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Structural Study of Aldose Reductase Inhibitors. Ten Oxazolecarbamate Derivatives

BY TOSHIMASA ISHIDA, YASUKO IN, CHIAKI TANAKA AND MASATOSHI INOUE

Osaka University of Pharmaceutical Sciences, 2-10-65 *Kawai, Matsubara, Osaka* 580, *Japan*

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Abstract

(1) Benzyl 4-isopropyl-5-phenyl-2-oxazolecarbamate, $C_{20}H_{20}N_2O_3$, $M_r = 336{\cdot}39$, $P\bar{1}$, $a = 19{\cdot}469\ (7)$, $b = 11{\cdot}270\ (3)$, $c = 8{\cdot}667\ (3)$ Å, $\alpha = 95{\cdot}48\ (3)$, $\beta = 99{\cdot}61\ (3)$, $\gamma = 104{\cdot}96\ (3)^\circ$, $V = 1792\ (1)$ Å^3, $Z = 4$, $D_m = 1{\cdot}266\ (2)$, $D_x = 1{\cdot}247$ g cm^{-3}, λ(Cu $K\alpha$) = 1·5418 Å, $\mu = 6{\cdot}49$ cm^{-1}, $F(000) = 712$, $T = 288$ K, $R = 0{\cdot}048$ for 5244 reflections. (2) Benzyl 4-ethyl-5-phenyl-2-oxazolecarbamate, $C_{19}H_{18}N_2O_3$, $M_r = 322{\cdot}37$, $P2_1/n$, $a = 9{\cdot}131\ (7)$, $b = 18{\cdot}81\ (1)$, $c = 9{\cdot}680\ (8)$ Å, $\beta = 101{\cdot}07\ (3)^\circ$, $V = 1631\ (2)$ Å^3, $Z = 4$, $D_m = 1{\cdot}310\ (2)$, $D_x = 1{\cdot}313$ g cm^{-3}, λ(Cu $K\alpha$) = 1·5418 Å, $\mu = 6{\cdot}92$ cm^{-1}, $F(000) = 680$, $T = 288$ K, $R = 0{\cdot}063$ for 2535 reflections. (3) Benzyl 4-methyl-5-phenyl-2-oxazolecarbamate, $C_{18}H_{16}N_2O_3$, $M_r = 308{\cdot}34$, $P2_1/n$, $a = 9{\cdot}210\ (7)$, $b = 8{\cdot}785\ (6)$, $c = 19{\cdot}800\ (9)$ Å, $\beta = 99{\cdot}60\ (3)^\circ$, $V = 1580\ (2)$ Å^3, $Z = 4$, $D_m = 1{\cdot}299\ (3)$, $D_x = 1{\cdot}300$ g cm^{-3}, λ(Cu $K\alpha$) = 1·5418 Å, $\mu = 6{\cdot}93$ cm^{-1}, $F(000) = 648$, $T = 288$ K, $R = 0{\cdot}057$ for 2190 reflections. (4) Benzyl 5-phenyl-2-oxazolecarbamate, $C_{17}H_{14}N_2O_3$, $M_r = 294{\cdot}31$, $P2_1/c$, $a = 6{\cdot}928\ (1)$, $b = 17{\cdot}255\ (6)$, $c = 25{\cdot}406\ (9)$ Å, $\beta = 92{\cdot}90\ (4)^\circ$, $V = 3033\ (2)$ Å^3, $Z = 8$, $D_m = 1{\cdot}270\ (2)$, $D_x = 1{\cdot}289$ g cm^{-3}, λ(Cu $K\alpha$) = 1·5418 Å, $\mu = 6{\cdot}99$ cm^{-1}, $F(000) = 1232$, $T = 288$ K, $R = 0{\cdot}055$ for 3318 reflections. (5) Benzyl 5-*tert*-butyl-2-oxazolecarbamate, $C_{15}H_{18}N_2O_3$, $M_r = 274{\cdot}33$, $C2/c$, $a = 19{\cdot}38\ (2)$, $b = 6{\cdot}458\ (4)$, $c = 26{\cdot}22\ (3)$ Å, $\beta = 109{\cdot}81\ (9)^\circ$, $V = 3087\ (5)$ Å^3, $Z = 8$, $D_m = 1{\cdot}201\ (5)$, $D_x = 1{\cdot}180$ g cm^{-3}, λ(Cu $K\alpha$) = 1·5418 Å, $\mu = 6{\cdot}44$ cm^{-1}, $F(000) = 1168$, $T = 288$ K, $R = 0{\cdot}049$ for 2169 reflections. (6) Benzyl 4,5-dimethyl-2-oxazolecarbamate, $C_{13}H_{14}N_2O_3$, $M_r = 246{\cdot}27$, $P\bar{1}$, $a = 11{\cdot}086\ (4)$, $b = 8{\cdot}544\ (6)$, $c = 7{\cdot}406\ (4)$ Å, $\alpha = 110{\cdot}51\ (4)$, $\beta = 103{\cdot}49\ (3)$, $\gamma = 94{\cdot}35\ (4)^\circ$, $V = 629{\cdot}2\ (7)$ Å^3, $Z = 2$, $D_m = 1{\cdot}299\ (2)$, $D_x = 1{\cdot}300$ g cm^{-3}, λ(Cu $K\alpha$) = 1·5418 Å, $\mu = 7{\cdot}36$ cm^{-1}, $F(000) = 260$, $T = 288$ K, $R = 0{\cdot}065$ for 1938 reflections. (7) Benzyl 5-methyl-2-oxazolecarbamate, $C_{12}H_{12}N_2O_3$, $M_r = 232{\cdot}24$, $P2_1/c$, $a = 4{\cdot}663\ (6)$, $b = 10{\cdot}48\ (2)$, $c = 23{\cdot}28\ (6)$ Å, $\beta = 90{\cdot}9\ (1)^\circ$, $V = 1137\ (4)$ Å^3, $Z = 4$, $D_m = 1{\cdot}329\ (5)$, $D_x = 1{\cdot}357$ g cm^{-3}, λ(Cu $K\alpha$) = 1·5418 Å, $\mu = 7{\cdot}84$ cm^{-1}, $F(000) = 488$, $T = 288$ K, $R = 0{\cdot}058$ for 1569 reflections. (8) Ethyl 5-phenyl-2-oxazolecarbamate, $C_{12}H_{12}N_2O_3$, $M_r = 232{\cdot}24$, $Pbcn$, $a = 26{\cdot}44\ (1)$, $b = 12{\cdot}206\ (8)$, $c = 7{\cdot}206\ (4)$ Å, $V = 2326\ (2)$ Å^3, $Z = 8$, $D_m = 1{\cdot}321\ (4)$, $D_x = 1{\cdot}327$ g cm^{-3}, λ(Cu $K\alpha$) = 1·5418 Å, $\mu = 7{\cdot}67$ cm^{-1}, $F(000) = 976$, $T = 288$ K, $R = 0{\cdot}050$ for 1650 reflections. (9) Benzyl 4-methyl-2-phenyl-5-oxazolecarbamate, $C_{18}H_{16}N_2O_3$, $M_r = 308{\cdot}34$, $P\bar{1}$, $a = 14{\cdot}99\ (4)$, $b = 9{\cdot}16\ (4)$, $c = 6{\cdot}00\ (2)$ Å, $\alpha = 107{\cdot}8\ (3)$, $\beta = 92{\cdot}6\ (5)$, $\gamma = 96{\cdot}2\ (4)^\circ$, $V = 776\ (5)$ Å^3, $Z = 2$, $D_m = 1{\cdot}319\ (4)$, $D_x = 1{\cdot}319$ g cm^{-3}, λ(Cu $K\alpha$) = 1·5418 Å, $\mu = 7{\cdot}05$ cm^{-1}, $F(000) = 324$, $T = 288$ K, $R = 0{\cdot}065$ for 1605 reflections. (10) Benzyl 2-phenyl-4-oxazolecarbamate, $C_{17}H_{14}N_2O_3$, $M_r = 294{\cdot}32$, $P2_1/a$, $a = 12{\cdot}017\ (2)$, $b = 9{\cdot}745\ (2)$, $c = 13{\cdot}923\ (3)$ Å, $\beta = 113{\cdot}65\ (1)^\circ$, $V = 1493{\cdot}6\ (5)$ Å^3, $Z = 4$, $D_m = 1{\cdot}318\ (6)$, $D_x = 1{\cdot}309$ g cm^{-3}, λ(Cu $K\alpha$) = 1·5418 Å, $\mu = 7{\cdot}10$ cm^{-1}, $F(000) = 616$, $T = 288$ K, $R = 0{\cdot}055$ for 2547 reflections. These related molecules exhibit different inhibitory activities for aldose reductase. In addition to the crystal and molecular structures, the correlation between the molecular conformation and inhibitory activity is reported.

