A GENERAL SYNTHESIS OF 6-AZASTEROIDS

by

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Date September 7, 1961
ABSTRACT

The ozonization of 7-ketocholesteryl acetate has yielded 5-keto-5,7-seco-6-nor-3-cholesten-7-oic acid, an intermediate useful in the preparation of 6-azacholestane. Catalytic hydrogenation converted this intermediate to 5-keto-5,7-seco-6-norcholestan-7-oic acid which, upon treatment with benzyl amine, gave N-benzyl-6-aza-4-cholesten-7-one. Catalytic reduction of this enol-lactam yielded N-benzyl-6-azacholestan-7-one which was reduced with lithium aluminum hydride to N-benzyl-6-azacholestane.

The generality of this route was shown when it was applied to compounds of the androstane series. Ozonization of 3β,17β-dihydroxy-5-androsten-7-one diacetate gave 17β-hydroxy-5-keto-5,7-seco-6-nor-3-androsten-7-oic acid which was hydrogenated catalytically to 17β-hydroxy-5-keto-5,7-seco-6-norandrostan-7-oic acid. This saturated acid ring-closed with benzyl amine to yield 17β-hydroxy-N-benzyl-6-aza-4-androsten-7-one. Catalytic hydrogenation of this enol-lactam gave 17β-hydroxy-N-benzyl-6-azandrostan-7-one which was reduced with lithium aluminum hydride to N-benzyl-6-azaandrostan-17β-ol. A mild chromic acid oxidation converted the alcohol to the keto compound, N-benzyl-6-azaandrostan-17-one.
ACKNOWLEDGEMENT

The time spent working on this thesis under the guidance of Dr. James P. Kutney has been a very valuable experience; the writer expresses his appreciation of this to Dr. Kutney.

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INTRODUCTION (1)

The steroidal compounds of nature, like other natural products, have provided chemists with the subjects for many fascinating structural determinations as well as a number of complex syntheses. Their usefulness to the chemist has not stopped at this point, however, and the steroids have been used as a basis for a large number of chemical studies. Among these are determination of absorptions of typical functional groups and chromophores in infrared and ultra-violet spectra, conformational analysis studies, utilization of optical rotatory dispersion as a means of determining configurations of asymmetric carbons, and use as pharmaceutical agents in the field of medicine. Today, their usefulness continues to occupy the interest of chemists.

The initial work on steroids was quite naturally concerned with their structural elucidation and chemists used the easily interrelated bile acids, cholesterol, and ergosterol as a basis of study. The correct structure of desoxycholic acid was proposed in 1932 (2)(3) and this led to the immediate formulation of cholesterol as I. (see figure 1) In the following years the sex hormones and the adrenal cortical hormones were isolated and their structures quickly determined. Table I illustrates the more common steroid types.
The structural elucidations of the steroids were essentially completed by 1940. The next decade found the major research efforts directed toward determination of the stereochemistry of the steroids and at the end of this period, cortisone, for example, could be represented as in formula II. (see figure 2) The substituents at the asymmetric carbons of a steroid are designated as $\alpha$ (below the plane of the molecule as drawn) or $\beta$ (above the plane of the molecule). The nomenclature of steroids depends on the configuration of carbon atom five; table I gives the nomenclature of some common steroids.

**Table I**

THE NOMENCLATURE OF SOME COMMON STEROIDS

<table>
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<tr>
<th>Configuration of $C_5$</th>
<th>Steroid Name</th>
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<tr>
<td>$\alpha$</td>
<td>Cholestane</td>
</tr>
<tr>
<td>$\beta$</td>
<td>Coprostanone</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>Allocholane</td>
</tr>
<tr>
<td>$\beta$</td>
<td>Cholane</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>Androstane</td>
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<tr>
<td>$\beta$</td>
<td>Testane</td>
</tr>
<tr>
<td>$\beta$</td>
<td>Estrane</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>Allopregnane</td>
</tr>
<tr>
<td>$\beta$</td>
<td>Pregnane</td>
</tr>
</tbody>
</table>
Figure 1. Cholesterol and the numbering system of steroids

Figure 2. Cortisone and its stereochemistry
The discovery of the great physiological activities of certain steroids (such as the sex hormones and the adrenal cortico hormones) when administered to animals as well as to humans has stimulated much research designed towards synthesis of these hormones and of analogous steroidal compounds which may have similar physiological effects. This has led to the synthesis of many different types of altered steroid molecules, some of which have exhibited remarkable physiological activity.

The first hormone analogs which had greater activity than the parent compounds were discovered accidentally when some 9-halogenated cortisol intermediates were included in tests for physiological activity and were found to be highly active. (4) All the 9α-halogen derivatives of cortisol and cortisone were prepared and the decreasing size of the halogen substituent was found to increase glucocorticoid (liver glycogen deposition) properties of the cortisone greatly. (5) Thus, 9α-fluorocortisone acetate was found to be nine times as active as cortisone acetate. Following this discovery, many other cortisone analogs were quickly prepared.

Certain methylated cortisols and cortisones also show greater anti-inflammatory properties than do the natural hormones. The compounds, 2α-methyl-cortisol and its 9α-fluoro derivative, have such properties but also have greatly enhanced mineralocorticoid (salt and water retention) activity. (6) However, 6α-methyl-prednisolone (1-dehydrocortisol)
eliminates this undesirable salt and water retention while maintaining a high level of glucocorticoid activity. (7)

Combination of several substituents in the same hormone analog may give additive or complementary physiological properties. Some C₁₆-hydroxylated cortisols in combination with a 9α-fluoro atom have high glucocorticoid activity as well as greatly reduced salt retention. (8) These hydroxylated steroids illustrate a third type of hormone analog.

In contrast to the addition of a substituent to the hormone molecule, the preparation of certain norsteroids (those in which carbon atoms have been removed from the normal steroid skeleton) has also led to compounds of increased biological activity. For example, 19-norprogesterone (9) has 4-8 times the activity of progesterone whereas 17α-ethynyl-19-nortestosterone has about five times the progestational activity of 17α-ethynyltestosterone. (10)

Another mode of alteration of the steroid molecule has been the introduction of nitrogen into the steroid ring system thereby producing a heterocyclic steroid analog. Several methods have been used in the synthesis of these aza-steroids. The first and more common of these is the utilization of the Beckmann rearrangement of an oxime in which the size of the heterocyclic ring in the product has been increased by one atom. (11-20) (see figure 3) A similar
method is the Schmidt reaction in which the rearrangement of an azide to an amine has been utilized to prepare an azasteroid. (12, 20-22)

A third method of preparation of azasteroids has utilized the ring closure of a keto-acid to a lactam by reaction with bases such as ammonia or amines. (14, 23-31) This method must yield a heterocyclic ring possessing one more atom than the starting keto-acid. Thus, if a heterocyclic six-membered ring A, B, C or five-membered D ring is desired, a carbon atom must first be eliminated from that ring of the steroid used as starting material. Such an elimination has been accomplished in ring A of the steroids by ozonization of an $\alpha,\beta$-unsaturated ketone. (23, 27-32) (see figure 4)

The preparation of 6-azasteroids was undertaken since such a synthesis would provide a steroid molecule with the usual functional groups at $C_3$ and $C_{17}$, a condition important to the physiological activity of most steroidal compounds, in addition to a basic nitrogen in the B ring. These properties had not been combined in any azasteroid reported before 1960; however, since that time, Jacobs and Brownfield (28) have prepared 6-azacholestane and Lettre and Knof (21) have prepared 6-azacholesterol.

