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Structure of the *n*-Butyl Acetate Solvate of 11β-[4-(Dimethylamino)phenyl]-17β-hydroxy-17α-(1-propynyl)estra-4,9-dien-3-one

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Abstract. $C_{29}H_{35}NO_2.C_6H_{12}O_2$, $M_r = 545{\cdot}77$, orthorhombic, $P2_12_12_1$, $a = 8{\cdot}4479\ (8)$, $b = 17{\cdot}011\ (3)$, $c = 21{\cdot}284\ (1)$ Å, $V = 3058{\cdot}7\ (3)$ Å^3, $Z = 4$, $D_x = 1{\cdot}185$ g cm^{-3}, λ(Mo $K\alpha$) = 0·71073 Å, μ(Mo $K\alpha$) = 0·7 cm^{-1}, $F(000) = 1184$, room temperature, $R = 0{\cdot}061$ for 3146 unique reflections with $I \geq 2{\cdot}5\sigma(I)$. While $\Delta^{4,9}$ steroids are known with strongly bent conformations, the title compound has a rather flat skeleton. There is a very short intramolecular contact of 3·108 (4) Å between the C atom of the phenyl ring attached to C(11) and C(18) of the methyl group. The phenyl ring is perpendicular to the steroid skeleton and approximately coplanar with C(9)–C(11). The steroid molecules are hydrogen bonded head to tail. The solvent molecule is not involved in hydrogen bonding.

Introduction. The title compound (RU 38 486) was the first steroid for which remarkable antiprogestational and antiglucocorticoid activities were found (*e.g.* Sakiz, Euvrard & Baulieu, 1984). We undertook the structure analysis of RU 38 486 to support an investigation aimed at finding more potent drugs with the same pharmacological profile. Despite numerous attempts by various other groups no X-ray analysis of this key compound was possible because of serious crystallization problems. We succeeded in co-crystallization of RU 38 486 with *n*-butyl acetate.

Experimental. Sample obtained through the Scientific Development Group of Organon, Oss, The Netherlands. A solution containing 10 mg of RU 38 486 in 700 µl methylcyclohexane (McH) and 70 µl *n*-butyl acetate (BuAc) was evaporated slowly, resulting in a deposit of amorphous material along with a few very small crystalline aggregates. This crystalline material was collected, pulverized and used as seeds in the next step. For that purpose 5 mg of RU 38 486 was suspended in 100 µl McH and 50 µl BuAc was added to obtain a clear solution. The addition of 100 µl McH resulted in a turbid solution to which the seeds were added. Small single crystals appeared within a few hours and heating the solution until a few crystals were left, followed by slow cooling, resulted in crystals large enough to be studied by X-ray diffraction.

Data measured on a parallelepiped crystal of dimensions 0·87 × 0·50 × 0·02 mm on an Enraf–Nonius CAD-4 diffractometer with Zr-filtered Mo $K\alpha$ radiation; lattice parameters refined by least-squares fitting of 2θ values of 25 reflexions in the range $11{\cdot}2° < 2\theta < 18{\cdot}2°$; ω–2θ scan mode, $\Delta\omega = (0{\cdot}55 + 0{\cdot}35\tan\theta)°$, 4953 independent reflexions measured up to $\theta = 30°$, h,k,l (max. range 11, 23, 29), 3146 of these considered observed [$I \geq 2{\cdot}5\sigma(I)$] and used for structure refinement. Four periodically measured standard reflexions ($\bar{1}2\bar{3}$, $12\bar{3}$, 123, $\bar{1}23$) showed a decrease in intensity less than 2%; Lp corrections, no correction for absorption.

Structure solved by direct methods using a preliminary version of *SHELXS*84 (Sheldrick, 1984). Best E map, for 1451 E values with $|E| > 1{\cdot}2$ and $R_E = 0{\cdot}34$, revealed almost all non-H atoms, except those of the solvent molecule. Tangent refinement and peak optimization (Sheldrick, 1982) using coordinates of the 20 uppermost peaks resulted in an E map, for 986 E values with $|E| > 1{\cdot}4$ and $R_E = 0{\cdot}22$, which gave all non-H-atom positions.

