of mercuric acetate with 1-allyl-1-phenylamino-cyclohexane that a sterically unhindered six-membered chelate with coordination of the mercury atom at the nitrogen atom should be formed. This is possibly the reason for the addition to the allyl group that is not in accordance with the Markownikoff rule.

EXPERIMENTAL

The IR spectra were recorded with UR-20 (KBr pellets) and Specord IR-75 (thin films) spectrometers. The mass spectra were obtained with an MKh-1303 spectrometer. The PMR spectra of solutions in $CDCl_3$ were recorded with a Tesla BS-487c spectrometer (60 MHz) with tetramethylsilane (TMS) as the standard. Azomethines I-IX were described in [10,11].

The characteristics of the synthesized compounds are presented in Tables 3 and 4. The results of elementary analysis of III, IV, and X-XXIV for C, H, and N were in agreement with the calculated values.

4-Allyl-4-arylaminopiperidines III, IV, and X-XIV. A solution of 0.1 mole of the imine in absolute ether was added dropwise with vigorous stirring at room temperature to allylmagnesium bromide, prepared from 0.3 mole of freshly distilled allyl bromide and 0.7 mole of magnesium in absolute ether containing a catalytic amount (1.0-1.5% with respect to the amine) of DB-18-K-6, and the mixture was heated for 5 h. It was then treated with ice water and a saturated solution of ammonium chloride and extracted with ether (three 40-ml portions). The extract was dried with magnesium sulfate and evaporated, and the residue was fractionated in vacuo. Compounds III, IV, and X-XIV were pale-yellow liquids. In TLC they showed up in the form of two or three spots, which indicated the presence of isomers.

1,2,3,4-Tetrahydrospiro[quinoline-2,4'-piperidines] XV-XVIII and 1',2',4,5'-Tetramethyl-1,2,3,4-tetrahydrospiro[benz(f)quinoline-2,4'-piperidine] (XIX). A solution of 0.1 mole of the starting 4-allyl-4-arylaminopiperidine in 10 ml of concentrated H_2SO_4 was maintained at 80-90°C for 2-6 h. The course of the reaction was monitored by means of TLC. Ice (10 cm^3) was added to the reaction mass, and the mixture was poured over ice ($\sim$50 cm^3). Ether (50 ml) was added, and the mixture was neutralized with 25% ammonium hydroxide. The ether layer was separated, the aqueous layer was extracted with ether (three 30-ml portions), and the extract was dried with magnesium sulfate. The ether extract was evaporated, and the residue was fractionated (in the case of XV, XVI, and XVIII) or crystallized (in the case of XVIII and XIX).

Spiro compounds XXII and XXIII were similarly obtained.

1-Phenylspiro[pyrrolidine-2-cyclohexane] (XXIV). A solution of 2.15 g (0.01 mole) of amine XX in tetrahydrofuran (THF) was added dropwise with stirring at room temperature to a suspension of 8.04 g (0.025 mole) of mercuric acetate in 26 ml of THF–water (1:1), after which the mixture was stirred for 10 h and allowed to stand overnight. It was then treated with cooling with ice water with 0.85 g (0.018 mole) of sodium borohydride in 12 ml of 2.5 N NaOH solution. The solvent was removed by distillation, and the aqueous layer was treated with 2.5 N NaOH solution to pH 11-12 and extracted with ether. The solvent was removed by distillation, and the residue was chromatographed [activity II Al_2O_3, hexane–ether (50:1)] to give 0.5 g (23%) of XXIV in the form of a colorless liquid that turned red in air, as well as 0.3 g of starting amine XX,

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