Investigations on Sterols. 38.^{1a} Synthesis of $1,2\beta$ -Methylene- 17α -acetoxy- 9β , 10α -pregnanes, a Class of Potent Progestational Agents

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In this paper the synthesis of $1,2\beta$ -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 $(9\alpha, 10\beta)$ 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 ,10 α 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 methylide⁹ we tried to introduce the 1,2methylene 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 $1,2\beta$ 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 $1,2\beta$ 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 Cl₂² 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 $1,2\beta;6,7\beta$ -bis(methylene) derivative 5c was obtained. This compound could be prepared also by treatment of 6cwith the Corey reagent. Conversion of 5c into its acetate 5bwas accomplished by known methods. Reaction of compound 12a with the Corey reagent gave the 6α -chloro- $6,7\beta$ methylene compound 15a. In this case protection of the 17 α -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 \geq 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 $1,2\beta$ -methylene compounds by previously published methods.^{13,14} Enol etherification of 7 gave 16, which, after reaction with CBrCl₃ 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 MnO₂ 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-3oxo-4,6-diene¹⁵ or a 4-chloro-3-oxo-4,6-diene¹⁷ into a 4,6dichloro-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 ester²² was unsuccessful. We succeeded, however, in dehydrating 23 with *p*-chlorobenzenesulfonyl chloride²³ 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[†] (9 β ,10 α -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.



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 1,2methylene 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 1,2 β -methylene-9 β ,10 α series more than a chlorine atom does. This is in contrast to what has been reported for the normal series, where the 6chloro 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-9 β ,10 α -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

Compounds	Potency	95% confidence limits	Relative potencies ($prog sc = 1$)	
			9β ,10 α (retro)	9α,10β (normal)
Dydrogesterone	1		0.07	
Progesterone sc	14	11-17 ^c		1
1b , 3-0x0, $\Delta^{4,6}$	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, 2 β -CH ₂	400	230-680 ^d	30	4^f
1c, 3-0x0, 6-Cl, $\Delta^{4,6}$	1250	900-1750 ^d	90	30, ^f 33, ^{g,h} 37 ⁱ
2c , 3-oxo, 6-Cl, $\Delta^{1,4,6}$	$\sim 800^{e}$		60	$35_{i,m}^{i,m}2^{k}$
12b , 3-0x0,6-Cl, $\Delta^{4,6}$,1,2 β -CH,	1500	$1,000-2,400^d$	110	$110,^{l}110,^{f}16^{k}$
26 , 3-oxo-6 α -Cl, Δ^4 ,6,7 β -CH, \tilde{b}	600	300-1,900	45	
15b , 3-0x0, 6α -Cl, Δ^4 , 1, 2β ; 6, 7β -diCH,	6000	3,000-12,000	430	
25 , 3-oxo, 4, 6-diCl, $\Delta^{4,6}$, 1, 2 β -CH,	2200	1,700-2,800	160	
1d, 3-0x0,6-F, $\Delta^{4,6}$	1250	$950-1,700^{d}$	90	1 5 ^{j, n}
2c , 3-oxo, 6-F, $\Delta^{1,4,6}$	860	570-1,330	60	6 ^{<i>m</i>, <i>n</i>}
14 , 3-0x0,6-F, $\Delta^{4,6}$, 1,2 β -CH,	8400	6,500-10,800 ^c	600	35^{f}
5b , 3-0x0, Δ^4 ,1,2 β ;6,7 β -diCH ₂	~3000 ^e		200	
21 , 3-0x0,6-CH ₃ , $\Delta^{4,6}$,1,2 β -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-17 α -hydroxy-9 β ,10 α -pregna-4,6-diene-3,20-dione³ 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 26. ^{*k*}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 -9 β ,10 α 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 9 α ,10 β 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-3,20dione (1a) (30 g) in dioxane (750 ml) containing 1 mg of HCl/ml was stirred at room temp for 90 min. After addn of CaCO₃ (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 CH₂Cl₂. After work-up, the residue was crystd from Me₂CO to give 2a (20.8 g): mp 195.5-197.5°. *Anal.* (C₂₁H₂₆O₃) H; C: calcd, 77.27; found, 76.84.

