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ACRYLONITRILE PHOTOADDITION ON 1-BENZYL-1,4-DIHYDRONICOTINAMIDE

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Abstract – Stereospecific acrylonitrile photoaddition on enamide moiety of 1-benzyl-1,4-dihydronicotinamide I followed by catalytic hydrogenation affords 2-benzyl-7- and -8-cyano-2-azabicyclo-[4.2.0]octane-6-carboxamide IV and V. Both compounds show a trans configuration between cyano and carbamoyl groups.

As a part of our interest in the photochemistry of NADH model compounds, we previously reported that 1-benzyl-1,4-dihydronicotinamide (BNAH), when irradiated in non-oxidizing media ($\lambda \geq 365$ nm) underwent a head-to-tail-syn cycloaddition on 2,3 and 5,6 double bonds of two molecules. Further irradiation at $\lambda \leq 313$ nm of the resulting adducts affords the centrosymmetric cage dimer.[1]

In order to gain more insight into the regio- and stereochemical features involved in the photoaddition of polarized alkenes on the BNAH moieties, we irradiated compound I in presence of an excess of acrylonitrile.

Monitoring the progress of the reaction by uv spectroscopy, we observed the disappearance of the BNAH maximum (355 nm) and the lack of any significant absorption at $\lambda > 250$ nm. This fact suggested the addition of acrylonitrile on, at least, 2,3 double bond, since the N-substituted 1,4,5,6-tetrahydronicotinamides showed a strong absorption near 300 nm.[2] In the ir spectrum of the residue obtained by removing the excess of acrylonitrile, a neat band at 2235 cm^{-1} , attributable to the unconjugated CN group, was found. Signals of two non-equivalent N-benzyl groups (singlets at 4.1 and 4.2 ppm) and olefinic protons of CH_2-CH=CH-N moieties (two coupled multiplets at 4.5 and 6.3 ppm) were observed in the nmr spectrum of the residue (N_2 bubbled, $CDCl_3$). Tlc analysis (silica gel, $CHCl_3$ /MeOH 9:1 as eluent) showed the presence of two main products; however, an attempt to separate individual components on preparative scale was unsuccessful, due to their low stability on silica gel (two dimensional tlc evidenced the formation of several new products during the elution).

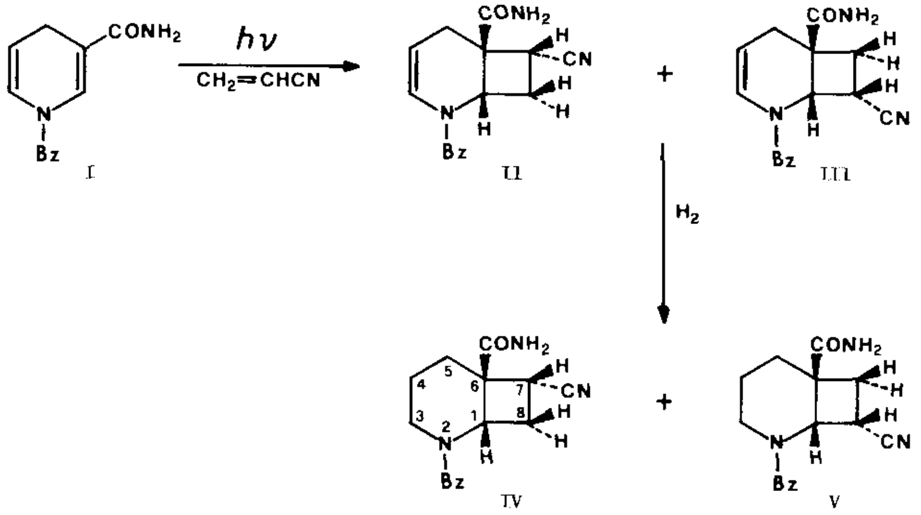
Catalytic hydrogenation of the mixture gave two isolable isomers IV and V, both evidencing in the ir spectrum bands attributable to CN and $CONH_2$ groups, and for which 2-benzyl-7- and/or 8-cyano-2-azabicyclo [4.2.0] octane-6-carboxamide structure could be reasonably proposed. Nmr data (200 MHz) (table 1) supported this hypothesis and allowed the assignment of the cyano group position. Thus, the multiplicity of angular methine protons (H_1) , confirmed by decoupling experiments,

Table 1 - 200 MHz ^1H - N.M.R. Data ($CDCl_3$) of 2-Azabicyclo [4.2.0] octanes IV and V.

