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Crystal structure of the sesquihydrate of dehydroepiandrosterone propan-2-ylidene hydrazone: Participation of the hydrazonyl nitrogen atoms as acceptors in the elaborate hydrogen bond scheme

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ABSTRACT

The crystal structure of the sesquihydrate of dehydroepiandrosterone propan-2-ylidene hydrazone, $[(7)_2{\cdot}(H_2O)_3]$, isolated from a solution of dehydroepiandrosterone propan-2-ylidene hydrazone, (7), in moist ethanol at room temperature, has been determined from data collected at 100 K. The sesquihydrate recrystallizes in the orthorhombic space group, $P2_12_12_1$ with Z = 8. The asymmetric unit of $[(7)_2{\cdot}(H_2O)_3]$ consists of two independent molecules of the steroid, Mol A and Mol B, and three moles of water. The six membered saturated rings, A and C, in both molecules have ideal or near ideal chair shapes, the unsaturated rings, B, have the expected half-chair shapes, while the five-membered rings, D, have envelope shapes with flaps at C114 and C214 for Mol A and Mol B, respectively. Differences in the conformations of the two molecules reside essentially completely within the hydrazonyl fragments with significantly different torsional angles, C117-N120-N121-C122 (in Mol A) and C217-N220-N221-C222 (in Mol B), of 149.19(14) and -93.08(17)°, respectively. The difference in this torsional angle is reflected in the hydrogen bonds involving the nitrogen atoms in the hydrazonyl units: it is of interest that the hydrazonyl nitrogen atoms partake as acceptors in hydrogen bonding with water molecules. The only intermolecular interactions in these molecules are hydrogen bonds -all classical O-H-O and OH···N hydrogen bonds with just one exception, a $C\text{-}H{\cdots}O_{(water)}$ hydrogen bond. Of interest, there are no direct steroid-steroid links: molecules are linked solely by hydrogen bonds involving the hydrate molecules. All three hydrate molecules take part in the indirect linking of the steroid molecules, but each has its own set of contacts.

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1. Introduction

Determination of the crystal structures of hydrazones and acyl hydrazones, especially of compounds having potentially useful biological activities has been an interest for some while, especially with aromatic and heteroaromatic compounds, [1-6], but also including steroidal hydrazonyl compounds, such as di- and tri-hydrates of (5α,17*E*)-17-hydrazonoandrostan-3-ol (**1**), [7] and the acetohydrazide (**2**), and hydrazone derivatives (**3**), of 5-methoxy-des-A-estra-5,7,9-triene-17-one) [8], see Figure 1.

As is evident from such studies of compound **1** [7] and the solvates of 3α-hydroxy-16α-bromoandrostan-17-one (**4**), [9] and 3β,19-dihydroxyandrost-5-en-17-one (**5**), [10] the solvate molecules have major influences on the packing of the steroid molecules, in particular on the linking of the steroid moieties. Compounds, such as 5α-androstane-3α-ol-17-one, and epi-androsterone, with a hydroxyl donor group, at one end of the molecule, e.g., on C-3, and an acceptor group, such as a carbonyl group at the other end of the molecule on C-17 [11-14], link directly in a head-to-tail linked via C-H---O hydrogen bonds, however on solvation, the prevalence of the direct head-to-tail links is reduced with an corresponding increase in the percentages of solvent linked steroids. The greater the mole ratio of the solvate to steroid, the greater is the effect, and of course the more powerful the solvate, the more significant is the effect too.

We have turned our attention to dehydroepiandrosterone propan-2-ylidene hydrazone (**7**), a compound used previously in antitumor activity studies [15,16]. We have obtained the crystal structure of the sesqui hydrate of compound **7** $[(\mathbf{7})_{1.5}{\cdot}(H_2O)]$, isolated from a solution of compound **7** from a moist ethanol solution.

2. Experimental

2.1. General

Melting points were determined using a Buchi instrument and are uncorrected. High-resolution mass spectra were determined using a Water Mass Spec. Model Xevo G2 QT of instrument with MassLynx version 4.1 software.

