SUBSTITUTED SPIRO[PYRROLIDINE-5,2'-TRICYCLO[3.3.1.1^{3,7}]DECANE] DERIVATIVES

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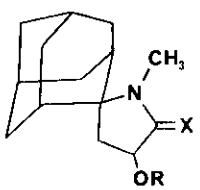
Abstract - The synthesis of a series of novel substituted spiro[pyrrolidine-5,2'-tricyclo[3.3.1.1^{3,7}]decane] derivatives 5-13 is described. When tested in the carrageenin-induced rat paw edema assay, several analogues elicited anti-inflammatory activity.

In recent years, we have been studying in some depth the synthesis and biological activity of various adamantane-spiro-heterocycles.[1-8] One efficient approach towards their preparation has been the 1,3-dipolar cycloaddition reaction of 2-adamantanone nitrone (1) with appropriate dipolarophiles.[5-7] Using this approach we accomplished the synthesis of a number of substituted spiro[isoxazolidine-3,2'-tricyclo[3.3.1.1^{3,7}]decanes] (3) starting with 1 and the substituted olefins 2 (Scheme I).[7] Now, as further extension of this study, we report the preparation and biological activity of a series of novel substituted spiro[pyrrolidine-5,2'-tricyclo[3.3.1.1^{3,7}]decanes] (5-13).

The synthesis of 5-13 (Scheme I) was straightforward and involved a catalytic hydrogenolysis[9,10] of the nitrogen-oxygen bond of the isoxazolidine ring of the adamantane-spiro-isoxazolidines 3 to furnish the corresponding aminoalcohols 4 which were not isolated but rather underwent an intramolecular cyclization to produce the substituted spiro[pyrrolidine-5,2'-tricyclo[3.3.1.1^{3,7}]decanes] 5 and 12 (Table I).

Table I. Substituted Spiro[pyrrolidine-5,2'-tricyclo[3.3.1.1^{3,7}]decane] Derivatives (5-13)



5-13

No	R	X	No	R	X
5	H	O	10	$COCH_2OC_6H_5$	O
6	$CO(CH_2)_{14}CH_3$	O	11	$COCH{=}CHC_6H_5$	O
7	$COCH_3$	O	12	H	H_2
8	$COCH_2CH_3$	O	13	$CO(CH_2)_{14}CH_3$	H_2
9	COC_6H_5	O			