Preliminary reports have suggested that certain 4-azasteroids exhibit biological activities (33) and that 6-aza-3,5-cholestadiene has a cytotoxic activity. (21)
Figure 3. Azasteroid synthesis using the Beckman rearrangement

Figure 4. Azasteroid synthesis using the ring closure of a keto-acid
The initial requirement of the synthesis of a 6-azasteroid is the removal of C₆ from the steroid B ring. The unsaturation of cholesterol at C₅ renders that ring vulnerable to various methods of attack which may be used to open the ring and remove C₆. Thus cholesteryl acetate, readily prepared by the acetylation of cholesterol, was used as a starting material in the synthesis of N-benzyl-6-azacholestane.

Chromic acid oxidation of cholesteryl acetate was the first method of attack attempted since this leads to the oxidation of ring B to the keto-acid, III, in addition to formation of 7-ketocholesteryl acetate, IV. (34) The keto-acid, III, has been converted to the lactone, V, which upon heating goes to 3-acetoxy-B-norcholest-5-ene, VI. (35) (see figure 5) Various oxidative reactions could then be applied to VI in order to obtain the keto-acid, VII. However, the number of steps required, many of only moderate yields, plus further work using different approaches on 7-ketocholesteryl acetate caused us to abandon this route to a keto-acid.

Several attractive alternatives utilizing 7-ketocholesteryl acetate, IV, as an intermediate in the elimination of C₆ were considered in view of the fact that this material can be prepared in higher yield. (36) One
Figure 5. Theoretical route to intermediate keto-acid

Figure 6. Epoxidation reactions
method of approach involved epoxidation of the C5 double bond. Since both cholestenone, VIII, (37) and 3-hydroxyestra-1,3,5 (10),16-tetraen-20-one, IX, (38) readily undergo epoxidation when treated with 30-35% hydrogen peroxide in an alkaline solution, (see figure 6) these conditions were attempted with 7-ketocholesterol acetate. However, epoxidation did not occur and 7-ketocholesterol (39) was recovered in good yield. Following a procedure using peroxytrifluoroacetic acid (40), the epoxidation was achieved in 33% yield after chromatography of the product on silicic acid-celite. (41) It was already known that periodic acid is an excellent hydrolytic agent for 5,6-epoxycholesterols (42) giving the diols in high yield. It was therefore assumed that the epoxy ketone, X, via the intermediate diol, XI, would result directly in the keto-acid, VII, when treated with periodic acid. (see figure 7) Several attempted cleavages of the epoxide with periodic acid gave no well defined products and in view of the subsequent successful ozonization of 7-ketocholestereryl acetate, this approach was not further studied.

Ozonization of an \( \alpha, \beta \)-unsaturated ketone system in ring A of compounds such as cholestenone gives good yields of the \( \delta \)-keto-acids. (32) When 7-ketocholestereryl acetate, IV, was treated with ozone at room temperature in an acetic acid solution followed by oxidative decomposition of the ozonide with hydrogen peroxide and water, approximately 50% of the material was extractable with base. Chromatography on a
Figure 7. Attempted route to intermediate keto-acid

Figure 8. Compounds containing enol-lactam chromophore
silica gel column gave the desired keto-acid in 18-22% yields as well as a more polar fraction which was not characterized. If the extraction of the acidic components before chromatography was done with aqueous potassium carbonate, the 3-acetoxy group was retained in the molecule as shown by an ester carbonyl band at 1730 cm$^{-1}$ and a C-O stretching band at 1250 cm$^{-1}$ in its infrared spectrum. (43) Treatment of this compound with 5% aqueous sodium hydroxide caused elimination of acetic acid to give 5-keto-5,7-seco-6-nor-3-cholesten-7-oic acid, XII. This compound was also obtained by direct sodium hydroxide extraction of the ozonization product. The infrared absorption maxima at 1726 cm$^{-1}$, 1675 cm$^{-1}$, and 1655 cm$^{-1}$ are characteristic of a carboxyl and an $\alpha,\beta$-unsaturated carbonyl system as demanded by structure XII. The presence of the unsaturated ketone system is further shown by the ultra-violet spectrum of this compound (XII) which has a maximum at 227 m$\mu$. The expected position of the ultra-violet maximum for this compound as calculated by Woodward's rules is also at 227 m$\mu$. (44) The neutralization equivalent of the compound showed the presence of one carboxyl group which, along with analytical data, confirmed structure XII.

The keto-acid, XII, did not react when treated with ammonia in a benzene solution at room temperature although these conditions were sufficient to form a ring A lactam from the corresponding keto-acid. (27) The failure of
the ring B keto-acid to form the lactam with ammonia is not unexpected since the two reactive centers are on different rings and so will tend to be further separated than in the rigid ring A keto-acid. Such a situation has been well illustrated when exceptions to the Blanc rule \(^{(45)}\) of cyclopentanone and anhydride formation from six carbon and five carbon diacids (respectively) were found. \(^{(3,46)}\) The six carbon "B ring" diacid, thilobilianic acid, was found to form a seven membered cyclic anhydride more easily than the predicted cyclopentanone. The angular methyl group at \(C_{10}\) in these situations will react sterically with the adjacent ring when the reactive centers are brought together as in formation of the lactam or the cyclopentanone.

When refluxed with benzyl amine \(^{(24)}\), the keto-acid, XII, gave an uncharacterized oil which had an ultraviolet absorption maxima at 293 \(\mu\) which is probably due to a 2,4 diene in conjugation with the B ring lactam. Jacobs and Brownfield subsequently reported that 6-aza-2,4-cholestadien-7-one has an ultra-violet maximum at 299 \(\mu\). \(^{(28)}\) The acid retaining the 3-acetoxy function was also treated with benzyl amine and yielded an oily product having the same ultraviolet spectrum as described above. This could easily result from acetic acid elimination in the basic benzyl amine solution followed by cyclization of the keto-acid with the amine.

The keto-acid, XII, was readily converted to the corresponding saturated keto-acid, XIII, by catalytic
Figure 9. Synthetic route to N-benzyl-6-azacholestane
hydrogenation. The success of the hydrogenation was evidenced by a shift of the ketone carbonyl absorption to 1700 cm.\(^{-1}\) in the infrared and by disappearance of any absorption in the ultra-violet spectrum.

Reaction of the saturated keto-acid, XIII, with benzyl amine at reflux temperature gave the neutral enol-lactam, XIV, as a crystalline product. Again, characterization of this compound was made by consideration of its spectral properties and its elemental analysis. Its infrared spectrum had a lactam carbonyl band at 1640 cm.\(^{-1}\) and an olefinic band at 1662 cm.\(^{-1}\); that the olefin band is at the higher wave number was shown by its disappearance upon hydrogenation. If the amide was the result of the reaction of only the carboxyl group with benzyl amine, the compound would be expected to have no ultra-violet spectrum other than that of the benzyl group. However, the ultra-violet maximum of XIV at 237 \(\mu\) is very similar to those of analogous enol-lactam chromophores such as 4a-phenyl-\(\Delta^8\)-octahydro-2-quinolone (\(\lambda_{\text{max}} = 231 \mu\)), XV, N-methyl-4a-phenyl-\(\Delta^8\)-octahydro-2-quinolone, XVI, (\(\lambda_{\text{max}} = 233 \mu\)) (47), and for 4-azacholest-5-en-3-one, (XVII), (\(\lambda_{\text{max}} = 233 \mu\)). (27) (see figure 8) Catalytic hydrogenation of the enol-lactam, XIV, yielded the lactam, XVIII, having a lactam carbonyl band in the infrared at 1644 cm.\(^{-1}\) and having an ultra-violet spectrum characteristic of the benzyl amine group, (211 \(\mu\)). Reduction of the enol-lactam, XIV, with lithium aluminum hydride gave an unstable
oil as a product. It exhibited an infrared band at 1634 cm.\(^{-1}\) which is probably due to the C\(_4\) olefin.

