PHOTOCHEMICAL ROUTE TO CYCLOBUT[b]ISOXAZOLO[4,5-e]PYRIDINE, A NEW HETEROCYCLIC SYSTEM

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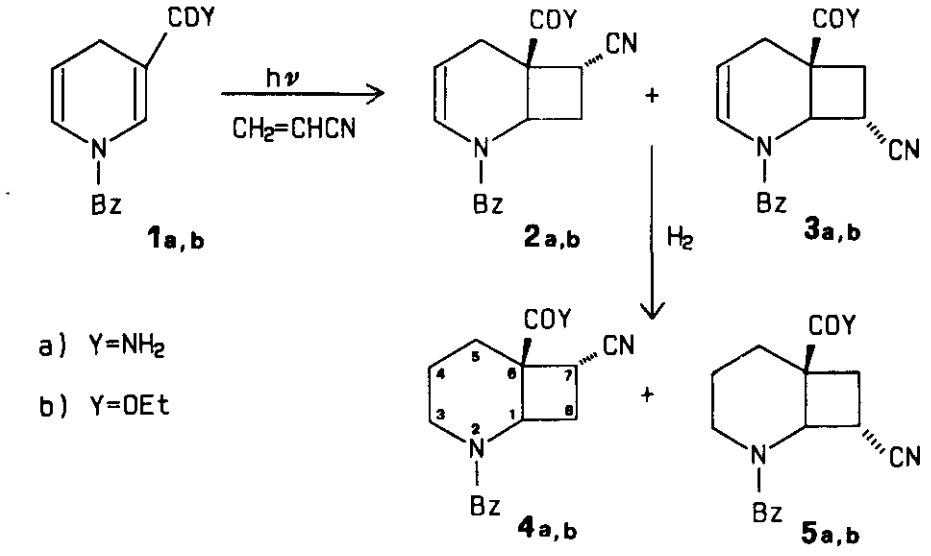
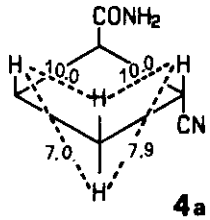
Abstract - Photochemical adducts between 3-carbamoyl- or 3-ethoxycarbonyl-1-benzyl-1,4-dihydropyridine and CH_2=CH-CN were transformed to derivatives of title compound (**6a,b** and **7a,b**) via regio- and stereospecific 1,3-dipolar addition of p-Cl-benzonitriloxide. Isomers **8** and **9** with inverted configuration at carbon bearing CN group can be obtained in EtOH/EtO^- solution.

As recently reported [1], irradiation of 1-benzyl-1,4-dihydronicotinamide **1a** in presence of acrylonitrile, give two photoadducts (**2a,3a**) deriving from 2+2 cycloaddition on the 2-3 double bond. A trans configuration between -CN and -$CONH_2$ groups was demonstrated for both compounds, after catalytic hydrogenation of the residue double bond (scheme 1). The 7-cyano-2-azabicyclo[4.2.0]octane-6-carboxamide **4a** so obtained, non-competitively inhibited the lactoperoxidase [2]. Such preliminary result, suggesting pharmacological interest for this type of compounds, prompted us to extend the above reaction to the ethyl 1-benzyl-1,4-dihydronicotinate **1b** in order to obtain more versatile intermediates.
Photochemical addition of acrylonitrile on **1b** displayed an analogous trend in respect to **1a** both from the regio- and stereochemical point of view.In fact we isolated compounds **4b** and **5b** , after hydrogenation of the crude reaction mixture.

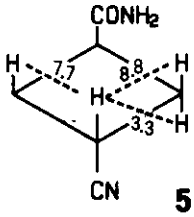


Scheme 1

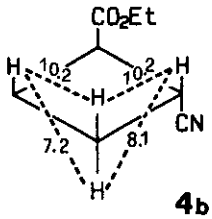
The CN group position was assigned at C_7 for compound **4b** and at C_8 for compound **5b** on the basis of the multiplicity of the H_1 signal in the ^{1}H-nmr spectrum. The trans configuration of the CN group in respect to the COOEt group followed from the comparison of the coupling constants of cyclobutane protons between carbetoxy and carbamoyl derivatives, whose structure was previously demonstrated [1]. The similarity between the coupling constants (fig. 1) exclude any different configuration.



