Investigations on Sterols. 38.[1a] Synthesis of 1,2β-Methylene-17α-acetoxy-9β,10α-pregnanes, a Class of Potent Progestational Agents

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In this paper the synthesis of 1,2β-methylene-17α-acetoxy-6-dehydro-9β,10α-progesterone and some of its 6-substituted derivatives is described. Some of these retro derivatives possess highly progestational activities when tested orally in the rabbit. Remarkable differences in activity in comparison with analogous compounds of the normal (9α,10β) series were found.

Introduction of a 1,2-methylene group leads to a remarkable increase in progestational activity of 17α-acetoxyprogesterone and some of its derivatives.[1b] This induced us to investigate the influence of such a substitution in the 9β,10α series, where, in previous studies,[2,3] interesting biological activities had been found.

Chemistry. Conversion of compound **1a**[4] into its 1-dehydro derivative **2a** was performed by means of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in dioxane in the presence of HCl.[3] Attempts to introduce the 1,2-methylene group by allowing compound **2a** to react with CH_2N_2[5,6] were not successful.[7] As good results[7,8] were obtained with dimethylsulfoxonium methylide[9] we tried to introduce the 1,2-methylene group by this route. Application of the reagent to **2a** according to the reaction conditions described in the literature gave a mixture containing, besides the 1,2β-methylene compound **6a**, starting material and a more polar compound (tlc). Prolongation of the reaction time—in order to complete the conversion of the difficult to remove starting material—led to greatly increased formation of the polar compound.

However, protection of the 17-OH group by conversion of **2a** into the tetrahydropyranyl (THP) ether **2c** gave a compound which could easily be converted into the 1,2β-methylene compound **6c** with the Corey reagent. The acetate **2b** led in this reaction to a mixture of the butenolide **3** and the β-hydroxy lactone **4**.[10] Hydrolysis of the THP ether **6c** under acidic conditions gave **6a**. This compound was converted into the 17α-acetate **6b** with an overall yield of 50%, based on **2a**. Hydrogenation of the 6,7-double bond, with $Pd/CaCO_3$ as a catalyst, provided compound **7**. Conversion of **7** into **8** was accomplished by means of isopropenyl acetate. Treatment of this enol acetate with Cl_2[2] gave the 6α- and 6β-chloro compounds **9**, while a reaction with $FClO_3$[2] furnished the 6α- and 6β-fluoro compounds **10**. When the 6-halo compounds thus obtained were treated with ethyl orthoformate, the enol ethers **11** and **13** were formed. These compounds were, without purification, treated with MnO_2 and HOAc[3,11] to yield respectively the 6-chloro compound **12b** and the 6-fluoro compound **14**.

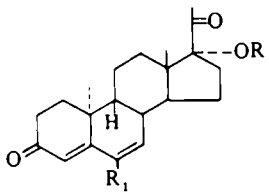
If the reaction of the Corey reagent with **2c** was allowed to proceed, a second methylene group was introduced and the 1,2β;6,7β-bis(methylene) derivative **5c** was obtained. This compound could be prepared also by treatment of **6c** with the Corey reagent. Conversion of **5c** into its acetate **5b** was accomplished by known methods. Reaction of compound **12a** with the Corey reagent gave the 6α-chloro-6,7β-methylene compound **15a**. In this case protection of the 17α-hydroxyl group was not required, as the Δ^6 bond in the 6-chloro-3-oxo-4,6-diene system proved to be much more reactive than the Δ^1 bond in the 3-oxo-1,4,6-triene system (reaction times respectively were 1.75 hr and ≥36 hr).[7b]

Studies of the normal series have shown that the introduction of a 6-methyl group can lead to compounds with interesting biological properties.[12] For this reason we introduced this substituent in our 1,2β-methylene compounds by previously published methods.[13,14] Enol etherification of **7** gave **16**, which, after reaction with $CBrCl_3$ and chromatography, did not give the expected **17** but the dehydrohalogenated compound **18**. Reduction of **18** afforded the 6-methyl-substituted compound **19**. Enol etherification of **19** gave **20**, and treatment of this enol ether with MnO_2 gave compound **21**. Because of the recently published, interesting biological properties of some 4,6-dihalo compounds in the normal series,[15,16] we synthesized such a derivative. The procedures reported for the conversion of a 6-chloro-3-oxo-4,6-diene[15] or a 4-chloro-3-oxo-4,6-diene[17] into a 4,6-dichloro-3-oxo-4,6-diene proved, however, to be unsuccessful. Reaction of compound **22** (obtained from **6b** by a reaction with SO_2Cl_2[18]) with chromyl chloride gave **23**,[19] which could also be prepared from **22** by reaction with peracid to **24** and opening of the epoxide with HCl. Dehydration of **23** with acid or *via* the tosylate[20,21] or mesylate ester[22] was unsuccessful. We succeeded, however, in dehydrating **23** with *p*-chlorobenzenesulfonyl chloride[23] to give **25**.

