in Table III leads to a correct qualitative prediction of the predominant anomer at equilibrium in every case. This generalization, previously found applicable in the cases of poly-*O*-acetylglycopyranosyl halides and alkyl glycopyranosides, thus also appears valid in the case of poly-*O*-acetylglycopyranoses.

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF CALIFORNIA, LOS ANGELES, AND THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF SYDNEY, AUSTRALIA]

Allylic Rearrangements. XLII. The Preparation and Some Reactions of 3β-Chlorocholest-4-ene and 3α-Chlorocholest-4-ene[1]

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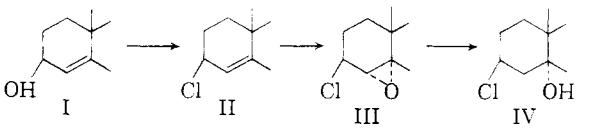
RECEIVED JUNE 23, 1958

The allylic chlorides named above have been prepared from 3β-hydroxycholest-4-ene and 3α-hydroxycholest-4-ene, respectively, and their structures established. The chlorides, by solvolysis in ethanol–dioxane (1:1) at 25°, exhibit kinetics of the first order with respect to the steroid and show closely similar rate constants (3β > 3α). The products of solvolysis under various conditions have been examined.

3β-Chlorocholest-4-ene (I, Cl quasiequatorial) was the sole isolatable product obtained by treatment of 3β-hydroxycholest-4-ene (I) with thionyl chloride in ether at 0° using the procedure of Plattner, *et al.*[2] A plot of the first-order kinetics obtained from solvolysis of the total product in alcohol–dioxane (1:1) at 25° gave a stright line between the limits 0–75% reaction. Beyond this point there was considerable drift in the rate, probably due to the presence in minor amount of a second allylic chloride. However, after several recrystallizations of this crude material, purer 3β-chlorocholest-4-ene (II) was obtained, as indicated by the almost complete elimination of this drift. The same chloride (II) was also obtained by use of phosphorus pentachloride in carbon tetrachloride; this result recalling the conversion of 7α-hydroxycholest-5-en-3β-yl acetate into 7α-chlorocholest-5-en-3β-yl acetate, with both thionyl chloride in ether and phosphorus pentachloride.[3]

The structure of the chloride II was established by conversion with perbenzoic acid to the 4α, 5α-epoxide (III), and reduction thereof with lithium aluminum hydride in ether to the known 3β-chloro-5α-cholestan-5-ol (IV).[4] This, by hydrogenation with platinum in ethyl acetate, gave 5α-cholestane. The 3β-configuration and quasiequatorial conformation[5] of the chlorine atom in II is confirmed by the infrared absorption spectrum, which exhibited a strong band at 760 cm.$^{-1}$ associated with the C-Cl stretching vibration (equatorial Cl, 736–856 cm.$^{-1}$; axial Cl, 646–730 cm.$^{-1}$[1,6a,b]).

Solvolysis of pure 3β-chlorocholest-4-ene in aqueous acetone at 45–55° in the presence of sodium bicarbonate, or in moist ether at 20° in the presence of silver hydroxide, gave cholesta-3,5-diene (*ca.* 15%), and 3β-hydroxycholest-4-ene (I) and 3α-hydroxycholest-4-ene (V) in approximately equal proportions (*ca.* 40% of each isomer). These reactions thus appear to proceed by an $S_{N}1$ heterolysis; the carbonium ion produced can acquire extra stability by resomerism and may therefore be sufficiently long-lived to assume its stable plane-trigonal form, so that the ultimate attack by the substituting agents affords an almost completely racemized product. However, use of potassium acetate in acetic acid at 20° afforded cholesta-3,5-diene (*ca.* 15%), with a marked preponderance of 3α-acetoxycholest-4-ene (70%) over the 3β-epimer (<10%); this predominant inversion of configuration suggests the incursion of $S_{N}2$ displacement despite the relatively weak nucleophilic power of the anion (OAc^{-}) involved.



