SYNTHESIS, CHEMICAL TRANSFORMATIONS, AND STRUCTURE OF 1,2,3,4-TETRAHYDROSPIRO(QUINOLINE-2-CYCLOALKANES)

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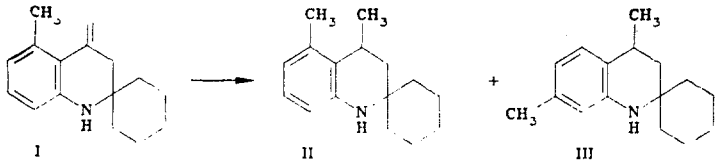
The cyclization of 1-(m-toluidino)-1-allylcyclohexane under acid-catalysis conditions gave 4,5- and 4,7-dimethyl-1,2,3,4-tetrahydrospiro(quinoline-2-cyclohexanes). The bromination, nitration, N-acylation, and N-allylation of 4-methyl-1,2,3,4-tetrahydrospiro[quinoline-2-cyclohexane(cyclopentane)] were studied. It was established that nitration takes place in the 6 and 7 positions, while bromination occurs in the 6 and 8 positions. The amino-Claisen rearrangement of N-allyltetrahydroquinolines is accompanied by quantitative allyl-vinyl isomerization. The stereochemistry of the synthesized spiro(tetrahydroquinolinecycloalkanes) was studied by PMR spectroscopy.

The cyclization of 1-anilino-1-allylcyclohexane(cyclopentane) under acid-catalysis conditions is a convenient method for the synthesis of previously unknown spiro compounds that contain 1,2,3,4-tetrahydroquinoline and carbocycle fragments [1].

In the present paper we describe the analogous cyclization of 1-(m-toluidino)-1-allylcyclohexane (I), obtained from N-cyclohexylidene-m-toluidine and allylmagnesium bromide. As one should have expected, the cyclization reaction takes place in the 2 and 6 positions of the toluidine fragment. We obtained, in quantitative yield, a mixture of 4,5-dimethyl- and 4,7-dimethyl-1,2,3,4-tetrahydrospiro(quinoline-2-cyclohexanes) (II and III) in a ratio (according to PMR data) of 1:1, from which II was isolated in individual form by chromatography.



I II III

The chemical transformations of the spiro(tetrahydroquinoline-2-cycloalkanes) were studied in the case of 4-methyl-1,2,3,4-tetrahydrospiro(quinoline-2-cyclohexane) (IV) and its analog (V) with a cyclopentane fragment. N-Acetyl derivatives VI and VII were obtained in yields close to the theoretical values by treatment of these compounds with acetic anhydride. A mixture of 32% 7-nitro- and 7% 6-nitro-4-methyl-1,2,3,4-tetrahydrospiro(quinoline-2-cyclohexane) (VIII and IX) is formed in the nitration of IV. Compounds VIII and IX were isolated in individual form by column chromatography. Nitration is accompanied by the formation of a significant amount of resinous products. The position of the nitro group in VIII and IX was established from the multiplicities of the signals of the aromatic protons in their PMR spectra. The signal of the 5-H proton was assigned on the basis of the existence of a long-range $^4J_{4a,5}$ spin-spin coupling constant (Tables 1 and 2).

The bromination of IV with N-bromosuccinimide in methylene chloride in the presence of acetic acid takes place int he 6 and 8 positions to give a mixture of 6- and 8-bromo derivatives, as well as 6,8-dibromo-substituted derivatives (X, XI, XII). According to the PMR spectral data monobromo-substituted tetrahydroquinoline X and dibromo-substituted XII are formed in a ratio of 1:20 in 44% overall yield. Compounds XI (2% yield) and XII (40% yield) were isolated in individual form by chromatography.

The alkylation of spiro compounds IV and V with allyl bromide in acetone leads to, respectively, 4-methyl-1-allyl-1,2,3,4-tetrahydrospiro(quinoline-2-cyclohexane) (XIII) and spiro(quinoline-2-cyclopentane) XIV.

