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PHOTOCHEMISTRY OF 1-(2,6-DICHLOROBENZYL)-1,4-DIHYDRONICOTINAMIDE

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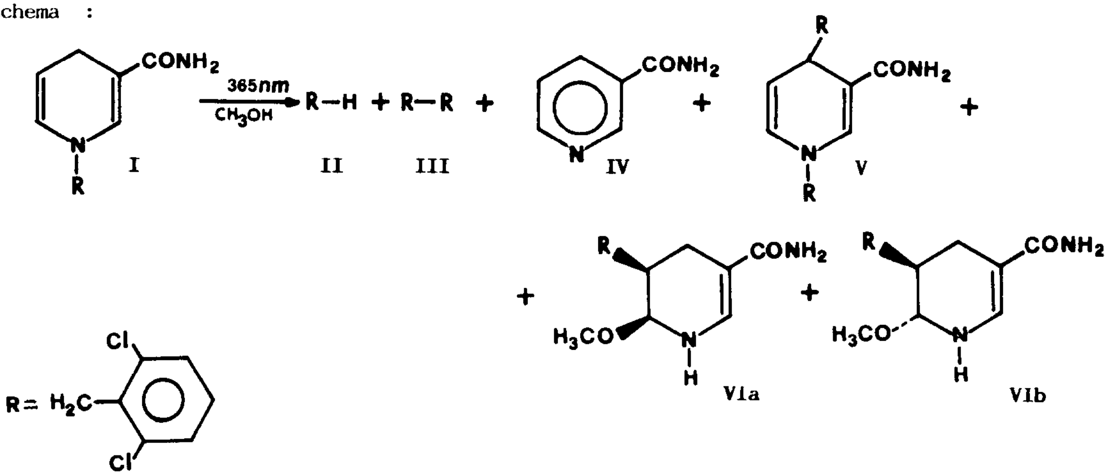
Summary: The cleavage of the N-benzyl bond characterizes the photochemical behaviour of I in methanol. Beside the coupling or the hydrogen abstraction products, the interconvertible 1,4,5,6-tetrahydropyridines VIa and VIb were obtained.

The investigation on the photochemistry of NADH and model compounds is centered around the electron-transfer processes and the reducing properties of these substances.[1] Few works are devoted to the photocycloadditions of 1,4-dihydropyridines which take place in non-oxidizing conditions, with high regio- and stereo-specificity: 1,4-dihydropyridine-3,5-dicarboxylate dimerizes giving head-to-tail-<u>syn</u> and head-to-tail-<u>anti</u> dimers,[2] 1-benzyl-1,4-dihydronicotinamide (BNAH) give head-to-tail-<u>syn</u> dimer[3] or, in the presence of acrylonitrile, photoadducts across the 2-3 double bond.[4]

We found that the photoreactivity of the title compound I[5] differs from that of the analogous BNAH. Instead of the photodimerization products, we identified the compounds reported in the schema :



The compounds II, III and IV were recognized by comparison of the spectral data of authentic samples. The structure of V (m.p. 184-186°C, from methanol) was established by elemental analysis, by the U.V. spectrum (λmax. = 265 and 337 nm, logε = 3.55 and 3.70) typical of 1,4-dihydronicotinamides, and by the coupling pattern in the ^{1}H-N.M.R. spectrum (200 MHz). An AB system centered at 3.21 ppm ($J_{A,B}$ = 13.2), attributable to the diastereotopic benzylic CH_2 in the 4-position, is coupled ($J_{A,H-4}$ = 7.3, $J_{B,H-4}$ = 6.2) with a proton at 4.63 ppm (H-4), which in turn is coupled with a proton at 4.97 ppm (J = 5.8, H-5), further on coupled with a proton at 6.24 ppm (J = 9.5, H-6). The presence of an AB system centered at 4.53 ppm ($J_{A,B}$ = 14.3) attributable to the benzylic CH_2 in the 1-position, a signal at 5.24 (2H, exch, NH_2) and a multiplet in the 7.0-7.4 region (7H, aromatic protons and H-2), confirmed the structure of V.

Compounds VIa and VIb were isolated as a single chromatographic fraction, and treatment of the mixture with $CHCl_3$ gave pure VIb (m.p. 142-145°C, from methanol). Elemental analysis and ^{1}H-N.M.R. spectrum suggested the MeOH addition and the 6-methoxy-1,4,5,6-tetrahydronicotinamide structure. However, the spectroscopic data[6] were inconclusive for the localization of the benzyl moiety and for the stereochemistry of the compound. For this reason a diffractometric analysis of VIb was undertaken[7] and the structure of <u>trans</u>-5-(2,6-dichlorobenzyl)-6-methoxy-1,4,5,6-tetrahydronicotinamide was established (fig. 1). The presence of the <u>cis</u> isomer was deduced by comparison of the N.M.R. spectra of the mixture with that of pure VIb. An ABX system centered at 3.10 ppm ($J_{A,B}$ = 13.9, $J_{A,X}$ = 6.7, $J_{B,X}$ = 5.7), a singlet at 3.36 ppm and a broad doublet at 4.22 ppm may be attributed to the benzylic CH_2, to the methoxy group and to the H-6, respectively.