Scheme I

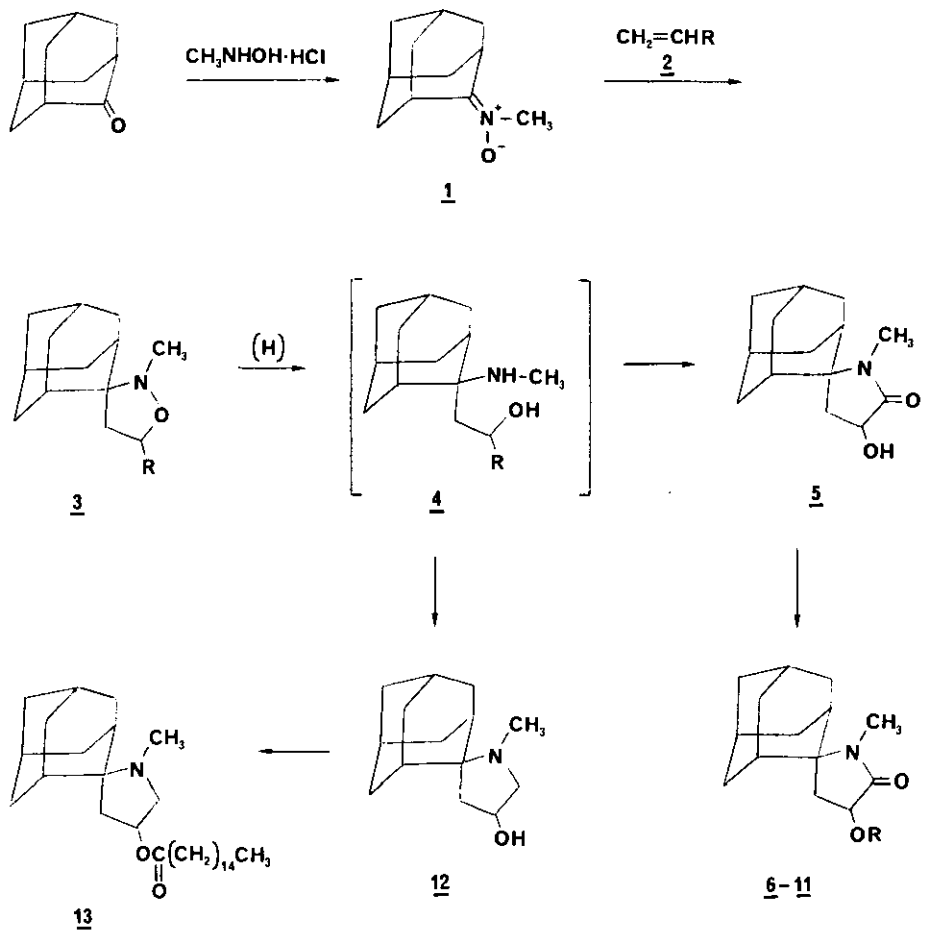


Table II. Anti-inflammatory Activity of the Substituted Spiro[pyrrolidine-5,2'-tricyclo[3.3.1.1^{3,7}]-decanes] in the Carrageenin-Induced Rat Paw Edema Assay

Compound	Dose (mg/kg, oral)	Paw Edema (mean ± S.E.)	Inhibition (%)
5	50	8.3 ± 0.2 - 13.5 ± 0.6	13.3
6	50	8.0 ± 0.3 - 13.3 ± 0.4	11.7
8	50	9.5 ± 0.2 - 14.0 ± 0.4	37.5 [a]
13	50	8.5 ± 0.2 - 13.3 ± 0.6	20.0
Indomethacin	4	9.2 ± 0.2 - 14.2 ± 0.3	30.6 [b]

[a] Statistically significant ($p<0.01$); [b] Statistically significant ($p>0.05$).

Treatment of alcohols 5 and 12 with appropriate acid chlorides provided the corresponding ester derivatives 6-11 and 13, respectively.

When tested in the carrageenin-induced rat paw edema assay, some of the title adamantane-spiro-pyrrolidine analogues showed anti-inflammatory activity (Table II). The two most active compounds of this series were the propionyl and n-hexadecanoyl esters 8 and 13, respectively, which when given orally at doses of 50 mg/kg, reduced the edema by 37.5 and 20%, respectively. Under similar conditions, indomethacin showed 30.6% inhibition of edema at a dose of 4 mg/kg (oral administration). When compared to its 2-carbonyl counterpart 6, the hydrogenated analogue 13 was the more active of the two.[11]

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The infrared spectra were obtained on a Nicolet MX-1 FT spectrophotometer as KBr discs. The proton nuclear magnetic resonance spectra were taken on a Varian EM-360A (60 MHz) spectrometer using tetramethylsilane as an internal standard. All spectra were consistent with the assigned structures. Elemental analyses were within the acceptable limits of 0.4% of theory.

2-Methyl-5-hydroxymethylspiro[isoxazolidine-3,2'-tricyclo[3.3.1.1^{3,7}]decane] (3; R = CH_2OH)

Under a nitrogen atmosphere, 36.0 g (0.24 mol) of 2-adamantanone and 20.02 g (0.240 mol) of N-methylhydroxylamine hydrochloride were dissolved in 600 ml of absolute ethanol. Sodium bicarbonate (21.1 g, 0.251 mol) was added and the resulting suspension was refluxed for 3 h. Upon cooling to ambient temperature, the solvent was removed under reduced pressure leaving a crude solid residue containing 2-adamantanone nitrone (1). The solid was suspended in 600 ml of toluene and filtered. Allyl alcohol (2; R = CH_2OH) (25 ml, 1.5 equiv) was added to the filtrate and the solution was refluxed under nitrogen atmosphere for 18 h. Upon cooling to ambient temperature, the solution was washed with water then dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure to give a yellow oil which crystallized from ether-pentane (1:1) affording 30.08 g (53%) of isoxazolidine 3. Recrystallization from pentane furnished a pure sample melting at 93-96 °C. Compound 3 was used in the next step without further purification.

