Absolute Configurations of Three *ent*-Beyerene* Derivatives

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Abstract. (1): 11β,17-Bis(4-bromobenzoyloxy)-9β-hydroxy-*ent*-beyerene, $C_{34}H_{38}Br_2O_5$, $M_r = 686\cdot5$, orthorhombic, $P2_12_12_1$, $a = 6\cdot1686$ (12), $b = 14\cdot613$ (3), $c = 32\cdot935$ (7) Å, $V = 2969$ (1) Å^3, $Z = 4$, $D_x = 1\cdot536$ g cm^{-3}, λ(Mo $K\alpha$) = 0·71069 Å, $\mu = 27\cdot43$ cm^{-1}, $F(000) = 1408$, $T = 173$ K, $R = 0\cdot0347$ and $wR = 0\cdot0358$ for 3064 reflections $[I_o \geq 3\sigma(I_o)]$. (2): 7β,17-Bis(4-bromobenzoyloxy)-9β-hydroxy-*ent*-beyerene, $C_{34}H_{38}Br_2O_5$, $M_r = 686\cdot5$, monoclinic, $P2_1$, $a = 12\cdot6424$ (15), $b = 6\cdot8353$ (12), $c = 18\cdot496$ (2) Å, $\beta = 101\cdot901$ (9)°, $V = 1564\cdot0$ (4) Å^3, $Z = 2$, $D_x = 1\cdot458$ g cm^{-3}, λ(Mo $K\alpha$) = 0·71073 Å, $\mu = 26\cdot03$ cm^{-1}, $F(000) = 704$, $T = 173$ Å, $R = 0\cdot0336$ and $wR = 0\cdot0361$ for 4610 reflections $[I_o \geq 3\sigma(I_o)]$. (3): 17-(4-Bromobenzoyloxy)-9β,11β-epoxy-7β-hydroxy-*ent*-beyerene, $C_{27}H_{33}BrO_4$, $M_r = 501\cdot5$, orthorhombic, $P2_12_12_1$, $a = 6\cdot1315$ (7), $b = 18\cdot389$ (3), $c = 21\cdot109$ (3) Å, $V = 2380\cdot0$ (6) Å^3, $Z = 4$, $D_x = 1\cdot399$ g cm^{-3}, λ(Mo $K\alpha$) = 0·71073 Å, $\mu = 17\cdot38$ cm^{-1}, $F(000) = 1048$, $T = 198$ K, $R = 0\cdot0325$ and $wR = 0\cdot0344$ for 2292 reflections $[I_o \geq 3\sigma(I_o)]$. The absolute configurations of (1), (2) and (3) were determined by the η (chirality/polarity) refinement which indicated that the molecular models refined belong to the correct configuration, namely, the *ent*-beyerene skeletal type. As a result, the biosynthetic pathways of (4) (9β,11β,17-trihydroxy-*ent*-beyerene), (5) (7β,9β,17-trihydroxy-*ent*-beyerene) and (6) (9β,11β-epoxy-7β,17-dihydroxy-*ent*-beyerene) are established as the *ent*-diterpenoid pathway. The three cyclohexane rings *A*, *B* and *C* are in chair conformations, whereas the five-membered rings are in envelope conformations. The hydroxyl group in each compound is involved in hydrogen bonding: (1) one intramolecular and one intermolecular bond; (2) one intramolecular bond; and (3) one intermolecular bond.

Introduction. As part of our chemical investigation of the genus *Helianthus* (Compositae), a new diter-

penoid alcohol, compound (4), was isolated from *Helianthus iaciniatus* A. Gray. Neither ^{1}H nor ^{13}C NMR spectra could be used to assign the hydroxyl substituents at C(9), C(11) and C(17) as axial or equatorial, nor to determine the absolute stereochemistry [whether (4) was an *ent*-beyerene (+)-hibaene, (7), or a (−)-hibaene compound, (8)]. Its relative configuration was established by an X-ray study (Watson, Tavanaiepour, Lee & Mabry, 1986). In (5) and (6), the presence of the single secondary hydroxyl substituent was established by ^{1}H and ^{13}C NMR studies of acetylated and unacetylated derivatives, but its position could not be determined because of the similarity of the chemical environments at C(7) and C(12) (von Carstenn-Lichterfelde, Valverde & Rodriguez, 1974; Garcia-Granados, Martinez, Onorato & Socorro, 1984; von Carstenn-Lichterfelde, Pascual, Pons, Rabanal, Rodriguez & Valverde, 1975; Garcia-Granados, Martinez, Onorato & Santoro, 1986).
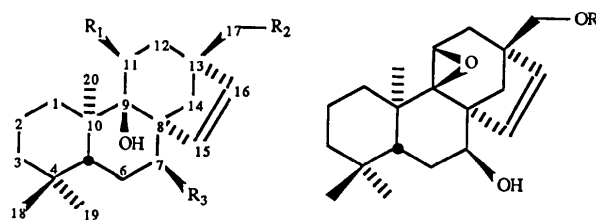
(1) $R_1 = R_2 = OC(O)C_6H_4Br$; $R = H$ (3) $R = C(O)C_6H_4Br$
(2) $R_1 = H$, $R_2 = R_3 = OC(O)C_6H_4Br$ (6) $R = H$
(4) $R_1 = R_2 = OH$, $R_3 = H$
(5) $R_1 = H$, $R_2 = R_3 = OH$
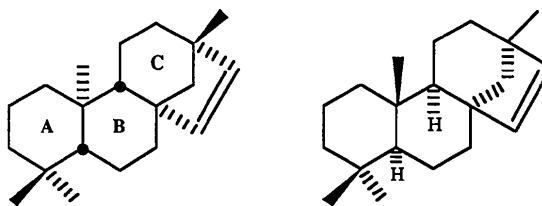
(7) *ent*-Beyeren [(+)-hibaene]   (8) (−)-Hibaene

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* Beyerene is (8β,13β)-13-methyl-17-norkaur-15-ene.

