Synthesis and Antiviral Activity Evaluation of Some Aminoadamantane Derivatives

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The synthesis of some spiro[cyclopropane-1,2′-adamantan]-2-amines and methanamines and some spiro[pyrrolidine-2,2′-adamantanes] is described. The title compounds were evaluated against a wide range of viruses (influenza A, influenza B, parainfluenza 3, RSV, HSV-1, TK⁻ HSV-1, HSV-2, vaccinia, vesicular stomatitis, polio 1, coxsackie B4, sindbis, semliki forest, Reo 1, HIV-1, and HIV-2), and some of them (compounds **6b**, **6c**, **9a**, **16a**, **16b**, and **17**) inhibited the cytopathicity of influenza A virus at a concentration significantly lower than that of amantadine and also significantly lower than the concentrations at which they proved cytotoxic to the host cells. None of the new aminoadamantane derivatives was active against influenza B virus or any of the other viruses tested, which points to their specificity as anti–influenza A virus agents.

Introduction

Amantadine (1-adamantanamine) has been established as effective in the prophylaxis and treatment of influenza A infections.[1–4] Although initially licensed in 1966, the clinical use of amantadine has been limited by the excess rate of CNS side effects.[5,6] On the other hand, the amantadine structural analog rimantadine (α-methyl-1-adamantanemethanamine) has been reported to be more active against influenza A in vitro in laboratory experiments in animals and also in human beings. Rimantadine has been considered to possess fewer side effects and appears to be the drug of choice for the chemoprophylaxis of influenza A.[4,7,8]

It has recently been demonstrated that the target of this selective, strain-specific antiviral activity is the hydrophobic, membrane-spanning domain of the small M2 protein and that these adamantanamines inhibit virus replication by blocking its ion-channel function and subsequently its ability to modulate the pH of the intracellular compartment in virus-infected cells. This may account for the lack of activity against influenza B, which does not possess this protein.[9–14]

The above-memtioned interesting activities of the aminoadamantane derivatives prompted us to synthesize some 2-spiro analogs of rimantadine **6a-c** and **9a-c** in order to investigate their antiviral properties.

In addition, some spiro[pyrrolidine-3,2′-adamantanes] have been found to be potent against influenza A, parainfluenza Sendai, rhinovirus, and coxsackie A21 viruses.[15–17] These findings prompted us to synthesize a novel heterocycle, spiro[pyrrolidine-2,2′-adamantane] (**14**), and its derivatives **16a-c** and **17** in order to investigate their antiviral properties.

Chemistry

The synthesis of the spiro[cyclopropane-1,2′-adamantan]-2-amines **6** and methanamines **9** is depicted in Scheme 1. 2-Methyleneadamantane (**3**)[18] was the starting material, and it was prepared by treatment of 2-adamantanone (**1**) with methylmagnesium iodide to provide 2-methyl-2-adamantanol (**2**),[18] which was dehydrated by heating at 100 °C in the presence of $KHSO_4$ under reduced presure (150–200 mmHg).

The [2 + 1]cycloaddition reaction of ethyl diazoacetate with 2-methyleneadamantane **3** in the presence of catalytic amounts of copper–bronze gave the ethyl spiro[cyclopropane-1,2′-adamantane]-2-carboxylate, which was saponificated to the corresponding carboxylic acid **4**. The action of ethyl chloroformate on the carboxylic acid **4**, in the presence of triethylamine, afforded the corresponding mixed anhydride, which was transformed to the azide of the acid **4**. Curtius rearrangement of this acyl azide by heating in dry toluene resulted in the isocyanate **5**, which was then converted into the primary amine **6a** by acidic hydrolysis. On the other hand, reduction of the isocyanate **5** with $LiAlH_4$ gave the *N*-methyl derivative **6b**. *N*,*N*-Dimethyl derivative **6c** was prepared by reductive methylation of the primary amine **6a** with formaldehyde and sodium cyanoborohydride.[19]

The methanamines **9** were prepared by conversion of the carbonyl chloride **7** into the corresponding carboxamides **8**, followed by reduction with $LiAlH_4$.

The structures of the compounds were confirmed by elemental analysis and IR and ^{1}H- and ^{13}C-NMR spectroscopy. The use of 2D NMR (XHCORR and COSY) proved to be helpful to the elucidation of the structure of some derivatives.

As far as amines **6** are concerned it is apparent that the adamantane 1′-H is strongly shielded and its signal is found to occur from δ 0.65 to 0.81 ppm (Scheme 2). The cyclopropane protons appeared as an AMX pattern, with the coupling constant between 2-H and 3-H_{cis} being larger than that between 2-H and 3-H_{trans}, i.e., $J_{MX} > J_{AX}$.[20] The chemical shift of 2-H (H_X) is found progressively upfield from the **6a** to **6c** derivative, and a considerable difference of 0.72 ppm is observed. On the contrary, the study of the ^{13}C-NMR spectra of these

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Scheme 1

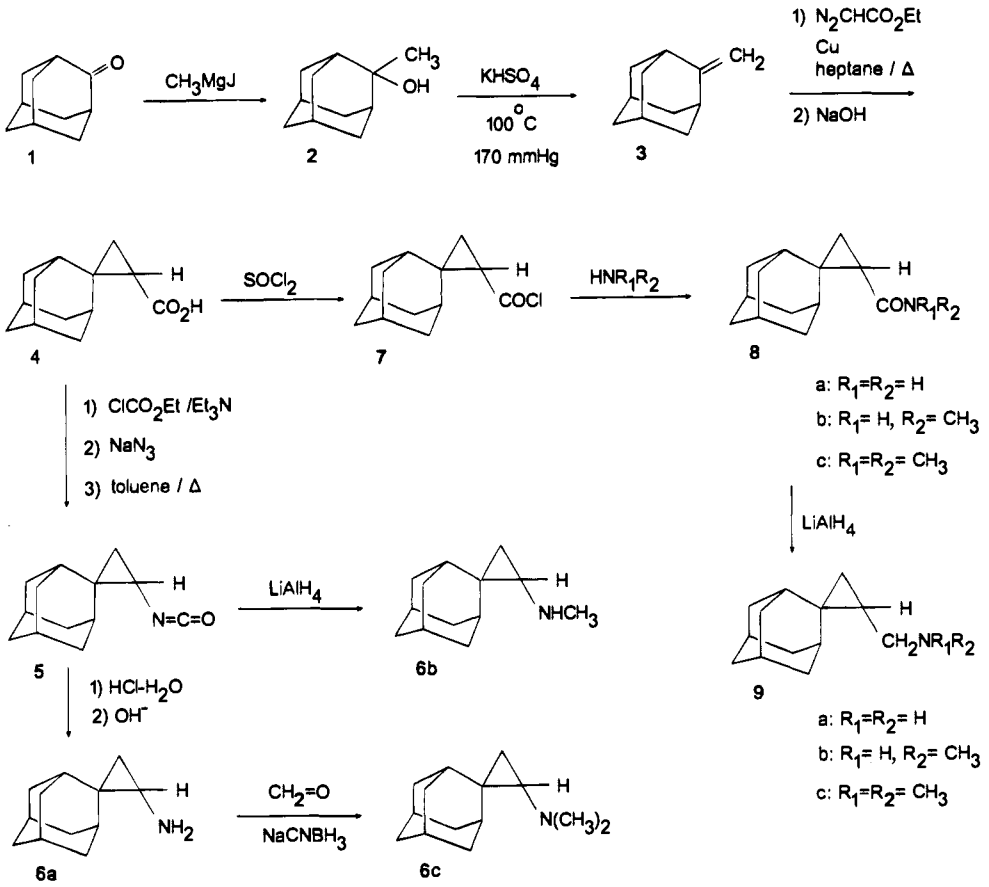


Table 1. Antiviral Activity and Cytotoxicity of Various Sprio[cyclopropane-1,2′-adamantan]-2-amines, Spiro[cyclopropane-1,2′-adamantane]-2-methanamines, and Spiro[pyrrolidine-2,2′-adamantanes]

