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Two Methylated Ribonucleosides: 3-Methyluridine and 1-Methylinosine

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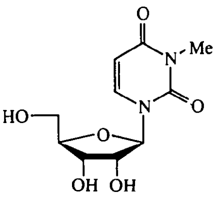
Abstract

3-Methyluridine, $C_{10}H_{14}N_2O_6$, (1), and 1-methylinosine, $C_{11}H_{14}N_4O_5$, (2), adopt conformations generally consistent with those of published ribonucleoside and ribonucleotide crystal structures. (1) has a C(2′)-*endo* ribofuranose pucker (Altona–Sundaralingam pseudorotation angle P = 175.5°); the glycosidic conformation is *anti* ($\chi_{CN} = -133.1°$). (2) has two molecules in the asymmetric unit of which both are C(2′)-*endo* (P = 159.8, 156.9°) with *syn* glycosidic conformations (χ_{CN} = 67.2, 53.6°).

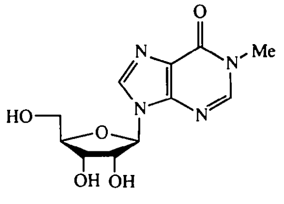
Comment

Nucleoside analogues in which functional groups are replaced by H atoms or are modified by alkylation provide a means of probing mechanisms of molecular recognition involving nucleic acids. Changes in affinity for regulatory proteins that result from systematic removal or hindrance of potentially interacting groups in the target nucleic acid have been used to identify intermolecular contacts in DNA– and RNA–protein complexes (Iwai, Pritchard, Mann, Karn & Gait, 1992). This strategy has also been applied to describe at the molecular level the catalytic activity of ribozymes (Bratty, Chartrand, Ferbeyre & Cedergren, 1993). Structural comparability between these synthetic analogues and their unmodified counterparts is critical to the correct interpretation of experimental results and begins at the nucleoside level.

N-Methylated nucleosides are also natural products; they can result from the action of various chemical carcinogens and mutagens, but many examples are normal components of undamaged DNA and especially RNA. The two ribonucleosides whose structures are described here are minor constituents of transfer RNA. 3-Methyluridine, (1), was detected *inter alia* in human and yeast tRNAs (0.03 and 0.01 mol%, respectively) (Hall, 1971), and 1-methylinosine, (2), has been shown to occur in yeast tRNA (0.05 mol%) (Holley *et al.*, 1965). More specifically, the latter nucleoside is located 3′- to the anticodon of alanine tRNA in yeast and *T. utilis* (Takemura, Ogawa & Nakazawa, 1973).



(1)



(2)

In the case of compounds (1) and (2), the key structural parameters of glycosidic torsion angle (χ_{CN}) and ribofuranose ring pucker are within the ranges typical of ribonucleosides (Saenger, 1984). A survey of purine and pyrimidine ribofuranosides in the Cambridge Structural Database (CSD; Allen *et al.*, 1991) shows in each case glycosidic torsion angles clustered about the values corresponding to *syn* and *anti*. The preference generally for *anti* conformations is less marked in the purine series (69 of 90 for purines; 84 of 94 for pyrimidines); since geometry about the five-membered ring is less sterically demanding, the clash between atoms of the sugar moiety and N(3) of purine is reduced compared to that with O(2) in pyrimidine nucleosides (Haschemeyer & Rich, 1967). Published structures of C(1′)-substituted ribofuranoses are almost equally distributed between two populations corresponding to C(2′)-*endo* and C(3′)-*endo* conformations. C(3′)-*endo* ribofuranose is, however, a characteristic of double-helical RNA (Saenger, 1984).

3-Methyluridine, (1), has an *anti* glycosidic conformation ($\chi_{CN} = -133.1°$) and an unsymmetrical C(2′)-*endo*–C(3′)-*exo* twist ($^2T_3$) described by an Altona–Sundaralingam pseudorotation angle (Altona & Sundaralingam, 1972) of P = 175.5°. All published structures of uridine are also *anti* but have sugar conformations within the C(3′)-*endo* envelope: $^3T_2$, P = 3.7, 14.0° (CSD Refcode: BEURID10), and $^3T_4$, P = 24.9° (CSD Refcode: GIDZIC10).

