REACTION OF TRIFLUOROACETIC ANHYDRIDE WITH *N*-(2-HYDROXYBENZYL)-α-AMINO ACIDS : AN ENTRY IN THE NEW [1,3]OXAZOLO[2,3-*b*][1,3]BENZOXAZINE RING SYSTEM

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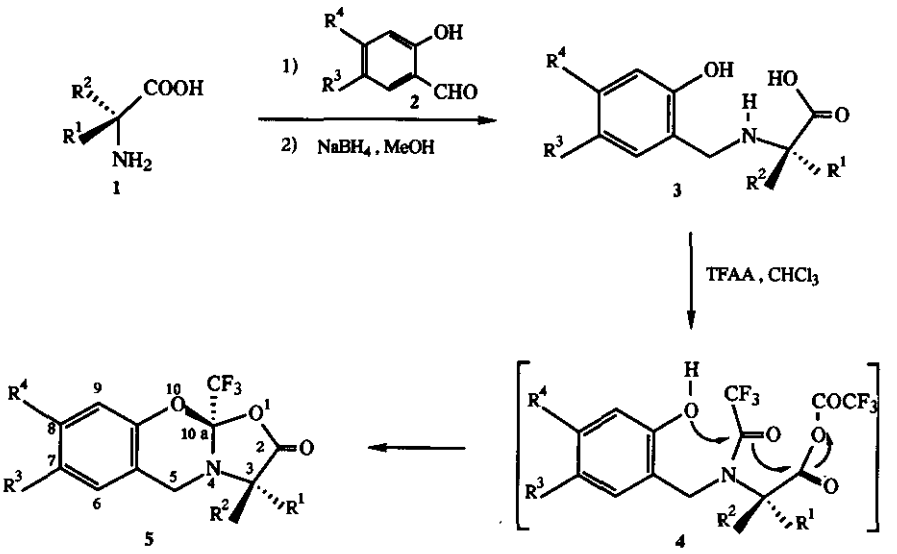
Abstract - The diastereospecific double ring closure of *N*-(2-hydroxybenzyl)-α-amino acids with trifluoroacetic anhydride leads to the formation of 10a-trifluoromethyl-2,3,4,10a-tetrahydro-[1,3]oxazolo[2,3-*b*][1,3]benzoxazin-2(5*H*)-ones. The chemical structures are supported by ir, ^{1}H-nmr and ^{13}C-nmr spectra and X-ray analysis.

In a program aimed at the study of the influence of 4-methylthio-2-oxobutanoic acid and its transaminase on the growth of methionine dependent cells in culture, we have synthesized some reduced Schiff bases of α-amino acids or α-amino esters and described their utilization as transaminase inhibitors.[1] As a part of this program, we became interested in the synthesis of structurally related compounds. We report here the synthesis of [1,3]oxazolo[2,3-*b*][1,3]benzoxazinone derivatives (**5**) from reduced Schiff bases of α-amino acids (**3**) (Scheme).

A few years ago, it was reported that the reaction of *N*-(2-hydroxybenzyl)anthranilic acids with trifluoroacetic anhydride (TFAA) allowed the synthesis of 6a-trifluoromethyl-6a,12-dihydro[3,1]benzoxazino[2,1-*b*][1,3]benzoxazin-5-ones by a double ring closure.[2,3] The structural features of *N*-(2-hydroxybenzyl)anthranilic acids (NH, COOH and OH functionalities) could be compared with those of *N*-(2-hydroxybenzyl)-α-amino acids (**3**) and therefore the reaction of compounds (**3**) with TFAA should provide a facile entry in the new [1,3]oxazolo[2,3-*b*]-[1,3]benzoxazine ring system.

