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INTERACTIONS OF HORMONAL STEROIDS: PROGESTOGENS*

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SUMMARY

An analysis of crystallographic data about progestogens derived from progesterone and testosterone has been carried out. Four features liable to be directly linked to the binding mechanisms of progestogen on their receptors can be pointed out: the orientation of 17βOH group and as a consequence its H-bond geometry, the directional interactions of 17 ethynyl groups, the H-bond geometry on 3-keton group and the mobility of the general molecular conformation.

INTRODUCTION

The binding of progestogens to specific proteins [1–5] is a prerequisite for hormonal activity. This binding is generally non-covalent and involves both van der Waals forces and hydrogen bonds. The van der Waals forces are numerous but weak. The hydrogen bond strengths are from 3 to 5 kcal per mole [6] and these bonds have specific geometric characteristics. Since the energy of binding of progesterone to its receptor is approx. 12–15 kcal [5,7], two hydrogen bonds would represent half of this energy.

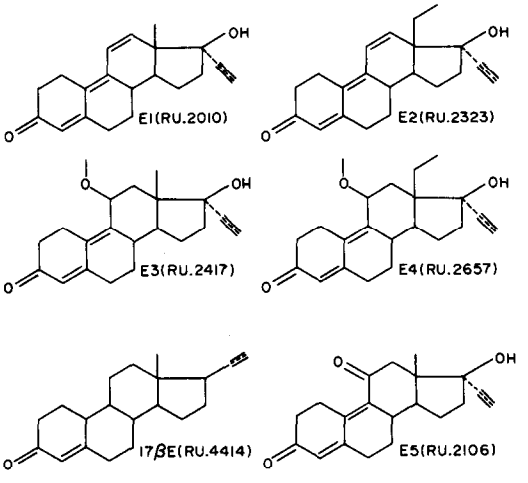
Under these conditions every structural modification (chemical or conformational) can affect the formation of a protein–progestogen complex and consequently disturbs the biological response. So we note that molecules chemically different from progesterone 17α ethynyl-19-nor testosterone and 17β-ethynyl-19-nor-4-androsten-3-one [17βE] [8] may have similar behaviour. Moreover very similar compounds (Scheme 1) can be active [E1, E2, E3] or completely inactive [E4] [9]. It is interesting to underline some structural parameters which may be connected with the affinity or the activity of these compounds.

EXPERIMENTAL

A Fortran program was developed to carry out this work. To make the comparison of molecular conformation possible, a rectangular coordinates system related to the molecule and presenting a high stability with regard to the various progestogen steroids was chosen. Here is the system: origin at the centre of gravity of the D ring; x axis parallel to the projection of (C13, middle of C15-C16) on the mean plane of the D ring and positively directed towards C15-C16; *y* axis perpendicular to *x* in the above mean plane and positively directed towards C14-C17; *z* axis perpendicular to *xoy* plane in order to get a right-handed coordinates system.

The constitutive atoms of the D ring are always in the same electronic state (particularly for progestogens). They are concerned by strong hindrances from the C ring and the 18 methyl group. These characteristics give a great stability to the D ring conformation (with regard to the purpose of section C) as shown in Table 1.

The mean coordinates of D ring atoms are recorded in the reference system previously described (this system is noted D). Each coordinate is given in Å together with its standard deviation. These data are calculated from 20 progesterone derivatives (upper figure) and from 25 testosterone derivatives (lower figure). These molecules are referenced in Figs. 7(a), 7(b) and 8.



Scheme 1.

* Part of this paper was presented at the annual meeting of the French Crystallographic Association at Liege (Belgium), 26–28th of May 1975, and at the Tenth International Congress of Crystallography at Amsterdam, 12th of August 1975.

Table 1.

	$\bar{x}_D$	σ^*	$\bar{y}_D$	σ	$\bar{z}_D$	σ
C13	−1.266	0.011	−0.016	0.004	0.287	0.012
	−1.251	0.008	−0.012	0.005	0.299	0.013
C14	−0.397	0.009	−1.160	0.009	−0.277	0.016
	−0.402	0.012	−1.162	0.011	−0.267	0.017
C15	1.032	0.014	−0.786	0.005	0.141	0.021
	1.034	0.012	0.783	0.007	0.120	0.018
C16	1.049	0.020	0.754	0.007	0.033	0.025
	1.044	0.011	0.760	0.010	0.057	0.018
C17	−0.417	0.011	1.209	0.013	−0.184	0.017
	−0.419	0.013	1.198	0.011	−0.208	0.017

* Standard deviation

The choice of another reference system (e.g. one derived from C5 to C17 mean plane) may be more difficult to use: several progestogens possess unsaturated B and C rings. The choice of the D ring is completely independent of any speculation concerning its behaviour during binding to receptors. Evidently the following results can be obtained with other reference systems.

Moreover several energy calculations have been done by using CNDO/2 program (a classical program for computing molecular energy in quantum mechanics). The aim of these calculations is to measure the variations in molecular energy caused by the rotation of a substituent, for example OH of 17βOH around C17-O17. Calculations have been limited to the molecular part most directly involved. This restriction can only have a very small effect on the results obtained. The atomic positions experimentally observed in the crystal structures have been introduced. The variations in shape caused by the rotation of the studied substituent have not been accounted for. Although this approximation artificially increases the energy differences, we feel the variations are foreseeable for the most important.

The energy variations have also been measured under the same conditions for the 'artificial' molecules defined as follows: e.g. the 17α ethynyl experimental group was replaced by an artificial H-atom (fixed at 1.05 Å from C17 along the C17-C17α bond). Under these conditions a disturbance in energy variations was introduced. With regard to the variations which will be obtained for a natural 17αH molecule, this disturbance appears to be slight. It is useful to note that CNDO/2 calculations give good values for energy variations in atomic systems without delocalized electrons, like the system studied here. A D ring connected with a 17α ethynyl group cannot be considered as a delocalized system. Electronic delocalization of the triple bond is small and limited to the nearest C–C bond. In every case absolute levels of energy cannot be obtained.

The calculations with program CNDO have been made on molecules considered as isolated. The areas calculated as having the higher stability are always in accordance with experimental positions. On the other hand the H-bonds are also in their best geometry for these positions (OH...O angle maxima) Such a situation is general; however, it has been noted for a steroid possessing a 11βOH group [95] an equilibrium state between internal orientation and the best geometry of an intermolecular H-bond.

Remarks about the H atoms

X-ray diffraction reveals the gravity centres of the electronic distributions and not the position of the nuclei themselves. In the case of the H-atom there is a systematic error tending to shorten the distance between the H atom and the atom to which it is bound. There is also quite a big random error due to the weak scattering power of H atoms. As these facts may modify the CNDO/2 energy two calculations have been undertaken: one requiring experimental H positions and the other with theorical H positions (distances C-H and O-H are equal to those obtained by neutronic diffraction). The differences in energy may be about 0.5–1.0 kcal but do not greatly modify relatives values of results (cf. Fig. 3, difference curves E1B, E1B').

In this paper the essential results of CNDO calculation are related to the *differences* between the energy variation calculated with the experimental molecule and its 'artificial' correspondent. Therefore most of the above approximations do not play an important part in such results.

All calculations have been executed on the IBM 370–168 computer of the CIRCE at Orsay.

Experimental data existing before this work

The following results have been used:

1. The results of our experiments especially the crystal structures of [E1–E5] [10–14] and partly those of 6 other progestogen structures not yet published [15–20]. The study of these crystal structures was suggested to us by the Roussel-UCLAF company who gave us the corresponding samples. Roussel-UCLAF references are indicated above, formula E1–E5, (Scheme 1) and in the molecular references given at the end of this paper.

2. The results of experiments about the progestogen structures and their near related compounds, particularly [21–23] for progesterone, [24] for d-norgestrel, [25] for (17βE), and [26, 27] for RU2453 and

RU5020. The other studies are referenced from [28] to [42].

3. For comparison, results of other steroids (steroids possessing a 17βOH function and/or an O3 H-bond system), androgens and related compounds are referenced from [43] to [64], estrogens and related compounds are referenced from [65] to [75], corticosteroids are referenced from [76] to [90] and various steroids from [91] to [95].

In all figures the following symbols have been used: ● our studies of progestogens, ○ other studies of progestogens and related compounds, △ androgens and related compounds, □ estrogens and related compounds, ⊙ corticosteroids, ▽ various steroids.

