SYNTHESIS AND NITRATION OF 4,6(4,8)-DIMETHYL-4-METHYL-6(8)-METHOXY-1,2,3,4-TETRAHYDROSPIRO[QUINOLINE-2-CYCLOHEXANES]

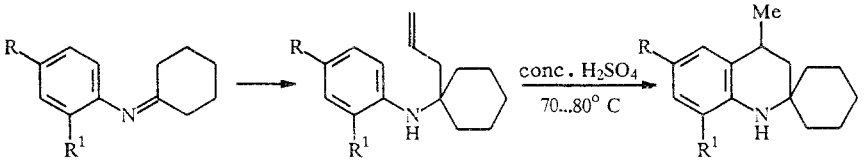
V. V. Kuznetsov, A. Pal'ma, A. É. Aliev, M. Fernandes, N. S. Prostakov, and A. V. Varlamov

The cyclization of 1-allyl-1-arylaminocyclohexanes under conditions of acid catalysis afforded 1,2,3,4-tetrahydro-4-methylspiro[quinoline-2-cyclohexanes] methyl (methoxy)-substituted in the phenylene ring. Their mono- and dinitro derivatives were synthesized, and their structure was established. Propositions on the direction of the nitration reaction of these heterocyclic compounds were expressed.

In the continuation of work on the synthesis and study of 1,2,3,4-tetrahydro-4-methylspiro[quinoline-2-cyclohexanes], for which we previously developed a method of isolation [1], we turned to the synthesis of 1,2,3,4-tetrahydro-4-methylspiro[quinoline-2-cyclohexanes] substituted in the phenylene ring and the study of the electrophilic substitution of compounds of this series using the example of their nitration. The synthesized methoxy and nitro derivatives present interest as potentially biologically active substances [2, 3].

The initial compounds — 1-allyl-1-p-tolyl (o-tolyl, p- and o-anisyl) aminocyclohexanes — were obtained from the corresponding N-cyclohexylidenarylamines and allylmagnesium bromide. Their cyclization was performed in concentrated sulfuric acid.

The 1,2,3,4-tetrahydro-4,6- and 1,2,3,4-tetrahydro-4,8-dimethylspiro[quinoline-2-cyclohexanes] (I) and (II) were obtained with corresponding yields of 75 and 85%; their methoxy-substituted analogs (III) and (IV) were obtained with yields of 23 and 35% (for the data of their PMR spectra, cf. Table 1).



I-IV

I R = CH_3; II, IV R = H; III R = OCH_3; I, III R^1 = H; II R^1 = CH_3; IV R^1 = OCH_3

The values of the $^3J_{34}$ SSCC (Table 2) indicate that the formation of the spiro compounds (I)-(IV) proceeds stereospecifically, and they exist in the form of one conformer with the equatorial methyl group at the position 4.

The nitration of the synthesized heterocyclic system was studied using the example of the compounds (I), (II), and 4-methyl-1-acetyl-1,2,3,4-tetrahydrospiro[quinoline-2-cyclohexane] (V). We previously established [4] that the nitration of the N-unsubstituted analog of compound (V) at 20°C proceeds ambiguously: 7-nitro- and 6-nitro-4-methyl-1,2,3,4-tetrahydrospiro-quinolines were obtained in respective yields of 32 and 7%, and the total yield was 39%. It can be assumed that the protonated and unprotonated forms of the initial base are subjected to the nitration. The predominating 7-nitro derivative is probably formed

Russian University of the Friendship of Peoples, Moscow 117198. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 784-788, June, 1993. Original article submitted February 24, 1993.

