(29) D. I. C. Scopes, U. Zarnack, N. J. Leonard, R. Y. Schmitz, and F. Skoog, *Phytochemistry*, **15**, 1523 (1976).
(30) Complete information regarding conditions of reaction, yields, analyses, and UV and NMR spectra may be found in the Ph.D. thesis of G. C. Walker, University of Illinois, 1974.
(31) T. Fujii and T. Saito, *Chem. Pharm. Bull.*, **21**, 1954 (1973).
(32) N. J. Leonard and R. A. Laursen, *J. Org. Chem.*, **27**, 1778 (1962).
(33) N. J. Leonard, K. L. Carraway, and J. P. Helgeson, *J. Heterocycl. Chem.*, **2**, 291 (1965).
(34) E. Fischer, *Ber. Dtsch. Chem. Ges.*, **31**, 104 (1898).
(35) R. N. Prasad and R. K. Robins, *J. Am. Chem. Soc.*, **79**, 6401 (1957).
(36) E. C. Taylor and P. K. Loeffler, *J. Org. Chem.*, **24**, 2035 (1959).
(37) J. A. Montgomery and C. Temple, Jr., *J. Am. Chem. Soc.*, **83**, 630 (1961).
(38) J. A. Montgomery, K. Hewson, and C. Temple, Jr., *J. Med. Pharm. Chem.*, **5**, 15 (1962).
(39) A. D. Broom, L. B. Townsend, J. W. Jones, and R. K. Robins, *Biochemistry*, **3**, 494 (1964).
(40) H. J. Schaeffer and R. Vince, *J. Med. Chem.*, **8**, 710 (1965).
(41) M. Rasmussen and N. J. Leonard, *J. Am. Chem. Soc.*, **89**, 5439 (1967).
(42) N. J. Leonard and M. Rasmussen, *J. Org. Chem.*, **33**, 2488 (1968).
(43) H. Suda, T. Takeuchi, T. Nagatsu, M. Matsuzaki, I. Matsumoto, and H. Umezawa, *Chem. Pharm. Bull.*, **17**, 2377 (1969).
(44) G. D. Hartman, S. E. Biffar, L. M. Weinstock, and R. Tull, *J. Org. Chem.*, **43**, 960 (1978).
(45) T. A. Jacob, R. P. Buhs, A. Rosegay, J. Carlin, W. J. A. VandenHeuvel, and F. J. Wolf, *Fed. Proc., Fed. Am. Soc. Exp. Biol.*, **37**, 3139, abstract (1978).
(46) F. J. Wolf, J. J. Steffens, R. F. Alvaro, and T. A. Jacob, *Fed. Proc., Fed. Am. Soc. Exp. Biol.*, **37**, 3141, abstract (1978).
(47) R. W. Fuller, P. P. K. Ho, Ch. Matsumoto, and J. A. Clemens, *Adv. Enzyme Regul.* **15**, 267–281.

Structural Requirements for Progestational Activity. Synthesis and Properties of *rac*-8α,9β,10α,14β-Progesterone[1-3]

A. J. Solo,* Virendra Kumar, Vitauts Alks,

Department of Medicinal Chemistry, School of Pharmacy, State University of New York at Buffalo, Amherst, New York 14260

and William L. Duax

Medical Foundation of Buffalo, Inc., Buffalo, New York 14203. *Received April 10, 1978*

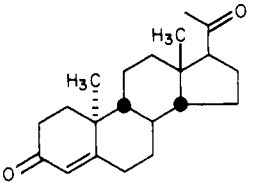
rac-8α,9β,10α,14β-Progesterone, 1, has been synthesized and subjected to X-ray crystallographic analysis which established that the ring conformations are A, 1β-sofa; B, chair; C, chair; and D, intermediate between an envelope and a half-chair. This compound is 10% as active as progesterone in the Clauberg assay and has an affinity for the uterine cytosol (rabbit) receptor for progesterone 2% as great as that of progesterone.

This work is part of a continuing investigation into the mode of binding of progesterone analogues to the uterine receptor.[4,5] Earlier, we put forward[4] an extension of Ringold's hypothesis on the mode of binding of gestogens to the uterine receptor.