Although the majority of the diterpenoid constituents isolated from *Helianthus* are of the *ent*-diterpenoid biosynthetic pathway, some *nor*-diterpenoid compounds have been isolated from members of the Compositae (Seaman, Bohlmann, Zdero & Mabry, 1989). Determination of the absolute stereochemistry of (4), (5) and (6) was necessary in order to establish their biosynthetic pathways; *i.e.* a (−)-hibaene skeleton indicates a *nor*-terpenoid pathway, whereas a (+)-hibaene skeleton indicates an *ent*-terpenoid pathway. Until the present study, the *ent*-beyerene skeleton had been observed only once in *Helianthus* (Lee, 1990). Bisbromobenzoate esters, (1) and (2) of (4) and (5), and the mono-bromobenzoate ester (3) of (6) were synthesized and their crystal structures and absolute configurations determined, leading to the correct absolute configurations of the parent compounds (4), (5) and (6).

Experimental. The bromobenzoate esters of the diterpenoid alcohols (4), (5) and (6) were prepared according to established procedures (Kupchan, Davies, Fujita, Cox, Restivo & Bryan, 1973). 104 mg of (4) was dissolved in 2 ml of anhydrous pyridine and 377 mg of *p*-bromobenzoyl chloride was added at room temperature under a stream of nitrogen. The solution was stirred for 24 h in the dark and then diluted with CH_2Cl_2, quenched with ice cold 0·3 M sulfuric acid, and the resultant solution was worked up. The crude product was purified using normal phase semi-preparative HPLC, using 2:1 hexane: EtOAc as the eluent. Recrystallization of the purified product from EtOAc to obtain suitable crystals for data collection yielded 167 mg (72%) of (1). Samples of (5) (120 mg) and (6) (122 mg) were treated similarly except that the reaction mixtures for these two compounds were stirred 48 h before work up. Semi-preparative HPLC purification followed by recrystallization from EtOAc afforded 156 mg (61%) of (2) and 150 mg (78%) of (3).

Details of data collection and structure refinement of the three compounds are summarized in Table 1. All data were collected on a Nicolet $R3m/V$ diffractometer equipped with a graphite monochromator and a Nicolet LT-2 low-temperature delivery system. Data for (1) and (2) were collected at 173 K and data for (3) were collected at 198 K, using the ω-scan technique. Four reflections were remeasured every 96 reflections to monitor instrument and crystal stability (maximum corrections on I for all data were < 1·1%). All structures were refined by full-matrix least squares using *SHELX*76 (Sheldrick, 1976), $\sum w(|F_o| - |F_c|)^2$ was minimized; $w = 1/[\sigma(F_o)]^2$, $\sigma(F_o) = 0·5kI^{-1/2}\{[\sigma(I)]^2 + (0·02I)^2\}^{1/2}$, I(intensity) = $(I_{peak} - I_{background}) \times$ (scan rate) and $\sigma(I)$ = (scan rate) $\times (I_{peak} + I_{background})^{1/2}$, k is the correction due to decay and Lp effects, 0·02 is a factor used to down-weight

Table 1. *Crystallographic data*

	(1)	(2)	(3)
Data collection			
Crystal size (mm)	0·29 × 0·46 × 0·50	0·19 × 0·31 × 0·35	0·19 × 0·35 × 0·48
Scan range (ω,°)	1·5	1·2	1·0
Scan rate (° min⁻¹)	4·0–8·0	4·0–8·0	3·0–6·0
2θ range (°)	4·0–55·0	3·0–60·0	3·0–55·0
Range of *hkl*	$-8 \le h \le 8$	$-17 \le h \le 17$	$-7 \le h \le 7$
	$-18 \le k \le 18$	$-3 \le k \le 9$	$-23 \le k \le 23$
	$0 \le l \le 24$	$-26 \le l \le 26$	$0 \le l \le 27$
	$-5 \le h \le 0$		$-2 \le h \le 0$
	$-8 \le k \le 0$		$-3 \le k \le 0$
	$-10 \le l \le 0$		$-5 \le l \le 0$
Mode		ω scan	
Background measurement	Stationary crystal and stationary counter at beginning and end of scan, each for 50% of total scan time.		
Total reflections measured	8397	13890	6350
Unique reflections	4334	6943	3197
Min. transmission	0·3739	0·5051	0·6179
Max. transmission	0·5413	0·6440	0·7459
Structure refinement			
Absolute configuration (η)	1·05 (2)	1·01 (2)	0·98 (2)
Extinction correction (χ)†	0·00014 (5)	0·0008 (1)	0·0012 (1)
Weighting scheme		$w^{-1} = \sigma^2(F) + 0·0004F^2$	
S, goodness of fit	1·23	1·18	1·13
Number of variables	524	523	423
R, wR (%, all data)	6·07, 4·42	6·96, 7·86	5·66, 4·18
R_{int} (I) (%)	3·01	2·21	1·67
Max. & mean shift/e.s.d.	0·004, 0·0	0·003, 0·0,	0·001, 0·0
Min. peak in difference Fourier map (e Å⁻³)	−0·54	−0·50	−0·31
Max. peak in difference Fourier map (e Å⁻³)	0·47	0·56	0·26

† $F^* = F[1 + 0·002\chi F^2/\sin(2\theta)]^{1/4}$.

intense reflections and to account for instrument instability. Data reduction was performed using the Nicolet XRD *SHELXTL-Plus* software package (Sheldrick, 1987). The linear absorption coefficients were calculated from values from *International Tables for X-ray Crystallography* (1974, Vol. IV, p. 55). Scattering factors for non-H atoms were taken from Cromer & Mann (1968) with anomalous-dispersion corrections from Cromer & Liberman (1970), while those of H atoms were from Stewart, Davidson & Simpson (1965). All structures were solved by Patterson syntheses using *SHELXTL-Plus*. The positions of all H atoms were determined from difference Fourier maps. Non-H atoms were treated anisotropically, whereas H atoms were refined with isotropic thermal parameters. Lattice parameters were obtained by least-squares refinement of 50 reflections with $31·46 \le 2\theta \le 34·81°$ for (1), $22·00 \le 2\theta \le 25·39°$ for (2) and $17·81 \le 2\theta \le 21·93°$ for (3). The thermal ellipsoid plots were all generated using *SHELXTL-Plus*.