H atoms were included in the refinement at calculated positions riding on their bonded atoms, except for the hydroxyl-group H atom which was located on a difference map. In the final cycles of two-block full-matrix refinement, using *SHELX*76 (Sheldrick, 1976), 93 and 278 parameters, respectively, were varied, including an overall scale factor, positional and individual anisotropic parameters for C, O and N atoms, positional parameters for H[O(17)], orientational parameters for the rigid C(22) (see Fig. 1) methyl group, and two overall thermal parameters for H atoms of the steroid molecule and of the solvent molecule, respectively. The refinement on F converged at $R = 0{\cdot}061$ and $wR = 0{\cdot}049$, where $w = 1/\sigma^2(F)$. Overall thermal parameters for steroid and solvent H atoms refined to 0·083 (2) and 0·211 (8) Å^2 respectively. $\Delta/\sigma = 0{\cdot}03$ (3) (av.) and 0·19 (max.) for non-H-atom parameters. $\Delta/\sigma = 0{\cdot}08$ (8) (av.) and 0·26 (max.) for H-atom parameters; final residual electron density $-0{\cdot}25 < \Delta\rho < 0{\cdot}27$ e Å^{-3}. Scattering factors were taken from Cromer & Mann (1968) for C, O and N atoms and from Stewart, Davidson & Simpson (1965) for H atoms.

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Discussion. The final atomic parameters are given in Table 1.* The conformation of the steroid molecule and atom numbering are shown in Fig. 1. The intramolecular dimensions involving non-hydrogen atoms of the steroid molecule are given in Table 2. A scan through the Cambridge Crystallographic Database on steroids (class 51) having $\Delta^{4,9}$ unsaturation gave 12 hits, comprising 14 crystal structures of 11 different steroids. The data of one crystal structure, form III of 11β,17β-dihydroxy-18-methyl-19-norpregna-4,9-dien-20-yn-3-one (Mornon, Delettré & Lepicard, 1982), was excluded from analysis, because of the poor reliability ($R = 0.134$). This resulted in data for 19 $\Delta^{4,9}$ steroid molecules. All bond lengths and angles of RU 38 486 correspond well within min. and max. values observed for these $\Delta^{4,9}$ steroids, except bond C(11)–C(12),

* Lists of structure factors, torsion angles, anisotropic thermal parameters, molecular dimensions of the *n*-butyl acetate molecule and H-atom coordinates have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 42986 (28 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

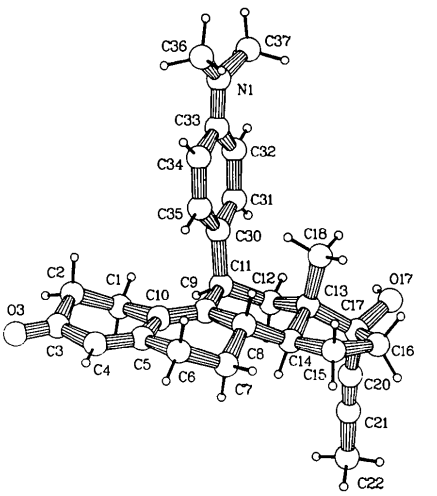

Fig. 1. Molecular structure with atom numbering of 11β-[4-(dimethylamino)phenyl]-17β-hydroxy-17α-(1-propynyl)estra-4,9-dien-3-one.

Table 1. *Positional and equivalent isotropic thermal parameters* (Å^2) *for non-*H *atoms with e.s.d.'s in parentheses*