In essence, the modified hypothesis[4] states that gestogens bind to the uterine receptor via their β face and that the most important binding points are the A-ring enone and the C-20 carbonyl oxygen of progesterone derivatives or the C-17β hydroxyl of 17α-ethinyltestosterone derivatives. With the molecule in the conformation which it would occupy while complexed to the receptor (with the critical A and D ring substituents in positions similar to those which the corresponding groups of progesterone or ethinyltestosterone would occupy), the bulk at C-10β must be equal to, or preferably less than, that of a methyl group, and some bulk must be present at C-13β. The hypothesis implies that the detailed stereochemistry at centers other than C-13 is unimportant, except as determinants of the β-face topography of the molecule. Kontula[6] has presented studies showing that the enone system and the acetyl side chain of progesterone each contribute approximately 3 kcal to its binding energy and an additional 6 kcal of binding energy derives from interaction of the rest of the nucleus with the receptor. The latter 6 kcal may derive, as Kontula suggests, from a loose fit between the gestogen and the receptor or it may arise from a relatively tight fit to some portion of the steroid nucleus with little or no contribution from the remaining portions.

Figure 1 depicts similar projections of the X-ray crystal structures[7] reported for progesterone and for 9β,10α-pregna-4,6-diene-3,20-dione. With the exception of the protuberance of the C-10β methyl of progesterone, the similarity of the β-face topography of these gestogens is marked. We assume that for optimal fit to the uterine receptor the β-face of a steroid must have a shape similar to these as shown in Figure 1. However, our hypothesis, in its present form, does not adequately define limits on that shape. Therefore, an extension of the hypothesis based on additional data seems to be required.

8α,9β,10α,13β,14β,17β-Progesterone (1) differs from



1

progesterone in stereochemistry at four of the six chiral centers. Examination of Dreiding-type models of 1 reveal that if this structure has its C ring in a twist conformation the β-face, although slightly concave upward in contrast to the convex surfaces of the structures depicted in Figure 1, appears to meet the requirements for binding to the uterine receptor for progesterone. However, if the C ring of the model is converted to a chair form, the β face becomes strongly concave upward over the A, B, and C rings but bends sharply downward at the C/D junction. This contour is very different from that of any known gestogen and was not expected to be capable of binding to the receptor.

An X-ray crystallographic study of 3β-[(*p*-bromobenzoyl)oxy]-13α-androst-5-en-17-one, a compound having an enantiomorphic relationship to 1 at the C-8, -9, -10, -13,

0022-2623/79/1822-0129$01.00/0

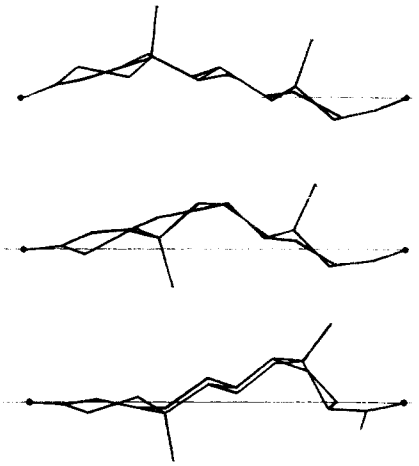
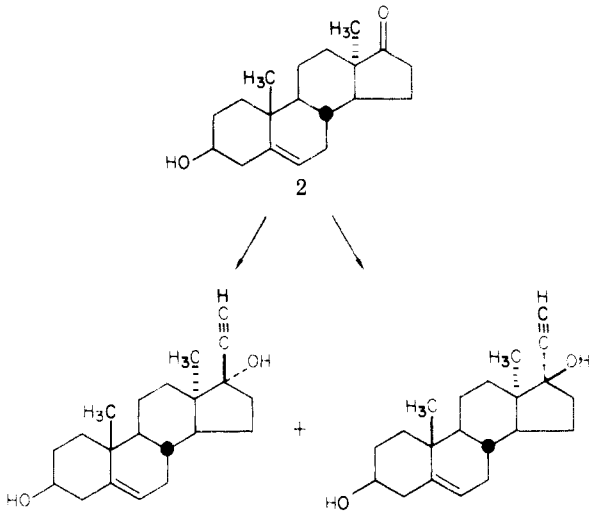


Figure 1. Projections of the X-ray crystal structures of progesterone, 9β,10α-pregna-4,6-diene-3,20 dione, and 8α,9β,10α,-14β-progesterone. Progesterone is viewed parallel to the least-squares plane through atoms C-5 to C-17. 9β,10α-Pregna-4,6-diene-3,20-dione is viewed parallel to a line joining the midpoints of the bonds C-11–C-12 and C-8–C-14. 8α,9β,10α,14β-Progesterone is viewed parallel to the least-squares plane through atoms C-1 to C-14. The projections have been oriented to place the line joining the oxygens at C-3 and C-20 horizontal.

