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STEROID STRUCTURE AND FUNCTION—II. CONFORMATIONAL TRANSMISSION AND RECEPTOR BINDING OF MEDROXYPROGESTERONE ACETATE

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SUMMARY

The A-ring of medroxyprogesterone acetate (MPA) has been determined by single crystal X-ray analysis to be in the inverted $1\beta,2\alpha$ half-chair conformation. Steric interaction of the 17α-acetate substituent with the 17β side chain virtually immobilizes the latter and introduces strain into the backbone that is transmitted to the primary region of flexibility in the molecule, the unsaturated A-ring. The inversion of the A-ring conformation appears to be the result of this long range influence coupled with steric strain introduced by the 6α-methyl group. The differences in overall conformation and electronic nature of the A-rings in MPA and progesterone will have a significant influence upon susceptibility to metabolism and may well be related to the 30-fold higher affinity of MPA for the progestogen receptor in the rabbit uterus. Furthermore the structure demonstrates that ring inversion does not necessitate a distortion of the 4-ene-3-one conjugation, and caution must be exercised in interpreting A-ring conformation from the ORD spectrum which is primarily a measure of ene-one helicity.

Crystals of MPA ($C_{24}H_{34}O_4$) are monoclinic, space group $P2_1$, with cell dimensions $a = 11.0780(5)$Å, $b = 10.5010(4)$Å, $c = 9.2690(3)$Å and $\beta = 103.23(3)^\circ$. The structure was solved by direct methods and refined by full-matrix least-squares procedures to a final R of 0.052.

INTRODUCTION

The crystal structure of medroxyprogesterone acetate, MPA, was undertaken in the hope of uncovering structural differences between MPA and progesterone that might account for the 30-fold difference in the affinity of these two steroids for the progestogen receptor in rabbit uterus [1].

Analysis of conformational data on over 200 steroids [2, 3, 4] indicates that crystallographically observed conformations are largely independent of crystal packing forces and consequently provide suitable models for attempting to correlate structural features with specific functions. In steroids having the 4-ene-3-one configuration the principal conformational variations involve the A-ring. In the majority of these structures (59/73) the A-ring varies in conformation from an ideal half chair (Fig. 1a) to an ideal sofa (Fig. 1b). A significantly different A-ring conformation (Fig. 1c) has been observed in 2β-acetoxy derivatives of testosterone [5].

This unusual conformation is adopted to avoid repulsive diaxial interactions between the 2β-substituent and the 19-methyl group, and anomalies observed in the ORD, CD and NMR spectra [6–9] were resolved on the basis of the X-ray findings. In the ORD spectra of the 2β-acetoxy-4-ene-3-one steroids the two peaks at longest wavelength are inverted in sign compared with the parent compounds [6]. This sign change is primarily due to the fact that the inversion of the A-ring significantly disrupts the conjugation of the ene-one system. It was presumed that the distortion of the O(3)—C(3)—C(4)—C(5) torsion angle was a necessary consequence of A-ring inversion and that similar ORD changes could be taken as indicative of this A-ring conformation in other structures.

EXPERIMENTAL

MPA was crystallized from methanol. Crystal data: $a = 11.0780(5)$Å, $b = 10.5010(4)$Å, $c = 9.2690(3)$Å, $\beta = 103.228(3)^\circ$, $V = 1049.7$ Å^3, $M = 386.50$, $Z = 2$, $P2_1$. Cell constants were determined from θ values for 15 reflections. The intensities of 2274 reflections having $2\theta < 150^\circ$ were measured on an Enraf Nonius CAD-4 diffractometer using CuKα radiation without monochromator. The structure was solved by direct methods using MULTAN [10] and NQEST [11], and it was refined by full-matrix least-squares procedures. The positions of all hydrogen atoms were determined from a difference Fourier map and refined isotropically. All other atoms were refined anisotropically. The final conventional R indices were 0.052 for all 2274 data and 0.042 for 2164 observed reflections

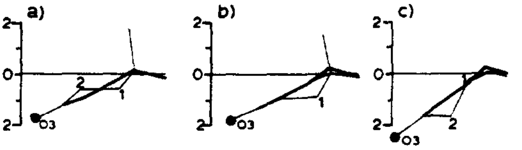

Fig. 1. $1\alpha,2\beta$ Half-chair, (b) 1α-sofa and (c) $1\beta,2\alpha$ inverted half-chair conformations of the A-ring in 4-ene-3-one steroids.

