CH_2), 2.12 (dt, $J_1 = J_2 = 6.2$ Hz, 2 H, CH_2), 3.61 (t, $J = 6.2$ Hz, 2 H, CH_2), 4.99 (dm, $J = 9.3$ Hz, 1 H), 5.06 (dm, $J = 17.8$ Hz, 1 H), 5.85 (m, 1 H, CH=).

3-Pentenol (12). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.68 (dm, $J = 7.1$ Hz, 1 H), 2.24 (dt, $J_1 = J_2 = 6.2$ Hz, 2 H, CH_2), 3.68 (t, $J = 6.2$ Hz, 2 H, CH_2OH), 5.45 (m, 1 H, CH=), 5.57 (dt, $J = 15.3$, 6.1 Hz, 1 H, CH=).

Registry No. **4a**, 143775-62-6; **4b**, 143775-67-1; **6**, 143775-63-7; **7**, 143775-64-8; **8**, 143775-65-9; **9**, 143775-66-0; **10**, 143790-34-5; **11**, 821-09-0; **12**, 39161-19-8; CH_3OH, 67-56-1; 1,4-pentadiene, 591-93-5; dipropylchloroborane, 22086-53-9; cyclopentanone, 120-92-3.

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Molecular Recognition Using Bioorganometallic Probes: NMR, X-ray Crystallographic, and Molecular Modeling Study of the Conformations of $Cr(CO)_3$ Derivatives of Hexestrol and Their Relevance to Estradiol–Receptor Binding

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The structures of the *meso*-hexestrol derivatives $R^1OC_6H_4CHEtCHEtC_6H_4OR^2$, where $R^1 = R^2 = H$, **1**; $R^1 = R^2 = CH_2Ph$, **6**; $R^1 = HO(CH_2)_3$, $R^2 = H$, **7**, have been investigated both by molecular modeling techniques and by ^{1}H NMR spectroscopy at 500 MHz; the centrosymmetric antiperiplanar conformation **10** is favored. The tricarbonylchromium complexes of **6** and **7**, viz. **9** and **8**, respectively, as well as the DES derivative $PhCH_2OC_6H_4CEt{=}CEtC_6H_4[Cr(CO)_3]OCH_2Ph$, **13**, have also been prepared. Crystals of **8** are monoclinic, of space group *Cc* with $a = 15.449$ (6) Å, $b = 21.077$ (5) Å, $c = 7.623$ (3) Å, $\beta = 113.41$ (3)°, and $V = 2278$ (1) Å^3 for $Z = 4$. For **13**, $a = 14.905$ (7) Å, $b = 8.558$ (2) Å, $c = 26.084$ (13) Å, $\beta = 115.58$ (3)°, and $V = 3001$ (2) Å^3 for $Z = 4$ in the monoclinic space group $P2_1/n$. In **8** the phenyl rings are not parallel; the twist angle is 25°. In **13**, the phenyl rings are within 11° of being parallel (as is the case for DES itself) but are almost orthogonal to the plane containing the central double bond. The relative binding affinity of **7** is 15% of the RBA for the natural hormone, 17β-estradiol, and this diminishes slightly upon incorporation of the $Cr(CO)_3$ group, as in **8**. The RBA's for the series of hexestrol derivatives have been measured and are discussed in terms of the favored molecular conformers. IR spectroscopy in the ν_{CO} region is used to demonstrate not only that the $Cr(CO)_3$ tripod remains attached but also that the organometallic derivative of hexestrol is still well recognized by the estradiol receptor.

Introduction

The interactions of organometallic moieties with systems of significance to molecular biology have become a new and important area of study. In this burgeoning area, one of the concepts which is of increasing current importance involves the utilization of metal fragments as cold (i.e. nonradioactive) markers.[1] Typically, cobalt and molybdenum carbonyl cluster derivatives of the mycotoxin zearalenone have high binding affinities for specific antibodies and provide the basis of new immunoassay techniques.[2] The pivotal factor in such studies is the recognition of the particular protein receptor site by a biological molecule *even when modified by the incorporation of the organometallic fragment*. It is thus apparent that the influence of the organometallic bioprobe on the molecular geometry of these systems needs to be understood at a rather fundamental level so that some measure of steric control may be achieved. We here describe how a combination of molecular modeling techniques and high-field NMR spectroscopy, together with X-ray crystallographic structural determinations for some key molecules, allows the rationalization of the relative binding affinities (RBA's) of a series of nonsteroidal hormones.

Results and Discussion

Nonsteroidal hormones such as hexestrol, **1**, and diethylstilbestrol (DES), **2**, occupy an important place in studies of the hormone ⇄ estradiol receptor system.[3] This topic has gained in significance with the recognition that the mechanism of the development of certain types of breast cancer is hormone dependent. Moreover, this knowledge has been exploited not only in terms of early diagnosis of such cancers but also in hormonal treatment therapy.

The nonsteroidal hormones possess two important characteristics. First of all they have in general a very good

† Ecole Nationale Supérieure de Chimie de Paris.
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(3) *Estrogen/Antiestrogen Action and Breast Cancer Therapy*; Jordan, V. C., Ed.; University of Wisconsin Press: Madison, WI, 1986.

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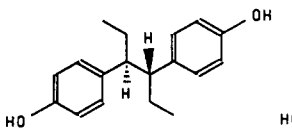
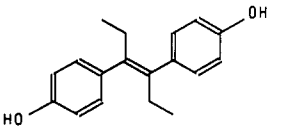
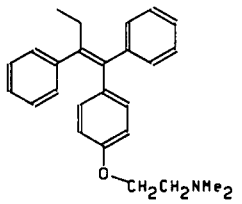


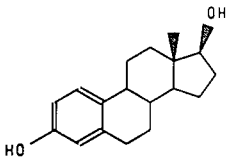
1 *meso*-hexestrol



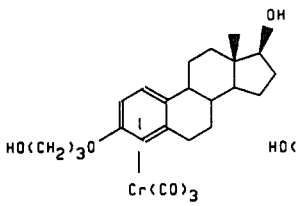
2 diethylstilbestrol (DES)



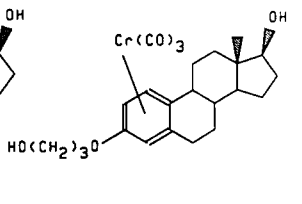
3 tanoxifen



4 β-estradiol



5α

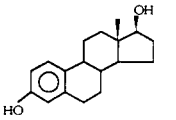


5β

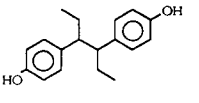
affinity for the specific receptor site—in some cases better than estradiol itself. Secondly, they can be chemically modified in a facile manner to yield a wide variety of derivatives. Tamoxifen, **3**, constitutes a typical example of this series, and it is widely used in the hormonal treatment of breast cancer.[4] Particularly noteworthy are the contributions of Katzenellenbogen et al. concerning the chemical, biological, and structural features of nonsteroidal hormones;[5] recently, these workers have focused their efforts on molecules which allow them to assay estradiol receptor sites by using fluorescence techniques.[6] These different approaches have shown that the relative binding affinity (RBA)—a quantifiable measure of the ability of the molecule under investigation to attach itself to the specific receptor site—is extremely sensitive to the identity, the site of incorporation, and the spatial requirements of the substituents. (In these studies the RBA of estradiol itself is assigned a value of 100%.) An understanding of these geometric constraints, which play a crucial role in determining steric hindrance to effective binding at the receptor site, can guide the synthetic chemist toward more effective molecular targets.

