[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SYNTEX, S. A.]

Steroids. LXXXII.[1] Synthesis of 4-Halo Hormone Analogs

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4-Chloro and 4-bromo derivatives of testosterone, methyltestosterone, progesterone, desoxycorticosterone, hydrocortisone, and cortisone have been prepared by hydrogen halide opening of the steroidal 4β,5β-oxido-3-keto compounds, in turn obtained by alkaline hydrogen peroxide oxidation of the corresponding hormones. In the case of the cortical series the ketol side chain was protected during epoxidation either by the C-21 dihydropyran adduct or by the C-20 cycloethylene ketal. Molecular rotation differences of some of the α and β epoxides are discussed.

Interest in halogenated steroid hormone analogs has been markedly stimulated by the discovery that certain types of hormonal activity are potentiated by the substitution of halogen for hydrogen at positions C-9,[2] C-12[3], and C-21[4] of the steroid nucleus. The recent report[5] of a facile synthesis of 4-bromo- and 4-chloro-cholestenone by hydrogen halide opening of the epoxide group in 4β, 5β-oxido-coprostanone and concomitant elimination of the resulting C-5 hydroxyl group has prompted us to apply and to extend this reaction[6] to the biologically important testosterone, progesterone, desoxycorticosterone, hydrocortisone, and cortisone series.

Thus, treatment of testosterone (Ia), 17α-methyltestosterone (Ib), and progesterone (IV) with alkaline hydrogen peroxide in methanol[7] gave in each case a crystalline mixture of the corresponding α- and β- C-4,5 epoxides. While isomer separation could be effected, it was advantageous to utilize the only once crystallized epoxidation mixture for the subsequent reaction with hydrogen halide. Epoxide opening was conveniently effected with aqueous hydrochloric or hydrobromic acid in acetone solution at room temperature, leading directly to 4-chloro- and 4-bromo-testosterone (IIIa, IIIb,)-17α-methyltestosterone (IIIc, IIId), and -progesterone (VIa, VIb), the structure of the product being proven in each instance by elemental analysis and the ultraviolet absorption maximum (254–256 mμ for 4-chloro and 260–262 mμ for 4-bromo).[8]

For preparation of the 4,5-epoxides from desoxycorticosterone, hydrocortisone and cortisone it was found expedient to protect the alkali-sensitive ketol side chains with a base-resistant group that would be removed during the acid epoxide openings. Two such reaction schemes were devised and their application to the cortical hormone series is exemplified by the following transformations. Desoxycorticosterone was converted to the C-21-dihydropyran adduct (VIIa) which smoothly underwent epoxidation with alkaline hydrogen peroxide. Treatment of the total epoxide mixture (VIIIa) with hydrogen halide, as described above, followed by acetylation gave 4-chloro- and 4-bromo-desoxycorticosterone acetate (IXa, IXb). Similarly, but with elimination of the acetylation step, hydrocortisone was converted to 4-chlorohydrocortisone (IXc). Finally, cortisone-20-cycloethylene ketal (X)[9] on epoxidation, followed by hydrogen halide treatment in acetone solution, directly yielded 4-chlorocortisone (XII).

Some comment on the configuration and molecular rotation differences of the epoxides obtained is pertinent (Table II). While no particular effort was made to isolate the pure 4β, 5β- and 4α, 5α-oxides, in each series, with the exception of desoxycorticosterone and hydrocortisone, a sample of crude epoxide was crystallized to constant melting point. In the case of 17α-methyltestosterone two isomers were readily isolated by fractional crystallization, one of m.p. 190–194°, $[\alpha]_D$ −88° and the other of m.p. 134–136°, $[\alpha]_D$ +113°. Inspection of molecular rotation data for these compounds and for cholestenone and the known 4β, 5β-oxidocoprostanone allows assignment of the β-configuration to the dextrorotatory isomer and conversely the α-configuration to the levorota-

(1) Paper LXXXI, G. Rosenkranz, O. Mancera, F. Sondheimer, and C. Djerassi, *J. Org. Chem.*, **21**, 520 (1956).

