# AZA STEROIDS

## II. SYNTHESIS OF 6-AZA STEROIDS—A NOVEL CLASS OF AZAANDROSTANE ANALOGUES

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ABSTRACT

A synthesis of N-benzyl-6-azacholestane is described and the generality of the approach is exemplified by the successful synthesis of 17β-hydroxy-N-benzyl-6-azaandrostane. This represents the first synthesis of a 6-aza derivative in the androstane series.



In recent years there have been numerous investigations concerned with the effect of substituents attached to the normal steroid skeleton on the biological properties of these important substances. These investigations have brought forth the realization that very dramatic alterations in these properties are indeed encountered when such substituents as halogen, particularly fluorine, hydroxyl, and methyl are placed at rather specific positions in the molecule (1–3). These steroidal derivatives still possess the basic steroid skeleton so that the nature of the molecule is not altered to a very significant extent. In this connection, it appeared of interest to us to consider a more substantial alteration in the chemical nature of steroidal substances in order to determine whether any appreciable differences in the biological activity of these molecules are associated with this change. We therefore considered the replacement of one or more carbon atoms of the cyclopentanoperhydrophenanthrene system by a hetero atom.

The introduction of a nitrogen atom into the steroid nucleus has attracted the interests of chemists for some time. However, inspection of the older literature reveals that most of the aza steroids represent analogues in which one of the rings of the skeleton has been expanded from a 6- to a 7-membered ring or in the case of ring D from a 5- to a 6-membered cycle. Very recently some successful syntheses of 4-aza steroids possessing the true steroid skeleton have been reported (4) and some interesting biological properties of these compounds have been described (5).

Our interest in the chemistry and biological properties of aza steroids led us to initiate studies in this area. Our initial considerations were directed toward the synthesis of ring B aza steroids since we felt that the introduction of a nitrogen atom in this ring would allow the retention of a $\Delta^4$-3-keto moiety in ring A—a structural feature present in most of the active steroidal hormones. At the time that our work was initiated, there were no ring B aza steroids known although, since that time, two laboratories have independently reported some work on 6-aza cholestane derivatives (6, 7). Our own work in this area has been briefly described, in part, in a preliminary communication (8). This paper outlines, in detail, a general approach to the synthesis of 6-aza steroids and describes the first synthesis of a 6-aza derivative in the androstane series.

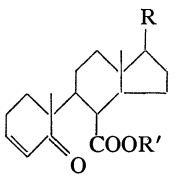
In considering a synthetic approach to this class of compounds, it became apparent that investigations in the cholesterol series would be of distinct advantage since larger quantities of the appropriate starting materials were obviously available. In this regard, a particularly attractive sequence involved the utilization of intermediates in which ring B had been opened since it was clear that the appropriate cyclization of such compounds

would lead to substances possessing the nitrogen atom in the ring system. This type of cyclization had been observed in ring A in the elegant researches of Woodward and co-workers on the total synthesis of steroids (9) and more recently by Uskokovic and Gut (4). The application of this reaction to ring B has been independently completed by Jacobs and Brownfield (6) and by the present authors (8).

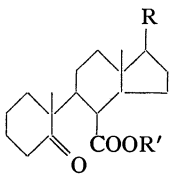
Of a number of alternatives which could be used to open ring B, the ozonization of the appropriate $\alpha,\beta$-unsaturated ketone system appeared most attractive since the ozonization of such systems had been studied in ring A (10) and, in one instance, in ring B (11).

Oxidative ring opening of 7-oxocholesteryl acetate to 5-oxo-5,7-seco-6-nor-3-cholesten-7-oic acid (I) was initially conducted by ozonolysis in glacial acetic acid followed by oxidative hydrolysis of the intermediate ozonide with aqueous hydrogen peroxide and treatment of the reaction mixture with sodium hydroxide in order to separate the desired acidic components from any neutral products. The initial intermediate, 3$\beta$-acetoxy-5-oxo-5,7-seco-6-norcholestan-7-oic acid (VI), readily lost the elements of acetic acid to provide I, a result also obtained by the American workers (6). The conjugated carbonyl chromophore present in I was reflected in its spectral data (226 m$\mu$, 5.97 $\mu$), and other evidence cited below served to establish the chemical structure. Since the ozonization product was an attractive intermediate for the preparation of 6-aza steroids it became necessary to obtain significant yields in this reaction. Under the reaction conditions mentioned above, the yield of I was low (22%) and in spite of numerous experiments wherein such reaction conditions as temperature and quantity of ozone used were varied, we were not able to raise the yield of acidic material. This difficulty was subsequently overcome by conducting the ozonolysis reaction under conditions where the ester was generated directly and is discussed in the later portion of this paper.