RESULTS

Orientation of 17βOH group

As the hydrogen atom of the OH function imposes the action directions (H-bonds donor or acceptor) various experimental orientations have been collected in different molecules (progestogens, androgens, estrogens and their related compounds and various other steroids). This shows, not surprisingly, three preferential directions relatively close to the staggered positions. We note them OH1, OH2, OH3 (Fig. 1). The OH1 direction is by far the most common. This arrangement remains valid for each of the biochemical categories studied. In addition, whatever the category may be, a correlation between the valency angles at C17 and the 17βOH orientations is noticeable.

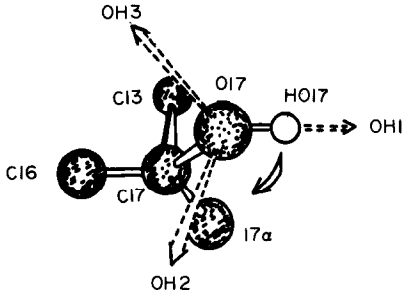


Fig. 1. Schematic representation of the three preferential orientations of the 17βOH group.

To our knowledge 49 X-ray studies (totaling 60 crystallographically independent molecules) have been made for steroids possessing a 17βOH group. Five of them are published as abstracts without coordinates and cannot be used at this time. For the others the orientation of the 17βOH group can be obtained directly from the atomic coordinates of HO17 (when they are published) or it can be estimated with the H-bonds geometry. The hydrogen position whose angle O17-HO17...X is maxima has been adopted as theoretical position (HO17 is kept at 0.99 Å from O17 with an angle C17-O17-HO17 of 113°, (the mean experimental value). The H-bonds geometry also allows a checking of the published coordinates of HO17 reducing the incidence of errors. From the 54 molecules which can be taken into account the following repartition can be observed. 34 molecules in OH1 orientation, 8 in OH2 and 8 in OH3. One molecule cannot be classified in one of these orientations; it is "B" estriol molecule [74B], for which C16-C17-O17-HO17(exp) = 224°. Undetermined orientations occur with 3 molecules: [63] (OH3 or OH1), [70] (OH3 or OH1), [72A] (OH1, OH2, or OH3).

Several molecules have been eliminated from quantitative 17βOH data because they show large discrepancies for C17-O17 bond length with regard to the mean experimental value obtained from 49 molecules (1.429 Å, σ = 0.011 Å) ([50B]: 1.394 Å; [55]: 1.504 Å; [65]: 1.492 Å; [72A]: 1.475 Å). Molecule [44] has also been eliminated since its C16-C17 bond length possesses an abnormal value: 1.462 Å. C13-C17-O17 and C16-C17-O17 angles have not been taken into account in the case of molecule [47] because the Hg-O17 bond may introduce large variations to these sensitive parameters. As the above perturbations have small incidence on the gross geometry of the H-bond system, seen from keton-3, molecules eliminated in this section have been reintroduced in the keton-3 section. The remaining molecules can be classified as shown in Table 2.

From the magnitudes of the C16-C17-O17 and C13-C17-O17 angles, the position of the 17βOH hydrogen can be deduced with relative certainty in

Table 2.

	OH1		OH2		OH3	
HO17 orientation obtained from experimental position	[10A, 11A, 11B, 12A, 12B, 15, 18A, 18B, 20, 24, 42, 43A, 46, 51, 52, 53, 54B, 56, 57, 58, 66, 67, 71, 72B, 74A, 75]		[13, 14, 19, 59 73, 91, 93]		[10B, 17, 28A, 28B, 43B, 54A, 64]	
HO17 orientation estimated from H-bonds geometry	[45, 49, 50A, 68]		[69]		[47]	
total	30 molecules		8 molecules		8 molecules	
	< >	σ	< >	σ	< >	σ
C13-C17-O17	115.4°	1.1°	111.5°	1.5°	115.2°	0.9°
C16-C17-O17	109.5°	1.1°	113.7°	1.5°	114.0°	0.7°

numerous cases. Fig. 2 illustrates the correlation between these angle values. Concerning the 16 molecules possessing a 17α ethynyl group, the mean valency angle CE1-C17-O17 (cf. Fig. 5 for CE1 notation) is 109.1° with $\sigma = 0.8°$ when 17βOH is in the OH1 or OH2 orientation (14 cases) and 105.1° with $\sigma = 0.9°$ when it is in the OH3 orientation (2 cases). These angular differences can be explained perfectly in the three cases by the distribution of the strongest steric repulsions.

Energy calculations done on isolated molecules with program CNDO/2 show a rotation barrier for 17βOH of about 1–4 kcal. One can see (Fig. 3) that the presence of an ethynyl or a methyl group at 17α makes the access to OH3 orientation easier (17βOH rotation barrier lowered by 1 or 2 kcal). A further study of CNDO/2 calculations shows up the main factor which is responsible for the above phenomenon. When OH3 orientation is reached, only six individual contributions to the molecular energy are obviously affected by the replacement of a 17α Hydrogen by 17α Carbon (e.g. a CH_3 group for the follow-

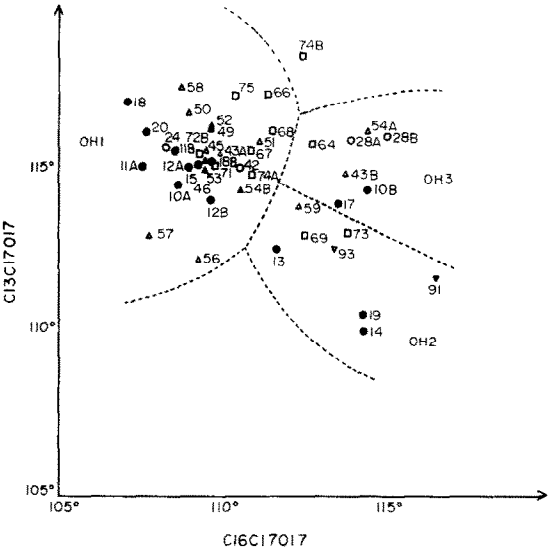


Fig. 2. Correlation between valency angles C16-C17-O17 and C13-C17-O17 relative to the three main orientations of HO17.

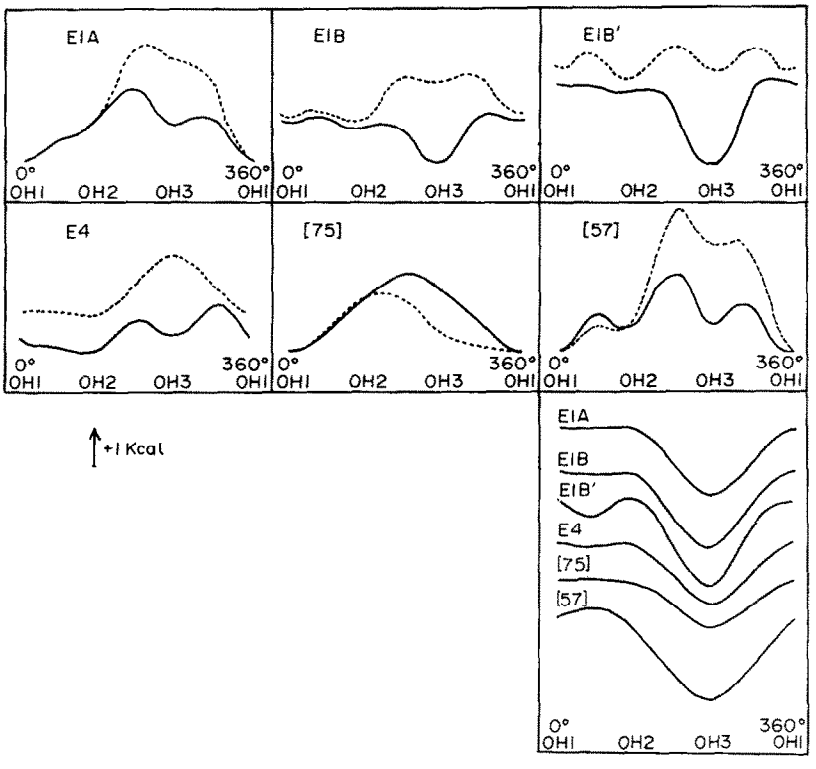


Fig. 3. Barriers of rotation for 17βOH group calculated with CNDO/2 program for real (solid line) and artificial (broken line) molecules as explained in experimental section (six upper cases). Differences between these barriers are reported in the lower right case for the six groups of calculations. They show the energy lowering effect of the replacement of a H17α atom by a C17α one. All curves are at relative and arbitrary absolute level of energy. The scale of variation for +1kcal is indicated by the arrow on the left. E1A*: E1A molecule is experimentally in OH1 orientation, −17αC ≡ CH,... 17αH. E1B: molecule experimentally in OH3 orientation, −17αC ≡ CH,... 17αH (experimental H-positions). E1B′: same calculations as E1B but for theoretical C–H and O–H lengths (cf. experimental section). E4: molecule experimentally in OH2 orientation, −17αC ≡ CH,... 17αH. [75]: calculation for steroid referenced [75], in OH1 orientation but note for this case the reverse situation, −17 H,... 17αC ≡ CH.