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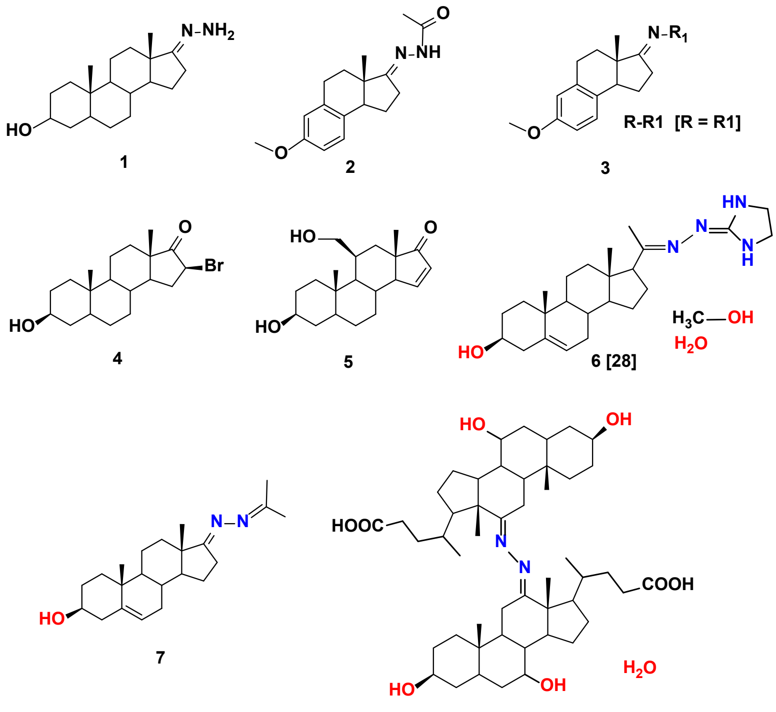
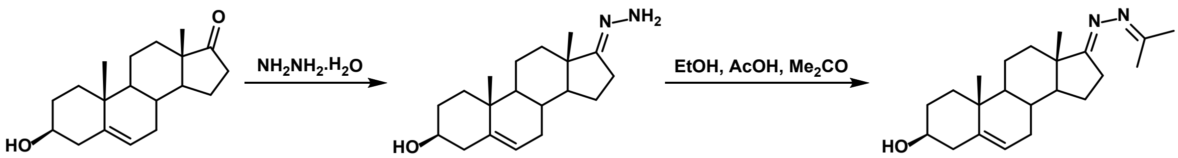


Figure 1. Compounds mentioned in this article.



Scheme 1. Synthesis of the title compound.

2.2. Synthesis

Compound **7** was prepared following the method of Cui *et al.* [15], and as outlined in Scheme 1. The physical and spectral properties of the products of each step were in agreement with those reported. Crystals of [(**7**)$_2$·(H_2O)$_3$] were collected on slow evaporation at room temperature of a moist ethanol solution of compound **7**.

(3*S*, 10*R*, 13*S*, *E*)-10, 13-dimethyl-17-(propan-2-ylidene hydrazineylidene)-2, 3, 4, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17-tetradecahydro-1*H*-cyclopenta[a]phenanthren-3-ol: Chemical formula: [($C_{22}H_{34}N_2O$)·1.5(H_2O)]. HRESI-MS *(m/z)*: 343.2742 [M+H]$^+$.

2.3. Crystallography

All details are listed in Table 1 [17-24].

2.4. Hirshfeld surface analyses

The Hirshfeld surfaces were generated using Crystal Explorer 3.1 [26]. The Hirshfeld surface, mapped over d_{norm}, is scaled between −0.7322 and 1.6141.

3. Results and discussion

3.1. General and molecular conformations

Crystals of [(**7**)$_2$·(H_2O)$_3$] were collected by slow evaporation at room temperature of a moist ethanol solution of compound **7**. The sesqui-hydrate crystallizes in the orthorhombic space group, $P2_12_12_1$ with Z = 8. The asymmetric unit of [(**7**)$_2$·(H_2O)$_3$] consists of two independent molecules of the steroid, Mol A and Mol B and 3 moles of water. The atom arrangements and numbering schemes of the steroidal molecules are shown in Figure 2.

The six membered saturated rings, A and C, in both molecules have ideal or near ideal chair shapes, the unsaturated rings, B, have the expected half-chair shapes, while the five-membered rings, D, have envelope shapes with flaps at C114 and C214 for Mol A and Mol B, respectively. The overlaps of the two independent molecules are shown in Figure 3 for the complete molecules and also without the terminal hydrazonyl moieties.

As illustrated the differences in the conformations of the molecules reside essentially completely within the hydrazonyl fragments, see also Table 2. The torsional angles, C117-N120-N121-C122 (in Mol A) and C217-N220-N221-C222 (in Mol B), of 149.19(14) and -93.08(17)°, respectively, are significantly different. Bond angles within the hydrazonyl unit are essentially the same in both molecules. The difference in this torsional angle is reflected in the hydrogen bonds involving the nitrogen atoms in the hydrazonyl units. Thus, there is an intramolecular hydrogen bond present in Mol A but not in Mol B. There are also consequences arising from the different spatial arrangements of the hydrazonyl unit shown by the intermolecular hydrogen bonds in the two molecules, see the following paragraph.

