New Substituted 4-Azatricyclo[4.3.1.1^{3,8}]undecane Derivatives

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The synthesis of a series of new substituted 4-azatricyclo[4.3.1.1^{3,8}]undecane and 4-azatricyclo[4.3.1.1^{3,8}]-undecan-5-one derivatives is described. Compounds **4f** and **4g** displayed antiviral activity.

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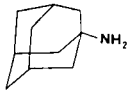
A number of nitrogen-containing adamantane derivatives such as amantadine (**1**) have long been known for their antiviral activity [1]. The introduction of a nitrogen into the lipophilic adamantane moiety to form analogs of structures such as the 4-azatricyclo[4.3.1.1^{3,8}]-undecan-5-one (**2**) [2-8] and its 5-dihydro analog **3** [2,7-9] have also provided compounds that exerted either antiviral [2,4-7], antiarrhythmic [6], anti-inflammatory [6] or cardiovascular [4,5] activities.



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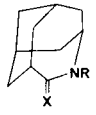


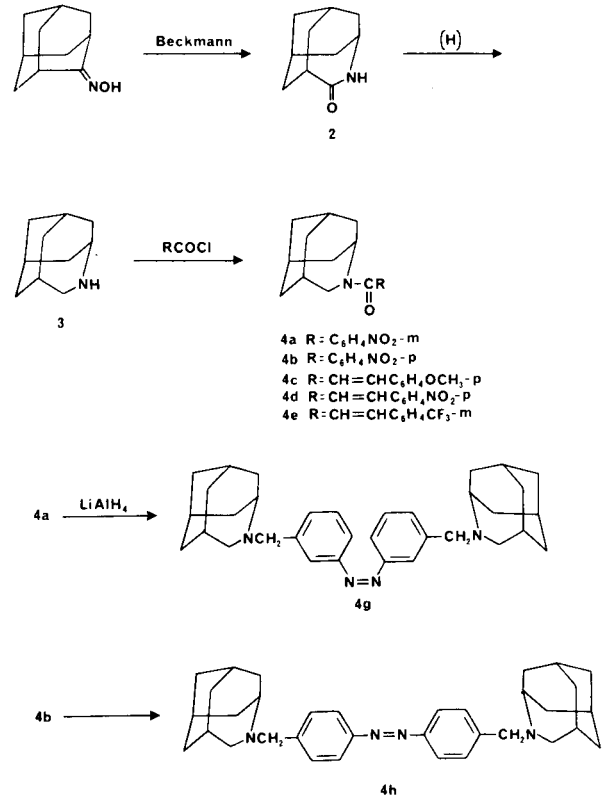
2 R= H, X= O

3 R= H, X= H_2

The present work describes the preparation and biological activity of a series of new substituted 4-azatricyclo-[4.3.1.1^{3,8}]undecanes **4a-4h** and 4-azatricyclo[4.3.1.1^{3,8}]-undecan-5-one derivatives.

The synthesis of derivatives **4a-4h** was straightforward and involved an initial Beckmann rearrangement of 2-adamantanone oxime to form the 4-azatricyclo[4.3.1.1^{3,8}]-undecan-5-one (**2**). Catalytic reduction of compound **2** furnished the 4-azatricyclo[4.3.1.1^{3,8}]undecane (**3**). The latter was *N*-acylated with appropriate acid chlorides to furnish derivatives **4a-4e**. Lithium aluminum hydride reduction of the *N*-(*m*-nitrobenzoyl) analog **4a** led to the preparation of the corresponding azobenzene compound **4g**. Similarly, the reduction of the *N*-(*p*-nitrobenzoyl) derivative **4b** produced the azobenzene analog **4h** (Scheme I).