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TABLE 1. PMR Spectra of Substituted 4-Methyl-1,2,3,4-tetrahydrospiro(quinoline-2-cycloalkanes)

Compound	Chemical shifts, δ, ppm										
	Tetrahydroquinoline ring protons							2,2-Cycloalkane protons	4-CH_3 (or 5-, 7-CH_3)	N-Substituents
	3a	3e	4-H	5-H	6-H	7-H	8-H			
II	1,92	1,78	3,10	—	6,53	6,90	6,41	1,42...1,63	1,32 (4-CH_3); 2,30 (5-CH_3)	3,75 (NH)
III	1,35	1,91	2,90	7,06	7,49	—	6,35	1,42...1,63	1,34 (4-CH_3); 2,25 (7-CH_3)	3,76 (NH)
IV	1,34	1,89	2,90	7,15	6,63	6,96	6,47	1,45...1,59	1,32	3,89 (NH)
V	1,61	1,78	2,93	7,15	6,65	6,97	6,44	1,60...1,76	1,34	3,81 (NH)
VI	0,95	2,33	2,69		6,94÷7,16*			1,18...3,03	1,33	2,01 ($COCH_3$)
VII	1,32	2,04	2,78		6,97÷7,18*			1,30...2,46	1,31	2,07 ($COCH_3$)
VIII	1,33	1,94	2,92	7,21	7,42	—	7,30	1,50...1,60	1,36	4,27 (NH)
IX	1,29	1,98	2,89	8,06	—	7,90	6,38	1,50...1,60	1,39	4,81 (NH)
X	—**			7,52	—	7,23	6,57	1,39...1,64		4,68 (NH)
XI	1,37	1,87	2,94	7,09	6,49	7,24	—	1,39...1,65	1,33	4,12 (NH)
XII	1,30	1,86	2,91	7,18	—	7,36	—	1,39...1,64	1,32	4,68 (NH)
XIII	1,27	2,40	2,87	7,15	6,63	7,04	6,53	1,15...1,81	1,37	3,68, 4,16 (NH_aH_b); 5,89 (H_c); 5,13 (H_d); 5,24 (H_e)
XIV	1,60	1,87	2,91	7,14	6,63	7,04	6,50	1,47...2,05	1,36	3,69, 3,98 (NH_aH_b); 5,92 (H_c); 5,15 (H_d); 5,24 (H_e)
Z-XV			2,93	7,09	6,64	6,91	—	1,50...1,80	1,37 (4-CH_3); 1,77 (CH_3C=)	4,02 (NH); 6,26 (H_c); 5,90 (H_d)
E-XV	1,36		2,93	7,08	6,63	7,03	—	1,45...1,80	1,35 (4-CH_3); 1,93 (CH_3C=)	4,02 (NH); 6,38 (H_c); 6,06 (H_d)
Z-XVI	1,65	1,78	2,95	7,11	6,64	6,84	—	1,59...1,78	1,37 (4-CH_3); 1,74 (CH_3C=)	3,87 (NH); 6,21 (H_c); 5,87 (H_d)
E-XVI	1,61	1,79	2,95	7,09	6,63	7,02	—	1,59...1,78	1,35 (4-CH_3); 1,90 (CH_3C=)	3,87 (NH); 6,32 (H_c); 6,03 (H_d)
Z-XVII	1,78	2,11	3,16	7,20	6,75	7,03	6,56	7,30...8,64 Pyridine	1,37	3,98 (NH)
E-XVII	2,05	1,86	2,94	7,10	6,70	7,04	6,58	7,28...8,64	1,37	4,12 (NH)

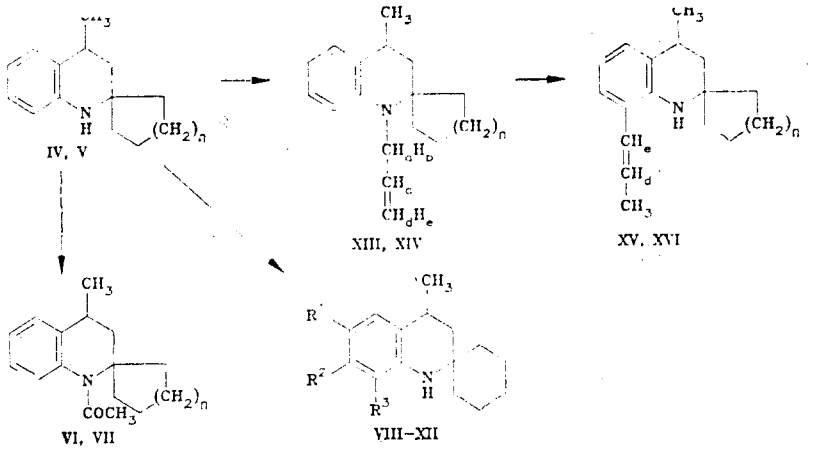
*A strongly coupled system of protons of the ABCD type.