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Introduction

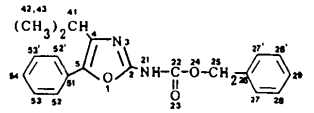
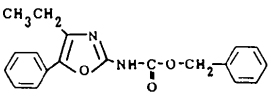
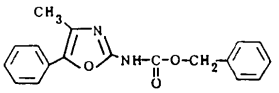
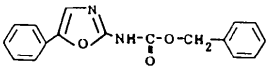
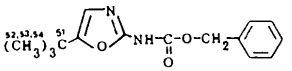
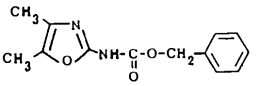
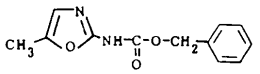
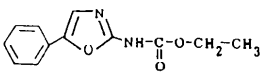
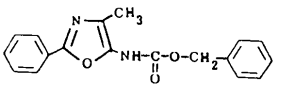
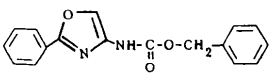
To develop a pharmaceutically useful compound, it is important to know they key atom or key structure and the spatial disposition of this atom or structure responsible for the emergence of biological activity. When information on the binding mode of a drug to the receptor molecule is lacking, a possible method to achieve this end is to compare the conformational characteristics or differences in a series of compounds having structural and physicochemical similarities but exhibiting different pharmacological activities. The structural characteristic thus obtained should be useful in the molecular design of new active compounds.

Aldose reductase (EC1.1.1.21) involved in the sorbitol pathway, an important mechanism in the regulation of mammalian glucose metabolism, has been found to play a physiologically significant role in the initiation of diabetic complications (Gabbay, 1975; Kador, Robinson & Kinoshita, 1985; Cohen, 1987). Therefore, the development of an aldose reductase inhibitor (ARI) has been increasingly required as a means to reduce diabetic complications. Several compounds with different chemical structures such as sorbonil (Sarges, Bordner, Dominy, Peterson & Whipple, 1985) and epalrestat (Terashima, Hama, Yamamoto, Tsuboshima, Kikkawa, Hatanaka & Shigeta, 1984) have already been developed. Benzyl 2-oxazolecarbamate derivatives have also been found to exhibit ARI activities (Tanimoto, Fukuda, Kawamura, Nakao, Shimada, Yamada & Tanaka, 1984; Tanimoto, Fukuda, Yamada, Ohmomo, Nakao & Tanaka, 1986). This paper deals with the X-ray crystal analyses of ten oxazolecarbamate derivatives exhibiting different ARI activities; their chemical structures and ARI activities are given in Table 1. The conformational comparison of these compounds was carried out to provide useful information for considering the structural characteristics of ARI's (Ishida, In, Ohishi, Yamamoto, Inoue, Tanaka, Ueno, Ohmomo, Kanda, Tanaka & Tanimoto, 1988).

Experimental

All compounds were chemically synthesized by the method of Tanaka *et al.* (Tanaka & Asai, 1971; Tanaka & Shibakawa, 1971), and recrystallized from ethanol/ethyl acetate (1), benzene/*n*-hexane (2), chloroform/*n*-hexane [(3), (4), (7)] or methanol/water [(5), (6), (8)–(10)]. Crystal size (mm): (1) 0·3 × 0·3 × 0·2; (2) 0·1 × 0·2 × 0·3; (3) 0·2 × 0·2 × 0·4; (4) 0·2 × 0·3 × 0·3; (5) 0·1 × 0·3 × 0·2; (6) 0·3 × 0·3 × 0·2; (7) 0·4 × 0·4 × 0·2; (8) 0·1 × 0·2 × 0·2; (9) 0·2 × 0·2 × 0·1; (10) 0·4 × 0·4 × 0·3. D_m by flotation using a benzene/carbon tetrachloride mixture. Rigaku four-circle diffractometer with graphite-monochromated

Table 1. *Chemical structures, atomic numbering and AR inhibitory activities of the oxazolecarbamate derivatives*

Compound	Chemical structure	IC_{50} (μM)*
(1)		0·35
(2)		0·84
(3)		2·45
(4)		15·6
(5)		89·5
(6)		418
(7)		770
(8)		1000
(9)		4010
(10)		∞

* The concentration of inhibitor expressing 50% inhibition of AR (rabbit lens) activity.

Cu $K\alpha$ radiation. Cell parameters from 20 to 25 reflections with $30 < 2\theta < 60°$. Intensity data measured by ω–2θ continuous scan mode; scan speed 1–2° min^{-1} (θ); scan range $(A + 0{\cdot}15\tan\theta)°$ with A 0·8 to 1·9°; 5 s stationary background counts; 2θ range 2–130°; hkl range: (1) 0–22, −13–13, −10–10; (2) −10–10, 0–22, 0–11; (3) 0–10, 0–10, −23–23; (4) 0–8, 0–20, −29–29; (5) 0–22, 0–7, −30–30; (6) −13–13, −10–10, 0–8; (7) 0–5, 0–12, −27–27; (8) 0–31, 0–14, 0–8; (9) −16–16, −10–10, 0–6; (10) 0–14, 0–11, −16–16. Four standard reflections monitored every 100 reflections; no significant variation of intensities. Corrections for Lorentz and polarization effects; no absorption corrections. Number of measured reflections, criterion for observed reflections $I \geq n\sigma(I)$, number of reflections used for structure

Table 2. *Fractional coordinates and equivalent isotropic temperature factors* (Å^2) *of compounds* (1)–(10)

The suffix letters *A* and *B* in compounds (1) and (4) represent two crystallographically independent molecules. $B_{eq} = \frac{4}{3}\sum_i\sum_j \mathbf{a}_i\mathbf{a}_j B_{ij}$.

