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Synthesis of Some New 17-Spiro-Substituted Steroids

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Iodolactonization of derivatives of 3β-hydroxypregna-5,20-dien-17α-acetic acid (**7**) afforded the corresponding 21-iodo-20β-hydroxy lactones (**8a**, **9a**, and **9b**). Displacement of the iodide by various nucleophiles afforded the corresponding 21-substituted analogs (**8b**, **8c**, **8f**, **9d–h**, and **12**), and catalytic reduction yielded the 21-unsubstituted compounds (**8d**, **8e**, and **9c**). Other spiro systems were prepared from 3β-hydroxy-5α-pregn-20-en-17α-acetic acid (**7b**) by ozonolysis followed by reduction (**18**) and oxidation (**19**).

The discovery in 1957 that the introduction of a spirolactone system at the C_{17} position of the steroid nucleus (*e.g.*, **1a**) produced a compound which inhibited the effects of aldosterone[1] led to the synthesis of steroids having other spiro ring systems at C_{17}. Several of these analogs (**1b**,[2] **1c**,[3] **2**,[4] and **3**[5]) have also been reported to be aldosterone inhibitors, while other variations of the spiro ring system (**1d**,[6,7] **1e**,[7] **4**,[8] **5**,[9] and **6**[10]) led to inactive compounds. In particular, the activity shown by **2** and **3** demonstrated that the 17β-oxygen linkage of the parent compounds (**1a–c**) could be replaced by a carbon linkage in a spirocyclic compound. In a preceding paper[11] we reported a convenient synthesis for a versatile steroid intermediate (**7**) bearing two functionalized carbon-linked substituents at C_{17}. We wish to report now the synthesis of a variety of new 17-spirocyclic steroids prepared from this intermediate by effecting ring closure between the two substituents at C_{17}.

Treatment of the sodium salts of the 17β-vinyl-17α-acetic acid derivatives (**7a**, **c**, and **d**) with iodine afforded the corresponding 21-iodo-20β-hydroxy-17α-acetic acid lactones (**8a** and **9a** and **b**) in good yield. This γ-lactone structure was assigned these compounds rather than the isomeric 20-iodo-21-hydroxy δ-lactone structure (**10**) on the basis of their infrared and nmr spectra. The infrared spectra exhibited carbonyl frequencies (see Table I) at 1775–1785 cm^{-1} (in the range of γ-lactones[12]), and the nmr spectra exhibited multiplets at *ca.* 3.4 and 4.7 ppm for the 21- and 20-protons, respectively. (The C_{21} methylene group, which is attached to an asymmetric carbon atom, exhibits this complex pattern because the two protons are in differing chemical environments.[13]) Although it is difficult to assign these peaks due to protons on an iodine-bearing carbon and to protons on an oxygen-bearing carbon with any degree of certainty, a comparison of this spectrum with those of the derived 21-substituted lactones **8b**, **d**, and **f** and **9d** easily clears up this uncertainty. The spectra (see Table II) of all these 21-substituted lactones (**8a**, **b**, **d**, and **f** and **9d**) show that the one-proton peak at *ca.* 4.6, which remains fairly constant in all these spectra, must be due to a proton on the oxygen-bearing carbon, whereas the two-proton peak, which shifts position with varying substitution at C_{21}, must be produced by the two protons on the substituent-bearing carbon. This rules out the isomeric 20-iodo δ-lactone structure **10**. This is corroborated by the nmr spectrum of the 21-unsubstituted lactone **8e** (see Table II). Reductive removal of the iodine atom increases the ratio of these peak areas from 2:1 to 3:1, confirming that the iodine and not the lactone oxygen was attached to the CH_2 group.

TABLE I
INFRARED FREQUENCIES OF γ-LACTONES

Compd no.	ν, cm^{-1}
8a	1775
8c	1762
9a	1784
9b	1783
16a	1762

(1) (a) J. A. Cella and C. M. Kagawa, *J. Am. Chem. Soc.*, **79**, 4808 (1957); (b) C. M. Kagawa, J. A. Cella, and C. G. Van Arman, *Science*, **126**, 1015 (1957).

(2) G. E. Arth, H. Schwam, L. H. Sarett, and M. Glitzer, *J. Med. Chem.*, **6**, 617 (1963).

(3) (a) D. Bertin and J. Perronnet, *Bull. Soc. Chim. France*, 564 (1964); (b) W. F. Johns and E. A. Brown, *J. Org. Chem.*, **31**, 2099 (1966).

(4) A. A. Patchett, U. S. Patent 3,257,390 (1966).

(5) B. Patelli and R. Sciaky, French Patent 1,383,204 (1965).