$$U_{eq} = (U_{11} + U_{22} + U_{33})/3.$$

	x	y	z	U_{eq}
O(3)	0·5919 (3)	0·4712 (1)	0·0913 (1)	0·062 (1)
O(17)	0·0840 (3)	0·9362 (1)	0·3850 (1)	0·050 (1)
N(1)	0·6275 (4)	1·0180 (2)	0·0915 (2)	0·066 (1)
C(1)	0·5647 (4)	0·6343 (2)	0·1990 (2)	0·056 (2)
C(2)	0·6304 (5)	0·5948 (2)	0·1420 (2)	0·071 (2)
C(3)	0·5324 (5)	0·5276 (2)	0·1179 (2)	0·049 (1)
C(4)	0·3626 (4)	0·5361 (2)	0·1252 (2)	0·044 (1)
C(5)	0·2947 (4)	0·5949 (2)	0·1579 (2)	0·039 (1)
C(6)	0·1176 (4)	0·6063 (2)	0·1534 (2)	0·053 (1)
C(7)	0·0535 (4)	0·6458 (2)	0·2118 (2)	0·049 (1)
C(8)	0·1376 (4)	0·7235 (2)	0·2248 (2)	0·038 (1)
C(9)	0·3181 (4)	0·7110 (2)	0·2269 (2)	0·034 (1)
C(10)	0·3569 (4)	0·6507 (2)	0·1963 (2)	0·040 (1)
C(11)	0·4189 (4)	0·7729 (2)	0·2603 (1)	0·036 (1)
C(12)	0·3372 (4)	0·8092 (2)	0·3192 (1)	0·035 (1)
C(13)	0·1654 (4)	0·8329 (2)	0·3063 (2)	0·036 (1)
C(14)	0·0759 (4)	0·7593 (2)	0·2858 (2)	0·039 (1)
C(15)	−0·0998 (4)	0·7843 (2)	0·2869 (2)	0·050 (1)
C(16)	−0·1076 (4)	0·8464 (2)	0·3402 (2)	0·049 (1)
C(17)	0·0649 (4)	0·8565 (2)	0·3652 (2)	0·041 (1)
C(18)	0·1548 (4)	0·9013 (2)	0·2592 (1)	0·046 (1)
C(20)	0·0889 (4)	0·8037 (2)	0·4197 (2)	0·043 (1)
C(21)	0·0962 (5)	0·7639 (2)	0·4645 (2)	0·054 (1)
C(22)	0·1042 (6)	0·7137 (2)	0·5209 (2)	0·081 (2)
C(30)	0·4788 (3)	0·8357 (2)	0·2140 (1)	0·037 (1)
C(31)	0·5632 (4)	0·9013 (2)	0·2354 (2)	0·041 (1)
C(32)	0·6136 (4)	0·9598 (2)	0·1961 (2)	0·047 (1)
C(33)	0·5827 (4)	0·9574 (2)	0·1309 (1)	0·046 (1)
C(34)	0·5051 (4)	0·8903 (2)	0·1087 (2)	0·047 (1)
C(35)	0·4549 (4)	0·8321 (2)	0·1496 (1)	0·046 (1)
C(36)	0·5913 (6)	1·0134 (2)	0·0248 (2)	0·078 (2)
C(37)	0·6707 (6)	1·0939 (2)	0·1164 (2)	0·076 (2)
O(101)	0·0790 (4)	0·3687 (2)	0·4593 (1)	0·095 (1)
O(102)	0·1126 (5)	0·2634 (2)	0·3997 (2)	0·136 (2)
C(101)	−0·2013 (7)	0·6081 (3)	0·4025 (3)	0·127 (3)
C(102)	−0·1483 (6)	0·5304 (3)	0·3806 (3)	0·104 (2)
C(103)	−0·0622 (6)	0·4844 (3)	0·4317 (2)	0·097 (2)
C(104)	−0·0087 (6)	0·4060 (3)	0·4091 (2)	0·100 (2)
C(105)	0·1372 (7)	0·2978 (3)	0·4493 (3)	0·096 (2)
C(106)	0·2357 (6)	0·2667 (3)	0·5012 (2)	0·116 (3)

Table 2. *Bond distances* (Å) *and bond angles* (°) *for non-*H *atoms of the steroid molecule with e.s.d.'s in parentheses*

O(3)–C(3)	1·222 (4)	C(8)–C(14)	1·526 (6)	C(30)–C(31)	1·400 (5)
O(17)–C(17)	1·429 (4)	C(9)–C(10)	1·347 (5)	C(30)–C(35)	1·387 (3)
N(1)–C(33)	1·382 (5)	C(9)–C(11)	1·529 (5)	C(31)–C(32)	1·368 (5)
N(1)–C(37)	1·443 (5)	C(11)–C(12)	1·559 (4)	C(32)–C(33)	1·413 (5)
N(1)–C(36)	1·454 (6)	C(11)–C(30)	1·539 (4)	C(33)–C(34)	1·399 (5)
C(1)–C(2)	1·494 (6)	C(12)–C(13)	1·531 (5)	C(34)–C(35)	1·385 (5)
C(1)–C(10)	1·529 (5)	C(13)–C(14)	1·526 (5)		
C(2)–C(3)	1·502 (5)	C(13)–C(17)	1·566 (6)		
C(3)–C(4)	1·450 (5)	C(13)–C(18)	1·538 (5)		
C(4)–C(5)	1·347 (5)	C(14)–C(15)	1·544 (5)		
C(5)–C(6)	1·512 (5)	C(15)–C(16)	1·552 (5)		
C(5)–C(10)	1·475 (5)	C(16)–C(17)	1·561 (5)		
C(6)–C(7)	1·513 (6)	C(17)–C(20)	1·481 (6)		
C(7)–C(8)	1·526 (5)	C(20)–C(21)	1·171 (6)		
C(8)–C(9)	1·540 (5)	C(21)–C(22)	1·475 (6)		