[57]: molecule in OH1 orientation but possessing a 17αCH_3 group, −17αCH_3,... 17αH.

* Two independent molecules present in the same crystal structure are noted A and B.

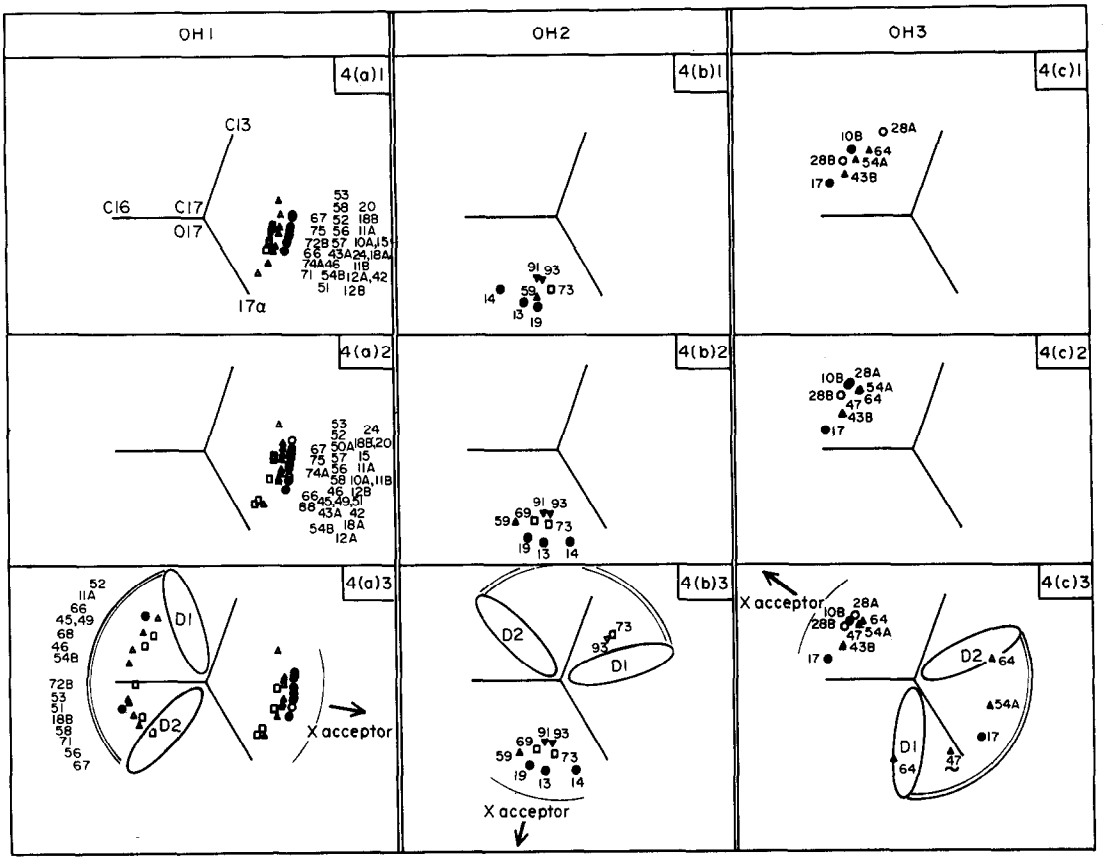


Fig. 4. 4(a)1, 4(b)1, 4(c)1: HO17 experimental orientations. 4(a)2, 4(b)2, 4(c)2; HO17 theoretical orientations. 4(a)3, 4(b)3, 4(c)3: O17 → X and X → O17 H-bond orientations. The normal area where O17 may be acceptor can be defined as being the zone which lies between D_1 and D_2 (D_1 and D_2 are the schematic representations of the lone pairs of O17). Experimental data are in agreement with this hypothesis. 4(c)3, ref [47]: HG—O17 bond. (To keep Fig. 4 clear, different categories of steroids have been recorded on concentric circles, the values of their radii are meaningless.)

ing results). E(HO17-C17)* E(C17-C17)† and E(C17-17α) are raised, on the contrary E(O17-17α), E(17α-17α) and E(O17-C17) are lowered. It is by far the latest contribution which strongly disturbs the rotation barrier of 17βOH by a lowering of about 2 kcal when a 17αC is present. This result is probably not specific for 17βOH and must be of general validity for OH groups in other molecules.

It must be emphasized that the stabilization of OH3 orientation by a 17αC substituent in the case of an isolated and rigid molecule, is not supported by crystallographic results. OH1, OH2 and OH3 orientations are distributed with approximately the same proportions for 17αH or 17αC molecules. Since many crystalline and molecular parameters are evidently not taken into account, a definite conclusion cannot be proposed. A list of the crystallographic 17βOH H-bond orientations has been established. This group is involved to a maximum in three H-bonds. When 17βOH is donor in direction OH1 and is also acceptor, it is acceptor in directions lying between D1 and D2. D1 and D2 representing the lone pairs of O17 (Fig. 4(a)3). The same behaviour is likely for OH2 and OH3 orientations (Figs. 4(b)3, 4(c)3).

From the figures given in Table 3 two main results which are of great importance for the possibilities of interaction of 17βOH can be deduced:

1. The magnitudes of most parameters are comparable to those normally observed for a tetrahedral oxygen.

2. OH1, OH2 and OH3 are not distributed with a ternary symmetry; the absolute angle differences between these directions, defined for each of them as the mean dihedral angle C16-C17-O17...X (acceptor), are the following:

$$\text{OH1} \xrightarrow[93^\circ]{} \text{OH2} \xrightarrow[111^\circ]{} \text{OH3} \xrightarrow[156^\circ]{} \text{OH1}.$$

C18 partly explains this dissymetry. The same data for C16-C17-O17-HO17 are

$$\text{OH1} \xrightarrow[97^\circ]{} \text{OH2} \xrightarrow[116^\circ]{} \text{OH3} \xrightarrow[147^\circ]{} \text{OH1}$$

(HO17 experimental).

* E(HO17-C17) is the energy of the HO17-C17 'bond' and †E(C17-C17) is that of atom C17 in CNDO notation.

Table 3. Some numerical results concerning the geometrical characteristics of 17βOH orientations

Kind of data	nc*	OH1 < >†	σ§	nc	OH2 < >	σ	nc	OH3 < >	σ
1 : C16-C17-O17-HO17 (exp)	26	168°	12°	7	71°	11°	7	315°	16°
2 : C16-C17-O17-HO17 (theo)	28	168°	15°	8	75°	12°	8	325°	12°
|1 minus 2|	24	7°	8°	7	14°	15°	7	8°	9°
3 : C16-C17-O17...X (acceptor)	28	169°	15°	8	76°	12°	8	325	13°
|2 minus 3|	28	1.4°	0.7°	8	1.3°	0.7°	8	1.3°	0.8°
4 : C16-C17-O17...X (donor)	16	349°	37°		(cf. Fig. 4b3)			(cf. Fig. 4c3)	
5 : X...O17...X (acceptor) (donor)	14	120°	11°	2	109°	11°	4	111°	11°
6 : C17-O17...X (acceptor)	28	111°	6°	8	108°	8°	8	114°	4°
7 : C17-O17...X (donor)	16	120°	7°	2	137°	4°	4	118°	11°
8 : O17...X (acceptor)	28	2.80Å	0.09Å	6	2.87Å	0.10Å	8	2.82Å	0.09Å
9 : O17...X (donor)	16	2.79Å	0.08Å	2	2.77Å	0.01Å	4	2.83Å	0.12Å
10 : O17-HO17...X (exp)	24	165°	10°	6	148°	24°	7	166°	10°
11:O17-HO17...X (theo)	27	172°	6°	8	168°	8°	8	175°	3°
12:O17-HO17 (exp)	26	0.84°A	0.16°A	7	0.85Å	0.09Å	7	0.88Å	0.12Å
13:C17-OH-HO17 (exp)	26	112°	9°	7	114°	14°	7	117°	5°

* Number of contributors.
† Mean value.
§ Standard deviation.
Positive rotation for dihedral angles is the standard one (0 to 180° *via* the α side). The data of table 3 are based on same references as table 1. X = O or N, but data 8 and 9 have been limited to oxygen.

