80772-30-1; **21**, 80772-32-3; **22**, 80772-46-9; **23**, 80772-34-5; **24**, 80772-35-6; **25**, 80772-71-0; **26**, 80772-36-7; **27**, 80772-22-1; **28**, 80772-37-8; **29**, 80772-38-9; **30**, 80772-39-0; **31**, 80772-40-3; **32**, 80772-41-4; **33**, 80772-25-4; **34**, 80772-44-7; **35**, 80772-45-8; **36**, 80772-24-3; **37**, 80772-61-8; **38**, 80772-52-7; **39**, 123963-99-5; **40**, 80772-54-9; **41**, 80772-55-0; **42**, 80772-59-4; **43**, 80772-51-6; **44**, 80772-56-1; **45**, 80772-57-2; **46**, 80772-58-3; *cis*-hexahydrophthalide, 6939-71-5; 2-(hydroxymethyl)pyridine, 586-98-1; *N*-(2-hydroxyethyl)morpholine, 622-40-2; 3-(hydroxymethyl)pyridine, 100-55-0; 2-(2-hydroxyethyl)pyridine, 103-74-2.

Supplementary Material Available: A table listing ^{1}H NMR data for H6a and H10a of **6a,b–13a,b** (1 page). Ordering information is given on any current masthead page.

Aldosterone Antagonists. 3. Synthesis and Activities of Steroidal 7α-(Alkoxycarbonyl)-15,16-methylene Spirolactones

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Several A- and D-ring substituted steroidal 7α-alkoxycarbonyl spirolactones were synthesized with the purpose of increasing the aldosterone antagonistic potency and reducing the endocrinological side effects relative to the standard drug spironolactone. It was found that the 15β,16β-methylene derivative **17** exhibited a 2-fold higher aldosterone antagonistic activity compared to either spironolactone or the 15,16-unsubstituted derivative **29** while showing remarkably reduced antiandrogenicity.

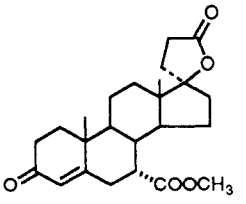
In a previous paper of this series,[1] we described the synthesis and pharmacological activity of some spironolactone derivatives. We have shown that introduction of a 15β,16β-cyclopropane ring in the spironolactone molecule enhances the aldosterone antagonistic activity. The endocrinological side effects are reduced by the introduction of a 1,2-double bond. It was known that the replacement of the 7α-acetylthio moiety by the 7α-alkoxycarbonyl function leads also to potent aldosterone antagonists.[2] In this paper we report our results with A- and D-ring substituted 7α-alkoxycarbonyl spirolactones in regard to their aldosterone antagonistic and endocrinological activity.

Chemistry

Although 7α-alkoxycarbonyl steroids have been prepared previously,[2-4] the reported methods result in only low yields under drastic conditions. We therefore sought a mild and efficient synthesis of these compounds. As starting material for our efforts we chose the known double unsaturated ketones **1–4**.[1] By reacting these ketones with diethylaluminum cyanide[5] in tetrahydrofuran (THF), a cyano group could be introduced stereoselectively at the 7α-position of the steroid framework in high yields (Scheme I, Table I). In case of the 1α,2α:15β,16β-dimethylene derivative **2** the introduction of a 7α-cyano group accessed in higher yields by using potassium cyanide in dimethylformamide. The reduction of the cyano ketones **5–8** with diethylaluminum hydride in THF or dichloromethane led directly to the aldehydes **9–12**. These compounds were obtained as mixtures of diastereomeric alcohols at the 3- and 5′-positions and were further transformed without purification. Jones oxidation of aldehydes **9–12** gave the carboxylic acid derivatives **13–16**. For the subsequent esterification, three different methods were employed. The methyl esters were prepared by reaction of the carboxylic acids with diazomethane. The higher esters were obtained either by preparing the mixed anhydride with butyl chloroformate followed by reaction with the appropriate alcohol[2] or directly by reaction of the carboxylic acids with an alkyl halide and silver oxide catalysis. The introduction of the 1,2-double bond was achieved by treatment of the α,β-unsaturated ketones **17–19** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to afford **26–28** (Table II).

