tallization from dilute methanol; yield 0.78 g., m.p. 160–162°. The analytical sample was obtained from dilute acetone as needles with m.p. 161–162°, $[\alpha]^{22}D$ −124°, $\lambda_{max}^{CHCl_3}$ 2.80 and 5.90 μ.

Anal. Calcd. for $C_{27}H_{42}O_4$: C, 75.30; H, 9.83. Found: C, 75.18; H, 9.94.

The stability of the hydrogenation product was demonstrated when 150 mg. of VIIa was refluxed with 12 g. of potassium hydroxide, 10 cc. of water and 65 cc. of methanol for 2 hours. Dilution with water and one recrystallization from dilute alcohol furnished 130 mg. of crystals with m.p. 158–161°, which after one additional recrystallization was raised to m.p. 161–162°, undepressed on admixture with the starting material. The same results were obtained when sodium ethoxide in ethanol was used.

Propionylation of VIIIa in the usual manner followed by recrystallization from dilute methanol afforded the **propionate VIIIb** with m.p. 196–198°, $[\alpha]^{22}D$ −119°.

Anal. Calcd. for $C_{30}H_{46}O_5$: C, 74.03; H, 9.53. Found: C, 74.32; H, 9.60.

In order to determine whether there exists a difference in the rate of hydrogenation of the Δ^8-11-ketone depending upon the configuration at C-14, a sample of the 14-iso propionate IVb was hydrogenated with the same catalyst and solvent simultaneously with the above described hydrogenation of the 14-"normal" propionate IIIb. In contrast to the latter which was reduced to the extent of *ca.* 90% after 20 hours, the former had undergone only about 20% hydrogenation during the same period.

22a-5α-14-Iso(β)-spirostan-3β-ol-11-one (VIIa)[19].—A suspension of 0.44 g. of the Δ^8-14-iso propionate IVb in 20 cc. of ether was added in one portion with stirring to a solution of 20 mg. of lithium metal in 80 cc. of liquid ammonia. After disappearance of the blue color (less than 10 minutes), an additional 10 mg. of lithium was added and after 30 minutes, the excess metal was decomposed by the addition of a few drops of *t*-butyl alcohol followed by 0.5 g. of ammonium chloride. The ammonia was evaporated and 10 cc. of ethanol and 2 cc. of water were added to the residue and the mixture was allowed to stand at room temperature for 12 hours in order to complete the saponification of the propionate. The ethanol was removed under reduced pressure, the remainder was extracted with chloroform, washed well with water, dried and evaporated. Measurement of the ultraviolet absorption spectrum of the residue (0.42 g.) indicated the presence of less than 5% of unreduced starting material. For effective purification, it was necessary to chromatograph this material on 15 g. of alumina (activity II[18]); elution with benzene–ether (1:1) afforded 0.2 g. of colorless crystals of VIIa with m.p. 231–234°. The analytical sample was recrystallized once from dilute methanol and twice from ligroin and finally sublimed at 150° and 0.008 mm.; m.p. 234.5–235.5°, $[\alpha]^{22}D$ −3.3°, $\lambda_{max}^{CHCl_3}$ 2.78 and 5.88 μ.

Anal. Calcd. for $C_{27}H_{42}O_4$: C, 75.30; H, 9.83. Found: C, 74.91; H, 9.94.

The **propionate** VIIb after recrystallization from dilute methanol and sublimation at 180° and 0.008 mm. exhibited m.p. 238–239°, $[\alpha]^{22}D$ −4.6°, $\lambda_{max}^{CHCl_3}$ 5.80 and 5.88 μ.

Anal. Calcd. for $C_{30}H_{46}O_5$: C, 74.03; H, 9.53. Found: C, 74.35; H, 9.59.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE UNIVERSITY AND THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Synthesis and Reactions of Chlorinated 3-Ketosteroids

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Chlorination of 3-ketoallosteroids by means of chlorine, sulfuryl chloride, pyridine perchloride hydrochloride or most advantageously *t*-butyl hypochlorite leads to the corresponding 2-chloro-3-ketones which can also be synthesized in one step from 3β-hydroxyallosteroids by simultaneous oxidation and chlorination. The position of the chlorine atom was proved by dehydrochlorination with 2,4-dinitrophenylhydrazine and by conversion *via* the pyridinium salt to the known nitrone. Evidence has also been adduced that the 2-chlorine atom possesses the α-configuration. Similar chlorination of 3-ketosteroids of the "5β" configuration produced the 4-chloroketones. A number of reactions of steroidal chloro ketones has been studied and compared with those of the brominated analogs.

4-Bromo-3-ketosteroids have proved to be of considerable importance[4] in the synthesis of Δ^4-3-ketosteroids and estrogens, while 2-iodoketones of the allo (5α) series represent the key intermediates[5] in the elaboration of the important Δ^4-keto moiety from allo ketones. Since bromo- and iodoketones differ markedly in some of their reactions, it appeared of interest to extend this work to the previously unknown chloro-3-ketosteroids and such an investigation was started at Wayne University (J.J.B. and C.D.). Independently, a study was undertaken at Harvard (D.G. and L.F.F.) to see if certain reactions of *t*-butyl hypochlorite reported in another connection[6] would be applicable to steroids, for example, to the chlorination of 3-ketosteroids.[7] Learning of each other's activities, we decided to complete the work in a joint investigation, which is reported in this paper.