**Could not be measured because of overlapping of the signals.

TABLE 2. Spin-Spin Coupling Constants (SSCC)

Compound	J_{HH}, Hz*										
	3a, 3e	3a, 4	3e, 4	4,5	4,7	5,6	5,7	6,7	6,8	7,8	4-CH_3, Hz
II	−13,6	7,1	5,6		—		—	7,5	1,2	7,9	7,1
III	−13,1	12,3	5,5	1,1	7,7			1,7			6,8
IV	−13,1	12,3	5,6	1,2	0,7	7,7	1,7	7,2	1,2	7,9	6,7
V	−12,7	12,1	5,5	1,2	0,7	7,7	1,6	7,2	1,3	7,9	6,8
VI	−13,1	11,2	3,7								6,7
VII	−13,1	11,0	3,9	0,9	—						6,9
VIII	−13,1	12,5	5,4	1,2	0,7	8,4	—	—	2,3	—	6,7
IX	−13,1	12,6	5,1	1,2	0,8	—	2,6	—	—	8,9	6,7
X							2,3			8,8	
XI	−13,0	12,3	5,4	1,1	0,9	7,7	1,5	7,9	—	—	6,7
XII	−13,2	12,4	5,4	1,2	0,9	—	2,2	—	—	—	6,8
XIII	−13,3	12,7	4,4	1,2		7,5	1,8	7,3	1,2	8,2	6,6
XIV	−12,9	12,3	4,3	1,2	0,9	7,6	1,7	7,2	1,1	8,2	6,7
Z-XV				1,0		7,5	1,5	7,5	—	—	6,7
E-XV	−12,7	12,6		1,0	0,8	7,6	1,5	7,5	—	—	6,7
Z-XVI	−12,7	12,0	5,5	0,9	0,8	7,5	1,5	7,5	—	—	6,7
E-XVI	−12,7	12,0	5,6	0,9	0,8	7,5	1,5	7,6	—	—	6,7
Z-XVII	−12,9	11,8	5,4	1,2	0,8	7,7	1,0	7,2	1,3	7,9	6,8
E-XVII	−13,1	5,3	3,6	0,7	0,8	7,7	1,6	7,3	1,2	7,9	7,1

*XIII J_{HH} = −18.5 (a, b); 4.1 [a(b), c]; 2.0 [a(b), d(e)]; 10.4 (c, d); 17.2 (c, e); −2.0 Hz (e, d). XIV J_{HH} = −18.5 (a, b); 3.8 [a(b), c]; 2.0 [a(b), d(e)]; 10.4 (c, d); 17.2 (c, e); −2.0 Hz (e, d). Z-XV J = 11.1 Hz (c, d). E-XV J_{HH} = 15.4 Hz (c, d). Z-XVI J_{HH} = 11.3 Hz (c, d). E-XVI J_{HH} = 15.4 Hz (c, d).

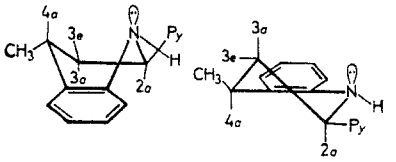


IV, VI, XIII, XV n=2; V, VII, XIV, XVI n=1; VIII R^1=R^3=H, R^2=NO_2; IX R^1=NO_2, R^2=R^3=H; X R^1=Br, R^2=R^3=H; XI R^1=R^2=H, R^3=Br; XII R^1=R^3=Br, R^2=H

The amino-Claisen rearrangement [2] of N-allyl-substituted spiro compounds XIII and XIV in the presence of boron trifluoride etherate is accompanied by quantitative allylvinyl isomerization. 4-Methyl-8-(1′-propenyl)-1,2,3,4-tetrahydrospiro(quinoline-2-cyclohexane) (XV) and -(quinoline-2-cycloheptane) (XVI) were obtained in 47% and 38% yields, respectively. According to the PMR data, they are mixtures of Z and E isomers with respect to the orientation of the substituents attached to the exocyclic double bond with a ratio of 1.0:4.5 for XV and a ratio of 1.0:4.3 for XVI.

