247. *Modified Steroid Hormones. Part III.* Some 4-Chloro-3-oxo-Δ⁴-derivatives.*

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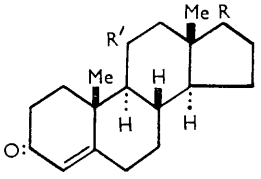
Chlorination of some 3-oxo-Δ⁴-steroids (I) in ether–propionic acid leads to the formation of 4ξ : 5ξ-dichlorides (II), which pass readily under the influence of basic reagents into the corresponding 4-chloro-3-oxo-Δ⁴-steroids (III). The latter may also be obtained directly from the ketones (I) by chlorination in the presence of proton acceptors such as pyridine, dimethylformamide, and ethylene or propylene oxide.

When our studies of the halogenation of steroid hormones began (1954), bromination of 3-oxo-Δ⁴-steroids in ether–acetic acid was known to occur by allylic substitution.[1] On bromination in the presence of proton acceptors, however, we observed formation of 4-bromo-3-oxo-Δ⁴-steroids (see Part I [2]). Concurrent studies on the chlorination of 3-oxo-Δ⁴-steroids (I) are now reported.

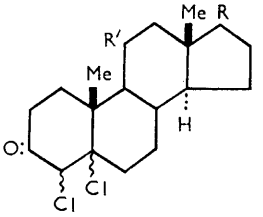


(I)

(*a*) R =  , R′ = H₂.

(*b*) R =  , R′ = H₂.

(*c*) R = :O, R′ = H₂.



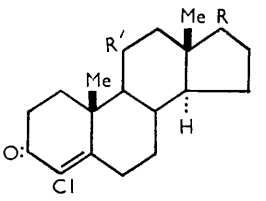
(II)

(*d*) R =  , R′ = H₂.

(*e*) R = , R′ = H₂.

(*f*) R =  , R′ =  .

(*j*) R =  , R′ = H₂.



(III)

(*g*) R = , R′ = H₂.

(*h*) R = , R′ = :O.

(*i*) R = , R′ = :O.

Chlorination of cholest-4-en-3-one (I*a*) in ether–propionic acid led to a dichloride, $C_{27}H_{44}OCl_2$, spectroscopically transparent from 220 to 300 mμ and hence formulated as 4ξ : 5ξ-dichlorocholestan-3-one (II*a*). Reaction of this compound with basic reagents such as pyridine led to formation of a new αβ-unsaturated ketonic product, $C_{27}H_{43}OCl$, which differed from the known 2- and 6-chlorocholest-4-en-3-one [3,4] and is consequently assigned the constitution 4-chlorocholest-4-en-3-one (III*a*).[5] This structure is established by (i) the ultraviolet absorption which reaches a maximum at 256 mμ [α-chlorination of an αβ-unsaturated ketone ($\lambda_{max.}$ 240 mμ) is known [3] to result in a bathochromic shift of the absorption maximum of *ca.* 16 mμ (cf. also Part I [2])], and (ii) its reaction with *o*-phenylenediamine in acetic acid solution to give the quinoxaline derivative [6] of cholestane-3 : 4-dione. Extension of the reaction to the steroid hormones (I*b*—*i*) led to the formation of the corresponding chlorides (II), severally converted into the 4-chloro-hormones (III*b*—*i*).

* Part II, preceding paper.

[1] Djerassi, Rosenkranz, Romo, Kaufmann, and Pataki, *J. Amer. Chem. Soc.*, 1950, **72**, 4534.
[2] Part I, *J.*, 1956, 627.
[3] Ellis and Petrow, *J.*, 1953, 3869.
[4] Barton and Miller, *J. Amer. Chem. Soc.*, 1950, **72**, 370.
[5] Cf. the preparation of 4-bromotestosterone reported by Bremer, Congress Handbook, XIVth Internat. Congr. Pure and Applied Chemistry, p. 162. This abstract became available after completion of our work.
[6] Butenandt, Schramm, Wolff, and Kudszus, *Ber.*, 1936, **69**, 2779; Inhoffen, *ibid.*, 1937, **70**, 1695.