(2) J. Fried and E. Sabo, *J. Am. Chem. Soc.*, **75**, 2273 (1953); **76**, 1455 (1954). J. Fried, J. Herz, E. Sabo, A. Borman, F. Singer, and P. Numerof, *J. Am. Chem. Soc.*, **77**, 1068 (1955); R. F. Hirschmann, R. Miller, R. E. Beyler, L. H. Sarett, and M. Tishler, *J. Am. Chem. Soc.*, **77**, 3166 (1955); J. Fried, K. Florey, E. Sabo, J. Herz, A. Restivo, A. Borman, and F. Singer, *J. Am. Chem. Soc.*, **77**, 4181 (1955).

(3) J. Herz, J. Fried, and E. Sabo, *J. Am. Chem. Soc.*, **78**, 2017 (1956).

(4) Private communication from Dr. E. Jensen of The Ben May Laboratory for Cancer Research.

(5) J. I. Shaw and R. Stevenson, *J. Chem. Soc.*, 3549 (1955).

(6) After completion of our work the synthesis of 4-bromoprogesterone and 4-bromotestosterone propionate, by a different route, was reported by D. N. Kirk, D. K. Patel, and V. Petrow, *J. Chem. Soc.*, 627 (1956).

(7) *Cf.* J. I. Shaw and R. Stevenson, reference 5.

(8) J. I. Shaw and R. Stevenson (reference 5) report $\lambda_{max.}$ 256 mμ for 4-chlorocholestenone and 260 mμ for 4-bromocholestenone. In a study of the effect of bromine substitution on ultraviolet absorption spectra, A. L. Nussbaum, O. Mancera, R. Daniels, G. Rosenkranz, and C. Djerassi [*J. Am. Chem. Soc.*, **73**, 3263 (1951)] estimated $\lambda_{max.}$ *ca.* 265 mμ for 4-bromocholestenone.

(9) R. Antonucci, S. Bernstein, M. Heller, R. Lenhard, R. Littell, and J. H. Williams, *J. Org. Chem.*, **18**, 70 (1953).

TABLE I

CONSTANTS OF 4-HALO HORMONE ANALOGS

Steroid	m.p., °C	$[\alpha]_D$ $CHCl_3$	$\lambda_{max.}$, mμ (95% EtOH)	log ε	Recryst. solvent[a]	Formula	Analyses C Calc'd	C Found	H Calc'd	H Found	Halogen Calc'd	Halogen Found
Testosterone												
4-Chloro	188–190	+148°	256	4.13	A-H	$C_{19}H_{27}ClO_2$	70.68	70.35	8.43	8.29	10.98	11.21
4-Bromo	160	+113°	262	4.10	A-W	$C_{19}H_{27}BrO_2$	62.13	61.96	7.36	7.50	21.76	21.46
17α-Methyl-testosterone												
4-Chloro	142–144	+90°	256	4.12	A-H	$C_{20}H_{29}ClO_2$	71.29	71.58	8.68	8.70	10.52	10.14
4-Bromo	148–151	+87°	262	4.06	A-H	$C_{20}H_{29}BrO_2$	62.98	63.07	7.66	7.79	20.85	21.15
Progesterone												
4-Chloro	219–220	+198°	256	4.15	A	$C_{21}H_{29}ClO_2$	72.28	72.52	8.37	8.44	10.16	10.10
4-Bromo	186–188[b]	+192°[b]	260[b]	4.07[b]	E	$C_{21}H_{29}BrO_2$	64.11	64.33	7.43	7.63	20.31	20.02
Desoxycorticosterone Acetate												
4-Chloro	178–179	+177°	256	4.12	A-H	$C_{23}H_{31}ClO_4$	67.88	67.81	7.68	7.99	8.71	8.63
4-Bromo	180–181	+183	260	4.08	A-H	$C_{23}H_{31}BrO_4$	61.19	61.22	6.92	7.10	17.70	17.83
Hydrocortisone												
4-Chloro	225–227		254	4.12	C-M	$C_{21}H_{29}ClO_5$	63.55	63.37	7.31	7.19	8.95	8.73
Cortisone												
4-Chloro	210–212		254	4.11	A	$C_{21}H_{27}ClO_5$	63.88	64.15	6.90	6.92	8.98	8.80

[a] A = acetone, C = chloroform, E = ether, H = hexane, M = methanol, W = water. [b] Reported, Ref. 6, m.p. 192–193°, $[\alpha]_D$ +185°, $\lambda_{max.}$ 261 mμ, log ε 4.07.

tory compound. The epoxide obtained from testosterone, m.p. 157–158°, $[\alpha]_D$ +136° may likewise be assigned the β-configuration while the constant melting product of 122–124°, $[\alpha]_D$ +157°, obtained in the progesterone case appears to be a mixture of isomers with the β form predominating. The pure isomer, m.p. 235–237°, $[\alpha]_D$ −13° derived from the crystallization of epoxidized cortisone ketal is undoubtedly the α-epoxide. The purified 4α,5α-epoxides did not lead to the 4-halo unsaturated ketones on treatment with hydrogen halide, and thus, in the mixtures of epoxides utilized only the β-epoxides served as a source of 4-halo hormones.