Unlike its β-epimer, 3α-hydroxycholest-4-ene (V) could form a quasiaxial chlorosulfinate in which the chlorine would have relatively unhindered approach to C_5 enabling the operation of an $S_{N}1'$ mechanism. However, 3α-chlorocholest-4-ene (VI) was the major product from the reaction of the allylic alcohol (V) with thionyl chloride. Solvolysis of the total product and a plot for first-order kinetics gave a straight line between the limits 0–70% beyond which point there was considerable drift, presumably due to the presence of a second non-isolable allylic chloride, the rate of solvolysis of which was considerably slower than that of 3β-chlorocholest-4-ene (II). This minor product may be 5α-chlorocholest-3-ene (IX) resulting from an $S_{N}1'$ reaction. Lithium aluminum hydride reduction of the allylic chloride mixture afforded solely cholest-4-ene. The infrared spectrum of this total product showed no absorption at 773 and 671 cm.$^{-1}$ expected for cholest-3-ene,[7] the

(1) This investigation was commenced independently at the University of California (W.G.Y., R.E.I., T.I.W.) and at the University of Wales (C.W.S., B.D.A., G.H.R.S.); learning of each others' work we decided to publish our results jointly.

(2) P. A. Plattner, H. Heusser and A. B. Kulkarni, *Helv. Chim. Acta*, **32**, 265 (1949).

(3) A. E. Bide, H. B. Henbest, E. R. H. Jones and P. A. Wilkinson, *J. Chem. Soc.*, 1788 (1948).

(4) C. W. Shoppee, R. J. Bridgwater, D. N. Jones and G. H. R. Summers, *ibid.*, 2492 (1956).

(5) D. H. R. Barton, R. C. Cookson, W. Klyne and C. W. Shoppee, *Chemistry & Industry*, 21 (1954).

(6) (a) J. E. Page, *J. Chem. Soc.*, 2017 (1955); (b) D. H. R. Barton, J. E. Page and C. W. Shoppee, *ibid.*, 331 (1956).

(7) H. B. Henbest, G. D. Meakins and G. W. Wood, *ibid.*, 800 (1954).

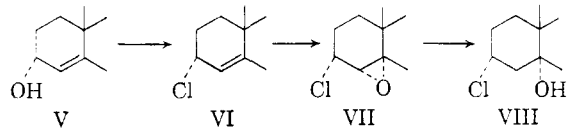
normal hydride reduction product of the tertiary allylic chloride IX. This does not rule out the possible formation of the latter, as hydride reduction by an S_{N2}' displacement may have occurred to give cholest-4-ene. 3α-Chlorocholest-4-ene (VI) was also obtained as principal product by treatment of 3α-hydroxycholest-4-ene (V) with phosphorus trichloride in chloroform at 20°.

TABLE I

RATE CONSTANTS FOR THE SOLVOLYSIS OF 0.017 M 3β-CHLOROCHOLEST-4-ENE AND 3α-CHLOROCHOLEST-4-ENE IN ETHANOL-DIOXANE (1:1) AT 25.0°

	10^4k, sec.$^{-1}$
3β-Chlorocholest-4-ene (II)	6.20 ± 0.04
3α-Chlorocholest-4-ene (VI)	4.94 ± 0.04

Proof of the structure of 3α-chlorocholest-4-ene (VI) was obtained by employing the same reaction sequence of epoxidation followed by lithium aluminum hydride reduction, as with the β-epimer, to give 3α-chlorocholestan-5α-ol (VIII).[8] Hydrogenation of the allylic chloride (VI) with platinum oxide in ether gave 5β-cholestane.



V VI VII VIII

Experimental

Melting points were recorded on a Kofler block and are corrected. Rotations were determined in 1% chloroform solutions. The petroleum ether referred to is the fraction with boiling point 67–68°. The deactivated alumina was prepared by treatment of activated alumina with 5% of its weight of 10% aqueous acetic acid; the alkaline alumina used was Spence (activity ~ II).

3β-Chlorocholest-4-ene.—(A) A solution of 3β-hydroxycholest-4-ene (6.2 g., m.p. 131–132°, $[\alpha]^{25}D$ + 42°) in anhydrous ether (50 ml.) was treated with purified thionyl chloride (1.5 ml.) at 0° for 6 min. It was thoroughly washed with sodium bicarbonate solution and the steroid was then isolated as a colorless solid (6.13 g.). Three crystallizations from ether gave fairly pure allylic chloride (3.1 g.), m.p. 116–120°, $[\alpha]^{25}D$ + 26°). Modified Volhard titrations indicated 96% chloride ion.