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All are consistent with the observation that for *anti*-pyrimidines, the glycosidic angle is correlated with the mode of the sugar pucker (Viswamitra, Reddy, Lin & Sundaralingam, 1971); χ_{CN} ranges from -180 to $-138°$ for C(3′)-*endo* (as is found for all the published structures) and from -144 to $-115°$ for C(2′)-*endo*, as in (1).

1-Methylinosine, (2), has two molecules in the asymmetric unit, both of which have similar conformations. Sugar pucker is an unsymmetrical C(2′)-*endo*–C(1′)-*exo* twist ($^2T_1$) with P = 159.8, 156.9°. Glycosidic conformations are *syn* with χ_{CN} = 67.2, 53.6°. These structures are somewhat different from those of the parent nucleoside inosine, where an *anti* glycosidic C(3′)-*endo* conformation (P = 7.9°, χ_{CN} = $-174.3°$) has been reported (CSD Refcode: INOSIN10), as well as C(2′)-*endo* in *anti* and high-*anti* glycosidic conformations (P = 149.7, 163.3°, χ_{CN} = -133.2, $-58.4°$) (CSD Refcode: INOSND10).

Guanosine, for which (2) is a model compound deficient in hydrogen-bond donors, has been observed as broadly C(2′)-*endo* in *anti* and high-*anti* glycosidic conformations: P = 138.4, 161.0°, χ_{CN} = -137.2, $-58.0°$ (CSD Refcode: GUANSH10). Singly and doubly methylated guanosines, however, have been found with *syn*-glycosidic conformations: P = 167.8°, χ_{CN} = 69.2° (CSD Refcode: MGUOSM01), P = 173.6°, χ_{CN} = 70.6° (CSD Refcode: DMGUAN10).

Molecular packing in both crystals involves extensive hydrogen bonding. Molecules of 3-methyluridine are connected by a network of hydrogen bonds into layers, which in turn are linked by stacking between pyrimidine rings. A twofold axis causes adjacent bases along this direction to have opposite orientations with N(1) positioned above the centre of the neighbouring six-membered ring. No stacking interactions are evident in the extended structure of 1-methylinosine.

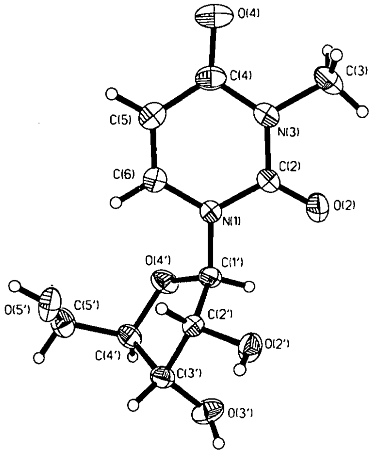

Fig. 1. Displacement ellipsoid plot of 3-methyluridine showing the numbering of the non-H atoms. The ellipsoids are scaled to the 50% probability level.

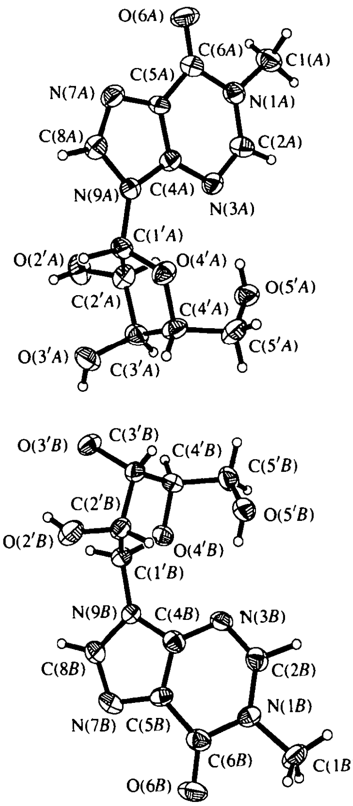

Fig. 2. Displacement ellipsoid plot of the two molecules in the asymmetric unit of 1-methylinosine showing the numbering of the non-H atoms. The ellipsoids are scaled to the 50% probability level.

