SYNTHESIS OF ADAMANTANE DERIVATIVES. 51.1 SYNTHESIS OF 2,4-DIAZA-BRIDGED-NORADAMANTANE, -PROTOADAMANTANE, AND -ADAMANTANE DERIVATIVES VIA INTRAMOLECULAR 1,3-DIPOLAR CYCLOADDITIONS

Tadashi Sasaki,* Shoji Eguchi, and Takanori Suzuki
Institute of Applied Organic Chemistry, Faculty of Engineering, Nagoya University, Furo-cho, Chikusa-ku, Nagoya, 464, Japan

Abstract—N-Acyl-N'-methyl-2,4-diaza-bridged noradamantane (4), -protoadamantane (7), and -adamantane derivatives (10a,b) were obtained via intramolecular 1,3-dipolar cycloadditions of the corresponding C-bicycloalkenylazomethine imines (3, 6, 9a and 9b).

The use of intramolecular 1,3-dipolar cycloadditions in organic synthesis has developed quite rapidly in recent years,2 however, while the use of nitrones has been reported extensively,3 the utilization of other 1,3-dipoles has received much less attention. With azomethine imines,4 Oppolzer showed that the intramolecular 1,3-dipolar cycloadditions of acyclic N-alkenylazomethine imines provide a simple method for synthesis of some diazabicyclic ring systems.5 We wish to describe in this paper the intramolecular 1,3-dipolar cycloadditions of C-bicycloalkenylazomethine imines (3, 6, 9a and 9b), which provided a convenient and facile route to 2,4-diaza-bridged noradamantane (4), -protoadamantane (7) and -adamantane derivatives (10a and 10b).6 C-Bicycloalkenylazomethine imines 3, 6, 9a and 9b were generated conveniently in situ simply by heating bicycloalkenylcarboxaldehydes 1, 5, and 8 with 1-methyl-2-phenylacetylhydrazine (2a)7 or 1-methyl-2-acetylhydrazine (2b)8 in the presence of a molecular sieve (type 4A, 1/16 inch beads) in xylene under reflux. The intramolecular cycloadditions of these azomethine imines proceeded smoothly under these conditions. Thus, heating of bicyclo[3.2.1]oct-6-ene-3-endo-carboxaldehyde (1)9 and 2a (1.2 fold-excess) in xylene under reflux for 11 h yielded 4-phenylacetyl-5-methyl-4,5-diazatetracyclo[5.3.1.0.0^2,6]undecane (trivial N-phenyl-
acetyl-N'-methyl-2,4-diaza-bridged noradamantane \(^6\) (4) as colorless crystals, mp 90.0-91.0°C,\(^{10}\) after chromatography (silica gel, n-hexane-ether) in 89% yield (Scheme I). The given structure 4 was supported by analysis\(^{11}\) and spectral data: IR(KBr) 3040, 2940, 2870, 2800, 1630, 1500, 1440, 1410, 1360, 1180, 1070, 1050, 1020, 720 and 680 cm\(^{-1}\); \(^1\)H NMR[(CD\(_3\)]\(_2\)SO, 130°C) \(\delta \) 7.26 (br s, 5, C\(_6\)H\(_5\)), 4.40 (d, d, 1, \(J_{3,2}=7.5\) Hz, \(J_{3,9}=4.5\) Hz, C\(_3\)H), 3.78 (ABq, 2, \(J=15.0\)Hz, \(\Delta\delta/J=1.200\), COCH\(_2\)), 3.50-2.85 (m, 2, C\(_2\)H and C\(_6\)H) and 2.59 (s, 3, N-CH\(_3\)) and 2.6-1.2 (m, 9, other protons) mass spectrum m/z (rel intensity) 282 (19.5, M\(^+\)), 164 (56.1), 163 (100), 91 (31.7) and 83 (29.3). \(^1\)H NMR spectrum of 4 at 25°C in CDCl\(_3\) revealed two benzylic methylene signals at \(\delta \) 3.97 (ABq, \(J=15.0\)Hz, \(\Delta\delta/J=1.211\)) and 3.66 (s) as well as N-CH\(_3\) signals at \(\delta \) 2.83 (s) and 2.62 (s) both in ca.2:1 ratio. These signals coalesced to the signals at \(\delta \) 3.78 for benzylic methylene and 2.59 for N-CH\(_3\), respectively at 130°C. These phenomena may be ascribable to restricted rotations of the amide group and to slow nitrogen inversions at 25°C.\(^{12}\)