	x	y	z	B_{eq}
(1)				
O(1)*A*	0·12811 (8)	0·0260 (1)	0·5241 (2)	4·38 (5)
C(2)*A*	0·1806 (1)	0·0978 (2)	0·6407 (2)	3·98 (7)
N(3)*A*	0·18337 (9)	0·0579 (2)	0·7762 (2)	4·15 (6)
C(4)*A*	0·1253 (1)	−0·0513 (2)	0·7484 (3)	4·28 (7)
C(5)*A*	0·0922 (1)	0·0717 (2)	0·5947 (3)	4·27 (7)
N(21)*A*	0·2240 (1)	0·2046 (2)	0·6088 (2)	4·38 (6)
C(22)*A*	0·2226 (1)	0·2376 (2)	0·4595 (3)	4·77 (8)
O(23)*A*	0·1931 (1)	0·1712 (2)	0·3382 (2)	7·59 (8)
O(24)*A*	0·25981 (8)	0·3562 (1)	0·4722 (2)	4·86 (5)
C(25)*A*	0·2608 (1)	0·4089 (2)	0·3249 (3)	5·27 (9)
C(26)*A*	0·1975 (1)	0·4604 (2)	0·2844 (3)	4·86 (8)
C(27)*A*	0·1342 (2)	0·3892 (3)	0·1844 (3)	6·8 (1)
C(27′)*A*	0·2016 (2)	0·5793 (2)	0·3478 (3)	6·3 (1)
C(28)*A*	0·0760 (2)	0·4394 (3)	0·1516 (4)	8·3 (1)
C(28′)*A*	0·1434 (2)	0·6265 (3)	0·3154 (4)	7·9 (1)
C(29)*A*	0·0809 (2)	0·5571 (3)	0·2175 (4)	8·1 (1)
C(41)*A*	0·1077 (1)	−0·1273 (2)	0·8763 (3)	5·31 (9)
C(42)*A*	0·1500 (2)	0·2236 (3)	0·8886 (4)	7·0 (1)
C(43)*A*	0·1203 (2)	−0·0453 (3)	1·0355 (3)	7·3 (1)
C(51)*A*	0·0312 (1)	−0·1615 (2)	0·4886 (3)	4·57 (8)
C(52)*A*	−0·0023 (2)	−0·2759 (3)	0·5290 (3)	6·8 (1)
C(52′)*A*	0·0048 (1)	−0·1331 (2)	0·3413 (3)	5·01 (8)
C(53)*A*	0·0615 (2)	−0·3575 (3)	0·4238 (4)	7·9 (1)
C(53′)*A*	0·0532 (1)	0·2172 (3)	0·2378 (3)	6·1 (1)
C(54)*A*	−0·0869 (1)	−0·3289 (3)	0·2780 (3)	6·8 (1)
O(1)*B*	0·39404 (7)	0·3722 (1)	1·1352 (1)	3·75 (4)
C(2)*B*	0·3417 (1)	0·3009 (2)	1·0168 (2)	3·54 (6)
N(3)*B*	0·31816 (9)	0·3590 (1)	0·9078 (2)	3·70 (5)
C(4)*B*	0·3588 (1)	0·4828 (2)	0·9564 (2)	3·60 (6)
C(5)*B*	0·4055 (1)	0·4918 (2)	1·0930 (2)	3·53 (6)
N(21)*B*	0·31630 (9)	0·1762 (1)	1·0234 (2)	3·92 (6)
C(22)*B*	0·3574 (1)	0·1078 (2)	1·0983 (2)	4·15 (7)
O(23)*B*	0·41837 (9)	0·1462 (1)	1·1699 (2)	5·48 (6)
O(24)*B*	0·31690 (9)	−0·0106 (1)	1·0750 (2)	5·23 (6)
C(25)*B*	0·3518 (1)	−0·0968 (2)	1·1478 (3)	5·5 (1)
C(26)*B*	0·3497 (1)	−0·0946 (2)	1·3205 (3)	4·29 (7)
C(27)*B*	0·4081 (1)	−0·1113 (2)	1·4215 (3)	5·21 (9)
C(27′)*B*	0·2898 (1)	0·0826 (2)	1·3793 (3)	5·47 (9)
C(28)*B*	0·4072 (1)	−0·1172 (2)	1·5783 (3)	6·1 (1)
C(28′)*B*	0·2888 (2)	−0·0884 (2)	1·5392 (4)	6·2 (1)
C(29)*B*	0·3472 (2)	−0·1062 (2)	1·6364 (3)	6·4 (1)
C(41)*B*	0·3495 (1)	0·5830 (2)	0·8597 (3)	4·23 (7)
C(42)*B*	0·3872 (1)	0·5774 (2)	0·7190 (3)	4·99 (9)
C(43)*B*	0·2691 (1)	0·5743 (2)	0·8061 (3)	5·42 (9)
C(51)*B*	0·4616 (1)	0·5906 (2)	1·1992 (2)	3·58 (6)
C(52)*B*	0·5053 (1)	0·6871 (2)	1·1390 (3)	4·40 (7)
C(52′)*B*	0·4731 (1)	0·5909 (2)	1·3619 (2)	4·08 (7)
C(53)*B*	0·5584 (1)	0·7802 (2)	1·2404 (3)	4·94 (8)
C(53′)*B*	0·5269 (1)	0·6842 (2)	1·4626 (3)	4·56 (8)
C(54′)*B*	0·5698 (1)	0·7794 (2)	1·4020 (3)	4·76 (8)
(2)				
O(1)	0·4046 (2)	0·93368 (9)	0·1693 (2)	3·87 (7)
C(2)	0·4375 (3)	0·9531 (1)	0·3043 (3)	3·8 (1)
N(3)	0·3850 (3)	1·0139 (1)	0·3323 (2)	5·3 (1)
C(4)	0·3114 (4)	1·0394 (2)	0·1995 (3)	5·9 (1)
C(5)	0·3199 (3)	0·9896 (1)	0·1019 (3)	4·3 (1)
N(21)	0·5283 (2)	0·9106 (1)	0·3997 (2)	3·87 (8)
C(22)	0·5858 (3)	0·8466 (1)	0·3659 (3)	3·8 (1)
O(23)	0·5437 (2)	0·8125 (1)	0·2616 (2)	5·31 (9)
O(24)	0·6960 (2)	0·82796 (9)	0·4724 (2)	4·15 (7)
C(25)	0·7780 (3)	0·7632 (1)	0·4512 (3)	4·3 (1)
C(26)	0·9050 (3)	0·7805 (1)	0·3785 (3)	3·61 (9)
C(27)	0·8869 (3)	0·7778 (1)	0·2329 (3)	4·3 (1)
C(27′)	1·0419 (3)	0·7998 (2)	0·4574 (3)	4·8 (1)
C(28)	1·0056 (4)	0·7949 (2)	0·1675 (3)	5·0 (1)
C(28′)	1·1579 (3)	0·8182 (2)	0·3907 (4)	5·8 (1)
C(29)	1·1402 (3)	0·8154 (2)	0·2478 (4)	5·4 (1)
C(41)	0·2603 (4)	1·1212 (2)	0·1821 (3)	6·7 (2)
C(42)	0·1143 (6)	1·1208 (3)	0·2121 (5)	9·4 (3)
C(51)	0·2735 (3)	0·9827 (1)	−0·0498 (3)	4·1 (1)
C(52)	0·1729 (4)	1·0303 (2)	−0·1277 (3)	5·5 (1)
C(52′)	0·3323 (3)	0·9289 (1)	0·1213 (3)	4·8 (1)
C(53)	0·1359 (4)	1·0243 (2)	−0·2735 (3)	6·2 (1)
C(53′)	0·2924 (4)	0·9235 (2)	−0·2661 (3)	5·5 (1)
C(54)	0·1947 (4)	0·9717 (2)	−0·3429 (3)	5·8 (1)
(3)				
O(1)	0·9330 (2)	0·1527 (2)	0·06337 (9)	4·67 (8)
C(2)	0·9584 (3)	0·2940 (3)	0·0431 (1)	4·3 (1)
N(3)	0·8800 (2)	0·3358 (2)	−0·0140 (1)	4·65 (9)
C(4)	0·7916 (3)	0·2083 (3)	0·0348 (1)	4·8 (1)
C(5)	0·8222 (3)	0·0976 (3)	0·0119 (1)	4·5 (1)
N(21)	1·0637 (2)	0·3811 (2)	0·0817 (1)	4·81 (9)
C(22)	1·1407 (3)	0·3397 (3)	0·1444 (1)	5·0 (1)
O(23)	1·1195 (3)	0·2295 (3)	0·1767 (1)	7·3 (1)
O(24)	1·2434 (2)	0·4457 (2)	0·16400 (9)	5·33 (8)
C(25)	1·3447 (3)	0·4145 (4)	0·2275 (1)	5·6 (1)
C(26)	1·4710 (3)	0·3215 (3)	0·2138 (1)	4·7 (1)
C(27)	1·4731 (3)	0·1653 (4)	0·2219 (2)	6·6 (2)
C(27′)	1·5893 (4)	0·3906 (4)	0·1912 (2)	6·5 (2)
C(28)	1·5931 (5)	0·0811 (4)	0·2064 (2)	8·8 (2)
C(28′)	1·7057 (4)	0·3087 (5)	0·1774 (2)	8·7 (2)
C(29)	1·7082 (4)	0·1561 (5)	0·1850 (2)	8·5 (2)
C(41)	0·6848 (4)	0·2128 (4)	−0·1003 (2)	7·6 (2)
C(51)	0·7730 (3)	−0·0573 (3)	0·0223 (1)	4·7 (1)
C(52)	0·6566 (4)	0·1206 (4)	−0·0224 (2)	6·7 (2)
C(52′)	0·8405 (3)	0·1432 (3)	0·0773 (2)	5·7 (1)
C(53)	0·6118 (4)	0·2685 (4)	−0·0124 (2)	7·8 (2)
C(53′)	0·7929 (4)	0·2899 (3)	0·0872 (2)	6·7 (2)
C(54)	0·6800 (4)	0·3528 (3)	0·0425 (2)	7·1 (2)
(4)				
O(1)*A*	1·0130 (3)	0·0941 (1)	0·88484 (7)	4·5 (1)
C(2)*A*	0·9954 (4)	0·0532 (2)	0·9294 (1)	4·0 (1)
N(3)*A*	0·9838 (4)	0·0933 (1)	0·97110 (9)	4·6 (1)
C(4)*A*	0·9910 (5)	0·1695 (2)	0·9539 (1)	4·7 (2)
C(5)*A*	1·0078 (4)	0·1713 (2)	0·9013 (1)	4·2 (1)
N(21)*A*	1·0010 (4)	−0·0258 (1)	0·92840 (9)	4·7 (1)
C(22)*A*	0·9922 (4)	0·0735 (2)	0·8859 (1)	4·3 (1)
O(23)*A*	0·9728 (4)	0·0552 (1)	0·84080 (8)	6·1 (1)
O(24)*A*	1·0053 (3)	0·1473 (1)	0·90438 (7)	5·5 (1)
C(25)*A*	0·9852 (6)	−0·2058 (2)	0·8641 (1)	5·7 (2)
C(26)*A*	0·9999 (5)	0·2831 (2)	0·8907 (1)	5·3 (2)
C(27)*A*	1·1462 (5)	−0·3335 (2)	0·8795 (1)	6·6 (2)
C(27′)*A*	0·8614 (5)	−0·3071 (2)	0·9238 (1)	6·2 (2)
C(28)*A*	1·1517 (6)	−0·4072 (2)	0·9007 (2)	7·9 (2)
C(28′)*A*	0·8711 (6)	0·3787 (2)	0·9468 (2)	7·6 (2)
C(29)*A*	1·0148 (6)	−0·4299 (2)	0·9335 (2)	8·0 (2)
C(51*A*)	1·0297 (4)	0·2305 (2)	0·8615 (1)	4·7 (2)
C(52*A*)	0·9984 (5)	0·3079 (2)	0·8740 (1)	5·7 (2)
C(52′)*A*	1·0851 (6)	0·2107 (2)	0·8114 (1)	6·1 (2)
C(53)*A*	1·0216 (5)	0·3645 (2)	0·8365 (2)	7·1 (2)
C(53′)*A*	1·1106 (7)	0·2680 (2)	0·7742 (1)	7·9 (2)
C(54)*A*	1·0759 (6)	0·3441 (2)	0·7857 (1)	7·6 (2)
O(1)*B*	0·4795 (3)	0·8061 (1)	−0·00477 (8)	4·7 (1)
C(2)*B*	0·4969 (5)	0·8838 (2)	−0·0065 (1)	4·3 (1)
N(3)*B*	0·5175 (4)	0·9179 (1)	0·03824 (9)	4·9 (1)
C(4)**B**	0·5106 (5)	0·8568 (2)	0·0744 (1)	5·1 (2)
C(5)*B*	0·4864 (4)	0·7892 (2)	0·0490 (1)	4·5 (1)
N(21)*B*	0·4923 (4)	0·9215 (1)	−0·05402 (9)	5·0 (1)
C(22)*B*	0·4855 (4)	0·8916 (2)	−0·1032 (1)	4·5 (1)
O(23)*B*	0·4937 (4)	0·8239 (1)	0·11524 (9)	6·7 (1)
O(24)*B*	0·4711 (3)	0·9501 (1)	−0·13749 (8)	5·8 (1)
C(25)*B*	0·4701 (5)	0·9288 (2)	−0·1933 (1)	6·1 (2)
C(26)*B*	0·4581 (5)	1·0025 (2)	−0·2245 (1)	5·9 (2)
C(27)*B*	0·2988 (5)	1·0184 (2)	−0·2567 (1)	6·9 (2)
C(27′)*B*	0·6128 (5)	1·0553 (3)	−0·2218 (2)	7·9 (2)
C(28)*B*	0·2955 (6)	1·0844 (3)	−0·2875 (2)	7·9 (2)
C(28′)*B*	0·6039 (6)	1·1211 (3)	−0·2521 (2)	8·9 (3)
C(29)*B*	0·4492 (6)	1·1363 (3)	−0·2849 (1)	7·8 (2)
C(51)*B*	0·4664 (4)	0·7085 (2)	0·0641 (1)	5·2 (2)
C(52)*B*	0·4980 (5)	0·6875 (2)	0·1164 (1)	6·9 (2)
C(52′)*B*	0·4119 (6)	0·6515 (2)	0·0274 (1)	6·8 (2)
C(53)*B*	0·4737 (5)	0·6099 (3)	0·1320 (2)	7·8 (2)
C(53′)*B*	0·3914 (6)	0·5772 (2)	0·0432 (2)	8·1 (3)
C(54)*B*	0·4194 (5)	0·5559 (2)	0·0956 (2)	7·7 (2)
(5)				
O(1)	0·89457 (5)	0·4586 (1)	0·36853 (3)	5·09 (4)
C(2)	0·93329 (7)	0·4852 (2)	0·42067 (5)	4·59 (6)
N(3)	0·97785 (6)	0·3368 (2)	0·44287 (4)	5·22 (5)
C(4)	0·96842 (7)	0·1957 (2)	0·40007 (5)	5·16 (7)
C(5)	0·91831 (7)	0·2662 (2)	0·35576 (5)	4·88 (6)
N(21)	0·92686 (6)	0·6613 (2)	0·44767 (4)	5·29 (5)
C(22)	0·86680 (7)	0·7908 (2)	0·43461 (5)	4·64 (6)
O(23)	0·81515 (5)	0·7899 (2)	0·39425 (3)	6·23 (5)
O(24)	0·87917 (5)	0·9203 (1)	0·47644 (3)	5·89 (5)
C(25)	0·82338 (8)	1·0734 (2)	0·47318 (5)	6·05 (8)
C(26)	0·83618 (7)	1·1406 (2)	0·53026 (5)	5·21 (7)
C(27)	0·81002 (9)	1·0223 (2)	0·56367 (6)	6·61 (8)
C(27′)	0·87427 (8)	1·3192 (3)	0·55004 (6)	6·53 (8)
C(28)	0·82231 (9)	1·0820 (3)	0·61682 (6)	8·2 (1)
C(28′)	0·88679 (9)	1·3794 (3)	0·60328 (6)	8·1 (1)
C(29)	0·86077 (9)	1·2609 (3)	0·63608 (6)	8·3 (1)
C(51)	0·88269 (8)	0·1925 (2)	0·29890 (5)	6·12 (7)