The *N*-(2-hydroxybenzyl)-α-amino acids (**3**) were prepared by reaction of various α-amino acids (**1**) with salicyl aldehydes (**2**) followed by reduction of the intermediate Schiff bases with sodium borohydride. When treated with an excess TFAA at room temperature, compounds (**3**) were rapidly converted into oxazolobenzoxazinones (**5a-j**) with fair yields (66-81%). The gross structure of compounds (**5**) is consistent with the ir (ν_{CO} =1825-1810 cm^{-1}), ^{1}H- and ^{13}C-nmr spectra and microanalysis (see Experimental); the tricyclic structure is mainly evidenced by the ^{13}C-nmr spectra with the resonance of only one carbonyl group at 168.5-174.0 ppm, the trifluoromethyl resonance at 120.0-120.6 ppm (q, $^1J_{CF}$ = 284.8-287.5 Hz) and the C-10a resonance at 104.2-107.9 ppm (q, $^2J_{CF}$ = 36.5-37.2 Hz).

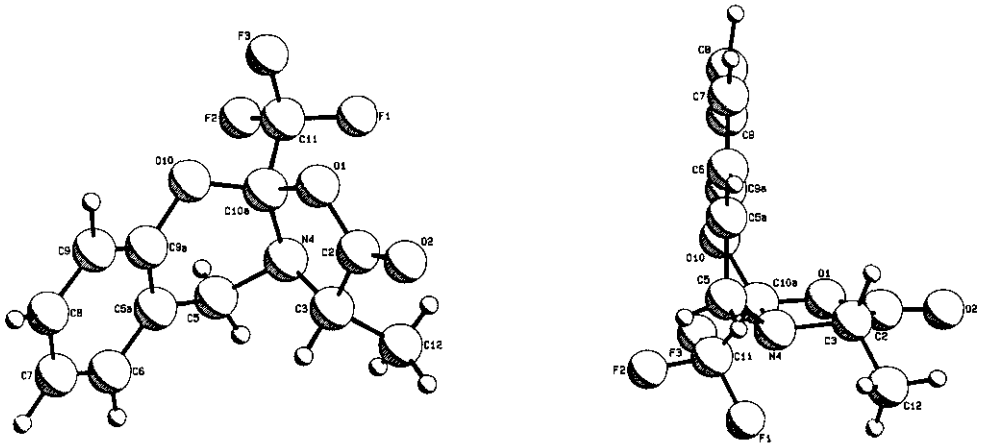
Scheme



1	3, 4 and 5	R^1	R^2	R^3	R^4
L-Ala	a	CH_3	H	H	H
L-2-Phenyl-Gly	b	C_6H_5	H	H	H
L-Val	c	$(CH_3)_2CH$	H	H	H
L-Met	d	$CH_3S(CH_2)_2$	H	H	H
L-Phe	e	$C_6H_5CH_2$	H	H	H
L-Ala	f	CH_3	H	Cl	H
L-Ala	g	CH_3	H	H	OCH_3
2-Methyl-Ala	h	CH_3	CH_3	H	H
1-Amino-1-cyclohexane-carboxylic acid	i	$(CH_2)_5$		H	H
D-Ala	j	enantiomer of a			

The reaction appears to be diastereospecific since when an optically active amino acid was used as starting material, a single diastereoisomer (**5a-g, j**) was detected in the ^1H- and ^{13}C-nmr spectra (one set of signals). Furthermore L-alanine and D-alanine gave rise respectively to the enantiomeric oxazolobenzoxazinones (**5a**) and (**5j**) as indicated by their superposable ir, ^1H- and ^{13}C-nmr spectra and their opposite specific rotations (- 38.6° and + 38.3° respectively, in chloroform).

The cis stereochemistry of the trifluoromethyl and R^1 substituents was established by X-ray analysis of the oxazolobenzoxazinone (**5a**) (Figure 1). The molecular structure of **5a** approximates a L shape with a dihedral angle of 92.1(2)° between the aromatic and the oxazole mean planes (Figure 1, view 2). The oxazine ring adopts a half-twist boat conformation with N4 and C10a respectively displaced by 0.967(4) and 0.705(5) Å from the mean plane of the C5-C5a-C9a-O10 atoms. Displacement of N4 by 0.260(4) Å from the mean plane of the C10a-O1-C2-C3 atoms indicates an envelope conformation for the oxazole ring.



