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Structure of the 4-Oxo-2-butenoic Acid Alkyl Ester Moiety. I. Structures of Diethyl 4,4′-(1,4-Piperazinediyl)bis(4-oxo-2-butenoate) and Dimethyl 4,4′-(2,5-Dioxo-1,4-piperazinediyl)bis(4-oxo-2-butenoate)

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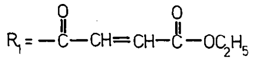
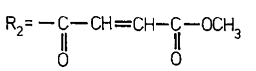
Abstract. $C_{16}H_{22}N_2O_6$, $M_r = 338{\cdot}4$, monoclinic, $P2_1/c$, $a = 8{\cdot}282\ (1)$, $b = 9{\cdot}357\ (1)$, $c = 11{\cdot}288\ (2)$ Å, $\beta = 93{\cdot}09\ (1)^\circ$, $V = 873{\cdot}5$ Å^3, $Z = 2$, $D_x = 1{\cdot}286$ Mg m^{-3}, $\lambda(\mathrm{Cu}\ K\alpha) = 1{\cdot}54178$ Å, $\mu = 0{\cdot}74$ mm^{-1}, $F(000) = 360$, room temperature, $R = 0{\cdot}050$ for 1369 reflections. $C_{14}H_{14}N_2O_8$, $M_r = 338{\cdot}3$, monoclinic, $P2_1/c$, $a = 24{\cdot}350\ (6)$, $b = 6{\cdot}973\ (1)$, $c = 9{\cdot}212\ (1)$ Å, $\beta = 91{\cdot}74\ (1)^\circ$, $V = 1563{\cdot}4$ Å^3, $Z = 4$, $D_x = 1{\cdot}437$ Mg m^{-3}, $\lambda(\mathrm{Cu}\ K\alpha) = 1{\cdot}54178$ Å, $\mu = 0{\cdot}99$ mm^{-1}, $F(000) = 704$, room temperature, $R = 0{\cdot}055$ for 2037 reflections. The fumaramate groups are approximately planar in both structures with the ester group *syn* to the double bond in the first and *anti* in the second structure. Substitution of 1,4-piperazine by the 2,5-dioxo-1,4-piperazine ring affects not only the ring conformation but also conjugation at the adjacent amide groups.

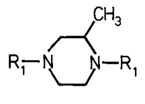
Introduction. 4,4′-(2-Methyl-1,4-piperazinediyl)bis(4-oxo-2-butenoic acid deithyl ester) (1) has been shown to inhibit the growth of transplantable neoplasms in mice: leukemias L1210 and P388, and sarcoma Sa180 (Graczyk, Pakulska, Groszkowski & Najman, 1980; Groszkowski & Najman, 1983). It has been suggested that the —CH═CH—C═O fragment may be responsible for antimitotic and cytostatic properties of compound (1) (Groszkowski & Najman, 1979) and cytostatic active acrylates (Lee, Kim, Piantadosi, Huang & Geissman, 1974; Loeffler, Sajadi & Hall, 1977). Consequently, a series of other piperazides, 2-methylpiperazides, 2,5-dimethylpiperazides and piperazide-2,5-diones of α,β-unsaturated carboxylic acids and their esters have been synthetized and tested against leukemias (Groszkowski, Najman & Sienkiewicz, 1972; Groszkowski & Najman, 1972; Andrzejewska-Golec, Broda & Najman, 1977; Groszkowski & Najman, 1979; Graczyk, Pakulska, Groszkowski & Najman, 1980; Groszkowski & Najman, 1983; Groszkowski & Najman, 1986). The investigations showed that even a slight change in the chemical structure of the 'carrier' piperazine unit affects antileukemic properties of the agent and therefore our X-ray studies attempt to determine the conformation and electronic structure of 4,4′-(1,4-piperazinediyl)bis(4-oxo-2-butenoic acid diethyl ester) (2) and 4,4′-(2,5-dioxo-1,4-piperazinediyl)bis(4-oxo-2-butenoic acid dimethyl ester) (3). The only known structures containing a similar 'active' —N—C(O)—CH═CH—C(O)— moiety are α- and β-funaltrexamines (Griffin, Larson & Porthoghese, 1986).



