Steroid Structure and Function.
III. Conformational Transmission in 1,3,5(10)-Estratrienes

By William L. Duax, Douglas C. Rohrer, Robert H. Blessing and Phyllis D. Strong

Medical Foundation of Buffalo, Inc., 73 High Street, Buffalo, New York 14203, USA

and Albert Segaloff

Alton Ochsner Medical Foundation, New Orleans, Louisiana 70121, USA

Abstract

The crystal structure determinations of four estranes were undertaken to determine conformational transmission effects of specific structure modifications. 3-Methoxy-1,3,5(10)-estratrien-17-one $(C_{19}H_{24}O_2)$ crystallizes in space group $P2_12_12_1$ with $Z = 4$, $a = 11\cdot8258$ (3), $b = 18\cdot4749$ (5), and $c = 6\cdot9852$ (3) Å, $R = 5\cdot4\%$. 1,3,5(10),14-Estratetraene-3,17β-diol hemihydrate $(C_{18}H_{22}O_2.\frac{1}{2}H_2O)$ crystallizes in space group $P2_12_12$ with $Z = 4$, $a = 12\cdot1234$ (9), $b = 19\cdot761$ (1), $c = 6\cdot3601$ (4) Å, $R = 6\cdot5\%$. 3-Methoxy-1,3,5(10),14-estratetraen-17β-ol $(C_{19}H_{24}O_2)$ crystallizes in space group $P2_12_12_1$, with $Z = 4$, $a = 12\cdot591$ (1), $b = 21\cdot661$ (2), $c = 5\cdot751$ (1) Å, $R = 3\cdot7\%$. 3-Methoxy-1,3,5(10),14-estratetraen-17-one $(C_{19}H_{22}O_2)$ crystallizes in space group $P2_12_12_1$, with $Z = 4$, $a = 9\cdot0595$ (5), $b = 29\cdot504$ (2), $c = 5\cdot8960$ (5) Å, $R = 5\cdot4\%$. Analysis of conformational data on these and 21 other 1,3,5(10)-estratriene structures illustrates that exocyclic nonbonded interactions play a decisive role in determining overall steroid conformation. This is particularly true of interactions across the A/C- and B/D-bay regions of the steroid backbone. Interactions between C(1) and C(11) stabilize the $7\alpha,8\beta$-half-chair conformation of the flexible B ring in 1,3,5(10)-estratrienes. 4-Bromo substitution and C(14)—C(15) dehydrogenation introduce strains at the C(6) and C(7) positions that are relieved by a shift in B-ring conformation to the 8β-sofa form.

Introduction

The activity of steroid hormones is dependent upon a number of factors including solubilization, motility, transport, metabolism, and complementarity of fit between hormone and receptor. Functional differences caused by structural modifications may be due to influence upon any or all of these factors. In many cas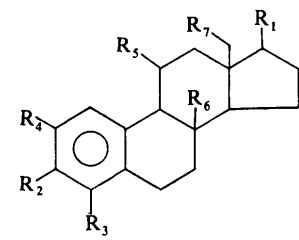es a structural change in one part of a steroid alters the rate of reaction at a distant point, a phenomenon that Barton (1955) labeled conformational transmission. The activities of certain estrogenic and androgenic steroids are significantly altered by C(14)—C(15) dehydrogenation and methylation of the C(3) hydroxyl. The influence of these structural modifications upon the overall geometry and conformation of the steroid backbone is being investigated by X-ray crystal structure analysis.

The three most important natural human estranes are the principal estrogen, estradiol (I), and its primary metabolites, estrone (VIII) and estriol (XIII). Crystal structure determinations of these hormones and nine derivatives thereof have been reported (Table 1). These determinations include urea, propanol, and hemihydrate complexes of estradiol, three polymorphic forms of estrone, two polymorphic forms of 2,4-dibromoestradiol (IX), and crystal forms containing two molecules in the asymmetry unit of estrone, 2,4-dibromoestradiol, and 17-epiestradiol (XII). In addition, we report here the determination of the structures of 3-methoxy-1,3,5(10)-estratrien-17-one (XI), 3-methoxy-1,3,5(10),14-estratetraen-17-one (XVI), 3-methoxy-1,3,5(10),14-estratetraen-17β-ol (XV) and 1,3,5(10),14-estratetraene-3,17β-diol (XIV). The latter structures provide information about the influence of C(14)—C(15) dehydrogenation upon overall conformation and the influence of methyl-ether formation on steroid geometry.
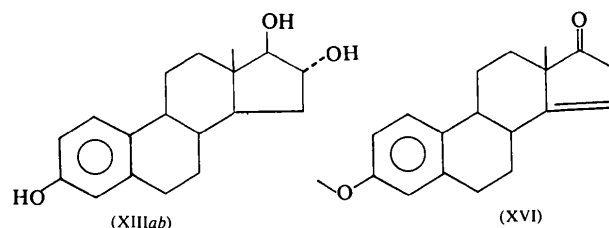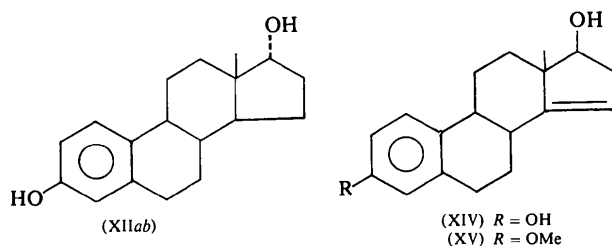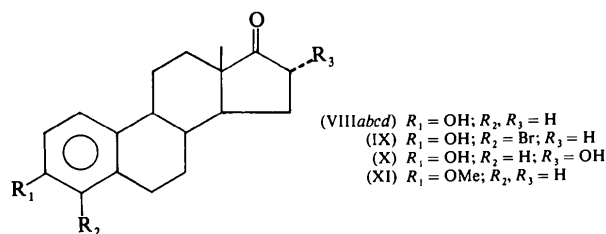
Experimental