view 1 **view 2**

Figure 1 : Crystal structure of **5a** and numbering scheme

The *S* configuration of C-3 in **5a** results from the *S* configuration of the stereocenter of the starting L-alanine which remains unchanged in the sequence **1** → **3** → **5**. According to the cis stereochemistry, the configuration (3*S*,10a*S*) was attributed to the oxazolobenzoxazinone (**5a**) and the configuration (3*R*,10a*R*) to the enantiomeric oxazolobenzoxazinone (**5j**). By analogy with **5a**, compounds (**5b-g**) must have the configuration (3*S*,10a*S*).
The diastereospecific formation of the oxazolobenzoxazinones (**5**) can be rationalized through the intermediate formation of the open chain mixed anhydride (**4**)[4] followed by a double ring closure proceeding in a quite concerted manner (Scheme).[5] The attack of the phenolic oxygen onto the amide carbonyl group might occur on the opposite side of the nitrogen lone pair in a conformation permitting a concerted interaction between the amide carbonyl oxygen and the anhydride carbonyl carbon (Figure 2). In the case of **5a-g**, the transition state **A** would lead to the (3*S*,10a*S*) oxazolobenzoxazinone (**5**) whereas the transiton state **B** would result in its (3*S*,10a*R*) isomer. The transition state **B** appears to be strongly disfavoured and this could presumably be due to the steric interaction between the R^1 substituent and the aromatic ring.

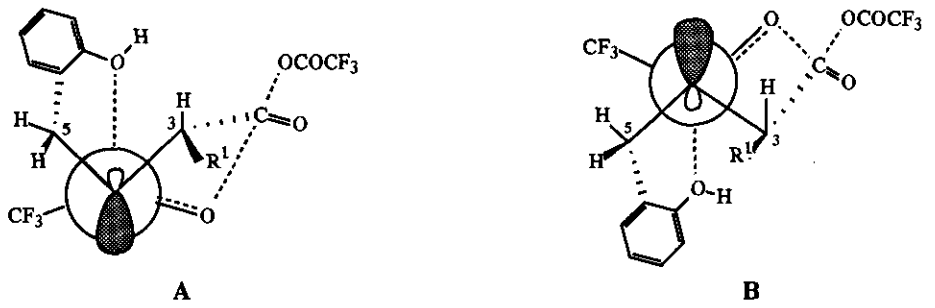


Figure 2 : Newman projection along the N4-C10a bond of the postulated transition states in the case of **5a-g**

EXPERIMENTAL

All melting points were determined on a Kofler block apparatus. The infrared spectra were obtained with a Perkin Elmer 1310 infrared spectrophotometer. The nmr spectra were recorded on a Bruker AC 200 spectrometer. The chemical shifts reported are in parts per million from internal TMS. Optical rotations were measured with a Beckmann 241 polarimeter. Elemental Analysis were performed by Microanalytical Laboratory, Centre National de la Recherche Scientifique, 69390 Vernaison, France. Silica gel (Kieselgel 60, 70-230 mesh ASTM, Merck) was employed for column chromatography. The α-amino acids and TFAA were obtained from Aldrich Chemical Co.

N-(2-Hydroxybenzyl)-α-amino acids (3)

To a stirred suspension of the α-amino acid (1) (30 mmol) in methanol (60 ml) was added a 1 M solution of methanolic potassium hydroxide (30 ml). After 10 min, the solution was filtered to eliminate a small quantity of undissolved material and the aldehyde (2) (salicyl aldehyde, 5-chlorosalicyl aldehyde or 4-methoxysalicyl aldehyde ; 30 mmol) in methanol (60 ml) was added. After stirring for 0.5 h at room temperature, the solution was cooled in a water ice bath and the intermediate Schiff base was reduced[6] with an excess sodium borohydride (1 g, 26.4 mmol). After 0.5 h at room temperature, the solution was neutralized to pH 4-5 with acetic acid. The solid was filtered off, washed with anhydrous ether and dried under vacuum (Yields of crude products : 80-90% except for **3g** 45%). The crude *N*-(2-hydroxybenzyl)-α-amino acids (3) were pure enough for the next step as indicated by the ^{1}H-nmr (D_2O + Na_3PO_4) :

3a δ 1.36 (d, 3H, J = 7.1 Hz), 3.42 (q, 1H, J = 7.1 Hz), 3.88 and 4.01 (AB system, 2H, J_{AB} = 13.2 Hz), 6.63-6.73 (m, 2H), 7.12-7.22 (m, 2H).