Biological Results and Discussion

In the 15β,16β-methylene series (**17–19**), the methyl ester **17** showed clearly the highest aldosterone antagonistic activity exhibiting a 2-fold higher potency than spironolactone (Table III). On the basis of in vitro experiments, **17–19** have similar affinities for the androgen and progesterone receptors. As it was found in other series,[1,6] the introduction of a 15β,16β-methylene moiety led to a remarkable enhancement of the aldosterone antagonistic potency (**17** compared to **29**). The affinity for the androgen receptor was practically the same, whereas the affinity for the progesterone receptor was increased.



29 (SC 25152)

By introduction of a 1,2-double bond (compounds **26–28**) the affinities for the androgen and progesterone receptors were significantly decreased; however, the aldosterone

(1) Nickisch, K.; Bittler, D.; Laurent, H.; Casals-Stenzel, J.; Losert, W.; Nishino, Y.; Schillinger, E.; Wiechert, R. *J. Med. Chem.* **1987**, *30*, 1403.
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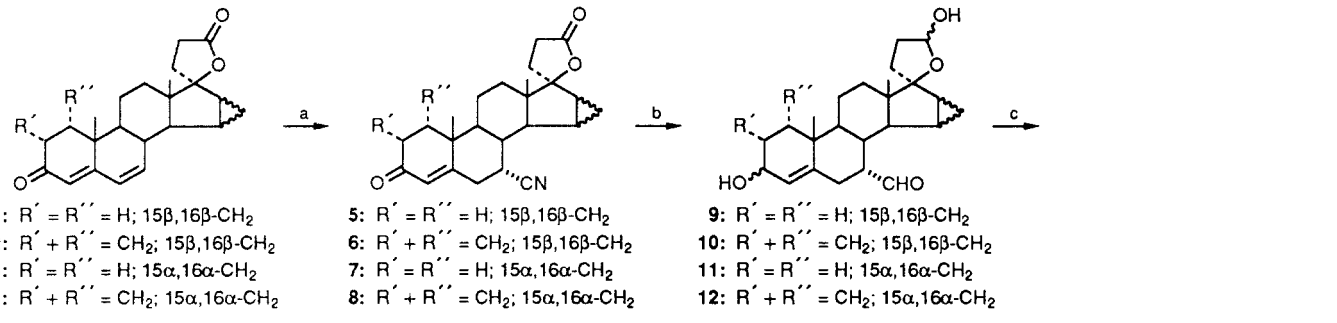
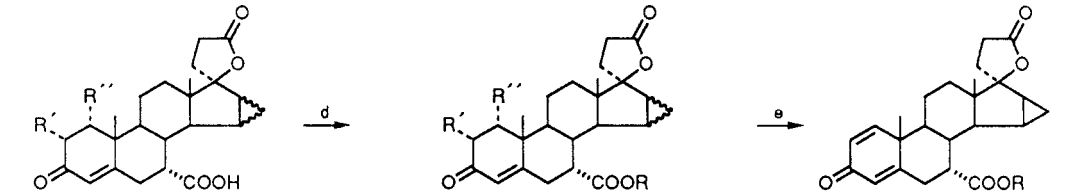
Scheme I[a]



1: R′ = R″ = H; 15β,16β-CH_2
2: R′ + R″ = CH_2; 15β,16β-CH_2
3: R′ = R″ = H; 15α,16α-CH_2
4: R′ + R″ = CH_2; 15α,16α-CH_2

5: R′ = R″ = H; 15β,16β-CH_2
6: R′ + R″ = CH_2; 15β,16β-CH_2
7: R′ = R″ = H; 15α,16α-CH_2
8: R′ + R″ = CH_2; 15α,16α-CH_2

9: R′ = R″ = H; 15β,16β-CH_2
10: R′ + R″ = CH_2; 15β,16β-CH_2
11: R′ = R″ = H; 15α,16α-CH_2
12: R′ + R″ = CH_2; 15α,16α-CH_2



13: R′ = R″ = H; 15β,16β-CH_2
14: R′ + R″ = CH_2; 15β,16β-CH_2
15: R′ = R″ = H; 15α,16α-CH_2
16: R′ + R″ = CH_2; 15α,16α-CH_2

