[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY]

MOLECULAR REARRANGEMENTS IN THE STEROLS. VII. THE CHEMISTRY OF THE *EPI-I*-STEROLS AND THEIR REARRANGEMENT PRODUCTS

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In a recent communication from this laboratory (1) certain experimental observations were reported on the reaction in ether solution of lithium aluminum hydride with *i*-cholestanone. The preparation of the C_6-epimer of *i*-cholesterol, designated as *epi-i*-cholesterol, was described, and the product of its acid rearrangement recorded. In this paper we wish to describe the preparation and properties of the epimeric 3,5-cyclo-androstan-6,17β-diols (Ic, IIIc). Certain derivatives of these compounds have been characterized and the results of certain configurational studies on the *i*-stanols in general are being reported.

When the 3,5-cyclo-stanones, *i*-cholestan-6-one (IIa), *i*-androstan-6-one (IIg), and *i*-androstan-6,17-dione (IIe) are treated in ether solution with an excess of lithium aluminum hydride the strongly dextrorotatory compounds, *epi-i*-cholesterol, m.p. 80.5–81.5°, $[\alpha]_D^{20}$ +80.9° (IIIa), *epi-i*-androstan-6-ol, m.p. 114–114.5°, $[\alpha]_D^{20}$ +80.5° (IIIg), and *epi-i*-androstan-6,17β-diol, m.p. 176–177°, $[\alpha]_D^{20}$ +64.5° (IIIc) are produced.

In the case of *epi-i*-cholesterol the stereospecificity of the reaction and the stereochemical purity of the product was demonstrated by chromatographic analysis on acid washed alumina. Not a trace of *i*-cholesterol (Ia) was found in a 99.5% recovery of the reduction product. Acetylation of *epi-i*-cholesterol (IIIa) in pyridine with acetic anhydride yielded the acetate (IIIb) m.p. 47–48°, $[\alpha]_D^{20}$ +100.8°. Similar treatment of *epi-i*-androstan-6,17β-diol (IIIc) yielded the diacetate (IIId) m.p. 130–130.5°, $[\alpha]_D^{20}$ +95.6°. Chromic acid oxidation of the free alcohols produced in each case the parent ketones (IIa, e, g).

The results of the acid rearrangement of the epimeric 3,5-cyclostanols and their acetates clearly support the concept of a unimolecular reaction (X, XI) as developed in this laboratory and elsewhere (2, 3).

Initial qualitative experiments on the sulfuric acid-catalyzed rearrangement of *epi-i*-cholestan-6-ol (IIIa) in glacial acetic acid revealed that this epimer formed the same *normal* 3β-derivative (IVb) as is produced by rearrangement of *i*-cholestan-6-ol (Ia). Similarly, *epi-i*-androstan-6,17β-diol (IIIc) yields on rearrangement and saponification the same Δ^5-androsten-3β, 17β-diol (IVc) as is formed in the rearrangement of *i*-androstan-6,17β-diol (Ic). The stereospecificity of the rearrangement was again demonstrated by a quantitative study of the reaction

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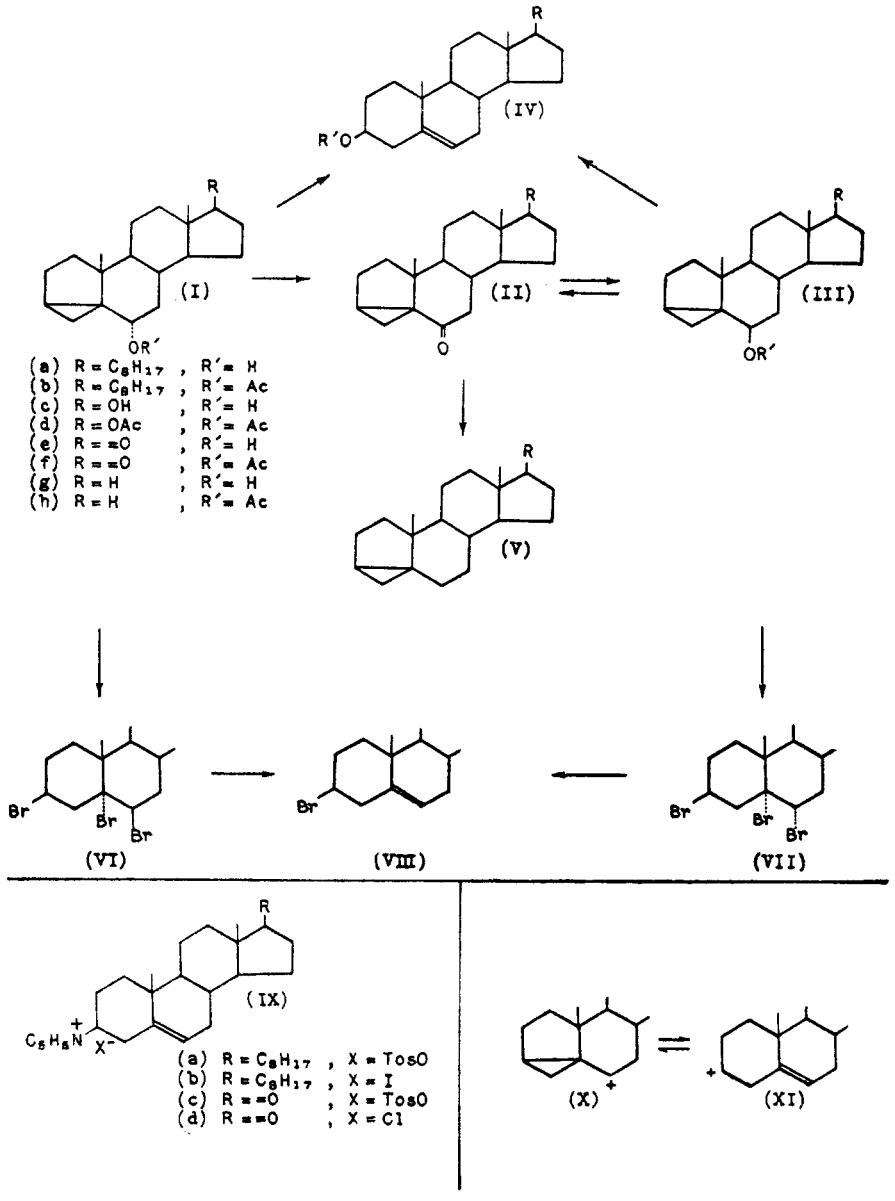
using digitonin as the separating agent. By this method it was found that the steroid having the *normal* 3β-Δ^5-configuration was produced in at least a 96% yield. No Δ^5-cholesten-3α-ol could be isolated from the rearrangement products.



