*Acta Cryst.* (1976). B32, 321

# Methyl 3,4-Dihydroisocoumarin-3-carboxylate

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(*Received* 18 *July* 1975; *accepted* 25 *September* 1975)

**Abstract.** $C_{11}H_{10}O_4$. M.W. 206·20; monoclinic, space group $P2_1/c$; $a=8{\cdot}747$, $b=13{\cdot}266$, $c=8{\cdot}588$ Å, $\beta=96{\cdot}42°$; $D_m=1{\cdot}388$, $D_c=1{\cdot}382$ g cm$^{-3}$ for $Z=4$. $R=0{\cdot}044$ for 1141 observed reflexions. Values of conformation angles are compared with those of a related enzyme substrate.

**Introduction.** The crystal, 0·2×0·3×0·2 mm, was colourless, elongated on **c**. The space group was determined from precession photographs and confirmed on a CAD-4 Nonius automatic diffractometer. 2022 reflexions were measured with Cu $K\alpha$ radiation by the $\omega$–$2\theta$ scan method. Two standard intensities were counted every 40 reflexions. In the range $2\theta\leq144°$, 1141 reflexions had intensities greater than $3\sigma$ above background, where $\sigma(I)$ is defined by $\sigma^2(I)=S+B+(0{\cdot}03S)^2$, $S$ being the scan and $B$ the background count. Lorentz and polarization factors were applied, but no absorption correction. *E*-Statistics confirmed the centrosymmetric space group. Scattering factors were those of Cromer & Mann (1968) for non-hydrogen atoms, and Stewart, Kruger, Ammon, Dickinson & Hall (1972) for H. The structure was solved with *MULTAN* (Germain, Main & Woolfson, 1971). A partial structure containing six of the fifteen atoms was used to compute structure factors; subsequent Fourier maps revealed the positions of the other non-hydrogen atoms.

The structure was refined by the full-matrix least-squares program *CRYLSQ* of the X-RAY 72 system. The final $R$ was 0·044.

With anisotropic temperature factors for all non-hydrogen atoms, $R_w=\{\sum w(|F_o|-|F_c|)^2/\sum w|F_o|^2\}^{1/2}$, was 0·047, where $w=(0{\cdot}1146-0{\cdot}0044|F_o|+0{\cdot}00004|F_o|^2)^{-1}$. Final atomic positions and temperature factors are given in Table 1.* Fig. 1 and Table 4 give bond lengths and angles.

Table 1. *Parameters derived from the final least-squares refinement* (*all* × $10^4$)

The expressions used for the temperature factors are: $\exp[-2\pi^2(U_{11}h^2a^{*2}+U_{22}k^2b^{*2}+U_{33}l^2c^{*2}+2U_{12}hka^*b^*+2U_{13}hla^*c^*+2U_{23}klb^*c^*)]$ and $\exp[-2\pi^2U(2\sin\theta/\lambda)^2]$.

| | *x* | *y* | *z* | $U_{11}$ | $U_{22}$ | $U_{33}$ | $U_{12}$ | $U_{13}$ | $U_{23}$ |
|---|---|---|---|---|---|---|---|---|---|
| O(1) | 921 (6) | 3424 (4) | 3706 (7) | 1107 (44) | 1149 (47) | 840 (41) | 635 (37) | 552 (36) | 481 (36) |
| O(2) | 908 (5) | 4432 (3) | 1632 (5) | 647 (28) | 620 (31) | 658 (28) | 252 (32) | 200 (25) | 150 (25) |
| O(3) | 380 (4) | 611 (3) | 2589 (6) | 698 (33) | 408 (25) | 1270 (50) | −34 (22) | 177 (32) | 220 (39) |
| O(4) | 2690 (4) | 2089 (3) | 2478 (5) | 464 (24) | 422 (23) | 698 (32) | −14 (20) | 186 (22) | 130 (22) |
| C(1) | 3836 (7) | 1465 (5) | 2106 (8) | 476 (38) | 452 (36) | 701 (49) | −57 (30) | 37 (36) | 54 (34) |
| C(2) | 5062 (6) | 1894 (4) | 1286 (7) | 441 (33) | 361 (33) | 478 (35) | 10 (26) | 17 (28) | 14 (28) |
| C(3) | 6168 (8) | 1248 (5) | 770 (8) | 610 (44) | 489 (42) | 709 (50) | 87 (35) | 103 (39) | −32 (28) |
| C(4) | 7369 (8) | 1630 (6) | 73 (6) | 582 (49) | 743 (52) | 192 (42) | 784 (60) | 152 (45) | −33 (43) |
| C(5) | 7505 (7) | 2661 (6) | −123 (9) | 439 (36) | 867 (56) | 773 (59) | −11 (40) | 193 (38) | 173 (46) |
| C(6) | 6431 (7) | 3305 (5) | 392 (8) | 461 (37) | 502 (45) | 758 (46) | 10 (33) | 179 (34) | 65 (36) |
| C(7) | 5189 (6) | 2930 (4) | 1081 (7) | 348 (31) | 383 (31) | 506 (37) | 6 (26) | 66 (27) | 42 (29) |
| C(8) | 4002 (6) | 3595 (5) | 1659 (9) | 449 (35) | 392 (33) | 628 (48) | 14 (27) | 136 (25) | 19 (36) |
| C(9) | 2497 (6) | 3042 (4) | 1629 (8) | 416 (32) | 455 (36) | 495 (37) | 35 (27) | 83 (29) | 67 (31) |
| C(10) | 1346 (7) | 3625 (5) | 2477 (8) | 455 (37) | 623 (42) | 551 (42) | 86 (33) | 126 (24) | 109 (37) |
| C(11) | −207 (9) | 5093 (7) | 2272 (10) | 626 (51) | 795 (53) | 738 (59) | 291 (68) | 108 (50) | −4 (57) |

