Water related				
O_5—HA_5···O_11	0.93	1.78	2.695 (5)	167
O_5—HB_5···O_9	1.02	1.71	2.725 (5)	172
O_6—HA_6···O10_3	1.00	1.90	2.775 (4)	145
O_6—HB_6···O_10	0.99	1.67	2.664 (5)	178
O_7—HA_7···O9_2	0.97	1.73	2.707 (4)	178
O_7—HB_7···O2_1	0.98	1.77	2.746 (4)	176
O_8—HA_8···O_7	0.95	1.80	2.757 (5)	179
O_8—HB_8···O2_2	0.98	2.16	3.138 (4)	173
O_9—HA_9···O10_1	0.98	1.90	2.874 (5)	173
O_9—HB_9···O10_4	0.97	1.83	2.803 (4)	175
O_10—HA_10···O10_1	1.01	1.72	2.724 (4)	174
O_10—HB_10···O10_4	1.01	1.92	2.928 (5)	175
O_11—HA_11···O10_3	0.99	1.82	2.814 (5)	176
O_11—HB_11···O10_2	0.97	1.72	2.688 (5)	179
O_12—HA_12···O_13	1.03	2.11	3.140 (18)	176
O_12—HB_12···O2_4	0.96	2.17	3.128 (8)	178
O_12—HA_12···N10_3	1.03	2.86	3.167 (11)	98
O_13—HA_13···O10T_3	0.96	1.89	2.831 (10)	169
O_13—HB_13···O9_4	1.07	1.93	2.983 (9)	170
O_14—H_14···O10T_4	1.00	1.86	2.850 (3)	177

Symmetry codes: (i) $\frac{1}{2}-x, \frac{1}{2}-y, z-\frac{1}{2}$; (ii) $x, y, 1+z$; (iii) $1-x, -y, z-\frac{1}{2}$; (iv) $x, -y, 1-z$.

The title structure was solved using *LODEM* (Matsugaki & Shiono, 1998), which is a density modification program designed to produce an *ab initio* solution by refining random phase sets. The program transforms the density (ρ) by $\rho' = \rho[1-\exp\{-0.5(\rho/0.2\rho_c)^2\}]$, if $\rho > 0$, or $\rho' = 0$, if $\rho < 0$, where ρ_c is the expected average peak height of light atoms in the structure. The results of structure determinations are given in terms of phases or peak positions in an asymmetric unit. The basic idea of the procedure is to remove negative density and also to sharpen peaks. Ten peaks remained in the final difference Fourier map. One of them (O_14) was located on a special position. These peaks were assigned as water molecules since no atom was found within covalent bond distance. The Flack (1983) parameter is consistent with the known absolute stereochemistry of the starting materials.

Data collection: *MSC/AFC Diffractmeter Control Software* (Molecular Structure Corporation, 1991). Cell refinement: *MSC/AFC Diffractmeter Control Software*. Data reduction: *MSC/AFC Diffractmeter Control Software*. Program(s) used to solve structure: *LODEM* (Matsugaki & Shiono, 1998). Program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997). Molecular graphics: *ORTEP*III (Burnett & Johnson, 1996). Software used to prepare material for publication: *PARST* (Nardelli, 1983).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: SX1078). Services for accessing these data are described at the back of the journal.

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Hexamethylenetetramine is a fourfold acceptor of O—H···N hydrogen bonds in its 1:2 adduct with 2,2′-biphenol

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Abstract

In hexamethylenetetramine–2,2′-biphenol (1/2), $C_6H_{12}N_4{\cdot}2C_{12}H_{10}O_2$, the biphenol acts as a double donor of O—H···N hydrogen bonds and the hexamethylenetetramine acts as a fourfold acceptor. The molecules are assembled into deeply puckered pseudo-tetragonal nets built from $R_8^8(44)$ rings.

Comment

In hydrogen-bonded systems, hexamethylenetetramine (HMTA, $C_6H_{12}N_4$) generally acts as a double acceptor of hydrogen bonds (Dahl & Hassel, 1971; Mak *et al.*, 1978; Mahmoud & Wallwork, 1979; Ferguson *et al.*, 1995; Coupar, Glidewell & Ferguson, 1997; Meehan *et al.*, 1997). Rather less frequently, HMTA behaves as an acceptor of just one hydrogen bond (Mak *et al.*, 1986; Coupar, Glidewell & Ferguson, 1997) or of three

