

Synthesis of 4-Azatricyclo[4.3.1.1<sup>3,5</sup>]undecane (4-Azahomoadamantane)

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Efficient routes for the synthesis of 4-azahomoadamantane (V) *via* the Beckmann and Schmidt rearrangements are described. The lactam III is unusual in that it forms a stable crystalline hydrochloride IV.

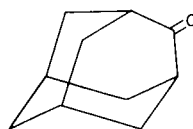
The growing interest in recent years in the syntheses of "homo" (1) and "hetero" (2) adamantanes led us to explore the synthesis of 4-azatricyclo[4.3.1.1<sup>3,5</sup>]undecane (V), a novel heterocyclic system, for which we suggest the trivial name "4-azahomoadamantane". Since our preliminary communication (3) regarding the synthesis of 4-azahomoadamantane *via* the Beckmann rearrangement of adamantanone oxime, two other reports on the synthesis of V, utilizing different catalysts, have appeared (4).

The recent reports of Sasaki, *et al.*, (5) on the Schmidt reaction of adamantanone (I), describing the formation of abnormal and normal products, prompts us to report our observations and to outline the details for the synthesis of 4-azahomoadamantane. We have found that the reaction of equimolar amounts of adamantanone and sodium azide at 65-70°, with polyphosphoric acid as catalyst, leads to a normal Schmidt rearrangement to give exclusively 4-azatricyclo[4.3.1.1<sup>3,5</sup>]undecan-5-one (III) in good yields (*ca.* 70%). The rearrangement was easily monitored by observing the disappearance of the characteristic infrared absorption of the ketone at 5.8  $\mu$  and the corresponding appearance of an absorption at 6.0  $\mu$ , characteristic of the lactam. By such means, it was noted that in 0.25 hours the rearrangement occurred to the extent of 25% and was complete in less than 12 hours. The structure of III is supported by microanalysis, its molecular ion (165<sup>+</sup>), and the spectral data. The ir spectrum shows a broad band at 3.0-3.3  $\mu$  (NH), and a peak at 6.0  $\mu$  (C=O). The nmr spectrum shows broad signals at  $\tau$  2.15-2.75 (1, NH); 6.45-6.80 (1, CH adjacent to NH); 7.15-7.40 (1, CH adjacent to C=O); and a complex multiplet at 7.75-8.30 (12H). The proton at  $\tau$  2.15-2.75 can be readily exchanged for deuterium by shaking with deuterium oxide.

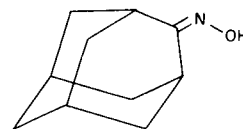
Surprisingly, the lactam III readily forms a stable crystalline hydrochloride IV which can be recrystallized and easily transformed to III by treatment with base. The structure of IV is further supported by elemental analysis and the spectral data; ir 4.0-5.0 (br, NH<sub>2</sub><sup>+</sup>); 6.04  $\mu$  (C=O); nmr  $\tau$  2.30-2.70 (br, 2, NH<sub>2</sub><sup>+</sup>), 6.10-6.45 (br, 1, CH adjacent to NH<sub>2</sub><sup>+</sup>), 7.05-7.25 (br, 1, CH adjacent to

C=O), 7.60-8.35 (m, 12H); mass spectrum *m/e* 165 (M<sup>+</sup>-HCl). An explanation for the unusual basicity of III may stem from the fact that the resonance delocalization of the electron pair on the nitrogen is restricted because of the steric requirements of a -NH=C-O<sup>-</sup> system in the tricyclic lactam.