The hexestrol series has attracted our attention since organometallic fragments can be readily affixed to the molecular skeleton; these complexes are of special interest since they allow the assaying of hormonal receptor sites while avoiding the inconveniences of radiolabeling. This novel approach takes advantage of the very intense metal carbonyl infrared vibrations in a spectral region (≈2100–1900 cm^{-1}) in which absorption by the proteins is minimal. The carbonyl absorptions in this "window" are conveniently monitored by FTIR techniques, and this approach has already been utilized for $Cr(CO)_3$, $Co_2(CO)_6$, $Cp_2Mo_2(CO)_4$, and $Os_3(CO)_{10}$ complexes of estradiol, **4**, and related molecules.[1,7]

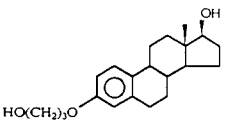
Table I. Relative Binding Affinities for Estradiol and Hexestrol Derivatives



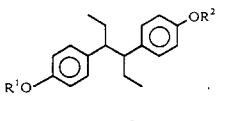
4 17β-estradiol
R.B.A. = 100 %



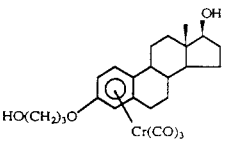
1 Hexestrol
R.B.A. = 70 %



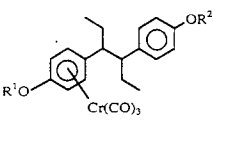
R.B.A. = 37 %



7 $R^1 = HO(CH_2)_3$, $R^2 = H$; R.B.A. = 15%
6 $R^1 = R^2 = PhCH_2$; R.B.A. = 0.12%



5α: R.B.A. = 28%
5β: R.B.A. = 2%



8 $R^1 = HO(CH_2)_3$, $R^2 = H$; R.B.A. = 10%
9 $R^1 = R^2 = PhCH_2$; R.B.A. = 0%

It has already been demonstrated that the effect of complexation of a tricarbonylchromium moiety to estradiol is very sensitive to the site of attachment. Thus, the RBA values for the α- and β-$Cr(CO)_3$ complexes of (3-hydroxypropyl)estradiol, **5**α and **5**β, are 28% and 2%, respectively.[8] Of course, diastereomers such as **5**α and **5**β are not interconvertible and are readily distinguished by high-field NMR spectroscopy.[9] In contrast, one might envisage that this problem could be circumvented in the hexestrol system by the simple expedient of allowing rotation about the phenyl–C_α bond. Moreover, since the RBA value of *meso*-hexestrol (300%)[10] is reported to exceed that of the natural hormone, viz. β-estradiol, one can hope for a good response from a suitably chosen metal complex.

Synthetic Aspects and RBA Values. In order to enhance the stability of the hexestrol system during the complexation of the organometallic fragments the phenolic groups can be protected either as benzyloxy substituents, as in **6**, or by addition of a hydroxypropyl chain as in **7**. However, we note that the RBA value for **7** has fallen to only 15% from 70% in **1**. Moreover, addition of the π-complexed $Cr(CO)_3$ group, as in **8**, causes a further small decrease of the RBA to 10%. When **6** is treated with chromium hexacarbonyl to yield the doubly-protected complex **9**, the resultant molecule is not recognized at all by the receptor site. These decreases in RBA values in the hexestrol series may be compared with the behavior of the analogous derivatives of β-estradiol as shown in

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(5) (a) Katzenellenbogen, J. A.; McGorrin, R. J.; Tatee, T.; Kempton, R. J.; Carlson, K. E.; Kinder, D. H. *J. Med. Chem.* **1981**, *24*, 435. (b) Landvatter, S. W.; Katzenellenbogen, J. A. *J. Med. Chem.* **1982**, *25*, 1300. (c) Katzenellenbogen, J. A. ref 3, p 73.

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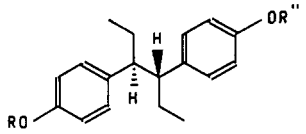
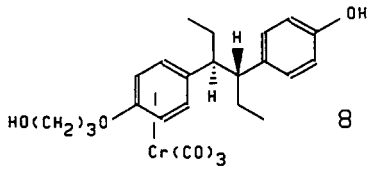
(8) Vessières, A.; Top, S.; Ismail, A. A.; Butler, I. S.; Louer, M.; Jaouen, G. *Biochemistry* **1988**, *27*, 6659.

(9) Top, S.; Jaouen, G.; Vessières, A.; Abjean, J.-P.; Davoust, D.; Rodger, C. A.; Sayer, B. G.; McGlinchey, M. J. *Organometallics* **1985**, *4*, 2143.

(10) Value quoted in ref 6b; in this laboratory, the RBA value for *meso*-hexestrol is found to be ≈70%.



6 R = R'' = CH_2Ph 7 R = $HO(CH_2)_3$; R'' = H



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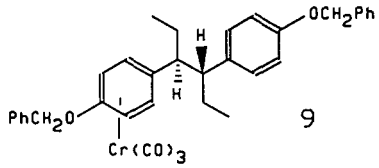
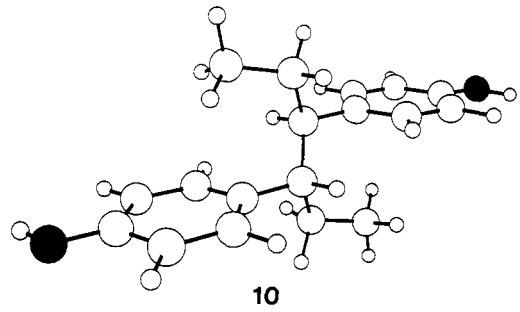


9

Table I. The alert reader will already have realized that complexation of a metal to one of the rings of *meso*-hexestrol not only destroys the centrosymmetric character of the molecule but also generates an enantiomeric mixture since the metal can bind to a phenyl attached to an *R* or to an *S* benzylic carbon center. Clearly, only one of these isomers has the same absolute configuration at the benzylic positions as is found in estradiol and so one might imagine that the RBA value would be affected. Nevertheless, previous work using pure enantiomers in the hexestrol series seems to show that RBA values of *d* and *l* forms are rather similar.[11] So even taking into account the fact that only one of the enantiomers is active this diminution of the RBA is too great to be attributed entirely to the use of a racemate. A plausible explanation for this reduced recognition factor may lie in the conformational changes induced by the presence of the relatively bulky $Cr(CO)_3$ group. We need to establish the true role of the $Cr(CO)_3$ moiety in these systems. Let us begin by examining the conformers which are energetically available to hexestrol itself.

Molecular Modeling, NMR Spectroscopy, and Conformations of Hexestrol. The conformations of *meso*- and *d,l*-hexestrol in solution were first analyzed a decade ago in an important pioneering study by Katzenellenbogen et al.[12] They used a combination of force field calculations and ^1H NMR spectroscopy on a series of molecules closely analogous to hexestrol and were able to show that the meso isomer adopts the antiperiplanar conformation (see Figure 1); this contrasts with the situation for the chiral molecule (3*S*,4*S*)-hexestrol for which the (−)-synclinal rotamer is favored. Gratifyingly, this latter result was in excellent accord with the X-ray crystallographically determined geometry for *d,l*-hexestrol.[13] These workers then went on to conclude that the conformational preferences provide a straightforward rationale for the markedly different RBA values for the meso and *d,l* forms, viz. 70% and 3.2%, respectively. It is readily seen that the superposition of a molecule of estradiol and the antiperiplanar form of *meso*-hexestrol reveals an excellent correspondence.