3-*Methoxy*-1,3,5(10)-*estratrien*-17-*one* (XI) $(C_{19}H_{24}O_2)$

Crystals of (XI) were grown from a 95% ethanol solution. Crystallographic data were measured on an Enraf–Nonius CAD-4 diffractometer using Ni-filtered Cu $K\alpha$ radiation ($\lambda = 1\cdot5418$ Å) and the ω–2θ scan technique. The specimen crystal of dimensions 0·18 ×

Table 1. *Crystallographic determinations of estradiol, estrone, estriol and derivatives*

	R_1	R_2	R_3	R_4	R_5	R_6	R_7
(Iabc)	OH	OH	–	–	–	–	–
(II)	OH	Br benzoate	–	–	–	–	–
(III)	OH	OH	Br	–	–	–	–
(IVabc)	OH	OH	Br	Br	–	–	–
(V)	OH	OH	–	–	OMe	–	–
(VI)	Br acetate	OMe	–	–	–	CH_3	–
(VII)	OH	OH	–	–	–	–	CH_3

(VIII$abcd$) $R_1 = OH; R_2, R_3 = H$
(IX) $R_1 = OH; R_2 = Br; R_3 = H$
(X) $R_1 = OH; R_2 = H; R_3 = OH$
(XI) $R_1 = OMe; R_2, R_3 = H$

(XIIab)

(XIV) $R = OH$
(XV) $R = OMe$

(XIIIab)

(XVI)

References: (Ia) (Busetta & Hospital, 1972); (Ib) (Busetta, Courseille, Geoffre & Hospital, 1972); (Ic) (Duax, 1972); (II), (VI) (Tsukuda, Sato, Shiro & Koyama, 1968); (III) (Norton, Kartha & Lu, 1964); (IVabc) (Cody, DeJarnette, Duax & Norton, 1971); (V) (Courseille, Busetta, Precigoux & Hospital, 1973); (VII) (Barrans, Courseille, Busetta & Precigoux, 1976); (VIII$abcd$) (Busetta, Courseille & Hospital, 1973); (IX) (Norton, Kartha & Lu, 1963; Strong, Duax & Engel, 1976); (XIIab) (Busetta, Barrans, Precigoux & Hospital, 1976); (XIIIab) (Cooper, Norton & Hauptman, 1969); (XI), (XIV), (XV), (XVI) (this work).

0.20×0.67 mm showed systematic absences in the diffraction data consistent with the orthorhombic space group $P2_12_12_1$ ($Z = 4$). The refined lattice parameters, $a = 11.8258$ (3), $b = 18.4749$ (5) and $c = 6.9852$ (3) Å, were obtained by a least-squares fit to a set of measured 2θ values for 60 reflections in the interval $70° < 2\theta < 90°$. Integrated relative intensities for the 1819 independent reflections accessible with $2\theta < 150°$ were measured; 1564 of these reflections were calculated to be observed above background ($I > 2\sigma_I$).

The intensities were reduced to structure-factor amplitudes, and phase angles sufficient to locate the nonhydrogen atoms were derived using the programs MULTAN (Germain, Main & Woolfson, 1971) and NQEST (DeTitta, Edmonds, Langs & Hauptman, 1975). The H atoms were located on difference electron density maps prepared at an intermediate stage of least-squares refinement of structural parameters. In the final cycles of full-matrix, least-squares refinement, positional parameters for all atoms, anisotropic thermal vibration parameters for the nonhydrogen atoms, and isotropic thermal vibration parameters for the H atoms were varied. The quantities $(1/\sigma_F^2)$, where σ_F was as defined by Stout & Jensen (1968, p. 457, eq. H14) but with an instrumental instability factor of 0.06, were used to weight the least-squares differences for the observed data; differences for data measured as unobserved above background were given zero weight. The final values of the residual, $R = \sum ||F_o| - |F_c||/ \sum |F_o|$, were 0.054 for the observed data and 0.064 for all the measured data. Final positional parameters are listed in Table 2.*

1,3,5(10),14-*Estratetraene*-3,17β-*diol* (XIV) *hemihydrate* ($C_{18}H_{22}O_2 \cdot \frac{1}{2}H_2O$)

Crystals of (XIV) were grown from an ethanol–water solution. A crystal with dimensions $0.1 \times 0.1 \times 0.4$ mm was used for crystallographic-data collection employing the same procedure used for (XI). The space group is $P2_12_12$ ($Z = 4$). The lattice parameters are $a = 12.1234$ (9), $b = 19.761$ (1) and $c = 6.3601$ (4) Å, refined using 25 reflections in the range $40° < 2\theta < 56°$. 1155 reflections were calculated to be observed ($I > 2\sigma_I$) from the 1815 measured.

The space group and lattice parameters for (XIV) indicated that this structure was nearly isomorphous with the structure of 1,3,5(10)-estratriene-3,17β-diol (Ia) hemihydrate (Busetta & Hospital, 1972). The coordinates for (Ia), corrected for the slight differences in the lattice parameters, and isotropic thermal parameters of 4.0 Å^2 produced an R of 0.288. The refinement

---

Table 2. *Atomic coordinates for* 3-*methoxy*-1,3,5(10)-*estratrien*-17-*one* (XI)