 17α -Hydroxy-9 β , 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 Ac₂O (104 ml) was kept at room temp for 3.5 hr. Decompn of the excess Ac₂O was accomplished with H₂O. The mixt was extd with CH₂Cl₂ and worked up. Crystn from Me₂CO-*n*-hexane gave 2b (10 g): mp 217-219°; [α]D 375°. Anal. (C₂₃H₂₈O₄) 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 CH₂Cl₂ (125 ml) and C₆H₆ (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 SiO₂ to give two compds: 17α -hydroxy-1,2 β -methylene-3-oxo-24-nor-9 β ,10 α -chola-4,6,20(22)trien-23-oic acid lactone (3), mp 263-267°, nmr δ 2.16 (21-CH₃), 5.86 (22-CH) ppm; 17α ,20 ξ -dihydroxy-1,2 β -methylene-3-oxo-24nor-9 β ,10 α -chola-4,6-dien-23-oic acid lactone (4), mp 264-268°, nmr δ 1.52 (21-CH₃), 4.10 (21-OH).

 17α -Hydroxy-1,2 β -methylene-9 β ,10 α -pregna-4,6-diene-3,20dione 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 H₂O and extd with CH₂Cl₂. Work-up and crystn from Me₂CO gave 6c: mp 210°. Anal. (C₂₇H₃₆O₄) C, H.

17α-Hydroxy-1,2β-methylene-9β,10α-pregna-4,6-diene-3,20dione (6a). The ether 6c (16.9 g) in boiling EtOH (300 ml) was treated with 2 N H₂SO₄ (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-3,20dione 17-Acetate (6b). To a mixt of AcOH (520 ml), Ac₂O (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 Me₂CO gave 6b (10 g): mp 253-254°; $[\alpha]D - 657°$. Anal. (C₂₄H₃₀O₄) C, H.

 17_{α} ·Hydroxy-1,2 β ;6,7 β -bis(methylene)-9 β ,10 α -pregn-4-ene-3,20dione 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° (Me₂CO). Anal. (C₂₅H₃₂O₄) 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 PhCH₃ (100 ml) was added Pd-CaCO₃ (5%) (2 g). This mixt was shaken in a H₂ atm. When 260 ml of H₂ had been consumed, the reaction mixt was worked up, chromatographed, and crystd from Me₂CO-Et₂O to give pure 7 (3.2 g): mp 205-205.5°. Anal. (C₂₄H₃₂O₄) 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 $CDCl_3$ (Me₄Si). 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 N₂ atm, and solns were dried over anhyd Na₂SO₄. Elemental analyses were performed in the Mikroanalytisches Laboratorium, Dr. F. Pascher (53 Bonn, West Germanty). Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

3,17 α -Dihydroxy-1,2 β -methylene-9 β ,10 α -pregna-3,5-dien-20one 3,17-Diacetate (8). From a soln of 7 (12.2 g) and TsOH (5 g) in abs C₆H₆ (800 ml) 50 ml was distd off to remove traces of H₂O. 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 H₂O (800 ml) and piperidine (200 ml). After work-up, the crude product was filtered over SiO₂ to give the enol acetate 8 (12.3 g): mp 118-119.5° (MeOH). Anal. (C₂₆H₃₄O₅) C, H.