Similarly, the reaction of bicyclo[3.2.1]oct-6-ene-3-endo-acetaldehyde (5) prepared from the corresponding known alcohol\(^{13}\) with 2a in refluxing xylene for 10h gave an adduct 7, mp 75.0-76.0°C, in 56% yield after chromatography (silica gel,
n-hexane-ether). The adduct \( \mathcal{A} \) was characterized as 4-phenylacetyl-5-methyl-4,5-
diazatetracyclo[6.3.1.0.2\(^{6}\) 6.0\(^{5}\) 10]dodecane (trivial N-phenylacetyl-N'-methyl-2,4-
diaza-bridged protoadamantane)\(^6\) on the basis of analysis\(^1\) and spectral data:

IR(KBr) \( 3040, 2920, 2860, 1620, 1500, 1430, 1360, 820, 710 \) and \( 690 \) cm\(^{-1}\); \( ^1\)H NMR(CDC\(_3\), 25°C) \( \delta 7.45-7.10 \) (m, \( 5, \text{C}_6\text{H}_5 \)), \( 4.31 \) (d,d, \( 1, J_3,2 = 9.0 \text{Hz}, J_3,10 = 4.5 \text{Hz}, \text{C}_3\text{H} \)), \( 3.83 \) (ABq, \( 2, J = 14.5 \text{Hz}, \delta_{6}/J = 1.241 \)), \( 3.39 \) (t, \( 1, J_{2,3} = 9.0 \text{Hz}, J_{2,6} = 6.5 \text{Hz}, \text{C}_2\text{H} \)), \( 2.96 \) (d,d, \( 1, J_6,7x = 9.0 \text{Hz}, J_6,7n = 0 \text{Hz}, J_6,2 = 6.5 \text{Hz}, \text{C}_6\text{H} \)), \( 2.55 \) (s, \( 3, \text{N-CH}_3 \)), and \( 2.7-0.9 \) (m, 11, other protons); mass spectrum \( m/z \) (rel intensity) \( 296 \) (8.7, \( \text{M}^\text{+} \)), \( 281 \) (13.0), \( 177 \) (52.2), and \( 162 \) (100). The double 
resonance experiments supported above \( ^1\)H NMR assignments: a doublet of 
triplets at \( \delta 3.39 \) collapses to a triplet (\( J = 6.5 \text{Hz} \)) on irradiation at the \( \delta 4.31 \) signal, while this signal (d,d) becomes a broad doublet (\( J = 4.5 \text{Hz} \)) on irradiation at the \( \delta 3.39 \) signal.

