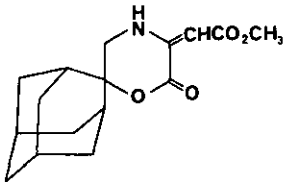
SYNTHESIS OF SUBSTITUTED SPIRO[AZETIDIN-2-ONE-4,2'(OR 3,2')-TRICYCLO[3.3.1.1^{3,7}]DECANE] DERIVATIVES

George B. Mullen and Vassil St. Georgiev*

Department of Organic Chemistry, Pennwalt Corporation,
Pharmaceutical Division, Rochester, New York 14623, U.S.A.

Abstract - The synthesis of two novel adamantane-spiro-azetidin-2-one systems, the spiro[azetidin-2-one-4,2'(or 3,2')-tricyclo[3.3.1.1^{3,7}]decanes] (7-10 and 15, respectively), is described.

Recently [1,2], we have described the preparation 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] (1 and 2). When tested for anti-inflammatory activity, derivative 2, at an oral dose of 50 mg/kg, elicited a 27.9% ($p < 0.05$) inhibition of the carrageenin-induced rat paw edema [2].



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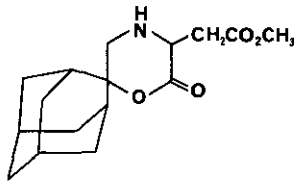

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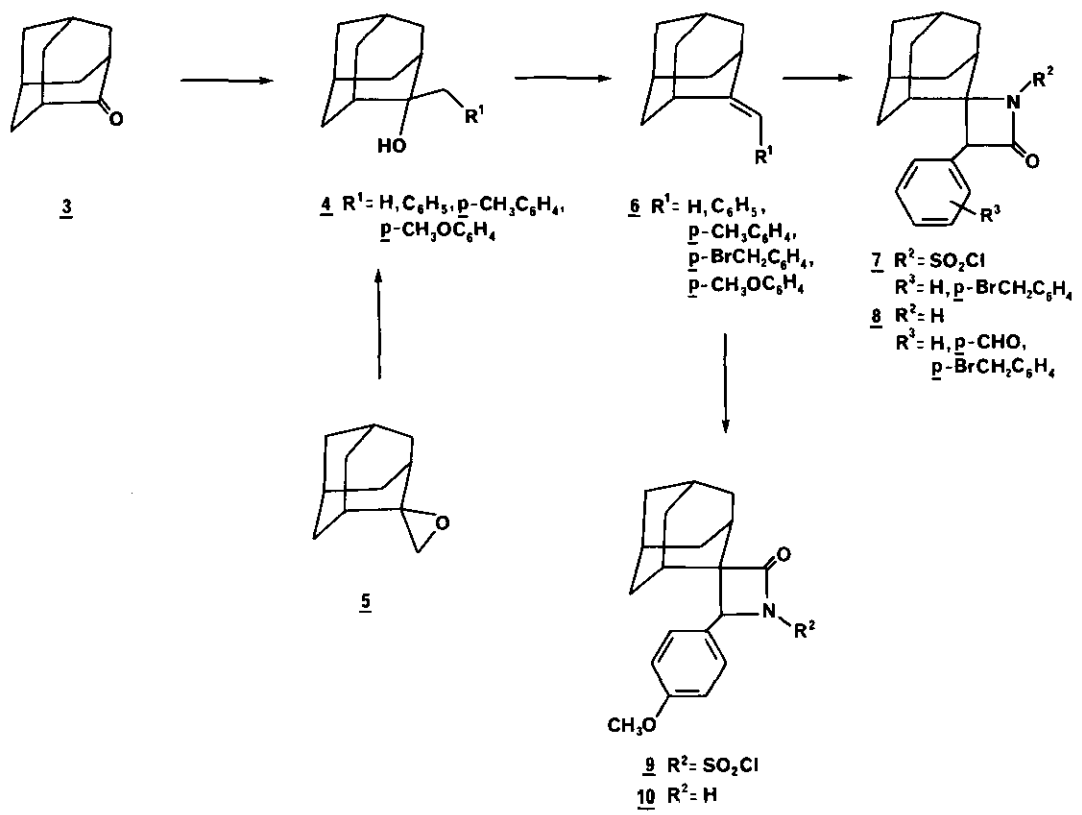
In this communication we wish to report the synthesis of a number of novel adamantane-spiro-β-lactam derivatives, the spiro[azetidin-2-one-4,2'(or 3,2')-tricyclo[3.3.1.1^{3,7}]decanes] 7-10 and 15. Thus, Grignard reaction of 2-adamantanone (3) with benzylmagnesium halide provided the corresponding 2-benzyl-tricyclo[3.3.1.1^{3,7}]decan-2-ol (4; $R^1 = C_6H_5$). Alternatively, a similar treatment of spiro[oxirane-2,2'-tricyclo[3.3.1.1^{3,7}]decane] (5) with p-methoxyphenylmagnesium bromide yielded the 2-(p-methoxyphenyl)-methyltricyclo[3.3.1.1^{3,7}]decan-2-ol (4; $R^1 = p\text{-}CH_3OC_6H_4$). Dehydration of compounds 4 led to the preparation of the corresponding methylene analogs 6. Cycloaddition reaction of compound 6 ($R^1 = C_6H_5$, $p\text{-}BrCH_2C_6H_4$) with chlorosulfonyl isocyanate [3-5,8] provided in a regiospecific manner the N-chlorosulfonyl-adamantane-spiro-azetidin-2-one compound 7. Conversely, the condensation of 2-(p-methoxyphenyl)-methylene-tricyclo[3.3.1.1^{3,7}]decane (6; $R^1 = p\text{-}CH_3OC_6H_4$) with chlorosulfonyl isocyanate gave rise to the 1-chlorosulfonyl-4-(p-methoxyphenyl)-spiro[azetidin-2-one-3,2'-tricyclo-[3.3.1.1^{3,7}]decane] (9). Reductive dechlorosulfonylation of derivatives 7 and 9 furnished the β-lactam analogs 8 and 10, respectively (Scheme I).