10

Figure 1. The energy-minimized antiperiplanar conformation, 10, of *meso*-hexestrol.

In that study the force field calculations were carried out on *meso*-3,4-diphenylhexane and yielded a relatively symmetrical structure for the antiperiplanar conformer; the synclinal rotamers were found to lie 1.3 kcal mol^{-1} above the minimum energy value. We have repeated these calculations (but for *meso*-hexestrol) using the programs MACROMODEL,[14] PCMODEL,[15] and ALCHEMY,[16] all of which give essentially the same result. In accord with the original report, the antiperiplanar conformation **10** is the favored structure. In particular, the dihedral angles between the two benzylic protons and between each benzylic proton and its neighboring methylene hydrogens are 180°, 170° and 71°, respectively. The barrier to interconversion of antiperiplanar and synclinal forms is ≈3 kcal mol^{-1} (in agreement with the findings of Katzenellenbogen), but the energy requirement for small rotations of the ethyl groups relative to the C_α–$C_{\alpha'}$ vector is almost negligible.

Any attempt to measure the dihedral angle between the benzylic hydrogens in *meso*-hexestrol by using NMR spectroscopy must overcome the symmetry equivalence of these two nuclei.[17] Katzenellenbogen et al. chose to break the symmetry by incorporating an ester function, as in *erythro*-methyl 3,4-bis(4-methoxyphenyl)hexanoate, 11. This molecule yielded a value for the coupling constant $J_{H\alpha-H\alpha'}$ of 10.5 Hz while the couplings from H_α to the methylene protons were reported as 10.5 and 5.0 Hz.[12] With the advent of higher field spectrometers and multipulse techniques,[18] it is now possible to extract information from molecules in which perturbations from the idealized symmetry are minimal. That is, coupling constants can be obtained even from systems exhibiting severe peak overlap. The 500-MHz ^1H NMR spectrum of **7**, the hydroxypropyl derivative of *meso*-hexestrol, appears as in Figure 2 and yields a value of 10.3 Hz for $J_{H\alpha-H\alpha'}$ and coupling constants of 10.3 and 3.6 Hz for both sets of benzylic H–methylene H interactions. We note parenthetically that the methylene groups of the hydroxypropyl chain in **7** can also be unequivocally assigned. The central

(11) Landvatter, S. W.; Katzenellenbogen, J. A. *Mol. Pharmacol.* **1981**, *20*, 43.
(12) Kilbourn, M. R.; Arduengo, A. J.; Park, J. T.; Katzenellenbogen, J. A. *Mol. Pharmacol.* **1981**, *19*, 388.
(13) Weeks, C. M.; Pokrywiecki, S.; Duax, W. L. *Acta Crystallogr.* **1973**, *B29*, 1729.
(14) MACROMODEL: written by W. C. Still, Columbia University, New York.
(15) PCMODEL: available from Dr. K. Gilbert, Serena Software, Bloomington, IN.
(16) ALCHEMY: available from Tripos Associates, St. Louis, MO.
(17) The measurement of $J_{H\alpha-H\alpha'}$ in unsubstituted hexestrol is nontrivial since these two symmetry-related protons obviously resonate at the same frequency. One possible approach could be to incorporate one $Cr(CO)_3$ group which would activate its neighboring benzylic proton toward base-catalyzed H/D exchange. Subsequent removal of the organometallic fragment will yield hexestrol possessing one benzylic deuterium site. Now the ^1H NMR signal of the remaining benzylic hydrogen will be triplet split by deuterium ($I = 1$) such that $J_{H\alpha-D\alpha'}$ will be directly measurable. This H–D coupling constant is reduced relative to the invisible $J_{H\alpha-H\alpha'}$ value by the factor 6.51 (i.e., γ_H/γ_D, where γ is the magnetogyric ratio for the particular nucleus).
(18) Derome, A. E. *Modern NMR Techniques for Chemistry Research*; Pergamon Press: Oxford, 1986.

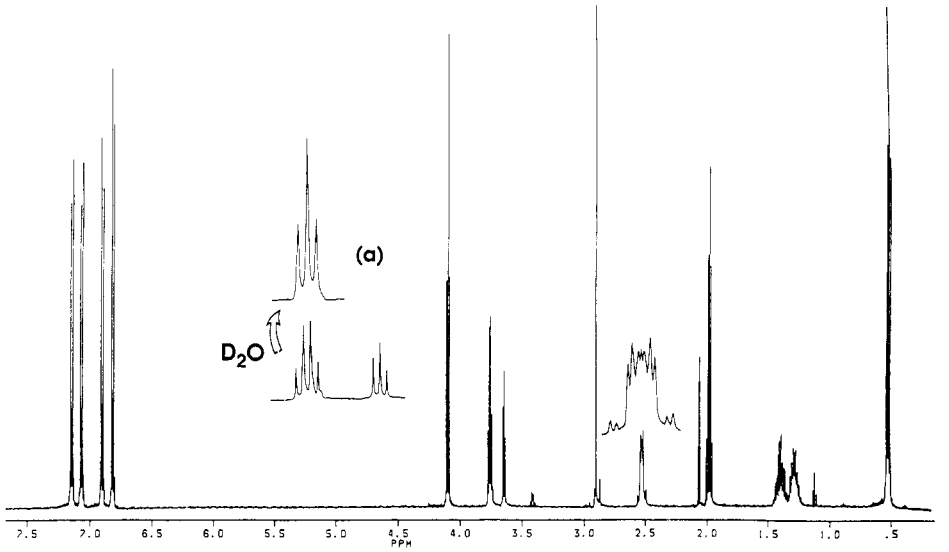


Figure 2. 500-MHz ^1H NMR spectrum of $HO(CH_2)_3OC_6H_4CHEtCHEtC_6H_4OH$, **7**; inset (a) shows an expansion of the region δ 3.8–3.6 and the effect of adding D_2O.

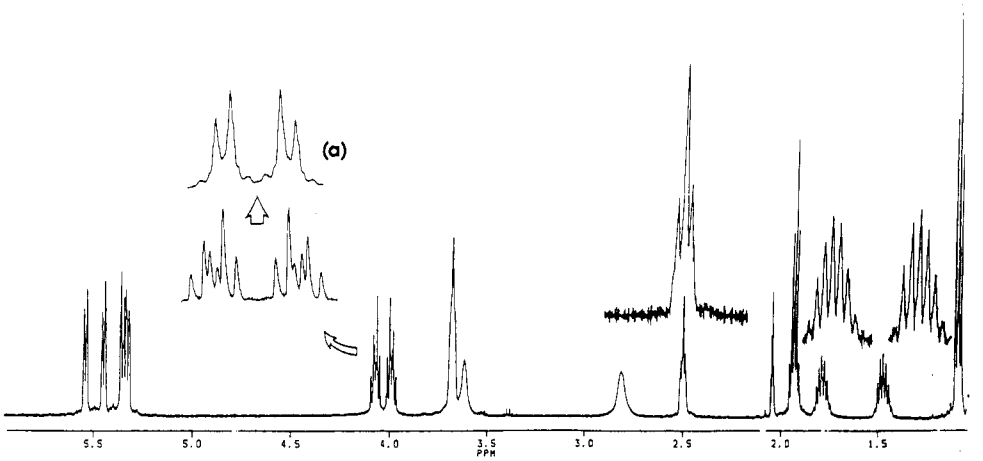


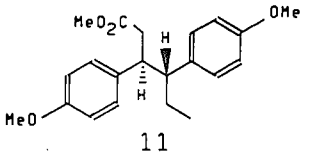
Figure 3. 500-MHz ^1H NMR spectrum of $HO(CH_2)_3OC_6H_4CHEtCHEtC_6H_4(CH_2)_3OH[Cr(CO)_3]_2$, **12**; inset (a) shows an expansion of the peaks in the region δ 4.1–3.9 and the effect of decoupling the central methylene group.

