4-Methyl-3,4-dihydrospiro[cycloheptane-1',2(1H)-quinoline] and 4-Methyl-3,4-dihydrospiro[cyclooctane-1',2(1H)-quinoline]. Synthesis of Derivatives and Chemical Transformations

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New derivatives of 3,4-dihydrospiro[cycloalkane-1',2(1H)-quinolines] were obtained from cycloheptanone and cyclooctanone *via* facile three steps hetero spiro annulation process. Their nitro derivatives were prepared through electrophilic substitution reactions.

Introduction.

The chemistry of quinoline and its hydrogenated derivatives, mainly, tetrahydroquinolines, has been the center of attention of chemists for a long time [1,2]. This is due to the wide and diverse use of such compounds in industry [3-6], agriculture and, principally, in medicine. Tetrahydroquinoline derivatives act as potent virucides [7] and analgesics [8,9], possess a high antibacterial [10], antiarrhithmic [11] and anti-hypertensive [12] activities. The alkaloids pumiliotoxin C [13], lepadin A [14], cuspareine [15], and virantmycin [16] have the tetrahydroquinoline moiety as a basic skeleton, while the alkaloids discorhabdins and prianosins possess more complex structures with a tetrahydroquinoline fragment which is spiro annulated to the cyclohexadiene ring [17].

Nevertheless, among the various methods for the construction of hydrogenated quinoline rings only a few examples of spirotetra(di-, deca)hydroquinoline synthesis may be mentioned [1,2]. Elsewhere, we reported an effective method to prepare dihydrospiro[cyclopentane-1',2(1H)-quinolines] and dihydrospiro[cyclohexane-1',2(1H)-quinolines] from readily available N-cycloalkylidenarylamines [18,19] and demonstrated that these spiro compounds possessed diverse biological activity [20-22].
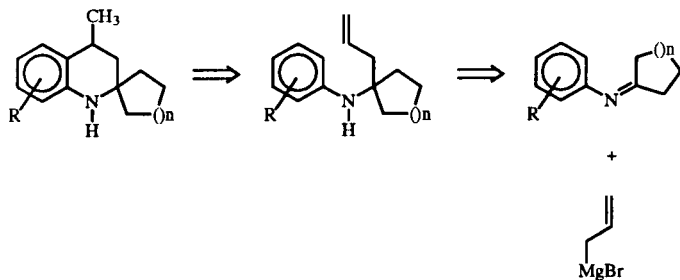
It has been envisaged that a facile access to these compounds is due to an intramolecular electrophilic cyclization of the N-(1-allylcycloalkyl)arylamines which are readily available from ketimines and allylmagnesium bromide, as

shown in Scheme 1. On the basis of this synthetic route we report the synthesis of two novel spiro-heterocyclic ring systems named in the title derived from the *ortho-(para)*-substituted anilines and cycloheptanone or cyclooctanone and their electrophilic nitration and acetylation.
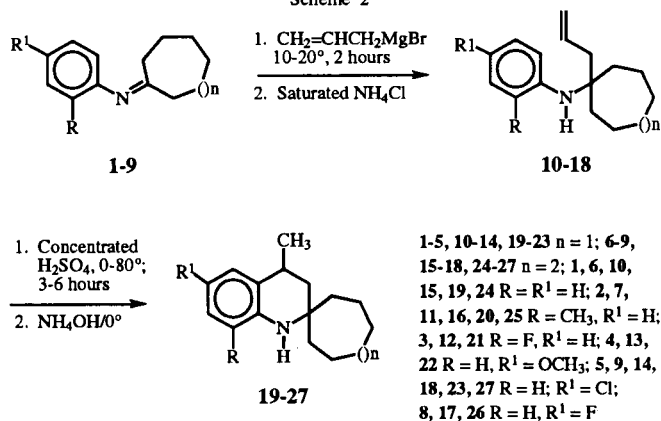
Discussion and Results.

The N-(1-allylcycloheptyl)arylamines and cyclooctyl analogues **10-18** were obtained by the nucleophilic addition of allylmagnesium bromide to the imine C=N bond of the Schiff bases **1-9**; hence, slow addition of a solution of imine **1-9** to the freshly prepared Grignard reagent at 10°, followed by stirring at room temperature for 2 hours, and aqueous workup resulted in the formation of homoallylamines **10-18** with 33-77% yields after distillation at reduced pressure (Scheme 2).