Table 1. Crystal data and details of the structure refinement for compound **7**·1.5(H_2O).

Parameters	**Compound 7**
Empirical formula	[($C_{22}H_{34}N_2O$)·1.5(H_2O)]
Formula weight	369.53
Temperature (K)	116.42
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
a, (Å)	7.4541 (1)
b, (Å)	18.7851 (1)
c, (Å)	30.1345 (2)
Volume (Å^3)	4219.61 (7)
Z	8
ρ_{calc} (g/cm^3)	1.163
μ (mm^{-1})	0.59
F(000)	1624
Crystal size (mm^3)	0.18 × 0.14 × 0.03
Radiation	MoKα (λ = 0.71073)
2Θ range for data collection (°)	2.772 -68.232
Index ranges	$-8 \le h \le 8$, $-22 \le k \le 22$, $-36 \le l \le 36$
Reflections collected	38813
Independent reflections	7699 [R_{int} = 0.024, R_{sigma} = 0.602]
Data/restraints/parameters	7699/0/518
Goodness-of-fit on F^2	1.04
Final R indexes [I≥2σ (I)]	R_1 = 0.026, wR_2 = 0.026
Final R indexes [all data]	R_1 = 0.069, wR_2 = 0.069
Largest diff. peak/hole (e Å^{-3})	0.14, -0.12
Flack parameter	0.0(4)

Computer programs: CrysAlis PRO 1.171.39.34b [17]; OSCAIL [18]; SHELXT [19]; ShelXle [20]; OLEX2 [21]; MERCURY [22]; CrysAlis PRO 1.171.39.9g [23]; PLATON [24].

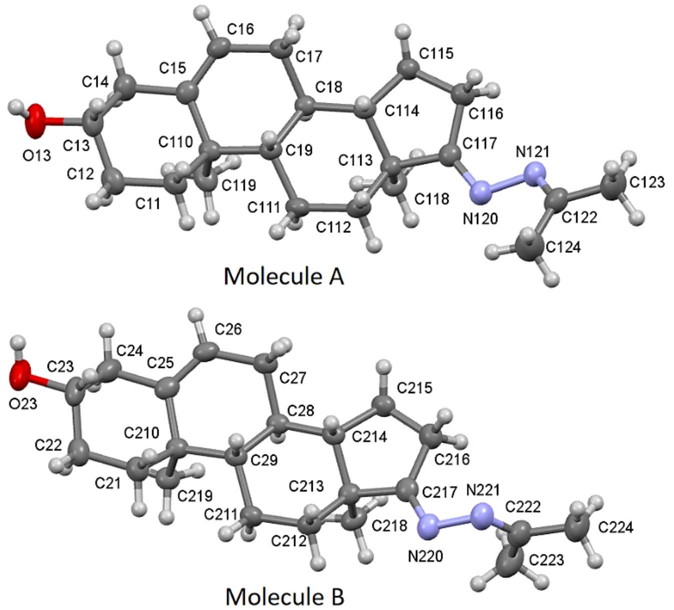


Figure 2. Atom arrangements and numbering schemes for two independent molecules.

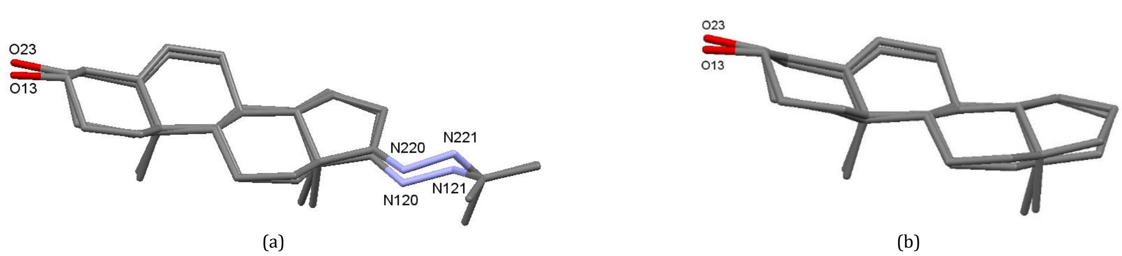


Figure 3. Overlays of Mol A and Mol B: (a) Complete molecules, (b) without the hydrazonyl units.

3.2. Crystal structure

The only intermolecular interactions in these molecules are hydrogen bonds -all classical O-H-O and O-H···N hydrogen bonds with just one exception, a C-H···O$_{(water)}$ hydrogen bond, see Table 3.