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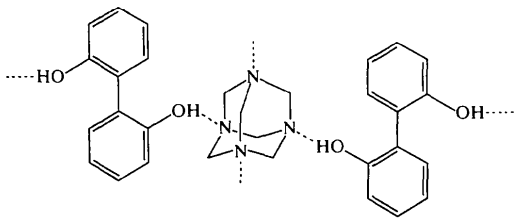
hydrogen bonds (Jordan & Mak, 1970; de Bruyn *et al.*, 1996; Coupar, Ferguson *et al.*, 1997). The perfect tetrahedral disposition of the nitrogen lone pairs in the HMTA molecule makes this an attractive candidate as a tetrahedral building block for supramolecular chemistry, but there appear to be no examples so far recorded in which HMTA acts as a fourfold acceptor of hydrogen bonds. Since hydrogen-bond formation effects only a very modest electronic perturbation in HMTA, as judged from the C—N bond lengths (Coupar, Glidewell & Ferguson, 1997), there appears to be no good reason why such behaviour should not be observed. We reasoned that by use of an appropriate bis-phenol, it should be possible to generate four hydrogen bonds per HMTA molecule. 2,2′-Biphenol was selected since, although the pure substance contains intramolecular O—H···hydrogen bonds (Byrne *et al.*, 1998), in both its hydrate (Chen *et al.*, 1996) and its adduct with 4,4′-bipyridyl (Lavender *et al.*, 1999), 2,2′-biphenol forms only intermolecular hydrogen bonds. In addition, it has a marked flexibility about the central C—C bond which increases its structural versatility. We report here the synthesis and structural characterization of the 1:2 adduct hexamethylenetetramine–2,2′-biphenol (1/2) $C_6H_{12}N_4 \cdot 2C_{12}H_{10}O_2$, (1), which exhibits the hydrogen-bonding features we sought.



(1)

Cocrystallization of HMTA and 2,2′-biphenol from methanol produces the desired 1:2 adduct in which the numbers of hydrogen-bond-donor hydroxyl groups and hydrogen-bond-acceptor N atoms are identical. The asymmetric unit of (1) (Fig. 1) consists of one molecule of HMTA and two of the biphenol, all lying in general positions. Each biphenol forms O—H···N hydrogen bonds with two different HMTA units, and each HMTA is an acceptor of four O—H···N hydrogen bonds from four different biphenol molecules (Fig. 2 and Table 2); as expected, there are no O—H···O hydrogen bonds. Within the asymmetric unit, the O1 and O3 atoms are hydrogen-bond donors to N51 and N53, respectively (Table 2); in addition, O2 and O4 at (x, y, z) are donors to N510 and N55 at $(1+x, y, z)$ and $(x, y, -1+z)$, respectively. Hence, a two-dimensional net parallel to (010) containing just a single type of $R_8^8(44)$ ring is generated by translation only (Fig. 2); two such nets, related by the 2_1 axis, run through each unit cell. The tetrahedral disposition of the hydrogen bonds around the HMTA units means that these nets are deeply puckered (Figs. 2 and 3) and successive nets are stacked like egg trays.

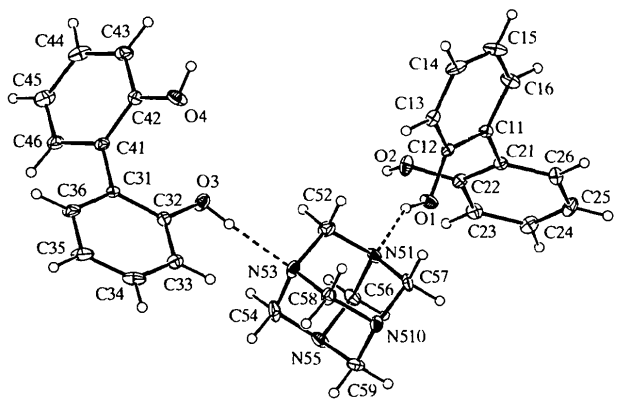


Fig. 1. The asymmetric unit of compound (1) showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 30% probability level.

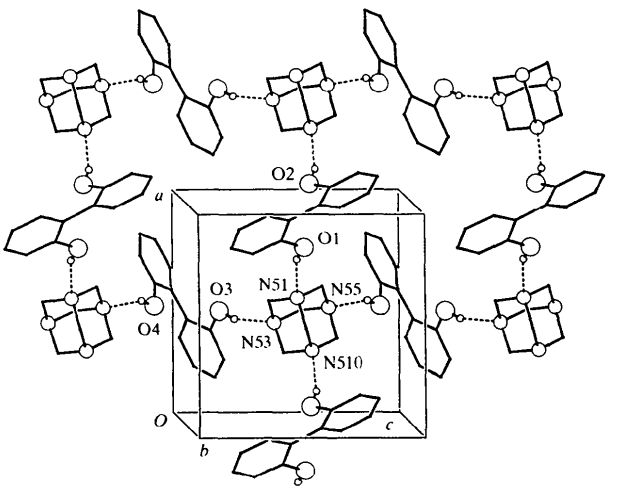


Fig. 2. Part of the crystal structure of (1), showing one of the (010) nets built from $R_8^8(44)$ rings.

