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The co-crystal structure of (17*b*)-estra-1,3,5(10)-triene-3,17diol – acetamide (1/1), a $Z' = 4$ structure, $C_{20}H_{29}NO_3$

Figure 1: Molecular structure of title compound. Thermal ellipsoids are drawn at 40% level.

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Abstract

$C_{20}H_{29}NO_3$, monoclinic, $P2_1$ (no. 4), $a = 16.167(3)$ Å, $b = 9.3424(19)$ Å, $c = 25.656(5)$ Å, $\beta = 108.27(3)^\circ$, $V = 3679.8(14)$ Å³, $Z = 8$, $R_{gt}(F) = 0.1030$, $wR_{ref}(F^2) = 0.2296$, $T = 153(2)$ K.

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The crystal structure is shown in the figure. Tables 1 and 2 contain details on crystal structure and measurement conditions and a list of the atoms including atomic coordinates and displacement parameters.

Table 1: Data collection and handling.

Crystal:	Colorless block
Size:	$0.23 \times 0.21 \times 0.2$ mm
Wavelength:	Mo $K\alpha$ radiation (0.71073 Å)
μ :	0.08 mm^{-1}
Diffractometer, scan mode:	Multiwire proportional, φ and ω -scans
$\theta_{\max}$, completeness:	27.5° , >99%
$N(hkl)_{\text{measured}}$, $N(hkl)_{\text{unique}}$, R_{int} :	25351, 15800, 0.053
Criterion for I_{obs} , $N(hkl)_{\text{gt}}$:	$I_{\text{obs}} > 2 \sigma(I_{\text{obs}})$, 14183
$N(\text{param})_{\text{refined}}$:	873
Programs:	CrystalClear [1], SHELX [2]

Source of material

An amount of (50 mg, 0.183 mmol) (17*b*)-estra-1,3,5(10)-triene-3,17-diol was dissolved in methanol (2 mL) at 50 °C, then acetamide (10.9 mg, 0.183 mmol) was added to the above solution slowly. The solution was cooled at room temperature and then it was volatilized slowly at room temperature for 8 days to get the (17*b*)-estra-1,3,5(10)-triene-3,17-diol-acetamide co-crystal.

Experimental details

Hydrogen atoms were obtained geometrically and treated as riding on the parent atoms or were constrained in the locations during refinements.

Discussion

The compound (17*b*)-estra-1,3,5(10)-triene-3,17-diol (estradiol) (systematic name: (8*R*,9*S*,13*S*,14*S*,17*S*)-13-methyl-7,8,9,11,12,

Table 2: Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å²).

