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Synthesis and Transformations of 20-Isoxazolyl Steroids with Modified Ring D: II.* Synthesis of 16α-Acetoxy Derivatives**

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Abstract—A procedure was developed for preparation of compounds of the cholestane and 26,27-dinorcholestane series with 16-acetoxy-substited ring **D** and functionalized side chain, starting from 16α,17α-epoxypregnenolone.

In the framework of our studies on the synthesis of possible haptenes of natural steroids, in particular brassinosteroids, we develop procedures for regio- and stereoselective chemical modification of steroid molecules containing an additional functional group in ring **D**. Starting from dehydropregnenolone acetate, we have syntheseized 16α,17α-epoxy-20-isoxazolyl steroids and studied methods of their transformations into compounds with open side chain [1]. However, the yields of the target products were poor, and the selectivity of some reactions in the above scheme was low. Therefore, we turned our attention to another approach, namely that involving opening of the oxirane ring in **I** [1] and subsequent application of the scheme described in the preceding communication. For this purpose, epoxy ketone **I** was treated with aluminum amalgam [2] to obtain 3β,16α-dihydroxy-20-oxo derivative **II**. Acetylation of the latter with acetic anhydride in pyridine gave 3,16-diacetoxy compound **III**. The reaction was accompanied by side reduction of the 20-oxo group with formation of 3,16,20-triacetoxy steroid **IV** as an epimeric mixture with respect to C^{20} (Scheme 1). Diacetate **III** characteristically shows in the ^{1}H NMR spectrum three-proton singlets from the acetyl methyl groups at δ 2.03 and 2.06 ppm, two one-proton signals from 3-H and 16-H at δ 3.49 and 4.78 ppm, and a three-proton singlet at δ 2.20 ppm, belonging to the methyl group attached to the ketone carbonyl. The IR spectrum of **III** contained three carbonyl absorption bands at 1750, 1735, and 1715 cm^{-1}.

Triacetate **IV** was separated into individual epimers **IVa** and **IVb** which differed from each other by the positions of signals in the ^{1}H NMR spectra (three singlets from the acetyl groups, three-proton doublet from the 21-methyl group, and three one-proton signals at δ 4.60, 4.87, and 5.02 ppm from protons at the carbon atoms attached to acetoxy groups). The main difference between the C^{20}-epimers is observed in the position of the 21-methyl signal which appears in a weaker field for the (20*S*)-isomer [3].

Further transformations of 16α-acetoxy-20-oxo compound **III** were accomplished according to the scheme proposed in [1] for 16α,17α-epoxy analogs. The scheme includes synthesis of acetylenic alcohol **V**, 1,3-dipolar cycloaddition to **V** of nitrile oxides (the reactions with acetonitrile oxide and isobutyronitrile oxide were studied [4]) to form 20-isoxazolyl steroids **VI** and **VII**, respectively, dehydration of the latter to $\Delta^{20(21)}$-derivatives **VIII** and **IX** by the action of thionyl chloride, and reductive cleavage of the isoxazole ring over Raney nickel in ethanol. We thus obtained products **X** and **XII**, as well as compounds **XI** and **XIII** which were formed by subsequent reduction of the 20(21)-double bond (Scheme 1).

In the ^{1}H NMR spectra of compounds **VI** and **VII** we observed a signal from the isoxazole ring proton at δ 6.00 and 6.02 ppm, respectively, whereas the signal

* For communication I, see [1].