and -14 positions, shows the C ring to be a chair.[8] Models of the X-ray structure show that with the C ring in the chair conformation the β face of the C-17 carbonyl group is severely hindered by the 8β- and 11β-hydrogen atoms. In spite of this, Nambara and Goto report that 13-isodehydroepiandrosterone (2) reacts with ethinylmagnesium



bromide to give a mixture containing two parts of the product of β attack to one part of the product of α attack.[9] Nambara and Goto's results would not be unexpected if the C ring were in a twist form but seem at variance with what would be expected with the form seen in the crystal. Moreover, Chinn has reported that an NMR study of 13α,17α-testosterone implies that the C ring of this related compound is intermediate between a chair and a twist boat form.[10]

To probe the requirements for binding to the uterine receptor for progesterone and in the hope of finding compounds with good Clauberg activity but little other endocrine activity,[11] we have undertaken a study of 1 and its derivatives. Because of the uncertainty regarding the preferred geometry of 1, it was decided to first synthesize and assay the parent compound and to attempt to obtain an X-ray crystal structure of it. The X-ray structure would then be used to predict the substitution required to produce a compound whose structure would be in better accord with the requirements for progestational activity.

Since steroidal intermediates from natural sources seem ill suited to the synthesis of 1, we determined to proceed by total synthesis. The enantiomer of 1 is 13α,17α-progesterone (**1a**) a compound potentially available by variants of Johnson's or Nagata's syntheses.[15,16]

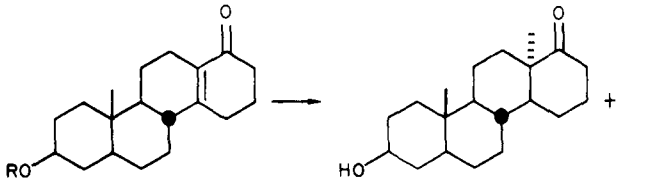
Johnson has reported that angular methylation of steroidal intermediates which lack 9(11) unsaturation favors formation of the 13α isomer.[17] We began by investigating the possibility that reductive methylation[18] of **3b** might shift the α/β ratio still further in favor of the α isomer while permitting us to shorten Johnson's synthesis.[15] *rac*-3β-Hydroxy-10β-methyl-5α-*D*-homo-13-(14)-gonen-17a-one, **3a**, was converted to the tetrahydropyranyl ether which was subjected to reductive methylation at −33 °C in liquid ammonia–tetrahydrofuran solution using a threefold ratio of lithium or potassium and a large excess of methyl iodide. The reaction was also attempted at 25 °C (in THF) using a three- to fivefold excess of potassium. In all cases, the crude yield of alkylated material was less than 50%, the dominant material was the β isomer **4b**, and substantial amounts of crystalline α-isomer **4a** proved prohibitively difficult to isolate.

Because of the unfavorable result obtained in the above attempt to shorten Johnson's synthesis, we decided to attempt to achieve our synthetic goal as expeditiously as possible. By following other procedures of Johnson,[19] we synthesized the known *rac*-5β,13α,17α-pregnane-3,20-dione (**10**) from 5-methoxy-2-tetralone by way of intermediates **5** to **9**. Compound **8** was isolated more easily and in slightly higher yield by using thin-layer chromatography in place of the column chromatography employed by Johnson.[19]

Because hydrocyanation of **7** produced equal amounts of the α and β isomers, this approach necessitated a tedious separation and limited the yield of **8**.[19,20] Therefore, we attempted to add lithium dimethylcuprate directly to **7** or to its protected derivatives in the hope of directly and stereoselectively introducing the methyl group. With **7a–c**, we were unable to effect this conjugate addition even though the reaction conditions employed worked well with a variety of model compounds. The failure of this reaction may be the result of a steric interaction between the 12β-hydrogen atom and the acetyl side chain which prevents the enone from becoming coplanar and thereby increases its reduction potential.[21]

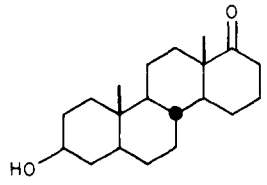
rac-5β,13α,17α-Pregnane-3,20-dione (**10**) was dehydrogenated by 2,3-dichloro-5,6-dicyanobenzoquinone[22] to **11** which was selectively hydrogenated in the presence of tris(triphenylphosphine)rhodium chloride[23] to the required *rac*-13α,17α-4-pregnene-3,20-dione (**1a**).