The initial study of chlorination conditions was carried out with cholestane-3-one (Ia). Chlorine gas in carbon tetrachloride solution affords the 2-chloro derivative IIa in 35% yield while sulfuryl chloride under free radical conditions produces IIa in slightly higher yield; pyridine perchloride hydrochloride gives essentially the same results. *t*-Butyl hypochlorite proved to be the reagent of choice since in acetic acid solution up to 90% of 2-chlorocholestanone (IIa) can be isolated. Cholestane-3-one (Ia) itself is usually prepared by oxidation[8] of cholestane-3β-ol with sodium dichromate or chromic anhydride, but *t*-butyl hypochlorite is equally efficacious. It was thus found

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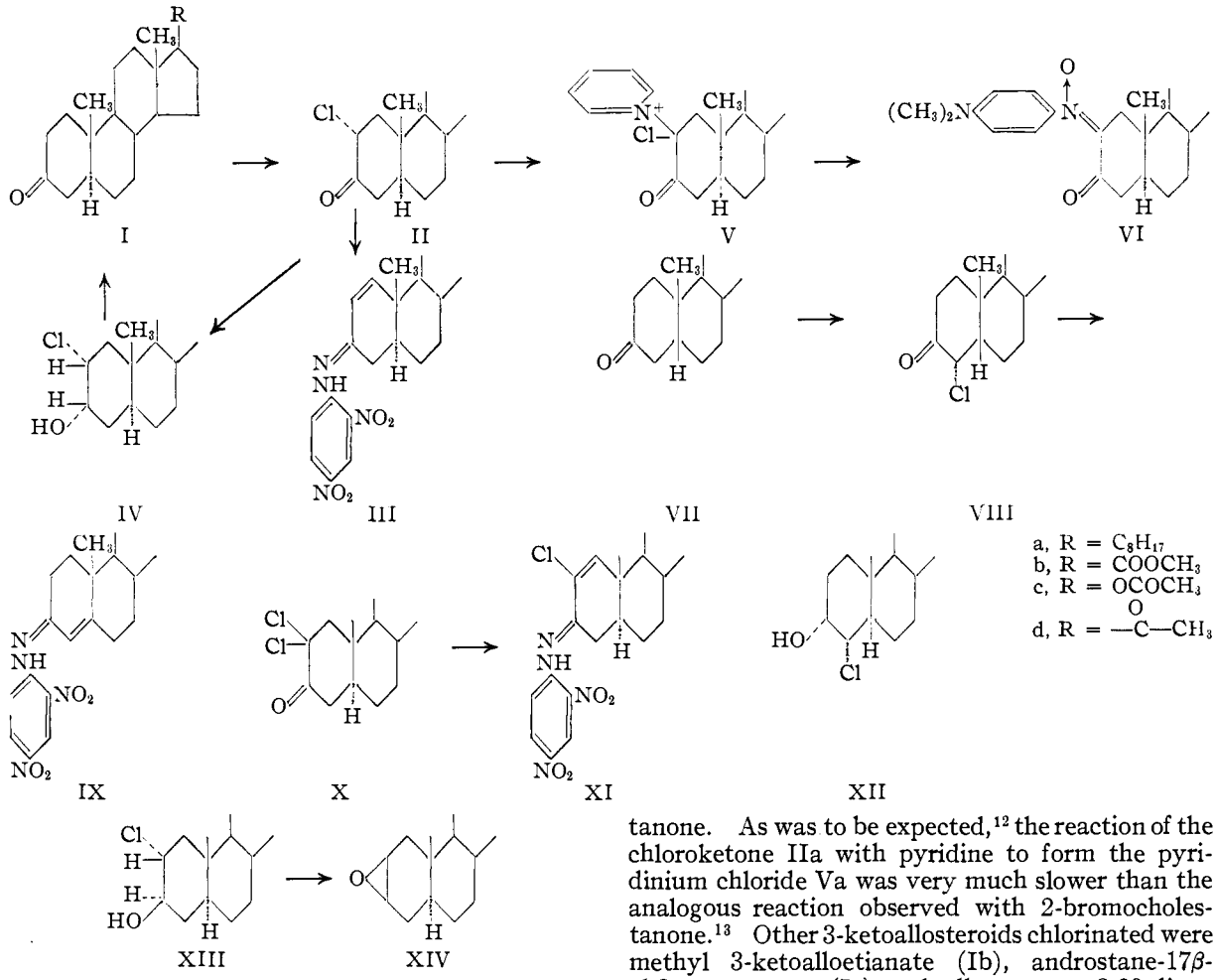
(4) See C. Djerassi, THIS JOURNAL, **71**, 1003 (1949) for leading references.

(5) G. Rosenkranz, C. Djerassi, *et al.*, *ibid.*, **72**, 1046, 4077, 4081 (1950); *Nature*, **168**, 28 (1951).

(6) J. J. Ritter and D. Ginsburg, THIS JOURNAL, **72**, 2381 (1950); D. Ginsburg, *ibid.*, **73**, 702, 2723 (1951); *Experientia*, **7**, 95 (1951).

(7) *Cf.* D. Ginsburg, *Bull. Res. Council Israel*, in press.

(8) W. F. Bruce, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., p. 139, and references cited therein.



possible to combine the steps of oxidation and chlorination and to convert cholestane-3β-ol directly into 2-chorocholestanone (IIa). One of the by-products in the *t*-butyl hypochlorite chlorination is a dichloro derivative which is assigned the 2,2-dichloro structure Xa because it exhibits the typical high positive rotation characteristic[9] of 2,2-dibromosteroids and loses only one chlorine atom upon treatment with 2,4-dinitrophenylhydrazine.[4] The ultraviolet absorption spectrum of the resulting Δ^1-2-chlorocholestene-3-one 2,4-dinitrophenylhydrazone (XIa) is identical with that of the corresponding bromo analog.[10]

The position of the chlorine atom in 2-chlorocholestanone (IIa) was established by two independent methods. Dehydrochlorination with 2,4-dinitrophenylhydrazine proceeds at essentially the same rate as the corresponding reaction[4] with 2-bromocholestanone and yields the known Δ^1-cholestene-3-one 2,4-dinitrophenylhydrazone IIIa in high yield. Alternately, 2-chlorocholestanone (IIa) was converted to the corresponding pyridinium salt Va, which upon treatment with *p*-nitrosodimethylaniline affords cholestane-3-one-2-(*p*-dimethylaminophenyl)-nitrone (VIa), identical with a sample prepared[11] from 2-bromocholestanone. As was to be expected,[12] the reaction of the chloroketone IIa with pyridine to form the pyridinium chloride Va was very much slower than the analogous reaction observed with 2-bromocholestanone.[13] Other 3-ketoallosteroids chlorinated were methyl 3-ketoalloetianate (Ib), androstane-17β-ol-3-one acetate (Ic) and allopregnane-3,20-dione (Id). In the first instance, the position of the chlorine atom in IIb was demonstrated by conversion to the known[4] methyl Δ^1-3-ketoalloetienate 2,4-dinitrophenylhydrazone (IIIb), while in the other two cases (IIc and IId) it was assumed by analogy.

