with 200 ml of 10% HCl. The organic layer was washed twice with a 5% soln of Na_2CO_3 and dried (Na_2SO_4), and the solvent removed. The residue, 20.18 g, did not crystallize.

The crude 2-(1-hydroxy-1-naphthylpropyl)-6-ethylbenzoic acid lactone (24) was dissolved in 300 ml of EtOH, 70 ml of a 30% aqueous soln of NaOH was added, and the EtOH was removed under reduced pressure. To the residue, 400 ml of H_2O, 70 ml of concd NH_4OH, and 70 g of Zn dust were added, and the mixture was refluxed with stirring for 47 hr. The mixture was filtered and the cold filtrate was acidified with HCl. The precipitate was filtered off and washed with H_2O. The dried product (17.00 g), crystd from C_6H_6–hexane: first crop 6.18 g, mp 133–134.5°, second crop 2.25 g, mp 131–133°: yield 33.6%. Mp of the analytical sample was 139–139.5°. *Anal.* ($C_{22}H_{22}O_2$) C, H.

8,12-Diethylbenz[*a*]anthr-7-one (26). Ten g (0.031 mole) of 25 was dissolved in 50 ml of anhyd HF. The excess reagent was allowed to evaporate overnight. The residue was dissolved in Et_2O, the soln was washed with a 5% Na_2CO_3 soln and with H_2O. The dried (Na_2SO_4) soln was evaporated. The remaining material (7.72 g) did not crystallize.

8,12-Diethylbenz[*a*]anthr-7-ol (27). The crude anthrone 26 was dissolved in 50 ml of toluene. To the soln, 125 ml of a 15% NaOH soln and 28 g of Zn–Cu couple were added, and the mixture was boiled for 48 hr with stirring. The organic layer was washed twice with H_2O and dried (Na_2SO_4). After evaporation of the solvent, a cryst residue (6.39 g) was obtained. For analysis, a sample was recrystd twice from hexane: mp 121–123°. *Anal.* ($C_{22}H_{22}O$) C, H.

8,12-Diethylbenz[*a*]anthracene (28). The soln of the crude anthrol (5.0 g) in 75 ml of C_6H_6 was refluxed with 0.75 g of TsOH for 1 hr. The cooled soln was washed with a 5% Na_2CO_3 soln and with H_2O. After drying (Na_2SO_4), the solvent was evaporated, and the residue (4.47 g) was crystd from hexane: yield 1.19 g, mp 104–105° and 1.84 g, mp 100–102.5°. Yield was 34% based on 25. The analytical sample melted at 104–105°: nmr δ 1.45 (t, 3), 1.82 (t, 3), 3.24 (q, 2), 3.81 (q, 2). *Anal.* ($C_{22}H_{20}$) C, H.

Acknowledgment. We are indebted to Professor Charles B. Huggins, The University of Chicago, for permission to cite the biological test data obtained in his laboratory.

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14α,17α-Alkylidenedioxyprogesterone Derivatives

Dirk van der Sijde,* Herman J. Kooreman, Kapil D. Jaitly, and Arthur F. Marx

Gist-Brocades Research and Development Division, Delft, Netherlands

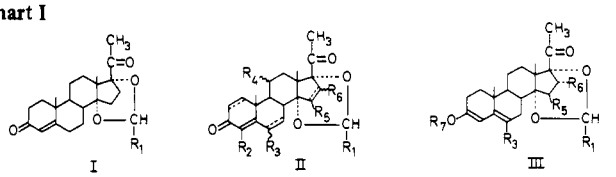
14α,17α-Alkylidenedioxyprogesterone derivatives, having interesting progestational and anticonceptive activities, were prepared by reaction of 14α,17α-dihydroxyprogesterone derivatives with aldehydes and orthoformates. Reaction with ketones did not yield the corresponding alkylidenedioxy compounds because of steric hindrance. The structure–activity relationship of the new compounds is discussed.

In the past there have been several attempts to enhance the pharmacological activity of steroids by attaching a new ring to the D ring of the steroid molecule. In the field of progestational hormones this has been carried out by Solo, *et al.*,[1] who synthesized 14α,17α-etheno derivatives by means of a Diels–Alder reaction and by Fried, *et al.*,[2a] who found that 16α,17α-alkylidenedioxy groups, normally used as protecting groups or for characterization purposes, showed an enhancing effect on certain pharmacological activities. Steroids with alkylidenedioxy groups in various positions, in most cases 16 and 17 or 17 and 21, have been described.[2] 14α,17α-Dihydroxy steroids have hydroxyl groups in a suitable position for condensation with carbonyl compounds and the bridging alkylidenedioxy group, together with carbon atoms 13, 14, and 17, would incorporate a new six-membered ring on the α side of the molecule. 14α,17α-Dihydroxy steroids were readily available to us and it was of interest to determine whether such compounds possessed biological activity. This communication describes the preparation and biological activity of a number of new 14α,17α-alkylidenedioxyprogesterone derivatives.

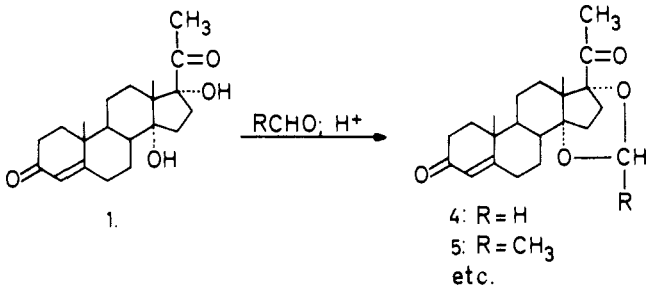
Chemistry. Most of the products were derived from the parent compound 14α,17α-dihydroxyprogesterone (**1**)[3] which was obtained from the 21-hydroxy analog according to the method described by Cooley, *et al.*[3] Some of the initially prepared products had promising progestational properties. Therefore the influence on activity of variation in the alkylidenedioxy moiety was investigated by the synthesis of a series of derivatives of the general formula I (Chart I), in which R_1 is an alkyl or aryl group or in some cases an alkoxy group. Also studied was the influence of substituents in the steroid skeleton such as double bonds, halogens, hydroxyl, or alkyl groups. The compounds of general formula II or III (Chart I) resulted. These compounds were, in some cases, synthesized from two other parent compounds, 11β,14α,-17α-trihydroxypregn-4-ene-3,20-dione (**2**)[4] and 6α-fluoro-16α-methyl-14α,17α-dihydroxypregn-4-ene-3,20-dione (**3**),[5] which were also derived from the corresponding 21-hydroxy analogs.[3] The key reaction for the preparation of these products is condensation of the parent compounds with aldehydes[2a] or ortho esters[2b] as shown in Schemes I and II.

