Articles

Aldosterone Antagonists. 1. Synthesis and Activities of 6β,7β:15β,16β-Dimethylene Steroidal Spirolactones

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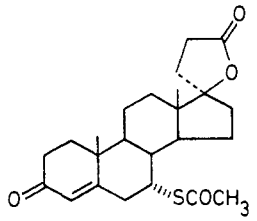
Several derivatives of the highly active aldosterone antagonists dihydrospirorenone (**2**) and spirorenone (**3**) were synthesized. The purpose of these efforts was to prepare compounds exhibiting reduced endocrinological properties with the same or better aldosterone antagonistic activity than that of spirorenone. The 1α,2α-methylene derivative **20** has a similar aldosterone antagonistic potency compared to that of spirorenone but does not show decreased endocrinological side effects. Other substituents as in compounds **4–11**, **15–19**, and **21** sharply decreased the aldosterone antagonistic activity of **2** or **3**, respectively.

In the late 1950s Cella, Tweit, and Kagawa[1] reported on the synthesis and the antialdosterone activity of the steroidal spirolactone derivative 1. Since its discovery, spironolactone (1) has been to date the only orally active aldosterone antagonist on the market. This compound



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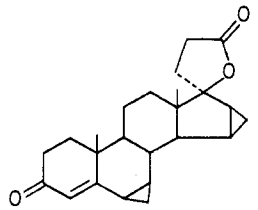
is found to antagonize the action of aldosterone and other mineralocorticoids at the distal tubule of the kidney. Therapy with this drug increases elimination of sodium and retention of potassium. For this reason, spironolactone has been used for the treatment of primary hyperaldosteronism, diseases related to secondary hyperaldosteronism (edema) and hypertension. A more extensive use of spironolactone for the treatment of these diseases is limited because of its endocrinological side effects.

Gynaecomastia and impotence[2-5] resulting from the antiandrogenic activity of spironolactone[2,4] are among the most frequently observed disturbances in male patients. Spironolactone is also active as a weak progestational agent[6] and women undergoing therapy with this drug exhibit menstrual cycle irregularities.[7,8] For these reasons, a great effort has been undertaken to develop aldosterone antagonists that are devoid of these side effects.[9-13]

Chemistry. Our research efforts during the past years have been primarily concerned with the development of new potent antialdosterone derivatives and have culminated in the synthesis of 6β,7β:15β,16β-dimethylene spirolactones **2** and **3**.[14,15] Both compounds, when tested in



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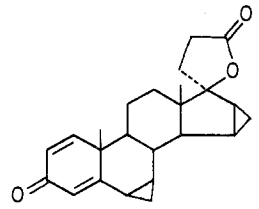

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the rat, exhibited a 7-fold increase of antialdosterone activity compared to that of spironolactone (1).[16] Compound **2** could not be developed as an aldosterone antagonist because of its progestational activity as measured in the Clauberg and pregnancy maintenance test.[17] In contrast, the 1,2-dehydro derivative **3** (spirorenone) showed a markedly reduced affinity for the androgen receptor and

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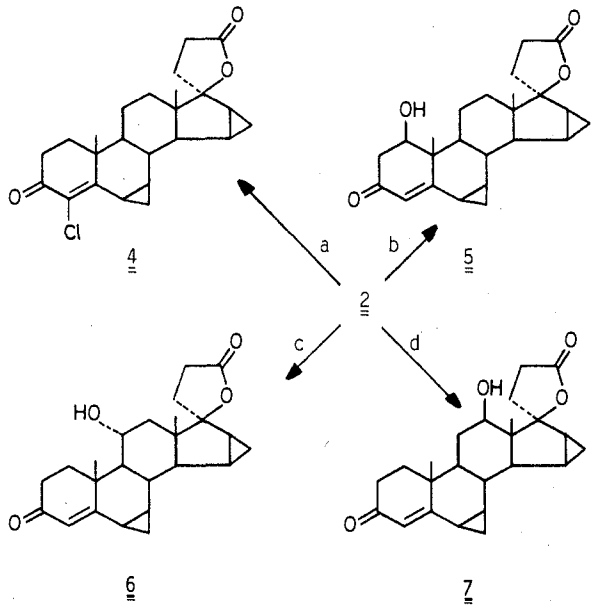
Scheme I