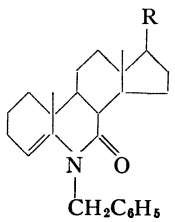
The conversion of the unsaturated keto acid to the saturated keto acid (II) was readily accomplished by catalytic hydrogenation and this provided us with the necessary intermediate for investigating the appropriate cyclization reactions to generate 6-aza steroidal analogues. As anticipated, the mild reaction conditions of Uskokovic and Gut (4) wherein anhydrous ammonia at room temperature is utilized were unsuccessful with our keto acid, II. However, when II was treated with refluxing benzylamine for 18 hours (9), an excellent yield of the expected enol lactam (III) was obtained. This material possessed the characteristic infrared absorption and, in particular, had an ultraviolet spectrum typical of these types of lactams (4, 6). The enol lactam was readily reduced to give an excellent yield of the expected product, N-benzyl-6-aza-5$\xi$-cholestan-7-one (IV), which possessed no absorption in the ultraviolet but still retained the lactam absorption in its infrared spectrum. Finally, reduction of IV with lithium aluminum hydride afforded the desired N-benzyl-6-aza-5$\xi$-cholestane (V).



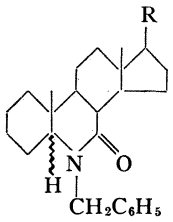

I, R′ = H
VII, R′ = $CH_3$
IX, R′ = H



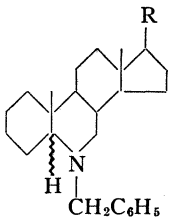

II, R′ = H
VIII, R′ = $CH_3$
X, R′ = H



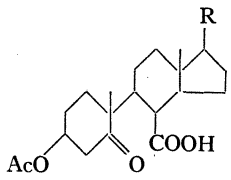

III, XI




IV, XII




V, XIII
I–VIII, R = $C_8H_{17}$
IX–XIII, R = OH




VI

It is pertinent to point out that in contrast to the American workers (6), who have devoted most of their attention to the parent 6-aza cholestane, we have concentrated our efforts on the N-benzyl-6-aza analogues. We feel that the presence of a tertiary nitrogen atom, as in the N-benzyl series provides more suitable intermediates for the reintroduction of an oxygen function at $C_3$ since undesirable double-bond migrations might be expected when a secondary nitrogen atom is present. Indeed, Jacobs and co-workers (6) have already suggested a migration of the $C_4$–$C_5$ double bond in their isolation of 6-aza-5-cholestene, a situation quite unlikely to occur in the N-benzyl series.

We would now like to exemplify the generality of the above approach by presenting the first synthesis of a 6-aza derivative in the androstane series.

The appropriate starting material 3$\beta$,17$\beta$-diacetoxy-5-androsten-7-one was readily converted to 17$\beta$-hydroxy-5-oxo-5,7-seco-6-nor-3-androsten-7-oic acid (IX) by ozonolysis and hydrolysis of the ozonide, as indicated above. As in the cholestane series, the yield of the desired product was quite low when the reaction was conducted under various conditions in acetic acid as solvent. The spectral data were again consistent with the structural assignment. Catalytic reduction of IX proceeded smoothly at room temperature to yield 17$\beta$-hydroxy-5-oxo-5,7-seco-6-norandrostan-7-oic acid (X), which, on treatment with refluxing benzylamine, provided an excellent yield of the desired enol lactam (XI). The unsaturated lactam on reduction with Adams catalyst in glacial acetic acid yielded 17$\beta$-hydroxy-N-benzyl-6-aza-5$\xi$-androstan-7-one (XII). As expected, the characteristic absorption of the enol lactam was no longer present in the ultraviolet spectrum of the reduction product but the typical lactam absorption was still evident in the infrared spectrum. This substance was finally reduced with lithium aluminum hydride to the desired 6-aza compound, 17$\beta$-hydroxy-N-benzyl-6-aza-5$\xi$-androstane (XIII).