X-Ray Crystal Structure. A single crystal taken from *rac*-**1** was determined to be in space group $P2_12_12_1$, which indicates that the crystal contains only one enantiomer. The unit cell constants were determined from a least-squares analysis of the θ values for 32 reflections to be a = 12.8727 (8), b = 17.957 (1), and c = 7.5684 (5) Å resulting in a unit cell volume of 1750 Å^3. The density was calculated to be 1.19 g cm^{-3} based on the presence of four molecules (Z = 4), each of molecular weight 314.47, in the cell. Integrated intensities for 2034 independent reflections having $\theta < 75°$ were measured on an Enraf-Nonius CAD-4 diffractometer using CuKα radiation. After the Lorentz and polarization corrections [1 + cos^2 2θ/2 sin 2θ] had been applied to the intensity data, normalized structure factor

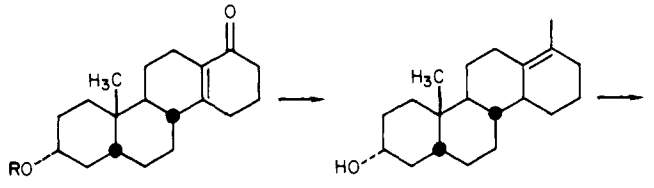


3a, R = H
b, R = THP

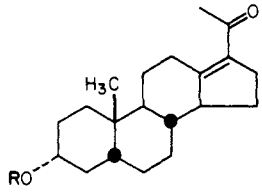
4a



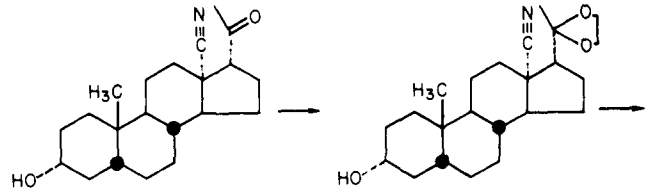
4b



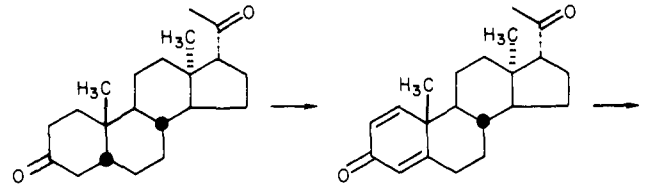
5 6



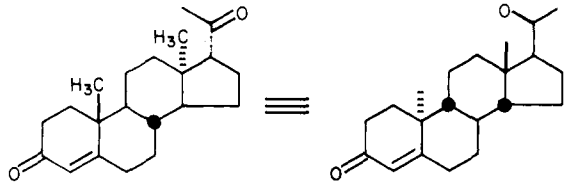
7a, R = H
b, R = THP
c, R = Ac



8 9



10 11



1a 1

amplitudes were computed, and the structure was solved by direct methods using the MULTAN program.[24]

The positional and anisotropic thermal parameters of all nonhydrogen atoms were refined by full-matrix least squares using the 1540 reflections for which the observed intensity was greater than twice the corresponding standard deviation. These reflections were regarded as having intensities significantly greater than the background. The weights used were the quantities $(1/\sigma_F^2)$, where σ_F is defined by equation H.14 of Stout and Jensen[25]

Table I. Fractional Atomic Coordinates and Estimated Standard Deviations for 8α,9β,10α,14β-Progesterone

atom	X/A	Y/B	Z/C
C(1)	0.2043 (2)	0.3127 (2)	0.0902 (4)
C(2)	0.1115 (2)	0.2617 (2)	0.0657 (4)
C(3)	0.0270 (2)	0.2737 (2)	0.2040 (5)
C(4)	0.0620 (2)	0.3020 (2)	0.3734 (5)
C(5)	0.1617 (2)	0.3165 (2)	0.4137 (4)
C(6)	0.1922 (2)	0.3373 (2)	0.5987 (4)
C(7)	0.2581 (2)	0.4071 (2)	0.6030 (4)
C(8)	0.3555 (2)	0.3983 (2)	0.4914 (4)
C(9)	0.3240 (2)	0.3799 (1)	0.2997 (3)
C(10)	0.2503 (2)	0.3121 (2)	0.2791 (3)
C(11)	0.4222 (2)	0.3735 (2)	0.1850 (4)
C(12)	0.4850 (2)	0.4452 (2)	0.1901 (4)
C(13)	0.5164 (2)	0.4704 (2)	0.3746 (4)
C(14)	0.4227 (2)	0.4692 (2)	0.5022 (4)
C(15)	0.4740 (3)	0.4765 (2)	0.6858 (4)
C(16)	0.5767 (3)	0.4365 (2)	0.6726 (4)
C(17)	0.5937 (2)	0.4172 (2)	0.4754 (4)
C(18)	0.5624 (3)	0.5499 (2)	0.3643 (5)
C(19)	0.3067 (2)	0.2377 (2)	0.3122 (5)
C(20)	0.7061 (2)	0.4242 (2)	0.4134 (5)
C(21)	0.7367 (2)	0.3818 (2)	0.2524 (6)
O(3)	−0.0623 (2)	0.2579 (2)	0.1760 (4)
O(20)	0.7687 (2)	0.4611 (2)	0.4923 (5)