Scheme I

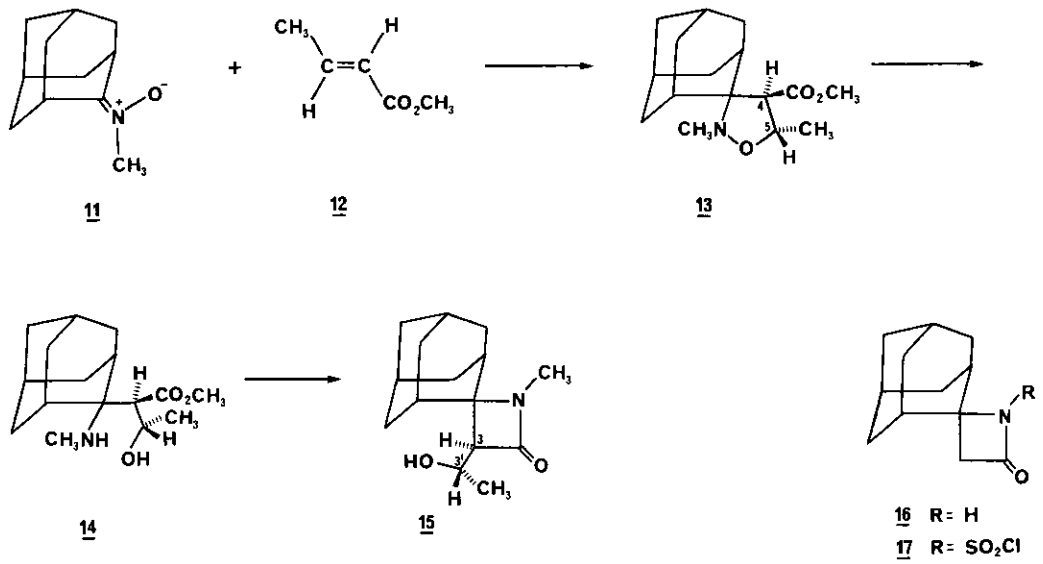


In another synthetic approach to the preparation of spiro[azetidin-2-one-4,2'-tricyclo[3.3.1.1^{3,7}]-decanes], treatment of N-methyladamantanyl nitrone (11) with methyl crotonate (12) gave rise to the spiro[isoxazolidine-3,2'-tricyclo[3.3.1.1^{3,7}]decane] ester 13. Catalytic hydrogenation of the latter resulted in a ring opening to provide the aminoalcohol ester 14. Subsequent treatment of compound 14 with ethylmagnesium bromide furnished the 1-methyl-3-(α-hydroxyethyl)-spiro[azetidin-2-one-4,2'-tricyclo[3.3.1.1^{3,7}]decane] (15) (Scheme II).

The stereochemical relationship between the hydrogens at C-3 and C-3' of the β-lactam derivative 15 is determined by the stereochemical relationship between the hydrogens at C-4 and C-5 of the isoxazolidine precursor 13 [6]. It is well known [7] that 1,3-dipolar cycloaddition of nitrones with olefins proceeds with retention of the configuration of the latter, that is, trans-1,2-disubstituted olefins such as 12 will give trans-4,5-disubstituted isoxazolidines such as 13. Indeed, the cycloaddition of methyl crotonate (12) and nitrone 11 produced exclusively the isoxazolidine derivative 13 as evidenced by the ^{1}H-NMR spectrum. The hydrogenolysis of compound 13 and the subsequent ring closure furnished the β-lactam derivative 15; no other stereoisomer of compound 15 was detected.

The synthesis of spiro[azetidin-2-one-4,2'-tricyclo[3.3.1.1^{3,7}]decane] (16) and its N-chlorosulfonyl analog 17 was reported previously by Sasaki et al. [8]

Scheme II



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

2-(Phenylmethyl)tricyclo[3.3.1.1^{3,7}]decan-2-ol (4: R^1= C_6H_5)