17: R′ = R″ = H; 15β,16β-CH_2; R = CH_3
18: R′ = R″ = H; 15β,16β-CH_2; R = C_2H_5
19: R′ = R″ = H; 15β,16β-CH_2; R = $CH(CH_3)_2$
20: R′ + R″ = CH_2; 15β,16β-CH_2; R = CH_3
21: R′ + R″ = CH_2; 15β,16β-CH_2; R = C_2H_5
22: R′ + R″ = CH_2; 15β,16β-CH_2; R = C_3H_7
23: R′ + R″ = CH_2; 15β,16β-CH_2; R = $CH(CH_3)_2$
24: R′ = R″ = H; 15α,16α-CH_2; R = CH_3
25: R′ + R″ = CH_2; 15α,16α-CH_2; R = CH_3

26: R = CH_3
27: R = C_2H_5
28: R = $CH(CH_3)_2$

[a] (a) 1. Et_2AlCN, THF; 2. K_2CO_3, MeOH. (b) (*i*-Bu_2)AlH, THF or CH_2Cl_2, −40 °C. (c) CrO_3, H_2SO_4, acetone. (d) CH_2N_2 or RX, Ag_2O, DMF or 1. ROCOCl, NEt_3, THF; 2. ROH, reflux. (e) DDQ, toluene, reflux.

Table I. 7α-Cyano Carbolactones

compd	prep method	yield, %	mp, °C	formula	anal.	^{1}H NMR (100 MHz, $CDCl_3$), δ 18-CH_3	19-CH_3	other	IR (KBr), cm^{-1}	UV max (MeOH), nm (ε)
5	1A	64	241	$C_{24}H_{29}NO_3$	C, H, N	1.05	1.21	3.27 (m, 1, H-7), 5.83 (s (br), 1, H-4)	2240, 1765, 1675, 1620	236 (15000)
6	1B	89	288	$C_{25}H_{29}NO_3$	C, H, N	1.05	1.30	3.20 (m, 1, H-7), 5.66 (s (br), 1, H-4)	2240, 1775, 1665	232 (13700)
7	1A	58	260	$C_{24}H_{29}NO_3$	C, H, N	1.21	1.21	3.32 (m, 1, H-7), 5.80 (s, H-4)	2220, 1760, 1660, 1620	234 (16000)
8	1A	68	>300	$C_{25}H_{29}NO_3$	C, H, N	1.10	1.20	3.22 (m, 1, H-7), 5.64 (s (br), 1, H-4)	2240, 1780, 1665	231 (12050)