The stereochemistry of the synthesized spiro(tetrahydroquinolinecycloalkanes) was studied by means of PMR spectroscopy. According to the results of x-ray diffraction analysis [3], the tetrahydropyridine ring of 2,2,4-trimethyl-6-acetoxy-1,2,3,4-tetrahydroquinoline has a half-chair conformation. On the basis of $A^{1,2}$-allyl strain [4], Johanson erroneously concluded that the methyl group in the 4 position has a pseudoaxial orientation, despite the fact that the x-ray diffraction data and the figure presented provide evidence that it has a pseudoequatorial orientation. We selected 4-methyl-1,2,3,4-tetrahydro-2-(3′-pyridyl)quinoline (XVIII), obtained by the method in [1], as a model compound. It is produced in the form of a mixture of two isomers with cis and trans orientations of the substituents in the tetrahydropyridine fragment. This mixture, without separation, was analyzed by means of PMR spectroscopy.

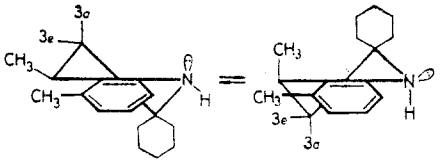
The following two conformations can be assumed for the predominant isomer of XVIII on the basis of the $J_{2,3}$ SSCC, taking into account the Karplus dependence [5]: a boat with a cis orientation of the 2*a*-H and 3*a*-H protons ($\varphi \approx 0°$) and a half chair with a trans orientation of these protons ($\varphi \approx 180°$C). in conformity with [5], the $^3J_{2a3a}$ values should be approximately equal in both cases.



To establish the mutual orientation of the 2*a*-H and 3*a*-H protons we used the differential spectra of the nuclear Overhauser effect (NOE), viz., NOEDIFF [6]. The NOE effect between the 2*a*-H and 3*a*-H protons is absent in the case of saturation of the 2*a*-H proton. However, the magnitude of this effect between the 2*a*-H and 4*a*-H protons is $\approx$ 10%, which unambiguously indicates the trans orientation of the 2*a*-H and 3*a*-H protons and the cis orientation of the 2*a*-H and 4*a*-H protons. Thus the preponderant isomer of XVIII exist in a half-chair conformation with a cis orientation of the substituents attached to the $C_{(2)}$ and $C_{(4)}$ atoms. The vicinal SSCC $^3J_{3a4a}$ = 11.8 Hz confirms the pseudoequatorial orientation of the methyl group attached to the $C_{(4)}$ atom. In accordance with the $^3J_{2a3a}$ and $^3J_{3e4e}$ SSCC (see Table 2), the minor isomer of XVIII also exists in a half-chair conformation but with a trans orientation of the substituents. This isomer has an equatorial substituent attached to the $C_{(2)}$ atom and an axial substituent attached to the $C_{(4)}$ atom.

The nonobservance of the $A^{1,2}$-allyl-strain rule [4] in the case of the preponderant isomer of XVIII and 2,2,4-trimethyl-6-acetoxy-1,2,3,4-tetrahydroquinoline is evidently due to the cis orientation of the substituents attached to the $C_{(2)}$ and $C_{(4)}$ atoms. The agreement between the $^3J_{3e4}$ and $^3J_{3a4}$ SSCC of spirotetrahydroquinolinecycloalkanes II-VII, XIII, and XIV and the corresponding SSCC values of the cis isomer of XVII indicates that the tetrahydroquinoline fragment in these compounds has a half-chair conformation with a pseudoequatorial methyl group attached to the $C_{(4)}$ atom.

The $^3J_{3,4}$ SSCC in the PMR spectrum of II (see Table 2) constitutes evidence for the existence of the conformational equilibrium IIA $\rightleftarrows$ IIB, which is evidently due to steric interaction of the methyl groups attached to the $C_{(4)}$ and $C_{(5)}$ atoms.



IIA IIB

Taking $^3J_{3a4a}$ = 12.3 Hz (for II) and $^3J_{3e4e}$ = 3.6 Hz (the trans isomer of XVII) as the boundary SSCC values, we used the method of averaged parameters to carry out a semiqualitative evaluation of the populations of the conformers: $n_A \approx 40\%$ and $n_B \approx 60\%$.