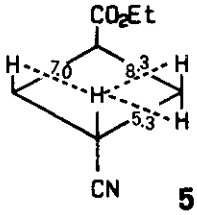
4a



5a



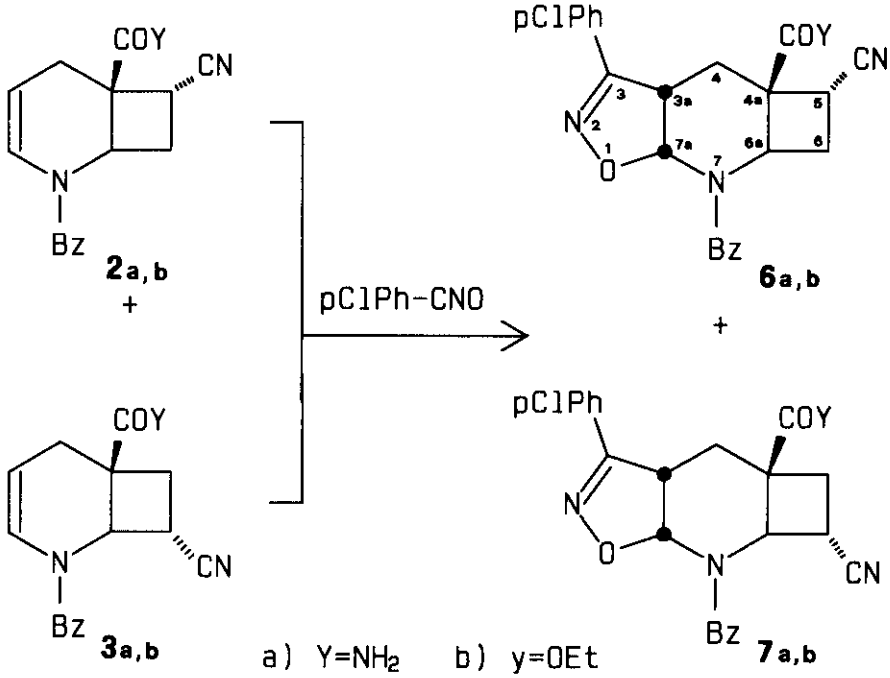
4b



5b

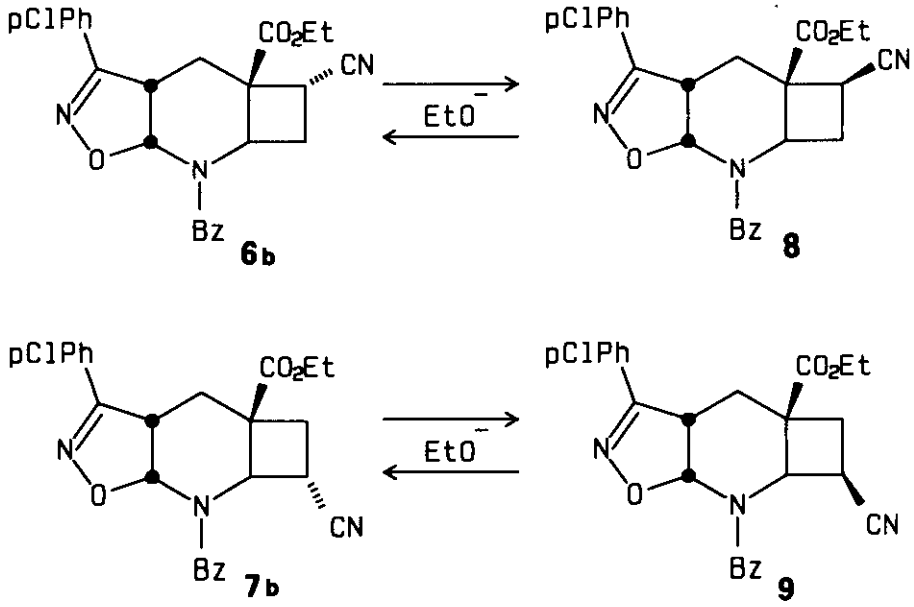
Fig 1:
Coupling constants between cyclobutane ring protons.