It was observed that a positive Liebermann reaction occurred in all the reactions with sulfuric acid — a fact which can well account for small losses of the material.

Epi-i-cholesteryl acetate (IIIb) was rearranged to cholesteryl acetate (IVb)

under similar conditions. Both *i*- and *epi-i*-cholestan-6-ol were found to rearrange to cholesteryl chloride in the presence of excess hydrochloric acid in glacial acetic acid solution. In all rearrangements recorded so far the *i*- and *epi-i*-sterols produce identical products. We have observed, however, that when rearrangement is carried out in ethereal bromine solution there is a difference in the stereochemistry of the resulting tribromides. It has been observed previously (4) that *i*-cholesterol is converted to a 3,5,6-tribromo-cholestane (m.p. 111.5–112°) by the action of a 1% ethereal solution of bromine. It has been noted also that the rearrangement is not acid-catalyzed and can be carried out in the presence of potassium acetate. On similar treatment, we have found that when *epi-i*-cholestan-6-ol is made to rearrange, an isomeric tribromide melting at 160° with decomposition can be isolated. On debromination in absolute ethanol with sodium iodide each isomeric tribromide produces the same 3β-bromo-Δ^5-cholestene

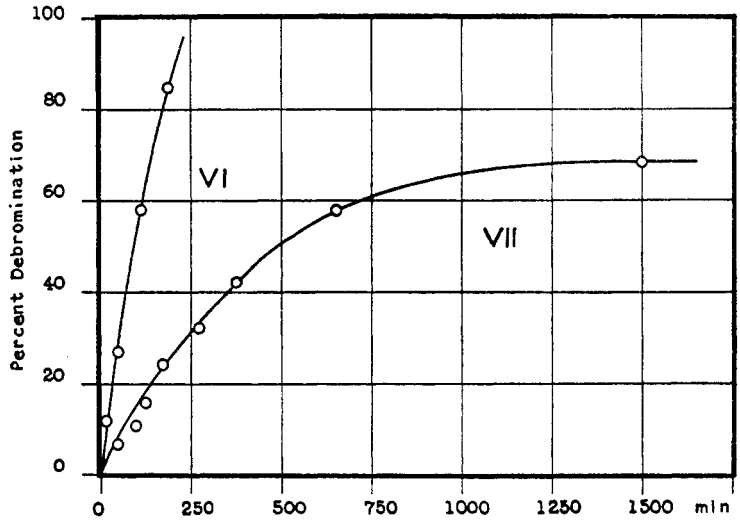


FIGURE 1. RATE OF DEBROMINATION OF THE ISOMERIC 3,5,6-TRIBROMO-CHOLESTANES

(VIII), identified by melting point, rotation, and mixture melting point with an authentic specimen of cholesteryl bromide. Therefore we can conclude that each isomer is a 3,5,6-tribromide possessing a β-configuration at C_3.

Stereochemical investigation of the 5- and 6-positions of the isomeric tribromides was initiated by studying the rate of sodium iodide debromination. This reaction, regarded as involving a four-centered transition state (5), demands that the four participating centers all lie in one plane for minimum activation energy requirements. Barton (6) has recently shown that the 5α,6β-sterol dihalides fulfill this requirement for facile elimination of bromine and regeneration of the double bond. These investigators have shown in addition that, with a 5α,6α- or 5β,6α-configuration this requirement is not met and a marked difference in reaction rates is noted.

Our results of a rate study are presented in Fig. 1. If one grants the argument

of Barton (6) these results demonstrate that the tribromide (VI) derived from *i*-cholestan-6-ol has the *trans*, 5α,6β-configuration. The slower rate observed with the isomeric tribromide (VII) formed from *epi-i*-cholestan-6-ol supports either the *cis*, 5α,6α-, or *trans*, 5β,6α-configuration at these centers.

To distinguish between the two possibilities for the second isomeric tribromide (VII) the dehydrohalogenation in pyridine was studied at room temperature. This reaction, involving the C_5-bromine and the C_6-hydrogen, is only possible with the 5α,6α-configuration, and as noted by Barton (6), the 5β,6α-isomer will eliminate hydrogen bromide only under even more drastic conditions than those required for the 5α,6β-isomer. The tribromide (VII) was found to lose hydrogen bromide on treatment with pyridine at room temperature to give a product melting at 141° with decomposition, $[\alpha]_D^{20}$ −22.4°; the tribromide (VI) was recovered unchanged on similar treatment.

From these data it may be concluded that *i*-cholestan-6-ol is rearranged to 3β,5α,6β-tribromocholestane (VI) by the action of a 1% ethereal solution of bromine. This is in accord with the synthesis of this tribromide from 3β-bromo-Δ^5-cholestene by the addition of bromine (6, 7). Under similar conditions *epi-i*-cholestan-6-ol rearranges to 3β,5α,6α-tribromo-cholestane (VII).