Table II. 7α-Alkoxycarbonyl Carbolactones

compd	prep method	yield,[a] %	mp, °C	formula	anal.	^{1}H NMR (100 MHz, $CDCl_3$), δ 18-CH_3	19-CH_3	other
17	2A-B-C	33	266	$C_{25}H_{32}O_5$	C, H, O	1.00	1.22	3.65 (s, 3, CH_3OCO), 5.7 (s (br), 1, H-4)
18	2A-B-D	34	185	$C_{26}H_{34}O_5$	C, H, O	1.04	1.30	1.31 (t, 3, CH_3CH_2OCO), 4.2 (q, 6, (CH_3CH_2OCO), 5.75 (s, (br), H-4)
19	2A-B-D	26	208	$C_{27}H_{36}O_5$	C, H, O	1.02	1.25	1.23 (d, 6, $(CH_3)_2CHOCO$), 5.09 (quin, 1, $(CH_3)_2CHOCO$), 5.72 (s (br), H-4)
20	2A-B-E	29	261	$C_{26}H_{32}O_5$	C, H, O	1.00	1.30	3.68 (s, 3, CH_3OCO), 5.5 (s (br), 1, H-4)
21	2A-B-E	34	233	$C_{27}H_{34}O_5$	C, H, O	1.00	1.20	1.2 (t, 3, CH_3CH_2OCO), 4.05 (q, 2, (CH_3CH_2OCO), 5.45 (s (br), H-4)
22	2A-B-E	23	181	$C_{28}H_{36}O_5$	C, H, O	1.00	1.24	0.9 (t, 3, $CH_3CH_2CH_2OCO$), 3.97 (t, 2, ($CH_3CH_2CH_2OCO$), 5.51 (s (br), H-4)
23	2A-B-E	28	214	$C_{28}H_{36}O_5$	C, H, O	0.98	1.28	1.2 (d, 6, $(CH_3)_2CHOCO$), 4.97 (quin, 1, $(CH_3)_2CHOCO$), 5.4 (s (br), H-4)
24	2A-B-C	18	187	$C_{25}H_{32}O_5$	C, H, O	1.20	1.17	3.67 (s, 3, CH_3OCO), 5.7 (s (br), 1, H-4)
25	2A-B-C	40	237	$C_{26}H_{32}O_5$	C, H, O	1.20	1.25	3.55 (s, 3, CH_3OCO), 5.45 (s (br), 1, H-4)
26	3	39	273	$C_{25}H_{30}O_5$	C, H, O	1.05	1.25	3.65 (s, 3, CH_3OCO), 6.02 (s (br), 1, H-4), 6.22 (dd, 1, H-1), 7.02 (d, 1, H-1)
27	3	32	238	$C_{26}H_{32}O_5$	C, H, O	1.04	1.27	1.25 (t, 3, CH_3CH_2OCO), 4.08 (q, 2, (CH_3CH_2OCO), 6.00 (s (br), H-4), 6.18 (dd, 1, H-2), 6.95 (d, 1, H-1)
28	3	29	255	$C_{27}H_{34}O_5$	C, H, O	1.02	1.25	1.24 (d, 6, $(CH_3)_2CHOCO$), 4.95 (quin, 1, $(CH_3)_2CHOCO$), 6.00 (s (br), H-4), 6.17 (dd, 1, H-2), 6.96 (d, 1, H-1)

[a] The yield was calculated for the transformation of the cyano derivatives 5–8 to the esters 17–25 and for the preparation of 26–28 by DDQ dehydrogenation of 17–19.

Table III. Biological Activities of Spirolactones

compd	antialdosterone act.: maximal rel potency[a] (spironolactone = 100; 95% confidence limits)	androgen receptor competition factor[c] (dihydrotestosterone = 1)	progesterone receptor competition factor[c] (progesterone = 1)
17	217 (169–309)	112	25
18	<50[b]	98	33
19	<50[b]	67	12
20	140 (130–150)	29	92
21	187 (166–231)	28	34
22	39 (23–49)	33	19
23	140 (113–156)	40	19
24	≈50[b]	121	10
25	140 (116–171)	53	98
26	<50[b]	no affinity	no affinity
27	<50[b]	no affinity	85
28	<50[b]	266	113
29[d]	104 (87–122)	142	130

[a] Relative potency calculated for the hour of maximal activity after oral administration. [b] <, ≈: less than, not significantly different relative potency estimated from single-dose experiments in which the test compound was administered at a 2-fold higher dose (53.6 mg/kg) than the standard spironolactone (26.8 mg/kg). [c] The competition factor is defined as the ratio of concentration of the test compound which causes specific displacement of the radiolabeled standard from the receptor (measured at 50% displacement). [d] Compound **29** (SC 25152) was synthesized for comparison following literature procedures.[2]

antagonistic activity was also diminished. These results stand in contrast to our findings in the 15β,16β-methylene spironolactone series[1] in which the introduction of a 1,2-double bond led not only to a reduced affinity for the androgen and progesterone receptors but also to a slightly increased aldosterone antagonistic activity. The 15α,16α-methylene analogue of **17**, compound **24**, exhibited an aldosterone antagonistic activity similar to or somewhat lower than that of spironolactone. This shows that the 15β,16β-methylene series is superior to the 15α,16α-methylene series.

The introduction of a 1α,2α-methylene moiety instead of a 1,2-double bond yielded compounds **20**, **21**, **23**, and **25**, in which a somewhat higher aldosterone antagonistic activity compared to spironolactone was observed. In contrast to the 1,2-dihydro series **17–19**, the same variation of the ester function in the 7α-position did not result in a reduction of the aldosterone antagonistic activity (**20**, **21**, **23**). With the exception of **20**, the affinities for the progesterone receptor were the same as in the 1,2-dihydro series **17–19**, whereas the affinities for the androgen receptor were higher.