The presence of an enamino system renders the adducts 2a,b and 3a,b suitable intermediates towards policyclic condensed piperidines via 1,3-dipolar addition. To this purpose we investigated the 1,3 dipolar addition of p-Cl-benzonitriloxide on the photoadducts 2a,b and 3a,b.



Scheme 2

In both cases only two isomers with ciclobut[b]isoxazolo[4,5-e]pyridine structure **6a,b** and **7a,b** were obtained (scheme 2).[1]H-nmr spectra of these compounds indicate the presence of a N-CH-CH_2-CHCN (**6a,b**) or N-CH-CHCN-CH_2 skeleton (**7a,b**) as expected for the cyclobutane ring system. The regiochemistry of attack followed unequivocally from the chemical shift of the 7a' proton, whose doublet was found in the range 5.57-5.70 ppm [3]. Indications on the stereochemistry of the isoxazoline ring fusion (endo or exo in respect to the cyclobutane ring) were found analysing the H_{3a}-H_4 and H_{3a}-$H_{4'}$ coupling constants. In fact modellistic considerations strongly suggest that the hypothetical endo configuration compels H_{3a} and one of the C_4 protons (H_4 or $H_{4'}$) in axial conformation as a consequence of steric hindrance. However the values of $J_{3a,4}$ and $J_{3a,4'}$, ranging between 0.7-3.7 Hz and 5.9-6.7 Hz respectively, exclude the presence of protons in axial conformation [4]. On this basis we may assume exo configuration between cyclobutane and isoxazoline rings [5]. Compounds **6b** and **7b** , on heating in EtOH solution with catalytic amount of EtO^-, undergoes an isomerization process leading to an equilibrium mixture of compounds **6b -8** (65:35) or **7b -9** (40:60)[6] (scheme 3). The structures of **8** and **9** were demonstrated performing the reaction in EtOD. [1]H-nmr spectra of the equilibrium mixtures showed deuterium exchange in the CH-CN moiety, so indicating that the **8** and **9** isomers differ from **6b** and **7b** respectively, in the C_5 or C_6 configuration.
In this way it was possible to prepare also stereoisomers having cis configuration between CN an COOEt groups, whereas only trans configuration was directly attainable from the photoreaction.