Although any considerations of mechanism for this reaction must be accepted with reservation until an adequate kinetic survey is carried out, the stereochemistry of the products suggests the formation of a 6-bromo-3,5-cyclo-steroid in the first step. The *i*-steryl bromide so formed should be more susceptible[2] to the addition of bromine across the three-membered ring than the parent alcohol. *Trans*-addition across the ring should prevail providing for the same configuration in both compounds at the 3- and 5-position. The 3β,5α-configuration found in both compounds supports this contention.

Following directly from this postulated mechanism a reasonable assumption can be made regarding the stereochemistry of the C_6-hydroxyl groups of the epimeric 3,5-cyclo-stanols. Replacement of the hydroxyl group by bromine in this reaction should lead to inversion at the 6-position; from this it can be predicted that *i*-sterols are 6α-ols and *epi-i*-sterols are 6β-ols. It should be pointed out that these stereochemical conclusions are in opposition to those of Dodson and Riegel (3) based upon model studies and those of Shoppee (8) based on molecular rotation differences of the saturated 6-cholestanols obtained from *i*- and *epi-i*-cholesterol on hydrogenation. This evidence must be considered with reservation in the light of known rearrangements of the 3,5-cylco-steroids on catalytic hydrogenation (9, 10, 11). Furthermore, we wish to point out that the molecular rotation reported by Shoppee for *epi-i*-cholesterol is 182 units lower than that found in this laboratory. To check the validity of the molecular rotation data of the *i*- and *epi-i*-sterols, we have calculated the ΔM_D values for the 6α-OH, 6β-OH, 6α-OAc, 6β-OAc, and 6=O groups in the *i*-steroids by the method of Barton (12). These data are listed in Table I and show the consistency of the

[2] *Cf.* the instability of the 3,5-cyclo-sterol derivatives of highly electronegative R-groups, *e.g.*, the 3,5-dinitrobenzoate (10), and the *p*-toluenesulfonate which is discussed in this article.

ΔM_D values for each group with the exception of *i*-androstan-6α,17β-diol (Ic) which crystallizes with one mole of ethanol. (See Experimental).

To substantiate further our reasoning on the configuration of the 3,5-cyclosterols it appeared desirable to prepare the epimeric 3,5-cyclo-androstan-6,17β-diols. From model studies it can be seen that the 6β,17β-diol should have a dipole moment and therefore a higher dielectric constant than its epimer, the 6α, 17β-diol. *i*-Androstan-6,17-diol (Ic) was prepared by lithium aluminum hydride reduction of *i*-androstan-6-ol-17-one (Ie). Its epimer was obtained in a similar reduction of *i*-androstan-6,17-dione (IIe).

The C_{17}-hydroxyl group in each case is known to possess a β-configuration when formed by reduction of a C_{17}-carbonyl with lithium aluminum hydride (13). The reaction proceeds almost exclusively by opening of the rear member of the double bond. Acid-rearrangement of both diols produced the same Δ^5-androsten-3β,17β-diol, identified by melting point, rotation, and mixture melting point with an authentic specimen.

The epimeric 3,5-cyclo-diols (Ic) and (IIIc) showed marked differences in their solubilities in non-polar solvents. Whereas the *i*-compound (Ic) dissolves

TABLE I

ΔM_D VALUES FOR THE EPIMERIC 3,5-CYCLO-STEROLS

COMPOUND	6β—OH	6α—OH	6β—OAc	6α—OAc	6 =O
3,5-Cyclo-cholestan-6-ol	+21	−199	+140	−87	—
3,5-Cyclo-androstan-6-17β-diol	+17	−16	+120	−84	—
3,5-Cyclo-androstan-6-ol	+2	−129	+103	−78	—
3,5-Cyclo-androstan-6-ol-17-one	—	−117	—	−81	—
3,5-Cyclo-androstan-6-one	—	—	—	—	−126
3,5-Cyclo-cholestan-6-one	—	—	—	—	−134
3,5-Cyclo-androstan-6,17-dione	—	—	—	—	−144

readily in chloroform, carbon tetrachloride, and benzene, the *epi-i*-compound (IIIc) is but sparingly soluble. Since the more polar molecule must be less soluble in non-polar solvents, it is evident that the *epi-i*-androstan-6,17β-diol is the more polar of the epimeric pair. This is in accord with a 6β,17β-configuration for this molecule.

To support this conclusion the dielectric constants of the epimeric diol-diacetates were measured in carbon tetrachloride. The latter was found to be the only common, non-polar solvent for the epimeric derivatives. Identical solutions were prepared and *epi-i*-androstan-6,17-diol-diacetate showed a dielectric constant 0.0288 $\pm$0.0005 units higher than its epimer (Id) at a concentration of 0.0078 mole-fractions in steroid.

On the basis of the bromine rearrangement, solubility properties, and dielectric constant measurements we are compelled to assign a 6α-configuration to the *i*-sterols and a 6β-configuration to the *epi-i*-sterols and their acetates.

Our attention was next turned to the preparation of the *p*-toluenesulfonates of *i*-sterols; but in all cases only rearrangement products of these compounds were obtained.

