which would reflect geometrical requirements or spatial requirements of the receptor. The absence of these changes in our study suggests the concept that dopamine acts directly on the dopamine receptor.

The substitution of two hydrogens by deuterium is one of the smallest possible changes that can be made on an organic molecule. Apparently, the substitution of deuterium for hydrogen does not affect the conformational requirements needed for dopamine action *in vivo*. The deuterium-labeled dopamine compounds described in this study should be valuable for studies of the enzymatic mechanism of the metabolism of dopamine.

References

(1) J. L. McNay and L. I. Goldberg, *J. Pharmacol. Exp. Ther.*, **151**, 23 (1966).
(2) L. I. Goldberg, F. Sonneville, and J. L. McNay, *ibid.*, **163**, 188 (1968).
(3) M. Tanabe, D. Yasuda, S. LeValley, and C. Mitoma, *Life Sci.*, 8, 1123 (1969) (paper I).
(4) L. C. Mark, L. Brand, S. Heiber, and J. M. Perel, *Fed. Proc., Fed. Amer. Soc. Exp. Biol.*, **30**, 442 (1971).
(5) C. Mitoma, D. M. Yasuda, J. Tagg, and M. Tanabe, *Biochem. Biophys. Acta*, **136**, 566 (1967).
(6) C. Elison, H. W. Elliott, M. Look, and H. Rapoport, *J. Med. Chem.*, **6**, 237 (1963).
(7) R. L. Foreman, F. P. Siegel, and R. G. Mrtek, *J. Pharm. Sci.*, **58**, 189 (1969).
(8) T. B. Vree, J. P. M. C. Gorgels, A. Th. J. M. Muskens, and J. M. Van Rossum, *Clin. Chim. Acta*, **34**, 333 (1971).
(9) D. J. Triggle and J. F. Moran, *Nature (London)*, **211**, 307 (1966); B. Belleau and J. Moran, *Ann. N. Y. Acad. Sci.*, **107**, 822 (1963); B. Belleau, "Isotopes in Experimental Pharmacology," L. P. Roth, Ed., University of Chicago Press, Chicago, Ill., 1965, p 469.
(10) M. Goldstein, T. H. Joh, and T. Q. Garvey, III, *Biochemistry*, 7, 2724 (1968); S. Kaufman and S. Friedman, *Pharmacol. Rev.*, 17, 71 (1965).
(11) H. Blaschko, *Enzymes*, 8, 313 (1963).
(12) R. F. Nystrom and W. G. Brown, *J. Amer. Chem. Soc.*, **70**, 3738 (1948).
(13) L. H. Amundsen and L. S. Nelson, *ibid.*, **73**, 242 (1951).
(14) R. F. Nystrom, *ibid.*, 77, 2544 (1955).
(15) R. Stoermer, *Ber.*, **41**, 321 (1908).
(16) G. Barger and A. J. Ewins, *J. Chem. Soc.*, 97, 284 (1910).
(17) C. Schopf and H. Bayerle, *Justus Liebigs Ann. Chem.*, **513**, 190 (1934).
(18) F. H. Schneider and C. N. Gillis, *Biochem. Pharmacol.*, 14, 623 (1965).
(19) D. J. G. Ives, *J. Chem. Soc.*, 81 (1938).
(20) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 5th ed, Wiley, New York, N. Y., 1964.
(21) A. Kaufman and H. Müller, *Ber.*, **51**, 123 (1918).
(22) H. C. Brown and P. Heim, *J. Amer. Chem. Soc.*, **86**, 3566 (1964).
(23) F. C. Whitmore and D. P. Langlois, *ibid.*, **54**, 3438 (1932).
(24) H. Decker and R. Pschorr, *Ber.*, **37**, 3396 (1904).
(25) S. Senoh, C. R. Creveling, S. Udenfriend, and B. Witkop, *J. Amer. Chem. Soc.*, 81, 6236 (1959).
(26) R. J. McDonald and L. I. Goldberg, *J. Pharmacol. Exp. Ther.*, **140**, 60 (1963).
(27) J. M. Perel, D. K. Dawson, P. G. Dayton, and L. I. Goldberg, *Pharmacologist*, 11, 232 (1969).
(28) L. B. Kier and E. B. Truitt, Jr., *J. Pharmacol. Exp. Ther.*, 174, 94 (1970).
(29) J. M. George, L. B. Kier, and J. R. Hoyland, *Mol. Pharmacol.*, 7, 328 (1971).
(30) "Proceedings of the Symposium on Isotope Mass Effects, Chemistry and Biology," International Union of Pure and Applied Chemistry, Butterworths, London, 1964.
(31) K. B. Wiberg, *Chem. Rev.*, **55**, 713 (1955).

Synthesis and Biological Activity of 17-Esters of 6-Dehydro-16-methylene-17α-hydroxyprogesterones

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The progestational and antiandrogenic activities of 6-dehydro-6-halo(fluoro, bromo, chloro)-16-methylene-17α-acetoxyprogesterones (1), as well as related activities of 17-esters of the 6-chloro compounds (1), are reported. A convenient synthesis for this class of compounds is also described.

