STEROID NITROGEN COMPOUNDS. I. SYNTHESIS, STRUCTURE, AND PROPERTIES OF METHYL 3α,7α-DIACETOXY-11α-CHLORO-12α-NITRO-5β-CHOLANOATE[1]

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ABSTRACT

The reaction between methyl 3α,7α-diacetoxy-5β-chol-11-enoate (I) and nitrosyl chloride is shown to give methyl 3α,7α-diacetoxy-11α-chloro-12α-nitro-5β-cholanoate (III) in moderate yield. In the presence of nitrogen dioxide the nitro-chloride III is formed rapidly, probably by a free radical mechanism. On treatment of III with zinc dust in acetic acid, chloro and nitro groups are expelled to regenerate the 11-ene in good yield. In contrast with 5α-chloro-6β-nitro steroids the cis nitro-chloride shows remarkable resistance towards dehydrochlorination, and treatment with refluxing γ-collidine affords only the starting nitro-chloride unchanged. The action of sodium carbonate on III yields 3α-hydroxy-7α-acetoxy-11α-chloro-12α-nitro-5β-cholanoic acid (IV), the chloro nitro moiety being unattacked. The methyl ester V and the acetate VI of IV, and the 3-one VII derived from V are described. The stereochemistry of the nitro-chloride, III, was confirmed by a detailed X-ray crystallographic structure analysis, the results of this analysis being described in detail.

It has been reported that the addition of nitrosyl chloride to cholesteryl acetate and other steroid 5-enes preceeds stereospecifically to lead to 5α-chloro-6β-nitro compounds.[2,3,4] It has also been shown that when cholesteryl acetate was treated with only one molar equivalent of nitrosyl chloride, a mixture of starting olefin and the nitro-chloride was obtained.[4] Since nitroso alkanes are known to be oxidized to nitro compounds with nitrosyl chloride,[5] it is postulated that 5α-chloro-6β-nitro steroids are formed by oxidation of initially formed 5α-chloro-6β-nitroso adduct. [2,3,4] Reactions of nitrosyl chloride and nitryl chloride with cholest-2-ene have been studied, whereby the latter was shown to yield no nitro compound at all.[6]

In connection with our studies on the syntheses and reactions of steroids having nitrogen functionality, we have investigated the addition of nitrosyl chloride to various steroid olefins. In this paper we wish to describe the reaction of methyl 3α,7α-diacetoxy-5β-chol-11-enoate (I)[7] with nitrosyl chloride in methylene chloride or carbon tetrachloride to give methyl 3α,7α-diacetoxy-11α-chloro-12α-nitro-5β-cholanoate (III), mp 243-244°, in moderate yield. Except for the stereochemistry of the adduct, the formation of a nitro-chloride rather than a nitroso-chloride from the 11-ene shows an interesting analogy with the reaction between nitrosyl chloride and steroid 5-enes. From the facts described below, the formation of the nitro-chloride is explained by the initial formation of a nitroso-chloride followed by the oxidation with nitrosyl chloride.

Evidently, this is the first example of steroid cis nitro-chloride and the formation of III suggests that the addition reaction of nitrosyl