The only derivative that was synthesized in the 1α,2α:15α,16α-dimethylene series, compound **25**, exhibited no difference in either aldosterone antagonistic activity or progesterone receptor affinity compared to the 15β,16β-methylene analogue **20**.

Further endocrinological evaluation of the most active compound **17** relative to spironolactone was carried out in the following in vivo models. The antiandrogenic activity was determined in the standard antiandrogen test[7] with orchidectomized rats and in the fetal feminization test[7] in the rat. The progestational activity was determined in rabbits.[8] The inhibitory effects on gonatrophin release were determined in the ovulation inhibition test.[8]

The low antiandrogenic activity of **17** (Table IV) was in agreement with its low affinity for the androgen receptor. This compound showed a remarkably reduced antiandrogenic activity compared to spironolactone when measured in the orchidectomized rat. Further confirmation of this finding was obtained in the feminization test in which a female transformation of male fetuses (reduction of the anogenital distance) is evaluated following treatment of the pregnant mother animals. All male fetuses excised from oil-treated pregnant animals (control) showed normal development of sexual differentiation. When pregnant animals were treated orally with spironolactone (50 mg/rat per day), 29 of 30 male fetuses excised were feminized, showing hypospadia, a developmental abnormality in the male, in which the urethra opens on the undersurface of the penis or in the perineum. Thereby, spironolactone caused a significant decrease in the anogenital distance and in the length of the urethra of males (Table V): the perineum was diminished in its width, and the urethra became straighter compared with that of control males which had a typical S-shaped urethra. The treatment of pregnant animals with compound **17** at the oral dose of 50 mg/rat per day also led to a decrease in the anogenital distance and the length of the urethra in male fetuses (Table V), but this feminizing effect of **17** was distinctly less pro-

Table IV. Antiandrogenic Activity in Orchidectomized Rats after Oral Administration[a]

compd	dose, mg/day	n	organ wt (mg/100 g body weight) x ± SD (% inhibn) seminal vesicle	prostate
17 + TP	96 + 0.1	6	42 ± 9 (16)	30 ± 5 (35)*
	48 + 0.1	6	47 ± 6 (5)	41 ± 6 (0)
	24 + 0.1	6	37 ± 2 (29)*	33 ± 2 (24)
	12 + 0.1	6	44 ± 10 (11)	38 ● 4 (8)
spironolactone + TP	96 + 0.1	6	6 ± 1 (98)*	10 ± 2 (92)*
	48 + 0.1	6	15 ± 5 (77)*	16 ± 5 (73)*
	24 + 0.1	6	23 ± 4 (61)*	19 ± 2 (64)*
	12 + 0.1	6	32 ± 4 (40)*	28 ± 3 (38)*
TP control	0.1	6	50 ± 8	41 ± 8
orchidectomized control		6	5 ± 0.7*	7 ± 2*

[a] TP = testosterone propionate (0.1 mg/day, subcutanously. SD = standard deviation. n = number of animals treated. * = significant difference in comparison with TP control.

Table V. Fetal Feminization Test in Rats after Oral Treatment[a]

compd	dose (for 4 days) mg/animal per day	n	no. of male evaluated fetuses	anogenital distance, mm
control		5	10	2.30 ± 0.16
17	50	5	16	2.00 ± 0.16*
spironolactone	50	5	19	1.46 ± 0.13*

[a] n = number of mother animals used. * = significant difference to control.

(7) Wiechert, R.; Steinbeck, H.; Elger, W.; Neumann, F. *Arzneim.-Forsch. (Drug Res.)* **1967**, *17*, 1103.
(8) Neumann, F.; Elger, W.; Nishino, Y.; Steinbeck, H. *Arzneim.-Forsch. (Drug Res.)* **1977**, *27*, 296.