6β-Chloro-17α-hydroxy-1,2β-methylene-9β, 10α-pregn-4-ene-3,20dione 17-Acetate (9). A stirred soln of the enol acetate 8 (13.3 g) in Et₂O (214 ml) was cooled to -15° . To this soln was added a cold soln of KOAc (24.6 g) in AcOH (540 ml) and H₂O (90 ml). Then 46 ml of a soln of Cl₂ in HOAc containing 53.4 mg of Cl₂/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 Me₂CO gave pure 9: mp 222.5-223°. Anal. (C₂₄H₃₁ClO₄) 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 MnO₂ (22 g) in a mixt of AcOH (240 ml) and H₂O (18 ml). After 25 min, the reaction mixt was filtered and dild with H₂O (1.5 l). After work-up and chromatography, compd 12b (3.1 g) was obtained: mp 243.5-244.5° (Me₂CO-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-CH₃), 0.9 and 1.3, m (cycloprop), 1.54, s (19-CH₃) 2.10, s (21-CH₃ and 17α-OAc), 6.18, s (4-CH), and 6.28, d (7-CH), ppm. Anal. (C₂₄H₂₂CIO₄) C, H.

6-Chloro-17 α -hydroxy-1,2 β -methylene-9 β ,10 α -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 NaClO₄ (1.78 g). After stirring for 4.5 hr at room temp, the reaction mixt was poured out into H₂O and worked up. Chromatography gave 12a (1.15 g): mp 219-219.5° (Me₂CO). Anal. (C₂₂H₂₇ClO₃) C, H.

6-Fluoro-17α-hydroxy-1,2β-methylene-9β,10α-pregn-4-ene-3,20dione 17-Acetate (10). A slow stream of FClO₃ mixed with N₂ (1:1)[§] was led at 0° through a mixed soln of the enol acetate 8 (1.95 g) in dry Me₂CO (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 N₂ was bubbled through the soln for 2 hr. The mixt was poured out into H₂O and worked up. Chromatography on SiO₂ 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° (Et₂O-hexane) [Anal. (C₂₄H₃₁FO₄) C, H]; and 6β fluoro compd 10 (0.57 g), mp 239-240° (Et₂O-hexane) [Anal. (C₂₄H₃₁FO₄) 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 MnO₂ to give, after chromatography and crystn from Et₂O, 0.37 g of 14: mp 249-251°; [α]D -459°; λ_{max} 283.5 nm (e 16,600); ν_{max} 3060, 1740, 1720, 1673, 1650, 1600, and 863 cm⁻¹; nmr δ 0.75, s (18-CH₃), 0.8 and 1.3, m (cycloprop), 1.55, s (19-CH₃), 2.07, s (21-CH₃ and 17α-OAc), 5.66, 2d (7-CH), and 5.91, s (4-CH) ppm. Anal. (C₂₄H₂₉FO₄) 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° (CH₂Cl₂-Et₂O). Anal. ($C_{13}H_{29}ClO_3$) C, H.

6-Chloro-17α-hydroxy-1,2β;6,7β-bis(methylene)-9β,10α-pregn-4ene-3,20-dione 17-Acetate (15b). Compd 15a was acetylated as described for 6b. Work-up, chromatography, and crystn from Et₂O-CH₂Cl₂ gave pure 15b: mp 203-205°. Anal. (C₂₅H₃₁ClO₄) C, H.

 17α -Hydroxy-6-methyl-1,2 β -methylene-9 β ,10 α -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 CCl₃Br (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 CH₂Cl₂, and worked up. After chromatography, compd 18 was obtained (3.25 g).

§Warning: As a violent explosion occurred once,² all fluorination experiments were carried out in an explosion-guarded hood. This compd was dissolved in Methyl Cellosolve (113 ml) and CH_2Cl_2 (35 ml) and then added to a prehydrogenated mixt of Pd-SrCO₃ (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 SiO₂ 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), MnO₂ (3.65 g), and H_2O (2.9 ml). After stirring for 1 hr, the reaction mixt was worked up and chromatographed over SiO₂ to give 21 (0.4 g): mp 255-256° (Me₂CO). Anal. (C₂₈H₃₂O₄) C, H.

4-Chloro-17 α -hydroxy-1,2 β -methylene-9 β ,10 α -pregna-4,6-diene-3,20-dione 17-Acetate (22). To a soln of 6b (0.6 g) in pyridine (6 ml) SO₂Cl₂ (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 Et₂O gave 90 mg of 22: mp 229-230°. Anal. (C₂₄H₂₉ClO₄) H; C: calcd, 69.13; found, 68.64.