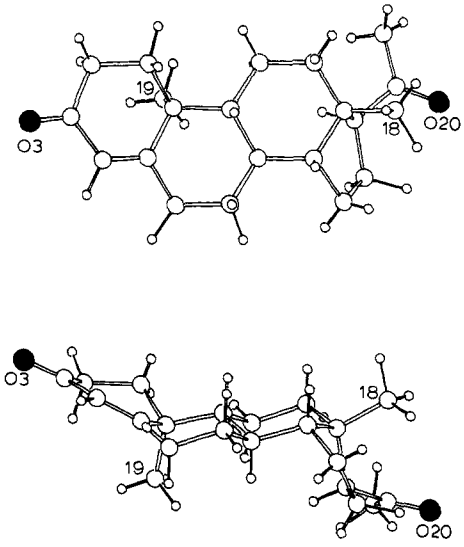


Figure 2. Perspective drawings of the 8α,9β,10α,14β-progesterone molecule.

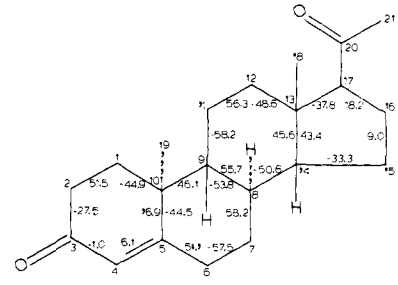


Figure 3. Endocyclic torsion angles in 8α,9β,10α,14β-progesterone. A torsion angle α–β–γ–δ is positive if, when viewed down the β–γ bond, the α–β bond will eclipse the γ–δ bond when rotated less than 180° in a clockwise direction.

using 0.06 rather than 0.01 as the instability correction. The hydrogen atoms were located on a Fourier difference map and refined during the final two cycles. The final reliability index, R (defined as $\sum||F_o| - |F_c||/\sum F_o$), was 4.8% for the 1540 reflections used in the refinement and 9.2% for all data. The final fractional coordinates for the nonhydrogen atoms listed in Table I correspond to the

Table II. Progestational Activity in a Modified Clauberg Assay[a] (Subcutaneous Injection)

material admin	total dose, mg	no. of rabbits	mean uterine wt, g	range of prolif index	mean prolif index
progesterone	0.2	2	1.49	0.5⁺–1.0⁺	0.75⁺
	0.5	2	2.34	3.5⁺	3.5⁺
compd 1	0.4	2	0.79	0	0
	4.0	2	1.24	1.0⁺–3.0⁺	2.0⁺

[a] Progestational proliferation was evaluated histologically according to the procedure of McPhail. For details see T. Miyake, *Methods Horm. Res.* 2, 135.

8α,9β,10α,14β enantiomer. Figure 2 shows the perspective drawings of this structure. Figure 3 gives the calculated endocyclic torsional angles for the molecule.

Biological Activity. The results of a preliminary Clauberg assay of *rac*-1 are shown in Table II.[26] These data indicate that *rac*-1 is approximately 10% as active as progesterone in this assay.

Professor Lars Terenius, at the University of Uppsala, Sweden, has measured the ability of *rac*-1 to inhibit specific binding of tritiated progesterone by uterine cytosol of rabbit. In this assay,[27] Professor Terenius found *rac*-1 to have an affinity for this receptor approximately 2% as great as that of progesterone.[28]

Discussion

The crystallographic study showed 1 to have ring conformations which are A, 1β-sofa; B, chair; C, chair; and D, intermediate between an envelope and a half-chair. The structure shows the C-17 position to be hindered and makes the findings of Nambara and Goto[9] appear to result from reaction with a conformer present in solution but not yet demonstrated in the solid state.