Experimental

The title compounds were prepared by methylation of the parent nucleosides using dimethylformamide dimethylacetal in methanol (uridine) and dimethylformamide (inosine) (Zemlicka, 1979). Crystals were obtained in each case as elongated regular blocks on cooling an aqueous ethanolic solution of the chromatographically purified product. Data were collected from specimens mounted with epoxy resin on glass fibres.

Compound (1)

Crystal data

$C_{10}H_{14}N_2O_6$
M_r = 258.23
Monoclinic
$C2$
a = 20.019 (4) Å
b = 6.8780 (10) Å
c = 8.923 (2) Å
β = 112.87 (3)°
V = 1132.0 (4) Å^3
Z = 4
D_x = 1.515 Mg m^{-3}

Mo $K\alpha$ radiation
λ = 0.71073 Å
Cell parameters from 48 reflections
θ = 11.5–12.5°
μ = 0.126 mm^{-1}
T = 293 (2) K
Block
0.38 × 0.33 × 0.28 mm
Colourless

Data collection

Siemens Stoe AED four-circle diffractometer

$R_{\rm int}$ = 0.0090
$\theta_{\rm max}$ = 24.98°

ω/θ scans
Absorption correction: none
2182 measured reflections
2003 independent reflections
1964 observed reflections $[I > 2\sigma(I)]$
$h = -23 \rightarrow 21$
$k = -8 \rightarrow 8$
$l = 0 \rightarrow 10$
3 standard reflections
frequency: 60 min
intensity decay: 2%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.0345$
$wR(F^2) = 0.1029$
$S = 0.946$
2003 reflections
166 parameters
H atoms riding on attached C; hydroxyl H atoms riding on attached O and rotating about the C—O bond
$w = 1/[\sigma^2(F_o^2) + (0.0951P)^2 + 0.3094P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{\max} = -0.043$
$\Delta\rho_{\max} = 0.549$ e Å^{-3}
$\Delta\rho_{\min} = -0.604$ e Å^{-3}
Extinction correction: none
Atomic scattering factors from *International Tables for Crystallography* (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4)
Absolute configuration: Flack (1983)

Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters* (Å^2) *for* (1)

$U_{\rm eq} = (1/3)\Sigma_i\Sigma_j U_{ij}a_i^*a_j^*\mathbf{a}_i.\mathbf{a}_j$.

	x	y	z	$U_{\rm eq}$
N(1)	0.95799 (10)	0.8624 (3)	0.7575 (2)	0.0264 (4)
C(2)	1.00399 (12)	1.0088 (3)	0.7492 (3)	0.0330 (5)
O(2)	0.99479 (14)	1.1782 (3)	0.7725 (4)	0.0634 (7)
N(3)	1.06089 (10)	0.9487 (3)	0.7077 (2)	0.0337 (5)
C(3)	1.1097 (2)	1.1028 (5)	0.6970 (5)	0.0601 (9)
C(4)	1.07778 (11)	0.7567 (4)	0.6883 (3)	0.0325 (5)
O(4)	1.13293 (9)	0.7197 (3)	0.6621 (2)	0.0474 (5)
C(5)	1.02737 (13)	0.6155 (4)	0.6999 (3)	0.0353 (5)
C(6)	0.97048 (13)	0.6716 (3)	0.7329 (3)	0.0318 (5)
C(1′)	0.89837 (10)	0.9155 (3)	0.8078 (2)	0.0248 (4)
C(2′)	0.82324 (10)	0.9027 (3)	0.6706 (2)	0.0235 (4)
O(2′)	0.80492 (9)	1.0796 (2)	0.5827 (2)	0.0311 (4)
C(3′)	0.77541 (11)	0.8540 (3)	0.7652 (2)	0.0267 (5)
O(3′)	0.76218 (9)	1.0216 (3)	0.8418 (2)	0.0406 (5)
C(4′)	0.82484 (11)	0.7180 (3)	0.8981 (3)	0.0286 (5)
O(4′)	0.89813 (8)	0.7792 (3)	0.9258 (2)	0.0318 (4)
C(5′)	0.81565 (14)	0.5031 (4)	0.8629 (3)	0.0373 (5)
O(5′)	0.80923 (10)	0.4642 (3)	0.6999 (2)	0.0391 (4)