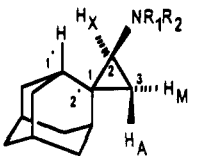
		MIC$_{50}$[c] (μg/mL)												
virus[a]	cell[b]	**6a**	**6b**	**6c**	**9a**	**9b**	**9c**	**14**	**16a**	**16b**	**16c**	**17**	amantadine	ribavirin
influenza A	MDCK	30	1.2	6.0	0.8	>20	>40	>30	0.56	2.4	≥40	2.4	100	1.2
influenza B	MDCK	>100	>100	>100	>20	>20	>100	>200	>200	>200	>100	>20	>200	4.0
parainfluenza 3	Vero	>40	>70	100	>20	>20	>70	>200	>400	>400	>400	>70	–	70
RSV	HeLa	30	>150	>200	≥15	30	40	>200	>200	>200	≥150	>20	>100	2.8
HSV-1	HEF	>20	>70	>200	>20	>20	>20	200	≥400	>400	300	>20	–	200
TK$^-$ HSV-1	HEF	>20	>40	>200	>20	>20	>20	>200	≥400	≥400	≥400	>20	–	≥200
HSV-2	HEF	>20	>70	>200	>20	>20	>20	>200	>400	>400	>400	>20	–	>400
vaccinia	HEF	>20	>70	>200	>20	>20	>20	>200	>400	>400	100	>20	–	70
vesicular stomatitis	HEF	>20	>40	>200	>20	>20	>20	>200	≥400	≥400	150	>20	–	20
polio 1	HeLa	>20	>100	>400	>10	>20	>70	>200	>400	>400	>400	>70	–	70
coxsackie B4	Vero	>40	>70	>400	>20	>20	>70	>200	>400	>400	>400	>70	–	300
sindbis	Vero	>40	>70	>400	>20	>20	>70	>200	>400	>400	>400	>70	–	70
semliki forest	Vero	>40	>70	>400	>20	>20	>70	>200	>400	>400	>400	>70	–	20
Reo 1	Vero	>40	>70	400	>20	>20	>70	>200	>400	>400	>400	>70	–	20
HIV-1	CEM	>8	>8	>200	>8	>8	>40	>40	>200	>200	>200	>1.6		
HIV-2	CEM	>8	>8	>200	>8	>8	>40	>40	>200	>200	>200	>1.6		
morphology	MDCK	100	100	100	20	20	70	>200	>200	>200	100	20	>100	>200
morphology	Vero	100	100	>400	40	40	100	≥400	>400	>400	>400	100	–	>400
morphology	HeLa	40	200	≥400	20	40	100	>200	>400	>400	>400	100	100	>200
morphology	HEF	40	100	≥400	40	40	40	≥400	>400	>400	>400	40	–	>400
proliferation	HEF	80	90	>200	28	50	95	>50	>50	>200	>200	150	–	–
viability	CEM	32	75	>200	14	4	23	100	>200	>200	>200	3.4	–	–

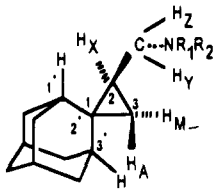
[a] Abbreviations and virus strains: influenza A (Ishikawa); influenza B (Singapore); RSV, respiratory syncytial virus (Long); HSV-1, herpes simplex virus type 1 (KOS); TK$^-$ HSV-1, thymidine kinase-deficient HSV-1 (B2006); HSV-2, herpes simplex virus type 2 (G); HIV-1, human immunodeficiency virus type 1 (IIIB/LAI); HIV-1, human immunodeficiency virus type 2 (ROD). [b] Abbreviations: MDCK, Madin–Darby canine kidney; HEF, human embryonic fibroblasts [either embryonig lung (for cell proliferation studies) or embryonic skin-muscle (for cell morphology studies and antiviral studies)]. Vero, HeLa, and MT-4 represent African green monkey kidney cells, human epithelial cells, and human T-lymphocytes, respectively. [c] Minimum inhibitory concentration required to reduce virus-induced cytopathicity by 50%, to cause a microscopically detectable alteration of normal cell morphology, or to reduce cell proliferation or cell viability by 50%. All data represent average values for at least two separate experiments.

compounds showed that 2-C was recognized downfield as the number of the nitrogen substituents was increased, resulting in a difference of 16.34 ppm from **6a** to **6c**.

Similar results were obtained from the NMR spectra of the methanamines **9**, where both 1′-H and 3′-H are shielded. The cyclopropane 2-H and 3-H and the methylene protons of the side chain CH_2N appeared as

Scheme 2





6a R_1:R_2:H
1'-H, δ:0.65 ppm
H_A, δ:0.03 ppm
H_M, δ:0.37 ppm
H_X, δ:2.08 ppm
2-C, δ:37.55 ppm

6b R_1:CH_3, R_2:H
1'-H, δ:0.73 ppm
H_A, δ:0.06 ppm
H_M, δ:0.32 ppm
H_X, δ:~1.78 ppm*
2-C, δ:45.15 ppm

6c R_1:R_2:CH_3
1'-H, δ:0.81 ppm
H_A, δ:0.11 ppm
H_M, δ:0.36 ppm
H_X, δ:1.36 ppm
2-C, δ:53.89 ppm

9a R_1:R_2:H
1'-H, δ:0.77 ppm, 3'-H, δ:1.26 ppm
H_A, δ:0.01 ppm, H_M, δ:0.37 ppm
H_X, δ:0.64 ppm, H_Y, δ:2.43 ppm
H_Z, δ:2.87 ppm
$\underline{C}H_2N$, δ:41.44 ppm

9b R_1:CH_3, R_2:H
1'-H, δ:0.82 ppm, 3'-H, δ:1.29 ppm
H_A, δ:0.05 ppm, H_M, δ:0.45 ppm
H_X, δ:0.69 ppm, H_Y, δ:2.32 ppm
H_Z, δ:2.87 ppm
$\underline{C}H_2N$, δ:51.55 ppm

9c R_1:R_2:CH_3
1'-H, δ:0.82 ppm, 3'-H, δ:1.30 ppm
H_A, δ:0.11 ppm, H_M, δ:0.52 ppm
H_X, δ:0.74 ppm, H_Y, δ:~1.85 ppm*
H_Z, δ:2.80 ppm
$\underline{C}H_2N$, δ:58.94 ppm

* experimental value obtained from 2D-NMR (^1H-^{13}C).

an AMXYZ pattern. It can be noted (Scheme 2) that as the number of the nitrogen substituents is increased, the H_Y proton is shielded, whereas the corresponding carbon atom (CH_2N) is deshielded.