Table VI. Progestational Activity in Rabbits and Ovulation Inhibition in Rats after Oral Administration

	progestational activity			ovulation inhibn	
compd	dose, mg	n^a	McPhail index	dose, mg	% inhibn
17	30	6	1.4	30	0
	100	6	1.8	100	0
	300	6	1.8		
spironolactone	30	6	1.5		
	100	6	1.5	100	100
	300	6	1.9		

[a] n = number of animals used.

nounced than that of spironolactone: six of 16 males examined showed normal development, four had a hypospadia, and six had a short perineum with its wide orifice, but no hypospadia.

The progestational activity of 17 compared to that of spironolactone as determined in rabbits was very weak, and there was no significant difference noticed (Table VI). Within the dose range tested, 17 did not exhibit any antiovulatory effect, and therefore suggesting that 17 has no antigonadotrophic effect. In contrast spironolactone was found to exhibit an inhibitory effect on ovulation in 100% of animals.

All in vitro and in vivo results clearly show that 17 can be described as a new aldosterone antagonist with an enhanced antimineralocorticoid activity and remarkably reduced endocrinological effects relative to the standard drug spironolactone. An extended evaluation of the antimineralocorticoid activity has been published elsewhere.[9]

Methods

Determination of Antialdosterone Activity in Rats. The methods used for evaluation of the antialdosterone activity in rats were described previously.[6,9,10] Adrenalectomized male rats (Wistar strain) with a body weight of 140–160 g were treated with glucocorticoids (1 mg of fluocortolone caproate/kg sc on the day of surgery and 10 mg of fluocortolone/kg sc 1 day before the diuresis experiment which was performed 5 days after adrenalectomy). These glucocorticoid-substituted rats were infused intravenously with a saline–glucose solution (0.05% NaCl, 5% glucose) containing aldosterone (50 μg/L) at a rate of 3 mL/h for 15 h. The aldosterone antagonist was administered 1 h before the start of the aldosterone infusion. Urine excretion was measured in fractions of 1 h. Sodium and potassium concentrations in urine were determined by flame photometry. The antialdosterone activity was assessed by the ability of the compounds to reverse the aldosterone effect on the urinary Na/K ratio. The various antialdosterone derivatives and spironolactone were administered at three oral doses of 6.7, 13.4, and 26.8 mg/kg. The dose–response relationship was tested for each fraction by regression analysis after logarithmic transformation of the doses. The potency of the standard substance, spironolactone, was allocated the value of 100.

Binding to Progesterone and Androgen Receptor.[11] For the determination of the affinity of the test substance to the progesterone and androgen receptor isolated from the rabbit uterus and the rat prostate gland, respectively, tritiated progesterone and dihydrotestosterone were used as ligands, and the competition factors are defined as the multiple of the concentration to obtain displacement equivalent to the standard. A high competition factor indicates low binding strength, and a low competition factor indicates high affinity.

Determination of Antiandrogenic Activity in Rats.[7] Castrated male rats (Wistar strain) weighing about 100 g were treated once a day with varying doses of test compounds (12, 24, 48, 96 mg/rat per day, po) in combination with 0.1 mg of testosterone propionate (TP)/rat per day (sc) for 7 days. Control animals obtained only 0.1 mg of TP/rat per day (sc). One day after the last treatment (day 8), the animals were sacrificed and the fresh weights of seminal vesicles and ventral prostates were evaluated. Data obtained were subjected to regression/covariance analysis to compare the relative potencies of test compounds.

Determination of Intrauterine Feminizing Effect in Rats.[12] Mature female rats (Wistar strain) weighing about 200 g were mated on the day of proestrus. Successful copulation was proved by the detection of spermatozoa and this indicated day 1 of pregnancy. The treatment of pregnant animals (50 mg/rat per day, po) was initiated on day 17 and continued for 4 days. On day 22, the fetuses were removed from the uterus, cut through at the umbilical level, and fixed in Bouin's solution. Sagittal slices were then prepared by cutting, bilaterally to the clitoris, in the ventrodorsal direction with a razor blade. The 2–3-mm-thick median slices were embedded in paraffin: every 10th section with 6 μm thickness was mounted and stained with hematoxylin–eosin. To evaluate the feminizing effect of the test substances, the anogenital distance, length of urethra, and length of vaginal part, evolved from the sinus urogenitalis, were measured by means of the MOP device (MOP-AM02/hp9815A/Kontron) combined with a microscope. The significance of differences between groups were evaluated by an analysis of variance.

