SYNTHESIS OF *trans* β-LACTAMS OF ESTRANE SERIES

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17,17-Ethylenedioxy-1,3,5(10)-estratrien-3β-ol (*I*) was converted into ethyl ester *II* by reaction with ethyl chloroacetate in the presence of potassium. The ethyl ester *II* on reaction with hydrazine gave hydrazide *III*, which on condensation with aromatic aldehydes gave Schiff bases *IVa–IVd*. The reaction of Schiff bases *IVa–IVd* with chloroacetyl chloride in the presence of triethylamine afforded β-lactams *Va–Vd*.

The β-lactam unit is the central functionality in a large number of antibiotics including penicillin and cephalasporin[1]. Consequently their preparation and further transformations are of interest[2,3]. In continuation of our work on extranuclear modification of steroids[4,5], we report here the synthesis of *trans* β-lactams of estrane series.

The reaction of imines with acid chlorides in the presence of amine base is one of the most versatile methods for the synthesis of β-lactams[6]. However, it is often difficult to predict the stereochemistry of the product[7]. The cycloaddition may be stereospecific or nonstereospecific with variable ratios of *cis* and *trans* isomers of β-lactams, depending on the order of addition of reactants[8]. The products having *trans* stereochemistry appear to be preferred when amine is added to a solution of imine and acid chloride, while *cis* products often predominates when acid chloride is added to a solution of imine and amine. It is generally assumed that the former method involve an acyliminium ion and the later a ketene intermediate[9].

17,17-Ethylenedioxy-1,3,5(10)-estratrien-3β-ol (*I*) on reaction with ethyl chloroacetate in the presence of potassium gave ethyl 17,17-ethylenedioxy-1,3,5(10)-estratrien-3β-*O*-acetate (*II*) (Scheme 1). The ^{1}H NMR spectrum of *II* gave a singlet at δ 4.8 (OCH_2CO_2), a quartet at δ 4.1 (CO_2CH_2) and a triplet at δ 1.2 (CH_3). The ethyl ester *II* on treatment with hydrazine gave hydrazide *III* whose ^{1}H NMR spectrum showed broad

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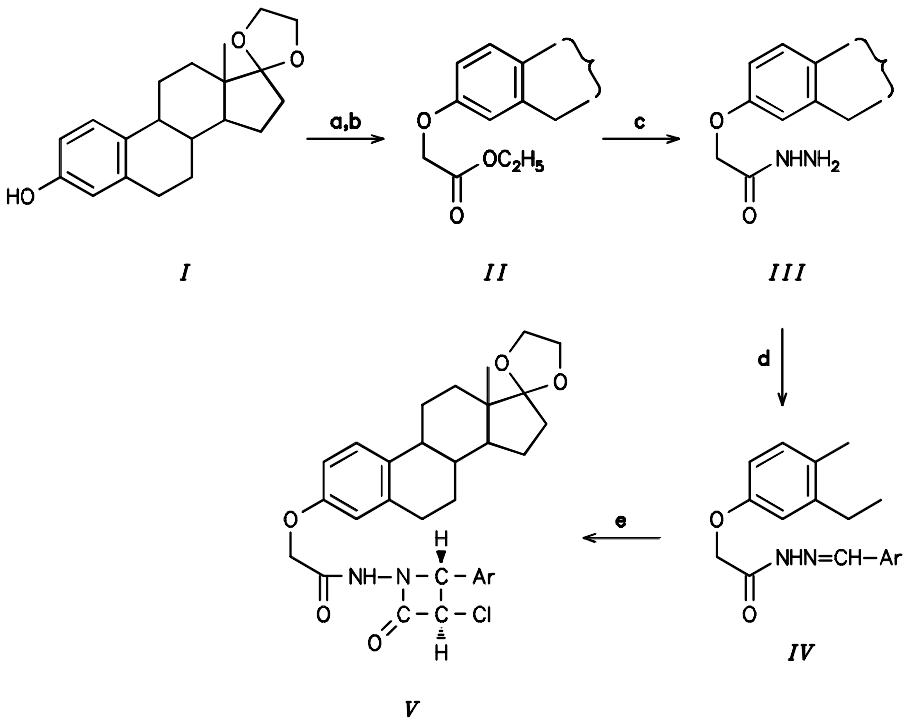
singlets at δ 4.3 (NH_2) and at δ 8.5 (CONH) which disappeared upon treatment with deuterium oxide. The hydrazide *III* on condensation with aromatic aldehydes such as benzaldehyde, 4-nitrobenzaldehyde, 4-chlorobenzaldehyde, and 4-methoxybenzaldehyde gave Schiff bases *IVa–IVd*. The ^{1}H NMR spectra of *IVa–IVd* showed a singlet at δ 6.1 for N=CH proton and multiplets in the region of δ 7.3–7.7 for aromatic protons.