We have long been interested in the chemistry and pharmacology of 16-alkyl and alkylidene derivatives of 17α-hydroxyprogesterone.[1,2] Our early work[1] showed that 16-methylene substitution enhances progestational activity far more than either 16α-methyl or 16β-methyl in this series. Investigations of 6-chloro-16-methylene-17α-hydroxy-4,6-pregnadiene 17-acetate (**1**, X = Cl; R = CH_3CO) reported by us§ and by others[6] indicated that introduction of the 6-chloro-6-dehydro function into the preferred parent structure appeared to lead to a compound of exceptional progestational and antiandrogenic activity. In this article we now describe a systematic study of the influence of the alteration of halogen at 6 and the acyl group at 17 on the progestational and antiandrogenic activities of the resulting structures (generic formula **1**) (Table I). We also present a convenient general method for the synthesis of all of the members of the generic family **1** from the precursors in common, **3** and **4a**.[7,#]

From the readily available 16-methyl-3β-hydroxy-5,16-pregnadien-20-one (**2**),[9] a five-step reaction sequence *via* **3**, **4a**, **5**, and **6** may be utilized to afford the members of the generic structure **1** (Scheme I). A less satisfactory alternative route **7** → **8**[10] → **4a** was abandoned because chloranil dehydrogenation of **7** to **8** was accompanied by objectionable amounts of simultaneous 16α,17α-oxide opening.[11] The presence of exocyclic methylene at 16 prior to epoxidation of the 6,7 double bond was not permissible since the 16-unsaturation represented an undesirable point of competitive attack by the epoxidizing agent.

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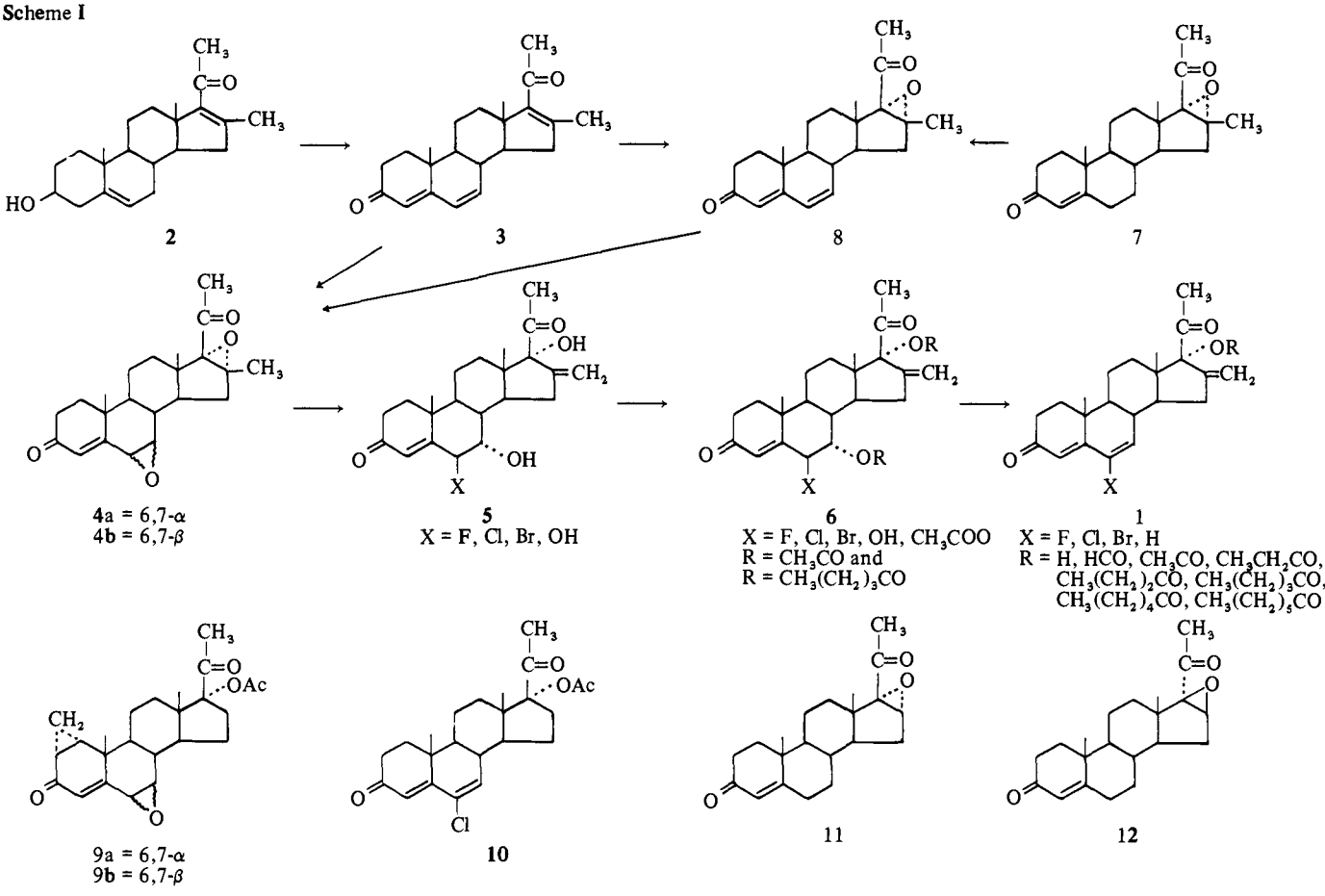
§ The antiandrogenic activity of 1 (X = Cl, R = CH_3CO) has been reported by Rocky and Neri,[3] Casmer, *et al.*,[4] and Neri.[5]

#Syhora and Mazac[8a] report the preparation of 1 (X = Cl, R = CH_3CO) by other routes. Syhora, *et al.*,[8b] report also 1, X = Br and F, R = CH_3CO, without constants and 1, X = Cl, R = caproyl (see Experimental Section).

