The Formation and X-Ray Structure of 6a-Trifluoromethyl-6a,12-dihydro[3,1]benzoxazino[2,1-b][1,3]-benzoxazin-5-ones, a New Heterocyclic Ring System [1]

Maria C. Aversa* [a], Placido Giannetto [a], and Giuseppe Bruno [b]

[a] Dipartimento di Chimica organica e biologica and [b] Dipartimento di Chimica inorganica e Struttura molecolare, Università di Messina, 98100 Messina, Italy

Four representatives of the new ring system [3,1]benzoxazino[2,1-b][1,3]benzoxazine, as determined by X-ray crystallography, were prepared by reaction of N-(2-hydroxybenzyl)anthranilic acids with trifluoroacetic anhydride.

Trifluoroacetic anhydride (TFAA) is a common dehydrating agent, and is used to protect hydroxyl and amino groups as their trifluoroacetates. In a previous communication [2] two of us reported the conversion of N-(2-hydroxybenzyl)-β-aminoacids into 3,4-dihydro-3-(2'-hydroxybenzyl)-2H-1,3-benzoxazines in the presence of a number of dehydrating agents, included TFAA. However, when other Mannich-type products, such as N-(2-hydroxybenzyl)anthranilic acids **1** [3], were treated with an excess of TFAA, without solvent at room temperature (or in boiling benzene), they were converted in excellent yields (>70%) to the tetracyclic benzoxazinobenzoxazinone system **2**, where a two-carbon fragment from TFAA is located at the fusion of the two heterocyclic rings.

The structure of the products **2** was revealed mainly by ^{13}C nmr spectral data. For example, in the 100.6 MHz ^{13}C nmr spectrum (deuteriochloroform) of **2d**, the resonance attributable to C-6a at 102.2 ppm was typical of a carbon in the vicinity of three heteroatoms: the analogous shift for triethylorthoformate is 112.5 ppm [4]. Moreover the resonance at 102.2 ppm appears in the ^{1}H decoupled spectrum of **2d** as a quartet, due to J_{CCF} = 36.6 Hz, while the C-15 resonance at 121.6 ppm shows J_{CF} = 295.7 Hz.
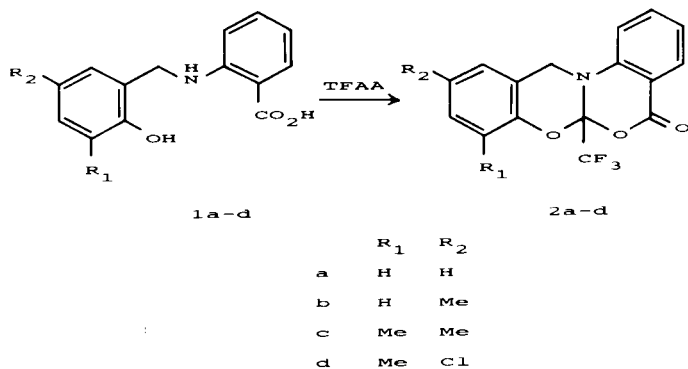
The structure of the compounds **2** was confirmed by X-ray crystallographic analysis of **2d**. The final atomic coordinates for non-hydrogen atoms, bond distances and
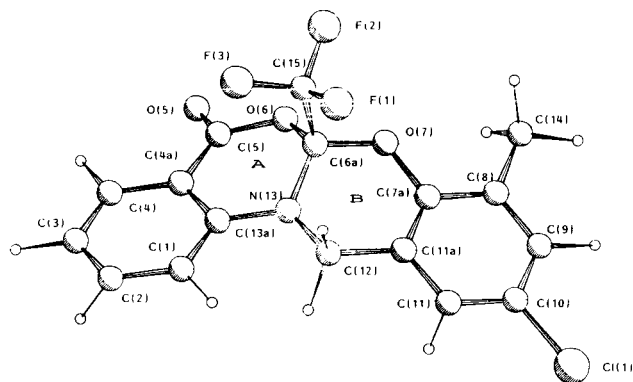

Figure. A perspective drawing of **2d** with the numbering scheme.

