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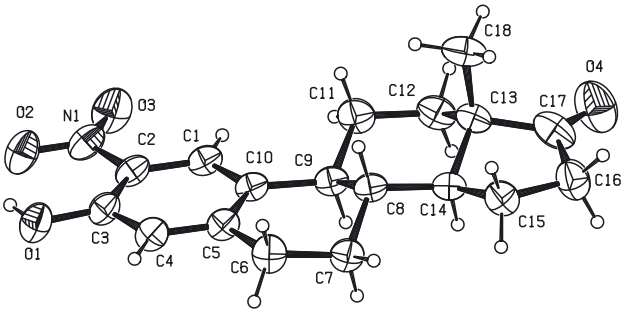
The crystal structure of 3-hydroxy-2-nitroestra-1,3,5(10)-trien-17-one, $C_{18}H_{21}NO_4$



https://doi.org/10.1515/ncrs-2022-0602
Received December 26, 2022; accepted January 15, 2023;
published online January 24, 2023

Abstract

$C_{18}H_{21}NO_4$, orthorhombic, $C222_1$ (no. 20), a = 10.6891(2) Å, b = 11.8375(2) Å, c = 25.4410(4) Å, V = 3219.11(10) Å^3, Z = 8, $R_{gt}(F)$ = 0.0483, $wR_{ref}(F^2)$ = 0.1449, T = 295 K.

CCDC no.: 2236340

The molecular structure of 3-hydroxy-2-nitroestra-1,3,5(10)-trien-17-one (2-nitroestrone) is shown in the figure. Table 1 contains crystallographic data, and Table 2 contains the list of the atoms including atomic coordinates and displacement parameters.

Table 1: Data collection and handling.

Crystal:	Yellow block
Size:	0.41 × 0.30 × 0.17 mm
Wavelength:	Cu *K*α radiation (1.54184 Å)
μ:	0.75 mm^{-1}
Diffractometer, scan mode:	Gemini S (Oxford Diffraction), φ and ω
θ_{max}, completeness:	71.9°, >99%
$N(hkl)_{measured}$, $N(hkl)_{unique}$, R_{int}:	11,459, 3106, 0.033
Criterion for I_{obs}, $N(hkl)_{gt}$:	$I_{obs} > 2\sigma(I_{obs})$, 2673
$N(param)_{refined}$:	213
Programs:	CrysAlis^{PRO} [1], SHELX [2, 3], PLATON [4]

Source of material

The synthesis of 2-nitroestrone was performed according to the procedure reported by Poirier & Vottero [5]. This procedure was preferred to classical nitrating procedures employing nitric acid in boiling acetic acid, as it was found to yield little or no 4-nitroestrone and/or 2,4-dinitroestrone. Suitable single crystals of the title compound were formed due to recrystallizing from 95% ethanol.

Experimental details

Coordinates of carbon-bonded hydrogen atoms were introduced in idealized positions and refined using a riding model. Their U_{iso} values are approximated as $U_{iso} = kU_{eq}$ of the parent atom (k = 1.2 for CH and CH_2 groups; 1.5 for CH_3 group). The hydrogen atom of the hydroxyl group was located using residual density map and refined freely.

Comment

Introduction

Organic chemistry in the late 1920s and mid-1930s was marked by the discovery and structural elucidation of steroid hormones. A fruitful period of research into their chemistry and biochemistry followed from this hallmark achievement, with many steroid structures being developed into pharmaceuticals [6]. To date, the steroid core is still considered a privileged motif in medicinal chemistry, and novel steroidal natural products continue to be reported [7].

Mononitrated estrone is first referenced in a US patent submitted by Niederl in 1948 [8], where its synthesis was

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Table 2: Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2).