Scheme 2

1-5, 10-14, 19-23 n = 1; 6-9, 15-18, 24-27 n = 2; 1, 6, 10, 15, 19, 24 R = R¹ = H; 2, 7, 11, 16, 20, 25 R = CH₃, R¹ = H; 3, 12, 21 R = F, R¹ = H; 4, 13, 22 R = H, R¹ = OCH₃; 5, 9, 14, 18, 23, 27 R = H; R¹ = Cl; 8, 17, 26 R = H, R¹ = F

The structure of these intermediates was established using ir and nmr spectroscopy and also mass spectrometry. Their ir spectra showed bands of the amine group in the region of 3388-3459 cm⁻¹. The mass spectra registered the molecular ion peaks corresponding to their formulae. In the ¹H nmr spectra of these compounds, the signals of

Scheme 1

cycloheptane (cyclooctane) protons appeared between 0.87-2.43 ppm. The allyl radical protons generated three groups of signals: a doublet of the CH_2-group was observed in the region of 2.27-2.69 ppm and multiplet signals of $=CH_2$ and $CH=$ groups, respectively, appeared at low fields, between 4.90-5.02 and 5.69-6.05 ppm.

In order to transform the homoallylamines **10-18** into spiro compounds **19-27**, these amines were subjected to heating in the presence of concentrated sulfuric acid. In this manner, the slow addition of sulfuric acid to amines at 0°, followed by vigorous stirring at 80° for 3-5 hours and basic workup, led to the desired derivatives. After chromatographic purification these spiro compounds were isolated as brownnish oils in 20-68% yields.

Their structures were also confirmed by spectroscopic methods in a similar manner as for intermediates **10-18**. Significantly, the ^1H nmr spectra of the final products showed the presence of 4-CH_3- proton doublet signals (1.29-1.40 ppm), which were the most characteristic evidence of the intramolecular electrophilic cyclization. The axial 3-H protons of the tetrahydroquinoline ring appeared at higher field than those corresponding to equatorial 3-H protons, and appeared as multiplets. The value of vicinal coupling constants permitted us to assign a semichair conformation to the tetrahydroquinoline fragment.

Mass spectral data also confirmed the structure of the heterocycles prepared. The stability of molecular ions (W_M), of medium intensity (20-43%) oscillated between 5.3 and 12.5% and depended slightly on the chemical nature of substituents R and R^1 (Table 1).

Nitration of compound **24** using a nitric and acetic acid mixture produced 4-methyl-6,8-dinitro-3,4-dihydrospiro[cyclooctane-1',2(1H)-quinoline] (**28**) as the major product. A small amount of the 8-mononitro derivative **30** was also observed in this reaction. In the case of nitration of the 6-chloro derivative **27** only one isomer was formed, the 8-nitro substituted was formed (Scheme 3). The regiochemistry of these products was in agreement with the aromatic splitting in the proton nmr.

For the biological tests, the acetamide **31-33** were prepared from the spiro compounds **24, 25, 27** and acetic anhydride.

Conclusion.

We have proposed a simple three-step route for the hetero spiro annulation of cycloheptanone or cyclooctanone which leads to the new substituted 3,4-dihydrospiro[cycloheptane(cyclooctane)-1',2(1H)-quinolines] via readily available N-arylcycloheptylidene(octylidene)amines. Although the overall yields in these syntheses remain moderate, the simplicity of the process, the accessibility and moderate cost of the starting materials are worthy of mention. The electrophilic nitration of these spiranes occurs regioselectively at C-8 of the phenyl ring affording the 8-nitro derivatives.
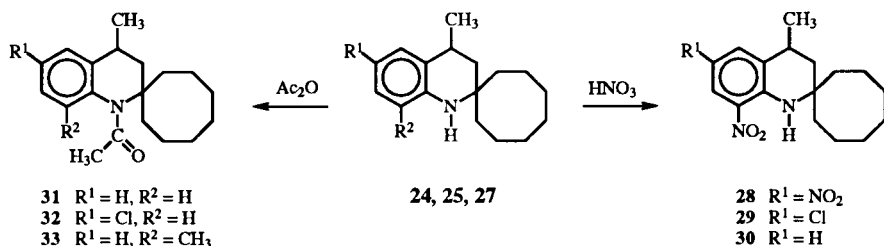
Scheme 3

31 $R^1 = H, R^2 = H$
32 $R^1 = Cl, R^2 = H$
33 $R^1 = H, R^2 = CH_3$

24, 25, 27

28 $R^1 = NO_2$
29 $R^1 = Cl$
30 $R^1 = H$

Table 1

Relative intensities (%) of the characteristic ions in the mass spectra of the spiranes **19-27**.

No.	MW	T_R [a]	$W_M,\%$[b]	M^+	ϕ_1[c]	ϕ_2	ϕ_3	ϕ_4	ϕ_5	ϕ_6	ϕ_7	ϕ_8	ϕ_9	ϕ_{10}
19	229	28.1	7.5	26	65	3	24	100	12	9	0	23	10	0
20	243	28.9	7.2	28	64	3	24	100	13	8	0	23	11	0
21	247	27.7	7.6	24	66	3	22	100	10	8	0	19	8	0
22	259	31.9	12.5	43	60	2	24	100	15	8	0	19	4	0
23	263 [d]	30.6	7.6	25	65	3	21	100	13	7	0	16	7	0
24	243	27.6	7.4	33	96	3	15	10	0	100	56	10	35	10
25	257	30.3	7.2	36	94	3	15	10	0	100	60	60	38	13
26	261	29.7	5.3	22	72	2	12	9	0	100	58	10	32	11
27	277 [d]	32.6	6.8	28	91	3	13	9	0	100	60	10	27	8