The synthesis of the spiro[pyrrolidine-2,2′-adamantanes] **14** and **16** is illustrated in Scheme 3.

2-Nitroadamantane (**11**) was the starting material and can be easily deprotonated to the carbanion, which undergoes 1,4-addition reactions with conjugated esters.

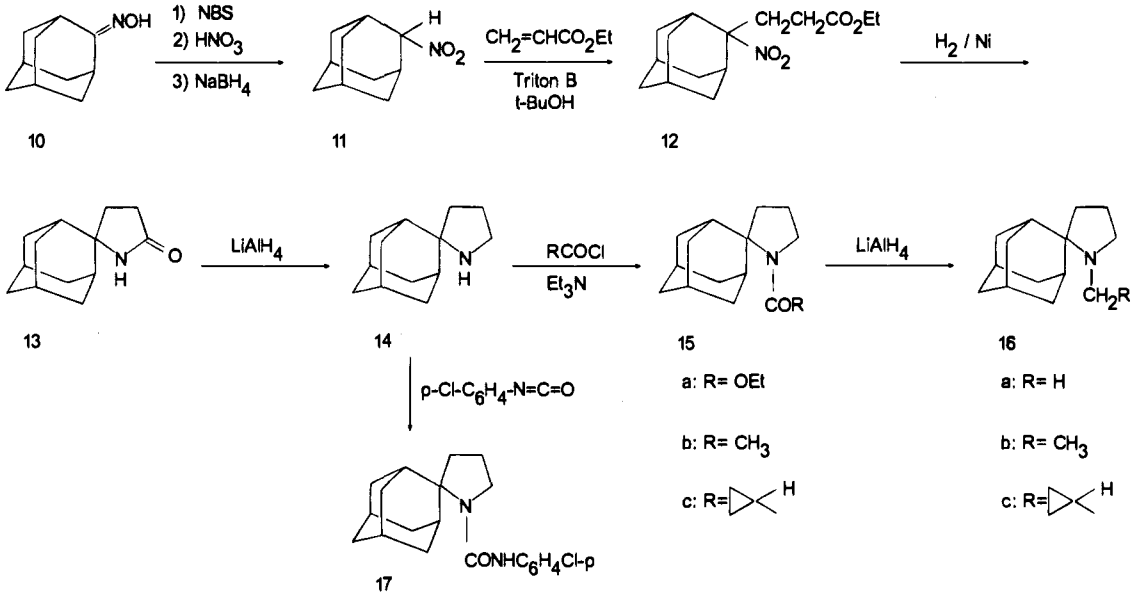
The literature procedure for the preparation of 2-nitroadamantane[21] by treatment of 2-adamantanone oxime with NBS, followed by $NaBH_4$ reduction, gave only a mixture of products with an undefined melting point. However, 2-nitroadamantane (**11**) was obtained in good yield according to the general method for the preparation of nitrocycloalkanes,[22,23] which involves NBS reaction with 2-adamantanone oxime (**10**), followed by oxidation of the intermediate 2-bromo-2-nitrosoadamantane with nitric acid. The 2-bromo-2-nitroadamantane thus formed was reductively debrominated to give the desired product **11**.

Michael condensation of 2-nitroadamantane (**11**) with ethyl acrylate in the presence of Triton B afforded ethyl 2-nitro-2-adamantanepropanoate (**12**). Hydrogenation of the nitro ester **12** over Raney nickel catalyst provided, with concomitant γ-lactam formation, the spiro[pyrrolidine-2,2′-adamantan]-5-one (**13**). Subsequent reduction of γ-lactam **13** with $LiAlH_4$ gave the spiropyrrolidine **14** which was then converted into the amides **15** through N-acylation. Finally, reduction of the amides **15** with $LiAlH_4$ led to the corresponding N-substituted spiropyrrolidines **16**. The preparation of **17** was achieved by treatment of the pyrrolidine **14** with 4-chlorophenyl isocyanate.

Results and Discussion

The aminoadamantane derivatives and the urea prepared were evaluated according to previously reported methods[24-29] against the following viruses: influenza A, influenza B, parainfluenza 3, RSV, HSV-1, TK^- HSV-1, HSV-2, vaccinia, vesicular stomatitis, polio 1, coxsackie B4, sindbis, semliki forest, reo 1, HIV-1, and HIV-2. Compounds **6b**, **6c**, **9a**, **16a**, **16b**, and **17** inhibited the cytopathicity of influenza A virus at a concentration that was (i) significantly lower than that of amantadine and (ii) significantly lower than the concentrations at which they proved cytotoxic to the host cells (MDCK or others). Particularly striking was the potency and selectivity of **16a** which inhibited influenza A virus-induced cytopathicity at a concentration of 0.56

Scheme 3



μg/mL, while not being toxic to the host cells at a concentration as high as 400 μg/mL. None of the new aminoadamantane derivatives (i.e., **6b**, **6c**, **9a**, **16a**, **16b**, and **17**) that proved active against influenza A virus were active against influenza B virus or any of the other viruses tested, which points to their specificity as anti-influenza A virus agents. Their potency is such that they should be further evaluated against influenza A virus infections *in vivo*, and these experiments are now underway. It may be surmised that the new aminoadamantane derivatives inhibit influenza A virus infection by a similar mechanism as amantadine itself. Amantadine is assumed to block virus assembly as well as disassembly (uncoating) through an interaction with the viral M2 protein followed by a lowered pH in the Golgi compartment resulting in an altered hemagglutinin conformation.[9-14]

Experimental Part

Melting points were determined using a Büchi capillary apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 833 spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were recorded on a BRUKER AC 200 spectrometer at 200 and 50 MHz, respectively, using $CDCl_3$ as solvent and TMS as internal standard. Carbon multiplicities were established by DEPT experiments. Microanalyses were performed by the Service Central de Microanalyse (CNRS) France, and the results obtained had a maximum deviation of ±0.4% from the theoretical value. 2-Methyl-2-adamantanol (**2**)[18] was prepared in 93% yield by the reaction of 2-adamantanone (1) with methylmagnesium iodide: mp 208–209 °C (petroleum ether).

2-Methylenetricyclo[3.3.1.1^{3,7}]decane (3).[18] A mixture of 2-methyl-2-adamantanol (**2**) (2 g, 12 mmol) and anhydrous $KHSO_4$ (2 g, 14.5 mmol) was subjected to sublimation at 100 °C (150–200 mmHg). A 1.7-g yield (96%) of a white solid was collected: mp 135–136 °C; IR (Nujol) ν(C–H) 3060, (CH_2=), ν(C=C) 1642 cm^{-1}; ^{1}H-NMR δ (ppm) 1.53–1.96 (m, 10H, adamantane H), 2.06–2.21 (m, 2H, 5,7-adamantane H), 2.39–2.48 (m, 2H, 1,3-adamantane H), 4.47 (s, 2H, =CH_2).