Atom	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> _{iso} */ <i>U</i> _{eq}
O1	0.2004(3)	0.2885(6)	0.47978(19)	0.0341(11)
H1	0.247797	0.276940	0.504946	0.041*
O2	0.2121(3)	0.3848(6)	0.05552(19)	0.0355(11)
H2	0.158455	0.367021	0.045816	0.043*
C1	0.2101(4)	0.2777(8)	0.4289(3)	0.0299(14)
C2	0.1391(4)	0.2352(8)	0.3853(3)	0.0295(14)
H2A	0.085351	0.210606	0.390706	0.035*
C3	0.1487(4)	0.2297(7)	0.3334(3)	0.0292(14)
H3	0.099546	0.202838	0.303430	0.035*
C4	0.2257(4)	0.2609(7)	0.3226(3)	0.0259(13)
C5	0.2968(4)	0.3015(8)	0.3672(3)	0.0308(15)
C6	0.2889(4)	0.3111(8)	0.4196(3)	0.0309(15)
H6	0.337521	0.340533	0.449470	0.037*
C7	0.3841(4)	0.3424(11)	0.3609(3)	0.043(2)
H7A	0.392408	0.447065	0.365958	0.052*
H7B	0.431197	0.294680	0.390102	0.052*
C8	0.3916(4)	0.3009(11)	0.3053(3)	0.046(2)
H8A	0.442325	0.350083	0.299635	0.055*
H8B	0.401177	0.196444	0.304375	0.055*
C9	0.3102(4)	0.3414(8)	0.2600(3)	0.0300(14)
H9	0.297669	0.444633	0.264589	0.036*
C10	0.2325(4)	0.2522(7)	0.2649(3)	0.0254(13)
H10	0.245652	0.150106	0.258913	0.030*
C11	0.1481(4)	0.2900(9)	0.2193(3)	0.0342(16)
H11A	0.100849	0.226227	0.222246	0.041*
H11B	0.131435	0.389646	0.224648	0.041*
C12	0.1568(4)	0.2757(9)	0.1620(3)	0.0343(16)
H12A	0.102394	0.308644	0.134401	0.041*
H12B	0.165511	0.173754	0.154560	0.041*
C13	0.2343(4)	0.3647(8)	0.1565(3)	0.0307(15)
C14	0.3165(4)	0.3211(8)	0.2028(3)	0.0304(15)
H14	0.323125	0.215776	0.198429	0.036*
C15	0.3895(5)	0.3916(12)	0.1857(3)	0.052(2)
H15A	0.444685	0.337646	0.200325	0.062*
H15B	0.399077	0.491491	0.199078	0.062*
C16	0.3563(5)	0.3869(11)	0.1215(3)	0.045(2)
H16A	0.356145	0.483976	0.106029	0.054*
H16B	0.393709	0.323918	0.107415	0.054*
C17	0.2640(4)	0.3274(8)	0.1066(3)	0.0323(15)
H17	0.266262	0.220942	0.103338	0.039*
C18	0.2148(6)	0.5230(8)	0.1569(3)	0.0417(18)
H18A	0.161779	0.545112	0.126779	0.063*
H18B	0.263695	0.577944	0.152266	0.063*
H18C	0.206403	0.548596	0.191952	0.063*
O3	0.7779(3)	0.4775(7)	0.9810(2)	0.0429(13)
H3A	0.760639	0.483618	1.008574	0.052*
O4	0.3485(3)	0.2593(6)	0.56120(19)	0.0369(12)
H4	0.389728	0.297327	0.552904	0.044*
C19	0.6295(4)	0.4555(8)	0.9208(3)	0.0302(14)
H19	0.607169	0.473204	0.950306	0.036*
C20	0.7192(5)	0.4515(8)	0.9307(3)	0.0325(15)
C21	0.7505(4)	0.4218(8)	0.8877(3)	0.0309(14)
H21	0.811333	0.411373	0.894241	0.037*
C22	0.6929(4)	0.4070(8)	0.8348(3)	0.0310(14)
H22	0.715778	0.392072	0.805371	0.037*

Table 2 (continued)

