N-p-tolylsulphonylsulphilimine (Kálmán & Sasvári, 1972). The fact that in both structures (*i.e.* the title compound and the sulphilimine) there is a somewhat weaker S^{VI}–N bond than in other sulphilimines (Kálmán, Párkányi & Kucsman, 1980, and references therein) seems to corroborate Kálmán's (1974) conjecture that the involvement of the lone pair of a bridging N atom in any intra- or intermolecular contact (*e.g.* hydrogen bonding in the title compound) weakens the S^{VI}–N bond. Theoretical considerations on bond-length controlling factors in these systems have been presented (Náray-Szabó & Kucsman, 1979).

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2-Acetamido-3,6-dioxo-5-isopropyl-10b-methoxy-2-methylperhydro-8*H*-oxazolo[3,2-*a*]-pyrrolo[2,1-*c*]pyrazine: a Cyclol Tripeptide Related to Ergot Alkaloids*

BY M. PRZYBYLSKA AND F. R. AHMED

Division of Biological Sciences, National Research Council of Canada, Ottawa, Canada K1A 0R6

Abstract

$C_{16}H_{25}N_3O_5$, $M_r = 339.40$, orthorhombic, $P2_12_12_1$, $a = 13.859$ (3), $b = 16.770$ (2), $c = 7.861$ (2) Å, $V = 1827.0$ Å^3, $Z = 4$, $D_c = 1.234$, $D_m = 1.227$ Mg m^{-3} (flotation in toluene and CCl$_4$ mixture). Final $R = 0.035$, $R_w = 0.040$ for 1618 observed reflexions. The stereochemistry of the tripeptide has been found to differ from that in the natural product, ergotamine, by inversions at two asymmetric centres. The molecules are linked by N—H···O hydrogen bonds into continuous spirals along **a**.

Introduction

The peptide portion of the ergot alkaloids has a profound influence on their physiological activity.

Photochemical generation of *N*-acyl imines (Court, Edwards, Grieco, Rank & Sano, 1975) provided a possible synthesis of the cyclol system common to these peptides, distinct from the approach of Stadler, Frey, Ott & Hofmann (1964). Indeed, an appropriately substituted diketopiperazine (I), when irradiated in methanol, with subsequent acid treatment in that solvent, gave a low yield of the crystalline derivative of one such tripeptide with the correct analyses and spectra for (II) (Edwards, 1980).

The present analysis has established that the chemical formula (II) is correct, but that the stereo-

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(I)   (II)
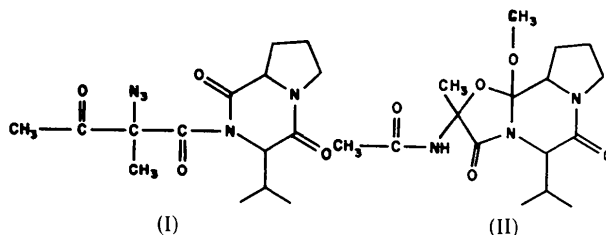
chemistry is not as originally expected. Two asymmetric centres are inverted relative to a corresponding derivative with natural stereochemistry.

Experimental

Colourless prisms (m.p. 449–451 K) were obtained from acetone and ether mixture. X-ray data were

Table 1. *Final fractional coordinates with e.s.d.'s in parentheses* ($\times 10^4$ *for* C, N, O; $\times 10^3$ *for* H) *and isotropic temperature factors* (Å^2)