Spiro[cyclopropane-1,2′-tricyclo[3.3.1.1^{3,7}]decane]-2-carboxylic Acid (4). A stirred mixture of 2-methyleneadamantane (**3**) (2.07 g, 14.0 mmol) and freshly prepared and dried copper–bronze dust[30] (0.5 g) in heptane (30 mL) was heated to reflux under nitrogen in an oil bath at 105 °C, and ethyl diazoacetate (6.2 g, 54.1 mmol) was then added dropwise over a 30-min period. The heating was continued for an additional hour, and the mixture was then stirred at room temperature for 15 h. The organic layer was separated, and the catalyst was washed with hexane. The combined organic phase was evaporated to dryness, and the viscous residue was refluxed with a solution of NaOH (5 g) in water (30 mL) and ethanol (80 mL) for 4 h. After removal of the ethanol, water was added and the aqueous phase was washed with ether and acidified with a 18% HCl solution. The precipitate was filtered, washed several times with water, and dried to give 2.35 g (81%) of the carboxylic acid **4**: mp 153–155 °C (Et_2O); IR (Nujol) ν(C=O) 1677 cm^{-1}; ^{1}H-NMR δ (ppm) 0.87–1.01 (m, 2H, 3-H, 1′-H), 1.15 (t, 1H, 3-H), 1.16 (q, 1H, 2-H), 1.54–1.98 (complex m, 13H, adamantane H), 9.45–11.85 (very br s, 1H, CO_2H); ^{13}C-NMR δ (ppm) 21.76 (3-C), 26.77 (2-C), 27.33 (5′-C), 27.68 (7′-C), 30.14 (3′-C), 36.20 (4′-C), 36.35 (10′-C), 36.59 (8′-C), 36.66 (9′-C), 37.44 (6′-C), 39.12 (1′-C), 39.77 (1,2′-C), 179.25 (C=O). Anal. ($C_{13}H_{18}O_2$) C, H.

Spiro[cyclopropane-1,2′-tricyclo[3.3.1.1^{3,7}]dec-2-yl] Isocyanate (5). Triethylamine (1.02 g, 10.1 mmol) in acetone (17 mL) was added dropwise under cooling to a solution of the carboxylic acid **4** (1.8 g, 8.7 mmol) in acetone (25 mL) and water (2 mL). While maintaining the temperature at 0 °C, ethyl chloroformate (1.19 g, 11 mmol) in acetone (5 mL) was slowly added. The mixture was stirred for 30 min at 0 °C, and then a solution of sodium azide (0.73 g 11 mmol) in water (4 mL) was added. The mixture was stirred at 0 °C for 1 h and was then poured into 100 g of ice–water and extracted with ether. The ether extracts were washed with water, dried over Na_2SO_4, and evaporated under vacuum without heating to give 2.2 g of the azide of the carboxylic acid **4**. The azide was dissolved in dry toluene (10 mL), and the solution was heated in an oil bath at 100 °C until no more nitrogen was evolved. Removal of the toluene under vacuum afforded 1.9 g (93%) of the isocyanate **5**: IR (film) ν(N=C=O) 2268 cm^{-1}, which was used for the preparation of the amines **6a** and **6b** without purification.

Spiro[cyclopropane-1,2′-tricyclo[3.3.1.1^{3,7}]decan]-2-amine (6a). A mixture of the isocyanate **5** (2 g, 10 mmol) and 20% hydrochloric acid (10 mL) was stirred at 80–90 °C for 3 h and was then allowed to stand for 12 h at ambient temperature. The reaction mixture was diluted with water and extracted with ether. The water phase was made alkaline with solid Na_2CO_3 and extracted with ether. The compined organic extracts were washed with water and dried (Na_2CO_3). Removal of the solvent under reduced pressure gave 1.66 g (94%) of the amine **6a** as a clear oil: IR (film) ν(NH_2) 3390–3300 cm^{-1}; ^{1}H-NMR δ (ppm) 0.03 (t, 1H, A region AMX, J_{AM} = J_{AX} = 4.5 Hz, 3-H), 0.37 (q, 1H, M region AMX, J_{AM} = J_{AX} = 4.5 Hz, J_{MX} = 7.5 Hz, 3-H), 0.65 (br s, 1H, 1′-H), 1.22–1.92

(complex m, 15H, adamantane H, NH_2), 2.08 (q, 1H, X region AMX, $J_{AM} = J_{AX} = 4.5$ Hz, $J_{MX} = 7.5$ Hz, 2-H); ^{13}C-NMR δ (ppm) 20.86 (3-C), 27.56 (5′-C), 28.32 (7′-C), 31.05 (3′-C), 32.00 (1,2′-C), 35.57 (4′-C), 36.01 (1′-C), 36.30 (10′-C), 36.57 (8′-C), 36.90 (9′-C), 37.41 (6′-C), 37.55 (2-C). Hydrochloride: mp 255 °C dec (EtOH−Et_2O). Anal. ($C_{12}H_{20}ClN$) C, H, N.

***N*-Methylspiro[cyclopropane-1,2′-tricyclo[3.3.1.1^{3,7}]decan]-2-amine (6b).** A solution of the isocyanate **5** (2 g, 10 mmol) in dry THF (20 mL) was added dropwise to a stirred slurry of $LiAlH_4$ (1.35 g, 35.5 mmol) in dry THF (50 mL). The reaction mixture was refluxed for 3 h and was then hydrolyzed with water and a 5% NaOH solution under ice-cooling. The inorganic precipitate was filtered off and washed with THF, and the filtrate was evaporated under vacuum. Water (20 mL) and a 5% HCl solution (10 mL) were added to the residue, which was then washed with ether. The aqueous phase was made alkaline with solid Na_2CO_3, and the separated oil was extracted into ether, dried (Na_2SO_4), and evaporated to dryness under vacuum to give 1 g (52%) of the amine **6b** as an oil: IR (film) ν(NH) 3380−3350 cm^{-1}; ^{1}H-NMR δ (ppm) 0.06 (t, 1H, A region AMX, $J_{AM} = J_{AX} = 4.5$ Hz, 3-H), 0.32 (q, 1H, M region AMX, $J_{AM} = J_{AX} = 4.5$ Hz, $J_{MX} = 7.5$ Hz, 3-H), 0.73 (br s, 1H, 1′-H), 1.35−1.92 (complex m, 15H, adamantane H, 2-H, NH), 2.42 (s, 3H, CH_3); ^{13}C-NMR δ (ppm) 18.89 (3-C), 27.62 (5′-C), 28.38 (7′-C), 31.65 (3′-C), 32.79 (1,2′-C), 35.64 (4′-C, 10′-C), 36.49 (8′C,CH_3), 37.07 (9′-C), 37.58 (1′-C, 6′-C), 45.15 (2-C). Hydrochloride: mp 240 °C (EtOH−Et_2O). Anal. ($C_{13}H_{22}ClN$) C, H, N.