The reaction of Schiff bases *IVa–IVd* with chloroacetyl chloride in the presence of triethylamine afforded β-lactams *Va–Vd*. The structure of β-lactams *Va–Vd* were established on the basis of IR, ^{1}H NMR and ^{13}C NMR. The IR spectra showed absorption bands at 3 225 (NH), 1 740 (C=O), 1 650 (CONH), 1 600 (C=C), 1 140 (ketal), 730



I *II* *III* *IV* *V*

In formulae *IV* and *V*: *a*, Ar = C_6H_5
b, Ar = 4–$NO_2C_6H_4$
c, Ar = 4–ClC_6H_4
d, Ar = 4–$CH_3OC_6H_4$

a) K, C_6H_6; b) $ClCH_2CO_2C_2H_5$; c) NH_2NH_2; d) ArCHO; e) $ClCH_2COCl/(C_2H_5)_3N$

SCHEME 1

(C-Cl) cm^{-1}. The ^1H NMR spectra gave a singlet at δ 6.3 for H-3′ (J = 2 Hz), doublet at δ 4.3 for H-4′ (J = 2 Hz) and other signals are attributed to CONH and aromatic protons. The stereochemistry at C-3′ and C-4′ of the β-lactam ring was established by ^1H NMR and was found to be *trans* on the basis[10] of coupling constant (J = 1–2 Hz). The ^{13}C NMR spectra further supported their structures and showed signals at δ 66.48 (OCH_2CH_2O), 70.61 (C-4′), 80.20 (C-3′), 84.50 (OCH_2), 167.10 (β-lactam C=O) and 168.20 (CONH).

EXPERIMENTAL

Melting points are uncorrected. The infrared spectra were obtained as KBr pellets using Perkin–Elmer 137 spectrometer. ^1H NMR were recorded in $CDCl_3$ on a Varian XL-200 spectrometer (200 MHz) and ^{13}C NMR in $CDCl_3$ on Gemini 200 instrument (50 MHz) with tetramethylsilane as internal standard. Chemical shifts are given in ppm (δ-scale), coupling constants (J) in Hz. The purity of analytical samples was checked by TLC (silica gel). 17,17-Ethylenedioxy-1,3,5(10)-estratrien-3β-ol (*I*) was prepared according to the literature procedure[11].

Ethyl 17,17-ethylenedioxy-1,3,5(10)-estratrien-3β-*O*-acetate (*II*)

To a solution of 17,17-ethylenedioxy-1,3,5(10)-estratrien-3β-ol (*I*) (2.0 g; 6.4 mmol) in benzene (50 ml) was added potassium metal (0.72 g; 18.4 mmol) and the mixture was refluxed for 1 h. After cooling ethyl chloroacetate (4.5 g; 36.7 mmol) was added and the mixture was further refluxed for 3 h. Excess potassium metal was destroyed by the addition of methanol (1 ml), the mixture was concentrated under reduced pressure and then poured onto ice and extracted with ether. The ether extract was concentrated and the material obtained was crystallized from ethanol to give 1.96 g (77%) of product *II* as colorless solid, m.p. 139–140 °C. IR spectrum: 1 735, 1 245 (acetate); 1 600 (C=C); 1 140 (OCH_2CH_2O). ^1H NMR spectrum: 0.79 s, 3 H (3 × H-18); 1.25 t, 3 H ($CO_2CH_2\mathbf{CH}_3$); 3.88 s, 4 H (OCH_2CH_2O); 4.12 q, 2 H ($CO_2\mathbf{CH}_2CH_3$); 4.84 s, 2 H (OCH_2CO_2); 6.58 d, 1 H, J = 2.4,(H-4); 6.69 dd, 1 H, J = 2.4, 8.7, (H-2); 7.07 d, 1 H, J = 8.7, (H-1). For $C_{24}H_{32}O_5$ (400.5) calculated: 71.97% C, 8.05% H; found: 72.12% C, 8.15% H.