Possibilities of intermolecular interaction of ethynyl group

The ethynyl group is an H-bond donor of the C ≡ CH ... O type. The 16 molecules possessing a 17α ethynyl group and the two steroids [25, 94] show 14 C ≡ C-H ... O interactions. $\langle C \ldots O \rangle = 3.30$ Å, $\sigma = 0.15$ Å; $\langle H \ldots O \rangle = 2.47$Å, $\sigma = 0.19$ Å; $\langle C\text{-}H \ldots O \rangle = 151°$, $\sigma = 12°$; $\langle C \equiv C \ldots O \rangle = 158°$, $\sigma = 12°$.

The ethynyl group is also a short contact receptor of the C–H ... C ≡ C type [96]. These contacts are probably similar to those also smaller than the sum of van der Waals radii, which occur in crystals between the CH group and the sp_2 carbon. In steroid structures they have a relative stable shape. As the steric hindrances in the ethynyl area are not very restrictive, the directions of approach lie in a cone (summit CE2, mean apex angle about 76°) (Fig. 5). These numerous contact possibilities might explain the 'dissolving power' of the ethynyl group [97]. No obvious intra or intermolecular bond such as OH ... C≡ or NH ... C≡ has been found in previous crystallographic publications (our results, [94] and [98]). However intramolecular bonds of this kind seem to have been observed by spectroscopy [99]. The absence of such links in the crystals can be explained by the competition of stronger energy bonds of the OH ... O type.

A CNDO calculation, executed in order to study the approach of a CH_4 molecule towards an ethynyl group (one of the hydrogens of CH_4 pointing to CE2 with an Ω' angle of 120°) shows a small attractive interaction. The approach of a water molecule in the same conditions shows an attractive interaction ten times stronger. The interaction is maximal for a near symmetrical interaction on CE1 and CE2 and decreases regularly when Ω' gets bigger, reaching a repulsive value between 140 and 160°.

H-bonds distribution around keton-3

Keton-3 shares classical H-bonds with its crystalline neighbours; C ≡ C–H...O3 and O–H–...–O3 H-bonds, only this latter type is commented on in this section. (It also receives interactions of weak energy of C–H ... O type; they are not taken into account in the present paper.) The small steric hindrances inducted by ring A in the H-bond area must allow a relative uniform distribution of the H-bond directions; roughly on a cone of C3–O3 axis with an apex angle of about 60°. However the electronic resonance may be favorable to H-bonds situated in the plane of sp_2 carbon C3(O3–C3–C4 plane).

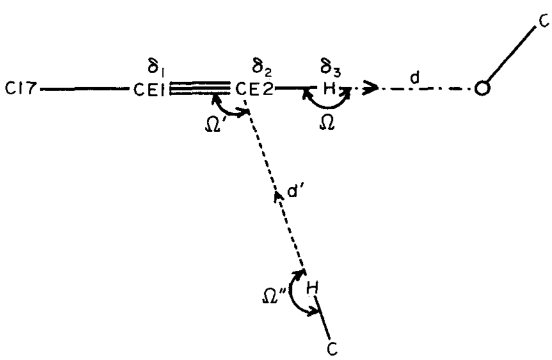


Fig. 5. Schematic representation of the ethynyl interactions: classical H-bonds CE2-H---O and low energy interactions C-H---CE2 ≡ . Mean values are: from 14 H-bonds, d = 2.47Å (σ = 0.19Å), Ω = 151° (σ = 12°); from 23 C-H---CE2 contacts: d' = 2.84Å (σ = 0.11Å), Ω' = 104° (σ = 12°), Ω'' = 143° (σ = 17°), d' may be as small as 2.6Å. CNDO calculations show that mean values for $\delta 1$, $\delta 2$, $\delta 3$ charges are approximately −0.05, −0.10, 0.05e.

The observed experimental distribution for 63 OH...O3 H-bonds is in agreement with the above remarks. Figure 6 shows a relative concentration in the plane of C3 and a gap near the orthogonal direction to this latter ($\theta = 90$ or 270°). Two particular concentrations are present: one for three molecules sharing an H-bond with a water molecule (ref. underlined is in Fig. 6), the other for molecules with OH1 orientation on 17βOH sharing an H-bond O17-HO17...O3 'head to tail' in respect to a 2_1 symmetry axis (drawing at bottom left in Fig. 6). In the first case the great similarity of crystalline environment may be an explanation for this concentration. In the second case if the above characteristics are fulfilled (OH1, head to tail bonding with molecular axis nearly parallel to a 2_1 axis) the only possible H-bond direction lies toward the 'C2 side', roughly in the plane of the ketone.

Corticosteroids seem to have a more aleatory distribution. This fact may be connected with the wider variety of H-bond systems existing in this case (O11, O16, O17, O21...O3) than those built by testosterone derivatives (mainly O17...O3). The distributions for other categories of steroids are not different between them. A specific study of corticosteroids can be found in the paper of the Liege group [100].

In order to get a clear view of this question several CNDO/2 calculations have been made with the following conditions:

Calculation of the energy variations caused by the rotation of a water molecule on a cone of C3–O3 *axis with an apex angle near to* 50° (*the* W...O3 *length being invariant* (2.9 Å) *and one H atom belonging to water being directed toward* O3 (W–H...O3 *of* 180°)). This calculation was done in three cases with the participation of experimental A and B rings (4–5, 9–10 diene [10], 4–5 ene [48], without any double bond [50]). The water molecule was chosen for the simplicity of its environment. In the three cases the energy variations are weak, two minima are situated in the plane of the ketone, two maxima in the perpendicular plane, the difference of energy between them being only of 0.05 to 0.1 kcal.

Calculation of the energy variations caused by the rotation of a water molecule. It stands on a circle centered on O3 and lies in the plane of C3, W–O3 being of 2.9 Å with W–H...O3 of 180°. This calculation shows a large area of stability for parameter θ' (Fig. 6) between 110° and 150° (the mean experimental value for C3-O3-X is 127°, $\sigma = 15°$). An H-bond with $\theta' = 180°$ looses an energy of only about 0.2 kcal with the best case.

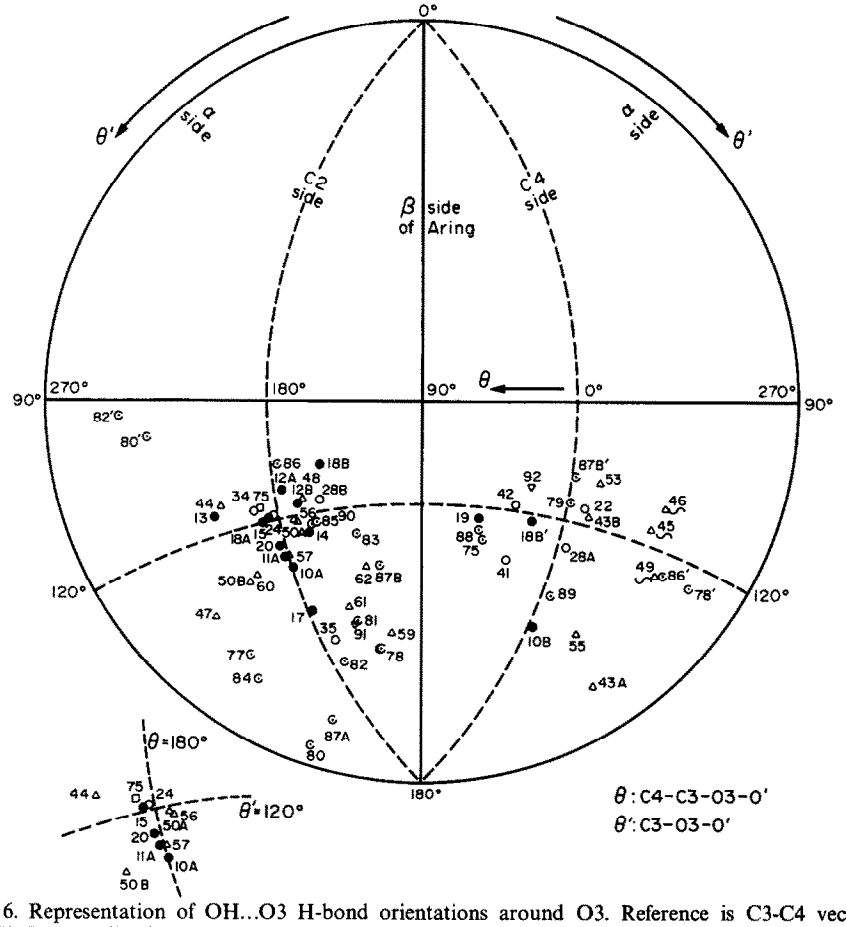


Fig. 6. Representation of OH...O3 H-bond orientations around O3. Reference is C3-C4 vector. θ: C4-C3-O3...O' dihedral angle, θ': C4-O3...O' angle. When O3 shares two H-bonds, the second is noted' (e.g. 78 and 78').

