SYNTHESIS OF ADAMANTANE DERIVATIVES. 51.[1] SYNTHESIS OF 2,4-DIAZA-BRIDGED-NORADAMANTANE, -PROTOADAMANTANE, AND -ADAMANTANE DERIVATIVES VIA INTRAMOLECULAR 1,3-DIPOLAR CYCLOADDITIONS

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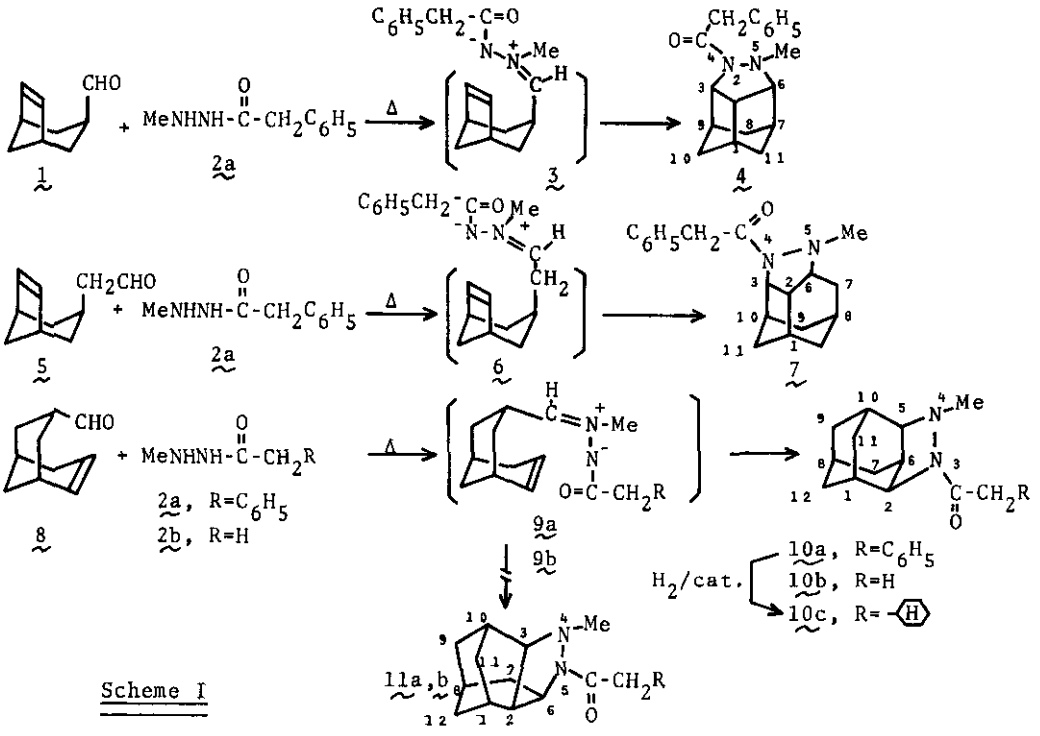
Abstract——N-Acyl-N'-methyl-2,4-diaza-bridged noradamantane (4), -protoadamantane (7), and -adamantane derivatives (10a,b) were obtained via intramolecular 1,3-dipolar cycloadditions of the corresponding C-bicycloalkenylazomethine imines (3, 6, 9a and 9b).

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 recieved 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.^{2,6}0^{3,9}]undecane (trivial N-phenyl-