Table 1 (*cont.*)

| | *x* | *y* | *z* | *U* |
|---|---|---|---|---|
| H(3) | 6083 (68) | 557 (47) | 864 (74) | 821 (200) |
| H(4) | 8170 (75) | 1202 (50) | −414 (80) | 1051 (225) |
| H(5) | 8328 (67) | 2933 (43) | −676 (72) | 578 (154) |
| H(6) | 6512 (6) | 4055 (37) | 359 (60) | 730 (211) |
| H(81) | 3789 (66) | 4187 (46) | 892 (73) | 507 (223) |
| H(82) | 4276 (70) | 3817 (48) | 2800 (80) | 727 (183) |
| H(9) | 2105 (60) | 2894 (40) | 411 (72) | 611 (170) |
| H(111) | 9507 (60) | 5517 (40) | 1424 (66) | 610 (167) |
| *H(112) | 267 | 5442 | 3188 | 400 |
| *H(113) | 8918 | 4726 | 1880 | 400 |

* Calculated positions: temperature factors have not been refined.

* A list of structure factors has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 31408 (19 pp., 1 microfiche). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

Table 2. *Torsion angles, compared with the corresponding angles of acetyltyrosine ethyl ester (Pieret, Durant, Germain & Koch, 1972)*

| Methyl 3,4-dihydroisocoumarin-3-carboxylate | | Acetyltyrosine ester | |
|---|---|---|---|
| C(9)–C(8)—C(7)–C(2) | 30 | $\chi_{21}$ | 62·6 |
| C(9)–C(8)—C(7)–C(6) | 210 | $\chi_{22}$ | 243·9 |
| O(4)–C(9)—C(8)–C(7) | −56·5 | $\chi_1$ | −62·9 |
| O(2)–C(10)–C(9)–O(4) | 170 | $\psi_1$ | 164·4 |
| O(1)–C(10)–C(9)–O(4) | 351 | $\psi_2$ | 343·6 |
| C(1)–O(4)—C(9)–C(10) | 189·5 | $\varphi$ | 75·2 |

Table 3. *Deviations of atoms from the aromatic plane*

Atoms in plane: C(2)–C(3)–C(4)–C(5)–C(6)–C(7)

| Deviations of the other atoms: | | | | |
|---|---|---|---|---|
| | C(1): | −0·07 Å | C(10): | 0·43 Å |
| | C(8): | −0·01 | O(1): | −0·28 |
| | O(3): | −0·34 | O(2): | 1·13 |
| | O(4): | 0·04 | C(11): | 1·05 |
| | C(9): | 0·67 | | |