Table 1. Atomic coordinates

Atom	X/A	Y/B	Z/C	U11	U22	U33	U12	U13	U23
C(1)	−0.1085(2)	1.0397	0.7455(3)	422(10)	626(14)	460(9)	84(11)	48(8)	28(11)
C(2)	−0.1936(2)	0.9406(3)	0.7886(3)	422(11)	597(14)	605(12)	0(11)	64(9)	−29(12)
C(3)	−0.2034(2)	0.9660(3)	0.9493(3)	339(9)	552(13)	648(12)	−74(10)	93(8)	31(11)
C(4)	−0.0875(2)	1.0016(3)	1.0512(2)	375(9)	482(11)	469(9)	−19(9)	134(7)	−33(9)
C(5)	0.0174(2)	1.0263(2)	1.0076(2)	350(8)	384(9)	361(7)	6(8)	81(6)	−18(7)
C(6)	0.1417(2)	1.0336(2)	1.1164(2)	320(8)	517(11)	368(7)	−44(8)	82(6)	−18(8)
C(7)	0.2185(2)	0.9191(2)	1.0838(2)	305(8)	528(11)	339(7)	2(9)	27(6)	13(8)
C(8)	0.2325(2)	0.9189(2)	0.9238(2)	253(6)	364(8)	357(7)	−15(7)	62(5)	2(7)
C(9)	0.1044(2)	0.9226(2)	0.8127(2)	292(7)	395(9)	326(7)	−4(7)	54(6)	9(7)
C(10)	0.0223(2)	1.0359(2)	0.8444(2)	358(8)	479(10)	334(7)	73(8)	87(6)	57(8)
C(11)	0.1182(2)	0.9190(3)	0.6511(2)	420(9)	568(12)	344(8)	153(10)	50(7)	49(9)
C(12)	0.1994(2)	0.8091(3)	0.6180(2)	381(9)	538(12)	351(8)	104(9)	45(7)	−24(9)
C(13)	0.3268(2)	0.8108(2)	0.7279(2)	316(8)	340(8)	388(7)	21(7)	85(6)	14(7)
C(14)	0.3032(2)	0.8034(2)	0.8869(2)	265(7)	366(9)	379(7)	0(7)	58(6)	21(7)
C(15)	0.4319(2)	0.7745(3)	0.9825(2)	299(8)	506(11)	456(9)	66(8)	4(8)	−29(9)
C(16)	0.4908(2)	0.6831(3)	0.8886(3)	358(9)	515(11)	478(10)	113(9)	1(8)	−17(9)
C(17)	0.4114(2)	0.6916(2)	0.7284(2)	298(7)	374(8)	427(8)	7(7)	56(6)	−4(8)
C(18)	0.4014(2)	0.9295(3)	0.7042(3)	504(10)	417(11)	599(10)	−33(9)	243(7)	22(10)
C(19)	0.0790(3)	1.1664(3)	0.8161(3)	712(13)	433(11)	567(10)	106(11)	248(9)	107(10)
C(20)	0.4884(2)	0.7000(3)	0.6083(3)	363(8)	408(10)	578(10)	5(8)	168(7)	−11(9)
C(21)	0.4220(2)	0.6799(3)	0.4493(3)	536(11)	506(13)	525(9)	11(10)	223(8)	−30(10)
C(22)	0.1363(2)	1.0366(3)	1.2799(2)	503(11)	775(17)	343(8)	−34(12)	72(8)	−80(11)
C(23)	0.3781(2)	0.4698(2)	0.6772(2)	496(10)	376(10)	445(9)	15(9)	138(7)	21(8)
C(24)	0.2841(3)	0.3652(3)	0.6515(3)	685(14)	435(11)	687(13)	−115(11)	270(10)	−36(11)
O(3)	−0.2972(2)	0.9447(4)	0.9939(3)	411(8)	1236(21)	857(11)	−258(11)	236(7)	−138(16)
O(17A)	0.3270(1)	0.5830(2)	0.6942(2)	360(6)	347(7)	507(7)	−27(6)	113(5)	−4(6)
O(20)	0.5958(2)	0.7317(3)	0.6400(2)	385(7)	704(12)	765(10)	−88(8)	199(6)	−74(10)
O(23)	0.4861(2)	0.4556(2)	0.6781(2)	450(8)	469(8)	774(10)	107(7)	107(7)	−17(9)