Atom	*x*	*y*	*z*	U_{iso}*/U_{eq}
O1	0.9111 (2)	0.4038 (2)	0.54727 (12)	0.0814 (7)
H1	0.912 (5)	0.346 (5)	0.528 (2)	0.111 (17)*
O2	0.7938 (3)	0.2492 (2)	0.49490 (13)	0.0912 (8)
O3	0.5944 (3)	0.2426 (3)	0.49328 (15)	0.1013 (9)
O4	−0.0176 (3)	0.6768 (4)	0.66796 (17)	0.1293 (13)
N1	0.6905 (3)	0.2855 (2)	0.50831 (11)	0.0729 (7)
C1	0.5672 (3)	0.4252 (2)	0.55648 (11)	0.0584 (7)
H1A	0.495770	0.388706	0.544350	0.070*
C2	0.6844 (3)	0.3836 (2)	0.54221 (11)	0.0609 (7)
C3	0.7945 (3)	0.4357 (2)	0.55940 (12)	0.0626 (7)
C4	0.7809 (3)	0.5291 (3)	0.59193 (13)	0.0644 (7)
H4	0.852497	0.564593	0.604529	0.077*
C5	0.6666 (3)	0.5711 (2)	0.60622 (12)	0.0589 (7)
C6	0.6639 (3)	0.6719 (3)	0.64222 (15)	0.0739 (9)
H6A	0.690638	0.648087	0.676935	0.089*
H6B	0.723964	0.726950	0.629591	0.089*
C7	0.5384 (3)	0.7284 (3)	0.64700 (13)	0.0656 (7)
H7A	0.524713	0.776234	0.616601	0.079*
H7AB	0.537844	0.776008	0.678020	0.079*
C8	0.4319 (3)	0.6419 (2)	0.65095 (11)	0.0564 (6)
H8	0.448338	0.591815	0.680825	0.068*
C9	0.4278 (3)	0.5709 (2)	0.60048 (11)	0.0566 (7)
H9	0.410327	0.624032	0.571877	0.068*
C10	0.5546 (3)	0.5185 (2)	0.58793 (10)	0.0546 (6)
C11	0.3176 (3)	0.4866 (3)	0.60090 (15)	0.0760 (9)
H11A	0.313035	0.449584	0.566939	0.091*
H11B	0.333618	0.429006	0.627167	0.091*
C12	0.1919 (3)	0.5423 (3)	0.61260 (15)	0.0762 (9)
H12A	0.169038	0.591483	0.583652	0.091*
H12B	0.127962	0.484649	0.615895	0.091*
C13	0.1983 (3)	0.6108 (3)	0.66316 (12)	0.0659 (7)
C14	0.3057 (3)	0.6969 (2)	0.65853 (10)	0.0562 (6)
H14	0.289556	0.738846	0.626009	0.067*
C15	0.2841 (3)	0.7809 (3)	0.70283 (13)	0.0717 (8)
H15A	0.327963	0.851154	0.696106	0.086*
H15B	0.312305	0.750270	0.736147	0.086*
C16	0.1430 (3)	0.7993 (4)	0.70316 (18)	0.0865 (11)
H16A	0.120935	0.867032	0.683771	0.104*
H16B	0.111886	0.806095	0.738831	0.104*
C17	0.0887 (4)	0.6917 (4)	0.67579 (16)	0.0928 (12)
C18	0.2066 (5)	0.5352 (4)	0.71194 (16)	0.0943 (12)
H18A	0.134910	0.486537	0.713315	0.141*
H18B	0.208969	0.581495	0.742922	0.141*
H18C	0.281317	0.490337	0.710150	0.141*

performed with 70% nitric acid as a nitrating agent in acetic acid, upon which the product crystallizes from the reaction mixture, albeit without specifying which regioisomer is obtained. A year later, a paper published by the same author identified the product to be 2-nitroestrone [9]. This procedure was later used by Hillmann–Elies and coworkers, who also noted that 4-nitroestrone could be isolated from the mother liquor after filtering out 2-nitroestrone [10]. However, several subsequently published works disputed the findings of both groups on the basis of further chemical transformations and IR spectroscopy, proposing that 4-nitroestrone is less soluble in acetic acid and separates out first [11–13]. An unequivocal assignment supported by ^{1}H NMR spectroscopy was put forward by Utne and coworkers in 1968; they identified the isomer crystallizing from the reaction mixture as 4-nitroestrone, while 2-nitroestrone was the one obtained from the mother liquor [14].

Structural comment

The absolute structure of 2-nitroestrone was assigned relative to the known stereochemistry of the steroid skeleton and was further confirmed by resonant scattering effects analyzed with Parsons' quotient method (z = −0.03(9)) [15].

The nitro group is co-planar with ring A probably due to the intramolecular hydrogen bond O1–H1···O2 (graph set descriptor $S_1^1(6)$ [16]) with the following parameters: d(O1–H1) = 0.84(6) Å; d(H1···O2) = 1.90(6) Å; d(O1···O2) = 2.588(4) Å; α(O1–H1···O2) = 138(5)°.