Determination of Progestational Activity in Rabbits.[8] Castrated infantile female rabbits (albino Neuseeland) weighing 800–1000 g were administered a daily subcutaneous dose of 0.5 μg of estradiol for 6 days (priming). Thereafter, the animals were treated with test compounds (total dose 30, 100, 300 mg/rabbit, po) for 5 days. On day 12, the animals were sacrificed, and the uteri were excised for histological studies. The rate of the glandular development in endometrium was evaluated by using the McPhail scale (1–4: 1 = inactive, 4 = maximal development of the glands).

Determination of Ovulation Inhibition in Rats.[8] Mature female rats (SPF, Wistar strain) weighing about 200 g were used in this experiment. Prior to the starting of the treatment, the estrus cycles of animals were monitored over a period of three cycles by means of vaginal smears. The daily treatment of animals showing a regular 4-day cycle with test compounds (30, 100 mg/rat per day, po) was initiated on the day of metestrus (day 1) and continued for 3 or 4 days. On day 4, animals were unilaterally ovarectomized, and the fallopian tube was dissected free. The tube was then microscopically examined by counting the number of ova to ascertain whether ovulation had occurred or not. When animals had had no ovulation, they were further treated on day 4. On day 5, animals were sacrificed, and the remaining tube was similarly examined as on day 4. The ovulation-inhibiting activity of test substances was expressed as the percent of animals in

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which ovulations were suppressed.

Experimental Section

All melting points were determined on a Büchi 510 melting point apparatus and are uncorrected. NMR spectra were taken in $CDCl_3$ on a Varian HA-100 spectrometer using tetramethylsilane as an internal standard unless otherwise stated. Ultraviolet spectra were obtained in methanol on a Cary 14 UV spectrophotometer. Infrared spectra were obtained in KBr tablet on Perkin-Elmer Model 621 and 580 B infrared spectrophotometer. Optical rotations are specific rotations taken in $CHCl_3$ (0.5%).

1. Typical Procedure for the Synthesis of 7α-Cyano-3-oxo 4-Enecarbolactones. A. A solution of 31.8 g (90.3 mmol) of 15β,16β-methylene-3-oxo-17α-pregna-4,6-diene-21,17-carbolactone (**1**) in 600 mL of THF was treated with 180 mL of a 1.8 N solution of diethylaluminum cyanide (0.32 mol) at room temperature, and stirring was continued for 3 h. The reaction mixture was poured into a solution of 28 g of potassium sodium tartrate in 420 mL of ice water and extracted with ethyl acetate. The combined extracts were washed with water, dried over sodium sulfate, and evaporated in vacuum. The crude mixture was dissolved in 200 mL of methanol and stirred with 2.59 g of potassium carbonate for 90 min. The mixture was poured into water and extracted with dichloromethane. The crude material was purified by column chromatography, yielding 22 g (64%) of 7α-cyano-15β,16β-methylene-3-oxo-17α-pregn-4-ene-21,17-carbolactone (**5**), mp 241 °C.

B. A solution of 4.0 g (10.9 mmol) of 1α,2α;15β,16β-dimethylene-3-oxo-17α-pregna-4,6-diene-21,17-carbolactone (**2**) in 80 mL of DMF and 8 mL of water was treated with 4.0 g of potassium cyanide and 2.0 g of ammonium chloride. The reaction mixture was stirred at 80 °C for 7 h and poured into ice water. The crude precipitate was purified by column chromatography, yielding 3.96 g (89%) of 7α-cyano-1α,2α;15β,16β-dimethylene-3-oxo-17α-pregn-4-ene-21,17-carbolactone (**6**), mp 288 °C.

