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Crystal Structure of Diethyl 2-[2,2,2-trifluoro-1-(indole-3-yl)-ethyl]-2-acetamidomalonate

The title compound ($C_{19}H_{21}F_3N_2O_5$) has been determined from three dimensional X-ray diffraction data. The crystals are monoclinic, $a = 7.626(4)\text{\AA}$, $b = 17.515(4)\text{\AA}$, $c = 15.066(3)\text{\AA}$, $\beta = 101.02(3)^\circ$, $V = 1975(1)\text{\AA}^3$, $Z = 4$, $D_{\text{calc}} = 1.393\text{g}\cdot\text{cm}^{-3}$, space group $P2_1/c$. The structure was solved by direct methods and refined by full-matrix least-squares method ($R = 0.039$).

Keywords: crystal structure, indole derivative, acetamidomalonate, hydrogen-bonding, trifluoromethyl, diastereoselective decarboxylation,

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1. Introduction

Recent studies have revealed that easy substitution of hydrogen atom by fluorine or trifluoromethyl group at a key position of a bioactive compound can exert a profound pharmacological effect (FILLER, 1993). Nowadays the syntheses and bioactivities of fluorine-substituted amino acids (SAKAI, 1996; YAMAZAKI, 1991) and their derivatives (CORRADI, 1998) have become important topics in this field, and 3-trifluoromethyltryptophan is considered to be one of the most interesting fluorine-containing amino acids for this purpose.

The target compound, 3-trifluoromethyltryptophan, could be prepared by hydrolysis and subsequent decarboxylation of diethyl 2-[2,2,2-trifluoro-1-(indol-3-yl)ethyl]-2-acetamidomalonate obtained from the replacement reaction of 2,2,2-trifluoro-1-(indole-3-yl)ethanol (MAKI, 1988) with diethyl acetamidomalonate in the presence of strong bases. Four stereoisomers were expected to be formed after the decarboxylation, but actually the product analysis showed clearly that two of the stereoisomers (a pair of enantiomers) were predominantly generated in the ratio of 97:3. It implies that the situation of the two ethoxycarbonyl groups of the diester molecule might be quite different. To our knowledge, this is the first observed case for the highly diastereoselective decarboxylation, so it is apparently necessary and interesting to account for the unexpected result. As a part of this work, the crystal structure of diethyl 2-[2,2,2-trifluoro-1-(indol-3-yl)ethyl]-2-acetamidomalonate (Fig.1), obtained by recrystallization from acetone as colorless needles, m.p. 162–163°C, was determined by X-ray analysis.

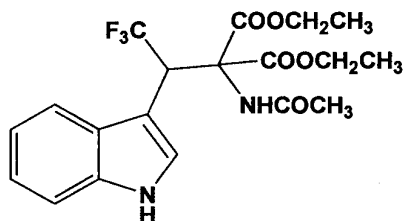


Fig. 1. Chemical structure of the compound

2. Experimental

All X-ray measurements were made at $23 \pm 0.1^\circ\text{C}$ on a Rigaku AFC5R diffractometer with graphite monochromated $\text{MoK}\alpha$ radiation ($\lambda = 0.71069 \text{ \AA}$) operating in $\omega/2\theta$ scanning mode using a single crystal suitable for data collection. Accurate lattice parameters were determined from least-squares refinement of the setting angles of 25 well-centered reflections in the range $20^\circ \leq 2\theta \leq 23^\circ$. During data collection, three standard reflections periodically observed showed no significant intensity variation. The ranges of h, k, l are $0 \leq h \leq 9, 0 \leq k \leq 22, -19 \leq l \leq 19$. 4536 unique reflections were measured. The final cycle of full-matrix least-squares refinement was based on 2544 observed reflections ($I > 3\sigma(I)$) and 346 variable of parameters. The refinement was performed based on (F) against all reflections. Corrections for Lorentz and polarization factors were applied to the intensity values but no absorption corrections were made. Table 1 shows the crystal and experimental data.

Crystal morphology	colorless, needles
Crystal dimensions (mm)	0.2 x 0.2 x 0.6
Chemical formula	$\text{C}_{19}\text{H}_{21}\text{F}_3\text{N}_2\text{O}_5$
Molecular weight (g/mol)	414.38
Crystal system	monoclinic
Space group	$P2_1/c$
Lattice parameters	
<i>a</i>	7.626(4) \AA
<i>b</i>	17.515(4) \AA
<i>c</i>	15.066(3) \AA
β	101.02(3) $^\circ$
Volume (\AA^3)	1975(1)
Number of formula units <i>Z</i>	4
Calculated density D_c ($\text{g}\cdot\text{cm}^{-3}$)	1.393
Absorption coefficient (cm^{-1})	1.19
$2\theta_{\text{max}}$	55.0 $^\circ\text{C}$
Unique data measured	4536 ($R_{\text{int}} = 0.016$)
Observed data	2544 ($I > 3\sigma(I)$)
$R(F)$	0.039
<i>w</i>	$1/\sigma^2(F_0)$
$wR(F^2)$	0.035
No. of parameters refined	346
Program system	TEXSAN(1985 & 1992)

Table 1: Crystal data for the title compound

3. Structure analysis

The structure was solved by direct methods (ALTORE, 1994 (SIR92)), expanded using Fourier techniques (BEURSKENS, 1994 (DIRDIF94)), and refined on (F) by full-matrix least-squares methods. The non-hydrogen atoms were refined anisotropically. The hydrogen atoms bonded to the carbon atoms were assigned based on the expected bonding geometry, and those bonded to the nitrogen atoms were found in a difference Fourier map. The hydrogen atoms were refined isotropically in the final least squares cycles. The final atomic parameters are listed in Table 2, and the molecular geometries for the non-H atoms are given in Table 3 and in Table 4, respectively. An ORTEP drawing of the molecular structure with atom numbering is shown in Fig.2.