(B) 3β-Hydroxycholest-4-ene (1 g.) in carbon tetrachloride (50 ml.) was shaken with phosphorus pentachloride (1 g., freshly sublimed at 50–70° (0.1 mm.) at 0° for 15 min. The usual working up gave 3β-chlorocholest-4-ene (0.8 g.), m.p. 111–113°, $[\alpha]^{25}D$ +25°.

Anal. Calcd. for $C_{27}H_{45}Cl$: C, 80.05; H, 11.20; Cl, 8.75. Found: C, 80.3; H, 11.1; Cl, 8.4.

Lithium Aluminum Hydride Reduction of 3β-Chlorocholest-4-ene.—3β-Chlorocholest-4-ene (0.170 g., m.p. 116–120°) in ether (15 ml.) was refluxed in the presence of lithium aluminum hydride (*ca.* 1 g.) for 20 min. The product was isolated with ether and chromatographed on alumina (5 g.). Elution with petroleum ether gave cholest-4-ene (0.108 g.), m.p. and mixed m.p. 81–82° (from acetone), $[\alpha]^{25}D$ + 71°.

3β-Chloro-4α-5-epoxy-5α-cholestane.—A benzene solution (15 ml.) of 3β-chlorocholest-4-ene (1.8 g.) was treated at 25° with perbenzoic acid (1.3 moles) in benzene (61 ml.). The ensuing reaction, followed titrimetrically, was complete in 2.5 hr. After washing with dilute sodium hydroxide solution the steroid was isolated as a crystalline solid (1.74 g.). Two recrystallizations from acetone yielded the pure epoxide, m.p. 114–115°, $[\alpha]^{25}D$ + 64°.

Anal. Calcd. for $C_{27}H_{45}OCl$: C, 77.01; H, 10.77; Cl, 8.42. Found: C, 76.81; H, 10.42; Cl, 8.11.

(8) A. J. Fudge, C. W. Shoppee and G. H. R. Summers, *J. Chem. Soc.*, 958 (1954).

3β-Chloro-5α-cholestan-5-ol.—The epoxide (0.4 g.) in ether (40 ml.) was refluxed with lithium aluminum hydride (0.2 g.) for 0.5 hr. The reaction product (0.38 g.) was chromatographed on alumina (15 g.). Elution with pentane gave cholesta-3,5-diene (54 mg.), m.p. and mixed m.p. 78–80°. Elution with ether–pentane (1:19) yielded 3β-chloro-5α-cholestan-5-ol (0.27 g.), m.p. 110–111°, $[\alpha]^{25}D$ +24°, giving no depression on admixture with an authentic sample.

Solvolysis Products of 3β-Chlorocholest-4-ene.—(A) 3β-Chlorocholest-4-ene (1.12 g., m.p. 116–120°) and sodium bicarbonate (3 g.) were placed in a 200 ml. r.b. flask and acetone (90 ml.) was added, the steroid easily dissolving. Water (10 ml.) was then added and the mixture was maintained at 45–55° for 1.5 hr. and vigorously shaken during this period. The steroid (1.01 g.) was isolated with ether as a crystalline solid. A sample of this material, after one recrystallization from ethanol, had m.p. 138–140°, $[\alpha]^{25}D$ +78°. The melting point of this material was not depressed upon admixture with a sample of the molecular compound of 3β-hydroxycholest-4-ene and 3α-hydroxycholest-4-ene.

A sample of the crude reaction product (0.618 g.) was chromatographed on alumina (35 g.). Elution with petroleum ether gave cholest-3,5-diene (0.062 g.), m.p. 78–79°, $[\alpha]^{25}D$ −118°. Elution with benzene–ether (10:1) gave (1) 3α-hydroxycholest-4-ene, m.p. 82–83°, $[\alpha]^{25}D$ + 119°; (2) the molecular compound, m.p. 139–140°, $[\alpha]^{25}D$ +83°; (3) 3β-hydroxycholest-4-ene, m.p. 131–132°, $[\alpha]^{25}D$ +43°.

(B) 3β-Chlorocholest-4-ene (0.5 g.) in ether (40 ml.) was shaken with moist, freshly precipitated silver oxide at 20° for 16 hr. The solid product, isolated in the usual way, was chromatographed on neutralized alumina (15 g.) in pentane to give by elution with pentane impure cholesta-3,5-diene (70 mg.), and by elution with ether–benzene (1:9) the molecular compound (0.4 g.), m.p. and mixed m.p. 140°.