Recently,[14] there was described a method for the determination of the configuration of bromine substituents in 3-ketosteroids and it was demonstrated[14b,c] that the bromine atom in 2-bromocholestanone has the α-configuration. Application of this procedure to 2-chlorocholestanone (IIa) has now shown that a similar situation exists in this instance. Thus, sodium borohydride reduction of IIa leads to a mixture of chlorohydrins, which is readily separable by chromatography on alumina. The initially eluted material gives no precipitate with digitonin and is thus assigned the 3α-configuration (IVa); from the later chromatogram fractions, there is obtained an isomer which produces an immediate precipitate with digitonin and which, therefore, is considered to be the 3β-epimer XIIIa. Treatment of the chlorohydrin IVa with base leads

(9) C. Djerassi and C. R. Scholz, THIS JOURNAL, **69**, 2404 (1947); *J. Org. Chem.*, **12**, 823 (1947); *ibid.*, **13**, 697 (1948).

(10) C. Djerassi and E. Ryan, THIS JOURNAL, **71**, 1000 (1949).

(11) L. Ruzicka, P. A. Plattner and M. Furrer, *Helv. Chim. Acta*, **27**, 524 (1944).

(12) *Cf.* R. G. Pearson, S. H. Langer, F. V. Williams and W. J. McGuire, THIS JOURNAL, **74**, 5130 (1952).

(13) L. Ruzicka, P. A. Plattner and R. Aeschbacher, *Helv. Chim. Acta*, **21**, 866 (1938).

(14a) L. F. Fieser and R. Ettore, THIS JOURNAL, **75**, 1700 (1953); (b) E. J. Corey, *ibid.*, in press; (c) L. F. Fieser and W. Y. Huang, *ibid.*, in press.

to cholestane-3-one (Ia), while a similar reaction with the isomer XIIIa yields 2β,3β-oxidocholestane (XIVa). On the justified assumption of a *trans* elimination mechanism, this would indicate the 2α-configuration for the chlorine atom in the chlorohydrins IVa and XIIIa and, *ipso facto*, in 2-chlorocholestanone (IIa). In contrast to the work of Fieser and Huang[14c] where the configuration of the hydroxyl groups of the intermediate bromohydrins was proved rigorously by catalytic debromination to cholestane-3β-ol and cholestane-3α-ol, it was not possible in our case to effect dechlorination. Nevertheless, the assigned configurations of the 3-hydroxyl groups in IVa and XIIIa (and hence of the chlorine atom) are fairly secure because they rest not only upon analogy to the bromine series[14b,c] and the characteristic behavior with digitonin, but also upon the order of elution in the chromatogram. Thus, chromatography of the *free* chlorohydrins yields first the *cis* chlorohydrin IVa followed by the *trans* epimer XIIIa while chromatography of the *acetates* results in exactly the reverse order of elution. Precisely the same observation has been made[14a] in the methyl 4-bromo-3-ketocholanate series. Finally, it should be noted that the infrared carbonyl band of the chloro ketone IIa as compared to cholestanone (Ia) is shifted toward higher frequency to exactly the same extent as has been observed[15] with the corresponding bromo compounds.

A number of reactions was carried out with 2-chlorocholestane-3-one (IIa) in order to compare it with the 2-bromo and 2-iodo analogs. Thus, refluxing of 2-bromocholestanone[9,15a] with γ-collidine for one hour results in complete *dehydrobromination* while similar treatment of 2-iodocholestanone[5] causes *deiodination*. 2-Chlorocholestanone (IIb), however, is recovered essentially unchanged after two hours and even after four hours only *ca.* 25% of collidine hydrochloride is isolated. A similar sluggishness was mentioned above in the reaction with pyridine which yields some recovered starting material (in addition to Va) after 16 hours, while the formation of cholestane-3-one pyridinium bromide is complete in less than two hours.[13] 2-Iodocholestanone is very readily reduced[5] with chromous chloride to cholestanone (Ia) and a similar behavior has now been noticed with the 2-bromo analog, but the 2-chloro derivative IIa is recovered to a large extent. The chlorine atom can be removed, however, with activated zinc and acetic acid. Finally, we examined the reaction of 2-chlorocholestanone (IIa) with sodium iodide in acetone solution, since in the case of the 2-bromo analog[5] quantitative interchange occurs after six hours of refluxing. Under these conditions, all of the chloro compound is recovered and it is necessary to carry out the reaction in methyl ethyl ketone solution for 20 hours before interchange could be effected. These results indicate a very considerable difference in reactivity between the chloro and bromo 3-ketosteroids which could make the use of mixed chloro–bromo or chloro–iodo ketones of interest in certain syntheses. Such a study is now in progress.

Representative 5β-ketones selected for study were coprostane-3-one (VIIa) and testane-17β-ol-3-one acetate (VIIc), which upon treatment with *t*-butyl hypochlorite yield the 4-chloro derivatives VIIIa and VIIIc, the structure of which was proved in the first instance by dehydrochlorination with 2,4-dinitrophenylhydrazine to the 2,4-dinitrophenylhydrazone of Δ^4-cholestene-3-one (IXa) and in the second case by dehydrochlorination with γ-collidine and subsequent formation of the 2,4-dinitrophenylhydrazone of testosterone acetate (IXa) and comparison with authentic samples.