[a] Retention time, t_R on the column HP-5 (30 x 0.25 mm i.d.) coated with 5% phenylpolymethylsiloxane (0.25 μm film thickness). Temperature program: from 100° (10 minutes) to 250° at 10°/minute. [b] Stability of molecule ion, W_M, ($W_M = I_M/\Sigma I_i$ x 100%; where I_M- molecule ion intensity; ΣI_i- sum of intensities of ions (m/z > 39) observed in mass spectrum). [c] $\phi_1 = M-CH_3$; $\phi_2 = M-C_2H_5$; $\phi_3 = M-C_3H_7$; $\phi_4 = M-C_4H_9$; $\phi_5 = M-C_5H_{10}$; $\phi_6 = M-C_5H_{11}$; $\phi_7 = M-C_6H_{12}$; $\phi_8 = C_6H_{13}$; $\phi_9 = C_7H_{15}$; $\phi_{10} = C_8H_{17}$. [d] ^{35}Cl.

EXPERIMENTAL

The purity of the substances and the composition of the reaction mixtures were controlled by thin-layer chromatography (tlc) on chromatoplates of Alufol 60 and Silufol uv$_{254}$. The separation was carried out by column chromatography on alumina, Brockmann activity II, using mixtures of ethyl acetate-heptane with gradual increase of polarity 1:30, 1:20, 1:10, 1:5 as eluents. The ir spectra were obtained on a Perkin Elmer 599B-FT spectrometer in potassium bromide. The ^{1}H- and ^{13}C nmr spectra were recorded on a Jeol EX-90 or on a Bruker AC-200 spectrometer, and are reported in ppm on the δ scale. Deuteriochloroform was used as a solvent and tetramethylsilane as the internal reference. Data are reported as follows: chemical shift (integral intensity, multiplicity, group, coupling constants). A Hewlett Packard 5890A Series II Gas Chromatograph interfaced to an HP 5972 Mass Selective Detector with an Hewlett Packard ms ChemStation Data system was used for ms identification. The column employed was an HP-5MS (Hewlett Packard) cross-linked fused silica capillary column (30 m, 0.25 mm ID) coated with 5%-phenylpolymethylsiloxane (0.25 μm phase thickness). The oven was programed from 100° (10 minute hold) to 250° at 10°/minute. The helium inlet pressure was 78 kPa, with linear velocity 38 cm/minute (split 10 ml/minute). The injector temperature was kept at 250° and the volume injected was 0.5 μl (20% in dichloromethane). The temperatures of the ionization chamber and of the transfer line were 180° and 285°, respectively. The electron beam energy was 70 eV. Mass spectra and reconstructed chromatograms were obtained by automatic scanning in the mass range m/z 50-400 a.m.u.'s at 2.2 scan/s. Elemental analyses were performed on a Leco CHN-600 analyzer. The difraction indexes were measured in a Schmidt Haensch 17452 apparatus. The melting points (uncorrected) were determined on a Fisher-Johns melting point apparatus. Solvents and common reagents were obtained from Merck and Aldrich and were reagent grade.

N-(1-Allylcycloheptyl(cyclooctyl))arylamines **10-18**.

Imines **1-9** (0.1 mole) [23] in 50 ml of ether at 10° were added slowly to 350 ml of an ether solution of allylmagnesium bromide prepared from 0.6 mole of magnesium and 0.3 mole of allyl bromide. The mixture was stirred for 2 hours at room temperature and then cooled and treated with saturated ammonium chloride solution. The products were extracted with ether (3 x 100 ml). The organic layer was dried (sodium sulfate) and the residue was fractionated at reduce pressure.

N-(1-Allylcycloheptyl)aniline (**10**).

This compound was obtained in 76% yield, bp 155-157°/10 mm Hg; n^{20} 1.5580; ir: ν NH 3415 cm^{-1} ; ^{1}H nmr: δ 1.25-1.73 (12H, m, cycloheptyl protons), 2.40 (2H, d, -CH$_2$), 3.05 (1H, s br, NH), 4.98 (2H, m, =CH$_2$), 5.75 (1H, m, CH=), 6.60-7.21 (5H, m, phenyl protons); ms: m/z 229 (M$^+$).

N-(1-Allylcycloheptyl)-*o*-toluidine (**11**).

This compound was obtained in 77% yield, bp 140-142°/10 mm Hg; n^{20} 1.5570; ir: ν NH 3448 cm^{-1}; ^{1}H nmr: δ 1.05-2.00 (12H, m, cycloheptyl protons), 2.12 (3H, s, CH$_3$-Ar), 2.50 (2H, d, -CH$_2$), 3.00 (1H, s br, NH), 4.92 (2H, m, =CH$_2$), 5.70 (1H, m, CH=), 6.60-7.21 (4H, m, phenyl protons); ms: m/z 243 (M$^+$).