3b δ 3.79 and 3.87 (AB system, 2H, J_{AB} = 13.6 Hz), 4.29 (s, 1H), 6.68-6.83 (m, 2H), 7.06-7.26 (m, 2H), 7.35 (s, 5H).

3c δ 0.94 (d, 6H, J = 6.9 Hz), 1.99 (m, 1H), 3.07 (d, 1H, J = 5.9 Hz), 3.75 and 4.04 (AB system, 2H, J_{AB} = 13.5 Hz), 6.61-6.69 (m, 2H), 7.08-7.20 (m, 2H).

3d δ 1.81-2.01 (m, 2H), 2.07 (s, 3H), 2.47-2.64 (m, 2H), 3,30 (t, 1H, J = 6.3Hz), 3.59 and 3.93 (AB system, 2H, J_{AB} = 14.3 Hz), 6.62-6.79 (m, 2H), 7.08-7.25 (m, 2H).

3e δ 2.93 (d, 2H, J = 6.9 Hz), 3.42 (t, 1H, J = 6.9 Hz), 3.57 and 3.78 (AB system, 2H, J_{AB} = 13.5 Hz), 6.60-6.71 (m, 2H), 7.03-7.20 (m, 2H), 7.20-7.43 (m, 5H).

3f δ 1.30 (d, 3H, J = 7.0 Hz), 3.34 (q, 1H, J = 7.0 Hz), 3.73 and 3.85 (AB system, 2H, J_{AB} = 13.5 Hz), 6.48-6.66 (m, 1H), 7.00-7.15 (m, 2H).

3g δ 1.31 (d, 3H, J = 7.1 Hz), 3.37 (q, 1H, J = 7.1 Hz), 3.70 (s, 3H), 3.73 and 3.84 (AB system, 2H, J_{AB} = 13.1 Hz), 6.11-6.26 (m, 2H), 7.00 (d, 1H, J = 8.0 Hz).

3h δ 1.44 (s, 6H), 3.95 (s, 2H), 6.61-6.72 (m, 2H), 7.13-7.22 (m, 2H).

3i δ 1.34-1.80 (m, 6H), 1.83-2.14 (m, 4H), 3.86 (s, 2H), 6.54-6.74 (m, 2H), 7.04-7.26 (m, 2H).

3j spectrum superposable with the spectrum of **3a**.

10a-Trifluoromethyl-2,3,4,10a-tetrahydro[1,3]oxazolo[2,3-*b*][1,3]benzoxazin-2(5*H*)-ones (5)
To a stirred suspension of the *N*-(2-hydroxybenzyl)-α-amino acid (3) (2 mmol) in chloroform (5 ml) was added a solution of TFAA (0.85 ml; 6 mmol) in chloroform (5 ml). The mixture became rapidly homogeneous and was stirred for 1 h at room temperature. The solvent was evaporated under reduced pressure and the residue was *purified by chromatography on silica gel eluting with methylene chloride to afford pure compounds* (5). Compounds (5) have the following characteristics :

5a Yield 74%. mp 84°C. $[\alpha]_D^{20}$ = -38.6° (c 0.86, $CHCl_3$). Ir ($CHCl_3$) 1820,1585. ^{1}H-Nmr ($CDCl_3$) δ 1.42 (d, 3H, J = 6.8 Hz), 3.54 (q, 1H, J = 6.8 Hz), 3.76 and 4.29 (AB system, 2H, J_{AB} = 16.5 Hz), 7.05-7.26 (m, 3H), 7.29-7.33(m, 1H). ^{13}C-Nmr ($CDCl_3$) δ 16.56, 43.92, 55.17, 107.36 (q, $^2J_{CF}$ = 36.7 Hz), 118.18, 120.30 (q, $^1J_{CF}$ = 284.8 Hz), 122.39, 124.22, 127.70, 129.66, 150.29, 171.15. Anal. Calcd for $C_{12}H_{10}NO_3F_3$: C 52.75, H 3.69, N 5.13 : Found C 52.93, H 3.60, N 5.15.