17,17-Ethylenedioxy-1,3,5(10)-estratrien-3β-*O*-acethydrazide (*III*)

To a solution of ethyl ester *II* (2.0 g; 5.0 mmol) in methanol (100 ml) was added hydrazine hydrate (6.41 g; 20 mmol) and the mixture was refluxed with a drop of acetic acid for 6 h. The mixture was concentrated in vacuo and then poured onto ice. The resulting precipitate was filtered, washed with water and recrystallized from methanol to give 1.54 g (80%) of hydrazide *III* as colorless solid, m.p. 156–157 °C. IR spectrum: 3 280, 3 170 (NH_2, NH); 1 640 (CONH); 1 600 (C=C); 1 138 (OCH_2CH_2O). ^1H NMR spectrum: 0.80 s, 3 H (3 × H-18); 3.90 s, 4 H (OCH_2CH_2O); 4.30 brs, 2 H (NH_2); 4.86 s, 2 H (OCH_2CO); 6.59 d, 1 H, J = 2.4, (H-4); 6.72 dd, 1 H, J = 2.4, 8.7, (H-2); 7.10 d, 1 H, J = 8.7, (H-1); 8.50 brs, 1 H (CONH). For $C_{22}H_{30}N_2O_4$ (386.5) calculated: 68.37% C, 7.82% H, 7.25% N; found: 68.48% C, 7.86% H, 7.32% N.

General Procedure for Reaction of Hydrazide *III* with Aromatic Aldehydes

A solution of hydrazide *III* (2.5 g; 5 mmol) and aromatic aldehyde (12.9 mmol) in benzene (40 ml) was refluxed with few drops of piperidine for 4 h. The mixture was concentrated under reduced

pressure and then poured onto ice and extracted with ether. The ether extract was concentrated and the residue obtained was crystallized from methanol to give Schiff bases *IVa–IVd*.

*17,17-Ethylenedioxy-3*β*-O-acethydrazinobenzyliden-1,3,5(10)-estratriene* (IVa): yield 70%; m.p. 167–168 °C. IR spectrum: 3 220 (NH); 1 643 (CONH); 1 630 (C=C); 1 140 (OCH_2CH_2O). ^{1}H NMR spectrum: 0.78 s, 3 H (3 × H-18); 3.92 s, 4 H (OCH_2CH_2O); 4.88 s, 2 H (OCH_2CO); 6.60 d, 1 H, *J* = 2.4 (H-4); 6.70 dd, 1 H, *J* = 2.4, 8.7 (H-2); 7.15 d, 1 H *J* = 8.7 (H-1); 7.4–7.7 m, 5 H (H-arom.); 8.55 brs, 1 H (CONH). For $C_{29}H_{34}N_2O_4$ (474.6) calculated: 73.39% C, 7.22% H, 5.90% N; found: 73.42% C, 7.34% H, 5.98% N.

*17,17-Ethylenedioxy-3*β*-O-acethydrazino(4-nitrobenzyliden)-1,3,5(10)-estratriene* (IVb): yield 68%; m.p. 175–176 °C. IR spectrum: 3 210 (NH); 1 645 (CONH); 1 625, 1 595 (C=C); 1 135 (OCH_2CH_2O). ^{1}H NMR spectrum: 0.80 s, 3 H (3 × H-18); 3.91 s, 4 H (OCH_2CH_2O); 4.88 s, 2 H (OCH_2CO); 6.62 d, 1 H, *J* = 2.4 (H-4); 6.70 dd, 1 H *J* = 2.4, 8.7 (H-2); 7.12 d, 1 H *J* = 8.7 (H-1); 7.4–7.8 m, 4 H (H arom.); 8.55 brs, 1 H (CONH). For $C_{29}H_{33}N_3O_6$ (519.6) calculated: 67.05% C, 6.40% H, 8.09% N; found: 67.12% C, 6.43% H, 8.15% N.

*17,17-Ethylenedioxy-3*β*-O-acethydrazino(4-chlorobenzyliden)-1,3,5(10)-estratriene* (IVc): yield 66%; m.p. 151–152 °C. IR spectrum: 3 215 (NH); 1 642 (CONH); 1 630, 1 590 (C=C); 1 135 (OCH_2CH_2O). ^{1}H NMR spectrum: 0.79 s, 3 H (3 × H-18); 3.92 s, 4 H (OCH_2CH_2O); 4.88 s, 2 H (OCH_2CO); 6.60 d, 1 H, *J* = 2.4 (H-4); 6.70 dd, 1 H, *J* = 2.4, 8.7 (H-2); 7.10 d, 1 H, *J* = 8.7 (H-1); 7.3–7.7 m, 4 H (H arom.); 8.55 brs, 1 H (CONH). For $C_{29}H_{33}ClN_2O_4$ (509.1) calculated: 68.43% C, 6.53% H, 5.50% N; found: 68.50% C, 6.58% H, 5.58% N.