N-(1-Allylcycloheptyl)-*o*-flouroaniline (**12**).

This compound was obtained in 34% yield; bp 127-129°/10 mm Hg; n^{20} 1.5400; ir: ν NH 3437 cm^{-1}; ^{1}H nmr: δ 1.25-1.78 (12H, m, cycloheptyl protons), 2.48 (2H, d, -CH$_2$), 3.51 (1H, s br, NH), 4.97 (2H, m, =CH$_2$), 5.76 (1H, m, CH=), 6.58-7.06 (4H, m, phenyl protons); ms: m/z 247 (M$^+$).

N-(1-Allylcycloheptyl)-*p*-anisidine (**13**).

This compound was obtained in 65% yield, bp 154-156°/10 mm Hg; n^{20} 1.5560; ir: ν NH 3404 cm^{-1}; ^{1}H nmr: δ 1.05-1.90 (12H, m, cycloheptyl protons), 2.33 (2H, d, -CH$_2$), 3.74 (3H, s, OCH$_3$), 5.02 (2H, m, =CH$_2$), 5.84 (1H, m, CH=), 6.74 (4H, s, phenyl protons); ms: m/z 259 (M$^+$).

N-(1-Allylcycloheptyl)-*p*-chloroaniline (**14**).

This compound was obtained in 37% yield, bp 153-155°/10 mm Hg; n^{20} 1.5630; ir: ν NH 3388 cm^{-1}; ^{1}H nmr: δ 1.26-1.70 (12H, m, cycloheptyl protons), 2.41 (2H, d, -CH$_2$), 3.34 (1H, s br, NH), 4.96 (2H, m, =CH$_2$), 5.72 (1H, m, CH=), 6.53-7.17 (4H, m, phenyl protons); ms: m/z 263 (M$^+$, ^{35}Cl).

N-(1-Allylcyclooctyl)aniline (**15**).

This compound was obtained in 61% yield, bp 140-141°/10 mm Hg; n^{20} 1.5590; ir: ν NH 3413 cm^{-1}; ^{1}H nmr: δ 1.25-1.84 (14H, m, cyclooctyl protons), 2.41 (2H, d, -CH$_2$), 3.05 (1H, s br, NH), 4.99 (2H, m, =CH$_2$), 5.79 (1H, m, CH=), 6.66-7.13 (5H, m, phenyl protons); ms: m/z 243 (M$^+$).

N-(1-Allylcyclooctyl)-*o*-toluidine (**16**).

This compound was obtained in 40% yield, bp 140-145°/10 mm Hg; n^{20} 1.5430; ir: ν NH 3448 cm^{-1}; ^{1}H nmr: δ 1.26-2.43 (14H, m, cyclooctyl protons), 2.52 (2H, d, -CH$_2$), 3.14 (1H, s br, NH), 4.95 (2H, m, =CH$_2$), 5.78 (1H, m, CH=), 6.53-7.15 (4H, m, phenyl protons); ms: m/z 257 (M$^+$).

N-(1-Allylcyclooctyl)-*p*-flouroaniline (**17**).

This compound was obtained in 59% yield, bp 150-153°/10 mm Hg; n^{20} 1.5380; ir: ν NH 3420 cm^{-1}; ^{1}H nmr: δ 0.87-1.65 (14H, m, cyclooctyl protons), 2.31 (2H, d, -CH$_2$), 2.97 (1H, s br, NH), 5.00 (2H, m, =CH$_2$), 5.87 (1H, m, CH=), 6.59-6.95 (4H, m, phenyl protons); ms: m/z 261 (M$^+$).

N-(1-Allylcyclooctyl)-*p*-chloroaniline (**18**).

This compound was obtained in 33% yield, bp 127-129°/10 mm Hg; n^{20} 1.5660; ir: ν NH 3420 cm^{-1}; ^{1}H nmr: δ 1.25-1.68 (14H, m, cyclooctyl protons), 2.33 (2H, d, -CH$_2$), 3.03 (1H, s br, NH), 4.98 (2H, m, =CH$_2$), 5.74 (1H, m, CH=), 6.54-7.24 (4H, m, phenyl protons); ms: m/z 277 (M$^+$, ^{35}Cl).

4-Methyl-3,4-dihydrospiro[cycloalkane-1',2(1*H*)-quinolines] **19-27**.

Concentrated sulfuric acid (2 ml) was added dropwise to 1.0 g of allylamines **10-17** at 0°. The mixture then was heated at 70-90° for 3-5 hours with vigorous stirring. Then, the mixture was cooled down to 0° and treated with a concentrated ammonium hydroxide solution. The products were extracted (ether, 2 x 50 ml). The organic layer was dried (sodium sulfate) and the residue purificated by a short chromatographic column (alumina). The compounds **19-27** were obtained as brownnish oils except compound **20** which is a white solid.