	x	y	z	B^*_{eq}/B
O(1)	4275 (1)	3096 (1)	2320 (2)	3·5
C(2)	4111 (2)	3147 (2)	510 (4)	3·5
C(3)	4904 (2)	3727 (2)	−74 (3)	3·4
N(4)	5284 (1)	4052 (1)	1350 (3)	2·9
C(5)	6267 (2)	4375 (2)	1354 (4)	2·9
C(6)	6914 (2)	3742 (2)	2108 (4)	3·0
N(7)	6554 (2)	3343 (1)	3424 (3)	3·1
C(8)	7049 (3)	2655 (2)	4178 (5)	4·8
C(9)	6410 (3)	2432 (2)	5674 (5)	5·3
C(10)	5411 (2)	2705 (2)	5141 (4)	4·0
C(11)	5600 (2)	3483 (2)	4208 (3)	2·8
C(12)	4848 (2)	3740 (2)	2860 (3)	2·9
C(13)	3115 (2)	3472 (2)	120 (5)	4·9
O(14)	5119 (2)	3873 (1)	−1533 (3)	4·8
O(15)	7720 (1)	3610 (1)	1518 (3)	4·8
O(16)	4258 (1)	4363 (1)	3498 (3)	3·6
C(17)	3662 (2)	4151 (2)	4920 (5)	5·2
N(18)	4229 (2)	2377 (1)	−233 (3)	3·9
C(19)	5098 (2)	2000 (2)	−279 (4)	3·9
O(20)	5823 (1)	2317 (1)	269 (3)	5·1
C(21)	5085 (3)	1182 (2)	−1037 (5)	5·2
C(22)	6360 (2)	5194 (2)	2194 (4)	3·3
C(23)	5655 (3)	5782 (2)	1427 (5)	5·5
C(24)	7400 (3)	5494 (2)	2047 (5)	4·9
H(5)	643 (2)	449 (2)	3 (4)	3·4 (0·6)
H(8,1)	704 (2)	222 (2)	335 (5)	5·8 (0·8)
H(8,2)	767 (3)	286 (2)	459 (5)	7·3 (1·0)
H(9,1)	639 (2)	184 (2)	579 (4)	5·3 (0·8)
H(9,2)	662 (3)	272 (2)	676 (5)	6·6 (0·9)
H(10,1)	518 (2)	230 (2)	436 (4)	4·6 (0·7)
H(10,2)	501 (2)	279 (2)	607 (4)	5·3 (0·8)
H(11)	564 (2)	397 (1)	495 (3)	2·4 (0·5)
H(13,1)	266 (2)	306 (2)	47 (4)	4·4 (0·7)
H(13,2)	303 (2)	406 (2)	67 (5)	5·5 (0·8)
H(13,3)	307 (3)	366 (2)	−120 (5)	6·7 (0·9)
H(17,1)	324 (3)	466 (2)	507 (5)	8·0 (1·1)
H(17,2)	330 (3)	365 (2)	468 (5)	6·9 (1·0)
H(17,3)	404 (4)	402 (3)	596 (8)	13·0 (1·7)
H(18)	373 (2)	217 (2)	−66 (5)	5·4 (0·8)
H(21,1)	458 (3)	97 (3)	−78 (7)	11·0 (1·5)
H(21,2)	555 (3)	85 (3)	−43 (7)	11·3 (1·5)
H(21,3)	531 (4)	110 (4)	−215 (9)	15·7 (2·2)
H(22)	619 (2)	513 (2)	340 (4)	2·9 (0·6)
H(23,1)	579 (2)	630 (2)	174 (4)	5·0 (0·8)
H(23,2)	585 (3)	585 (2)	10 (5)	7·4 (1·0)
H(23,3)	506 (2)	563 (2)	135 (5)	6·6 (0·9)
H(24,1)	751 (3)	562 (2)	81 (5)	6·5 (0·9)
H(24,2)	744 (3)	600 (2)	251 (5)	6·8 (1·0)
H(24,3)	787 (3)	505 (3)	257 (5)	7·9 (1·1)

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

measured on a Picker diffractometer with Ni-filtered Cu radiation [$\lambda(K\alpha_1) = 1\cdot54050$, $\lambda(K\alpha_2) = 1\cdot54434$ Å] and a crystal cut into a square plate ($0\cdot36 \times 0\cdot36 \times 0\cdot10$ mm) mounted along **c**. The cell parameters were based on the 2θ values of the $K\alpha_1$ and $K\alpha_2$ components of 14 reflexions measured with a narrow slit. The 1794 independent reflexions within $2\theta < 130°$ were scanned by the θ–2θ method and, of these, 1618 (90%) were observed above threshold. The background was measured for 20 s at the lower and upper limits of each scan, and two reflexions (160 and 810) were used as standards for scaling. The intensities were corrected for Lorentz and polarization effects but not for absorption [$\mu(\text{Cu } K\alpha) = 0\cdot775$ mm^{-1}].