Biological Activity. In Table I a survey is given of the oral progestational activity of the most interesting compounds as determined in a modified Clauberg assay in rabbits (see Experimental Section).

The potency of each compound, as shown in Table I, column 2, was estimated directly, in the same test, against the reference dydrogesterone† (9β,10α-pregna-4,6-diene-3,20-dione). The tests fulfilled all statistical criteria of the standard six-point assay,[28] if not otherwise indicated. For further information the 95% confidence limits are added in Table I, column 3. For comparative purposes the data have been recalculated on the basis of contemporary potency determinations of the reference (dydrogesterone oral) against progesterone (sc). The average value of three experiments (0.07, 0.06, and 0.10 times progesterone sc) has been used (Table I, column 4). In the last column we have collected from the literature data of some of the analogous

†Generic name. Registered Trademark name: Duphaston.



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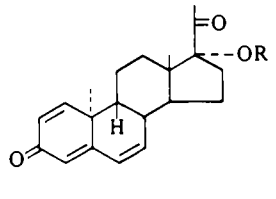
c, R = Ac; R_1 = Cl
d, R = Ac; R_1 = F



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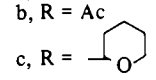
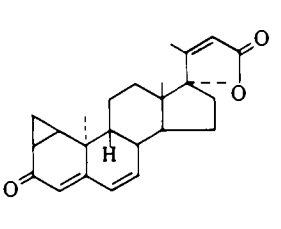
c, R = 



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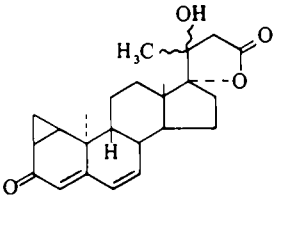

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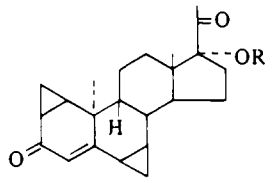

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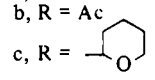
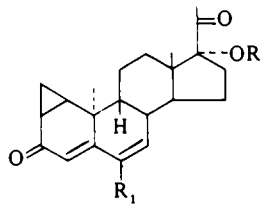
c, R = 



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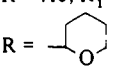
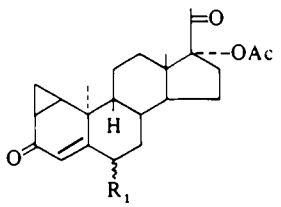
c, R =  ; R_1 = H
12a, R = H; R_1 = Cl
b, R = Ac; R_1 = Cl
14, R = Ac; R_1 = F
21, R = Ac; R_1 = CH_3



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9, R_1 = Cl
10, R_1 = F
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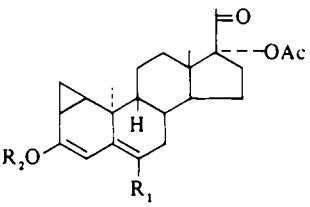
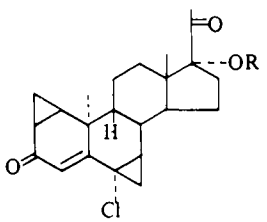
19, R_1 = CH_3



8, R_2 = Ac; R_1 = H
11, R_2 = C_2H_5; R_1 = Cl
13, R_2 = C_2H_5; R_1 = F
16, R_2 = C_2H_5; R_1 = H
20, R_2 = C_2H_5; R_1 = CH_3



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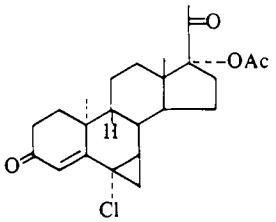

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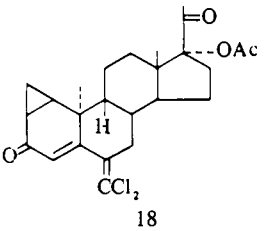

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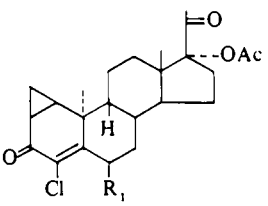
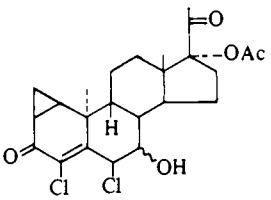


22, R_1 = H
25, R_1 = Cl



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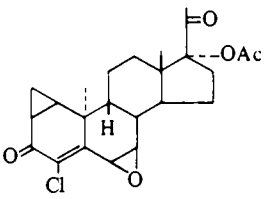

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compounds in the normal series. Most of these values were measured orally with progesterone sc as a standard; otherwise they have been recalculated on this basis.