4-Methyl-3,4-dihydrospiro[cycloheptane-1',2(1*H*)-quinoline] (**19**).

This compound was obtained in 59% yield; ir: ν NH 3387 cm^{-1}; ^{1}H nmr: (90 MHz) δ 1.23 (1H, tt, 3a-H, J = -12.87 Hz, J =

12.30 Hz), 1.40 (3H, d, 4-CH$_3$, J = 6.77 Hz), 1.23-1.90 (12H, m, cycloheptyl protons), 1.99 (1H, tt, 3e-H, J = -12.87 Hz, J = 5.76 Hz), 2.94 (1H, m, 4-H), 3.84 (1H, s br, NH), 6.52 (1H, dd, 8-H, J = 7.88 Hz, J = 1.20 Hz), 6.75 (1H, dd, 6-H, J = 7.70 Hz, J = 7.20 Hz), 7.05 (1H, dd, 7-H, J = 7.20 Hz, J = 7.88 Hz), 7.25 (1H, dd, 5-H, J = 7.70 Hz, J = 1.70 Hz).

Anal. Calcd. for C$_{16}$H$_{23}$N: C, 83.84; H, 10.04; N, 6.11. Found: C, 83.70; H, 10.12; N, 5.98.

4,8-Dimethyl-3,4-dihydrospiro[cycloheptane-1',2(1*H*)-quinoline] (20).

This compound was obtained in 64% yield; mp 59-61° (heptane) yield; ir: ν NH 3412 cm^{-1}; ^{1}H nmr: (90 MHz) δ 0.96 (1H, tt, 3a-H, J = -12.94 Hz, J = 12.70 Hz), 1.32 (3H, d, 4-CH$_3$, J = 6.84 Hz), 1.05-2.00 (12H, m, cycloheptyl protons), 2.10 (3H, s, 8-CH$_3$), 2.24 (1H, tt, 3e-H, J = -12.94 Hz, J = 5.60 Hz), 2.88 (1H, m, 4-H), 3.65 (1H, s br, NH), 6.58 (1H, dd, 6-H, J = 8.00 Hz, J = 7.56 Hz), 6.89 (1H, dd, 7-H, J = 8.00 Hz, J = 1.65 Hz), 7.06 (1H, dd, 5-H, J = 7.56 Hz, J = 1.65 Hz); ^{13}C nmr: (75.5 MHz) δ 17.5, 20.6, 27.2, 38.4, 22.0, 22.6, 29.5, 30.2, 44.0, 44.5, 54.3, 116.0, 124.7, 125.4, 127.8, 139.1, 141.5.

Anal. Calcd. for C$_{17}$H$_{25}$N: C, 83.95; H, 10.29; N, 5.76. Found: C, 83.94; H, 10.35; N, 5.71.

8-Fluoro-4-methyl-3,4-dihydrospiro[cycloheptane-1',2(1*H*)-quinoline] (21).

This compound was obtained in 20% yield; ir: ν NH 3426 cm^{-1}; ^{1}H nmr: (90 MHz) δ 1.27 (1H, tt, 3a-H, J = -13.50 Hz, J = 12.80 Hz), 1.34 (3H, d, 4-CH$_3$, J = 6.66 Hz), 1.10-1.90 (12H, m, cycloheptyl protons), 1.99 (1H, tt, 3e-H, J = -13.50 Hz, J = 5.49 Hz), 2.89 (1H, m, 4-H), 3.91 (1H, s br, NH), 6.40-7.00 (3H, m, phenyl protons).

Anal. Calcd. for C$_{16}$H$_{22}$FN: C, 77.73; H, 8.91; N, 5.67. Found: C, 77.58; H, 8.79; N, 5.52.

6-Methoxy-4-methyl-3,4-dihydrospiro[cycloheptane-1',2(1*H*)-quinoline] (22).

This compound was obtained in 50% yield; ir: ν NH 3364 cm^{-1}; ^{1}H nmr: (90 MHz) δ 1.17 (1H, tt, 3a-H, J = -13.05 Hz, J = 12.75 Hz), 1.30 (3H, d, 4-CH$_3$, J = 6.78 Hz), 1.92 (1H, tt, 3e-H, J = -13.05 Hz, J = 5.60 Hz), 1.10-2.00 (12H, m, cycloheptyl protons), 2.83 (1H, m, 4-H), 3.74 (3H, s, 6-OCH$_3$), 3.99 (1H, s br, NH), 6.39 (1H, d, 8-H, J = 8.00 Hz), 6.60 (1H, dd, 7-H, J = 8.00 Hz, J = 2.30 Hz), 6.77 (1H, d, 5-H, J = 2.30 Hz),

Anal. Calcd. for C$_{17}$H$_{25}$NO: C, 78.76; H, 9.65; N, 5.41. Found: C, 78.67; H, 9.54; N, 5.34.