Atom	x	y	z	Beq
F1	0.9487(2)	0.21337(9)	1.05259(9)	5.59(4)
F2	1.0174(2)	0.24380(10)	0.9255(1)	5.69(4)
F3	1.0651(2)	0.1303(1)	0.9776(1)	6.63(4)
O1	0.6024(2)	0.18983(10)	1.0716(1)	4.78(4)
O2	0.4314(2)	0.28401(9)	1.00028(9)	3.61(3)
O3	0.3595(2)	0.20652(9)	0.78684(10)	4.12(4)
O4	0.4152(2)	0.11009(8)	0.88629(10)	3.61(3)
O5	0.7775(2)	0.3522(1)	0.9907(1)	4.74(4)
N1	0.8255(3)	0.1292(1)	0.6824(1)	4.19(5)
N2	0.6311(2)	0.2885(1)	0.8691(1)	3.18(4)
C1	0.8158(3)	0.1756(1)	0.7544(2)	3.89(5)
C2	0.7846(3)	0.1327(1)	0.8255(1)	3.26(5)
C3	0.7731(3)	0.0546(1)	0.7957(1)	3.38(5)
C4	0.7985(3)	0.0552(1)	0.7054(1)	3.80(5)
C5	0.7978(4)	-0.0117(2)	0.6549(2)	4.91(6)
C6	0.7740(4)	-0.0791(2)	0.6965(2)	5.74(8)
C7	0.7492(4)	-0.0816(2)	0.7859(2)	5.41(7)
C8	0.7475(4)	-0.0155(1)	0.8356(2)	4.42(6)
C9	0.7674(3)	0.1605(1)	0.9186(1)	3.33(5)
C10	0.9474(3)	0.1881(2)	0.9684(2)	4.59(6)
C11	0.6072(3)	0.2169(1)	0.9137(1)	3.06(4)
C12	0.5517(3)	0.2285(1)	1.0066(1)	3.28(5)
C13	0.3683(3)	0.3016(1)	1.0839(1)	3.80(5)
C14	0.2639(5)	0.3741(2)	1.0676(2)	5.53(7)
C15	0.4448(3)	0.1779(1)	0.8534(1)	3.09(4)
C16	0.2750(4)	0.0640(1)	0.8313(2)	4.08(6)
C17	0.2541(5)	-0.0073(2)	0.8817(2)	5.19(7)
C18	0.7113(3)	0.3512(1)	0.9108(2)	3.61(5)
C19	0.7149(5)	0.4190(2)	0.8497(2)	5.74(8)

$$\text{Beq} = 8/3 \cdot \pi^2 [U_{11}(aa^*)^2 + U_{22}(bb^*)^2 + U_{33}(cc^*)^2 + 2U_{12}aa^*bb^*\cos\gamma + 2U_{13}aa^*cc^*\cos\beta + 2U_{23}bb^*cc^*\cos\alpha]$$

Table 2: Final atomic coordinates for non-hydrogen atoms and equivalent isotropic temperature parameters (\AA^2)

4. Discussion

An intramolecular hydrogen bond is found between N(2)–H and O(3). The distances of N(2)–H, N(2)⋯O(3) and O(3)⋯H are 0.81(2) Å, 2.628(2) Å and 2.19(2) Å, respectively. The angle of N(2)–H⋯O(3) is 114(2)°. A short contact is kept between N(1)–H⋯O(5) due to the intermolecular hydrogen bond, and the distances of N(1)–H, N(1)⋯O(5) and H⋯O(5) are 0.85(2), 2.860(2) and 2.06(2), respectively. The angle of N(1)–H⋯O(5) is 156(2)°. One of the ethoxycarbonyl groups with the intramolecular hydrogen bond is above the indole ring. The deviations of N(1), C(1) and C(2) from the weighted-least-squares plane through all the

ring atoms are 0.0101 Å, 0.0098 Å and 0.0025 Å, respectively. Both the benzene and the pyrrole rings of the indole ring system are planar, and the dihedral angle between the two rings is 178.57°. The acetamido group is trigonal and the angle between N(2)–C(18)–C(19) is 114.6(2)°.

The observations of the intramolecular hydrogen bond and the greatly different orientation of the ethoxycarbonyl groups are obviously important and helpful to understand the subsequent highly diastereoselective decarboxylation of the title compound.