Consideration of Dreiding models shows that the most

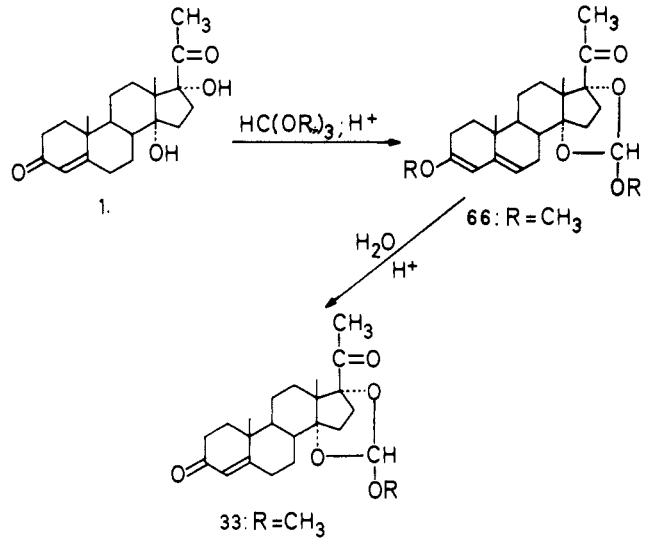
Chart I



Scheme I



Scheme II



probable conformation of the additional 1,3-dioxane ring is the chair form with the substituent R_1 in the equatorial position. The other possibilities—boat conformation and chair conformation with R_1 in axial position—show considerable steric hindrance. Therefore the former conformation is assumed to be correct. This was proved for one of the products, 6α-fluoro-15β-chloro-16α-methyl-14α,17α-ethylidenedioxypregn-4-ene-3,20-dione (**62**), by means of a study of the Nuclear Overhauser Effect.[5] In accordance with these findings 14α,17α-dihydroxy steroids could not be condensed with acetone. The other structural variations were made by known chemical and microbiological methods. The various products obtained are listed in Tables I, II, and III (referring to formulas I, II, and III, respectively). All compounds were identified by nuclear magnetic resonance, infrared, and ultraviolet spectra, and their empirical formulas were consistent with the elemental analyses (in all cases C and H and—if present—Cl and N). Typical examples of the reactions involved are given in detail in the Experimental Section. Physical data are given in the tables.

Pharmacology. The compounds were tested as solutions or suspensions in maize oil (50 mg/ml for rats; 5 mg/ml for rabbits). The rats used in these experiments were the Wistar-derived strain from T.N.O. (Zeist, Holland) and the rabbits were the "Bastard" strain bred by T.N.O. (Zeist, Holland).

The anticonceptive activity of our compounds was determined by means of the "pregnancy-delay" test[6] after subcutaneous injection of a single dose of 10 mg/rat. The test drugs were administered to groups of 6 regularly cycling female rats (weight approx 200 g) on the first day of diestrus. Males were introduced into the cages on the following

Table I. Compounds with Formula I

No.	R_1	Methods	Mp, °C	Formula	Anal.[a]	Pregnancy delay[b]	Claub test[c]	Decid weight, g[d]
4	H	A	172–174	$C_{22}H_{30}O_4$	C, H	11		
5	Me	A	178–181	$C_{23}H_{32}O_4$	C, H	27	3.8	175
6	Et	A	93–94	$C_{24}H_{34}O_4$	C, H	47	4.0	140
7	Vinyl	A	113–115	$C_{24}H_{32}O_4$	C, H	5	0.0	
8	Pr	A	88–98	$C_{25}H_{36}O_4$	C, H	40		282
9	Propenyl	A	119–120	$C_{25}H_{34}O_4$	C, H	24	3.8	
10	Bu	A	88–89	$C_{26}H_{38}O_4$	C, H	18	0.5	285
11	*tert*-Bu	A	122–125	$C_{26}H_{38}O_4$	C, H	15	0.0	275
12	Et_2CH	A	84–86	$C_{27}H_{40}O_4$	C, H	21	0.1	385
13	Heptyl	A	Oil	$C_{29}H_{44}O_4$	C, H	5		82
14	Cyclohexyl	A	75–79	$C_{28}H_{40}O_4$	C, H	21	0.2	206
15	$ClCH_2CH_2$	A	129–132	$C_{24}H_{33}O_4Cl$	C, H, Cl	40	1.3	
16	$MeOOCCH_2CH_2$	A	Oil	$C_{26}H_{36}O_6$	C, H	6	0.0	36
17	$HOOCCH_2CH_2$	A, W	174–176	$C_{25}H_{34}O_6$	C, H	5		8
18	2-Furyl	A	173–174	$C_{26}H_{32}O_5$	C, H	9		186
19	$PhCH_2CH_2$	A	153–155	$C_{30}H_{38}O_4$	C, H	10	0.2	
20	PhMeCH	A	136–138	$C_{30}H_{38}O_4$	C, H	17	0.0	
21	Ph	A	183–186	$C_{28}H_{34}O_4$	C, H	17	3.0	262[e]
22	*p*-Tolyl	A	145–146	$C_{29}H_{36}O_4$	C, H	18	0.0	263[e]
23	*p*-*i*-PrC_6H_4	A	140–142	$C_{31}H_{40}O_4$	C, H	8	0.0	
24	*p*-$MeOC_6H_4$	A	115–117	$C_{29}H_{36}O_5$	C, H	16	0.5	73[e]
25	3,4,5-$(MeO)_3C_6H_2$	A	122–125	$C_{31}H_{40}O_7$	C, H	15	0.5	6
26	*p*-ClC_6H_4	A	195–198	$C_{28}H_{33}O_4Cl$	C, H, Cl	37	3.4	274
27	*p*-FC_6H_4	A	134–140	$C_{28}H_{33}O_4F$	C, H	48	4.0	
28	*p*-$NO_2C_6H_4$	A	164–167	$C_{28}H_{33}O_6N$	C, H	23	3.6	234
29	*p*-$NH_2C_6H_4$	A, U	131–134	$C_{28}H_{35}O_4N$	C, H, N	9	0.1	18
30	*p*-$ClCH_2CONHC_6H_4$	A, U, V	130–155	$C_{30}H_{36}O_5NCl$	C, H	4		
31	*p*-$BrCH_2CONHC_6H_4$	A, U, V	130–155	$C_{30}H_{36}O_5NBr$	C, H	4	0.0	
32	1-Naphthyl	A	125–130	$C_{32}H_{36}O_4$	C, H	2	0.0	275
33	MeO	B1,2	130–132	$C_{23}H_{32}O_5$	C, H	8	0.7	297
34	EtO	B1,2	143–146	$C_{24}H_{34}O_5$	C, H	5		
	Progesterone[f]					12	3	330[e]
	Ethynylnortestosterone[f]					18	0.7	12