In the castrate immature rat, 4-chlorotestosterone exhibited approximately 50% of the androgenic activity of testosterone while the 4-bromo derivative showed a much lower order of activity. In the ovariectomized rabbit, 4-bromo- and 4-chloro-progesterone possessed only slight progestational activity. The biological activity of the other 4-halo hormone analogs will be published elsewhere.

TABLE II

MOLECULAR ROTATION DIFFERENCES OF 3-KETO-4,5-EPOXIDO STEROIDS

Substance	$[M]_D$	ΔM_D (Parent Compound)
Cholestenone[a]	+342	
4β,5β-Oxidocoprostanone	+528	+186
Testosterone[b]	+312	
4β,5β-Oxidoetiocholan-17β-ol-3-one	+450	+138
17α-Methyltestosterone[c]	+231	
4β,5β-Oxido-17α-methyletiocholan-17β-ol-3-one	+362	+131
4α,5α-Oxido-17α-methylandrostan-17β-ol-3-one	−278	−509
Progesterone[d]	+634	
Mixture of 4β,5β- and 4α,5α-Oxidopregnane-3,20-dione	+543	−91
Cortisone 20-cycloethylene ketal[e]	+623	
4α,5α-Oxidopregnane-17α,21-diol-3,11,20-trione 20-cycloethylene ketal	−46	−669

[a] Butenandt and Wolff, *Ber.*, **68**, 2091 (1935). [b] David, Dingemanse, Freud, and Laquer, *Z. physiol. Chem.*, **233**, 281 (1935). [c] Ruzicka, Goldberg, and Rosenberg, *Helv. Chim. Acta*, **18**, 1487 (1935). [d] Butenandt and Schmidt, *Ber.*, **67**, 2088 (1934). [e] Reference 9.

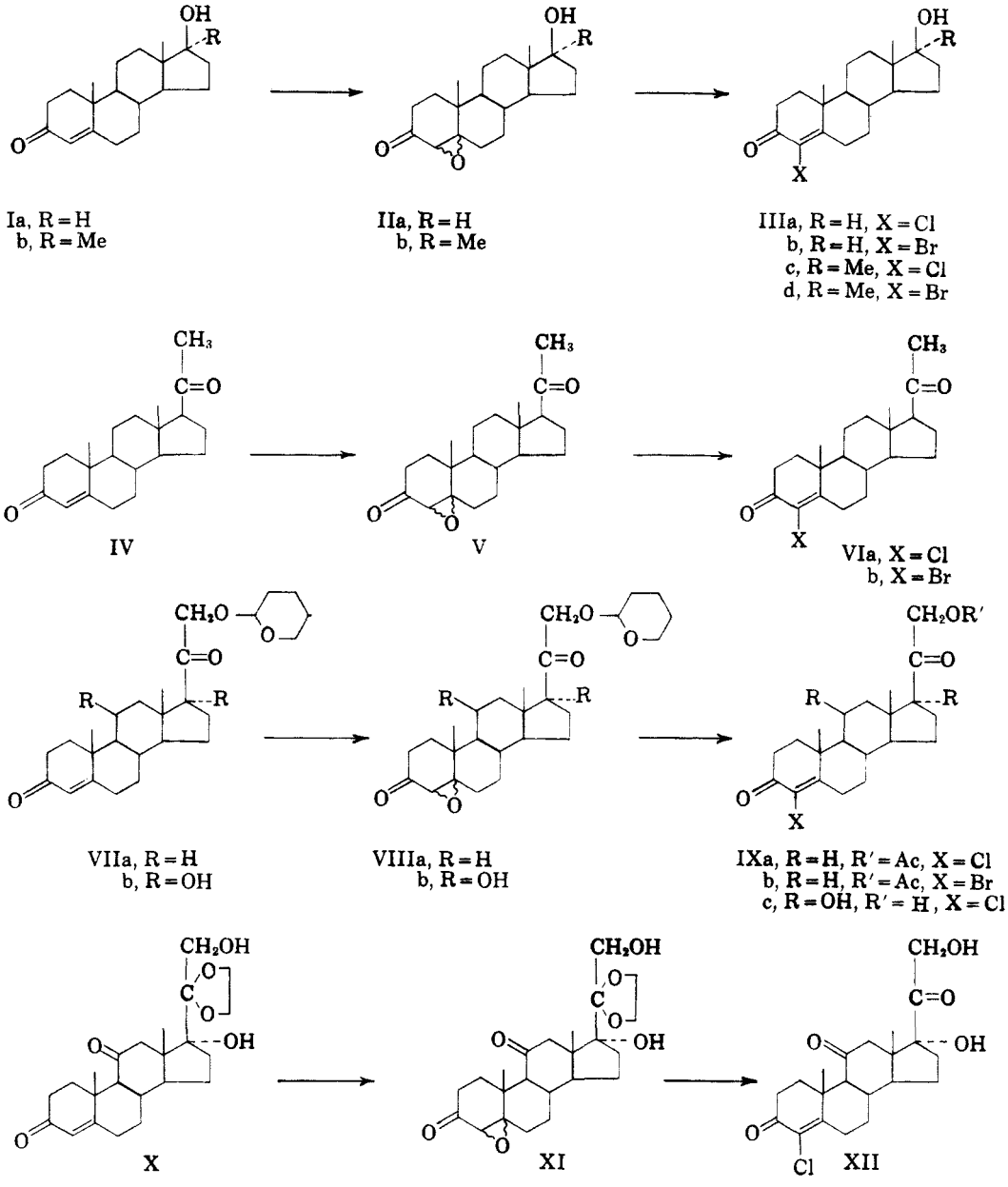
EXPERIMENTAL[10]