	R_1	R_2
a	H	H
b	H	Me
c	Me	Me
d	Me	Cl

Table 1

Final fractional atomic co-ordinates (x 10^4) for non-hydrogen atoms of **2d** with e.s.d.'s in parentheses

Atom	x/a	y/b	z/c
C(1)	12547(6)	11464(4)	1073(5)
C(2)	13294(7)	12722(5)	358(5)
C(3)	14954(7)	13030(5)	236(5)
C(4)	15938(6)	12086(5)	812(5)
C(4a)	15227(6)	10811(4)	1522(4)
C(5)	16310(7)	9776(5)	2058(5)
O(5)	17848(4)	9834(4)	1792(4)
O(6)	15466(4)	8610(3)	2925(3)
C(6a)	13633(6)	8459(4)	3373(5)
O(7)	13406(4)	7059(3)	3675(4)
C(7a)	12230(5)	6472(4)	3263(4)
C(8)	12252(5)	5047(4)	3496(4)
C(9)	11093(6)	4419(4)	3096(5)
C(10)	9974(6)	5187(4)	2487(5)
C(11)	9961(6)	6586(4)	2271(5)
C(11a)	11110(5)	7229(4)	2673(4)
C(12)	11200(6)	8762(4)	2394(5)
N(13)	12921(4)	9171(3)	2328(4)
C(13a)	13534(6)	10481(4)	1663(4)
C(14)	13516(6)	4240(4)	4128(5)
C(15)	2861(6)	8940(4)	4818(5)
Cl(1)	8556(2)	4348(1)	1978(2)
F(1)	1163(4)	8668(3)	5396(3)
F(2)	3612(4)	8326(3)	5748(3)
F(3)	3045(4)	10269(2)	4688(3)

angles are reported in Tables 1-3. Lists of thermal parameters, atomic coordinates for hydrogen atoms, and the observed and calculated structure factors are available on request. The Figure shows a projection of **2d** molecule which illustrates the assigned structure and stereochemistry. Both the heterocyclic rings adopt envelope conformations, with a slight distortion of the B envelope, so that an overall V-shape of the molecule results. The atoms C(6a) and N(13) are 0.093(5) and 0.543(4) Å respectively out of the mean plane defined by C(7a), C(11a), C(12), and O(7): N(13) shows the expected tetrahedral configuration, being 0.172(3) Å out of the plane defined by C(6a), C(12), and C(13a). The dihedral angle between the two benzene ring planes is 30.1(1)°. Bond distances and angles in the aromatic nuclei require no special comment. The reduced value of the bond angle O(5)–C(5)–O(6) [117.3(5)°] with respect to C(4a)–C(5)–O(5) [126.7(5)°] may be indicative of electronic effects due to the trifluoromethyl substituted aza-ortho-ester moiety of the molecule; the same phenomenon should be responsible for the value of the bond angle O(6)–C(6a)–O(7) [103.4(4)°].

Table 2

Bond lengths (Å) of **2d** with their e.s.d's in parentheses

C(1)–C(2)	1.389(6)	C(7a)–C(11a)	1.369(6)
C(1)–C(13a)	1.404(7)	C(7a)–O(7)	1.378(6)
C(2)–C(3)	1.371(8)	C(8)–C(9)	1.382(7)
C(3)–C(4)	1.373(7)	C(8)–C(14)	1.508(7)
C(4)–C(4a)	1.394(6)	C(9)–C(10)	1.385(7)
C(4a)–C(5)	1.462(6)	C(10)–C(11)	1.375(6)
C(4a)–C(13a)	1.397(7)	C(10)–Cl(1)	1.743(6)
C(5)–O(5)	1.184(6)	C(11)–C(11a)	1.384(7)
C(5)–O(6)	1.380(5)	C(11a)–C(12)	1.508(6)
C(6a)–C(15)	1.544(7)	C(12)–N(13)	1.468(6)
C(6a)–N(13)	1.431(7)	C(13a)–N(13)	1.393(5)
C(6a)–O(6)	1.417(6)	C(15)–F(1)	1.331(5)
C(6a)–O(7)	1.387(5)	C(15)–F(2)	1.329(6)
C(7a)–C(8)	1.401(6)	C(15)–F(3)	1.325(5)

The structural assignments made for **2a-d** are consistent with their elemental analyses and spectral data (see Experimental). From the mechanistic point of view, the formation of **2** from **1** may be rationalized in terms of an initial formation of trifluoroacetamide or mixed anhydride or trifluoroacetate derivatives of **1**, which are then transformed into products **2** by subsequent intramolecular nucleophilic attacks and dehydrations. Experiments are in progress to eventually support one (or more) of the suggested reaction schemes.