The reactions of bicyclo[3.3.1]non-6-ene-3-endo-carboxaldehyde (8)\(^1\) with \( \mathcal{A} \) and \( \mathcal{B} \) in refluxing xylene under the similar conditions gave only single adduct \( \mathcal{Aa} \) (a colorless oil, 72% yield\(^1\)) and \( \mathcal{Ab} \) (mp \( 81.0-82.0 \text{°C}, 70\% \) yield), respectively. These products were characterized as 3-phenylacetyl- (\( \mathcal{Aa} \)) and 3-acetyl-4-methyl-3,4-diazatetracyclo[6.3.1.0.2\(^{6}\) 6.0\(^{5}\) 10]dodecane (\( \mathcal{Ab} \)) respectively on the basis of analytical and the following spectral data. \( \mathcal{Aa}: \) IR(neat) \( 3040, 2920, 2870, 1640, 1600, 1500, 1460, 1410, 1340, 1100, 910 \) and \( 800 \text{ cm}^{-1}; \) \( ^1\)H NMR(CDC\(_3\), 130°C) \( \delta 4.34 \) and \( 4.08 \) (both t, each \( J = 4.5 \text{Hz}, \text{C}_2\text{H} \)), \( 3.02 \) (t, \( 1, J_{5,6} = 4.5 \text{Hz}, \text{C}_5\text{H} \)), \( 2.73 \) and \( 2.65 \) (both s, each \( 1.5, \text{N-CH}_3 \)), \( 2.22 \) and \( 2.05 \) (both s, each \( 1.5, \text{COCH}_3 \))), and \( 8.1-2.1 \) (m, 12, other protons); mass spectrum \( m/z \) (rel intensity) \( 221 \) (1.7), \( 220 \) (7.8, \( \text{M}^\text{+} \)), \( 178 \) (14.6), \( 177 \) (100) and \( 43 \) (32.9). At \( 25\% \) in CDC\(_3\), \( \mathcal{Aa} \) revealed also a pair of signals assignable to \( \text{C}_2\text{H} \), benzylic methylene, and \( \text{N-CH}_3 \) at \( \delta 4.37 \) and \( 4.12 \) (both t, each \( 0.5, J = 5.0 \text{Hz} \)), \( 3.91 \) and \( 3.60 \) (ABq, \( 1.0, J = 15.3 \text{Hz}, \delta_{6}/J = 1.209 \) and \( s, 1.0 \)), \( 2.73 \) and \( 2.65 \) (both s, each \( 1.5 \)), respectively.

Catalytic reduction of \( \mathcal{Aa} \) using Adams catalyst in glacial acetic acid afforded quantitatively the corresponding cyclohexylacetyl derivative \( \mathcal{Ac} \) as a liquid:

IR(neat) \( 2920, 2860, 1640, 1450, 1410 \) and \( 800 \text{ cm}^{-1}; \) \( ^1\)H NMR(CDC\(_3\), 25°C) \( \delta 4.55 \)
and 4.12 (both \( t \), each 0.5, \( J = 5.0 \text{Hz}, \text{C}_2\text{H} \)), 3.00 (\( t \), 1, \( J = 4.5 \text{Hz}, \text{C}_2\text{H} \)), 2.73 and 2.62 (both \( s \), each 1.5, N-CH\(_3\)), 2.73 and 2.62 (both \( s \), each 1.5, N-CH\(_3\)), and 2.9-0.7 (m, 25, other protons); mass spectrum \( m/z \) (rel intensity) 303 (1.7), 302 (7.6, \( M^+ \)), 178 (21.1) and 177 (100).

As described above, the intramolecular 1,3-dipolar cycloadditions of 3, 6, 9a and 9b provided a convenient route to N-acyl-N'-methyl-2,4-diaza-bridged tricarbo-cycles (4, 7, 10a and 10b). In the intramolecular cycloadditions of 9a and 9b, the selective formation of 2,4-diaza-bridged adamantane skeleton (10a,b) is of interest from the synthetic point of view since the corresponding cycloaddition of nitrone\(^{3c}\) yielded both adamantane and protoadamantane derivatives.

REFERENCES AND FOOTNOTES


2. For recent reviews, see (a) A. Padwa, Angew. Chem., Int. Ed. Engl., 1976, 15, 123; (b) W. Oppolzer, ibid., 1977, 16, 10.


6. We used these trivial names in this paper because the corresponding parent tricyclic hydrocarbons are well known as noradamantane, protoadamantane and adamantane, respectively.


10. All melting points were measured in a sealed tube and are uncorrected.

11. All new compounds described here had CHN microanalytical properties in agreement with the assigned structures.

12. Detailed variable temperature NMR studies are in progress and the coalescence temperature and the free energy of activation were not determined yet.


Received, 18th June, 1980