The lactam, XVIII, was the compound desired for the preparation of the azasteroid and was successfully converted to N-benzyl-6-azacholestane, XIX, by reduction with lithium aluminum hydride in a refluxing ether solution. The azasteroid was a crystalline compound which had no carbonyl bands in the infrared spectrum but which retained the absorption bands attributable to the aromatic ring.

Reduction of the lactam, XVIII, over platinum in an acetic acid-HCl solution gave a compound showing a melting point depression when mixed with starting material, although each had similar melting points. It also retains an amide infrared band which when taken with its analysis suggests that the compound may be N-acetyl-6-azacholestane, XX.
The successful utilization of cholesterol as a starting material in the synthesis of N-benzyl-6-azacholestane provided a synthetic sequence which it was hoped would be useful in the preparation of 6-aza steroidal hormones from starting materials having a 5,6 double bond. Dehydroepiandrosterone (androstenedione), is such a compound and is of the androgenic family of hormones; thus it was used as a starting material in a synthesis of N-benzyl-6-azaandrostan-17β-ol and N-benzyl-6-azaandrostan-17-one.

It was first necessary to protect the oxygen functions at C₃ and C₁₇ of androstenolone, XXI, since these would both be affected by subsequent reactions if left unprotected. Although the hydroxyl group at C₃ is lost during subsequent reactions, it must be protected during the allylic oxidation of C₇. Likewise, the C₁₇ ketonic function must be protected during reactions with amines. The hydroxyl group at C₃ was first converted to the known formate, XXII, and the ketone then reduced to an alcohol, XXIII, with sodium borohydride. (48) The alcohol was acetylated and the resulting compound, XXIV, oxidized with t-butyl chromate (36) to give the desired 7-keto-5-androsten-3β,17β-diol 3-formate 17-acetate, XXV. An equally successful route involving one less step to an ozonizable compound resulted when androstenolone
Figure 10. Protection of oxygen functions of androstenolone
was reduced with sodium borohydride to 5-androsten-3\(\beta\),17\(\beta\)-diol, XXVI. Acetylation of the diol followed by allylic oxidation with t-butyl chromate gave 7-keto-5-androsten-3\(\beta\),17\(\beta\)-diol diacetate. XXVII (36)

The unsaturated keto-acid, 17\(\beta\)-hydroxy-5-keto-5,7-seco-6-nor-5-androsten-7-oic acid, XXVIII, was obtained from ozonization of either XXVII or XXV followed by sodium hydroxide extraction. The results of the ozonization reaction were not consistent from experiment to experiment, however, and the course of the reaction has not been completely worked out. In addition to the keto-acid, XXI, characterized by its spectral characteristics, on one occasion a crystalline solid was isolated directly from the extract of the acidic material of the ozonization reaction. This material was unique in that it was crystallizable from hot water. It is a compound retaining five oxygens and having no ultra-violet spectrum. Its infrared spectrum showed the presence of alcoholic, ketonic, and acidic functions and the absence of any acetate group. It may be speculated that this material has the structure XXIX or XXX. A third reaction product was obtained in the form of an oil having a moderate ultra-violet absorption corresponding to that of the unsaturated keto-acid, XXVIII. This oil also had an acetoxy absorption band in its infrared spectrum and upon chromatography this oil separated into two fractions, both retaining similar spectral characteristics. Catalytic hydrogenation of this oily product
resulted in uptake of 0.5-0.7 of a mole of hydrogen. Treatment of the hydrogenated oil with refluxing benzyl amine gave the enol-lactam, XXXII, described below, and in addition it gave a glassy product when the acid extract of the product was basified. This product has an infrared absorption similar to that of the enol-lactam, XXXII, with peaks at 1657 and 1690 cm$^{-1}$ but, in addition, it has a strong absorption at 1505 cm$^{-1}$. The ultra-violet spectrum of this material has a maximum at 248 nm suggesting either a different chromophore in the molecule or a further conjugation of the enol-lactam system.

The desired keto-acid, XXVIII, was a crystalline solid retaining either organic solvents or water very tenaciously and requiring drying at 100°C. This drying had a marked effect on the position of the unsaturated ketone carbonyl absorption in the infrared spectrum, shifting it from 1637 cm$^{-1}$ to 1660 cm$^{-1}$. The hydrolysis of the 17-acetoxy group either during the ozonization or the work up is shown by the hydroxyl band at 3580 cm$^{-1}$ and the absence of the acetoxy C-O-band at 1250 cm$^{-1}$ in the infrared. The ultra-violet spectrum has a maximum at 227 nm corresponding to an $\alpha,\beta$-unsaturated ketone system.

Catalytic hydrogenation of the keto-acid, XXVIII, gave the saturated keto-acid, XXXI, as evidenced by its infrared spectrum. Cyclization of the keto-acid, XXXI, with benzyl amine proceeded as in the cholesterol series of
compounds to give the enol-lactam, XXXII. Likewise catalytic hydrogenation of the enol-lactam yielded the lactam, XXXV, having spectra similar to those of the corresponding lactam, XIV, in the cholesterol series.

Lithium aluminum hydride reduction of the lactam, XXXV, yielded crystalline N-benzyl-6-azaandrostan-17β-ol, XXXVI.

Oxidation of XXXVI using the mild conditions of chromium trioxide in acetone (49) yielded N-benzyl-6-azaandrostan-17-one, XXXVII. The appearance of the characteristic cyclopentanone carbonyl at 1730 cm\(^{-1}\) in the infrared spectrum of this compound confirmed the success of the oxidation.
CONCLUSION

A general synthesis of 6-azasteroids has been developed using cholesterol as a model starting compound. The synthesis includes reactions giving good yields of products with the exception of the ozonization. It seems likely that a thorough study of conditions for the ozonization reaction would improve the yield of this step. The synthesis has the disadvantage of the loss of the functional group at C\textsubscript{3}. The use of benzyl amine in the cyclization of the saturated keto-acids provides, in the enol-lactam, a compound which may be useful in further studies designed to re-introduce the C\textsubscript{3} oxygen function since the tertiary nitrogen will prevent double bond migrations which have been shown to occur if the nitrogen of the enol-lactam is secondary.\(^{(28)}\) It has been reported that N-bromosuccinimide substitutes a bromine at the olefinic C\textsubscript{4} position\(^{(28)}\), however further studies of both allylic bromination and allylic oxidation reactions on the enol-lactam system may lead to re-introduction of the C\textsubscript{3} oxygen function. The hydrogenolysis of N-benzyl is well known\(^{(50)}\) and if applied to N-benzyl-6-azasteroids it would provide a route to the 6-azasteroids.