[a] Analytical results obtained for the elements mentioned were within ±0.4% of the theoretical values. [b] The pregnancy delay is given in days after a single sc injection of 10 mg/rat. [c] The McPhail score is given after daily sc injection of 0.1 mg/rabbit for 5 days. [d] The deciduoma weight is given in mg after daily sc injection of 10 mg/rat for 9 days. [e] 5 mg/rat. [f] For comparison.

Table II. Compounds with Formula II

No.	R_1	C=C	R_2	R_3	R_4	R_5	R_6	Methods	Mp, °C	Formula	Anal.[a]	Pregnancy delay[b]	Claub test[c]	Decid weight, g[d]
35	Me		H	H	β-OH	H	H	A[e]	261-262	$C_{23}H_{32}O_5$	C, H	94	3.9[g]	36
36	Et		H	H	β-OH	H	H	A[e]	191-193	$C_{24}H_{34}O_5$	C, H	14		134
37	Bu		H	H	β-OH	H	H	A[e]	116-117	$C_{26}H_{38}O_5$	C, H	20		178
38	Me		H	α-F	H	H	α-CH_3	A[f]	214-217	$C_{24}H_{33}O_4F$	C, H	42	3.9	241
39	Me	Δ^1	H	H	H	H	H	A, C	213-215	$C_{23}H_{30}O_4$	C, H	20	3.9	
40	Me	Δ^1	H	α-F	H	H	α-CH_3	A, C[f]	237-239	$C_{24}H_{31}O_4F$	C, H	15	0.1	115
41	Me		Cl	H	H	H	H	A, E	177-179	$C_{23}H_{31}O_4Cl$	C, H, Cl	28	0.1	64
42	Me		H	β-Cl	H	H	H	A, D, G	84-92	$C_{23}H_{31}O_4Cl$	C, H	31		
43	Me		H	α-Cl	H	H	H	A, D, G, D, H	86-92	$C_{23}H_{31}O_4Cl$	C, H, Cl	36	3.9	
44	Et		H	α-Cl	H	H	H	A, D, G, D, H	131-134	$C_{24}H_{33}O_4Cl$	C, H, Cl	37		
45	Ph		H	α-Cl	H	H	H	A, D, G, D, H	107-113	$C_{28}H_{33}O_4Cl$	C, H, Cl	17		
46	Me	Δ^6	H	Cl	H	H	H	A, D, G, D, J	159-161	$C_{23}H_{29}O_4Cl$	C, H, Cl	32		
47	Me		H	α-CH_3	H	H	H	A, D, F, K	154-156	$C_{24}H_{34}O_4$	C, H	45	4.0	112
48	Me	Δ^6	H	H	H	H	H	A, L	187-188	$C_{23}H_{30}O_4$	C, H	11	3.9	434
49	Me	$\Delta^{1,6}$	H	H	H	H	H	A, L, C	212-213	$C_{23}H_{28}O_4$	C, H		3.3	
50	Me	Δ^6	H	CH_3	H	H	H	A, D, F, K, L	207-212	$C_{24}H_{32}O_4$	C, H	28	4.0	265
51	Me	Δ^6	H	H	H	H	α-CH_3	A, L[f]	171-172	$C_{24}H_{32}O_4$	C, H	16	0.1	
52	Me		H	H	α-OH	H	H	A, M or M, A	234-236	$C_{23}H_{32}O_5$	C, H	10	3.6	77[h]
53	Me	Δ^6	H	H	α-OH	H	H	A, M, L	232-236	$C_{23}H_{30}O_5$	C, H		2.0[i]	
54	Et		H	H	α-OH	H	H	M, A	170-172	$C_{24}H_{34}O_5$	C, H	6		178
55	p-$MeOC_6H_4$		H	H	α-OH	H	H	M, A	151-152	$C_{29}H_{36}O_6$	C, H	10	0.0	
56	Me		H	H	β-OAc	H	H	A, N[e]	217-218	$C_{25}H_{34}O_6$	C, H	17		88
57	Me		H	H	=O	H	H	A, M, P	184-187	$C_{23}H_{30}O_5$	C, H	13	3.6	125
58	Me		H	H	H	β-Cl	H	R, A	258-261	$C_{23}H_{31}O_4Cl$	C, H, Cl	2	0.1	6
59	Et		H	H	H	β-Cl	H	R, A	194-197	$C_{24}H_{33}O_4Cl$	C, H, Cl	21		56
60	Me		H	H	H	β-Br	H	R, A	239-240	$C_{23}H_{31}O_4Br$	C, H, Br		0.0	
61	Me		H	H	H	β-F	H	R, A	192-199	$C_{23}H_{31}O_4F$	C, H	12	0.0	
62	Me		H	α-F	H	β-Cl	α-CH_3	R, A[f]	228-230	$C_{24}H_{32}O_4FCl$	C, H	9		6
63	Me		H	α-F	H	β-Br	α-CH_3	R, A[f]	218-219	$C_{24}H_{32}O_4FBr$	C, H		0.5[i]	
64	Me		H	α-F	H	β-OH	α-CH_3	R, A[f]	246-248	$C_{24}H_{33}O_5F$	C, H	3		
65	Me	Δ^{15}	H	H	H	H	H	R, A, S	218-222	$C_{23}H_{30}O_4$	C, H		3.5	

[a]Analytical results obtained for the elements mentioned were within ±0.4% of the theoretical values. [b]The pregnancy delay is given in days after a single sc injection of 10 mg/rat. [c]The McPhail score is given after daily sc injection of 0.1 mg/rabbit for 5 days. [d]The deciduoma weight is given in mg after daily sc injection of 10 mg/rat for 9 days. [e]Prepared from 2. [f]Prepared from 3. [g]0.01 mg/rabbit. [h]2.5 mg/rat. [i]1.0 mg/rabbit.