Treatment of *epi-i*-cholesterol with *p*-toluenesulfonyl chloride in pyridine at room temperature did result in the isolation of a crystalline compound melting at 230° with decomposition. Similar treatment of *i*-cholesterol, however, produced the same compound which was weakly laevorotatory and found to contain nitrogen and sulfur. The compound was characterized as cholesteryl-pyridinium *p*-toluenesulfonate (IXa) on the basis of melting point, rotation, analysis, and conversion to cholesteryl-pyridinium iodide (IXb) by the action of sodium iodide in absolute ethanol (14). Δ^5-Androsten-pyridinium *p*-toluenesulfonate (IXc) was obtained under similar conditions from *i*-androstan-6-ol-17-one (Ie) together with 30% of the corresponding chloride (IXd) which was separated by chromatography. The pyridinium *p*-toluenesulfonate (IXc) was converted to the corresponding chloride on treatment with hydrochloric acid in ethanol.

Since the products were isolated under conditions eliminating the possibility of free acid formation, the only way to account for this rearrangement and salt formation is to consider the initial formation of the *i*- or *epi-i*-tosyl ester. The negative inductive effect of the *p*-tosyl group causes a displacement of the electron density of the C_3—C_5 bond in the direction of C_5 creating a partial positive center at C_3. The nucleophilic agent, in this case pyridine, can attack the C_3-position, resulting in heterolytic fission at the 6-position and regeneration of the 5–6 double bond. This will account for the difficulty experienced in this laboratory and by other workers in the attempted preparation of the tosyl esters of the 3,5-cyclo-sterols. Obviously in the light of the above results the rearrangement of *i*-steroid methyl ethers in a mixture of pyridine and *p*-toluenesulfonic acid as reported by King and co-workers (14) must proceed through the *i*-tosyl ester [See also (15)].

In a recent paper by Josien, Fuson, and Cary (16) the infrared spectra of certain *i*-steroid methyl ethers have been recorded. We are now able to present the infrared spectra of two *epi-i*-sterol acetates, their C_6-epimers and the spectrum of the *i*-steroid skeleton *i*-androstane (Fig. 2). These spectra were determined on a Baird Double Beam Instrument in carbon tetrachloride solution. Our compounds displayed similar absorption bands in the 890 and 860 cm^{-1} region as was found typical for *i*-methoxy-steroids. *Epi-i*-sterols, however, seem to have less pronounced peaks in these regions. The hydrocarbon *i*-androstane is characterized by its strong absorption in the C—H stretching region, the absence of the C—O band, and a shift in the "*i*-region."

EXPERIMENTAL[3]

3,5-Cyclo-cholestan-6β-ol (epi-i-cholesterol) (IIIa). *i*-Cholestan-6-one (21.5 g.) was dissolved in 500 ml. of dry ether and 200 ml. of a 0.15 *M* absolute ether solution of lithium aluminum hydride was added slowly with stirring. The solution was allowed to stand several hours. The excess lithium aluminum hydride was destroyed by the cautious dropwise addition of ethanol and then water. The mixture was shaken with 350 ml. of 20% aq. KOH and the ether layer separated. The alkaline liquors were twice extracted with 100-ml.

[3] All melting points are uncorrected, and were determined on a Kofler block; all rotations were taken in a 1-dm. tube.