For other gestogens, only one enantiomer possesses biological activity.[29] We assume this is also true of *rac*-1, and, on the basis of our hypothesis, we attribute the activity to 8α,9β,10α,14β-4-pregnene-3,20-dione. We believe that the low affinity of *rac*-1 for the rabbit uterine receptor results from the C ring of 1 existing in the chair form. The lack of complimentarity could result from the concave upward shape of the A, B, and C portion of 1, from the exaggerated bulk and novel orientation of C-13 and its β-methyl, or both.

We are attempting to differentiate among these possibilities by synthesizing and assaying derivatives of 1 which have their β face flattened by double bonds or methylene groups substituted at the 1,2 and/or 6,7 positions. 18-Nor analogues also will be studied. In addition, we shall try to resolve the most active of these compounds to test our assumption that the biological activity resides solely in the C-13β isomer.

Experimental Section

Melting points were determined in capillary tubes on a Mel-Temp apparatus and are uncorrected. IR spectra were determined on a Beckman IR-8 spectrometer. NMR spectra were determined on a Varian A-60 spectrometer. Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, Ga.

rac-3β-Hydroxy-*D*-homo-18-nor-5α-androst-13(14)-en-17a-one (**3a**), *rac*-3α-hydroxy-18-nor-13(17)-pregnen-20-one (**7a**), and *rac*-13α,17α-5β-pregnene-3,20-dione (**10**) were prepared according to the procedures of Johnson.[15,16] All intermediates had physical properties in good accord with literature values, appeared homogeneous by TLC, and had the expected IR and NMR spectra. Selected intermediates were submitted for elemental analysis with satisfactory results.

Attempted Addition of Lithium Dimethylcuprate to *rac*-3α-Hydroxy-18-nor-13(17)-pregnen-20-one (7a). (A) To a suspension of 1.9 g (0.01 mol) of cuprous iodide in 25 mL of anhydrous ether, cooled in an ice–salt bath, was added 10 mL of 2.2 M (0.02 mol) methyllithium in ether dropwise. **7a** (0.736 g, 2.5 mmol) in 30 mL of ether was added dropwise, and the mixture was stirred for 2 h before being poured into a concentrated ammonium hydroxide solution (cooled in an ice bath) and extracted with ether. The extract was washed (H_2O), dried ($MgSO_4$), and concentrated to give a glass (0.62 g) which was separated on thick-layer plates of silica gel using a mixture of benzene (80%) and ethyl acetate (20%) as solvent. The fastest moving band was extracted to yield starting material (195 mg). Extraction of a second band gave 125 mg of material which was shown by rechromatography and IR and NMR studies to consist of 1,2-addition product at C-20 contaminated by starting material. A third band was isolated (80 mg) but not identified. Its spectra were not consistent with those expected for the product of conjugated addition.

(B) The tetrahydropyranyl ether **7b** was formed by dissolving 212 mg (0.70 mmol) of **7a** in 10 mL of CH_2Cl_2 containing 0.25 mL of freshly distilled 2,3-dihydropyran and adding 1 drop of phosphorus oxychloride. The solution was stirred at room temperature for 3 h and then was diluted with CH_2Cl_2, washed (aqueous NaHCO and then H_2O), dried ($MgSO_4$), and concentrated to give 310 mg of crude product. Chromatography over Al_2O_3 using benzene–ethyl acetate as eluent gave 250 mg of **7b** of sufficient purity for use in the conjugate addition.

To a stirred suspension of 0.50 g (2.63 mmol) of cuprous iodide in 8 mL of anhydrous ether, under argon, at −5 °C was added 2.5 mL of 2.2 M methyllithium in ether solution. As this was just sufficient to cause the disappearance of a yellow precipitate, a small amount of cuprous iodide was slowly added to bring back the precipitate and thus assure that no excess methyllithium was present. This was stirred for 15 min at 5 °C, and then a solution of 275 mg (0.72 mmol) of **7b** in 6 mL of dry ether was added during 20 min. The reaction mixture was stirred for 1 h and then poured, with stirring, into a mixture of ice and concentrated ammonium hydroxide. Standard workup gave 260 mg of a crude product which showed no C-21 hydrogens in the methyl ketone region of the NMR and is, therefore, presumed to be mainly the 1,2-addition product.

The reaction was repeated at temperatures ranging from −78 to 0 °C and with reaction times of up to 2 h. No 1,4-addition product was detected, and the principal isolated product appeared to be the 1,2-addition product: NMR ($CDCl_3$) δ 0.85 (s, C-19 H's), 1.35 (s, C-21, C-22 H's).