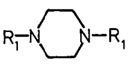
$$R_1 = -\overset{\overset{\displaystyle O}{\|}}{C}-CH{=}CH-\overset{\overset{\displaystyle O}{\|}}{C}-OC_2H_5$$



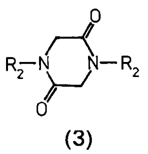
$$R_2 = -\underset{\underset{\displaystyle O}{\|}}{C}-CH{=}CH-\underset{\underset{\displaystyle O}{\|}}{C}-OCH_3$$



(1)



(2)



(3)

Experimental. Colourless crystals were grown by slow evaporation of a methanol–water (2) or an ethanol–chloroform (3) solution. Crystals of dimensions $0{\cdot}22 \times 0{\cdot}15 \times 0{\cdot}12$ mm (2) and $0{\cdot}32 \times 0{\cdot}25 \times 0{\cdot}21$ mm (3) were used for data collection on an Enraf–Nonius CAD-4 diffractometer fitted with an

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Ni filter. Unit-cell parameters were determined by least-squares refinement of 25 reflections in the range $15 \leq \theta \leq 32°$. The data were collected to a maximum $\theta = 75°$ using $\omega/2\theta$ scan and a maximum measurement time 200 s. Three standard reflections 332, $4\bar{2}1$, and $3\bar{2}0$ for (2) and $\bar{4}0\bar{6}$, $\bar{1}35$ and 514 for (3) were measured every hour, with no significant change in intensity. 1753 unique reflections for (2), 3204 for (3). For observed intensities, $0 \leq h \leq 10$, $0 \leq k \leq 11$, $-14 \leq l \leq 14$ for (2) and $-28 \leq h \leq 30$, $0 \leq k \leq 8$, $0 \leq l \leq 11$ for (3). The data were corrected for Lorentz and polarization effects but not for absorption.

The structures were solved by direct methods (*SHELXS*; Sheldrick, 1986). The initial E synthesis revealed the positions of all non-hydrogen atoms. Using 1369 and 2037 observed $[F > 3\sigma(F)]$ reflections for (2) and (3) respectively, the parameters were refined by full-matrix least squares (*SHELX76*; Sheldrick, 1976). The final cycles of refinement included coordinates of all atoms, anisotropic thermal parameters for non-hydrogen atoms, isotropic thermal parameters of hydrogen atoms and an isotropic extinction parameter, $g = 0{\cdot}027\,(5)$ for (2) and $0{\cdot}010\,(2)$ for (3) (Larson, 1967). $(\Delta/\sigma)_{\max} = 0{\cdot}03$ for (2) and 0·11 for (3). The final agreement factors $R(wR)$ were 0·050 (0·062) and 0·055 (0·060) for (2) and (3) respectively. $S = 1{\cdot}14$ for (2) and 0·98 for (3). The function minimized was $\sum w(|F_o| - |F_c|)^2$ where $w^{-1} = \sigma^2(F_o) + m(F_o)^2$ with $m = 0{\cdot}00068$ for (2) and 0·0025 for (3). The maximum peaks in the final difference Fourier syntheses were 0·17 (2) and 0·14 (3) e Å^{-3}. Scattering factors were from *International Tables for X-ray Crystallography* (1974).

The molecular conformations and atomic labelling schemes are shown in Fig. 1. The atomic coordinates for non-hydrogen atoms are given in Tables 1 and 2, and the bond distances and angles for these atoms are listed in Table 3.*

Discussion. The electronic structure of the 4-oxo-2-butenoate fragment seems to be well preserved as the bond lengths and angles in this planar group are very similar in all structures containing the fragment. However, the ester group is *syn* to the C(3)=C(4) double bond in (2) [C(3)=C(4)—C(5)—O(6) angle is 9·9 (6)°] and is *anti* in (3). The *anti* orientation is more stable for α,β-unsaturated carboxylic acid esters (Leiserowitz, 1976). Indeed, the C=C—C(O)—O*R* torsional angle is close to 180° in all other 4-oxo-2-butenoates; it is −179·2 (4) and 176·4 (3)° in

Table 1. *Final atomic coordinates and equivalent isotropic temperature parameters with e.s.d.'s in parentheses for non-hydrogen atoms of structure* (2)