Table 2 (*cont.*)

	x	*y*	*z*	B_{eq}
C(52)	0·79991 (9)	0·1699 (3)	0·28683 (6)	8·25 (9)
C(53)	0·8948 (1)	0·3510 (3)	0·25918 (6)	8·9 (1)
C(54)	0·9147 (1)	0·0158 (3)	0·29316 (6)	9·5 (1)
(6)				
O(1)	1·0545 (2)	0·9410 (3)	0·7740 (3)	4·69 (8)
C(2)	0·9562 (2)	0·8230 (3)	0·7074 (4)	3·04 (8)
N(3)	0·9415 (2)	0·7076 (2)	0·5238 (3)	2·66 (6)
C(4)	1·0442 (3)	0·7597 (4)	0·4663 (4)	3·62 (9)
C(5)	1·1125 (2)	0·9004 (3)	0·6173 (4)	3·23 (8)
N(21)	0·8715 (2)	0·8101 (3)	0·8113 (3)	3·67 (7)
C(22)	0·7586 (3)	0·7015 (3)	0·7343 (4)	2·29 (8)
O(23)	0·7159 (2)	0·5991 (3)	0·5679 (3)	5·44 (8)
O(24)	0·7009 (2)	0·7318 (2)	0·8807 (3)	3·90 (6)
C(25)	0·5864 (3)	0·6130 (4)	0·8374 (5)	3·85 (9)
C(26)	0·6184 (2)	0·4565 (3)	0·8752 (4)	3·27 (8)
C(27)	0·5658 (3)	0·2974 (4)	0·7326 (4)	4·2 (1)
C(27′)	0·6979 (3)	0·4719 (4)	1·0575 (5)	4·13 (9)
C(28)	0·5929 (3)	0·1546 (4)	0·7724 (5)	5·0 (1)
C(28′)	0·7261 (3)	0·3305 (4)	1·0971 (5)	4·7 (1)
C(29)	0·6739 (3)	0·1709 (4)	0·9530 (5)	4·6 (1)
C(41)	1·0521 (3)	0·6564 (5)	0·2626 (5)	5·1 (1)
C(51)	1·2301 (3)	1·0042 (4)	0·6304 (5)	4·8 (1)
(7)				
O(1)	0·7310 (4)	0·1993 (2)	0·50416 (7)	3·73 (8)
C(2)	0·8555 (6)	0·3140 (2)	0·5016 (1)	3·3 (1)
N(3)	0·7770 (6)	0·3951 (2)	0·5393 (1)	4·3 (1)
C(4)	0·5837 (7)	0·3268 (3)	0·5719 (1)	4·5 (1)
C(5)	0·5550 (6)	0·2077 (3)	0·5519 (1)	3·8 (1)
N(21)	1·0488 (6)	0·3395 (2)	0·45888 (9)	3·9 (1)
C(22)	1·1351 (6)	0·2577 (3)	0·4171 (1)	3·9 (1)
O(23)	1·0505 (5)	0·1501 (2)	0·40951 (9)	5·3 (1)
O(24)	1·3307 (4)	0·3160 (2)	0·38579 (8)	4·11 (9)
C(25)	1·4206 (7)	0·2459 (3)	0·3352 (1)	4·8 (2)
C(26)	1·6088 (6)	0·3311 (3)	0·3006 (1)	3·7 (1)
C(27)	1·6344 (8)	0·3018 (4)	0·2420 (1)	5·6 (2)
C(27′)	1·7589 (7)	0·4324 (3)	0·3240 (1)	4·4 (1)
C(28)	1·8146 (8)	0·3758 (4)	0·2080 (1)	5·7 (2)
C(28′)	1·9335 (8)	0·5053 (3)	0·2881 (2)	5·4 (2)
C(29)	1·9654 (8)	0·4779 (3)	0·2324 (1)	5·5 (2)
C(51)	0·3822 (8)	0·0938 (3)	0·5659 (1)	5·2 (2)
(8)				
O(1)	0·39868 (5)	0·8505 (1)	0·3701 (2)	4·58 (7)
C(2)	0·44108 (8)	0·9041 (2)	0·4232 (3)	4·2 (1)
N(3)	0·43777 (6)	1·0098 (2)	0·4167 (2)	4·51 (9)
C(4)	0·38881 (7)	1·0292 (2)	0·3541 (3)	4·5 (1)
C(5)	0·36453 (8)	0·9346 (2)	0·3251 (3)	4·1 (1)
N(21)	0·48262 (6)	0·8474 (1)	0·4817 (3)	4·9 (1)
C(22)	0·48885 (9)	0·7376 (2)	0·4832 (4)	4·7 (1)
O(23)	0·45813 (6)	0·6690 (1)	0·4368 (3)	6·17 (9)
O(24)	0·53541 (5)	0·7162 (1)	0·5466 (2)	5·49 (8)
C(25)	0·5506 (1)	0·6025 (2)	0·5409 (4)	6·2 (1)
C(26)	0·6016 (1)	0·5939 (2)	0·6209 (4)	7·4 (2)