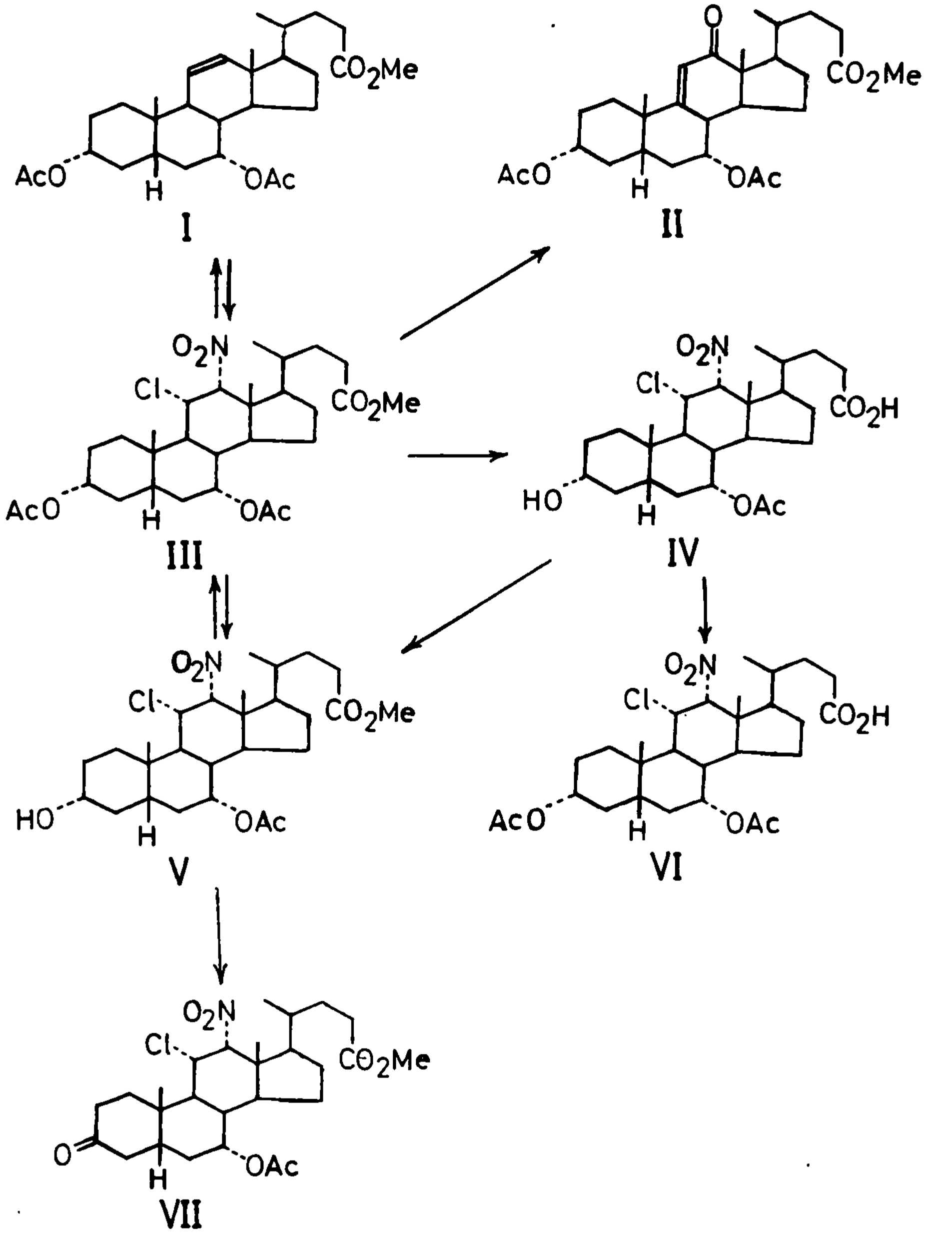

Figure 1

chloride to the 11-ene in these solvents proceeds from the α-site of the olefin in cis fashion, probably through a four-centered mechanism.[8]

Meinwald and co-workers investigated the stereochemistry of the dimeric nitroso-chlorides from the reaction of nitrosyl chloride with norbornene and norbornadiene and concluded that the products have the exo-cis stereochemistry.[8] Ohno and co-workers found that the steric course of the addition of nitrosyl chloride is dependent upon the solvent, the addition of the reagent to cyclohexene in nonpolar solvents gives the cis adduct, whereas the trans adduct is favored in polar solvents.[9]

The 11-ene I was treated with excess nitrosyl chloride (ca. 10 mol equiv) at 2° for 10 days in methylene chloride or carbon tetrachloride to give, in moderate yield, a crystalline product, which was assigned the 11α-chloro-12α-nitro structure III on the basis of elemental analysis and spectral data. In addition to the characteristic nitro absorption bands in the infrared, the compound showed an nmr spectrum (100 MHz) which consisted of a one-proton quartet at δ 4.36 with J = 11.1 and 4.4 Hz, and a one-proton doublet at δ 5.17 with J = 4.4 Hz. Since a proton attached to a carbon possessing a nitro group is known to absorb in a lower field than that carrying a chlorine atom in cyclohexane derivatives,[10] the quartet and doublet are attributable to the protons on C_{11} and C_{12} respectively. Coupling constants of these protons are also in good agreement with the literature data[11] which support the 11α-chloro-12α-nitro structure. Chemical evidence for the assigned structure III comes from the transformation of the adduct into methyl 3α,7α-diacetoxy-12-oxo-5β-chol-9(11)-enoate (II)[12] as described below.