	Compound IV		Compound V	
Assignment	δ ppm(multiplicity)	Coupling Constants, Hz	δ ppm(multiplicity)	Coupling Constants, Hz
$H_{8'}$	2.02(ddd)	$J_{8,8'} = 10.0$, $J_{7,8'} = 7.9$, $J_{1,8'} = 7.0^a$	---	---
H_8	2.41(q)	$J_{8,8'} = J_{7,8} = J_{1,8} = 10.0$	2.91(ddd)	$J_{1,8} = 7.7$, $J_{7,8} = 8.8$, $J_{7',8} = 3.3$
$H_{7'}$	---	---	2.14(dd)	$J_{7,7'} = 11.9$, $J_{7',8} = 3.3$
H_7	2.85(dd)	$J_{7,8} = 10.0$, $J_{7,8'} = 7.9$	2.30(dd)	$J_{7,7'} = 11.9$, $J_{7,8} = 8.8$
H_{5a}	2.02(td)	$J_{5a,5e} = J_{4a,5a} = 14.3$, $J_{4e,5a} = 4.3^a$	2.25(m)	obscured
H_{5e}	2.17(dt)	$J_{5a,5e} = 14.3$, $J_{4e,5e} = J_{4a,5e} = 3.0$		
$H_{4a,e}$	1.73(m)	unresolved	1.78(m)	unresolved
H_{3a}	2.43(td)	$J_{3e,3a} = J_{3a,4a} = 11.5$, $J_{3a,4e} = 3.6$	3.42(td)	$J_{3e,3a} = J_{3a,4a} = 11.8$, $J_{3a,4e} = 3.8$
H_{3e}	2.81(dt)	$J_{3e,3a} = 11.5$, $J_{3e,4e} = J_{3e,4a} = 3.0$	2.72(dt)	$J_{3e,3a} = 11.8$, $J_{3e,4e} = J_{3e,4a} = 3.8$
H_1	3.36(dd)	$J_{1,8} = 10.0$, $J_{1,8'} = 7.0$	3.60(d)	$J_{1,8} = 7.7$
CH_2	3.54(AB system)	$J_{A,B} = 13.1$	3.88(AB system)	$J_{A,B} = 13.3$
NH_2	6.19,5.99(br s)	---	6.38,5.90(br s)	---
C_6H_5	7.27(m)	unresolved	7.32(m)	unresolved

[a] Measured from the spectrum in pyridine-d_5

undoubtedly indicated the 7- and 8- position of the cyano group on the IV and V isomers, respectively.



Stereochemistry of the above compounds resulted from LIS experiments. In fact, different paramagnetic effects are expected, depending on the distance of different protons from $CONH_2$, as a consequence of the preferential binding of europium on this group.[3] For compound IV, the sequence of $Eu(FOD)_3$ induced shifts (table 2) ($H_7 \gg H_1 > H_8 > CH_2C_6H_5 \simeq H_{8'}$), requiring for H_7 the closest position to the amide, unequivocally demonstrated the <u>trans</u> configuration of carbamoyl and cyano groups.

Table 2 - LIS (%)[a] on cyclobutane and benzyl protons.

Compound	$C_6H_5CH_2$	H_1	H_7	$H_{7'}$	H_8	$H_{8'}$
IV	20	50	100	-	40	20
V	23	74	100	74	58	-

a) LIS (%): percent ratio between $Eu(FOD)_3$ induced shifts, relative to H_7

Further evidence followed from the values of the vicinal coupling constants between cyclobutane ring protons. As shown in table 1, the proposed configuration assigns the larger ones ($J_{1,8}$ and $J_{7,8}$) to the <u>cis</u> protons, in agreement with the values of several substituted cyclobutanes reported in the literature.[4]

In the case of compound V, the high LIS for the H_8 proton (table 2), indicated, also in this case, the <u>trans</u> configuration between the cyano and the carbamoyl groups. Further evidence supporting this structure, came from the value of $J_{1,8}$ (table 1), which better compares with the J <u>cis</u> of compound IV than with the corresponding J <u>trans</u>.

A noteworthy long range deshielding effect was observed for one of H_3 protons of compound V (table 1), attributable to CN effect. Examination of the corresponding molecular model (fig 1), suggests that a chair conformation, bringing one of H_3 protons, axially very close to CN group, in the deshielding zone, may explain the observed shift.