Scheme I



Compound **2** was converted to **3** in *ca.* 60% yield by the oxidative bromination-dehydrobromination technique of Dryden and Kalm using bromine in DMF in the presence of LiBr and Li_2CO_3 at 80°.**

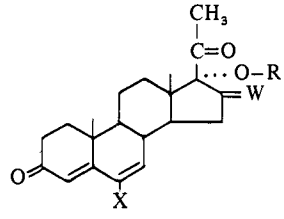
While alkaline hydrogen peroxide will conveniently epoxidize 16-methyl-Δ^{16}-20-keto steroids,†† epoxidation of a Δ^6, in a $\Delta^{4,6}$-3-keto steroid with this reagent, fails. Peracids on the other hand have been reported to epoxidize both classes of unsaturation (for Δ^6 see ref 14a; for Δ^{16} see ref 14b). With *m*-chloroperbenzoic acid, triene **3** was converted directly to the bisepoxide **4a** in 53% yield. In addition, approximately 5% of the 6β,7β-oxide **4b** was also isolated. The assignment of structure to **4a** is consistent with earlier literature on the preferred modes of epoxidation at Δ^6 and Δ^{16} and with the transformation of **4a** into **1** *via* the observed route.‡‡ See also Table II for nmr data of related compounds.

The procedure used was essentially that described by Dryden and Kalm.[12a] Syhora and Mazac[12b] report the preparation of **3 by an alternate route.

††See footnote 2 in ref 1 and also G. Nomine, *et al.*[13]

‡‡In the assignment of structure of the minor product **4b**, we have taken into account the possibilities of 6β,7β-epoxidation (with 16α,17α), 16β,17β-epoxidation (with 6α,7α), and both 6β,7β and 16β,17β simultaneously. The presence of a 16β,17β-epoxide was excluded because the expected chemical shift for the 13-methyl band was not observed (see Table II) when compared to compounds **3**, **7**, **8**, **11**, and particularly **12**. The presence of the 6β,7β-epoxide was suggested by the observed shift in the 10-methyl band following 6,7-epoxidation (*cf.* Laurent, *et al.*,[15] who report a chemical shift for the 10-CH_3 in **9a** as 1.18 ppm and for the 10-CH_3 in **9b** as 1.30 ppm, a difference of 0.12 ppm). The difference between **4a** and **4b** is 0.11 ppm. Also, the pronounced rotational shift for **4b** *vis a vis* **4a** (Experimental Section), is consistent with the shift for **9b** (+85°, $CHCl_3$) (*cf.* Laurent, *et al.*[15]) *vis a vis* **9a** (+160.2°, $CHCl_3$) (kindly supplied by Dr. T. L. Popper of these laboratories).

Table I. Progestational and Antiandrogenic Activities



X	R	W	Progestational,[a] Prog = 1 im	Progestational,[a] Prog = 1 po	Antiandrogenic[b,c] (as % of control)[d] SV	VP	LA
H	Acetyl	CH_2	1		76	81	94
Br	Acetyl	CH_2	42		46	73	89
F	Acetyl	CH_2	55		21	31	26
Cl	Acetyl	CH_2	77	55[f]	36	46	42
Cl	Formyl	CH_2	14.5		36	61	58
Cl	Propionyl	CH_2	14.5		23	49	40
Cl	Butyryl	CH_2	2.4		55	62	37
Cl	Valeryl	CH_2	3.0		103	108	86
Cl	Caproyl	CH_2	3.8		80	81	86
Cl	Heptanoyl	CH_2	0.3		105	100	127
Cl	H	CH_2	1		72	89	69
Cl	Acetyl	H_2[e]	50	13[g]	79	77	84

[a]Progestational activity was determined in immature rabbits by the method of McPhail.[19] Progesterone was administered im. Ref 11 cites the statistical method used to obtain the results presented here. [b]Daily dose, 10 mg/kg for 3 weeks. [c]Male rats (Charles River CD strain) 21–28 days old and weighing approximately 60 g were used to assess the ability of these compounds to inhibit endogenous androgens. The compound was suspended in a carboxymethyl cellulose solution and injected sc each day for 3 weeks. Twenty-four hours following the last drug treatment, the seminal vesicles (SV), ventral prostates (VP), and levator ani (LA) muscle were removed, freed of extraneous tissue, and weighed. [d]Controls taken as 100, with decreasing value signifying greater activity. [e]Chlormadinone. [f]Ref 6a reports a value of 75. [g]Ref 6a reports a value of 37.

Table II. Nmr, δ (ppm) (TMS = 0)

Compound	Solvent	13-CH_3	10-CH_3	16-CH_3	20-CH_3	4-H	6-H	7-H	16=CH_2	16-H
3	$CDCl_3$	1.04	1.14	2.30	2.08	5.69	6.15	6.15		
7	$CDCl_3$	1.05	1.20	1.43	2.21	5.72				
11	$CDCl_3$	1.08	1.20		2.05	5.72				3.72
12	$CDCl_3$	0.97	1.18		2.02	5.72				3.72, d (J = 3 Hz)
8	$CDCl_3$	1.13	1.13	1.49	2.22	5.69	6.10 or 3.46, d ($J_{6,7}$ = 3.5 Hz)	6.12 or 3.28, d of doublets ($J_{6,7}$ = 3.5 Hz; $J_{7,8}$ = 2 Hz)		
4a	$CDCl_3$	1.08	1.08	1.48	2.19	6.10				
4b	$CDCl_3$	1.09	1.19	1.49	2.19	6.15	3.35, d ($J_{6,7}$ = 3.5 Hz)	3.28, d ($J_{6,7}$ = 3.5 Hz)		