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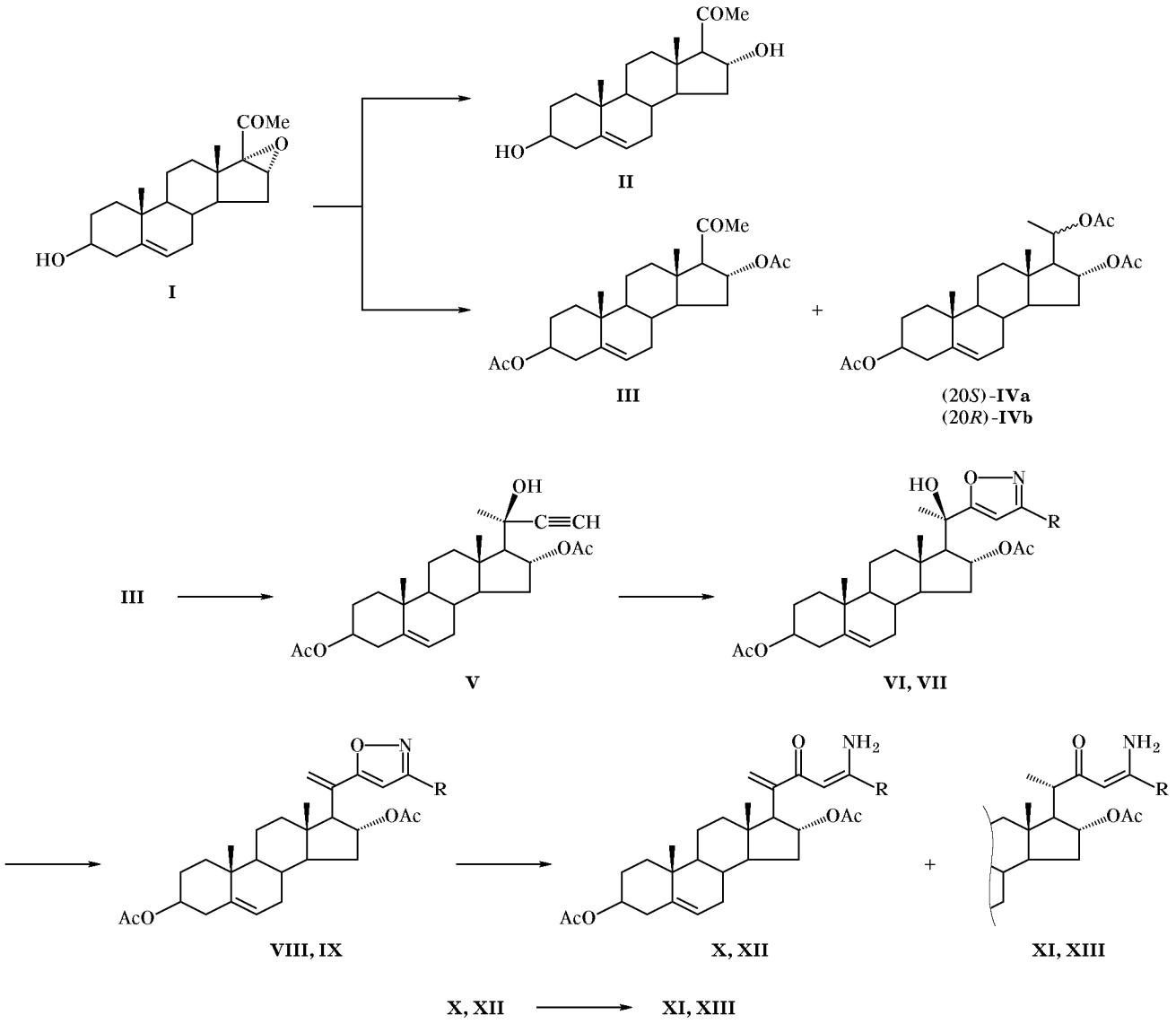
Scheme 1.