	x (×10⁴)	y (×10⁵)	z (×10⁴)
C(1)	9142 (2)	112921 (11)	8417 (3)
C(2)	9276 (2)	105508 (12)	8521 (3)
C(3)	8322 (2)	101072 (10)	8470 (3)
C(4)	7257 (2)	104157 (10)	8417 (3)
C(5)	7126 (2)	111654 (10)	8355 (3)
C(6)	5930 (2)	114613 (11)	8320 (4)
C(7)	5873 (2)	122820 (11)	8580 (4)
C(8)	6774 (2)	126411 (10)	7330 (3)
C(9)	7954 (2)	124411 (10)	8122 (3)
C(10)	8077 (2)	116230 (10)	8293 (3)
C(11)	8910 (2)	127943 (11)	6940 (4)
C(12)	8760 (2)	136186 (11)	6704 (4)
C(13)	7594 (2)	137846 (10)	5895 (3)
C(14)	6682 (2)	134613 (10)	7223 (3)
C(15)	5586 (2)	138289 (12)	6561 (3)
C(16)	5967 (2)	146122 (12)	6190 (4)
C(17)	7239 (2)	145772 (10)	5858 (4)
C(18)	7500 (2)	135342 (12)	3793 (3)
C(19)	7578 (2)	89073 (12)	8344 (3)
O(3)	8526 (1)	93748 (8)	8503 (3)
O(17)	7852 (2)	150936 (8)	5595 (3)
	x (×10³)	y (×10³)	z (×10³)
H(1)	986 (2)	1163 (1)	814 (3)
H(2)	1003 (2)	1035 (1)	857 (4)
T(4)*	656 (2)	1011 (1)	827 (4)
H(6A)	550 (3)	1126 (2)	956 (4)
H(6B)	555 (3)	1132 (1)	715 (4)
H(7A)	603 (2)	1239 (1)	995 (4)
H(7B)	509 (2)	1248 (1)	844 (4)
H(8B)	668 (2)	1245 (1)	604 (3)
H(9A)	797 (2)	1266 (1)	924 (4)
H(11A)	964 (2)	1271 (1)	767 (4)
H(11B)	896 (2)	1255 (1)	575 (4)
H(12A)	887 (2)	1385 (1)	807 (3)
H(12B)	936 (3)	1387 (1)	599 (5)
H(14A)	686 (2)	1368 (1)	850 (3)
H(15A)	497 (2)	1373 (1)	754 (4)
H(15B)	530 (2)	1362 (1)	533 (3)
T(16A)	584 (2)	1494 (1)	731 (4)
H(16B)	558 (2)	1486 (1)	499 (3)
T(18A)	760 (2)	1299 (2)	375 (5)
H(18B)	676 (3)	1361 (2)	324 (4)
H(18C)	810 (3)	1377 (2)	308 (4)
H(19A)	715 (3)	903 (1)	713 (4)
T(19B)	790 (3)	843 (2)	793 (5)
H(19C)	707 (3)	894 (2)	932 (5)

* *T* indicates a hydrogen atom placed at its geometrically expected position.

Table 3. *Atomic coordinates for* 1,3,5(10),14-*estratetraene*-3,17β-*diol* (XIV) *hemihydrate* (*all* × 10⁴)

	x	y	z
C(1)	1334 (4)	982 (3)	-2963 (9)
C(2)	2442 (5)	868 (3)	-3294 (10)
C(3)	3195 (5)	1086 (3)	-1768 (10)
C(4)	2832 (4)	1452 (3)	-63 (9)
C(5)	1710 (4)	1574 (2)	262 (8)
C(6)	1393 (5)	1966 (3)	2178 (10)
C(7)	163 (5)	2115 (3)	2332 (10)
C(8)	-508 (4)	1514 (3)	1550 (8)
C(9)	-302 (4)	1425 (2)	-815 (8)
C(10)	935 (4)	1335 (3)	-1183 (9)
C(11)	-995 (4)	859 (3)	-1717 (10)
C(12)	-2239 (4)	958 (3)	-1281 (10)
C(13)	-2479 (4)	1041 (3)	1065 (9)
C(14)	-1731 (5)	1566 (3)	2001 (9)
C(15)	-2256 (5)	1978 (3)	3329 (12)
C(16)	-3479 (5)	1832 (3)	3368 (11)
C(17)	-3618 (4)	1366 (3)	1435 (10)
C(18)	-2372 (5)	373 (3)	2237 (10)
O(3)	4303 (3)	933 (2)	-2075 (8)
O(17)	-4525 (3)	909 (2)	1648 (8)
O(20)	0000	5000	5041 (10)
H(1)	975	954	-4255
H(2)	2548	699	-4575
H(4)	3390	1460	1217
H(6A)	1782	2331	2113
H(6B)	1784	1691	3328
H(7A)	-39	2563	1483
H(7B)	-10	2167	3725
H(8B)	-183	1078	2388
H(9A)	-512	1951	-1682
H(11B)	-779	420	-1321
H(11A)	-881	756	-3275
H(12B)	-2610	596	-1850
H(12A)	-2511	1328	-1812
H(15)	-1975	2471	3701
H(16A)	-3788	2285	3330
H(16B)	-3761	1543	4387
H(17A)	-3836	1665	47
H(18A)	-1555	198	2084
T(18B)	-2565	480	3891
H(18C)	-2933	23	1663
H(17O)	-4613	508	1025
H(20O)	368	4778	5517
H(30)	4531	1203	-2045

procedure was nearly the same as that described for (XI), except the parameters for the H's were never refined. The final R for the observed data was 0·065 and 0·104 for all data. The final positional parameters are listed in Table 3.

3-*Methoxy*-1,3,5(10),14-*estratetraen*-17β-*ol* (XV) (C₁₉H₂₄O₂)

Crystals of (XV) were grown from a benzene–cyclohexane solution. The crystal dimensions were 0·12 ×

0·20 × 0·30 mm. See compound (XI) for other data-collection details. The space group is $P2_12_12_1$ ($Z = 4$) and the refined lattice parameters are $a = 12\cdot591$ (1), $b = 21\cdot661$ (2) and $c = 5\cdot751$ (1) Å. The 2θ values for 24 reflections in the range $50° < 2\theta < 80°$ were used in the lattice-parameter refinement. A total of 1887 data were measured; 1597 of these were calculated to be observed above background ($I > 2\sigma_I$).

The structure solution and refinement were the same as those described for (XI). The final R value for the observed data was 0·037 and 0·049 for all data. The final atomic positions are listed in Table 4.