(6) A. A. Patchett, F. Hofmann, F. F. Giarrusso, H. Schwam, and G. E. Arth, *J. Org. Chem.*, **27**, 3822 (1962).

(7) L. N. Nysted and R. R. Burtner, *ibid.*, **27**, 3175 (1962).

(8) (a) H.-J. Hess, *ibid.*, **27**, 1096 (1962); (b) K. Heusler, *Helv. Chim. Acta*, **45**, 1939 (1962).

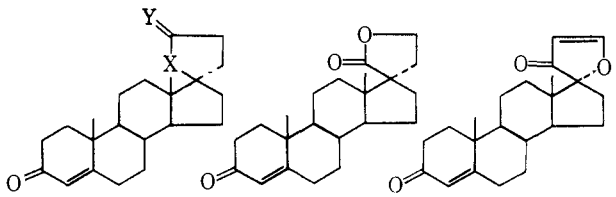
(9) (a) H. G. Lehmann, *Angew. Chem. Intern. Ed. Engl.*, **4**, 783 (1965); (b) N. H. Dyson, J. A. Edwards, and J. H. Fried, *Tetrahedron Letters*, 1841 (1966); (c) G. W. Moersch, D. E. Evans, and G. S. Lewis, *J. Med. Chem.*, **10**, 254 (1967).

(10) (a) E. Farkas and J. A. Swallow, *ibid.*, **7**, 739 (1964); (b) G. W. Moersch and P. L. Creger, *J. Heterocyclic Chem.*, **2**, 207 (1965).

(11) D. F. Morrow, T. P. Culbertson, and R. M. Hofer, *J. Org. Chem.*, **32**, 361 (1967).

(12) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1954, p 153.

(13) R. H. Bible, Jr., "Interpretation of NMR Spectra," Plenum Press, New York, N. Y., 1965, p 71.



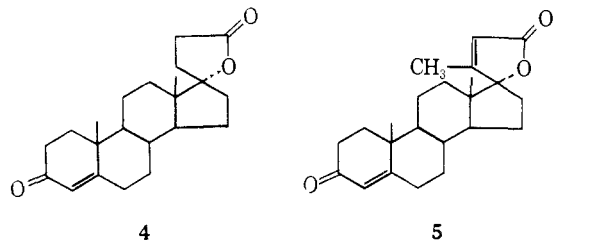
1a, X = Y = O **2** **3**

b, X = O; Y = H_2

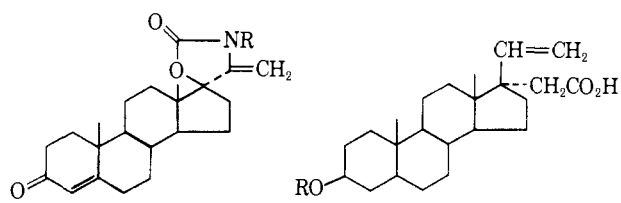
c, X = O; Y = H, OH

d, X = NR; Y = O

e, X = NR; Y = H_2



4 **5**



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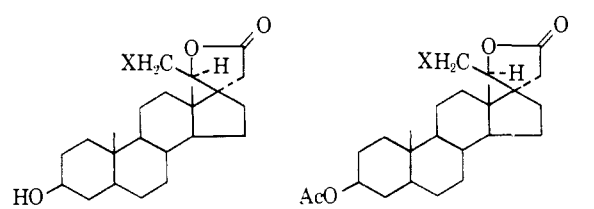
7a, Δ^5; R = H
b, 5α-H; R = H
c, Δ^5; R = Ac
d, 5α-H; R = Ac



8a, Δ^5; X = I
b, Δ^5; X = OAc
c, Δ^5; X = OH
d, Δ^5; X = H
e, 5α-H; X = H
f, 5α-H; X = NMe_2

9a, Δ^5; X = I
b, 5α-H; X = I
c, Δ^5; X = H
d, Δ^5; X = N_3
e, 5α-H; X = N_3
f, Δ^5; X = NH_2
g, 5α-H; X = NH_2
h, Δ^5; X = OTs

The 20β configuration was assigned on the basis of steric considerations. Examination of molecular models of **7a** revealed that the iodine atom would most likely attack the vinyl group on the side away from the bulky C_{18}-methyl group. Backside attack by the carboxylate anion on the resulting iodonium ion would then lead to the 20β-hydroxy stereochemistry of the lactone (**8a**). A Jones oxidation[14] of **8a** produced the Δ^4-3-keto derivative (**11a**).