The success of this last sequence allows entry into a novel class of androstane analogues and it should be of interest to determine whether any significant modifications in biological properties are associated with these compounds. It is clear that since the necessary starting substances are readily available in the progesterone series, the corresponding 6-aza derivatives should also be easily obtained in this series and, in turn, in the adrenocortical hormone series.

It was evident to us that although the above approach was of considerable applicability, it suffered from the fact that the ozonolysis reaction provided the desired product in low yield. Consequently, a considerable amount of experimentation was done to find optimum conditions for this reaction. Although we have not been able to obtain the corresponding acidic products in substantially higher yields, we have been able to overcome the difficulty by preparing the neutral esters directly from the ozonization. It appeared to us that it

may be of advantage to conduct the ozonolysis in non-acidic solvents and in particular in the presence of an alcohol so that the direct conversion of the ozonide to an ester would be possible. Indeed when we carried out this reaction in a solvent mixture of methylene chloride – methanol at −78°, we obtained the unsaturated keto ester (VII) from the neutral portion of the reaction product. In addition, the acidic portion contained a significant amount of unsaturated keto acid (I) so that the actual yield of starting material has been substantially increased.

It became necessary to confirm our suspicions that the unsaturated keto ester (VII) could be used effectively as a starting material. For this reason, we subjected VII to catalytic reduction and obtained the expected keto ester (VIII) as a beautifully crystalline substance. The structure of VIII was finally confirmed when the reduction product was treated with benzylamine, and the enol lactam which resulted was shown to be identical in every respect with N-benzyl-6-aza-4-cholesten-7-one (III). In this manner, the overall yield of the enol lactam from 7-oxocholesteryl acetate was raised to 40%. This marked improvement now makes the above approach a very attractive one indeed. It was not necessary to extend our studies to the androstane series since at the time that our investigations in the cholesterol series were being conducted Atwater, in his paper on 6-oxa-androstane derivatives (12), indicated that the analogous ozonolysis reaction provided the corresponding B-nor seco ester in yields up to 73%. It is now clear that the extension to the androstane series is valid.

## EXPERIMENTAL

All melting points were determined on a Fischer–Johns apparatus and are uncorrected. The ultraviolet spectra were recorded in 95% ethanol on a Cary 14 recording spectrophotometer and the rotations were taken in 1% chloroform solutions. The n.m.r. spectra were taken at 60 Mc on a Varian A60 instrument. The values are given in the Tiers $\tau$ scale with the signal of tetramethylsilane, which was used as the internal standard, set at 10.0 $\tau$ units. Analyses were performed by A. Bernhardt, Mulheim (Ruhr), Germany, and by Mrs. Aldridge, University of British Columbia.

*5-Oxo-5,7-seco-6-nor-3-cholesten-7-oic Acid (I)*

Solutions of 7-oxocholesteryl acetate (25.0 g) in glacial acetic acid (100 ml) were ozonized in 5-g portions at 25° over a period of 20 minutes at a rate of 0.1 mole per hour. The solution attained a bright yellow color during the course of the ozonization but this color slowly disappeared when the ozonide was treated with 30% hydrogen peroxide (19 ml) and water (50 ml, for each 5-g portion). After the solution had been allowed to stand for 15 hours at room temperature, the solvent was removed under reduced pressure and the residue was taken up in ether. The ether solution was washed with water and then extracted with 5% aqueous sodium hydroxide to remove all acidic components. The basic extract was acidified with dilute hydrochloric acid and this acid layer was extracted with ether. The ether extract was dried over anhydrous magnesium sulphate, the solvent was evaporated to yield 20.3 g of a viscous oil. Chromatography of this oil on silica gel (500 g) gave the keto acid (I) as an oil when elution with chloroform was carried out. Crystallization from hexane gave 4.86 g (22%) of virtually pure, crystalline keto acid, m.p. 179–183°. Three recrystallizations from hexane gave analytically pure acid (I) as colorless needles, m.p. 183–184°; $[\alpha]_D$+79°; $\lambda_{max}$ 226 m$\mu$ (log $\epsilon$ 3.93); infrared in chloroform: 5.86 $\mu$, 5.97 $\mu$; lit. (6). Found: C, 77.82; H, 10.46; O, 12.09; neutralization equivalent, 394; mol. wt. (Rast), 402. Calc. for $C_{26}H_{42}O_3$: C, 77.56; H, 10.51; O, 11.92; mol. wt., 402.

