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The crystal structure of 6-methyl-3,20-dioxo-19-norpregna-4,6-dien-17-yl acetate–2,4-dihydroxybenzoic acid (1/1), $C_{30}H_{36}O_8$

The molecular structure 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:	Colorless block
Size:	$0.21 \times 0.15 \times 0.14$ mm
Wavelength:	Mo $K\alpha$ radiation ($0.71073 \text{ \AA}$)
μ :	0.10 mm^{-1}
Diffractometer, scan mode:	Rigaku AFC10\SATURN 724+, φ and ω
$\theta_{\max}$, completeness:	27.5° , 99%
$N(hkl)_{\text{measured}}$, $N(hkl)_{\text{unique}}$, R_{int} :	9793, 5485, 0.040
Criterion for I_{obs} , $N(hkl)_{\text{gt}}$:	$I_{\text{obs}} > 2 \sigma(I_{\text{obs}})$, 5077
$N(\text{param})_{\text{refined}}$:	347
Programs:	CrystalClear [1], SHELX [2], Olex2 [3]

Source of material

6-Methyl-3,20-dioxo-19-norpregna-4,6-dien-17-yl acetate (50 mg; 0.135 mmol) and 2,4-dihydroxybenzoic (20.8 mg; 0.135 mmol) were added to a glass bottle; 2 mL methanol were then added to the bottle while stirring. The solution was heated to 60°C , until it changed to clear, after that the solution was cooled at room temperature 25°C . Crystals of the title compound were obtained by slow evaporation within 15 days.

Experimental details

The single crystal data collections were carried out on a Rigaku AFC-10/Saturn 724+ CCD diffractometer with graphite-monochromated Mo $K\alpha$ radiation ($\lambda = 0.71073 \text{ \AA}$) using the multi-scan technique. The structure was determined by direct methods using SHELXS-2014 and refined by full-matrix least-squares procedures on F_2 with SHELXL-2018 [2]. All non-hydrogen atoms were obtained from the difference Fourier map and subjected to anisotropic refinement by full-matrix least-squares on F_2 . Hydrogen atoms were placed geometrically and treated as riding on the parent atoms.

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Abstract

$C_{30}H_{36}O_8$, monoclinic, $P2_1$ (no. 4), $a = 10.899(2) \text{ \AA}$, $b = 11.002(2) \text{ \AA}$, $c = 11.847(2) \text{ \AA}$, $V = 1310.3(5) \text{ \AA}^3$, $Z = 2$, $R_{\text{gt}}(F) = 0.0504$, $wR_{\text{ref}}(F^2) = 0.1161$, $T = 163(2) \text{ K}$.

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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	0.4456(2)	0.5857(3)	0.6440(2)	0.0354(6)
O2	−0.2240(2)	0.6554(2)	−0.4182(2)	0.0402(6)
O3	0.0237(2)	0.4474(2)	−0.25088(18)	0.0244(5)
O4	−0.0277(2)	0.4449(3)	−0.4532(2)	0.0369(6)
C1	0.3731(3)	0.5896(3)	0.5338(3)	0.0277(7)
C2	0.2291(3)	0.5548(4)	0.4893(3)	0.0367(9)
H2A	0.176882	0.625486	0.497534	0.044*
H2B	0.218332	0.488517	0.541259	0.044*
C3	0.1746(3)	0.5131(4)	0.3561(3)	0.0337(8)
H3A	0.217570	0.435636	0.349594	0.040*
H3B	0.077711	0.498419	0.328226	0.040*
C4	0.1998(3)	0.6077(3)	0.2742(3)	0.0240(6)
H4	0.150112	0.682674	0.278892	0.029*
C5	0.3468(3)	0.6411(3)	0.3232(3)	0.0235(6)
C6	0.4238(3)	0.6308(3)	0.4444(3)	0.0264(7)
H6	0.515331	0.651658	0.471514	0.032*
C7	0.4022(3)	0.6894(3)	0.2371(3)	0.0236(6)
C8	0.5464(3)	0.7252(4)	0.2849(3)	0.0319(8)
H8A	0.560884	0.795387	0.339476	0.048*
H8B	0.571165	0.746505	0.216208	0.048*
H8C	0.601253	0.656992	0.330272	0.048*
C9	0.3233(3)	0.7047(3)	0.1185(3)	0.0243(7)
H9	0.361669	0.738533	0.066017	0.029*
C10	0.1780(3)	0.6715(3)	0.0636(3)	0.0209(6)
H10	0.125489	0.744869	0.067277	0.025*
C11	0.1485(3)	0.5702(3)	0.1384(3)	0.0213(6)
H11	0.198568	0.496019	0.132167	0.026*
C12	−0.0002(3)	0.5394(3)	0.0844(3)	0.0242(6)
H12A	−0.051256	0.610792	0.092926	0.029*
H12B	−0.017041	0.471597	0.131467	0.029*
C13	−0.0498(3)	0.5032(3)	−0.0517(3)	0.0241(6)
H13A	−0.006075	0.426671	−0.059663	0.029*
H13B	−0.146956	0.488679	−0.083619	0.029*
C14	−0.0196(3)	0.6027(3)	−0.1271(3)	0.0209(6)
C15	0.1310(3)	0.6312(3)	−0.0696(3)	0.0209(6)
H15	0.178171	0.553317	−0.069796	0.025*
C16	−0.1083(3)	0.7139(3)	−0.1358(3)	0.0276(7)
H16A	−0.087658	0.747150	−0.053700	0.041*
H16B	−0.202020	0.689434	−0.171555	0.041*
H16C	−0.091843	0.776016	−0.187533	0.041*
C17	−0.0332(3)	0.5697(3)	−0.2601(3)	0.0236(6)
C18	0.0562(3)	0.6640(3)	−0.2876(3)	0.0296(7)
H18A	0.001432	0.730654	−0.338593	0.036*
H18B	0.106018	0.625312	−0.332367	0.036*
C19	0.1537(3)	0.7143(3)	−0.1631(3)	0.0241(6)
H19A	0.246903	0.709201	−0.156707	0.029*
H19B	0.132825	0.799824	−0.151775	0.029*
C20	−0.1781(3)	0.5679(3)	−0.3531(3)	0.0286(7)
C21	−0.2632(3)	0.4599(3)	−0.3544(3)	0.0320(7)
H21A	−0.289489	0.417979	−0.433197	0.048*
H21B	−0.342846	0.487299	−0.342386	0.048*
H21C	−0.212624	0.404046	−0.288283	0.048*
C22	0.0247(3)	0.3969(3)	−0.3536(3)	0.0275(7)
C23	0.0966(4)	0.2788(3)	−0.3312(3)	0.0345(8)
H23A	0.076413	0.232430	−0.269858	0.052*