2. Typical Procedure for the Synthesis of 7α-(Alkoxycarbonyl)-3-oxo 4-Enecarbolactones. A. A solution of 3.4 g (8.9 mmol) of 7α-cyano-15β,16β-methylene-3-oxo-17α-pregn-4-ene-21,17-carbolactone (**5**) was dissolved in 200 mL of toluene. At −50 °C 39 mL of a 20% solution of diisobutylaluminum hydride was added, and the stirring was continued for 1 h at −40 °C. Five milliliters of amyl alcohol was added and the mixture was poured into ice-cold aqueous potassium sodium tartrate solution and extracted with ethyl acetate, dried, and evaporated in vacuum, yielding 3.41 g (100%) of 3,5′-dihydroxy-15β,16β-methylene-4-androstene-17-spiro-2′-(tetrahydrofuran)-7α-carbaldehyde (**9**).

B. A solution of 18.8 g (48.6 mmol) of 3,5′-dihydroxy-15β,16β-methylene-4-androstene-17-spiro-2′-(tetrahydrofuran)-7α-carbaldehyde (**9**) in 750 mL of acetone was treated at −15 °C with 58.9 mL of an 8 N Jones solution. After 30 min at −15 °C the mixture was quenched with 10 mL of methanol, diluted with ethyl acetate, and extracted with sodium hydroxide solution. The aqueous phase was washed with ethyl acetate, acidified with sulfuric acid, and extracted with ethyl acetate, yielding 10.1 g (53%) of 7α-carboxy-15β,16β-methylene-3-oxo-17α-pregn-4-ene-21,17-carbolactone (**13**).

C. A solution of 4.05 g (10.1 mmol) of 7α-carboxy-15β,16β-methylene-3-oxo-17α-pregn-4-ene-21,17-carbolactone (**13**) in 150 mL of dichloromethane was treated with ice cooling with an excess of diazomethane. The excess diazomethane was destroyed with acetic acid and the solvent was evaporated. The crude product was purified by column chromatography, yielding 2.8 g (66%) of 7α-(methoxycarbonyl)-15β,16β-methylene-3-oxo-17α-pregn-4-ene-21,17-carbolactone (**17**), mp 266 °C.

D. A solution of 150 mg (0.37 mmol) of 7α-carboxy-15β,16β-methylene-3-oxo-17α-pregn-4-ene-21,17-carbolactone (**13**) in 3 mL of THF was treated at 0 °C with 0.1 mL of triethylamine. This solution was treated with 0.05 mL of butyl chloroformate in 0.5 mL of THF and stirred for 1 h. The precipitate was filtered and the solvent was evaporated in vacuum. The residue was dissolved in ethanol and refluxed for 48 h. After evaporation of the solvent, the crude material was purified by thick-layer chromatography, yielding 109 mg (48%) of 7α-(ethoxycarbonyl)-15β,16β-methylene-3-oxo-17α-pregn-4-ene-21,17-carbolactone (**18**), mp 185 °C.

E. A solution of 500 mg (1.21 mmol) of 7α-carboxy-1α,2α:15β,16β-dimethylene-3-oxo-17α-pregn-4-ene-21,17-carbolactone (**14**) in 10 mL of DMF was treated with 1.0 g of silver oxide and 2 mL of bromoethane and stirred at room temperature for 4.5 h. The reaction mixture was filtered and poured into ice water and extracted with dichloromethane. The crude material was purified by column chromatography on silica gel, yielding 364 mg (68%) of 7α-(ethoxycarbonyl)-1α,2α:15β,16β-dimethylene-3-oxo-17α-pregn-4-ene-21,17-carbolactone (**21**), mp 233 °C.

3. Typical Procedure for the Synthesis of 7α-(Alkoxycarbonyl)-3-oxo 1,4-Dienecarbolactones. A solution of 360 mg (0.87 mmol) of 7α-(methoxycarbonyl)-15β,16β-methylene-3-oxo-17α-pregn-4-ene-21,17-carbolactone (**17**) in 25 mL of dioxane was refluxed with 250 mg of DDQ for 14 h. After dilution with diethyl ether, the solution was washed with aqueous $NaHCO_3$ and water. The crude product was purified by thick-layer chromatography, yielding 140 mg (39%) of 7α-(methoxycarbonyl)-15β,16β-methylene-3-oxo-17α-pregna-1,4-diene-21,17-carbolactone (**26**), mp 273 °C.

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