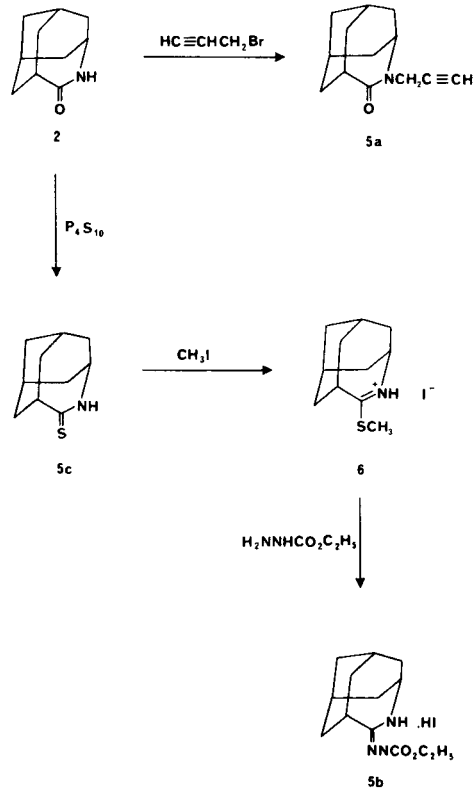
Scheme I



N-Alkylation of 4-azatricyclo[4.3.1.1^{3,8}]undecan-5-one (**2**) with propargyl bromide led to the preparation of 4-propargyl-4-azatricyclo[4.3.1.1^{3,8}]undecan-5-one (**5a**). The 4-azatricyclo[4.3.1.1^{3,8}]undecane-5-thione (**5c**) and its methylthio analog **6** were obtained by treatment of compound **2** with phosphorus pentasulfide and subsequent reaction with methyl iodide. Reaction of 5-methylthio-4-azatricyclo[4.3.1.1^{3,8}]undec-4-ene hydroiodide (**6**) with ethyl carbazate gave rise to the corresponding 5-[(ethoxycarbonyl)hydrazonyl]-4-azatricyclo[4.3.1.1^{3,8}]undecane hydroiodide (**5b**) (Scheme II).

When tested for its antiviral effect on Influenza A/NWS/33 virus in MDCK cells and on Type 2 Herpesvirus in MA104 cells, compound **4f** exerted *in vitro* a moderate activity with minimum inhibitory concentrations (MIC) of 1.0 and 3.2 μg/ml (virus rating 1.2 and 0.7), respectively. Derivative **4g** was also found to be moderately active against Type 1 Herpesvirus in MA104 cells with a MIC value of 3.2 μg/ml (virus rating 0.4).

Scheme II



EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The ir spectra were obtained on a Nicolet MX-1 FT spectrometer as potassium bromide discs. The ^{1}H nmr spectra were obtained on a Varian EM-360A (60 MHz) spectrometer using TMS as an internal standard. All spectra were consistent with the assigned structures.

4-Azatricyclo[4.3.1.1^{3,8}]undecan-5-one (**2**).

To a suspension of 3 g (18 mmoles) 2-adamantanone oxime in 36 ml of 20% aqueous sodium hydroxide were added 5 g (28 mmoles) benzenesulfonyl chloride with vigorous stirring at 20-30°. The temperature was maintained below 30° until the exothermic reaction ceased, then raised to 55° and held there for 2 hours. The reaction mixture was worked up leaving 2.0 g (67%) of 4-azatricyclo[4.3.1.1^{3,8}]undecan-5-one as white crystals melting at 306-308° (hexane) (lit mp 309-310° [7]).

Anal. Calcd. for $C_{10}H_{15}NO$: C, 72.69; H, 9.15; N, 8.47. Found: C, 72.29; H, 9.26; N, 8.34.

4-Azatricyclo[4.3.1.1^{3,8}]undecane (**3**).

4-Azatricyclo[4.3.1.1^{3,8}]undecan-5-one (2.45 g, 14 mmoles) was added to a suspension of lithium aluminum hydride (2.12 g, 56 mmoles) in 200 ml of anhydrous ether. The mixture was refluxed for 6 hours, then worked up as usual to afford compound **3** as white solid material which was recrystallized from hexane, mp 290° (lit mp 300° [7]), yield 1.90 g (85%).

4-(*p*-Nitrobenzoyl)-4-azatricyclo[4.3.1.1^{3,8}]undecane (**4b**).

A mixture of 4-azatricyclo[4.3.1.1^{3,8}]undecane (0.75 g, 5 mmoles) and *p*-nitrobenzoyl chloride (0.93 g, 5 mmoles) in 40 ml of anhydrous ethanol was refluxed for 4.5 hours. Following workup and recrystallization from 2-propanol, 1.25 g (84%) of compound **4b** were obtained as white crystals, mp 150°; ir (potassium bromide): 1596 cm^{-1} (aromatic), 1616 cm^{-1} (amide C=O), 1519 and 1348 cm^{-1} (NO_2); nmr (dimethyl sulfoxide-d_6): ppm 1.20-2.25 (m, 5 x CH_2, 4 x CH, 14H), 3.50-4.10 (cm, CH_2, 2H), 4.70-8.40 (dd, d, aromatic 4H).

