RING OPENING OF SPIRO[AZETIDIN-2-ONE-4,2'(OR 3,2')-TRICYCLO[3.3.1.1^{3,7}]DECANES]

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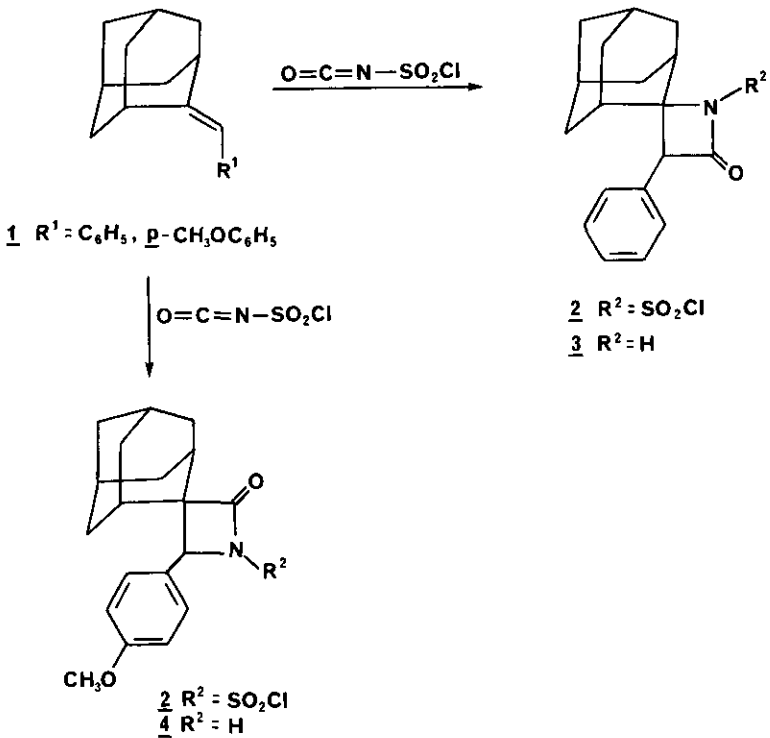
Abstract - The facile opening of the azetidin-2-one ring of the novel spiro[azetidin-2-one-4,2'(or 3,2')-tricyclo[3.3.1.1^{3,7}]decanes] 3 and 4 under acidic or alkaline conditions, is described. The reaction led to the preparation of two novel positional isomers, the heretofore difficult to obtain adamantylphenyl-β-alanines 5 and 8.

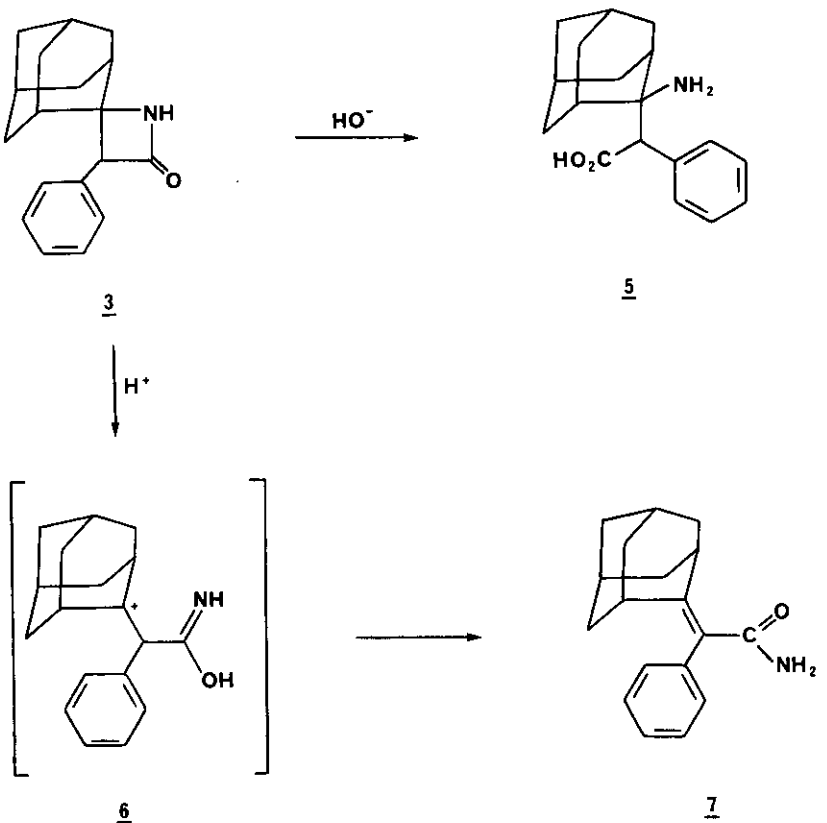
Recently, we have completed the synthesis of two novel adamantane-spiro-heterocyclic systems, the spiro[azetidin-2-one-4,2'(or 3,2')-tricyclo[3.3.1.1^{3,7}]decanes] (3 and 4) via the cycloaddition of chlorosulfonyl isocyanate to substituted 2-methylene-tricyclo[3.3.1.1^{3,7}]decanes (1), followed by a reductive dechlorosulfonylation of the resulting N-chlorosulfonyl-spiro[azetidin-2-one-4,2'(or 3,2')-tricyclo[3.3.1.1^{3,7}]decanes] 2 (Scheme 1) [1].