Heating the 21-iodide (**8a**) with potassium acetate in dimethylformamide produced the 21-acetoxy derivative **8b**. Saponification of **8b** afforded sodium 3β,20β,21-trihydroxypregn-5-en-17α-acetate, which when heated in water relactonized to the 21-hydroxy γ-lactone (**8c**), generating sodium hydroxide. An Oppenauer oxidation of the 21-acetate (**8b**) afforded a mixture of the 21-hydroxy and 21-acetoxy Δ^4-3-ketones (**11b** and **c**).

Catalytic reduction of the 21-iodo compounds (**8a** and **9a**) proceeded rapidly to give the 21-unsubstituted compounds (**8d** and **9c**). Investigation of the mother liquors from the reduction of **8a** afforded a small amount of the corresponding 5α-dihydro compound (**8e**). A Jones oxidation[14] of **8d** gave the Δ^4-3-keto derivative (**11d**).

Displacement of the 21-iodides (**9a** and **b**) with sodium azide afforded the 21-azido compounds (**9d** and **e**), which were reduced catalytically to the corresponding 21-amines (**9f** and **g**). These amines did not undergo readily the expected O → N acyl migration, even in refluxing toluene. However, the hydroxy lactam (**12**) was produced when the amino lactone (**9f**) was heated neat at 220°. Clarke-Eschweiler methylation[15] of **9g** afforded the 21-dimethylamino lactone (**8f**).

In an attempt to prepare 17α-substituted derivatives of progesterone, the 21-amino lactone (**9f**) was diazotized with amyl nitrite in tetrahydrofuran with 1 equiv of an acid. No trace of the desired enol lactone (**13**) or its hydrolysis product, 17α-carboxymethylpregnenolone, was seen in the infrared spectrum of the total crude acid-insoluble material obtained from this reaction. The product which was formed instead was that in which the anion of the acid (*p*-toluenesulfonic, trichloroacetic, or trifluoroacetic) had displaced the diazonium group (*e.g.*, **9h**). Why this diazonium group underwent this unusual displacement by these relatively poor nucleophiles rather than expelling the proton at C_{20} to give **13** is not clear.

Lithium aluminum hydride reduction of the 21-acetoxy (**8b**) and 21-unsubstituted lactones (**8d**) afforded the corresponding triols and tetrols (**14a** and **b**). Periodic acid oxidation of **14b** afforded the 17β-carboxaldehyde (**15**), isolated as a cyclic hemiacetal. Silver oxide oxidation yielded the lactone (**16a**), which constitutes an alternate synthetic route into this known active spirolactone series (*e.g.*, **2**).[4]

Ozonolysis of the 17β-vinyl-17α-acetic acid derivative (**7b**) afforded the aldehydo acid (**17**),[11] which was both reduced with sodium borohydride to the lactone (**18**) and oxidized with chromic acid to the cyclic anhydride (**19**).

N,N-Dimethyl-3-oxopregna-4,20-dien-17α-acetamide (**20**) was prepared by an Oppenauer oxidation of the corresponding Δ^5-3β-ol.[11]

The lactones **11b**, **c**, and **d** and **18**, the anhydride **19**, the amide **20**, and the acid **7d** were inactive, both

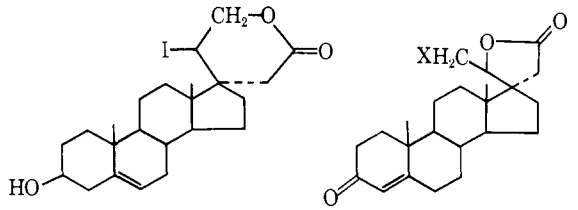
Table II
NMR Spectra of γ-Lactones

Compd no.	18-Me	$-CH_2CO_2-$	$C_{20}-CH_2O_2$	$C_{20}-H$
8a	0.84	2.52, 2.60[a]	3.2–3.6[b]	4.6–4.9[c]
8b	0.87	2.47, 2.58[a]	4.1–4.4[b]	4.5–4.8[c]
8d	0.83	2.39, 2.55[a]	1.29, 1.40[a]	4.6–4.8[c]
8e	0.81	2.37, 2.54[a]	1.27, 1.38[a]	4.6–4.8[c]
8f	0.82	2.25——2.67[b] (4 H)		4.6–4.8[c]
9d	0.89	2.54, 2.60[a]	3.5–3.7[b]	4.4–4.8[d]

[a] Doublet. [b] Multiplet. [c] Quartet. [d] Multiplet superimposed on broad 3α-H hump.

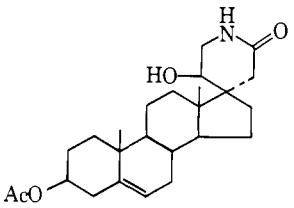
(14) C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

(15) M. L. Moore, *Org. Reactions*, **5**, 307 (1949).