The facility with which the dichloro-compounds (II) pass into the monochloro-compounds (III) led us to examine the chlorination of the unsaturated ketones (I) in the presence of proton acceptors such as pyridine, dimethylformamide, and ethylene and propylene oxide. In parallel with results recorded in Part I [2] on the bromination of 3-oxo-Δ^4-steroids, chlorination gave the 4-chloro-hormones in good yields. As the 4ξ : 5ξ-dichlorides (II) proved stable to dimethylformamide and ethylene and propylene oxide, the reaction under these experimental conditions evidently proceeds by direct substitution and not by an addition-dehydrochlorination mechanism.

Experimental

Ultraviolet absorption spectra were kindly determined by Mr. M. T. Davies, B.Sc. (figures in parentheses are log ε). Optical rotations were measured for $CHCl_3$ solutions in a 1 dm. tube.

Preparation of 4ξ : 5ξ-*Dichlorides* (II).—The steroid, dissolved in *ca.* 50 vols. ether and/or dioxan, was treated at 0° to −30° with chlorine in propionic acid (1·05—1·1 mols. of *ca.* M-solution), and the cooled mixture stored in the dark for *ca.* 12—16 hr., then poured into water, and the product isolated with ether and purified by crystallisation.

Preparation of 4-*Chloro*-3-*oxo*-Δ^4-*derivatives* (III).—(*a*) The 4ξ : 5ξ-dichloride (II) was dissolved in pyridine by gentle warming and the solution kept at room temperature for several hr. The product was isolated with ether, the ethereal solution washed with dilute hydrochloric acid and with water, and dried, and the solvent removed. The 4-chloro-steroid was purified by crystallisation.

(*b*) The steroid, dissolved in ethylene oxide (or propylene oxide) (*ca.* 10 vols.) and ether and/or dioxan (10—15 vols.), was treated at 0 to −30° with chlorine in propionic acid (1·05—1·1 mols. of *ca.* M-solution). After being kept in the dark for some hours the mixture was poured into water, and the 4-chloro-steroid isolated with ether and purified by crystallisation.

(*c*) As (*b*), but with a solution of the steroid in dimethylformamide.

(*d*) As (*b*), but with a solution of the steroid in pyridine.

4ξ : 5ξ-*Dichlorocholestan*-3-*one* (II*a*) crystallised from ether–methanol (1 : 4) in thick needles, m. p. 120—122°, $[\alpha]_D^{18}$ −4° (*c*, 0·46) (Found : C, 71·3; H, 9·7; Cl, 15·7. $C_{27}H_{44}OCl_2$ requires C, 71·2; H, 9·7; Cl, 15·6%).

4-*Chlorocholest*-4-*en*-3-*one* (III*a*) separated from ether–methanol (1 : 2) in needles, m. p. 126—127, $\lambda_{max.}$ 256 mμ (4·15) (in propan-2-ol), $[\alpha]_D^{20}$ +106° (*c*, 0·492) (Found : C, 77·8; H, 10·2; Cl, 8·6. $C_{27}H_{43}OCl$ requires C, 77·4; H, 10·3; Cl, 8·5%).

The quinoxaline derivative was prepared by heating the foregoing compound (500 mg.) with *o*-phenylenediamine (125 mg.) in acetic acid (5 ml.) under reflux for 2 hr., after which methanol (5 ml.) was added and the solution allowed to crystallise overnight at 0°. The derivative formed pale brown plates, m. p. 205—207°, $\lambda_{max.}$ 239 (4·48) and 321 mμ (4·00) (in EtOH) (Found : N, 6·0. Calc. for $C_{33}H_{48}N_2$: N, 5·9%), after crystallisation from ethyl acetate. The m. p. was not depressed in admixture with an authentic specimen.[6]

4ξ : 5ξ-*Dichloro*-4 : 5-*dihydrotestosterone propionate* (II*b*) formed needles, m. p. 143—144°, $[\alpha]_D^{24}$ −22° (*c*, 0·47) (Found : C, 63·5; H, 8·1; Cl, 16·8. $C_{22}H_{32}O_3Cl_2$ requires C, 63·5; H, 7·8; Cl, 17·1%), after crystallisation from methanol.