Atom	X/A	Y/B	Z/C	Biso	Atom	X/A	Y/B	Z/C	Biso
H(1A)	−0.142(2)	1.131(3)	0.741(3)	2.5(5)	H(16A)	0.495(3)	0.600(4)	0.923(4)	4.0(6)
H(1B)	−0.102(3)	1.029(4)	0.642(4)	4.8(7)	H(16B)	0.586(3)	0.693(5)	0.893(4)	5.0(8)
H(2A)	−0.135(4)	0.853(7)	0.793(6)	8.2(12)	H(18A)	0.352(4)	1.023(5)	0.704(5)	6.1(9)
H(2B)	−0.289(3)	0.942(4)	0.748(3)	4.4(7)	H(18B)	0.472(3)	0.947(5)	0.768(4)	5.9(9)
H(4)	−0.088(3)	1.005(4)	1.155(4)	4.8(7)	H(18C)	0.413(4)	0.928(8)	0.594(6)	9.2(12)
H(6)	0.189(2)	1.107(3)	1.110(3)	2.6(5)	H(19A)	0.034(4)	1.234(6)	0.844(5)	6.4(11)
H(7A)	0.184(2)	0.840(3)	1.104(3)	2.0(4)	H(19B)	0.173(3)	1.166(3)	0.856(3)	3.8(6)
H(7B)	0.301(2)	0.919(4)	1.143(3)	3.9(6)	H(19C)	0.062(3)	1.168(4)	0.717(4)	4.5(7)
H(8)	0.277(2)	1.002(3)	0.919(3)	3.2(5)	H(21A)	0.413(5)	0.784(7)	0.396(6)	9.4(14)
H(9)	0.063(2)	0.843(4)	0.834(3)	3.5(6)	H(21B)	0.448(5)	0.619(8)	0.375(6)	7.5(15)
H(11A)	0.160(3)	1.010(4)	0.643(4)	4.9(8)	H(21C)	0.328(4)	0.667(5)	0.416(5)	7.2(12)
H(11B)	0.038(2)	0.912(3)	0.580(3)	2.9(5)	H(22A)	0.104(3)	0.951(4)	1.307(3)	3.9(6)
H(12A)	0.201(2)	0.803(3)	0.520(3)	2.8(5)	H(22B)	0.214(3)	1.048(4)	1.335(4)	5.3(8)
H(12B)	0.157(3)	0.715(4)	0.648(4)	4.6(7)	H(22C)	0.074(4)	1.106(6)	1.314(6)	8.2(13)
H(14)	0.249(3)	0.733(4)	0.884(3)	4.0(6)	H(24A)	0.210(4)	0.387(6)	0.652(5)	6.9(10)
H(15A)	0.433(2)	0.745(3)	1.092(3)	2.6(5)	H(24B)	0.285(3)	0.324(4)	0.550(4)	5.0(7)
H(15B)	0.480(3)	0.843(4)	1.011(4)	4.0(6)	H(24C)	0.308(5)	0.307(8)	0.708(8)	9.2(17)

($|F_0| > 2\sigma$). The final atomic coordinates for the non-hydrogen atoms are listed in Table 1.*

RESULTS

The A-ring of MPA (Fig. 2) was found to be in the inverted 1β,2α half-chair conformation. The B- and C-rings have normal chair conformations and the D-ring has a symmetric 13β,14α half-chair conformation. The bond lengths, angles and torsion angles are given in Fig. 3, the ring asymmetry parameters [3] are listed in Table 2.

DISCUSSION

The inversion of the A-ring is remarkable because (1) it can be traced to long range transmission effects [12] involving the 17α acetate substituent, (2) it is achieved without distorting the planarity of the ene-one system, and (3) it suggests that the A-rings of 4-ene-3-one structures may be in this 1β,2α-half chair conformation when bound to progesterone receptors.

Long range transmission

A previous study of 17α-acetoxy progesterone (17α AP) [13] showed that the 17α substituent restricted

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*Material supplementary to this article (observed and calculated structure amplitudes) is available from the authors upon request.