Of interest, there are no direct steroid-steroid links; molecules are linked solely by hydrogen bonds involving the hydrate molecules. All three hydrate molecules take part in the indirect linking of the steroid molecules, but each has its own set of contacts.

Table 2. Geometric parameters.

Bond lengths (Å) and torsion angle (º)						
Mol A				**Mol B**		
C117-N120			1.275(2)	C217-N220		1.274(2)
N120-N121			1.4258(18)	N220-N221		1.4145(17)
N121-C122			1.288(2(	N221-C222		1.2882(2)
C113-C117-N120-N121			-179.45(13)	C213-C217-N220-N221		-179.05(13)
C116-C117-N120-N121			0.1(2)	C216-C217-N220-N221		0.8(2)
C117-N120-N121-C122			149.19(14)	C217-N220-N221-C222		-93.08(17)
Pucker parameters						
Ring	**Mol A**			**Mol B**		
	θ	**φ**	**Pucker**	**θ**	**φ**	**Pucker**
A	5 .80(17)	56.4(18)	Chair	11.29(18)	98.5(19)	Chair
B	50.59(19)	212.9(2)	Half Chair	49.9(2)	216.4(8)	Half Chair
C	9.26(16)	260.7(10)	Chair	5.90(16)	260.3(16)	chair
D	-	212.0(2)	E on C114	-	207.9(2)	E on C214

Table 3. Geometric parameters (Å, °) for hydrogen bonds.

Intramolecular hydrogen bonds					
D-H···A	**D-H**	**H···A**	**D···A**	**∠D-H···A**	
C124-H12H···N120	0.98	2.29	2.735(2)	107	
Intermolecular hydrogen bonds					
D-H···A	**D-H**	**H···A**	**D···A**	**∠D-H···A**	**Symmetry code**
O1W-H1W1···N120	0.88(3)	2.21(3)	3.0679(19)	162(2)	1.5-*x*, 1-*y*, -1/2+*z*
O1W-H2W1···N120	0.91(3)	2.03(3)	2.9094(19)	162(3)	1.5-*x*, 1-*y*, -1/2+*z*
O3W-H2W3···N120	0.87(3)	1.93(3)	2.783(2)	167(3)	*x*, *y*, *z*
O13-H13A···O2W	0.92(3)	1.77(3)	2.6887(19)	177.4(18)	*x*, *y*, *z*
O23-H23A···O3W	0.87(3)	1.78(3)	2.645(2)	173(2)	*x*, *y*, *z*
O2W-H1W2···O1W	0.95(3)	1.790(3)	2.8483(19)	178(3)	*x*, *y*, *z*
O2W-H2W2···N121	0.92(3)	2.06(3)	2.975(2)	174(3)	0.5-*x*, 1-*y*, -1/2+*z*
O3W-H1W3···O23	0.96(3)	173(3)	2.6947(18)	167	-0.5+*x*, 1.5-*y*, 1+*z*
C223-H22C···O1W	0.98	2.46	3.423(2)	175(2)	2-*x*, 0.5+*y*, 1.5-*z*

There are no differences in the roles in the hydrogen bonding of the hydroxyl groups in the two molecules: the oxygen atoms in the hydroxyl groups, O13 and O23, in each molecule, act as donors; each in in a single hydrogen bond. In contrast, there are differences in the roles of the hydrazonyl nitrogen atoms: both nitrogen atoms, N120 and N121 in Mol A partake in intermolecular hydrogen bonds with hydrate molecules, but only N221 in Mol B. - another consequence of the different spatial arrangements of the hydrazonyl units. The lack of any hydrogen bond involving N220 is apparently compensated by the C223-H22C···O1W hydrogen bond - the only C-H···O hydrogen bond present in the structure. It is noted that the participating CH bond in the C223-H22C···O1W hydrogen bond is a part of the propan-2-ylidene unit attached to the N220, N221 hydrazone unit.

A search of the CCDC database on 28th January 2021, for hydrated compounds containing the fragment C=N-N=C revealed 36 hits [27]. Twenty of these hits indicated compounds having hydrogen bonds involving a hydrazonyl nitrogen atom and a water molecule -and thus 16 hits without such a bond. However, one of the latter hits the mixed solvated steroidal compound, 20-(imidazolidin-2-ylidenehydrazono) pregnan-3-ol methanol solvate, [(**7**).(H_2O).(MeOH)] [CCDC codes: 659449: KATXIO] [28], did possess a hydrogen bond involving a hydrazonyl nitrogen and the methanol solvate, see Figure 1 for the chemical structure of compound **7**. Only one other hydrated steroidal compound was found in this search, namely, 12,12'-hydrazine-1,2-diylidene-*bis*(3α,7α-dihydroxy-24-carboxy-5β-cholan-24-oic acid) dihydrate, [(**8**).(H_2O)] [CCDC codes: 637989: GIVHAV] [29], and this solvate did not possess a hydrogen bond involving a hydrazonyl nitrogen and the water molecule, see Figure 1 for the chemical structure of compound **8**. Thus, it can be concluded that while occurring in ca 50% of the hydrated hydrazone structures, in general, very few occurrences are found examples are present in steroidal molecules.