5b Yield 66%. mp 144°C. $[\alpha]_D^{20}$ = +135.6° (c 3.40, $CHCl_3$). Ir ($CHCl_3$) 1825,1590. ^{1}H-Nmr ($CDCl_3$) δ 3.71 and 4.33 (AB system, 2H, J_{AB} = 16.5 Hz), 4.50 (s, 1H), 7.11-7.16 (m, 3H), 7.23-7.40 (m, 1H), 7.41 (s, 5H). ^{13}C-Nmr ($CDCl_3$) δ 43.78, 63.17, 107.02 (q, $^2J_{CF}$ = 36.8 Hz), 118.23, 120.41 (q, $^1J_{CF}$ = 285.2 Hz), 121.71, 124.16, 127.68, 127.71, 129.15, 129.47, 129.73, 133.14, 150.37, 168.48. Anal. Calcd for $C_{17}H_{12}NO_3F_3$: C 60.90, H 3.61, N 4.18 : Found C 60.81, H 3.38, N 4.25.

5c Yield 66%. oil. $[\alpha]_D^{20}$ = -33.7° (c 3.92, $CHCl_3$). Ir ($CHCl_3$) 1815,1590. ^{1}H-Nmr ($CDCl_3$) δ 1.06 (d, 3H, J = 6.9 Hz), 1.09 (d, 3H, J = 6.9 Hz), 2.03-2.19 (m, 1H), 3.38 (d, 1H, J = 3.7 Hz), 3.74 and 4.29 (AB system, 2H, J_{AB} = 16.3 Hz), 7.06-7.19 (m, 3H), 7.25-7.35 (m, 1H). ^{13}C-Nmr ($CDCl_3$) δ 17.47, 17.65, 30.71, 45.33, 64.15, 107.65 (q, $^2J_{CF}$ = 36.5 Hz), 118.41, 120.45 (q, $^1J_{CF}$ = 285.2 Hz), 123.35, 124.21, *127.52, 129.67, 150.16, 169.70.* Anal. Calcd for $C_{14}H_{14}NO_3F_3$: C 55.82, H 4.68, N 4.65 : Found C 55.82, H 4.67, N 4.74.

5d Yield 80%. oil. $[\alpha]_D^{20}$ = +5.4° (c 5.03, $CHCl_3$). Ir ($CHCl_3$) 1810,1585. ^{1}H-Nmr ($CDCl_3$) δ 2.00-2.15 (m, 2H), 2.11 (s, 3H), 2.52-2.82 (m, 2H), 3.72 (t, 1H, J = 5.7 Hz), 3.78 and 4.26 (AB system, 2H, J_{AB} = 16.2 Hz), 7.09-7.21 (m, 3H), 7.26-7.36 (m, 1H). ^{13}C-Nmr ($CDCl_3$) δ 15.17, 28.85, 30.52, 44.70, 57.89, 107.88 (q, $^2J_{CF}$ = 36.6 Hz), 118.38, 120.27 (q, $^1J_{CF}$ = 284.9 Hz), 123.31, 124.44, 127.60, 129.73, 149.96, 170.50. Anal. Calcd for $C_{14}H_{14}NO_3F_3S$: C 50.45, H 4.23, N 4.20, S 9.62 : Found C 50.68, H 4.31, N 4.20, S 9.85.