Table III. Compounds with Formula III

No.	R_1	R_3	R_5	R_6	R_7	Methods	Mp, °C	Formula	Anal.[a]
66	MeO	H	H	H	Me	B1	117-121	$C_{24}H_{34}O_5$	C, H
67	EtO	H	H	H	Et	B1	83-120	$C_{26}H_{38}O_5$	C, H
68	Me	H	H	H	Et	A, D	147-150	$C_{25}H_{36}O_4$	C, H
69	Me	F	H	α-CH_3	Et	A, D[b]	149-150	$C_{26}H_{37}O_4F$	C, H
70	Et	H	H	H	Et	A, D	128-131	$C_{26}H_{38}O_4$	C, H
71	Et	H	H	H	Cyclopentyl	A, D	92-98	$C_{29}H_{42}O_4$	C, H
72	Ph	H	H	H	Et	A, D	191-196	$C_{30}H_{38}O_4$	C, H
73	Ph	H	H	H	Cyclopentyl	A, D	125-132	$C_{33}H_{42}O_4$	C, H
74	p-FC_6H_4	H	H	H	Et	A, D	Amorph	$C_{30}H_{37}O_4F$	C, H
75	Ph	H	H	H	Me	A, D	126-127	$C_{29}H_{36}O_4$	C, H
76	Me	COH	H	H	Et	A, D, F	167-171	$C_{26}H_{36}O_5$	C, H
77	H	Cl	H	H	Et	A, D, G, D	187-188	$C_{24}H_{33}O_4Cl$	C, H
78	Me	Cl	H	H	Et	A, D, G, D	169-170	$C_{25}H_{35}O_4Cl$	C, H, Cl
79	Me	Cl	H	H	Cyclopentyl	A, D, G, D	125-129	$C_{28}H_{39}O_4Cl$	C, H, Cl
80	Et	Cl	H	H	Et	A, D, G, D	55-60	$C_{26}H_{37}O_4Cl$	C, H, Cl
81	Ph	Cl	H	H	Et	A, D, G, D	183-186	$C_{30}H_{37}O_4Cl$	C, H, Cl
82	1-Naphthyl	Cl	H	H	Et	A, D, G, D	180-183	$C_{34}H_{39}O_4Cl$	C, H, Cl
83	Me	H	β-Cl	H	Et	R, A, D	164-170	$C_{25}H_{35}O_4Cl$	C, H, Cl
84	Ph	H	H	H	Me	A, D, T[c]	190-200	$C_{29}H_{37}O_4N$	C, H

[a]Analytical results obtained for the elements mentioned were within ±0.4% of the theoretical values. [b]Prepared from 3. [c]20-Oxime.

day. The pregnancy delay was the period elapsing between administration of a drug and a successful mating. The day of successful mating was calculated by subtracting 22 days (the normal length of gestation) from the date on which delivery took place. The progestational activity was examined in the Clauberg test (McPhail score)[7] and the deciduoma-weight test[8] with daily doses of 0.1 mg/rabbit and 10 mg/rat (sc), respectively.

For the Clauberg test groups of 4 female rabbits (approx 1 kg in weight) were primed for 6 days with 5 μg of estradiol-17β sc, daily. This was followed by daily sc injections of the test substance for the next 5 days. The rabbits were sacrificed on the 12th day, and the middle portion of both uterine horns was removed for scoring (McPhail grading) of the endometrial proliferation.

For the deciduoma test, groups of 8 female rats (weight approx 200 g), ovariectomized a week earlier, were primed with 0.5 μg of estradiol benzoate sc daily for 4 days. The test compounds were injected sc, daily, for the next 9 days. On the 5th day of treatment with the test compound the rats were anesthetized with ether, and 0.1 ml of 1% histamine was injected in one uterine horn. The animals were

killed on the 10th day after starting treatment with the test drug. The difference in the weight of the two uterine horns represented the weight of the deciduoma. The results are given in Tables I and II.

Some of the initially prepared products appeared to be promising. Though the parent compound 14α,17α-dihydroxyprogesterone (**1**) did not show any hormonal activity, compound **5** showed activities of the same order as progesterone (Table I). This clearly demonstrates the activity-enhancing effect of the alkylidenedioxy moiety. This effect (especially on the pregnancy delay) could be influenced considerably by variation of the alkylidenedioxy moiety.

In the case of aliphatic R_1 chains optimum activity was found for R_1 = Et (**6**). The condensation products with aromatic aldehydes (*e.g.*, **21**) also had high activity which could be substantially improved by para-halogen (**26**, **27**) or para-nitro (**28**) substituents. Electron-donating substituents on the contrary appeared to have negative effects (**23**, **29**). Further the influence of various modifications in the steroid skeleton on pharmacological activity was investigated.

In the literature it has been reported[9-12] that enhancement of activity occurs when substituents such as 6α-halogen and 6α-methyl and double bonds at 6 are present, whereas 6β-halogens have been reported to have a decreasing effect and some other substituents, *e.g.*, 11β-halogen or hydroxyl, 16α-methyl, to have no noticeable effect. In general, these findings were confirmed, except that a double bond at position 6 was found to have a rather negative effect on anticonceptive activity (**48**, **50**). The positive effect of 6α-methyl is clearly demonstrated in compounds **47** and **50**. Some 15β substituents (**58–64**) and hydroxyl groups at 11α (**52–55**) showed a negative effect on activity. Very surprising was the large positive effect of 11β-hydroxyl in **35** (not seen in **36** and **37**). The very long pregnancy delay (94 days), induced in rats by compound **35**, appeared to be combined with considerable corticoid activity. Other promising long-acting agents are the compounds **6** and **27**. The various 3-enol ethers (Table III) were made with the intention of enhancing oral activity[13] and were therefore tested by the oral route only. The most active products were compounds **78** and **79**. Compound **79** caused a pregnancy delay of 26 days after administration of a single 50-mg dose (after a single dose of 10 mg, the delay was 19 days). Compound **78** showed a delay of 26 days with 50 mg (with 10 mg the delay was 6 days). Both compounds gave a McPhail score of 4 with a 1-mg dose. No correlation has been found between the results in the three tests used in this study.