The procedure applied above for the determination of configuration of the chlorine atom in 2-chlorocholestanone was used also in the case of 4-chlorotestane-17β-ol-3-one acetate. Reduction with sodium borohydride yields an apparently homogeneous chlorohydrin XIIc which does not give a precipitate with digitonin. Treatment of the chlorohydrin XIIc with base leads to a product which, after acetylation, is identical with testane-17β-ol-3-one acetate indicating that the 4-chlorine atom is *cis* with respect to the 3-hydroxyl group. The latter fact coupled with the observation that the chloroketone VIIIc may be dehydrochlorinated with collidine with the isolation of *ca.* 50% of the theoretical quantity of collidine hydrochloride would seem to indicate the 3α,4α-configuration in the chlorohydrin XIIc and the 4α-configuration in the chloroketone VIIIc. These assignments are only tentative since it was not found possible to effect dehalogenation[14] in order to establish rigorously the configuration of the hydroxyl group.

It should be noted, however, that in contrast to the analogous configurations obtaining in the cases of 2-chloro- and 2-bromocholestanone, there is a difference in configuration of the 4-halogen atom in the testane-17β-ol-3-one acetate series since the 4β-bromo configuration has been demonstrated[14c] in the corresponding bromoketone. Whether this difference can be attributed to the smaller size of the chlorine atom and hence ability to enter at the α-side remains to be seen and this point is being investigated further.

Experimental[16]

Cholestane-3-one (Ia).—To a solution of 5.0 g. of cholestane-3β-ol[17] in 250 cc. of carbon tetrachloride was added dropwise 3.0 g. of *t*-butyl hypochlorite[18] in 25 cc. of the same solvent. After stirring at room temperature for 4 hr. the solution was washed until neutral, dried and evaporated to give 4.8 g. of colorless solid, m.p. 122–124°. One recrystallization from ethanol furnished 3.82 g. of pure cholestane-3-one (Ia), m.p. 128–129°.

2-Chlorocholestane-3-one (IIa). (a) With Chlorine Gas.—An ice-cold solution of 15.0 g. of cholestanone (Ia) in 500 cc. of carbon tetrachloride was treated dropwise with stirring with 3.1 g. of liquid chlorine in 100 cc. of carbon tetrachloride and stirring was continued at 0° for 4 hr. Evaporation to dryness *in vacuo* and crystallization of the residue

(15) R. N. Jones, D. A. Ramsay, F. Herling and K. Dobriner, THIS JOURNAL, **74**, 2828 (1952).

(15a) A. Butenandt, L. Mamoli, H. Dannenberg, L. Masch and J. Paland, *Ber.*, **72**, 1617 (1939)

(16) Melting points are uncorrected. Rotations were determined *ca.* 10 mg. in 2 cc. of chloroform in 1-dm. tubes. Infrared spectra were measured on a Baird Associates recording spectrometer in chloroform solution in a 0.1-mm. sodium chloride cell.

(17) We are indebted to Drs. E. P. Oliveto and E. B. Hershberg, Schering Corporation, for supplying some of this material.

(18) H. M. Teeter and E. W. Bell, *Org. Syntheses*, **32**, 20 (1952).

from chloroform–ethanol afforded 5.70 g. (35%) of colorless crystals, m.p. 171–174°. The mother liquors, though crystalline, melted over a wide range and did not yield any additional 2-chlorocholestanone even after chromatography on alumina. Further recrystallization of the first crop furnished the analytical sample of IIa as long, colorless needles, m.p. 178–179°, $[\alpha]^{22}D$ +52°, $\lambda_{max}^{CHCl_3}$ 5.76 μ.

Anal. Calcd. for $C_{27}H_{45}OCl$: C, 77.01; H, 10.77; Cl, 8.42. Found: C, 76.83; H, 10.65; Cl, 8.10.

(b) **With Sulfuryl Chloride.**—A mixture of 5.0 g. of cholestanone, 1.27 cc. of redistilled sulfuryl chloride, 10 mg. of benzoyl peroxide and 300 cc. of carbon tetrachloride was refluxed for 12 hr. After washing with dilute bicarbonate solution and water, the solvent was removed *in vacuo* and the residue was recrystallized twice from chloroform–ethanol; yield 2.2 g., m.p. 176–178°.

(c) **With Pyridine Perchloride-Hydrochloride.**—Chlorine gas was passed with continuous stirring for two hours through 25 g. of molten pyridine hydrochloride at 90°. The resulting solid[19] was washed well with ether and 4.0 g. of it dissolved in 50 cc. of glacial acetic acid was added to a solution of 6.13 g. of cholestanone in 25 cc. of glacial acetic acid. After stirring at 25° for two hours, the precipitate was collected, washed well with water and dried; yield 3.2 g., m.p. 164–168°. Dilution of the filtrate with water and filtration yielded 3.1 g. of slightly impure, recovered, cholestanone, m.p. 125–128°. Two recrystallizations of the first crop from chloroform–ethanol gave 2.18 g. (32%) of 2-chlorocholestanone, m.p. 174–177°.

(d) **With *t*-Butyl Hypochlorite.**—A warm (65°) solution of 1.9 g. of cholestanone in 20 cc. of glacial acetic acid was treated with one portion of 0.6 cc. of *t*-butyl hypochlorite and warmed on the steam-bath for one hour. After standing overnight the solution was concentrated to about one-third of its volume. After cooling and filtering, 1.89 g. (90%) of pure 2-chlorocholestanone, m.p. 178–179°, was obtained.

(e) **From Cholestane-3β-ol with *t*-Butyl Hypochlorite.**—A warm (65°) solution of 5.0 g. of cholestanol in 150 cc. of glacial acetic acid was treated rapidly with 3.08 cc. (2.1 mole) of *t*-butyl hypochlorite and then heated at 70° for two hours. After cooling to slightly below room temperature and filtering, 2.43 g. (45%) of essentially pure 2-chlorocholestanone (IIa) was obtained with m.p. 177–179°. Chromatography of the mother liquors on 65 g. of silica gel (Fisher, 30–200 mesh) and elution with petroleum ether–benzene (40:60) afforded 0.6 g. of oily material. Elution with petroleum ether–benzene (50:50) gave an additional 5% of IIa while the subsequent fractions eluted with benzene melted below 170° and were not further characterized. The 0.6 g. of oily material eluted first crystallized readily from hexane and after two additional recrystallizations yielded 0.3 g. of colorless crystals of **2,2-dichlorocholestane-3-one (Xa)**, m.p. 145–146°, $[\alpha]^{22}D$ +111°, $\lambda_{max}^{CHCl_3}$ 5.78 μ.[20]

Anal. Calcd. for $C_{27}H_{44}OCl_2$: C, 71.18; H, 9.74; Cl, 15.57. Found: C, 71.16; H, 9.59; Cl, 15.64.