The structure was solved with the tangent formula (Karle & Hauptman, 1956). The E map computed with 170 E's out of a possible 191 with $|E| > 1\cdot5$ ($R_K = 0\cdot25$) revealed all non-hydrogen atoms but several weak peaks were not accepted until confirmed by difference maps. All H atoms were located from a difference map when R was $0\cdot08$. No other significant peaks were observed. Refinement was by block-diagonal least-squares calculations, minimizing $\sum w(|F_o| - |F_c|)^2$, where $w = \{1 + [(|F_o| - 10)/ 30]^2\}^{-1}$, excluding the unobserved reflexions. In the final cycle, $R = 0\cdot035$ for the observed reflexions and $R_w = 0\cdot040$. Mean and maximum shift/e.s.d. for the parameters of the non-hydrogen atoms were $0\cdot07$ and $0\cdot39$, respectively. The atomic parameters are presented in Table 1.* All calculations were carried out with the NRC program system (Ahmed, Hall, Pippy & Huber, 1973). Scattering factors were those of Hanson, Herman, Lea & Skillman (1964), except for H (Stewart, Davidson & Simpson, 1965).
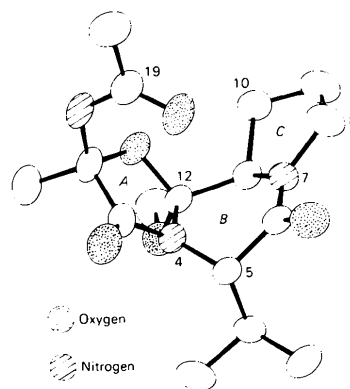
Fig. 1. An *ORTEP* parallel projection of the tripeptide showing thermal ellipsoids at the 50% probability level (Johnson, 1965).

Discussion

The molecular structure of the cyclol tripeptide is shown in Fig. 1 and in (III). Its stereochemistry (2S, 5S, 11R and 12S) differs from that in the natural product ergotamine (IV) in the configurations at C(2) and C(11).

(III)

R = lysergyl

(IV)

R = p − iodobenzoyl

(V)
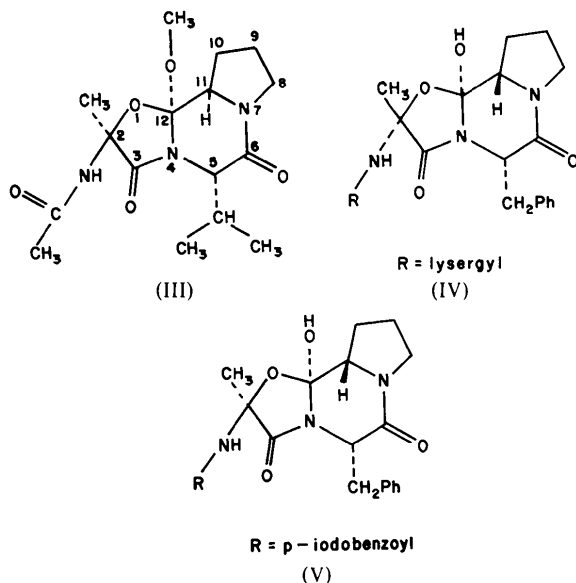
The structure of the peptide moiety of (IV) was established by chemical and spectroscopic methods as 2R, 5S, 11S and 12S (Hofmann, Ott, Griot, Stadler & Frey, 1963) and was confirmed recently by the X-ray analysis of (−)-dihydroergotamine methanesulphonate monohydrate (Hebert, 1979). The only other related structure determined by X-ray methods is the aci-p-iodobenzoylamino cyclol (V), obtained by isomerization of the parent alkaloid in acidic medium (McPhail, Sim, Frey & Ott, 1966). The sterochemistry of (V) differs from (IV) only in the inversion at C(2).

The inversions at C(2) and C(11) and the intermolecular N(18)···O(15′) hydrogen bond in the present compound appear to be responsible for

considerable conformational differences and a much less planar molecule than in (IV). The skeleton of (III) is V-shaped (Fig. 1), being folded at the C(5)···C(11) diagonal with an angle of 118·3° between the two mean planes.

The bond lengths and angles, not corrected for thermal vibration, are presented in Fig. 2. C−H bonds are 0·81–1·09 Å (0·99 Å average). The C(2)−C(3) length of 1·538 (4) Å agrees well with the corresponding value of 1·539 (7) Å in (IV), but both are longer than the expected value 1·516 (5) Å (Molecular Structures and Dimensions, 1972) for a C−CO bond.