CH_2 is found at δ 1.99 as a pseudoquintet while the two OCH_2 groups resonate at δ 3.73 and 4.07. The former is a pseudoquartet by virtue of coupling to the alcoholic proton which is itself a triplet (J = 5.3 Hz); addition of D_2O washes out the coupling to the terminal methylene group and thus confirms the assignments.

The careful measurement of vicinal proton coupling constants, $^3J_{H-H}$, in conjunction with the Bothner-By version of the Karplus equation,[19] can provide information concerning dihedral angles in H–C–C–H fragments. Relationships of this type have been widely invoked despite the cautionary remarks of their progenitor;[20] nonetheless, their use in conformational analysis is of unquestionable value.[21] As mentioned above, the coupling constant $J_{H\alpha-H\alpha'}$ between the benzylic protons of *erythro*-methyl 3,4-bis-(4-methoxyphenyl)hexanoate, **11** (analogous to *meso*-hexestrol), is approximately 10.5 Hz, but $J_{H\alpha-H\alpha'}$ is only about 5.0 Hz in the threo isomer (analogous to *d,l*-hexestrol). Moreover, there is a significant chemical shift difference between the methyl groups in the meso (δ 0.54) and *d,l* (δ 0.72) forms. These data are consistent with the assignment of the favored conformers as being antiperiplanar and (–)-synclinal, respectively.[12] The antiperiplanar structure not only mandates a large dihedral angle between the benzylic C–H bonds but also places the methyls in the shielding region of the cones of anisotropy associated with the arene rings. Likewise, the smaller $^3J_{H-H}$ value found in the threo molecule is in accord with the 68° dihedral angle observed in the solid-state structure of *d,l*-hexestrol.[13] In keeping with this trend, the methyl groups in the monoprotected *meso*-hexestrol **7** are found at δ 0.49, entirely consonant with the $J_{H\alpha-H\alpha'}$ value of 10.3 Hz.

Turning now to the bis-$Cr(CO)_3$ complex of *meso*-bis-(hydroxypropyl)hexestrol, **12**, the molecular modeling approach again tells us that the centrosymmetric geometry is favored. That is, we expect a structure similar to **10** in which each phenyl ring bears a tripodal moiety. Of course, the symmetry of the complex precludes observation of coupling between the two equivalent benzyl protons but the measured $^3J_{H-H}$'s for the interactions of H_α with the neighboring methylene protons are 5.9 and 6.0 Hz. Clearly, we no longer have a methylene proton oriented so as to make a dihedral angle of $\approx$180° with the benzylic proton; indeed, such J values are more in keeping with a twist angle of $\approx$50°. In this metal-complexed system the presence of the $Cr(CO)_3$ group on one face of each phenyl ring

(19) (a) Karplus, M. *J. Chem. Phys.* **1959**, *30*, 11. (b) Bothner-By, A. A. *Adv. Magn. Reson.* **1965**, *1*, 195.
(20) Karplus, M. *J. Am. Chem. Soc.* **1963**, *85*, 2870.
(21) (a) Booth, H. *Prog. NMR Spectroc.* **1969**, *5*, 149. (b) Colucci, W. J.; Jungk, S. J.; Gandour, R. D. *Magn. Reson. Chem.* **1985**, *23*, 335.



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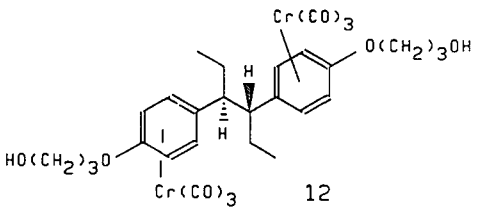

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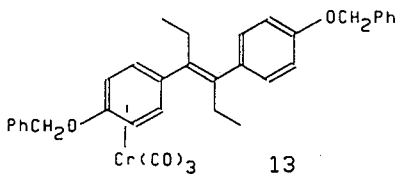

13

renders all four aromatic proton positions different since ring rotation no longer interconverts the ortho and ortho′ (and meta and meta′) environments (see Figure 3). Particularly noteworthy, however, is the marked diastereotopic character of the methylene protons attached to the phenolic oxygen. There is, of course, no need to invoke slowed rotation of the hydroxypropyl chain in a such a system,[22] but the observation caused us to consider the possibility that the hydroxyl group at the end of the chain might be involved in an interaction with the metal center as has been invoked for analogous ferrocenyl molecules.[23] Clearly, X-ray crystallographic data would be valuable in this case.

The questions raised concerning the molecular geometries of 7 and 12 can be answered to some extent as a result of an NMR spectroscopic and X-ray crystallographic study of the mono-$Cr(CO)_3$ complex of 7. The 500-MHz ^1H NMR spectrum of 8, the π-$Cr(CO)_3$-complexed hydroxylpropyl derivative of hexestrol, permits a very clear separation of the benzylic protons which resonate at δ 2.22 (H_α) and 2.64 ($H_{\alpha'}$). Furthermore, the diastereotopic character of the methylene pairs in each ethyl substituent is evident (see Figure 4) and allows the extraction of the appropriate coupling constants between these protons and their benzylic neighbors. Selective irradiation experiments yielded a $J_{H\alpha-H\alpha'}$ value of 6.7 Hz which is consistent with a dihedral angle of $\approx$40° or $\approx$130°; of these, the latter is greatly favored on steric grounds. The benzylic proton H_α adjacent to the $Cr(CO)_3$-complexed ring exhibits couplings to its methylene partners of 6.2 and 6.7 Hz, rather similar to the behavior of the bis-$Cr(CO)_3$ molecule 12. In contrast, the benzylic hydrogen $H_{\alpha'}$, which is next to the noncomplexed phenyl ring, reveals J values of 10.8 and $\approx$2 Hz; this parallels the situation for the noncomplexed molecule 7 in which one of the methylene protons is disposed at a dihedral angle of 180° to the benzylic C–H bond.