4-*Chlorotestosterone propionate* (III*b*) formed needles, m. p. 164°, $\lambda_{max.}$ 254 mμ (4·12) (in propan-2-ol), $[\alpha]_D^{22}$ +114° (*c*, 0·4) (Found : C, 69·8; H, 8·2; Cl, 9·1. $C_{22}H_{31}O_3Cl$ requires C, 69·8; H, 8·3; Cl, 9·4%), after crystallisation from methanol.

4ξ : 5ξ-*Dichloroandrostane*-3 : 17-*dione* (II*c*) separated from methylene chloride–methanol in plates, m. p. 187—188°, $[\alpha]_D^{25}$ +40° (*c*, 0·511) (Found : C, 63·4; H, 7·3; Cl, 20·2. $C_{19}H_{26}O_2Cl_2$ requires C, 63·8; H, 7·3; Cl, 19·8%).

4-*Chloroandrost*-4-*ene*-3 : 17-*dione* (III*c*) formed crystals, m. p. 180—182°, $\lambda_{max.}$ 254—255 mμ (4·19) (in propan-2-ol), $[\alpha]_D^{24}$ +206° (*c*, 0·42) (Found : C, 70·6; H, 7·8; Cl, 11·5. $C_{19}H_{25}O_2Cl$ requires C, 71·1; H, 7·9; Cl, 11·1%), after crystallisation from methanol.

4ξ : 5ξ-*Dichloro*-4 : 5-*dihydro*-17α-*methyltestosterone* (II*d*) crystallised from methanol in needles, m. p. 167°, $[\alpha]_D^{23}$ −26° (*c*, 0·409) (Found : C, 63·3; H, 8·2; Cl, 19·2. $C_{20}H_{30}O_2Cl_2$ requires C, 64·3; H, 8·0; Cl, 19·0%).

4-*Chloro*-17α-*methyltestosterone* (III*d*), crystallised from acetone–hexane, had m. p. 142—143°, $[\alpha]_D^{23}$ +99° (*c*, 0·387), $\lambda_{max.}$ 255—256 mμ (4·14) (in propan-2-ol) (Found : C, 71·1; H, 8·9; Cl, 10·7. $C_{20}H_{29}O_2Cl$ requires C, 71·3; H, 8·7; Cl, 10·5%).

4ξ : 5ξ-*Dichloro*-4 : 5-*dihydroprogesterone* (II*e*) formed needles, m. p. 172—174°, $[\alpha]_D^{25}$ +46°

(*c*, 0·354) (Found : C, 65·1; H, 8·1; Cl, 18·4. $C_{21}H_{30}O_2Cl_2$ requires C, 65·4; H, 7·8; Cl, 18·4%), after crystallisation from methylene chloride–methanol.

4-*Chloroprogesterone* (III*e*) separated from methanol in rods, m. p. 218—220·5°, $\lambda_{max.}$ 255 mμ (4·125) (in propan-2-ol), $[\alpha]_D^{25}$ +198° (*c*, 0·569) (Found : C, 71·8; H, 8·3; Cl, 10·8. $C_{21}H_{29}O_2Cl$ requires C, 72·3; H, 8·4; Cl, 10·2%).

4ξ : 5ξ-*Dichloro*-11α-*hydroxypregnane*-3 : 20-*dione* (II*f*) crystallised from aqueous acetone in needles, m. p. 174—175°, $[\alpha]_D^{24}$ +25° (*c*, 0·459) (Found : C, 63·0; H, 7·7; Cl, 17·8. $C_{21}H_{30}O_3Cl_2$ requires C, 62·9; H, 7·5; Cl, 17·7%).