VI, **VIII**, **X**, **XI**, R = Me; **VII**, **IX**, **XII**, **XIII**, R = *i*-Pr.

from the terminal acetylenic proton disappeared. The three-proton singlet from the methyl group at C^{18} shifts upfield to δ 0.94 ppm. In the ^1H NMR spectra of dehydrated products **VIII** and **IX** the 18-CH_3 signal was observed in a stronger field (δ 0.66–0.67 ppm), while signals from the isoxazole ring proton and 16-H were displaced downfield (δ 6.12–6.14 and 5.48 ppm). In addition, two singlets from the vinyl protons at C^{21} appeared at δ 5.40 and 5.96 ppm. The formation of compounds **X** and **XII** with open side chain gives rise to an upfield shift of the 18-CH_3 signal (δ 0.60–0.62 ppm), signals from the vinyl protons (δ 5.28–5.29 and 5.70–5.72 ppm), and signal from 16-H (δ 5.36 m.d.). The 23-H signal appears as a singlet at δ 5.36–5.38 ppm. The hydrogenation of the $\Delta^{20(21)}$-double bond in **X** and **XII** yields Δ^{23}-22-oxo steroids **XI** and **XIII**, respectively. As a result, the 18-CH_3 signal shifts downfield (δ 0.78 ppm), signals from 23-H and 16-H shift upfield (δ 5.06, 5.02 and 4.98, 4.92 ppm, respectively), and the 21-CH_3 signal appears as a doublet at δ 1.16–1.18 ppm.

Thus, starting from 16α,17α-epoxypregnenolone, we have developed a procedure for synthesis of 16α-acetoxy derivatives of cholestane and 26,27-dinorcholestane. The products can be subjected to further modifications with the goal of obtaining

haptenes of the series of natural polyhydroxy steroids and their derivatives at C^{16} without involving functional groups which are responsible for biological activity [5–8].

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were recorded on a Bruker A-200 instrument (200 MHz for ^1H) from solutions in $CDCl_3$ containing tetramethylsilane as internal reference. The IR spectra were obtained on a UR-20 spectrometer from samples prepared as thin films or KBr pellets. The mass spectra (70 eV) were run on a Hewlett–Packard HP-5890 instrument (linear oven temperature programming from 40 to 280°C at a rate of 10 deg/min). The UV spectra were measured on a Specord M-400 spectrophotometer from solutions in methanol or ethanol. The melting points were determined on a Koefler heating block. The progress of reactions was monitored by TLC on Silufol UV-254 and Kieselgel 60 F_{254} (Merck) plates. Kieselgel 60 silica gel (40/60 μm, Merck) was used for chromatographic separation.

Opening of the oxirane ring in 16α,17α-epoxy steroid I. Epoxy steroid **I**, 2 g (6.2 mmol), was dissolved in 100 ml of ethanol, 2 ml of a 10% solution of sodium hydrogen carbonate and aluminum amalgam prepared from 3.6 g of aluminum plates were added, and the mixture was stirred for 18 h at room temperature. Chloroform, 100 ml, was then added, the precipitate was filtered off, and the filtrate was evaporated to obtain 2 g of a crude product. Recrystallization gave 0.1 g of diol **II**. The residue (without additional purification) was acetylated with acetic anhydride in pyridine for 12 h at room temperature. The products were separated by chromatography on silica gel using toluene–ethyl acetate (9:1) as eluent. We isolated 1.66 g (67%) of 3,16-diacetoxy-20-oxo steroid **III** and 0.52 g (21%) of triacetate **IV**.

3β,16α-Dihydroxypregn-5-ene (II). mp 156–157°C (from methanol). ^1H NMR spectrum ($CDCl_3$–CD_3OD), δ, ppm: 0.65 s (3H, 18-Me), 1.01 s (3H, 19-Me), 2.20 s (3H, 21-Me), 2.58 d (1H, 17-H, J = 7 Hz), 3.49 m (1H, 3-H), 4.78 m (1H, 16-H), 5.38 m (1H, 6-H).

3β,16α-Diacetoxypregn-5-ene (III). mp 173–174°C (from methanol). IR spectrum (CCl_4), ν, cm^{-1}: 2980, 2960, 2920, 2860, 1750, 1735, 1715, 1370, 1255. ^1H NMR spectrum, δ, ppm: 0.64 s (3H, 18-Me), 1.04 s (3H, 19-Me), 2.03 s (3H, OAc), 2.06 s (3H, OAc), 2.20 s (3H, 21-Me), 2.68 d (1H, 17-H, J = 7 Hz), 4.62 m (1H, 3-H), 5.39 m (1H, 6-H), 5.51 t (1H, 16-H, J = 7 Hz).