0009-3122/93/2906-0671$12.50

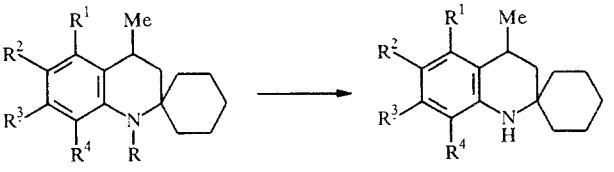
TABLE 1. Chemical Shifts of the Protons in the PMR Spectra of Substituted Spiro[tetrahydroquinoline-2-cyclohexanes] (I)-(IV) and (VII)-(XII)

Compound	δ, ppm										
	3α-H	3e-H	4-H	5-H	6-H	7-H	8-H	N—H	4-CH_3	CH_3 arom	Cyclohexane protons
I	1,31	1,90	2,88	6,95	—	6,78	6,38	3,65	1,30	2,20	1,45
II	1,31	1,88	2,88	7,02	6,58	6,88	—	3,74	1,32	2,09	1,50
III	1,30	1,85	2,85	6,70	—	6,59	6,40	3,42	1,30	3,72	1,50
IV	1,32	1,90	2,93	6,78	6,58	6,88	—	4,45	1,30	3,85	1,55
VII	1,33	1,96	2,95	—	8,24	—	8,02	5,52	1,41	—	1,45...1,61
VIII	1,39	2,04	2,99	8,15	—	9,03	—	9,35	1,46	—	1,51...1,67
IX	1,32	1,93	2,88	7,16	—	—	7,02	4,10	1,33	2,44	1,50
X	1,34	1,97	2,92	—	—	7,14	—	8,70	1,34	2,19	1,43...1,75
XI	1,34	1,98	2,90	7,99	—	7,87	—	4,35	1,37	2,13	1,54
XII	—*	1,91	3,01	7,22	—	7,09	—	3,81	1,40, 1.42	2,19	1,45...1,74

*It is superimposed by signals of the cyclohexane protons.

from the protonated form if it is taken into account that the consistent orientation of the quaternized amino group and the methylmethine fragment at the position 4 is realized in this case.

The 6-nitro-, 5,7-dinitro-, and 6,8-dinitro-4-methyl-1,2,3,4-tetrahydrospiro[quinoline-2-cyclohexanes] (VI), (VII), and (VIII) were isolated in respective fields of 10, 4, and 17% (the total yield of 31%) from the complex mixture of reaction products in the nitration of the compounds (V) at 0°C. It is apparent that the N-acetyl group determines the orientation in this case. The composition of the reaction products permits confirmation that the cleavage of the acetyl group occurs in the process of the isolation of these substances.



I, II, V VI - XI

I R = H, R^1 = H, R^2 = CH_3, R^3 = H, R^4 = H; II R = H, R^1 = H, R^2 = H, R^3 = H, R^4 = CH_3; V R = CH_3CO, R^1 = H, R^2 = H, R^3 = H, R^4 = H; VI R = H, R^1 = H, R^2 = NO_2, R^3 = H, R^4 = H; VII R = H, R^1 = NO_2, R^2 = = H, R^3 = NO_2, R^4 = H; VIII R = H, R^1 = H, R^2 = NO_2, R^3 = H, R^4 = NO_2; IX R = H, R^1 = H, R^2 = CH_3, R^3 = NO_2, R^4 = H; X R = H, R^1 = NO_2, R^2 = CH_3, R^3 = H, R^4 = NO_2; XI R = H, R^1 = H, R^2 = NO_2, R^3 = = H, R^4 = CH_3

It does not seem possible to draw any conclusions on the orientation in the nitration of the compounds (I) and (II) since the nitro derivatives were obtained in insignificant yield due to strong resinification. The nitration of compound (I) at 0°C led to the isolation of 7-nitro- and 5,8-dinitro-4,6-dimethyl-1,2,3,4-tetrahydrospiro[quinoline-2-cyclohexanes] (IX) and (X) with respective yields of 4 and 2%. The compound (II) afforded 6-nitro-4,8-dimethyl-1,2,3,4-tetrahydrospiro[quinoline-2-cyclohexane] (XI) with the yield of 8%.