The low electron density on C(2) and C(12), caused by attachment to O atoms, is probably responsible for the shortening of N(18)−C(2) and N(4)−C(12) (1·426, 1·431 Å) compared with N(7)−C(8) and N(7)−C(11) (1·467, 1·477 Å). The shortening of O(1)−C(12) [1·407 (3) Å] and the variations in the N−CO lengths [1·329 (4), 1·352 (4) and 1·361 (4) Å] seem to be also largely dependent on the differences in the electron-density distribution.

The differences in the C=O lengths in (III), in the dihydroergotamine cation (IV) and in the aci isomer (V) can be correlated with the hydrogen-bond formation. Table 2 shows a comparison of the corresponding C=O groups.

Such bond-length changes caused by hydrogen bonding have been reported by Ottersen (1975) and Stevens (1978), and have recently been confirmed by Jeffrey, Ruble, McMullan, DeFrees, Binkley & Pople

Table 2. The C=O lengths (Å) in this structure (III), in the dihydroergotamine cation (IV) and in the aci isomer (V)

	(III)	(IV)	(V)
C(19)=O(20)	1·215 (4)	1·232 (6)*	1·25 (3)†
C(3)=O(14)	1·210 (4)	1·220 (6)*	1·26 (3)*
C(6)=O(15)	1·230 (3)*	1·212 (7)	1·25 (3)*

* Oxygen acts as an acceptor in the hydrogen-bond formation.
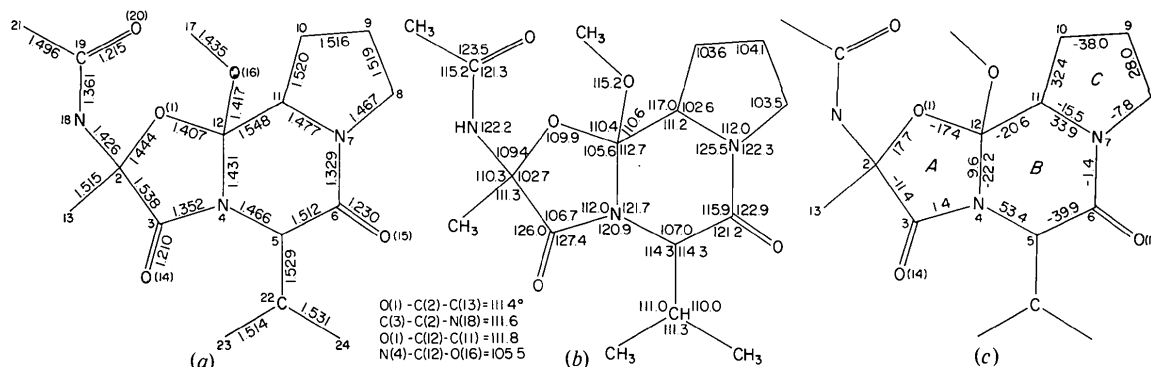† Bond affected by the substitution by a phenyl group.

Fig. 2. (a) Bond lengths (Å), σ = 0·003 to 0·005 Å; (b) valency angles (°), σ = 0·2–0·3°; (c) endocyclic torsion angles (°), σ ≤ 0·6°.

(III) O(20) $\xrightarrow[\text{(4)}]{1.215}$ C(19) $\xrightarrow[\text{(4)}]{1.361}$ N(18) $\xrightarrow[\text{(4)}]{1.426}$ C(2)

                       | H

                                      O(15')

(IV) O(20) $\xrightarrow[\text{(6)}]{1.232}$ C(19) $\xrightarrow[\text{(7)}]{1.341}$ N(18) $\xrightarrow[\text{(6)}]{1.443}$ C(2)

  : | H

  H   O

  O

(a)

(III) O(14) $\xrightarrow[\text{(4)}]{1.210}$ C(3) $\xrightarrow[\text{(4)}]{1.352}$ N(4) $\xrightarrow[\text{(4)}]{1.431}$ C(12) $\xrightarrow[\text{(3)}]{1.417}$ OCH₃