EXPERIMENTAL

The mass spectra of the synthesized compounds 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 of the compounds in $CDCl_3$ were recorded with a Bruker WM-400 spectrometer with tetramethylsilane (TMS) as the internal standard. Thin-layer chromatography (TLC) was carried out on Alufol and Silufol plates with development by iodine vapors. Brockmann activity II Al_2O_3 was used for column chromatography.

The results of elementary analysis for C, H, and N were in agreement with the calculated values.

4,5-Dimethyl- and 4,7-Dimethyl-1,2,3,4-tetrahydrospiro(quinoline-2-cyclohexanes) (II, III, $C_{16}H_{22}N$). A 4.6-g (0.02 mole) sample of I was heated in 10 ml of concentrated H_2SO_4 at 70°C for 2.5 h, after which the reaction mixture was poured over ice. The aqueous mixture was made alkaline with NH_4OH and extracted with ether. The ether was removed by distillation, and the residue was fractionated in vacuo to give 3.25 g (71%) of a mixture of II and III in the form of a viscous yellow liquid with bp 143-144°C (3 mm), n_D^{20} 1.5670, and R_f 0.82 and 0.68 [hexane—ethyl acetate (6:1)]. Double chromatography of this mixture with a column (H = 30 cm, d = 2.5 cm, elution with hexane) yielded 0.55 g of tetrahydroquinoline II in the form of a colorless oily liquid with R_f 0.68 [Alufol, hexane—ethyl acetate (6:1)].

4-Methyl-1,2,3,4-tetrahydro-1-acetylspiro(quinoline-2-cyclohexane) (VI, $C_{17}H_{23}NO$). A 2.3-g (0.1 mole) sample of tetrahydroquinoline IV was refluxed for 3 h in 7 ml of acetic anhydride, after which the reaction mixture was poured into water, and the aqueous mixture was made alkaline to pH $\approx$ 10 with sodium carbonate and extracted with ether. The extract was dried with $MgSO_4$, and the ether was removed by distillation to give 2.6 g (83%) of acetamide VI in the form of a pale-yellow vitreous mass with R_f 0.34 [Alufol, hexane—ethyl acetate (5:1)]. IR spectrum (film): 1670 cm^{-1} (ν_{CO}).

4-Methyl-1,2,3,4-tetrahydro-1-acetylspiro(quinoline-2-cyclopentane) (VII, $C_{16}H_{21}NO$). Similarly, the acetylation of 0.6 g (83%) of tetrahydroquinoline V gave 0.6 g (83%) of acetamide VII in the form of a pale-yellow vitreous mass with R_f 0.41 [Alufol, hexane—ethyl acetate (5:1)]. IR spectrum (film): 1665 cm^{-1}.

7-Nitro- and 6-Nitro-4-methyl-1,2,3,4-tetrahydrospiro(quinoline-2-cyclohexanes) VIII and IX, $C_{15}H_{20}N_{20}O_{20}$). A 1.62-g (7.5 mmole) sample of IV was dissolved in 2 ml of concentrated H_2SO_4, after which a mixture of 0.47 g of concentrated HNO_3 and 1.42 g of concentrated H_2SO_4 was added, and the mixture was stirred for 1 h at 20°C. It was then poured over ice, and the resulting aqueous solution was treated with sodium carbonate to bring the pH up to 7-8. This mixture was then extracted with ether, the ether was removed by distillation, and the residue was chromatographed with a column [H = 40 cm, d = 2 cm, elution with heptane—ethyl acetate (20:1)] to give, initially, 0.6 g of nitro compound VIII in the form of orange crystals with mp 75-77°C (from hexane) and R_f [Alufol, heptane—ethyl acetate (2:1)]. IR spectrum (KBr): 3415 (ν_{NH}), 1360, 1510 cm^{-1} (δ_{NO_2}). Subsequent elution gavel 0.14 g (7%) of nitro compound IX in the form of light-brown crystals with mp 105-107°C (from hexane) and R_f 0.47 [Alufol, heptane—ethyl acetate (2:1)]. IR spectrum (KBr): 3390 (ν_{NH}); 1360, 1505 cm^{-1} (δ_{NO_2}).