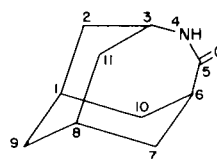
An alternate synthesis (3) for III involves the Beckmann rearrangement of adamantanone oxime (II), with polyphosphate ester as the catalyst. Reduction of III with lithium aluminum hydride in tetrahydrofuran furnishes 4-azahomoadamantane (V) in excellent yields (78%), isolated as the crystalline hydrochloride. The structure of V is supported by microanalysis and the spectral data; ir 3.30-4.10 (NH<sub>2</sub><sup>+</sup> and CH), no C=O at 6.0  $\mu$ ; nmr  $\tau$  0.60-



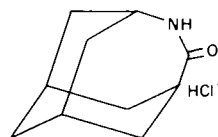
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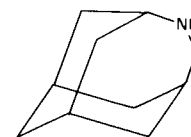
II



III



IV



V

0.80 (br, 2,  $\text{NH}_2^+$ ), 5.95-6.15 (br, 1, CH adjacent to  $\text{NH}_2^+$ ), 6.40-6.70 (br, 2,  $\text{CH}_2$  adjacent to  $\text{NH}_2^+$ ), 7.65-8.45 (m, 13H); mass spectrum  $m/e$  151 ( $\text{M}^+ - \text{HCl}$ ).

### EXPERIMENTAL

Melting points were determined on a Thomas-Hoover "Uni-Melt" apparatus and are uncorrected. Infrared spectra were determined on a Perkin-Elmer 21 Spectrometer in Nujol. Nmr spectra were obtained on a Varian A-60 Spectrometer in deuteriochloroform with TMS as the internal standard. Mass spectra were determined on an AEI MS-902 mass spectrometer.

4-Azatricyclo[4.3.1.1<sup>3,8</sup>]undecan-5-one (III) *via* the Schmidt Rearrangement.

To a well-stirred solution of 1.50 g. (10 mmoles) of adamantanone (6) (I) in 20 g. of polyphosphoric acid heated to 60-65°, 0.65 g. (10 mmoles) of sodium azide was added in portions. The reaction mixture was heated on an oil bath at 65-70° for 12 hours. The cooled mixture was poured into ice-water, made basic with 10% sodium hydroxide, and extracted with chloroform. The chloroform extracts were dried (magnesium sulfate) and evaporated to give 1.44 g. (87%) of white solid, which was crystallized from ether-hexane to give 1.19 g. (72%) of III as white crystals, m.p. 297-300°; ir 3.0-3.3 (NH), 6.0  $\mu$  (C=O); nmr  $\tau$  2.15-2.75, (br, 1, NH), 6.45-6.80 (br, 1, CH adjacent to NH), 7.15-7.40 (br, 1, CH adjacent to C=O), 7.75-8.30 (m, 12H); mass spectrum  $m/e$  165 ( $\text{M}^+$ ).

*Anal.* Calcd. for  $\text{C}_{10}\text{H}_{15}\text{NO}$ : C, 72.69; H, 9.15; N, 8.48. Found: C, 72.55; H, 9.30; N, 8.44.

The lactam hydrogen that appears at  $\tau$  2.85-3.2 is readily exchanged for deuterium by shaking with deuterium oxide.

4-Azatricyclo[4.3.1.1<sup>3,8</sup>]undecan-5-one Hydrochloride (IV).

Treatment of a solution of III in ethanol with hydrogen chloride-ether gave the stable lactam hydrochloride IV. Recrystallization from ethanol-ether yielded the analytical sample, m.p. 304-306°; ir 4.0-5.0 (br,  $\text{NH}_2^+$ ); 6.04  $\mu$  (C=O); nmr  $\tau$  2.30-2.70 (br, 2,  $\text{NH}_2^+$ ), 6.10-6.45 (br, 1, CH adjacent to  $\text{NH}_2^+$ ), 7.05-7.25 (br, 1, CH adjacent to C=O), 7.60-8.35 (m, 12H); mass spectrum  $m/e$  165 ( $\text{M}^+ - \text{HCl}$ ).

*Anal.* Calcd. for  $\text{C}_{10}\text{H}_{15}\text{NO} \cdot \text{HCl}$ : C, 59.56; H, 8.00; N, 6.95; Cl, 17.58. Found: C, 59.84; H, 8.00; N, 6.95; Cl, 17.25.

The free base liberated from the above lactam hydrochloride exhibited ir, nmr and mass spectra identical to III.