(IV) O(14) $\xrightarrow[\text{(6)}]{1.220}$ C(3) $\xrightarrow[\text{(7)}]{1.335}$ N(4) $\xrightarrow[\text{(6)}]{1.451}$ C(12) $\xrightarrow[\text{(6)}]{1.371}$ O(16) H
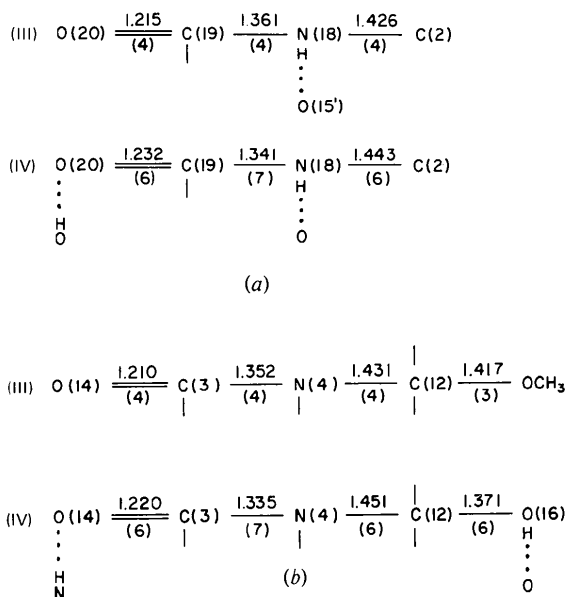
(b)

Fig. 3. Effect of hydrogen bonding in (a) N(18) and (b) N(4) peptides in the present structure (III) and in the dihydro-ergotamine derivative (IV), assuming the same numbering system.

Fig. 4. Newman projections down N(4)–C(12) and N(7)–C(11).

Table 3. Mean planes and atomic displacements

(a) Parameters for the planes $lX + mY + nZ = p$, where X,Y,Z are in Å

	l	m	n	p
Ring A	−0·6749	0·7373	−0·0289	0·0305
Ring B	−0·1060	−0·8547	−0·5081	−7·1712
Ring C	−0·4227	−0·6002	−0·6790	−9·0326

(b) Deviations from the mean planes (Å), e.s.d. = 0·004 Å

Ring A		Ring B		Ring C	
C(2)	0·004	N(4)	0·046	N(7)	0
C(3)	−0·007	C(6)	0·050	C(8)	0
N(4)	0·007	N(7)	0·048	C(11)	0
C(12)	−0·004	C(12)	−0·045	C(6)*	0·090
O(1)*	−0·254	C(5)*	−0·561	C(9)*	−0·199
C(5)*	−0·512	C(11)*	−0·324	C(10)*	0·395
O(14)*	0·005	C(3)*	1·138		
		C(8)*	0·660		
		O(15)*	0·256		

* Atoms not included in the calculation of the plane.

(1980), who compared acetamide bonds from a neutron diffraction analysis at 23 K with those for an isolated molecule arrived at by *ab initio* molecular-orbital calculations. The latter (C=O 1·215 and C—N 1·360 Å for a conformation of minimum energy) are in good agreement with the values for non-hydrogen-bonded C=O groups shown in Table 2, and with N(18)—C(19) and C(3)—N(4) [1·361 (4), 1·352 (4) Å].

On comparison of N(18) peptide bonds in (III) with those in (IV) (Fig. 3a), bond differences are observed, which are probably due to the hydrogen-bond formation by the carbonyl O atom found only in the latter. In (IV), as in crystalline acetamide, the shortening of the NH—C donor bond is displayed by N(18)—C(19) = 1·341 (7) Å, whereas in (III) this effect is shown by N(18)—C(2) rather than by N(18)—C(19), which is 1·361 (4) Å. The difference between N(18)—C(2) bonds ($\Delta = 0\cdot017$, $t = \Delta/\sigma = 2\cdot4$) in the two structures is possibly significant.

The N(4) peptides (Fig. 3b) present another example of bond-length differences between the two structures due to hydrogen-bond formation. In (IV), with C=O as an acceptor and O(16) as a donor, there is an alternate lengthening and shortening of bonds throughout the chain compared with the corresponding values in (III).