C(33)–N(1)–C(36)	119·7 (3)	C(17)–C(13)–C(18)	107·2 (3)
C(33)–N(1)–C(37)	120·9 (4)	C(8)–C(14)–C(13)	113·7 (3)
C(36)–N(1)–C(37)	117·4 (3)	C(8)–C(14)–C(15)	116·8 (3)
C(2)–C(1)–C(10)	114·6 (3)	C(13)–C(14)–C(15)	104·2 (3)
C(1)–C(2)–C(3)	114·5 (3)	C(14)–C(15)–C(16)	103·9 (3)
O(3)–C(3)–C(2)	121·9 (4)	C(15)–C(16)–C(17)	106·5 (3)
O(3)–C(3)–C(4)	122·3 (3)	O(17)–C(17)–C(13)	114·7 (3)
C(2)–C(3)–C(4)	115·6 (3)	O(17)–C(17)–C(16)	108·1 (3)
C(3)–C(4)–C(5)	123·4 (3)	O(17)–C(17)–C(20)	109·2 (3)
C(4)–C(5)–C(6)	119·0 (3)	C(13)–C(17)–C(16)	101·8 (3)
C(4)–C(5)–C(10)	122·6 (3)	C(13)–C(17)–C(20)	113·4 (3)
C(6)–C(5)–C(10)	118·4 (3)	C(16)–C(17)–C(20)	109·2 (3)
C(5)–C(6)–C(7)	111·0 (3)	C(17)–C(20)–C(21)	174·6 (4)
C(6)–C(7)–C(8)	111·5 (3)	C(20)–C(21)–C(22)	179·6 (4)
C(7)–C(8)–C(9)	110·3 (3)	C(11)–C(30)–C(31)	120·8 (2)
C(7)–C(8)–C(14)	109·9 (3)	C(11)–C(30)–C(35)	123·7 (3)
C(9)–C(8)–C(14)	111·6 (3)	C(31)–C(30)–C(35)	115·5 (3)
C(8)–C(9)–C(10)	121·2 (3)	C(30)–C(31)–C(32)	122·6 (4)
C(8)–C(9)–C(11)	118·0 (3)	C(31)–C(32)–C(33)	121·5 (3)
C(10)–C(9)–C(11)	120·6 (3)	N(1)–C(33)–C(32)	121·6 (3)
C(1)–C(10)–C(5)	115·0 (3)	N(1)–C(33)–C(34)	122·2 (3)
C(1)–C(10)–C(9)	123·0 (3)	C(32)–C(33)–C(34)	116·2 (3)
C(5)–C(10)–C(9)	122·0 (3)	C(33)–C(34)–C(35)	121·0 (3)
C(9)–C(11)–C(12)	113·6 (3)	C(30)–C(35)–C(34)	123·0 (3)
C(9)–C(11)–C(30)	111·3 (2)		
C(12)–C(11)–C(30)	112·7 (3)		
C(11)–C(12)–C(13)	112·3 (2)		
C(12)–C(13)–C(14)	107·7 (3)		
C(12)–C(13)–C(17)	116·0 (3)		
C(12)–C(13)–C(18)	111·8 (3)		
C(14)–C(13)–C(17)	99·8 (3)		
C(14)–C(13)–C(18)	113·9 (3)		