Table III

R	Mp, °C	[α]D, deg	λ_{max}, nm	ε	Empirical formula	Microanal.	*m/e*
H	170–172	−42	285	22,200	$C_{22}H_{27}O_3Cl$	C, H, Cl	
Formyl	197–199	−139	284	23,290	$C_{23}H_{27}O_4Cl$		402
Propionyl	156–158	−134	284	22,280	$C_{25}H_{31}O_4Cl$		430
Butyryl	160–162	−132	284	22,830	$C_{26}H_{33}O_4Cl$		444
Valeryl	180–182	−129	284	22,537	$C_{27}H_{35}O_4Cl$		458
Caproyl[a]	128–129	−124	284	22,700	$C_{28}H_{27}O_4Cl$		472
Heptanoyl		−114			$C_{29}H_{39}O_4Cl$		486

[a] Lit.[8b] mp 110–114°; $[\alpha]^{20}D$ −128° ($CHCl_3$).

From earlier work in our laboratories and elsewhere, it was clear that a hydrohalic acid (HF, HCl, HBr) would be expected to open a 6α,7α-epoxide to the 6β-halo-7α-hydroxy product[14a,16] and a 16β-methyl-16α,17α-epoxide to the 16-methylene-17α-hydroxy product.[1,††] With **4a** as anticipated, the two processes occurred simultaneously affording **5** (X = F, Cl, Br). The yield in the most favorable HCl case was 87%. Adventitious water present during the reaction with "anhydrous" HF caused the formation of some 6β,7α-diol **5**, which became the major product when 70% aqueous HF was used as the reagent.

Bisesterification of **5** (X = F, Cl, Br) with the appropriate alkanoic acid, trifluoroacetic anhydride (TFAA), and pTSA[17] afforded the desired 7,17-diesters **6** in good yield. Elimination of the 7-acetate from **6** (X = F, Cl, Br) with hydrogen chloride in chloroform gave **1** (X = F, Cl, Br; R = CH_3CO). The yield was best (80%) when X = Cl. With the 6-bromo compound **6**, a competing reaction was the concerted elimination of bromide from position 6 and acetate from position 7, presumably catalyzed by both Cl^- and H^+, to give **1** (X = H; R = CH_3CO).[18]

In the same way, elimination of higher alkanoate from **6** (*e.g.*, X = Cl; R = $CH_3CH_2CH_2CH_2CO$) with HCl in chloroform afforded the corresponding 6-chloro-6-dehydro-17-ester **1**.

Alternatively, a variety of 17-esters (formate, propionate, butyrate, hexanoate, and heptanoate) were prepared from **1** (X = Cl; R = H) which had been generated by alkaline saponification of **1** (X = Cl; R = CH_3CO). Reesterification was accomplished by exposure to the appropriate acid in the TFAA–pTSA medium (Table III).

Biology. In our hands, the 6-halo-6-dehydro-16-methylene-17-acetoxyprogesterones are among the most potent of all progestational compounds [see Table I; comparison with chlormadinone acetate (**10**)]. In our series progestational activity peaks with the 6-chloro substituent. The optimum acyl function (R) in the 6-chloro series is clearly CH_3CO, activity diminishing rapidly with larger or smaller esterifying groups. Antiandrogenic activity follows progestational activity in a general way, but is more difficult to evaluate other than semiquantitatively.

Generally speaking, potent progestational agents have been found to have useful contraceptive activity at the clinical level. We believe that **1** (X = Cl; R = CH_3CO), because of its structural similarity to chlormadinone acetate and its high progestational potency, will perform as a contraceptive just as chlormadinone acetate has done, and perhaps at a significantly lower dose.

Experimental Section§§

16-Methyl-4,6,16-pregnatriene-3,20-dione (3). To a suspension of 31.5 g of **2** (mp 188°), 95 g of Li_2CO_3, and 63 g of LiBr in 450 ml of DMF was added, with stirring, over a 30-min period, 30.8 g of Br_2 dissolved in 200 ml of dioxane. The reaction mixt was stirred for 2.25 hr at 80°, then cooled to room temp and filtered, and the filtrate added to 6.5 l. of water contg 12 g of $NaHCO_3$ and 12 g of $NaHSO_3$. The resulting yield of ppt of **3** was 28.8 g; analytical sample from Me_2CO–Et_2O; mp 216–218° (lit.[12b] mp 217–218°); $[\alpha]D$ +44.3°; λ_{max} 283 nm (ε 26,200). *Anal.* ($C_{22}H_{28}O_2$) C, H; *m/e* 324.

Preparation of 16β-Methyl-16α,17α-epoxy-4,6-pregnadiene-3,20-dione (8). A mixt of 33.0 g of **7**, 70.3 g of chloranil, and 28.7 g of $CaCO_3$ was refluxed, with stirring, in 1320 ml of *tert*-BuOH for 1 hr. It was then cooled to 25° and filtered, and the filtrate evapd to a residue *in vacuo*. This residue was dissolved in 2 l. of Et_2O–EtOAc

§§ All mps were detd on a Kofler hot stage microscope and are uncorrected. Rotations are in dioxane at 25° at about 1% concn, uv spectra are of MeOH soln, and ir spectra are in Nujol, unless otherwise stated. The nmr spectra were measured on a Varian A-60-A spectrometer in $CDCl_3$ (Me_4Si). Mass spectra were determined on a Varian-Mat CH5 spectrometer using an electron impact source at 70 eV and at 250°. Analyses were determined by the Physical Organic Chemistry Department of Schering Corporation. Where analyses are indicated by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

(1:1), washed with dil NaOH and with water, and then dried to a residue *in vacuo*. The residue, which weighed 23.3 g, was chromatogd on 2 kg of silica gel, eluting with $(CH_3)_2CO$–hexane mixts. Two compds were isolated: the less polar eluted with 15% Me_2CO–85% hexane, weighed 7.7 g, and was 8; the more polar, eluted with 20% Me_2CO–80% hexane, weighed 12.2 g, and was the 16-methylene-17α-hydroxy compd contaminated with Δ^{15}-16-methyl compd. Crystn of 8 from Et_2O gave 6.85 g (20.7%); mp 167–169°; [α]D +90°; λ_{max} 282 nm (ε 27,200); (lit.[11] mp 197–201°). *Anal.* ($C_{22}H_{28}O_3$) C, H.

