

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

Bernard Chantegrel,<sup>a</sup> Christian Deshayes,\*<sup>a</sup> and René Faure<sup>b</sup>

<sup>a</sup> Laboratoire de Chimie Organique, Bâtiment 403, Institut National des Sciences Appliquées, 20 Avenue Albert Einstein, 69621 Villeurbanne Cedex, France

<sup>b</sup> Laboratoire de Chimie Analytique II, Bâtiment 305, Université Claude-Bernard, Lyon I, 43 boulevard du 11 Novembre 1918, 69622 Villeurbanne Cedex, France

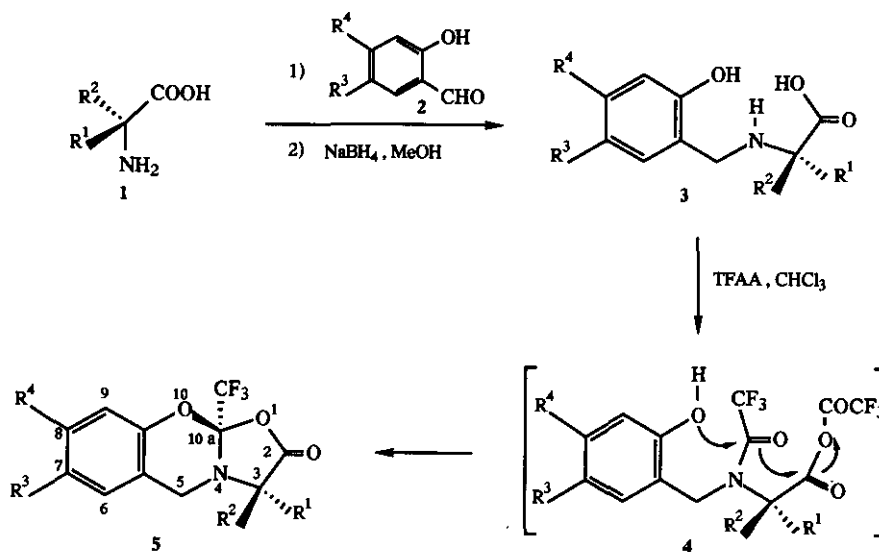
**Abstract** - The diastereospecific double ring closure of *N*-(2-hydroxybenzyl)- $\alpha$ -amino acids with trifluoroacetic anhydride leads to the formation of 10a-trifluoromethyl-2,3,4,10a-tetrahydro-[1,3]oxazolo[2,3-*b*][1,3]benzoxazin-2(5*H*)-ones. The chemical structures are supported by ir, <sup>1</sup>H-nmr and <sup>13</sup>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  $\alpha$ -amino acids or  $\alpha$ -amino esters and described their utilization as transaminase inhibitors.<sup>1</sup> 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  $\alpha$ -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.<sup>2,3</sup> The structural features of *N*-(2-hydroxybenzyl)anthranilic acids (NH, COOH and OH functionalities) could be compared with those of *N*-(2-hydroxybenzyl)- $\alpha$ -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)- $\alpha$ -amino acids (3) were prepared by reaction of various  $\alpha$ -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 ( $\nu_{\text{CO}} = 1825-1810 \text{ cm}^{-1}$ ), <sup>1</sup>H- and <sup>13</sup>C-nmr spectra and microanalysis (see Experimental); the tricyclic structure is mainly evidenced by the <sup>13</sup>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, <sup>1</sup>J<sub>CF</sub> = 284.8-287.5 Hz) and the C-10a resonance at 104.2-107.9 ppm (q, <sup>2</sup>J<sub>CF</sub> = 36.5-37.2 Hz).

## Scheme



1	3, 4 and 5	$\text{R}^1$	$\text{R}^2$	$\text{R}^3$	$\text{R}^4$
L-Ala	a	$\text{CH}_3$	H	H	H
L-2-Phenyl-Gly	b	$\text{C}_6\text{H}_5$	H	H	H
L-Val	c	$(\text{CH}_3)_2\text{CH}$	H	H	H
L-Met	d	$\text{CH}_3\text{S}(\text{CH}_2)_2$	H	H	H
L-Phe	e	$\text{C}_6\text{H}_5\text{CH}_2$	H	H	H
L-Ala	f	$\text{CH}_3$	H	Cl	H
L-Ala	g	$\text{CH}_3$	H	H	$\text{OCH}_3$
2-Methyl-Ala	h	$\text{CH}_3$	$\text{CH}_3$	H	H
1-Amino-1-cyclohexane-carboxylic acid	i	$(\text{CH}_2)_5$		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  $^1\text{H}$ - and  $^{13}\text{C}$ -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,  $^1\text{H}$ - and  $^{13}\text{C}$ -nmr spectra and their opposite specific rotations ( $-38.6^\circ$  and  $+38.3^\circ$  respectively, in chloroform).