(C) A solution of 0.15 g of **7a** in 10 mL of anhydrous pyridine plus 1 mL of acetic anhydride was stirred at room temperature for 12 h. Standard workup afforded the acetate **7c** as a gum sufficiently pure for further reaction: NMR ($CDCl_3$) δ 0.87 (s, C-19 H's), 2.03 (s, acetate H's), 2.24 (s, C-21 H's), 4.71 (m, C-3β H).

A solution of 4.37 g (0.023 mol) of cuprous iodide in 34 mL of water containing 44 g of potassium iodide was shaken for a few minutes with decolorizing charcoal and then filtered. The filtrate was stirred with 4.17 mL of tri-*n*-butylphosphine until the resulting greasy mass crystallized. The crystals were collected; washed with saturated aqueous potassium iodide solution, water, and 95% ethanol; and air-dried. Recrystallization from 33 mL of ethanol plus 25 mL of isopropyl alcohol gave 2.2 g (30%) of (tri-*n*-butylphosphine)copper iodide complex as fine needles, mp 72 °C (lit. mp 75 °C).

To a solution of 745 mg (1.9 mmol) of the above complex in 10 mL of anhydrous ether, at 0 °C under nitrogen, was added 0.7 mL of 1.8 M (1.3 mmol) methyl iodide in ether solution. After the yellow mixture had stirred for 10 min, a solution of 115 mg (0.3 mmol) of **7c** in 10 mL of anhydrous ether was added within a period of 20 min. The mixture was stirred for 1 h at 0 °C and then was subjected to the usual workup. The product was hydrolyzed in a solution of K_2CO_3 in methanol and water and chromatographed to give mainly starting material **7a**.

***rac*-13α,17α-4-Pregnene-3,20-dione (1a).** A solution of 0.55 g (1.74 mmol) of 5β,13α,17α-pregnane-3,20-dione (**10**) in 125 mL of dry dioxane containing 0.85 g (3.74 mmol) of 2,3-dichloro-5,6-dicyanobenzoquinone was refluxed, under nitrogen, for 16 h. The mixture was cooled, filtered through infusorial earth, and concentrated. The residue was partitioned between CH_2Cl_2 and

aqueous NaOH, washed (H_2O), dried ($MgSO_4$), and distilled to afford a brown gum (0.45 g). A sample (200 mg) was subjected to thick-layer chromatography over silica gel using benzene–ethyl acetate as solvent to give *rac*-13α,17α-1,4-pregnadiene-3,20-dione (11) in 37% yield: NMR ($CDCl_3$) δ 0.83 (s, C-18 H's), 1.22 (s, C-19 H's), 2.17 (s, C-21 H's), 6.15 (m, C-4 H), 6.15 and 6.30 (d, C-2 and C-1 H's).

Tris(triphenylphosphine)rhodium chloride (72 mg) was dissolved in 15 mL of anhydrous benzene and 15 mL of absolute ethanol and was hydrogenated for 1 h at room temperature. A solution of 72 mg (0.08 mmol) of 11 in 10 mL of anhydrous benzene and 10 mL of absolute ethanol was added to the catalyst solution, and hydrogenation was continued for 12 h at room temperature. The solution was distilled under reduced pressure, and the residue was dissolved in a mixture of petroleum ether and CH_2Cl_2 and filtered through Celite. The filtrate was concentrated. Chromatography on a thick-layer plate of silica using 80% benzene–20% ethyl acetate to develop the plate gave 35 mg of **1a** which was still slightly contaminated with catalyst.

The product of five hydrogenations afforded a total of 151 mg of crude product, from 450 mg of crude 11, which was rechromatographed on a thick-layer silica plate using ether as solvent. **1a** was obtained crystalline in a yield of 50 mg (11% based on 11). Recrystallization from ether–hexane and then from ether gave *rac*-**1a** as colorless crystals: mp 144–145 °C; IR ($CHCl_3$) 1700, 1665, and 1620 cm^{-1}; NMR ($CDCl_3$) δ 0.74 (s, C-18 H's), 1.18 (s, C-19 H's), 2.16 (s, C-21 H's), 5.75 (br s, C-4 H). Anal. ($C_{21}H_{30}O_2$) C, H.

Acknowledgment. The crystal structure determination performed at the Medical Foundation of Buffalo, Inc., was supported by Grant CA-10906 from the National Cancer Institute, DHEW. The synthetic work was supported, in part, by Training Grant CM-555 and by Grant AM-06900 from the National Institute of Arthritis and Metabolic Diseases, DHEW.

