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3,3'-Ethylenedioxyandrost-4-en-17 β -ol **1** was converted into the ethyl ester **2** by reaction with potassium metal and ethyl chloroacetate. The ethyl ester **2** on reaction with hydrazine gave the hydrazide **3**. Condensation of **3** with aryl aldehydes gave the Schiff bases **4**. The reaction of Schiff bases **4** with monochloroacetyl chloride in the presence of triethylamine afforded the β -lactams **5**.

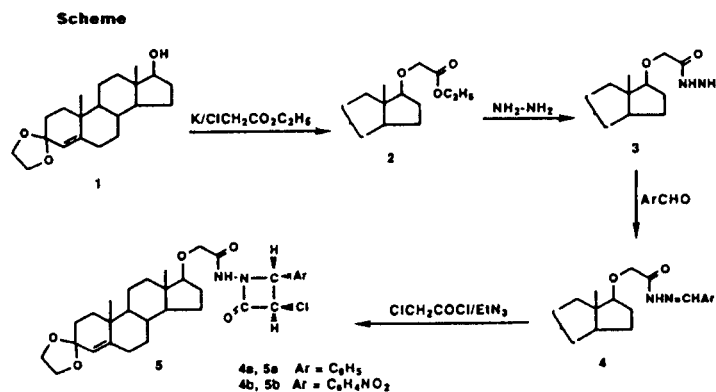
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In continuation of our work on steroidal β -lactams [2], it is considered of interest to investigate the reaction of C-17 Schiff bases with monochloroacetyl chloride in the presence of triethylamine.

The synthesis of β -lactams by the reaction of imines with acid halide in the presence of an amine base with respect to mechanism and stereochemical outcome have been proposed [3]. However, it is often difficult to confidently predict the stereochemistry of the product [4]. The degree of stereospecificity was found to depend upon the experimental conditions employed [5]. Generally, the β -lactams formed from the reactions between chloroacetyl chloride, phenylacetyl chloride or phthaloylacetyl chlo-

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 **4a-b** with monochloroacetyl chloride in the presence of triethylamine afforded β -lactams **5a-b**. The infrared spectra showed absorption bands at 1750 (C=O), 1660 (CONH) and 710 (C-Cl) cm^{-1} . The ^1H nmr spectra revealed a doublet at δ 6.3 for C'₃-H ($J = 2$ Hz), doublet at δ 4.3 for C'₄-H ($J = 2$ Hz) and other signals are attributed to NH 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 of coupling constant ($J_{\text{trans}} = 1-2$ Hz) [7].



ride with an imine in the presence of triethylamine are *trans* isomers [6].

3,3'-Ethylenedioxyandrost-4-en-17 β -ol (**1**) on reaction with potassium metal and ethyl chloroacetate gave 3,3'-ethylenedioxyandrost-4-en-17-ethyl-*O*-acetate (**2**). The ^1H nmr spectrum of **2** gave a singlet at δ 4.8 (OCH₂CO), quartet at δ 4.1 (CO₂CH₂), and a triplet at δ 1.2 (CH₂CH₃). The ethyl ester **2** on reaction with hydrazine gave hydrazide **3**, whose ^1H nmr spectrum showed broad singlets at δ 4.3 (NH₂) and at δ 8.5 (CONH) which disappeared upon treatment with deuterium oxide. Condensation of hydrazide **3** with aryl aldehydes gave Schiff bases **4a-b**. The ^1H nmr spectra of **4a-b** showed a

EXPERIMENTAL

Melting points are uncorrected. The Infrared spectra were recorded as potassium bromide pellets using Perkin-Elmer 137 spectrometer. The ^1H nmr spectra were obtained in deuteriochloroform on a varian FT-80 or on a Varian XL 200 spectrometer with TMS as internal standard. Chemical shifts are given in ppm (δ).

3,3'-Ethylenedioxyandrost-4-en-17 β -ol (**1**) was prepared according to the literature procedure [8].

3,3'-Ethylenedioxyandrost-4-en-17-ethyl-*O*-acetate (**2**).