From the values it is clear that introduction of a 1,2-methylene group has a considerable influence on the progestational activity, especially when this influence is compared with the diminishing effect of the introduction of a Δ^1 bond (compare: **1b**, **2b**, and **6b**; **1c**, **2d**, and **12b**; **1d**, **2e**, and **14**; **15b** and **26**).

Although we did not find much difference in progestational activity between the 6-chloro compound **12b** and its 9α,10β isomer cyproterone acetate, it was very remarkable that the retro compound was completely devoid of the antiandrogenic properties reported for the 9α,10β analog. Introduction of a 6,7-methylene group in compound **12b** again gave a considerable rise in progestational activity (**15b** compared with **12b**), which was found also in the nonchlorinated products (**5b** compared with **6b**).

Introduction of a fluorine atom at C-6 gives rise to a very active progestagen. As far as we know, the oral progestational activity of **14** is higher than that of any compound reported so far in the literature. It is noteworthy that substitution of hydrogen at position 6 by a fluorine atom should promote the progestational activity in the 1,2β-methylene-9β,10α series more than a chlorine atom does. This is in contrast to what has been reported for the normal series, where the 6-chloro compound is more active than the 6-fluoro compound (compare 9α,10β analogs of **14** and **12b** in Table I). A comparably favorable effect of this fluorine substitution at C-6 will be reported in a future paper from this laboratory, concerning 16-methylene-9β,10α-steroids.[29] In contrast to what has been reported for the 6-fluoro compound in the 9α,10β series,[30] the retro derivative **14** proved also to be completely free from any antiandrogenic activity, analogously to the 6-chloro derivative.

Introduction of a 6-methyl group, which in the normal series gives rise to compounds with interesting biological properties, led in the 9β,10α series to a sharp decrease in

Table 1. Progestational Potency after Oral Administration in the Clauberg Test[a]

Compounds	Potency	95% confidence limits	Relative potencies (prog sc = 1) 9β,10α (retro)	9α,10β (normal)
Dydrogesterone	1		0.07	
Progesterone sc	14	11–17[c]		1
1b, 3-oxo, $\Delta^{4,6}$	60	20–130	4	3,[f] 1.5[g]
2b, 3-oxo, $\Delta^{1,4,6}$	17	12–24	1	4[f]
6b, 3-oxo, $\Delta^{4,6}$, 1,2β-CH_2	400	230–680[d]	30	4[f]
1c, 3-oxo,6-Cl,$\Delta^{4,6}$	1250	900–1750[d]	90	30,[f] 33,[g,h] 37[i]
2c, 3-oxo,6-Cl,$\Delta^{1,4,6}$	~800[e]		60	35,[i,m] 2[k]
12b, 3-oxo,6-Cl,$\Delta^{4,6}$,1,2β-CH_2	1500	1,000–2,400[d]	110	110,[l] 110,[f] 16[k]
26, 3-oxo-6α-Cl,Δ^{4},6,7β-CH_2[b]	600	300–1,900	45	
15b, 3-oxo,6α-Cl,Δ^{4},1,2β;6,7β-diCH_2	6000	3,000–12,000	430	
25, 3-oxo,4,6-diCl,$\Delta^{4,6}$,1,2β-CH_2	2200	1,700–2,800	160	
1d, 3-oxo,6-F,$\Delta^{4,6}$	1250	950–1,700[d]	90	15[j,n]
2c, 3-oxo,6-F,$\Delta^{1,4,6}$	860	570–1,330	60	6[m,n]
14, 3-oxo,6-F,$\Delta^{4,6}$, 1,2β-CH_2	8400	6,500–10,800[c]	600	35[f]
5b, 3-oxo,Δ^{4},1,2β;6,7β-diCH_2	~3000[e]		200	
21, 3-oxo,6-CH_3,$\Delta^{4,6}$,1,2β-CH_2	~100[e]		7	

[a]For a detailed description of the performance of this test see Experimental Section. [b]This compound has been synthesized by the reaction of 6-chloro-17α-hydroxy-9β,10α-pregna-4,6-diene-3,20-dione[3] with the Corey reagent as described in this paper for **12a**: mp 205–206°; λ_{max} 255 nm (ε 9600). [c]Average of 3 experiments. [d]Average of 2 experiments. [e]Only 2 doses tested against one dose of the reference. [f]See ref 1. [g]See ref 24a. [h]In our own laboratory a value of 460 (95% confidence limits 360–610) against dydrogesterone was found. Recalcd to progesterone sc this gives the value of 33. [i]See ref 24b. [j]See ref 25. [k]See ref 26. [l]Determined in this laboratory. [m]See ref 27. [n]In these tests norlutin was used as standard and the activity of norlutin with respect to progesterone sc is given as 1.