5e Yield 81%. mp 90°C. $[\alpha]_D^{20}$ = +41.1° (c 4.05, $CHCl_3$). Ir ($CHCl_3$) 1820,1590. ^{1}H-Nmr ($CDCl_3$) δ 2.88 (ABX system, 1H, J_{AX} = 8.9 Hz, J_{AB} = 13.8 Hz), 2.99 and 3.98 (AB system, 2H, J_{AB} = 16.3 Hz), 3.22 (ABX system, 1H, J_{BX} = 3.8 Hz, J_{AB} = 13.8 Hz), 3.69 (ABX system, 1H, J_{BX} = 3.8 Hz, J_{AX} = 8.9 Hz,), 6.88-6.92 (m, 1H), 7.01-7.09 (m, 2H), 7.22-7.42 (m, 6H). ^{13}C-Nmr ($CDCl_3$) δ 38.29, 45.01, 60.94, 107.93 (q, $^2J_{CF}$ = 36.7 Hz), 118.38, 120.15 (q, $^1J_{CF}$ = 285.0 Hz), 123.57, 124.31, 127.34, 127.43, 128.83, 129.09, 129.63, 135.65, 149.93, 169.88. Anal. Calcd for $C_{18}H_{14}NO_3F_3$: C 61.89, H 4.04, N 4.01 : Found C 61.78, H 3.93, N 4.19.

5f Yield 69%. mp 46°C. $[\alpha]_D^{20}$ = -65.6° (c 1.33, $CHCl_3$). Ir ($CHCl_3$) 1825,1570. ^{1}H-Nmr ($CDCl_3$) δ 1.44 (d, 3H, J = 6.8 Hz), 3.53 (q, 1H, J = 6.8 Hz), 3.75 and 4.28 (AB system, 2H, J_{AB} = 16.7 Hz), 7.03 (d, 1H, J = 8.6 Hz), 7.17 (d, 1H, J = 2.2 Hz), 7.28 (dd, 1H, J = 2.2 Hz, J = 8.6 Hz). ^{13}C-Nmr ($CDCl_3$) δ 16.50, 43.59, 55.08, 107.10 (q, $^2J_{CF}$ = 37.0 Hz), 119.56, 120.11 (q, $^1J_{CF}$ = 284.9 Hz), 123.70, 127.48, 129.26, 129.64, 148.82, 170.65. Anal. Calcd for $C_{12}H_9NO_3F_3Cl$: C 46.85, H 2.95, N 4.55, Cl 11.52 : Found C 47.10, H 2.96, N 4.53, Cl 11.51.

5g Yield 77%. mp 45°C. $[\alpha]_D^{20}$ = +30.0° (c 5.54, $CHCl_3$). Ir ($CHCl_3$) 1825,1625,1590. ^{1}H-Nmr ($CDCl_3$) δ 1.42 (d, 3H, J = 6.8 Hz), 3.55 (q, 1H, J = 6.8 Hz), 3.70 and 4.24 (AB system, 2H, J_{AB} = 16.4 Hz), 3.79 (s, 3H), 6.61-6.68 (m, 2H), 7.02-7.26 (m, 1H). ^{13}C-Nmr ($CDCl_3$) δ 16.49, 43.42, 55.02, 103.95, 107.20 (q, $^2J_{CF}$ = 36.8 Hz), 110.24, 111.83, 119.96 (q, $^1J_{CF}$ = 284.8 Hz), 128.12, 151.12, 160.82, 171.24. Anal. Calcd for $C_{13}H_{12}NO_4F_3$: C 51.49, H 3.99, N 4.62 : Found C 51.44, H 3.90, N 4.74.

5h Yield 74%. mp 97°C. Ir ($CHCl_3$) 1815,1585. ^{1}H-Nmr ($CDCl_3$) δ 1.12 (s, 3H), 1.45 (s, 3H), 3.90 and 4.36 (AB system, 2H, J_{AB} = 17.7 Hz), 6.96-7.15 (m, 3H), 7.18-7.27 (m, 1H). ^{13}C-Nmr ($CDCl_3$) δ 22.73, 25.48, 39.66, 60.92, 104.74 (q, $^2J_{CF}$ = 37.2 Hz), 117.17, 120.54 (q, $^1J_{CF}$ = 287.1 Hz), 121.20, 123.45, 125.62, 128.96, 150.76, 173.97. Anal. Calcd for $C_{13}H_{12}NO_3F_3$: C 54.36, H 4.21, N 4.88 : Found C 54.54, H 4.01, N 4.78.

