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RESTRICTED INVERSION OF PYRAMIDAL NITROGEN IN SUBSTITUTED HYDRAZINE SYSTEM : ^{1}H NMR STUDY

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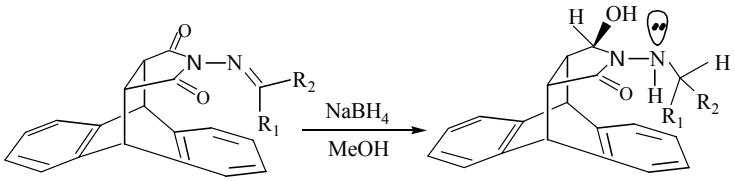
Abstract

An sp^3 non-inverting geometry of nitrogen in N-(cyclopentylamino) imide and N-(cyclohexylamino) imide stabilized by the asymmetric cage has been demonstrated through ^{1}HNMR spectroscopy. When the exocyclic nitrogen is transformed into sp^2 state a preferred conformation about N-N bond with the N'-acetyl in *anti* orientation has been observed. The anisotropic interaction of an olefinic system with the lone pair electrons of nitrogen is much weaker than an aromatic system, a small shield parameter indicates restricts inversion of pyramidal nitrogen.

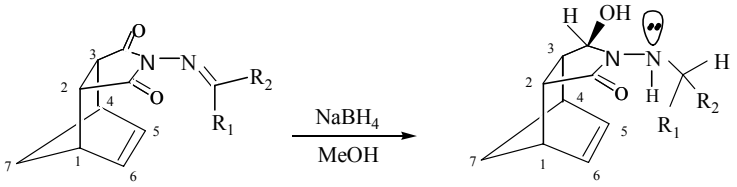
The rate of pyramidal nitrogen inversion in amines of type R_3N (1) is too fast of the order 10^{11}sec^{-1} to be measured by NMR spectroscopy[1-3]. Inversion of nitrogen atom is slow in three membered ring system and also when connected to another atom bearing an unshared pair of electrons[4-8]. Asymmetric magnetic environments provided by cage moieties of Diels-Alder adducts have been found to be very useful in conformational analysis about N-N[9-11]and N–C bonds[12,13]. Conformational analysis about the N–C (pyridyl) bond in (2) has shown that the effective size[14] of sp^2 -lone electron pair of pyridyl nitrogen is sufficient to restrict rotation about N-C bond[15]. The pyridyl ring has been proposed to be orthogonal to the succinimidyl plane with its nitrogen is in *anti* orientation to the cage. This behaviour demonstrated a strong electrostatic repulsion of the sp^2 lone electron pair of nitrogen from the cage phenyl ring.

On these considerations it was proposed to hold an sp^3-nitrogen over a phenyl ring (3) which may restrict pyramidal inversion. A pyramidal geometry of nitrogen in N-isopropylamine imide (4) was demonstrated in solution having its lone electron pair in *anti*- orientation to the cage with the help of ^{1}H NMR spectroscopy[16]. X-Ray crystallographic studies have stablished the sp^3- geometry of the exocyclic nitrogen in (4) in the solide state also. In this communication the geometry of compounds (II, IV) obtained by the reduction of compounds (I, III) with sodium borohydride on the basis of NMR spectral studies.



Ia, R_1 -C- R_2 = Cyclopentyl
Ib, R_1-C- R_2 = Cyclohexyl
Ic, R_1-C- R_2=2-Methylcyclohexyl

IIa, R_1 -C- R_2 = Cyclopentyl
IIb, R_1- C- R_2 = Cyclohexyl
IIc, R_1-C- R_2=2-Methylcyclohexyl



III, R_1-C- R_2 = Cyclopentyl

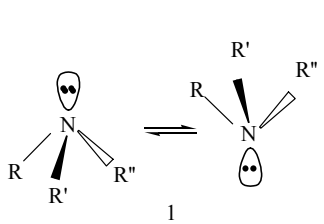
IV, R_1-C- R_2 = Cyclopentyl

Compound (IIa) was obtained by the reduction of (Ia)[17] with an excess of sodium borohydride, in methanol. It was characterized by its element analysis, IR and ^{1}H NMR spectral data. One of the carbonyls of the succinimidyl ring is reduced to –CHOH and the imine part –N=C– is transformed into –NH-CH-[18]. The 300 MHz ^{1}H NMR spectrum of the compound (IIa) exihibits multiplets at δ 0.7 (1H), 0.9 (2H), 1.3 (3H) and 1.5 (2H) for the 5', 4', 3', 2'- methylene protons, a multiplet at δ 2.4 (1H) for the methine proton along with the other resonances. The appearance of methylene resonances at shielded position suggests that the cyclopentyl moiety sits exactly over the phenyl ring which would be possible with the non-inverting geometry of the *exo* -cyclic nitrogen having the lone electron pair in *anti* orientation[16]. The spectral pattern clearly demonstrates the phenomenon of restricted pyramidal geometry of the *exo*-cyclic mitrogen resulting from a strong electronic repulsive interaction of the lone electron pair from the phenyl ring of the cage moiety (5).

