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Synthesis of Adamantane Spiro Sultones as Potential Antiviral Agents

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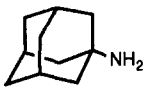
Abstract: Spiro adamantane derivatives functionalized with a γ-sultone moiety have been synthesized and evaluated as antivirals. The reaction pathway followed represents an alternative route to those previously described for the synthesis of β-keto-γ-sultones.

Since the discovery of the interesting antiviral properties of 1-adamantanamine (amantadine, **1**),[1] the preparation of adamantane analogues has recieved considerable attention.[2] The synthesis of 2-adamantanone encouraged chemists to investigate the possibilities of substitution at a bridge carbon atom of the adamantane nucleus and thus several secondarily substituted adamantanes, including spiro compounds, have been prepared.[3] Among the latter, the *N*-methyl-adamantane-spiro-3'-pyrrolidine (**2**) was found to be superior to amantadine in potency and spectrum of antiviral activity.[4]



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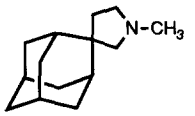

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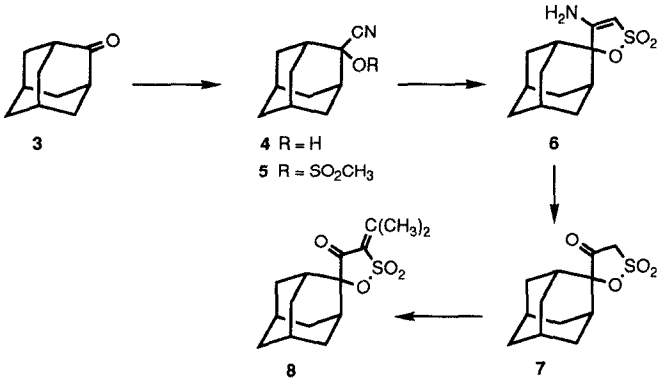
In the course of our studies on the synthesis of highly functionalized branched-chain sugars, we reported the unexpected behavior of α-mesyloxynitriles of sugars, which, under basic conditions, undergo an intramolecular aldol-type cyclocondensation to afford *C*-branched spiro derivatives.[5] We have recently reported the application of this reaction to 3'-α-mesyloxynitriles of nucleosides, which has led to the discovery of a novel class of potent and specific anti-HIV-1 agents, called TSAO derivatives.[6] With this in mind, we decided to apply this method to the α-mesyloxynitrile (**5**) prepared from 2-adamantanone. This reaction would lead to a new type of adamantane spiro compounds, functionalized at the bridge carbon atom with a γ-sultone moiety. Compounds with this moiety are known to have important biological activities.[7]

Reaction of 2-adamantanone (**3**) with sodium cyanide in a two phase ethyl ether/water (2:1) system in the presence of sodium bicarbonate, followed by mesylation (mesyl chloride/pyridine) of the resulting cyanohydrine (**4**) afforded the α-mesyloxynitrile **5** in 53% overall yield. Treatment of **5** under basic conditions (DBU/acetonitrile, Cs_2CO_3/acetonitrile or NaH/dimetoxyethane) gave the corresponding spiroadamantane derivative **6** (85% yield).[8] Hydrolysis of **6** with 0.1N-HCl in methanol afforded the β-keto-γ-sultone **7** in 77%

yield.[8] The hydrogen atoms of the sultone moiety in compound **7** must exhibit considerable acidity, as they are flanked by two strong electronwithdrawing groups. According to the literature data,[7] β-keto-γ-sultones can readily undergo aldol condensation and Mannich reactions. Thus, reaction of **7** with acetone in the presence of NaOAc afforded the condensation product **8**.[8]



The spiro adamantanes **6** and **7** were evaluated against human immunodeficiency virus type 1 (HIV-1), HIV-2 and several ortho- and paramyxoviruses (parainfluenza-3, influenza A, influenza B, respiratory syncytial and measles), but none of them showed significant antiviral activity at concentrations up to 200 $\mu g.mL^{-1}$.

In conclusion, we describe the synthesis of novel adamantane spiro sultones from the readily available α-mesyloxynitrile of 2-adamantanone. Among them, compound **7** represents a new example of substituted β-keto-γ-sultones that can be easily transformed by reaction at the carbonyl group or at the α-carbon atom.[7] These transformations and the biological activities of the resulting products will be the subject of further investigations.

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8. Selected data for **6**, **7** and **8**: **6**: m.p. 216-218°C (hexane:ethyl acetate); i.r. (KBr) (NH_2) 3475, 3360, (C=C-N) 1655, (SO_2) 1295, 1150 cm^{-1}; δ^1H [$(CD_3)_2SO$]: 1.50-2.43 (m, 14H, $C_{10}H_{14}$), 5.32 (s, 1H, H-3'), 6.45 (br s, 2H, NH_2); selected $\delta^{13}C$[$(CD_3)_2SO$]: 86.17 (C-3'), 93.16 (C-2), 161.46 (C-4'). **7**: m.p. 88-89°C ($CHCl_3$); i.r. (KBr) (CO) 1760, (SO_2) 1365, 1160 cm^{-1}; δ^1H ($CDCl_3$): 1.60-2.51 (m, 14H, $C_{10}H_{14}$), 3.95 (s, 2H, H-3'); selected $\delta^{13}C$($CDCl_3$): 53.34 (C-3'), 102.10 (C-2), 198.72 (C-4'). **8**: m.p. 113-115°C (hexane); i.r. (KBr) (CO) 1710, (C=C) 1610, (SO_2) 1340, 1175 cm^{-1}; δ^1H ($CDCl_3$): 1.51-2.45 (m, 14H, $C_{10}H_{14}$), 2.38, 2.41 [2s, 6H, $(CH_3)_2C$]; selected $\delta^{13}C$($CDCl_3$): 98.91 (C-2), 127.24 (C-3'), 170.17 [$C=C(CH_3)_2$], 191.79 (C-4').