Atom	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> _{iso} */ <i>U</i> _{eq}
C23	0.6036(4)	0.4134(7)	0.8237(3)	0.0267(13)
C24	0.5720(4)	0.4339(8)	0.8683(3)	0.0315(15)
C25	0.4756(4)	0.4260(12)	0.8621(3)	0.049(2)
H25A	0.460909	0.505118	0.883356	0.059*
H25B	0.463912	0.334821	0.878155	0.059*
C26	0.4166(5)	0.4354(10)	0.8029(3)	0.0409(19)
H26A	0.409499	0.537307	0.791740	0.049*
H26B	0.358347	0.397752	0.800722	0.049*
C27	0.4508(4)	0.3530(8)	0.7626(3)	0.0300(14)
H27	0.456377	0.249471	0.773079	0.036*
C28	0.5409(4)	0.4116(8)	0.7659(2)	0.0282(14)
H28	0.531003	0.514486	0.755035	0.034*
C29	0.5780(4)	0.3438(9)	0.7235(3)	0.0370(17)
H29A	0.632302	0.394258	0.724570	0.044*
H29B	0.592930	0.242648	0.733675	0.044*
C30	0.5145(4)	0.3498(10)	0.6651(3)	0.0392(17)
H30A	0.508416	0.450190	0.652099	0.047*
H30B	0.538350	0.293228	0.640482	0.047*
C31	0.4253(4)	0.2916(8)	0.6621(3)	0.0297(14)
C32	0.3915(4)	0.3672(8)	0.7044(2)	0.0284(14)
H32	0.389837	0.471585	0.695494	0.034*
C33	0.2959(5)	0.3188(12)	0.6891(3)	0.050(2)
H33A	0.259831	0.391356	0.700022	0.060*
H33B	0.290870	0.226462	0.706853	0.060*
C34	0.2684(5)	0.3029(12)	0.6256(3)	0.048(2)
H34A	0.246704	0.205013	0.614293	0.058*
H34B	0.222007	0.372378	0.607550	0.058*
C35	0.3505(5)	0.3330(8)	0.6103(3)	0.0319(15)
H35	0.353867	0.438163	0.603938	0.038*
C36	0.4308(6)	0.1282(9)	0.6689(3)	0.049(2)
H36A	0.453255	0.086495	0.640942	0.073*
H36B	0.372712	0.089606	0.664612	0.073*
H36C	0.470075	0.104173	0.705486	0.073*
O5	0.6986(3)	0.1714(6)	0.47119(19)	0.0350(11)
H5	0.747584	0.187256	0.494256	0.042*
O6	0.7182(3)	0.5172(6)	0.06391(18)	0.0347(11)
H6A	0.666405	0.514565	0.064137	0.042*
C37	0.7879(4)	0.2135(8)	0.4127(3)	0.0309(15)
H37	0.839350	0.198001	0.442694	0.037*
C38	0.7086(5)	0.2078(8)	0.4212(3)	0.0298(14)
C39	0.6340(5)	0.2336(7)	0.3778(3)	0.0313(15)
H39	0.578714	0.232860	0.383495	0.038*
C40	0.6398(4)	0.2604(8)	0.3258(3)	0.0296(14)
H40	0.588089	0.276809	0.296143	0.036*
C41	0.7202(4)	0.2638(8)	0.3162(3)	0.0289(14)
C42	0.7946(4)	0.2417(8)	0.3607(3)	0.0319(15)
C43	0.8846(4)	0.2589(10)	0.3547(3)	0.0412(19)
H43A	0.910392	0.349138	0.372838	0.049*
H43B	0.921851	0.179293	0.374415	0.049*
C44	0.8872(4)	0.2611(9)	0.2963(3)	0.0344(16)
H44A	0.883921	0.161826	0.282300	0.041*
H44B	0.943187	0.302820	0.295650	0.041*
C45	0.8110(4)	0.3497(8)	0.2583(3)	0.0276(13)
H45	0.813745	0.449247	0.273039	0.033*
C46	0.7256(4)	0.2807(8)	0.2584(3)	0.0289(14)
H46	0.727007	0.181165	0.244373	0.035*

Table 2 (continued)