Reaction of 2-Chlorocholestane-3-one (IIa) with 2,4-Dinitrophenylhydrazine.—To a hot solution of 0.5 g. of IIa in 20 cc. of glacial acetic acid was added 0.26 g. of 2,4-dinitrophenylhydrazine in 5 cc. of acetic acid. After refluxing for three minutes in an atmosphere of nitrogen, the mixture was cooled and the dark orange precipitate was collected; yield 0.57 g., m.p. 220–222°, undepressed upon admixture with an authentic specimen of **Δ^1-cholestene-3-one 2,4-dinitrophenylhydrazone (IIIa)**, $\lambda_{max}^{CHCl_3}$ 382 mμ, log ϵ 4.45. The infrared spectra of the two samples were identical.

Reaction of 2,2-Dichlorocholestane-3-one (Xa) with 2,4-Dinitrophenylhydrazine.—Thirty milligrams of the 2,2-dichloro derivative Xa in 3 cc. of glacial acetic acid was treated with 17 mg. of 2,4-dinitrophenylhydrazine for three minutes at 100° under nitrogen; yield 29 mg. of orange blades of **Δ^1-2-chlorocholestene-3-one 2,4-dinitrophenylhydrazone (XIa)**, m.p. 273–275°, $\lambda_{max}^{CHCl_3}$ 374 mμ, log ϵ 4.50; reported[10] for the Δ^1-2-bromo analog: $\lambda_{max}^{CHCl_3}$ 375 mμ, log ϵ 4.48.

Anal. Calcd. for $C_{33}H_{47}O_4ClN_4$: C, 66.15; H, 7.91; Cl, 5.92. Found: C, 65.77; H, 8.07; Cl, 6.03.

Cholestane-3-one Pyridinium Chloride (Va).—2-Chlorocholestane-3-one (2.39 g., m.p. 174–176°) was refluxed with 15 cc. of dry pyridine for six hours and filtered, yielding 0.74 g. of pyridinium chloride Va with m.p. 300° (dec.). The filtrate was refluxed for an additional 10 hours, whereupon filtration furnished 0.62 g. of Va of equal purity. Dilution with water, extraction with ether, washing until neutral, evaporation and recrystallization from chloroform–ethanol gave 0.57 g. of recovered chloroketone IIa with m.p. 175–178°.

A sample of the pyridinium salt Va was recrystallized from ethanol whereupon it exhibited m.p. 303–305° (dec.), 308–312° (Kofler).

Anal. Calcd. for $C_{32}H_{50}OClN$: C, 76.84; H, 10.08; N, 2.80; Cl, 7.09. Found: C, 76.72; H, 10.37; N, 2.62; Cl, 6.75.

Cholestane-3-one-2-(*p*-dimethylaminophenyl)-nitrone (VIa).—The above pyridinium chloride Va (0.3 g.) in 10 cc. of chloroform and 10 cc. of ethanol was mixed at 0° with 0.59 cc. of 1 *N* sodium hydroxide solution and 0.09 g. of freshly prepared *p*-nitrosodimethylaniline and the mixture was allowed to warm to room temperature over a period of one hour while stirring. Concentration *in vacuo* followed by filtration and recrystallization from hexane–acetone afforded 0.2 g. of bright orange, glistening plates of the nitrone VIa, m.p. 184–185°, undepressed on admixture with a sample (m.p. 183–185°) prepared from 2-bromocholestenone[11]; $\lambda_{max}^{CHCl_3}$ 6.00 μ.

Sodium Borohydride Reduction of 2-Chlorocholestane-3-one.—A suspension of 6.7 g. of 2-chlorocholestanone (IIa) in 350 cc. of ethanol was stirred with 1.21 g. of sodium borohydride for 14 hours at which time a clear solution resulted. After dilution with water and standing for 4 hours, the precipitate (no infrared carbonyl band) was filtered and chromatographed in petroleum ether-benzene (8:2) solution on 170 g. of unwashed alumina. Elution with petroleum ether-benzene (1:1) yielded 2.26 g. of solid which after recrystallization from ether-methanol furnished 1.88 g. of **2α-chlorocholestane-3α-ol** (IVa) with m.p. 120–122° (cor.), $[\alpha]^{29}D$ +32°; the product gave no precipitate with digitonin after standing for 24 hours.

Anal. Calcd. for $C_{27}H_{47}OCl$: C, 76.64; H, 11.20. Found: C, 76.63; H, 11.23.

Acetylation with acetic anhydride-pyridine in the usual manner led in nearly quantitative yield to an acetate with m.p. 192–192.5° (cor.) which proved to be identical (mixture melting point, infrared comparison) with the analytical sample described below.

Further development of the chromatogram yielded an intermediate semisolid fraction and elution with benzene-ether (8:2) furnished 2.66 g. of colorless solid with m.p. 108–112°. Recrystallization of this material from ether-methanol gave 2.43 g. of **2α-chlorocholestane-3β-ol** (XIIIa) with m.p. 119–119.5° (cor.), $[\alpha]^{29}D$ +15°, which gave an immediate precipitate (comparable to cholestane-3β-ol used as standard) when a solution of 10 mg. in 3 cc. of ethanol was treated with 1 cc. of a 1% ethanolic solution of digitonin.

Anal. Found: C, 76.45; H, 11.04.

Acetylation furnished an acetate with m.p. 121–122°, which was shown by direct comparison (including infrared spectrum) to be identical with the analytical sample described below.