The described reaction thus constitutes an efficient mean of access to the new *N*-bridgehead [3,1]benzoxazino-[1,3]benzoxazine system **2**, the synthesis of which is important, because of the biological significance [5] of oxazine derivatives [6]. As far as we are aware, few examples have been reported in the literature of heterocyclic systems [6,6,6,6] related to these new compounds. These previous examples of benzoxazinobenzoxazines [7] have different ring fusion and heteroatom arrangement as to the compounds prepared by us.

Table 3

Bond angles (°) of **2d** with their e.s.d's in parentheses

C(1)–C(2)–C(3)	121.6(5)	C(8)–C(7a)–C(11a)	122.3(4)
C(1)–C(13a)–C(4a)	118.7(4)	C(8)–C(7a)–O(7)	115.3(4)
C(1)–C(13a)–N(13)	122.5(4)	C(8)–C(9)–C(10)	120.4(4)
C(2)–C(1)–C(13a)	118.8(5)	C(9)–C(8)–C(14)	121.7(4)
C(2)–C(3)–C(4)	120.4(5)	C(9)–C(10)–C(11)	121.8(4)
C(3)–C(4)–C(4a)	119.1(5)	C(9)–C(10)–Cl(1)	118.7(3)
C(4)–C(4a)–C(5)	119.2(5)	C(10)–C(11)–C(11a)	118.4(5)
C(4)–C(4a)–C(13a)	121.2(4)	C(11)–C(10)–Cl(1)	119.5(4)
C(4a)–C(5)–O(5)	126.7(5)	C(11)–C(11a)–C(12)	120.3(4)
C(4a)–C(5)–O(6)	116.3(4)	C(11a)–C(7a)–O(7)	122.4(4)
C(4a)–C(13a)–N(13)	118.7(4)	C(11a)–C(12)–N(13)	109.0(4)
C(5)–C(4a)–C(13a)	119.5(4)	C(12)–N(13)–C(13a)	119.9(4)
C(5)–O(6)–C(6a)	122.3(4)	F(1)–C(15)–F(2)	107.5(4)
C(6a)–N(13)–C(12)	118.4(3)	F(1)–C(15)–F(3)	107.4(4)
C(6a)–N(13)–C(13a)	117.4(4)	F(2)–C(15)–F(3)	107.0(4)
C(6a)–O(7)–C(7a)	120.9(4)	N(13)–C(6a)–O(6)	112.2(4)
C(7a)–C(8)–C(9)	117.1(4)	N(13)–C(6a)–O(7)	114.7(4)
C(7a)–C(8)–C(14)	121.2(4)	O(5)–C(5)–O(6)	117.3(5)
C(7a)–C(11a)–C(11)	119.9(4)	O(6)–C(6a)–O(7)	103.4(4)
C(7a)–C(11a)–C(12)	119.7(4)		

EXPERIMENTAL

Melting points were recorded on a Kofler block and are uncorrected. Ir spectra were recorded in chloroform using a Perkin-Elmer 225 spectrophotometer, ¹H and ¹³C nmr spectra in deuteriochloroform using Varian EM360, FT80, and Bruker WH400 instruments with tetramethylsilane as internal standard. Mass spectra were obtained on a Kratos M25 spectrometer. For silica gel column chromatography, Kieselgel S 0.063-0.2 mm (Riedel - de Haën) was used, eluting with petroleum ether (bp 30-50°) containing increasing amounts of diethyl ether.