	x	*y*	*z*	B_{eq}
C(51)	0·31525 (7)	0·9014 (2)	0·2581 (3)	3·94 (9)
C(52)	0·27542 (7)	0·9763 (2)	0·2648 (3)	4·6 (1)
C(52′)	0·30691 (8)	0·7979 (2)	0·1832 (3)	4·8 (1)
C(53)	0·22783 (8)	0·9470 (2)	0·1982 (3)	5·4 (1)
C(53′)	0·2596 (1)	0·7695 (2)	0·1142 (3)	5·3 (1)
C(54)	0·22032 (8)	0·8437 (2)	0·1221 (3)	5·6 (1)
(9)				
O(1)	0·5780 (2)	0·2393 (3)	0·9861 (4)	3·3 (1)
C(2)	0·6513 (3)	0·1608 (4)	0·9173 (7)	3·2 (2)
C(3)	0·6670 (2)	0·0820 (4)	1·0624 (7)	3·0 (1)
N(4)	0·6045 (2)	0·1067 (4)	1·2299 (5)	3·2 (1)
C(5)	0·5539 (2)	0·1999 (4)	1·1762 (7)	2·9 (1)
N(21)	0·6922 (2)	0·1829 (4)	0·7260 (5)	3·5 (1)
C(22)	0·7731 (3)	0·2825 (5)	0·7605 (7)	3·5 (2)
O(23)	0·8139 (2)	0·3477 (4)	0·9482 (5)	5·3 (1)
O(24)	0·7942 (2)	0·2917 (3)	0·5537 (5)	3·8 (1)
C(25)	0·8770 (3)	0·3944 (5)	0·5572 (8)	4·4 (2)
C(26)	0·9582 (2)	0·3092 (5)	0·5315 (7)	3·6 (2)
C(27)	0·9790 (3)	0·2253 (6)	0·3104 (8)	5·1 (2)
C(27′)	1·0135 (3)	0·3140 (6)	0·7246 (8)	5·3 (2)
C(28)	1·0545 (3)	0·1481 (6)	0·2835 (9)	5·8 (2)
C(28′)	1·0891 (3)	0·2365 (6)	0·6974 (9)	6·1 (2)
C(29)	1·1075 (3)	0·1528 (6)	0·4782 (9)	5·7 (2)
C(31)	0·7389 (3)	−0·0183 (5)	1·0582 (8)	4·6 (2)
C(51)	0·4764 (2)	0·2634 (4)	1·2890 (7)	3·1 (1)
C(52)	0·4441 (3)	0·2158 (5)	1·4710 (7)	4·1 (2)
C(52′)	0·4372 (3)	0·3764 (5)	1·2238 (8)	4·2 (2)
C(53)	0·3718 (3)	0·2800 (6)	1·5837 (8)	5·0 (2)
C(53′)	0·3663 (3)	0·4389 (6)	1·338 (1)	5·5 (2)
C(54)	0·3340 (3)	0·3917 (6)	1·5157 (9)	5·9 (2)
(10)				
N(1)	0·3964 (1)	0·8272 (2)	0·3688 (1)	4·06 (6)
C(2)	0·3505 (2)	0·7349 (2)	0·4185 (1)	3·90 (6)
C(3)	0·3778 (2)	0·6067 (2)	0·4014 (2)	5·01 (8)
O(4)	0·4429 (1)	0·6161 (1)	0·3397 (1)	5·14 (6)
C(5)	0·4486 (2)	0·7521 (2)	0·3228 (1)	4·01 (7)
N(21)	0·2873 (1)	0·7845 (2)	0·4762 (1)	4·20 (6)
C(22)	0·2427 (2)	0·7008 (2)	0·5292 (1)	4·20 (7)
O(23)	0·2586 (2)	0·5789 (1)	0·5376 (1)	5·92 (7)
O(24)	0·1802 (1)	0·7734 (1)	0·5725 (1)	4·95 (6)
C(25)	0·1194 (2)	0·6971 (2)	0·6278 (2)	5·11 (9)
C(26)	0·1814 (2)	0·7194 (2)	0·7433 (2)	4·14 (7)
C(27)	0·1314 (2)	0·8076 (3)	0·7928 (2)	6·0 (1)
C(27′)	0·2874 (2)	0·6512 (3)	0·8016 (2)	6·4 (1)
C(28)	0·1904 (3)	0·8267 (4)	0·9021 (2)	8·5 (2)
C(28′)	0·3428 (3)	0·6699 (4)	0·9086 (2)	8·8 (2)
C(29)	0·2956 (3)	0·7554 (4)	0·9579 (2)	8·5 (1)
C(51)	0·5109 (2)	0·7941 (2)	0·2569 (1)	4·20 (7)
C(52)	0·5104 (2)	0·9317 (2)	0·2297 (2)	6·2 (1)
C(52′)	0·5702 (2)	0·7000 (2)	0·2200 (2)	5·05 (8)
C(53)	0·5682 (3)	0·9721 (3)	0·1660 (2)	7·6 (1)
C(53′)	0·6280 (2)	0·7420 (3)	0·1565 (2)	5·7 (1)
C(54)	0·6268 (2)	0·8759 (3)	0·1292 (2)	6·4 (1)

Table 3. *Hydrogen-bond distances* (Å) *and patterns*

	Donor (*D*) at *x*, *y*, *z*	Acceptor (*A*)	Symmetry operation of *A*	Distance *D*···*A*	H-bond pattern
(1)	N(21)*A*	N(3)*B*	*x*, *y*, *z*	3·001 (2)	
	N(21)*B*	N(3)*A*	*x*, *y*, *z*	2·981 (2)	NH···N cyclic dimer
(2)	N(21)	N(3)	1 − *x*, 2 − *y*, 1 − *z*	2·930 (3)	NH···N cyclic dimer
(3)	N(21)	N(3)	2 − *x*, 1 − *y*, − *z*	2·913 (3)	NH···N cyclic dimer
(4)	N(21)*A*	N(3)*A*	2 − *x*, − *y*, 2 − *z*	2·803 (3)	NH···N cyclic dimer
	N(21)*B*	N(3)*B*	1 − *x*, 2 − *y*, − *z*	2·801 (4)	NH···N cyclic dimer
(5)	N(21)	N(3)	2 − *x*, 1 − *y*, 1 − *z*	2·838 (2)	NH···N cyclic dimer
(6)	N(21)	O(1)	2 − *x*, 2 − *y*, 2 − *z*	2·935 (3)	NH···O cyclic dimer
(7)	N(21)	N(3)	2 − *x*, 1 − *y*, 1 − *z*	2·896 (3)	NH···H cyclic dimer
(8)	N(21)	N(3)	1 − *x*, 2 − *y*, 1 − *z*	2·829 (3)	NH···N cyclic dimer
(9)	N(21)	N(4)	*x*, *y*, *z* − 1	3·039 (5)	NH···N infinite chain
(10)	N(21)	O(23)	$\frac{1}{2}-x, \frac{1}{2}+y, 1-z$	2·913 (2)	NH···O infinite chain

refinement: (1) 6126, $n = 2$, 5244; (2) 2772, $n = 2$, 2535; (3) 2685, $n = 2$, 2190; (4) 5168, $n = 3$, 3318; (5) 2619, $n = 0$, 2619; (6) 2132, $n = 2$, 1938; (7) 1956, $n = 2$, 1569; (8) 1999, $n = 2$, 1650; (9) 2304, $n = 2$, 1605; (10) 2547, $n = 0$, 2547. All structures were solved by direct methods using the program *MULTAN*84 (Main, Gemain & Woolfson, 1984). All H atoms ideally calculated and ascertained on respective difference Fourier maps. Block-diagonal least-squares refinements with anisotropic temperature factors for non-H atoms and isotropic temperature factors for H atoms. The function minimized was