16β-Methyl-6α,7α:16α,17α-bisoxido-4-pregnene-3,20-dione (4a). A. From 8. To a refluxing soln of 200 g of 8 in 1.5 l. of C_6H_6, was added over 30 min a slurry of 250 g of *m*-chloroperbenzoic acid in 1.25 l. of C_6H_6. The reaction mixt was heated at reflux temp for an addnl 2 hr, then cooled to 30°, dild with Et_2O, and washed with 5% NaOH, then water. The organic layer was sepd, dried over $MgCO_3$, and concd *in vacuo* to a residue. Crystn (Et_2O) gave 4a, 112 g (53.5%).

B. From 3. To a stirred slurry consisting of 4,6,16-pregnatriene-3,20-dione (5 g) and *tert*-BuOH (25 ml) at reflux temp was added 7.98 g of *m*-chloroperbenzoic acid, as a solid in 4 equal portions over a 15-min period. After the addn was complete, the soln was refluxed, with stirring, for 30 min, then cooled to 40°. A 10% aqueous Na_2SO_3 soln was added until excess peracid could not be detected, as detd by testing with starch–iodide paper. The mixt was added to 80 ml of water, and then 50 ml of CH_2Cl_2 was added. The pH of the aqueous layer was adjusted to 11 by addn of aqueous NaOH. The organic layer was sepd and the aqueous layer extd with 20 ml of CH_2Cl_2. The combined exts were washed to neutrality with water and evapd to a residue of 4a. Crystn (CH_2Cl_2–Et_2O) gave 2.8 g of 4a; mp 188–191°; [α]D +88°; λ_{max} 238 nm (ε 15,330). *Anal.* ($C_{22}H_{28}O_4$) C, H; *m/e* 356.

16β-Methyl-6β,7β: 16α,17α-bisoxido-4-pregnene-3,20-dione (4b), From a combined collection of mother liquors of 4a, obtained from 1 kg of **3**, *ca.* 5% of **4b** was isolated; analytical sample (EtOAc), mp 226–227°; [α]D −35°; λ_{max} 243 nm (ε 16,848). *Anal.* ($C_{22}H_{28}O_4$) C, H; *m/e* 356.

6β-Chloro-7α,17α-dihydroxy-16-methylene-4-pregnene-3,20-dione (5, X = Cl). To a soln of 1.2 g of 4a in 21.6 ml of AcOH was added 7.2 ml of an 8% soln of HCl in glacial AcOH (wt/vol). The reaction mixt was stirred at room temp for 6 hr; then the resultant ppt was collected, washed with 50% aqueous AcOH, then water, and air-dried to give **5** (X = Cl), yield 1.15 g (87.1% theory); mp 250°; [α]D −59° (pyridine); λ_{max} 240 nm (ε 13,900); nmr, δ (ppm) DMSO-d_6, 4.90 and 5.08 (16-CH_2). *Anal.* ($C_{22}H_{29}O_4Cl$) Cl.

6β-Chloro-16-methylene-4-pregnene-7α,17α-diol-3,20-dione 7,17-Diacetate (6, X = Cl; R = CH_3CO). To a suspension of 70.0 g of **5** (X = Cl) in 700 ml of glacial AcOH, together with 7.0 g of pTSA·H_2O, at about 15–20° was rapidly added 250 ml of TFAA. The reaction mixt was warmed to room temp and stirred for 3.5 hr. Water was added to afford a ppt. Crystn (EtOAc) gave 55.2 g of **6** (X = Cl); mp 248–250°; [α]D −98°; λ_{max} 238 nm (ε 14,600); nmr, δ (ppm), 5.90 (4-H), 4.47, d (*J* = 2.5 Hz) (6-H), 5.03, t (*J* = 2.25 Hz) (7-H), 5.42 and 5.59 (16-CH_2), 2.04, 2.07 (7- and 17-$OCOCH_3$). *Anal.* ($C_{26}H_{33}O_6Cl$) C, H, Cl; *m/e* 476.

6-Chloro-16-methylene-4-pregnene-7α,17α-diol-3,20-dione 7,17-Divalerate (6, X = Cl; R = $CH_3(CH_2)_3CO$). The use of **5** for the prepn of diesters other than R = CH_3CO is illustrated with the divalerate. Using the procedure described for the prepn of **6** (X = Cl; R = CH_3CO), 1 g of **5** (X = Cl) with 10 ml of valeric acid and 100 mg of pTSA·H_2O gave after silica gel chromatography (Et_2O–hexane elution) 805 mg of the divalerate; mp 88–92°; [α]D −58°; λ_{max} 238 nm (ε 15,764) [with a minor contamination exhibited by λ_{max} 295 nm (ε 1900)]; nmr, δ (ppm), 0.88, t (*J* = 6 Hz) (17-$OCOCH_2(CH_2)_2CH_3$), 4.46, d (*J* = 3 Hz) (6-H), 5.05, broad (7-H), 5.45 and 5.62 (16-CH_2), 5.90 (4-H). *Anal.* ($C_{32}H_{45}O_6$) C, H, Cl; *m/e* 560.