In the ORD curve, the adduct exhibited a positive Cotton effect in the 280 mμ region due to n→π* transition of the nitro group. Inspection of Dreiding models showed that the least hindered conformation of the 12α-nitro group would have a positive torsion angle[13] compatible with the observed positive Cotton effect.

The nitro-chloride is also obtained more efficiently (a few days at 2°) by the similar reaction carried out in ether in the presence of potassium acetate, which decomposes nitrosyl chloride into nitrogen dioxide and nitric oxide.[3] Furthermore, in the presence of pure nitrogen dioxide,[3] the formation of the cis nitro-chloride is completed within several hours. Because of low solubility of the nitro-chloride in ether, the adduct was observed to separate as fine needles during the reaction. As suggested by Harrison and co-workers,[3] this marked effect shows that the nitro-chloride is formed by a different route, probably be a radical process, in which attack is initiated by nitrogen dioxide and nitrosyl chloride then acts as a source of chlorine atoms.

Of particular interest is the fact that the product precipitated also had cis configuration. This was rather unexpected since the addition reaction in the presence of nitrogen dioxide seemed to favor a trans addition[14] to give the 11β-chloro-12α-nitro compound.

In fact, on treatment with nitrosyl chloride in ether in the presence of nitrogen dioxide, 5α-cholest-3-ene, for example, afforded a trans nitro-chloride, 3α-nitro-4β-chloro-5α-cholestane in moderate yield, as well as a small amount of a cis adduct, 3α-nitro-4α-cholor-5α-cholestane, while with nitrosyl chloride alone in the same solvent it gave the cis nitro-chloride in low yield, and the formation of the trans nitro-chloride was not observed.[15] This. also suggest that the nitro compound formation from nitrosyl chloride addition to some steroid olefins arises from oxidation of the nitroso group by the reagent, and not by direct introduction of an NO_2 species. From this fact, it was assumed that the cis nitro-chloride formation in the presence of nitrogen dioxide seemed to be a rather exceptional case. The preferential formation of the cis nitro-chloride over the trans isomer in the presence of nitrogen dioxide can be explained by a steric hindrance due to the two angular methyl groups at the γ-carbon atoms which may inhibit the attack of the chlorine atom from the β-site of the intermediate radical.

Although a trans diaxial orientation for the 5α-chloro-6β-nitro steroids was suggested by ready reductive elimination using zinc dust in acetic acid to regenerate steroid 5-enes,[2,3,4] this redution seemed to have little stereospecificity, since the cis nitro-chloride III when treated with zinc dust in acetic acid also afforded the starting olefin I of high purity in 79% yield.

In contrast with the 5α-chloro-6β-nitro steroids, the cis nitro-chloride showed remarkable resistance towards dehydrochlorination, and even after treatment with refluxing γ-collidine for 6 hours, the dark colored reaction mixture afforded unchanged pure nitro-chloride in 88% recovery.

On treatment with sodium carbonate in aqueous methanol, the adduct III was hydrolyzed without being attacked at the chloro nitro moiety to give 3α-hydroxy-7α-acetoxy-11α-chloro-12α-nitro-5β-cholanoic acid (IV) in quantitative yield. Esterification of the hydroxy acid IV afforded the hydroxy ester V, which was also obtainable by acid hydrolysis of the adduct III with methanolic hydrogen chloride. Acetylation of the hydroxy ester V and the hydroxy acid IV with acetic anhydride in pyridine at room temperature afforded the adduct III and the diacetoxy acid VI respectively. Chromic acid oxidation in acetone[16] of the hydroxy ester V gave the 3-one VII in quantitative yield. By these transformations the chloro nitro group has been shown to be extremely stable under basic reaction conditions.