***N,N*-Dimethylspiro[cyclopropane-1,2′-tricyclo[3.3.1.1^{3,7}]decan]-2-amine (6c).** To a stirred mixture of the primary amine **6a** (1.04 g 5.6 mmol), acetonitrile (30 mL), and a 37% aqueous formaldehyde solution (0.86 g, 2.3 mL, 28 mmol) was added $NaCNBH_4$ (0.8 g, 13 mmol) in one portion. After stirring for 15 min, acetic acid was added until the solution's pH turned to neutral. Stirring was continued for an additional hour during which time the pH maintained as neutral by addition of acetic acid, if necessary. The solvents were evaporated under vacuum, and the residue was made alkaline by the addition of a 10% KOH solution. The aqueous phase was extracted with ether, and the ether extracts were washed with a 10% KOH solution. The ether layer was then treated with a 10% HCl solution, and the aqueous phase was washed with ether and made alkaline with solid Na_2CO_3. The oil formed was extracted into ether, washed with water, and dried over Na_2SO_4. Removal of the ether afforded 1.05 g (91%) of the amine **6c** as an oil: ^{1}H-NMR δ (ppm) 0.11 (t, 1H, A region AMX, $J_{AM} = J_{AX} = 4.5$ Hz, 3-H), 0.36 (q, 1H, M region AMX, $J_{AM} = J_{AX} = 4.5$ Hz, $J_{MX} = 7.5$ Hz, 3-H), 0.81 (br s, 1H, 1′-H), 1.36 (q, 1H, X region AMX, $J_{AM} = JA_X = 4.5$ Hz, $J_{MX} = 7.5$ Hz, 2-H), 1.52−1.96 (complex m, 13H, adamantane H), 2.34 (s, 6H, 2 × CH_3); ^{13}C-NMR δ (ppm) 18.46 (3-C), 27.01 (5′-C), 28.48 (7′-C), 31.68 (3′-C), 34.49 (1,2′-C), 35.84 (4′-C), 36.08 (10′-C), 37.11 (8′-C), 37.32 (1′-C, 9′-C), 37.84 (6′-C), 46.71 (2 × CH_3), 53.89 (2-C). Hydrochloride: mp 239 °C dec (EtOH−Et_2O). Anal. ($C_{14}H_{24}ClN$) C, H, N.

Spiro[cyclopropane-1,2′-tricyclo[3.3.1.1^{3,7}]decane]-2-carbonyl Chloride (7). A mixture of the acid **4** (4.12 g, 20 mmol) and thionyl chloride (8 mL, HCl-free) was heated at 40 °C for 20 min. The excess thionyl chloride was removed under vacuum, and the resulting chloride **7** (4.5 g, yield almost quantitative) was used for the preparation fo the amides **8** without purification.

Spiro[cyclopropane-1,2′-tricyclo[3.3.1.1^{3,7}]decane]-2-carboxamide (8a). The chloride **7** (2.25 g, 10 mmol) in dry THF (10 mL) was added dropwise with stirring to a 28% aqueous ammonia solution (30 mL). After the mixture was stirred for 10 min, water was added and the precipitate was filtered, washed with water, and dried to yield 2 g (98%) of the amide **8a**: mp 165 °C (THF−Et_2O); IR (Nujol) ν(NH) 3395, 3190, ν(C=O) 1655 cm^{-1}; ^{1}H-NMR δ (ppm) 0.75 (q, 1H, 3-H), 0.91 (br s, 1H, 1′-H), 1.13 (t, 1H, 3-H), 1.22−1.32 (m, 1H, 2-H), 1.61−1.93 (complex m, 13H, adamantane H), 5.61 (br s, 2H, NH_2); ^{13}C-NMR δ (ppm) 19.70 (3-C), 27.44 (5′-C), 27.74 (7′-C), 28.35 (2-C), 29.92 (3′-C), 36.24 (4′-C), 36.48 (10′-C), 36.59 (8′-C), 36.67 (9′-C), 37.43 (6′-C), 37.64 (1,2′-C), 39.13 (1′-C), 173.91 (C=O). Anal. ($C_{13}H_{19}NO$) C, H, N.

The following amides were obtained by the same procedure:

***N*-Methylspiro[cyclopropane-1,2′-tricyclo[3.3.1.1^{3,7}]decane]-2-carboxamide (8b).** After the reaction of the chloride **7** with a 40% aqueous methylamine solution was completed, the amide **8b** was extracted with benzene and the organic phase was washed with water, dried over Na_2SO_4, and evaporated under vacuum: yield 82%; mp 145 °C (THF−Et_2O); IR (Nujol) ν(NH) 3270, ν(C=O) 1630 cm^{-1}; ^{1}H-NMR δ (ppm) 0.68 (q, 1H, 3-H), 0.87 (br s, 1H, 1′-H), 1.09−1.22 (m, 2H, 2-H, 3-H), 1.45−1.92 (m, 13H, adamantane H), 2.78 (d, 3H, CH_3), 5.78 (br s, 1H, NH); ^{13}C-NMR δ (ppm) 19.04 (3-C), 26.45 (CH_3), 27.49 (5′-C), 27.76 (7′-C), 28.91 (2-C), 29.93 (3′-C), 36.29 (4′-C), 36.43 (10′-C), 36.53 (8′-C), 36.67 (9′-C, 1,2′-C), 37.76 (6′-C), 39.07 (1′-C), 172.02 (C=O). Anal. ($C_{14}H_{21}NO$) C, H, N.

***N,N*-Dimethylspiro[cyclopropane-1,2′-tricyclo[3.3.1.1^{3,7}]decane]-2-carboxamide (8c).** It was prepared by the same procedure that was described for compound **8b**: yield 93%; mp 86−87 °C (*n*-pentane); IR (Nujol) ν(C=O) 1630 cm^{-1}; ^{1}H-NMR δ (ppm) 0.65 (q, 1H, 3-H), 0.98 (br s, 1H, 1′-H), 1.25 (m, 1H, 3-H), 1.32−1.45 (br m, 1H, 3′-H), 1.57 (q, 1H, 2-H), 1.58−1.93 (complex m, 12H, adamantane H), 2.94 (s, 3H, CH_3), 3.18 (s, 3H, CH_3); ^{13}C-NMR δ (ppm) 19.02 (3-C), 26.33 (2-C), 27.51 (5′-C), 27.87 (7′-C), 29.94 (3′-C), 35.79 (CH_3), 36.41 (4′-C), 36.59 (8′-C, 10′-C), 37.35 (9′-C, 1,2′-C), 37.58 (6′-C), 37.84 (CH_3), 39.03 (1′-C), 170.85 (C=O). Anal. ($C_{15}H_{23}NO$) C, H, N.