Experimental Section

General. Melting points were determined on a Büchi melting point apparatus according to Tottoli. Elemental analyses were performed at the Laboratory of Organic Chemistry of the Technical University at Delft (Mr. M. v. Leeuwen). These data are given in the tables for compounds 4–84 and in the Experimental Section for compounds 86–88. The ir and nmr spectra and, if necessary, uv spectra of all compounds were measured. In all cases the absorption bands were as expected. Details of these spectra are not given. All reactions were controlled by thin-layer chromatography.

A. Condensation with Aldehydes.[2a] In general the 14α,17α-dihydroxy steroid was treated at room temp with an aldehyde in an organic solvent (such as dioxane, CH_2Cl_2), in the presence of a catalytic quantity of perchloric or other acid. At the end of the reaction the mixt was neutralized with pyridine or $NaHCO_3$. In most cases excess aldehyde had to be removed from the reaction mixt by some method such as treatment with bisulfite reagent, steam distn etc., and in many cases column chromatog was necessary. Some specific examples are given.

1. 14α,17α-Ethylidenedioxypregn-4-ene-3,20-dione (**5**). A soln of 200 g of 200 g of 14α,17α-dihydroxypregn-4-ene-3,20-dione (**1**) in 2.5 l. of dioxan was mixed with 350 ml of paraldehyde and 10 ml of 70% $HClO_4$ was added. The mixt was stirred at room temp for 2 hr, neutralized with pyridine, and dild with 5 l. of water. The crude cryst product was recrystd from MeOH–CH_2Cl_2 to yield 204 g (95%) of **5**.

2. 14α,17α-(3′-Methoxycarbonylpropylidenedioxy)pregn-4-ene-3,20-dione (**16**). A soln of 2 g of 14α,17α-dihydroxypregn-4-ene-3,-20-dione (**1**) in 90 ml of CH_2Cl_2 was mixed with 5 ml of 3-methoxycarbonylpropanal (prepd according to Borghero[14] and 0.05 ml of 70% $HClO_4$. The mixt was stirred at room temp for 1.5 hr, washed with $NaHCO_3$ soln, $NaHSO_3$ soln, and water, and evapd *in vacuo*. The residue was chromatographed on alumina with PhH–EtOH, 20:1. From the appropriate fractions 1 g (39%) of **16** was isolated as an oil

B. Condensation with Ortho Esters.[2b] 1. 3-Methoxy-14α,17α-Methoxymethylenedioxypregna-3,5-dien-20-one (**66**). A mixt of 20 g of 14α,17α-dihydroxypregn-4-ene-3,20-dione (**1**), 150 ml of dioxan, 150 ml of $HC(OMe)_3$, and 0.5 g of *p*-toluenesulfonic acid·H_2O was stirred at room temp. After 2 hr, 2.5 ml of pyridine was added, and the product was pptd by carefully adding 275 ml of water. The crude product (17.4 g) was recrystd twice from Me_2CO–water (with a trace of pyridine) to yield 8.64 g (37.2%) of **66**.

2. 14α,17α-Methoxymethylenedioxypregn-4-ene-3,20-dione (**33**). 3-Methoxy-14α,17α-methoxymethylenedioxypregna-3,5-dien-20-one (**66**) (9.65 g) was dissolved in a mixt of 225 ml of MeOH and 225 ml of CH_2Cl_2. This mixt was sufficiently acidic to hydrolyze the product in 2 hr at room temp. After addn of 5 ml of 1 *N* $NaHCO_3$ soln, the solvent was evapd *in vacuo*. The residue was crystd from MeOH–water to yield 6.70 g of crude product. This was recrystd twice from Me_2O–heptane (with a trace of pyridine) to yield 3.87 g (41.5%) of pure **33**.

C. Introduction of the Δ^1 Double Bond.[15] This bond was introduced by means of SeO_2 in pyridine and *tert*-BuOH[15a,b] or DDQ in *tert*-BuOH or dioxan.[5b] These methods can also be applied after introduction of a Δ^6 double bond.

14α,17α-Ethylidenedioxypregna-1,4-diene-3,20-dione (**39**). A mixt of 2.08 g of 14α,17α-ethylidenedioxypregn-4-ene-3,20-dione (**5**) and 1.63 g of DDQ in 24 ml of dioxan was refluxed for 5 hr. The reaction mixt was filtered, and the filtrate was evapd *in vacuo*. The residue was chromatographed on alumina with PhH–Me_2O, 20:1. From the appropriate fractions 0.94 g of the product was obtained by concn *in vacuo* and addn of heptane. The product was recrystd three times from PhH–heptane to yield 0.37 g (18%) of **39**.

D. Conversion of the Δ^4-3-Keto Moiety to 3-Alkylenol Ether Groups.[16] This conversion was effected with orthoformates analogous to B or with 2,2-dimethoxypropane and MeOH in DMF with acid catalysis. In most cases this was done after substitution at 14,17 according to A and in some cases after substitution with halogen at 6.

1. 3-Ethoxy-6-chloro-14α,17α-ethylidenedioxypregna-3,5-dien-20-one (**78**). A mixt of 19.5 g of 6β-chloro-14α,17α-ethylidenedioxypregn-4-ene-3,20-dione (**42**), 0.95 g of sulfosalicylic acid, 30 ml of triethyl orthoformate, and 225 ml of dioxan was stirred at room temp for 3 hr. After neutralization with 5 ml of pyridine, the reaction product was pptd with water. The water was removed from the oily ppt by vacuum distn with isobutyl methyl ketone and the residue was crystd from MeOH–water (with a trace of pyridine) to yield 16.1 g (77.3%) of **78**. An analytical sample was prepd by recrystn from MeOH–pyridine.