The position of the nitro groups in the spiro compounds (VII)-(XI) was established using PMR spectroscopy (Table 1). Increments in the chemical shifts of the nitro group and its anisotropic effect were considered for this purpose [5]. The anomalous low-field shift of the N—H proton (9.35 ppm) in the PMR spectrum of compound (VIII) is evidently caused by the formation of the hydrogen bond with the nitro group at the position 8. This effect served as a criterion for establishing the position of the nitro groups in the compound (X). It is difficult to assign the signal of the aromatic proton in its PMR spectrum. However, the position of the broad N—H signal at 8.7 ppm, by analogy with compound (VIII), may only be associated with the presence of the nitro group at the position 8.

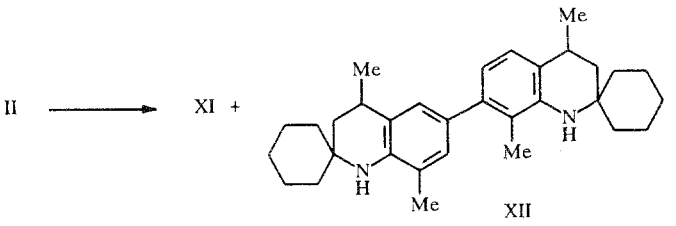
TABLE 2. Spin–Spin Coupling Constants in the PMR Spectra of Substituted Spiro[tetrahydroquinoline-2-cyclohexanes] (I)-(IV) and (VII)-(XII)

Compound	$J_{H,H}$, Hz							
	3a,3e	3a,4	3e,4	4CH3,4	5,6	5,7	6,7	7,8
I	-13,0	13,0	5,4	7,0	—	—*1	—	8,0
II	-13,0	12,8	5,8	7,0	8,0	—*1	8,0	—
III	-13,1	-*1	5,6	7,0	—	2,4	—	8,0
IV	-13,0	-*1	5,6	7,0	8,0	2,0	8,0	—
VII*2	-13,1	12,8	5,0	6,7	—	—	—	—
VIII*3	-13,6	13,0	4,7	6,7	—	2,6	—	—
IX	-13,1	—*1	5,6	6,7	—	—	—	—
X	-13,1	13,1	4,5	6,7	—	—	—	—
XI	-13,0	13,0	5,8	6,4	1,8			
XII*4	-13,5	—*1	6,5	6,7				

*1It could not be measured due to the strong superimposition of the signals.
*2The $^4J_{68}$ = 2.4 Hz.
*3The $^4J_{45}$ = 1.7 Hz.
*4The $^4J_{68}$ = 2.5 Hz.

The values of the $^3J_{34}$ SSCCs (Table 2) show that the nitro-substituted spiro compounds (VII)-(XII) exist in the form of one conformer with the equatorial methyl group.

Besides the nitro derivative (XI), the nitration of the compound (II) led to the isolation, with the yield of 11%, of a dark yellow crystalline substance, to which the structure di(1,2,3,4-tetrahydro-4,8-dimethylspiro[quinoline-2-cyclohexane]-6-yl) (XII) was assigned on the basis of analytical and spectral data. It is probably formed by oxidative dimerization at the sterically unencumbered position 6.



XII

The mass spectrum of compound (XII) contains the peak of the molecular ion with the m/z 456 (100%), corresponding with the empirical formula, as well as the fragment ion with the m/z 228 (4%) caused by the breakage at the $C_{(6)}-C_{(6')}$ bond. The IR spectrum of compound (XII) lacks bands in the region of vibrations of the NO_2 group. The aromatic region of the PMR spectrum (Table 1) contains singlet signals of the 5-H and 7-H protons at 7.20 and 7.09 ppm, broadened on account of the meta-interaction.