Benzylmagnesium chloride was prepared by reacting benzyl chloride (37.0 ml, 0.32 mol) with magnesium turnings (8.50 g, 0.35 mol) in 125 ml of anhydrous ether (under nitrogen atmosphere). Then, a solution of 2-adamantanone (3) (24.03 g, 0.16 mol) in 250 ml of anhydrous ether was added gradually over a period of 1 h. The resulting suspension was stirred at room temperature for 18 h, and then was quenched by cautious addition of 200 ml of 2 N hydrochloric acid. The organic layer was separated, washed with water, then dried over anhydrous magnesium sulfate and the solvent evaporated under reduced pressure to leave, after crystallization from pentane, 32.47 g (84%) of derivative 4 (R^1= C_6H_5), mp 58-60°C.

The 2-methyltricyclo[3.3.1.1^{3,7}]decan-2-ol (4: R^1= H) and the 2-(p-methylphenyl)-methyltricyclo[3.3.1.1^{3,7}]decan-2-ol (4: R^1= p-$CH_3C_6H_4$) were prepared according to the preceding procedure.

The spiro-oxirane-2,2'-tricyclo[3.3.1.1^{3,7}]decane (5) was prepared by the method of Fărcaşiu [9].

2-(p-Methoxyphenyl)-methyltricyclo[3.3.1.1^{3,7}]decan-2-ol (4: R^1= p-$CH_3OC_6H_4$)

A reaction of p-methoxyphenyl bromide (14.2 ml, 0.11 mol) with magnesium turnings (2.70 g, 0.11 mol) in 80 ml of anhydrous ether (under nitrogen atmosphere) provided the corresponding p-methoxyphenylmagnesium bromide. To this, a solution of epoxide 5 (17.4 g, 0.10 mol) in 100 ml of anhydrous ether was added at 0°C over a period of 40 min. The resulting suspension was stirred at room temperature for 2 h, and then was quenched by slow addition of 150 ml of 1 N hydrochloric acid. The organic layer was dried over anhydrous magnesium sulfate and the solvent was removed under reduced pressure

yielding 27.2 g (100%) of compound 4 (R^1= p-$CH_3OC_6H_4$) as an oil which was flash-chromatographed on silica gel using hexane-ethyl acetate (3:1) as an eluent.