Collectively, the hydrogen bonds form a complex array with indirect links to the steroid molecules. A view of the 3-dimensional array of hydrate and steroid molecules looking down the *a* axis is shown in Figure 4, in which Mol A and Mol B are colored green and blue, respectively.

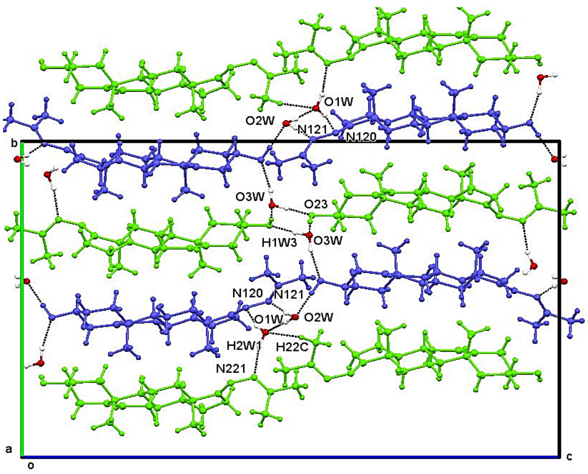


Figure. 4. A view of the arrangement of the hydrate and steroid molecules, looking down the *a* axis: Mol A and Mol B are colored green and blue, respectively.

There are no directly linked steroid molecules: the molecules in all three directions are separated by the complex array of hydrogen bonds. The arrangement in Figure 4 shows alternating layers of indirectly linked Mol A, and indirectly linked Mol B. Each layer of the 3-dimensional array extends throughout the structure. Views looking down other axes are much too cluttered to provide a good understanding of the packing arrangement.

As shown in the Hirshfeld surfaces in Figure 5, the contacts of the water molecules on the surfaces of the steroid molecules are clearly indicated by the red spots on the surface. In both Mol A and Mol B the major contacts at the hydroxyl and hydrazonyl sites with water molecules are shown, while in Mol B there is an additional red area indicating the C223-H22C···O1W contact.

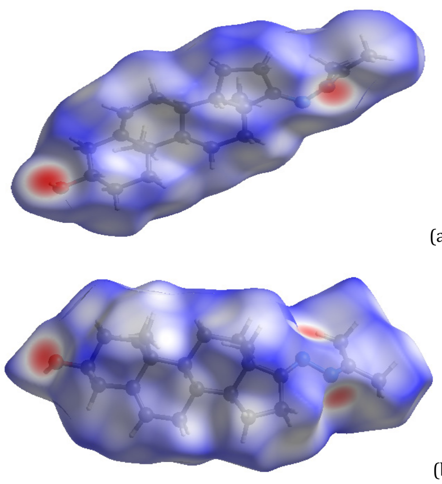


Figure 5. Hirshfeld surfaces of the steroid, showing red spots indicating contacts with water molecules. (a) Mol A, (b) Mol B.

4. Conclusion

While it is anticipated that the presence of water molecules in a hydrate could greatly reduce the occurrence of directly linked steroid molecules, it is still surprising that there were no directly linked steroid molecules in $[(\mathbf{7})_2{\cdot}(H_2O)_3]$, with a mole ratio of 1.0:1.5 steroid to water. From studies of other hydrates, to have no directly linked steroid molecules, a higher ratio of water: steroid would appear to be needed. The involvement of both nitrogen atoms of the hydrazonyl unit acting as acceptors, at least in the case of Mol A, but only one in Mol B is also of interest, as this is not frequently met. The differences in the arrangements of the hydrazonyl unit have impacts on the hydrogen bonding formation.

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Supporting information

CCDC-1914766 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via https://www.ccdc.cam.ac.uk/structures/, or by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0)1223-336033.

Disclosure statement

Conflict of interests: The authors declare that they have no conflict of interest.
Author contributions: All authors contributed equally to this work.
Ethical approval: All ethical guidelines have been adhered.
Sample availability: Samples of the compounds are available from the author.

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