An analogous conformation of the nitro group is found in the crystal structures of the structurally similar compounds 17α-ethynyl-2-nitroestradiol (CSD refcode MAKFUB) [17] and 2-nitroestradiol (CSD refcode MUVNIA) [18]. The latter crystal structure contains two crystallographically independent molecules in the asymmetric unit, and in one of them the phenol hydrogen atom is probably wrongly oriented towards the steroid backbone of the neighboring molecule, which leads to unreasonably short H···H contacts of 1.88 Å; a more plausible position is the one in which this hydrogen atom is oriented towards the oxygen atom of the nitro group of the neighboring molecule (O···O separation is 2.826 Å, indicative of hydrogen bonding).

Conversely, in the crystal structure of 4-nitroestrone (CSD refcode GEWXUE) [19] nitro groups are perpendicular to the A ring (there are two crystallographically independent molecules in the asymmetric unit). It is also worth noting that the phenol hydrogen atom position in one of the molecules in the structure of 4-nitroestrone is erroneously oriented; it points to the C9 hydrogen atom of the neighboring molecule, leading to H···H contacts of 1.88 Å, while a more reasonable position is the one in which it is pointed towards the C17-keto oxygen of the neighboring molecule (O···O distance is 2.705 Å, clearly suggesting the presence of a hydrogen bond).

Parameters of ring pucker were determined [20, 21] for rings B–D; the direction for calculation was clockwise for all

rings, starting from the lowest-numbered carbon, as per rules of preference given by Boeyens [22]. The conformation of ring B is a 7α,8β-half-chair ($^4H_5$); puckering parameters: Q = 0.497(3) Å, θ = 4.5(3)°, φ = 287(4)°. While ring C is a nearly perfect 8β,12α-chair ($^1C_4$) with puckering parameters: Q = 0.576(3) Å, θ = 133.5(3)°, φ = 15.1(5)°, ring D can be described as a 14α-envelope (E_5) with *ca.* 23% $^5T_4$ twisted form character (puckering parameters: q_2 = 0.412(4) Å, φ_2 = 328.2(6)°).

The intermolecular hydrogen bond O1–H1···O3(i) (symmetry code (i): x + 1/2, $-y$ + 1/2, $-z$ + 1) connects molecules of 2-nitroestrone in chains propagating along the crystallographic a axis; the corresponding graph set descriptor is $C_1^1(6)$. The structural parameters are d(O1–H1) = 0.84(6) Å, d(H1···O2) = 2.28(5) Å, d(O1···O2) = 2.812(4) Å, α(O1–H1···O2) = 122(4)°. Therefore, the O1 phenol group is involved in a bifurcated hydrogen bond. However, it would be misleading to recognize this as the basic structural motif of the crystal packing. The true hierarchy of intermolecular interactions is brought to light only after intermolecular energies are taken into account [23].

Hirshfeld surface analysis [24] revealed that there are 13 neighboring molecules in the first coordination shell of a molecule in the crystal structure of 2-nitroestrone. Estimation of intermolecular interaction energies with CE–B3LYP functional [25] showed that they have stabilizing energies ranging from –7 to –53 kJ mo1^{-1}. In all interactions the dispersion component is essentially dominant. The strongest interaction (–53 kJ mo1^{-1}) is found between the central molecule and its neighbor related by two-fold rotation axis (symmetry code x, $-y$ + 1, $-z$ + 1), with Cg···Cg distance of 5.60 Å. This interaction is mediated by π···π stacking of steroid A rings. The following two interactions are equal in strength (–32 kJ mo1^{-1}) and are formed between the central molecule and two molecules related by translations (symmetry codes x – 1/2, y + 1/2, z and x + 1/2, y – 1/2, z), both at a Cg···Cg separation of 7.97 Å. The mentioned intermolecular hydrogen bond belongs to the intermolecular dimer, the only one with an equal contribution of dispersion and electrostatic components. The Cg···Cg distance is 10.20 Å, while the corresponding interaction energy is significantly lower (–16 kJ mo1^{-1}) compared to the previously mentioned interactions.

Author contributions: All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

Research funding: The authors acknowledge the financial support of the Ministry of Education, Science and Technological Development of the Republic of Serbia (Grants No. 451-03-68/2022-14/200124 and 451-03-68/2022-14/200125).

Conflict of interest statement: The authors declare no conflicts of interest regarding this article.

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