Anal. Calcd. for $C_{17}H_{20}N_2O_3$: C, 67.98; H, 6.71; N, 9.32. Found: C, 67.53; H, 6.95; N, 9.17.

4-(*m*-Nitrobenzoyl)-4-azatricyclo[4.3.1.1^{3,8}]undecane (**4a**).

Compound **4a** was prepared by a procedure similar to that described for derivative **4b** starting with 4-azatricyclo[4.3.1.1^{3,8}]undecane (**3**) (0.75 g, 5 mmoles) and *m*-nitrobenzoyl chloride (0.93 g, 5 mmoles), yield 1.20 g (81%), white crystals, mp 122° (2-propanol); ir (potassium bromide): 820 and 725 cm^{-1} (aromatic γ-CH, confirms 1,3-disubstitution), 1617 cm^{-1} (amide C=O), 1370 cm^{-1} (amide C-N), 1528 and 1348 cm^{-1} (NO_2).

Anal. Calcd. for $C_{17}H_{20}N_2O_3$: C, 67.98; H, 6.71; N, 9.32. Found: C, 67.51; H, 6.96; N, 9.14.

4-(*p*-Methoxycinnamoyl)-4-azatricyclo[4.3.1.1^{3,8}]undecane (**4c**).

Compound **4c** was prepared by a procedure similar to that described for derivative **4b** starting with 4-azatricyclo[4.3.1.1^{3,8}]undecane (**3**) (0.80 g, 5.5 mmoles) and *p*-methoxycinnamoyl chloride (1.0 g, 5.5 mmoles), yield 1.30 g (79%), white crystals, mp 170-172° (anhydrous ethanol); ir (potassium bromide): 1585 cm^{-1} (aromatic), 822 cm^{-1} (aromatic γ-CH, confirms 1,4-disubstitution), 1639 cm^{-1} (amide C=O), 2985 and 1603 cm^{-1} (CH=CH), 985 cm^{-1} (δ CH-*trans*); nmr (deuteriochloroform): ppm 0.80-2.80 (cm, 6 x CH_2 and 1 x CH, 13H), 3.50-4.10 (s, OCH_3, cm, N-CH_2-C, 5H), 4.33 -5.10 (broad singlet, C-CH-C, 1H), 6.50-8.10 (cm, aromatic 6H).

Anal. Calcd. for $C_{20}H_{25}NO_2$: C, 77.13; H, 8.09; N, 4.49. Found: C, 77.04; H, 8.21; N, 4.40.

4-(*p*-Nitrocinnamoyl)-4-azatricyclo[4.3.1.1^{3,8}]undecane (**4d**).

Compound **4d** was prepared by a procedure similar to that described for derivative **4b** starting with 4-azatricyclo[4.3.1.1^{3,8}]undecane (**3**) (0.75 g, 5 mmoles) and *p*-nitrocinnamoyl chloride (1.13 g, 5.4 mmoles), yield 1.29 g (81%), beige crystals, mp 290-293° (anhydrous ethanol); ir (potassium bromide): 1590 cm^{-1} (aromatic), 844 cm^{-1} (aromatic γ-CH, confirms 1,4-disubstitution), 1641 cm^{-1} (amide C=O), 1514 and 1349 cm^{-1} (NO_2), 1602 cm^{-1} (CH=CH), 965 cm^{-1} (δ CH-*trans*); nmr (deuteriochloroform): ppm 0.70-3.40 (cm, 6 x CH_2 and 1 x CH, 13H), 3.70 (t, N-CH_2, 2H), 4.40-5.20 (broad singlet, 2 x CH, 2H), 6.60-8.80 (cm, aromatic 6H).

Anal. Calcd. for $C_{19}H_{22}N_2O_3$: C, 69.91; H, 6.79; N, 8.58. Found: C, 71.05; H, 6.77; N, 8.55.

4-[(*m*-Trifluoromethyl)cinnamoyl]-4-azatricyclo[4.3.1.1^{3,8}]undecane (**4e**).

Compound **4e** was prepared by a procedure similar to that described for derivative **4b** starting with 4-azatricyclo[4.3.1.1^{3,8}]undecane (**3**) (0.72 g, 4.7 mmoles) and (*m*-trifluoromethyl)cinnamoyl chloride (1.15 g, 4.9 mmoles), yield 1.24 g (75%), white crystals, mp 95-100° (petroleum ether); ir (potassium bromide): 1609 cm^{-1} (aromatic), 800 and 690 cm^{-1} (aromatic γ-CH, confirms 1,3-disubstitution), 1644 cm^{-1} (amide C=O), 1610 cm^{-1} (CH=CH), 1000 cm^{-1} (δ CH-*trans*); nmr (deuteriochloroform): ppm 1.40-2.90 (cm, 5 x CH_2 and 4 x CH, 14H), 3.95 (broad singlet, N-CH_2, 2H), 7.10-8.05 (cm, aromatic 6H).