Table 2 (continued)

Atom	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> _{iso} [*] / <i>U</i> _{eq}
H23B	0.192597	0.293731	−0.301261	0.052*
H23C	0.068195	0.232451	−0.407679	0.052*
O5	0.3391(2)	0.4879(2)	−0.20717(19)	0.0322(6)
H5	0.388389	0.516799	−0.240177	0.039*
O6	0.4346(2)	0.3103(2)	0.1775(2)	0.0381(6)
H6A	0.503016	0.299967	0.241376	0.046*
O7	0.6691(3)	0.3531(2)	0.3512(2)	0.0397(6)
O8	0.8101(2)	0.4767(3)	0.3105(2)	0.0396(6)
H8	0.846108	0.450995	0.382678	0.047*
C24	0.4277(3)	0.4736(3)	−0.0902(3)	0.0268(7)
C25	0.3915(3)	0.3989(3)	−0.0141(3)	0.0280(7)
H25	0.307850	0.358704	−0.044842	0.034*
C26	0.4774(3)	0.3826(3)	0.1075(3)	0.0263(7)
C27	0.6024(3)	0.4398(3)	0.1527(3)	0.0270(7)
C28	0.6361(3)	0.5136(3)	0.0727(3)	0.0313(7)
H28	0.720406	0.552572	0.102324	0.038*
C29	0.5517(3)	0.5318(3)	−0.0470(3)	0.0317(7)
H29	0.576844	0.582602	−0.099326	0.038*
C30	0.6934(3)	0.4187(3)	0.2786(3)	0.0316(8)

Comment

6-Methyl-3,20-dioxo-19-norpregna-4,6-dien-17-yl acetate (NOMAC) belongs to a new generation of synthetic progestins that possess high affinities for progesterone receptor and low or no affinities for estrogen, androgen, glucocorticoid or mineralocorticoid receptors [4–6]. Because of the very low solubility across the physiological pH range, NOMAC requires micronization or nanomization to improve dissolution. Therefore, it is important to establish effective methods for enhancing the dissolution and bioavailability of NOMAC. It is agreed that co-crystals form a vital part of the solid-state toolbox for improving the properties of older medicines [7–10]. To date, researchers have obtained many co-crystals of the steroids to improve their dissolution compared with the pure counterpart [11, 12]. Only one co-crystal of NOMAC has been reported to date to improve its dissolution profile about three to four times [12]. Therefore, increasing the dissolution of NOMAC through 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 NOMAC. The co-crystal structure of the title compound crystallized as colorless elongate prism-shaped crystals and was found to be a 1:1 co-crystal of NOMAC and 2,4-dihydroxybenzoic acid as revealed by the single crystal structure. The co-crystal crystallizes in the monoclinic *P*2₁ space group. The asymmetric unit consists of one NOMAC molecule and one 2,4-dihydroxybenzoic acid molecule. As expected, H-bonding

interactions are dominant in the crystal structure. The 2,4-dihydroxybenzoic acid molecule blends into the 1D chain of NOMAC molecules, in which each 2,4-dihydroxybenzoic acid molecule links two NOMAC molecules through two intermolecular hydrogen bonds [O8–H8A...O4 (D...A distance of 2.694(3) Å, D...A angle 157.2°; O1–H5...O5 (D...A distance of 2.683(4) Å, D...A angle 161.6°)]. An intramolecular hydrogen bond is found in 2,4-dihydroxybenzoic acid [O6–H6A...O7 (D...A distance of 2.631(3) Å, D...A angle 150.3°)] in 2,4-dihydroxybenzoic acid molecule. Bond lengths and angles of all moieties are in the expected ranges [12, 13].

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