SYNTHESIS OF SPIRO[3,4,5,6-TETRAHYDRO-1,4-OXAZIN-2-ONE-6,2'-TRICYCLO[3.3.1.1^{3,7}]DECANE]

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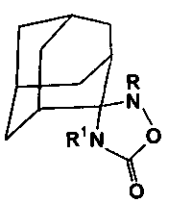
Abstract - The synthesis of spiro[3,4,5,6-tetrahydro-1,4-oxazin-2-one-6,2'-tricyclo[3.3.1.1^{3,7}]decane], a novel heterocyclic system is described.

From the vast amount of information on the synthesis of adamantane and its substituted analogs, only a relatively small part of it represents results dealing with the preparation of N-heterocyclic spiro-adamantanes. Thus, Zinner and Geister [1] reported the synthesis of a series of oxadiazolidinones (1). A number of adamantane-spiro-3'-pyrrolidine compounds (2) were found effective against influenza A, parainfluenza Sendai, coxsackie A21, and rhinovirus [2]. Derivative 3 was reported active as antimuricide (inhibition of the mouse-killing response) agent in rats [3].



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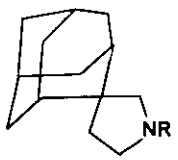

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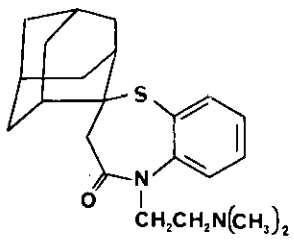

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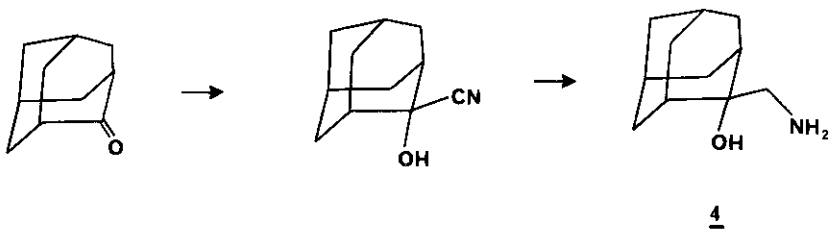
Now we wish to report the synthesis of a novel adamantane-spiro-heterocyclic system, the spiro[3,4,5,6-tetrahydro-1,4-oxazin-2-one-6,2'-tricyclo[3.3.1.1^{3,7}]decane] (compounds 6 and 7). The preparation of the latter was straightforward and involved the condensation of 2-aminomethyl-2-hydroxyadamantane (4) [4] with dimethyl acetylenedicarboxylate (5) to furnish the 3-(methoxycarbonyl)methylene-spiro[3,4,5,6-tetrahydro-1,4-oxazin-2-one-6,2'-tricyclo[3.3.1.1^{3,7}]decane] (6). Catalytic hydrogenation of compound 6 provided the corresponding 3-(methoxycarbonyl)methyl-spiro[3,4,5,6-tetrahydro-1,4-oxazin-2-one-6,2'-tricyclo[3.3.1.1^{3,7}]decane] (7) (Scheme). When tested for anti-inflammatory activity, derivative 7 at an oral dose of 50 mg/kg elicited a 27.9% ($p < 0.05$) inhibition of the carrageenin-induced rat paw edema [5].

Scheme



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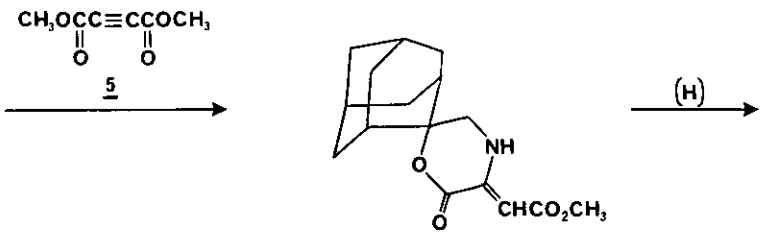

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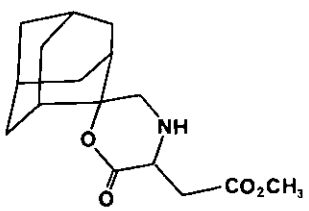

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EXPERIMENTAL

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 KBr discs. The ^{1}H nuclear magnetic resonance (NMR) spectra were taken on a Varian EM-360A (60 MHz) spectrometer using Me_4Si as an internal standard. All spectra were consistent with the assigned structures.

2-Aminomethyl-2-hydroxyadamantane (4)

To a well stirred solution of 2-adamantanone (45.0 g, 0.3 mol) in 200 ml of methanol were added 50 ml of concentrated sulfuric acid at a rate that caused the solution to reflux. Then, a saturated aqueous

solution of sodium cyanide (88.2 g, 0.6 mol) was added, and the mixture was, first, refluxed for 1 h, then stirred at room temperature for additional 3 h. Ether was added, and the organic solution was decanted from the precipitated salts. The ether solution was washed with aqueous solution of sodium chloride and water, then dried and evaporated to leave 43.0 g (81%) of 2-cyano-adamantan-2-ol as a beige crystalline solid, mp over 240°C (decomp.).

A solution of 2-cyanoadamantan-2-ol (6.0 g, 0.03 mol) in ether was added to a suspension of lithium aluminum hydride (3.9 g, 0.13 mol) in ether. The reaction mixture was refluxed for 6 h. Following workup, 4.1 g of 2-aminomethyl-2-hydroxyadamantane (4) were obtained as white crystals, mp 154-156°C (cyclohexane). Anal. Calcd for $C_{11}H_{19}NO.HCl$: C, 60.67; Cl, 16.28; H, 9.25; N, 6.43. Found: C, 60.75; Cl, 16.30; H, 9.59; N, 6.39.

3-(Methoxycarbonyl)methylene-spiro[3,4,5,6-tetrahydro-1,4-oxazin-2-one-6,2'-tricyclo[3.3.1.1^{3,7}]decane] (6)

2-Aminomethyl-2-hydroxyadamantane (4) (2.7 g, 0.015 mol) was dissolved in 40 ml of anhydrous ethanol. After stirring for several minutes at room temperature, the solution was treated dropwise with 1.84 ml (0.015 mol) of dimethyl acetylenedicarboxylate (5). The reaction mixture was stirred at room temperature for 2.5 h, then the solvent was removed in vacuo to yield 3.3 g (77%) of compound 6, mp 227-229°C (ethanol). Anal. Calcd for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.26; N, 4.81. Found: C, 65.80; H, 7.44; N, 4.85.

3-(Methoxycarbonyl)methyl-spiro[3,4,5,6-tetrahydro-1,4-oxazin-2-one-6,2'-tricyclo[3.3.1.1^{3,7}]decane] (7)

Derivative 6 (13.0 g) was dissolved in acetic acid and subjected to hydrogenation in a Parr apparatus over 2.62 g of platinum oxide. The hydrogenation was carried out at room temperature for 2.5 h at pressure that did not exceed 1 atm. After workup and recrystallization from methanol, 8.8 g of the pure 3-(methoxycarbonyl)methyl analog 7 were obtained, mp 103-107°C. Anal. Calcd for $C_{16}H_{23}NO_4$: C, 65.51; H, 7.90; N, 4.77. Found: C, 64.55; H, 7.53; N, 4.72.

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