X-ray Crystallography. An X-ray crystallographic structure determination of 8 was undertaken and confirmed (see Figure 5 and Tables S1, S2, S5, and S7, supplementary material) the general features of the geometry which had been deduced from the spectroscopic and molecular modeling approaches. In particular, the phenyl rings adopt an approximately antiperiplanar arrangement in which the dihedral angle C_{ar}–C_α–$C_{\alpha'}$–$C_{ar'}$ is 179°. In fact, the two ring planes are not perfectly parallel; the twist angle between the two is $\approx$25°. Likewise, the CH_2–C_α–$C_{\alpha'}$–CH_2 angle is 180° while the dihedral angle H_α–C_α–$C_{\alpha'}$–$H_{\alpha'}$ is 173°, i.e., approximately 40° larger than the value indicated from the NMR coupling constant data. Furthermore, the ethyl substituents seem to have twisted relative to their conformation in solution. The NMR data suggest that in solution the ethyl group attached to $C_{\alpha'}$ should have one of the methylene protons almost orthogonal to the $C_{\alpha'}$–$H_{\alpha'}$ bond. In the solid state, however, these methylene protons make $H_{\alpha'}$–$C_{\alpha'}$–C–H angles of 161° and 46°. The corresponding H_α–C_α–C–H angles are 153° and 91°. These data must however be put in perspective since the Karplus relationship is based on calculations for an isolated $-CH_2CH_2-$ fragment with normal bond angles. It is noteworthy that the C_α–C_β–C_γ and $C_{\alpha'}$–$C_{\beta'}$–$C_{\gamma'}$ bond angles in 8 have opened up from their normal values of 110–111° to approximately 120°. This undoubtedly arises as a result of steric interactions with the bulky $Cr(CO)_3$ group. Similar effects have been noted in $(C_6Et_6)Cr(CO)_3$ and related nitrosyl and thiocarbonyl complexes where the C_{ar}–CH_2–CH_3 angle is 112° for the *distal* ethyls but opens up to $\approx$117° for the ethyls *proximal* to the tripodal fragment.[24,25] In alkyl chains with potentially large angular distortions one should perhaps be rather circumspect when relating vicinal coupling constants to dihedral angles. Moreover, it is possible that another factor may come into play. The possibility has been raised that the hydroxypropyl chain may interact with the chromium center in 8. If such were to be the case, one would certainly anticipate minor differences between the solid state and solution structures. As is common with such systems, the crystal structure reveals the existence of intermolecular hydrogen bonds in the solid state. Thus, the distance between the hydroxypropyl oxygen of one molecule and the phenolic oxygen of the next molecule is 2.8 Å—a value entirely typical of weak hydrogen bonding interactions.[26] It seems to be the case that the solid-state structure is dominated by the *intermolecular* hydrogen bonding interactions, which are absent for the individual molecules in solution, and which may account for the small angular deviations between the structures in the two phases.

From the perspective of the organometallic chemist, we note that the orientation of the tricarbonylchromium moiety in 8 places the CO ligands such that they eclipse the C_{ar}–O bond and the arene carbons meta to this position. In effect, the chromium atom is in an octahedral environment and is bonded to the carbons which are ortho and para to the alkoxy substituent, i.e., the most electron-rich ring positions, as originally discussed by Sim et al. a number of years ago.[27]

The principal lesson to be drawn from the crystal structure of 8 is that the presence of the $Cr(CO)_3$ unit restricts somewhat the motion of the ethyl groups. This in turn destabilizes the perfect antiperiplanar alignment of the phenyl rings which is thought to be essential for hexestrol to bind effectively to the estradiol receptor site.

In order to ascertain the effect of placing sp^2- rather than

(22) Sanders, J. K. M.; Hunter, B. K. *Modern NMR Spectroscopy—A Guide for Chemists*; Oxford University Press: Oxford, 1987; p 299.
(23) Kotz, J.; Pedrotty, D. *Organomet. Chem. Rev. A* **1969**, *4*, 479 and references therein.
(24) Iverson, D. J.; Hunter, G.; Blount, J. F.; Damewood, J. R., Jr.; Mislow, K. *J. Am. Chem. Soc.* **1981**, *103*, 6073.
(25) Mailvaganam, B.; Frampton, C. S.; Top, S.; Sayer, B. G.; McGlinchey, M. J. *J. Am. Chem. Soc.* **1991**, *113*, 1177.
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(27) (a) Carter, O. L.; McPhail, A. T.; Sim, G. A. *J. Chem. Soc. A* **1966**, 822. (b) Carter, O. L.; McPhail, A. T.; Sim, G. A. *J. Chem. Soc. A* **1967**, 1619.

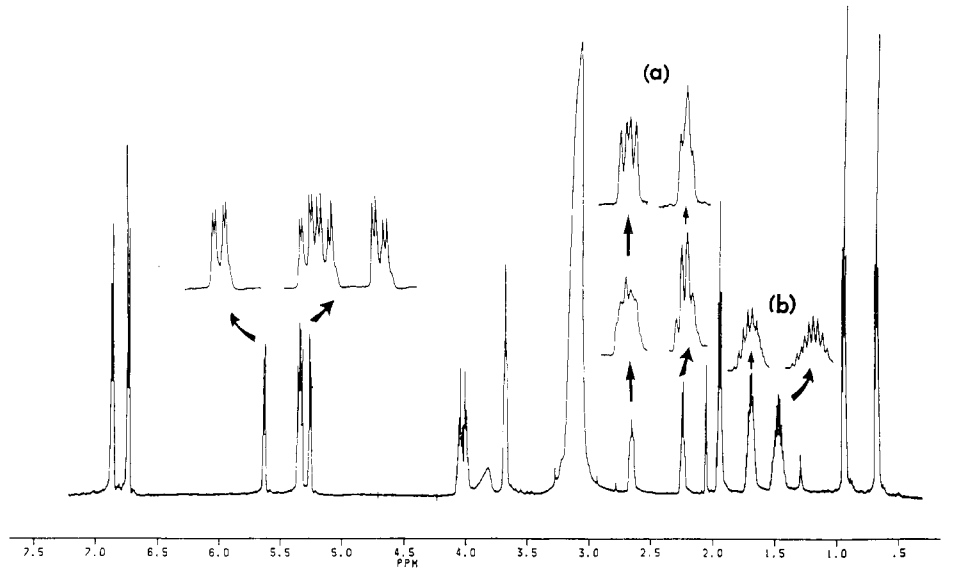

Figure 4. 500-MHz ^{1}H NMR spectrum of $HO(CH_2)_3OC_6H_4[Cr(CO)_3]CHEtCHEtC_6H_4OH$, **8**: inset (a) shows an expansion of the Hα and Hα' peaks in the region δ 2.2–2.8 and the effect in each case of decoupling one of the neighbouring methylene protons; inset (b) shows an expansion of the methylene peaks in the range δ 1.7–1.4.

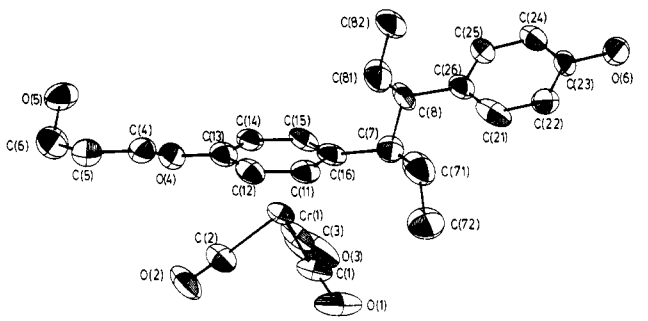

Figure 5. ORTEP view of $HO(CH_2)_3OC_6H_4[Cr(CO)_3]$-$CHEtCHEtC_6H_4OH$, **8**.