2-Methylenetricyclo[3.3.1.1^{3,7}]decane (6; R^1= H)

A solution of 2-methyltricyclo[3.3.1.1^{3,7}]decan-2-ol (4; R^1= H) (5.0 g, 0.03 mol) and p-toluenesulfonic acid monohydrate (0.58 g, 0.003 mol) in 60 ml of toluene was refluxed for 1 h (with separation of water), then cooled to ambient temperature and washed sequentially with water and saturated aqueous sodium chloride. The solvent was evaporated under reduced pressure leaving 2.90 g (65%) of derivative 6 (R^1= H) [10], mp 72-75°C (methanol).

2-(Phenyl)-methylenetricyclo[3.3.1.1^{3,7}]decane (6; R^1= C_6H_5)

Derivative 6 (R^1= C_6H_5) was prepared according to the procedure of Keul [11], starting with 2-benzyltricyclo[3.3.1.1^{3,7}]decan-2-ol (4; R^1= C_6H_5). Mp 28.5-30°C (methanol) (lit. [11] mp 30°C).

2-(p-Methoxyphenyl)-methylenetricyclo[3.3.1.1^{3,7}]decane (6; R^1= p-$CH_3OC_6H_4$)

Derivative 6 (R^1= p-$CH_3OC_6H_4$) was prepared according to the procedure of Keul [11], starting with 2-(p-methoxyphenyl)-methyltricyclo[3.3.1.1^{3,7}]decan-2-ol (4; R^1= p-$CH_3OC_6H_4$). Oil.

2-(p-Methylphenyl)-methylenetricyclo[3.3.1.1^{3,7}]decane (6; R^1= p-$CH_3C_6H_4$)

Derivative 6 (R^1= p-$CH_3C_6H_4$) was prepared according to the procedure of Keul [11], starting with 2-(p-methylphenyl)-methyltricyclo[3.3.1.1^{3,7}]decan-2-ol (4; R^1= p-$CH_3C_6H_4$). Mp 55-57°C (methanol).

2-[(p-Bromomethyl-phenyl)]-methylenetricyclo[3.3.1.1^{3,7}]decane (6; R^1= p-$BrCH_2C_6H_4$)

A solution of 1.65 g (6.9 mmol) of 2-(p-methylphenyl)-methylenetricyclo[3.3.1.1^{3,7}]decane (6; R^1= p-$CH_3C_6H_4$), 1.30 g of N-bromosuccinimide and 0.09 g of benzoyl peroxide in 20 ml of carbon tetrachloride was refluxed for 4 h, then cooled to ambient temperature and filtered. The filtrate was washed sequentially with 5% aqueous sodium bicarbonate and water, then dried over anhydrous magnesium sulfate and flash-chromatographed on silica gel using hexane-ethyl acetate (9.5:0.5) as an eluent. Derivative 6 (R^1= p-$BrCH_2C_6H_4$) (1.42 g; 65%) was obtained following recrystallization from acetone, mp 48-52°C.

1-Chlorosulfonyl-3-phenylspiro[azetidin-2-one-4,2'-tricyclo[3.3.1.1^{3,7}]decane] (7; R^3= H)

Under a nitrogen atmosphere, a solution of 2-(phenyl)-methylenetricyclo[3.3.1.1^{3,7}]decane (24.5 g, 0.109 mol) in 75 ml of ether was added dropwise over a period of 20 min to an ice-cold solution of chlorosulfonyl isocyanate (15.0 ml, 0.172 mol) in 250 ml of ether. The reaction mixture was stirred in ice-bath for 8 h and then at room temperature for 90 h. Following the addition of pentane, the resulting precipitate was filtered off. After recrystallization from ether, 21.5 g (68%) of compound 7 (R^3= H) were obtained; mp 96-101°C.