The endocyclic angles have mean values of 115·7° in the six-membered ring and 106·3° in the five-membered rings, the largest angles occurring at the N atoms. While the three bonds at N(7) are almost coplanar, those at N(4) are significantly non-planar,
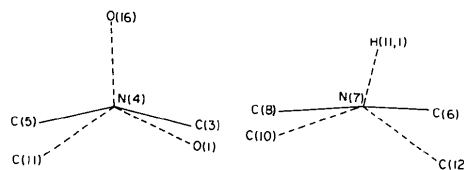
with N(4) at 0·191 Å from the plane of its three nearest C atoms, indicating a smaller resonance contribution of the type $-\overset{|}{N}{}^{+}=\overset{|}{C}-O^{-}$ at N(4) than at N(7). This is also supported by the differences in the corresponding C—N and C=O lengths in the two groups.

The Newman projections along N(4)—C(12) and N(7)—C(11), Fig. 4, indicate that both ring junctions are *cis*, although it is more pronounced for A/B than for B/C as shown by the near linearity of C(6)—N(7)—C(8) in the projection.

The torsion angles are presented in Fig. 2(c), with signs according to the IUPAC–IUB Commission on Biochemical Nomenclature (1970), and the details of the mean planes are in Table 3. Ring A has an envelope conformation with O(1) at −0·25 Å from the mean plane of the other four atoms and $\Delta C_s[O(1)] = 1\cdot3°$. Ring B is in a distorted boat form flattened at C(11) which is only 0·32 Å from the mean plane of N(4), C(6), N(7) and C(12). Ring C is half-chair with C(9) at −0·20 and C(10) at 0·40 Å from the plane of N(7), C(8) and C(11); $\Delta C_2[C(9)—C(10)] = 6\cdot3°$ (Duax & Norton, 1975). The torsion angles C(3)—C(2)—N(18)—C(19) and C(2)—N(18)—C(19)—C(21) are 46·4 and 177·5° ($\sigma \simeq 0\cdot6°$) respectively.

The conformational differences between the tripeptides in (III), (IV) and (V) are thus considerable. In the dihydroergotamine derivative ring A has a half-chair form with N(4) at -0.10 and C(12) at 0.16 Å from the plane of the other three atoms, B is an envelope at C(12) and C is half-chair with C(10) above ($+0.22$ Å) and C(11) below (-0.25 Å) the plane of N(7), C(8) and C(9). In the aci isomer (V) ring B is a distorted half-boat, and rings A and C are both envelopes at C(2) and C(10).

The hydrogen bond between N(18) and O(15') of a neighbouring molecule gives rise to spirals of H-bonded molecules parallel to **a**. The pertinent data are: N(18)···O(15') = 2.851 (3), N(18)—H(18,1) = 0.85 (3), H(18,1)···O(15') = 2.03 (3) Å and N(18)—H···O(15') = 165 (3)°. All other intermolecular contacts are longer than the sums of the corresponding van der Waals radii.

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Structure of the Unstable Monoclinic 1,2,3,5-Tetra-O-acetyl-β-D-ribofuranose*

By MÁTYÁS CZUGLER, ALAJOS KÁLMÁN, JÓZSEF KOVÁCS AND ISTVÁN PINTÉR

Central Research Institute of Chemistry, Hungarian Academy of Sciences, H-1525 Budapest 114, POB 17, Hungary

Abstract

The unstable A form of 1,2,3,5-tetra-O-acetyl-β-D-ribofuranose, $C_{13}H_{18}O_9$ (m.p. = 330–331 K), crystallizes in the monoclinic system, $a = 12.649$ (2), $b = 5.582$ (2), $c = 11.078$ (2) Å, $\beta = 97.92$ (1)°, space group $P2_1$, $Z = 2$, $D_c = 1.364$ Mg m^{-3}. Final $R = 0.045$ for 1142 reflexions. To shed light on the spontaneous and irreversible transition of form A into the stable orthorhombic form B (m.p. 358 K) the present structure determination of A is compared with that of B reported by James & Stevens [*Cryst. Struct. Commun.* (1973), **2**, 609–612] and Poppleton [*Acta Cryst.* (1976), B**32**, 2702–2705]. Neither the bonding of the molecules nor the puckering of the furanose rings reveals significant differences. However, two of the four acetyl moieties exhibit torsional parameters [C(4)—C(5)—O(5)—C(6) and C(1)—C(2)—O(2)—C(10)] which differ significantly ($\Delta = 92.5$ and 70.0°), indicating conformational dimorphism of A and B. There are three H···H intermolecular contacts in A which