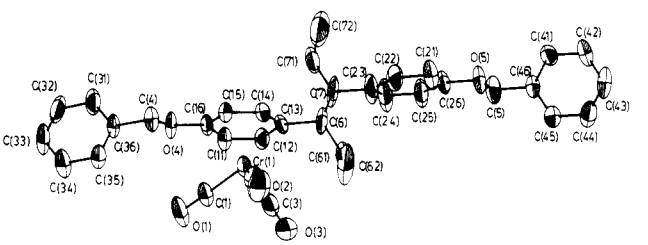

Figure 6. ORTEP view of $PhCH_2OC_6H_4[Cr(CO)_3]$-$CHEtCHEtC_6H_4OCH_2Ph$, **13**.

sp^3-hybridized carbons in the benzylic positions, a $Cr(CO)_3$ complex of a DES derivative was used. Crystals of the bis(benzyloxy) complex **13** were suitable for an X-ray diffraction study, and the resulting structure appears as Figure 6. The crystallographic data are collected in Tables S1, S7, S8, and S11 (supplementary material). In this case, the phenyl rings are twisted relative to each other by only 11° and so are close to adopting a perfect antiperiplanar geometry. In contrast, the benzyl rings are almost orthogonal to their phenyl neighbors. As with **8**, we note that the ethyls have opened up; the C_α–C_β–C_γ and $C_{\alpha'}$–$C_{\beta'}$–$C_{\gamma'}$ bond angles in **13** are 115.4° and 119.7°, respectively. It is noteworthy that the angles made by the benzyloxy substituents with the phenyl rings are markedly different; the angles C(11)–C(16)–O(4) and C(15)–C(16)–O(4) are 115° and 123°, respectively. A similar effect is seen with the $HO(CH_2)_3O$ chain in **8**. Once again we see that the steric requirements of the tricarbonylchromium fragment impose restrictions on the flexibility of the molecule.

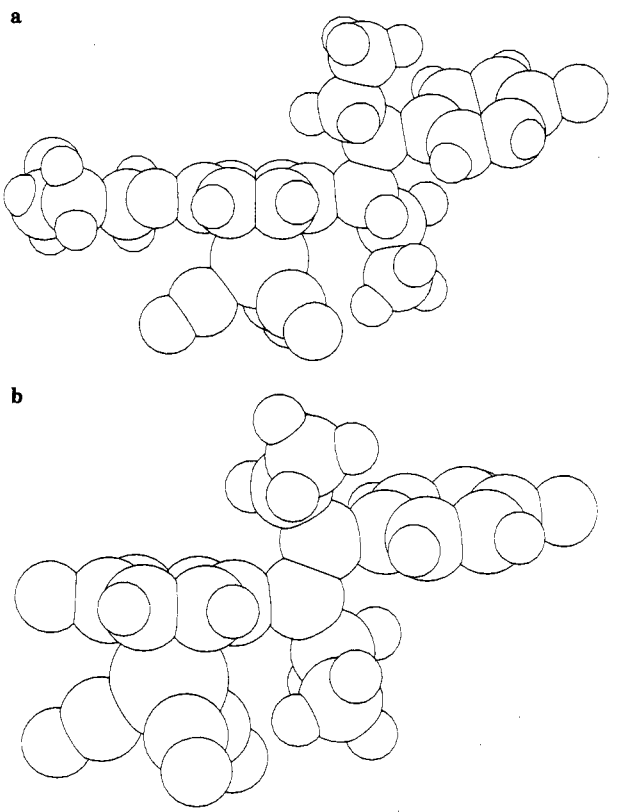

Figure 7. Space-filling models of (a) **8** and (b) **13**.

In comparison to the known solid-state structure of DES, we note that the planes of the phenyl rings in DES are parallel but not coplanar.[28] The rings are twisted by 62° relative to the plane containing the central double bond. The corresponding twist angles for **13** are 82° (for the complexed ring) and 84° (for ring C(21)–C(26)). It is readily apparent that the degree of ring twisting is greater for **13** than for DES. Moreover, the ethyl substituents in **13**, unlike those in **8** and in DES itself, are both oriented

(28) (a) Smiley, I. E.; Rossmann, M. G. *J. Chem. Soc., Chem. Commun.* **1969**, 198. (b) Weeks, C. M.; Cooper, A.; Norton, D. A. *Acta Crystallogr.* **1970**, *B26*, 429. (c) Busetta, B.; Courseille, C.; Hospital, M. *Acta Crystallogr.* **1973**, *B29*, 2456.

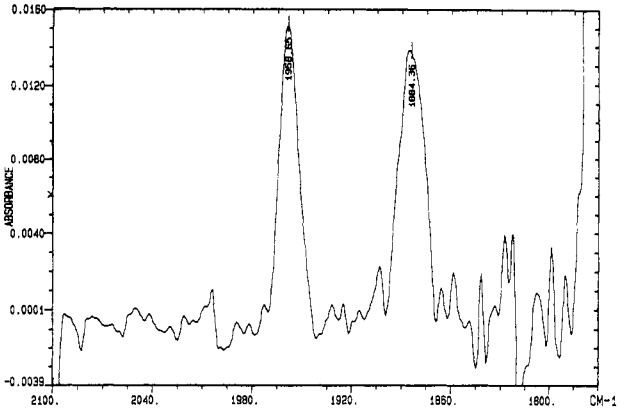

Figure 8. FTIR difference spectrum of $HO(CH_2)_3OC_6H_4[Cr(CO)_3]CHEtCHEtC_6H_4OH$, **8**, after incubation with lamb uterine cytosol (see text).

to the same face of the central double bond. This is clearly illustrated in Figure 7 which depicts space-filling representations of **8** and **13**.

In making comparisons between the natural hormone, 17β-estradiol, and nonsteroidal hormones, discussion has focused on the distance between the oxygens at C-3 and C-17 since these OH groups presumably control the attachment to the receptor site. In estradiol this distance is in the range 10.9–11.0 Å depending on the solvent used for the crystallization; in DES this distance is 12.13 Å. In **8** and **13** the separation between the oxygens attached to the phenyl rings is 11.97 and 11.98 Å, respectively. Consequently, the distance criterion is adequately satisfied in these systems. We note also that, in the solid state, the distance between the hydroxyl oxygen at C-17 in **8** and the oxygen at the end of the hydroxypropyl chain is 14.9 Å. However, molecular modeling reveals that twisting of the hydroxypropyl chain is rather facile and there is no problem in positioning the oxygen at the end of this chain in the range 11–12 Å from the phenolic moiety in the noncomplexed ring.

Finally, we wish to focus on the RBA values for the chromium complexes shown in Table I. Incorporation of a hydroxypropyl chain at C-3 of estradiol allows considerable flexibility in the separation of the two hydroxy groups, and it is found that the RBA for **7** is 37% of that for the natural hormone. We see from Table I that placement of a $Cr(CO)_3$ fragment on the α-face of the arene ring has a rather small effect on the RBA value, in sharp contrast to that for the β-complex, **5**β. In the hexestrol series, analogous attachment of a hydroxypropyl chain indeed reduces the RBA value, but recognition is still acceptable. Gratifyingly, incorporation of the $Cr(CO)_3$ unit into **7** to give **8** shows only a small decrease in RBA. We note, however, that it is the noncomplexed arene ring which possesses the phenolic group while the complexed ring bears the hydroxpropyl chain. It is not immediately apparent which of these hydroxy functionalities mimics which OH group in 17β-estradiol. It could well be the case that the complexed ring is modeling the D ring of the natural hormone; it is now well established[7b] that placement of an organometallic group in the 17α position of estradiol, or related molecules, yields RBA values in the same range as we have found for **8**.