In another experiment, 6.18 g. of 2-chlorocholestanone (IIa) was reduced with sodium borohydride and the entire crude reduction mixture was acetylated and chromatographed in petroleum ether solution on 300 g. of acid-washed alumina. An effective separation was accomplished by development with forty-five 100-cc. fractions of petroleum ether-benzene (1:1). Combination of fractions 25–29 and recrystallization from acetone-methylene chloride furnished 1.8 g. of **2α-chlorocholestane-3β-ol acetate**, m.p. 120–121° (cor.), $[\alpha]^{29}D$ +4.5°, which proved to be identical with the acetylation product of the digitonin-positive chlorohydrin (XIIIa) described above.

Anal. Calcd. for $C_{29}H_{49}O_2Cl$: C, 74.88; H, 10.62. Found: C, 74.69; H, 10.63.

Recrystallization of fractions 32–40 with the same solvent pair yielded 1.2 g. of **2α-chlorocholestane-3α-ol acetate**,

(19) S. M. McElvain and M. A. Goese, THIS JOURNAL, **65**, 2227 (1943).

(20) This is in agreement with the observation of R. N. Jones, P. Humphries and K. Dobriner (*ibid.*, **72**, 956 (1950)) that introduction of a second halogen atom into the *gem* position has no effect on the wave length of the infrared carbonyl band.

m.p. 193.5–194° (cor.), $[\alpha]^{29}D$ +59°, which was identical with the acetylation product of the above described digitonin-negative chlorohydrin (IVa).

Anal. Found: C, 75.05; H, 10.64.

Conversion of 2α-Chlorocholestane-3β-ol (XIIIa) to 2β,3β-Oxidocholestane (XIV).—A solution of 0.5 g. of the acetate of XIIIa (the free chlorohydrin was equally satisfactory) and 1 g. of potassium hydroxide in 45 cc. of ethanol was refluxed for 12 hours. The crude product, obtained on dilution and ether extraction, showed no infrared carbonyl band and on chromatographic purification yielded 91 mg. of 2β,3β-oxidocholestane (XIVa) with m.p. 87–89°, $[\alpha]^{29}D$ +58°; the product showed no infrared carbonyl or hydroxyl bands.

Conversion of 2α-Chlorocholestane-3α-ol (IVa) to Cholestanone (Ia).—The alkali treatment of 500 mg. of the acetate of IVa was carried out exactly as described above and on dilution with water led to a crude product with an infrared carbonyl band at 5.88 μ of an intensity comparable to that of the C–H band at 3.4 μ. Purification in the usual manner gave 2.16 mg. of cholestanone (Ia) (m.p. 127–129°) which was identified by direct comparison (mixture melting point and infrared absorption spectrum) with an authentic specimen.

Reactions of 2-Chlorocholestanone (IIa). (a) With Collidine.—When 0.18 g. of IIa was refluxed for two hours with 5 cc. of freshly distilled collidine, no collidine hydrochloride could be isolated and extraction with ether, washing with dilute acid, drying and evaporation gave 0.178 g. with m.p. 163–166°. One recrystallization from chloroform–ethanol raised the m.p. to 177–178° (0.16 g.) undepressed upon admixture with the original starting material. When the reflux period was doubled, 24% of collidine hydrochloride was isolated and over 50% of the starting material (m.p. 178–179°) could be recovered.

(b) With Chromous Chloride.—For comparison purposes, 0.2 g. of 2-bromocholestanone in 50 cc. of acetone was treated for 30 minutes in an atmosphere of carbon dioxide with 5 cc. of a chromous chloride solution prepared[21] from 5 g. of chromic chloride. Dilution with water and filtration produced 0.16 g. (85%) of cholestanone with m.p. 128–129°. A similar reaction with 2-chlorocholestanone resulted in a 50% recovery of the chloroketone with m.p. 175–177°. The remainder of the material was a mixture melting between 135–160°.

(c) With Zinc.—A mixture of 0.257 g. of IIa, 2 g. of activated zinc[22] and 25 cc. of glacial acetic acid was refluxed for 10 hours. After filtration of the zinc, the filtrate was diluted with water and the precipitate collected; yield 0.225 g., m.p. 120–123°. One recrystallization from ethanol raised the m.p. to 127–128°, undepressed upon admixture with cholestane-3-one (Ia).

When IIa was refluxed for 12 hr. with ordinary zinc dust in a mixture of dioxane and ethanol, 66% of pure chloroketone IIa was recovered.

(d) With Sodium Iodide.—Refluxing of IIa for 6 hr. with an equal weight of sodium iodide in acetone solution resulted in 95% recovery of unchanged chloroketone; under the same conditions, 2-bromocholestanone was converted[5] in 90% yield to the 2-iodo derivative. The iodide interchange could, however, be effected when IIa was refluxed in ethyl methyl ketone solution for 20 hr. whereupon the theoretical amount of sodium chloride was isolated. The identity of the 2-iodocholestanone thus obtained was established by mixed m.p. and infrared spectra comparison with an authentic specimen.[5]

Methyl 2-Chloro-3-ketoalloetianate (IIb).—Since this substance and the succeeding two (IIc, IId) were appreciably more soluble than 2-chlorocholestanone, the chlorination was carried out in more concentrated solution in order to make possible the separation of some pure chloroketone by direct crystallization from the reaction medium.

A solution of 0.7 g. of the ketone Ib in 10 cc. of glacial acetic acid was warmed for three hours with 3 cc. of an acetic acid solution of *t*-butyl hypochlorite (2.0 g. in 25 cc.). After 12 hr. at room temperature, the volume was reduced to 3 cc. and the resulting precipitate was filtered; yield 0.42 g., m.p. 197–200°. The analytical sample crystallized from chloroform–ethanol as needles with m.p. 212–213°, $[\alpha]D$ +96°.

Anal. Calcd. for $C_{21}H_{31}O_3Cl$: C, 68.74; H, 8.52; Cl, 9.66. Found: C, 68.85; H, 8.74; Cl, 10.04.