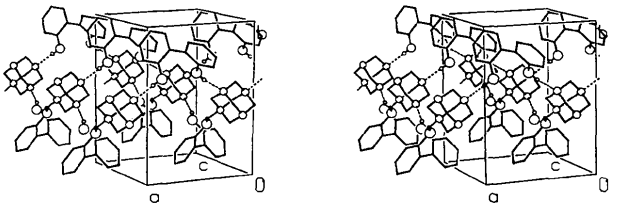


Fig. 3. Stereoview of part of the crystal structure of (1), showing the puckering of an (010) net.

Although compound (1) is unambiguously monoclinic, the supramolecular structure is pseudo-tetragonal (Fig. 2); indeed, after an appropriate axis transformation, the structure can be readily solved in the tetragonal space group $P4_2$, although successful refinement of the resulting disordered model is not possible. The principal deviation from tetragonal symmetry can be traced to the orientation of the HMTA unit; the local C_2 axis of the

HMTA molecule through C54 and C57 is tilted away from the direction of the screw axis by *ca* 8.7°, and this in turn causes a discrimination between the two axial directions normal to the screw axis. Associated with this tilt is the difference in the O1···N51 and O2···N510 distances (Fig. 2 and Table 2). The two independent 2,2′-biphenol molecules have very similar conformations; in the molecules containing atoms O1 and O3, the interplane dihedral angles are 55.6 (1) and 55.4 (1)°, respectively; however, the locations of the molecular centroids for these components differ significantly from those required by tetragonal symmetry.

In hydrogen-bonded neutral HMTA molecules, the C—N bonds are, in general, significantly longer for an N atom acting as a hydrogen-bond acceptor than for an N atom not involved in hydrogen bonding (Coupar, Glidewell & Ferguson, 1997). The C—N bond lengths in compound (1) [range 1.457 (4)–1.483 (4) Å, mean 1.469 (6) Å] are consistent with the ranges observed earlier (Coupar, Glidewell & Ferguson, 1997). The N—C—N angles in (1) are consistently larger than the C—N—C angles. In the biphenol units, the exocyclic C—C—O angles all show the usual dependence on the orientation of the substituent at oxygen; other bond lengths are typical of their types.

Examination of the structure with *PLATON* (Spek, 1999) showed that there were no solvent-accessible voids in the crystal lattice.

Experimental

Stoichiometric quantities of HMTA and 2,2′-biphenol were dissolved separately in methanol. The solutions were mixed and the resulting mixture was set aside to crystallize, producing compound (1) in analytically pure form. Analysis, found: C 70.0, H 6.6, N 10.8%; $C_{30}H_{32}N_4O_4$ requires: C 70.3, H 6.3, N 10.9%. Despite replicate preparations using a variety of crystallization regimes, the crystal quality was always rather poor and data collected at 100 (1) K using a conventional laboratory X-ray source did not lead to a satisfactory refinement. However, a data set collected at 150 (2) K on station 9.8 at the Synchrotron Radiation Source, Daresbury (Cernik *et al.*, 1997), using a very small crystal led to satisfactory structure solution and refinement.

Crystal data

$C_6H_{12}N_4{\cdot}2C_{12}H_{10}O_2$
M_r = 512.60
Monoclinic
$P2_1$
a = 9.7615 (9) Å
b = 13.0362 (12) Å
c = 9.7878 (9) Å
β = 90.199 (2)°
V = 1245.5 (2) Å^3
Z = 2
D_x = 1.367 Mg m^{-3}
D_m not measured
Synchrotron radiation
λ = 0.68880 Å
Cell parameters from 6608 reflections
θ = 2.02–29.42°
μ = 0.092 mm^{-1}
T = 150 (2) K
Plate
0.12 × 0.08 × 0.03 mm
Orange

Data collection

Bruker SMART CCD diffractometer
ω rotation with narrow frames
Absorption correction: multi-scan (*SADABS*; Sheldrick, 1997*a*)
T_{min} = 0.989, T_{max} = 0.997
12 298 measured reflections
3625 independent reflections (plus 2983 Friedel-related reflections)
5905 reflections with $I > 2\sigma(I)$
R_{int} = 0.036
θ_{max} = 29.42°
$h = -13 \rightarrow 13$
$k = -18 \rightarrow 18$
$l = -13 \rightarrow 13$
Intensity decay: negligible

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.066
$wR(F^2)$ = 0.144
S = 1.101
6608 reflections
348 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0348P)^2 + 1.2638P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.31 e Å^{-3}
$\Delta\rho_{min}$ = −0.27 e Å^{-3}
Extinction correction: *SHELXL*97 (Sheldrick, 1997*b*)
Extinction coefficient: 0.026 (4)
Scattering factors from *International Tables for Crystallography* (Vol. C)