6-Chloro-4-methyl-3,4-dihydrospiro[cycloheptane-1',2(1*H*)-quinoline] (23).

This compound was obtained in 29% yield; ir: ν NH 3405 cm^{-1}; ^{1}H nmr: (90 MHz) δ 1.19 (1H, tt, 3a-H, J = -12.91 Hz, J = 12.70 Hz), 1.31 (3H, d, 4-CH$_3$, J = 6.76 Hz), 0.91-1.90 (12H, m, cycloheptyl protons), 1.92 (1H, tt, 3e-H, J = -12.91 Hz, J = 5.76 Hz), 2.82 (1H, m, 4-H), 3.59 (1H, s br, NH), 6.38 (1H, d, 8-H, J = 8.04 Hz), 6.64 (1H, dd, 7-H, J = 8.04 Hz, J = 2.20 Hz), 6.98 (1H, d, 5-H, J = 2.20 Hz).

Anal. Calcd. for C$_{16}$H$_{22}$ClN: C, 72.86; H, 8.35; N, 5.31. Found: C, 72.70; H, 8.22; N, 5.18.

4-Methyl-3,4-dihydrospiro[cyclooctane-1',2(1*H*)-quinoline] (24).

This compound was obtained in 68% yield; ir: ν NH 3392 cm^{-1}; ^{1}H nmr: (90 MHz) δ 1.21 (1H, tt, 3a-H, J = -13.04 Hz, J = 12.35 Hz), 1.32 (3H, d, 4-CH$_3$, J = 6.84 Hz), 1.94 (1H, tt, 3e-H, J =

-13.04 Hz, J = 5.76 Hz), 1.00-2.00 (14H, m, cyclooctyl protons), 2.85 (1H, m, 4-H), 3.56 (1H, s br, NH), 6.46 (1H, dd, 8-H, J = 7.74 Hz, J = 1.20 Hz), 6.67 (1H, dd, 6-H, J = 7.65 Hz, J = 7.20 Hz), 6.93 (1H, dd, 7-H, J = 7.74 Hz, J = 7.20 Hz), 7.15 (1H, dd, 5-H, J = 7.65 Hz, J = 1.70 Hz).

Anal. Calcd. for C$_{17}$H$_{25}$N: C, 83.95; H, 10.29; N, 5.76. Found: C, 83.73; H, 10.10; N, 5.67.

4,8-Dimethyl-3,4-dihydrospiro[cyclooctane-1',2(1*H*)-quinoline] (25).

This compound was obtained in 43% yield; ir: ν NH 3377 cm^{-1}; ^{1}H nmr: (90 MHz) δ 1.21 (1H, tt, 3a-H, J = -13.50 Hz, J = 12.70 Hz), 1.32 (3H, d, 4-CH$_3$, J = 6.84 Hz), 1.00-1.90 (14H, m, cyclooctyl protons), 1.95 (1H, tt, 3e-H, J = -13.50 Hz, J = 5.60 Hz), 2.08 (3H, s, 8-CH$_3$), 2.86 (1H, m, 4-H), 3.62 (1H, s br, NH), 6.52 (1H, dd, 6-H, J = 8.00 Hz, J = 7.56 Hz), 6.67 (1H, dd, 7-H, J = 8.00 Hz, J = 1.60 Hz), 6.89 (1H, dd, 5-H, J = 7.56 Hz, J = 1.60 Hz).

Anal. Calcd. for C$_{18}$H$_{27}$N: C, 84.05; H, 10.51; N, 5.45. Found: C, 83.92; H, 10.40; N, 5.35.

6-Fluoro-4-methyl-3,4-dihydrospiro[cyclooctane-1',2(1*H*)-quinoline] (26).

This compound was obtained in 20% yield; ir: ν NH 3394 cm^{-1}; ^{1}H nmr: (90 MHz) δ 1.18 (1H, tt, 3a-H, J = -13.27 Hz, J = 12.85 Hz), 1.29 (3H, d, 4-CH$_3$, J = 6.86 Hz), 1.00-1.90 (14H, m, cyclooctyl protons), 1.93 (1H, tt, 3e-H, J = -13.27 Hz, J = 5.56 Hz), 6.82 (1H, d, 5-H, J = 2.28 Hz), 2.88 (1H, m, 4-H), 3.80 (1H, s br, NH), 6.39 (1H, d, 8-H, J = 8.10 Hz), 6.63 (1H, dd, 7-H, J = 8.10 Hz, J = 2.28 Hz).

Anal. Calcd. for C$_{17}$H$_{24}$FN: C, 78.16; H, 9.19; N, 5.36. Found: C, 78.01; H, 9.02; N, 5.12.

6-Chloro-4-methyl-3,4-dihydrospiro[cyclooctane-1',2(1*H*)-quinoline] (27).

