NOVEL SUBSTITUTED ADAMANTANE-SPIRO-5-OXAZOLIDINE DERIVATIVES

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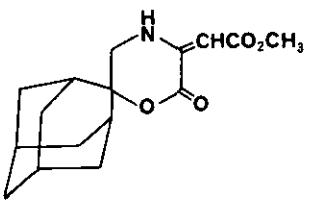
Abstract - The synthesis of a series of substituted adamantane-spiro-5-oxazolidin-2-one (3-6) and adamantane-spiro-5-oxazolidine (7-10) derivatives, is described. Compounds 7-10 represent novel adamantane-spiro-heterocyclic systems.

Recently, [1,2] we have reported the synthesis of spiro[3,4,5,6-tetrahydro-1,4-oxazin-2-one-6,2'-tricyclo[3.3.1.1^{3,7}]decane] (compounds 1 and 2), a novel adamantane-spiro-heterocyclic system. When tested for anti-inflammatory activity, at an oral dose of 50 mg/kg, derivative 2 exerted a 27.9% ($p \leq 0.05$) inhibition of the carrageenin-induced rat paw edema. [2]



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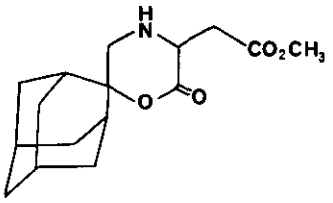

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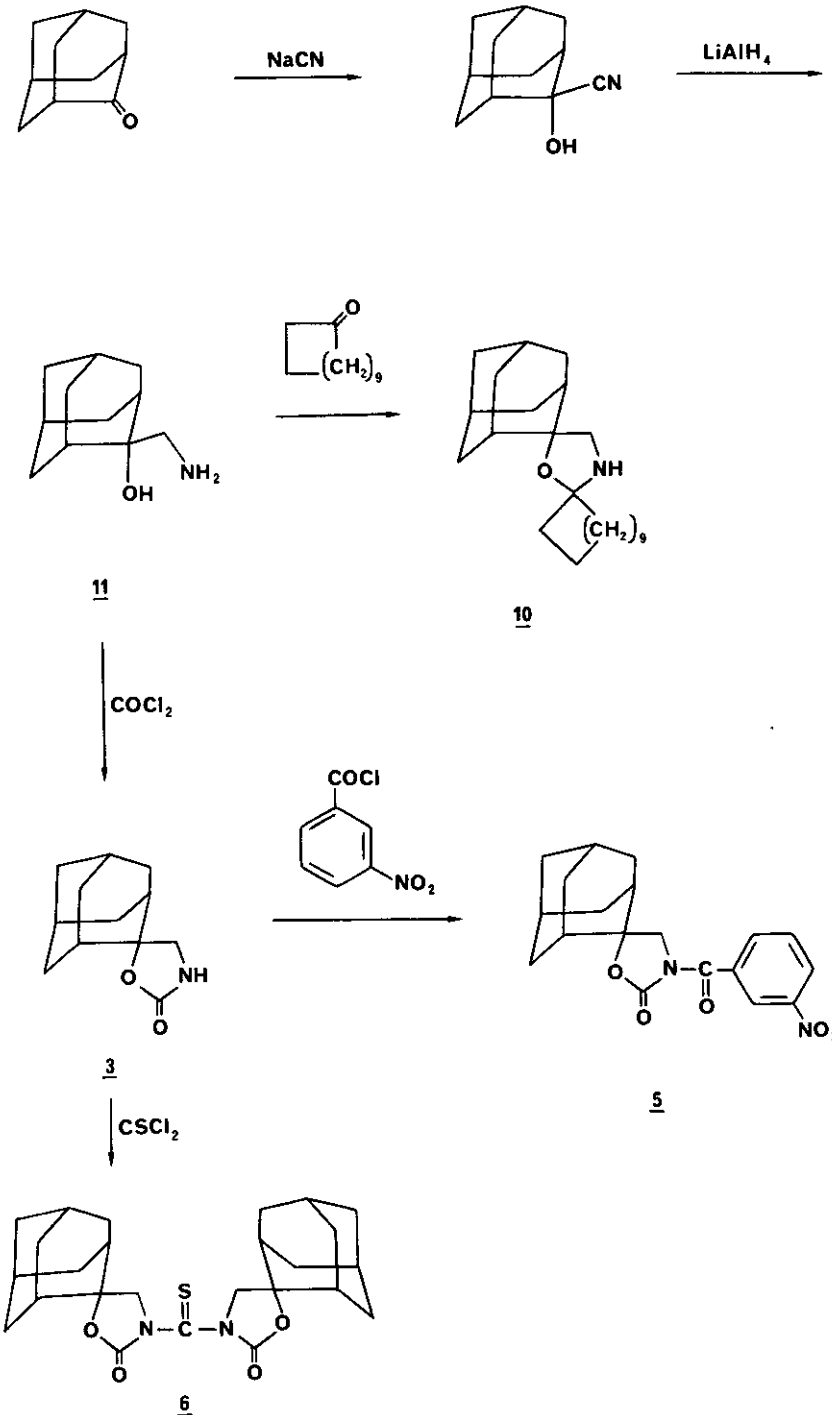
In the present communication we wish to report a further extension of our previous work, namely, the synthesis of a series of novel substituted adamantane-spiro-5-oxazolidin-2-one (3-6) and adamantane-spiro-5-oxazolidine (7-10) derivatives (Table I). The synthesis of the title compounds was straightforward and involved an initial reaction of 2-adamantanone with sodium cyanide in methanol-concentrated sulfuric acid, followed by a lithium aluminum hydride reduction of the resulting cyanohydrin derivative to afford the known 2-aminomethyl-2-hydroxyadamantane (11). [2] Condensation of the latter with either phosgene or an appropriate alicyclic ketone provided the corresponding adamantane-spiro-5-oxazolidine analogs 3 and 10, respectively. Furthermore, reaction of compound 3 with m-nitrobenzoyl chloride or thiophosgene furnished the N-substituted oxazolidin-2-one compounds 5 and 6, respectively (Scheme I).