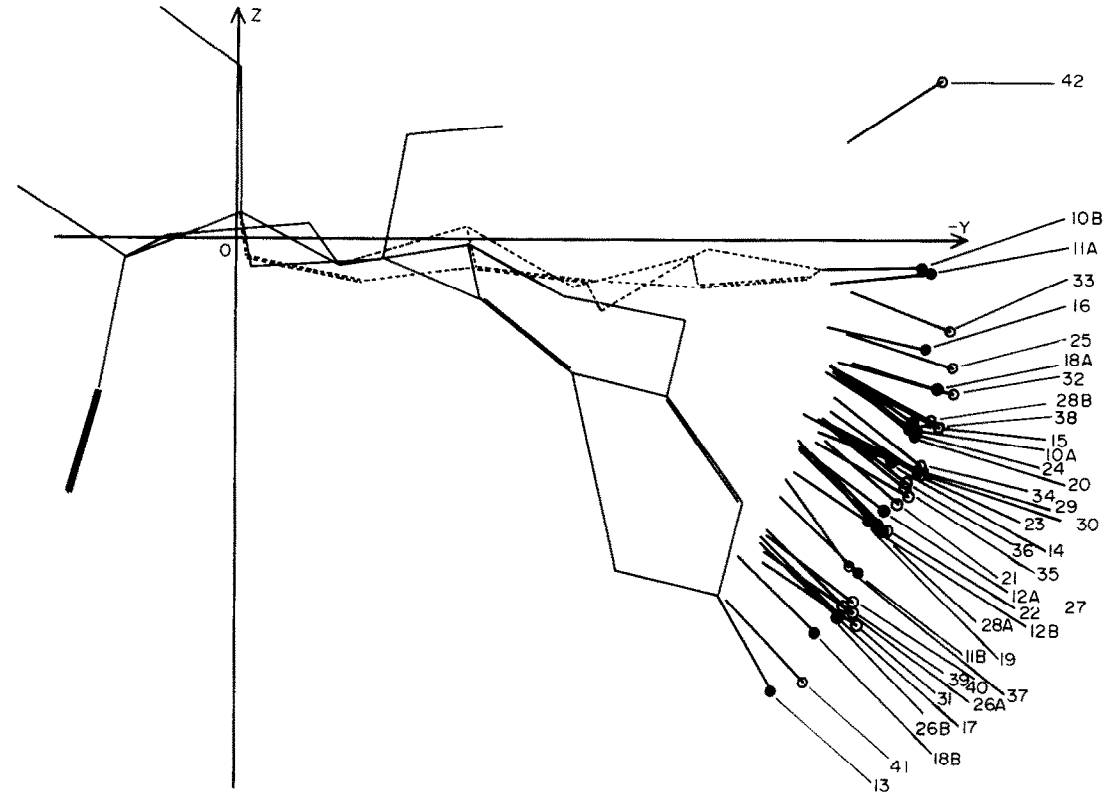


Fig. 7(a). Superposition of YOZ projections, in the reference system D (cf. experimental section), for progestogens and related compounds. Only two steroids, at the two extremities of the normal range of variation, are completely drawn to keep the fig. clear. For the other progestogens only the C3-O3 bond is represented.

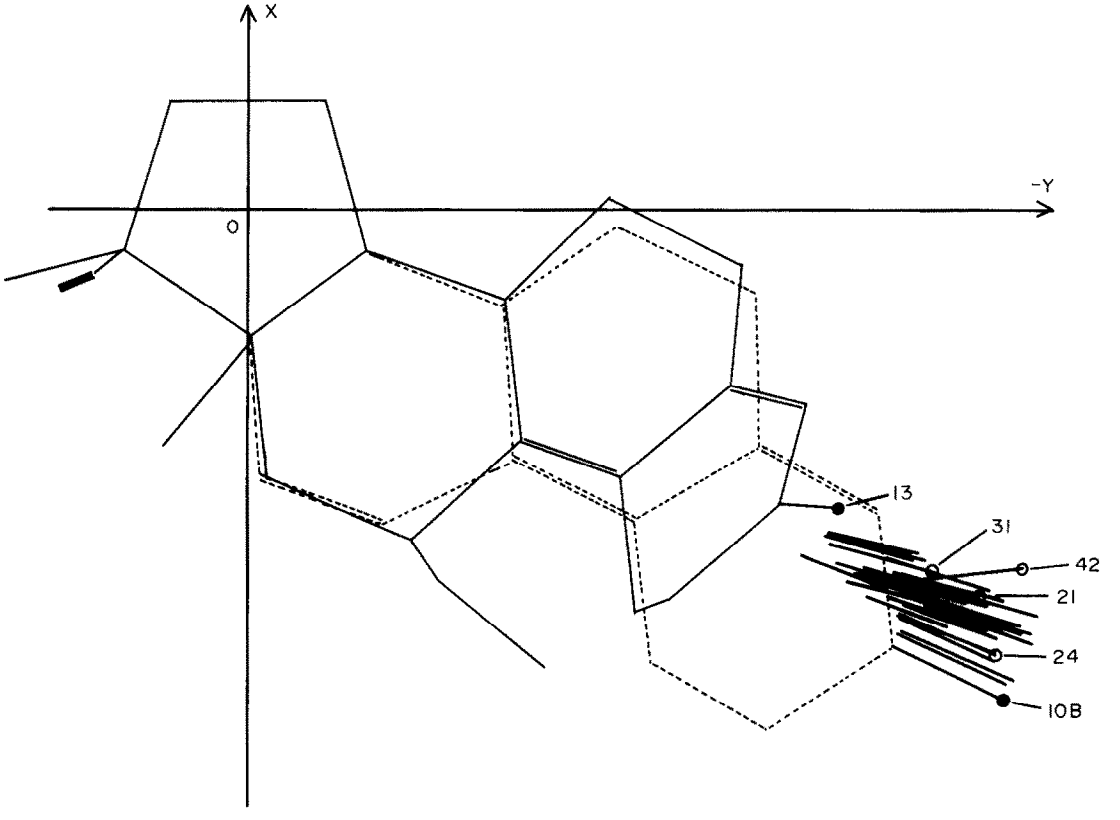


Fig. 7(b) Same data as for Fig. 7(a) but for XOY projections.

The mean experimental value for 64 OH...O3 bond length is 2.85 Å with $\sigma = 0.08$ Å. From six crystal structures for which O3 shares two H-bonds the mean O...O3...O′ angle is 92° ($\sigma = 20°$); this value appears to be sensibly smaller than the corresponding one for O17 (Table 3).

The experimental data and the estimation of energy variations implicated by the modifications of H-bond parameters for keton-3 suggest the following remarks. The relative concentration of the H-bond directions near the plane of C3 and the gap in the perpendicular direction are probably the result of two main factors: crystalline interactions and internal electronic behaviour but their proportion is difficult to specify with such small variations of energy. In conclusion keton-3 can accept one or two H-bonds with few restrictions.

General conformation of the molecules

Figure 7(a) shows the superposition of the $(YOZ)_D$ projections of published progestogens and close related compounds. Figure 7(b) shows the same data for $(XOY)_D$ projections. In these drawings we have recorded only the D ring and the orientation of C3-O3 of all molecules to simplify the Fig. A fluctuation of 4 Å for the 3-keton group is noticeable. Moreover the three crystalline forms of progesterone lie in the centre of this fluctuation range [21–23]. For comparison Fig. 8 shows the shape fluctuations of progesterone and testosterone in their different crystalline environments. The amplitudes of fluctuation in the two cases are of 0.9 Å with a common range of 0.3 Å. This figure can be put together with Fig. 3 of [101] built with another reference system.

It has been noticed that the compounds related to retroprogesterone are not bent more than the others [31, 33, 39–41]. This may partly constitute an explanation for their activity.

DISCUSSION

We suggest on one hand that synthetic progestogens can directly replace progesterone on its receptors and on the other hand that their bindings have to be mainly assumed by H-bonds on O3 and on a 17 substitute. Results shown above lead us to the following comments.