Scheme 3

Table 1

^{1}H-Nmr data for compounds 6a,b , 7a,b , 8 and 9

	δ (multiplicity,assignment)	Coupling constants (Hz)
6a	3.78(ddd,H_{3a}); 2.38(ABX,H_4,); 2.30(ABX,H_4); 3.07(t,H_5); 2.31(ABXY,H_6); 2.06(ABXY,H_6,); 3.73(t,H_{6a}); 5.70(d,H_{7a}); 3.98.3.91(AB,NCH_2); 5.4,5.8(br,NH_2); 7.34-7.58(m,Ar)	3a,4'=6.5; 3a,4=3.7; 3a,7a=10.1; 4,4'=14.4; 5,6=5,6'=9.6; 6,6'=12.3; 6a,6=6a,6'=7.2; NCH_2=13.2
6b	3.72(ddd,H_{3a}); 2.59(ABX,H_4); 2.38(ABX,H_4,); 2.98(dd,H_5); 2.36(ABXY,H_6); 2.11(ABXY,H_6,); 3.99(t,H_{6a}); 5.62(d,H_{7a}); 3.96,3.85(AB,NCH_2); 3.96,3.57(AMX$_3$,OCH_2); 0.84(t,CH_3); 7.31-7.37,7.40-7.60(m,Ar)	3a,4=1.9; 3a,4'=6.6; 3a,7a=10.5; 4,4'=14.1; 5,6=9.0; 5,6'=9.6; 6,6'=12.2; 6a,6=6a,6'=7.1; NCH_2=13.0; OCH_2=10.7; CH_2-CH_3=7.2
7a	3.67(ddd,H_{3a}); 2.41(ABX,H_4'); 2.35(ABX,H_4); 2.48(ABX,H_5); 2.28(ABX,H_5,); 3.26(ddd,H_6); 4.06(d,H_{6a}); 5.69(d,H_{7a}); 4.03,3.97(AB,NCH_2); 5.26,5.80(br,NH_2); 7.27-7.58(m,Ar)	3a,4'=5.9; 3a,4=2.8; 3a,7a=10.3; 4,4'=12.7; 5,5'=12.6; 5,6=9.9; 5',6=3.8; 6a,6=7.7; NCH_2=12.7
7b	3.60(ddd,H_{3a}); 2.63(ABX,H_4); 2.35(ABX,H_4,); 2.42(ABX,H_5); 2.23(ABX,H_5,); 3.31(ddd,H_6); 4.31(d,H_{6a}); 5.57(d,H_{7a}); 3.99,3.92(AB;NCH_2); 3.98,3.60(AMX$_3$,OCH_2); 0.85(t,CH_3); 7.25-7.55(m,Ar)	3a,4=0.7; 3a,4'=6.7; 3a,7a=9.9; 4,4'=14.3; 5,5'=12.7; 5,6=10.0; 5',6=4.4; 6a,6=7.6; NCH_2=12.7; OCH_2=10.9; CH_2-CH_3=7.1
8	3.71(ddd,H_{3a}); 2.76(ABX,H_4); 2.04(ABX,H_4,); 3.19(ddd,H_5); 2.52(dt,H_6); 2.34(ddd,H_6,); 4.03(ddd,H_{6a}); 5.56(d,H_{7a}); 3.91,3.81(AB,NCH_2); 3.50,3.98(AMX$_3$,OCH_2); 0.97(t,CH_3); 7.34-7.60(m,Ar)	3a,4=2.0; 3a,4'=5.7; 3a,7a=10.4; 4,4'=14.0; 5,6=7.5; 5,6'=9.1; 5,6a=1.0; 6,6'=12.8; 6a,6=7.5; 6a,6'=4.1; NCH_2=13.4; OCH_2=10.7; CH_2-CH_3=7.2
9	3.60(ddd,H_{3a}); 2.58(ABX,H_4); 1.95(ABX,H_4,); 2.31(ABX,H_5); 2.27(ABX,H_5,); 2.94(td,H_6); 4.37(d,H_{6a}); 5.56(d,H_{7a}); 4.10,3.96(AB,NCH_2); 3.71,4.08(AMX$_3$,OCH_2); 0.95(t,CH_3); 7.26-7.54(m,Ar)	3a,4=0.7; 3a,4'=6.8; 3a,7a=10.4; 4,4'=14.3; 5,5'=11.5; 5,6=5',6=9.5; 6a,6=6.6; NCH_2=13.6; OCH_2=10.8; CH_2-CH_3=7.1

EXPERIMENTAL

Ir spectra were run on a Perkin-Elmer 782 grating spectrometer. ^1H (200 MHz) and ^{13}C nmr spectra were recorded on a Varian XL200 instrument, in $CDCl_3$ solution using tetramethylsilane as internal standard; chemical shifts are reported in δ (ppm) and coupling constants in Hz. ^{13}C assignments were confirmed by off-resonance and selective decoupling experiments. Melting points were determined on a Kofler hot stage and are uncorrected. Irradiation were carried out with a medium pressure immersion mercury lamp (125 watts), filtered and cooled by a $CuSO_4$ saturated solution. N_2 was bubbled through the irradiated solution. Columm chromatographies were carried out on silica gel (230-400 mesh).

Preparation of Ethyl 1-Benzyl-1,4-dihydronicotinate (1b).

Compound **1b** was prepared following the procedure reported for the corresponding methyl ester [7]. The crude oily product was purified by flash-chromatography with neutral alumina eluting with ethyl ether and immediately used for the photoreaction.