A sample of IIb (25 mg.) on treatment with 2,4-dinitrophenylhydrazine in the usual manner afforded 31 mg. of methyl Δ^1-3-ketoalloetienate 2,4-dinitrophenylhydrazone (IIIb) with m.p. 272–273°, which gave no depression when mixed with an authentic specimen.[4]

2-Chloroandrostane-17β-ol-3-one Acetate (IIc).—The chlorination was performed exactly as above, except that the recrystallization was carried out from acetone–hexane solution; m.p. 185–187°, $[\alpha]^{22}D$ +37°.

Anal. Calcd. for $C_{21}H_{31}O_3Cl$: C, 68.74; H, 8.52; Cl, 9.66. Found: C, 68.84; H, 8.45; Cl, 9.51.

2-Chloroallopregnane-3,20-dione (IId).—Chlorination as described for IIb produced 0.4 g. of IId with m.p. 222–224° by direct crystallization from glacial acetic acid. Two recrystallizations from chloroform–ethanol gave the analytical sample, m.p. 228–229°, $[\alpha]^{22}D$ +137°.

Anal. Calcd. for $C_{21}H_{31}O_2Cl$: C, 71.87; H, 8.91; Cl, 10.11. Found: C, 72.03; H, 9.19; Cl, 9.87.

4-Chlorotestane-17β-ol-3-one Acetate.—To a warm (65°) solution of 1.8 g. of testane-17β-ol-3-one acetate in 20 cc. of glacial acetic acid was added 0.6 cc. of *t*-butyl hypochlorite. The solution was warmed on the steam-bath for two hours. Upon cooling, 1.65 g. (83%) of 4-chlorotestane-17β-ol-3-one acetate, m.p. 211–212°, was obtained, $[\alpha]^{21}D$ +18.4°, $\lambda_{max}^{CHCl_3}$ 5.82 μ. The chlorine substituent shifts the carbonyl band to the same position of absorption as the acetate.

Anal. Calcd. for $C_{21}H_{31}O_3Cl$: C, 68.74; H, 8.51; Cl, 9.66. Found: C, 68.68; H, 8.37; Cl, 9.78.

4-Chlorotestane-3,17β-diol 17-Acetate.—To a solution of 2.0 g. of 4-chlorotestane-17β-ol-3-one acetate in 60 cc. of ethanol was added a solution of 130 mg. of sodium borohydride in 25 cc. of the same solvent and the mixture was allowed to stand at room temperature for 20 hr. After working up in the usual manner, 1.64 g. (81%) of chlorohydrin was isolated, m.p. 132–133° (from methanol), $[\alpha]^{21}D$ +33.3°, $\lambda_{max}^{CHCl_3}$ 5.82 μ. The chlorohydrin did not give a precipitate with digitonin in alcoholic solution.

Anal. Calcd. for $C_{21}H_{33}O_3Cl$: C, 68.36; H, 9.02. Found: C, 68.24; H, 8.91.

Alkaline Treatment of Chlorohydrin.—A solution of 150 mg. of 4-chlorotestane-3,17β-diol 17-acetate and 350 mg. of potassium hydroxide pellets in 20 cc. of methanol was refluxed for 20 hr. After working up in the usual way the product showed λ_{ketone}^{Chf} 5.87 μ. The acetate absorption is missing because of the alkaline hydrolysis. Testane-17β-ol-3-one acetate shows λ_{max}^{Chf} 5.82 μ, 5.87 μ. On acetylation of the residue with acetic anhydride–pyridine, a product identical with testane-17β-ol-3-one acetate is obtained.

4-Chlorotestane-3,17β-diol Diacetate.—This product was formed on treating a pyridine solution of 4-chlorotestane-3,17β-diol 17-acetate with acetic anhydride. The **diacetate** melted at 156–157°, $[\alpha]^{21}D$ +37.2°.

Anal. Calcd. for $C_{25}H_{35}O_4Cl$: C, 67.20; H, 8.58. Found: C, 67.33; H, 8.51.

Chlorination of Coprostanone.—A warm (65°) solution of 1.9 g. of coprostanone in 20 cc. of glacial acetic acid was treated with one portion of 0.6 cc. of *t*-butyl hypochlorite and warmed on the steam-bath for one hour. The solution was then allowed to stand overnight and had darkened considerably. It was evident that some dehydrochlorination had taken place as the crude reaction product showed the presence of a double bond (infrared). The reaction product was an oily solid. Treatment of 150 mg. of this crude material with 80 mg. of 2,4-dinitrophenylhydrazine in 5 cc. of acetic acid solution yielded the 2,4-dinitrophenylhydrazone of Δ^4-cholestenone, m.p. 232° (ethanol–ethyl acetate). On admixture with an authentic sample, no depression was obtained.

Dehydrochlorination of 4-chlorotestane-17β-ol-3-one Acetate.—A solution of 300 mg. of 4-chlorotestane-17β-ol-3-one acetate was refluxed with 10 cc. of collidine for 4 hr. After removal of most of the solvent *in vacuo*, water was added

(21) G. Rosenkranz, O. Mancera, J. Gatica and C. Djerassi, THIS JOURNAL, **72**, 4077 (1950).

(22) 30-Mesh zinc was treated with concd. sulfuric acid containing a few drops of concd. nitric acid for 15 minutes at 90°. The acid was decanted, water was added and the zinc was exposed to this dilute acid for one minute. After washing with water five times and four times with acetone, the zinc was dried under high vacuum (*cf.* L. F. Fieser and W. S. Johnson, *ibid.*, **62**, 576 (1940)).

and the organic material was extracted with ether. Titration of the aqueous phase (Volhard) indicated that about 50% dehydrochlorination had been effected. The ether extract was washed with dilute hydrochloric acid to remove collidine and upon evaporation a crude residue (260 mg.) was obtained. This was dissolved in 5 cc. of acetic acid and a solution of 150 mg. of 2,4-dinitrophenylhydrazine in 5 cc. of acetic acid was added. After standing overnight the brick-red 2,4-dinitrophenylhydrazone was filtered, m.p. 219–220° (ethanol–ethyl acetate). The product was identical in m.p., mixed m.p. and infrared spectrum with testosterone acetate 2,4-dinitrophenylhydrazone.