Spiro[cyclopropane-1,2′-tricyclo[3.3.1.1^{3,7}]decane]-2-methanamine (9a). To a stirred solution of the amide **8a** (1.5 g, 7.3 mmol) in dry dimethoxyethane (30 mL) was added $LiAlH_4$ (1.11 g, 29.2 mmol). The mixture was refluxed for 20 h under nitrogen and was then hydrolyzed with water and a 10% NaOH solution under ice-cooling. The inorganic precipitate was filtered off and washed with THF, and the filtrate was evaporated under vacuum. The residue was disolved in ether and extracted with 5% HCl solution, and the aqueous phase was washed with ether and made alkaline with solid Na_2CO_3. The crude amine was extracted into methylene chloride, and the organic layer was dried over Na_2SO_4 and evaporated to dryness to give 1.25 g (90%) of the amine **8a**: mp 75 °C (*n*-pentane); IR (Nujol) ν(NH) 3300 cm^{-1}; ^{1}H-NMR δ (ppm) 0.01 (t, 1H, A region, AMXYZ, $J_{AM} = J_{AX} = 4.3$ Hz, 3-H), 0.37 (q, 1H, M region, AMXYZ, $J_{AM} = J_{AX} = 4.3$ Hz, $J_{MX} = 8.3$ Hz, 3-H), 0.64 (m, 1H, X region, AMXYZ, 2-H), 0.77 (br s, 1H, 1′-H), 1.14−1.28 (m, 3H, 3′-H, NH_2), 1.57−1.91 (complex m, 12H, adamantane H), 2.43 (q, 1H, Y region, AMXYZ, $J_{XY} = 8$ Hz, $J_{YZ} = 13$ Hz, CH_YH$_Z$N), 2.87 (q, 1H, Z region, AMXYZ, $J_{XZ} = 6$ Hz, $J_{YZ} = 13$ Hz, CH$_Y$H$_Z$N); ^{13}C-NMR δ (ppm) 16.90 (3-C), 27.64 (5′-C), 28.18 (7′-C), 28.74 (2-C), 31.55 (1,2′-C), 32.48 (3′-C), 36.15 (4′-C), 36.56 (8′-C, 10′-C), 37.14 (9′-C), 37.63 (6′-C), 39.06 (1′-C), 41.44 (CH_2N). Hydrochloride: mp >285 °C (EtOH−Et_2O). Anal. ($C_{13}H_{22}ClN$) C, H, N.

The amines **9b** and **9c** were prepared by an analogous procedure.

***N*-Methylspiro[cyclopropane-1,2′-tricyclo[3.3.1.1^{3,7}]decane]-2-methanamine (9b)**: yield 90%; IR (film) ν(NH) 3300 cm^{-1}; ^{1}H-NMR δ (ppm) 0.05 (t, 1H, A region, AMXYZ, $J_{AM} = J_{AX} = 4.5$ Hz, 3-H), 0.45 (q, 1H, M region, AMXYZ, $J_{AM} = J_{AX} = 4.5$ Hz, $J_{MX} = 8.3$ Hz, 3-H), 0.68−0.83 (m, 2H, X region, AMXYZ, 2-H, 1′-H), 1.19−1.33 (br d, 2H, 3′-H, NH), 1.49−1.89 (complex m, 12H, adamantane H), 2.32 (q, 1H, Y region, AMXYZ, $J_{XY} = 8.5$ Hz, $J_{YZ} = 13$ Hz, CH_YH$_Z$N), 2.46 (s, 3H, CH_3), 2.87 (q, 1H, Z region, AMXYZ, $J_{XZ} = 5.5$ Hz, $J_{YZ} = 13$ Hz, CH$_Y$H$_Z$N); ^{13}C-NMR δ (ppm) 17.32 (3-C), 24.81 (2-C), 27.53 (5′-C), 28.06 (7′-C), 30.67 (1,2′-C), 32.47 (3′-C), 36.05 (4′-C), 36.43 (8′-C, 10′-C, CH_3), 36.89 (9′-C), 37.50 (6′-C), 39.00 (1′-C), 51.15 (CH_2N). Hydrochloride: mp >285 °C (EtOH−Et_2O). Anal. ($C_{14}H_{24}ClN$) C, H, N.

***N,N*-Dimethylspiro[cyclopropane-1,2′-tricyclo[3.3.1.1^{3,7}]decane]-2-methanamine (9c)**: yield 92%; ^{1}H-NMR δ (ppm) 0.11 (t, 1H, A region AMXYZ, $J_{AM} = J_{AX} = 4.5$ Hz, 3-H), 0.52 (q, 1H, M region, AMXYZ, $J_{AM} = J_{AX} = 4.5$ Hz, $J_{MX} = 8.5$ Hz, 3-H), 0.59−0.74 (m, 1H, X region, AMXYZ, 2-H), 0.82 (br s, 1H, 1′-H), 1.30 (br s, 1H, 3′-H), 1.61−1.98 (m, 13H, adamantane H, CH_YH$_Z$N), 2.26 (s, 6H, 2 × CH_3), 2.80 (q, 1H, Z region, AMXYZ, $J_{XZ} = 3.7$ Hz, $J_{YZ} = 12$ Hz, CH$_Y$H$_Z$N); ^{13}C-NMR δ (ppm) 18.94 (3-C), 23.07 (2-C), 27.63 (5′-C), 28.15 (7′-C), 29.92 (1,2′-C), 32.67 (3′-C), 36.18 (4′-C), 36.51 (8′-C, 10′-C), 36.71 (9′-

C), 37.55 (6'-C), 39.24 (1'-C), 45.60 (2 × CH_3), 58.94 (CH_2N). Hydrochloride: mp 284 °C dec (EtOH–Et_2O). Anal. ($C_{15}H_{26}ClN$) C, H, N.

2-Nitrotricyclo[3.3.1.1^{3,7}]decane (11). A suspension of 2-adamantanone oxime[31] (10 g, 60.6 mmol) (**10**) and $NaHCO_3$ (11.8 g, 140 mmol) in a mixture of water (50 mL) and dioxane (60 mL) was added to a vigorously stirred suspension of NBS (25 g, 140 mmol) in water (100 mL) during a 10-min period at 10 °C. Stirring was continued for 15 additional min, and the mixture was extracted with petroleum ether (bp 40–65 °C). The combined extracts were concentrated to a volume of approximately 30 mL and were then worked up with nitric acid (100 mL, *d* 1.42) for 5 min. Cold water (~100 mL) was added, and the mixture was extracted with petroleum ether (bp 40–65 °C). The organic layer was washed with water and dried over Na_2SO_4. After removal of the solvent, 2-bromo-2-nitroadamantane was obtained as a crystalline blue solid, which was suspended without purification in a vigorously stirred mixture of methanol (75 mL) and water (15 mL). $NaBH_4$ (5.5 g, 145 mmol) was repidly added (highly exothermic reaction), and the mixture was allowed to cool to room temperature with stirring. The reaction mixture was then neutralized with acetic acid, a sufficient amount of water was added, and the precipitated 2-nitroadamantane was filtered, washed several times with water, and recrystallized from methanol/water: yield 9 g (82%); mp 167 °C; IR (Nujol) $\nu(NO_2)$ 1543 cm^{-1}; ^{1}H-NMR δ (ppm) 1.55–2.60 (m, 12H, 4,5,6,7,8,9,-10-H), 2.73 (s, 2H, 1,3-H), 4.36 (s, 1H, 2-H).