[a] (a) SO_2Cl_2/pyridine/0 °C. (b) Gibberella fujikuroi ATCC 14842, microbiologically. (c) Colletotrichum phomoides JFO 5257, microbiologically. (d) Botryodiplodia malorum CBS 13450, microbiologically.

only a slightly greater affinity for the progesterone receptor when compared to spironolactone (1). Spirorenone and spironolactone were inactive in the pregnancy maintenance test, whereas spirorenone had a greater activity than spironolactone in the Clauberg test.[18] A pharmacokinetic study did finally show that, in man[19] as well as in monkeys,[20] spirorenone is converted in vivo into the progestationally active spirolactone derivative **2** by hydrogenation of the 1,2-double bond. For these reasons, the development of spirorenone as an aldosterone antagonist has to be reconsidered.

In view of the progestational side effects associated with these two dimethylene spirolactone derivatives **2** and **3**, an attempt was undertaken to modify the structure of these highly active aldosterone antagonists. The goal we pursued was to reduce the affinity of such substances to the progesterone receptor while retaining the antialdosterone activity with structurally modified derivatives (Scheme I).

Starting from dihydrospirorenone (**2**), it was possible to prepare the 4-chloro derivative **4** by reaction with sulfuryl chloride in pyridine. The hydroxylated products **5–7** were prepared microbiologically from **2**.

Treatment of **2** with bis(dimethylamino)methane and acetyl chloride[21] in acetonitrile yielded the 2-methylene derivative **8**.

Hydrogenation of **8** with tris(triphenylphosphine)rhodium(I) chloride gave a mixture of the 2β- and 2α-methyl derivatives **9** and **10**, in a ratio of 3:1. The 2β-methyl derivative **9** was dehydrogenated with DDQ to yield 2-methylspirorenone (**11**, Scheme II).

Starting from spirorenone (**3**), the 2-chloro derivative **15** was prepared by epoxidation with hydrogen peroxide/sodium hydroxide followed by treatment with lithium chloride to yield the chlorohydrin **13**, formation of the methanesulfonate ester **14**, and elimination of the methanesulfonate in DMF/sodium acetate (Scheme III).

The sulfur-substituted spirolactone derivatives **16–18** were prepared by base-catalyzed 1,4-addition of thioacetic acid, methyl mercaptan, and hydrogen sulfide to spirorenone (**3**). The 1α-methyl derivative **19** was synthesized by reaction of **3** with methylmagnesium bromide in the presence of copper(I) chloride. The corresponding 1α,2α-methylene derivative **20** could be obtained by treating **3** with trimethylsulfoxonium iodide and sodium hydride.[22,23] The 1α-cyano derivative **21** was prepared by treatment of spirorenone (**3**) with diethylaluminum cyanide[24] (Scheme IV).

Table I. Biological Activities of Spirolactones

compd	antialdosterone act., MRP[a] (spironolactone = 100; 95% CL)	androgen receptor[b] competition factor[c] (dihydrotestosterone = 1.0)	progesterone receptor[b] competition factor[c] (progesterone = 1.0)
1	100	8.9	21
2	685 (549–1015)	66	2.7
3	745 (590–1510)	150	6.5
4	no act.[d]		
5	45 (35–57)	no affin[e]	19
6	no act.	no affin	195
7	no act.	no affin	25
8	no act.	no affin	18
9	≈100	no affin	30
10	<100	no affin	105
11	no act.		35
15	no act.		33
16	≈100		no affin
17	240 (218–260)	no affin	no affin
18	>100	63	5.8
19	≈100	70	
20	520 (300–1060)	25	2.1
21	no act.		

[a] Relative potency calculated for the hour of maximal activity after oral administration. <, ≈, >: lower, not significantly different, higher activity of a test compound with 53.3 mg/kg po compared to 26.7 mg/kg of spironolactone. [b] The tests were performed by Dr. Schillinger, Department of Biochemistry, Schering AG. [c] The competition factor is defined as the ratio of the concentration of the test compound that causes a specific displacement of the radiolabeled standard from the receptor vs. the concentration of the unlabeled standard that causes an equivalent displacement of the radiolabeled standard. [d] No activity. [e] No affinity.