5i Yield 73%. mp 104°C. Ir ($CHCl_3$) 1815,1590. ^{1}H-Nmr ($CDCl_3$) δ 0.98-2.16 (m, 10H), 3.90 and 4.30 (AB system, 2H, J_{AB} = 17.9 Hz), 6.94-7.09 (m, 3H), 7.18-7.26 (m, 1H). ^{13}C-Nmr ($CDCl_3$) δ 21.50, 21.78, 24.44, 31.97, 34.22, 39.11, 61.87, 104.17 (q, $^2J_{CF}$ = 37.0 Hz), 117.03, 120.61 (q, $^1J_{CF}$ = 287.5 Hz), 121.24, 123.16, 125.38, 128.88, 150.93, 171.91. Anal. Calcd for $C_{16}H_{16}NO_3F_3$: C 58.71, H 4.93, N 4.28 : Found C 58.34, H 4.97, N 4.41.

5j Yield 78%. mp 84°C. $[\alpha]_D^{20}$ = +38.3° (c 3.06, $CHCl_3$). The ir, ^{1}H-nmr and ^{13}C-nmr spectra are totally superposable with the corresponding spectra of **7a**.

X-Ray Analysis of 5a

Single crystals suitable for X-ray structure analysis were prepared from a dilute solution of **5a** in cylohexane by growth under slow evaporation at room temperature.

Crystal Data : $C_{12}H_{10}NO_3F_3$, MW = 273.2, monoclinic, group $P2_1$, a = 6.830(2), b = 6.853(1), c = 13.192(1) Å, β = 99.40(1)°, V = 609.2(3)Å^3, Z = 2, D_C = 1.490g.cm^{-3}, λ(CuKα) = 1.5424 Å, μ (CuKα) = 12.3 cm^{-1}.

The diffraction data were collected from a single crystal of 0.30x0.40x0.50 mm studied on a Nonius CAD4 diffractometer. The unit cell parameters were refined from setting angles of 25 selected reflections ($24.8 < \theta < 57.1°$). The intensities were collected using ω-θ scan in the range $1 < \theta < 73°$. Among the 1314 independent reflections, only 1246 were considered as observed according to the condition $I > 3\sigma(I)$. The intensity data were corrected for Lorentz and polarization. The data were corrected for absorption by means of an empirical method from ψ scan concerning 9 high χ reflections ($\chi > 80°$). The structure was solved by means of Multan. Full matrix refinements based on Fo were performed, weighted by $w=1/\sigma^2(Fo)$. All the hydrogen atoms were located from ΔF syntheses. The final refinement involved the x, y, z, β_{ij} parameters for the non-hydrogen atoms and the x, y, z for the hydrogen atoms.The final agreements were R = 0.060 and Rw = 0.059. Computing by means of Enraf-Nonius SDP system (B.A. Frenz & Associates inc., SDP Structure Determination Package, College station, Texas, USA, 1982) on MicroVax 3100-80 (Centre de Diffractométrie Automatique de l'Université Claude Bernard, Lyon I). Drawing by means of PLUTO (W.D.S. Motherwell & W. Clegg, PLUTO Program for Plotting molecular and crystal structures, University of Cambridge, England, 1978).

Table 1

Relative atomic coordinates and thermal Beq parameters of non-hydrogen atoms with their standard deviations in parentheses. $Beq = 4/3\Sigma i\ \Sigma j\ \beta_{ij}\ a_i\ a_j$