activity. Summarizing, it can be stated that the introduction of a 1,2-methylene group in the 17α-acetoxy-Δ^6-9β,10α-progesterones mentioned in this paper generally leads to highly active compounds. The effect of this substitution differs quantitatively as well as qualitatively from that in the normal series (see **12b** and **14** in comparison with their 9α,10β isomers).

In addition, the compounds described in this paper, and especially the 6-halo compounds **12b** and **14**, are very active in the pregnancy maintenance test and they have also a very interesting antiestrogenic and ovulation inhibitory activity. More extensive and detailed biological data of these compounds will be published in the near future.

Experimental Section‡

17α-Hydroxy-9β,10α-pregna-1,4,6-triene-3,20-dione (2a). A soln of DDQ (29 g) and 17α-hydroxy-9β,10α-pregna-4,6-diene-3,20-dione (1a) (30 g) in dioxane (750 ml) containing 1 mg of HCl/ml was stirred at room temp for 90 min. After addn of $CaCO_3$ (4 g), stirring was continued for 20 min. The reaction mixt was filtered, and the filtrate refluxed for 90 min. The dioxane was removed *in vacuo*, and the residue dissolved in CH_2Cl_2. After work-up, the residue was crystd from Me_2CO to give **2a** (20.8 g): mp 195.5–197.5°. *Anal.* ($C_{21}H_{26}O_3$) H; C: calcd, 77.27; found, 76.84.

17α-Hydroxy-9β,10α-pregna-1,4,6-triene-3,20-dione 17-Acetate (2b). A soln of **2a** (13 g) and TsOH (13 g) in a mixt of AcOH (520 ml) and Ac_2O (104 ml) was kept at room temp for 3.5 hr. Decompn of the excess Ac_2O was accomplished with H_2O. The mixt was extd with CH_2Cl_2 and worked up. Crystn from Me_2CO–*n*-hexane gave **2b** (10 g): mp 217–219°; [α]D 375°. *Anal.* ($C_{23}H_{28}O_4$) C, H.

17α-Hydroxy-9β,10α-pregna-1,4,6-triene-3,20-dione 17-THP Ether (2c). To a soln of **2a** (25 g) in a mixt of CH_2Cl_2 (125 ml) and C_6H_6 (100 ml) were added TsOH (250 mg) and 2,3-dihydropyran (DHP) (4.2 ml). The reaction mixt was stirred and, after 10 and 20 min, addnl portions of DHP (4.2 ml) were added. After 4.5 hr DHP (2.5 ml) was again added. After a total reaction time of 5.5 hr, H_2O was added and the organic layer sepd. The aqueous layer was extd with C_6H_6, and the combined organic layers were worked up. After drying and removal of the solvents, a cryst product, being a mixt of the two possible isomers of **2c**, was obtained by trituration with Et_2O.

Reaction of 2b with Dimethylsulfoxonium Methylide. A soln of trimethylsulfoxonium iodide (tmsi) (0.96 g) in DMSO (7 ml) was stirred for 2 hr at room temp with NaH (120 mg of a 50% oil suspension). To this *in situ* prepared soln of dimethylsulfoxonium methylide (dmsm) a soln of **2b** (0.4 g) in THF (4 ml) was added. After stirring for 3 hr, the reaction mixt was worked up and the crude product was chromatographed over SiO_2 to give two compds: **17α-hydroxy-1,2β-methylene-3-oxo-24-nor-9β,10α-chola-4,6,20(22)-trien-23-oic acid lactone (3)**, mp 263–267°, nmr δ 2.16 (21-CH_3), 5.86 (22-CH) ppm; **17α,20ξ-dihydroxy-1,2β-methylene-3-oxo-24-nor-9β,10α-chola-4,6-dien-23-oic acid lactone (4)**, mp 264–268°, nmr δ 1.52 (21-CH_3), 4.10 (21-OH).

17α-Hydroxy-1,2β-methylene-9β,10α-pregna-4,6-diene-3,20-dione 17-THP Ether (6c). To a soln of dmsm prepd from 7.5 g of tmsi, as described for **2b**, was added a soln of THP ether **2c** (7.5 g) in THF (60 ml). After a reaction time of 24 hr, no starting material was detectable (uv). The reaction mixt was poured out into H_2O and extd with CH_2Cl_2. Work-up and crystn from Me_2CO gave **6c**: mp 210°. *Anal.* ($C_{27}H_{36}O_4$) C, H.