10

11a, X = I
b, X = OH
c, X = OAc
d, X = H



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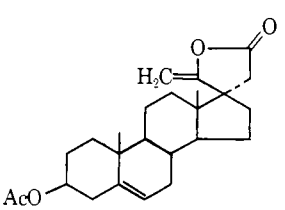

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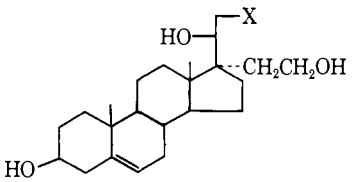
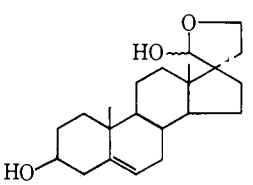


14a, X = H
b, X = OH



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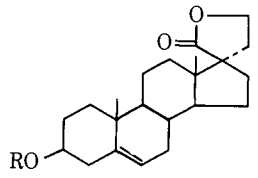
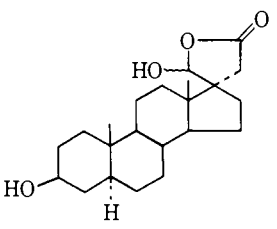


16a, R = H
b, R = Ac



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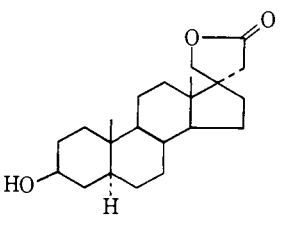

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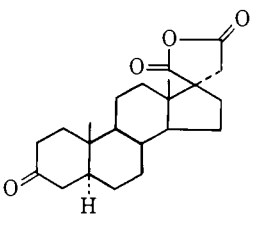

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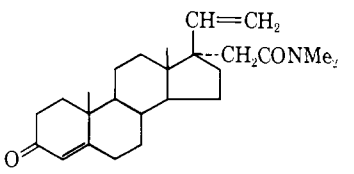

20

orally and subcutaneously, as inhibitors of aldosterone in adrenalectomized rats.[16] Compounds **7a** and **b**, **11b**, **c**, and **d**, **18**, and **20** were found to be ineffective orally in preventing litters in mice,[17] and in lowering serum cholesterol levels in rats.[18] The lactone **11d** exhibited no progestational activity either orally or subcutaneously in the Clauberg assay at doses as high as 10 mg/kg.

Experimental Section[19]

The physical properties and methods of preparation of the compounds are listed in Table III.

Procedure A.—A solution of 10.4 g of 3β-hydroxypregna-5,02-dien-17α-acetic acid (**7a**)[11] in 310 ml of methanol was treated first with a solution of 8.3 g of $KHCO_3$ in 200 ml of water and then with a solution of 7.9 g of iodine and 12.4 g of KI in 75 ml of water. The mixture was stirred in the dark at room temperature for 1 hr, and then poured into water. The precipitate was filtered, washed with dilute $NaHSO_3$ solution and with water, dried, and recrystallized.

Procedure B.—A solution of 4.90 g of 3β,20β-dihydroxy-21-iodopregn-5-en-17α-acetic acid lactone (**8a**) in 100 ml of dimethylformamide (DMF) was treated with 3.8 g of potassium acetate, and the mixture was stirred and refluxed for 1 hr. The cooled mixture was poured into water and the precipitate was filtered, dried, and recrystallized.

Procedure C.—A solution of 250 mg of 21-acetoxy-3β,20β-dihydroxypregn-5-en-17α-acetic acid lactone (**8b**) in 30 ml of ethanol was treated with 1.22 ml of 1.00 *N* NaOH solution and refluxed for 2 hr. The cooled solution was concentrated to dryness under reduced pressure. The solid residue was suspended in 25 ml of water and warmed on a steam bath. The **sodium 3β,20β,21-trihydroxypregn-5-en-17α-acetate** went into solution as another precipitate began to form. After 15 min on the steam bath, the mixture was cooled and filtered, and the crude product was recrystallized.

Procedure D.—A solution of 10.0 g of 3β,20β-dihydroxy-21-iodopregn-5-en-17α-acetic acid lactone (**8a**) in 1200 ml of 95% ethanol was treated with 1.0 g of 20% Pd–C and 2.0 g of sodium acetate, and the mixture was hydrogenated at 3.5 kg/cm² until 1 equiv of hydrogen was absorbed (*ca.* 25 min). The catalyst was removed by filtration and the filtrate was concentrated and poured into water. The precipitate was collected and recrystallized.

Procedure E.—A solution of 2.06 g of 3β-acetoxy-20β-hydroxy-21-iodopregn-5-en-17α-acetic acid lactone (**9a**) in 100 ml of DMF was treated with a solution of 1.25 g of NaN_3 in 8 ml of water and heated on a steam bath for 1 hr. The solution was poured into concentrated salt solution, and the precipitate was filtered, washed, dried, and recrystallized.