6-Chloro-16-methylene-4,6-pregnadiene-3,20-dione 17-Acetate (1, X = Cl; R = CH_3CO). Dry HCl gas was passed into 760 ml of dry $CHCl_3$, contg 38 g of **6** (X = Cl; R = Ac), at room temp for 1 hr. Stirring was maintained for an addnl 3.5 hr. The product was isolated after water and $NaHCO_3$ washing, concn to low vol, and addn of MeOH, affording 1 (X = Cl; R = CH_3CO); 27,0 g (80%); analytical sample (EtOAc), mp 195–198°; [α] −134°; λ_{max} 285 nm (ε 22,550); nmr, δ (ppm), 0.80 (13-CH_3), 1.18 (10-CH_3), 2.16 (20-CH_3), 6.38 (4-H), 6.35, broad (7-H), 5.53 and 5.66 (16-CH_2), 2.06 (17-$OCOCH_3$) [lit.[8a] mp 198–200°; [α]D −137° ($CHCl_3$), λ_{max} 285 mμ (log e 4.32)]. *Anal.* ($C_{24}H_{29}O_4Cl$) C, H, Cl.

6-Chloro-16-methylene-4,6-pregnadiene-3,20-dione 17-Valerate (1, X = Cl; R = $CH_3(CH_2)_3CO$). In a similar manner to the prepn of 1 (X = Cl; R = CH_3CO) the 7,17-divalerate **6** with HCl gave the corresponding 17-valerate 1. For consts see under General Procedure for 17-ester prepns.

6β-Bromo-16-methylene-4-pregnene-7α,17α-diol-3,20-dione (5, X = Br). To a soln of 10.0 g of **4a** in 112 ml of AcOH was added 8 ml of a 30% soln of HBr in AcOH (wt/vol). The reaction was stirred at 25° for 3 hr, and the solids collected by filtration to yield 4.63 g (37.6%); mp 180° dec; [α]D −43°; [α]D −36° (pyridine); λ_{max} 247 nm (ε 13,470); nmr, δ (ppm), DMSO-d_6, 4.80 (6-H), 3.77 (7-H), 4.91 and 5.10 (16-CH_2). *Anal.* ($C_{22}H_{29}O_4Br$) Br.

6β-Bromo-16-methylene-4-pregnene-7α,17α-diol-3,20-dione 7,17-Diacetate (6, X = Br; R = CH_3CO). To a mixt consisting of 4.50 g of **5** (X = Br), 45 ml of AcOH, and 0.45 g of pTSA·H_2O, at 15°, was added rapidly 18 ml of TFAA. After 3 hr at room temp, water was added. The resulting solids were collected by filtration to afford 5.01 g. Crystn (EtOAc) gave 2.80 g (55.9%) of **6** (X = Br; R = CH_3CO); mp 198° dec; [α]D −76°; λ_{max} 245 mμ (ε 13,600); nmr, δ (ppm), 4.64, d (*J* = 2.5 Hz) (6-H), 5.10, t (*J* = 2 Hz) (7-H), 5.46 and 5.63 (16-CH_2), 2.03, 2.06 (7- and 17-$OCOCH_3$). *Anal.* ($C_{26}H_{39}O_6Br$) C, H, Br.

6-Bromo-16-methylene-17α-hydroxy-4,6-pregnadiene-3,20-dione 17-Acetate (1, X = Br; R = CH_3CO). A soln of 2.36 g of **6** (X = Br; R = CH_3CO) in 24 ml of $CHCl_3$ was satd with anhyd HCl. After 18 hr at 25°, the soln was dild to 200 ml with CH_2Cl_2 and washed with water. The organic phase was evapd *in vacuo* to give a crude product which was chromatogd on 200 g of 100–200 mesh silica gel. Elution with mixt of Et_2O–hexane (3:2 to 7:3) gave 1.59 g, which by bromine analysis contd *ca.* 75% 6-bromo. This was then chromatogd on 200 g of Florisil, again eluting with Et_2O–hexane mixt giving 1.0 g of the 6-bromo, 82.4% by bromine analysis. Two crystns (EtOAc) gave 690 mg of pure 6-bromide; mp 152–154°; [α]D −105°; λ_{max} 286 nm (ε 21,085). *Anal.* ($C_{24}H_{29}O_4Br$) C, H, Br.

The contaminant, present to the extent of 25% in the crude product, was identified after further purification by preparative silica gel tlc ($CHCl_3$–EtOAc, 9:1), as 1 (X = H; R = CH_3CO), by tlc, ir, and nmr, δ (ppm), 5.72 (4-H), 6.15 (6-H), 6.15 (7-H), 5.50 and 5.64 (16-CH_2), 2.05 (17-$OCOCH_3$).

6β-Fluoro-16-methylene-4-pregnene-7α,17α-diol-3,20-dione (5, X = F). To a soln consisting of 10 ml of HF and 20 ml of THF at −20° was added 2 g of **4a**. The reaction was stirred at −20° for 15 min, and then slowly added to a mixt of 45 g of K_2CO_3 and 450 ml of ice water. The resulting mixt was extd with 1.2 l. of CH_2Cl_2. The organic phase afforded, after water washing and evapn, a residue which was sludged with EtOAc, affording 131 mg of **5** (X = F); 6.2%; mp 268–272°; [α]D −68° (pyridine); λ_{max} 235 mμ (ε 11,330); nmr, δ (ppm), DMSO-d_6, 1.20, (*J* = 1 Hz) (10-CH_3). *Anal.* ($C_{22}H_{29}O_4F$) C, H, F.