(20*S*)-3β,16α,20-Triacetoxypregn-5-ene (IVa) was isolated as an oily substance. IR spectrum (film), ν, cm^{-1}: 2960, 2920, 2870, 1745, 1730, 1450, 1375, 1260. ^1H NMR spectrum, δ, ppm: 0.72 s (3H, 18-Me), 1.02 s (3H, 19-Me), 1.26 d (3H, 21-Me, J = 7 Hz), 2.04 s (6H, $2CH_3CO$), 4.60 m (1H, 3-H), 5.04 m (1H, 16-H), 5.22 m (1H, 21-H), 5.38 m (1H, 6-H).

(20*R*)-3β,16α,20-Triacetoxypregn-5-ene (IVb). Oily substance. IR spectrum (film), ν, cm^{-1}: 2960, 2920, 2870, 1745, 1730, 1450, 1375, 1260. ^1H NMR spectrum, δ, ppm: 0.70 s (3H, 18-Me), 1.02 s (3H, 19-Me), 1.17 d (3H, 21-Me, J = 7 Hz), 2.04 s (6H, $2CH_3CO$), 4.60 m (1H, 3-H), 4.87 m (1H, 21-H), 5.02 m (1H, 16-H), 5.38 m (1H, 6-H).

3β,16α-Diacetoxy-20-hydroxy-24-norchol-25-en-22-yne (V). Ethyl bromide, 0.74 ml (8.4 mmol), was added dropwise to a mixture of 0.2 g (8.4 mmol) of magnesium and 30 ml of anhydrous tetrahydrofuran. When the magnesium dissolved completely, the mixture was stirred for 10 min, and acetylene was passed through the mixture over a period of 30 min (the mixture warmed up to 40°C). The mixture was then cooled to room temperature, a solution of 0.7 g (1.68 mmol) of oxo steroid **III** in 20 ml of tetrahydrofuran was added, and the mixture was stirred for 2 h at room temperature and was treated with 100 ml of a saturated solution of ammonium chloride. The products were extracted into ethyl acetate, the extract was dried over sodium sulfate, the solvent was evaporated, and the residue was subjected to column chromatography on silica gel using toluene–ethyl acetate (4:1) as eluent. Yield 0.68 g (92%). mp 174–175°C (from methanol). IR spectrum (KBr), ν, cm^{-1}: 3480, 2970, 2950, 2910, 2870, 1740, 1725, 1450, 1380, 1260. ^1H NMR spectrum, δ, ppm: 1.01 s (3H, 18-Me), 1.03 s (3H, 19-Me), 1.53 s (3H, 21-Me), 2.03 s (6H, $2CH_3CO$), 2.54 s (1H, 23-H), 4.61 m (1H, 3-H), 5.36 m (2H, 6-H and 16-H). ^{13}C NMR spectrum, δ_C, ppm: 14.1 q, 19.2 q, 20.4 t, 21.4 d.q, 27.6 t, 30.6 q, 30.8 t, 31.6 d, 32.7 t, 36.5 s, 36.6 t, 38.0 t, 40.1 t, 44.3 s, 49.7 d, 53.3 d, 65.1 s, 69.7 s, 73.8 d, 74.0 s, 76.4 d, 87.3 d, 122.1 d, 139.7 s, 170.5 s, 170.9 s.

1,3-Dipolar cycloaddition of nitrile oxides to acetylenic alcohol V. Several drops of pyridine were added to a suspension of 0.8 g (6 mmol) of *N*-chlorosuccinimide in 5 ml of chloroform, and a solution of 6 mmol of acetaldehyde oxime or isobutyraldehyde oxime in 2 ml of chloroform was added. The mixture was stirred for 15 min, and 0.68 g (2 mmol) of compound **V** in 2 ml of chloroform was added. The mixture was stirred for 10 min, 0.85 ml (6 mmol) of triethylamine in chloroform was added dropwise over a period of 4 h, and the mixture was left overnight.