Biological Results and Discussion

Incorporation of various substituents into the dimethylene spirolactones **2** and **3** led to derivatives that exhibited practically no affinity for the progesterone receptor. Unfortunately, in most instances, a marked decrease in antialdosterone activity compared to that of spirorenone (**3**) was also noted (Table I). A chlorine substituent at the 2- (compound **15**) or 4-position (compound **4**) led to a total loss of activity. The 2β- and 2α-methyl derivatives **9** and **10** were only weakly active. The 1α-hydroxy compound **5** was less active than spironolactone (**1**); the two other hydroxylated derivatives **6** and **7** were inactive. In contrast to the above-mentioned derivatives, the activity of the 1α,2α-methylene compound **20** was comparable to that of dihydrospirorenone (**2**) and

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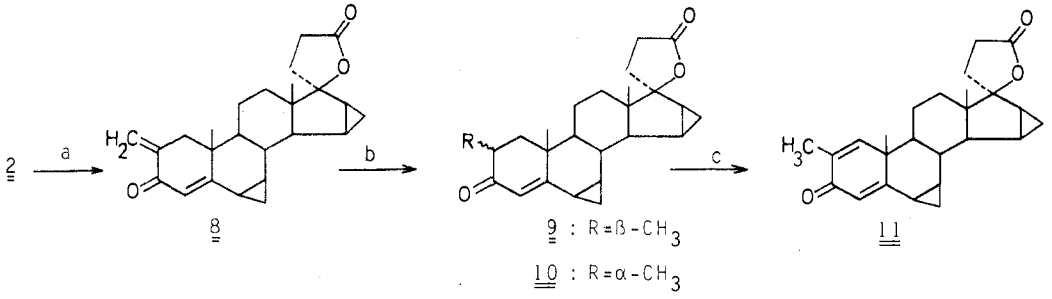
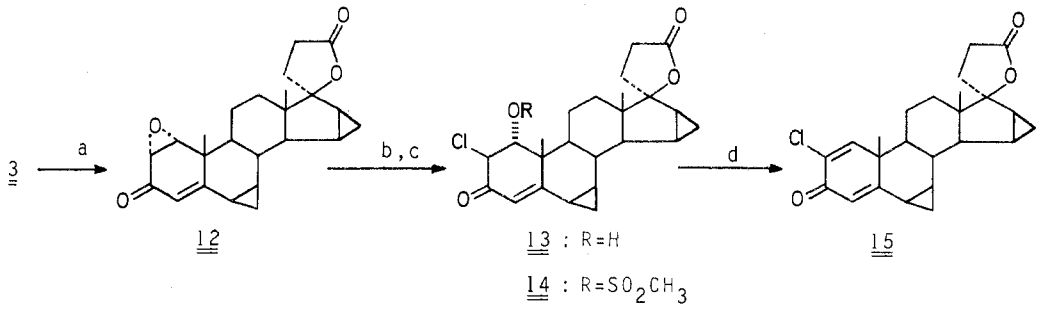
Scheme II[a]



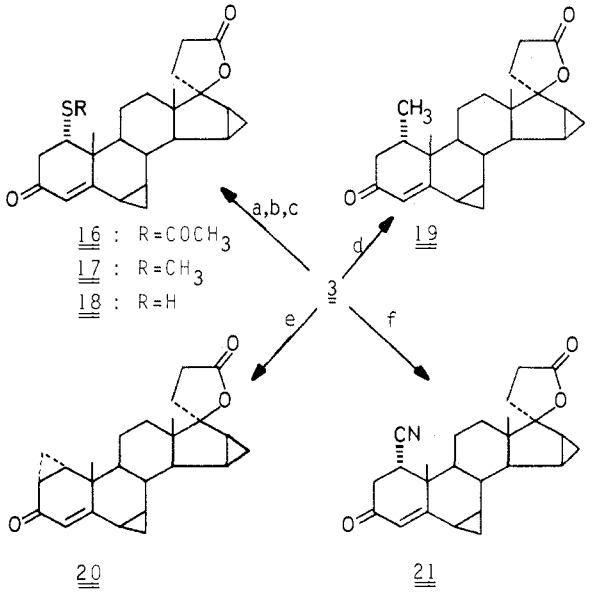
[a] (a) $CH_3COCl/[(CH_3)_2N]_2CH_2$/ether/80 °C. (b) $H_2/(Ph_3P)_3RhCl$/THF/toluene. (c) DDQ/dioxane/reflux.

Scheme III[a]



[a] (a) $H_2O_2/NaOH/CH_2Cl_2$/MeOH/25 °C. (b) LiCl/CH_3COOH/25 °C. (c) $CH_3SO_2Cl/NEt_3/CH_2Cl_2$/25 °C. (d) NaOAc/DMF/80 °C.