Table 2. *Selected geometric parameters* (Å, °) *for* (1)

N(1)—C(6)	1.370 (3)	C(5)—C(6)	1.339 (3)
N(1)—C(2)	1.386 (3)	C(1′)—O(4′)	1.411 (3)
N(1)—C(1′)	1.475 (3)	C(1′)—C(2′)	1.529 (3)
C(2)—N(3)	1.391 (3)	C(2′)—C(3′)	1.539 (3)
N(3)—C(4)	1.391 (3)	C(3′)—C(4′)	1.533 (3)
N(3)—C(3)	1.469 (3)	C(4′)—O(4′)	1.452 (3)
C(4)—C(5)	1.433 (3)	C(4′)—C(5′)	1.507 (3)
C(2)—N(3)—C(4)	125.4 (2)	O(4′)—C(1′)—N(1)	107.5 (2)
C(2)—N(3)—C(3)	115.9 (2)	O(4′)—C(1′)—C(2′)	105.8 (2)
C(4)—N(3)—C(3)	118.5 (2)	N(1—C(1′)—C(2′)	113.8 (2)

Compound (2)

Crystal data

$C_{11}H_{14}N_4O_5$
$M_r = 282.26$
Orthorhombic
$P2_12_12_1$
$a = 10.622$ (2) Å
$b = 13.662$ (3) Å
$c = 16.525$ (3) Å
$V = 2398.1$ (8) Å^3
$Z = 8$
$D_x = 1.564$ Mg m^{-3}
Cu $K\alpha$ radiation
$\lambda = 1.54178$ Å
Cell parameters from 25 reflections
$\theta = 25$–36°
$\mu = 1.071$ mm^{-1}
$T = 293$ (2) K
Block
0.25 × 0.1 × 0.1 mm
Colourless

Data collection

Rigaku AFC-5*R* four-circle diffractometer
$2\theta/\omega$ scans
Absorption correction: ψ scans
$T_{\min} = 0.876$, $T_{\max} = 0.947$
2035 measured reflections
2035 independent reflections
1691 observed reflections $[I > 2\sigma(I)]$
$\theta_{\max} = 60.06°$
$h = 0 \rightarrow 11$
$k = 0 \rightarrow 15$
$l = 0 \rightarrow 18$
3 standard reflections
monitored every 150 reflections
intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.0500$
$wR(F^2) = 0.1287$
$S = 0.980$
2022 reflections
367 parameters
H atoms riding on attached C; hydroxyl H atoms riding on attached O and rotating about the C—O bond
$w = 1/[\sigma^2(F_o^2) + (0.0683P)^2 + 3.5767P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{\max} = 0.086$
$\Delta\rho_{\max} = 0.272$ e Å^{-3}
$\Delta\rho_{\min} = -0.364$ e Å^{-3}
Extinction correction: none
Atomic scattering factors from *International Tables for Crystallography* (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4)
Absolute configuration: Flack (1983)

Table 3. *Fractional atomic coordinates and equivalent isotropic displacement parameters* (Å^2) *for* (2)

$U_{\rm eq} = (1/3)\Sigma_i\Sigma_j U_{ij}a_i^*a_j^*\mathbf{a}_i.\mathbf{a}_j$.