Anal. Calcd. for $C_{20}H_{22}FNO$: C, 68.75; H, 6.34; F, 16.31; N, 4.00. Found: C, 68.94; H, 6.45; F, 15.77; N, 4.02.

4-(3'-Phenylpropen-2'-yl)-4-azatricyclo[4.3.1.1^{3,8}]undecane (**4f**).

A mixture consisting of 4-azatricyclo[4.3.1.1^{3,8}]undecane (**3**) (0.75 g, 5 mmoles) and cinnamyl chloride (0.76 g, 5 mmoles) in 40 ml of anhydrous ethanol was refluxed for 8 hours. Then, the solvent was evaporated under reduced pressure leaving 1.05 g (70%) of derivative **4f** as white solid, mp 273° (2-propanol); ir (potassium bromide): 1580 cm^{-1} (aromatic), 760 cm^{-1} (aromatic γ-CH, confirms a monosubstitution), 1635 cm^{-1} (CH=CH).

Anal. Calcd. for $C_{19}H_{26}ClN$: C, 75.12; H, 8.59; Cl, 11.68; N, 4.61. Found: C, 75.02; H, 8.84; Cl, 11.56; N, 4.62.

4,4'-Bis(4''-methylene-4''-azatricyclo[4.3.1.1^{3,8}]undecane)azobenzene (**4h**).

4-(*p*-Nitrobenzoyl)-4-azatricyclo[4.3.1.1^{3,8}]undecane (0.37 g, 1.2 mmoles) was added to a suspension of lithium aluminum hydride (0.37 g, 9.8 mmoles) in 100 ml of anhydrous ether and the reaction mixture was refluxed for 7.5 hours. After workup, 0.54 g (86%) of derivative **4h** was obtained as white solid, mp 196-198° (2-propanol); ir (potassium bromide): 1600 cm^{-1} (aromatic), 838 cm^{-1} (aromatic γ-CH, confirms 1,4-disubstitution), 1351 cm^{-1} (NH_2).

Anal. Calcd. for $C_{34}H_{44}N_4$: C, 80.27; H, 8.71; N, 11.01. Found: C, 79.76; H, 8.68; N, 10.91.

3,3'-Bis(4''-methylene-4''-azatricyclo[4.3.1.1^{3,8}]undecane)azobenzene (**4g**).

Compound **4g** was prepared by a procedure similar to that described for derivative **4h** starting with 4-(*m*-nitrobenzoyl)-4-azatricyclo-[4.3.1.1^{3,8}]undecane (**4a**) (1.84 g, 6 mmoles) and lithium aluminum hydride (1.86 g, 4.9 mmoles), yield 2.51 g (81%), white crystals, mp 127° (anhydrous ethanol); ir (potassium bromide): 1605 cm^{-1} (aromatic), 800 and 695 cm^{-1} (aromatic γ-CH, confirms 1,3-disubstitution); nmr (deuteriochloroform): ppm 1.20-2.30 (cm, 12 x CH_2, 24H), 2.50-3.20 (cm, 8 x CH, 8H), 4.90 (s, 2 x N-CH_2-C, 4H), 7.30-8.00 (cm, aromatic 8H).

Anal. Calcd. for $C_{34}H_{44}N_4$: C, 80.27; H, 8.71; N, 11.01. Found: C, 79.94; H, 8.93; N, 10.88.

4-Propargyl-4-azatricyclo[4.3.1.1^{3,8}]undecan-5-one (**5a**).