which is 0·02 Å longer in RU 38 486 than the observed mean value. The Δ^4 *A* ring has a 1α,2β-half-chair conformation as illustrated by the asymmetry parameter ΔC_2[C(1)–C(2)] = 4·9 (5)° (Duax & Norton, 1975) and the Δ^9 *B* ring has a 7α-sofa conformation as illustrated by ΔC_s[C(7)] = 2·3 (4)°. The *C* ring is in the usual, distorted, chair conformation {ΔC_s[C(8)] = 19·1 (3), ΔC_s[C(9)] = 3·5 (3), ΔC_s[C(11)] = 15·7 (3), ΔC_2[C(8)–C(9)] = 15·9 (4), ΔC_2[C(9)–C(11)] = 8·7 (4), ΔC_2[C(11)–C(12)] = 24·6 (4)°} and the *D* ring has a 13β-envelope conformation {ΔC_s[C(13)] = 4·0 (4)°}. In general $\Delta^{4,9}$ steroids have a wide variety of conformations (Delettré, Mornon, Lepicard, Ojasoo & Raynaud, 1980), varying from the unusual flat conformation of 11β,17β-dihydroxy-19-norpregna-4,9-dien-20-yn-3-one (Lepicard, Mornon & Delettré, 1982) to the strongly bent conformation of 17β-hydroxy-11β-methoxy-18-methyl-19-norpregna-4,9-dien-20-yn-3-one (Mornon, Lepicard & Delettré, 1974). The overall conformation of $\Delta^{4,9}$ steroids is related to the conformation of the *A* ring, which is a 1α,2β-half chair in the flat conformation and a (inverted) 1β,2α-half chair or 1β-sofa in the bent conformations. The conformation of the *B* ring, which is normally a 6β,7α-half chair or a 7α-sofa, can be inverted to a 6α,7β-half chair and this also influences the overall conformation (see Delettré, Lepicard, Surcouf & Mornon, 1981). The overall conformation of RU 38 486 is flat and this is in agreement with the relation between *A*-ring conformation and overall shape. The 11β-[4-(dimethylamino)phenyl] group is perpendicular to the steroid skeleton and is coplanar with C(9)–C(11) as indicated by torsion angle C(9)–C(11)–C(30)–C(31) = 175·0 (3)°, and seems to be fixed in this position by the 1,3-diaxial interaction with the C(18) methyl group. The torsion angles C(36)–N(1)–C(33)–C(34) = 1·1 (5) and C(37)–N(1)–C(33)–C(32) = −15·8 (5)° show that the amino group is significantly distorted from planarity and coplanarity with the phenyl ring; N(1), C(36) and C(37) are 0·08 (3), 0·13 (3) and 0·45 (3) Å out of the phenyl plane respectively. The orientation of the propynyl group is given by torsion angle C(15)–C(16)–C(17)–C(20) = −93·8 (4)°.

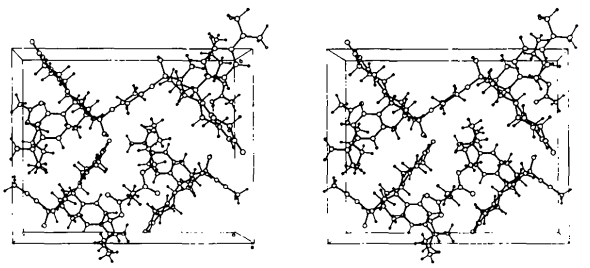

Fig. 2. Stereo packing diagram viewed down **a**.

The shortest intramolecular C···H contact distance is C(30)···H[C(18)] = 2·33 Å, whereas C(30)···C(18) = 3·108 (4) Å. There are no other $\Delta^{4,9}$ steroids with an angular C atom at C(11) in the Cambridge Database; however, the O···C(18) contact distance for 11β-hydroxy- or 11β-methoxy-substituted $\Delta^{4,9}$ steroids is rather constant [mean = 3·04 (7) Å for 5 different compounds, comprising 10 molecules] and gives no indication that this distance is correlated with the overall shape of the molecule.

The molecular packing is illustrated in Fig. 2, which shows a stereoview down **a**. The steroid molecules are hydrogen bonded from head to tail; O(17)→O(3)-($1-x,\frac{1}{2}+y,\frac{1}{2}-z$) with an O···O distance of 2·847 (4) Å and an O–H···O angle of 177 (3)°. The BuAc solvent molecule with bond distances and angles within the normal range has an all-*trans* conformation and is not involved in hydrogen bonding (see deposition footnote). There are several H···H contact distances between steroid and solvent molecules of about 2·3 Å, but, because of calculated H-atom positions, these distances should be considered with some care.

Considering the extreme flexibility of the *A* and *B* rings for $\Delta^{4,9}$ steroids we cannot exclude the possibility that a bent conformation of RU 38 486 is preferred in solution, the observed flat conformation in the crystal being due to packing forces.

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