(C) 3β-Chlorocholest-4-ene (0.65 g.) was treated with a solution of freshly fused potassium acetate (0.36 g.) in acetic acid (20 ml.) at 20° for 24 hr. The resultant oil (0.66 g.) was chromatographed on neutralized alumina (30 g.) in pentane. Elution with pentane (50 ml.) gave cholesta-3,5-diene (104 mg.), m.p. 80–81°, $[\alpha]^{25}D$ −105°. Further elution with pentane (10 × 50 ml.) gave 3α-acetoxycholest-4-ene (0.47 g.), m.p. and mixed m.p. 83–84°, $[\alpha]^{25}D$ +177°, after crystallization from acetone. A portion of this material was converted by treatment with lithium aluminum hydride in ether at 20° into 3α-hydroxycholest-4-ene, m.p. 80–84°, $[\alpha]^{25}D$ + 110°; after crystallization from acetone. 3β-Hydroxycholest-4-ene could not be isolated.

3α-Chlorocholest-4-ene.—(A) Thionyl chloride (0.6 ml.) was added to an ether solution (25 ml.) of 3α-hydroxycholest-4-ene (1.35 g., m.p. 82–84°, $[\alpha]^{25}D$ +122°) maintained at 0°. After 6 min. the steroid (1.29 g.) was isolated with ether and recrystallized from acetone to give fairly pure 3α-chlorocholest-4-ene, m.p. 89–95°, $[\alpha]^{25}D$ +169°. Modified Volhard titrations indicated 89% chloride ion.

(B) 3α-Hydroxycholest-4-ene (0.3 g.) in chloroform (15 ml.) was treated with excess phosphorus trichloride (5 ml.) dissolved in chloroform (10 ml.) at 20° for 7 hr. The product, isolated with ether, crystallized readily and by recrystallization from acetone gave 3α-chlorocholest-4-ene, m.p. 96–98°, $[\alpha]^{25}D$ +140°.

Anal. Calcd. for $C_{27}H_{45}Cl$: C, 80.05; H, 11.20; Cl, 8.75. Found: C, 80.22; H, 11.28; Cl, 8.55.

Lithium Aluminum Hydride Reduction of 3α-Chlorocholest-4-ene.—The hydride (*ca.* 0.1 g.) was added to a solution of the crude allylic chloride (0.198 g., m.p. 89–95°) in ether (25 ml.), the mixture then being heated under reflux for 30 min. The steroid was isolated with ether and chromatographed on alumina (10 g.). Elution with petroleum ether gave cholest-4-ene m.p. and mixed m.p. 79–81° (from acetone), $[\alpha]^{25}D$ × 69°.

Hydrogenation of 3α-Chlorocholest-4-ene.—The pure chloride (65 mg.) was hydrogenated with platinum oxide (20 mg.) in ether (20 ml.); the solid product by recrystallization from acetone furnished 5β-cholestane, m.p. 69–70°, mixed m.p. 69–71° with a genuine sample.

3α-Chloro-5α-cholestan-5-ol.—A solution of 3α-chlorocholest-4-ene (2.81 g., m.p. 88–94°) in benzene (30 ml.) was treated with perbenzoic acid (1.25 moles) in benene (85 ml.) and maintained at room temp. for 3 hr. The product (2.79 g.) was isolated as an oil and treated with lithium aluminum hydride (1.5 g.) in refluxing ether (80 ml.) for 2.5 hr.

After decomposition of the excess hydride by cautious addition of ethyl acetate, the steroid was isolated with ether and chromatographed on alumina (120 g.). Elution with petroleum ether–benzene (10:1) afforded an oil (0.48 g.) which failed to crystallize. Elution with petroleum ether–benzene (1:1) have a gummy solid (1.21 g.), $[\alpha]^{25}D$ +37°, which after five recrystallizations from aqueous acetone gave 3α-chloro-5α-cholestan-5-ol, m.p. 115-118°, $[\alpha]^{25}D$ +17°. The melting point of this material was depressed upon admixture with a sample of 3β-chloro-5α-cholestan-5-ol.

Acknowledgment.—C.W.S. wishes to acknowledge a gift of cholesterol from Glaxo Laboratories Limited, London.