Ethyl 2-Nitro-2-tricyclo[3.3.1.1^{3,7}]decanepropanoate (12). To a stirred mixture of 2-nitroadamantane (9.2 g, 50.8 mmol) (11) in *tert*-butyl alcohol (40 mL) and ethyl acrylate (10.2 g, 101.6 mmol) was added dropwise a 40% methanolic solution of Triton B (8 mL). The reaction mixture was heated at 55 °C for 2 h and was then acidified, after thorough cooling, with a 10% HCl solution. Water was added, and the mixture was extracted with dichloromethane. The combined organic layers were washed with water and dried over Na_2SO_4, and the solvent was evaporated, leaving a viscous oil which was then saponificated with NaOH (3.6 g) in ethanolic solution (80 mL of ethanol/40 mL of water). Most of the ethanol was removed under vacuum, and the residue was diluted with water and extracted with petroleum ether (bp 40–65 °C). The aqueous layer was acidified under cooling with a 18% HCl solution, and the precipitated 2-nitro-2-adamantanepropanoic acid was filtered, washed with water, and dried: yield 9 g (~70%); mp 124 °C (ether–*n*-pentane); IR (Nujol) ν(C=O) 1725, $\nu(NO_2)$ 1530 cm^{-1}; ^{1}H-NMR δ (ppm) 1.68–2.00 (m, 12H, 4,5,6,7,8,9,10-H), 2.27–2.32 (m, 4H, CH_2CH_2CO), 2.47–2.56 (s, 2H, 1,3-H), 10.03 (br s, 1H, CO_2H). Anal. ($C_{13}H_{19}NO_4$) C, H, N.

2-Nitro-2-adamantanepropanoic acid (8.1 g, 32 mmol) was esterificated in an ethanolic solution of gaseous HCl to result in 8.43 g (~94%) of ethyl 2-nitro-2-adamantanepropanoate (**12**) as a clear oil: IR (film) ν(C=O) 1735, $\nu(NO_2)$ 1530 cm^{-1}.

Spiro[pyrrolidine-2,2'-tricyclo[3.3.1.1^{3,7}]decan]-5-one (13). A solution of the nitro ester **12** (11.3 g, 40.2 mmol) in ethanol (40 mL) was hydrogenated in the presence of Raney nickel catalyst under a pressure of 45 psi, at 50 °C, for 8 h. The solution was filtered to remove catalyst, and the filtrate was evaporated to dryness. The residue was then worked up with ether–*n*-pentane, under cooling, to yield 7.83 g (~95%) of the γ-lactam as a pure crystalline solid: mp 212–214 °C; IR (Nujol) ν(NH) 3460, 3210, ν(C=O) 1670 cm^{-1}; ^{1}H-NMR δ (ppm) 1.58–1.90 (m, 14H, adamantane H), 1.95 (t, 2H, ~A_2X_2, J_{AX} ~ 8 Hz, 3-H), 2.30 (t, 2H, ~A_2X_2, J_{AX} ~ 8 Hz, 4-H), 8.05 (br s, 1H, 1-H); ^{13}C-NMR δ (ppm) 26.45 (7'-C), 26.62 (5'-C), 30.22 (3-C), 31.49 (4-C), 33.49 (4'-C, 9'-C), 34.07 (8'-C, 10'-C), 37.56 (1'-C, 3'-C), 37.71 (6'-C), 64.22 (2,2'-C), 177.44 (5-C). Anal. ($C_{13}H_{19}NO$) C, H, N.

Spiro[pyrrolidine-2,2'-tricyclo[3.3.1.1^{3,7}]decane] (14). To a stirred suspension of $LiAlH_4$ (2.22 g, 58.5 mmol) in dry THF (50 mL) was added a solution of the lactam **13** (4 g, 19.5 mmol) in dry THF (40 mL). The reaction mixture was refluxed for 20 h and was then hydrolyzed with water and a 20% NaOH solution under ice-cooling. The inorganic precipitate was filtered off and washed with THF, and the filtrate was evaporated under vacuum. The residue was dissolved in ether and extracted with a 10% HCl solution. The aqueous phase was made alkaline with solid K_2CO_3, and the oil which separated was extracted into ether, dried (K_2CO_3), and evaporated to dryness under vacuum to give 3.7 g (yield almost quantitative) of **14** as an oil: IR (film) ν(NH) 3320 cm^{-1}; ^{1}H-NMR δ (ppm) 1.43–1.84 (complex m, 17H, 1, 3, 4-H, adamantane H), 1.88–2.02 (br d, 2H, 4', 9'-H_A), 2.86 (~t, 2H, J ~ 6 Hz, 5-H); ^{13}C-NMR δ (ppm) 25.65 (3-C), 27.12 (7'-C), 27.33 (5'-C), 34.06 (4'-C, 9'-C), 35.40 (8'-C, 10'-C), 35.73 (4-C), 37.47 (1'-C, 3'-C), 38.13 (6'-C), 45.46 (5-C), 85.62 (2,2'-C). Hydrochloride: 265 °C dec (EtOH–Et_2O). Anal. ($C_{13}H_{22}ClN$) C, H, N.

1-(Ethoxycarbonyl)spiro[pyrrolidine-2,2'-tricyclo-[3.3.1.1^{3,7}]decane] (15a). To a stirred solution of the amine **14** (0.95 g, 4.97 mmol) and triethylamine (1.8 g, 17.6 mmol) in dry ether (15 mL) was added dropwise under ice-cooling ethyl chloroformate (0.95 g, 8.8 mmol) in dry ether (15 mL), and the mixture was stirred at room temperature for 15 h. The precipitated triethylamine hydrochloride was filtered off and washed with ether, and the filtrate was washed with a 2% HCl solution and water, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography on neutral aluminum oxide using ether as eluent. After removal of the solvent, 1.25 g (~96%) of the carbamate **15a** was obtained as an oil, which was used without further purification for the preparation of the derivative **16a**: IR (film) ν(C=O) 1700–1695 cm^{-1}; ^{1}H-NMR δ (ppm) 1.22 (t, 3H, A_3X_2, J_{AX} ~ 7 Hz, CH_3CH_2), 1.53–1.83 (complex m, 14H, adamantane H, 3-H), 2.12–2.30 (m, 4H, 4',9'-H_A, 4-H), 3.58 (~t, 2H, J ~ 7 Hz, 5-H), 4.03 (q, 2H, A_3X_2, J_{AX} ~ 7 Hz, CH_3CH_2).

1-Acetylspiro[pyrrolidine-2,2'-tricyclo[3.3.1.1^{3,7}]-decane] (15b). **15b** was prepared by the procedure used for the compound **15a**, by the reaction of acetylcholide with the pyrrolidine **14** in the presence of triethylamine. The product was purified by column chromatography on neutral aluminum oxide using a mixture of ether–*n*-hexane (1:2) as eluent: yield 85%; mp 99 °C (*n*-pentane); IR (Nujol) ν(C=O) 1655–1640 cm^{-1}; ^{1}H-NMR δ (ppm) 1.57–2.02 (complex m, 14H, adamantane H, 3-H), 2.04 (s, 3H, CH_3), 2.14–2.27 (m, 4H, 4',9'-H_A, 4-H), 3.47 (t, 2H, J ~ 7 Hz, 5-H). Anal. ($C_{15}H_{23}NO$) C, H, N.