Scheme I

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}; ^1H NMR[$(CD_3)_2SO$, 130°C] δ 7.26 (br s, 5, C_6H_5), 4.40 (d, d, 1, $J_{3,2}$=7.5Hz, $J_{3,9}$=4.5Hz, C_3H), 3.78 (ABq, 2, J=15.0Hz, Δδ/J =1.200, $COCH_2$), 3.50-2.85 (m, 2, C_2H and C_6H), 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). ^1H NMR spectrum of 4 at 25°C in $CDCl_3$ revealed two benzylic methylene signals at δ 3.97 (ABq, J=15.0Hz, Δδ/J =1.211) and 3.66 (s) as well as N-CH_3 signals at δ 2.83 (s) and 2.62 (s) both in ca. 2:1 ratio. These signals coalesced to the signals at δ 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 7 was characterized as 4-phenylacetyl-5-methyl-4,5-diazatetracyclo[6.3.1.0.^{2,6}0^{3,10}]dodecane (trivial N-phenylacetyl-N'-methyl-2,4-diaza-bridged protoadamantane)[6] on the basis of analysis[11] and spectral data: IR(KBr) 3040, 2920, 2860, 1620, 1500, 1430, 1360, 1030, 820, 710 and 690 cm^{-1}; ^{1}H NMR($CDCl_3$, 25°C) δ 7.45-7.10 (m, 5, C_6H_5), 4.31 (d,d, 1, $J_{3,2}$=9.0Hz, $J_{3,10}$=4.5 Hz, C_3H), 3.83 (ABq, 2, J=14.5Hz, Δδ/J =1.241, $COCH_2$), 3.39 (d,t, 1, $J_{2,3}$=9.0Hz, $J_{2,1}$=$J_{2,6}$=6.5Hz, C_2H), 2.96 (d,d, 1, $J_{6,7x}$=9.0Hz, $J_{6,7n}$=0Hz, $J_{6,2}$=6.5Hz, C_6H), 2.55 (s, 3, N-CH_3), and 2.7-0.9 (m, 11, other protons); mass spectrum m/z (rel intensity) 296 (8.7, M^+), 281 (13.0), 177 (52.2), and 162 (100). The double resonance experiments supported above NMR assignments: a doublet of triplets at δ 3.39 collapses to a triplet (J=6.5Hz) on irradiation at the δ 4.31 signal, while this signal (d,d) becomes a broad doublet (J=4.5Hz) on irradiation at the δ 3.39 signal.

The reactions of bicyclo[3.3.1]non-6-ene-3-endo-carboxaldehyde (8)[14] with 2a and 2b in refluxing xylene under the similar conditions gave only single adduct 10a (a colorless oil, 72% yield) and 10b (mp 81.0-82.0°C, 70% yield), respectively. These products were characterized as 3-phenylacetyl- (10a) and 3-acetyl-4-methyl-3,4-diazatetracyclo[6.3.1.0.^{2,6}0^{5,10}]dodecane (10b) respectively on the basis of analytical and the following spectral data. 10a: IR(neat) 3040, 2920, 2870, 1640, 1600, 1500, 1460, 1410, 720 and 690 cm^{-1}; ^{1}H NMR[$(CD_3)_2SO$, 130°C] δ 7.23 (br s, C_6H_5), 4.23 (t, 1, $J_{2,1}$=$J_{2,6}$=5.0Hz, C_2H), 3.72 (br s, 2, $COCH_2$), 3.04 (t, 1, $J_{5,6}$=$J_{5,10}$=4.5Hz, C_5H), 2.64 (s, 3, N-CH_3) and 2.7-1.1 (m, 12, other protons); mass spectrum m/z (rel intensity) 297 (2.9), 296 (11.8, M^+), 205 (1.6), 178 (15.4), 177 (100) and 91 (15.4). 10b: IR(KBr) 2920, 2860, 1620, 1410, 1340, 1100, 910 and 800 cm^{-1}; ^{1}H NMR($CDCl_3$, 25°C) δ 4.34 and 4.08 (both t, each 0.5, J=4.5Hz, C_2H), 3.02 (t, 1, J=4.5Hz, C_5H), 2.73 and 2.65 (both s, each 1.5, N-CH_3), 2.22 and 2.05 (both s, each 1.5, $COCH_3$), and 2.8-1.2 (m, 12, other protons); mass spectrum m/z (rel intensity) 221 (1.7), 220 (7.8, M^+), 178 (14.6), 177 (100) and 43 (32.9). At 25°C in $CDCl_3$, 10a revealed also a pair of signals assignable to C_2H, benzylic methylene, and N-CH_3 at δ 4.37 and 4.12 (both t, each 0.5, J=5.0Hz), 3.91 and 3.60 (ABq, 1.0, J=15.3Hz, Δδ/J =1.209 and s, 1.0), 2.73 and 2.65 (both s, each 1.5), respectively.

Catalytic reduction of 10a using Adams catalyst in glacial acetic acid afforded quantitatively the corresponding cyclohexylacetyl derivative 10c as a liquid: IR(neat) 2920, 2860, 1640, 1450, 1410 and 800 cm^{-1}; ^{1}H NMR($CDCl_3$, 25°C) δ 4.35

and 4.12 (both t, each 0.5, J=5.0Hz, C_2H), 3.00 (t, 1, J=4.5Hz, C_5H), 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 tricarbocycles (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.

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