Compounds 7-10 represent novel adamantane-spiro-heterocyclic systems.

When tested for anti-inflammatory activity, the adamantane-spiro-5-oxazolidin-2-one (3), at a dose of 100 mg/kg administered orally, elicited a 47.1% inhibition of the rat carrageenin-induced paw edema. [3]

Scheme I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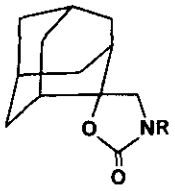
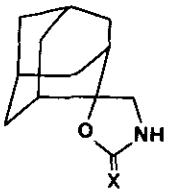
LiAlH4
CN
OH
NH2
OH
(CH2)9
O
NH
(CH2)9
11
10
COCl2
COCl
NO2
O
NH
O
3
5
CSCl2
S
O
N
C
N
O
O
O
6

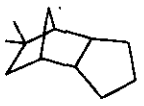
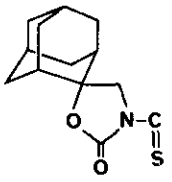
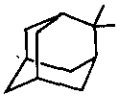
Table I. Substituted Adamantane-spiro-5-oxazolidin-2-one (3-6) and Adamantane-spiro-5-oxazolidine (7-10) Derivatives



3-6



7-10

Compd	R	Compd	>X
3	H	7	
4	CH_3		
5	$COC_6H_4NO_2$-m		
		8	
6		9	
		10	cyclododecyl

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The infrared (IR) spectra were obtained on a Nicolet MX-1 FT spectrometer as KBr discs. The proton nuclear magnetic resonance (^{1}H NMR) spectra were taken on a Varian Em-360A (60 MHz) spectrometer using tetramethylsilane as an internal standard. All spectra were consistent with the assigned strucres. All compounds gave elemental analyses which were within conventional limits for expected values.