Table 4. *Distances and angles involving* H *atoms*

| | | | |
|---|---|---|---|
| C(3)—H(3) | 0·92 (6) Å | C(2)—C(3)—H(3) | 118·7 (40)° |
| C(4)—H(4) | 1·02 (6) | C(4)—C(3)—H(3) | 120·8 (40) |
| C(5)—H(5) | 0·97 (6) | C(3)—C(4)—H(4) | 124·5 (38) |
| C(6)—H(6) | 0·99 (5) | C(5)—C(4)—H(4) | 115·1 (38) |
| C(8)—H(81) | 1·02 (6) | C(4)—C(5)—H(5) | 120·2 (34) |
| C(8)—H(82) | 1·02 (6) | C(6)—C(5)—H(5) | 119·5 (34) |
| C(9)—H(9) | 1·08 (6) | C(9)—C(8)—H(81) | 105·4 (36) |
| C(11)–H(111) | 1·09 | C(9)—C(8)—H(82) | 105·4 (32) |
| C(11)–H(112) | 1·10 (6) | C(7)—C(8)—H(81) | 108·7 (35) |
| C(11)–H(113) | 1·09 | C(7)—C(8)—H(82) | 113·0 (35) |
| | | C(81)—C(8)—H(82) | 113·5 (49) |
| | | O(4)—C(9)—H(9) | 109·4 (29) |
| | | C(8)—C(9)—H(9) | 106·7 (30) |
| | | C(10)—C(9)—H(9) | 113·6 (29) |
| | | O(2)—C(11)–H(112) | 110·8 (31) |
| | | O(2)—C(11)–H(113) | 109·9 |
| | | O(2)—C(11)–H(111) | 109·9 |
| | | H(112)–C(11)–H(113) | 109·9 |
| | | H(112)–C(11)–H(111) | 109·9 |
| | | H(113)–C(11)–H(111) | 109·4 |

**Discussion.** The action of α-chymotrypsin on a series of locked substrates seems to be essentially determined by their overall geometry. Within the framework of a general conformational analysis of substrates and inhibitors of enzymes we have determined the crystal structure of methyl 3,4-dihydroisocoumarin-3-carboxylate by X-ray diffraction. This compound is one of the locked substrates of α-chymotrypsin and subtilisin BPN′. The most important features of the molecular structure are the position of C(10) with respect to the aromatic ring and the distortion of the heterocycle (Fig. 2). Dihedral angles are compared with those in acetyltyrosine ethyl ester in Table 2. Deviations from coplanarity with the aromatic ring for different atoms are given in Table 3.

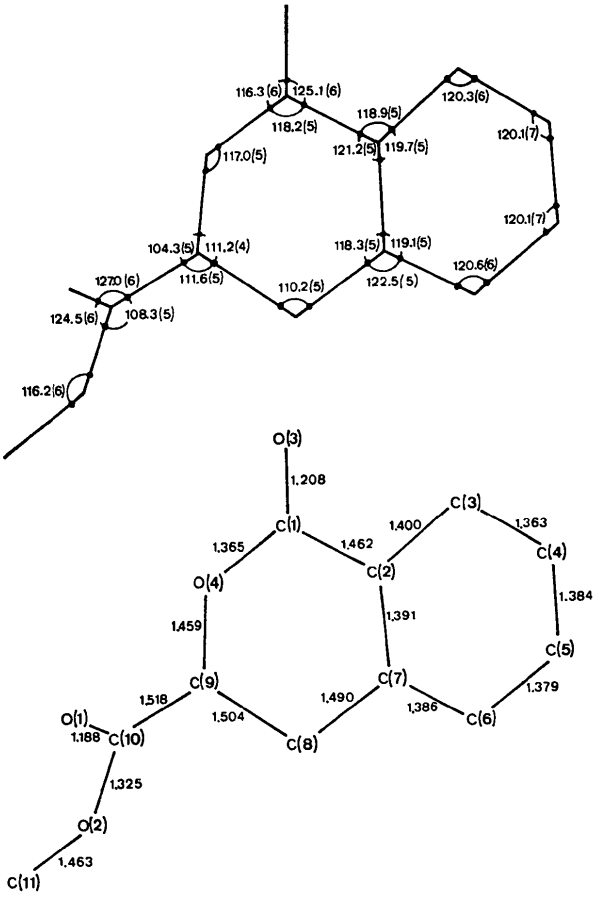


Fig. 1. Numbering, intramolecular distances and angles. $\sigma = 0{\cdot}006$ for C–C and 0·005 Å for C–O.