1-(Cyclopropylcarbonyl)spiro[pyrrolidine-2,2'-tricyclo-[3.3.1.1^{3,7}]decane] (15c). **15c** was prepared by the procedure used for the compound **15a**, by the reaction of cyclopropanecarbonyl chloride with the pyrrolidine **14** in the presence of triethylamine. The product was purified by column chromatography on neutral aluminum oxide using a mixture of ether–*n*-hexane (1:2) as eluent: yield 92%; mp 85 °C (acetone–H_2O); IR (Nujol) ν(C=O) 1650–1630 cm^{-1}; ^{1}H-NMR δ (ppm) 0.62–0.72 (m, 2H, cyclopropane H), 0.84–0.93 (m, 2H, cyclopropane H), 1.50–1.92 (complex m, 15H, 1-cyclopropane H, adamantane H, 3-H), 2.08–2.34 (m, 4H, 4',9'-H_A, 4-H), 3.72 (~t, 2H, J ~ 7 Hz, 5-H). Anal. ($C_{17}H_{25}NO$) C, H, N.

1-Methylspiro[pyrrolidine-2,2'-tricyclo[3.3.1.1^{3,7}]-decane] (16a). To a stirred suspension of $LiAlH_4$ (1.8 g, 47.4 mmol) in dry THF (50 mL) was added the carbamate **15a** (1.1 g, 4.2 mmol) in dry THF (40 mL). The reaction mixture was refluxed for 20 h and was then hydrolyzed with water and a 20% NaOH solution under ice-cooling. The inorganic precipitate was filtered off and washed with THF, and the filtrate was evaporated under vacuum. The residue was dissolved in ether and extracted with a 5% HCl solutionm The aqueous phase was made alkaline with solid Na_2CO_3, and the oil formed was extracted into ether. The ether extracts were dried (Na_2SO_4) and evaporated to dryness to give 0.82 g (95%) of **16a** as an oil: ^{1}H-NMR δ (ppm) 1.44 (br s, 1H, 1'-H), 1.50 (br s, 1H, 3'-H), 1.59–1.85 (complex m, 14H, 3, 4-H, adamantane H), 2.08–2.20 (m, 2H, 4', 9'-H_A), 2.15 (s, 3H, CH_3), 2.75–2.87 (m, 2H, 5-H); ^{13}C-NMR δ (ppm) 21.41 (3-C), 27.30 (5'-C, 7'-C), 28.90 (4-C), 33.25 (1'-C, 3'- C), 33.47 (4'-C, 9'-C), 35.07 (8'-C, 10'-C), 37.45 (CH_3), 38.16 (6'-C), 52.94 (5-C), 70.71 (2,2'-C). Hydrochloride: mp 111 °C (EtOH–Et_2O). Anal. ($C_{14}H_{24}ClN$) C, H, N.

1-Ethylspiro[pyrrolidine-2,2'-tricyclo[3.3.1.1^{3,7}]-decane] (16b). **16b** was prepared by the reduction of the amide **15b**, using the above-mentioned procedure: yield 95%; ^{1}H-NMR δ (ppm) 1.02 (s, 3H, A_3X_2, J_{AX} ~ 7 Hz, CH_3), 1.42 (br

s, 1H, 1'-H), 1.47 (br s, 1H, 3'-H), 1.58–1.87 (complex m, 14H, 3, 4-H, adamantane H), 2.14–2.28 (br d, 2H, 4', 9'-H_A), 2.27 (q, 2H, A_3X_2, $J_{AX} \sim 7$ Hz, CH_2CH_3), 2.76–2.85 (m, 2H, 5-H); ^{13}C-NMR δ (ppm) 15.42 (CH_3), 21.42 (3-C), 27.48 (7'-C), 27.58 (5'-C), 30.65 (4-C), 33.43 (1'-C, 3'-C, 4'-C, 9'-C), 35.01 (8'-C, 10'-C), 38.21 (6'-C), 39.95 (CH_2CH_3), 47.27 (5-C), 70.79 (2,2'-C). Hydrochloride: mp 245 °C (EtOH–Et_2O). Anal. ($C_{15}H_{26}ClN$) C, H, N.

1(Cyclopropylmethyl)spiro[pyrrolidine-2,2'-tricyclo[3.3.1.1^{3,7}]decane] (16c). **16c** was prepared by the reduction of the amide **15c**, using the above-mentioned procedure: yield 92%; ^{1}H-NMR δ (ppm) 0.05–0.12 (m, 2H, cyclopropane H), 0.42- 0.50 (m, 2H, cyclopropane H), 0.72–0.92 (m, 1H, 1-cyclopropane H), 1.39 (br s, 1H, 1'-H), 1.45 (br s, 1H, 3'-H), 1.58–1.82 (complex m, 14H, 3, 4-H, adamantane H), 2.13 (~d, 2H, $J \sim 6$ Hz, CH_2N), 2.18–2.25 (br d, 2H, 4', 9'-H_A), 2.95–3.06 (m, 2H, 5-H); ^{13}C-NMR δ (ppm) 3.92 (2,3-cyclopropane C), 11.35 (1-cyclopropane C), 21.33 (3-C), 27.44 (7'-C), 27.47 (5'-C), 30.56 (4-C), 33.31 (1'-C, 3'-C), 33.42 (4'-C, 9'-C), 35.01 (8'-C, 10'-C), 38.17 (6'-C), 47.73 (5-C), 50.96 (CH_2N), 70.70 (2,2'-C). Hydrochloride: mp 235 °C (EtOH–Et_2O). Anal. ($C_{17}H_{28}ClN$) C, H, N.

1-[[(4-Chlorophenyl)amino]carbonyl]spiro[pyrrolidine-2,2'-tricyclo[3.3.1.1^{3,7}]decane] (17). To a stirred solution of the amine **14** (0.67 g, 3.5 mmol) in dry ether (20 mL) was added a solution of 4-chlorophenyl isocyanate (0.53 g, 3.5 mmol) in dry ether (10 mL) in one portion. The mixture was refluxed for 20 min and then cooled at 0 °C. The precipitate was filtered and washed with ether to yield 0.85 g (~70%) of **17**: mp 164 °C (Et_2O–*n*-pentane); IR (Nujol) ν(NH) 3200–3180, ν(C=O) 1640–1625, ν(C=C) 1580 (aromatic), δ(C–H) 820 cm^{-1} (aromatic); ^{1}H-NMR δ (ppm) 1.59–1.96 (complex m, 14H, adamantane H, 3-H), 2.08 (br d, 2H, 4',9'-H_A), 2.26–2.35 (m, 2H, 4-H), 3.52 (t, 2H, $J \sim 7$ Hz, 5-H), 6.25 (s, 1H, NH), 7.12-7.32 (m, 4H, aromatic H). Anal. ($C_{17}H_{25}NO$) C, H, N.

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