17α-Hydroxy-1,2β-methylene-9β,10α-pregna-4,6-diene-3,20-dione (6a). The ether **6c** (16.9 g) in boiling EtOH (300 ml) was treated with 2 *N* H_2SO_4 (30 ml) for 1 hr. Work-up gave a crude product (13 g) which was used in the subsequent reactions. Pure **6a** was obtained by chromatography and crystn from CH_2Cl_2–Me_2CO: mp 243.5–244.5°. *Anal.* ($C_{22}H_{28}O_3$) C, H.

17α-Hydroxy-1,2β-methylene-9β,10α-pregna-4,6-diene-3,20-dione 17-Acetate (6b). To a mixt of AcOH (520 ml), Ac_2O (104 ml), and TsOH (13 g) was added **6a** (13 g). After stirring for 3 hr at room temp, the reaction mixt was worked up. Chromatography and crystn from Me_2CO gave **6b** (10 g): mp 253–254°; [α]D −657°. *Anal.* ($C_{24}H_{30}O_4$) C, H.

17α-Hydroxy-1,2β;6,7β-bis(methylene)-9β,10α-pregn-4-ene-3,20-dione 17-Acetate (5b). To a soln of dmsm, prepd from tmsi (1 g) as described for **2b**, was added THP ether **6c** (0.5 g). After 36 hr, the reaction mixt was worked up, the crude THP ether **5c** was hydrolyzed, as described for **6a**, and the resulting hydroxy compd **5a** was acetylated, as described for **6b**. Chromatography gave **5b** (0.15 g): mp 274–276° (Me_2CO). *Anal.* ($C_{25}H_{32}O_4$) C, H.

17α-Hydroxy-1,2β-methylene-9β,10α-pregn-4-ene-3,20-dione 17-Acetate (7). To compd **6b** (3.8 g) in $PhCH_3$ (100 ml) was added Pd–$CaCO_3$ (5%) (2 g). This mixt was shaken in a H_2 atm. When 260 ml of H_2 had been consumed, the reaction mixt was worked up, chromatographed, and crystd from Me_2CO–Et_2O to give pure **7** (3.2 g): mp 205–205.5°. *Anal.* ($C_{24}H_{32}O_4$) C, H.

‡All melting points were measured in glass capillaries on a Büchi apparatus (W. Büchi, Glassapparate Fabrik, Flawil, Switzerland) and are uncorrected. Rotations were determined in $CHCl_3$ at 25° at about 1% concn; uv spectra are of MeOH solns and ir spectra are in KBr. The nmr spectra were recorded on a Varian HA-100 in $CDCl_3$ (Me_4Si). In those cases in which no complete uv, ir, and nmr spectral data are given, they were consistent with the assigned structures. All reactions were carried out in a N_2 atm, and solns were dried over anhyd Na_2SO_4. Elemental analyses were performed in the Mikroanalytisches Laboratorium, Dr. F. Pascher (53 Bonn, West Germany). Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

3,17α-Dihydroxy-1,2β-methylene-9β,10α-pregna-3,5-dien-20-one 3,17-Diacetate (8). From a soln of **7** (12.2 g) and TsOH (5 g) in abs C_6H_6 (800 ml) 50 ml was distd off to remove traces of H_2O. Then isopropenyl acetate (120 ml) was added. From this reaction mixt 250 ml was distd off in 3.5 hr. The reaction mixt was poured out into a mixture of H_2O (800 ml) and piperidine (200 ml). After work-up, the crude product was filtered over SiO_2 to give the enol acetate **8** (12.3 g): mp 118–119.5° (MeOH). *Anal.* ($C_{26}H_{34}O_5$) C, H.

6β-Chloro-17α-hydroxy-1,2β-methylene-9β,10α-pregn-4-ene-3,20-dione 17-Acetate (9). A stirred soln of the enol acetate **8** (13.3 g) in Et_2O (214 ml) was cooled to −15°. To this soln was added a cold soln of KOAc (24.6 g) in AcOH (540 ml) and H_2O (90 ml). Then 46 ml of a soln of Cl_2 in HOAc containing 53.4 mg of Cl_2/ml was added dropwise. After 1 hr, the reaction mixt was worked up and the residue chromatographed. This gave a fraction consisting of a mixt of 6α- and 6β-chloro compd **9** (8.14 g) and a fraction of the pure 6β compd **9** (0.86 g). Crystn of the latter fraction from Me_2CO gave pure **9**: mp 222.5–223°. *Anal.* ($C_{24}H_{31}ClO_4$) H; C: calcd, 68.80; found, 68.27.