The *cis* stereochemistry of the trifluoromethyl and R<sup>1</sup> 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.

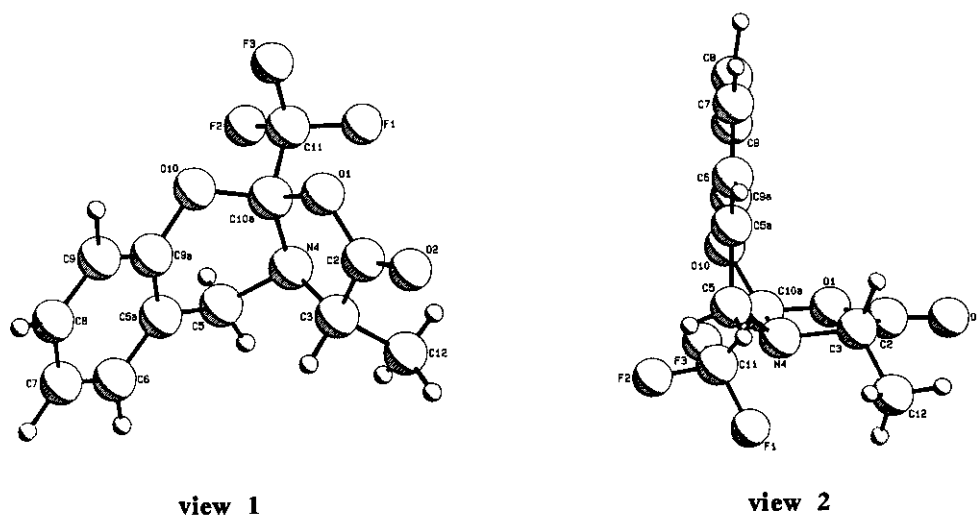


Figure 1 : Crystal structure of **5a** and numbering scheme

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*,10*aS*) was attributed to the oxazolobenzoxazinone (**5a**) and the configuration (3*R*,10*aR*) to the enantiomeric oxazolobenzoxazinone (**5j**). By analogy with **5a**, compounds (**5b-g**) must have the configuration (3*S*,10*aS*). The diastereospecific formation of the oxazolobenzoxazinones (**5**) can be rationalized through the intermediate formation of the open chain mixed anhydride (**4**)<sup>4</sup> followed by a double ring closure proceeding in a quite concerted manner (Scheme).<sup>5</sup> 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*,10*aS*) oxazolobenzoxazinone (**5**) whereas the transition state **B** would result in its (3*S*,10*aR*) isomer. The transition state **B** appears to be strongly disfavoured and this could presumably be due to the steric interaction between the R<sup>1</sup> substituent and the aromatic ring.

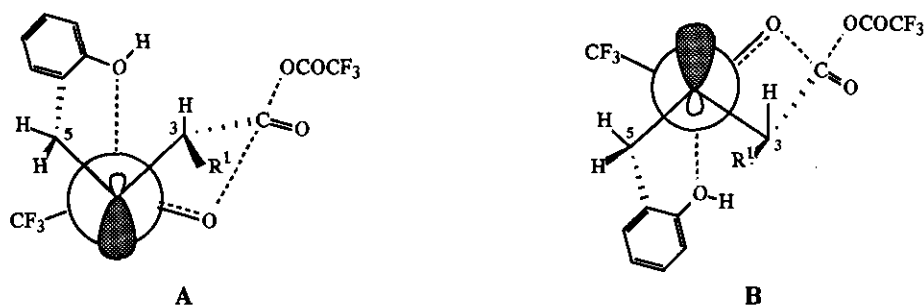


Figure 2 : Newman projection along the N4-C10a bond of the postulated transition states in the case of 5a-g

## 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  $\alpha$ -amino acids and TFAA were obtained from Aldrich Chemical Co.

### *N*-(2-Hydroxybenzyl)- $\alpha$ -amino acids (3)

To a stirred suspension of the  $\alpha$ -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<sup>6</sup> 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)- $\alpha$ -amino acids (3) were pure enough for the next step as indicated by the <sup>1</sup>H-nmr (D<sub>2</sub>O + Na<sub>3</sub>PO<sub>4</sub>) :

**3a**  $\delta$  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**  $\delta$  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**  $\delta$  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**  $\delta$  1.81-2.01 (m, 2H), 2.07 (s, 3H), 2.47-2.64 (m, 2H), 3.30 (t, 1H,  $J = 6.3$ Hz), 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**  $\delta$  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**  $\delta$  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**  $\delta$  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**  $\delta$  1.44 (s, 6H), 3.95 (s, 2H), 6.61-6.72 (m, 2H), 7.13-7.22 (m, 2H).