The absolute configurations of (1), (2) and (3) were determined by refining η, a coefficient multiplying f'' (Rogers, 1981). The rigid-body motion for (1), (2) and (3) was analyzed by the method of Schomaker & Trueblood (1968). A maximum correction of 0·001 Å (less than 20% of σ for a few bonds) was needed. Consequently, librational corrections were not applied. Thermal ellipsoid drawings with the atom labelling schemes of (1), (2) and (3) are shown in Figs. 1, 2 and 3, respectively. The positional param-

eters with the equivalent isotropic thermal param-eters of the non-H atoms are in Table 2* and bond lengths and angles of the non-H atoms are in Table 3.

Discussion. Compounds (1), (2) and (3) are deriva-tives of ent-beyerene which can be described as having three trans-fused six-membered rings labelled A, B and C. An ethylene unit bridges C(8) and C(13) forming a five-membered ring and a seven-membered ring. The five-membered rings in (1), (2) and (3) are in envelope conformations (Toromanoff, 1980), while the rest of the rings are in chair conformations except ring C in (3) which exhibits a half-boat con-formation because of the effect of the epoxy moiety. Compound (4) exhibits similar ring conformations (Watson et al., 1986). Close interactions are observed between substituents in the axial positions of the α-faces of the three compounds. The C(20) methyl group interacts with H(2a), H(6b), C(19) methyl group and the C(15)—C(16) ethylene moiety. The C(20)···C(19) distances in (1), (2) and (3) are 3·26, 3·23 and 3·25 Å, while the C(20)···C(15) distances are 3·18, 3·10 and 3·20 Å. These distances are compa-rable with their counterparts in (4) [3·24 and 3·08 Å, for C(20)···C(19) and C(20)···C(15), respectively] and in a similar beyerene derivative [3·38 and 3·26 Å; Hanson, McLaughlin & Sim (1972)]. Short contacts are also observed between the C(20) methyl H atoms and the rest of the axial substituents of the α-faces. [For (1), (2) and (3), the H(20A)···H(2A) distances are 2·27, 2·17 and 2·31 Å, respectively. Also in (1), H(20C)···H(6A) = 2·08 and H(20C)···H(18A) = 2·10 Å; in (2), H(20B)···H(6A) = 2·14 Å; and in (3), H(20C)···H(6B) and H(20B)···H(18B) = 2·13 Å.] These close contacts would be expected to lead to flattening of the rings which should in turn be reflected by smaller endocylic torsion angles. Ring A has torsion angles that range between 48·7 (6) and 57·3 (8)° in (1), 49·9 (4) and 59·1 (5)° in (2) and 50·8 (5) and 59·0 (5)° in (3); compared to 48·6 and 56·8° in (4), 50 to 60° in a similar derivative (Hanson et al., 1972) and an angle of 56° in a normal chair (Bucourt, 1974). The torsion-angle ranges for the B rings are 47·7 (5)–61·8 (6), 45·4 (4)–59·8 (4) and 41·5 (5)–63·6 (5)°; and for the C rings 44·4 (5)–76·9 (4), 41·9 (5)–75·1 (3) and 2·2 (6)–74·2 (4)°, respectively. These ranges show the flattening effect of the epoxide moiety and the puckering effect of the ethylene moiety in each compound.

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* Lists of structure factors, anisotropic thermal parameters, bond lengths, bond angles and torsion angles involving H atoms and H-atom parameters have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 53407 (109 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

The C(8)—C(9) and C(9)—C(10) bond distances [1·573 (6) and 1·586 (6) Å in (1); 1·571 (5) and 1·584 (5) Å in (2)], although normal compared to similar compounds (Hall & Maslen, 1965; Hanson et al., 1972; Muir & Sim, 1968; Murakami, Tanaka, Iida & Iitaka, 1981), are significantly longer than an
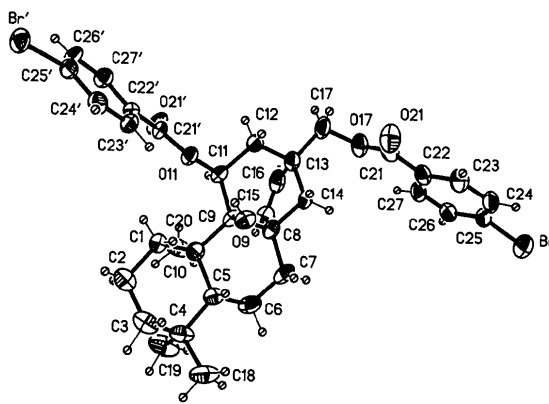

Fig. 1. Molecular structure of (1), with 50% probability ellipsoids, showing the atom numbering scheme.
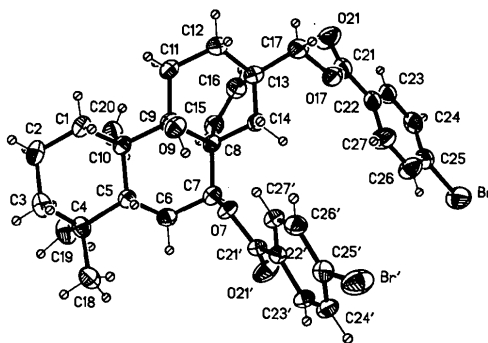

Fig. 2. Molecular structure of (2), with 50% probability ellipsoids, showing the atom numbering scheme.
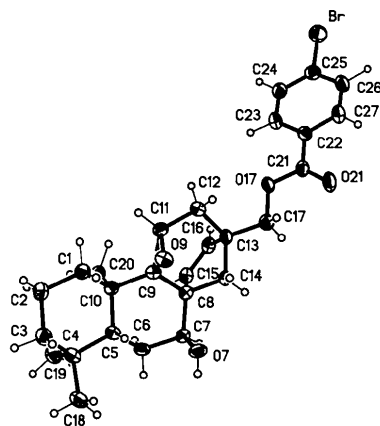

Fig. 3. Molecular structure of (3), with 50% probability ellipsoids, showing the atom numbering scheme.