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

C12—O1	1.364 (3)	N53—C54	1.466 (4)
C22—O2	1.367 (3)	N53—C58	1.465 (4)
C32—O3	1.353 (3)	N55—C54	1.462 (4)
C42—O4	1.353 (3)	N55—C56	1.469 (4)
N51—C52	1.466 (4)	N55—C59	1.471 (3)
N51—C56	1.483 (4)	N510—C57	1.457 (4)
N51—C57	1.465 (4)	N510—C58	1.472 (4)
N53—C52	1.474 (4)	N510—C59	1.474 (3)
O1—C12—C13	121.9 (2)	N55—C59—N510	111.6 (2)
O1—C12—C11	117.3 (2)	C52—N51—C56	109.1 (2)
O2—C22—C23	122.1 (2)	C52—N51—C57	107.9 (2)
O2—C22—C21	117.2 (2)	C56—N51—C57	108.2 (2)
O3—C32—C33	122.0 (2)	C52—N53—C54	108.7 (2)
O3—C32—C31	117.5 (2)	C52—N53—C58	108.5 (2)
O4—C42—C43	122.0 (2)	C54—N53—C58	108.2 (2)
O4—C42—C41	117.5 (2)	C54—N55—C56	107.4 (2)
N51—C52—N53	110.8 (2)	C54—N55—C59	108.1 (2)
N51—C56—N55	111.2 (2)	C56—N55—C59	109.0 (2)
N51—C57—N510	112.6 (2)	C57—N510—C58	108.3 (2)
N53—C54—N55	112.8 (2)	C57—N510—C59	108.1 (2)
N53—C58—N510	111.3 (2)	C58—N510—C59	108.4 (2)

Table 2. *Hydrogen-bonding geometry (Å, °)*

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O1—H1···N51	0.84	2.05	2.827 (3)	154
O2—H2···N510^{i}	0.84	1.99	2.771 (3)	156
O3—H3···N53	0.84	2.00	2.809 (3)	161
O4—H4···N55^{ii}	0.84	2.05	2.819 (3)	152

Symmetry codes: (i) $1 + x, y, z$; (ii) $x, y, z - 1$.

Compound (1) crystallized in the monoclinic system; space groups $P2_1$ or $P2_1/m$ from the systematic absences. $P2_1$ was chosen and confirmed by the analysis. H atoms were treated as riding atoms with C—H = 0.95 and 0.99 Å, and O—H = 0.84 Å. With this all-light atom structure, the Flack (1983) parameter [−0.6 (13)] did not allow determination of the direction of the polar axis.

Data collection: *SMART* (Siemens, 1994). Cell refinement: *LSCELL* (Clegg, 1995). Data reduction: *SAINT* (Siemens, 1994). Program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997*c*). Program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997*b*). Molecular graphics: *PLATON* (Spek, 1999). Software used to prepare material for publication: *SHELXL*97 and *WordPerfect* macro *PRPKAPPA* (Ferguson, 1999).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: SK1324). Services for accessing these data are described at the back of the journal.

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The 17-spiro lactide of cortienic acid: a probe for studying the active sites of steroidal receptors

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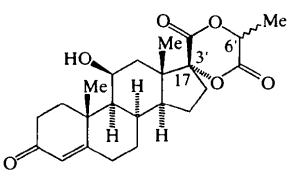
Abstract

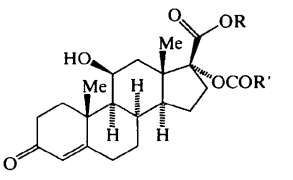
The steroid (5′*R*,17*R*)-11β-hydroxy-5′-methylspiro-[androst-4-ene-17,2′-[1,4]dioxane]-3,3′,6′-trione (cortienic acid lactide), $C_{23}H_{30}O_6$, adopts an arched conformation towards the β side of the molecule. The spiro lactide ring is in the half-chair conformation, with the two ester carbonyl groups aligned and directly opposing each other. A hydrogen bond between the hydroxyl group of ring *C* and the carbonyl group of ring *A* links the molecules, forming chains along **b**.

Comment

Soft drugs (Bodor, 1984) based on hydrocortisone (Little *et al.*, 1999) are important topical anti-inflammatory agents which are presently being tested in clinical trials (Hochhaus *et al.*, 1992; Bodor *et al.*, 1992). These compounds are of a structural type which is represented by scheme (II). In the process of developing these drugs, several candidates were considered, one of which is the subject of the present communication. This compound, (I), is an interesting cyclic modification in which the *R* groups of the 17α, 17β-diesters, (II), are joined into one alkyl group.



(I)



(II)

Although not active in *in vivo* tests, the spiro lactide, which was formed as a mixture of epimers which were separated by column chromatography, is useful as a probe of the active sites of steroidal receptors such as corticosteroid binding globulin (CBG) and the gluco-