**3i**  $\delta$  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)- $\alpha$ -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.  $[\alpha]_D^{20} = -38.6^\circ$  (c 0.86, CHCl<sub>3</sub>). Ir (CHCl<sub>3</sub>) 1820,1585. <sup>1</sup>H-Nmr (CDCl<sub>3</sub>)  $\delta$  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). <sup>13</sup>C-Nmr (CDCl<sub>3</sub>)  $\delta$  16.56, 43.92, 55.17, 107.36 (q, <sup>2</sup> $J_{CF} = 36.7$  Hz), 118.18, 120.30 (q, <sup>1</sup> $J_{CF} = 284.8$  Hz), 122.39, 124.22, 127.70, 129.66, 150.29, 171.15. Anal. Calcd for C<sub>12</sub>H<sub>10</sub>NO<sub>3</sub>F<sub>3</sub> : 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.  $[\alpha]_D^{20} = +135.6^\circ$  (c 3.40, CHCl<sub>3</sub>). Ir (CHCl<sub>3</sub>) 1825,1590. <sup>1</sup>H-Nmr (CDCl<sub>3</sub>)  $\delta$  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). <sup>13</sup>C-Nmr (CDCl<sub>3</sub>)  $\delta$  43.78, 63.17, 107.02 (q, <sup>2</sup> $J_{CF} = 36.8$  Hz), 118.23, 120.41 (q, <sup>1</sup> $J_{CF} = 285.2$  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<sub>17</sub>H<sub>12</sub>NO<sub>3</sub>F<sub>3</sub> : C 60.90, H 3.61, N 4.18 : Found C 60.81, H 3.38, N 4.25.

**5c** Yield 66%. oil.  $[\alpha]_D^{20} = -33.7^\circ$  (c 3.92, CHCl<sub>3</sub>). Ir (CHCl<sub>3</sub>) 1815,1590. <sup>1</sup>H-Nmr (CDCl<sub>3</sub>)  $\delta$  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). <sup>13</sup>C-Nmr (CDCl<sub>3</sub>)  $\delta$  17.47, 17.65, 30.71, 45.33, 64.15, 107.65 (q, <sup>2</sup> $J_{CF} = 36.5$  Hz), 118.41, 120.45 (q, <sup>1</sup> $J_{CF} = 285.2$  Hz), 123.35, 124.21, 127.52, 129.67, 150.16, 169.70. Anal. Calcd for C<sub>14</sub>H<sub>14</sub>NO<sub>3</sub>F<sub>3</sub> : C 55.82, H 4.68, N 4.65 : Found C 55.82, H 4.67, N 4.74.