Table 2. *Atomic coordinates for* (1), (2) *and* (3) ($\times 10^4$) *and equivalent isotropic displacement coefficients* ($\mathring{A}^2 \times 10^3$)

U_{eq} is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U_{eq}
(1)				
Br'	6213 (1)	6513 (1)	8474 (1)	67 (1)
Br'	513 (1)	−5447 (1)	10036 (1)	44 (1)
O(9)	3655 (6)	−576 (3)	8619 (1)	33 (1)
O(11)	341 (5)	−1342 (2)	9071 (1)	31 (1)
O(17)	1464 (6)	2773 (2)	9283 (1)	45 (1)
O(21)	4846 (6)	2495 (3)	9503 (1)	61 (2)
C(21')	−3194 (6)	−1442 (2)	9230 (1)	44 (1)
C(1)	1103 (13)	−1992 (4)	8245 (2)	51 (2)
C(2)	985 (15)	−2642 (5)	7882 (2)	63 (3)
C(3)	2565 (12)	−2375 (5)	7560 (2)	57 (2)
C(4)	2268 (9)	−1395 (4)	7403 (2)	44 (2)
C(5)	2308 (8)	−740 (4)	7776 (2)	35 (2)
C(6)	2119 (12)	277 (4)	7661 (2)	49 (2)
C(7)	2815 (12)	866 (4)	8015 (2)	46 (2)
C(8)	1564 (8)	694 (3)	8403 (1)	31 (2)
C(9)	1462 (7)	−354 (3)	8512 (1)	27 (1)
C(10)	791 (8)	−979 (3)	8138 (1)	33 (2)
C(11)	−10 (7)	−447 (4)	8883 (1)	29 (2)
C(12)	378 (10)	251 (3)	9220 (2)	35 (2)
C(13)	601 (9)	1236 (3)	9060 (1)	34 (2)
C(14)	2522 (9)	1205 (4)	8768 (2)	34 (2)
C(15)	−715 (9)	1112 (3)	8403 (2)	42 (2)
C(16)	−1229 (10)	1427 (4)	8763 (2)	42 (2)
C(17)	761 (11)	1876 (3)	9419 (2)	44 (2)
C(18)	4233 (12)	−1185 (7)	7133 (2)	61 (3)
C(19)	283 (12)	−1330 (7)	7138 (2)	67 (3)
C(20)	−1621 (10)	−862 (7)	8036 (2)	59 (3)
C(21)	3558 (10)	2971 (3)	9324 (2)	42 (2)
C(22)	4142 (9)	3833 (3)	9118 (2)	37 (2)
C(23)	6188 (10)	4183 (4)	9168 (2)	44 (2)
C(24)	6822 (10)	4980 (4)	8981 (2)	49 (2)
C(25)	5341 (9)	5435 (4)	8735 (2)	43 (2)
C(26)	3288 (10)	5101 (4)	8680 (2)	43 (2)
C(27)	2713 (9)	4298 (4)	8869 (2)	41 (2)
C(21')	−1393 (9)	−1754 (3)	9240 (1)	32 (2)
C(22')	−795 (8)	−2620 (3)	9438 (1)	28 (1)
C(23')	1214 (8)	−3045 (3)	9395 (1)	32 (1)
C(24')	1592 (10)	−3871 (3)	9577 (2)	37 (2)
C(25')	16 (8)	−4275 (3)	9808 (1)	35 (2)
C(26')	−1942 (9)	−3855 (3)	9865 (2)	37 (2)
C(27')	−2359 (9)	−3039 (3)	9675 (2)	35 (2)
(2)				
Br	8803 (1)	10123	5774 (1)	69 (1)
Br'	13974 (1)	−2832 (1)	3472 (1)	50 (1)
O(7)	9409 (2)	1934 (4)	1838 (1)	30 (1)
O(9)	8050 (2)	−1352 (4)	1374 (1)	33 (1)
O(17)	7081 (2)	1762 (5)	3972 (1)	39 (1)
O(21)	5441 (2)	2832 (5)	4098 (2)	59 (1)
O(21')	10398 (2)	4616 (4)	2195 (2)	46 (1)
C(1)	6854 (3)	−1058 (7)	−95 (2)	38 (1)
C(2)	6845 (3)	−600 (8)	−899 (2)	40 (1)
C(3)	7894 (3)	371 (7)	−965 (2)	39 (1)
C(4)	8133 (3)	2285 (7)	−521 (2)	33 (1)
C(5)	8049 (2)	1860 (6)	296 (2)	27 (1)
C(6)	8282 (3)	3640 (6)	802 (2)	31 (1)
C(7)	8413 (3)	3103 (6)	1612 (2)	28 (1)
C(8)	7512 (2)	1845 (5)	1796 (2)	25 (1)
C(9)	7196 (2)	104 (6)	1238 (2)	28 (1)
C(10)	7005 (3)	773 (6)	401 (2)	28 (1)
C(11)	6222 (2)	−1007 (7)	1424 (2)	36 (1)
C(12)	6274 (3)	−1338 (7)	2253 (2)	41 (1)
C(13)	6656 (3)	510 (7)	2713 (2)	34 (1)
C(14)	7786 (3)	996 (6)	2581 (2)	29 (1)
C(15)	6515 (3)	3049 (6)	1866 (2)	33 (1)
C(16)	6049 (3)	2281 (8)	2373 (2)	37 (1)
C(17)	6620 (3)	114 (8)	3516 (2)	41 (1)
C(18)	9304 (3)	2874 (8)	−528 (3)	44 (2)
C(19)	7397 (4)	3924 (7)	−897 (2)	46 (2)
C(20)	5987 (3)	2054 (9)	199 (2)	41 (1)
C(21)	6414 (3)	3042 (7)	4204 (2)	41 (1)
C(21')	10322 (3)	2874 (6)	2158 (2)	30 (1)
C(22)	7010 (3)	4720 (7)	4593 (2)	38 (1)
C(22')	11199 (3)	1464 (6)	2460 (2)	28 (1)
C(23)	6460 (3)	6050 (7)	4929 (2)	38 (1)
C(23')	12249 (3)	2180 (8)	2699 (2)	33 (1)
C(24)	6980 (3)	7687 (7)	5283 (2)	43 (2)
C(24')	13087 (3)	918 (6)	3006 (2)	35 (1)