Procedure F.—A solution of 2.35 g of 3β-acetoxy-21-azido-20β-hydroxypregn-5-en-17α-acetic acid lactone (**9d**) in 60 ml of ethyl acetate and 60 ml of methanol was added to a suspension of 0.90 g of 20% Pd–C in 60 ml of methanol. The resulting mixture was stirred under hydrogen at atmospheric pressure for 5 hr. The solution was filtered, and the filtrate was concentrated to dryness under reduced pressure. The crystalline residue afforded a clean, sharp infrared spectrum which was transparent at 2108 (N_3) and at 1650 cm^{-1} (lactam), and exhibited peaks at 3400 (NH), 1780 (lactone), and 1735 cm^{-1} (3-OAc).

Procedure G.—A solution of 200 mg of 3β-acetoxy-21-amino-20β-hydroxypregn-5-en-17α-acetic acid lactone (**9f**) in 20 ml of tetrahydrofuran (THF) was treated with 92 mg of *p*-toluenesulfonic acid monohydrate and 0.20 ml of isoamyl nitrite. The mixture was stirred overnight at room temperature under an atmosphere of nitrogen. It was concentrated under reduced pressure and poured into water. The precipitate was filtered, washed, and dried; λ_{max} 273 mμ (ε 477), 261 (670), and 22ᵥ (8020); ν_{max} 1786 (lactone), 1732 (3-OAc), 1600 (C_6H_5), 1368 and 1178 cm^{-1} (SO_2).

Procedure H.—A flask containing 2.18 g of dry 3β-acetoxy-21-amino-20β-hydroxypregn-5-en-17α-acetic acid lactone (**9f**) was

(16) The procedure used was a modification of that developed by C. M. Kagawa, F. M. Sturtevant, and C. G. Van Arman, *J. Pharmacol. Exptl. Therap.*, **126**, 123 (1959).

(17) R. Q. Thompson, M. Sturtevant, and O. D. Bird, *Science*, **118**, 657 (1953).

(18) G. Rodney, M. L. Black, and O. D. Bird, *Biochem. Pharmacol.*, **14**, 445 (1965).

(19) Analyses and physical data are listed in Table III. Melting points were determined on a Fisher-Johns block and are corrected. The ultraviolet spectra were run in methanol. The nmr spectra were obtained on a Varian A-60 instrument in $CDCl_3$, and the shifts are expressed as parts per million downfield from Me_4Si used as an internal standard. All compounds had infrared spectra which agreed with the assigned structures. The crude materials obtained from the generalized procedures were purified by recrystallization from the appropriate solvent noted in Table III.