6-Chloro-17α-hydroxy-1,2β-methylene-9β,10α-pregna-4,6-diene-3,20-dione 17-Acetate (12b). After the addn of freshly distd $(EtO)_3CH$ (31 ml) and TsOH (0.78 g) to a soln of a mixt of 6α- and 6β-chloro compd **9** (4.4 g) in abs dioxane (78 ml), the reaction mixt was stored for 18 hr at room temp. After that time, the enol ether **11** was added to a stirred suspension of MnO_2 (22 g) in a mixt of AcOH (240 ml) and H_2O (18 ml). After 25 min, the reaction mixt was filtered and dild with H_2O (1.5 l.). After work-up and chromatography, compd **12b** (3.1 g) was obtained: mp 243.5–244.5° (Me_2CO–*n*-hexane); λ_{max} 285 nm (ε 15,800); [α]D −516°; ν_{max} 3050, 1740, 1715, 1660, 1625, 1595, 998, 885 cm^{-1}; nmr δ 0.74, s (18-CH_3), 0.9 and 1.3, m (cycloprop), 1.54, s (19-CH_3) 2.10, s (21-CH_3 and 17α-OAc), 6.18, s (4-CH), and 6.28, d (7-CH), ppm. *Anal.* ($C_{24}H_{29}ClO_4$) C, H.

6-Chloro-17α-hydroxy-1,2β-methylene-9β,10α-pregna-4,6-diene-3,20-dione (12a). To a soln of **12b** (1.78 g) in 0.5 *N* NaOH in MeOH (178 ml) was added $NaClO_4$ (1.78 g). After stirring for 4.5 hr at room temp, the reaction mixt was poured out into H_2O and worked up. Chromatography gave **12a** (1.15 g): mp 219–219.5° (Me_2CO). *Anal.* ($C_{22}H_{27}ClO_3$) C, H.

6-Fluoro-17α-hydroxy-1,2β-methylene-9β,10α-pregn-4-ene-3,20-dione 17-Acetate (10). A slow stream of $FClO_3$ mixed with N_2 (1:1)§ was led at 0° through a mixed soln of the enol acetate **8** (1.95 g) in dry Me_2CO (40 ml) and dry KOAc (0.9 g) in abs EtOH (25.7 ml). After 4 hr, no starting material could be detected (tlc). Then a stream of N_2 was bubbled through the soln for 2 hr. The mixt was poured out into H_2O and worked up. Chromatography on SiO_2 gave in addition to a mixture of 6α- and 6β-fluoro compd **10** (0.2 g) the pure compds: 6α-fluoro compd **10** (0.52 g), mp 178–179° (Et_2O–hexane) [*Anal.* ($C_{24}H_{31}FO_4$) C, H]; and 6β-fluoro compd **10** (0.57 g), mp 239–240° (Et_2O–hexane) [*Anal.* ($C_{24}H_{31}FO_4$) C, H].

6-Fluoro-17α-hydroxy-1,2β-methylene-9β,10α-pregna-4,6-diene-3,20-dione 17-Acetate (14). In the same manner as described for compd **12b** a mixt of the 6α- and 6β-fluoro compds **10** (0.85 g) was converted into the enol ether **13**, which was then oxidized, as described in the same example, by MnO_2 to give, after chromatography and crystn from Et_2O, 0.37 g of **14**: mp 249–251°; [α]D −459°; λ_{max} 283.5 nm (ε 16,600); ν_{max} 3060, 1740, 1720, 1673, 1650, 1600, and 863 cm^{-1}; nmr δ 0.75, s (18-CH_3), 0.8 and 1.3, m (cycloprop), 1.55, s (19-CH_3), 2.07, s (21-CH_3 and 17α-OAc), 5.66, 2d (7-CH), and 5.91, s (4-CH) ppm. *Anal.* ($C_{24}H_{29}FO_4$) C, H.

6-Chloro-17α-hydroxy-1,2β;6,7β-bis(methylene)-9β,10α-pregn-4-ene-3,20-dione (15a). To a soln of dmsm, prepd from 3.2 g of tmsi as described for **2b**, was added a soln of **12a** (1.45 g) in dry DMSO (52 ml). After 1.75 hr, the reaction mixt was worked up. Chromatography gave **15a** (0.95 g): mp 230–231° (CH_2Cl_2–Et_2O). *Anal.* ($C_{23}H_{29}ClO_3$) C, H.