4-Chloro-17 α -hydroxy-1,2 β -methylene-6,7 ξ -oxido-9 β ,10 α -pregn-4ene-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 Et₂O-CH₂Cl₂, compd 24 (2.0 g): mp 238-240°. *Anal.* (C₂₄H₂₉O₅Cl) 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).

4,6 α -Dichloro-7 ξ ,17 α -dihydroxy-1,2 β -methylene-9 β ,10 α 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 NaHCO₃-H₂O and worked up. Crystn from Me₂CO-*n*-hexane gave compd 23 (1.53 g): mp 242-245°. Anal. (C₂₄H₃₀Cl₂O₅) C, H.

4,6-Dichloro-17 α -hydroxy-1,2 β -methylene-9 β ,10 α -pregna-4,6diene-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 Et₂O, compd 25: mp 223-224°. Anal. (C₂₄H₂₈Cl₂O₄) 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 $0.4 \, \mu g/day$ except on day 2. The compounds were tested orally as a solin in arachis oil. During administration of the test compound from day 10 until 14 a sustaining dose of $0.08 \, \mu g/day$ 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 $\mu g/animal$) and dydrogesterone orally (daily doses of 500, 1500, and 4500 $\mu g/animal$). 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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References

- (a) M. P. Rappoldt and Th. R. Rix, *Recl. Trav. Chim. Pays-Bas*, 90, 27 (1971) (paper 37); (b) R. Wiechert and F. Neumann, *Arzneim.-Forsch.*, 15, 244 (1965).
- (2) P. Westerhof, J. Hartog, and S. J. Halkes, Recl. Trav. Chim. Pays-Bas, 84, 863 (1965).
- (3) P. Westerhof and J. Hartog, ibid., 84, 918 (1965).
- (4) A. Smit and P. Westerhof, ibid., 82, 1107 (1962).

#C.P.B. = Centraal Proefdieren Bedrijf T.N.O.-Zeist, The Netherlands.

- (5) R. Wiechert and E. Kaspar, Chem. Ber., 93, 1710 (1960).
- (6) G. W. Krakower and H. A. Van Dine, J. Org. Chem., 31, 3467
- (1966).
- (7) H. van Kamp, private communication.
- (8) H. van Kamp, P. Nissen, and E. van Vliet, Tetrahedron Lett., 1457 (1967).
- (9) E. J. Corey and M. Chaykovsky, J. Amer. Chem. Soc., 84, 867 (1962); 87, 1353 (1965).
- (10) (a) T. L. Popper, J. N. Gardner, R. Neri, and H. L. Herzog, J. Med. Chem., 12, 393 (1969); (b) G. W. Moersch, D. E. Evans, and G. S. Lewis, ibid., 10, 254 (1967); (c) N. H. Dyson, J. A. Edwards, and J. H. Fried, Tetrahedron Lett., 1841 (1966); (d) H. G. Lehmann, Angew. Chem., Int. Ed. Engl., 4, 783 (1965).
- (11) Searle and Company, British Patent 871.487; Chem. Abstr., 54, 22732i (1960).
- (12) (a) G. W. Duncan, S. C. Lyster, J. W. Hendrix, J. J. Clark, and H. D. Webster, Fert. Steril., 15, 419 (1964); (b) J. C. Babcock, E. S. Gutsell, M. E. Herr, J. A. Hogg, J. C. Stucki, L. E. Barnes, and W. E. Dublin, J. Amer. Chem. Soc., 80, 2904 (1958); (c) H. J. Ringold, E. Batres, and G. Rosenkranz, J. Org. Chem., 22,99 (1957).
- (13) S. Liisberg, W. O. Godtfredsen, and S. Vangedal, Tetrahedron Lett., 9, 149 (1960).
- (14) H. van Kamp and S. J. Halkes, Recl. Trav. Chim. Pays-Bas, 84,904 (1965).
- (15) R. Wiechert, Experientia, 24, 767 (1968).
- (16) A. Boris, L. Demartino, and T. Trmal, Acta Endrocrinol.,

63, 476 (1970).