2. 3-Cyclopentyloxy-14α,17α-benylidenedioxypregna-3,5-dien-20-one (**73**). A mixt of 5 g of 14α,17α-benzylidenedioxypregn-4-ene-3,20-dione (**21**), 5 ml of cyclopentanol, 550 ml of isooctane, and 250 mg of *p*-toluenesulfonic acid·H_2O was refluxed *via* a water absorption trap for 23 hr and, after an addnl 100 mg of the catalyst, for 8 hr. The reaction mixt was cooled, neutralized with pyridine, washed with water, and concd *in vacuo*. The residue was crystd from MeOH–pyridine to yield 1.64 g (28.4%) of **73**.

E. Introduction of 4-Cl.[17] 4-Chloro-14α,17α-ethylidenedioxypregn-4-ene-3,20-dione (**41**). To a stirred soln of 22.5 g of 14α,17α-ethylidenedioxypregn-4-ene-3,20-dione (**5**) in 225 ml of pyridine 21.3 ml of SO_2Cl_2 was added dropwise at 0° in approx 1 hr. The reaction mixt was poured into 1.5 l. of ice-cold 3 *N* H_2SO_4. The crystd product was filtered, washed with water, and dried (25.5 g). This product was chromatographed on alumina with PhH–Me_2O mixtures. By evapn of the appropriate fractions *in vacuo* and crystn from EtOH 15.5 g of the product was obtained. Recrystn from EtOH afforded 12.6 g (51.2%) of pure **41**.

F. Introduction of 6-CHO.[3] 3-Ethoxy-6-formyl-14α,17α-ethylidenedioxypregna-3,5-dien-20-one (**76**). To a stirred mixt of 2.5 ml of DMF and 16.4 ml of 1,2-dichloroethane a soln of 1 g of $COCl_2$ in 6 ml of 1,2-dichloroethane was added dropwise at 0°. To this mixt

was added dropwise a soln of 2.7 g of 3-ethoxy-14α,17α-ethylidenedioxypregna-3,5-dien-20-one (68) in 12.5 ml of 1,2-dichloroethane together with a drop of pyridine. After 2.5 hr at room temp, a soln of 4 g of NaOAc in 6 ml of water and 25 ml of MeOH was added, and the mixt was stirred for another 0.5 hr. After extn with 1,2-dichloroethane, washing, and evapn of the exts, 1.5 g (56.1%) of 76 was obtained.

G. Introduction of 6β-Cl.[18] 14α,17α-Substituted 3-alkyl enol ethers were chlorinated and hydrolyzed by treatment with *N*-chlorosuccinimide and $HClO_4$.

6β-Chloro-14α,17α-ethylidenedioxypregn-4-ene-3,20-dione (42). A mixt of 2 g of 3-ethoxy-14α,17α-ethylidenedioxypregna-3,5-dien-20-one (68), 1.4 g of NCS, 20 ml of dioxan, and 1 ml of 0.68 *N* $HClO_4$ was stirred at room temp for 15 min and poured into 60 ml of water, contg 2 g of $Na_2S_2O_5$. The pptd oil was dissolved in CH_2Cl_2, and the soln was washed with Na_2CO_3 and $NaHSO_3$ soln and evapd *in vacuo*. The residue was crystd from MeOH–water to yield 1.4 g (68.9%) of 42.

H. Introduction of 6α-Cl.[19] 6α-Chlorides have been obtained by hydrolysis of 6-chloroenol ethers; for preparation *cf.* G and D.

6α-Chloro-14α,17α-ethylidenedioxypregn-4-ene-3,20-dione (43). A soln of 1 g of 3-ethoxy-6-chloro-14α,17α-ethylidenedioxypregna-3,5-dien-20-one (78) in 10 ml of Me_2O, acidified with 0.25 ml of concd HCl, was refluxed for 10 min. The product was crystd in pure form by pouring the soln into 200 ml of water: yield, 0.87 g (93%) of 43.

J. Conversion of 6-Chloro Enol Ether to 6-Chloro-4,6-diene.[20] **6-Chloro-14α,17α-ethylidenedioxypregna-4,6-diene-3,20-dione (46).** A soln of 6 g of 3-ethoxy-6-chloro-14α,17α-ethylidenedioxypregna-3,5-dien-20-one (78) in 50 ml of dioxan was added dropwise to a stirred suspension of 20 mg of MnO_2 in 250 ml of AcOH at room temp. After 0.5 hr, the mixt was filtered, and the filtrate was dild with water to yield 4.6 g of cryst product. This was purified by chromatog on silica gel with PhH–Me_2O, 20:1. After evapn of the appropriate fractions and crystn from MeOH–water, 1.6 g (28.6%) of 46 was obtained.

K. Introduction of 6α-CH_3.[3] **6α-Methyl-14α,17α-ethylidenedioxypregn-4-ene-3,20-dione (47).** A mixt of 5 g of 3-ethoxy-6-formyl-14α,17α-ethylidenedioxypregna-3,5-dien-20-one (76), 100 ml of EtOH, 30 ml of cyclohexene, 10 ml of AcOH, and 5 g of 5% Pd/C was refluxed for 48 hr. At that time the conversion was complete. In shorter runs a considerable amt of the 6-methyl-$\Delta^{4,6}$ compd (50) was found. The catalyst was removed by filtration, and the filtrate was evapd *in vacuo*. The residue was crystd from EtOH to yield 2.52 g of the product. Recrystn from MeOH yielded 1.8 g (40%) of 47.

L. Introduction of Δ^6 Double Bond.[21] This introduction was effected with chloranil in *tert*-BuOH, PhH, or xylene, in some cases with acid catalysis, or with DDQ in dioxan–HCl. The reaction occurred with retention of 11α-OH or 6-CH_3, but in one case with loss of 6-F.

1. **14α,17α-Ethylidenedioxypregna-4,6-diene-3,20-dione (48).** A mixt of 48.4 g of 14α,17α-ethylidenedioxypregn-4-ene-3,20-dione (5), 145.2 g of chloranil, and 3.4 l. of *tert*-BuOH was refluxed for 2 hr. The mixt was filtered, and the ppt was washed with $CHCl_3$. The combined filtrates were evapd *in vacuo*. The residue was chromatographed on alumina with PhH–Me_2O mixtures. The appropriate fractions were evapd *in vacuo* and the residue was crystd from $CHCl_3$–MeOH. The product (18.6 g) was recrystd from MeOH to yield 16.2 g (33.7%) of 48.