*17,17-Ethylenedioxy-3*β*-O-acethydrazino(4-methoxybenzyliden)-1,3,5(10)-estratriene* (IVd): yield 72%; m.p. 147–148 °C. IR spectrum: 3 210 (NH); 1 640 (CONH); 1 630, 1 600 (C=C); 1 138 (OCH_2CH_2O). ^{1}H NMR spectrum: 0.81 s, 3 H (3 × H-18); 3.90 s, 4 H (OCH_2CH_2O); 4.86 s, 2 H (OCH_2CO); 6.58 d, 1 H, *J* = 2.4 (H-4); 6.70 dd, 1 H, *J* = 2.4, 8.7 (H-2); 7.12 d, 1 H, *J* = 8.7 (H-1); 7.4–7.8 m, 4 H (H-arom.); 8.60 brs, 1 H (CONH). For $C_{30}H_{36}N_2O_5$ (504.6) calculated: 71.41% C, 7.19% H, 5.55% N; found: 71.50% C, 7.28% H, 5.62% N.

General Procedure for Reaction of Schiff Bases *IVa–IVd* with Chloroacetyl Chloride in the Presence of Triethylamine

To a solution of Schiff base *IV* (2.1 mmol) in dioxane (30 ml) was added chloroacetyl chloride (0.95 g; 8.4 mmol) and the solution was refluxed for 10 min. After cooling triethylamine (0.85 g; 8.4 mmol) was added drop by drop and the solution was further refluxed for 2 h. The resultant triethylammonium chloride was filtered and the filtrate was evaporated in vacuo to give an oily residue. The residue was purified by chromatography (neutral alumina; 40 g) using petroleum ether–benzene (1 : 1) as eluting solvent and the material obtained was crystallized from methanol to give β-lactams *Va–Vd*.

*17,17-Ethylenedioxy-3*β*-O-acetamido(3′-chloro-2′-oxo-4′-phenylazetidinyl)-1,3,5(10)-estratriene* (Va): yield 71%; m.p. 132–133 °C. IR spectrum: 3 220 (NH); 1 740 (C=O); 1 645 (CONH); 1 600 (C=C); 1 140 (OCH_2CH_2O); 740 (C–Cl). ^{1}H NMR spectrum: 0.78 s, 3 H (3 × H-18); 3.88 s, 4 H (OCH_2CH_2O); 4.35 d, 1 H, *J* = 1.8 (H-4′); 4.84 s, 2 H (OCH_2CO); 6.35 d, 1 H *J* = 1.8 (H-3′); 6.58 d, 1 H, *J* = 2.4 (H-4); 6.69 dd, 1 H, *J* = 2.4, 8.7 (H-2); 7.07 d, 1 H, *J* = 8.7 (H-1); 7.3–7.7 m, 5 H (H-arom.); 8.50 brs, 1 H (CONH). ^{13}C NMR spectrum: 11.80 (C-18); 66.53 (OCH_2CH_2O); 70.64 (C-4′); 80.15 (C-3′); 84.52 (OCH_2); 112.72 (C-2); 115.32 (C-4); 126.47 (C-1); 135.80–126.31 (arom. carbons); 138.20 (C-5); 153.53 (C-3); 167.13 (β-lactam C=O); 168.24 (CONH). For $C_{31}H_{35}ClN_2O_5$ (551.1) calculated: 67.57% C, 6.40% H, 5.08% N; found: 67.64% C, 6.44% H, 5.16% N.

*17,17-Ethylenedioxy-3*β*-O-acetamido[3′-chloro-2′-oxo-4′-(4-nitrophenyl)azetidinyl]-1,3,5(10)-estratriene* (Vb): yield 70%; m.p. 153–154 °C. IR spectrum: 3 225 (NH); 1 738 (C=O); 1 645 (CONH); 1 600 (C=C); 1 138 (OCH_2CH_2O); 730 (C–Cl). ^{1}H NMR spectrum: 0.80 s, 3 H (3 × H-18);