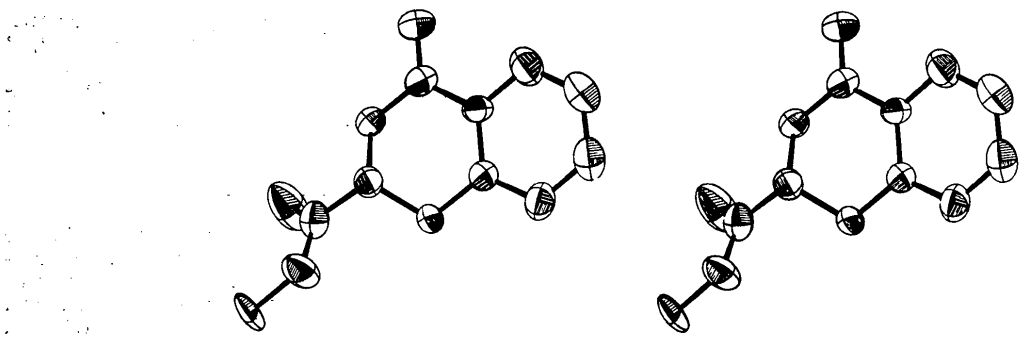

Fig. 2. *ORTEP* stereo diagram with non-hydrogen atoms represented by thermal ellipsoids at 50% probability.

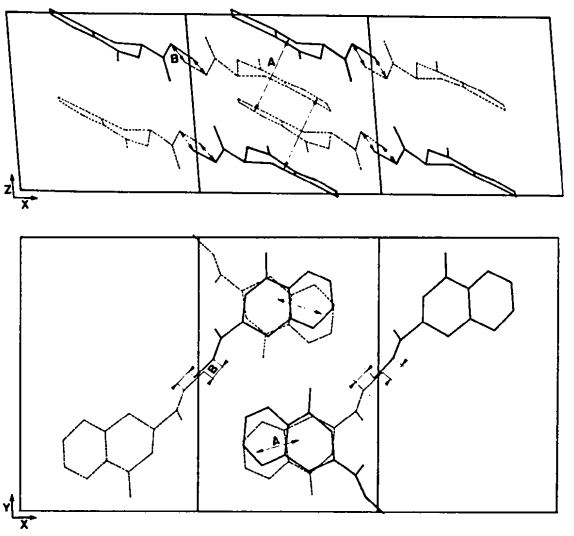

Fig. 3. Views of the unit cell along **b** and **c**.

Because of the absence of proton donors in the molecule, short intermolecular distances are not expected.

Packing by interaction between aromatic rings ($A$ = 3·65 Å) is shown in Fig. 3. The shortest intermolecular distances ($B$ = 3·35 Å) are van der Waals contacts between ester groups. This network of intermolecular bonds is very loose and must be related to the low melting point (91°) compared with that of the analogous compound where –CO– is substituted by –NH– (139°).

We are grateful to Professor V. K. Antonov, USSR Academy of Sciences, Moscow, for supplying the compound.

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*Acta Cryst.* (1976). B**32**, 323

# D-Methyl 3,4-Dihydroisocarbostyril-3-carboxylate

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(*Received* 18 *July* 1975; *accepted* 25 *September* 1975)

**Abstract.** $C_{11}H_{11}O_3N$; M.W. 205·2; orthorhombic, space group $P2_12_12_1$; $a$ = 8·914, $b$ = 21·050, $c$ = 5·398 Å; $D_m$ = 1·350, $D_c$ = 1·346 g cm$^{-3}$ for $Z$ = 4. $R$ = 0·042 for 849 observed reflexions. The structure is compared with those of related enzyme substrates.

**Introduction.** The crystal, 0·3 × 0·3 × 0·5 mm, was centred on the goniometer and treated automatically. With the SEARCH and INDEX routines of the CAD-4 Nonius system, the space group and crystallographic parameters were determined; Table 1 gives experimental conditions for the data collection. 1199 reflexions were measured and 849 had intensities greater than 2·5$\sigma$ above background; Lorentz and polarization factors were applied, but no absorption correction. For the non-hydrogen atoms, the scattering factors were those of Cromer & Mann (1968), and Stewart, Kruger, Ammon, Dickinson & Hall (1972) for H. The structure was solved by direct methods: the phases of 450 normalized structure factors with $E$ > 1·5 were assigned with *MULTAN* (Germain, Main & Woolfson, 1971). The Fourier transform of one of the 16 most probable sets gave the position of all the non-hydrogen atoms. Fourier refinement improved the atomic coordinates till $R$ was 23%. Full-matrix least-squares refinement was then performed with *CRYLSQ* from the X-RAY 72 system.

Table 1. *Experimental conditions*

Source: Cu $K\bar{\alpha}$, $\lambda$ = 1·5418 Å: $\omega$–2$\theta$ scan
Graphite monochromator
Scanning (°): 0·7 + 0·25 tg $\theta$
$\theta$ min: 2°; $\theta$ max: 72°
Aperture: 3·0 + 0·5 tg $\theta$
Confidence level: 2·5$\sigma$
Total number of independent reflexions: 1199
Total observed: 849