The preparation of N-benzyl-6-azaandrostan-17-ol and N-benzyl-6-azaandrostan-17-one provides the first known examples of ring B aza steroidal hormones and demonstrates the
generality of the synthetic sequence. A more thorough study of the ozonization step here is required, however, in order to define the several products obtained and the conditions under which they result.
EXPERIMENTAL

The melting points were determined on a Fisher-Johns melting point block and are uncorrected. All ultraviolet spectra were recorded on a Cary 11 recording spectrophotometer in solutions of 95% ethanol. Rotations were determined in chloroform solutions. Infrared spectra were recorded on a Perkin-Elmer 21 spectrophotometer. Analyses were performed by A. Bernhardt, Mulheim-Ruhr, Germany.

Cholesteryl acetate. The acetylation procedure described by Fieser (51) was used. Cholesterol, I, (40 g.) was dissolved in pyridine (40 ml.) and acetic anhydride (40 ml.) and heated on a steam bath for 0.5 hour. The solution was then poured into cold water and stirred several hours. The resulting white solid was filtered off and dried. Recrystallization of the solid from acetone yielded cholesteryl acetate as colorless needles, m.p. 112-114.5°; $\tilde{\nu}_{C=O} 1727$ cm.$^{-1}$ (5.79µ) in KBr and in Nujol; $\tilde{\nu}_{C=C} 1470$ cm.$^{-1}$ (6.80µ) in KBr; $\tilde{\nu}_{C=O} 1250$ cm.$^{-1}$ (8.00µ) in KBr and in Nujol. Reported m.p. 116°. (51)

7-Ketocholesteryl acetate (IV). The allylic oxidation procedure of Heusler and Wettstein (36) was used. A solution of cholesteryl acetate (50.0 g., 0.113 mole) in 240 ml. of carbon tetrachloride was heated to 70°C. and treated with
275 ml. of a solution of t-butyl chromate in carbon tetrachloride mixed with 125 ml. of glacial acetic acid and 50 ml. of acetic anhydride. The oxidizing solution was added to the reaction over a period of 0.5 hour. The reaction mixture was then warmed to 76-79° with constant stirring for ten hours after which the dark green solution was cooled to 5° in an ice bath. Eighty grams of oxalic acid in 400 ml. of water were slowly added to the cooled reaction with vigorous stirring. A further 50 g. of solid oxalic were then added and the mixture allowed to warm to room temperature. The carbon tetrachloride layer was separated and the aqueous layer extracted with more carbon tetrachloride. The organic extracts were combined and washed with aq. sodium bicarbonate and with water and then dried over magnesium sulfate. The carbon tetrachloride solution was filtered and the solvent removed under reduced pressure to yield a greenish-yellow solid. Crystallization from ether yielded, in three crops, 31.1 g. of 7-ketocholesteryl acetate, m.p. 150-152°, 161-163° C.; \( \nu_C = 0 \) 1732, 1670 cm.\(^{-1}\) (577, 5.99\( \mu \)) in KBr; \( \nu_C = c \) 1640 cm.\(^{-1}\) (6.10\( \mu \)) in KBr. Reported m.p. 157-159°. (39)

7-Ketocholesterol. Saponification of 7-ketocholesteryl acetate with methanolic sodium hydroxide for twelve hours at room temperature gave a white solid when the reaction was diluted with water. Crystallization of the solid from acetone gave small, colorless needles of 7-ketocholesterol,
m.p. 173-174\degree; \( \lambda_{\text{max}} \) 236 \text{ m}\mu \ (\log\varepsilon \ 4.19). \ Reported \ m.p. \ 170-172\degree, (39).

3\beta\text{-Hydroxy-5,6-epoxycholestan-7-one 3-acetate (X).}

A. \textit{Methods} of Plattner, et al. (37) and Zaffaroni, et al. (38).

When 7-ketocholesteryl acetate (1.0 g., 2.3 mmoles) was treated with 4-8 ml. of 30\% hydrogen peroxide in a methanolic sodium hydroxide solution at either 0\degree C. or at room temperature, there was obtained 0.89 g. (2.2 mmoles, 97\%) of a white solid product. This product was crystallized from acetone and had m. p. 171-173\degree; mixed m.p. with 7-ketocholesterol, 171-173\degree.

B. \textit{Method} of Bergmann and Meyers, (41). The epoxidizing reagent was made up as follows: 3.0 ml. of trifluoroacetic anhydride in 5 ml. of methylene chloride was mixed at 0\degree C. with stirring with a solution of 4.5 ml. of 98\% hydrogen peroxide in 10 ml. of methylene chloride. This reagent was added by dropping over a period of forty minutes to a solution of 1.0 g. (2.3 mmoles) of dried 7-ketocholesteryl acetate in 30 ml. of methylene chloride over 5 g. of anhydrous sodium hydrogen phosphate at the reflux temperature of methylene chloride. The solution was refluxed another forty minutes, then cooled and treated with 50 ml. of water. The layers were separated, the aqueous layer was washed twice with methylene chloride, and the combined organic extracts were dried over magnesium sulfate. Filtration of the dry solution followed by removal of the solvent under
reduced pressure yielded 1.02 g. of a glassy solid. This material was chromatographed on a column made of 50 g. of celite mixed with 50 g. of silicic acid (100 mesh) packed in hexane. Elution of the column with 50% benzene in hexane yielded 0.36 g. of a white solid. Crystallization from methanol gave a first crop of crystals, m.p. 122-129\(^\circ\), after recrystallization, \([\alpha]_D^{25} +77^\circ\) and a second crop having m.p. 127-131\(^\circ\) and \([\alpha]_D^{25} +99^\circ\) after recrystallization. Reported m.p. 130-131.5\(^\circ\); \([\alpha]_D^{25} +78.9^\circ\) for 3\(\beta\)-acetoxy-5,6\(\alpha\)-epoxycholestan-7-one. (41)

Periodic acid oxidation of the epoxide, X. A solution of the epoxide, X, (0.040 g.) in 4 ml. of acetone was added to a solution of 0.625 g. of periodic acid in 3 ml. of water and refluxed for 12 hours. The reaction mixture slowly turned brown in color and upon removing the acetone and cooling the solution, a dark oil separated. This oil solidified and was dissolved in acetone and then poured into water yielding a creamy-white solid. The solid was taken up in ether and dried after which a whitish solid resulted; \(\lambda_{\text{max}}\) 234 m\(\mu\) (log \(\epsilon\) 4.01); \(\nu_{\text{c}=0}\) 1730, 1670 cm\(^{-1}\) (5.78, 599\(\mu\)) in Nujol.

5-Keto-5,7-seco-6-nor-3-cholestan-7-oic acid (XII). Solutions of 7-ketocholesteryl acetate (25.0 g., 0.0565 mole) in glacial acetic acid (100 ml.) were ozonized in five gram portions.
Ozonizing conditions using a Welsbach ozonator were:
5.5 p.s.i. of oxygen pressure, 110 volts, 0.06 rotameter setting, 20 minutes, 25°C. The solution became bright yellow during the ozonization. This color slowly disappeared when the ozonide was treated with 10 ml. of 30% hydrogen peroxide and 50 ml. of water (for each 5 g. lot) and allowed to stand for 15-18 hours. The excess solvent was removed under reduced pressure and the residue was taken up in ether. The ether solution was washed twice with water and then extracted with 5% aq. sodium hydroxide. The initial basic extracts removed the remaining acetic acid; after this the extracts were bright yellow-orange in color with some orange, oily material observed between the aqueous and ether layers which was included in the basic extract. Basic extraction was continued until only slightly yellow extracts were obtained. The basic extract was acidified with dil. aqueous hydrochloric acid which resulted in the formation of an oily white mixture. The acidic material was taken up in ether and dried over magnesium sulfate. Removal of the ether gave 20.3 g. of viscous oil. Chromatography of the oil on BDH silica gel (500 g.) gave the keto-acid, XII, as an oil when eluted with 100% chloroform. Crystallization from hexane gave 4.86 g. (0.012 mole, 22%) of colorless crystalline keto-acid, m.p. 179-183°C. Three recrystallizations from hexane gave 5-keto-5,7-seco-6-nor-3-cholesten-7-oic acid as colorless needles, m.p. 181-184°C;
$\lambda_{\text{max.}}$ 226 m$\mu$ ($\log \varepsilon$ 3.93); $[\alpha]_D +78.9^\circ$; $\tilde{\nu}_C = 0$ 1726, $1677$ cm.$^{-1}$ ($5.79$, $5.96\mu$) in Nujol, $1705$, $1675$ cm.$^{-1}$ ($5.86$, $5.97\mu$) in CHCl$_3$; $\tilde{\nu}_C = 0$ 1655 cm.$^{-1}$ ($6.04\mu$) (shoulder) in Nujol.