6-Chloro-17α-hydroxy-1,2β;6,7β-bis(methylene)-9β,10α-pregn-4-ene-3,20-dione 17-Acetate (15b). Compd **15a** was acetylated as described for 6b. Work-up, chromatography, and crystn from Et_2O–CH_2Cl_2 gave pure **15b**: mp 203–205°. *Anal.* ($C_{25}H_{31}ClO_4$) C, H.

17α-Hydroxy-6-methyl-1,2β-methylene-9β,10α-pregna-4,6-diene-3,20-dione 17-Acetate (21). Compd **7** (8 g) was converted to its enol ether **16** by the method described for compd **11**. To the crude **16** pyridine (2.8 ml) and CCl_3Br (10.3 g) were added. This reaction mixt was stored for 7 days in daylight. After filtration of the ppt, the filtrate was dild with 2 *N* HCl (950 ml), extd with CH_2Cl_2, and worked up. After chromatography, compd **18** was obtained (3.25 g). This compd was dissolved in Methyl Cellosolve (113 ml) and CH_2Cl_2 (35 ml) and then added to a prehydrogenated mixt of Pd–$SrCO_3$ (3.12 g) in Methyl Cellosolve (76 ml) and $(C_2H_5)_3N$ (1.85 ml). After an uptake of 468 ml of H_2, the mixt was filtered, and the solvent evapd *in vacuo*. Chromatography over SiO_2 gave **19** (0.73 g). To a soln of this compd in abs dioxane (11 ml) were added $(EtO)_3CH$ (7.1 ml) and TsOH (0.14 g). After a reaction time of 20 hr, the mixt was added to a mixt of HOAc (36.5 ml), MnO_2 (3.65 g), and H_2O (2.9 ml). After stirring for 1 hr, the reaction mixt was worked up and chromatographed over SiO_2 to give **21** (0.4 g): mp 255–256° (Me_2CO). *Anal.* ($C_{25}H_{32}O_4$) C, H.

4-Chloro-17α-hydroxy-1,2β-methylene-9β,10α-pregna-4,6-diene-3,20-dione 17-Acetate (22). To a soln of **6b** (0.6 g) in pyridine (6 ml) SO_2Cl_2 (0.2 ml) was added at 0°. After stirring for 15 min, the reaction mixt was poured out into ice water–2 *N* HCl and worked up. Chromatography and crystn fron Et_2O gave 90 mg of **22**: mp 229–230°. *Anal.* ($C_{24}H_{29}ClO_4$) H; C: calcd, 69.13; found, 68.64.

4-Chloro-17α-hydroxy-1,2β-methylene-6,7ξ-oxido-9β,10α-pregn-4-ene-3,20-dione 17-Acetate (24). *m*-Chloroperbenzoic acid (2.25 g) was added to a soln of **22** (3 g) in dichloroethane (75 ml). After a reaction time of 65 hr, the mixt was worked up to give, after crystn from Et_2O–CH_2Cl_2, compd **24** (2.0 g): mp 238–240°. *Anal.* ($C_{24}H_{29}O_5Cl$) C, H.

A soln of **22** (0.5 g) in CH_2Cl_2 (90 ml) was slowly added at −15° to CrO_2Cl_2 (3.2 ml) in CH_2Cl_2 (15 ml). After stirring for 2.5 hr at −15°, the reaction mixt was poured out into H_2O and worked up. Chromatography gave **24** (0.14 g) and **23** (0.81 g).

4,6α-Dichloro-7ξ,17α-dihydroxy-1,2β-methylene-9β,10α-pregn-4-ene-3,20-dione 17-Acetate (23). Compd **24** (2 g) was dissolved in a soln of HCl in HOAc (50 ml) containing 5.5% HCl (w/v). After 3 min, the mixt was poured out into $NaHCO_3$–H_2O and worked up. Crystn from Me_2CO–*n*-hexane gave compd **23** (1.53 g): mp 242–245°. *Anal.* ($C_{24}H_{30}Cl_2O_5$) C, H.

4,6-Dichloro-17α-hydroxy-1,2β-methylene-9β,10α-pregna-4,6-diene-3,20-dione 17-Acetate (25). Compd **23** (1.3 g) and *p*-chlorobenzenesulfonyl chloride (1.3 g) in pyridine (6 ml) were allowed to react for 20 hr at 80°. Work-up and chromatography gave 0.6 g of the esterified product. Heating of this ester in DMSO (5 ml) for 6 hr at 150° gave, after work-up, chromatography, and crystn from Et_2O, compd **25**: mp 223–224°. *Anal.* ($C_{24}H_{28}Cl_2O_4$) C, H.