IR (KBr): 1810 cm^{-1} (C=O). ^{1}H-NMR ($CDCl_3$): δ= 0.9-2.8 (cm, 14H, 5 x ring CH_2 and 4 x ring CH), 4.32 (s, 1H, C^3-H), 7.37 (m, 5H, aromatic).

1-Chlorosulfonyl-3-(p-bromomethylphenyl)spiro[azetidin-2-one-4,2'-tricyclo[3.3.1.1^{3,7}]decane] (7; R^3= p-$BrCH_2$)

Derivative 7 (R^3= p-$BrCH_2$) was prepared according to the preceding procedure, starting from 2-[(p-bromomethylphenyl)]-methylenetricyclo[3.3.1.1^{3,7}]decane (6; R^1= p-$BrCH_2$) and chlorosulfonyl isocyanate. Mp. 85-93°C (decomp.) (ether-pentane, 1:1).

^{1}H-NMR ($CDCl_3$): δ= 0.9-2.90 (cm, 14H, 5 x ring CH_2 and 4 x ring CH), 4.29 (s, 1H, C^3-H), 4.45 (s, 2H, CH_2Br), 7.33 (m, 4H, aromatic).

1-Chlorosulfonyl-4-p-methoxyphenyl-spiro[azetidin-2-one-3,2'-tricyclo[3.3.1.1^{3,7}]decane] (9)

Derivative 9 was prepared according to the procedure described for the synthesis of compound 7 (R^3= H), starting from 2-(p-methoxyphenyl)-methylenetricyclo[3.3.1.1^{3,7}]decane (6; R^1= p-$CH_3OC_6H_4$) and chlorosulfonyl isocyanate. Mp 128-134°C (decomp.) (ether-pentane, 1:1).

IR (KBr): 1798 cm^{-1} (C=O). ^{1}H-NMR ($CDCl_3$): δ= 0.9-2.7 (cm, 14H, 5 x ring CH_2 and 4 x ring CH), 3.80

(s, 3H, CH_3O), 4.91 (s, 1H, C^4-H), 7.13 (m, 4H, aromatic).

3-Phenylspiro[azetidin-2-one-4,2'-tricyclo[3.3.1.1^{3,7}]decane] (8; R^3= H)

A 20% aqueous solution of sodium sulfite (700 ml) was added dropwise over a period of 45 min to a solution of 7 (R^3= H) (16.95 g) in 250 ml of tetrahydrofuran. During the addition the pH of the reaction mixture was maintained at 7-8 by the dropwise addition of 200 ml of 10% aqueous potassium hydroxide. The reaction mixture was stirred vigorously at ambient temperature for an additional 2 h, followed by addition of ether. The organic layer was separated, dried over anhydrous magnesium sulfate, then evaporated under reduced pressure to give 11.31 g (91%) of compound 8 (R^3= H) as white granules, mp 218-221°C (ethyl acetate). Anal. Calcd for $C_{18}H_{21}NO$: C, 80.86; H, 7.92; N, 5.24. Found: C, 80.64; H, 8.18; N, 5.23.

IR (KBr): 3200 cm^{-1} (NH), 1746 cm^{-1} (C=O). ^{1}H-NMR ($CDCl_3$): δ= 0.50-3.20 (cm, 14H, 5 x ring CH_2 and 4 x ring CH), 4.15 (s, 1H, C^3-H), 6.10-7.75 (m, 5H, aromatic), 8.05 (bs, 1H, NH).

3-(p-Bromomethyl)-phenylspiro[azetidin-2-one-4,2'-tricyclo[3.3.1.1^{3,7}]decane] (8; R^3= p-$BrCH_2$)

Derivative 8 (R^3= p-$BrCH_2$) was prepared according to the preceding procedure, starting from 1-chlorosulfonyl-3-(p-bromomethyl)-phenylspiro[azetidin-2-one-4,2'-tricyclo[3.3.1.1^{3,7}]decane] (7: R^3= $BrCH_2$). Mp 198-200°C (ethyl acetate). Anal. Calcd for $C_{19}H_{22}BrNO$: C, 63.34; H, 6.15; Br, 22.18; N, 3.89. Found: C, 63.06; H, 6.12; Br, 22.55; N, 3.53.