4ξ,5ξ-Oxidoandrostan-17β-ol-3-one (IIa). A solution of 10 g. of testosterone (Ia) in 300 cc. of methanol was cooled to 0° and treated successively with 60 cc. of cold Perhydrol (30% H_2O_2) and 20 cc. of cold aqueous 10% sodium hydroxide. After standing for 48 hours at 0° the solution was poured into water, and the resultant oil was extracted with methylene dichloride and crystallized from acetone–hexane, yielding 8.5 g. (81%) of a mixture of epoxides (IIa), m.p. 138–150°, which was utilized without further purification for the preparation of the 4-halotestosterones. A sample crystallized from ether to constant melting point gave the pure 4β,5β-isomer, m.p. 157–158°, $[\alpha]_D$ +136°, no high selective ultraviolet absorption.

Anal. Calc'd for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 74.97; H, 9.37.

4-Chlorotestosterone (IIIa). The epoxide mixture (IIa) (1 g.) in 10 cc. of acetone was treated with 1 cc. of 37% hydrochloric acid for 30 minutes at room temperature, water then was added to turbidity, and the mixture was chilled

(10) Melting points are uncorrected. Rotations were determined, at 20°, in chloroform and ultraviolet absorption spectra in 95% ethanol solution.



and the crystalline 4-chlorotestosterone (IIIa) collected. Yield, 0.9 g. (85%), m.p. 184–186°.

4-Bromotestosterone (IIIb). Substitution of 30% aqueous hydrobromic acid for hydrochloric acid gave 0.52 g. (43%) of 4-bromotestosterone (IIIb), m.p. 150°.

4ξ,5ξ-Oxido-17α-methylandrostan-17β-ol-3-one (IIb). Treatment of 10 g. of 17α-methyltestosterone (Ib) exactly as in the preparation of IIa, gave, after crystallization from acetone–hexane, 7.4 g. (71%) of epoxide mixture (IIb), m.p. 122–130°. Fractional crystallization from acetone gave the pure α-epoxide, m.p. 190–194°, $[\alpha]_D$ −88°.

Anal. Calc'd for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.21; H, 10.07, while from the mother liquors, the 4β,5β-epoxide of m.p. 134–136°, $[\alpha]_D$ +113° was obtained.

Anal. Calc'd for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.17; H, 9.87.