This compound was obtained in 25% yield; ir: ν NH 3392 cm^{-1}; ^{1}H nmr: (90 MHz) δ 1.17 (1H, tt, 3a-H, J = -13.10 Hz, J = 12.80 Hz), 1.29 (3H, d, 4-CH$_3$, J = 6.84 Hz), 1.93 (1H, tt, 3e-H, J = -13.10 Hz, J = 5.70 Hz), 1.10-1.95 (14H, m, cyclooctyl protons), 2.80 (1H, m, 4-H), 3.38 (1H, s br, NH), 6.37 (1H, d, 8-H, J = 8.00 Hz), 6.59 (1H, dd, 7-H, J = 8.00 Hz, J = 2.40 Hz), 6.96 (1H, d, 5-H, J = 2.40 Hz).

Anal. Calcd. for C$_{17}$H$_{24}$ClN: C, 73.51; H, 8.65; N, 5.05. Found: C, 73.28; H, 8.51; N, 4.90.

4-Methyl-6,8-dinitro-3,4-dihydrospiro[cyclooctane-1',2(1*H*)-quinoline] (28) and 4-Methyl-8-nitro-3,4-dihydrospiro[cyclooctane-1',2(1*H*)-quinoline] (30).

Acetic acid (5 ml) was chilled in an ice-bath and 24 (1.9 g, 7.8 mmoles) was added. Nitric acid (1.5 ml, 3.7 mmoles) was added dropwise over a period of 10 minutes to yield a brown reaction mixture which was allowed to warm to room temperature and then heated at 50° for 30 minutes with continous stirring. The reaction mixture was poured over ice, basified with concentrated ammonium hydroxide and extracted with dichlorometane (3 x 20 ml). The organic layer was dried (sodium sulfate) and evaporated to afford a brown oil residue (1.2 g). The residue was separated by column chromatography (alumina; heptane-ethyl acetate, 3:1 as eluent) to give compound 28 and compound 30 in 35% (0.85 g) and 6% (0.14 g) yield, respectively.

Compound 28 was obtained as orange crystals, mp 107-109° (heptane) ir: ν NH 3328, δ NO$_2$ 1526, 1347 cm^{-1}; ^{1}H nmr: (200

MHz) δ 1.32 (1H, t, 3a-H), 1.47 (3H, d, 4-CH$_3$), 1.55-1.90 (14H, m, cyclooctyl protons), 2.10 (1H, dd, 3e-H), 2.95 (1H, m, 4-H), 8.15 (1H, s, 5-H), 9.04 (1H, s, 7-H), 9.20 (1H, s br, NH); ^{13}C nmr: (75.5 MHz) δ 19.7, 21.7, 21.8, 24.9, 27.1, 28.0, 28.0, 34.8, 37.9, 39.7, 56.1, 122.5, 126.1, 129.1, 130.6, 134.9, 145.3; ms: m/z 333 (10), 318 (88), 304 (2), 290 (8), 276 (4), 262 (100).

Anal. Calcd. for C$_{17}$H$_{23}$N$_3$O$_4$: C, 61.26; H, 6.91; N, 12.61. Found: C, 61.12; H, 6.75; N, 12.49.

Compound **30** was obtained as yellow crystals, mp 55-57° (heptane) ir: ν NH 3339, δ NO$_2$ 1521, 1341 cm^{-1}; ^{1}H nmr: (200 MHz) δ 1.35 (1H, t, 3a-H), 1.38 (3H, d, 4-CH$_3$), 1.50-1.80 (14H, m, cyclooctyl protons), 2.05 (1H, dd, 3e-H), 2.90 (1H, m, 4-H), 6.53 (1H, t, 6-H), 7.33 (1H, d, 5-H), 8.01 (1H, d, 7-H), 8.73 (1H, s br, NH); ^{13}C nmr: (75.5 MHz) δ 20.1, 21.7, 21.9, 24.9, 26.9, 28.2, 30.0, 34.6, 38.2, 40.6, 54.7, 113.9, 124.5, 129.8, 130.5, 132.4, 142.4; ms: m/z 288 (19), 273 (88), 259 (2), 245 (10), 217 (100), 204 (40).

Anal. Calcd. for C$_{17}$H$_{24}$N$_2$O$_2$: C, 70.83; H, 8.33; N, 9.72. Found: C, 70.71; H, 8.18; N, 9.56.

6-Chloro-4-methyl-8-nitro-3,4-dihydrospiro[cyclooctane-1',2(1H)-quinoline] (29).