Table 4. *Bond lengths* (Å) *and angles* (°) *of the 2-oxazolecarbamate moiety*

	(1*A*)	(1*B*)	(2)	(3)	(4*A*)	(4*B*)	(5)	(6)	(7)	(8)	(9)	(10)	Mean
O(1)—C(2)	1·339 (3)	1·344 (2)	1·334 (3)	1·337 (3)	1·345 (3)	1·347 (4)	1·329 (2)	1·297 (4)	1·337 (3)	1·353 (3)	1·350 (5)	1·353 (2)	1·339 (15)
O(1)—C(5)	1·396 (3)	1·402 (2)	1·392 (3)	1·402 (3)	1·397 (3)	1·397 (4)	1·404 (2)	1·407 (4)	1·395 (3)	1·405 (2)	1·386 (5)	1·378 (3)	1·397 (8)
C(2)—N(3)	1·295 (3)	1·288 (3)	1·289 (4)	1·290 (3)	1·270 (4)	1·282 (4)	1·289 (2)	1·335 (3)	1·280 (4)	1·294 (3)	1·302 (5)	1·288 (2)	1·292 (15)
N(3)—C(4)	1·408 (3)	1·399 (3)	1·414 (4)	1·405 (3)	1·388 (4)	1·401 (4)	1·409 (2)	1·399 (4)	1·386 (4)	1·391 (3)	1·390 (5)	1·378 (2)	1·397 (10)
C(4)—C(5)	1·349 (3)	1·345 (3)	1·343 (4)	1·340 (4)	1·349 (4)	1·339 (4)	1·317 (2)	1·339 (4)	1·338 (4)	1·337 (3)	1·318 (6)	1·338 (3)	1·338 (10)
C(2)—N(21)	1·362 (3)	1·374 (3)	1·372 (3)	1·365 (3)	1·364 (4)	1·371 (4)	1·368 (2)	1·366 (4)	1·378 (3)	1·365 (3)			1·369 (5)
N(21)—C(22)	1·379 (3)	1·378 (3)	1·377 (3)	1·372 (4)	1·356 (4)	1·350 (4)	1·379 (2)	1·368 (4)	1·362 (4)	1·351 (3)	1·402 (5)	1·347 (3)	1·368 (15)
C(22)—O(23)	1·192 (3)	1·190 (3)	1·196 (3)	1·194 (4)	1·190 (4)	1·209 (4)	1·185 (2)	1·191 (4)	1·206 (4)	1·213 (3)	1·202 (5)	1·202 (3)	1·198 (8)
C(22)—O(24)	1·330 (3)	1·341 (3)	1·342 (3)	1·338 (3)	1·359 (4)	1·335 (4)	1·335 (2)	1·344 (4)	1·326 (3)	1·339 (3)	1·319 (5)	1·338 (2)	1·337 (9)
O(24)—C(25)	1·459 (3)	1·455 (3)	1·463 (3)	1·461 (3)	1·439 (4)	1·464 (4)	1·446 (2)	1·460 (4)	1·456 (4)	1·446 (3)	1·469 (5)	1·460 (3)	1·457 (8)
C(25)—C(26)	1·496 (3)	1·502 (3)	1·504 (4)	1·483 (4)	1·495 (5)	1·498 (5)	1·496 (2)	1·510 (4)	1·496 (4)		1·504 (6)	1·492 (3)	1·498 (7)
C(5)—C(51)	1·455 (3)	1·456 (3)	1·454 (4)	1·460 (4)	1·450 (4)	1·452 (4)				1·448 (3)			1·454 (4)
C(2)···O(1)—C(5)	104·8 (1)	103·9 (1)	104·7 (2)	104·2 (2)	104·1 (2)	104·0 (2)	104·1 (1)	104·3 (2)	103·9 (2)	104·1 (1)	104·0 (2)	104·7 (1)	104·2 (3)
O(1)—C(2)—N(3)	114·9 (1)	115·3 (1)	115·2 (1)	115·3 (1)	115·4 (2)	115·8 (2)	115·3 (1)	115·0 (2)	115·9 (1)	114·6 (1)	113·3 (2)	113·7 (1)	115·0 (7)
C(2)—N(3)—C(4)	104·2 (1)	104·1 (1)	104·0 (2)	104·0 (2)	104·4 (2)	103·3 (2)	103·6 (1)	104·1 (2)	103·2 (2)	104·1 (1)	105·0 (2)	104·6 (1)	104·1 (5)
N(3)—C(4)—C(5)	109·1 (1)	109·6 (1)	108·8 (2)	109·4 (2)	109·8 (2)	110·4 (2)	109·7 (1)	107·9 (2)	110·7 (2)	110·6 (1)	109·0 (2)	110·1 (1)	109·6 (8)
O(1)—C(5)—C(4)	107·1 (1)	107·0 (1)	107·4 (2)	107·1 (1)	106·2 (2)	106·6 (2)	107·4 (1)	108·7 (2)	106·2 (2)	106·6 (1)	108·7 (2)	106·9 (1)	107·2 (8)
O(1)—C(2)—N(21)	118·6 (1)	118·9 (1)	119·6 (1)	119·7 (1)	120·2 (1)	120·2 (2)	121·4 (1)	124·9 (2)	119·7 (1)	120·6 (1)			119·9 (8)*
N(3)—C(2)—N(21)	126·5 (1)	125·7 (1)	125·2 (2)	125·0 (1)	124·3 (2)	124·0 (2)	123·3 (1)	120·0 (2)	124·3 (2)	124·8 (1)			124·7 (9)*
C(2)—N(21)—C(22)	124·0 (1)	123·8 (1)	123·9 (2)	124·8 (2)	128·4 (20	129·1 (2)	126·4 (1)	125·7 (2)	126·6 (2)	127·1 (1)			126·0 (18)
N(21)—C(22)—O(23)	125·9 (1)	126·4 (1)	126·4 (1)	126·4 (2)	127·2 (2)	127·2 (2)	127·3 (1)	127·5 (2)	126·4 (2)	126·9 (1)	124·8 (2)	124·7 (1)	126·4 (9)
N(21)—C(22)—O(24)	108·9 (1)	107·8 (1)	108·1 (1)	108·2 (1)	107·1 (2)	108·2 (2)	105·9 (1)	107·7 (2)	108·4 (1)	107·9 (1)	107·9 (2)	110·2 (1)	108·0 (10)
O(23)—C(22)—O(24)	125·1 (1)	125·8 (1)	125·5 (1)	125·5 (2)	125·7 (2)	124·6 (2)	126·8 (1)	124·8 (2)	125·2 (2)	125·2 (1)	127·3 (2)	125·1 (1)	125·6 (7)
C(22)—O(24)···C(25)	116·3 (1)	115·4 (1)	116·0 (2)	116·0 (2)	114·2 (2)	116·1 (2)	117·2 (1)	116·2 (2)	115·0 (2)	115·6 (2)	115·4 (3)	117·3 (1)	115·9 (8)
O(24)—C(25)—C(26)	111·0 (1)	112·9 (1)	110·3 (1)	110·7 (1)	107·6 (2)	107·3 (2)	105·8 (1)	110·6 (2)	108·3 (2)	108·2 (1)	111·5 (2)	110·8 (1)	109·6 (20)
O(1)—C(5)—C(51)	114·3 (1)	116·7 (1)	115·7 (1)	115·2 (1)	117·3 (2)	117·4 (2)				116·8 (1)			116·2 (11)
C(4)—C(5)—C(51)	138·6 (1)	136·3 (1)	136·8 (2)	137·7 (2)	136·4 (2)	136·0 (2)				136·6 (1)			136·9 (8)

* The O(1)—C(2)—N(21) and N(3)—C(2)—N(21) bond angles for (6) were omitted from the calculations of the mean values because of their different bonding character.

$\sum w(|F_o| - |F_c|)^2$, where the following w was used: $w = m_1$ for $|F_o| = 0.0$ and $w = 1.0/[\sigma(F_o)^2 + m_2|F_o| + m_3|F_o|^2]$ for $|F_o| > \sigma(F_o)$; values of m_1, m_2 and m_3: (1) 0, 0·0264, −0·0003; (2) 0, 0·0641, −0·0009; (3) 0, 0·0481, −0·0005; (4) 0, 0·0326, −0·0002; (5) 0·8099, −0·0326, 0·0003; (6) 0, 0·0445, −0·0005; (7) 0, 0·0277, −0·0002; (8) 0, 0·0399, −0·0004; (9) 0, 0·0217, −0·0003; (10) 2·7195, 0·0282, −0·0002. Final wR and S: (1) 0·044, 1·108; (2) 0·052, 1·265; (3) 0·046, 1·054; (4) 0·032, 1·148; (5) 0·025, 1·090; (6) 0·093, 1·212; (7) 0·054, 1·205; (8) 0·023, 1·158; (9) 0·037, 1·120; (10) 0·048, 1·101. $(\Delta/\sigma)_{max}$: (1) 0·46; (2) 0·35; (3) 0·40; (4) 0·37; (5) 0·30; (6) 0·65; (7) 0·51; (8) 0·64; (9) 0·51; (10) 0·55. The values of $(\Delta/\rho)_{min}$ and $(\Delta\rho)_{max}$ were all in the range −0·30 to 0·35 e Å^{-3}. Scattering factors from *International Tables for X-ray Crystallography* (1974, Vol. IV). All numerical computations performed on a MicroVAX II computer at the Computation Center, Osaka University of Pharmaceutical Sciences, using *The Universal Crystallographic Computing System – Osaka* (1979).*

Discussion

Table 2 lists final coordinates and B_{eq} values for the non-H atoms. The H-bond distances observed in the crystal packing are summarized in Table 3.