When the ozonization was carried out as above with the exception that the acidic materials were extracted from the reaction mixture with dilute potassium carbonate instead of sodium hydroxide, another acidic oil was obtained from the carbonate layer after acidification and ether extraction. This oil (3.51 g from 5.0 g of starting material) on chromatography on silica gel and elution with chloroform yielded a fraction (3.5 g) which crystallized from ether – petroleum ether, m.p. 171–177°. Although not pure, this material is beyond doubt predominantly 3$\beta$-acetoxy-5-oxo-5,6-seco-6-norcholestan-7-oic acid (VI) as evidenced by no absorption in the ultraviolet and its infrared spectrum in (KBr): 5.75 $\mu$, 5.78 $\mu$, 5.83 $\mu$, 5.88 $\mu$, 8.03$\mu$.

This was further confirmed when the above material was converted, in essentially quantitative yield, to the unsaturated keto-acid (I) by merely shaking an ether solution of this substance with 5% aqueous sodium hydroxide, acidifying the alkaline layer, and extracting again with ether.

*5-Oxo-5,7-seco-6-norcholestan-7-oic Acid (II)*

The unsaturated keto-acid (I) (0.398 g) was reduced over 10% palladium on charcoal (0.4 g) in ethanol (30 ml) at room temperature and atmospheric pressure. The hydrogen uptake was virtually complete in 15

minutes, after which time the catalyst was filtered off and the solvent removed under reduced pressure. The remaining white solid crystallized from hexane yielding 0.237 g of the saturated keto-acid (II), m.p. 188–193°. Three additional recrystallizations from hexane gave an analytical sample, m.p. 192–194°; $[\alpha]_D$+91°; infrared in KBr: 5.83 $\mu$, 5.89 $\mu$; lit. (6). Found: C, 76.80; H, 10.84; O, 12.11. Calc. for $C_{26}H_{44}O_3$: C, 77.17; H, 10.98; O, 11.86.

*N-Benzyl-6-aza-4-cholesten-7-one (III)*

The saturated keto-acid (II) (4.0 g) was dissolved in benzylamine (19 ml) and refluxed for 18 hours in a nitrogen atmosphere. The cooled yellow reaction mixture was taken up in ether and extracted with aqueous hydrochloric acid until the extract was acidic to litmus. The ether layer was then washed once with 5% aqueous sodium hydroxide and once with a saturated salt solution and then dried over anhydrous magnesium sulphate. Evaporation of the solvent, after removal of the drying agent by filtration, yielded a light yellow oil. Crystallization from methanol afforded 3.93 g (84%) of colorless crystals, m.p. 135–140°. Three recrystallizations from methanol gave pure N-benzyl-6-aza-4-cholesten-7-one (III) as long, flat crystals, m.p. 139–141°; $[\alpha]_D$ +93°; $\lambda_{max}$ 237 m$\mu$ (log $\epsilon$ 4.05); infrared in KBr: 6.10 $\mu$, 6.02 $\mu$; lit. (6). Found: C, 82.92; H, 10.33; N, 3.01; O, 3.48. Calc. for $C_{33}H_{49}NO$: C, 83.31; H, 10.38; N, 2.94; O, 3.36.

*N-Benzyl-6-aza-5ξ-cholestan-7-one (IV)*

The enol lactam (III) (0.50 g) was hydrogenated in acetic acid (40 ml) over 0.05 g of platinum oxide at room temperature and atmospheric pressure. The uptake of hydrogen stopped after 1 hour, and the catalyst was filtered off. The solvent was removed *in vacuo* and the remaining oil was placed in a vacuum desiccator and allowed to stand, over solid potassium hydroxide, for several hours. The oil (0.487 g, 90%) crystallized from ether–methanol and melted at 141–145°. Three recrystallizations from ether–methanol provided an analytical sample of the lactam (IV), m.p. 143–145°; $[\alpha]_D$+63°; infrared in Nujol: 6.08 $\mu$. Found: C, 83.19; H, 10.53; N, 3.19; O, 3.50. Calc. for $C_{33}H_{51}NO$: C, 82.96; H, 10.76; N, 2.93; O, 3.35.