Clauberg Test. Immature female rabbits, C.P.B. strain,# 6 weeks old, body weight 800–1000 g, were pretreated with oestradiol monobenzoate for 8 days, in a subcutaneous dose of 0.4 μg/day except on day 2. The compounds were tested orally as a soln in arachis oil. During administration of the test compound from day 10 until 14 a sustaining dose of 0.08 μg/day of oestradiol monobenzoate was given. As a rule the compounds were orally administered to groups of 4 animals at 4 dose levels, against 3 dose levels of the standards, *i.e.*, progesterone subcutaneously (daily doses of 50, 150, and 450 μg/animal) and dydrogesterone orally (daily doses of 500, 1500, and 4500 μg/animal). The progestational effect was judged in 4–8 slices of different parts of each uterus on the basis of the histological development of the endometrium. The relative potency was calculated in terms of the standard, by rank numbering of the microphotographs of the uterine sections of each animal.[28]

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§ **Warning:** As a violent explosion occurred once,[2] all fluorination experiments were carried out in an explosion-guarded hood.

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Investigations on Sterols. 39.[1] Synthesis and Progestational Activities of Some 16-Methylene-17α-acetoxy-9β,10α-pregna-4,6-diene-3,20-dione Derivatives

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The syntheses and progestational activities of some 16-methylene-9β,10α-steroids are reported. Introduction of a 16-methylene group leads to compounds with orally high progestational activity in rabbits, in particular introduction into **16c** resulted in a very potent progestational agent (**8d**). Comparison of structure–activity relationships reveals a striking difference between the natural (9α,10β) and the retro (9β,10α) series as far as substitution at position 6 is concerned.

Introduction of a 16-methylene group into 17α-acetoxypregnanes leads to an enhancement of progestational activity.[2] Furthermore our own studies[3] of steroids having an unnatural configuration showed that 9β,10α-pregnanes possessed interesting hormonal properties. This prompted us to investigate a number of 16-methylene- and 1,2β;16-bis(methylene)-17α-acetoxy-9β,10α-pregnanes.[1] The synthesis and the remarkable progestational properties of this new class of retrosteroids form the subject of this paper.

Chemistry. The introduction of the 17α-hydroxy-16-methylene moiety has been accomplished by the following method (Chart I). The 16-en-20-one system in compound **1**[4] was converted into the 16α,17α-pyrazolino structure **2** with CH_2N_2.[5] Thermolysis[5] at 190° in paraffin oil yielded the 16-methyl-16-en-20-one derivative **3**. Epoxidation of **3** with *m*-Cl-$C_6H_4CO_3H$ afforded as a major product the 16,17α-epoxy-16-methyl compound **4**. The corresponding 4-en-3-one **6** was prepared by Pd–$CaCO_3$ catalyzed hydrogenation of the 4,6-dien-3-one **3**, followed by similar epoxidation of the 16-en-20-one system. Isomerization of **4** and **6** with TsOH[6] in boiling $PhCH_3$ gave the 17α-hydroxy-16-methylene compounds **8a** and **9e**, which on treatment with Ac_2O, AcOH, and TsOH afforded the 17α-acetoxy-16-methylene derivatives **8b** and **9f**. The TsOH-catalyzed treatment of **6** with boiling $PhCH_3$ in the presence of Ac_2O[7] resulted in a high yield of the diacetate **7a**. Fluorination of **7a** with perchloryl fluoride ($FClO_3$)[3b] in Me_2CO–EtOH solution furnished, in addition to the 6α- and 6β-fluoro-4-en-3-ones **9b** and **9c**, a small amount of the 6β-hydroxy-4-en-3-one **9d**. The 6β-chloro compound **9a** could be obtained by treatment of **7a** with Cl_2[3b] in Et_2O–AcOH. The final dehydrogenation of **9a**, **9b**, and **9c** was performed by treatment of the 3-enol ethers **7b** and **7c** with MnO_2 in AcOH,[3a,8] resulting in the 6-halo-4,6-dien-3-ones **8c** and **8d**.

The introduction of the 1,2β-methylene substituent was carried out as reported before.[1] For this purpose the 1-dehydro derivative **11a** was prepared by dehydrogenation of **8a** with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in dioxane.[3a] The 1,4,6-trien-3-one **11a** was converted into the 1,2β-methylene compound **12a** with the Corey ylide reagent.[1,9] Acetylation of **12a** with AcOH, Ac_2O, and TsOH afforded the 17-acetate **12b**. The syntheses of respectively the 6-chloro and 6-fluoro derivatives **12c** and **12d** were realized as outlined before and as described in ref 1.

In the natural series, introduction of a 6-methyl[10] or a 4-chloro[11] substituent, as well as conversion of the 4,6-dien-3-one system into a 3-acetoxy-4,6-diene[12] moiety, results in enhanced biological activity. For that reason some of the