Atom	x	y	z	U_{iso}^*/U_{eq}
C47	0.6463(4)	0.3523(9)	0.2178(3)	0.0344(16)
H47A	0.593335	0.297275	0.216518	0.041*
H47B	0.639712	0.449969	0.231008	0.041*
C48	0.6536(4)	0.3619(8)	0.1602(3)	0.0326(15)
H48A	0.651534	0.264289	0.144850	0.039*
H48B	0.603280	0.416215	0.136439	0.039*
C49	0.7367(4)	0.4341(8)	0.1601(3)	0.0287(14)
C50	0.8144(4)	0.3562(8)	0.1997(2)	0.0275(13)
H50	0.809942	0.254782	0.186706	0.033*
C51	0.8937(5)	0.4187(11)	0.1875(3)	0.045(2)
H51A	0.942002	0.348640	0.196026	0.053*
H51B	0.914114	0.506826	0.209132	0.053*
C52	0.8605(5)	0.4526(10)	0.1250(3)	0.0398(18)
H52A	0.871923	0.553759	0.118083	0.048*
H52B	0.889226	0.390074	0.104693	0.048*
C53	0.7613(4)	0.4225(8)	0.1077(3)	0.0317(15)
H53	0.750858	0.321887	0.093893	0.038*
C54	0.7356(5)	0.5939(8)	0.1748(3)	0.0384(17)
H54A	0.684709	0.640099	0.149015	0.058*
H54B	0.788830	0.639981	0.172566	0.058*
H54C	0.732573	0.603140	0.212223	0.058*
O7	1.2745(3)	0.3947(6)	0.9704(2)	0.0408(13)
H7	1.256528	0.385117	0.997620	0.049*
O8	0.8411(3)	0.1742(6)	0.55566(19)	0.0386(12)
H8	0.890716	0.181339	0.551931	0.046*
C55	1.2115(4)	0.4006(8)	0.9200(3)	0.0304(14)
C56	1.2360(4)	0.4427(8)	0.8750(3)	0.0308(14)
H56	1.293792	0.474443	0.879960	0.037*
C57	1.1765(4)	0.4383(7)	0.8236(3)	0.0304(14)
H57	1.194707	0.464798	0.793128	0.037*
C58	1.0891(4)	0.3959(7)	0.8140(2)	0.0235(12)
C59	1.0649(4)	0.3608(8)	0.8605(3)	0.0291(14)
C60	1.1258(4)	0.3609(8)	0.9121(3)	0.0334(15)
H60	1.108554	0.333263	0.942782	0.040*
C61	0.9722(4)	0.3146(10)	0.8560(3)	0.0388(18)
H61A	0.953631	0.364920	0.884440	0.047*
H61B	0.971700	0.210567	0.863187	0.047*
C62	0.9072(4)	0.3474(9)	0.7992(3)	0.0360(17)
H62A	0.851269	0.298098	0.795116	0.043*
H62B	0.895916	0.451614	0.795429	0.043*
C63	0.9448(4)	0.2962(7)	0.7550(2)	0.0246(12)
H63	0.965124	0.195318	0.763498	0.029*
C64	1.0247(4)	0.3901(7)	0.7566(2)	0.0246(13)
H64	1.002515	0.489734	0.747053	0.029*
C65	1.0653(4)	0.3433(9)	0.7127(3)	0.0330(15)
H65A	1.091815	0.247429	0.722135	0.040*
H65B	1.112221	0.411144	0.712355	0.040*
C66	0.9976(5)	0.3380(9)	0.6551(3)	0.0366(16)
H66A	0.977199	0.436390	0.643499	0.044*
H66B	1.025542	0.300146	0.628691	0.044*
C67	0.9197(4)	0.2450(7)	0.6534(3)	0.0272(14)
C68	0.8805(4)	0.3001(7)	0.6969(3)	0.0267(13)
H68	0.865988	0.403201	0.688200	0.032*
C69	0.7930(4)	0.2209(9)	0.6847(3)	0.0361(17)
H69A	0.750903	0.276983	0.697317	0.043*
H69B	0.800881	0.125666	0.702545	0.043*

Table 2 (continued)