The foregoing discussion is predicated on the assumption that the chromium tripod is not lost during the reaction of the modified hexestrol with the receptor. It is obviously crucial to establish that the $Cr(CO)_3$ moiety remains firmly attached to the hexestrol system *even after binding has occurred*. To demonstrate this point, we have obtained an IR spectrum after incubation of 5×10^{-7} M **8** with lamb uterine cytosol. Figure 8 shows the result obtained by subtraction of the spectrum obtained with a pure protein pellet (obtained by precipitating pure lamb uterine cytosol proteins without incubation in the presence of an organometallic hormone) from that obtained after incubation with the complex. This spectrum clearly shows the two characteristic ν_{CO} bands of the $Cr(CO)_3$ tripod. This experiment establishes that the organometallic derivative of hexestrol is still well recognized by the estradiol receptor; moreover, its stability is sufficient to allow biochemical experiments.

In conclusion, we have used a combination of molecular modeling, high-resolution NMR spectroscopy, and X-ray crystallography to probe the conformational behavior of *meso*-hexestrol and several related complexes bearing tricarbonylchromium moieties. The incorporation of one or more $Cr(CO)_3$ fragments leads to unfavorable steric interactions between the tripod and the ethyl groups. The net result is that the antiperiplanar arrangement of the phenyl groups, which is a requirement for hormone–receptor binding, is disrupted. It is apparent that the RBA's of these molecules are crucially dependent on small changes in molecular geometry. Finally, it has been conclusively shown that the $Cr(CO)_3$ marker remains attached to the hexestrol system even after binding to the receptor site has occurred.

Experimental Section

All reactions were carried out under an atmosphere of dry nitrogen employing conventional benchtop and glovebag techniques. All solvents were dried according to standard procedures before use.[29] ^1H NMR spectra were recorded at 500 MHz by using a Bruker AM 500 spectrometer equipped with a 5-mm dual frequency $^1H/^{13}C$ probe.

***O*-(3-Hydroxypropyl)hexestrol, 7.** Following the procedure of Brewster and Putman,[30] hexestrol (0.54 g, 2 mmol) and NaOH (0.08 g, 2 mmol) were heated at reflux in acetone (50 mL) for 3 h. 3-Bromopropanol (0.42 g, 3 mmol) was added to the mixture, and the heating was continued for 48 h. After filtration and evaporation of the solvent the residual oil was chromatographed on silica gel plates (eluent: ether/pentane, 5:1) to yield **7** as a colorless solid (0.236 g, 0.72 mmol; 36%), mp 148 °C after recrystallization from ether/pentane. ^1H NMR (acetone-d_6): δ 8.05 (s, 1 H, phenolic OH), 7.11 (d, 2 H), 7.04 (d, 2 H), 6.87 (d, 2 H), 6.73 (d, 2 H) (aromatic protons), 4.07 (t, J = 6.3 Hz, 2 H, OCH_2), 3.73 (quartet, J = 6.3 Hz, 2 H, $HOCH_2$), 3.61 (t, 1 H, OH), 2.49 (m, 2 H, $J_{H\alpha-H\alpha'}$ = 10.3 Hz, Hα, Hα'), 1.99 (quintet, 2 H, J = 6.3 Hz, central CH_2), 1.34, 1.25 (m, m, 4 H, $J_{H\alpha-H\beta}$ = 3.6 and 10.3 Hz, CH_2-β, CH_2-β'), 0.49 (t, 6 H, J = 6.3 Hz, CH_3's). Anal. Calcd for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 75.26; H, 8.67. Mass spectrum: m/z 328 $(M)^+$, 193 $(HO(CH_2)_3OC_6H_4CHEt)^+$, 135 $(HOC_6H_4CHEt)^+$.

[*O*-(3-Hydroxypropyl)hexestrol]tricarbonylchromium(0), 8. Hexestrol (0.54 g, 2 mmol) and $Cr(CO)_6$ (0.66 g, 3 mmol) were heated at reflux in di-*n*-butyl ether for 5 h. The yellow solution obtained was filtered under argon and evaporated to dryness under vacuum. NaOH (0.08 g, 2 mmol) and acetone (50 mL) were added, and the mixture was heated under reflux for 1 h. 3-Bromopropanol (0.42 g, 2 mmol) was added to the mixture, and the heating was continued for 24 h. After cooling, the mixture was poured into water. The solution was extracted with diethyl ether and, after workup, chromatography on silica gel plates (eluent: ether/pentane, 2:1) yielded **8** as a yellow solid (0.27 g, 0.58 mmol; 29%), mp 162 °C after recrystallization from ether/pentane. ^1H NMR (acetone-d_6): δ 8.40 (s, 1 H, phenolic OH), 6.87 (d, 2 H), 6.74 (d, 2 H) (free aromatic protons), 5.64, 5.36, 5.33, 5.26 (dd,

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(30) Brewster, C. M.; Putman, I. J., Jr. *J. Am. Chem. Soc.* **1939**, *61*, 3083.

dd, dd, dd, 4 H, complexed aromatic protons), 4.04 (m, 1 H), 3.99 (m, 1 H) (OCH_2), 3.82 (br, 1 H, OH), 3.68 (m, 2 H, $HOCH_2$), 2.64 (ddd, 1 H, $J_{H\alpha-H\alpha'}$ = 6.7 Hz, $J_{H\alpha'-H\beta'}$ = 2.0 and 10.8 Hz, Hα'), 2.22 (ddd, 1 H, $J_{H\alpha-H\alpha'}$ = 6.7 Hz, $J_{H\alpha-H\beta}$ = 6.7 and 6.2 Hz, Hα), 1.99 (quintet, 2 H, J = 6.3 Hz, central CH_2), 1.67, 1.42 (m, m, 2 H, CH_2-β), 1.66 and 1.45 (m, m, 2 H, CH_2-β'), 0.91 (t, 3 H, J = 6.3 Hz, CH_3-γ), 0.65 (t, 3 H, J = 6.3 Hz, CH_3-γ'). Anal. Calcd for $C_{24}H_{28}O_6Cr$: C, 62.06; H, 6.08. Found: C, 61.86; H, 5.98. Mass spectrum: m/z 464 $(M)^+$, 380 $(M - 3CO)^+$, 328 $(M - 3CO - Cr)^+$, 193 $(HO(CH_2)_3OC_6H_4CHEt)^+$, 135 $(HOC_6H_4CHEt)^+$.

Bis-*O*-(3-hydroxypropyl)hexestrol. The procedure is analogous to that for **7** and gave the product in 58% yield, mp 142 °C (after recrystallization from dichloromethane). ^1H NMR (DMSO): δ 7.03 (m, 8 H, aromatic H's), 4.53 (t, 2 H, OH's), 4.05 (t, 4 H, OCH_2's), 3.63 (quartet, 4 H, $HOCH_2$'s), 1.88 (quintet, 4 H, central CH_2's), 1.23 (m, 4 H, CH_2CH_3's), 0.45 (t, 6 H, CH_2CH_3's). Anal. Calcd for $C_{24}H_{34}O_4$: C, 74.57; H, 8.86. Found: C, 73.67; H, 8.56. Mass spectrum: m/z 386 $(M)^+$, 193 $(HO(CH_2)_3OC_6H_4CHEt)^+$.