IR (KBr): 3220 cm^{-1} (NH), 1789 cm^{-1} (C=O). ^{1}H-NMR ($CDCl_3$): δ= 0.94-2.46 (cm, 14H, 5 x ring CH_2 and 4 x ring CH), 3.98 (s, 1H, C^3-H), 4.48 (s, 2H, CH_2Br), 7.14-7.38 (m, 4H, aromatic), 7.73 (bs, 1H, NH).

4-(p-Methoxyphenyl)-spiro[azetidin-2-one-3,2'-tricyclo[3.3.1.1^{3,7}]decane] (10)

Derivative 10 was prepared according to the procedure described for the synthesis of compound 8 (R^3= H), starting from 1-chlorosulfonyl-4-p-methoxyphenyl-spiro[azetidin-2-one-3,2'-tricyclo[3.3.1.1^{3,7}]-decane] (9). Mp 179-180°C (ethyl acetate). Anal. Calcd for $C_{19}H_{23}NO_2$: C, 76.74; H, 7.79; N, 4.71. Found: C, 76.82; H, 7.74; N, 4.55.

IR (KBr): 3190 cm^{-1} (NH), 1727 cm^{-1} (C=O). ^{1}H-NMR ($CDCl_3$): δ= 0.90 (m, 2H, 2 x ring CH), 1.10-2.33 (cm, 12H, 5 x ring CH_2 and 2 x ring CH), 3.70 (s, 3H, CH_3O), 4.30 (s, 1H, C^4-H), 6.60-7.50 (m, 4H, aromatic), 8.15 (bs, 1H, NH).

3-(4-Formylphenyl)-spiro[azetidin-2-one-4,2'-tricyclo[3.3.1.1^{3,7}]decane] (8; R^3= 4-CHO)

3-(p-Bromomethylphenyl)-spiro[azetidin-2-one-4,2'-tricyclo[3.3.1.1^{3,7}]decane] (8: R^3= p-$BrCH_2$) (4.63 g, 12.8 mmol) was added under nitrogen atmosphere to a suspension of 1.20 g of sodium bicarbonate in 55 ml of anhydrous dimethyl sulfoxide, and the reaction mixture was stirred at 120°C for 4 h. Following cooling to ambient temperature, the reaction mixture was poured into ice-water and extracted with chloroform. The organic extract was dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure, followed by flash chromatography of the oily residue on silica gel using hexane-ethyl acetate (2:1) as an eluent. Pure derivative 8 (R^3= 4-CHO) (1.16 g; 31%) was obtained. Mp 209-212°C (decomp.) (ethyl acetate). Anal. Calcd for $C_{18}H_{21}NO_2$: C, 77.28; H, 7.17; N, 4.74. Found: C, 76.84; H, 7.35; N, 4.67.

IR (KBr): 3240 cm^{-1} (NH), 1739 cm^{-1} (C=O), 1700 cm^{-1} (C=O). ^{1}H-NMR ($CDCl_3$): δ= 0.80-1.50 (m, 2H, 2 x ring CH), 1.60-2.30 (cm, 12H, 5 x ring CH_2 and 2 x ring CH), 4.07 (s, 1H, CH), 7.65 (m, 5H, aromatic and NH), 10.03 (s, 1H, CHO).

Methyl 2,5-Dimethyl-spiro[isoxazolidine-3,2'-tricyclo[3.3.1.1^{3,7}]decane]-4-carboxylate (13)

A solution of N-methyladamantanyl nitrone (11) [prepared by reacting 36.09 g (0.24 mol) of 2-adamantanone, 20.63 g (0.247 mol) of N-methylhydroxylamine hydrochloride and 20.79 g (0.247 mol) of sodium bicarbonate in 600 ml of ethanol] and methyl crotonate (12) (50 ml, 2.0 equivalents) in 600 ml of benzene was refluxed for 20 h. The dark-colored reaction mixture was cooled to room temperature and then washed sequentially with water and saturated aqueous solution of sodium chloride. After drying

over anhydrous magnesium sulfate, the solvent was removed under reduced pressure leaving 22.91 g (34%) of derivative 13, mp 123-124°C (methanol). Anal. Calcd for $C_{16}H_{25}NO_3$: C, 68.79; H, 9.02; N, 5.01. Found: C, 69.06; H, 9.23; N, 4.98.