EXPERIMENTAL

The PMR spectra were recorded on the Bruker WP-80 instrument (80 MHz) for the compounds (I)-(IV) and the Bruker WM-400 (400 MHz) for the compounds (VI)-(XII) using $CDCl_3$; the internal standard was TMS. The mass spectra were obtained on the MX-1303 and LKB-9000 instruments supplied with a system of direct sample input to the ion source at the ionizing voltage of 70 eV. The IR spectra were recorded on the UR-20 spectrometer using tablets with KBr. Column chromatography utilized Al_2O_3 with the Brockmann 2 grade. The TLC utilized plates with a fixed layer of Al_2O_3 or silica gel of the Alufol and Silufol UV-254 types; development was effected using iodine vapor.

The data of the elemental analysis for C, H, and N correspond with the calculated data.

N-Cyclohexylidenarylamines. The solution of 0.14 mole of the arylamine and 0.15 mole of cyclohexanone in 150 ml of toluene is boiled in the presence of 0.1 ml of glacial acetic acid in apparatus with the Dean–Stark attachment until the separation of water ceases. The solvent is distilled off, and the residue is fractionated in vacuo. The products are as follows: **N-cyclohexylidene-p-toluidine** with the yield of 74%, the bp 116-119°C (2 mm), and the n_D^{20} 1.5530, **N-cyclohexylidene-o-toluidine** with the yield of 76%, the bp 120-123°C (4 mm), and the n_D^{20} 1.5490, **N-cyclohexylidene-p-anisidine** with the yield of 82%, the bp 144-146°C (3 mm), and the n_D^{20} 1.5620, and **N-cyclohexylidene-o-anisidine** with the yield of 81%, the bp 153-158°C (8 mm), and the n_D^{20} 1.5630.

1-Allyl-1-arylaminocyclohexanes. To the solution of allylmagnesium bromide, obtained from 0.6 mole of magnesium activated with iodine and 0.3 mole of allyl bromide in 200 ml of abs. ether, is added, at 20°C, the solution of 0.1 mole of the freshly distilled N-cyclohexylidenarylamine in 40 ml of abs. ether. The mixture is boiled for 4 h prior to the decomposition with a saturated aqueous solution of ammonium chloride. The mixture is extracted with ether (3 × 50 ml) and dried with Mg_2SO_4. The residue is fractionated in vacuo after the distillation of the ether. The 1-allyl-1-arylaminocyclohexanes are obtained in the form of light yellow liquids. The products are as follows: **1-allyl-1-(p-tolylamino)cyclohexane ($C_{16}H_{23}N$)** with the yield of 86%, the bp 140-143°C (3 mm), the R_f 0.60 (Alufol, the 20:1 mixture of heptane–ethyl acetate), the n_D^{20} 1.5485, and the IR spectrum characterized at 3405 cm^{-1} (NH), **1-allyl-1-(o-tolylamino)cyclohexane ($C_{16}H_{23}N$)** with the yield of 72%, the bp 125-128°C (2 mm), the R_f 0.70 (Alufol, the 20:1 mixture of heptane–ethyl acetate), the n_D^{20} 1.5440, and the IR spectrum characterized at 3440 cm^{-1} (NH), **1-allyl-1-(p-anisylamino)cyclohexane ($C_{16}H_{23}NO$)** with the yield of 61%, the bp 152-156°C (2 mm), the R_f 0.77 (Silufol, the 2:1 mixture of heptane–ethyl acetate), the n_D^{20} 1.5505, and the IR spectrum characterized at 3410 cm^{-1} (NH), and **1-allyl-1-(o-anisylamino)cyclohexane ($C_{16}H_{23}NO$)** with the yield of 68%, the bp 155-156°C (3 mm), the R_f 0.80 (Silufol, the 2:1 mixture of heptane–ethyl acetate), the n_D^{20} 1.5520, and the IR spectrum characterized at 3425 cm^{-1} (NH).