* Lists of structure factors, anisotropic temperature factors, H-atom parameters, bond lengths and angles, and stereoscopic packing views have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 54208 (95 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

It is a structural characteristic of 2-oxazolecarbamate derivatives that they have a high tendency to form an N(21)—H···N(3) H-bonded dimer in their molecular associations. In spite of different packing environments, dimers are observed between the two crystallographically independent molecules (1), or between the centrosymmetrically related molecules [(2)–(5), (7) and (8)]. The predominant formation of this type of dimer over the N—H···O one [observed only in (6)] clearly suggests that the proton-accepting ability of the N(3) atom is superior to that of the O(1) or O(23) atoms, or that the spatial positioning of the N(3) atom is suitable for forming such a dimer. Conversely, compounds (9) or (10) show different H-bonding patterns from the 2-oxazolecarbamate compounds; they are infinitely linked with one another by 'linear' N(21)—H···N(4) or N(21)—H···O(23) H-bond formation, respectively. As a whole, all of the compounds are stabilized by these H bonds and van der Waals contacts.

The bond lengths and angles of the 2-oxazolecarbamate moieties of (1)–(10) are listed in Table 4; the mean values are given in the last column. These values are, within their e.s.d.'s, all in the expected range (Kennard, 1983), and the molecular dimensions of oxazole ring are little affected by covalent bond formation with different groups such as alkyl or phenyl groups. As a result of the resonance between the 5-phenyl and oxazole rings, the C(5)—C(51) bond lengths in (1)—(4) and (8) (average length = 1·454 Å) are in the partial double-bond region, and this leads to the coplanar orientation of both rings. A similar tendency is also

observed for (9) and (10). The dihedral angles between the rings are: (1) 12·5 (1) and 36·0 (1); (2) 11·1 (2); (3) 4·3 (2); (4) 11·6 (2) and 9·4 (2); (8) 21·4 (1); (9) 7·1 (2); (10) 5·6 (1)°. The oxazole, phenyl, carbamoyl and benzyl groups are almost planar, and the deviations of individual atoms from their least-squares planes are not significant.

The molecular conformations of compounds (1)–(10) are shown in Fig. 1. The conformational torsion angles are given in Table 5. As can easily be seen, it is a conformational characteristic commonly observed in the benzyl 2-oxazolecarbamate compounds [(1)–(8)] that the carbamate group is almost coplanar with the oxazole ring, thus forming an extended conformation. The dihedral angles between the carbamate and oxazole groups are: (1) 18·6 (1) and 26·6 (1); (2) 18·4 (1); (3) 10·3 (1); (4) 11·6 (2) and 9·1 (2); (5) 18·7 (1); (6) 9·2 (2); (7) 2·4 (2); (8) 3·0 (1)°. This is due to the partial double-bond character of C(2)–N(21) (average length = 1·369 Å). The torsion angles ω_1, ω_2, ω_3 and ω_4 in 2-oxazolecarbamate derivatives are mostly restricted to the *trans, cis,*

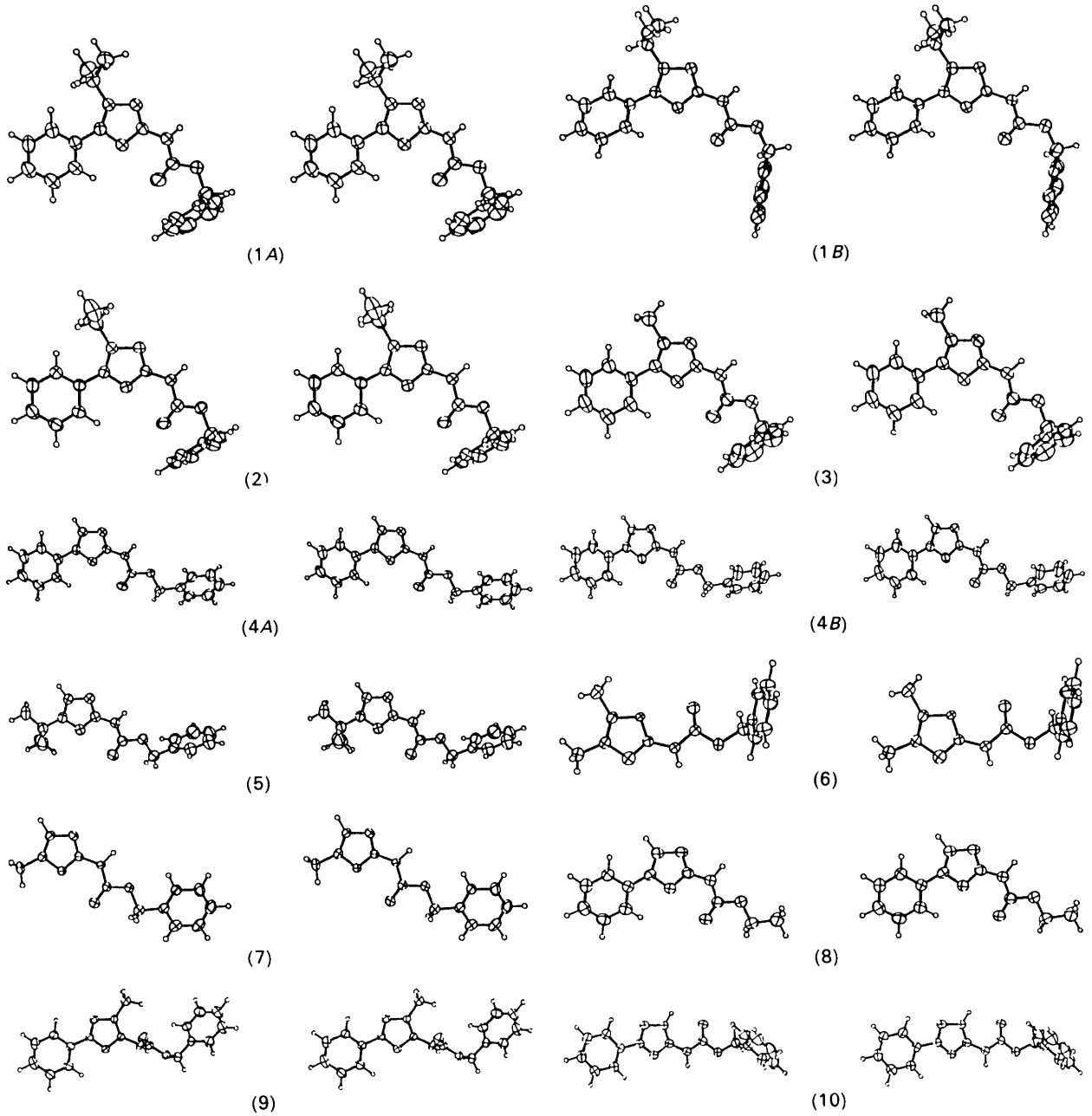


Fig. 1. Stereoscopic views of the molecular conformations of compounds (1)–(10).

Table 5. *Selected torsion angles* (°)

ω_1: O(1)—C(5)—C(51)—C(52); ω_2: O(1)—C(2)—N(21)—C(22); ω_3: C(2)—N(21)—C(22)—O(24); ω_4: N(21)—C(22)—O(24)—C(25); ω_5: C(22)—O(24)—C(25)—C(26); ω_6: O(24)—C(25)—C(26)—C(27). ω_1 and ω_2 of compound (10) correspond to the N(1)—C(5)—C(51)—C(52) and N(1)—C(2)—N(21)—C(22) torsion angles, respectively.