Scheme IV[a]



[a] (a) CH_3COSH/THF/MeOH/H_2O/25 °C. (b) $KOCH_3$/CH_3SH/THF/25 °C. (c) piperidin/H_2S/THF/MeOH/25 °C. (d) $LiCH_3/Cu_2I_2$/THF/DMF/0 °C. (e) $(CH_3)_3SOI$/NaH/$(CH_3)_2SO$/25 °C. (f) Et_2AlCN/THF/25 °C.

spirorenone (**3**). However, this substance **20** exhibits also a pronounced affinity to the progesterone receptor, a fact that renders impossible the use of this trimethylene derivative as an aldosterone antagonistic drug.

The thio ester, thioether, and mercapto derivatives **16–18** were, by far, the most promising compounds in this series since they appeared to fulfill the requirement for a highly active aldosterone antagonist with low endocrinological side effects. Although these derivatives exhibited a low affinity for the progesterone receptor, it can be assumed, in analogy to the metabolism of spironolactone (**1**), that the sulfur substituent at C-1 would be eliminated in vivo to yield spirorenone (**3**).[25,26] For this reason, the progestational activity of **17** and **18** was determined in the Clauberg test (Table II). The progestational activity found for these derivatives stands in contradiction to the low affinity of these compounds for the progesterone receptor. This result is consistent with the assumption that the elimination of sulfur under formation of the 1,2-double bond does indeed take place.

Table II. Progestational Activity in Rabbits after Oral Administration[a]

compd	dose, mg	McPhail index
1	100	1.1
	300	1.7
3	0.3	1.0
	1.0	2.2
	3.0	2.7
17	30	3.8
18	30	3.5

[a] A standard Clauberg test was used following literature procedures.[17]

To summarize our results, it has not been possible to reduce the endocrinological side effects to a greater extent without reducing concomitantly the antialdosterone activity of these spirorenone derivatives.

Methods

Determination of Antialdosterone Activity in Rats. The methods used for evaluation of the antialdosterone activity in rats were described previously.[27] Adrenalectomized Wistar rats with a body weight of 140–160 g were substituted with 1 mg of fluocortolone caproate/kg at the day of surgery and 10 mg of fluocortolone/kg sc 1 day before the diuresis experiment. These glucocorticoid-substituted rats were infused intravenously with a sa-

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line–glucose solution (0.05% NaCl, 5% glucose) containing aldosterone (50 μg/L) at a rate of 3 mL/h for 6 h in the first and for 10–15 h in the second screen. 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 anti-aldosterone activity was assessed by the ability of the compounds to reverse the aldosterone effect on the urinary Na/K ratio. Substances which, at a dosage of 53.3 mg/kg, showed similar or stronger effects than spironolactone at 26.7 mg/kg in a preliminary test were examined in a second diuresis experiment over a period of 10 or 15 h to determine their relative potency in comparison to spironolactone after oral administration. 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. 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.[21]

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 Bruker MX 90 or a Varian HA-100 spectrometer using tetramethylsilane as an internal standard. Ultraviolet spectra were obtained in methanol on a Cary 14 UV spectrophotometer. Infrared spectra were obtained in KBr tablet on a Perkin-Elmer Model 621 and 580 B infrared spectrophotometer. Optical rotations are specific rotations taken in $CHCl_3$ (0.5%).

4-Chloro-6β,7β:15β,16β-dimethylene-3-oxo-17α-pregn-4-ene-21,17-carbolactone (4). A solution of 500 mg (1.36 mmol) of **2** in 5 mL of pyridine was treated at 4 °C with 0.35 mL of sulfuryl chloride and the resulting mixture stirred for 1 h at room temperature. The reaction mixture was poured into ice water. The resultant solid was collected, washed with water, and dried. The crude product was purified by thick-layer chromatography with hexane/EtOAc, yielding 306 mg of **4**. Recrystallization from diisopropyl ether/acetone yielded 165 mg (30%) of **4**: mp 224–225 °C; $[\alpha]^{25}_D$ −263.9°; UV ϵ_{274} = 16 760; IR 1770, 1678, 1570 cm^{-1}; NMR 1.0 (C-18), 1.1 (C-19) ppm. Anal. ($C_{24}H_{29}ClO_3$) C, H, O, Cl.