Table III
Tabulation of Physical Data

Compd	Method of prepn	Starting material	Yield, %	Mp, °C	Solvent[a]	$[\alpha]^{25}D$	Formula	Calcd, % C	Calcd, % H	Calcd, % Other	Found, % C	Found, % H	Found, % Other
3β-Acetoxy-5α-pregn-20-en-17α-acetic acid (7d)	*c*	7b	63	200–201	A	−36	$C_{25}H_{38}O_4$	74.59	9.51		74.60	9.47	
3β,20β-Dihydroxy-21-iodopregn-5-en-17α-acetic acid lactone (8a)	A	7a	94	215–216.5	A	−24[c]	$C_{23}H_{31}IO_3$	57.03	6.87	26.20[b]	57.07	6.91	26.12[b]
21-Acetoxy-3β,20β-dihydroxypregn-5-en-17α-acetic acid lactone (8b)	B	8b	83	193–195	A	−65[d]	$C_{25}H_{38}O_5$	72.08	8.70		72.02	8.74	
3β,20β,21-Trihydroxypregn-5-en-17α-acetic acid lactone (8c)	C	8b	79	255–257	A	−99	$C_{23}H_{34}O_4$	73.76	9.15		73.46	9.20	
3β,20β-Dihydroxypregn-5-en-17α-acetic acid lactone (8d)	D	8a	44	246–249	A	−111	$C_{23}H_{34}O_3$	77.05	9.56		77.06	9.56	
3β,20β-Dihydroxy-5α-pregnan-17α-acetic acid lactone (8e)	D[e]	8a	2.6	201–205	A–W	−42	$C_{23}H_{36}O_3$	76.62	10.07		76.51	9.95	
3β,20β-Dihydroxy-21-dimethylamino-5α-pregnan-17α-acetic acid lactone (8f)	*g*	9g	56	86–88	M	−18	$C_{25}H_{41}NO_4$	74.40	10.24	3.47[b]	74.36	10.29	3.36[b]
3β-Acetoxy-20β-hydroxy-21-iodopregn-5-en-17α-acetic acid lactone (9a)	A	7c	88	208–210	M	−39	$C_{25}H_{33}IO_4$	57.04	6.70	24.10[b]	57.28	6.85	24.36[b]
3β-Acetoxy-20β-hydroxy-21-iodo-5α-pregnan-17α-acetic acid lactone (9b)	A	7d	80	222–223	M	+11	$C_{25}H_{37}IO_4$	56.81	7.06	24.02[b]	56.88	7.20	24.14[b]
3β-Acetoxy-20β-hydroxypregn-5-en-17α-acetic acid lactone (9c)	D	9a	38	172–173	M	−101	$C_{25}H_{36}O_4$	74.96	9.06		75.24	9.15	
3β-Acetoxy-21-azido-20β-hydroxypregn-5-en-17α-acetic acid lactone (9d)	E	9a	75[f]	186–188	A	−81	$C_{25}H_{35}N_3O_4$	68.00	7.99	9.52[b]	68.18	8.00	9.66[b]
3β-Acetoxy-21-azido-20β-hydroxy-5α-pregnan-17α-acetic acid lactone (9e)	E	9b	76	203–204.5	A	−17	$C_{25}H_{37}N_3O_4$	67.69	8.41	9.47[b]	67.67	8.58	9.57[b]
3β-Acetoxy-21-amino-20β-hydroxypregn-5-en-17α-acetic acid lactone (9f)	F	9d	100[f]				$C_{25}H_{37}NO_4$						
3β-Acetoxy-21-amino-20β-hydroxy-5α-pregnan-17α-acetic acid lactone (9g)	F	9e	100[f]				$C_{25}H_{39}NO_4$						
3β-Acetoxy-20β-hydroxy-21-*p*-toluenesulfonyloxypregn-5-en-17α-acetic acid lactone (9h)	G	9f	44	215–217	E	−47	$C_{32}H_{42}O_7S$	67.34	7.42	5.62[b]	67.61	7.56	5.39[b]
20β-Hydroxy-21-iodo-3-oxopregn-4-en-17α-acetic acid lactone[g] (11a)	*m*	8a	18	209–210	Et	+85	$C_{23}H_{31}IO_4$	57.26	6.48	26.31[c]	57.19	6.69	26.07[c]
20β,21-Dihydroxy-3-oxopregn-4-en-17α-acetic acid lactone[g] (11b)	*o*	8b	27	257–260	A	+41	$C_{23}H_{32}O_4$	74.16	8.66		74.23	8.43	

TABLE III (*Continued*)

Compd	Method of prepn	Starting material	Yield, %	Mp, °C	Solvent[a]	$[\alpha]^{25}D$[b]	Formula	Calcd, % C	Calcd, % H	Calcd, % Other	Found, % C	Found, % H	Found, % Other
21-Acetoxy-20β-hydroxy-3-oxopregn-4-en-17α-acetic acid lactone[p] (11c)	*q*	8b	10[r]	187–189	M	+53	$C_{25}H_{34}O_5$	72.43	8.27		72.28	8.36	
20β-Hydroxy-3-oxopregn-4-en-17α-acetic acid lactone[s] (11d)	*m*	8d	65	221–223	E	+27	$C_{23}H_{32}O_3$	77.49	9.05		77.38	9.13	
3β-Acetoxy-21-amino-20β-hydroxypregn-5-en-17α-acetic acid lactam (12)	H	9f	58	>300	P		$C_{25}H_{37}NO_4$	72.25	8.98	3.37[h]	72.25	8.98	3.47[h]
2-(3β,20β-Dihydroxypregn-5-en-17α-yl)-ethanol (14a)	I	8d	77	240–242	M	−45[d]	$C_{23}H_{38}O_3$	76.19	10.57		76.05	10.58	
2-(3β,20β,21-Trihydroxypregn-5-en-17α-yl)ethanol (14b)	I	8b	79	273–275	M		$C_{23}H_{38}O_4$	72.97	10.12		72.54	9.98	
3β,21-Dihydroxy-17α-pregn-5-ene-17β-carboxylic acid lactone (16a)	J	14b	34	239–241	M	−80	$C_{22}H_{32}O_3$	76.70	9.36		76.75	9.16	
3β-Acetoxy-21-hydroxy-17α-pregn-5-ene-17β-carboxylic acid lactone (16b)	*q*	16a	76	200–202	M	−73	$C_{24}H_{34}O_4$	74.57	8.87		74.31	8.69	
3β,20β-Dihydroxy-21-nor-5α-pregnan-17α-acetic acid lactone (18)	K	17	67	212–213	Et–W	−13	$C_{22}H_{34}O_3$	76.26	9.89		76.11	9.83	
17β-Carboxy-3-oxo-5α,17α-pregnan-21-oic anhydride (19)	L	17	75	243–245	D–E	+17	$C_{22}H_{30}O_4$	73.71	8.44		73.44	8.39	
N,N-Dimethyl-3-oxopregna-4,20-dien-17α-acetamide[t] (20)	*o*		40	179–180	B–H	+56	$C_{25}H_{37}NO_2$	78.29	9.73	3.65[h]	78.12	9.70	3.63[h]