17βOH Orientations and interactions of 17 ethynyl group

In accordance with this hypothesis the H-bond on the $COCH_3$ side chain of progesterone must be assumed by either 17βOH or 17βOH-17αC ≡ CH functions. The 17βOH H-bond highly directional character associated with the special hindrances of O20 for progesterone will only allow a narrow fluctuating freedom to the binding geometry. As far as 17βOH is connected, usual OH1, OH2 or OH3 orientations are probably involved.

Because the CNDO/2 calculations indicate that 17α carbon substitution decreases the relative conformational energy of an isolated and rigid molecule having the 17βOH in the OH3 position and because this substitution confers progestational activity on androstenes [3, 4], a direct structural correlation between these two effects may be proposed.

The ethynyl group might assume part or complete binding either by usual H-bonds C ≡ C–H...X, by directional interactions C–H...C ≡ C or by hypothetical H-bond type interaction X–H...C ≡ C. As 17α ethynyl derivatives are the best progestogens, among testosterone derivatives, an interaction between 17βOH and 17α C ≡ C–H parameters may occur.

General conformation and O3 H-bond

Progesterone and nearly all progestogens have an identical A ring. This suggests that, for this molecular

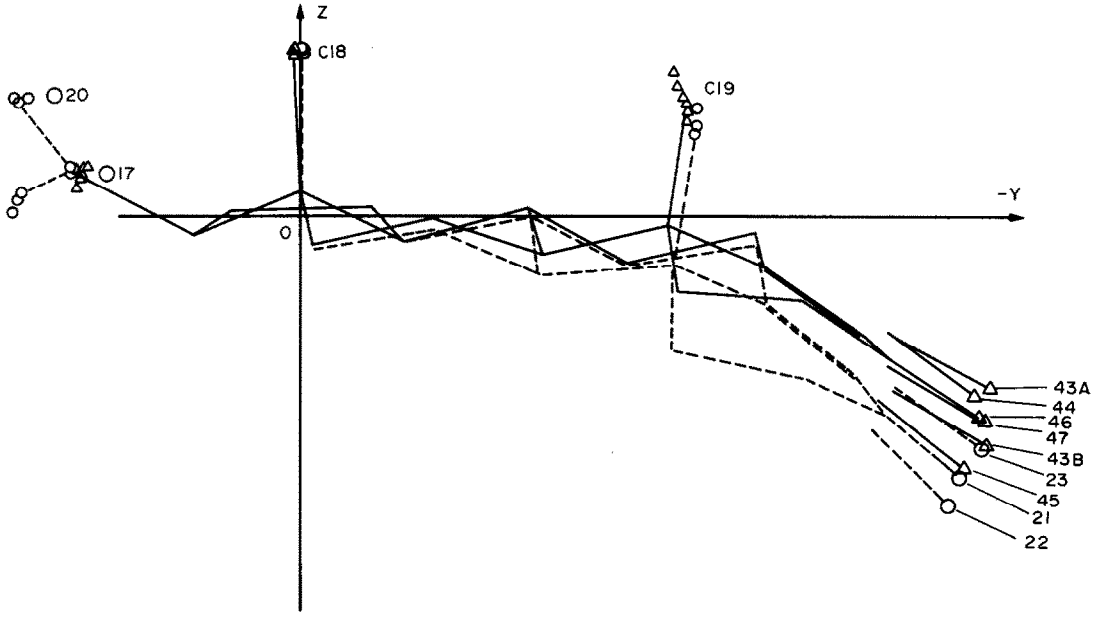


Fig. 8. YOZ projections for testosterone and progesterone in their different crystalline forms.

extremity, the binding geometry is the same in the natural hormone as well as in its substitutes. This hypothesis would imply that the synthetic progestogens must adopt a molecular conformation close to the progesterone one. This specifically occurs if an H-bond takes place on O3. Effectively with the O3...X length possible fluctuations are strictly limited. This hypothesis seems to be supported by Figs. 7(a) and 7(b). It seems apparent that a small amount of energy is sufficient during interconversion from one conformer to the other, relative to the couples (10A, 10B), (11A, 11B), (18A, 18B), (28A, 28B). Furthermore, couple conformations are widely apart. Therefore it may suggest active compounds are able to take a conformation close to the progesterone one.

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REFERENCES

1. Raynaud J. P., Philibert D. and Azadian-Boulanger G.: In *The Physiology and Genetics of Reproduction.* Plenum Press, New York. Vol. 1 (1974) pp. 142–160.
2. Terenius L.: *Steroids* **23** (1974) 909–919.
3. Smith H. E., Smith R. G., Toft D. D., Neergaard J. T., Burrows E. P. and O'Malley B. W.: *J. biol. Chem.* **249** (1974) 5924–5932.
4. McGuire J. L., Bariso C. D. and Shroff A. P.: *Biochemistry* **13** (1974) 319–322.
5. Kontula K., Janne O., Vihko R., De Jager E., De Visser J. and Zeelen F.: *Acta endocr. (Copenh).* **78** (1975) 574–592.
6. Pimentel C. and McClellan A. L.: *The Hydrogen Bond.* Freeman & Co. (1960) pp 206–225.
7. Bucourt R.: *Topics in Stereochemistry* **8** (1974) p. 205.
8. Bucourt R., Nedelec L., Gasc J. C., Rousseau G., Philibert D. and Tournemine C.: Fourth International Congress on Hormonal Steroids, Mexico City (1974) (Communication to the congress).
9. Azadian-Boulanger G.: Private communication.
10. Lepicard G., Delettré J. and Mornon J.-P.: *Acta Crystallogr.* **B30** (1974) 2751–2753.
11. Delettré J., Mornon J.-P. and Lepicard G.: *Acta Crystallogr.* **B31** (1975) 450–453.
12. Delettré J., Mornon J.-P. and Lepicard G.: *Acta Crystallogr.* **B31** (1975) 2858–2861.
13. Mornon J.-P., Lepicard G. and Delettré J.: *Acta Crystallogr.* **B30** (1974) 2754–2756.
14. Lepicard G., Delettré J. and Mornon J.-P.: *Acta Crystallogr.* **B29** (1973) 1723–1725.
15. Mornon J.-P., Lepicard G. and Delettré J.: *C.R. hebd. Séanc. Acad. Sci., Paris* (1976) t. **282,** série C 387–390.
16. Delettré L., Mornon J.-P. and Bally R.: *Acta Crystallogr.* in press.
17. Lepicard G., Delettré J. and Mornon J.-P.: *Acta Crystallogr.* in press.
18. Mornon J.-P., Lepicard G. and Bally R.: *Acta Crystallogr.* in press.
19. Bally R., Lepicard G. and Surcouf E.: *Acta Crystallogr.* in press.
20. Delettré J., Lepicard G. and Mornon J.-P.: *Acta Crystallogr.* in press.
21. Campsteyn H., Dupont L. and Dideberg O.: *Acta Crystallogr.* **B28** (1972) 3032–3042.
22. Dideberg O., Dupont L. and Campsteyn H.: *Acta Crystallogr.* **B31** (1975) 637–640.
23. Serantoni E. F., Krajewski A., Pongiorgi R., Riva Di Sanseverino L. and Cameroni R.: *Cryst. Struct. Commun.* **4** (1975) 189–192.
24. Deangelis N. J., Doyn T. H. and Grob R. L.: *Acta Crystallogr.* **B31** (1975) 2040–2043.
25. Precigoux G., Courseille C., Geoffre S. and Busetta B.: *Acta Crystallogr.* **B30** (1974) 2757–2759.
26. Courseille C., Busetta B., Precigoux G. and Hospital M.: (1975) private communication, and *Acta Crystallogr.* **B31** (1975) 2290–2294.
27. Busetta B., Comberton G., Courseille C. and Hospital M.: *Acta Crystallogr.* **B30** (1974) 2759–2761 and private communication for H coordinates.
28. Precigoux G., Busetta B., Courseille C. and Hospital M.: *Acta Crystallogr.* **B31** (1975) 1527–1532.
29. Chandross R. J. and Bordner J.: *Acta Crystallogr.* **B30** (1974) 1581–1584.
30. Chandross R. J. and Bordner J.: *Acta Crystallogr* **B31** (1975) 928–931.
31. Romers C., Hesper B., Van Heijkoop E. and Geise H. J.: *Acta Crystallogr.* **20** (1966) 363–368.
32. Gopalakrishna E. M., Cooper A. and Norton D. A.: *Acta Crystallogr.* **B25** (1969) 639–645.
33. Weber H. P. and Galantay E.: *Helv. Chem. Acta* **57** (1974) 187–192.
34. Isaacs N. W., Motherwell W. D. S., Coppola J. C. and Kennard O.: *J. Chem. Soc. Perkin* **II** (1972) 2331–2335.
35. Declercq J. P., Germain G. and Van Meerssche M.: *Cryst. Struct. Commun.* **1** (1972) 9–11.
36. Watson W. H., Kuan Tee Go and Purdy R. H.: *Acta Crystallogr.* **B29** (1973) 199–204.
37. Cooper A. and Norton D. A.: *Acta Crystallogr.* **B24** (1968) 811–824.
38. Weeks M., Strong P. and Duax W. L.: *Cryst. Struct. Commun.* **3** (1974) 515–518.
39. Braun P. B., Hornstra J. and Leenhouts J. I.: *Philips Res. Reports* **24** (1969) 431–436.
40. Braun P. B., Hornstra J. and Leenhouts J. I.: *Philips Res. Reports* **24** (1969) 441–445.
41. Braun P. B., Hornstra J. and Leenhouts J. I.: *Philips Res. Reports* **24** (1969) 445–449.
42. Mc Phail A. T. and Miller R. W.: *J. Chem. Soc. Perkin* **II** (1975) 1180–1184.
43. Roberts P. J., Pettersen R. C., Sheldrick G. M., Isaacs N. W. and Kennard O.: *J. Chem. Soc. Perkin* **II** (1973) 1978–1984.
44. Cooper A., Kartha G. and Gopalakrishna E. M.: *Acta Crystallogr.* **B25** (1969) 2409–2411.
45. Busetta B., Courseille C., Leroy F. and Hospital M.: *Acta Crystallogr.* **B28** (1972) 3293–3299.
46. Precigoux G., Hospital M. and Van Den Bosche G., *Cryst. Struct. Commun.* **3** (1973) 435–439.
47. Cooper A., Gopalakrishna E. M. and Norton D. A., *Acta Crystallogr.* **B24** (1968) 935–941.
48. Isaacs N. W., Motherwell D. S., Coppola J. C. and Kennard O.: *J. Chem. Soc. Perkin* **II** (1972) 2335–2339.
49. Busetta B., Courseille C., Fornies-Marquina J. M. and Hospital M.: *Cryst. Struct. Commun.* **1** (1972) 43–45.
50. Courseille C., Precigoux G., Leroy F. and Busetta B.: *Cryst. Struct. Commun.* **2** (1973) 441–446.
51. Precigoux G., Busetta B., Courseille C. and Hospital M.: *Cryst. Struct. Commun.* **1** (1972) 265–268.
52. Precigoux G. and Fornies-Marquina J.: *Cryst. Struct. Commun.* **2** (1973) 287–290.
53. Duax W. L., Norton D. A., Rokrywiecki S. and Eger C.: *Steroids* **18** (1971) 525–544 and Duax W. L. and Norton D. A.: *Atlas of Steroid Structure.* Plenum,