6β-Fluoro-16-methylene-4-pregnene-7α,17α-diol-3,20-dione 7,17-Diacetate (6, X = F; R = CH_3CO). Following the procedure for the prepn of **6** (X = Cl; R = CH_3CO), 625 mg of **5** (X = F) with 12.6 ml of AcOH, 126 mg of pTSA·H_2O, and 5 ml of TFAA, gave, after crystn (EtOAc), 438 mg (57.2%) of **6** (X = F; R = CH_3CO); mp 258–259°; [α]D −139°; λ_{max} 233 nm (ε 12,890); nmr, δ (ppm), 1.32, d (*J* = 2 Hz), 4.8, d of d ($J_{H,F}$ = 45 Hz; $J_{6,7}$ = 4 Hz) (6-H), 5.10 (7-H), 5.45 and 5.60 (16-CH_2), 2.02, 2.05 (7- and 17-$OCOCH_3$). *Anal.* ($C_{26}H_{33}O_6F$) C, H, F.

6-Fluoro-16-methylene-17α-hydroxy-4,6-pregnadiene-3,20-dione 17-Acetate (1, X = F; R = CH_3CO). A soln of 1.58 g of **6** (X = F; R = CH_3CO) in 32 ml of $CHCl_3$ was satd with dry HCl. After a total of 31 hr at 25°, the reaction was dild to 150 ml with CH_2Cl_2, washed neutral with water, and dried with $MgSO_4$ to afford a residue, which after 2 crystns (MeOH) gave 623 mg (45.5%) of 1 (X = F; R = CH_3CO); mp 234–238°; [α]D −191°; λ_{max} 283 nm (ε 23,790); nmr, δ (ppm), 5.50 and 5.61 (16-CH_2), 5.77 (7-H), 6.08 (4-H). *Anal.* ($C_{24}H_{29}O_4F$) C, H, F.

6β,7α,17α-Trihydroxy-16-methylene-4-pregnene-3,20-dione 6,7,-17-Triacetate (6, X = CH_3COO; R = CH_3CO). A soln of 1.0 g of 4a in 5 ml of DMF was added to 8 ml of 70% aqueous HF at −5°. The mixt was allowed to warm to 25° and remain at room temp for 3 hr, then carefully poured into 200 ml of water which contd 20 g of K_2CO_3. The resulting solids and CH_2Cl_2 extract of the filtrate were concd to a residue which after sludging with EtOAc yielded 390 mg of insoluble compounds. By tlc (silica gel) there appeared to be more 6,7-diol than 6-fluoro-7-ol. The combined mixt (370 mg) was exposed to TFAA, Ac_2O, and pTSA, to give after purification by prep silica gel plate ($CHCl_3$–EtOAc; 3:1) and Et_2O slurry, 114 mg of the triacetate **6**; mp 204–207°; [α]D −67°; λ_{max} 234 nm (ε 13,500); nmr, δ (ppm), 5.27, d (*J* = 3 Hz) (6-H), 4.96, d (*J* = 3 Hz, broadened) (7-H), 5.45 and 5.60 (16-CH_2), 2.02,

2.05, 2.09 (6-, 7-, and 17-$OCOCH_3$). *Anal.* ($C_{28}H_{36}O_8$) *m/e* 500.

General Procedure for the Preparation of 17-Esters of 6-Chloro-16-methylene-4,6-pregnadiene-17α-ol-3,20-dione (1, X = Cl). A soln, or suspension, of 1.0 g of 6-chloro-16-methylene-17α-hydroxy-4,6-pregnadiene-3,20-dione## and 100 mg of pTSA·H_2O in 10 ml of the esterifying acid is prepd and cooled to 15° with stirring. Four ml of TFAA is added as rapidly as possible, but maintaining the temp below 20°. After 30 min the reaction is poured into 100 ml of water and stirred for 30 min. When a ppt results, it is collected by filtration, washed, and dried: 1 (X = Cl; R = CH_3CO and CH_3CH_2CO). When preparing the butyrate, valerate, caproate, and heptanoate, the presence of the excess acid makes it desirable to extract with an organic solvent, wash 1 time with 5% NaOH and 3 times with water (the formate prepn never goes to completion; the reaction is extd as with the higher acids). The dried organic exts are then chromatogd on 100 g of 100–200 mesh silica gel, eluting with Et_2O–hexane. The fractions contg the desired ester (detd by tlc) are combined and crystd (MeOH) to yield the desired product. Yields of esters were: formate, 14%; propionate, 71%; butyrate, 77%; valerate, 82%; caproate, 84%; heptanoate, 64% (Table III).