2-Methyl-5-methoxycarbonylspiro[isoxazolidine-3,2'-tricyclo[3.3.1.1^{3,7}]decane] (3; R = CO_2CH_3)

Compound 3 (R = CO_2CH_3) was obtained by a procedure similar to that described in the above example by replacing allyl alcohol with methyl acrylate (2; R = CO_2CH_3). Recrystallization from methanol furnished a pure sample melting at 166-170 °C. Yield - 19%.

2-Methyl-5-(methanesulfonyloxy)methylspiro[isoxazolidine-3,2'-tricyclo[3.3.1.1^{3,7}]decane] (3; R = $CH_2OSO_2CH_3$)

Under a nitrogen atmosphere, 6.02 g (25.4 mmol) of compound 3 (R = CH_2OH) were dissolved in 75 ml of anhydrous pyridine. The solution was cooled in an ice bath, then 10.0 ml (5.0 equiv) of methanesulfonyl chloride were added dropwise over 15 min. The resulting yellow solution was stirred for 1 h at 5 °C, then for 2 h at ambient temperature. The reaction mixture was poured into water, then cautiously neutralized with solid K_2CO_3 and extracted with methylene dichloride. The organic layer was dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure. Crystallization from petroleum ether (bp 40-60 °C) gave 6.79 g (85%) of compound 3, mp 88-90 °C, which was used in the next step without further purification.

1-Methyl-3-hydroxyspiro[pyrrolidin-2-one-5,2'-tricyclo[3.3.1.1^{3,7}]decane] (5)

Compound 3 (R = CO_2CH_3) (8.16 g, 31 mmol) was dissolved in 200 ml of glacial acetic acid and hydrogenolyzed in a Parr apparatus at 2 atm over 0.8 g of 10% palladium-on-carbon catalyst. After 18 h, the suspension was suction-filtered through celite. Vacuum evaporation of the solvent yielded a yellow

oil which was taken up in water, then made alkaline (pH 10) with 2 N sodium hydroxide and extracted with chloroform. The organic layer was dried over anhydrous magnesium sulfate and evaporated under reduced pressure leaving 6.47 g (89%) of compound 5, mp 145-147 °C (ethanol). Anal. Calcd for $C_{14}H_{21}NO_2$: C, 71.46; H, 8.99; N, 5.95. Found: C, 71.73; H, 9.05; N, 5.95.

1-Methyl-3-n-hexadecanoyloxyspiro[pyrrolidin-2-one-5,2'-tricyclo[3.3.1.1^{3,7}]decane] [6; R = $CO(CH_2)_{14}CH_3$]

Under a nitrogen atmosphere, 2.1 ml (1.5 equiv) of triethylamine and 3.63 g (1.1 equiv) of palmitoyl chloride were added to a solution of 2.82 g (12 mmol) of pyrrolidinone 5 in 50 ml of anhydrous tetrahydrofuran. The mixture was stirred for 20 h at ambient temperature, then poured into ice-water and extracted with ether. The organic layer was dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure yielding an oily residue which was flash-chromatographed on neutral silica gel (Kieselgel 60, 230-400 mesh) using a 19:1 mixture of methylene dichloride and methanol as eluent. 3.64 g (64%) of ester 6 [R = $CO(CH_2)_{14}CH_3$] were obtained, mp 35.5-37.5 °C (pentane). Anal. Calcd for $C_{30}H_{51}NO_3$: C, 76.06; H, 10.85; N, 2.96. Found: C, 76.15; H, 10.94; N, 2.80.

1-Methyl-3-methylcarbonyloxyspiro[pyrrolidin-2-one-5,2'-tricyclo[3.3.1.1^{3,7}]decane] (7; R = $COCH_3$)

Compound 7 was obtained by a procedure similar to that described for 6 by using acetyl chloride in place of palmitoyl chloride. Crystallization from methanol-ether (1:19) provided an analytical sample, mp 146-149 °C. Yield - 43%. Anal. Calcd for $C_{16}H_{23}NO_3$: C, 69.29; H, 8.36; N, 5.05. Found: C, 69.33; H, 8.49; N, 5.04.