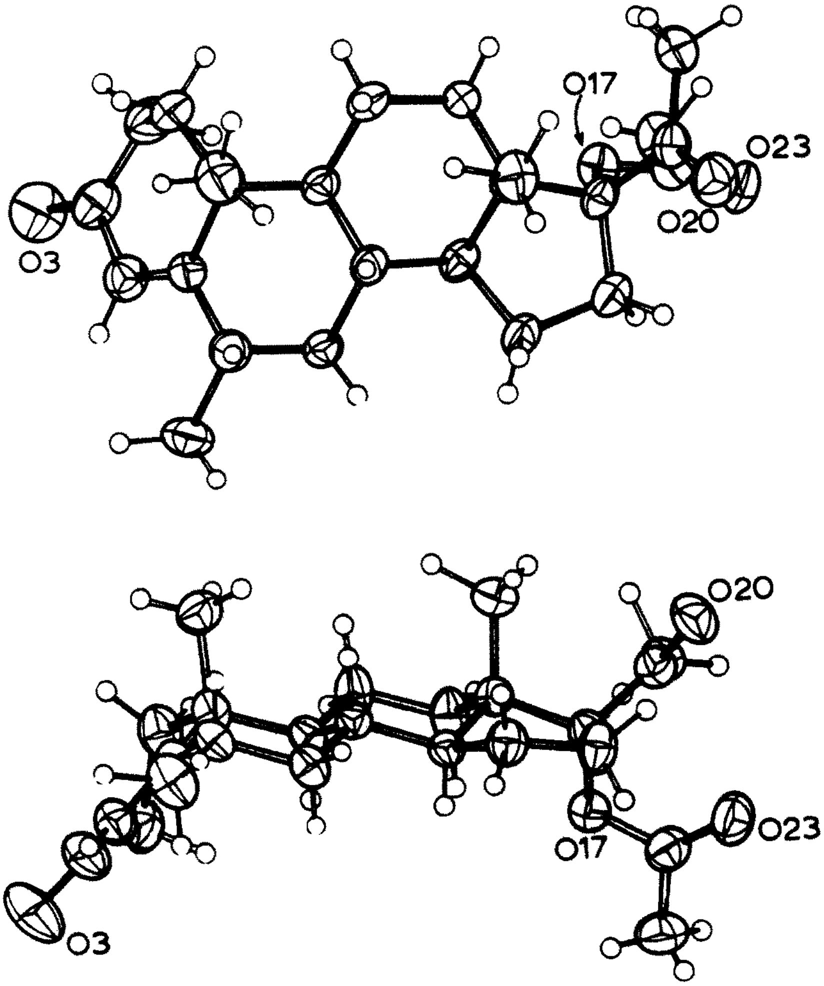

Fig. 2. Two views of the molecular conformation of MPA prepared from the observed atomic coordinates illustrating the inverted A-ring conformation with 50% probability thermal vibrational ellipsoids.

the flexibility of the progesterone side chain, introduced strain into the steroid nucleus that was reflected in bond length changes in the C and D rings, and caused the A-ring to adopt a highly symmetric sofa conformation (Fig. 1b). The conformations of the 17α-acetate group, the progesterone side chain, and the D-ring in MPA are nearly identical to those observed in 17α AP and two other structures of similar composition [14, 15] despite appreciable variation in their crystal packing patterns.

In MPA, nine bond lengths differ by more than three standard deviations (0.009Å) from the average bond lengths for 27 steroids having a 4-ene-3-one configuration recorded in the *Atlas of Steroid Structure* [3]. The most remarkable deviation is the 0.045Å lengthening of the C(2)—C(3) bond. Because of sp^2 hybridization at C(3) and the presence of the conjugated double bonds, the average C(2)—C(3) bond length is 1.496(3)Å in structures having normal A-ring conformations. The C(2)—C(3) bond length in MPA is 1.541Å. This pattern of bond length alteration suggests a path of transmission of the 17α acetate substitution effect through the fused ring system to the unsaturated A-ring, the region of maximum flexibility in 4-ene-3-one structures.