**Anal. Calcd. for C$_{26}$H$_{42}$O$_3$ (402.60):** C, 77.56; H, 10.51; O, 11.92. Found: C, 77.82; H, 10.46; O, 12.09; neutralization equivalent, 394; M.W. (Rast), 402. Reported m.p. 164-165$^\circ$; $[\alpha]_D +81 \pm 1^\circ$. (28)

When the ozonization was carried out as above with the exception that the basic extraction was done with dilute potassium carbonate, an oil was obtained which was eluted from a silica gel column with 100% chloroform to yield crystals from ether-petroleum ether (30-60$^\circ$), m.p. 171-177$^\circ$C. Two further recrystallizations from ether-petroleum ether (30-60$^\circ$) gave colorless needles, m.p. 173-178$^\circ$C; $\tilde{\nu}_C = 0$ 1740, 1730, 1715, and 1702 cm.$^{-1}$ ($5.75$, $5.78$, $5.83$, $5.88\mu$) in KBr.

**Anal. Calcd. for C$_{28}$H$_{46}$O$_5$ (462.65):** C, 72.69; H, 10.02; O, 17.30. Found: C, 72.08; H, 9.84; O, 18.02. When this compound was taken up in ether and extracted with 5% aqueous sodium hydroxide, it was converted to 5-keto-5,7-seco-6-nor-3-cholesten-7-oic acid as shown by appearance of an ultraviolet absorption maxima at 227 m$\mu$. and a similar melting point of the solid.
5-Keto-5,7-seco-6-norcholestan-7-oic Acid (XIII). The \( \alpha,\beta \)-unsaturated keto-acid, XII, (0.398 g., 0.990 mmole) was hydrogenated over 10% palladium-on-charcoal (0.4 g.) in an ethanol solution at room temperature and atmospheric pressure. The hydrogen uptake was complete in 15 minutes and totalled 18.6 cc. (calculated volume for one mole uptake is 22.2 cc). The catalyst was filtered off and the solvent removed under reduced pressure leaving a white solid. This solid crystallized from hexane yielding 0.237 g. (0.587 mmole, 59%) of saturated keto-acid, m.p. 188-193°. Three additional crystallizations from hexane gave 5-keto-5,7-seco-6-norcholestan-7-oic acid as colorless needles, m.p. 192-194°; \([\alpha]_D +91.3^0\); \(\nu_C = 0 1715, 1697\) cm.\(^{-1}\) (5.83, 5.89\(\mu\)) in KBr, 1722, 1703 cm.\(^{-1}\) (5.81, 5.87\(\mu\)) in Nujol; shoulder at 1736 cm.\(^{-1}\) (5.76\(\mu\)) in KBr, 1745 cm.\(^{-1}\) (5.73\(\mu\)) in Nujol.

Anal. Calcd. for \(C_{26}H_{44}O_3\) (404.61): C, 77.17; H, 10.98; O, 11.86. Found: C, 76.40; H, 10.84; O, 11.86. Reported m.p. 186.6-189.2°; \([\alpha]_D +93 \pm 2^0\). (28) A mixed m.p. of these two samples was 189-192° and their infrared spectra were identical.

N-Benzyl-6-aza-4-cholesten-7-one (XIV). The saturated keto-acid, XIII, (4.0 g., 9.9 mmole) was dissolved in 10 ml. of benzyl amine and refluxed gently for 18 hours in a nitrogen atmosphere. (24) The cooled yellow reaction solution was taken up in ether and extracted with aqueous hydrochloric acid.
until the extract remained acidic to litmus. It was then washed once with 5% aqueous sodium hydroxide and once with a saturated salt solution. The neutral ether layer was dried over magnesium sulfate, filtered, and the ether evaporated to yield a light yellow solid. Crystallization from methanol yielded, in two crops, 3.93 g. (8.3 mmole, 84%) of colorless crystals, m.p. 135-140°. Three recrystallizations from methanol gave N-benzyl-6-aza-4-cholesten-7-one as long, flat colorless crystals, m.p. 139-141°; λ max. 211 mμ (log ε 4.06), 237 mμ (log ε 4.05); [α] D +93.0°; β C = 0 1640 cm. -1 (6.10 μ) in KBr, 1645 cm. -1 (6.08 μ) in Nujol; β C = C 1662 cm. -1 (6.02 μ) in KBr, 1670 cm. -1 (5.99 μ) in Nujol; β aromatic 1495, 728 cm. -1 (6.69, 13.7 μ) in KBr, 1500, 733 cm. -1 (6.67, 13.6 μ) in Nujol.

Anal. Calcd. for C33H49NO (475.73): C, 83.31; H, 10.38; N, 2.94; O, 3.36. Found: C, 82.42; H, 10.33; N, 3.01; O, 3.48. Reported m.p. 136.3-137.3°; [α] D +107 ± 1°. (28)

Mixed m.p. of the two samples was 135-137° and their infrared spectra were identical.

N-Benzyl-6-aza-cholestan-7-one (XVIII). The enol-lactam, XIV, (0.500 g., 1.05 mmole) was hydrogenated in acetic acid (40 ml) over 0.050 g. of pre-reduced platinum oxide at room temperature and atmospheric pressure. The total uptake of hydrogen was 31.0 cc. (calculated for one mole, 24 cc.) and was complete in one hour. The catalyst was filtered off, the acetic acid was
removed under reduced pressure, and the remaining oil was placed in a vacuum desiccator over potassium hydroxide for several hours. The oil (0.497 g., 1.04 mmole, 99%) crystallized from ether-methanol, m.p. 141-145°. Three recrystallizations from ether-methanol gave an analytical sample of N-benzyl-6-azacholestan-7-one, m.p. 143-145°; [α]D +63°; νC=0 1644 cm.⁻¹ (6.08μ) in Nujol; νaromatic 1500, 732 cm.⁻¹ (6.67, 13.6μ) in Nujol.

Anal. Calcd. for C33H51NO: C, 82.96; H, 10.76; N, 2.93; O, 3.35. Found: C, 83.19; H, 10.53; N, 3.19; O, 3.50.