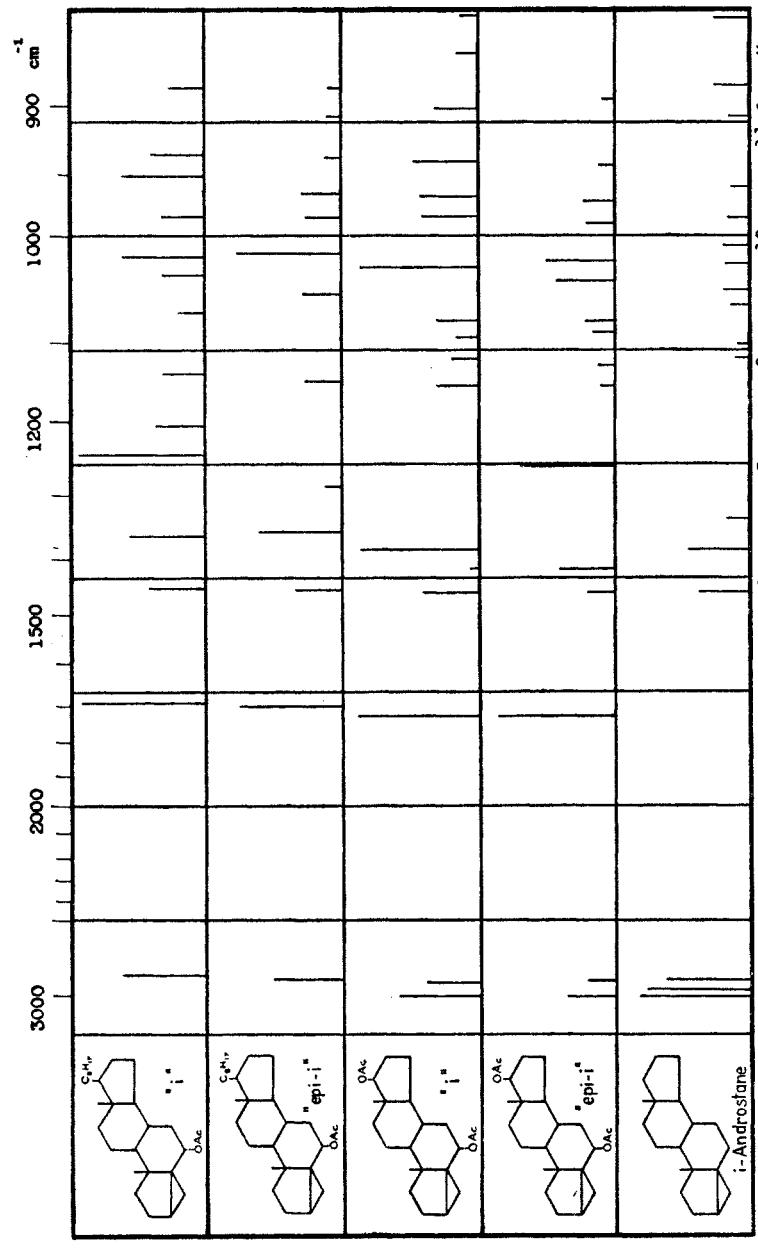


FIGURE 2. INFRARED SPECTRA OF TWO EPIMERIC PAIRS OF 3,5-CYCLO-STEROIDS AND THE *i*-STEROID SKELETON

portions of ether and the combined ether extracts were washed with water and dried over magnesium sulfate. The ether solution was evaporated to dryness on the water-bath using a stream of nitrogen. The residual oil was taken up in ethanol (60 ml.) and cooled in an ice-salt bath where crystallization took place. The crystalline material was filtered off and dried *in vacuo*. Yield: 18.5 g., m.p. 80.5–81.5°, $[\alpha]_D^{25}$ +80.9° ($CHCl_3$; *c*, 1.83).

Anal. Calc'd for $C_{27}H_{46}O$ (386.64): C, 83.85; H, 11.92.
Found: C, 84.08; H, 11.90.

6β-Acetoxy-3,5-cyclo-cholestane (IIIb). One g. of IIIa dissolved in 15 ml. of pure dry pyridine and 5 g. of pure acetic anhydride (magnesium distilled) was allowed to stand at room temperature overnight. The mother liquors were evaporated to dryness *in vacuo* at 30–40° and the residual oil was taken up in ether, washed with 5% aq. NaOH, and dried over magnesium sulfate. The dried ether solution was evaporated to dryness on a water-bath using a stream of nitrogen and the residual oil was taken up in 30 ml. ethanol and cooled to 0°. The crystalline material was filtered off and dried *in vacuo*. Yield: 0.9 g., m.p. 47–48°, $[\alpha]_D^{25}$ +100.8°, ($CHCl_3$; *c*, 1.27).

Anal. Calc'd for $C_{29}H_{48}O_2$ (428.66): C, 81.23; H, 11.29.
Found: C, 81.16; H, 11.10.

Acid rearrangement of epi-i-cholesterol (IIIa). Thirty drops of concentrated sulfuric acid were added to a solution of 2.95 g. of IIIa dissolved in 300 ml. of glacial acetic acid. The solution was warmed at 50–55° for one hour. Within five minutes a curdy precipitate began to form and a faint red tinge appeared throughout the solution. At the end of one hour the mixture was poured into 600 ml. of water and extracted with 500 ml. of ether. The ether solution was neutralized by shaking with dilute aq. potassium carbonate. The ether solution was evaporated to dryness on the water-bath, taken up in 600 ml. ethanol, and treated with 200 ml. of 10% ethanolic KOH at 45° for one hour. The alcoholic liquors were poured into 1600 ml. of water, extracted with two 500-ml. portions of ether, and the extracts evaporated to dryness. The crystalline residue was taken up in hot ethanol and 1200 ml. of a 1% alcoholic solution of digitonin was added at 65°. The mixture was allowed to stand overnight. The precipitated digitonide was filtered off and dried *in vacuo*. Wt. of digitonide: 11.56 g., equiv. wt. of cholesterol precipitated: 2.76 g. The alcoholic liquors from the digitonin separation were worked up in the usual manner and a residue of 0.045 g. was isolated. Total amount of steroid: 2.81 g. (95.4% recovery). Percent of recovered material rearranged to 3β-cholesterol (IVa): 98.2.

Acid rearrangement of the acetate IIIb. 6β-Acetoxy-3,5-cyclo-cholestane (IIIb) (0.2 g.) was dissolved in 20 ml. of glacial acetic acid and four drops of concentrated sulfuric acid were added. The solution was warmed on a steam-bath for one hour. At the end of the hour water was added until turbidity developed. The mother liquors were allowed to cool slowly to room temperature. The crystalline material was filtered off and recrystallized from methanol. Yield 0.18 g., m.p. 110–110.5°; no depression was observed when this material was admixed with 3β-acetoxy-Δ^5-cholestene (IVb).

Rearrangement of IIIa *to 3β-chloro-Δ^5-cholestene.* To a solution of 0.1 g. of *epi-i*-cholesterol (IIIa) dissolved in 30 ml. of glacial acetic acid was added 0.1 ml. of concentrated hydrochloric acid. The solution was allowed to stand at room temperature overnight. The acid liquors were taken up in 50 ml. of ether, washed with 5% aq. sodium bicarbonate, and dried over sodium sulfate. The ether was evaporated *in vacuo* and the residual solid was recrystallized from acetone; m.p. 95–95.5°, $[\alpha]_D^{20}$ −26.5°, ($CHCl_3$; *c*, 1.02). No depression of melting point was observed when a sample was admixed with an authentic sample of cholesteryl chloride.

Chromic acid oxidation of epi-i-cholesterol (IIIa). To a solution of 0.2 g. of IIIa in 7 ml. of glacial acetic acid was added dropwise with constant agitation 140 mg. of CrO_3 in 5 ml. of glacial acetic acid and 14 drops of water. The reaction mixture was allowed to stand overnight. The excess chromic acid was destroyed by the addition of ethanol and the solution poured into water and extracted with ether. The ether solution was washed with 2 *N* aq. NaOH and water and dried over magnesium sulfate. The ether was evaporated on the

steam-bath and the solid residue was crystallized from methanol. Yield 0.12 g., m.p. 96.5–97.5°, $[\alpha]_D^{20}$ +44.9° ($CHCl_3$; *c*, 0.7). No depression of melting point was observed when a sample was admixed with 3,5-cyclo-cholestan-6-one (IIa).