Scheme 1



In this communication we wish to describe some examples of a facile β-lactam ring opening of the spiro[azetidin-2-one-4,2'(or 3,2')-tricyclo[3.3.1.1^{3,7}]decanes] 3 and 4 that led to the preparation of two novel positional isomers, the heretofore difficult to obtain adamantylphenyl-β-alanines 5 and 8. Thus, treatment of 3-phenyl-spiro[azetidin-2-one-4,2'-tricyclo[3.3.1.1^{3,7}]decane] (3) with 10% aqueous potassium hydroxide resulted in a nucleophilic cleavage of the amide bond [2,3] to provide the corresponding (±)-adamantylphenyl- β-alanine analog 5. Alternatively, refluxing of compound 3 with concentrated hydrochloric acid gave rise to the α-(tricyclo[3.3.1.1^{3,7}]dec-2-ylidene)phenylacetamide derivative 7, presumably through the intermediacy of the carbonium ion 6 (Scheme 2).

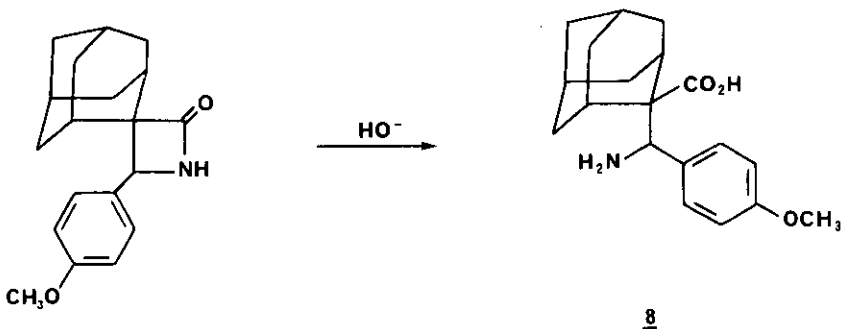
Scheme 2



3 5 6 7

As in the case with the β-lactam derivative 3, the exposure of 3-(p-methoxyphenyl)-spiro[azetidin-2-one-3,2'-tricyclo[3.3.1.1^{3,7}]decane] (4) to 10% aqueous solution of potassium hydroxide furnished the (±)-2-[amino-(p-methoxyphenyl)methyl]-tricyclo[3.3.1.1^{3,7}]decane-2-carboxylic acid (8) (Scheme 3).

Scheme 3



4 8

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 nuclear magnetic resonance (^{1}H-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.

(±)-α-(2'-Aminotricyclo[3.3.1.1^{3,7}]dec-2-yl)phenylacetic Acid (5)

A 10% aqueous solution of potassium hydroxide (30 ml) was added to a solution of 3.22 g (12 mmol) of 3-phenyl-spiro[azetidin-2-one-4,2'-tricyclo[3.3.1.1^{3,7}]decane] (3) in 30 ml of ethanol, and the resulting mixture was refluxed for 18 h. After cooling to ambient temperature, the product was precipitated with concentrated hydrochloric acid. Following a recrystallization from water, 2.85 g (83%) of compound (±)-5 were obtained; mp 169-172°C (decomp.). Anal. Calcd for $C_{18}H_{23}NO_2.H_2O$: C, 71.25; H, 8.31; N, 4.62. Found: C, 71.80; H, 8.23; N, 4.41.

IR (KBr): ν = 3700-2200 (NH_3^+); 1603 (CO_2^-); 1578 (phenyl).

^{1}H-NMR (DMSOd_6/TFA): δ = 1.10-2.80 (m, 14H, 5 x ring CH_2 and 4 x ring CH); 4.62 (s, 1H, =C-CH-C); 7.40 (s, 5H, phenyl).

α-(Tricyclo[3.3.1.1^{3,7}]dec-2-ylidene)phenylacetamide (7)

A solution of 1.88 g (7 mmol) of 3-phenyl-spiro[azetidin-2-one-4,2'-tricyclo[3.3.1.1^{3,7}]decane] (3) in 25 ml of ethanol and 25 ml of concentrated hydrochloric acid was refluxed for 4.5 h. The solvent was removed under reduced pressure leaving 1.90 g (100%) of derivative 7, mp 147-148°C (aqueous ethanol). Anal. Calcd for $C_{18}H_{21}NO$: C, 80.86; H, 7.92; N, 5.24. Found: C, 80.99; H, 8.03; N, 5.13.

IR (KBr): ν=3480, 3420 (NH_2); 1658, 1641 (C=O); 1608 (phenyl); 1379 (amide III).

^{1}H-NMR ($CDCl_3/D_2O$): δ = 1.20-2.20 (m, 12H, 5 x ring CH_2 and 2 x ring CH); 2.45, 3.45 (br s, 2H, 2 x ring CH); 5.30, 6.20 (br s, 2H, NH_2); 7.25 (br s, 5H, phenyl).

(±)-2-[Amino-(p-methoxyphenyl)methyl]-tricyclo[3.3.1.1^{3,7}]decane-2-carboxylic Acid (8)

The racemic derivative 8 was prepared according to the procedure described for the synthesis of compound 5, starting from 3-(p-methoxyphenyl)-spiro[azetidin-2-one-3,2'-tricyclo[3.3.1.1^{3,7}]decane] (4) (3.86 g, 13 mmol). Yield: 3.46 g (84%); mp 205-213°C (water) (decomp.). Anal. Calcd for $C_{19}H_{25}NO_3.HCl$: C, 61.70; H, 7.63; Cl, 9.68; N, 3.79. Found: C, 61.48; H, 7.94; Cl, 9.75; N, 3.69.

IR (KBr): ν = 3280-2200 (NH_3^+); 1721 (CO_2^-); 1585 (phenyl).
^{1}H-NMR ($CDCl_3$/TFA):δ = 1.40-2.60 (m, 14H, 5 x ring CH_2 and 4 x ring CH); 3.80 (br s, 3H, OCH_3); 5.25 (br s, 1H, H-CNH_2); 6.50-7.30 (dd, 4H, phenyl).

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