Table 2 (*cont.*)

	x	y	z	U_{eq}
C(25)	8067 (3)	7929 (7)	5295 (2)	44 (1)
C(25')	12856 (3)	−1044 (6)	3063 (2)	33 (1)
C(26)	8631 (3)	6605 (8)	4958 (3)	51 (2)
C(26')	11829 (3)	−1781 (7)	2830 (2)	32 (1)
C(27)	8101 (3)	4990 (8)	4602 (2)	50 (2)
C(27')	11004 (3)	−509 (6)	2539 (2)	31 (1)
(3)				
Br	8692 (1)	8249 (1)	541 (1)	51 (1)
O(7)	55 (5)	1894 (2)	2304 (2)	33 (1)
O(9)	940 (5)	2463 (1)	802 (1)	27 (1)
O(17)	3675 (5)	5090 (1)	1434 (1)	30 (1)
O(21)	1161 (5)	5886 (1)	1760 (2)	41 (1)
C(1)	3027 (8)	1245 (2)	328 (2)	28 (1)
C(2)	3575 (10)	451 (2)	194 (2)	36 (1)
C(3)	2543 (8)	−45 (2)	692 (2)	33 (1)
C(4)	3247 (7)	137 (2)	1372 (2)	28 (1)
C(5)	2865 (7)	966 (2)	1487 (2)	22 (1)
C(6)	3433 (8)	1217 (2)	2161 (2)	26 (1)
C(7)	2406 (7)	1947 (2)	2312 (2)	24 (1)
C(8)	3019 (6)	2530 (2)	1832 (2)	21 (1)
C(9)	2928 (6)	2263 (2)	1138 (2)	21 (1)
C(10)	3822 (7)	1497 (2)	986 (2)	22 (1)
C(11)	2953 (7)	2845 (2)	658 (2)	25 (1)
C(12)	2977 (8)	3643 (2)	827 (2)	26 (1)
C(13)	3064 (7)	3780 (2)	1553 (2)	25 (1)
C(14)	1620 (7)	3217 (2)	1886 (2)	25 (1)
C(15)	5280 (7)	2851 (2)	1942 (2)	25 (1)
C(16)	5294 (7)	3555 (2)	1796 (2)	26 (1)
C(17)	2290 (8)	4531 (2)	1724 (2)	30 (1)
C(18)	1799 (9)	−301 (3)	1827 (3)	39 (2)
C(19)	5619 (8)	−96 (3)	1487 (3)	37 (2)
C(20)	6340 (8)	1554 (2)	980 (2)	27 (1)
C(21)	2901 (7)	5765 (2)	1508 (2)	28 (1)
C(22)	4339 (7)	6345 (2)	1252 (2)	27 (1)
C(23)	6388 (8)	6203 (2)	996 (2)	30 (1)
C(24)	7682 (8)	6765 (3)	782 (2)	34 (1)
C(25)	6914 (8)	7476 (2)	827 (2)	32 (1)
C(26)	4890 (8)	7624 (2)	1078 (2)	35 (1)
C(27)	3618 (9)	7063 (2)	1287 (2)	33 (1)

Table 3. *Bond lengths* ($\mathring{A}$) *and angles* (°) *for* (1), (2) *and* (3)

(1)

Br—C(25)	1·874 (6)	Br'—C(25')	1·895 (5)
O(9)—C(9)	1·435 (5)	O(11)—C(11)	1·462 (6)
O(11)—C(21')	1·348 (6)	O(17)—C(17)	1·452 (6)
O(17)—C(21)	1·331 (7)	O(21)—C(21)	1·209 (7)
O(21')—C(21')	1·201 (6)	C(1)—C(2)	1·527 (9)
C(1)—C(10)	1·533 (7)	C(2)—C(3)	1·494 (10)
C(3)—C(4)	1·534 (9)	C(4)—C(5)	1·557 (7)
C(4)—C(19)	1·507 (9)	C(4)—C(18)	1·534 (9)
C(5)—C(6)	1·538 (8)	C(5)—C(10)	1·557 (7)
C(6)—C(7)	1·511 (9)	C(7)—C(8)	1·514 (8)
C(8)—C(9)	1·573 (6)	C(8)—C(14)	1·535 (7)
C(8)—C(15)	1·533 (7)	C(9)—C(10)	1·586 (6)
C(9)—C(11)	1·530 (6)	C(10)—C(20)	1·535 (8)
C(11)—C(12)	1·526 (7)	C(12)—C(13)	1·540 (7)
C(13)—C(14)	1·525 (7)	C(13)—C(16)	1·519 (8)
C(13)—C(17)	1·511 (7)	C(15)—C(16)	1·312 (8)
C(21)—C(22)	1·475 (7)	C(22)—C(23)	1·371 (8)
C(22)—C(27)	1·383 (8)	C(23)—C(24)	1·374 (9)
C(24)—C(25)	1·391 (8)	C(25)—C(26)	1·369 (8)
C(26)—C(27)	1·375 (8)	C(21')—C(22')	1·470 (6)
C(22')—C(23')	1·393 (7)	C(22')—C(27')	1·383 (7)
C(23')—C(24')	1·368 (7)	C(24')—C(25')	1·368 (7)
C(25')—C(26')	1·369 (7)	C(26')—C(27')	1·372 (7)

(2)

Br—C(25)	1·886 (4)	Br'—C(25')	1·903 (4)
O(7)—C(7)	1·477 (4)	O(7)—C(21')	1·346 (4)
O(9)—C(9)	1·452 (4)	O(17)—C(17)	1·455 (5)
O(17)—C(21)	1·345 (5)	O(21)—C(21)	1·213 (5)
O(21')—C(21')	1·195 (5)	C(1)—C(2)	1·517 (6)
C(1)—C(10)	1·540 (6)	C(2)—C(3)	1·511 (6)
C(3)—C(4)	1·541 (6)	C(4)—C(5)	1·565 (5)
C(4)—C(18)	1·538 (6)	C(4)—C(19)	1·528 (6)
C(5)—C(6)	1·526 (5)	C(5)—C(10)	1·561 (5)
C(6)—C(7)	1·519 (5)	C(7)—C(8)	1·521 (5)
C(8)—C(9)	1·571 (5)	C(8)—C(14)	1·536 (5)
C(8)—C(15)	1·533 (5)	C(9)—C(10)	1·584 (5)
C(9)—C(11)	1·544 (5)	C(10)—C(20)	1·537 (6)

Table 3 (*cont.*)