Atom	x	y	z	U_{iso}^*/U_{eq}
C70	0.7622(5)	0.2067(9)	0.6211(3)	0.0377(17)
H70A	0.746688	0.106254	0.609973	0.045*
H70B	0.710678	0.267988	0.604484	0.045*
C71	0.8401(4)	0.2561(8)	0.6029(3)	0.0294(14)
H71	0.831279	0.359115	0.591963	0.035*
C72	0.9461(5)	0.0846(8)	0.6619(3)	0.0346(15)
H72A	0.969234	0.053258	0.632790	0.052*
H72B	0.894847	0.026943	0.660730	0.052*
H72C	0.990752	0.072342	0.697677	0.052*
O9	0.0435(3)	0.3004(6)	0.0242(2)	0.0369(11)
N1	0.0432(4)	0.0679(8)	0.0020(3)	0.0436(16)
H1A	0.096725	0.068973	0.004184	0.052*
H1B	0.013965	−0.009067	−0.006496	0.052*
C73	0.0049(5)	0.1875(8)	0.0120(3)	0.0334(15)
C74	−0.0904(5)	0.1770(9)	0.0066(4)	0.0444(19)
H74A	−0.096843	0.142974	0.041248	0.067*
H74B	−0.118915	0.109664	−0.022856	0.067*
H74C	−0.117503	0.271515	−0.002167	0.067*
O10	0.4856(3)	0.3410(6)	0.5273(2)	0.0352(11)
N4	0.4615(4)	0.5761(7)	0.5091(3)	0.0399(15)
H4A	0.410999	0.571523	0.515251	0.048*
H4B	0.479779	0.657953	0.499781	0.048*
C79	0.5095(5)	0.4608(8)	0.5139(3)	0.0350(16)
C80	0.5940(5)	0.4735(10)	0.5019(4)	0.049(2)
H80A	0.631564	0.542784	0.527132	0.073*
H80B	0.582868	0.505945	0.464017	0.073*
H80C	0.622871	0.379960	0.506750	0.073*
O11	1.0115(4)	0.6508(6)	0.4721(2)	0.0407(13)
N3	1.0457(4)	0.4210(7)	0.4940(3)	0.0398(15)
H3B	1.089058	0.436532	0.482757	0.048*
H3C	1.019888	0.340822	0.491337	0.048*
C77	0.9933(4)	0.5320(7)	0.4870(3)	0.0294(14)
C78	0.9079(5)	0.5071(10)	0.4970(4)	0.048(2)
H78A	0.895556	0.587222	0.518087	0.071*
H78B	0.910857	0.418038	0.517706	0.071*
H78C	0.861446	0.499696	0.461767	0.071*
O12	0.5416(3)	0.5355(6)	0.0305(2)	0.0382(12)
N2	0.5531(4)	0.7649(7)	0.0074(3)	0.0367(14)
H2B	0.529151	0.846545	−0.000195	0.044*
H2C	0.608081	0.766035	0.014465	0.044*
C75	0.5075(4)	0.6524(8)	0.0125(3)	0.0309(14)
C76	0.4111(5)	0.6682(9)	−0.0041(4)	0.0440(19)
H76A	0.383563	0.590620	−0.029239	0.066*
H76B	0.394225	0.760533	−0.022451	0.066*
H76C	0.392040	0.663859	0.028594	0.066*

13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthrene-3,17-diol) is a member of the estrogen family of hormones, which was widespread used in hormonal replacement therapy for the treatment of postmenopausal symptoms and the protection against long-term consequences of estrogen deficiency (osteoporosis and cardiovascular disease) [3, 4]. According to the Biopharmaceutics Classification System (BCS), estradiol belongs to BCS class II compounds with very low

solubility across physiological pH range. Different oral formulation technology of Estradiol has been employed to increase its solubility [5, 6]. The design and synthesis of suitable pharmaceutical co-crystals provide a new door for improving the bioavailability of potential poorly soluble drugs [7, 8]. Therefore, increasing the solubility of estradiol via co-crystallization and consequently improving its bioavailability through the preparation of pharmaceutical acceptable co-crystals is of interest for the development of new dosage forms of estradiol.

The co-crystal structure of the title compound contains four estradiol and for acetamide molecules in the asymmetric unit. As expected, H-bonding interactions are dominant in the crystal structure. The intermolecular hydrogen bonding O6—H3A···—O3 (distance of 2.632 Å) links two estradiol molecules to form parallel chains. Finally, chains interact through O9—H2A···—O2 (distance of 2.706 Å), O9—H1B···—N1 (distance of 2.841 Å) and O3—H1A···—N1 (distance of 2.912 Å) to give a two dimension sheet framework. Bond lengths and angles of all moieties are in perfect accord with the directly related formamide solvate of the title estradiol [9].

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