4-*Chloro*-11α-*hydroxypregn*-4-*ene*-3 : 20-*dione* (III*f*) formed needles, m. p. 181—183°, $\lambda_{max.}$ 256 mμ (4·12) (in propan-2-ol), $[\alpha]_D^{24}$ +163° (*c*, 0·637) (Found : C, 68·7; H, 7·7; Cl, 10·3. $C_{21}H_{29}O_3Cl$ requires C, 69·0; H, 8·0; Cl, 9·7%).

4ξ : 5ξ-*Dichloro*-21-*acetoxypregnane*-3 : 20-*dione* (II*g*) separated from methylene chloride–methanol (1 : 4) in needles, m. p. 185—186°, $[\alpha]_D^{24}$ +55° (*c*, 0·717) (Found : C, 62·1; H, 7·3; Cl, 16·3. $C_{23}H_{32}O_4Cl_2$ requires C, 62·3; H, 7·3; Cl, 16·0%).

21-*Acetoxy*-4-*chloropregn*-4-*ene*-3 : 20-*dione* (III*g*) crystallised from methylene chloride–methanol (1 : 10) in needles, m. p. 183—184°, $\lambda_{max.}$ 255 mμ (4·12) (in EtOH), $[\alpha]_D^{24}$ +191° (*c*, 0·662) (Found : C, 67·4; H, 7·8; Cl, 8·6. $C_{23}H_{31}O_4Cl$ requires C, 67·9; H, 7·7; Cl, 8·7%).

4ξ : 5ξ-*Dichloropregnane*-3 : 11 : 20-*trione* (II*h*) crystallised from methylene chloride–methanol as needles, m. p. 189—190°, $[\alpha]_D^{25}$ +48° (*c*, 0·605) (Found : C, 62·8; H, 6·9; Cl, 18·4. $C_{21}H_{28}O_3Cl_2$ requires C, 63·2; H, 7·1; Cl, 17·8%).

4-*Chloropregn*-4-*ene*-3 : 11 : 20-*trione* (III*h*) separated from methylene chloride–methanol (1 : 10) in needles, m. p. 198—200°, $\lambda_{max.}$ 257 mμ (4·12) (in EtOH), $[\alpha]_D^{24}$ +275° (*c*, 0·654) (Found : C, 69·8; H, 7·8; Cl, 9·6. $C_{21}H_{17}O_3Cl$ requires C, 69·5; H, 7·5; Cl, 9·8%).

4ξ : 5ξ-*Dichloro*-4 : 5-*dihydrocortisone acetate* (II*i*) had m. p. 235—236° (decomp.), $[\alpha]_D^{24}$ +57° (*c*, 0·211 in dioxan) (Found : C, 58·1; H, 6·6; Cl, 14·9. $C_{23}H_{30}O_6Cl_2$ requires C, 58·3; H, 6·4; Cl, 15·0%), after purification from acetone–ether.

4-*Chlorocortisone acetate* (III*i*) separated from acetone–hexane (1 : 3) in plates, m. p. 232—234° (decomp.), $\lambda_{max.}$ 253 mμ (4·11) (in EtOH), $[\alpha]_D^{24}$ +214° (*c*, 0·202 in dioxan) (Found : C, 63·8; H, 7·1; Cl, 7·8. $C_{23}H_{39}O_6Cl$ requires C, 63·2; H, 6·7; Cl, 8·1%).

4-*Chloro*-17α-*hydroxypregn*-4-*ene*-3 : 20-*dione* (III*j*) separated from methylene chloride–methanol (1 : 10) in needles, m. p. 216—218°, $\lambda_{max.}$ 255 mμ (4·12) (in EtOH), $[\alpha]_D^{25}$ +102° (*c*, 0·98) (Found : C, 68·9; H, 8·3; Cl, 10·2. $C_{21}H_{29}O_3Cl$ requires C, 69·0; H, 8·0; Cl, 9·7%).

The authors thank the directors of the British Drug Houses Ltd. for permission to publish this work.

Chemical Research Laboratories,
The British Drug Houses Ltd., London, N.1. [*Received, October 6th,* 1955.]