Ir: 1680 (CO) cm^{-1}; ^1H nmr δ : 7.11(d,J=1.8, H_2), 3.13(m, H_4, $H_{4'}$),4.74(dt, $J_{4,5}$= $J_{4',5}$=3.2, $J_{5,6}$=8.4, H_5), 5.66(dq, $J_{2,6}$=$J_{4,6}$=$J_{4',6}$=1.8,$J_{5,6}$=8.4, H_6), 4.26(s, $\underline{CH_2}$-C_6H_5), 7.15-7.39 (m,C_6H_5), 4.13(q,J=6.6, OCH_2), 1.23(t,J=6.6, CH_3).

Photoaddition of Acrylonitrile on 1b .

Ethyl 1-benzyl-1,4-dihydronicotinate (**1b**) (5 g) and acrylonitrile (13 g) in anhydrous ethyl ether were irradiated and hydrogenated as previously reported for **1a** [1]. Evaporation of ethyl acetate afforded an oily residue which was column chromatographed with light petroleum-ethyl ether 1:1 to give, in order of mobility:

-Ethyl trans-2-benzyl-7-cyano-2-azabicyclo[4.2.0]octane-6-carboxylate (4b)

(0.40 g); ir: 2235 (CN), 1725 (CO) cm^{-1}; ^1H nmr δ : 3.53 (dd,$J_{1,8}$=10.2, $J_{1,8'}$=7.2, H_1), 2.51 (td, $J_{3a,3e}$=$J_{3a,4a}$=11.7, $J_{3a,4e}$=2.0, H_{3a}), 2.74 (dt, $J_{3a,3e}$=11.7, $J_{3e,4a}$ =$J_{3e,4e}$=2.2, H_{3e}), 1.6-1.9,2.3-2.5(m, H_{4a}, $H_{4e}$and H_{5a}, H_{5e}), 3.07 (dd, $J_{7,8}$=10.2, $J_{7,8'}$=8.1, H_7), 2.44 (q, $J_{1,8}$=$J_{7,8}$=$J_{8,8'}$=10.2, H_8), 2.05 (ddd, $J_{1,8'}$=7.2, $J_{7,8'}$=8.1, $J_{8,8'}$=10.2, $H_{8'}$), 3.59,3.54 (AB, J=13.7, $\underline{CH_2}$-C_6H_5), 4.18 (q, J=7.2, OCH_2), 1.28 (t, J=7.2, CH_3), 7.25-7.32 (m, C_6H_5).

^{13}C nmr δ :172.9 (CO), 138.0-127.2 (C_6H_5), 119.0 (CN),61.3 (OCH_2), 58.2 (NCH_2), 55.5 (C_1), 48.7 (C_6), 46.6 (C_3), 25.7 (C_5), 25.3 (C_7), 23.5 (C_8), 21.45 (C_4), 14.2 (CH_3). mp (picrate) = 68-71 °C; Anal. Calcd for $C_{24}H_{25}N_5O_9.H_2O$: C, 52.85; H, 4.95; N, 12.83. Found: C, 53.14; H, 4.65; N, 12.90.

-Ethyl trans-2-benzyl-8-cyano-2-azabicyclo[4.2.0]octane-6-carboxylate (5b)

(0.60 g); ir: 2235 (CN), 1725 (CO) cm^{-1}; ^1H nmr δ : 3.73 (dd, $J_{1,7}$=1.0, $J_{1,8}$=7.0, H_1); 3.15 (ddd, $J_{3a,3e}$=11.5, $J_{3a,4a}$=8.1, $J_{3a,4e}$=3.9,H_{3a}), 2.39 (m,H_{3e}), 1.58-1.77 (m,H_{4a} and H_{4e}), 1.95-2.18 (m,H_{5a} and H_{5e}), 2.41 ($\underline{A}$BXY, $J_{7,7'}$=11.7, $J_{7,8}$=8.8, $J_{1,7}$=1.0, H_7), 2.26 (A$\underline{B}$X, $J_{7,7'}$=11.7, $J_{7',8}$=5.4, $H_{7'}$), 3.01 (ddd, $J_{1,8}$=7.0, $J_{7,8}$=8.8, $J_{7',8}$=5.4, H_8), 3.97, 3.62(AB, J_{AB}=13.6, $\underline{CH_2}$-C_6H_5), 4.16 (q, J= 7.2, OCH_2), 1.26 (t, J= 7.2 CH_3), 7.25-7.48 (m, C_6H_5).