New York, Vol 1 (1975) p. 326 and Duax W. L., private communication
54. Weeks C. M., Cooper A. and Norton D. A.: *Acta Crystallogr.* **B27** (1971) 531–538.
55. McKechnie J. S., Kubina L. and Paul I. C.: *J. chem. Soc.* **(B)** (1970) 1476–14
56. Rendle D. F. and Trotter J.: *J. chem. Soc. Perkin* **II** (1974) 847–852.
57. Cooper A., Lu C. T. and Norton D. A.: *J. chem. Soc. Perkin* **II** (1968) 1228–1237.
58. Weeks C. M., Cooper A., Norton D. A., Hauptman H. and Fisher J.: *Acta Crystallogr.* **B27** (1971) 1562–1572
59. Rendle D. F. and Trotter J.: *J. chem. Soc. Perkin* **II** (1975) 1361–1365.
60. Peck D. N., Langs D. A., Eger C. and Duax W. L.: *Cryst. Struct. Commun.* **3** (1974) 451–454
61. Duax W. L., Eger C. and Pokrywiecki S.: *J. med. Chem.* **14** (1971) 295–300.
62. Duax W. L., Eger C., Pokrywiecki S. and Osawa Y.: *J. med. Chem.* **14** (1971) 295–300.
63. Duax W. L.: private communication.
64. Duax W. L.: private communication.
65. Tsukuda Y., Sato T., Shiro M. and Koyama H.: *J. chem. Soc.* **(B)** (1968) 1387–1393.
66. Busetta B. and Hospital M.: *Acta Crystallogr.* **B28** (1972) 560–567.
67. Duax W. L.: *Acta Crystallogr.* **B28** (1972) 1864–1871.
68. Busetta B., Courseille C., Geoffre S. and Hospital M.: *Acta Crystallogr.* **B28** (1972) 1349–1351.
69. Courseille C., Busetta B., Precigoux G. and Hospital M.: *Acta Crystallogr.* **B29** (1973) 2462–2465.
70. Norton D. A., Kartha G. and Chia Tang LY: *Acta Crystallogr.* **17** (1964) 77–82.
71 and 72. Cody C., Dejarnette F., Duax W. L. and Norton D. A.: *Acta Crystallogr.* **B27** (1971) 2458–2468.
73. Brown J. N. and Trefonas L. M.: *J. Am. chem. Soc.* **94** (1972) 4311–4314.
74. Cooper A., Norton D. A. and Hauptman H.: *Acta Crystallogr.* **B25** (1969) 814–828.
75. Sobti R. R., Levine S. G. and Bordner J.: *Acta Crystallogr.* **B28** (1972) 2292–2297.
76. Weeks C. M. and Duax W. L.: *Acta Crystallogr.* **B29** (1973) 2210–2213.
77. Declercq J. P., Germain G. and Van Meerssche M.: *Cryst. Struct. Commun.* **1** (1972) 13–15.
78. Duax W. L., Cooper A. and Norton D. A.: *Acta Crystallogr.* **B27** (1971) 1–6.
79. Campsteyn H., Dupont L. and Dideberg O.: *Acta Crystallogr.* **B29** (1973) 1726–1728.
80. Dupont L., Dideberg O. and Campsteyn H.: *Acta Crystallogr.* **B29** (1973) 205–215.
81. Krakower G. W., Keeler B. T. and Gougoutas J. Z.: *Tetrahedron lett.* **4**, (1971) 291–294.
82. Roberts R. J., Coppola J. C., Isaacs N. W. and Kennard O.: *J. chem. Soc. Perkin* **II** (1973) 774–781.
83. Duax W. L. and Norton D. A.: *Atlas of Steroid Structure*, Plenum, New York, Vol. 1 (1975) p. 446.
84. Dupont L., Dideberg O. and Campsteyn H.: *Acta Crystallogr.* **B28** (1972) 3023–3032. and Duax W. L. and Norton D. A.: *Atlas of Steroid Structure.* Plenum, New York, Vol. 1 (1975) p. 450.
85. Duax W. L. and Hauptman H.: *J. Am. chem. Soc.* **94** (1972) 5467–5471.
86. Declercq J. P., Germain G. and Van Meerssche M.: *Cryst. Struct. Commun.* **1** (1972) 5–7.
87. Dideberg O., Dupont L. and Campsteyn H.: *Acta Crystallogr.* **B30** (1974) 702–710.
88. Nassimbeni L. R., Sheldrick G. M. and Kennard O.: *Acta Crystallogr.* **B30** (1974) 2401–2406.
89. Dideberg O., Dupont L. and Campsteyn H.: *Acta Crystallogr.* **B30** (1974) 2064–2066.
90. Dupont L., Dideberg O. and Campsteyn H.: *Acta Crystallogr.* **B30** (1974)
91. Chaney M. O. and Jones N. O.: *Cryst. Struc. Commun.* **1** (1972) 197–202.
92. Green M. J., Abraham N. A., Fleischer E. B., Molin-Case J. and Fried J.: *Chem. Commun.* (1970) 234–235.
93. Rendle D. F. and Trotter J.: *Acta Crystallogr.* **B31** (1975) 1678–1683.
94. Chiaroni A., Riche C. and Pascard-Billy C.: *Acta Crystallogr.* **B31** (1975) 2122–2123.
95. Terzis A. and Theophanides T.: *Acta Crystallogr.* **B31** (1975) 796–801.
96. Jungk A. E.: *Chemicalia* **105** (1972) 1595–1613.
97. Rutledge T. F.: *Acetylenic Compounds.* Reinhold book corporation (1969) p. 314.
98. Brassy C.: private communication.
99. Prey V., Berbalk H.: *Monatsh.* **82** (1951) 990–1007.
100. Dideberg O., Dupont L. and Campsteyn H.: *J. steroid Biochem.* **7** (1976) 757–760.
101. Duax W. L., Weeks C. M., Rohrer D. C. and Yoshio Osawa: *J. steroid Biochem.* **6** (1975) 195–200.