Potassium metal (0.71 g, 18.1 mmoles) was added to a solution of 3,3'-ethylenedioxyandrost-4-en-17 β -ol (**1**) (2 g, 6.02 mmoles) in dry benzene (50 ml) and the mixture was refluxed

for 1 hour. After cooling ethyl chloroacetate (4.42 g, 36.2 mmoles) was added and the mixture was further refluxed for 3 hours. 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 recrystallized from ethanol to give 2.01 g of **2** as a colorless solid (80%), mp 191-192°; ir: ν max 1740 (ester), 1600 (C=C), 1080 (ketal) cm^{-1} ; ^1H nmr: δ 5.70 (m, 1H, C₄-H), 4.84 (s, 2H, OCH₂CO₂), 4.12 (q, 2H, CO₂CH₂CH₃), 3.86 (s, 4H, OCH₂CH₂O), 3.60 (t, 1H, C₁₇- α H), 1.25 (t, 2H, CO₂CH₂CH₃), 1.18 (s, 3H, C₁₉-H₃), 0.80 ppm (s, 3H, C₁₈-H₃).

Anal. Calcd. for C₂₅H₃₈O₅: C, 71.74; H, 9.15. Found: C, 71.80; H, 9.24.

3,3'-Ethylenedioxyandrost-4-en-17-O-acetylrazide (**3**).

A solution of ethyl ester **2** (2 g, 4.78 mmoles) and hydrazine hydrate (6.12 g, 19.12 mmoles) in methanol (100 ml) was refluxed with a drop of acetic acid for 6 hours. 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 1.45 g of **3** as a colorless solid (75%), mp 201-202°; ir: ν max 3280, 3170 (NH₂, NH), 1640 (CONH), 1600 (C=C) cm^{-1} ; ^1H nmr: δ 8.50 (br s, 1H, CONH), 5.72 (m, 1H, C₄-H), 4.85 (s, 2H, OCH₂CO₂), 4.32 (br s, 2H, NH₂), 3.88 (s, 4H, OCH₂CH₂O), 3.62 (t, 1H, C₁₇- α H), 1.20 (s, 3H, C₁₉-H₃), 0.79 ppm (s, 3H, C₁₈-H₃).

Anal. Calcd. for C₂₃H₃₆N₂O₄: C, 68.29; H, 8.97; N, 6.92. Found: C, 68.35; H, 8.91; N, 6.98.

General Procedure for the Preparation of Schiff Bases **4a-b**.

A solution of hydrazide **3** (2 g, 4.95 mmoles) and an aromatic aldehyde (9.9 mmoles) in benzene (40 ml) was refluxed with few drops of piperidine for 4 hours. The mixture was concentrated under reduced pressure and then poured onto ice and extracted with ether. The organic layer was concentrated and recrystallized from methanol.

3,3'-Ethylenedioxy-17-O-acetylrazinobenzylidenandrost-4-ene (**4a**).

This compound was obtained as colorless needles from methanol (75%), mp 197-198°; ir: ν max 3220 (NH), 1645 (CONH), 1630 (C=N), 1600 (C=C) cm^{-1} ; ^1H nmr, δ 8.50 (br s, 1H, CONH), 7.3-7.7 (m, 5H, Ar-H), 6.10 (s, 1H, CH=N), 5.74 (m, 1H, C₄-H), 4.85 (s, 2H, OCH₂CO₂), 4.32 (br s, 2H, NH₂), 3.88 (s, 4H, OCH₂CH₂O), 3.63 (t, 1H, C₁₇- α H), 1.20 (s, 3H, C₁₉-H₃), 0.81 ppm (s, 3H, C₁₈-H₃).

Anal. Calcd. for C₃₀H₄₀N₂O₄: C, 73.14; H, 8.18; N, 5.69. Found: C, 73.22; H, 8.24; N, 5.80.

3,3'-Ethylenedioxy-17-O-acetylrazino(*p*-nitrobenzyliden)-androst-4-ene (**4b**).

This compound was obtained as colorless needles from methanol (73%), mp 188-189°; ir: ν max 3210 (NH), 1640 (CONH), 1630 (C=N), 1600 (C=C) cm^{-1} ; ^1H nmr: δ 8.50 (br s, 1H, CONH), 7.3-7.7 (m, 4H, Ar-H), 6.14 (s, 1H, CH=N), 5.75 (m, 1H, C₄-H), 4.86 (s, 2H, OCH₂CO₂), 3.90 (s, 4H, OCH₂CH₂O), 3.62 (t, 1H, C₁₇- α H), 1.20 (s, 3H, C₁₉-H₃), 0.80 ppm (s, 3H, C₁₈-H₃).

Anal. Calcd. for C₃₀H₃₉N₃O₆: C, 67.02; H, 7.31; N, 7.82. Found: C, 67.10; H, 7.35; N, 7.88.