When treated with methanolic potassium hydroxide, however, the nitro-chloride III was transformed into a carboxylic acid mixture, which gave a negative Beilstein test. Its infrared spectrum indicated both the presence of an unconjugated nitro group and an α,β-unsaturated ketone system. Esterification and acetylation of the mixture afforded, after percolation over alumina, methyl 3α,7α-diacetoxy-12-oxo-5β-chol-9(11)-enoate (II)[12] in low yield. The formation of II also supports the assigned structure III for the adduct.

Conformation of the molecule of methyl 3α,7α-diacetoxy-11α-chloro-12α-nitro-5β-cholanoate (III).

The overall structure of III, as obtained from the detailed X-ray crystallographic study, confirms that obtained in the chemical study: the A/B ring junction is *cis*, rings A, B, and C, have chair conformations, and the D-ring is a slightly distorted β-envelope. The 3, 7, 11, and 12-substitutents are all in the α-configuration, and the 17-side chain has the β-configuration. Both the B and the C rings are somewhat distorted, the C-ring being more so than the B-ring. In the B-ring, the torsional angles involving atom C_5, that is, $\phi(C_{10}-C_5-C_6-C_7)$, and $\phi(C_6-C_5-C_{10}-C_9)$, have been reduced to -44.4° and +45.9°

respectively. In the C-ring, those torsional angles involving atom C_{11} have also been reduced: $\phi(C_{14}-C_8-C_9-C_{11}) = -46.2°$, $\phi(C_8-C_9-C_{11}-C_{12}) = +42.8°$, and $\phi(C_9-C_{11}-C_{12}-C_{13}) = -48.7°$. The bond distance at the B/C ring junction, C_8-C_9, has been increased to 1.67 Å, with the bond angle $C_9-C_{11}-C_{12}$ also being increased to 121.3°.

The C_{11}-Cℓ bond length of 1.85 Å is a little longer than those observed in 2α,3β- and 2β,3α-dichloro-5α-cholestane (1.76-1.82 Å).[17,18] The C_{12}-N bond length of 1.59 Å is also about 0.1 Å longer than expected.[19] In the nitro-group, the two oxygen atoms are not equivalent, the nitrogen-oxygen bonds showing single and double bond character, with the N=O bond pointing outward from the molecule. These conclusions are demonstrated by the torsional angles $\phi(C_{11}-C_{12}-N{=}O) = +136.9°$, $\phi(C_{11}-C_{12}-N-O) = -47.1°$, and the bond distances N=O = 1.17 Å, and N-O = 1.26 Å.

The conformations of the various substitutents may be seen clearly in figure 2. Referred to the flat portions of the respective chairs C_1, C_2, C_4, C_5 in ring A; C_6, C_7, C_9, C_{10} in ring B; and C_{11}, C_{12}, C_{14}, C_8 in ring C), the plane of the 3α-acetate group makes an angle of 54.4° with ring A, the plane of the 7α-acetate group makes an angle of 62.2° with the plane of ring B, and the plane of the 12α-nitro group makes an angle of 76.9° with ring C. The torsional angle $\phi(C\ell_{11}-C_{11}-C_{12}-N)$ is -52.3°. The conformations of these substitutents are also given in the Newman projections in figure 3.