3,5-Cyclo-androstan-6α,17β-diol (*i-androstan-diol*) (Ic). *i*-Androstan-6α-ol-17-one (Ie)[4] (1.5 g.) dissolved in 60 ml. of anhydrous ether was treated with an excess of lithium aluminum hydride dissolved in anhydrous ether at room temperature. After three hours the solution was worked up as described for IIIa. Recrystallized twice from ethanol, prisms, m.p. 97–98°, $[\alpha]_D^{20}$ +53° ($CHCl_3$; *c*, 1.00). Yield: 1.1 g. Very soluble in chloroform, carbon tetrachloride, benzene, and ether.

Anal. Calc'd for $C_{19}H_{30}O_2 \cdot C_2H_5OH$ (336.50): C, 74.96; H, 10.78.

Found: C, 74.64; H, 10.57.

Attempted sublimation at 1 mm. produced a clear glassy substance; benzene-petroleum ether yielded an oil which on addition of one drop of ethanol formed a crystalline compound, m.p. 96–98°. Oxidation of Ic with 1.5 moles of CrO_3 in glacial acetic acid at room temperature yielded needles melting at 179–182° (from ethyl acetate), $[\alpha]_D^{20}$ +113.5° ($CHCl_3$). A mixture melting point determination with an authentic sample of 3,5-cyclo-androstan-6, 17-dione (IIe) showed no depression.

Acid rearrangement of Ic. 3,5-Cyclo-androstan-6α,17β-diol (0.5 g.) was dissolved in 10 ml. of glacial acetic acid. Three drops of concentrated sulfuric acid were added and the solution was heated for ten minutes on a water-bath. A white precipitate soon formed. A pink coloration also occurred. After working up the solution in the usual manner followed by hydrolysis of the crude steroid material in ethanolic KOH a product melting at 175–178° (from ethyl acetate) was obtained; $[\alpha]_D^{20}$ −55° (dioxane), yield: 0.42 g. A mixture melting point with Δ^5-androsten-3β,17β-diol, m.p. 177–178° (IVc) prepared by the reduction of Δ^5-androsten-3β-ol-17-one with lithium aluminum hydride, showed no depression.

6α,17β-Diacetoxy-3,5-cyclo-androstane (Id). Compound Ic (600 mg.) dissolved in a mixture of 7 ml. of dry pyridine and 7 ml. of acetic anhydride was allowed to stand overnight. The solution was then poured on a mixture of ice and sodium bicarbonate. The precipitate was filtered and washed. Three crystallizations from ethanol gave a product melting at 128–128.5°, $[\alpha]_D^{25}$ +41.8° ($CHCl_3$; *c*, 1.02). Yield: 580 mg.

Anal. Calc'd for $C_{23}H_{34}O_4$ (374.5): C, 73.76; H, 9.15.

Found: C, 73.72; H, 9.20.

6α-Acetoxy-3,5-cyclo-androstane (Ih). This compound was prepared by a modified Wolff-Kishner reduction (18) of Ie. On working up the reaction mixture an oily residue was obtained which was acetylated in pyridine with acetic anhydride. The crude acetate was taken up in methanol and on standing for two days in a Dry Ice-acetone bath it finally crystallized in needles. Two more crystallizations produced a product, m.p. 59–60°, $[\alpha]_D^{20}$ +44.8° ($CHCl_3$; *c*, 1.00).

Anal. Calc'd for $C_{21}H_{32}O_5$ (316.47): C, 79.70; H, 10.19.

Found: C, 79.90; H, 9.84.

3,5-Cyclo-androstan-6α-ol (Ig). Compound Ih described above (800 mg.) was refluxed for one hour in 5% ethanolic KOH and was worked up in the usual manner. Crystallization from methanol gave a compound, m.p. 52–53°, plates, $[\alpha]_D^{20}$ +33.2° ($CHCl_3$; *c*, 1.02). Oxidation of this material in glacial acetic acid yielded the ketone IIg which melted at 121–122.5°, $[\alpha]_D^{20}$ +35.2° ($CHCl_3$). It had physical properties identical with the 3,5-cyclo-androstan-6-one described by Butenandt (17).

3,5-Cyclo-androstan-6β,17β-diol (*epi-i-androstan-diol*) (IIIc). One g. of 3,5-cyclo-androstan-6,17-dione (m.p. 183°, IIe) was refluxed in 200 ml. anhydrous ether for eight hours with one g. of lithium aluminum hydride. After destroying the excess reductant with ethanol and water, 150 ml. of 5% aq. sodium hydroxide was added. The ether layer, containing solid organic and inorganic material, was separated and evaporated to dryness. The remaining white residue was washed with water, filtered, and dried. After triturating this material

[4] Prepared by the method of Butenandt and Surányi (17).

with three portions of 30 ml. of boiling ethanol, the crude diol solution was filtered from its inorganic residue, evaporated to dryness, and recrystallized from ethyl acetate. A product, m.p. 166–171°, was isolated. Yield: 0.9 g. Two more crystallizations raised the melting point to 176–177°, plates, $[\alpha]_D^{20}$ +64.5° (dioxane; *c*, 1.01). Slightly soluble in chloroform, carbon tetrachloride, benzene, and ether.

Anal. Calc'd for $C_{19}H_{30}O_2$ (290.43): C, 78.57; H, 10.41.
Found: C, 78.87; H, 10.38.

Acid rearrangement of IIIc. This rearrangement was carried out with 500 mg. of material as described for Ic. Δ^5-Androsten-3β,17β-diol was isolated in good yield, and was identified by its melting point, rotation, and a mixture melting point with an authentic specimen.