General Procedure for Preparation of 6a-Trifluoromethyl-6a,12-dihydro-[3,1]benzoxazino[2,1-*b*][1,3]benzoxazin-5-ones **2a-d**.

Trifluoroacetic anhydride (TFAA) (23.8 mmoles) was added to *N*-(2-hydroxybenzyl)anthranilic acid **1** (4 mmoles) [3], and the obtained deep red solution was allowed to stand under stirring at room temperature avoiding the contact with the atmosphere moisture. After about 6 hours, the reaction mixture was diluted with benzene (20 ml), and made alkaline with a slight excess of 10% sodium bicarbonate aqueous solution. Stirring was continued for 4 hours, the benzene layer was then separated, and the aqueous phase extracted again with benzene. The combined organic layers were washed with water, dried with sodium sulfate, and evaporated *in vacuo* to give the benzoxazinobenzoxazinone **2**. According to circumstances, the products **2** were purified by column chromatography. The yields were always very good (>70%) even though the reaction was carried out in benzene solution at reflux for 6 hours using 2:1 molar amounts of TFAA and **1**.

6a-Trifluoromethyl-6a,12-dihydro[3,1]benzoxazino[2,1-*b*][1,3]benzoxazin-5-one (**2a**).

This compound had mp 123-125°; ir: 1750 (C = O) cm⁻¹; ¹H nmr: δ 4.67 (2H, br s, CH₂), 6.5-8.2 (8H, m, benzene H) ppm; ¹³C nmr: δ 44.1 (C-12), 112.9 (C-3), 117.4 (C-8), 121.3 (C-1), 123.6 (C-10), 125.7 (C-11), 129.3 (C-9), 130.7 (C-4), 136.5 (C-2), 144.2 (C-13a) ppm.

Anal. Calcd. for C₁₆H₁₀F₃NO₃: C, 59.82; H, 3.14; N, 4.36. Found: C, 59.66; H, 3.14; N, 4.31.

10-Methyl-6a-trifluoromethyl-6a,12-dihydro[3,1]benzoxazino[2,1-*b*][1,3]-benzoxazin-5-one (**2b**).

This compound had mp 162-164°; ^{1}H nmr: δ 2.35 (3H, s, CH$_3$), 4.62 (2H, br s, CH$_2$), 6.7-8.0 (7H, m, benzene H) ppm.

Anal. Calcd. for C$_{17}$H$_{12}$F$_3$NO$_3$: C, 60.90; H, 3.61; N, 4.18. Found: C, 61.05; H, 3.68; N, 4.32.

8,10-Dimethyl-6a-trifluoromethyl-6a,12-dihydro[3,1]benzoxazino[2,1-*b*]-[1,3]benzoxazin-5-one (**2c**).

This compound had mp 150-152°; ir: 1750 (C = O) cm^{-1}; ^{1}H nmr: δ 2.28 (6H, s, 2 x CH$_3$), 4.53 (2H, br s, CH$_2$), 6.7-8.2 (6H, m, benzene H) ppm; ^{13}C nmr: δ 15.0 (C-14), 20.7 (C-16, *i.e.* 10-Me), 44.7 (C-12), 111.5 (C-4a), 113.3 (C-3), 121.1 (C-1), 123.3 (C-11), 126.9 (C-8), 130.5 (C-9), 131.2 (C-4), 132.5 (C-11a), 132.7 (C-10), 136.5 (C-2), 144.3 (C-7a), 144.6 (C-13a), 151.3 (C-5) ppm.

Anal. Calcd. for C$_{18}$H$_{14}$F$_3$NO$_3$: C, 61.89; H, 4.04; N, 4.01. Found: C, 61.91; H, 4.27; N, 4.12.

10-Chloro-8-methyl-6a-trifluoromethyl-6a,12-dihydro[3,1]benzoxazino-[2,1-*b*][1,3]benzoxazin-5-one (**2d**).