3.87 s, 4 H (OCH_2CH_2O); 4.32 d, 1 H, *J* = 1.8 (H-4′); 4.81 s, 2 H (OCH_2CO); 6.32 d, 1 H, *J* = 1.8 (H-3′); 6.59 d, 1 H, *J* = 2.4 (H-4); 6.70 dd, 1 H, *J* = 2.4, 8.7 (H-2); 7.10 d, 1 H, *J* = 8.7 (H-1); 7.4–7.8 m, 4 H (H arom.); 8.60 brs, 1 H (CONH). ^{13}C NMR spectrum: 11.77 (C-18); 66.48 (OCH_2CH_2O); 70.61 (C-4′); 80.18 (C-3′); 84.54 (OCH_2); 112.73 (C-2); 115.32 (C-4); 126.47 (C-1); 135.85–126.30 (arom. carbons); 138.21 (C-5); 153.51 (C-3); 167.12 (β-lactam C=O); 168.22 (CONH). For $C_{31}H_{34}ClN_3O_7$ (596.1) calculated: 62.47% C, 5.75% H, 7.05% N; found: 62.54% C, 5.85% H, 7.12% N.

*17,17-Ethylenedioxy-3*β*-O-acetamido[3′-chloro-2′-oxo-4′-(4-chlorophenyl)azetidinyl]-1,3,5-(10)-estratriene* (Vc): yield 68%; m.p. 145–146 °C. IR spectrum: 3 225 (NH); 1 736 (C=O); 1 642 (CONH); 1 610 (C=O); 1 140 (OCH_2CH_2O); 730 (C–Cl). ^{1}H NMR spectrum: 0.81 s, 3 H (3 × H-18); 3.89 s, 4 H (OCH_2CH_2O); 4.30 d, 1 H, *J* = 2 (H-4′); 4.82 s, 2 H (OCH_2CO); 6.28 d, 1 H, *J* = 2 (H-3′); 6.61 d, 1 H, *J* = 2.4 (H-4); 6.72 dd, 1 H, *J* = 2.4, 8.7 (H-2); 7.13 d, 1 H *J* = 8.7 (H-1); 7.4–7.8 m, 4 H (H arom.); 8.60 brs, 1 H (CONH). ^{13}C NMR spectrum: 11.78 (C-18); 66.45 (OCH_2CH_2O); 70.60 (C-4′); 80.20 (C-3′); 84.51 (OCH_2); 112.69 (C-2); 115.30 (C-4); 126.50 (C-1); 135.90–126.32 (arom. carbons); 138.22 (C-5); 153.54 (C-3); 167.10 (β-lactam C=O); 168.20 (CONH). For $C_{31}H_{34}Cl_2N_2O_5$ (585.5) calculated: 63.59% C, 5.85% H, 4.78% N; found: 63.66% C, 5.92% H, 4.84% N.

*17,17-Ethylenedioxy-3*β*-O-acetamido[3′-chloro-2′-oxo-4′-(4-methoxyphenyl)azetidinyl]-1,3,5(10)-estratriene* (Vd): yield 72%; m.p. 151–152 °C. IR spectrum: 3 220 (NH); 1 740 (C=O); 1 648 (CONH); 1 590 (C=C); 1 140 (OCH_2CH_2O); 738 (C–Cl). ^{1}H NMR spectrum: 0.80 s, 3 H (3 × H-18); 3.60 s, 3 H (Ar–OCH_3); 3.86 s, 4 H (OCH_2CH_2O); 4.32 d, 1 H, *J* = 1.8 (H-4′); 4.80 s, 2 H (OCH_2CO); 6.30 d, 1 H, *J* = 1.8 (H-3′); 6.60 d, 1 H, *J* = 2.4 (H-4); 6.70 dd, 1 H, *J* = 2.4, 8.7 (H-2); 7.10 d, 1 H, *J* = 8.7 (H-1); 7.4–7.8 m, 4 H (H-arom.); 8.55 brs, 1 H (CONH). ^{13}C NMR spectrum: 11.74 (C-18); 55.16 (OCH_3); 66.48 (OCH_2CH_2O); 70.61 (C-4′); 80.20 (C-3′); 84.50 (OCH_2); 112.70 (C-2); 115.33 (C-4); 126.50 (C-1); 135.92–126.28 (arom. carbons); 138.20 (C-5); 153.52 (C-3); 167.12 (β-lactam C=O); 168.19 (CONH). For $C_{32}H_{37}ClN_2O_6$ (581.1) calculated: 66.14% C, 6.42% H, 4.82% N; found: 66.22% C, 6.38% H, 4.90% N.

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