IR (KBr): 1722 cm^{-1} (C=O). ^{1}H-NMR ($CDCl_3$): δ= 1.25 (d, 3H, J= 6 Hz, CH-C$\underline{H}_3$), 1.40-2.75 (cm, 14H, 5 x ring CH_2 and 4 x ring CH), 2.80 (s, 3H, NCH_3), 2.85 (d, 1H, J= 5 Hz, C^3-H), 3.60 (s, 3H, CO_2CH_3), 4.50 (m, 1H, C$\underline{H}$-CH_3).

Methyl α-(1-Hydroxyethyl)-2-methylamino-tricyclo[3.3.1.1^{3,7}]decane-2-acetate (14)

Compound 13 (9.99 g, 0.036 mol) in 200 ml of glacial acetic acid was hydrogenated over 1.06 g of palladium-on-carbon in a Parr apparatus at 45 psi. After 24 h the reaction mixture was filtered through celite and the solvent was removed under reduced pressure to yield 10.10 g (100%) of compound 14 as colorless oil. The corresponding hydrochloric salt of derivative 14 was crystallized from methanol and melted at 193-198°C (decomp.). Anal. Calcd for $C_{16}H_{28}ClNO_3$: C, 60.46; H, 8.88; Cl, 11.15; N, 4.41. Found: C, 60.82; H, 8.71; Cl, 11.26; N, 4.36.

IR of 14.HCl (KBr): 1725 cm^{-1} (C=O). ^{1}H-NMR ($CDCl_3$): δ= 1.15 (d, 3H, J= 6 Hz, CH-C$\underline{H}_3$), 1.40-2.40 (cm, 14H, 5 x ring CH_2 and 4 x ring CH), 2.60 (s, 3H, NCH_3), 3.00 (d, 1H, J= 10 Hz, C$\underline{H}$-CO_2CH_3), 3.64 (s, 3H, CO_2CH_3), 3.90-4.60 (bm, 3H, C$\underline{H}$-CH_3, O$\underline{H}$, N$\underline{H}$).

1-Methyl-3-(α-hydroxyethyl)-spiro[azetidin-2-one-4,2'-tricyclo[3.3.1.1^{3,7}]decane] (15)

Ethylmagnesium bromide (3 N solution in anhydrous ether) (22 ml, 4.0 equivalents) was added at -20°C and over a period of 35 min, to a solution of 4.68 g (16.6 mmol) of ester 14 in 75 ml of anhydrous tetrahydrofuran. A precipitate was formed during the addition. The reaction mixture was warmed to ambient temperature and stirred for an additional 4 h, then cooled in an ice-bath and quenched cautiously with 50 ml of saturated aqueous ammonium chloride. Following the addition of methylene chloride and water, the organic layer was washed sequentially with water and saturated aqueous sodium chloride, then dried over anhydrous magnesium sulfate and the solvent evaporated under reduced pressure to give, after recrystallization from ether-hexane, 1.36 g (33%) of compound 15, mp 131-132°C. Anal. Calcd for $C_{15}H_{23}NO_2$: C, 72.25; H, 9.30; N, 5.62. Found: C, 72.42; H, 9.49; N, 5.58.

IR (KBr): 3404 cm^{-1} (OH), 1717 cm^{-1} (C=O). ^{1}H-NMR ($CDCl_3$): δ= 1.46 (d, 3H, J= 6.5 Hz, CH-C$\underline{H}_3$), 1.58-2.41 (cm, 15H, alkyl hydrogens), 2.76 (d, 1H, J= 7.0 Hz, C^3-H), 3.10 (s, 3H, NCH_3), 4.14 (m, 1H, C$\underline{H}$-CH_3).

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