- 5d** Yield 80%. oil.  $[\alpha]_D^{20} = +5.4^\circ$  (c 5.03,  $\text{CHCl}_3$ ). Ir ( $\text{CHCl}_3$ ) 1810,1585.  $^1\text{H-Nmr}$  ( $\text{CDCl}_3$ )  $\delta$  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).  $^{13}\text{C-Nmr}$  ( $\text{CDCl}_3$ )  $\delta$  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  $\text{C}_{14}\text{H}_{14}\text{NO}_3\text{F}_3\text{S}$ : 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  $90^\circ\text{C}$ .  $[\alpha]_D^{20} = +41.1^\circ$  (c 4.05,  $\text{CHCl}_3$ ). Ir ( $\text{CHCl}_3$ ) 1820,1590.  $^1\text{H-Nmr}$  ( $\text{CDCl}_3$ )  $\delta$  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).  $^{13}\text{C-Nmr}$  ( $\text{CDCl}_3$ )  $\delta$  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  $\text{C}_{18}\text{H}_{14}\text{NO}_3\text{F}_3$ : C 61.89, H 4.04, N 4.01: Found C 61.78, H 3.93, N 4.19.
- 5f** Yield 69%. mp  $46^\circ\text{C}$ .  $[\alpha]_D^{20} = -65.6^\circ$  (c 1.33,  $\text{CHCl}_3$ ). Ir ( $\text{CHCl}_3$ ) 1825,1570.  $^1\text{H-Nmr}$  ( $\text{CDCl}_3$ )  $\delta$  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).  $^{13}\text{C-Nmr}$  ( $\text{CDCl}_3$ )  $\delta$  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  $\text{C}_{12}\text{H}_9\text{NO}_3\text{F}_3\text{Cl}$ : 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  $45^\circ\text{C}$ .  $[\alpha]_D^{20} = +30.0^\circ$  (c 5.54,  $\text{CHCl}_3$ ). Ir ( $\text{CHCl}_3$ ) 1825,1625,1590.  $^1\text{H-Nmr}$  ( $\text{CDCl}_3$ )  $\delta$  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).  $^{13}\text{C-Nmr}$  ( $\text{CDCl}_3$ )  $\delta$  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  $\text{C}_{13}\text{H}_{12}\text{NO}_4\text{F}_3$ : C 51.49, H 3.99, N 4.62: Found C 51.44, H 3.90, N 4.74.
- 5h** Yield 74%. mp  $97^\circ\text{C}$ . Ir ( $\text{CHCl}_3$ ) 1815,1585.  $^1\text{H-Nmr}$  ( $\text{CDCl}_3$ )  $\delta$  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).  $^{13}\text{C-Nmr}$  ( $\text{CDCl}_3$ )  $\delta$  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  $\text{C}_{13}\text{H}_{12}\text{NO}_3\text{F}_3$ : C 54.36, H 4.21, N 4.88: Found C 54.54, H 4.01, N 4.78.
- 5i** Yield 73%. mp  $104^\circ\text{C}$ . Ir ( $\text{CHCl}_3$ ) 1815,1590.  $^1\text{H-Nmr}$  ( $\text{CDCl}_3$ )  $\delta$  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).  $^{13}\text{C-Nmr}$  ( $\text{CDCl}_3$ )  $\delta$  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  $\text{C}_{16}\text{H}_{16}\text{NO}_3\text{F}_3$ : C 58.71, H 4.93, N 4.28: Found C 58.34, H 4.97, N 4.41.
- 5j** Yield 78%. mp  $84^\circ\text{C}$ .  $[\alpha]_D^{20} = +38.3^\circ$  (c 3.06,  $\text{CHCl}_3$ ). The ir,  $^1\text{H-nmr}$  and  $^{13}\text{C-nmr}$  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 cyclohexane 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,  $\beta = 99.40(1)^\circ$ ,  $V = 609.2(3)$  Å<sup>3</sup>,  $Z = 2$ ,  $D_C = 1.490$  g.cm<sup>-3</sup>,  $\lambda(\text{CuK}\alpha) = 1.5424$  Å,  $\mu(\text{CuK}\alpha) = 12.3$  cm<sup>-1</sup>.

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 ( $24.8 < \theta < 57.1^\circ$ ). The intensities were collected using  $\omega$ - $\theta$  scan in the range  $1 < \theta < 73^\circ$ . 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  $\psi$  scan concerning 9 high  $\chi$  reflections ( $\chi > 80^\circ$ ). The structure was solved by means of Multan. Full matrix refinements based on  $F_o$  were performed, weighted by  $w=1/\sigma^2(F_o)$ . All the hydrogen atoms were located from  $\Delta F$  syntheses. The final refinement involved the  $x$ ,  $y$ ,  $z$ ,  $\beta_{ij}$  parameters for the non-hydrogen atoms and the  $x$ ,  $y$ ,  $z$  for the hydrogen atoms. The final agreements were  $R = 0.060$  and  $R_w = 0.059$ . 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.  $Beq = 4/3 \sum_i \sum_j \beta_{ij} a_i a_j$

Atom	x	y	z	Beq (Å <sup>2</sup> )
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)		

## REFERENCES AND NOTES

- 1 G. Ogier, J. Chantepie, C. Deshayes, B. Chantegrel, C. Charlot, A. Doutheau, and G. Quash, *Biochem. Pharm.*, 1993, **45**, 1631.
- 2 M. C. Aversa, P. Giannetto, and G. Bruno, *J. Heterocycl. Chem.*, 1988, **25**, 297.
- 3 M. C. Aversa, M. C. Bonaccorsi, and P. Giannetto, *J. Heterocycl. Chem.*, 1989, **26**, 1383.
- 4 J. Bergman, G. Lidgren, and A. Gogoll, *Bull. Soc. Chim. Belg.*, 1992, **101**, 643 and references cited therein.
- 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-2H[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 <sup>1</sup>H- and <sup>13</sup>C-nmr. Therefore the presence of the mixed anhydride functionality seems necessary to induce the benzoxazine ring closure.
- 6 E. S. Severin, N. N. Gulyaev, E. N. Khurs, and R. M. Khomutov, *Biochemical and Biophysical Research Communications*, 1969, **35**, 318 and references cited therein.

Received, 26th July, 1993