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References

(1) E. L. Shapiro, T. Legatt, L. Weber, M. Steinberg, A. Watnick, M. Eisler, M. G. Hennessey, C. T. Coniglio, W. Charney, and E. P. Oliveto, *J. Med. Pharm. Chem.*, **5**, 975 (1962).
(2) E. P. Oliveto, R. Rausser, and E. B. Hershberg, U. S. Patent 3,312,692 (April 4, 1967).
(3) S. Rocky and R. Neri, *Fed. Proc., Fed. Amer. Soc. Exp. Biol.*, **27**, 624 (1968).
(4) C. Casmer, F. Fielder and R. Neri, Northeast Conference of Comparative Endocrinology, Boston University, Boston, Mass., 1968.
(5) R. Neri, *Proc. Int. Congr. Horm. Steroids, 3rd*, 1970, 1022 (1971).
(6) (a) Z. Cekan, M. Seda, J. Mikulaskova, and K. Syhora, *Steroids*, 8, 205 (1966); (b) Z. Cekan and O. Horesovsky, *Acta Endocrinol.*, **66**, 317 (1971).
(7) E. L. Shapiro, H. L. Herzog, and L. Weber, U. S. Patent, 3,493,588 (Feb 3, 1970).
(8) (a) K. Syhora and R. Mazac, *Collect. Czech. Chem. Commun.*, **31**, 2768 (1966); (b) K. Syhora, M. Seda, R. Mazac, and Z. Cekan, Czechoslovakian Patent 125,136 (Dec 15, 1967); *Chem. Abstr.*, 69, 97008*u* (1968).
(9) A. Wettstein, *Helv. Chim. Acta*, **27**, 1803 (1944).
(10) (a) K. Syhora, Czechoslovakian Patent 104,667 (Aug 15, 1962); *Chem. Abstr.*, **60**, 8100 (1963); (b) D. N. Kirk, V. Petrow, M. Stansfield, and D. M. Williamson, *J. Chem. Soc.*, 2385 (1960).
(11) E. L. Shapiro, T. L. Popper, L. Weber, R. Neri, and H. L. Herzog, *J. Med. Chem.*, **12**, 631 (1969).
(12) (a) H. L. Dryden and M. J. Kalm, U. S. Patent 3,270,009 (Aug 30, 1966); (b) K. Syhora and R. Mazac, Belgium Patent 664,224 (Sept 16, 1965); *Chem. Abstr.*, **65**, 3943*c* (1966).
(13) G. Nominé, D. Bertini, and A. Pierdet, *Tetrahedron*, 8, 217 (1960).
(14) (a) A. L. Nussbaum, G. Brabazon, T. L. Popper, and E. P. Oliveto, *J. Amer. Chem. Soc.*, **80**, 2722 (1958); (b) D. Taub, R. D. Hoffsommer, and N. L. Wendler, *J. Org. Chem.*, **25**, 2258 (1960); **29**, 3486 (1964).
(15) H. Laurent, G. Schulz, and R. Wiechert, *Chem. Ber.*, 2570 (1969).
(16) K. Brückner, B. Hampel, and U. Johnsen, *ibid.*, 94, 1225 (1961).
(17) E. L. Shapiro, L. Finckenor, H. Pluchet, L. Weber, C. H. Robinson, E. P. Oliveto, H. L. Herzog, I. I. A. Tabachnick, and E. Collins, *Steroids*, 9, 143 (1967).
(18) H. J. Mannhardt, F. v. Werder, K. H. Bork, H. Metz, and K. Brückner, *Tetrahedron Lett.*, **16**, 21 (1960).
(19) M. K. McPhail, *J. Physiol. (London)*, **83**, 145 (1934).

##Obtained by saponification of the 17-acetate with KOH in aqueous MeOH.

1-Phenyl-2-phenethyl-1,2,3,4-tetrahydroisoquinolines. A New Series of Nonsteroidal Female Antifertility Agents

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Upon finding (±)-1-phenyl-2-phenethyl-1,2,3,4-tetrahydroisoquinoline·HCl (1) active as a female antifertility agent in the rat, a series of analogs was synthesized. Whereas 1 and most of its analogs were frank estrogens, four analogs, of which (±,±)-1-{*p*-[2-(1-pyrrolidinyl)ethoxy]phenyl}-2-(β-methylphenethyl)-1,2,3,4-tetrahydroisoquinoline · 2HCl (**62**) was the most active, proved to be impeded estrogens.

The success of various steroids in the control of human reproduction has elicited considerable interest[1] in finding nonsteroidal female antifertility agents. In particular, research has been directed toward reducing or eliminating hormonal side effects; thus far these efforts have not met with success. During a search for a nonsteroidal compound, 1-phenyl-2-phenethyl-1,2,3,4-tetrahydroisoquinoline hydrochloride (**1**) was found to be active in female rats as an antifertility agent. A study was undertaken to improve its activity and lower its estrogenicity.

Chemistry. Two synthetic schemes were used to make the 2-unsubstituted tetrahydroisoquinolines. If a phenethylamine had substituents which activated the position ortho to the ethylamine side chain, the Pictet–Spengler reaction, Scheme I, path A, was used. Trifluoroacetic acid proved to be a much better cyclization catalyst than the usual acids[2] used in this reaction. When there was no activation ortho to the ethylamine, the Bischler–Napieralski reaction, Scheme I, path B, was used. Here the procedure of Cannon and Webster[3] using polyphosphoric acid worked well if there were no methoxy groups in the starting amide. With methoxy groups $POCl_3$ was used in place of polyphosphoric acid. Initially the tetrahydroisoquinolines I were alkylated directly to II but the yields were low. Using the two-step procedure, Scheme I, path D, of acylating with phenylacetyl chloride followed by reduction with BH_3–THF,[4] much better yields were obtained.

The pyrrolidinoethoxy derivatives were prepared *via* Scheme II. A sample of 1-phenyl-1,2,3,4-tetrahydroisoquinoline† was resolved by the method of Leithe[5] and both isomers alkylated by Scheme I, path C. Table I lists the analogs

†Unless otherwise noted, all compounds capable of optical activity are racemic.