C(11)—C(12)	1·537 (6)	C(12)—C(13)	1·544 (6)
C(13)—C(14)	1·535 (5)	C(13)—C(16)	1·501 (6)
C(13)—C(17)	1·519 (5)	C(15)—C(16)	1·316 (6)
C(21)—C(22)	1·475 (6)	C(21')—C(22')	1·488 (6)
C(22)—C(23)	1·369 (6)	C(22)—C(27)	1·388 (5)
C(22')—C(23')	1·399 (5)	C(22')—C(27')	1·384 (6)
C(23)—C(24)	1·391 (6)	C(23')—C(24')	1·393 (5)
C(24)—C(25)	1·381 (6)	C(24')—C(25')	1·381 (6)
C(25)—C(26)	1·378 (7)	C(25')—C(26')	1·376 (5)
C(26)—C(27)	1·386 (7)	C(26')—C(27')	1·380 (5)

(3)

Br—C(25)	1·890 (4)	O(7)—C(7)	1·445 (5)
O(9)—C(9)	1·458 (5)	O(9)—C(11)	1·452 (5)
O(17)—C(17)	1·467 (5)	O(17)—C(21)	1·339 (5)
O(21)—C(21)	1·213 (5)	C(1)—C(2)	1·525 (6)
C(1)—C(10)	1·544 (5)	C(2)—C(3)	1·528 (6)
C(3)—C(4)	1·535 (6)	C(4)—C(5)	1·561 (5)
C(4)—C(18)	1·536 (7)	C(4)—C(19)	1·536 (7)
C(5)—C(6)	1·537 (6)	C(5)—C(10)	1·553 (5)
C(6)—C(7)	1·517 (6)	C(7)—C(8)	1·522 (5)
C(8)—C(9)	1·546 (5)	C(8)—C(14)	1·530 (5)
C(8)—C(15)	1·525 (6)	C(9)—C(10)	1·545 (5)
C(9)—C(11)	1·474 (5)	C(10)—C(20)	1·547 (6)
C(11)—C(12)	1·511 (5)	C(12)—C(13)	1·554 (6)
C(13)—C(14)	1·534 (6)	C(13)—C(16)	1·518 (6)
C(13)—C(17)	1·503 (6)	C(15)—C(16)	1·331 (6)
C(21)—C(22)	1·485 (6)	C(22)—C(23)	1·392 (6)
C(22)—C(27)	1·394 (6)	C(23)—C(24)	1·379 (6)
C(24)—C(25)	1·394 (6)	C(25)—C(26)	1·377 (7)
C(26)—C(27)	1·367 (6)		

(1)

C(11)—O(11)—C(21')	117·2 (4)	C(17)—O(17)—C(21)	117·1 (4)
C(2)—C(1)—C(10)	114·6 (5)	C(1)—C(2)—C(3)	111·3 (6)
C(2)—C(3)—C(4)	113·9 (6)	C(3)—C(4)—C(5)	107·9 (4)
C(3)—C(4)—C(18)	106·7 (6)	C(5)—C(4)—C(18)	108·8 (5)
C(18)—C(4)—C(19)	107·1 (5)	C(3)—C(4)—C(19)	110·5 (6)
C(5)—C(4)—C(19)	115·5 (5)	C(4)—C(5)—C(6)	113·5 (4)
C(4)—C(5)—C(10)	117·2 (4)	C(6)—C(5)—C(10)	111·1 (4)
C(5)—C(6)—C(7)	109·9 (5)	C(6)—C(7)—C(8)	114·3 (5)
C(7)—C(8)—C(9)	112·0 (4)	C(7)—C(8)—C(14)	112·6 (4)
C(9)—C(8)—C(14)	108·1 (4)	C(7)—C(8)—C(15)	113·6 (4)
C(9)—C(8)—C(15)	110·5 (4)	C(14)—C(8)—C(15)	99·2 (4)
O(9)—C(9)—C(8)	103·8 (3)	O(9)—C(9)—C(10)	107·8 (3)
C(8)—C(9)—C(10)	113·2 (4)	O(9)—C(9)—C(11)	110·0 (3)
C(8)—C(9)—C(11)	107·0 (4)	C(10)—C(9)—C(11)	114·4 (4)
C(1)—C(10)—C(5)	108·4 (4)	C(1)—C(10)—C(9)	110·3 (4)
C(5)—C(10)—C(9)	108·0 (4)	C(1)—C(10)—C(20)	106·2 (3)
C(5)—C(10)—C(20)	112·9 (4)	C(9)—C(10)—C(20)	111·0 (5)
O(11)—C(11)—C(9)	109·3 (4)	O(11)—C(11)—C(12)	105·5 (3)
C(9)—C(11)—C(12)	115·4 (4)	C(11)—C(12)—C(13)	112·9 (4)
C(12)—C(13)—C(14)	104·9 (4)	C(12)—C(13)—C(16)	109·1 (4)
C(14)—C(13)—C(16)	100·3 (4)	C(12)—C(13)—C(17)	108·3 (4)
C(14)—C(13)—C(17)	117·4 (4)	C(16)—C(13)—C(17)	116·0 (4)
C(8)—C(14)—C(13)	102·0 (4)	C(8)—C(15)—C(16)	111·2 (5)
C(13)—C(16)—C(15)	109·7 (5)	O(17)—C(17)—C(13)	109·7 (4)
O(17)—C(21)—O(21)	124·2 (5)	O(17)—C(21)—C(22)	112·1 (5)
O(21)—C(21)—C(22)	123·7 (5)	C(21)—C(22)—C(23)	119·2 (5)
C(21)—C(22)—C(27)	122·4 (5)	C(23)—C(22)—C(27)	118·3 (5)
C(22)—C(23)—C(24)	121·6 (6)	C(23)—C(24)—C(25)	118·6 (6)
Br—C(25)—C(24)	118·8 (4)	Br—C(25)—C(26)	120·3 (4)
C(24)—C(25)—C(26)	121·0 (5)	C(25)—C(26)—C(27)	118·9 (5)
C(22)—C(27)—C(26)	121·5 (5)	O(11)—C(21')—O(21')	123·6 (4)
O(11)—C(21')—C(22')	111·7 (4)	O(21')—C(21')—C(22')	124·7 (5)
C(21')—C(22')—C(23')	124·1 (4)	C(21')—C(22')—C(27')	117·2 (4)
C(23')—C(22')—C(27')	118·7 (4)	C(22')—C(23')—C(24')	120·0 (5)
C(23')—C(24')—C(25')	120·3 (5)	Br'—C(25')—C(24')	119·7 (4)
Br'—C(25')—C(26')	119·5 (4)	C(24')—C(25')—C(26')	120·7 (5)
C(25')—C(26')—C(27')	119·4 (5)	C(22')—C(27')—C(26')	120·8 (5)