*N-Benzyl-6-aza-5ξ-cholestane (V)*

N-Benzyl-6-aza-5ξ-cholestan-7-one (0.50 g) was dissolved in anhydrous ether (100 ml) and refluxed for 24 hours with lithium aluminum hydride (0.6 g), which was initially placed in a Soxhlet extractor and gradually brought into the vessel by the refluxing ether. The excess hydride was decomposed by cautious addition of moist ether and water, followed by refluxing for 0.5 hours. The inorganic solids were filtered off and the ether solution was dried over anhydrous magnesium sulphate. Removal of the solvent yielded 0.423 g (87%) of a light yellow oil which crystallized from ether–methanol (0.410 g), m.p. 65–68°. Two further recrystallizations from ether–methanol yielded N-benzyl-6-aza-5ξ-cholestane, m.p. 68–69°; $[\alpha]_D$+71°. Found: C, 85.42; H, 11.27; N, 3.30. Calc. for $C_{33}H_{53}N$: C, 85.46; H, 11.52; N, 3.02.

*17β-Hydroxy-5-oxo-5,7-seco-6-nor-3-androsten-7-oic Acid (IX)*

A solution of 3β,17β-diacetoxy-5-androsten-7-one (3.42 g) in glacial acetic acid (125 ml) was treated with ozone for 15 minutes at room temperature at a rate of 0.1 mole per hour. The resulting yellow solution was treated with dilute hydrogen peroxide (3 ml) and water (15 ml) after 20 minutes and then allowed to stand at room temperature for 20 hours. During this time, the solution lost its yellow color. The excess acetic acid was then removed *in vacuo* and the oily residue was taken up in ether. The ether solution was washed with 5% aqueous sodium hydroxide and water to remove acidic components. The alkaline extracts were made acidic by the addition of dilute hydrochloric acid and this acidic material was then extracted with ether. The ether extract was dried over anhydrous magnesium sulphate, the drying agent removed by filtration, and the solvent evaporated to yield 1.6 g of a glassy acidic material. This material was chromatographed on silica gel (100 g) and elution with chloroform – 2½% methanol yielded a glassy material (0.96 g, 36%) which crystallized from ether – petroleum ether (0.92 g), m.p. 142–148°. Two further recrystallizations from ether – petroleum ether gave shiny crystals which appeared to have a double melting point, 145–150° and 195–200°, probably due to strong solvation. However, after the crystals had dried at 100°/0.1 mm for several hours, the melting point was greatly improved and a pure sample melted at 203–204°; $[\alpha]_D$+88°; $\lambda_{max}$ 227 m$\mu$ (log $\epsilon$ 3.98); infrared in KBr: 2.94 $\mu$, 5.81 $\mu$, 6.04 $\mu$. Found: C, 70.65; H, 8.52; O, 21.14. Calc. for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55; O, 20.89.

*17β-Hydroxy-5-oxo-5,7-seco-6-norandrostan-7-oic Acid (X)*

A solution of the unsaturated keto-acid (IX) (0.896 g) in 95% ethanol (50 ml) was hydrogenated over 0.54 g of 10% palladium on charcoal at room temperature and atmospheric pressure. After the uptake of hydrogen was complete (20 minutes), the catalyst was filtered off and the solvent removed *in vacuo* to yield an oily product (0.75 g). Chromatography of this oil on silica gel (50 g) gave the product as an oil by elution with chloroform – 2½% methanol. This oil (0.70 g) slowly crystallized when it was left standing and after two recrystallizations from hexane gave pure 17β-hydroxy-5-oxo-5,7-seco-6-norandrostan-7-oic acid (0.65 g), m.p. 228–229; $[\alpha]_D$+96°; infrared in KBr: 2.90 $\mu$, 5.81 $\mu$, 5.93 $\mu$. Found: C, 69.67; H, 9.01; O, 21.23. Calc. for $C_{18}H_{28}O_4$: C, 70.09; H, 9.15; O, 20.76.