MOLECULAR REFERENCES

10. [E1] 17β-hydroxy-19-nor-17α-pregna-4,9,11-trien-20-yne-3-one (RU2010)
11. [E2] 17β-hydroxy-19-nor-17α-pregna-4,9,11-trien-20-yne-18-methyl-3-one (RU2323)
12. [E3] 17β-hydroxy-19-nor-17α-pregna-4,9-dien-20-yne-11β-methoxy-3-one (RU2417)
13. [E4] 17β-hydroxy-19-nor-17α-pregna-4,9-dien-20-yne-11β-methoxy-18-methyl-3-one (RU2657)
14. [E5] 17β-hydroxy-19-nor-17α-pregna-4,9-dien-20-yne-3,11-dione (RU2106)
15. 17β-hydroxy-19-nor-17α-4-pregnene-20-yne-3-one (Norethindrone)
16. 19-nor-pregna-4,9,11-trien-3,20-dione (RU2061)
17. 11β-17β-dihydroxy-19-nor-17α-pregna-4,9-dien-20-yne-18-methyl-3-one-ethanol(1:1) (RU2732)
18. 11β-17β-dihydroxy-19-nor-17α-pregna-4,9-dien-20-yne-18-methyl-3-one (RU2732)
19. 17β-hydroxy-19-nor-17α-4-pregnene-20-yne-11β-methoxy-3-one (RU4843)
20. 17β-hydroxy-19-nor-17α-4-pregnene-20-yne-18-methyl-3-one (RU1364)
21. 4-pregnene-3,20-dione (progesterone)
22. 4-pregnene-3,20-dione resorcinol (1:1)
23. 4-pregnene-3,20-dione (second form)
24. 17β-hydroxy-19-nor-17α-4-pregnene-20-yne-18-methyl-3-one (Norgestrel)
25. [17βE] 17β-ethynyl-19-nor-4-androsten-3-one (RU4414)
26. 17-methyl-19-nor-pregna-4,9-diene-3,20-dione (RU2453)
27. 17,21-dimethyl-19-nor-pregna-4,9-diene-3,20-dione (RU5020)
28. 17β-hydroxy-19-nor-4-androsten-3-one (19-nor-testosterone)
29. 6-chloro-17α-acetoxy-1α,2α-methylene-4,6-pregnadiene-3,20-dione (cyproterone acetate)
30. 6-chloro-17α-acetoxy-4,6-pregnadiene-3,20-dione (chlormadinone acetate)

31. 4-bromo-9β-10α-pregna-4,6-diene-3,20-dione (4 bromo-duphaston)
32. 6β-bromo-4-pregnene-3,20-dione
33. 9α-methyl-10α-pregn-4-ene-3,20-dione (Ψ-retroprogesterone)
34. 20(S)-hydroxypregn-4-en-3-one
35. 17α-hydroxy-4-pregnene-3,20-dione
36. 17α-(9′-OXO-10′-chlorodecanoyloxy)-4-pregnene-3,20-dione
37. 12α-bromo-11β-hydroxy-4-pregnene-3,20-dione
38. 6-chloro-21-fluoro-17α-acetoxy-16-methylene-4,6-pregnadiene-3,20-dione
39. 9β,10α-pregna-4,6-diene-3,20-dione
40. 6α-methyl-9β,10α-pregn-4-ene-3,20-dione
41. 11α-hydroxy-9β,10α-pregn-4-ene-3,20-dione
42. 17α-ethynyl-17β-hydroxy-6-dimethyl-6-sila-5α-estr-1(10)-en-3-one
43. 17β-hydroxy-4-androsten-3-one (testosterone)
44. 17β-hydroxy-4-androsten-3-one p-bromophenol (1:1)
45. 17β-hydroxy-4-androsten-3-one monohydrate
46. 17β-hydroxy-4-androsten-3-one monohydrate
47. 17β-hydroxy-4-androsten-3-one mercuric chloride (2:1)
48. 17α-hydroxy-4-androsten-3-one
49. 17β-hydroxy-5α-androstan-3-one monohydrate
50. 17β-hydroxy-5α-androstan-3-one
51. 3α,17β-dihydroxy-5α-androstan
52. 3β,17β-dihydroxy-5α-androstan monohydrate
53. 17β-hydroxy-1,4-androstadien-3-one p-bromophenol (1:1)
54. 3β-chloro-5-androsten-17β-ol methanol (2:1)
55. 6α-bromo-17β-hydroxy-17α-methyl-4-oxa-5α-androstan-3-one
56. 17β-hydroxy-17α-methyl-5α-androst-1-en-3-one
57. 9α-bromo-17β-hydroxy-17α-methyl-4-androstene-3,11-dione
58. 3α,17β-dihydroxy-5β-androstane
59. 17β-hydroxy-17α-methyl-2-oxa-5α-androstan-3-one
60. 1,4,6-androstatriene-3,17-dione p-bromophenol (1:1)
61. 17β-chloroacetoxy-2β-acetoxy-4-androsten-3-one methanol (1:1)
62. 2β,17β-diacetoxy-4-androsten-3-one p-bromophenol (1:1)
63. [19R]-19-methyl-5-androstene-3β,17β,19-triol
64. [19S]-19-methyl-5-androstene-3β,17β,19-triol dihydrate
65. 1,3,5(10)-estratriene-3,17β-diol 3-p-bromobenzoate
66. 1,3,5(10)-estratriene-3,17β-diol hemihydrate (Estradiol)
67. 1,3,5(10)-estratriene-3,17β-diol urea (1:1)
68. 1.3.5(10)-estratriene-3,17β-diol propanol (1:1)
69. 1,3,5(10)-estratriene-3,17β-diol-11β-methoxy
70. 4-bromo-1,3,5(10)-estratriene-3,17β-diol methanol (1:1)
71. 2,4-dibromo-1,3,5(10)-estratriene-3,17β-diol (crystal 1)
72. 2,4-dibromo-1,3,5(10)-estratriene-3,17β-diol (crystal 2)
73. D,L-8-aza-1,3,5(10)-estratriene-3,17β-diol
74. 1,3,5(10)-estratriene-3,16α,17β-triol
75. 17β-hydroxy-5(10)-estren-3-one
76. 9α-bromo-11β,17α,21-trihydroxy-4-pregnene-3,20-dione
77. 17α,21-dihydroxy-4-pregnene-3,11,20-trione (cortisone)
78. 4-chloro-17α,21-dihydroxy-4-pregnene-3,11,20-trione
79. 11β,21-dihydroxy-4-pregnene-3,20-dione (corticosterone)
80. 17α,21-dihydroxy-4-pregnene-3,20-dione (Reichstein's S substance)
81. 21-bromo-9α-fluoro-11β-hydroxy-16α,17α-[22R]-methylphenylmethylenedioxy-4-pregnene-3,20-dione methanol (1:1)
82. 11β,17α,21-trihydroxy-4-pregnene-3,20-dione methanol (1:1) (cortisol)
83. 6α-fluoro-11β,17α,21-trihydroxy-4-pregnene-3,20-dione
84. 9α-fluoro-11β,17α,21-trihydroxy-4-pregnene-3,20-dione
85. (18R,20S)-18,11-acetal-20,18-hemiketal of 11β,21-dihydroxy-3,20-dioxo-4-pregnen-18-al monohydrate (aldosterone)
86. 6α-methyl-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione
87. 9α-fluoro-6α-methyl-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione
88. 9α-fluoro-16β-methyl-6-azido-11β,17α,21-trihydroxy-1,4,6-pregnatriene-3,20-dione-21-acetate
89. 11β,16α,17α,21-tetrahydroxy-1,4-pregnadiene-3,20-dione
90. 9α-fluoro-16α-methyl-11β,21-dihydroxy-1,4-pregna-diene-3,20-dione
91. 17β-hydroxy-8[9 → 10β]-abeo-estr-4-en-3,10-dione
92. dl-17β-hydroxy-D-homo-12,18-dinor-8α,13α,14β-androst-4-en-3-one
93. [3S-(3β,3aβ,5aα,5bR,5cR,7R,9aR,10aα,11aβ,11bα)]-tetradecahydro-3,7-dihydroxy-3a-methyl-1H-5b,7-methano-8H-az-indeceno-[3′,2′; 4,5]-furo-[2,3-b]-pyran-8-one
94. 2β-ethynyl-5β,17β-dihydroxy-3,4-bisnorandrostane-17-acetate
95. 9α-fluoro-16α-methyl-11β,17,21-trihydroxy-1,4-pregnadiene-3,20-dione-21-acetate monohydrate