1-Methyl-3-ethoxycarbonyloxyspiro[pyrrolidin-2-one-5,2'-tricyclo[3.3.1.1^{3,7}]decane] (8; R = COC_2H_5)

Pyrrolidinone 8 was prepared by a procedure similar to that described for 6 by substituting propionyl chloride for palmitoyl chloride; mp 157-159 °C (2-propanol). Yield - 39%. Anal. Calcd for $C_{17}H_{25}NO_3$: C, 70.07; H, 8.65; N, 4.81. Found: C, 70.04; H, 8.77; N, 4.70.

1-Methyl-3-phenylcarbonyloxyspiro[pyrrolidin-2-one-5,2'-tricyclo[3.3.1.1^{3,7}]decane] (9; R = COC_6H_5)

The 3-phenylcarbonyloxy analogue 9 was obtained by a procedure similar to that described for 6 by using benzoyl chloride in place of palmitoyl chloride; mp 113-115 °C (2-propanol). Yield - 67%. Anal. Calcd for $C_{21}H_{25}NO_3$: C, 74.31; H, 7.42; N, 4.13. Found: C, 74.32; H, 7.72; N, 4.05.

1-Methyl-3-phenoxymethylcarbonyloxyspiro[pyrrolidin-2-one-5,2'-tricyclo[3.3.1.1^{3,7}]decane] (10; R = $COCH_2OC_6H_5$)

Derivative 10 was synthesized by a similar procedure as described for 6 using phenoxyacetyl chloride in place of palmitoyl chloride; mp 129-132 °C (2-propanol). Yield - 46%. Anal. Calcd for $C_{22}H_{27}NO_4$: C, 71.52; H, 7.37; N, 3.79. Found: C, 71.56; H, 7.49; N, 3.74.

1-Methyl-3-cinnamoyloxyspiro[pyrrolidin-2-one-5,2'-tricyclo[3.3.1.1^{3,7}]decane] (11; R = $COCH{=}CHC_6H_5$)

Analogue 11 was made by a procedure similar to that described for 6 by substituting cinnamoyl chloride for palmitoyl chloride; mp 117-119 °C (ethyl acetate). Yield - 55%. Anal. Calcd for $C_{23}H_{27}NO_3$: C, 75.59; H, 7.45; N, 3.83. Found: C, 75.53; H, 7.58; N, 3.83.

1-Methyl-3-hydroxyspiro[pyrrolidine-5,2'-tricyclo[3.3.1.1^{3,7}]decane] (12)

Compound 3 (R = $CH_2OSO_2CH_3$) (10.6 g, 31.7 mmol) was dissolved in 90 ml of glacial acetic acid and hydrogenated over 1.0 g of 5% palladium-on-carbon catalyst in a Parr apparatus at 40 psi. After 6 h, the suspension was filtered and the solvent was removed under reduced pressure. The residual oil was dissolved in water, then made basic with solid K_2CO_3 and extracted with methylene chloride. The organic layer was dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure. Crystallization from ligroin (bp 90-100 °C) gave 5.98 g (85%) of derivative 12, mp 90-92 °C. Anal. Calcd for $C_{14}H_{23}NO$: C, 75.97; H, 10.47; N, 6.33. Found: C, 76.02; H, 10.50; N, 6.30.

1-Methyl-3-n-hexadecanoyloxyspiro[pyrrolidine-5,2'-tricyclo[3.3.1.1^{3,7}]decane] (13)

Compound 13 was prepared by treating the pyrrolidine alcohol 12 with palmitoyl chloride as described

for 6; mp 50-53 °C (pentane). Yield - 44%. Anal. Calcd for $C_{30}H_{53}NO_2$: C, 78.37; H, 11.62; N, 3.05. Found: C, 78.50; H, 11.56; N, 2.78.

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