Analysis of 33 4-ene-3-one steroids having no additional unsaturation in the A-, B- and C-rings showed that the A-rings of these structures had conformations that fluctuated about the midpoint between the ideal half-chair and sofa forms and that, with one exception, they did not adopt ideal forms. The sole exception is the structure of 17α-AP, which has a nearly perfect sofa A-ring conformation [13]. Apparently strain introduced by the 17α-acetate substituent is transmitted to the A-ring and relieved by this ring adjusting to a slightly less favored conformation. In MPA, the additional strain of the 6α-methyl group in a position *cis* to the C(4)—C(5) bond coupled with the 17α-acetoxy substitution causes the A-ring to adopt an inverted conformation. In this

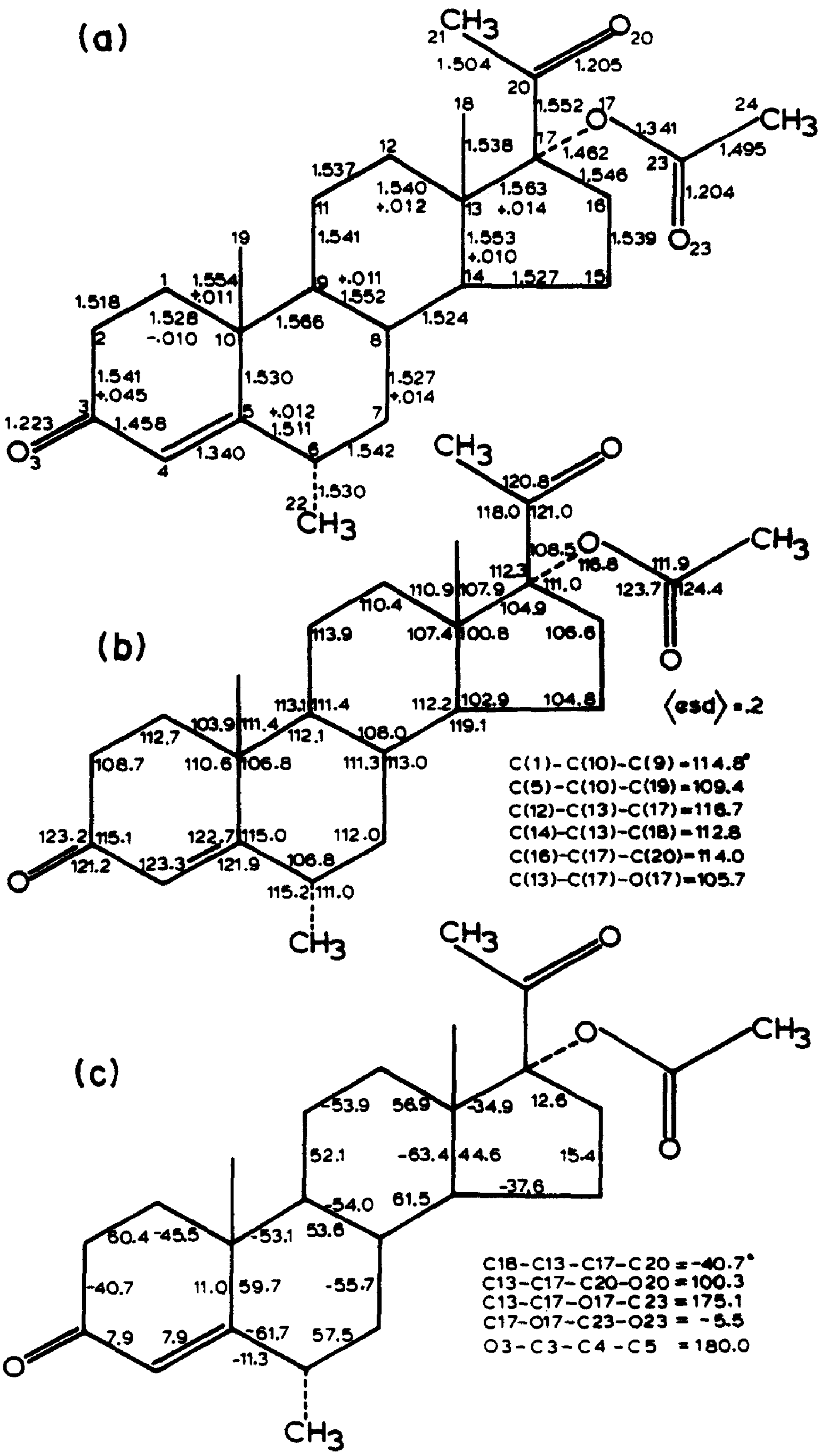

Fig. 3. (a) Observed bond lengths in MPA. The significant deviations of nine bond lengths from average values for 27 steroids having 4-ene-3-one configurations are noted. (b) Observed bond angles in MPA. (c) Observed torsion angles in MPA.