A solution of potassium hydroxide (0.56 g, 10 mmoles) in 3 ml of anhydrous methanol was added to 4-azatricyclo[4.3.1.1^{3,8}]undecan-5-one (1.65 g, 10 mmoles) and the solvent was slowly removed under reduced pressure with the internal temperature not exceeding 25°. When a solid began to separate, anhydrous toluene was added and the solvent removal continued - a total of 30 ml toluene were removed, then the temperature was raised to 90° (with the distillation continuing at atmospheric pressure - a total of 10 ml toluene were distilled). The reaction mixture was cooled to 40° and propargyl bromide (0.9 ml, 10 mmoles) was added dropwise. The temperature was raised to 65° and the mixture was stirred for 4 hours. The solid precipitate that formed was filtered off and the filtrate was evaporated under reduced pressure to yield 1.82 g (90%) of compound **5a**, mp 168-170° (petroleum ether-ethanol); ir (potassium bromide): 3208 and 2115 cm^{-1} (C≡CH), 1633 cm^{-1} (amide C=O), 1375 cm^{-1} (amide C-N); nmr (dimethyl sulfoxide-d_6): ppm 1.40-2.40 (cm, 5 x CH_2 and 1 x CH, 11H), 2.66-3.00 (cm, 2 x CH, 2H), 3.00-3.15 (t, ≡CH, 1H), 4.20 (d, N-CH_2, 2H).

Anal. Calcd. for $C_{13}H_{17}NO$: C, 76.81; H, 8.42; N, 6.89. Found: C, 76.68; H, 8.82; N, 6.85.

5-[(Ethoxycarbonyl)hydrazonyl]-4-azatricyclo[4.3.1.1^{3,8}]undecane Hydroiodide (**5b**).

A mixture of the hydroiodide salt **6** (0.5 g, 2.56 mmoles) and ethyl carbazate (0.31 g, 3 mmoles) in 50 ml toluene was refluxed for 6 hours. The resulting precipitate was filtered off and then recrystallized from ethyl acetate leaving 0.24 g (41%) of compound **5b** as white crystalline material melting at 185-187°; ir (potassium bromide): 1746 cm^{-1} (carbamate C=O), 1575 cm^{-1} (amide II), 1250 cm^{-1} (amide III), 1654 cm^{-1} (imine C=N), 3400-2400 cm^{-1} (NH_2^+); nmr (dimethyl sulfoxide-d_6): ppm 1.40 (t, C-CH_3, 3H), 1.66-2.70 (cm, 5 x CH_2 and 1 x CH, 11H), 3.20 (broad singlet, 2 x CH, 2H), 3.90-4.60 (q, cm, O-CH_2-C, ring CH, 3H).

Anal. Calcd. for $C_{13}H_{22}IN_3O_2$: C, 41.17; H, 5.85; I, 33.46; N, 11.08. Found: C, 40.81; H, 5.85; I, 33.23; N, 11.14.

Azatricyclo[4.3.1.1^{3,8}]undecane-5-thione (**5c**).

4-Azatricyclo[4.3.1.1^{3,8}]undecan-5-one (3.0 g, 18 mmoles) and phosphorus pentasulfide (4.65 g, 21 mmoles) were dissolved in 100 ml pyridine and the resulting solution was refluxed for 45 minutes. The mixture was poured into 150 ml of ice-cold saturated aqueous sodium chloride solution with continuing stirring. The precipitate that formed was filtered off and washed with water, then dissolved in methylene chloride. The organic solution was filtered through activated alumina and then evaporated under reduced pressure to yield 1.72 g (52%) of the 5-thione analog **5c**, mp 184-185° (anhydrous ethanol); ir (potassium bromide): 3175 cm^{-1} (thiolactam NH), 1560 cm^{-1} (C-N), 1122 cm^{-1} (thiolactam C=S).

Anal. Calcd. for $C_{10}H_{15}NS$: C, 66.25; H, 8.34; N, 7.73; S, 17.68. Found: C, 66.31; H, 8.46; N, 7.74; S, 18.00.

5-Methylthio-4-azatricyclo[4.3.1.1^{3,8}]undec-4-ene Hydroiodide (**6**).

A mixture of the 5-thione derivative **5c** (1.45 g, 8 mmoles) and methyl iodide (1.21 g, 8.5 mmoles) in 100 ml methanol was refluxed for 6 hours. The solvent was evaporated under reduced pressure yielding the hydroiodide salt **6** (2.0 g, 78%) as white solid, mp 235-238° (anhydrous ethanol); ir (potassium bromide): 1620 cm^{-1} (C=N), 622 cm^{-1} (SCH_3); nmr (deuteriochloroform): ppm 1.10-2.40 (cm, 5 x CH_2 and 2 x CH, 12H), 2.50-3.30 (broad singlet, SCH_3, N=C-CH, 4H), 4.80 (broad singlet, N-CH-C, 1H).

Anal. Calcd. for $C_{11}H_{18}INS$: C, 40.87; H, 5.61; I, 39.26; N, 4.33; S, 9.92. Found: C, 40.86; H, 5.76; I, 38.95; N, 4.32; S, 9.86.

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