3-*Methoxy*-1,3,5(10),14-*estratetraen*-17-*one* (XVI) (C₁₉H₂₂O₂)

Crystals of (XVI) were grown from an ethanol–water solution. A crystal measuring 0·10 × 0·56 ×

Table 4. *Atomic coordinates for* 3-*methoxy*-1,3,5(10),-14-*estratetraen*-17β-*ol* (XV)

	$x (\times 10^4)$	$y (\times 10^5)$	$z (\times 10^4)$
C(1)	4000 (2)	−12513 (8)	−3733 (3)
C(2)	4334 (1)	−6532 (8)	−3260 (4)
C(3)	3939 (1)	−3420 (7)	−1334 (4)
C(4)	3191 (1)	−6283 (8)	70 (4)
C(5)	2847 (1)	−12295 (8)	−417 (3)
C(6)	2018 (2)	−15016 (8)	1195 (3)
C(7)	1567 (1)	−21140 (8)	368 (4)
C(8)	2425 (1)	−25217 (8)	−678 (3)
C(9)	2886 (1)	−22087 (7)	−2875 (3)
C(10)	3259 (1)	−15529 (7)	−2319 (3)
C(11)	3742 (2)	−26205 (8)	−3979 (4)
C(12)	3294 (2)	−32559 (8)	−4626 (4)
C(13)	2798 (1)	−35976 (7)	−2552 (3)
C(14)	2059 (1)	−31681 (7)	−1237 (3)
C(15)	1151 (1)	−34402 (8)	−687 (4)
C(16)	1123 (2)	−40990 (9)	−1503 (4)
C(17)	2001 (2)	−41103 (8)	−3308 (4)
C(18)	3661 (2)	−38532 (9)	−920 (4)
C(19)	4018 (2)	5543 (9)	1045 (5)
O(3)	4333 (1)	2408 (6)	−989 (4)
O(17B)	2449 (1)	−47076 (6)	−3685 (3)

	$x (\times 10^3)$	$y (\times 10^4)$	$z (\times 10^3)$
H(1)	429 (1)	−1473 (8)	−511 (5)
H(2)	491 (2)	−447 (9)	−417 (4)
H(4)	287 (2)	−436 (9)	135 (4)
H(6A)	144 (1)	−1195 (9)	140 (4)
H(6B)	235 (2)	−1562 (10)	274 (6)
H(7A)	94 (2)	−2062 (10)	−88 (5)
H(7B)	119 (2)	−2311 (10)	159 (4)
H(8B)	305 (1)	−2568 (8)	48 (3)
H(9A)	235 (1)	−2173 (9)	−407 (4)
H(11A)	399 (2)	−2425 (9)	−538 (5)
H(11B)	434 (2)	−2678 (9)	−283 (4)
H(12A)	271 (2)	−3191 (10)	−591 (4)
H(12B)	388 (2)	−3498 (9)	−536 (6)
H(15)	58 (2)	−3271 (9)	18 (5)
H(16A)	46 (2)	−4250 (10)	−217 (4)
H(16B)	128 (1)	−4395 (8)	−25 (4)
H(17A)	167 (2)	−3978 (9)	−482 (5)
H(18A)	416 (2)	−3500 (9)	−36 (5)
H(18B)	327 (2)	−4065 (10)	36 (5)
H(18C)	413 (2)	−4133 (12)	−180 (5)
H(19A)	421 (2)	337 (11)	251 (6)
H(19B)	430 (2)	931 (10)	99 (4)
H(19C)	324 (2)	629 (12)	96 (5)
H(17O)	255 (4)	−4907 (15)	−225 (9)

Table 5. *Atomic coordinates for* 3-*methoxy*-1,3,5(10),-14-*estratetraen*-17-*one* (XVI)

	$x (\times 10^4)$	$y (\times 10^5)$	$z (\times 10^4)$
C(1)	3926 (3)	50123 (10)	9791 (6)
C(2)	3741 (4)	54807 (11)	9560 (7)
C(3)	4423 (4)	57049 (10)	7767 (7)
C(4)	5230 (4)	54662 (11)	6215 (6)
C(5)	5424 (3)	49990 (10)	6434 (5)
C(6)	6352 (4)	47578 (12)	4668 (7)
C(7)	6832 (4)	42838 (11)	5296 (6)
C(8)	5579 (4)	40260 (11)	6450 (5)
C(9)	5131 (3)	42658 (10)	8665 (5)
C(10)	4794 (3)	47652 (10)	8254 (5)
C(11)	3912 (4)	40032 (10)	9885 (5)
C(12)	4364 (4)	35138 (10)	10421 (6)
C(13)	4834 (4)	32645 (11)	8249 (6)
C(14)	5928 (4)	35389 (10)	6928 (6)
C(15)	7140 (5)	33044 (14)	6468 (9)
C(16)	7082 (6)	28282 (14)	7371 (12)
C(17)	5725 (5)	28348 (12)	8782 (10)
C(18)	3486 (5)	31226 (13)	6810 (9)
C(20)	4972 (5)	64130 (12)	5998 (12)
O(3)	4249 (3)	61685 (8)	7742 (6)
O(17)	5400 (4)	25544 (9)	10239 (8)

	$x (\times 10^3)$	$y (\times 10^4)$	$z (\times 10^3)$
H(1)	346 (3)	4861 (9)	1092 (5)
H(2)	320 (3)	5646 (9)	1076 (5)
H(4)	570 (3)	5594 (9)	475 (6)
H(6A)	708 (5)	4923 (14)	446 (9)
H(6B)	576 (4)	4760 (12)	357 (7)
H(7A)	772 (3)	4319 (10)	627 (6)
H(7B)	704 (3)	4090 (9)	388 (5)
H(8)	469 (3)	4060 (10)	523 (6)
H(9)	609 (3)	4255 (10)	976 (7)
H(11B)	297 (3)	4017 (10)	885 (5)
H(11A)	375 (3)	4110 (9)	1118 (5)
H(12B)	361 (4)	3320 (10)	1112 (7)
H(12A)	514 (3)	3509 (9)	1129 (5)
H(15)	801 (3)	3443 (10)	584 (6)
H(16A)	806 (4)	2751 (11)	844 (7)
H(16B)	772 (9)	2588 (14)	649 (10)
H(18A)	281 (4)	3372 (12)	632 (7)
H(18B)	378 (5)	2954 (14)	530 (11)
H(18C)	302 (5)	2915 (12)	748 (8)
H(20A)	477 (5)	6292 (13)	425 (10)
H(20B)	473 (5)	6781 (14)	620 (8)
H(20C)	612 (4)	6369 (12)	632 (7)

0·72 mm was used for crystallographic-data collection using the procedure described for (XI). The space group is $P2_12_12_1$ ($Z = 4$). The 2θ values for 26 reflections in the interval $50° < 2\theta < 79°$ were used to obtain the refined lattice parameters: $a = 9·0595$ (5), $b = 29·504$ (2) and $c = 5·8960$ (5) Å. A total of 1916 reflections were measured; 1202 of these were calculated to be observed above background ($I > 2\sigma_I$).