(2)

C(7)—O(7)—C(21')	118·0 (3)	C(17)—O(17)—C(21)	119·1 (3)
C(2)—C(1)—C(10)	113·0 (4)	C(1)—C(2)—C(3)	109·9 (3)
C(2)—C(3)—C(4)	114·1 (4)	C(3)—C(4)—C(5)	108·2 (3)
C(3)—C(4)—C(18)	107·5 (3)	C(5)—C(4)—C(18)	108·3 (3)
C(3)—C(4)—C(19)	110·3 (3)	C(5)—C(4)—C(19)	114·8 (3)
C(18)—C(4)—C(19)	107·5 (4)	C(4)—C(5)—C(6)	113·6 (3)
C(4)—C(5)—C(10)	115·9 (2)	C(6)—C(5)—C(10)	114·4 (3)
C(5)—C(6)—C(7)	112·3 (3)	O(7)—C(7)—C(6)	108·9 (3)
O(7)—C(7)—C(8)	105·3 (3)	C(6)—C(7)—C(8)	115·0 (3)
C(7)—C(8)—C(9)	112·5 (3)	C(7)—C(8)—C(14)	113·0 (2)
C(9)—C(8)—C(14)	108·2 (3)	C(7)—C(8)—C(15)	112·4 (3)
C(9)—C(8)—C(15)	111·1 (2)	C(14)—C(8)—C(15)	98·7 (3)
O(9)—C(9)—C(8)	109·0 (2)	O(9)—C(9)—C(10)	108·9 (3)
C(8)—C(9)—C(10)	112·9 (3)	O(9)—C(9)—C(11)	102·9 (3)
C(8)—C(9)—C(11)	109·4 (3)	C(10)—C(9)—C(11)	113·1 (2)

Table 3 (*cont.*)

C(1)—C(10)—C(5)	108·4 (3)	C(1)—C(10)—C(9)	108·8 (3)
C(5)—C(10)—C(9)	107·3 (2)	C(1)—C(10)—C(20)	108·9 (3)
C(5)—C(10)—C(20)	112·7 (3)	C(9)—C(10)—C(20)	110·7 (3)
C(9)—C(11)—C(12)	115·0 (3)	C(11)—C(12)—C(13)	111·9 (4)
C(12)—C(13)—C(14)	106·6 (3)	C(12)—C(13)—C(16)	110·7 (3)
C(14)—C(13)—C(16)	99·9 (3)	C(12)—C(13)—C(17)	108·9 (4)
C(14)—C(13)—C(17)	114·2 (3)	C(16)—C(13)—C(17)	116·0 (3)
C(8)—C(14)—C(13)	101·3 (2)	C(8)—C(15)—C(16)	110·1 (4)
C(13)—C(16)—C(15)	110·8 (3)	O(17)—C(17)—C(13)	109·8 (4)
O(17)—C(21)—O(21)	123·5 (4)	O(17)—C(21)—C(22)	111·8 (3)
O(21)—C(21)—C(22)	124·7 (4)	O(7)—C(21')—O(21')	123·5 (3)
O(7)—C(21')—C(22')	111·1 (3)	O(21')—C(21')—C(22')	125·4 (3)
C(21)—C(22)—C(23)	118·8 (3)	C(21)—C(22)—C(27)	121·0 (3)
C(23)—C(22)—C(27)	120·2 (4)	C(21')—C(22')—C(23')	118·5 (4)
C(21')—C(22')—C(27')	122·3 (3)	C(23')—C(22')—C(27')	119·1 (3)
C(22)—C(23)—C(24)	120·8 (4)	C(22')—C(23')—C(24')	120·3 (4)
C(23)—C(24)—C(25)	118·4 (4)	C(23')—C(24')—C(25')	118·5 (3)
Br—C(25)—C(24)	119·7 (3)	Br—C(25)—C(26)	118·9 (3)
C(24)—C(25)—C(26)	121·3 (4)	Br'—C(25')—C(24')	120·2 (2)
Br'—C(25')—C(26')	117·7 (3)	C(24')—C(25')—C(26')	122·2 (3)
C(25)—C(26)—C(27)	119·6 (4)	C(25')—C(26')—C(27')	118·7 (4)
C(22')—C(27')—C(26')	121·2 (3)	C(22)—C(27)—C(26)	119·6 (4)

(3)