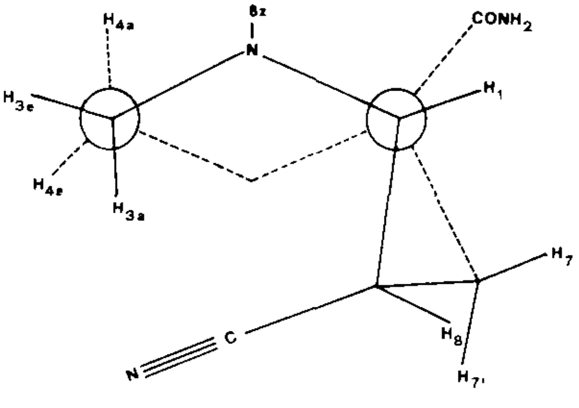


Fig. 1 : schematic drawing of the conformation of compound V.

The axial conformation for this proton was confirmed also by the high value of the vicinal coupling constant ($J_{3,4}$), according to an axial-axial interaction. Similar modellistic considerations *justify the lack of deshielding effects for the* H_3 *protons in compound IV.*

It is worth nothing some aspects in the photocycloaddition of BNAH. First of all, only the enamidic 2,3 double bond participates in the photoaddition. However, the cross-conjugated enaminic 5,6 double bond, participating to the primary photochemical events, is required for the reactivity: attempts to obtain compounds IV and V by direct irradiation of 1-benzyl-1,4,5,6-tetrahydronicotinamide, were unsuccessful. In the second place, the isomers IV and V were characterized by the trans configuration of the CN and $CONH_2$ groups. Thus, the photocycloaddition on the 2,3 double bond does not shown any significant regioselectivity, whereas the repulsive force between the CN and $CONH_2$ groups controls the stereochemistry of the photoreaction. Taking into account the good yields, this photoreaction represents a valuable route to functionalized policyclic reduced pyridines.

EXPERIMENTAL

Ir spectra were run on a Perkin-Elmer 782 grating spectrometer. Uv spectra were recorded on a Perkin-Elmer 124 instrument. Nmr spectra were recorded on Perkin-Elmer R600 (60 MHz) or Varian XL200 (200 MHz) instruments, using tetramethylsilane as internal standard. Melting points were determined on a Köfler hot stage and are uncorrected. Irradiation was carried out with a medium pressure immersion mercury lamp (125 watts), filtered and cooled by a $CuSO_4$ solution (200 g/l). N_2 was bubbled through the irradiated solution.

Photoaddition of Acrylonitrile on BNAH-

1-Benzyl-1,4-dihydronicotinamide (I) (5 g) and acrylonitrile (12.3 g) in anhydrous tetrahydrofuran (250 ml) were irradiated until the starting material disappeared (tlc). Solvent was removed *in vacuo under nitrogen and the residue was dissolved in ethyl acetate (200 ml, acids free).*

10% Pd on charcoal (1 g) was then added and the mixture shaked in a Parr apparatus under a 25 psi hydrogen pressure. Catalyst was removed by filtration and solvent evaporated to give a gummy residue which was exhaustively extracted with ether. Evaporation of the solvent afforded a white-yiellow solid (4 g, 64%) containing (tlc) two main components (IV and V) in the ratio ca. 2:3 (nmr). The mixture was dissolved in dichloromethane (30 ml) and extracted with glycine/HCl buffer solution (pH = 3.1) (2 x 15 ml). Neutralization and extaction with dichloromethane gave, on evaporation, trans-2-benzyl-7-cyano-2-azabicyclo[4.2.0]octane-6-carboxamide IV (1.1 g); ir 3420, 3330,3250,3200 (NH_2), 2230 (CN), 1670 (CO). An analytical sample of IV (as hydrochloride) melted at 200-205°C (dec); Anal. Calcd. for $C_{16}H_{19}N_3O.HCl$: C,62.84; H,6.59; N,13.74. Found: C,62.68; H,6.59; N,13.81%. Evaporation of the former dichloromethane solution gave trans-2-benzyl-8-cyano-2-azabicyclo[4.2.0]octane-6-carboxamide V (2 g), contaminated for a small amount (tlc) of the isomer IV. An analytical sample was obtained by flash chromatography on silica gel ($CHCl_3$/MeOH 95:5 as eluent) and crystallization from hexane, m.p. 70-75°C; ir 3420,3360,3200 (NH_2), 2230 (CN), 1660 (CO); Anal. Calcd. for $C_{16}H_{19}N_3O$: C,71.35; H,7.11; N,15.60. Found: C,70.54; H,6.80; N,15.74%.

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