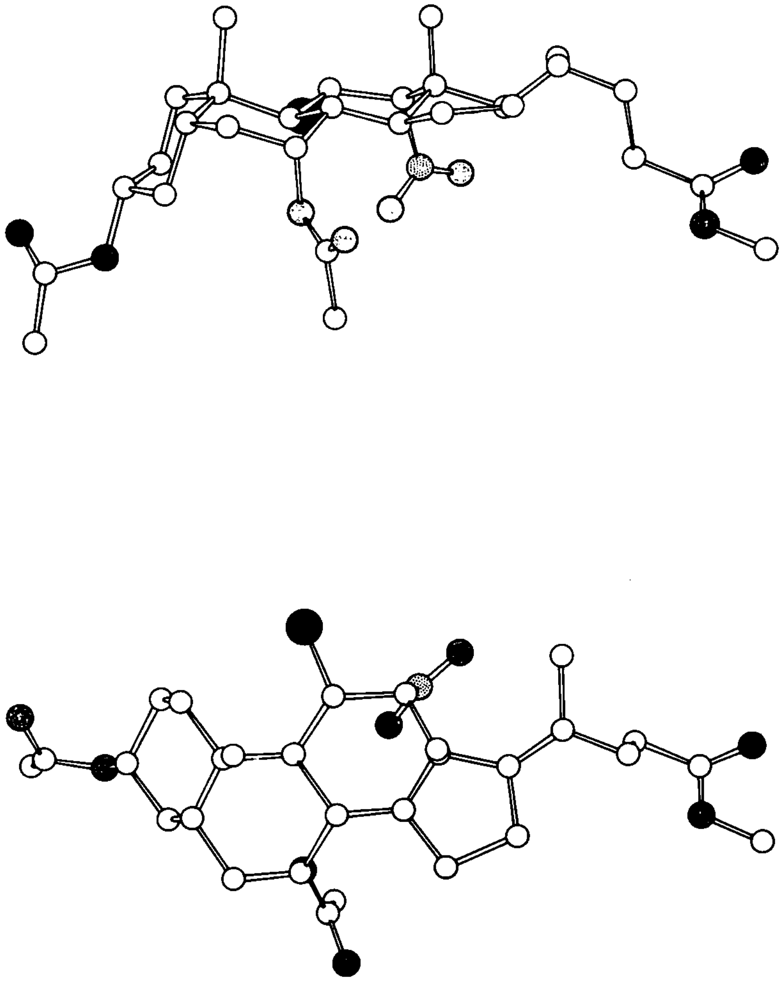

Figure 2

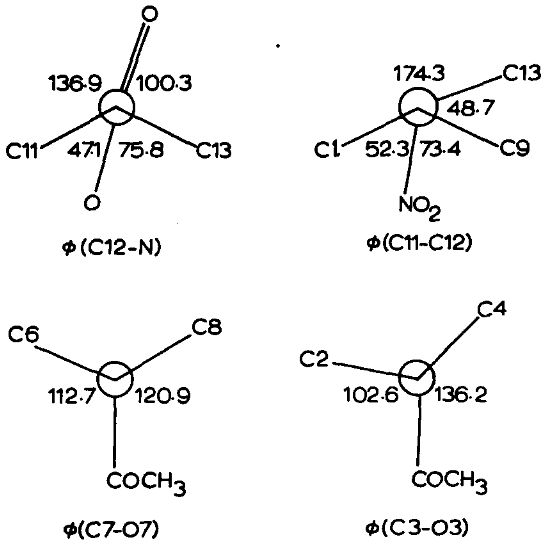

Figure 3

EXPERIMENTAL[20]

Methyl 3α,7α-Diacetoxy-11α-chloro-12α-nitro-5β-cholanoate (III).

A. Using nitrosyl chloride and potassium acetate. - Into an ice cooled solution of 24.5 g (0.050 mol) of methyl 3α,7α-diacetoxy-5β-chol-11-enoate (I)[7] in 490 ml of absolute ether was passed a slow stream of 34 g (0.52 mol) of nitrosyl chloride under exclusion of moisture. To the solution was added 7.5 g of commercial anhydrous potassium acetate, and the mixture was allowed to stand at 2° for 7 days in the dark. Within 2 days crystals of III began to separate as fine needles. The excess of nitrosyl chloride and the solvent were removed under reduced pressure and to the residue was added 25 ml of methanol. The crystalline product was collected, washed with a small amount of methanol and thoroughly with water to remove remaining potassium acetate, and dried. It weighed 16.5 g (58%) and melted at 218-223°. Two crystallizations from methanol gave III as colorless needles: mp 243-244°; $[\alpha]_D^{25}$ +31.5° (c 1); ν^{KBr} 1738 (ester), 1553 (NO_2) cm^{-1}; $[\alpha]_{650}$ +40°, $[\alpha]_{589}$ +49°, $[\alpha]_{300}$ +577° (peak), $[\alpha]_{258}$ -284° (trough), $[\alpha]_{240}$ -80° (c 0.1, Chf, 24°). The nmr spectrum (100 MHz, Varian HA-100) had peaks at δ 0.89 (s, C18-H), 1.08 (s, C19-H), 2.00 and 2.08 (s, acetate Me), 3.61 (s, OMe), 4.36 (q. C11-H, J = 11.1 and 4.4, axial), 4.62 (m, C3-H, W1/2 = 23, a), 4.92 (m, C7-H, W1/2 = 8, equatorial), 5.17 (d, C12-H, J = 4.4, e).