Table 2. Ring conformations

Ring	Description	Relevant Asymmetry Parameters
A	Inverted 1β,2α-half chair	$\Delta C_2(1\text{–}2) = 4.0$, $\Delta C_s(1) = 21.2$
B	Chair	$\Delta C_2(5\text{–}6) = 2.4$, $\Delta C_s(7) = 6.1$
C	Chair	$\Delta C_s(11) = 2.3$, $\Delta C_2(8\text{–}9) = 9.5$
D	13β,14α-Half chair	$\Delta C_2(16) = 2.8$

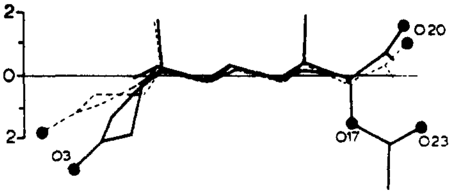

Fig. 4. Projections perpendicular to the least-squares planes through steroids atoms C(5) to C(17) in progesterone (---) and MPA (——), overlapped to illustrate the dramatic conformational difference.

conformation the C(6)—C(6α) bond no longer eclipses the C(4)—C(5) double bond and the C(4)—C(5)—C(6α) torsion angle is −11.3°.

In addition to the study of 17α-AP, the crystal structure of 6α-methyl-17α-hydroxy progesterone has been determined in this laboratory [16], and its A-ring is in an unstrained intermediate sofa-half-chair (1α,2β) conformation. Repeated efforts to crystallize polymorphs of MPA from other solvent systems have produced only crystals similar to the one reported here indicating that the inverted A-ring is a minimum energy conformation of MPA. These facts support the contention that the inversion of the A-ring in MPA is a result of strain from the 17α-acetate substituent being transmitted to the flexible A-ring.

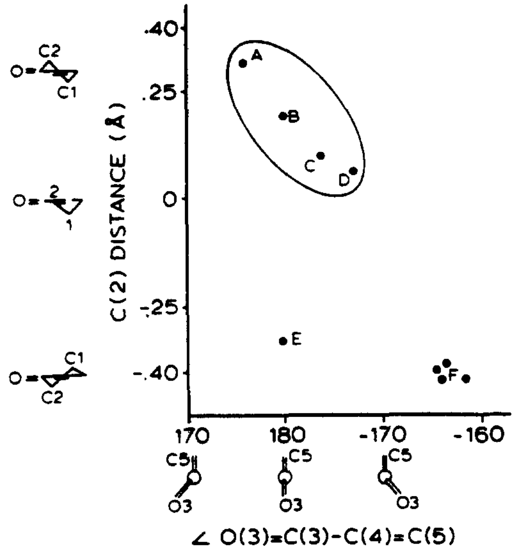

Fig. 5. A-ring conformation versus 4-ene-3-one conjugation. When the distance of C(2) from the plane of C(3), C(4), C(5), and C(10) is plotted *versus* the O(3)—C(3)—C(4)—C(5) torsion angle, almost all 4-ene-3-one structures fall within the ellipse at the top of the diagram. (1) the most symmetric ring forms have the most distorted conjugation. (2) The A-ring of progesterone (A,B,C) is observed in conformations that span the normal range. (3) The 4-ene-3-one group of 17α-acetoxy progesterone (D) has a significant loss of conjugation and its A-ring is in a perfect sofa conformation. (4) The A-ring of MPA (E) is inverted and 4-ene-3-one conjugation is restored. (5) The inverted A-ring of 2β-acetoxy derivatives of testosterone (F) have extensive loss of conjugation causing the sign change in the c.d. spectra of their $n \rightarrow \pi^*$ transition.