6β,7β:15β,16β-Dimethylene-1β-hydroxy-3-oxo-17α-pregn-4-ene-21,17-carbolactone (5). A 3-g (8.18 mmol) sample of **2** was fermented in a 40-L glass fermentor with Gibberella fujikuroi ATCC 14842 until the starting material had disappeared and was worked up by extraction with isobutyl methyl ketone. The crude reaction product was purified by column chromatography on silica gel. Recrystallization from hexane/acetone yielded 867 mg (27.7%) of **5**: mp 243.5 °C; $[\alpha]^{25}_D$ −172.8°; IR 3420, 1770, 1655, 1590 cm^{-1}; NMR (pyridine-d_5) 6.32 (C-4), 4.18 (m, C-1), 1.18 (C-19), 0.92 (C-18) ppm. Anal. ($C_{24}H_{30}O_4$) C, H, O.

6β,7β:15β,16β-Dimethylene-11α-hydroxy-3-oxo-17α-pregn-4-ene-21,17-carbolactone (6). A 3-g (8.18 mmol) sample of **2** was fermented in a 40-L glass fermentor with Colletotrichum phomoides JFO 5257 until the starting material had disappeared and was worked up by extraction with isobutyl methyl ketone. The crude reaction product was purified by column chromatography on silica gel. Recrystallization from hexane/acetone yielded 865 mg (27.6%) of **6**: mp 238.8 °C; $[\alpha]^{25}_D$ −194.9°; IR 3400, 1760, 1645, 1595 cm^{-1}; NMR (pyridine-d_5) 6.22 (C-4), 3.98 (m, C-11), 1.17 (C-19), 1.01 (C-18) ppm. Anal. ($C_{24}H_{30}O_4$) C, H, O.

6β,7β:15β,16β-Dimethylene-12β-hydroxy-3-oxo-17α-pregn-4-ene-21,17-carbolactone (7). A 3-g (8.18 mmol) sample of **2** was fermented in a 40-L glass fermentor with Botryodiplodia malorum CBS 13450 until the starting material had disappeared and was worked up by extraction with isobutyl methyl ketone. The crude reaction product was purified by column chromatography on silica gel. Recrystallization from hexane/acetone yielded 124 mg (4%) of **7**: mp 190.7 °C; $[\alpha]^{25}_D$ −150.9°; IR 3440, 1665, 1660, 1595 cm^{-1}; NMR (pyridine-d_5) 6.20 (C-4), 3.91 (dd, J = 9 and 4 Hz, C-12), 1.23 (C-18), 0.96 (C-19) ppm. Anal. ($C_{24}H_{30}O_4$) C, H, O.

3-Oxo-2:6β,7β:15β,16β-trimethylene-17α-pregn-4-ene-21,17-carbolactone (8). An ice-cold solution of 1.85 mL (20.3 mmol) of acetyl chloride in 24 mL of absolute ether was treated with a solution of 3.9 mL of bis(dimethylamino)methane (28.5 mmol) in 48 mL of ether and the mixture stirred for 30 min. The resulting precipitate was rapidly filtered and suspended in 42 mL of acetonitrile. This suspension was treated with a solution of 6 g of **2** (16.45 mmol) in 42 mL of tetrahydrofuran and stirred for 28 h at 80 °C. The reaction mixture was evaporated in a vacuum and suspended in 50 mL of tetrahydrofuran. Filtration and evaporation provided a crude product, which was chromatographed on silica gel with hexane/acetone to yield 2.76 g (44.4%) of **8** as an oil: $[\alpha]^{25}_D$ −124.7°; UV ϵ_{287} = 15 750; IR 1770, 1665, 1615, 1595 cm^{-1}; NMR 6.1 (C-4), 6.00 and 5.25 (C=CH_2), 1.0 (C-18), 1.0 (C-19) ppm. Anal. ($C_{25}H_{30}O_3$) C, H, O.