C(9)—O(9)—C(11)	60·9 (2)	C(17)—O(17)—C(21)	113·3 (3)
C(2)—C(1)—C(10)	112·5 (3)	C(1)—C(2)—C(3)	110·7 (4)
C(2)—C(3)—C(4)	113·3 (4)	C(3)—C(4)—C(5)	108·4 (3)
C(3)—C(4)—C(18)	107·9 (4)	C(5)—C(4)—C(18)	109·1 (3)
C(3)—C(4)—C(19)	110·7 (4)	C(5)—C(4)—C(19)	112·9 (3)
C(18)—C(4)—C(19)	107·6 (4)	C(4)—C(5)—C(6)	113·8 (3)
C(4)—C(5)—C(10)	116·8 (3)	C(6)—C(5)—C(10)	110·9 (3)
C(5)—C(6)—C(7)	111·4 (3)	O(7)—C(7)—C(6)	110·7 (3)
O(7)—C(7)—C(8)	106·6 (3)	C(6)—C(7)—C(8)	112·4 (3)
C(7)—C(8)—C(9)	113·4 (3)	C(7)—C(8)—C(14)	113·1 (3)
C(9)—C(8)—C(14)	108·2 (3)	C(7)—C(8)—C(15)	113·3 (3)
C(9)—C(8)—C(15)	107·5 (3)	C(14)—C(8)—C(15)	100·3 (3)
O(9)—C(9)—C(8)	114·2 (3)	O(9)—C(9)—C(10)	115·2 (3)
C(8)—C(9)—C(10)	118·3 (3)	O(9)—C(9)—C(11)	59·4 (2)
C(8)—C(9)—C(11)	114·8 (3)	C(10)—C(9)—C(11)	121·1 (3)
C(1)—C(10)—C(5)	107·8 (3)	C(1)—C(10)—C(9)	110·4 (3)
C(5)—C(10)—C(9)	107·3 (3)	C(1)—C(10)—C(20)	109·1 (3)
C(5)—C(10)—C(20)	115·2 (3)	C(9)—C(10)—C(20)	107·0 (3)
O(9)—C(11)—C(9)	59·8 (2)	O(9)—C(11)—C(12)	115·4 (3)
C(9)—C(11)—C(12)	122·9 (3)	C(11)—C(12)—C(13)	113·0 (3)
C(12)—C(13)—C(14)	108·8 (3)	C(12)—C(13)—C(16)	108·6 (3)
C(14)—C(13)—C(16)	100·4 (3)	C(12)—C(13)—C(17)	112·1 (3)
C(14)—C(13)—C(17)	109·1 (3)	C(16)—C(13)—C(17)	117·0 (3)
C(8)—C(14)—C(13)	101·5 (3)	C(8)—C(15)—C(16)	110·3 (4)
C(13)—C(16)—C(15)	109·8 (4)	O(17)—C(17)—C(13)	111·1 (4)
O(17)—C(21)—O(21)	122·2 (4)	O(17)—C(21)—C(22)	114·4 (4)
O(21)—C(21)—C(22)	123·4 (3)	C(21)—C(22)—C(23)	122·8 (3)
C(21)—C(22)—C(27)	118·1 (4)	C(23)—C(22)—C(27)	119·0 (4)
C(22)—C(23)—C(24)	120·3 (4)	C(23)—C(24)—C(25)	119·2 (4)
Br—C(25)—C(24)	119·3 (3)	Br—C(25)—C(26)	119·6 (3)
C(24)—C(25)—C(26)	121·1 (4)	C(25)—C(26)—C(27)	119·3 (4)
C(22)—C(27)—C(26)	121·1 (4)		

expected C_{sp^3}–C_{sp^3} bond distance. The C(8), C(9) and C(10) atoms are the only fully substituted C atoms. Apparently, steric effects play a role in elongating the bonds between these atoms.

Each compound has one hydroxyl group and each is involved in H bonding in the crystalline state. H(9) of (1) participates in a bifurcated hydrogen bond, one an intramolecular H bond with O(11) [H(9)···O(11) = 2·36 (6), O(9)···O(11) = 2·77 (1) Å, O(9)—H(9)···O(11) = 117 (5)°] and the other an intermolecular one with O(21') [H(9)···O(21') (1 + x, y, z) = 2·55 (5), O(9)···O(21') = 3·07 (1) Å, O(9)—H(9)···O(21') = 131 (6)°]. H(9) of (2) is involved in one intramolecular H bond with O(7) [H(9)···O(7) = 2·20 (5), O(9)···O(7) = 2·85 (1) Å, O(9)—H(9)···O(7) = 143 (5)°]. H(7) of (3) is involved in one strong intermolecular H bond as evidenced by the linearity of the O(7), H(7) and O(21) atoms [H(7)···O(21) =

2·05 (4), O(7)···O(21) $(-x, y - \frac{1}{2}, \frac{1}{2} - z) = 2·81$ (1) Å, O(7)—H(7)···O(21) = 177 (4)°].

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Structure of Two Polymorphs of 2-Methyl-3,4'-bipyridin-6(1H)-one

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Abstract. $C_{11}H_{10}N_2O$, $M_r = 186·22$. Polymorph (I) monoclinic, $P2_1/c$, $a = 7·574$ (1), $b = 11·132$ (2), $c = 11·437$ (2) Å, $\beta = 94·90$ (1)°, $V = 960·8$ (5) Å^3, $Z = 4$, $D_x = 1·287$ Mg m^{-3}, $\lambda(\text{Mo } K\alpha) = 0·71069$ Å, $\mu = 0·079$ mm^{-1}, $F(000) = 392$, $T = 293$ K, $R = 0·058$ for 2335 observed reflections. Polymorph (II) monoclinic, $P2_1/c$, $a = 6·7897$ (7), $b = 13·449$ (2), $c = 10·736$ (1) Å, $\beta = 108·644$ (8)°, $V = 928·9$ (2) Å^3, $Z = 4$, $D_x = 1·331$ Mg m^{-3}, $\lambda(\text{Mo } K\alpha) = 0·71069$ Å, $\mu = 0·082$ mm^{-1}, $F(000) = 392$, $T = 293$ K, $R = 0·047$ for 1952 observed reflections. The molecular conformations in the two polymorphs are similar and the torsion angle C(2)—C(1)—C(1')—C(2') is 58·9 (2) and 54·1 (2)° for (I) and (II), respectively. Both structures contain centrosymmetric hydrogen-bonded dimers of molecules with the pyridone ring NH groups acting as donors and the keto O atoms as acceptors with N···O distances of 2·776 (2) and 2·765 (1) Å for (I) and (II), respectively.

Introduction. Bipyridine derivatives, a new class of nonglycosidic cardiac positive inotropic agents which inhibit phosphodiesterase isozyme III activity (Baim, McDowell, Cherniles, Monrad, Parker, Edelson, Braunwald & Grossman, 1983), have been developed for the treatment of congestive heart failure. The most potent inotropic agent in the series, milrinone (2-methyl-6-oxo-1,6-dihydro-3,4'-bipyridine-5-carbonitrile), also stimulates rabbit myocardial membrane Ca^{2+}ATPase activity *in vitro* in a way similar to that of thyroid hormones (Mylotte, Cody, Davis, Davis, Blas & Schoenl, 1985). Milrinone, revealing structural homology to thyroxine (Cody, 1987), competes with thyroid hormones for their binding sites on human serum transthyretin (thyroxine-binding prealbumin) (Davis, Cody, Davis, Warnick, Schoenl & Edwards, 1987). We have determined the struc-

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