2. **11α-Hydroxy-14α,17α-ethylidenedioxypregna-4,6-diene-3,20-dione (53).** 11α-Hydroxy-14α,17α-ethylidenedioxypregn-4-ene-3,20-dione (52) (1 g) and 0.65 g of DDQ were mixed with 30 ml of 4 *N* HCl in dioxan. After 0.5 hr, the mixt was filtered, and the ppt was washed with CH_2Cl_2. The combined filtrates were washed with 1 *N* NaOH and with water and evapd *in vacuo*. The residue crystd on trituration with ether (0.25 g). Recrystn from MeOH–water yielded 0.105 g (16.2%) of 53.

3. **16α-Methyl-14α,17α-ethylidenedioxypregna-4,6-diene-3,20-dione (51).** A mixt of 10 g of 6α-fluoro-16α-methyl-14α,17α-ethylidenedioxypregn-4-ene-3,20-dione (38), 10 g of chloranil, and 0.25 g of *p*-toluenesulfonic acid·H_2O was refluxed for 28 hr in 1 l. of xylene. The mixt was chromatographed on alumina (eluted by PhH–Me_2O mixtures), and the appropriate fractions were evapd *in vacuo*. The residue was crystd from Me_2O–heptane to yield 3.85 g (38%) of almost pure product. An analytical sample was prepd by crystn from MeOH–water and isobutyl methyl ketone.

4. **6-Methyl-14α,17α-ethylidenedioxypregna-4,6-diene-3,20-dione (50).** Impure 6α-methyl-14α,17α-ethylidenedioxypregn-4-ene-3,20-dione (47) (3 g), from an incomplete reaction according to method K, was refluxed for 5 hr with 3 g of chloranil and 150 mg of *p*-nitrophenol in 108 ml of *tert*-BuOH. The reaction mixt was filtered, and the filtrate was evapd *in vacuo*. The residue was chromatographed on alumina (elution with PhH–Me_2O mixtures), and the appropriate fractions were evapd *in vacuo*. The residue was crystd from Et_2O to yield 0.65 g (21.8%) of 50.

M. Introduction of 11α-OH.[22] 11α-Hydroxyl could be introduced microbiologically with *Aspergillus ochraceus* before–or eventually after–introduction of the alkylidenedioxy group.

1. **11α-Hydroxy-14α,17α-ethylidenedioxypregn-4-ene-3,20-dione (52).** 14α,17α-Ethylidenedioxypregn-4-ene-3,20-dione (5) (400 g) was dissolved in 13 l. of Me_2O and added to a 1300-l. culture of *Aspergillus ochraceus*. After an incubation time of 22 hr and the usual recovery process, 241 g (57.8%) of the 11-hydroxylated product was obtained. An analytical sample was prepd by recrystn from MeOH–water and from isobutyl methyl ketone.

2. **11α,14α,17α-Trihydroxypregn-4-ene-3,20-dione (85).** In a similar way 300 g of 14α,17α-dihydroxypregn-4-ene-3,20-dione (1) was converted with *Aspergillus ochraceus* to 194 g (61.8%) of 85.

N. Introduction of 11β-OAc.[23] **11β-Acetoxy-14α,17α-ethylidenedioxypregn-4-ene-3,20-dione (56).** A mixture of 20 g of 11β-hydroxy-14α,17α-ethylidenedioxypregn-4-ene-3,20-dione (35), 200 ml of CH_2Cl_2, 10 ml of Ac_2O, and 2 ml of 70% $HClO_4$ was stirred at room temp for 1 hr. The mixt was dild with CH_2Cl_2, washed with 0.1 *N* NaOH and with water, and evapd *in vacuo*. The residue was crystd from MeOH to yield 17.7 g (79.9%) of 56. An analytical sample was prepd by crystn from isobutyl methyl ketone.

P. Oxidation of 11-OH to 11-Keto Group. **11-Keto-14α,17α-ethylidenedioxypregn-4-ene-3,20-dione (57).** 11α-Hydroxy-14α,-17α-ethylidenedioxypregn-4-ene-3,20-dione (52) (20 g) was treated with a soln of 7 g of CrO_3 in 70 ml of water and 210 ml of AcOH for 15 min at room temp. Then the mixt was stirred with a soln of 20 g of $NaHSO_3$ in 500 ml of water and extd with 3 × 300 ml of isobutyl methyl ketone. The ext was washed with K_2CO_3 soln and water and evapd *in vacuo*. The residue was crystd from MeOH to yield 15.0 g. Recrystn from MeOH yielded 11.7 g (58.8%) of pure 57. An analytical sample was prepd by crystn from isobutyl methyl ketone.

R. Introduction of 15β-Halogen or Hydroxyl Groups.[3,24] 1. **6α-Fluoro-16α-methyl-17α-hydroxypregna-4,14-diene-3,20-dione (86).** A suspension of 80 g of 6α-fluoro-16α-methyl-14α,17α-dihydroxypregn-4-ene-3,20-dione (3) in 4 l. of Me_2O and 40 ml of 70% $HClO_4$ was stirred for 5 hr at room temp. After neutralization with $NaHCO_3$, the product was crystd by the addn of 12 l. of water: yield, 63 g (82.7%) of 86.

2. **6α-Fluoro-14α,15α-epoxy-16α-methyl-17α-hydroxypregn-4-ene-3,20-dione (87).** To a stirred, ice-cooled soln of 62.9 g of the preceding compd (86) in 800 ml of $CHCl_3$ was added in 15 min a soln of 0.36 mole of monoperphthalic acid in Et_2O.[25] After 3 hr, the mixt was filtered, and the filtrate was washed with $NaHCO_3$ soln and with water, treated with charcoal, and evapd *in vacuo*. The cryst residue was recrystd several times from MeOH–water to yield 45.3 g (69.0%) of 87.

3. **6α-Fluoro-15β-chloro-16α-methyl-14α,17α-dihydroxypregn-4-ene-3,20-dione (88).** A suspension was made of 6 g of the epoxide (87) in 90 ml of Me_2O, and 12 ml of 12 *N* HCl was added at 0°. After an hour, the product was crystd by addn of 180 ml of water: yield, 6.0 g (91%) of 88. The 15β-Br,15β-F, and 15β-OH compds were prepd in a similar way, using HBr (20 ml of 50% HBr in 100 ml of THF), HF (2:1, v/v in DMF), and H_2SO_4 (0.6 *N* in Me_2O–water), respectively.