Catalytic reduction of N-benzyl-6-azacholestan-7-one. A solution of the lactam, XVIII, (0.148 g., 0.309 mmole) in 29 ml. of acetic acid and 4.8 ml. of IN hydrochloric acid was hydrogenated over 0.120 g. of platinum oxide (pre-reduced) for 14 hours. The measured hydrogen uptake was 21.6 cc. The catalyst was filtered off and water was added to the solution which caused a cloudy solid to form. After 48 hours, small crystals had formed. These were filtered off and dried. They weighed 0.115 g. and had m.p. 142-145°. Two recrystallizations from methanol gave long colorless needles, m.p. 150-152°; mixed melting point with N-benzyl-6-azacholestan-7-one, 130-145°; νC=0 1629 cm.⁻¹ (6.14μ) in KBr.

N-Benzyl-6-azacholestane (XIX). N-Benzyl-6-azacholestane-7-one (0.50 g., 105 mmole) was dissolved in dry ether and treated with lithium aluminum hydride (0.6 g) extracted from a Soxhlet cup with refluxing ether for 24 hours. The excess lithium aluminum hydride was decomposed with moist ether and water followed by refluxing for 0.5 hour. The inorganic solids were filtered off by suction and the ether solution dried over magnesium sulfate. Removal of the ether yielded 0.423 g. (0.915 mmole, 87%) of light yellow oil which crystallized from ether-methanol, m.p. 65-68°. Two further recrystallizations from ether-methanol yielded N-benzyl-6-azacholestane as colorless, chunky crystals, m.p. 67-69°; \( \lambda_{\text{max}} \) 210 m\( \mu \) (log \( E \) 3.98); [\( \alpha \)]\( D\) +71°; \( \gamma \) aromatic 1493, 736 cm\(^{-1}\) (6.70, 13.6\( \mu \)) in KBr.


3\( \beta \)-Hydroxyandrost-5-en-17-one formate (XXII). The procedure of Ringold, et al., (48) was used to prepare the formate. Dehydroepiandrosterone, XXI, (5.00 g., 17.4 mmole) was dissolved in 60 ml. of 85% formic acid and heated to 60-65° for one hour. Dilution of the reaction mixture gave a white solid which was filtered off and dried to yield 5.34 g. of crude product, m.p. 135-140°. A sample crystallized from acetone-hexane gave 3\( \beta \)-hydroxyandrost-5-en-17-one formate, m.p. 143-146°; 

\[ \gamma_C = 0 \] 1700, 1734 cm\(^{-1}\) (5.88, 5.77\( \mu \)) in KBr; 

\[ \gamma_{C-O} = 1174 \] cm\(^{-1}\)
Androst-5-en-3β,17β-diol 3-formate (XXIII). The method described by Ringold, et al. (48) was used for the reduction. A solution 3β-hydroxyandrost-5-ene-17-one formate, XII, (5.34 g., 16.9 mmole) in 100 ml. of tetrahydrofuran was treated with 0.25 g. of sodium borohydride dissolved in 0.5 ml. of water for three hours at room temperature with constant stirring. The excess sodium borohydride was decomposed with formic acid and the inorganic material was filtered off and washed with fresh tetrahydrofuran. The solvent was removed under reduced pressure leaving an oily residue which slowly crystallized. A sample recrystallized from acetone-hexane had m.p. 157-169°; ν₀-H 3460 cm⁻¹ (2.89µ) in KBr; ν₀=₀ 1698 cm⁻¹ (5.89µ) in KBr. Reported m.p. 170-172°. (48)

Androst-5-en-3β,17β-diol 3-formate 17-acetate (XXIV). The procedure of Ringold, et al. (48) was followed for this acetylation. A solution of androst-5-en-3β,17β-diol 3-formate, XXIII, (5.35 g., 0.0168 mole) and 1.83 g. of p-toluenesulfonic acid in 50 ml. of acetic anhydride was stirred at room temperature for 15 hours. The clear, brown solution was poured into an aqueous sodium acetate solution and thoroughly stirred. A yellow solid precipitated and was filtered off to yield 5.14 g. (0.0143 mole, 85%) of crude androst-5-en-3β,17β-diol 3-formate 17-acetate. A sample was recrystallized from
hexane and had m.p. 141-145°; \( \nu_{C=O} \) 1725, 1704 cm.\(^{-1}\) (5.80, \\
5.87\( \mu \)) in KBr; \( \nu_{C-O-} \) 1270, 1255, 1248 and 1163 cm.\(^{-1}\) (7.88, \\
7.97, 8.01, 8.60\( \mu \)) in KBr. Reported m.p. 146-148, 149-151°. \\
(48)

3\( \beta \),17\( \beta \)-Dihydroxyandrost-5-en-7-one 3-formate 17-acetate.

The oxidation procedure of Heusler and Wettstein (36) was used to prepare this compound. A solution of androst-5-en-3\( \beta \),17\( \beta \)-diol 3-formate 17-acetate, XXIV, (5.13 g., 0.0143 mole) in 26 ml. of carbon tetrachloride was treated with a mixture of 36 ml. t-butyl chromate solution, 12.5 ml. of acetic acid, and 5 ml. of acetic anhydride. The reaction was then carried out and worked up in the way described for the preparation of 7-ketocholesteryl acetate. Recrystallization of the reaction product from ether gave a total of 2.55 g. (0.0067 mole, 48%) of crystalline solid, m.p. 180-205°. Two further recrystallizations from ether gave 3\( \beta \),17\( \beta \)-dihydroxyandrost-5-en-7-one 3-formate 17-acetate as shiny, colorless needles, m.p. 225-227°; \( \lambda_{max} \) 235 \( \mu \) (log \( \varepsilon \) 4.05); \( \nu_{C=O} \) 1727, 1715, 1663 cm.\(^{-1}\) in KBr; \( \nu_{C=C} \) 1625 cm.\(^{-1}\) in KBr.

Anal. Calcd. for \( C_{22}H_{30}O_5 \) (374.46): C, 70.56; H, 8.07; O, 21.37. Found: C, 70.47; H, 7.68; O, 21.41.

Androst-5-en-3\( \beta \),17\( \beta \)-diol (XXVI). Dehydroepiandrosterone, XXI, (5.00 g., 0.017 mole) was dissolved in 100 ml. of tetrahydrofuran and stirred with 0.5 g. of sodium borohydride in 1.0 ml.
of water for four hours. Formic acid was used to decompose the excess sodium borohydride and the inorganic solids were filtered off. Removal of the solvent under reduced pressure yielded androst-5-en-3β,17β-diol as a white solid. Crystallization from acetone gave the product with m.p. 173-179°; \( \nu_{O-H} \) 3200, 3380, 3450 cm\(^{-1}\) (3.12, 2.96, 2.90\( \mu \)) in KBr. Reported m.p. 184°C. (52)

Androst-5-en-3β,17β-diol diacetate. The procedure of Fieser (51) was used as described for the acetylation of cholesterol. The diacetate was crystallized from hexane and had m.p. 155-160°; \( \nu_{C=O} \) 1727 cm\(^{-1}\) (5.79\( \mu \)) in KBr; \( \nu_{C-O} \) 1248 cm\(^{-1}\) (8.01\( \mu \)) in KBr. Reported m.p. 165-166°C. (53)

3β,17β-Dihydroxyandrost-5-en-7-one diacetate (XXVIII). The procedure of Heusler and Wettstein (36) was used in a manner identical to that described for the preparation of 7-ketocholesteryl acetate, p. 25. Crystallization from ether gave 3β,17β-dihydroxyandrost-5-en-7-one diacetate, m.p. 220-225°; \( \nu_{C=O} \) 1730, 1687 cm\(^{-1}\) (5.78, 5.93\( \mu \)); \( \nu_{C=C} \) 1623 cm\(^{-1}\) (6.16\( \mu \)); \( \nu_{C-O} \) 1240 cm\(^{-1}\) (8.06\( \mu \)) in KBr. Reported m.p. 219-221°C. (36)
Ozonization of $3\beta,17\beta$-dihydroxyandrost-5-en-7-one diacetate.