The structure solution and refinement were the same as those described for (XI). The final R value for the observed data was 0·054 and 0·108 for all data. The final positional parameters are listed in Table 5.

Results

The observed conformations of the four molecules are illustrated in the stereodiagram (Fig. 1). The bond lengths and valence and torsion angles are presented in Fig. 2. The methoxy methyl consistently eclipses C(2) with one H antiperiplanar to C(3)—O(3) causing a slight opening of the O(3)—C(3)—C(4) angle. No specific effect on bond lengths in the A ring or on the conformation of the B ring can be correlated with the methoxy substitution. Dehydrogenation at the C(14)—C(15) bond stabilizes the 17α-envelope conformation of the D ring and results in a twisting of the D ring out

XVI

XI

XV

XIV

Fig. 1. *ORTEP* II stereodiagrams of 3-methoxy-1,3,5(10)-estratrien-17-one (XI), 1,3,5(10),14-estratetraene-3,17β-diol (XIV), 3-methoxy-1,3,5(10),14-estratetraen-17β-ol (XV), and 3-methoxy-1,3,5(10),14-estratetraen-17-one (XVI).

of the general plane of the molecules, an effect most pronounced in the 17-one structure. The C(8)—C(14)—C(15) angle, which is expanded to approximately 119° in most steroids, due to *C/D* ring fusion, is further opened in these structures (average angle = 129·1°). The *B* rings of all three of the Δ^{14} structures have conformations intermediate between a sofa and a half chair which are significantly different from the 7α,8β-half-chair conformation observed in most 1,3,5(10)-estratrienes. Despite this correlation between *B*-ring conformation and *D*-ring unsaturation the overall bowing of the three Δ^{14} structures varies somewhat (Fig. 3).

A uniform perspective of the immediate environments of the Δ^{14} steroids reported here and the estradiol hemihydrate which is isomorphous with (XIV) is presented in Fig. 4. Tail-to-tail hydrogen bonding generates infinite stacks of steroids in (XV) while water molecules link the head-to-tail hydrogen-bonded chains of (XIV) into infinite sheets. It is noteworthy that despite vastly different crystal packing the conformational differences in the three Δ^{14} steroids are smaller than the conformational differences between

Fig. 2. Bond distances (Å, σ range = 0·003–0·006 Å), bond angles (°, σ range = 0·1–0·4°), and endocyclic torsion angles (°, σ range = 0·3–0·6°) for (*a*) (XI), (*b*) (XIV), (*c*) (XV) and (*d*) (XVI). A torsion angle α–β–γ–δ is positive if, when viewed down the β–γ bond, the α–β bond will eclipse the γ–δ bond when rotated less than 180° in a clockwise direction.

(I*a*) and (XIV) *which have isomorphous crystal packing.*

The orientation of hydrogen bonds around O(17) appears similar in (XIV) and (XV). However, as illustrated in Fig. 2, H(O17) is antiperiplanar to H(17a) in (XV) [H(17a)—C(17)—O(17)—H(O17) = −160·2°] and antiperiplanar to C(16) in (XIV) [C(16)—C(17)—O(17)—H(O17) = −154·7°]. Consequently the donor and acceptor directions are different in the two structures. All three of the hydrogen bonds in (XIV) are shorter than the hydrogen bonds in (XV).

Discussion

Most of the conformational flexibility in the 1,3,5(10)-estratriene backbone is located in the *B*-ring region. The *B* rings of 1,3,5(10)-estratriene steroids have been observed in $7\alpha,8\beta$-half-chair conformations in which atoms C(9), C(10), C(5) and C(6) are coplanar and atoms C(7) and C(8) are equidistant from that plane on opposite sides and in ideal 8β-sofa conformations in which atoms C(9), C(10), C(5), C(6) and C(7) are

coplanar and C(8) is on the β side of that plane. Since the symmetry of these forms (rotation axis in the half chair and mirror in the sofa) is manifested in the intraring torsion angles, the torsion angles can be used to evaluate the deviation of a given conformer from the ideal form (Duax, Weeks & Rohrer, 1976).

The asymmetry parameter $\Delta C_s(5)$, which measures the deviation of the *B* ring from mirror symmetry across a plane intersecting the C(5) and C(8) atoms, is defined by the formula $\Delta C_s(5) = \{[(\varphi_{5-6} + \varphi_{6-7})^2 + (\varphi_{5-10} + \varphi_{7-8})^2 + (\varphi_{9-10} + \varphi_{8-9})^2]/3\}^{1/2}$, in which the φ's are the intraring torsion angles. The asymmetry

Fig. 3. Bowing of the molecules. Although the *B* and *C* rings of the Δ^{14}-steroids (XIV, XV and XVI) are very similar, the overall bowing differs.