[a] A = acetonitrile, B = C_6H_6, D = CH_2Cl_2, E = ether, Et = ethanol, H = hexane, M = methanol, P = pyridine, W = water. [b] Run as 1% solutions in $CHCl_3$ unless otherwise noted. [c] See preparation of **5e** in ref 11. [d] Run as a 1% solution in methanol. [e] Iodine analysis. [f] Isolated by fractional crystallization of the mother liquors from the recrystallization of **8d**. [g] See ref 15. [h] N analysis. [i] Also prepared in 89% over-all yield from **8a** by procedure E followed by acetylation. [j] Because of anticipated problems with O → N acyl migration at higher temperatures, the product was not recrystallized but was used directly for the succeeding reactions. [k] S analysis. [l] λ_{max} 240 mμ (ε 16,100). [m] See ref 14. [n] λ_{max} 240 mμ (ε 15,800). [o] C. Djerassi, *Org. Reactions*, **6**, 207 (1951). [p] λ_{max} 240 mμ (ε 15,400). [q] See preparation of **6b** in ref 11. [r] Obtained by acetylation of the mother liquors from the recrystallization of **11b**. [s] λ_{max} 240 mμ (ε 16,300). [t] λ_{max} 241 mμ (ε 17,100).

heated at 220° in a Woods metal bath. An atmosphere of nitrogen was maintained over the steroid. After 3.5 hr, the flask was cooled and the unreacted starting material was washed out with boiling chloroform. The insoluble residue was recrystallized.

Procedure I.—A solution of 0.54 g of 3β,20β-dihydroxypregn-5-en-17α-acetic acid lactone (**8d**) in 50 ml of THF was treated with 0.50 g of $LiAlH_4$, and the mixture was stirred and refluxed overnight. The excess reagent was decomposed with ethanol, and the mixture was poured into dilute HCl. The precipitate was filtered, washed, dried, and recrystallized.

Procedure J.—A suspension of 1.14 g of 2-(3β,20β,21-trihydroxypregn-5-en-17α-yl)ethanol (**14b**) in 162 ml of dioxane was cooled and treated with a solution of 1.62 g of periodic acid in 33 ml of water. The mixture was stirred at 0° overnight, allowed to warm to room temperature, and poured into concentrated salt solution. The precipitate was filtered, washed, dried, and recrystallized from methanol, affording 0.85 g (82%) of **3β,21-dihydroxy-17α-pregn-5-ene-17β-carboxaldehyde hemiacetal form (15)**, mp 194–210°. The infrared spectrum of this material was transparent in the 6-μ region, indicating that this hydroxyaldehyde existed completely in the cyclic hemiacetal form. This intermediate was not further characterized and the stereochemistry produced at C_{20} was not determined.

A solution of 0.83 g of **15** in 63 ml of ethanol was treated with a solution of 1.0 g of $AgNO_3$ in 9 ml of water. The solution was stirred and treated dropwise with a solution of 1.25 g of NaOH in 25 ml of water. The resulting mixture was stirred and refluxed overnight. The mixture was filtered and the precipitate was washed with 125 ml of ethanol. The filtrate and washings were combined, treated with 3 ml of 12 *N* HCl, and refluxed for 2 hr. The cooled solution was concentrated under reduced pressure and poured into water. The precipitate was filtered and recrystallized.

Procedure K.—A solution of 0.25 g of 3β,20,20-trihydroxy-21-nor-5α-pregnan-17α-acetic acid lactone (**17**)[11] in 20 ml of ethanol was treated with 2 drops of 50% NaOH solution and 200 mg of $NaBH_4$ and left at room temperature for 1 hr. The solution was poured into dilute HCl, and the precipitate was filtered, washed, and dried. The infrared spectrum indicated some hydroxy acid to be present as well as lactone, so the crude material was dissolved in 50 ml of ethanol, treated with 4 drops of 12 *N* HCl, and refluxed for 1 hr. The cooled solution was concentrated to dryness under reduced pressure, and the residue was recrystallized.