6β,7β:15β,16β-Dimethylene-2β-methyl-3-oxo-17α-pregn-4-ene-21,17-carbolactone (9) and 6β,7β:15β,16β-Dimethylene-2α-methyl-3-oxo-17α-pregn-4-ene-21,17-carbolactone (10). A solution of 1 g (2.64 mmol) of **8** in 50 mL of tetrahydrofuran/toluene (1:1) was hydrogenated with 500 mg of tris(triphenylphosphine)rhodium(I) chloride, yielding after chromatography on silica gel with hexane/acetone 620 mg (61.8%) of **9** [mp 166.5–171.5 °C; $[\alpha]^{25}_D$ −176.2°; UV λ_{265} = 17 950; IR 1775, 1665, 1600 cm^{-1}; NMR 6.02 (C-4), 1.24 (d, J = 7 Hz, 2β-CH_3), 1.16 (C-19), 0.99 (C-18) ppm; anal. ($C_{25}H_{32}O_3$) C, H, O] and 200 mg (19.9%) of **10** [mp 199–202 °C; $[\alpha]^{25}_D$ −133.3°; UV ϵ_{264} = 1770; IR 1770, 1665, 1600 cm^{-1}; NMR 6.0 (C-4), 1.13 (d, J = 7 Hz, 2α-CH_3), 1.12 (C-19), 1.00 (C-18) ppm; anal. ($C_{25}H_{32}O_3$) C, H, O].

6β,7β:15β,16β-Dimethylene-2-methyl-3-oxo-17α-pregna-1,4-diene-21,17-carbolactone (11). A solution of 500 mg (1.31 mmol) of **9** in 10 mL of dioxane was refluxed with 500 mg (1.2 mmol) of DDQ for 4 h. The solution was dissolved with ether washed with saturated aqueous $NaHCO_3$ and water and dried over sodium sulfate. Chromatography on silica gel with hexane/acetone yielded 405 mg (81%) of **11**: mp 228.9 °C; $[\alpha]^{25}_D$ −134°; UV ϵ_{253} = 13 790, ϵ_{286} = 7370; IR 1770, 1660, 1630, 1620 cm^{-1}; NMR 6.58 (q, J = 1 Hz, C-1), 6.28 (C-4), 1.85 (d, J = 1 Hz, CH_3C=), 1.08 (C-18), 1.02 (C-19) ppm. Anal. ($C_{25}H_{30}O_3$) C, H, O.

6β,7β:15β,16β-Dimethylene-1α,2α-epoxy-3-oxo-17α-pregn-4-ene-21,17-carbolactone (12). A solution of 2 g (5.49 mmol) of **3** in 60 mL of dichloromethane/methanol (1:1) was stirred with 4 mL of aqueous 2 N NaOH and 12 mL of 30% hydrogen peroxide solution for 4 h at room temperature. After neutralization with sulfuric acid, the solution was diluted with ether and washed with water. Chromatography with dichloromethane/acetone yielded, after crystallization from diisopropyl ether, 825 mg (39.2%) of **12**: mp: 290–293 °C; $[\alpha]^{25}_D$ −7.7°; UV ϵ_{269} = 16 000; IR 1760, 1705, 1595 cm^{-1}; NMR (pyridine-d_5) 6.18 (d, J = 2 Hz, C-4), 3.76 (dd, J = 4 + 2 Hz, C-2), 3.38 (d, J = 4 Hz, C-1), 0.98 (C-18), 0.94 (C-19) ppm. Anal. ($C_{24}H_{28}O_4$) C, H, O.

2-Chloro-6β,7β:15β,16β-dimethylene-3-oxo-17α-pregna-1,4-diene-21,17-carbolactone (15). A solution of 1 g (2.63 mmol) of **12** in 40 mL of acetic acid was stirred with 3 g (70.8 mmol) of lithium chloride for 17 h. The solution was poured into ice water and the resulting precipitate was filtered, dissolved in dichloromethane, washed with saturated aqueous $NaHCO_3$ and water, and evaporated in vacuum. The crude product of 1.1 g (2.63 mmol) of **13** was dissolved in 24 mL of dichloromethane and treated with 1.26 mL (9.1 mmol) of triethylamine and 0.63 mL (8.0 mmol) of methanesulfonyl chloride and the mixture stirred 1 h at room temperature. The solution was dissolved in dichloromethane and washed with water. The crude product of 1.3 g (2.63 mmol) was dissolved in 13 mL of dimethylformamide and stirred with 3.9 g of sodium acetate for 18 h at 80 °C. The solution was poured into ice water and the resulting precipitate was filtered off and dried. Chromatography on silica gel with hexane/acetone yielded 728 mg (69.2%) of **15** as a colorless oil: $[\alpha]^{25}_D$ −130.7°; UV ϵ_{256}

= 11 800, ϵ_{291} = 6350; IR 1760, 1655, 1585 cm^{-1}; NMR 7.0 (C-1), 6.38 (C-4), 1.18 (C-19), 1.04 (C-18) ppm. Anal. ($C_{24}H_{27}ClO_3$) C, H, O, Cl.