(c)

(d)
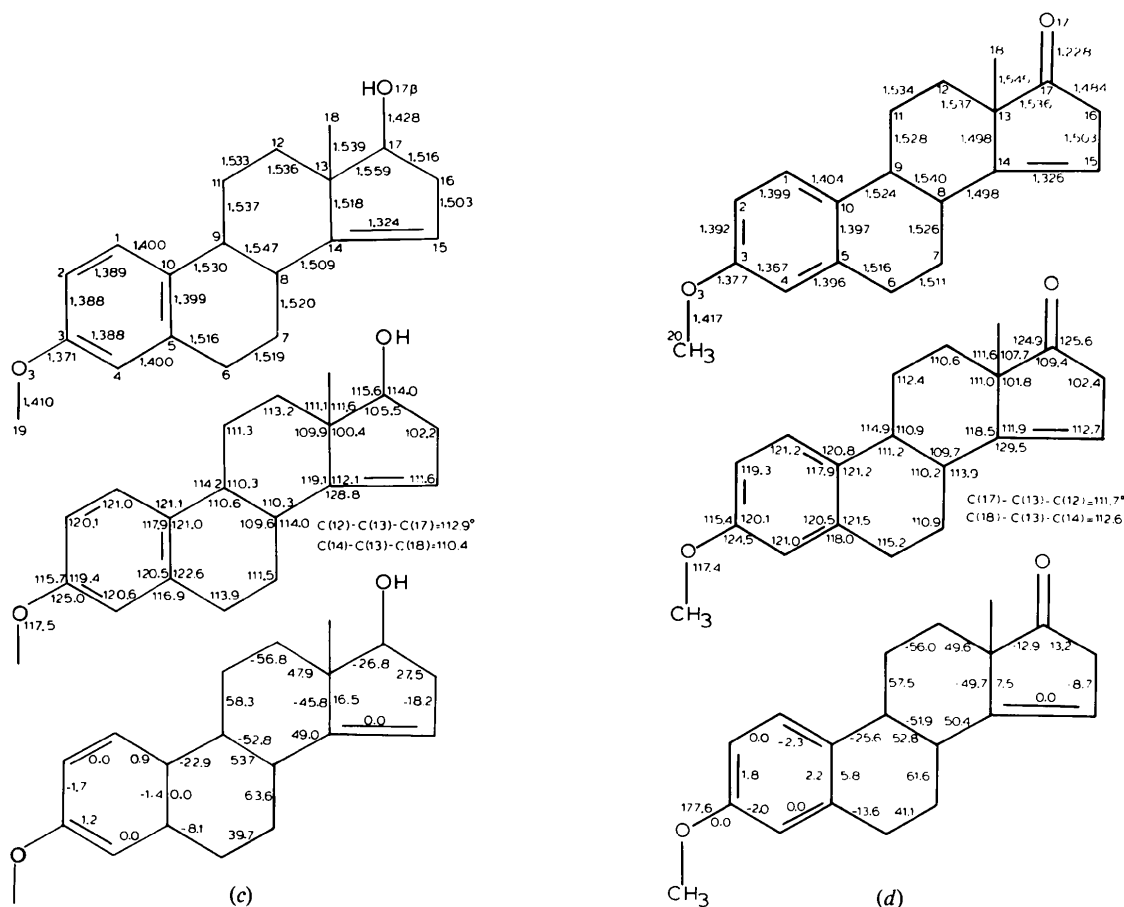
Fig. 2 (*cont.*)
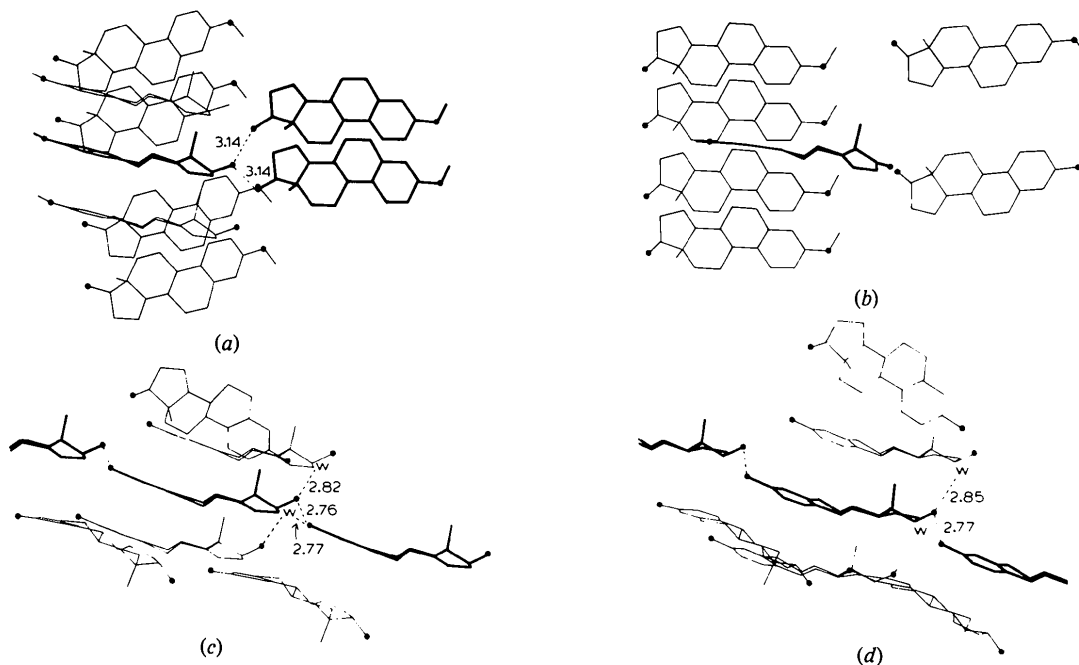
Fig. 4. The crystalline environment and hydrogen bonding of (a) (XV), (b) (XVI), (c) (XIV), and (d) (Ia). The central molecule is viewed along a vector parallel to its width, C(14)→C(12). Small differences in atomic coordinates of atoms C(12) and C(14) in the isomorphous structures (XIV) and (Ia) distort the isomorphism.