Compound (IIb) was obtained from the reduction of the compound (Ib) with an excess of sodium borohydirde in methanol. The ^{1}H NMR spectrum exhibits characterstic absorption at δ 0.57 (1H), 0.75 (2H), 0.95 (3H), a doublet at 1.2 (1H) and a multiplet at 1.55 (3H) for the methylene protons of the cyclohexyl ring, a multiplet at δ2.75 (1H) for the methine proton, a singlet at δ 4.6 (1H) for the *CH*OH along with the other resonances. Considering the shielding parameters of the methylene protons it is evident that the cyclohexyl group falls in the shielding zone of the cage phenyl ring (6) which would be possible with the non-inverting pyramidal geometry of *exo*-cyclic nitrogen

having the lone pair in *anit*-orientation. A strong electronic repulsive interaction of *exo*-cyclic nitrogen lone electron pair from the phenyl ring of the cage moiety may result in the restricted pyramidal geometry of *exo*-cyclic nitrogen.

^{1}H NMR spectrum of the compound (IIc) obtained by the reduction of compound (Ic) shows a doublet at δ 0.7 (3H) for the 2'–methyl protons and multiplets at 0.5 (1H), 0.82 (2H), 0.95 (2H), 1.2 (2H), 1.45 (2H) for methylene and the methine protons of N^1-2- methyl cyclohexyl substituent, along with other resonances. The spectrum shows that one of the carbonyls of the succinimidyl ring has been reduced to –CHOH and the imine part –N=C< is reduced to –NH–CH<. The shielding parameters cyclohexyl protons suggests that it lies in the shielding zone of the cage phenyl ring. The spectral pattern is similar to (IIb) and suggests restricted pyramidal geometry of nitrogen having the lone pair in *anti* orientation (6).



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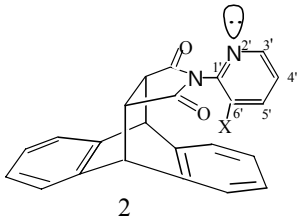

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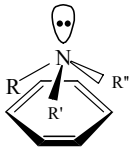

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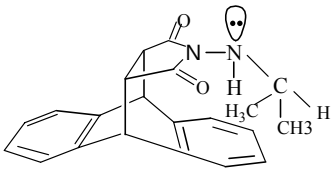

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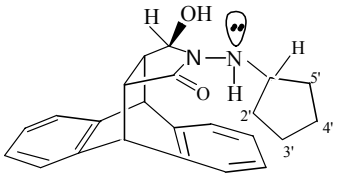

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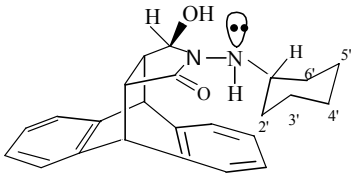
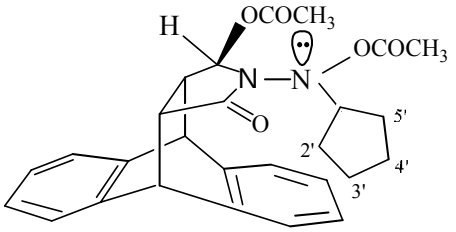


6

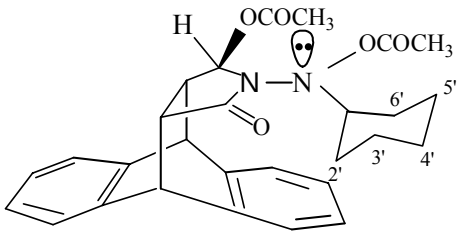
Transformation of sp^3 nitrogen into sp^2 state

The proposed pyramidal geometry of nitrogen (6) has been further supported by transformation of the *exo*-cyclic nitrogen (sp^3) into (sp^2) state by acetylation. Acetylation of compound (IIb) gave 5-acetoxy-N'-acetyl derivative (VI) where the exocyclic nitrogen is transformed into sp^2 state. The ^{1}H NMR spectrum of the compound (VI) exhibits a broad multiplet at δ 0.7-1.6 (10H) for the cyclohexyl methylene protons, two singlets at δ.190 (3H) and 2.11 (3H) for

the N'-acetyl and O-acetyl protons respectively and a multiplet at δ 3.55 (1H) for the cyclohexyl ring methine proton along with other resonances.