A. 17\(\beta\)-Hydroxy-5-keto-5,7-seco-6-nor-3-androsten-7-oic acid (XXVIII). A solution of $3\beta,17\beta$-dihydroxyandrost-5-en-7-one diacetate (or $3\beta$-formate 17-acetate) (3.42 g., 8.8 mmole) in glacial acetic acid was treated with ozone from a Welsbach ozonator operating under the conditions: 5.5 p.s.i. of oxygen pressure, 110 volts, rotameter setting of 0.06, 15 minutes, 25°. A yellow solution resulted which was treated with 3 ml. of dilute hydrogen peroxide and 15 ml. of water after 20 minutes. The solution became clear as it stood at room temperature for 20 hours. The excess acetic acid was then removed under reduced pressure leaving an oily residue. The oil was taken up in ether and extracted with 5% aqueous sodium hydroxide. This basic extract was yellow-orange in color but became colorless after acidification with dilute hydrochloric acid. The acidic material was extracted five times with 15 ml. portions of ether, the ether extract was dried over magnesium sulfate and then filtered. Removal of the solvent yielded 1.6 g. of a glassy material. This was chromatographed on 100 g. of BDH silica gel packed in benzene. The material was applied to the column in chloroform and elution with 2½% methanol in chloroform yielded a total of 0.960 g. (3.14 mmole, 36%) of glassy material. This product crystallized from ether-petroleum ether (30-60°) and had m.p., 142-148°. Exhaustive ether extraction of the acidic aqueous solution yielded a further 1.2 g. of material. When this was chromatographed on 100 g. of BDH silica gel,
elution with 2½% methanol in chloroform failed to yield a significant quantity of material. Two recrystallizations of the above solid from ether-petroleum ether (30-60°) gave shiny, chunky crystals melting 145-150°, 195-200° and only after drying at 100° in high vacuum did they have a sharper melting point. The crystals of 17β-hydroxy-5-keto-5,7-seco-6-nor-3-androsten-7-oic acid after drying were colorless, opaque chunks, m.p. 200-204°; λ_{max} 227 μ (log ε 3.98); [α]_D +88.2°; V_{O-H} 3400 cm.⁻¹ (2.94μ) (Broad) in KBr; V_{C=O} 1720, 1657 cm.⁻¹ (5.81, 6.04μ) in KBr. Infrared absorption before drying: V_{O-H} 3580, 3200 to 3400 cm.⁻¹ (2.79, 2.94 to 3.12μ) (broad) in KBr; V_{C=O} 1726, 1635 cm.⁻¹ (5.79, 6.12μ) in KBr; V_{C=C} 1710 cm.⁻¹ (6.21μ) in KBr.

Anal. Calcd. for C_{18}H_{26}O_{4} (306.39): C, 70.56; H, 8.55; O, 20.89. Found: C, 70.65; H, 8.52; O, 21.14.

B. "C_{18}H_{26}O_{5} acid." A solution of 3β,17β-dihydroxyandrost-5-en-7-one diacetate (2.290 g., 5.90 mmole) in 100 ml. of glacial acetic acid was treated with ozone from the Welsbach ozonator for 15 minutes at room temperature under the following conditions: 5.5 p.s.i. of oxygen pressure, 110 volts, and the rotameter opened to 0.06. The resulting yellow solution was left at room temperature for thirty minutes, then it was treated with 3 ml. of 30% hydrogen peroxide and 10 ml. of water and left standing at room temperature for 18 hours. The excess solvent was removed under reduced pressure leaving an oil which
was taken up in ether and washed twice with water. The ether solution was then extracted three times with 5% aqueous sodium hydroxide giving a yellow-orange extract. The basic extract was treated with 60 ml. of a dilute hydrochloric acid solution made up of 5 ml. of concentrated hydrochloric acid in 90 ml. of water. This resulted in a clear, colorless solution from which small needles slowly crystallized. The mixture was cooled to aid further crystallization. The crystals were filtered off and dried in a vacuum desiccator. The yield of crystalline product was 0.524 g. (1.62 mmole, 28%) having a melting point of 212-217° preceded by a loss of sharp needle form at 110°-125°. The neutral ether layer from the ozonization workup gave, after drying, 0.38 g. of colorless oil. Ether extraction of the acidic aqueous solution yielded 0.2 g. of colorless oil. The above crystalline material was recrystallized three times from hot water giving shiny colorless needles which became smaller and opaque white upon drying, m.p. 233-234°; \( \lambda_{\text{max}} \), none; \( \tilde{\nu}_{\text{O-H}} \) 3540 cm.\(^{-1}\) (2.83\( \mu \)) in KBr; \( \tilde{\nu}_{\text{O=O}} \) 1727, 1692 cm.\(^{-1}\) (5.79, 5.91\( \mu \)) (broad) in KBr.

**Anal. Calcd. for C\(_{18}\)H\(_{26}\)O\(_{5}\) (322.39):** C, 67.05; H, 8.13; O, 24.82; for C\(_{18}\)H\(_{28}\)O\(_{5}\) (324.40): C, 66.64; H, 8.68; O, 24.68. **Found:** C, 67.02; H, 8.00; O, 25.06; neutralization equivalent, 308.
C. Mixture of products. Several ozonizations carried out as either of those described above gave as a product an oil having an ultra-violet maximum at 227 m\(\mu\) with an \(\epsilon\) value of 2,000-3,000. Chromatography of this oil on silica gel gave two fractions, the first eluting with 100% chloroform and having a slightly increased ultra-violet \(\epsilon\) value (3,000-5,000) and the second eluting with 2½% methanol in chloroform and having an \(\epsilon\) value of 2,000-3,000, both maxima occurring at 227 m\(\mu\). Infrared; \(\nu\) \(O=H\) not distinct in chloroform; \(\nu\) \(O=O\) 1700 to 1725 cm.\(^{-1}\) (5.80 to 5.88\(\mu\)) in chloroform; \(\nu\) \(-C-O\) 1255 cm.\(^{-1}\) (7.97\(\mu\)) in chloroform.

Hydrogenation of the combined fractions above in ethanol over 10% palladium-on-charcoal resulted in hydrogen uptake corresponding to 0.5 to 0.7 of a mole.

17\(\beta\)-Hydroxy-5-keto-5,7-seco-6-norandrostan-7-oic acid (XXXI). A solution of the unsaturated keto-acid, XXVIII, (0.896 g., 2.93 mmole) in 95% ethanol was hydrogenated over 0.540 g. of 10% palladium-on-charcoal at room temperature and atmospheric pressure. The catalyst was filtered off and the solvent distilled off under reduced pressure to give an oil (0.75 g.). Chromatography of the oil on 50 g. of silica gel gave the product as an oil by elution with 2½% methanol in chloroform. This oil (0.70 g.) slowly crystallized and was recrystallized twice from hexane to give 17\(\beta\)-hydroxy-5-keto-5,7-seco-6-norcholestan-7-oic acid as chunky, very faint yellow crystals,
m.p. 226-229°; [α]_D +96.5°; ν OH 3450 cm.⁻¹ (2.90 μ) in KBr; ν C=O 1722, 1687 cm.⁻¹ (5.81, 5.93 μ) in KBr.