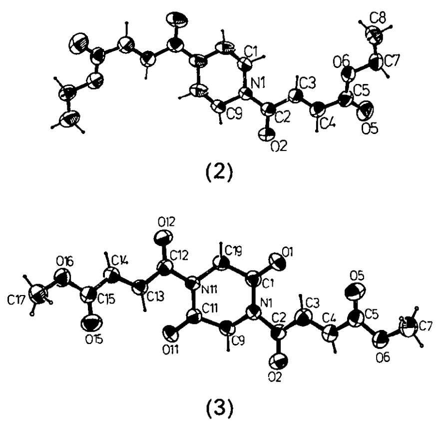
$$B_{\rm eq} = \tfrac{8}{3}\pi^2\textstyle\sum_i\sum_j U_{ij}a_i^*a_j^*\mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	$B_{\rm eq}$(Å^2)
N(1)	0·0576 (2)	0·8648 (2)	0·5371 (1)	4·59 (5)
C(1)	−0·0101 (3)	0·8871 (3)	0·4147 (2)	5·03 (7)
C(2)	0·1358 (3)	0·7461 (2)	0·5758 (2)	4·39 (6)
O(2)	0·1557 (3)	0·7201 (2)	0·6821 (1)	6·30 (6)
C(3)	0·2037 (3)	0·6487 (2)	0·4868 (2)	4·30 (6)
C(4)	0·2380 (3)	0·5156 (2)	0·5159 (2)	5·02 (6)
C(5)	0·3094 (3)	0·4093 (2)	0·4376 (2)	4·91 (6)
O(5)	0·3211 (3)	0·2849 (2)	0·4623 (2)	7·65 (7)
O(6)	0·3606 (2)	0·4648 (2)	0·3389 (1)	5·13 (5)
C(7)	0·4342 (4)	0·3677 (3)	0·2568 (2)	5·16 (7)
C(8)	0·4911 (5)	0·4556 (4)	0·1575 (3)	6·45 (8)
C(9)	−0·0122 (4)	0·9613 (3)	0·6225 (2)	5·09 (7)

Table 2. *Final atomic coordinates and equivalent isotropic temperature parameters with e.s.d.'s in parentheses for non-hydrogen atoms of structure* (3)

$$B_{\rm eq} = \tfrac{8}{3}\pi^2\textstyle\sum_i\sum_j U_{ij}a_i^*a_j^*\mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	$B_{\rm eq}$(Å^2)
N(1)	0·2032 (1)	0·4164 (4)	0·5418 (3)	3·17 (6)
C(1)	0·2471 (1)	0·3549 (5)	0·4615 (3)	3·40 (8)
O(1)	0·2435 (1)	0·2407 (4)	0·3638 (3)	5·22 (7)
C(2)	0·1518 (1)	0·3251 (5)	0·5485 (3)	3·65 (8)
O(2)	0·1142 (1)	0·4063 (4)	0·6054 (3)	5·09 (7)
C(3)	0·1457 (1)	0·1289 (5)	0·4883 (4)	4·06 (9)
C(4)	0·0972 (1)	0·0524 (6)	0·4682 (4)	4·16 (9)
C(5)	0·0897 (1)	−0·1415 (5)	0·4050 (3)	3·62 (7)
O(5)	0·1260 (1)	−0·2448 (4)	0·3689 (3)	4·70 (7)
O(6)	0·0367 (1)	−0·1869 (4)	0·3933 (3)	4·82 (7)
C(7)	0·0243 (2)	−0·3703 (7)	0·3247 (6)	5·98 (13)
C(9)	0·2099 (1)	0·6012 (5)	0·6159 (4)	3·36 (8)
N(11)	0·3060 (1)	0·5166 (3)	0·6515 (2)	2·82 (6)
C(11)	0·2615 (1)	0·6138 (4)	0·7067 (3)	3·09 (7)
O(11)	0·2638 (1)	0·7094 (4)	0·8166 (3)	4·58 (7)
C(12)	0·3570 (1)	0·4965 (5)	0·7231 (4)	3·40 (7)
O(12)	0·3967 (1)	0·4515 (5)	0·6558 (3)	5·08 (7)
C(13)	0·3592 (1)	0·5139 (5)	0·8832 (3)	3·47 (7)
C(14)	0·4063 (1)	0·5133 (5)	0·9582 (3)	3·68 (8)
C(15)	0·4072 (1)	0·5165 (5)	1·1180 (4)	3·92 (8)
O(15)	0·3675 (1)	0·5276 (6)	1·1906 (3)	6·49 (10)
O(16)	0·4580 (1)	0·5042 (4)	1·1731 (2)	4·71 (7)
C(17)	0·4640 (2)	0·4979 (10)	1·3300 (4)	5·67 (12)
C(19)	0·3015 (1)	0·4465 (5)	0·5011 (3)	3·19 (7)



(2)

(3)

Fig. 1. Views (Johnson, 1976) of molecules (2) and (3) with labelling schemes of the atoms.