The mixture was washed with water, dried over sodium sulfate, and evaporated, and the residue was subjected to column chromatography on silica gel using toluene–ethyl acetate [(1–2) : 1] as eluent.

(20*R*)-3β,16α-Diacetoxy-20-hydroxy-20-(3-methylisoxazol-5-yl)pregn-5-ene (VI) was obtained from 0.3 g (0.7 mmol) of compound **V** and acetaldehyde oxime. Yield 0.34 g (94%). mp 240–241°C (from methanol). IR spectrum (film), ν, cm^{-1}: 3470, 2980, 2960, 2920, 2860, 1740, 1510, 1480, 1455, 1380, 1260. ^{1}H NMR spectrum, δ, ppm: 0.94 s (3H, 18-Me), 1.02 s (3H, 19-Me), 1.54 s (3H, 21-Me), 2.04 s (3H, OAc), 2.26 s (3H, OAc), 2.77 s (3H, 3′-Me), 4.62 m (1H, 3-H), 5.38 m (2H, 6-H and 16-H), 6.00 s (1H, 4′-H).

(20*R*)-3β,16α-Diacetoxy-20-hydroxy-20-(3-isopropylisoxazol-5-yl)pregn-5-ene (VII) was obtained from 0.3 g (0.7 mmol) of compound **V** and isobutyraldehyde oxime. Yield 0.275 g (83%). mp 244–245°C (from methanol). IR spectrum (KBr), ν, cm^{-1}: 3470, 2980, 2960, 2920, 2860, 1745, 1505, 1480, 1460, 1380, 1255. ^{1}H NMR spectrum, δ, ppm: 0.94 s (3H, 18-Me), 1.02 s (3H, 19-Me), 1.14 d (6H, CH**Me**$_2$, *J* = 7 Hz), 1.75 s (3H, 21-Me), 2.04 s (6H, 2CH_3CO), 2.98 m (1H, C**H**Me_2), 4.62 m (1H, 3-H), 5.38 m (2H, 6-H and 16-H), 6.02 s (1H, 4′-H).

Dehydration of 20-hydroxy-20-isoxazolyl steroids by the action of thionyl chloride. Pyridine, 0.3 ml, was added with stirring to a solution of 1 mmol of 20-hydroxy-20-isoxazolyl steroid in 20 ml of tetrahydrofuran. The mixture was cooled to –50°C, and 0.33 ml (1.84 mmol) of freshly distilled thionyl chloride in 5 ml of tetrahydrofuran was added. The mixture was allowed to warm up to room temperature over a period of 1 h, and 100 ml of a 5% solution of sodium hydrogen carbonate was added. The mixture was treated with ethyl acetate, and the extract was washed with water and a solution of sodium hydrogen carbonate, dried over anhydrous sodium sulfate, and evaporated. The residue was subjected to column chromatography on silica gel using hexane–ethyl acetate [(1–3) : 1] as eluent.

3β,16α-Diacetoxy-20-(3-methylisoxazol-5-yl)-pregna-5,20(21)-diene (VIII) was synthesized from 0.34 g (0.7 mmol) of 20-hydroxy-20-isoxazolyl steroid **VI**. Yield 0.191 g (58%). mp 146–147°C (from methanol–chloroform). IR spectrum (CCl_4), ν, cm^{-1}: 2980, 2960, 2920, 2860, 1745, 1585, 1450, 1370, 1255. UV spectrum (EtOH): λ_{max} 249 nm, ε 8430. ^{1}H NMR spectrum, δ, ppm: 0.67 s (3H, 18-Me), 1.02 s (3H, 19-Me), 2.02 s (3H, $OCOCH_3$), 2.04 s (3H, $OCOCH_3$), 2.29 s (3H, 3′-Me), 4.62 m (1H, 3-H), 5.38 m (1H, 6-H), 5.48 t (1H, 16-H, *J* = 7 Hz), 5.40 s and 5.96 s (2H, 21-H), 6.12 s (1H, 4′-H).