4-Chloro-17α-methyltestosterone (IIIc). Reaction of 1 g. of epoxide mixture (IIb) as described above for IIIa gave, after acetone–water crystallization of the crude product, 0.8 g. (76%) of 4-chloro-17α-methyltestosterone (IIIc), m.p. 140–142°.

4-Bromo-17α-methyltestosterone (IIId). One gram of epoxide mixture treated as above (see IIIb) yielded, after acetone–hexane recrystallization, 0.5 g. (42%) of IIId, m.p. 142–147°.

4ξ,5ξ-Oxidopregnane-3,20-dione (V). Progesterone (10 g.) processed exactly as in IIa furnished 8.8 g. (84%) of epoxide mixture (V), m.p. 116–120°. A sample thrice crystallized from acetone–hexane melted at 122–124°, $[\alpha]_D$ +157° and apparently was still a mixture of the two isomers (see Table II and discussion).

Anal. Calc'd for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.14; H, 9.03.

4-Chloroprogesterone (VIa). Treatment of crude epoxide (V) (1 g.) in the described manner and recrystallization of the total product from acetone gave 0.62 g. (59%) of 4-chloroprogesterone (VIa), m.p. 214–217°.

4-Bromoprogesterone (VIb). Reaction of 1 g. of V as above and ether crystallization of the crude product gave 0.49 g. (41%) of 4-bromoprogesterone (VIb), m.p. 180–182°.

4-Chlorodesoxycorticosterone acetate (IXa). Desoxycorticosterone (5.0 g.) was dissolved in 100 cc. of benzene and 10 cc. of dihydropyran and a few cc. of the solution was distilled to remove moisture. *p*-Toluenesulfonic acid hydrate

(200 mg.) was added to the cooled solution which then was allowed to stand at room temperature for 20 hours, at which time the triphenyltetrazolium test[11] was negative. The mixture was poured into saturated bicarbonate solution, and the organic phase was separated, washed with water, and evaporated to dryness *in vacuo*, yielding the 21-dihydropyran adduct of desoxycorticosterone (VIIa)[12] as an oil. Treatment of VIIa with Perhydrol, as in the other series, gave the noncrystalline epoxide(s) (VIIIa) which, after a 30 minute reaction with 5 cc. of concentrated hydrochloric acid in 75 cc. of acetone, acetylation of the total crude 4-chloro compound with acetic anhydride–pyridine (25 cc., 25 cc., 15 hours, 25°) and chromatographic separation on neutral alumina, gave, in the hexane–benzene fractions, 0.91 g. (15%) of 4-chlorodesoxycorticosterone acetate (IXa), m.p. 178–179°.

4-Bromodesoxycorticosterone acetate (IXb). Substitution of 30% hydrobromic acid for hydrochloric acid in the above reaction sequence furnished 4-bromodesoxycorticosterone acetate (IXb), m.p. 180–181°.

4-Chlorohydrocortisone (IXc). Treatment of hydrocortisone, as above, with (1) dihydropyran, (2) Perhydrol, and (3) hydrochloric acid–acetone, followed by silica gel chromatography of the total crude reaction product, furnished, in the ethyl acetate–chloroform fractions, 4-chlorohydrocortisone (IXc), m.p. 225–227°.

4-Chlorocortisone (XII). Cortisone 20-cycloethylene ketal (X)[9] was epoxidized in the usual manner, yielding a mixture of epoxides (XI) from which one crystalline isomer, the 4α,-5α, m.p. 235–237°, $[\alpha]_D$ −13° could be readily separated by acetone crystallization.

Anal. Calc'd for $C_{23}H_{32}O_7$: C, 65.69; H, 7.67. Found: C, 65.63; H, 7.62.

Treatment of the mixture (XI) with hydrochloric acid–acetone followed by partial dilution with water and 4-hour repose at room temperature to allow complete hydrolysis of the ketal moiety, and finally chromatographic purification of the product on silica gel, led to 4-chlorocortisone (XII), m.p. 210–212°.

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(11) R. B. Burton, A. Zaffaroni, and E. H. Keutmann, *J. Biol. Chem.*, **188**, 763 (1951).

(12) Since addition of dihydropyran would be expected to lead to two isomers, no purification of the reaction product was attempted. A. C. Ott, M. F. Murray, and R. L. Pederson, (*J. Am. Chem. Soc.*, **74**, 1239 (1952)) reported the isolation in 37% yield of an apparently homogeneous isomer, m.p. 108–111°.