	x	y	z	$U_{\rm eq}$
C(1*A*)	1.3029 (7)	0.1753 (6)	0.3961 (5)	0.043 (2)
N(1*A*)	1.1964 (5)	0.2438 (4)	0.4053 (3)	0.0319 (14)
C(2*A*)	1.0879 (6)	0.2243 (6)	0.3649 (4)	0.034 (2)
N(3*A*)	0.9875 (5)	0.2804 (4)	0.3640 (4)	0.0337 (14)
C(4*A*)	1.0023 (6)	0.3630 (5)	0.4098 (4)	0.0279 (14)
C(5*A*)	1.1039 (6)	0.3873 (5)	0.4570 (4)	0.031 (2)
C(6*A*)	1.2168 (7)	0.3273 (6)	0.4542 (4)	0.036 (2)
O(6*A*)	1.3170 (5)	0.3438 (4)	0.4866 (4)	0.053 (2)
N(7*A*)	1.0811 (5)	0.4731 (4)	0.4989 (4)	0.0366 (15)
C(8*A*)	0.9687 (6)	0.5000 (5)	0.4755 (4)	0.031 (2)
N(9*A*)	0.9162 (5)	0.4362 (4)	0.4202 (3)	0.0297 (13)
C(1′*A*)	0.7937 (6)	0.4480 (5)	0.3833 (4)	0.030 (2)
C(2′*A*)	0.7918 (6)	0.4403 (5)	0.2917 (4)	0.031 (2)
O(2′*A*)	0.8371 (5)	0.5233 (4)	0.2510 (3)	0.0432 (13)
C(3′*A*)	0.6530 (7)	0.4147 (5)	0.2774 (4)	0.035 (2)
O(3′*A*)	0.5829 (5)	0.5046 (4)	0.2824 (3)	0.0495 (15)
C(4′*A*)	0.6218 (7)	0.3491 (5)	0.3493 (4)	0.035 (2)
O(4′*A*)	0.7135 (4)	0.3732 (3)	0.4122 (3)	0.0338 (11)
C(5′*A*)	0.6304 (7)	0.2394 (5)	0.3352 (5)	0.042 (2)
O(5′*A*)	0.7478 (5)	0.2104 (4)	0.3028 (3)	0.0422 (13)
N(1*B*)	−0.2257 (5)	0.1919 (4)	0.1151 (3)	0.0296 (13)
C(1*B*)	−0.3154 (7)	0.1115 (5)	0.1258 (5)	0.041 (2)
C(2*B*)	−0.1042 (6)	0.1796 (5)	0.1397 (4)	0.034 (2)
N(3*B*)	−0.0140 (5)	0.2436 (4)	0.1330 (4)	0.0325 (13)

C(4*B*)	−0.0535 (7)	0.3290 (5)	0.0978 (4)	0.031 (2)
C(5*B*)	−0.1733 (6)	0.3504 (5)	0.0731 (4)	0.0277 (15)
C(6*B*)	−0.2722 (7)	0.2818 (5)	0.0841 (4)	0.035 (2)
O(6*B*)	−0.3847 (4)	0.2913 (4)	0.0692 (3)	0.0460 (14)
N(7*B*)	−0.1806 (6)	0.4435 (5)	0.0399 (4)	0.0372 (14)
C(8*B*)	−0.0640 (7)	0.4749 (5)	0.0439 (4)	0.034 (2)
N(9*B*)	0.0183 (5)	0.4093 (4)	0.0791 (3)	0.0290 (13)
C(1′*B*)	0.1502 (6)	0.4293 (5)	0.0962 (4)	0.0288 (15)
C(2′*B*)	0.1799 (6)	0.4352 (5)	0.1856 (4)	0.031 (2)
O(2′*B*)	0.1495 (4)	0.5255 (4)	0.2210 (3)	0.0417 (13)
C(3′*B*)	0.3200 (6)	0.4098 (5)	0.1849 (4)	0.030 (2)
O(3′*B*)	0.3928 (5)	0.4956 (3)	0.1686 (3)	0.0354 (11)
C(4′*B*)	0.3304 (6)	0.3340 (5)	0.1172 (4)	0.031 (2)
O(4′*B*)	0.2207 (4)	0.3489 (3)	0.0663 (3)	0.0303 (11)
C(5′*B*)	0.3309 (7)	0.2293 (5)	0.1443 (5)	0.039 (2)
O(5′*B*)	0.2289 (5)	0.2070 (4)	0.1971 (3)	0.0427 (13)

Table 4. *Selected geometric parameters* (Å, °) *for* (2)