This compound had mp 194-196°; ir: 1760 (C = O) cm^{-1}; ^{1}H nmr: δ 2.33 (3H, s, CH$_3$), 4.56 (2H, br s, CH$_2$), 6.9-8.1 (6H, m, benzene H) ppm; ^{13}C nmr: δ 15.1 (C-14), 44.3 (C-12), 102.2 (C-6a), 111.8 (C-4a), 113.3 (C-3), 121.6 (C-1), 121.6 (C-15), 122.0 (C-8), 123.0 (C-11), 128.5 (C-10), 129.3 (C-11a), 130.5 (C-9), 130.7 (C-4), 136.7 (C-2), 144.1 (C-13a), 145.5 (C-7a), 158.3 (C-5) ppm; ms: m/z (% relative intensity) 369 (10, M$^+$), 156 (62), 155 (14), 154 (100), 146 (33), 128 (12), 126 (46), 125 (10), 91 (90), 90 (66), 89 (15), 77 (20), 69 (24), 51 (20), 39 (24).

Anal. Calcd. for C$_{17}$H$_{11}$ClF$_3$NO$_3$: C, 55.23; H, 3.00; Cl, 9.59; N, 3.79. Found: C, 55.58; H, 3.30; Cl, 9.35; N, 3.61.

Crystallography.

Crystal Data for **2d**: C$_{17}$H$_{11}$ClF$_3$NO$_3$, M = 369.73, triclinic, space group P1̄, a = 8.174(1), b = 10.017(2), c = 10.162(2) Å, α = 78.69(2), β = 69.78(2), γ = 85.99(2)°, U = 765.6 Å^3, Z = 2, D$_c$ = 1.605 gcm^{-3}. Diffraction intensities were measured on a Siemens-Stoe four-circle diffractometer with graphite monochromatized Mo-K$_\alpha$ radiation using a crystal with dimensions of 0.20 x 0.24 x 0.18 mm. A total of 2460 reflections were collected to 3 < 2θ < 50°, of which 1463 had $|F_o| > 3\sigma(F_o)$ and were used in the refinement. The intensity data were corrected for Lorentz and polarization effects but not for absorption [μ(Mo-K$_\alpha$) 3.1 cm^{-1}]. The structure was solved by direct methods (MULTAN-80) and refined by full-matrix least-squares (SHELX 76). All the hydrogen atoms were included in the scattering model in calculated idealized positions [d(C-H) = 1.08 Å] with a common thermal parameter. The weighting scheme used was w = 2.922/(σ^2F$_o$ + 0.000227F$_o^2$). The final R index was 0.054.

REFERENCES AND NOTES

[1] Presented in part at the Giornate di chimica organica fisica e meccanicistica, Catania, October 22-25th, 1986.

[2] M. C. Aversa, P. Giannetto, C. Caristi, and A. Ferlazzo, *J. Chem. Soc., Chem. Commun.*, 469 (1982).

[3] M. C. Aversa and P. Giannetto, *J. Chem. Res.* (S), 200 (1984).

[4] L. F. Johnson and W. C. Jankowski, "Carbon-13 NMR Spectra", Wiley-Interscience, New York, 1972, p 279.

[5] Several oxazine and thiazine derivatives show interesting activity as tranquilizers, sedatives, antitubercular, antiepileptic, antitumour, parasiticidal and bacteriocidal agents.

[6] M. Sainsbury, in "Comprehensive Heterocyclic Chemistry", Vol **3**, A. R. Katritzky and C. W. Rees, eds, Pergamon, Oxford, 1984, p 1037.

[7] J. M. Bakke, *Acta Chem. Scand.*, **B29**, 1063 (1975); S. Morimura, *Heterocycles*, **14**, 1331 (1980); F. M. Abdelrazek, Z. E. Kandeel, K. M. H. Hilmy, and M. H. Elnagdi, *Chem. Ind. (London)*, 439 (1983); J. Barluenga, F. Aznar, R. Liz, M. P. Cabal, F. H. Cano, and C. Foces-Foces, *Chem. Ber.*, **119**, 887 (1986); E. Tauer, K. H. Grellmann, E. Kaufmann, and M. Noltemeyer, *ibid.*, **119**, 3316 (1986); F. Fülöp, G. Bernàth, and I. Pelczer, *Tetrahedron Letters*, **27**, 2517 (1986).