1α-(Acetylthio)-6β,7β:15β,16β-dimethylene-3-oxo-17α-pregn-4-ene-21,17-carbolactone (16). A solution of 200 mg (0.55 mmol) of **3** in 4 mL of tetrahydrofuran/methanol (1:1) was stirred with 0.2 mL of water and 0.4 mL of thioacetic acid for 45 min. The reaction mixture was diluted with dichloromethane, washed with water, saturated aqueous $NaHCO_3$, and water, and evaporated in vacuum. The crude product was recrystallized from diisopropyl ether, yielding 230 mg (94.9%) of **16**: mp 212 °C; $[\alpha]^{25}_D$ −141.1°; UV ϵ_{266} = 15 700; IR 1770, 1680, 1665, 1595 cm^{-1}; NMR 6.0 (C-4), 392 (dd, J = 5 and 4 Hz, C-1), 2.34 ($SC(O)CH_3$), 1.26 (C-11), 0.98 (C-18) ppm. Anal. ($C_{26}H_{32}O_4S$) C, H, S.

6β,7β:15β,16β-Dimethylene-1α-(methylthio)-3-oxo-17α-pregn-4-ene-21,17-carbolactone (17). A solution of 750 mg (2.05 mmol) of **3** in 25 mL of tetrahydrofuran was treated with 75 mg of potassium methylate and during 2 h with a constant stream of methyl mercaptan. The reaction mixture was diluted with ether, washed with water, and evaporated under reduced pressure. The crude product was recrystallized from diisopropyl ether, yielding 720 mg (84.8%) of **17**: mp 122.7 °C; $[\alpha]^{25}_D$ −156.4°; UV ϵ_{263} = 14 930; IR 1770, 1665, 1600 cm^{-1}; NMR 6.02 (C-4), 2.06 (SCH_3), 1.21 (C-19), 0.98 (C-18) ppm. Anal. ($C_{25}H_{32}O_3S$) C, H, S.

6β,7β:15β,16β-Dimethylene-1α-mercapto-3-oxo-17α-pregn-4-ene-21,17-carbolactone (18). A solution of 500 mg (1.37 mmol) of **3** in 375 mL of methanol/tetrahydrofuran (2:1) and 0.3 mL of piperidine was treated at room temperature with H_2S for 1.5 h. The reaction mixture was poured into ice water and the resulting precipitate was filtered off and dried. Chromatography on silica gel with dichloromethane/acetone yielded, after recrystallization from diisopropyl ether, 216 mg (39.4%) of **18**: mp 242.2 °C; $[\alpha]^{25}_D$ −136.5°; UV ϵ_{266} = 14 500; IR 2550, 1760, 1660, 1600 cm^{-1}; NMR 6.08 (C-4), 3.37 (m, C-1), 1.22 (C-19), 0.98 (C-18) ppm. Anal. ($C_{24}H_{30}O_3S$) C, H, S.

6β,7β:15β,16β-Dimethylene-1α-methyl-3-oxo-17α-pregn-4-ene-21,17-carbolactone (19). A suspension of 2.2 g (11.5 mmol) of cuprous iodide in 23 mL of ether was treated at 0 °C with 15 mL of a 1.5 M methyllithium solution in ether and the mixture stirred until all the cuprous iodide had dissolved. This solution was treated with a solution of 640 mg (1.75 mmol) of **3** in dimethylformamide/tetrahydrofuran (1:1) and stirred for 3 h at 0 °C. The reaction mixture was diluted with ether, washed with diluted sulfuric acid and water, and evaporated under reduced pressure. Chromatography on silica gel with hexane/acetone yielded, after recrystallization from diisopropyl ether, 64 mg (9.6%) of **19**: mp 252.1 °C; UV ϵ_{267} = 15 050; IR 1770, 1660, 1595 cm^{-1}; NMR 6.02 (C-4), 1.16 (C-19), 0.98 (C-18) ppm. Anal. ($C_{25}H_{30}O_3$) C, H, O.