3β,16α-Diacetoxy-20-(3-isopropylisoxazol-5-yl)-pregna-5,20(21)-diene (IX) was synthesized from 0.34 g (0.68 mmol) of 20-hydroxy-20-isoxazolyl steroid **VII**. Yield 0.32 g (99%). mp 168–169°C (from methanol). IR spectrum (KBr), ν, cm^{-1}: 2980, 2960, 2910, 2860, 1740, 1590, 1460, 1455, 1380, 1255. UV spectrum (EtOH): λ_{max} 249 nm, ε 9260. ^{1}H NMR spectrum, δ, ppm: 0.66 s (3H, 18-Me), 1.02 s (3H, 19-Me), 1.32 d (6H, CH**Me**$_2$, *J* = 7 Hz), 2.04 s (3H, $OCOCH_3$), 2.06 s (3H, $OCOCH_3$), 3.06 m (1H, C**H**Me_2), 4.62 m (1H, 3-H), 5.38 m (1H, 6-H), 5.40 s and 5.95 s (2H, 21-H), 5.48 t (1H, 16-H, *J* = 8 Hz), 6.14 s (1H, 4′-H). ^{13}C NMR spectrum, δ_C, ppm: 13.8 q, 19.3 q, 20.5 t, 21.2 q, 21.4 q, 21.7 d.q, 26.5 d, 27.7 t, 31.6 d, 31.8 t, 33.3 t, 36.6 s, 36.9 t, 38.0 t, 38.1 t, 43.7 s, 50.0 d, 54.3 d, 58.7 d, 73.8 d, 76.6 d, 98.8 d, 117.2 t, 122.1 d, 132.7 s, 139.8 s, 169.5 s, 170.5 s, 170.9 s, 171.1 s.

Reductive cleavage of isoxazolyl steroids. Raney nickel (W-2), 100 mg, was saturated with hydrogen while stirring in 10 ml of ethanol over a period of 2 h. $\Delta^{20,21}$-20-isoxazolyl steroid, 0.1 mmol, in 10 ml of ethanol was added, and the mixture was stirred for 2–3 h at room temperature under hydrogen. When the reaction was complete, the catalyst was filtered off, the filtrate was evaporated, and the residue was subjected to chromatography on silica gel using toluene–ethyl acetate [(2–3) : 1] as eluent. From 0.18 g (0.38 mmol) of compound **VIII** we obtained 0.16 g (90%) of 24-amino-20(21),23-dien-22-one **X** and 0.01 g (5%) of 24-amino-23-en-22-one **XI**.

3β,16α-Diacetoxy-24-amino-26,27-dinorcholesta-5,20(21),23-trien-22-one (X). mp 103–105°C (ethyl acetate–hexane). IR spectrum (KBr), ν, cm^{-1}: 2980, 2960, 2920, 2860, 1745, 1635, 1535, 1450, 1380, 1255. ^{1}H NMR spectrum, δ, ppm: 0.60 s (3H, 18-Me), 1.00 s (3H, 19-Me), 2.00 s (3H, $OCOCH_3$), 2.04 s (3H, $OCOCH_3$), 2.06 s (3H, 25-Me), 3.18 d (1H, 17-H, *J* = 7 Hz), 4.60 m (1H, 3-H), 5.16 br.s (1H, NH), 5.29 s and 5.70 s (2H, 21-H), 5.36 m (2H, 16-H and 23-H), 5.38 m (1H, 6-H), 9.90 br.s (1H, NH).