Anal. Calcd. for $C_{27}H_{34}O_6N_4$: C, 63.51; H, 6.71. Found: C, 63.87; H, 6.65.

Dehydrobromination of 4-Bromotestane-17β-ol-3-one Acetate.—A solution of 50 mg. of bromoketone and 25 mg. of 2,4-dinitrophenylhydrazine in 3 cc. of acetic acid was heated on the steam-bath for one hour. After cooling, 55 mg. of pure testosterone acetate 2,4-dinitrophenylhydrazone, m.p. 219–220°, identical with the product described above, was obtained.

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

Steroids. XLV.[1] Introduction of the 11-Keto and 11α-Hydroxy Groups into Ring C Unsubstituted Steroids (Part 8).[2] Performic Acid Oxidation of 7,9(11)-Dienes[3]

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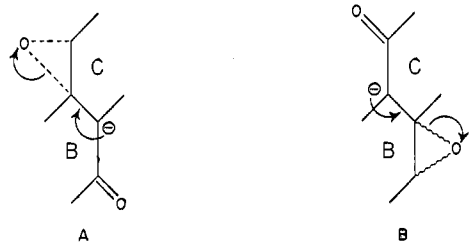
As illustrated with $\Delta^{7,9(11)}$-dienes of the 20β-hydroxy, 20-keto and 16α,17α-oxido-20-ketoallopregnane series as well as with a sapogenin derivative, performic acid oxidation leads to 9α,11α-oxido-7-ketones which are useful intermediates for the synthesis of 11-keto and 11α-hydroxy steroids.

During the past two years there have been developed a number of syntheses of 11-oxygenated steroids, notably cortisone, from ring C unsubstituted precursors which occur abundantly in a variety of plant sources. All of these methods[5] proceed through some type of oxidation of a steroidal $\Delta^{7,9(11)}$-diene I followed by appropriate manipulations leading eventually to the desired 11-ketosteroid. One of the methods developed in this Laboratory involves performic acid oxidation of such dienes and the present paper is concerned with a description of the experimental details in four different series.[6]

The starting material for our initial experiments was $\Delta^{7,9(11)}$-allopregnadiene-3β,20β-diol diacetate (IA)[7] since it was felt that the absence of carbonyl groups (aside from the acetate functions) would facilitate infrared examination of the oxidation products. The diacetate IA proved indeed a fortuitous choice since all of the subsequent transformation products were nicely crystalline. Oxidation of the diene IA with hydrogen peroxide in formic acid solution, with or without an additional solvent,[8] resulted in the introduction of two oxygen atoms. Since the product exhibited no ultraviolet absorption and showed no infrared hydroxyl band but did possess carbonyl bands at 1736 cm.$^{-1}$ (acetate) and 1718 cm.$^{-1}$ (unconjugated 6-membered ring carbonyl band), only three possible structures were considered: (a) saturated 7,11-dione; (b) 8,9-oxido-11-ketone, and (c) 9,11-oxido-7-ketone IIA. The subsequent transformations[9] served to establish the correctness of the last structure IIA. Thus mild alkaline treatment resulted in saponification *cum* rearrangement yielding a trihydroxy ketone, which formed a triacetate and exhibited a pronounced ultraviolet absorption maximum at 254 mμ (log ε 4.11). Such a reaction excludes a 7,11-dione structure and can be rationalized only with an epoxyketone (A or B) rearranging to an unsaturated ketol.



A B

Catalytic hydrogenation with palladized charcoal resulted in smooth reduction of the double bond and a modified[10] Wolff–Kishner reduction produced a triol which could be oxidized to the known allopregnane-3,11,20-trione (VIIIa).[11] The oxidation to the ketone demonstrated that the triol was allopregnane-3β,11α,20β-triol (VIIa), the 11α-configuration being proved by the facile preparation of a 3,11,20-triacetate VIIb. This in turn requires the placement of the reactive (to Wolff–Kishner conditions and Girard complex formation) keto

(1) Paper XLIV, F. Sondheimer, G. Rosenkranz, O. Mancera and C. Djerassi, THIS JOURNAL, **75**, 2601 (1953).

(2) Part 7, F. Sondheimer, O. Mancera, G. Rosenkranz and C. Djerassi, *ibid.*, **75**, 1282 (1953).

(3) We are greatly indebted to Dr. Gilbert Stork of Columbia University for valuable suggestions.

(4) Department of Chemistry, Wayne University, Detroit 1, Michigan.

(5) For a recent review, see L. Velluz, A. Petit and J. Mathieu, *Bull. soc. chim. France*, 1 (1952).

(6) Part of this material has been announced in a preliminary Communication to the Editor (G. Stork, J. Romo, G. Rosenkranz and C. Djerassi, THIS JOURNAL, **73**, 3546 (1951)).

(7) J. Romo, G. Rosenkranz and C. Djerassi, *ibid.*, **73**, 5489 (1951).

(8) Similar oxidations recently also have been described in the ergosterol (R. Budziarek, G. T. Newbold, R. Stevenson and F. S. Spring, *J. Chem. Soc.*, 2892 (1952); R. C. Anderson, R. Stevenson and F. S. Spring, *ibid.*, 2901 (1952)) and cholesterol series (L. F. Fieser and J. E. Herz, THIS JOURNAL, **75**, 121 (1953)).

(9) An independent proof of structure has already been presented in the sapogenin series (C. Djerassi, E. Batres, M. Velasco and G. Rosenkranz, THIS JOURNAL, **74**, 1712(1952)) where the epoxyketone II was converted to the 7-cycloethylene mercaptal and desulfurized to the known 9α,11α-oxido-22a-5α-spirostan-3β-ol (C. Djerassi, H. Martinez and G. Rosenkranz, *J. Org. Chem.*, **16**, 1278 (1951)).

(10) Huang-Minlon, THIS JOURNAL, **71**, 3301 (1949).

(11) M. Steiger and T. Reichstein, *Helv. Chim. Acta*, **21**, 161 (1938), obtained this substance VIIIa by degradation of corticosterone.