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[CONTRIBUTION FROM THE DIVISION OF CHEMICAL RESEARCH OF G. D. SEARLE & CO.]

Azasteroids. I[1,2]

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RECEIVED AUGUST 25, 1958

The conversion of the readily available plant steroid, hecogenin, to a C-ring lactam is described. The latter could serve as the precursor for modified steroid hormones.

Hecogenin (I), 3β-hydroxy-5α,22a-spirostan-12-one,[3] is among the most readily available sapogenins, being found in various species of Agave.[4] It has been used successfully as a starting material for the synthesis of cortisone[5] and would seem to be an attractive substance for the preparation of steroids modified in ring C.[6,7] One such modification could be the introduction of nitrogen into ring C.

The physiological activity of steroid hormones depends on a number of factors. Among those of primary importance are stereochemistry and the over-all shape of the molecule. Thus, any really fundamental change in the steroid nucleus should alter the stereochemistry as little as possible. Models indicate that expansion of ring C from six- to seven-membered has little effect on the molecule's general shape and no change in the configuration at any asymmetric center need be made.

The preparation of steroids containing nitrogen in the ring system has been limited to few examples. Bolt[8] synthesized 4-aza analogs of cholestane and 17β-hydroxypregnane. Schenck[9] has carried out Beckmann rearrangements of ring ketoximes derived from bile acids. Barnes, *et al.*,[10] and Falco, *et al.*,[11] have prepared B-ring lactams in the lanosterol series while Kaufmann,[12] Heusser, *et al.*,[13] Regan and Hayes[1] and the present author[1] have synthesized various 17a-aza-D-homo steroids.

Hecogenin (I) was converted to the acetate II which gave the oxime III. The oxime failed to rearrange at room temperature with *p*-toluenesulfonyl chloride in pyridine, but heating at 100° gave 3β-acetoxy-12a-aza-C-homo-5α,22a-spirostan-12-one (IV). An examination of models showed that although the assigned structure of the oxime and resulting lactam was the more probable, the alternative oxime (*syn* to the C-18 methyl group) and lactam (a 12-aza-12a-one) was not precluded. More about the structure of the lactam was learned from the following sequence of reactions.

Hecogenin acetate was oxidized by selenium dioxide in *t*-butyl alcohol[14] to 3β-acetoxy-5α,22a-spirost-9(11)-en-12-one (V).[15] The oxime VI was more reactive than its saturated analog III and yielded with *p*-toluenesulfonyl chloride in pyridine at room temperature 3β-acetoxy-12a-aza-C-homo-5α,22a-spirost-9(11)-en-12-one (VII). The latter on catalytic hydrogenation gave IV. Thus, the two series II→III→IV and II→V→VI→VII→IV both lead to a common end-product and the second sequence goes through an intermediate whose structure should be capable of unambiguous proof, namely, the unsaturated lactam VII. It should be possible to distinguish between VII and the alternative 12-aza-9(11)-en-12a-one (an enamine lactam) by the ultraviolet spectrum.

Not enough examples of α,β-unsaturated amides and lactams and of α,β-unsaturated amines are in the literature to permit an unambiguous interpretation of the ultraviolet spectrum of VII. The more pertinent data, summarized in Table I, lead to the tentative conclusion that α,β-unsaturated lactams have their strong maxima at low wave lengths (around 200 mμ) while α,β-unsatu-

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(2) R. H. Mazur, U. S. Patent 2,806,028 (September 10, 1957).

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(4) R. E. Marker, R. B. Wagner, P. R. Ulshafer, E. L. Wittbecker, D. P. J. Goldsmith and C. H. Ruof, *ibid.*, **69**, 2167 (1947).

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(6) E. S. Rothman and M. E. Wall, THIS JOURNAL, **77**, 2229 (1955). These authors have prepared a series of compounds containing a 12-carboxy-13-hydroxy-lactone by peracid oxidation of 12-keto steroids.

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(12) S. Kaufmann, THIS JOURNAL, **73**, 1779 (1951).

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(14) C. Meystre, H. Frey, W. Voser and A. Wettstein, *ibid.*, **39**, 734 (1956); S. A. Szpilfogel, T. A. P. Posthmus, M. S. deWinter and D. A. van Dorp, *Rec. trav. chim.*, **75**, 475 (1956).

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