*17β-Hydroxy-N-benzyl-6-aza-4-androsten-7-one (XI)*

A solution of the saturated keto-acid (X) (0.553 g) in benzylamine (10 ml) was refluxed gently for 15

hours in a nitrogen atmosphere. The cooled, yellow solution was taken up in ether and washed with dilute hydrochloric acid until the aqueous layer was acidic. The ether solution was then washed once with 5% aqueous sodium hydroxide followed by water and finally dried over anhydrous magnesium sulphate. The drying agent was filtered off and the ether evaporated to yield a light yellow oil (0.56 g). Chromatography of this oil on silica gel (50 g) gave 0.46 g (68%) of an oil when the column was eluted with benzene–chloroform (1:1). This oil crystallized from ether–hexane as colorless needles, m.p. 105–109°. Three further recrystallizations gave an analytical sample, m.p. 109–110°; $[\alpha]_D$+102; $\lambda_{max}$ 237 m$\mu$ (log $\epsilon$ 4.02); infrared in KBr: 6.11 $\mu$, 6.02 $\mu$. Found: C, 79.49; H, 8.82; N, 3.72; O, 8.30. Calc. for $C_{25}H_{33}NO_2$: C, 79.11; H, 8.76; N, 3.69; O, 8.43.

*17β-Hydroxy-N-benzyl-6-aza-5ξ-androstan-7-one (XII)*

A solution of the enol lactam (0.185 g) in glacial acetic acid (30 ml) was hydrogenated over platinum oxide (0.050 g) at room temperature and atmospheric pressure for 2 hours. The catalyst was filtered off and the acetic acid was removed *in vacuo* to yield 0.168 g (90%) of an oil. The oil was chromatographed on silica gel (19 g) and the oily product was eluted with benzene–chloroform (1:1). This oil crystallized upon standing and was recrystallized from acetone – petroleum ether as colorless needles, m.p. 134–136°; $[\alpha]_D$−1°; infrared in KBr: 2.93 $\mu$, 6.13 $\mu$. Found: C, 78.73; H, 9.61; N, 3.90; O, 8.66; active H, 0.27. Calc. for $C_{25}H_{35}NO_2$: C, 78.69; H, 9.25; N, 3.67; O, 8.38; active H, 0.264.

*17β-Hydroxy-N-benzyl-6-aza-5ξ-androstane (XIII)*

The saturated lactam (XII) (0.90 g) was dissolved in anhydrous ether (100 ml) and refluxed for 24 hours with lithium aluminum hydride (1.0 g), which was initially placed in a Soxhlet extractor and gradually brought into the reaction vessel by the refluxing ether. The reaction mixture was then allowed to stand for a further 56 hours at room temperature. The excess hydride was decomposed by the dropwise addition of an ether–acetone solution. Water (1 ml) was then added cautiously and the reaction mixture was warmed on a steam bath for 0.5 hour. The inorganic salts were filtered off and washed with ether and the combined ether solutions were dried over anhydrous magnesium sulphate. Filtration and evaporation of the solvent gave a colorless oil which slowly crystallized. The yield of solid crystalline product was 0.843 g (97%). Recrystallization of the solid from petroleum ether gave needles, melting point 109–111°, which, after two more recrystallizations from the same solvent, provided a pure sample of the aza steroid, m.p. 111–112°; $[\alpha]_D$ +67°. Found: C, 81.57; H, 10.34; N, 4.14; O, 4.51. Calc. for $C_{25}H_{37}NO$: C, 81.69; H, 10.15; N, 3.81; O, 4.35.

*Methyl 5-Oxo-5,7-seco-6-nor-3-cholesten-7-oate (VII)*

A solution of 7-oxocholesteryl acetate (5.0 g) in dichloromethane (75 ml) and absolute methanol (25 ml) was ozonized at −78° until the solution had attained a blue color (about 20 minutes at a rate of 0.1 mole per hour). The solution was allowed to warm to room temperature, 30% aqueous hydrogen peroxide (0.7 ml) and water (1.7 ml) were added, and the mixture was then allowed to stand at room temperature for 16 hours. The organic phase was separated and the aqueous phase was extracted several times with dichloromethane. The organic extracts were combined, washed with water, and then dried over anhydrous magnesium sulphate. Evaporation of the solvent after removal of the drying agent by filtration provided a viscous clear oil. This oil was taken up in ether and the ethereal solution was washed with 5% aqueous sodium hydroxide to remove any acidic materials. The workup of this aqueous layer is given below.