V



VI

The appearance of a singlet for N'-acetyl protons suggests the presence of only one conformation exhibed usual restrticted and non-planar conformation about N−N bond[9]. A preferred conformation with the N'–cyclohexyl moiety in *syn*- orientation (towards the cage) having the magnetic environment similar to that in (IIb) and N'-acetyl in *anti*-orientation (away from the cage) is exhibited. Normal O-acetyl resonances indicate that it is not influenced by the anisotropy of the cage and support the *exo*-configuration of the OH group. The *exo*-orientation of the –OH group suggests the hydride attack on the carbonyl from the *endo* side which seems to be very hard due to steric repulsion of the phenyl group. It appears that the reduction occurred from the *exo*-side and then the *endo*-hydroxy compound was isomerized to *exo*- hydroxyl compound by thermodynamic control through the ring opened intermediate.

Acetylation of compound (IIa) yielded (V). The spectrum exhibits a broad multiplet at δ 0.7-1.8 for the ring methylene protons, two singlets at δ1.95 and 2.18 for N'−acetyl and O-acetyl protons along with the other resonances. The spectral pattern is very much similar to that of (VI) and suggests the acetyl in *anti* orientation and cyclopentyl moiety in *syn* configuration.

Interaction of the Nitrogen Lone Pair with an Olefinic Bond:

π-Electronic system of an olefinic bond has been shown to have some repulsive interaction with the lone electron pair of nitrogen and a preferred conformation about N−C (pyridyl) bond has been reported[15]. With this consideration, the pyramidal nitrogen is held over an olefinic system and the stereochemistry of the compound (IV) has been investigated by ^{1}H NMR spectral studies.

Reduction of the compound (III) with excess of sodium borohydride in methanol gave a compound (IV) where one of the carbonyls of the succinimidyl ring is transformed into−CHOH and –N=C< is reduced to –NH −CH<. ^{1}H NMR of compound (IV) exhibits a broad multiplet at δ1.0 −1.7 (8H) for the 5', 4', 3',

2’ –methylene protons of the cyclopentyl moiety along with the other resonances. Methylene signals are not very much shielded by the anisotropy of the oelfinic bond and it appears that it is not a very effective system for demonstrating the geometry of the cyclopentyl amino moiety. Some shielding observed on the resonances of methylene protons suggests interaction of these protons with the cage olefinic moiety. Further it may be inferred that cyclopentyl ring in syn- orientation and nitrogen lone pair is *anti* to the cage system

EXPERIMENTAL

Melting points were determined in open capillary tubes and are uncorrected. IR spectra were recorded as neat samples on a Perkin-Elmer Spectrum 100 FT-IR spectrophotometer. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on JOEL AL 300 FT-NMR (300 MHz) spectrometer using chloroform-d as a solvent. Chemical shifts were reported in δ units, as parts per million downfield from tetramethylsilane (δ 0.0) used as an internal standard for ^{1}H NMR spectra. Analytical thin layer chromatography was performed using E. Merck silica gel G. Visualization was accomplished with UV light or iodine vapour. Elemental analysis was performed using a Vario-EL elemental analyzer.

N-(Cyclopentylamino)- α, β -*endo*-(9’,10’-dihydroanthracene-9’,10’-diyl)-5- *exo*-hydroxy- 2- pyrrolidone (IIa) : Imide (Ia**)** (1 mol) was dissolved in excess methanol, and $NaBH_4$ (3 moles) was added portionwise while the mixture was stirrerd over a period of 30 min.. After 6 hrs at 25^{0}C, the borate complex was hydrolysed with water and extracted with Et_2O. The ether extract was dried over Na_2SO_4 and concentrated to give the crystalline product in 45%: mp 160-63, IR: 3415m, 3150m, 1667m cm^{-1}, ^{1}H NMR: δ 0.7 (m, 1H), 0.9 (nm, 2H), 1.3 (m, 3H), 1.5 (m, 2H), 5’, 4’, 3’, 2’-CH_2], 2.4 (dd, 1H, α-H), 2.6 (m, 1H, N-CH), 3.0 (dd, 1H, β-H), 3.8 (d, 2H, -OH & -NH), 4.5 (d, 1H, 9-H), 4.7 (t, 2H, 10-H & -*CHOH*), 7.2-7.5 (m, 8H, ArH).