Procedure L.—A solution of 0.62 g of 3β,20,20-trihydroxy-21-nor-5α-pregnan-17α-acetic acid lactone (**17**)[11] in 65 ml of acetic acid was treated with 1.9 ml of 4 *N* chromic acid solution and

stirred at room temperature for 1 hr. The solution was poured into dilute HCl, NaCl was added, and the precipitate was filtered, washed, dried, and recrystallized.

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Synthetic Estrogens, Implantation Inhibitors, and Hypocholesterolemic Agents. I. Tetrahydronaphthalene Series[1]

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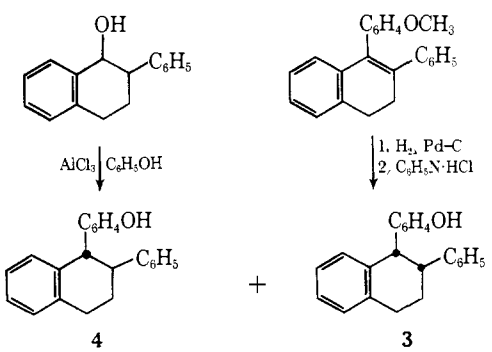
The stereochemistry of 1,2-diaryl-substituted tetrahydronaphthalene derivatives has been studied. Basic phenolic ethers and phenoxyacetic acid derivatives have been prepared in this series to achieve separation of estrogenic, antifertility, and hypocholesterolemic activities. Only partial separation of these biological features has been attained.

Several years ago a number of 3-pyridyl substituted dihydro- and tetrahydronaphthalene derivatives prepared in our laboratories were shown to inhibit the 11β- or the 17-hydroxylase enzyme systems in the biosynthesis of adrenal cortical and gonadal steroid hormones.[2]

The present report deals with the synthesis, stereochemistry, and endocrine-screening results of a number of tetrahydronaphthalene derivatives.

Chemistry.—Catalytic reduction of 1,2-disubstituted 3,4-dihydronaphthalenes resulted in tetrahydronaphthalene derivatives in which the substituents on the carbon atoms 1 and 2 are in the *cis* configuration. However, Friedel–Crafts-type alkylation of phenol by means of the carbonium ion produced by the action of a Lewis acid on 1-hydroxy-2-substituted 1,2,3,4-tetrahydronaphthalene afforded a mixture of *para*-alkylated phenols from which both the *cis* and *trans* isomers of 1,2-disubstituted tetrahydronaphthalenes could be isolated.



Thus, when 1-hydroxy-2-phenyl-1,2,3,4-tetrahydronaphthalene was used to alkylate phenol, the *cis* and *trans* products (**3** and **4**) could readily be isolated by fractional crystallization. The *cis* isomer (**3**) was identical with the product obtained by demethylation of **5** (see Table I) which, in turn, was prepared by catalytic hydrogenation of the corresponding 3,4-dihydronaphthalene derivative.[3] A further proof of structure for the *cis* isomer **3** was accomplished by reductive elimination of the phenolic hydroxy group *via* the phosphate ester **7** to afford the *cis* hydrocarbon **1**, which was found to be identical with 1,2-diphenyl-1,2,-3,4-tetrahydronaphthalene prepared according to the procedure of Bergmann, *et al.*[4]

Isolation of the *cis* isomer of phenol **11** from the Friedel-Crafts alkylation reaction mixture by crystallization was unsuccessful. However, subsequent to removal of most of the *trans* isomer **12** by crystallization, the residual mixture was methylated, and the phenolic methyl ethers **13** and **14** could be separated by fractional crystallization from 2-propanol. Again **13** was found to be identical with the product of catalytic hydrogenation of the corresponding 3,4-dihydronaphthalene derivative.

The most convincing evidence for the correct stereochemical assignment of the *cis* and *trans* configurations of the 1,2-disubstituted 1,2,3,4-tetrahydronaphthalene isomers was furnished by the nmr spectra of the pure compounds.

Figure 1 illustrates the four possible conformations of the tetrahydronaphthalene derivative assuming that the alicyclic ring is in the pseudo-chair form. The *trans* form, in which the two substituents are in the equatorial positions is depicted as structure A. Flipping the bulky aromatic substituents in axial positions would result in the *thermodynamically less stable* conformation B. In the stable *trans* form A the vicinal tertiary hydrogen atoms on carbons 1 and 2 are located *trans* to each other and would be expected to show a large coupling constant in their nmr doublet signal. Indeed, $J_{1,2}$ for the C_1 hydrogen signal was found to be approximately 10 cps, which confirms the *trans* diaxial relationship of the $C_{1,2}$ hydrogen atoms. Whereas nmr clearly establishes conformation A for the *trans* isomer, the coupling constant $J_{1,2} = 5$ cps for the *cis* isomer cannot distinguish between the two conformations C and D.

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