N1—C1	1.369(3)	N1—C4	1.367(3)
C1—C2	1.367(3)	C2—C3	1.437(3)
C2—C9	1.514(3)	C3—C4	1.410(3)
C3—C8	1.398(3)	C4—C5	1.398(3)
C5—C6	1.365(4)	C6—C7	1.396(4)
C7—C8	1.379(4)	C9—C10	1.513(3)
C9—C11	1.563(3)	C10—F1	1.341(3)
C10—F2	1.337(3)	C10—F3	1.344(3)
C11—C12	1.552(3)	C11—C15	1.547(3)
C11—N2	1.450(3)	C12—O1	1.193(3)
C12—O2	1.327(3)	O2—C13	1.464(3)
C13—C14	1.494(4)	C15—O3	1.196(2)
C15—O4	1.323(3)	O4—C16	1.464(3)
C16—C17	1.485(4)	N2—C18	1.351(3)
C18—O5	1.213(3)	C18—C19	1.506(4)

Table 3: Interatomic distances(Å)

C1—N1—C4	109.2(2)	N1—C1—C2	109.7(2)
N1—C4—C5	129.9(2)	N1—C4—C3	107.9(2)
C1—C2—C3	106.8(2)	C1—C2—C9	127.5(2)
C2—C3—C4	106.4(2)	C2—C3—C8	135.0(2)
C3—C2—C9	125.8(2)	C3—C4—C5	122.2(2)
C4—C3—C8	118.5(2)	C4—C5—C6	117.5(2)
C5—C6—C7	121.6(3)	C6—C7—C8	121.0(3)
C7—C8—C3	119.1(2)	C10—C9—C11	116.6(2)
C9—C10—F1	114.7(2)	C9—C10—F2	113.7(2)
C9—C10—F3	109.6(2)	F1—C10—F2	106.6(2)
F1—C10—F3	105.5(2)	F2—C10—F3	106.2(2)
C9—C11—N2	113.8(2)	N2—C11—C12	112.6(2)
N2—C11—C15	105.5(2)	C11—C12—O1	124.4(2)
O1—C12—O2	125.9(2)	C12—O2—C13	115.4(2)
C11—C15—O3	123.6(2)	O3—C15—O4	125.8(2)
C15—O4—C16	116.2(2)	C11—N2—C18	125.0(2)
N2—C18—O5	122.6(2)	N2—C18—C19	114.6(2)
O5—C18—C19	122.8(2)		

Table 4 : The bond angles (°)

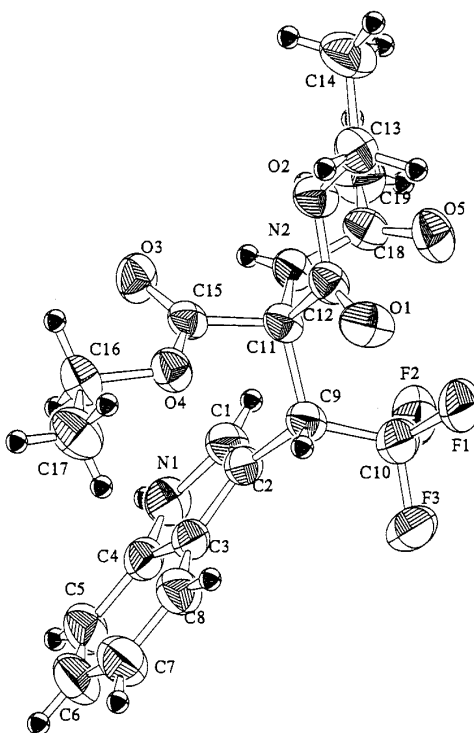


Fig. 2: An ORTEP drawing of the compound with 50% probability ellipsoids and the numbering system

References

- ALTOMARE, A., BURLA, M. C., CAMALLI, M., CASCARANO, M., GIACOVAZZO, C., GUAGLIARDI, A. and POLIDORI, G.: *J. Appl. Cryst.*, **27** (1994) 435
- BEURSKENS, P. T., ADMIRAAL, G., BEURSKENS, G., BOSMAN, W. P., DE GELDER, R., ISRAEL, R. and SMITS, J. M. M.: *The DIRDIF-94 program system*, Technical Report of the Crystallography Laboratory, University of Nijmegen, The Netherlands (1994)
- CORRADI, E., BRAVO, P., PESENTI, C., VERGANI, B., VIANI, F., VOLONTERIO, A. and ZANDA, M.: *Tetrahedron: Asymmetry* **9**(21) (1998) 3731
- FILLER, R., KOBAYASHI Y. and YAGUPOLSKII L. M.: "Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications", Elsevier, Amsterdam (1993)
- MAKI, Y., KIMOTO, H. and FUJII, S.: *J. Fluorine Chem.*, **39** (1988) 47
- SAKAI, T., YAN, F., KASHINO, S. and UNEYAMA, K.: *Tetrahedron* **52**(1) (1996) 233
- YAMAZAKI, T., HAGA, J. and KITAZUME, T.: *Bioorganic & Medicinal Chemistry Letters*, **1** (1991) 271
- TEXSAN: Crystal Structure Analysis Package, Molecular Structure Corporation (1985 & 1992)

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