Atom	x	y	z	Beq (Å^2)
F1	0.4275(6)	0.109	0.1392(3)	6.8(1)
F2	0.2665(7)	0.1559(7)	0.2620(4)	8.9(1)
F3	0.5775(6)	0.1010(7)	0.2955(3)	8.1(1)
O1	0.5288(5)	- 0.2567(7)	0.1988(3)	4.48(9)
C2	0.4624(8)	- 0.383(1)	0.1231(4)	4.3(1)
O2	0.5691(6)	- 0.4752(8)	0.0784(4)	6.5(1)
C3	0.2348(7)	- 0.3843(9)	0.1067(4)	3.6(1)
N4	0.1921(5)	- 0.2183(7)	0.1668(3)	3.13(8)
C5	0.0174(7)	- 0.242(1)	0.2199(4)	4.3(1)
C5a	0.0668(7)	- 0.381(1)	0.3085(4)	3.7(1)
C6	- 0.0545(8)	- 0.523(1)	0.3380(4)	4.7(1)
C7	0.0091(9)	- 0.640(1)	0.4217(5)	5.2(1)
C8	0.2015(9)	- 0.616(1)	0.4781(4)	4.8(1)
C9	0.3271(8)	- 0.478(1)	0.4485(4)	4.2(1)
C9a	0.2599(7)	- 0.3610(9)	0.3660(4)	3.5(1)
O10	0.3787(5)	- 0.2083(7)	0.3406(3)	4.59(9)
C10a	0.3708(7)	- 0.1659(9)	0.2373(4)	3.3(1)
C11	0.412(1)	0.051(1)	0.2334(5)	5.2(1)
C12	0.1454(9)	- 0.368(1)	- 0.0071(4)	5.6(2)

Table 2

Bond lengths (Å) and bond angles (°) with their standard deviations in parentheses

Bond	Distance	Bond	Distance	Bond	Distance
F1-C11	1.325(7)	C3-N4	1.443(8)	C6-C7	1.379(9)
F2-C11	1.332(9)	C3-C12	1.529(7)	C7-C8	1.411(8)
F3-C11	1.328(7)	N4-C5	1.488(7)	C8-C9	1.375(9)
O1-C2	1.342(7)	N4-C10a	1.454(6)	C9-C9a	1.371(8)
O1-C10a	1.410(7)	C5-C5a	1.503(8)	C9a-O10	1.398(7)
C2-O2	1.192(8)	C5a-C6	1.373(9)	O10-C10a	1.386(6)
C2-C3	1.534(7)	C5a-C9a	1.417(6)	C10a-C11	1.514(9)

Bond	Angle	Bond	Angle	Bond	Angle
C2-O1-C10a	111.5(4)	C5-C5a-C9a	115.2(5)	O1-C10a-C11	105.2(5)
O1-C2-O2	123.4(5)	C6-C5a-C9a	118.0(5)	N4-C10a-O10	118.1(4)
O1-C2-C3	108.7(5)	C5a-C6-C7	120.9(5)	N4-C10a-C11	111.3(4)
O2-C2-C3	127.9(5)	C6-C7-C8	120.0(6)	O10-C10a-C11	105.2(4)
C2-C3-N4	102.0(4)	C7-C8-C9	120.0(6)	F1-C11-F2	106.3(5)
C2-C3-C12	111.8(5)	C8-C9-C9a	119.1(5)	F1-C11-F3	108.2(6)
N4-C3-C12	113.4(5)	C5a-C9a-C9	122.0(5)	F1-C11-C10a	111.8(5)
C3-N4-C5	115.0(5)	C5a-C9a-O10	118.0(5)	F2-C11-F3	106.5(5)
C3-N4-C10a	108.8(4)	C9-C9a-O10	119.8(4)	F2-C11-C10a	111.6(6)
C5-N4-C10a	112.3(4)	C9a-O10-C10a	117.5(4)	F3-C11-C10a	112.2(5)
N4-C5-C5a	109.8(4)	O1-C10a-N4	105.8(4)		
C5-C5a-C6	126.8(4)	O1-C10a-O10	110.6(4)		

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5 The transformation of **4** into **5** could also occur by a stepwise mechanism through the intermediate and reversible formation of a 3,4-dihydro-2-hydroxy-2-trifluoromethyl-2*H*[1,3]benzoxazine derivative and subsequent ring closure. However by treating the *N*-(2-hydroxybenzyl)alanine methyl ester by one equivalent of TFAA in chloroform, we detected no trace of a benzoxazine derivative but only *N*-trifluoroacetyl *N*-(2-hydroxybenzyl)alanine methyl ester as the sole product. The structure of this compound, which appears to be constituted by a 56:44 mixture of amide rotamers, was supported by ^{1}H- and ^{13}C-nmr. Therefore the presence of the mixed anhydride functionality seems necessary to induce the benzoxazine ring closure.

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