1,2,3,4-Tetrahydro-4-methylspiro[quinoline-2-cyclohexanes] (I)-(IV). To 12 mmoles of the 1-allyl-1-arylaminocyclohexane are added, dropwise and with the cooling of the mixture with ice, 9 ml of concentrated H_2SO_4. The mixture is heated for 3-4 h at 70-80°C with the monitoring by TLC. The mixture is cooled and poured onto ice; it is neutralized with aqueous ammonia prior to the extraction with ether and the drying with Mg_2SO_4. The residue remaining after the distillation of the ether is fractionated in vacuo, for the compounds (I), (II), and (IV), or chromatographed on Al_2O_3. The compounds (I)-(IV) are viscous yellow liquids. The products are as follows: **1,2,3,4-tetrahydro-4,6-dimethylspiro[quinoline-2-cyclohexane] (I) ($C_{16}H_{23}N$)** with the yield of 75%, the bp 165-167°C (3 mm), the R_f 0.83 (Alufol, the 6:1 mixture of heptane–ethyl acetate), the n_D^{20} 1.5620, and the IR spectrum characterized at 3390 cm^{-1} (NH), **1,2,3,4-tetrahydro-4,8-dimethylspiro[quinoline-2-cyclohexane] (II) ($C_{10}H_{23}N$)** with the yield of 85%, the bp 160-163°C (3 mm), the R_f 0.93 (Alufol, the 6:1 mixture of heptane–ethyl acetate), the n_D^{20} 1.5625, and the IR spectrum characterized at 3425 cm^{-1} (NH), **1,2,3,4-tetrahydro-6-methoxy-4-methylspiro[quinoline-2-cyclohexane] (III) ($C_{16}H_{23}NO$)** with the yield of 23%, the R_f 0.82 (Silufol, the 1:1 mixture of heptane–ethyl acetate), and the IR spectrum characterized at 3400 cm^{-1} (NH), and **1,2,3,4-tetrahydro-8-methoxy-4-methylspiro[quinoline-2-cyclohexane] (IV) ($C_{16}H_{23}NO$)** with the yield of 35%, the bp 153-154°C (3 mm), the R_f 0.85 (Silufol, the 1:1 mixture of heptane–ethyl acetate), the n_D^{20} 1.5660, and the IR spectrum characterized at 3410 cm^{-1} (NH).

1,2,3,4-Tetrahydro-6-nitro-4-methylspiro[quinoline-2-cyclohexane] (VI), 1,2,3,4-Tetrahydro-5,7-dinitro- and 6,8-Dinitro-4-methylspiro[quinoline-2-cyclohexane] (VII) ($C_{15}H_{19}N_3O_4$) and (VIII) ($C_{15}H_{19}N_3O_4$). To the solution of 2 g (7.7 mmoles) of the N-acetyl-substituted spiro compound (V) in 3 ml of glacial acetic acid at 0°C is added the mixture of 0.5 g of concentrated HNO_3 and 1.52 g of concentrated H_2SO_4. The mixture is maintained for 4 h at 20°C and poured onto ice prior to the neutralization with sodium carbonate solution to the pH 7-8. The mixture is extracted with ether and dried with Mg_2SO_4. The residue remaining after the distillation of the ether is chromatographed on a column with Al_2O_3 using the 25:1 mixture of heptane–ethyl acetate as the eluent. Compound (VII) is isolated with the yield of 0.12 g (4%) as red crystals with the mp 130-132°C (heptane), the R_f 0.86 (Alufol, the 5:2 mixture of heptane–ethyl acetate), and the IR spectrum characterized at 1360, 1510 (NO_2), and 3410 (NH) cm^{-1}. Compound (VIII) is obtained with the yield of 0.48 g (16.8%) as yellow crystals with the mp 140-142°C (heptane), the R_f 0.57 (Alufol, the 5:2 mixture of heptane–ethyl acetate), and the IR spectrum characterized at 1360, 1500 (NO_2), and 3405 (NH) cm^{-1}. Compound (VI) is obtained with the yield of 0.24 g (10%) as light brown crystals with the mp 105-107°C (hexane) and the R_f 0.47 (Alufol, the 2:1 mixture of heptane–ethyl acetate). The mixed melting test with a sample of known structure [4] does not give a depression of the melting temperature.