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* Lists of anisotropic thermal parameters for non-H atoms, coordinates and thermal parameters for H atoms, and structure factors have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 52694 (19 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 3. *Bond lengths* (Å), *and bond and torsion angles* (°)

	(2)	(3)		(2)	(3)
N(1)—C(1)	1·478 (3)	1·383 (4)	C(4)—C(5)	1·475 (4)	1·485 (5)
N(11)—C(11)		1·386 (4)	C(14)—C(15)		1·473 (5)
N(1)—C(2)	1·347 (3)	1·403 (4)	C(5)—O(5)	1·200 (3)	1·192 (4)
N(11)—C(12)		1·396 (4)	C(15)—O(15)		1·191 (4)
N(1)—C(9)	1·462 (3)	1·468 (5)	C(5)—O(6)	1·320 (3)	1·329 (4)
N(11)—C(19)		1·473 (5)	C(15)—O(16)		1·324 (4)
C(2)—O(2)	1·226 (3)	1·207 (4)	O(6)—C(7)	1·455 (3)	1·460 (6)
C(12)—O(12)		1·205 (4)	O(16)—C(17)		1·456 (5)
C(2)—C(3)	1·490 (3)	1·488 (6)	C(1)—C(19)	1·494 (3)	1·502 (4)
C(12)—C(13)		1·479 (5)	C(11)—C(9)		1·488 (4)
C(3)—C(4)	1·315 (3)	1·299 (6)	C(1)—O(1)		1·206 (5)
C(13)—C(14)		1·317 (4)	C(11)—O(11)		1·213 (4)
			C(7)—C(8)	1·488 (4)	
C(1)—N(1)—C(2)	124·9 (2)	126·2 (3)	C(4)—C(5)—O(5)	123·0 (2)	124·9 (3)
C(11)—N(11)—C(12)		124·9 (3)	C(14)—C(15)—O(15)		124·9 (3)
C(1)—N(1)—C(9)	112·7 (2)	116·2 (3)	C(4)—C(5)—O(6)	113·4 (2)	110·8 (3)
C(11)—N(11)—C(19)		118·0 (3)	C(14)—C(15)—O(16)		111·5 (3)
C(2)—N(1)—C(9)	119·7 (2)	117·4 (3)	O(5)—C(5)—O(6)	123·6 (2)	124·3 (3)
C(12)—N(11)—C(19)		116·8 (3)	O(15)—C(15)—O(16)		123·6 (3)
N(1)—C(2)—O(2)	121·3 (2)	119·9 (3)	C(5)—O(6)—C(7)	117·1 (2)	115·4 (3)
N(11)—C(12)—O(12)		119·9 (3)	C(15)—O(16)—C(17)		116·5 (3)
N(1)—C(2)—C(3)	118·5 (2)	118·7 (3)	O(6)—C(7)—C(8)	107·2 (2)	
N(11)—C(12)—C(13)		118·0 (2)	N(1)—C(1)—C(19)	110·5 (3)	115·6 (3)
O(2)—C(2)—C(3)	120·1 (2)	121·4 (3)	N(11)—C(11)—C(9)		115·0 (3)
O(12)—C(12)—C(13)		121·9 (3)	N(1)—C(9)—C(11)	110·0 (3)	113·2 (3)
C(2)—C(3)—C(4)	119·7 (2)	120·9 (3)	N(11)—C(19)—C(1)		114·0 (3)
C(12)—C(13)—C(14)		121·9 (3)	N(1)—C(1)—O(1)		124·0 (3)
C(3)—C(4)—C(5)	125·2 (2)	122·0 (4)	N(11)—C(11)—O(11)		123·8 (3)
C(13)—C(14)—C(15)		120·8 (3)	O(1)—C(1)—C(19)		120·3 (3)
			O(11)—C(11)—C(9)		121·1 (3)