Preparation of III *via* the Beckmann Rearrangement. Adamantanone Oxime (II).

A solution of 37.5 g. (0.25 mole) of I and 35.0 g. of hydroxylamine hydrochloride in 300 ml. of 95% ethanol was treated with a solution of 20 g. of sodium hydroxide in 80 ml. of water. The reaction mixture was heated on the steam bath for 15 minutes and cooled, then the product was filtered. Crystallization from a mixture of 300 ml. of ethanol and 150 ml. of water yielded 31.1 g. (76%) of II as shiny white needles, m.p. 164-166°; ir 3.03-3.24 (OH), 6.01  $\mu$  (C=O); nmr  $\tau$  5.35 (S, 1, OH); 6.30-6.55 (1, H); 7.35-7.60 (1, H); 7.95-8.25 (S, 12H).

*Anal.* Calcd. for  $\text{C}_{10}\text{H}_{15}\text{NO}$ : C, 72.69; H, 9.15; N, 8.48. Found: C, 72.53; H, 9.10; N, 8.51.

Concentration of the mother liquor gave an additional 4.29 g. of II (total yield 86%), m.p. 162-164°.

Beckmann Rearrangement.

To a cooled solution of 2.47 g. of II (15 mmoles) in 10 ml. of chloroform, 10 g. of freshly prepared polyphosphate ester (7) (PPE) was added. The solution turned dark, with the evolution of bubbles. The reaction mixture was refluxed, with stirring, for 5-7 minutes. After cooling, water was added and the two-phase system was stirred overnight to decompose the excess PPE. The mixture was extracted with chloroform, dried (magnesium sulfate) and concentrated *in vacuo* to give 2.20 g. (81%) of III as an off-white solid. Recrystallization from ether-hexane yielded 1.60 g. (65%) of pure III, m.p. 298-300°.

*Anal.* Calcd. for  $\text{C}_{10}\text{H}_{15}\text{NO}$ : C, 72.69; H, 9.15; N, 8.48. Found: C, 72.98; H, 9.00; N, 8.43.

Ir, nmr and mass spectra of this product were identical to those of III obtained *via* the Schmidt rearrangement.

4-Azatricyclo[4.3.1.1<sup>3,8</sup>]undecane (4-Azahomoadamantane) (V).

To a well-stirred suspension of 2.4 g. of lithium aluminum hydride (LAH) in 50 ml. of dry tetrahydrofuran (THF) cooled in ice, a solution of 3.0 g. (18 mmoles) of III in 50 ml. of dry THF was added dropwise. The reaction mixture was then refluxed overnight. After cooling, the excess LAH was decomposed by the addition of water. A 10% solution of sodium hydroxide was added until the gelatinous precipitate had become granular. The precipitate was filtered and washed with THF. The combined extract was concentrated *in vacuo*. The oily aqueous layer was extracted with chloroform and dried (magnesium sulfate). The dried chloroform solution was filtered, concentrated, and treated with hydrogen chloride-ether to give a white solid, which was crystallized from ethanol-ether to give 2.1 g. (78%) of IV as white crystals, m.p. 350°; ir 3.30-4.10 ( $\text{NH}_2^+$  and CH), no C=O at 6.0  $\mu$ ; nmr  $\tau$  0.60-0.80 (br, 2,  $\text{NH}_2^+$ ), 5.95-6.15 (br, 1, CH adjacent to  $\text{NH}_2^+$ ), 6.40-6.70 (br, 2,  $\text{CH}_2$  adjacent to  $\text{NH}_2^+$ ), 7.65-8.45 (m, 13H); mass spectrum  $m/e$  151 ( $\text{M}^+ - \text{HCl}$ ).

*Anal.* Calcd. for  $\text{C}_{10}\text{H}_{17}\text{N} \cdot \text{HCl}$ : C, 63.99; H, 9.67; N, 7.47; Cl, 18.89. Found: C, 63.83; H, 9.89; N, 7.47; Cl, 18.85.

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