6β,17β-Diacetoxy-3,5-cyclo-androstane (IIId). This diacetate was prepared as described for Id. On recrystallization from ethanol the product obtained melted at 130–130.5°, $[\alpha]_D^{25}$ +95.6° ($CHCl_3$; *c*, 1.00).

Anal. Calc'd for $C_{23}H_{34}O_4$ (374.50): C, 73.76; H, 9.15.
Found: C, 73.69; H, 9.12.

3,5-Cyclo-androstan-6β-ol (*epi-i-androstan-6-ol*) (IIIg). A solution of 1.5 g. of 3,5-cyclo-androstan-6-one (IIg), m.p. 121–122.5°[4] was reduced with an excess of lithium aluminum hydride in the same manner as described for IIIc. Working up the product afforded 1.2 g. of felty needles, melting at 114–114.5° (from ethanol), $[\alpha]_D^{20}$ +80.5° ($CHCl_3$; *c*, 1.00). Acid rearrangement and saponification of IIIg produced a crystalline material melting at 131°, $[\alpha]_D^{20}$ −47.6° which had the same physical properties as Δ^5-androsten-3β-ol, described by Butenandt and Surányi (17). Chromic acid oxidation in glacial acetic acid produced the same parent ketone (IIg) as obtained from 3,5-cyclo-androstan-6α-ol (Ig). The oxidation product was identified by melting point, rotation, and mixture melting point with an authentic sample.

6β-Acetoxy-3,5-cyclo-androstane (IIIh). Acetylation in pyridine of compound IIIg above as described for Id afforded needles (from ethanol) m.p. 93–93.5°, $[\alpha]_D^{20}$ +102° ($CHCl_3$; *c*, 1.02).

Anal. Calc'd for $C_{21}H_{32}O_5$ (316.47): C, 79.70; H, 10.19.
Found: C, 79.88; H, 9.87.

3,5-Cyclo-androstane (*i-androstane*) (Vg). One g. of 3,5-cyclo-androstan-6,17-dione (IIe) was reduced to the parent hydrocarbon Vg in the same manner as Ie by a modified Wolff-Kishner reaction (18). Careful addition of water to the cold reaction mixture produced a crystalline compound. Four crystallizations from acetone produced needles, m.p. 66–67°, $[\alpha]_D^{25}$ +85.1° ($CHCl_3$; *c*, 1.00).

Anal. Calc'd for $C_{19}H_{30}$ (258.43): C, 88.30; H, 11.70.
Found: C, 88.15; H, 11.62.

3β,5α,6β-Tribromo-cholestane (VI). *i*-Cholesterol (600 mg.) was rearranged as described by Beynon, Heilbron, and Spring (4). On working up the product the tribromide VI was obtained in crystalline form melting at 111.5–112.0°, $[\alpha]_D^{25}$ −49.6°, ($CHCl_3$; *c*, 1.11). This compound showed no depression in melting point when admixed with a specimen of tribromo-cholestane prepared by the method of Kolm (7).

3β,5α,6α-Tribromo-cholestane (VII). To a solution of 2.0 g. of *epi-i*-cholesterol in 800 ml. of dry ether was added 300 ml. of a 1% ethereal solution of bromine. The solution, after standing overnight at room temperature, was washed with 300 ml. of 1% aq. sodium hydroxide, then with water, and dried over magnesium sulfate. On evaporation to dryness on the steam-bath a white oil was obtained which on treatment with boiling ethanol yielded crystalline material melting at 155° with decomposition. Yield: 0.55 g. Recrystallization from acetone raised the melting point to 160° dec., $[\alpha]_D^{25}$ −50.0° ($CHCl_3$; *c*, 1.24).

Anal. Calc'd for $C_{27}H_{45}Br_3$ (609.38): C, 53.21; H, 7.44.
Found: C, 53.18; H, 7.26.

In certain runs difficulty was encountered in the isolation of this compound in pure form because of the instability of this tribromo-derivative. Chromatographic methods were unsuccessful because of decomposition on the column.

Sodium iodide debromination of the isomeric tribromides VI *and* VII. In each case a solution of 870 mg. of the tribromide, dissolved in 150 ml. of dry acetone, was refluxed for five hours with 5 g. of sodium iodide in 85 ml. of pure dry acetone. The solution was poured into 200 ml. of water and extracted with 100 ml. of ether. The ether solution was washed with 1% aq. sodium sulfite and worked up in the usual manner. The residual oil crystallized from acetone in the form of needles. Yield from either tribromide, 300–400 mg. Compound VIII from VI: m.p. 100°, $[\alpha]_D^{20}$ −23.6° ($CHCl_3$; *c*, 3.09). Compound VIII from VII: m.p. 99°, $[\alpha]_D^{20}$ −22.3° ($CHCl_3$; *c*, 2.92). Each product, when admixed with cholesteryl bromide, showed no depression in melting point.

Rates of debromination of VI *and* VII. The rates were followed spectrophotometrically using 1.64×10^{-3} *M* solutions of the tribromides in dry benzene and a 0.0532 *M* solution of NaI in absolute ethanol. The iodine concentration was determined at 450 millimicrons and per cent debromination was calculated from a standard iodine calibration curve (See Fig. 1).