Supplementary Material Available: Tables of the anisotropic thermal parameters of the nonhydrogen atoms, coordinates of the hydrogens, interatomic distances, valency angles, and observed and calculated structure factors (14 pages). Ordering information is given on any current masthead page.

References and Notes

(1) Portions of this work are taken from the Ph.D. dissertations of V. Kumar and V. Alks.
(2) A part of this work was presented as paper 100 before the Division of Medicinal Chemistry at the 172nd American Chemical Society National Meeting in San Francisco in September, 1976.
(3) Portions of this work were presented at the symposium "New Approaches in Steroid Synthesis" at the Medical Foundation of Buffalo, Buffalo, New York, April 22, 1977.
(4) A. J. Solo and B. Singh, *J. Med. Chem.*, **10**, 1048 (1967).
(5) A. J. Solo and J. N. Kapoor, *J. Med. Chem.*, **16**, 270 (1973) and loc. cit.
(6) K. Kontula et al., *Acta Endocrinol.*, **78**, 544 (1975).
(7) "Atlas of Steroid Structure", Vol. 1, W. L. Duax and D. A. Norton, Ed., Plenum Press, New York, N.Y., 1975, pp 416 and 512.
(8) J. C. Portheine and C. Romers, *Acta Crystallogr., Sect. B* **26**, 1791 (1970). Also in ref 6, p 370.
(9) T. Nambara and J. Goto, *Chem. Pharm. Bull.*, **19**, 1937 (1971).
(10) L. J. Chinn, *J. Org. Chem.*, **30**, 4165 (1965).
(11) Compounds having high progestational activity have been found to have a variety of endocrine profiles.[12-14] Some of the compounds with highest progestational activity and useful endocrine profiles in lower animals have been found to lack progestational activity in humans.[14]
(12) R. A. Edgren, H. Smith, D. L. Peterson, and D. L. Carter, *Steroids*, **2**, 318 (1963).
(13) J. Hartog, S. J. Halkes, L. Morsink, A. M. DeWachter, and J. L. M. A. Schlatmann, *J. Steroid Biochem.*, **6**, 577 (1975).
(14) L. Morsink, A. M. deWachter, P. Brenner, S. Z. Cekan, R. Guerrero, K. Hagenfeldt, and E. Diczfalusy, *Acta Endocrinol. (Copenhagen)* **82**, 193 (1976).
(15) W. S. Johnson et al., *J. Am. Chem. Soc.*, **78**, 6278, 6331, and 6354 (1956).
(16) W. Nagata, T. Terasawa, and T. Aoki, *Tetrahedron Lett.*, 865 (1963).
(17) W. S. Johnson and Duff S. Allen, Jr., *J. Am. Chem. Soc.*, **79**, 1261 (1957).
(18) G. Stork, P. Rosen, N. Goldman, R. V. Coombs, and J. Tsuji, *J. Am. Chem. Soc.*, **87**, 275 (1965).
(19) W. S. Johnson, J. A. Marshall, J. F. W. Keana, R. W. Frank, D. G. Martin, and V. J. Bauer, *Tetrahedron, Suppl.*, **8**, 541 (1966).
(20) (a) W. Nagata, M. Yoshioka, and M. Murakami, *J. Am. Chem. Soc.*, **94**, 4654 (1972).
(21) H. O. House and M. J. Umen, *J. Am. Chem. Soc.*, **94**, 5495 (1972).
(22) G. Muller, J. Martel, and C. Huynh, *Bull. Soc. Chim. Fr.*, 2000 (1961).
(23) C. Djerassi and J. Gutzwiller, *J. Am. Chem. Soc.*, **88**, 4537 (1966).
(24) G. Germain, P. Main, and M. M. Woolfson, *Acta Crystallogr., Sect. A*, **27**, 368 (1971).
(25) G. H. Stout and L. H. Jensen, "X-Ray Structure Determination", Macmillan, New York, N.Y., 1968, p 168.
(26) The Clauberg assay was performed at the Endocrine Laboratory, Madison, Wis.
(27) L. Terenius, *Steroids*, **23**, 909 (1974).
(28) Private communication to A.J.S. We thank Professor Terenius for running this assay and for his permission to publish these results.
(29) R. A. Edgren, H. Smith, G. A. Hughes, L. L. Smith, and G. Greenspan, *Steroids*, **2**, 731 (1963).