N-(Cyclohexylamino)- α, β -*endo*-(9’,10’-dihydroanthracene-9’,10’-diyl) -5- *exo*-hydroxy-2- pyrrolidone (IIb) was obtained by the reduction of hydrazone (Ib) with excess of $NaBH_4$ (3 moles) in methanol at 25^{0}C in the same way as described for (IIa) in 50%: mp197-199^{0}C IR: 3435m, 3140m, 1670m cm^{-1} ,^{1}H NMR: δ 0.5 (m, 1H), 0.7 (m, 2H), 0.95 (m, 3H), 1.25 (d, 1H), 1.50 (m, 3H) for 6’, 5’, 4’, 3’ & 2’-CH_2, 2.20 (m, 1H, N-CH<), 2.61 (dd, 1H, α-H), 3.05 (dd, 1H, β-H), 3.95 (d, 2H, -NH & -OH), 4.45 (d, 1H, 9-H), 4.63 (s, 1H, -C*H*OH), 4.67 (d, 1H, 10-H), 7.1-7.4 (m, 8H, ArH).

N-(2-Methylcyclohexylamino)- α, β -*endo*-(9',10'-dihydroanthracene-9',10'-diyl) -5- *exo*-hydroxy-2- pyrrolidone (IIc) was obtained by the reduction of hydrazone (Ic) with excess of $NaBH_4$ (3 moles) in methanol at 25^0C in the same way as described for (IIa) in 57%: mp.182-83, IR: 3442m, 3130m, 1670m cm^{-1}, ^{1}H NMR: δ0.5 -1.45 (m, 9H, 6', 5', 4', 3' –CH_2 & 2' -CH), 0.7 (d, 3H, -CH_3), 2.1 (bs, 1H, N-CH), 2.57 (dd, 1H, α-H), 3.0 (dd, 1H, β-H), 3.9 (bs, 1H, -NH), 4.35 (d, 1H, -OH), 4.44 (d, 1H, 9-H), 4.6 (dd, 2H, -CH & 10-H), 7.19-7.4 (m, 8H, ArH).

N-(Cyclopentylamino) [2.2.1] bicyclo -5-heptene- 2, 3-*endo*-5-exo-hydroxy-2- pyrrolidone (IV) was obtained by the reduction of hydrazone (III) with excess of $NaBH_4$ (3 moles) in methanol at 25^0C in the same way as described for (IIa), in 40% yield: mp.150-152^{0}C, IR: 3423m, 3160m, 1665m cm^{-1}, ^{1}H NMR: δ1.0-1.7 (bm, 8H, 5', 4', 3' & 2'-CH_2), 1.72 (ABq, 2H, 7-CH_2), 2.34 (m, 1H, 3-H), 2.88 (m, 1H, 2-H), 3.26 (m, 3H, 1, 4-H), 3 .40 (m, 1H, 1'-CH), 4.36 (bs, 2H, -NH & -OH, D_2O exchangeable), 4.65 (s, 1H, -*CH*OH), 5.8 8 (t, 2H, 5 & 6-H).

1-(N - Acetyl - N - cyclopentylamino)-α, β - *endo* - (9', 10'- dihydroanthracene-9', 10'-diyl) -5- *exo*-acetoxy-2- pyrrolidone (V) was obtained by refluxing (IIa) with an excess of acetic anhydride for about 2h. The excess of acetic anhydride was removed under reduced pressure to give a solid which was recrystallised from ethanol in 60% yield: mp.189-191^{0}C, IR: 1735s, 1670s, ^{1}H NMR: δ0.7-1.8 (m, 9H, 2', 3', 4' & 5', –CH_2), 1.95 (s, 3H, -$NCOCH_3$), 2.18 (s, 3H, -$OCOCH_3$), 2.65 (m, 1H, α-H), 3.07 (m, 1H**,** 1'-CH), 3.11 (dd, 1H, β-H), 4.71 (d, 1H, 9'-H), 4.75 (d, 1H, 10'-H), 5.69 (s, 1H, -*CHOAc*), 7.04-7.45 (m, 8H, ArH).

(N-Acetyl- N-cyclohexylamino)- α, β -*endo*-(9',10'-dihydroanthracene-9',10'-diyl) -5- *exo*-acetoxy-2- pyrrolidone (VI) was obtained by acetylation of (IIb) as described for ( )in 70% yield: mp. 210-214 ^{0}C, IR: 1735s, 1670s, ^{1}H NMR: δ 0.85-1.6 (m, 10H, 6', 5', 4', 3' & 2'-CH_2), 1.90 (s, 3H, -$NCOCH_3$), 2.11 (s, 3H, -$OCOCH_3$), 2.67 (m, 1H, α-H), 3.12 (dd, 1H, β-H), 3.55 (m, 1H**,** 1'-CH), 4.61 (d , 1H, 9'-H) , 4.93 (d , 1H, 10'-H), 5.71 (s, 1H, -*CHOAc*), 7.05-7.4 (m, 8H, ArH).

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