^{13}C nmr δ :174.5 (CO), 137.9-126.0 (C_6H_5), 122.1 (CN), 61.1 (OCH_2), 59.0 (C_1), 58.6 ($\underline{CH_2}C_6H_5$), 46.7 (C_3), 46.6 (C_6), 30.9 (C_7), 28.7 (C_5), 23.3 (C_8), 21.9 (C_4), 14.2 (CH_3). mp (hydrochloride)= 106-108 °C; Anal. Calcd for $C_{18}H_{22}N_2O_2$.HCl: C, 64.57; H, 6.62; N, 8.37. Found: C, 65.02; H, 6.85; N, 8.53.

Cycloaddition of p-Cl-Benzonitriloxide on Compounds 2a,b and 3a,b

1-Benzyl-1,4-dihydronicotinamide (1a) (5 g) or ethyl 1-benzyl-1,4-dihydronicotinate (**1b**) (5 g) and acrylonitrile (13 g) were irradiated as above described. After evaporation of the solvent, the reaction mixture of the enamines **2a** ,**3a** or 2b, 3b was dissolved in tetrahydrofurane or anhydrous ether (50 ml), respectively. A 0.23 M solution of p-chlorobenzonitriloxide[7] (100 ml or 50 ml respectively) was added and the solution kept under nitrogen overnight. Solvent was then removed and the reaction mixture column chromatographed to yield compounds **6a**, 7a, or **6b**, 7b respectively.

- (3aRS,4aSR,5RS,6aSR,7aSR)-**7-benzyl-3-(p-chlorophenyl)-5-cyano-3a,4,4a,5,6,6a,7,7a-octahydrocyclobut[b]isoxazolo[4,5-e]pyridin-4a-carboxamide** (6a)

was obtained by elution with ethyl ether; yield 0.70 g , mp 203-207 °C (from ethanol). Anal. Calcd for $C_{23}H_{21}N_4O_2Cl$. 1/2 H_2O : C, 64.26; H,5.16; N,13.03 . Found: C,64.24; H,4.81; N,12.86; ir: 3480, 3420, 3180 (NH_2), 2235 (CN), 1680 (CO) cm^{-1} ; ^{13}C nmr (DMSO-d_6) δ : 172.6 (CO), 157.4 (C_3), 137.5-127.3 (Arom.), 119.4 (CN), 94.1 (C_{7a}), 54.8 (CH_2-C_6H_5), 50.1 (C_{6a}), 45.8 (C_{4a}), 29.6 (C_5), 28.1 (C_4), 22.2 (C_6).

-(3aRS,4aRS,6SR,6aSR,7aSR)-**7-benzyl-3-(p-chlorophenyl)-6-cyano-3a,4,4a,5,6,6a,7,7a-octahydrocyclobut[b]isoxazolo[4,5-e]pyridin-4a-carboxamide** (7a)

was obtained by elution with ethyl ether/methanol 95:5; yield 2.40 g ; mp 206-215 °C (from ethanol). Anal. Calcd for $C_{23}H_{21}N_4O_2Cl$.1/2 H_2O: C, 64.26; H, 5.16; N, 13.03. Found : C, 63.87; H,5.26; N,13.00; ir: 3470,3380,3200 (NH_2), 2235 (CN), 1670 (CO) cm^{-1};^{13}C nmr (DMSO-d_6) δ :173.5 (CO), 157.1 (C_3), 136.8-127.5 (Arom.), 121.4 (CN), 91.7 (C_{7a}), 53.8 (CH_2-C_6H_5), 51.8 (C_{6a}), 42.8 (C_{4a}), 33.3 (C_5), 25.1 (C_4), 24.2 (C_6).