Anal. Calcd. for $C_{29}H_{44}O_8NCl$: C, 61.06; H, 7.78; N, 2.46; Cl, 6.22. Found: C, 60.89; H, 7.77; N, 2.71; Cl, 5.93.

B. Using nitrosyl chloride. - Into an ice cooled solution of 1.00 g of the 11-ene I in 20 ml of dried methylene chloride was passed 1.8 g (13 mol equiv) of nitrosyl chloride. The ampoule was sealed, and kept at 2° for 10 days in the dark. The excess of nitrosyl chloride and the solvent were removed under reduced pressure to leave almost colorless oil which on treatment with methanol afforded 0.49 g (42%) of III as needles, mp 227-231°. Two crystallizations from methanol brought the mp to 243-244°. The product was identified by mixed mp and comparison of infrared spectra with authentic material described above.

In carbon tetrachloride the 11-ene afforded the same cis nitrochloride in yield of about 40%.

C. Using nitrogen dioxide and nitrosyl chloride. - To an ice cooled solution of 7.25 g (0.111 mol) of nitrosyl chloride and 5.47 g (0.119 mol as NO_2 monomer) of nitrogen dioxide in 100 ml of absolute ether was added 5.00 g (0.0102 mol) of the 11-ene I, and the mixture was kept at 2° for 24 hours in the dark. Within 2 hours large crystals of III began to separate. The excess of reagents and the solvent were removed under reduced pressure, and the crystalline residue was triturated with 50 ml of ether. The mixture was cooled and filtered to give 3.80 g (65%) of crude III, mp 195-200°. Crystallizations from methanol afforded pure III as colorless needles, mp 243-244°. The product was identical in every respect with the authentic material described above.

Treatment of the Nitro-chloride III with Zinc-dust in Acetic Acid. - A solution of 202 mg of the nitro-chloride III in 10 ml of acetic acid was heated under reflux with 0.4 g of zinc dust for 2 hours. The reaction mixture was cooled to room temperature, and the zinc was filtered off. The filtrate was diluted with water, and the needles precipitated were collected, washed with water, and dried to yield 137 mg (79%) of the 11-ene I, mp 140-141°. The product was identified by mixed mp and comparison of infrared spectra with authentic material.

Treatment of the Nitro-chloride III with γ-Collidine. - A solution of 0.50 g of III in 20 ml of γ-collidine was heated under reflux for 6 hours, and the solvent was distilled under reduced pressure. Dark colored crystals obtained were dissolved in 10 ml of pyridine, and diluted with water. The product precipitated was collected, washed with 40% aqueous pyridine and water, and dried to yield 0.44 g (88%) of unchanged starting material III, mp 242.5-243.5°, as colorless needles.

3α-Hydroxy-7α-acetoxy-11α-chloro-12α-nitro-5β-cholanoic Acid (IV). - To a refluxing solution of 2.00 g of the nitro-chloride III in 200 ml of methanol was added a hot solution of 2.0 g of anhydrous sodium carbonate in 120 ml of water, and refluxing was continued for 2 hours. The methanol was removed by distillation and the resulting solution was filtered, diluted with water to 200 ml, and the solution was made acid to Congo red by addition of dilute hydrochloric acid. The precipitate was collected, washed with water, and dried to yield 1.8 g (100%) of colorless crystals, mp 250-255° dec. Crystallization from methanol afforded analytical sample of IV, mp 270-271° dec, as needles: $[\alpha]_D^{25}$+ 33.7° (c 0.4, MeOH); ν^{Nujol} 3560 and 3440 (OH), 1738 (acetate), 1703 (carboxyl), 1550 (NO_2) cm^{-1}. The nmr spectrum in deuteropyridine had peaks at δ 0.87 (s, C18-H), 1.06 (s, C19-H), 1.88 (s, acetate Me), 4.67 (q, C11-H, J = 10.8 and 4.8, a), 5.02 (m, C7-H, W1/2 = 7.2, e), 5.42 (d, C12-H, J = 4.8, e).