3-Oxo-1α,2α:6β,7β:15β,16β-trimethylene-17α-pregn-4-ene-21,17-carbolactone (20). A solution of 2.2 g (10 mmol) of trimethylsulfoxonium iodide in 35 mL of dimethyl sulfoxide was stirred with 393 mg (9 mmol) of a 55% suspension of sodium hydride in oil for 1.5 h. This solution was treated with 729 mg (2 mmol) of **3** and stirred for 21 h at room temperature. The reaction mixture was poured into ice water and acidified with sulfuric acid, and the resulting precipitate was filtered and dried. Chromatography on silica gel yielded after, recrystallization from diisopropyl ether/acetone, 540 mg (71.4%) of **20**: mp 261.7 °C; $[\alpha]^{25}_D$ −9.7°; UV ϵ_{259} = 14 800; IR 1770, 1655, 1605 cm^{-1}; NMR 5.85 (C-4), 1.15 (C-19), 1.0 (C-18) ppm. Anal. ($C_{25}H_{30}O_3$) C, H, O.

1α-Cyano-6β,7β:15β,16β-dimethylene-3-oxo-17α-pregn-4-ene-21,17-carbolactone (21). A solution of 1 g (2.75 mmol) of **3** in 33 mL of dry tetrahydrofuran was treated with 3 mL of a 1.8 M solution of diethylaluminum cyanide in toluene. After 5 min the reaction mixture was poured in cooled sodium potassium tartrate solution. Extraction with methylene chloride and column chromatography yielded, after recrystallization from diisopropyl ether, 950 mg (88.1%) of **21**: mp 271.4 °C; $[\alpha]^{25}_D$ −147°; UV ϵ_{264} = 17 380; IR 2240, 1760, 1665, 1595 cm^{-1}; NMR 6.16 (C-4), 1.16 (C-19), 0.98 (C-18) ppm. Anal. ($C_{25}H_{29}NO_3$) C, H, N, O.

Registry No. **2**, 67392-87-4; **3**, 74220-07-8; **4**, 95218-05-6; **5**, 95218-06-7; **6**, 95218-07-8; **7**, 95218-08-9; **8**, 95218-09-0; **9**, 95218-10-3; **10**, 95340-87-7; **11**, 95218-11-4; **12**, 95218-12-5; **13**, 95218-13-6; **14**, 95218-14-7; **15**, 95218-15-8; **16**, 95218-16-9; **17**, 95218-17-0; **18**, 95218-18-1; **19**, 95218-19-2; **20**, 95218-20-5; **21**, 95218-21-6; CH_3SO_2Cl, 124-63-0; CH_3COSH, 507-09-5; CH_3SH, 74-93-1; H_2S, 7783-06-4; $LiCH_3$, 917-54-4; $(CH_3)_3SOI$, 1774-47-6; Et_2AlCN, 5804-85-3; aldosterone, 52-39-1.

Synthesis and Antiviral Activity of the Carbocyclic Analogues of (*E*)-5-(2-Halovinyl)-2′-deoxyuridines and (*E*)-5-(2-Halovinyl)-2′-deoxycytidines

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The carbocyclic analogues of the potent and selective antiherpes agents (*E*)-5-(2-bromovinyl)-2′-deoxyuridine (BVDU), (*E*)-5-(2-iodovinyl)-2′-deoxyuridine (IVDU), and (*E*)-5-(2-bromovinyl)-2′-deoxycytidine (BVDC) were synthesized by conventional methods with use of carbocyclic 2′-deoxyuridine as starting material. C-BVDU, C-IVDU, and C-BVDC were equally selective, albeit slightly less potent, in their antiherpes action than BVDU, IVDU, and BVDC. Although resistant to degradation by pyrimidine nucleoside phosphorylases, C-BVDU did not prove more effective than BVDU in the systemic (oral, intraperitoneal) or topical treatment of HSV-1 infections in mice.

(*E*)-5-(2-Bromovinyl)-2′-deoxyuridine (BVDU) is a highly potent and selective antiherpes agent,[1] which inhibits herpes simplex virus type 1 (HSV-1),[2] varicella-zoster virus (VZV),[3] pseudorabies virus (suid herpesvirus type 1),[4] infectious bovine rhinotracheitis virus (bovid herpesvirus type 1),[5] and simian varicella virus,[6] at a concentration of 0.001–0.01 μg/mL, while not being toxic for the host cell at concentrations up to 50–100 μg/mL.[1-7] The selectivity of BVDU as an antiherpes agent depends primarily on a specific phosphorylation by the virus-induced 2′-deoxythymidine (dThd) kinase,[8] and its antiviral action would

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