C(1*A*)—N(1*A*)	1.476 (9)	N(1*B*)—C(2*B*)	1.363 (9)
N(1*A*)—C(2*A*)	1.359 (9)	N(1*B*)—C(6*B*)	1.419 (9)
N(1*A*)—C(6*A*)	1.415 (9)	N(1*B*)—C(1*B*)	1.465 (8)
C(2*A*)—N(3*A*)	1.313 (8)	C(2*B*)—N(3*B*)	1.301 (9)
N(3*A*)—C(4*A*)	1.368 (8)	N(3*B*)—C(4*B*)	1.369 (9)
C(4*A*)—C(5*A*)	1.373 (9)	C(4*B*)—N(9*B*)	1.371 (9)
C(4*A*)—N(9*A*)	1.366 (8)	C(4*B*)—C(5*B*)	1.368 (9)
C(5*A*)—N(7*A*)	1.383 (9)	C(5*B*)—N(7*B*)	1.387 (9)
C(5*A*)—C(6*A*)	1.453 (10)	C(5*B*)—C(6*B*)	1.419 (10)
N(7*A*)—C(8*A*)	1.308 (9)	N(7*B*)—C(8*B*)	1.313 (9)
C(8*A*)—N(9*A*)	1.381 (8)	C(8*B*)—N(9*B*)	1.381 (9)
N(9*A*)—C(1′*A*)	1.445 (8)	N(9*B*)—C(1′*B*)	1.455 (8)
C(1′*A*)—O(4′*A*)	1.414 (8)	C(1′*B*)—O(4′*B*)	1.419 (8)
C(1′*A*)—C(2′*A*)	1.519 (9)	C(1′*B*)—C(2′*B*)	1.514 (9)
C(2′*A*)—C(3′*A*)	1.533 (10)	C(2′*B*)—C(3′*B*)	1.528 (9)
C(3′*A*)—C(4′*A*)	1.525 (10)	C(3′*B*)—C(4′*B*)	1.527 (9)
C(4′*A*)—O(4′*A*)	1.461 (8)	C(4′*B*)—O(4′*B*)	1.452 (8)
C(4′*A*)—C(5′*A*)	1.520 (10)	C(4′*B*)—C(5′*B*)	1.500 (9)
C(2*A*)—N(1*A*)—C(6*A*)	124.6 (6)	C(2*B*)—N(1*B*)—C(6*B*)	122.9 (6)
C(2*A*)—N(1*A*)—C(1*A*)	118.4 (6)	C(2*B*)—N(1*B*)—C(1*B*)	119.2 (6)
C(6*A*)—N(1*A*)—C(1*A*)	116.9 (6)	C(6*B*)—N(1*B*)—C(1*B*)	117.7 (6)
O(4′*A*)—C(1′*A*)—N(9*A*)	108.7 (5)	O(4′*B*)—C(1′*B*)—N(9*B*)	107.1 (5)
O(4′*A*)—C(1′*A*)—C(2′*A*)	106.1 (5)	O(4′*B*)—C(1′*B*)—C(2′*B*)	105.7 (5)
N(9*A*)—C(1′*A*)—C(2′*A*)	115.1 (6)	N(9*B*)—C(1′*B*)—C(2′*B*)	113.6 (5)

For both compounds, program(s) used to solve structures: *SHELXS*86 (Sheldrick, 1990); program(s) used to refine structures: *SHELXL*93 (Sheldrick, 1993).

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Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: AB1267). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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trans-(±)-2-(4-Methoxyphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-yl Acetate

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Abstract

The title compound, $C_{18}H_{17}NO_4S$, is a diltiazem-related compound. The molecular packing is predominantly stabilized by hydrogen bonding; amide groups hydrogen bond with adjacent molecules to form centrosymmetric dimers. The seven-membered ring is distorted, showing a twist-boat conformation. The benzene ring is planar but the methoxyphenyl ring deviates significantly from planarity. The relative configuration of the methoxyphenyl and acetoxy groups is *gauche*.

Comment

The title compound, (I), is a drug intermediate in the synthesis of diltiazem, (II), an enantiomerically pure