Anal. Calcd. for $C_{26}H_{40}O_7NCl$: C, 60.75; H, 7.84; N, 2.72. Found: C, 60.67; H, 7.74; N, 2.65.

Methyl 3α-Hydroxy-7α-acetoxy-11α-chloro-12α-nitro-5β-cholanoate (V).

A. From the adduct III. - A solution of 2.0 g of III in 360 ml of methanol containing 3.6 g of hydrogen chloride was heated under reflux for 1.5 hours, and the solution was concentrated under reduced pressure to a small volume. Crystals separated were collected, washed with a small amount of methanol, and dried over soda-lime to yield 1.4 g (76%) of V as needles, mp 219-220°. Crystallization from methanol furnished the analytical sample: mp 222-223° $[\alpha]_D^{23}$ + 19.1° (c 1); ν^{Nujol} 3590 (OH), 1737 and 1718 (ester), 1554 (NO_2) cm^{-1}. The nmr spectrum had peaks at δ 0.87 (s, C18-H), 1.07 (s, C19-H), 2.06 (s, acetate Me), 3.58 (s, OMe), 4.33 (q, C11-H, J = 10.8 and 4.8, a), 4.86 (m, C7-H, W1/2 = 7.2, e), 5.11 (d, C12-H, J = 4.8, e).

Anal. Calcd. for $C_{27}H_{42}O_7NCl$: C, 61.41; H, 8.02; N, 2.65; Cl, 6.71. Found: C, 61.14; H, 8.09; N, 2.68; Cl, 6.86.

B. From the hydroxy acid IV. - A solution of 2.0 g of IV in 40 ml of methanol containing 1% of hydrogen chloride was refluxed for 15 minutes, and the solution was concentrated to a volume of about 20 ml. Crystals separated were collected by filtration, washed with a small amount of methanol, and dried over soda-lime to yield 1.67 g of V as needles, mp 222-223°. Further 0.20 g of V was obtained from the mother liquor, and the total yield was 1.87 g (91%). The identity was confirmed by mixed mp and comparison of the infrared spectra with authentic material.

Acetylation of the Hydroxy Ester V. - A solution of 3.0 g of V in 60 ml of pyridine-acetic anhydride (1:1) was allowed to stand over night at room temperature. The mixture was diluted with water under occasional cooling, and the precipitated crystals were collected, and washed with water. One crystallization from methanol afforded 2.6 g (80%) of III, mp 242-243°, which was identical in every respect with an authentic sample prepared above.

3α,7α-Diacetoxy-11α-chloro-12α-nitro-5β-cholanoic Acid (VI). - After a solution of 1.00 g of the hydroxy acid IV in 30 ml of pyridine-acetic anhydride (1:1) had been left at room temperature overnight, 100 ml of water was added dropwise under cooling. The resulting precipitate was collected, washed with water, and dried to give VI, mp 279-280° dec, in quantitative yield. One crystallization from methanol afforded 1.00 g (97%) of analytical sample of VI as colorless needles: mp 284-285° dec; $[\alpha]_D^{25}$ + 28.7° (c 0.6); ν^{Nujol} 3320 (OH), 1737 (acetate), 1706 (carboxyl), 1553 (NO_2) cm^{-1}. The nmr spectrum in deuteropyridine had peaks at δ 0.87 (s, C18-H), 1.03 (s, C19-H), 1.97 and 2.02 (s, acetate Me), 4.66 (q, C11-H, J = 10.8 and 4.8, a), 4.70 (m, C3-H, W1/2 = ca. 24, a), 5.01 (m, C7-H, W1/2 = 7.2, e), 5.42 (d, C12-H, J = 4.8, e).