Table 6. *Asymmetry parameters for estradiol, estrone, estriol and their derivatives* (°)

Struc-ture	$\Delta C_s(5)$	$\Delta C_2(5-10)$	Struc-ture	$\Delta C_s(5)$	$\Delta C_2(5-10)$
(XIIa)	21·2	2·4	(II)	13·2	9·5
(VII)	19·2	4·5	(IVc)	11·6	11·4
(VIIIa)	20·5	4·1	(XVI)	11·3	11·8
(VIIId)	19·2	4·6	(XV)	12·2	14·4
(XIIIb)	18·2	3·5	(XIIb)	11·3	15·8
(III)	19·8	5·8	(XIV)	10·8	19·5
(X)	19·2	6·7	(IVa)	9·2	20·8
(V)	17·9	5·7	(VIIIc)	7·8	19·3
(VIIIb)	16·3	7·6	(XIIIa)	4·2	24·0
(Ib)	17·4	7·9	(IX)	3·4	22·3
(XI)	17·8	9·4	(IVb)	2·3	27·0
(Ia)	17·1	9·5	(VI)	0·5	31·8
(Ic)	14·6	7·6			

parameter $\Delta C_2(5-10)$ which is a measure of the deviation of the B ring from rotation symmetry about an axis joining the midpoints of the C(5)—C(10) and C(7)—C(8) bonds is defined by the formula $\Delta C_2(5-10)$ $= \{[(\varphi_{5-6} - \varphi_{9-10})^2 + (\varphi_{6-7} - \varphi_{8-9})^2]/2\}^{1/2}$. The deviations of the B rings of the steroids of Table 1 from the ideal forms as measured by these parameters are given in Table 6 and displayed graphically in Fig. 5.

Exocyclic nonbonded interactions appear to play a decisive role in determining overall steroid conformation and long-range conformational transmission
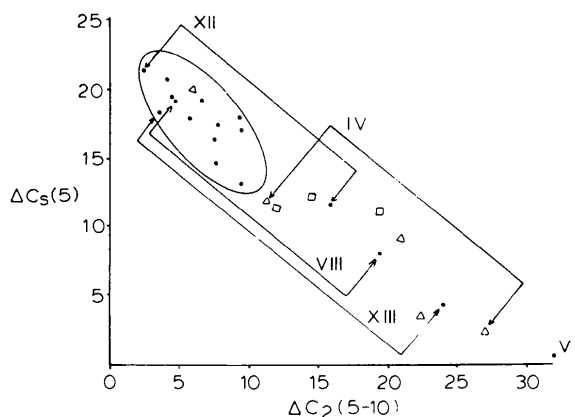
Fig. 5. Correlated variation in principal asymmetry parameters of the B rings in 1,3,5(10)-estratriene structures. The rotational asymmetry parameter $\Delta C_2(5-10)$ is plotted *versus* the mirror asymmetry parameter, $\Delta C_s(5)$. Over half of the observed structures have $7\alpha,8\beta$-half-chair conformations. Structures with Δ^{14} composition (□), with 4-bromo substitution (△), or with two molecules in the asymmetric unit tend to be outside this region. The brackets link the molecules that occur together in single crystals.

effects. The B rings of the first fourteen structures of Table 1 have $7\alpha,8\beta$-half-chair conformations that fall within the ellipse on Fig. 5. Thus this conformation appears to be most stable. In eight of the eleven structures that fall outside this range it is possible to
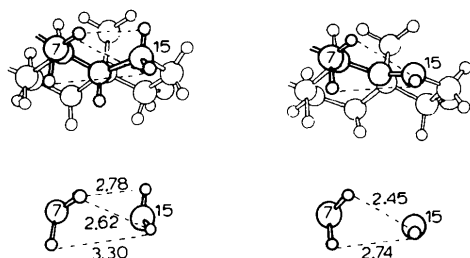
Fig. 6. Effect of introduction of a double bond at C(14)—C(15), resulting in enhanced acceptability of the 7β position and increased shielding of the 7α position from equatorial approach to the steroid.

dehydro derivatives) or substitution (4-bromoestrone) will stabilize an alternative conformation.

In addition to these general observations the data offer some insight into the stereochemistry of reaction at the C(7) position. Methyl addition to C(7) is greatly influenced by the presence of a double bond at C(14)—C(15). When this bond is saturated a mixture of 7α- and 7β-methyl substitution is obtained and in 14-ene structures only 7β-methyl derivatives are produced. Structural details show that the H atoms of a saturated C(15) atom shield the 7α position. The introduction of the double bond moves C(15) into the plane of C(7) and the lone H on C(15) now lies between the H atoms of C(7). The net result is to make the 7β position more vulnerable to approach than the 7α position (Fig. 6).

rationalize the conformational differences. The 8β-sofa conformation is generally less favorable because it requires the near eclipsing of the C(1)—C(10) and the C(9)—C(11) bonds.

In three of the four structures with a 4-bromo substituent, the 8β-sofa conformation minimizes the effect of the steric interactions with the bromo substituent. When the B ring is in an 8β-sofa conformation the 6α- and 6β-H's are nearly equidistant from the 4-bromo substituent. When the B ring is in the $7\alpha,8\beta$-half-chair conformation the 6α-H is closer to the bromine than is the 6β-H. This repulsive interaction between the 6α-H and the 4-bromo substituent induces a closing of the C(1)—C(10)—C(9)—C(11) torsion angle. In a similar fashion, C(14)—C(15) dehydrogenation shifts the B-ring conformation toward the 8β-sofa form in order to maximize the interatomic distance between H(15) and the 7β-H.