[Bis-*O*-(3-hydroxypropyl)hexestrol]bis[tricarbonylchromium(0)], 12. Bis[*O*-(3-hydroxypropyl)hexestrol] (0.39 g, 1 mmol) and $Cr(CO)_6$ (0.88 g, 4 mmol) were heated at reflux in di-*n*-butyl ether (120 mL) for 7 h. The yellow solution obtained was filtered and left overnight in the refrigerator to give **12** as yellow crystals (0.23 g, 0.35 mmol; 35%), mp 170 °C (after recrystallization from ether/pentane). ^1H NMR (acetone-d_6): δ 5.54, 5.33, 5.36, 5.36 (d, d, d, d, 8 H, complexed aromatic H's), 4.07 (d, J = 9.1, t, J = 6.4 Hz, 2 H) and 3.98 (d, J = 9.1, t, J = 6.4 Hz, 2 H) (OCH_2's), 3.67 (t, 4 H, $HOCH_2$'s), 3.61 (br, 2 H, OH's), 2.48 (pseudotriplet, J = 6 Hz, 2 H, Hα,Hα'), 1.92 (quintet, 4 H, central CH_2's), 1.77 and 1.46 (pseudoseptets, 4 H, CH_2-β), 1.08 (t, 6 H, J = 7.4 Hz, CH_3's). Anal. Calcd for $C_{30}H_{34}O_{10}Cr_2$: C, 54.71; H, 5.20. Found: C, 54.72; H, 5.32. Mass spectrum: m/z 658 $(M)^+$, 522 $(M - 3CO - Cr)^+$, 458 $(M - 6CO - Cr)^+$, 386 $(M - 6CO - 2Cr)^+$, 193 $(HO(CH_2)_3OC_6H_4CHEt)^+$.

[Bis(*O*-benzyl)hexestrol]tricarbonylchromium(0), 9. Hexestrol (0.54 g, 2 mmol) and $Cr(CO)_6$ (0.66 g, 3 mmol) were heated at reflux in di-*n*-butyl ether (120 mL) for 5 h. The yellow solution obtained was filtered under argon and evaporated to dryness under vacuum. NaOH (0.16 g, 4 mmol) and acetone (50 mL) were added, and the mixture was heated under reflux for 18 h. Benzyl bromide (1.36 g, 8 mmol) was added and the reflux continued for 2.5 h. After cooling, the solution was concentrated and then poured into water. The solution was extracted with diethyl ether and, after workup, chromatography on silica gel plates (eluent: ether/pentane, 2:3) yielded **9** as a yellow solid (0.46 g, 0.78 mmol; 39%), mp 162 °C after recrystallization from ether/pentane. ^1H NMR (acetone-d_6): δ 7.50 (m, 10 H, $PhCH_2$), 7.00 (m, 4 H, free aromatic H's), 5.58 (m, 4 H, complexed aromatic ring), 5.15, 5.05 (s, s, $PhCH_2$'s), 2.40 (m, 2 H, CHCH), 1.61 (m, 4 H, CH_2CH_3), 0.95 (t, 3 H, CH_3). Anal. Calcd for $C_{35}H_{34}O_5Cr$: C, 71.65; H, 5.84; Cr, 8.86. Found: C, 71.91; H, 5.89; Cr, 8.90. Mass spectrum: m/z 586 $(M)^+$, 502 $(M - 3CO)^+$, 450 $(M - 3CO - Cr)^+$, 411 $(M - 3CO - Cr - PhCH_2)^+$, 320 $(M - 3CO - Cr - 2PhCH_2)^+$, 225 $(PhCH_2OC_6H_4CHEt)^+$ $(PhCH_2)^+$.

Bis(*O*-benzyl)hexestrol, 6. A solution of [bis(*O*-benzyl)-hexestrol]tricarbonylchromium(0), **9**, in diethyl ether was exposed to sunlight for 2 h. After filtration and removal of solvent, **6** was obtained in quantitative yield, mp 218 °C.

X-ray Crystallography of 8 and 13. Yellow air-stable crystals of **8** (**13**) were grown from diethyl ether/pentane. In each case, a single crystal suitable for X-ray diffraction was selected, and precession photographs revealed that the crystal was monoclinic, and accurate cell parameters were determined from a least-squares fit to χ, φ, and 2θ for 25 (15) reflections in the range $78.5° < 2\theta < 80.0°$ ($14.1° < 2\theta < 24.9°$). Details of the data collection procedure are listed in Tables S1 and S7 (supplementary material). Measurements on **8** (**13**) were made on a Rigaku AFC6R (Nicolet P3) diffractometer with use of graphite-monochromated Cu Kα (Mo Kα) radiation. Data collection over h, k, $\pm l$ resulted in 1772 (3919) unique reflections and 1473 (1859) observed reflections with $I > 3\sigma(I)$. Data were corrected for Lorentz polarization effects, and for absorption. Considering only observed data, heavy-atom positions were found by direct methods (SHELXS-86).[31] Subsequent Fourier difference maps revealed the positions of all remaining atoms excluding the hydrogens which were placed at calculated positions (SHELX).[32] Anisotropic refinements of all non-hydrogen atoms by full-matrix least-squares methods resulted in final R_1 and R_2 values of 0.0696 (0.1247) and 0.0675 (0.1083), respectively. Scattering curves from ref 33 were applied during refinement of the structure, and anomalous dispersion corrections for Cr were applied from ref 34. All calculations were performed on a VAX 8650 computer. Programs XTAL[35] for data reduction, TAPER[36] for absorption correction, SHELXS-86[31] for structure solution, SHELX-76[32] for structure refinement, MOLGEOM[37] for molecular geometry, and SNOOPI[38] for drawing programs were used. Atomic positional parameters, temperature factors, and selected bond lengths and angles appear in the supplementary material.

Relative Binding Affinities. Relative binding affinities (RBA's) were determined as follows: Lamb uterine cytosol (0.2-mL fractions containing 4 mg of protein/mL) were incubated at 0 °C for 3 h with 2 nM[3*H*]-17β-estradiol (Amersham, England; specific activity 52 Ci/mmol) and increasing amounts of the competing steroids (10–1000-fold excess; nine concentrations in duplicate). Bound fractions were measured by protamine sulfate precipitation.[8] The RBA of the competitor is taken as the ratio [unlabeled estradiol]/[competitor] required to inhibit half of the specific [3*H*]-17β-estradiol binding, with the affinity of estradiol set at 100%.

FT-IR Analysis. Lamb uterine cytosol (8 mL) containing 4.8 mg/mL proteins were incubated for 4 h at 0 °C with the organometallic-labeled hexestrol derivative **7** to yield a final concentration of 5×10^{-7} M. At the end of the incubation period, an equal volume of protamine sulfate solution (2.4 mg/mL) was added to precipitate the proteins. The precipitates obtained were collected by centrifugation (3300*g*, 15 min). After elimination of the supernatants, the precipitates were washed three times with 1 mL of cold distilled water and lyophilized. This procedure yielded white powders which could be used directly for the FT-IR measurements. The receptor concentration in these samples was established by competitive binding assay with [3*H*]E2 to be in the range of 300 fmol/mg of total proteins. The solid samples were pressed into 3-mm pellets. The spectra were recorded on a Michelson-100 FT spectrometer (Bomem, Inc.) equipped with a liquid nitrogen cooled 1.0-mm InSb (indium antimonide) detector and a 1.0-mm diameter beam. The IR spectral data were processed on a NEC APC IV microcomputer. A total of 5000 coadded interferograms were apodized using a cosine function and then Fourier transformed to yield spectra of 4-cm^{-1} resolution.

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Supplementary Material Available: Tables listing crystal data, atomic and hydrogen positional parameters, temperature factors, and selected bond lengths and angles for **8** and **13** (11 pages). Ordering information is given on any current masthead page.

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