Adamantane-spiro-5-oxazolidin-2-one (3)

2-Aminomethyl-2-hydroxyadamantane (11) [2] (0.58 g, 3 mmol) was refluxed for 2 h with a toluene solution of phosgene (25%, 25 ml). Then, the solvent was evaporated under reduced pressure leaving 0.12 g of adamantane-spiro-5-oxazolidin-2-one (3), mp 203-206°C (petroleum ether). IR (KBr): 3280 cm^{-1} (NH, lactam); 1709 cm^{-1} (C=O); 1257 cm^{-1} (C-O-C). ^{1}H NMR (DMSO-d_6/D_2O): 1.30-2.30 ppm (cm, 14H, 5 x ring CH_2 and 4 x ring CH); 3.35 ppm (s, 2H, N-CH_2); 7.45 ppm (s, 1H labile, NH-C). Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.53; H, 8.26; N, 6.75. Found: C, 69.44; H, 8.53; N, 6.70.

Adamantane-spiro-5-(N-methyloxazolidin-2-one) (4)

Sodium methoxide (0.14 g, 25 mmol) was added to a solution of adamantane-spiro-5-oxazolidin-2-one (3) (0.41 g, 2 mmol) in 10 ml of anhydrous methanol. The reaction mixture was stirred at room temperature for 10 min, then the solvent was evaporated under reduced pressure. The solid residue was

dissolved in 60 ml of toluene and dimethyl sulfate (0.3 ml, 3 mmol) was added. The reaction mixture was refluxed for 75 min, then the solvent was evaporated to dryness and the crude derivative 4 was recrystallized from petroleum ether giving 0.69 g of crystalline material melting at 191-194°C (lit.[4] 191-192.5°C). IR (KBr): 2860 cm^{-1} ($N-CH_3$); 1750 cm^{-1} (C=O); 1100 and 1040 cm^{-1} (C-O-C). Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.55; H, 8.65; N, 6.32. Found: C, 70.77; H, 8.85; N, 6.39.

Adamantane-spiro-5-[(N-m-nitrobenzoyl)oxazolidin-2-one] (5)

Compound 3 (0.33 g, 1.6 mmol) was treated, first, with sodium methoxide (0.112 g) in anhydrous methanol, and then with m-nitrobenzoyl chloride (0.37 g, 2 mmol) as described in the preceding experiment. After the reaction was completed the solvent was removed under reduced pressure and the crude reaction product was recrystallized from ethanol leaving 0.50 g of pure compound 5, mp 174°C (ethanol). IR (KBr): 1615 cm^{-1} (aromatic); 765 and 711 cm^{-1} [γ(=CH) 4H, confirms aromatic 1,3-disubstitution]; 1778 cm^{-1} (O=C-O-); 1678 cm^{-1} (C=O, amide); 1524 and 1348 cm^{-1} (nitro). ^1H NMR ($CDCl_3$): 1.36-2.50 ppm (cm, 14H, 5 x ring CH_2 and 4 x ring CH); 4.00 ppm (s, 2H, $N-CH_3$); 7.10-8.50 ppm (cm, 4H, aromatic). Anal. Calcd for $C_{19}H_{20}N_2O_5$: C, 64.03; H, 5.65; N, 7.86. Found: C, 63.95; H, 5.60; N, 7.88.

1,1'-Thiocarbonylbis[adamantane-spiro-5"-(oxazolidin-2"-one)] (6)

Derivative 3 (0.90 g, 5 mmol) was treated with sodium methoxide (0.27 g, 5 mmol) in anhydrous methanol (stirring at ambient temperature for 15 min). Then, the solvent was removed under reduced pressure and the solid residue was suspended in toluene. Thiophosgene (0.2 ml) was added and the reaction mixture was refluxed for 2 h. Following completion of the reaction the solvent was evaporated *in vacuo* and the crude product was recrystallized from ethanol yielding 0.17 g of compound 6, mp 200-207°C (ethanol). IR (KBr): 1783 and 1710 cm^{-1} [NC(=O)O]. ^1H NMR ($CDCl_3$): 0.60-2.90 ppm (cm, 28H, 10 x ring CH_2 and 8 x ring CH); 3.50 and 4.10 ppm (ss, 2 x 2H, $N-CH_2$ - the different shifts for the oxazolidine ring methylene protons indicate that the latter are not equivalent). Anal. Calcd for $C_{25}H_{32}N_2O_4S$: C, 65.76; H, 7.06; N, 6.13. Found: C, 65.97; H, 7.20; N, 6.21.