The ether layer was washed with water and dried over anhydrous magnesium sulphate, and the solvent was removed to provide a viscous, neutral oil (3.3 g). This neutral oil was taken up in dioxane, treated with 5% aqueous sodium hydroxide (30 ml), and the whole mixture was stirred for 30 minutes. This mixture was then treated with 1.5 liters of water and extracted exhaustively with ether in a continuous extraction apparatus. The resulting ether extract was washed with water, and dried over anhydrous magnesium sulphate. The solvent was removed to yield a viscous oil (2.25 g). This oil was taken up in benzene and chromatographed on silica gel (80 g). The desired unsaturated keto ester was eluted with benzene as a clear viscous oil (1.76 g) and, in spite of numerous attempts, it resisted all efforts to obtain it in crystalline form. Infrared in $CCl_4$: 5.98 $\mu$, 5.81 $\mu$; $\lambda_{max}$ 227 m$\mu$ (log $\epsilon$ 3.84); $[\alpha]_D$ +83; n.m.r. signals ($CCl_4$): sharp signal at

6.5 $\tau$ (−$COOCH_3$), multiplets at 4.25 $\tau$ and 3.8 $\tau$ (—C=C—C=O). Found: C, 77.52; H, 10.31. Calc. for $C_{27}H_{44}O_3$: C, 77.83; H, 10.65.

The aqueous alkaline layer from the potassium hydroxide in dioxane treatment was acidified with hydrochloric acid and the resulting mixture was extracted with ether. The ethereal extract was washed with water, then dried over anhydrous magnesium sulphate. Removal of the solvent yielded an acidic material (0.7 g).

This acidic material (0.7 g) was reduced over 10% palladium on charcoal (0.4 g) in ethanol at room temperature and atmospheric pressure. The catalyst was filtered off and the solvent was removed under reduced pressure. This crude reduction product was chromatographed on silica gel (16 g) and a solid material (200 mg) which was obtained upon elution with benzene–chloroform turned out to be 5-oxo-5,7-seco-6-norcholestan-7-oic acid (II). This was identified by infrared comparison and mixed melting point with an authentic sample.

The original aqueous alkaline extract of the product resulting directly from the ozonization was acidified with hydrochloric acid and this acidic mixture was then extracted with ether. The ether extract was washed

with water, and dried over anhydrous magnesium sulphate. Removal of the solvent yielded an acidic material (1.94 g).

*Methyl 5-Oxo-5,7-seco-6-norcholestan-7-oate (VIII)*

The unsaturated keto ester, VII (1.65 g), was hydrogenated over 10% palladium on charcoal (1 g) in ethanol at room temperature and atmospheric pressure. The catalyst was removed by filtration and the solvent evaporated to yield a white solid. This solid was taken up in benzene and chromatographed on silica gel (60 g). Elution with benzene provided a white crystalline material (1.5 g) which on several recrystallizations from benzene yielded an analytical sample, m.p. 81–83°; $[\alpha]_D^{28}$ +97°; infrared in KBr: 5.90 $\mu$, 5.80 $\mu$; lit. (6). Found: C, 77.30; H, 10.96. Calc. for $C_{27}H_{46}O_3$: C, 77.46; H, 11.08.

*N-Benzyl-6-aza-4-cholesten-7-one from VIII*

The saturated keto ester, VIII (1 g), was refluxed in benzylamine (2.5 ml) for 20 hours in a nitrogen atmosphere. The resulting reaction mixture was taken up in ether and the ethereal solution was washed with dilute hydrochloric acid to remove any benzylamine. This solution was then washed with 5% aqueous sodium hydroxide, water, and finally dried over anhydrous magnesium sulphate. Removal of the solvent gave a white solid (1.1 g) which, upon recrystallization from ethanol, provided a pure sample of the enol lactam, III (0.95 g).

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