General Procedure for the Preparation of β -Lactams **5a-b**.

To a solution of Schiff base (1.5 mmoles) in dry dioxane (30 ml) was added monochloroacetyl chloride (3 mmoles) and the solution was refluxed for 10 minutes. After cooling triethylamine (3 mmoles) was added drop by drop and the solution was further refluxed for 2 hours. The resultant triethylammonium hydrochloride was filtered and the filtrate was evaporated *in vacuo* to give an oily residue. The residue was subjected to column chromatography (neutral alumina, 40 g) using petroleum ether-benzene (1:1). After the evaporation of eluting solvent, a solid product was obtained which was recrystallized from methanol.

3,3'-Ethylenedioxy-17-O-acetamido(3'-chloro-2'-oxo-4'-phenylazetidiny)androst-4-ene (**5a**).

This compound was obtained as colorless needles from methanol (71%), mp 207-208°; ir: ν max 3220 (NH), 1750 (C=O), 1650 (CONH), 1600 (C=C), 710 (C-Cl) cm^{-1} ; ^1H nmr: δ 8.55 (br s, 1H, CONH), 7.2-7.6 (m, 5H, Ar-H), 6.32 (d, 1H, J = 2 Hz, C'₃- α H), 5.74 (m, 1H, C₄-H), 4.30 (d, 1H, J = 1.8 Hz, C'₄- β H), 3.90 (s, 4H, OCH₂CH₂O), 3.62 (t, 1H, C₁₇- α H), 1.21 (s, 3H, C₁₉-H₃), 0.79 ppm (s, 3H, C₁₈-H₃).

Anal. Calcd. for C₃₂H₄₁N₂O₅Cl: C, 67.53; H, 7.26; N, 4.92. Found: C, 67.62; H, 7.29; N, 5.0.

3,3'-Ethylenedioxy-17-O-acetamido[3'-chloro-2'-oxo-4'-(*p*-nitrophenyl)azetidiny]androst-4-ene (**5b**).

This compound was obtained as colorless needles from methanol (68%), mp 198-199°; ir: ν max 3210 (NH), 1750 (C=O), 1650 (CONH), 1600 (C=C), 700 (C-Cl) cm^{-1} ; ^1H nmr: δ 8.55 (br s, 1H, CONH), 7.2-7.6 (m, 4H, Ar-H), 6.36 (d, 1H, J = 2.1 Hz, C'₃- α H), 5.72 (m, 1H, C₄-H), 4.28 (d, 1H, J = 2 Hz, C'₄- β H), 3.90 (s, 4H, OCH₂CH₂O), 3.60 (t, 1H, C₁₇- α H), 1.20 (s, 3H, C₁₉-H₃), 0.80 ppm (s, 3H, C₁₈-H₃).

Anal. Calcd. for C₃₂H₄₀N₃O₇Cl: C, 62.58; H, 6.57; N, 6.84. Found: C, 62.66; H, 6.64; N, 6.90.

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REFERENCES AND NOTES

- [1] Present address: Department of Biochemistry, Rice University, P. O. Box 1892, Houston, TX-77251, USA
- [2] A. U. Siddiqui, A. H. Siddiqui and T. Sundara Ramaiah, *J. Heterocyclic Chem.*, **31**, 61 (1993).
- [3] A. K. Bose, B. Dayal, H. P. S. Chawla and M. S. Manhas, *Tetrahedron Letters*, 2823 (1972); D. A. Nelson, *J. Org. Chem.*, **37**, 1447 (1972); H. W. Moore, L. Hernandez and R. Chambers, *J. Am. Chem. Soc.*, **100**, 2245 (1978); F. Duran and L. Ghosez, *Tetrahedron Letters*, 245 (1970).
- [4] A. K. Bose, G. Spiegelman and M. S. Manhas, *Tetrahedron*, **23**, 3167 (1967).
- [5] A. K. Bose, B. Anjaneyulu, S. K. Bhattacharya and M. S. Manhas, *Tetrahedron*, **23**, 4769 (1967).
- [6] A. K. Bose, Y. H. Chang and M. S. Manhas, *Tetrahedron*, **28**, 4091 (1972).
- [7] D. A. Nelson, *Tetrahedron Letters*, 2543 (1971); K. D. Barrow and T. M. Spotswood, *Tetrahedron Letters*, 3325 (1965).
- [8] J. I. Brown, R. H. Lenhard and S. Bernstein, *J. Am. Chem. Soc.*, **86**, 2183 (1964).