Dehydrohalogenation of the isomeric tribromides. The tribromide VII (m.p. 160° dec.) (350 mg.) was dissolved in 10 ml. of pure dry pyridine. Within one hour the pyridine solution became straw yellow. After standing overnight the solution was poured onto ice and acidified to Congo Red with cold, 1 *N* hydrochloric acid. The product was extracted with ether and the extract washed with water and dried over magnesium sulfate. The ether solution was evaporated to dryness at room temperature and the product crystallized from ethyl acetate-methanol. Yield: 150 mg., m.p. 136° dec. Further recrystallization from ether-methanol raised the melting point to 141° dec., $[\alpha]_D^{20}$ −22.4° ($CHCl_3$; *c*, 1.07). Similar treatment of the tribromide VI (m.p. 110.5–111°) with 10 ml. of dry pyridine, as described above, resulted in no reaction. The starting material was recovered unchanged.

Dielectric constant measurements of 6α,17β-diacetoxy-3,5-cyclo-androstane (Id) *and 6β, 17β-diacetoxy-3,5-cyclo-androstane* (IIId). Two identical solutions, each containing 0.00788 mole fractions of steroid, were prepared from Id and IIId in carbon tetrachloride. The dielectric constants were determined in a cylindrical gold cell on a 1000 cycle heterodyne beat-frequency oscillator. Temp., 23°.

6β,17β-Diacetoxy-3,5-cyclo-androstane solution: ϵ' 2.2624.

6α,17β-Diacetoxy-3,5-cyclo-androstane solution: ϵ' 2.2336. $\Delta\epsilon'$ 0.0288.

Action of p-toluenesulfonyl chloride on i-sterols. Δ⁵-Cholestenyl-3-pyridinium p-toluenesulfonate (IXa). *Epi-i*-cholesterol (2 g.) was dissolved in 4 ml. of pure dry pyridine. Then 2.0 g. of pure *p*-toluenesulfonyl chloride was added and the solution was allowed to stand at room temperature for 2 days. At the end of the first day a heavy precipitate had formed. The mixture was poured onto an ice-sodium bicarbonate mixture and a foamy emulsion formed. The addition of water produced a semisolid suspension which was filtered. The residue was triturated with an acetone-ethanol mixture and filtered. This solution on cooling produced well defined needles (450 mg.), m.p. 175° dec. Recrystallization from the same solvent mixture gave a product melting at 230° with decomposition, identical to the Δ⁵-cholestenyl-3-pyridinium *p*-toluenesulfonate described by King and co-workers (14).

In a similar experiment 5.8 g. of *i*-cholesterol, dissolved in 12 ml. of pure dry pyridine and 5.8 g. of pure *p*-toluenesulfonyl chloride, was allowed to stand for 2 days and was worked up in the manner as described above. Yield: 1.7 g., m.p. 230° dec., $[\alpha]_D^{20}$ −3° ($CHCl_3$; *c*, 1.10). A qualitative test for sulfur and nitrogen was positive.

Anal. Calc'd for $C_{39}H_{57}NO_3S$ (619.91): C, 73.44; H, 9.01.
Found: C, 73.72; H, 9.26.

The action of *p*-toluenesulfonyl chloride on *i*-androstan-6α-ol-17-one (Ie) was also studied. In this case again the pyridinium *p*-toluenesulfonate was obtained. Δ⁵-Androstenyl-3-pyridinium *p*-toluenesulfonate (IXc) melted at 139–140° with resolidification and final melting with decomposition at 192–193°. $[\alpha]_D^{20}$ +25.6° (ethanol; *c*, 1.00).

Anal. Calc'd for $C_{31}H_{39}NO_4S$ (521.69): C, 71.33; H, 7.56.
Found: C, 71.12; H, 7.52.

In this reaction, however, it was observed that the main product was always accom-

panied by some of the corresponding pyridinium chloride IXd, m.p. 124–126° dec., $[\alpha]_D^{20}$ +1.9° ($CHCl_3$; *c*, 1.06) which could be separated by chromatographic methods. Treatment of the pyridinium *p*-toluenesulfonate IXc with concentrated hydrochloric acid in ethanol also afforded the Δ^5-androstenyl-3-pyridinium chloride IXd.

Conversion of IXa *to the iodide* IXb. Sodium iodide (500 mg.) in 5 ml. of absolute ethanol was added dropwise to a solution of 350 mg. of the Δ^5-cholestenyl-3-pyridinium *p*-toluenesulfonate IXa. A precipitate of the pyridinium iodide formed immediately and was filtered. The product was recrystallized from ethanol and yielded 300 mg. of material, m.p. 258–260° dec., $[\alpha]_D^{25}$ −7.6° ($CHCl_3$; *c*, 1.19), identical to the Δ^5-cholestenyl-3-pyridinium iodide described by King and co-workers (14).

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SUMMARY

The preparation of the C_6-epimers of the 3,5-cyclo-stanols and their derivatives has been described. Experiments are cited to show that they are formed as sole products on reduction of the 3,5-cyclo-stanones with excess lithium aluminum hydride. The acid rearrangement of the epimeric pairs clearly supports the concept of a unimolecular reaction yielding 3β-Δ^5-derivatives in every case. Bromine in ether solution reacts with *i*-cholesterol to form 3β,5α,6β-tribromocholestane, whereas *epi-i*-cholesterol yields 3β,5α,6α-tribromocholestane. Stereochemical assignments for the six position have been advanced for the epimeric 3,5-cyclo-stanols. Mechanistic considerations of the bromine rearrangement of the epimeric cyclo-stanols and the dielectric constant measurements of two epimeric diacetates, showed that *i*-sterols possess a 6α-configuration, and *epi-i*-sterols a 6β-configuration. The action of *p*-toluenesulfonyl chloride on the *i*- and *epi-i*-stanols in pyridine resulted in rearrangement, and the formation of the same Δ^5-stenyl-pyridinium *p*-toluenesulfonate. Infrared spectra have been presented for two epimeric pairs of 3,5-cyclo-stanols and the 3,5-cyclo-steroid skeleton *i*-androstane.

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