- **ethyl** (3aRS,4aSR,5RS,6aSR,7aSR)-**7-benzyl-3-(p-chlorophenyl)-5-cyano-3a,4,4a,5,6,6a,7,7a-octahydrocyclobut[b]isoxazolo[4,5-e]pyridin-4a-carboxylate** (6b)

was obtained by elution with ethyl ether/light petroleum 1:1 and purified by column chromatography with benzene/ ethyl ether 20:3 as eluent; yield 0.03 g, mp 164-167 °C. Anal. Calcd for $C_{25}H_{24}N_3O_3Cl$: C, 66.74, H, 5.38; N, 9.34. Found: C, 66.32; H, 5.41; N, 9.15; ir: 2240 (CN), 1770 (CO) cm^{-1}; ^{13}C nmr δ : 171.1 (CO), 156.9 (C_3), 136.7-127.4 (arom.), 118.1 (CN), 94.0 (C_{7a}), 61.8 (OCH_2), 55.5 ($CH_2C_6H_5$), 50.3 (C_{6a}), 45.6 (C_{4a}), 40.8 (C_{3a}), 30.5 (C_4), 28.1 (C_5), 22.0 (C_6), 13.3 (CH_3).

- **ethyl** (3aRS,4aRS,6SR,6aSR,7aSR)-**7-benzyl-3-(p-chlorophenyl)-6-cyano-3a,4,4a,5,6,6a,7,7a-octahydrocyclobut[b]isoxazolo[4,5-e]pyridin-4a-carboxylate** (7b)

was obtained by further elution ; yield 1.60 g, mp 182-184 °C (from ethanol). Anal. Calcd for $C_{25}H_{24}N_3O_3Cl$: C, 66.74; H, 5.38; N, 9.34. Found C, 66.67; H, 5.34; N, 9.13; ir: 2240(CN), 1755 (CO) cm^{-1}; ^{13}C nmr δ :171.9 (CO), 157.2 (C_3), 135.7-127.1 (Arom.), 120.3 (CN), 92.2 (C_{7a}), 61.4 (OCH_2), 54.8 (CH_2-C_6H_5), 52.8 (C_{6a}), 42.9(C_{4a}), 40.8 (C_{3a}), 33.3 (C_5), 25.3 (C_6), 24.9 (C_4), 13.4(CH_3).

Isomerization of Compounds 6b and 7b

To a solution of sodium (15 mg) in anhydrous ethanol (5 ml) , 100 mg of compounds **6b** or **7b** was added. The mixture was refluxed for 30 min, cooled and neutralised wih acetic acid. Solvent was evaporated and the residue column chromatographed with ethyl ether/light petroleum 2:3 as eluent to give the starting materials **6b** (45 mg) or **7b** (25 mg) and the isomers **8** (25 mg) or **9** (40 mg) respectively.

- ethyl(3aRS,4aSR,5SR,6aSR,7aSR)-7-benzyl-3-(p-chlorophenyl)-5-cyano-3a,4,4a,5,6,6a,7,7a-octahydrocyclobut[b]isoxazolo[4,5-e]pyridin-4a-carboxylate (8)
mp 152-155 °C (from ether). Anal. Calcd. for $C_{25}H_{24}N_3O_3Cl$: C,66.74; H,5.38; N,9.34. Found: C,66.95; H,5.02; N,9.68; ir: 2235 (CN), 1725(CO) cm^{-1}.
- ethyl(3aRS,4aRS,6RS,6aSR,7aSR)-7-benzyl-3-(p-chlorophenyl)-6-cyano-3a,4,4a,5,6,6a,7,7a-octahydrocyclobut[b]isoxazolo[4,5-e]pyridin-4a-carboxylate (9)
mp 177-180 °C (from ether). Anal. Calcd. for $C_{25}H_{24}N_3O_3Cl$: C,66.74; H,5.38; N,9.34. Found: C,66.77; H,5.22; N,9.19; ir: 2235 (CN), 1730 (CO) cm^{-1}; ^{13}C nmr δ: 171.6 (CO), 157.2 (C_3),136.2-127.4 (Arom.), 119.9 (CN), 93.4 (C_{7a}), 61.6 (OCH_2), 57.1 (C_{6a}) , 55.7 ($CH_2C_6H_5$), 41.7 (C_{4a}), 41.1 (C_{3a}), 33.2 (C_5), 26.3 (C_6), 24.3 (C_4), 13.4 (CH_3).

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5) Preliminary results of RX diffractometric analysis for the compound **7b** confirm the assigned configuration.
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