Attempts to obtain pure VIa were unsuccessful, due to the easy elimination of methanol. In fact, in the N.M.R. spectra of the mixture in $CDCl_3$ we observed a decrease of the methyl signals and an increasing MeOH signal; in the N.M.R. spectrum of the pure VIb (CD_3OD) we noticed a slow exchange of the methyl signal and the increase of the peaks attributed to the VIa isomer. The deuterium exchange did not affect the H-5 proton, so that the 5-(2,6-dichlorobenzyl)-4,5-dihydronicotinamide was thought to be an intermediate in the cis/trans equilibrium. From the areas of the H-6 signals, a ratio of about 68/32 was measured between the trans/cis isomers at the equilibrium.

Unlike the known behaviour of 1,4-dihydronicotinamides, the homolytic cleavage of the N-benzyl bond characterizes the photochemical reactivity of I; the subsequent thermal reactions of the radicals obtained may explain the products reported in the scheme 1. Since no photodimerization products were found, this behaviour appears alternative in respect to photocyclization process. Comparison between BNAH and I emphasizes the role of the substituent on the nuclear nitrogen in the photochemical pathways of 1,4-dihydronicotinamides.

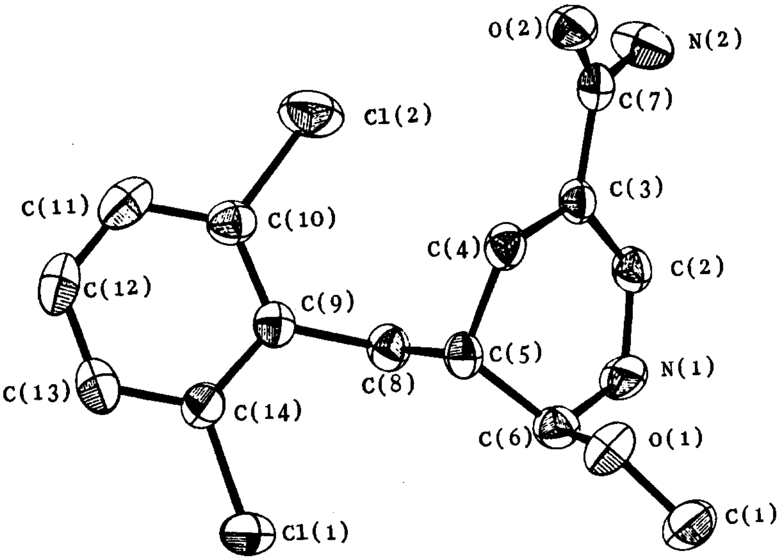


Figure 1 : ORTEP drawing of the compound VIb with 50% probability thermal ellipsoids and atom labelling system used in the crystallographic analysis.

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References and Notes

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5) Typically, 1g. of I (prepared according to C.S.Y.Kim and S.Chaykin, Biochemistry, 1968, 7, 2339) in 100 ml of anhydrous methanol, was irradiated under N_2 bubbling with a medium pressure mercury lamp, filtered by $CuSO_4$ solution (200 g/l). After ca 7 hrs, 70% of the starting material reacted; the solvent was evaporated at reduced pressure, under nitrogen. The

crude product was chromatographed on silica gel column, using $CHCl_3$ /MeOH 95/5 as eluent. Four main fractions were eluted in this order: A (150 mg), constituted by II and III, then column chromatographed on silica gel (*n*-hexane as eluent), gave II (60 mg) and III (70 mg); B (90 mg) afforded pure V by treatment with ethyl ether; C (250 mg), treated with chloroform, yielded pure VIb (80 mg); D (170 mg) was constituted by pure IV. Due to the low stability of V,VIa and VIb, a better evaluation of the yields was accomplished by integration of peaks in the N.M.R. spectrum of the crude material. The following yields, based on the reacted starting material, were obtained: II,10%; III,11%; IV,24%; V,13%; VIa,13%; VIb,29%.

6) Compound VIb: UV (MeOH) λ_{max} =275 nm (log ε =4.39) . ^1H NMR (200Mz, δ ,$CDCl_3$) 2.0-2.6 (m,3H,H-4 and H-5), 2.80 (<u>AB</u>X,2H,$J_{A,B}$ = 12.4, $J_{A,X}$ = 5.9, $J_{B,X}$ 6.8, benzylic CH_2), 3.30 (s , 3H, OCH_3), 4.18 (dd,1H,$J_{6,NH}$=4.1, $J_{6,5}$= 1.2, H-6),5.16 (exch. br. s , 3H, NH_2 and NH) , 7.05-7.32 (m, 3H, aromatic protons), 7.42 (dd, 1H, $J_{2,NH}$= 5.7, $J_{2,4}$ =1.2, H-2)

7) Crystal data: $C_{14}H_{16}N_2O_2Cl_2$, triclinic, space group $P\bar{1}$, a= 11.23(1), b=9.57(1), c=6.86(1) Å, α =102.59(3), β =87.93(3), γ =100.91(3) °, Z=2, λ=0.7107 (Mo-K_α graphite monochromated) μ (Mo-K_α)= 4.06 cm^{-1}. 2366 reflections having $I \geq 3\sigma(I)$ in the range $2\vartheta \leq 60°$, were collected on a Philips single crystals diffractometer. The structure was solved by direct methods of MULTAN80[8] and refined by full matrix least-squares techniques of SHELX76[9] program system. Final disagreement indexes R=0.041 and R_w =0.049 (weight schema w= $\sigma^{-2}(F)$), were obtained, with anisotropic thermal parameters for the non-hydrogen atoms and isotropic thermal parameters for all hydrogens.
Tables of fractional atomic coordinates, bond lenghts and bond angles have been deposited with the Cambridge Crystallographic Data Center.

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