Perhaps the most interesting structures with conformations outside the ellipse are estrone, estradiol and epiestradiol, all of which are found in crystal structures having double asymmetric units. In each case the other conformer present in the crystal is in the normally observed conformation. This striking difference in conformers is characteristic of crystals having more than one molecule in the asymmetric unit. These differences in the conformations of the four structures of that type in this sample, as reflected in the asymmetry parameters, are indicated by the brackets in Fig. 5. This conformational isomerism within crystals is in marked contrast to the similarity of conformation of estradiol in urea, propanol, and hemihydrate complexes. Also noteworthy is the fact that in two other crystal forms estrone resembles the commonly observed $7\alpha,8\beta$-half-chair conformer. These results suggest that (1) in general the $7\alpha,8\beta$-half-chair conformation is favored in 1,3,5(10)-estratriene structures, (2) in some structures (estrone, estradiol, epiestradiol) a second conformer is of comparable stability and that under favorable circumstances conformational isomers will be co-crystallized, (3) in some structures unsaturation (14,15-

References

BARRANS, Y., COURSEILLE, C., BUSETTA, B. & PRECIGOUX, G. (1976). Acta Cryst. B32, 1296–1298.
BARTON, D. H. R. (1955). Experientia, Suppl. II, 121–136.
BUSETTA, B., BARRANS, Y., PRECIGOUX, G. & HOSPITAL, M. (1976). Acta Cryst. B32, 1290–1292.
BUSETTA, B., COURSEILLE, C., GEOFFRE, S. & HOSPITAL, M. (1972). Acta Cryst. B28, 1349–1351.
BUSETTA, B., COURSEILLE, C. & HOSPITAL, M. (1973). Acta Cryst. B29, 298–313.
BUSETTA, B. & HOSPITAL, M. (1972). Acta Cryst. B28, 560–567.
CODY, V., DEJARNETTE, F. E., DUAX, W. L. & NORTON, D. A. (1971). Acta Cryst. B27, 2458–2468.
COOPER, A., NORTON, D. A. & HAUPTMAN, H. (1969). Acta Cryst. B25, 814–828.
COURSEILLE, C., BUSETTA, B., PRECIGOUX, G. & HOSPITAL, M. (1973). Acta Cryst. B29, 2462–2465.
DETITTA, G. T., EDMONDS, J. W., LANGS, D. A. & HAUPTMAN, H. (1975). Acta Cryst. A31, 472–479.

DUAX, W. L. (1972). *Acta Cryst.* B28, 1864–1871.
DUAX, W. L., WEEKS, C. M. & ROHRER, D. C. (1976). *Topics in Stereochemistry*, Vol. 9, edited by E. L. ELIEL & N. ALLINGER, pp. 271–383. New York: John Wiley.
GERMAIN, G., MAIN, P. & WOOLFSON, M. M. (1971). *Acta Cryst.* A27, 368–376.
NORTON, D. A., KARTHA, G. & LU, C. T. (1963). *Acta Cryst.* 16, 89–94.

NORTON, D. A., KARTHA, G. & LU, C. T. (1964). *Acta Cryst.* 17, 77–82.
STOUT, G. H. & JENSEN, L. H. (1968). *X-ray Structure Determination.* New York: Macmillan.
STRONG, P., DUAX, W. L. & ENGEL, L. L. (1976). *Cryst. Struct. Commun.* 5, 815–818.
TSUKUDA, Y., SATO, T., SHIRO, M. & KOYAMA, H. (1968). *J. Chem. Soc. B*, pp. 1387–1393.

The Structure of the Methyl Ester of 5,5-Dimethyl-2-(2-phenoxymethyl-5-oxo-1,3-oxazolin-4-ylidene)-1,3-thiazolidine-4-carboxylic Acid

BY P. A. C. GANE AND M. O. BOLES

*School of Mathematical Sciences, Plymouth Polytechnic, Plymouth PL4 8AA, England*

Abstract

$C_{17}H_{18}N_2O_5S$ is monoclinic, space group $P2_1/c$, with $a = 10.60$ (3), $b = 15.53$ (3), $c = 12.63$ (3) Å, $\beta = 61.97$ (2)°, $Z = 4$, $V = 1835.25$ Å^3, $\mu(Cu\ K\alpha) = 1.714$ mm^{-1}; $R = 0.097$ for 1738 observed reflexions. The crystallographic results confirm the structure reported by Bachi & Vaya [*Tetrahedron Lett.* (1977), pp. 2209–2212].

Introduction

$C_{17}H_{18}N_2O_5S$ was first reported by Brandt, Bassignani & Re (1976*a,b*) to have the configuration (I), *i.e.* that of a DL-5,6-didehydropenicillin, on the basis of spectroscopic data (IR, ^{1}H and ^{13}C NMR, mass spectrometry). Bachi & Vaya (1977) suggested configuration (II) on the basis of a comparative study of UV and IR spectra.

(I)

(II)
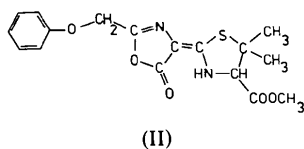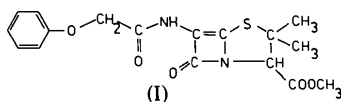
X-ray structure analysis was carried out as a preliminary to investigation of the reported weak antibacterial activity of the unsaturated dehydropenicillin. The analysis has confirmed structure (II).

Experimental

The compound was obtained from Snamprogetti Società per Azioni. Single crystals were prepared by dissolving 30 mg in 2 ml ethyl acetate. To this solution, 1 ml cyclohexane was added slowly to prevent clouding. The solution was placed in a water bath warmed to not more than 313 K and protected from light and rapid evaporation. The compound crystallized as clear needle-shaped single crystals on slow cooling of the solution.

The cell dimensions were determined from zero-level equi-inclination Weissenberg photographs, the camera radius being determined from high-angle reflexions from an annealed gold wire. Systematic absences $h0l$, $l = 2n + 1$ and $0k0$, $k = 2n + 1$ indicated space group $P2_1/c$.

Intensities were recorded by the equi-inclination method on Stoe and Nonius Weissenberg cameras with Ni-filtered Cu $K\alpha$ radiation ($\lambda = 1.5418$ Å) and the multiple-film technique. The crystals were rotated about c^* with the long edge of the crystal parallel to the rotation axis. The X-ray films showed severe reduction in intensity of reflexions at high sin θ after crystals had prolonged exposure to X-rays. Four crystals were used for collection of intensities which were measured by the Science Research Council microdensitometer at Daresbury. 1738 reflexions were of measurable intensity.

Structure determination and refinement

The major computations were performed on an ICL 1903A computer with *SHELX* (Sheldrick, 1976). The