- (17) R. W. Kierstead, J. Blount, K. E. Fahrenholtz, A. Faraone, R. A. LeMahieu, and P. Rosen, J. Org. Chem., 35, 4141 (1970).
- (18) N. Sugimoto, T. Fujita, N. Shigematsu, and A. Ayada, Chem. Pharm. Bull., 10, 427 (1962).
- (19) Syntex Corporation, U. S. Patent 3076823; Chem. Abstr., 59, 12880e (1963).
- (20) J. Fried and E. F. Sabo, J. Amer. Chem. Soc., 75, 2273 (1953).
- (21) G. Rosenkranz, O. Mancera, and F. Sondheimer, ibid., 76,
- 2227 (1954).
- (22) J. Fried and E. F. Sabo, *ibid.*, 79, 1130 (1957). (23) H. R. Nace, ibid., 81, 5428 (1959).
- (24) (a) Z. Cekan, M. Seda, J. Mikulaskova, and K. Syhora, Steroids, 4, 415 (1964); (b) 8, 205 (1966).
- (25) H. J. Ringold, E. Batres, A. Bowers, J. Edwards, and J. Zderic, J. Amer. Chem. Soc., 81, 3485 (1959).
- (26) E. L. Shapiro, T. L. Popper, L. Weber, R. Neri, and H. L. Herzog, J. Med. Chem., 12, 631 (1969).
- (27) F. A. Kincl, Endokrinologie, 40, 257 (1961).
- (28) R. van Strik, "Quantitative Methods in Pharmacology," H. de Jonge, Ed., North Holland Publishing Co., Amsterdam, 1961, p 88.
- (29) J. Hartog, J. I. G. M. Wittelaar, L. Morsink, and A. M. de Wachter, J. Med. Chem., 15, 1292 (1972).
- (30) Handbuch der experimentelle Pharmakologie, Band XXI, Teil 1 Die Gestagene, K. Junkmann-Springer Verlag, Berlin, 1968, p 870.

Investigations on Sterols. 39.¹ Synthesis and Progestational Activities of Some 16-Methylene-17 α -acetoxy-9 β ,10 α -pregna-4,6-diene-3,20-dione Derivatives

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The syntheses and progestational activities of some 16-methylene-9 β , 10 α -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 $(9\alpha, 10\beta)$ and the retro $(9\beta, 10\alpha)$ 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 studies³ 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 $1,2\beta$;16-bis-(methylene)-17 α -acetoxy-9 β ,10 α -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-16methylene 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 CH₂N₂⁵ Thermolysis⁵ at 190° in paraffin oil yielded the 16-methyl-16-en-20-one derivative 3. Epoxidation of 3 with m-Cl-C₆H₄CO₃H afforded as a major product the 16,17 α -epoxy-16-methyl compound 4. The corresponding 4-en-3-one 6 was prepared by Pd-CaCO₃ 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 TsOH⁶ in boiling PhCH₃ gave the 17α -hydroxy-16methylene compounds 8a and 9e, which on treatment with Ac₂O, AcOH, and TsOH afforded the 17α -acetoxy-16methylene derivatives 8b and 9f. The TsOH-catalyzed treatment of 6 with boiling PhCH₃ in the presence of Ac_2O^7 resulted in a high yield of the diacetate 7a. Fluorination of 7a with perchloryl fluoride (FClO₃)^{3b} in Me₂CO-EtOH solution furnished, in addition to the 6α - and 6β -fluoro-4-en-3ones **9b** and **9c**, a small amount of the 6β -hydroxy-4-en-3one 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 $1,2\beta$ -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 1,2 β -methylene compound 12a with the Corey ylide reagent.^{1,9} Acetylation of 12a with AcOH, Ac₂O, 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-methyl¹⁰ or a 4chloro¹¹ substituent, as well as conversion of the 4,6-dien-3-one system into a 3-acetoxy-4,6-diene¹² moiety, results in enhanced biological activity. For that reason some of the