17β-Hydroxy-N-benzyl-6-aza-4-androsten-7-one (XXXII).

A. From crystalline saturated keto-acid: A solution of 5-keto-5,7-seco-6-norandrostan-17-ol-7-oic acid, (XXXI), (0.553 g., 1.80 mmole) in 10 ml. of benzyl amine was refluxed gently in a nitrogen atmosphere for 15 hours. The cooled, yellow solution was taken up in ether and washed with dilute hydrochloric acid until the extract was acidic to pH paper. The ether solution was washed once with 5% aqueous sodium hydroxide and once with water. After drying over anhydrous magnesium sulfate, removal of the ether yielded a light oil weighing 0.56 gram.

Chromatography of the oil on a column of 50 g. silica gel gave 0.460 g. (1.21 mmole, 68%) of oil when the column was eluted with 50% chloroform in benzene. This oil crystallized from ether-n-hexane as heavy, round chunks covered with fluffy white needles, m.p. 105-109°. Three similar recrystallizations gave an analytical sample of 17β-hydroxy-N-benzyl-6-aza-4-androsten-7-one as a colorless solid, m.p. 107-110°; λ max 238 μ (log ε 4.02), 211 μ (log ε 403); [α]_D +102°; ν C=O 1637 cm.⁻¹ (6.11 μ) in KBr; ν C=C 1661 cm.⁻¹ (6.02 μ) in KBr.

Anal. Calcd. for C_{25}H_{33}NO_2 (379.52): C, 79.11; H, 8.76; N, 3.69; O, 8.43. Found: C, 79.49; H, 8.82; N, 3.72; O, 8.30.
B. From mixture of oily acids. When the reduced acidic material described under the ozonization (part C) of 3β,17β-dihydroxy-androst-5-en-7-one was treated with benzyl amine as above, the identical enol-lactam was obtained from the neutral fraction in approximately 50% yield. In addition, when the acidic extract of the benzyl amine reaction was neutralized with 5% aqueous sodium hydroxide, a reddish-brown oil precipitated. This oil had λ_max at 248 μ (log ε 3.85 to 3.98) in addition to the usual absorption maximum of the benzyl amine function. This oil did not readily re-dissolve in dilute aqueous hydrochloric acid. Its infrared spectrum had ν 1690, 1657, 1505, cm⁻¹.

17β-Hydroxy-N-benzyl-6-azaandrostan-7-one (XXXV). A solution of 17β-hydroxy-N-benzyl-6-aza-4-androsten-7-one, XXXII, (0.185 g., 0.488 mmole) in glacial acetic acid was reduced with hydrogen over platinum for two hours. The hydrogen uptake was 17 cc. (calculated, 11 cc.). The catalyst was filtered off and the acetic acid removed under reduced pressure and finally under high vacuum to yield 0.168 g. (0.441 mmole, 90%) of oil. The oil was chromatographed on 15 g. of silica gel and the product was eluted in 50% chloroform in benzene. It may also be chromatographed on alumina (activity III/IV) and elutes with 50% ether in petroleum ether (30-60°). The oil crystallized upon standing a short time and recrystallized from acetone-petroleum ether (30-60°) as colorless needles, m.p. 134-136°. Two further recrystallizations yield 17β-hydroxy-N-benzyl-6-azaandrostan-7-one as colorless needles, m.p. 135-137°;
\[ \lambda_{\text{max}} \] 211 (log \epsilon 4.03); \[ [\alpha]_D -1.1^0 \]; \[ \sqrt{\nu_{\text{O-H}}} 3410 \text{ cm}^{-1} \ (2.93\mu) \] (broad) in KBr; \[ \sqrt{\nu_{\text{C=0}}} 1630 \text{ cm}^{-1} \ (6.13\mu) \] in KBr; \[ \sqrt{\nu_{\text{aromatic}}} 1495 \text{ cm}^{-1} \ (6.69\mu) \] in KBr.

**Anal.** Calcd. for C\textsubscript{25}H\textsubscript{35}N\textsubscript{2}O (381.54): C, 78.69; H, 9.25; N, 3.67; O, 8.38; active H, 0.264. Found: C, 78.73; H, 9.61; N, 3.90; O, 8.66; active H, 0.27.

**N-Benzyl-6-azaandrostan-17\beta\text{-}ol (XXXVI).** 17\beta-Hydroxy-N-benzyl-6-azaandrostan-7-one, XXXV, (0.900 g., 2.36 mmoles) was dissolved in anhydrous ether and treated with lithium aluminum hydride by extraction of 1.0 g. placed in a Soxhlet cup. The total reaction time was 24 hours at ether reflux temperature and 56 hours at room temperature. The excess lithium aluminum hydride was decomposed with an acetone-ether solution. One ml. of water was added and the mixture warmed gently on a steam bath for 0.5 hour. The inorganic salts were filtered off and washed with ether. The combined ether solutions were dried over magnesium sulfate. Filtration and distillation of the ether gave a colorless oil which slowly crystallized. The yield of solid crystalline reduction product was 0.843 g. (2.30 mmoles; 97%). Recrystallization of 0.294 g. of the solid from petroleum ether (30-60\(^{\circ}\)) gave a first crop of 0.170 g. of needles, m.p. 109-111\(^{\circ}\). Two further recrystallizations gave N-benzyl-6-azaandrostan-17\beta\text{-}ol as colorless, flat needles, m.p. 110-112\(^{\circ}\); \[ [\alpha]_D +66.6^0 \]; \[ \sqrt{\nu_{\text{O-H}}} 3340 \text{ cm}^{-1} \ (330\mu) \] (broad) in KBr; \[ \sqrt{\nu_{\text{aromatic}}} 1495 \text{ cm}^{-1} \ (6.69\mu) \] in KBr.
Anal. Calcd. for $C_{25}H_{37}NO$ (367.56): C, 81.69; H, 10.15; N, 3.81; O, 43.5. Found: C, 81.57; H, 10.34; N, 4.14; O, 4.51.

N-Benzyl-6-azaandrostan-17-one (XXXVII). N-Benzyl-6-azaandrostan-17β-ol, (XXXVI), (0.265 g., 0.725 mmole) was dissolved in 10 ml. of distilled acetone and cooled to 10°C. It was treated with 0.5 ml. of a solution of 8N CrO$_3$ in sulfuric acid and water. (49) Within a minute a greenish precipitate had formed. After 15 minutes, 1 ml. of water was added and after 45 minutes, 100 ml. of water were added and the solution made basic with dilute aqueous sodium carbonate. The solution was extracted with ether, the ether was dried and after distillation gave 0.200 g. (0.55 mmole, 76%) of an oil product. Crystallization from aqueous methanol gave N-benzyl-6-azaandrostan-17-one as colorless needles, m.p. 110-112°C; $\nu_{C=O}$ 1730 cm.$^{-1}$ (5.78μ) in KBr; $\nu_{aromatic}$ 1493 cm.$^{-1}$ (670μ) in KBr.


5. Ibid., 76, 1455 (1954).


33. R.I. Dorfman, M. Uskokovic, and M. Gut, Abstracts of the 137th Meeting of the American Chemical Society, Cleveland, Ohio, April, 1960, p. 19-N.


45. H.G. Blanc, Compt. rend., 144, 1356 (1907).


52. Fieser and Fieser, op. cit., pp. 519.