A-ring conformation and ene-one conjugation

When an inverted A-ring was observed for the first time in two 2β-acetoxy derivatives of testosterone, it was noted that a significant loss in conjugation accompanied the ring inversion [4]. The values of the O(3)—C(3)—C(4)—C(5) torsion angles in these two structures were observed to be −161° and −163°. This distortion of the conjugation, or abnormally negative helicity, about the C(3)—C(4) bond, gave rise to a sign change in the two highest wavelength peaks in the CD spectra, wavelengths generally attributed to the $n \rightarrow \pi^*$ transition [17]. It was presumed that the loss of conjugation was a necessary result of ring inversion. In MPA, the conjugation (or helicity) of the ene-one system is unperturbed despite the inversion of the A-ring. For this reason it is not surprising to find that the CD spectra of MPA are similar to that of progesterone [18] despite the dramatic difference in A-ring conformation (Fig. 4).

The correlation between A-ring conformation and ene-one conjugation is displayed graphically in Fig. 5. The relative conformation of the A-ring is moni-

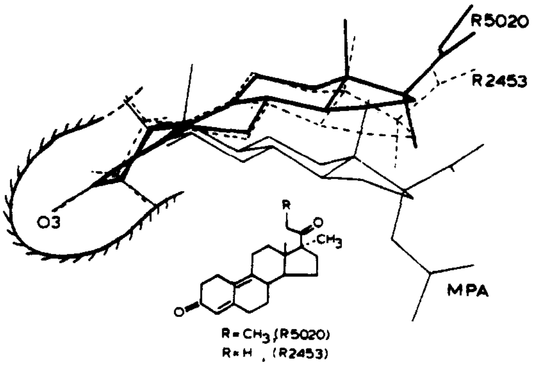

Fig. 6. The superposition of the nearly identical A-rings of the high affinity binders MPA, R2453 and R5020 suggests a receptor site for progestins that provides intimate contact over the β face of atoms C(2) through C(6) and the α face of the conjugated system and far less specific binding on the remainder of the steroid.

tored by the distance of the C(2) atom from the plane of atoms C3, C4, C5, C10. If the β face is considered the positive side of the plane, the distance from C(2) to the plane will be positive for 1β,2α half chair conformers, near zero for 1β sofa conformers and negative for 1α,2β half chair conformers.

Figure 5 illustrates (1) that symmetric forms of the ring are generally achieved at the expense of the conjugation of the ene-one system and visa versa, (2) that the A-rings of progesterone molecules [19, 20] have been observed at each extreme of the normal range, (3) that the A-ring of 17α AP was observed in a symmetric form with attendant loss of conjugation, (4) that inversion of the A-ring in MPA allows the conjugation of the ene-one system to be restored, and (5) that despite the similarity of the A-ring conformation between MPA and the 2β-acetoxy derivative of testosterone, the loss of conjugation of the latter is not observed in the MPA structure.

Because the ene-one conjugation and the O(3)—C(3) bond length in MPA are not unlike those observed in testosterone, the solution spectra sensitive to these parameters can be expected to be normal. Consequently it appears likely that the marked difference between the overall structures of progesterone and MPA (Fig. 4) would have escaped notice in solution.

Progesterone receptor binding

A dramatic dependence of A-ring conformation on 17α-acetate substitution as suggested by this investigation has significant implications concerning biological activity. Acetate derivatives are often administered in hormone therapy because they are resistant to metabolic breakdown [1]. While the 6α-methyl and the 17α-acetoxy groups may play a significant role in directly influencing transport properties, binding affinities, and metabolism, it is nonetheless true that if the inverted A-ring conformation seen in the solid state persists *in vivo*, the overall conformation and electronic properties of MPA will be so different from those of progesterone (Fig. 4) that it may not compete effectively for active sites on many metabolizing enzymes. Furthermore, the fact that the affinity of MPA for the progestogen receptor in rabbit uterus is 30 times greater than that of progesterone [1] suggests that the stereochemistry and electronic character of the inverted A-ring conformation are at least partially responsible for this high affinity. Additional support for this view is provided by the fact that many 19-nor steroids, including R5020, show dramatic enhancement of affinity for receptors in the human uterus [21, 22], and the A-rings of 19-nortestosterone [23] and R5020 [24] have also been observed in the unusual inverted 1β,2α half-chair conformation. The superposition of the A-rings of the high affinity binders MPA, R5020, and R2453 (Fig. 6) suggests a preference of the progestogen receptor for the inverted A-ring, and far less structural complementarity between protein and steroid over the rest of the molecule.

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