6-Bromo- (X, $C_{15}H_{20}BrN$), 8-Bromo- (XI, $C_{15}H_{20}BrN$), and 6,8-Dibromo-(XII, $C_{15}H_{19}Br_2N$)-4-methyl-1,2,3,4-tetrahydrospiro(quinoline-2-cyclohexanes). A 1.46-g (8 mmole) sample of N-bromosuccinimide was added in portions at 20°C to a solution of 1.76 g (8 mmole) of tetrahydroquinoline IV in a mixture of 20 ml of methylene chloride and 8 ml of acetic acid, after which the mixture was refluxed at 20°C for 6 h (monitoring by TLC). The methylene chloride was then removed by distillation, the residue was poured into water, and the aqueous mixture was mad alkaline with sodium carbonate and extracted with ether. The ether was removed by distillation, and the residue was chromatographed with a column packed with silica gel (H = 30 cm, d = 2.5 cm, elution with hexane). Subsequent elution yielded 0.2 g (8%) of XI in the form of a pale-yellow oily substance with R_f 0.60 (Alufol, hexane) and 1.05 g of starting IV. Crystallization of the mixture of X and XII gave XII in the form of colorless crystals with mp 60-62°C (from hexane) and R_f 0.54 (Alufol, hexane). IR spectrum (KBr): 3440 (ν_{NH}); 1495, 1470 ($\nu_{C=C}$); 620 cm^{-1} (ν_{C-B}).

4-Methyl-1-allyl-1,2,3,4-tetrahydrospiro(quinoline-2-cyclohexane) (XIII, $C_{18}H_{25}N$). A 2.9-g (13 mmole) sample of IV and 2.4 g (20 mmole) of allyl bromide were heated with 5 g of potassium carbonate in absolute acetone for 5 h, after which the acetone was evaporated, and 20 ml of water was added to the residue. The aqueous mixture was extracted with ether, the ether was removed by distillation, and the residue was chromatographed with a column to give 1.9 g (56%) of XIII in the form of an oily liquid with R_f 0.87 (Alufol, hexane). IR spectrum (film): 1600, 1580 cm^{-1} ($\nu_{C=C}$). The final substance eluted was 1.0 g (29%) of starting IV.

4-Methyl-1-allyl-1,2,3,4-tetrahydrospiro(quinoline-2-cyclopentane) (XIV, $C_{17}H_{23}N$). Similarly, the reaction of 1.35 g (6.7 mmole) of tetrahydroquinoline V and 0.9 g (7.4 mmole) of allyl bromide in the presence of 2.5 g of sodium carbonate gave 1.03 g (64%) of allylamine XIV in the form of an oily liquid with R_f 0.61 (Alufol, hexane). IR spectrum (film): 1600, 1580 cm^{-1} ($\nu_{C=C}$). Workup of the reaction mixture also yielded 0.3 g (18%) of starting V.

4-Methyl-8-(1′-propenyl)-1,2,3,4-tetrahydrospiro(quinoline-2-cyclohexane) (XV, $C_{18}H_{25}N$). A 1.9-g (7.4 mmole) sample of allylamine XIII was heated for 3 h at 170°C in 3 ml of $BF_3O\cdot(C_2H_5)_2$ (monitoring by TLC), after which 20 ml of ether and 20 ml of water were added, and the mixture was neutralized with sodium carbonate. The ether layer was separated, and the reaction products were extracted the aqueous layer with ether. The ether extract was dried with $MgSO_4$, the ether was removed by distillation, and the residue was purified on aluminum oxide by elution with ether—hexane (1:1) to give 0.9 g (47%) of XV in the form of a pale-yellow liquid with R_f 0.59 (Alufol, hexane). IR spectrum (film): 3400 (ν_{NH}); 1580 cm^{-1} ($\nu_{C=C}$).

4-Methyl-8-(1′-propenyl)-1,2,3,4-tetrahydrospiro(quinoline-2-cyclopentane) (XVI), $C_{17}H_{23}N$). Similarly, form 1.6 g (6.6 mmole) of allylamine XIV in 3 ml of $BF_3\cdot O(C_2H_5)_2$ we obtained 0.61 g (38%) of XVI in the form of a pale-yellow liquid with R_f 0.24 (Alufol, hexane). IR spectrum (film): 3400 (ν_{NH}), 1580 cm^{-1} ($\nu_{C=C}$).

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