	(2)	(3)
C(1)—N(1)—C(2)—O(2)	−162·9 (4)	−169·4 (3)
C(11)—N(11)—C(12)—O(12)		−162·0 (3)
C(9)—N(1)—C(2)—O(2)	−3·1 (7)	5·1 (5)
C(19)—N(11)—C(12)—O(12)		11·5 (5)
C(1)—N(1)—C(2)—C(3)	19·4 (4)	12·1 (5)
C(11)—N(11)—C(12)—C(13)		23·1 (5)
C(9)—N(1)—C(2)—C(3)	179·2 (4)	−173·5 (3)
C(19)—N(11)—C(12)—C(13)		−163·3 (3)
N(1)—C(2)—C(3)—C(4)	−160·4 (4)	−167·6 (4)
N(11)—C(12)—C(13)—C(14)		−173·9 (3)
O(2)—C(2)—C(3)—C(4)	21·8 (6)	13·9 (6)
O(12)—C(12)—C(13)—C(14)		11·3 (5)
C(2)—C(3)—C(4)—C(5)	−178·4 (4)	178·4 (3)
C(12)—C(13)—C(14)—C(15)		−175·3 (3)
C(3)—C(4)—C(5)—O(5)	−170·9 (5)	1·1 (6)
C(13)—C(14)—C(15)—O(15)		−3·1 (6)
C(3)—C(4)—C(5)—O(6)	9·9 (6)	−179·2 (4)
C(13)—C(14)—C(15)—O(16)		176·4 (3)
C(4)—C(5)—O(6)—C(7)	179·5 (4)	176·8 (4)
C(14)—C(15)—O(16)—C(17)		−177·5 (3)
O(5)—C(5)—O(6)—C(7)	0·2 (7)	−3·5 (5)
O(15)—C(15)—O(16)—C(17)		2·1 (5)
C(19)—C(1)—N(1)—C(2)	−142·5 (6)	−165·1 (3)
C(9)—N(11)—C(11)—C(12)		−174·6 (3)
C(19)—C(1)—N(1)—C(9)	56·2 (7)	20·4 (4)
C(9)—C(11)—N(11)—C(19)		11·9 (4)
N(11)—C(19)—C(1)—N(1)	54·9 (7)	25·3 (4)
N(1)—C(9)—C(11)—N(11)		34·2 (4)
C(1)—N(1)—C(9)—C(11)	−56·6 (6)	−51·6 (4)
C(11)—N(11)—C(19)—C(1)		−42·8 (4)
C(2)—N(1)—C(9)—C(11)	141·7 (6)	133·2 (3)
C(12)—N(11)—C(19)—C(1)		143·1 (3)
C(5)—O(6)—C(7)—C(8)	−176·4 (4)	
N(11)—C(19)—C(1)—O(1)		−156·1 (3)
N(1)—C(9)—C(11)—O(11)		−148·6 (3)
O(1)—C(1)—N(1)—C(2)		16·4 (5)
O(11)—C(11)—N(11)—C(12)		8·3 (5)
O(1)—C(1)—N(1)—C(9)		−158·1 (3)
O(11)—C(11)—N(11)—C(19)		−165·2 (3)

(3), 173·4 in α- and −160·5° in β-funaltrexamine (Griffin, Larson & Porthoghese, 1986). The other structural difference between the two structures concerns the piperazine moiety and is due to its different chemical composition. Substitution of 1,4-piperazine [in (2)] by 2,5-dioxo-1,4-piperazine [in (3)] affects not only the piperazine ring (which is evidenced by the difference of about 0·1 Å in the N—C ring-bond lengths) but also the adjacent carbonyl group of the 4-oxo-2-butenoate fragment. The N(1)—C(2) and C(2)=O(2) bond lengths are 1·347 (3) and 1·226 (3) Å in (2), and 1·403 (4), 1·396 (4) Å (N—C), 1·207 (4) and 1·205 (4) Å (C=O) in (3), indicating the possible conjugation of π electrons of C(2) (carbonyl group) with the lone pair at N(1) in (3).

There are some C—H···O contacts with H···O distance well below 2·4 Å, deserving remark. The *intramolecular* contacts with H···O separations of 2·30 Å for C(9)—H···O(2) in (2), and 2·26 Å for C(9)—H···O(2), 2·35 Å for C(19)—H···O(12), 2·23 Å for C(3)—H···O(1) and 2·23 Å for C(13)—H···O(11) in (3), all result from the planarity of fumaramate groups. There are also short H···O *intermolecular* contacts: C(1)—H···O(2) ($x,1{\cdot}5-y,z-0{\cdot}5$) of 2·29 Å in (2) and C(9)—H···O(5) ($x,0{\cdot}5-y,0{\cdot}5+z$) of 2·22 Å in (3).

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