3β,16α-Diacetoxy-24-amino-26,27-dinorcholesta-5,23-dien-22-one (XI). mp 193–195°C (from MeOH). IR spectrum (KBr), ν, cm^{-1}: 2980, 2960, 2920, 2860, 1745, 1630, 1540, 1460, 1380, 1260. UV spectrum, (EtOH): λ_{max} 300 nm, ε 18235. ^{1}H NMR spectrum, δ, ppm: 0.78 s (3H, 18-Me), 1.03 s (3H, 19-Me), 1.16 d (3H, 21-Me, *J* = 7 Hz), 1.90 s (3H, $OCOCH_3$), 1.95 s (3H, $OCOCH_3$), 2.10 s (3H, 25-Me), 4.62 m (1H, 3-H), 4.98 m (2H, NH and 16-H), 5.00 s (1H, 23-H), 5.36 m (1H, 6-H), 9.87 br.s (1H, NH). ^{13}C

NMR spectrum, δ_C, ppm: 13.1 q, 16.8 q, 19.2 q, 20.6 t, 20.8 q, 21.4 q, 22.3 q, 27.6 t, 31.2 d, 31.6 t, 34.1 t, 36.5 s, 36.8 t, 38.0 t, 39.3 t, 43.3 s, 46.8 d, 49.7 d, 53.5 d, 59.1 d, 73.8 d, 79.0 d, 95.3 d, 122.2 d, 139.7 s, 170.5 s, 171.0 s, 201.6 s.

In a similar way, from 0.1 g (0.21 mmol) of 24-amino-20(21),23-dien-22-one **X** we obtained 0.082 g (82%) of 24-amino-23-en-22-one **XI**; from 0.14 g (0.27 mmol) of $\Delta^{20(21)}$-20-isoxazolyl steroid **IX**, 0.099 g (70%) of 24-amino-20(21),23-dien-22-one **XII** and 0.01 g (7%) of 24-amino-23-en-22-one **XIII**; and from 0.05 g (0.09 mmol) of 24-amino-20(21),23-dien-22-one **XII**, 0.035 g (70%) of 24-amino-23-en-22-one **XIII**.

3β,16α-Diacetoxy-24-aminocholesta-25,20(21),23-trien-22-one (XII). mp 188–190°C (from methanol). IR spectrum (KBr), ν, cm^{-1}: 2980, 2960, 2920, 2860, 1745, 1620, 1535, 1480, 1450, 1380, 1255. UV spectrum (EtOH): λ_{max} 305 nm, ε 7250. ^{1}H NMR spectrum, δ, ppm: 0.62 s (3H, 18-Me), 1.00 s (3H, 19-Me), 1.20 d (6H, CH**Me**$_2$, *J* = 7 Hz), 2.00 s (3H, $OCOCH_3$), 2.02 s (3H, $OCOCH_3$), 2.48 m (1H, C**H**Me_2), 3.18 d (1H, 17-H, *J* = 7 Hz), 4.60 m (1H, 3-H), 5.12 br.s (1H, NH), 5.28 s and 5.72 s (2H, 21-H), 5.36 m (2H, 6-H and 16-H), 5.38 s (1H, 23-H), 10.04 br.s (1H, NH).

3β,16α-Diacetoxy-24-aminocholesta-5,23-dien-22-one (XIII). mp 216–218°C (from methanol). IR spectrum (film), ν, cm^{-1}: 2980, 2960, 2920, 2860, 1740, 1625, 1540, 1470, 1450, 1380, 1255. UV spectrum (EtOH): λ_{max} 301 nm, ε 23180. ^{1}H NMR spectrum, δ, ppm: 0.78 s (3H, 18-Me), 1.02 s (3H, 19-Me), 1.18 d (9H, 21-Me and CH**Me**$_2$, *J* = 7 Hz), 1.86 s (3H, $OCOCH_3$), 2.03 s (3H, $OCOCH_3$), 2.42 m (1H, C**H**Me_2), 4.61 m (1H, 3-H), 4.92 t (1H, 16-H, *J* = 7 Hz), 5.02 s (1H, 23-H), 5.13 br.s (1H, NH), 5.38 m (1H, 6-H), 10.08 br.s (1H, NH).

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