Anal. Calcd. for $C_{28}H_{42}O_8NCl$: C, 60.48; H, 7.61; N, 2.52. Found: C, 60.85; H, 7.73; N, 2.47.

Methyl 7α-Acetoxy-11α-chloro-12α-nitro-3-oxo-5β-cholanoate (VII). - To a solution of 1.00 g of the hydroxy ester V in 100 ml of acetone and 5 ml of water was added dropwise 2 ml of 8N-chromic acid at room temperature. Stirring was continued for an additional 15 minutes, and then diluted with 400 ml of water. The fine needles separated were collected, washed with water, and dried to yield 1.00 g (100%) of the 3-one VII, mp 181-182°. Two crystallizations from aqueous acetone furnished the analytical sample: mp 182-183°; $[\alpha]_D^{22}$ +27.2° (c 1); ν^{Nujol} 1742 (ester), 1720 (C=O), 1552 (NO_2) cm^{-1}. The nmr spectrum had peaks at δ 0.96 (s, C18-H), 1.22 (s, C19-H), 2.12 (s, acetate Me), 3.67 (s, OMe), 4.47 (q, C11-H, J = 11.2 and 4.8, a), 5.03 (m, C7-H, W1/2 = 10, e), 5.22 (d, C12-H, J = 4.8, e).

Anal. Calcd. for $C_{27}H_{40}O_7NCl$: C, 61.65; H, 7.66; N, 2.66; Cl, 6.74. Found: C, 61.42; H, 7.82; N, 2.60; Cl, 6.87.

Methyl 3α,7α-Diacetoxy-12-oxo-5β-chol-9(11)-enoate (II). - A solution of 2.00 g of the nitro-chloride III in 200 ml of methanol containing 2 g of potassium hydroxide was heated under reflux for

5 hours, and the solvent was removed under reduced pressure. The residue was dissolved in 80 ml of water, and the solution was made acid to Congo red by addition of dilute hydrochloric acid. The resulting precipitate was collected, washed with water, and dried. The amorphous product (1.45 g) was dissolved in 4.4 ml of methanol containing 1% of hydrogen chloride, and heated under reflux for 15 minutes. The solvent was removed under reduced pressure, and the residue was extracted with methylene chloride. The extract was washed with water, dried over magnesium sulfate, and evaporated to dryness. The resulting oil was acetylated with 10 ml of acetic anhydride in 15 ml of pyridine at room temperature. Standard work-up afforded brown oil which was percolated over 75 g of alumina with 300 ml of ether, and the 0.31 g of clear oil obtained was crystallized from methanol to afford 0.17 g of II: mp 158-159°, lit.[12] mp 159-161°; ν^{Nujol} 1734 (ester) 1668 and 1607 (O=C-C=C) cm^{-1}. The product was identified by mixed mp and comparison of infrared spectra with authentic material.

Crystal Structure of Methyl 3α,7α-Diacetoxy-11α-chloro-12α-nitro-5β-cholanoate (III). - Crystals of III, prepared as in the experimental section, are orthorhombic (space group $P2_12_12_1$), with unit cell dimensions, a = 11.821, b = 24.741, c = 10.477 Å. Full three-dimensional diffraction data were collected using copper-Kα radiation and the structure was solved by application of the "heavy atom" method. The atomic positional and anisotropic thermal parameters were refined by a block-diagonal approximation to the least-squares normal equations. The refined parameters and a full discussion of the structure will be presented elsewhere.

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20. Melting points were determined in capillary tubes and are uncorrected. Infrared spectra were recorded on a Hitachi EPI-S2 spectrophotometer. Optical rotations were measured in chloroform solutions (except where noted) on an Applied Electric Lab. MP-1T polarimeter. Proton nmr spectra were recorded in deuterochloroform (except otherwise noted) on a Hitachi R-20 (60MHz) spectrometer, and are reported in parts per million downfield from a tetramethylsilane internal standard. Coupling constants and half-band widths are quoted in Hz. Optical rotatory dispersion was recorded on a JASCO ORD/UV-5 recorder.

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