1,2,3,4-Tetrahydro-7-nitro-4,6-dimethyl- and 5,8-Dinitro-4,6-dimethylspiro[quinoline-2-cyclohexane] (IX) ($C_{16}H_{22}N_2O_3$) and (X) ($C_{16}H_{21}N_3O_4$). Using the method described above, 3.4 g (15 mmoles) of the spiro compound (I) are nitrated.

The mixture is chromatographed on Al_2O_3 in the 20:1 system of heptane–ethyl acetate prior to the isolation of 0.1 g (2%) of the dinitro-substituted spiro compound (X) as red crystals with the mp 133-134°C (heptane), the R_f 0.51 (Silufol, the 5:1 mixture of heptane–ethyl acetate), and the IR spectrum characterized at 1340, 1540 (NO_2), and 3370 (NH) cm^{-1}. The compound (IX) is isolated with the yield of 0.14 g (4%) as orange crystals with the mp 125-126°C (heptane), the R_f 0.35 (Silufol, the 5:1 mixture of heptane–ethyl acetate), and the IR spectrum characterized at 1345, 1535 (NO_2), and 3425 (NH) cm^{-1}.

1,2,3,4-Tetrahydro-6-nitro-4,8-dimethylspiro[quinoline-2-cyclohexane] (XI) ($C_{16}H_{22}N_2O_2$) and Di(1,2,3,4-tetrahydro-4,8-dimethylspiro[quinoline-2-cyclohexane]-6-yl) (XII) ($C_{32}H_{44}N_2$). To 2 g (8.7 mmoles) of the spiro compound (II) is added, dropwise, the mixture of 0.5 g of concentrated HNO_3 and 1.52 g of concentrated H_2SO_4, and the mixture is heated for 1 h at 50°C with the monitoring by TLC. The mixture is poured onto ice and neutralized with aqueous sodium carbonate solution to the pH 7-8. The mixture is extracted with ether and dried with $MgSO_4$. The residue remaining after the distillation of the ether is chromatographed on Al_2O_3 with the 20:1 mixture of heptane–ethyl acetate as the eluent. The dimer (XII) is isolated with the yield of 0.43 g (11%) as dark yellow crystals with the mp 149-150°C (heptane), the R_f 0.66 (Alufol, the 5:1 mixture of heptane–ethyl acetate), and the IR spectrum characterized at 3420 cm^{-1} (NH); compound (XI) is isolated with the yield of 0.19 g (8%) as brown crystals with the mp 122-123°C (heptane), the R_f 0.57 (Alufol, the 5:1 mixture of heptane–ethyl acetate), and the IR spectrum characterized at 1345, 1525 (NO_2), and 3380 (NH) cm^{-1}.

REFERENCES

1. V. V. Kuznetsov, E. E. Stashenko, and N. S. Prostakov, Khim. Geterotsikl. Soedin., No. 11, 1514 (1989).
2. S. I. Murahashi, I. Yasushi, and H. Yoshiaki, Bull. Chem. Soc. Jpn., **62**, No. 9, 2968 (1989).
3. Zh. V. Shmireva, Kh. S. Shikhalev, and E. V. Shpaneg, Izv. Vyssh. Uchebn. Zaved., Khim. Khim. Tekhnol., **31**, No. 9, 45 (1988).
4. V. V. Kuznetsov, A. É. Aliev, A. R. Pal'ma, A. V. Varlamov, and N. S. Prostakov, Khim. Geterotsikl. Soedin., No. 7, 947 (1991).
5. N. S. Prostakov, A. A. Fomichev, N. I. Golovtsov, A. V. Varlamov, N. Islan, and V. M. Polosin, Khim. Geterotsikl. Soedin., No. 11, 1532 (1985).