6α-Fluoro-15β-chloro-16α-methyl-14α,17α-ethylidenedioxypregn-4-ene-3,20-dione (62). The dihydroxy compound 88 (5.9 g) was condensed with paraldehyde, *cf.* method A, to yield 2.0 g (32.2%) of 62.

S. Introduction of Δ^{15} Double Bond.[26] **14α,17α-Ethylidenedioxypregna-4,15-diene-3,20-dione (65).** A suspension of 1.5 g of 15β-bromo-14α,17α-ethylidenedioxypregn-4-ene-3,20-dione (60) and 1.5 g of *tert*-BuOK in 75 ml of dry xylene, satd with N_2, was refluxed for 15 min. The mixt was cooled, dild with xylene, washed with AcOH and water, and evapd *in vacuo*. The residue was treated with 0.1 *N* HCl in Me_2O for 0.5 hr (to restore the partially deconjugated Δ^4-3-keto system). The solvent was evapd *in vacuo*, and the residue was dissolved in isobutyl methyl ketone, washed with $NaHCO_3$ soln and water, and again evapd *in vacuo*. The residue was chromatographed on alumina with PhH–Me_2O mixtures. From the appropriate fractions the product was obtained by evapn *in vacuo* and crystn from MeOH: yield, 0.35 g (28.4%).

T. Conversion of 20-Keto to 20-Oxime. **3-Methoxy-14α,17α-benzylidenedioxy-20-oximinopregna-3,5-diene (84).** A mixt of 4.88 g of 3-methoxy-14α,17α-benzylidenedioxypregna-3,5-dien-20-

one (75), 12.2 g of hydroxylamine·HCl, 97.6 ml of 10% NaOH, and 290 ml of EtOH was refluxed for 15 min. The reaction mixt was poured into 1.25 l. of water to yield 5.05 g (100%) of 84.

U. Reduction of the *p*-Nitrobenzylidenedioxy Group to the *p*-Aminobenzylidenedioxy Group.[27] 14α,17α-Aminobenzylidenedioxypregn-4-ene-3,20-dione (29). A mixt of 31.5 g of 14α,17α-*p*-nitrobenzylidenedioxypregn-4-ene-3,20-dione (28), 1.2 l. of PhH, and 300 g of Fe (activated with HCl) was refluxed and ten 6-ml portions of water were added in the course of 5 hr. The mixt was stirred for another 2 hr and filtered. The filtrate was washed with water and evapd *in vacuo*. The oily residue (32 g) was crystd from 80 ml of PhH to yield 19.5 g (66%) of 29.

V. Acylation of the *p*-Aminobenzylidenedioxy Group. 14α,17α-[*p*-(*N*-Chloroacetylamino)benzylidenedioxy]pregn-4-ene-3,20-dione (30). To a soln of 3 g of 14α,17α-*p*-aminobenzylidenedioxypregn-4-ene-3,20-dione (29) in 27 ml of 1,2-dichloroethane and 1.5 ml of ethyldiisopropylamine a mixt of 0.85 ml of chloroacetyl chloride and 2.5 ml of 1,2-dichloroethane was added dropwise at 0°. After 45 min, the reaction mixt was dild with 1,2-dichloroethane, washed with NaOH soln, H_2SO_4 soln, and water, and evapd *in vacuo*. The residue was chromatographed on silica gel with PhH-Me_2O, 9:1. By evapn of the appropriate fractions and crystn from Et_2O 2.55 g (72.7%) of 30 was obtained. In a similar way the *N*-bromoacetyl compound (31) was prepd with bromoacetyl chloride.

W. Hydrolysis of 3'-Methoxycarbonylpropylidenedioxy Group. 14α,17α-(3'-Carboxypropylidenedioxy)pregn-4-ene-3,20-dione (17). A mixt of 1 g of 14α,17α-(3'-methoxycarbonylpropylidenedioxy)-pregn-4-ene-3,20-dione (16), 8 ml of EtOH, and 2 ml of 10% NaOH was refluxed for 0.5 hr. The mixt was cooled, dild with water, and acidified to pH 2 with HCl. The cryst product was filtered and recrystd several times from MeOH–water and once from $CHCl_3$–heptane to yield 0.20 g (20.7%) of 17.

Acknowledgment. The authors wish to acknowledge the valuable assistance of Mrs. A. B. Bakker-Vader, N. C. M. E. Barendse, C. A. M. Gijben, P. J. Jaarsma, F. Looyer, Mrs. M. M. Lorsheyd-Janssen, Mrs. J. M. W. van Middelkoop-Hoek, S. A. Spaans, W. F. C. Vlaardingerbroek, Mrs. K. de Vries-Kragt, and B. de Wreede. The authors are indebted to Dr. E. Talman, Centraal Laboratorium T. N. O., Delft, for assistance in the interpretation of spectra.

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5-Hydroxy-3-piperidylidenemethane Derivatives as Spasmolytics

Mitsutaka Kawazu,* Takeshi Kanno, Seiichi Saito, and Hajime Tamaki

Research Laboratories, Tanabe Seiyaku Co., Ltd., Toda, Saitama, Japan. *Received January 5, 1972*

N-Methyl-3-piperidylidenedithienylmethane methobromide (VIII) was found to be as potent a spasmolytic agent as atropine. In order to search for active compounds with lessened anticholinergic side effects (dryness of mouth, mydriasis), some 5-hydroxy, acyloxy, and methoxy derivatives of VIII were synthesized. (The results of the comparative studies *in vitro* on those compounds are discussed.) As a result of the *in vivo* test, *N*-methyl-5-methoxy-3-piperidylidenedithienylmethane methobromide (VIIIb) proved to be an excellent spasmolytic and its side effects were considerably weaker than those of the parent compound (VIII).

Although a number of anticholinergic agents have been synthesized, the continued use of atropine in spite of its unpleasant side effects seems to indicate that the available synthetic drugs are not entirely satisfactory. One of the drawbacks is undoubtedly due to their poor absorbability from the intestinal tract, a characteristic of quaternary ammonium compounds. In order to obtain a sufficient response by oral administration relatively high doses are required, whereas an adequate potency is obtained at low doses by injection. The problem of the poor absorption may have