Adamantane-spiro-5-(oxazolidine-2-spiro-dodecane) (10)

Cyclododecanone (0.91 g, 5 mmol) was added to a solution of 2-aminomethyl-2-hydroxyadamantane (11) (0.90 g, 5 mmol) in 30 ml of toluene. After the reaction mixture was refluxed for 7 h (Dean-Stark separator), the solvent was evaporated under reduced pressure to furnish derivative 10 as a brown oil which crystallized from 2-propanol leaving 1.08 g of crystalline compound melting at 241-245°C (2-propanol). IR (KBr): 3440 and 1100 cm^{-1} (amine); 1080 cm^{-1} (C-O-C). ^1H NMR ($CDCl_3$): 0.20-2.80 ppm (cm, 36H, 16 x ring CH_2 and 4 x ring CH); 3.00 ppm (s, 2H, $N-CH_2$). Anal. Calcd for $C_{23}H_{29}NO$: C, 79.94; H, 11.38; N, 4.05. Found: C, 79.87; H, 11.22; N, 4.09.

Adamantane-spiro-5-[oxazolidine-2-spiro-(8'-ketotricyclo[5.2.1.$0^{2,6}$]decane] (7)

Compound 7 was prepared in a similar manner as described in the preceding experiment by reacting 2-aminomethyl-2-hydroxyadamantane (11) (0.90 g, 5 mmol) with 8-ketotricyclo[5.2.1.$0^{2,6}$]decane (0.75 g, 5 mmol) in toluene solution (40 ml). After refluxing for 4.5 h the reaction mixture was evaporated under reduced pressure and the resultant oil was crystallized from petroleum ether yielding 0.40 g of pure compound 7, mp 110-112°C (petroleum ether). IR (KBr): 3400 and 1160 cm^{-1} (amine); 1071 cm^{-1} (C-O-C). Anal. Calcd for $C_{21}H_{31}NO$: C, 80.46; H, 9.97; N, 4.47. Found: C, 80.45; H, 10.10; N, 4.31.

Adamantane-spiro-5-(oxazolidine-2-spiro-adamantane) (8)

Compound 8 was obtained by a similar procedure as described in the synthesis of derivative 10 by reacting 2-aminomethyl-2-hydroxyadamantane (11) (0.45 g, 2.5 mmol) and 2-adamantanone (0.37 g, 2.5 mmol) in chloroform solution (30 ml). Following a reflux for 4 h, the solvent was removed *in vacuo* and the residual solid was recrystallized from 2-propanol yielding 0.65 g of derivative 8 as white crystals melting at 110-112°C (2-propanol). IR (KBr): 3270 and 1358 cm^{-1} (amine); 1120 cm^{-1} (C-O-C). Anal. Calcd for $C_{21}H_{31}NO$: C, 80.46; H, 9.96; N, 4.46. Found: C, 80.58; H, 10.40; N, 4.18.

Adamantane-spiro-5-[oxazolidine-2-spiro-(2-norbornane)] Hydrochloride (9)

Derivative 9 was synthesized according to the procedure described for the preparation of compound 10 by reacting 2-aminomethyl-2-hydroxyadamantane (11) (0.90 g, 5 mmol) with 2-norbornanone (0.55 g, 5 mmol) in toluene solution (40 ml). The reaction mixture was refluxed for 8 h and then stirred at ambient temperature for 64 h. Following completion, the solvent was removed under reduced pressure and the resulting oil was converted into the hydrochloric salt and recrystallized from ethanol giving 0.27 g of compound 9, mp 234-235°C (ethanol). IR (KBr): 3100-2100 cm^{-1} (NH_2^+); 1582 cm^{-1} (NH); 1105 cm^{-1} (C-O-C). Anal. Calcd for $C_{18}H_{28}ClNO$: C, 69.76; H, 9.10; N, 4.51. Found: C, 69.65; H, 9.34; N, 4.56.

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