According to the procedure described above from 0.63 g (2.3 mmoles) of **27** and acetic (5 ml) and nitric (1 ml, 2.5 mmoles) acids, 0.36 g (49%) of nitro product **29** was obtained after column chromatography (alumina; heptane-ethyl acetate, 1:5 as eluent) as orange crystals, mp 88-90° (heptane) yield; ir: ν NH 3347, δ NO$_2$ 1515, 1336 cm^{-1}; ^{1}H nmr: (200 MHz) δ 1.27 (1H, t, 3a-H), 1.36 (3H, d, 4-CH$_3$), 1.50-1.90 (14H, m, cyclooctyl protons), 2.02 (1H, dd, 3e-H), 2.90 (1H, m, 4-H), 7.20 (1H, s, 5-H), 8.00 (1H, s, 7-H), 8.71 (1H, s br, NH); ^{13}C nmr: (75.5 MHz) δ 21.6, 22.1, 23.0, 29.5, 29.9, 31.3, 35.1, 39.8, 42.6, 48.7, 63.2, 125.5, 126.0, 127.9, 130.0, 137.0, 144.0; ms: m/z 322 (^{35}Cl, 14), 307 (74), 293 (2), 279 (9), 265 (6), 251 (100), 238 (45).

Anal. Calcd. for C$_{17}$H$_{23}$ClN$_2$O$_2$: C, 63.25; H, 7.13; N, 8.68. Found: C, 63.11; H, 7.03; N, 8.53.

1-Acetyl-4-methyl-3,4-dihydrospiro[cyclooctane-1',2(1H)-quinoline] (31).

A solution of **24** (1.02 g, 4.2 mmoles) in acetic anhydride (7 ml) was allowed to reflux for 2 hours. The mixture was cooled to 0° and treated with 3 N ammonium hydroxide solution. The products were extracted (ether, 2 x 25 ml). The organic layer was dried (sodium sulfate) and the residue purified by a short chromatographic column (alumina). Acetamide **31** (0.84 g, 70%) was obtained as a pale yellow oil; ir: ν CO 1657 cm^{-1}; ^{1}H nmr: (90 MHz) δ 1.05 (1H, t, 3a-H), 1.33 (3H, d, 4-CH$_3$), 1.57-1.81 (14H, m, cyclooctyl protons), 2.01 (3H, s, CH$_3$CO), 2.26 (1H, dd, 3e-H), 2.67 (1H, m, 4-H), 6.97-7.19 (4H, m, phenyl protons); ms: m/z 285 (40), 270 (32), 256 (1), 242 (38), 228 (94), 214 (8), 200 (27), 172 (94), 162 (100).

Anal. Calcd. for C$_{19}$H$_{27}$NO: C, 80.00; H, 9.47; N, 4.91. Found: C, 79.88; H, 9.39; N, 4.78.

1-Acetyl-6-chloro-4-methyl-3,4-dihydrospiro[cyclooctane-1',2(1H)-quinoline] (32).

In the same manner as described above, from **27** (1.0 g, 3.6 mmoles) acetamide **32** (0.67 g, 58%) was obtained as white crystals, mp 83-85° (heptane), ir: ν CO 1651 cm^{-1}; ^{1}H nmr: (200 MHz) δ 0.97 (1H, t, 3a-H), 1.35 (3H, d, 4-CH$_3$), 1.40-1.75 (14H, m, cyclooctyl protons), 2.09 (3H, s, CH$_3$CO), 2.30 (1H, dd, 3e-H), 2.68 (1H, m, 4-H), 6.85 (1H, d, 8-H), 7.15 (1H, d, 7-H), 7.28 (1H, d, 5-H); ^{13}C nmr: (75.5 MHz) δ 16.7, 22.4, 23.4, 23.9,

26.4, 27.6, 28.9, 29.0, 30.8, 36.6, 47.4, 66.3, 123.1, 127.0, 130.8, 138.4, 143.2, 171.6; ms: m/z 319 (^{35}Cl, 49), 304 (20), 276 (30), 262 (94), 248 (8), 234 (19), 220 (11), 206 (80), 196 (100).

Anal. Calcd. for C$_{19}$H$_{26}$ClNO: C, 71.36; H, 8.14; N, 4.38. Found: C, 71.18; H, 8.03; N, 4.24.

1-Acetyl-4,8-dimethyl-3,4-dihydrospiro[cyclooctane-1',2(1H)-quinoline] (33).

In the same manner as described above, from **25** (0.77 g, 3.0 mmoles) acetamide **33** (0.79 g, 88%) was obtained as a brownnish oil, ir: ν CO 1666 cm^{-1}; ^{1}H nmr: (90 MHz) δ 1.05 (1H, t, 3a-H), 1.30 (3H, d, 4-CH$_3$), 1.15-1.70 (14H, m, cyclooctyl protons), 2.27 (3H, s, CH$_3$CO), 2.30 (1H, dd, 3e-H), 2.65 (1H, m, 4-H), 7.05-7.45 (3H, m, phenyl protons); ms: m/z 299 (23), 284 (6), 270 (0.5), 256 (28), 242 (33), 228 (1), 214 (8), 200 (7), 186 (32), 176 (100).

Anal. Calcd. for C$_{20}$H$_{29}$NO: C, 80.27; H, 9.69; N, 4.68. Found: C, 79.93; H, 9.23; N, 4.14.

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[23]   The synthesis of imines **1-9** was realized using standard procedures, heating equimolar quantities of the reagents in toluene in the presence of glacial acetic acid (see, for example, ref 18).