	(1*A*)	(1*B*)	(2)	(3)	(4*A*)	(4*B*)	(5)	(6)	(7)	(8)	(9)	(10)
ω_1	167·8 (3)	143·8 (2)	171·8 (3)	175·2 (3)	170·9 (3)	171·4 (4)				160·7 (2)	174·2 (4)	174·6 (2)
ω_2	− 7·1 (2)	− 29·2 (2)	− 2·1 (2)	5·5 (2)	11·6 (3)	5·2 (3)	25·3 (1)	170·3 (3)	0·6 (3)	4·9 (2)	101·9 (4)	− 178·2 (2)
ω_3	167·3 (2)	− 177·1 (2)	165·3 (3)	174·2 (3)	179·3 (3)	176·2 (3)	169·5 (1)	− 177·6 (3)	177·5 (3)	178·4 (3)	175·6 (4)	176·3 (2)
ω_4	− 176·9 (2)	179·4 (2)	− 176·0 (2)	− 175·2 (2)	176·1 (2)	177·5 (3)	179·5 (1)	− 171·8 (2)	− 173·3 (2)	− 174·3 (2)	178·9 (3)	176·4 (2)
ω_5	88·2 (2)	81·0 (2)	87·6 (2)	86·4 (2)	179·2 (3)	− 178·6 (3)	159·6 (1)	82·5 (3)	172·4 (3)	− 178·1 (3)	89·8 (4)	109·1 (2)
ω_6	94·3 (2)	144·7 (2)	92·1 (3)	− 96·9 (3)	− 118·4 (3)	114·6 (3)	81·4 (1)	− 130·0 (3)	157·8 (3)		97·7 (4)	78·2 (2)

trans and *trans* regions, respectively, and the *trans* conformation of ω_2 in (6), which results from NH···O cyclic H-bond formation, is rather exceptional; it is interesting to note that this *trans* conformation makes the O(1)—C(2)—N(21) bond angle much larger than the N(3)—C(2)—N(21) angle, though in other structures the latter is much larger than the former. Such an extended conformation is also observed in the molecular conformation of (10), although the carbamate plane of (9) is almost at right angles to the oxazole ring [the dihedral angles of both the groups are: (9) 75·4 (2); (10) 4·9 (1)°].

The ω_6 torsion angle is in the range −80 to −160°, usually close to −90°. This conformation has frequently been observed in the torsion angles around the C—C single bond covalently bonded to the aromatic ring. The ω_5 torsion angle is mainly restricted to either of ~90 or ~180°, irrespective of whether or not the normal single O(24)—C(25) bond (average length = 1·457 Å) allows free rotation.

The molecular geometries observed in the crystal structures may not represent the actual conformations bound to the enzyme. Nevertheless, it would be interesting to consider the possible molecular conformation–activity relationship using the present X-ray data, particularly as structural data on the binding site of the enzyme are almost lacking at present. The molecular structures of (1)–(3), which exhibit high ARI activities, all show a common conformational characteristic irrespective of the different substituents at the oxazole C(4) site: $\omega_1 = \sim -180$, $\omega_2 = \sim 0$, $\omega_3 = \omega_4 = \sim 180$, $\omega_5 = \sim 90$ and $\omega_6 = \sim -90$°. Since the respective torsion angles are in the usual regions, it therefore seems resonable to imagine this conformation as a suitable form for binding with enzyme. In order to test this hypothesis, each conformational difference of the van der Waals volume (CDV, Å^3) from a standard compound (1) was calculated using a numerical integration method (Pearlstein, 1983), in which a common overlap volume was set for the oxazole ring. Further, the molecular surface area (MSA, Å^3) of each compound was calculated using the accepted van der Waals radii for the respective atoms (Hopfinger, 1980). These values are given in Table 6. As was expected, a high correlation with the activity was observed for the CDV parameter [see equation (1)], while the correlation of the MSA was not so high. When only the 2-oxazolecarbamate derivatives [(1)–(8)] are considered, however, the correlation of both parameters with activity becomes significant, as can be seen in equation (2). This shows clearly that, in addition to the chemical structural requirements such as a phenyl ring at the oxazole C(5) site and benzylcarbamate at the oxazole C(2) site (Ishida, In, Ohishi, Yamamoto, Inoue, Tanaka, Ueno, Ohmomo, Kanda, Tanaka & Tanimoto, 1988), the molecular conformation and dimensions are very important for ARI activity. These insights should be useful for designing potent ARI's (Yasukawa, Satoh, Gotoh, Ishida, Sumiya & Kitamura, 1990).

Table 6. *Conformational parameters and their correlation coefficients* (r) *with aldose reductase inhibitory activities expressed as* $\log_{10}1/IC_{50}$

Compound	MSA (Å^2)	CDV (Å^3)	Activity
(1*A*)	337·09	0·00	0·456
(1*B*)	349·95	0·43	0·456
(2)	335·94	15·54	0·076
(3)	342·28	31·76	0·389
(4*A*)	314·66	47·34	−1·193
(4*B*)	315·45	48·65	−1·193
(5)	322·76	45·83	1·952
(6)	279·35	81·18	2·621
(7)	251·66	98·13	2·887
(8)	285·29	97·37	3·000*
(9)	344·29	33·27	−3·000*
(10)	315·46	50·03	−3·000*

Linear correlation coefficient (r) with activity [$\log(1/IC_{50})$], and correlation equation with e.s.d's in parentheses

	MSA	CDV		
For all compounds				
r	0·626	0·843		
$\log(1/IC_{50}) =$	3·857 + 0·011MSA (2·540) (0·008)	0·027CDV (0·007)	$r = 0·870$ (0·622)	(1)
For compounds (1)–(8)				
r	0·960	0·932		
$\log(1/IC_{50}) =$	−5·649 + 0·017MSA (2·323) (0·007)	−0·022CDV (0·007)	$r = 0·960$ (0·340)	(2)

* IC_{50} values of (8), (9) and (10) were treated as $\times 10^3$, respectively.

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SHORT COMMUNICATIONS

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Crystals of isoenzyme 3-3 of rat liver glutathione S-transferase with and without inhibitor.

By JIAN-HUA FU, JOHN ROSE and YONG-JE CHUNG, *Department of Crystallography, University of Pittsburgh, Pittsburgh, PA* 15260, *USA*, MING F. TAM, *Institute of Molecular Biology, Academia Sinica, Nankang, Taipei* 11529, *Taiwan*, and BI-CHENG WANG,* *Departments of Crystallography and Biological Sciences, University of Pittsburgh, Pittsburgh, PA* 15260, *USA*

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Abstract

The isoenzyme 3-3 of rat liver glutathione S-transferase (GST 3-3) isolated from a baculovirus expression system has been crystallized with and without inhibitor. The crystals grown in the absence of an inhibitor belong to space group $P2_1$ with cell dimensions $a = 119{\cdot}7$, $b = 96{\cdot}2$, $c = 136{\cdot}7$ Å and $\beta = 103{\cdot}3°$, and diffract to 3 Å resolution. The crystals grown in the presence of an inhibitor belong to space group $C2$ with cell dimensions $a = 88{\cdot}3$, $b = 69{\cdot}7$, $c = 81{\cdot}4$ Å and $\beta = 105{\cdot}3°$, and diffract to at least 2·5 Å resolution. The inhibitor used is either methylmercury chloride or ethylmercury chloride; both are weak inhibitors.

Introduction

Glutathione S-transferases (GST's, E.C. 2.5.1.18) are a group of dimeric proteins, catalyzing the conjugation of glutathione to a wide variety of electrophilic alkylating agents. They are also involved in the reduction of organic hydroperoxides, isomerization of prostaglandins and binding of non-substrate hydrophobic ligands such as bile acids, bilirubin, a number of drugs and thyroid hormones. These isoenzymes are believed to be responsible for the detoxification of chemical carcinogens such as xenobiotics and endogenous compounds, as well as metabolic products from oxidative metabolism. A recent review on the structure and catalytic activity of GST has been given by Mannervik & Danielson (1988).

* Author for correspondence.

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The diversity of the enzyme's action provides a unique opportunity to study the relationship between structure and the mechanism of molecular detoxification. An understanding of the structure–function relationship will require the detailed structural information of GST's and their conformational changes. Crystallization and preliminary X-ray diffraction studies have been reported for several classes of GST complexed with inhibitors of glutathione (GSH) analogs (Sesay, Ammon & Armstrong, 1987; Schaffer, Gallay & Ladenstein, 1988; Cowan *et al.*, 1989; Parker, Bello & Federici, 1990). To our knowledge, there are no reports on crystals of GST uncomplexed with inhibitor. We report here the crystallization of rat liver GST 3-3 without inhibitor and in the presence of two non-GSH-based weak inhibitors.

Experimental

For preparation of protein samples, a full-length GST 3 cDNA clone of rat liver GST was expressed in *Spodoptera frugiperda* (*Sf* 9) cells using a baculovirus expression system (Hsieh, Liu, Chen & Tam, 1989) which allows isolation of large quantities of functionally active homogeneous GST 3-3 of high purity without contamination by the closely related isoenzyme(s). The expressed proteins were purified using existing procedures (Mannervik & Guthenberg, 1981).

For the crystallization set-ups, the sample was dialyzed against 20 m*M* tris-HCl buffer (pH 7·0) containing 20 m*M* NaCl, 1 m*M* EDTA and 0·02% (*w*/*v*) sodium azide, and then concentrated to about 20 mg ml^{-1}. Crystallization