# The Synthesis of a Steroidal β-Lactam

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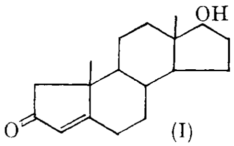
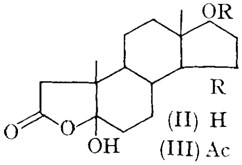
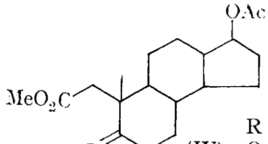
THE $\beta$-lactam ring-system is rare in Nature. Penicillin, cephalosporin, and the recently described Pachysandra alkaloids,[1] pachystermine-A and -B possess this system. We report the synthesis of a new steroidal ring system possessing a fused $\beta$-lactam as ring A.[2] The details for the chemical conversion of A-nortestosterone (I) into the steroidal $\beta$-lactam (XIV) are described.

Hydroxylation of (I) with osmium tetroxide, followed by oxidation with periodic acid, gave the lactonol (II),[3] which was treated at room temperature with acetic anhydride in pyridine to give (III) (m.p. 187·5—188·5°; $[\alpha]_{\rm D}$ + 24°; $\lambda$ 3·07, 5·69, 5·79 $\mu$; $\tau$ 9·18 (s,18-Me), 8·87 (s,19-Me), 7·97 (s,17$\beta$-OAc), and 5·48 (m,17$\alpha$-H).† Esterification with diazomethane gave the oily methyl ester (IV) [$\tau$ 9·15 (s,18-Me), 8·84 (s,19-Me), 7·97 (s,17$\beta$-OAc), and 5·40 (m,17$\alpha$-H)], which was treated with hydroxylamine hydrochloride in pyridine at room temperature to afford the oxime (V) (m.p. 155—157°; $\lambda$ 2·95, 5·80 (b)$\mu$; $\tau$ 9·18 (s,18-Me), 8·81 (s,19-Me) 7·97 (s,17$\beta$-OAc), 6·38 (s,2-$CO_2Me$), and 5·40 (m,17$\alpha$-H). Beckmann rearrangement of the oxime (thionyl chloride–dioxan at 10°), followed by hydrolysis with 25% aqueous potassium hydroxide solution gave the lactam acid (VI) (m.p. 275—276°; $[\alpha]_{\rm D}$ + 30°; $\lambda$ 3·00, 3·08, 5·86, and 6·09 $\mu$). Diazomethane esterification of (VI), followed by reduction with $LiAlH_4$ in tetrahydrofuran, gave the dihydroxyamine (VII) (m.p. 170·5—171°; $[\alpha]_{\rm D}$ − 16°; $\lambda$ 3·02 $\mu$; $\tau$ 9·25 (s,18-Me), and 8·82 (s,19-Me). Room temperature acetylation with acetic anhydride in pyridine gave the *N*-acetyl diacetate (VIII) (m.p. 139—140°; $[\alpha]_{\rm D}$ − 41°; $\lambda$ 5·78 and 6·11 $\mu$; $\tau$ 9·20 (s,18-Me), 8·63 (s,19-Me), 7·97 (s,17$\beta$- and 2-OAc), 7·93 (s,5-*N*-Ac), and 5·42 (m,17$\alpha$-H), which was selectively hydrolyzed with potassium carbonate in methanol to the *N*-acetyl diol (IX) (m.p. 172—172·5°; $[\alpha]_{\rm D}$ − 47°; $\lambda$ 2·93 3·12 and 6·23 $\mu$; $\tau$ 9·25 (s,18-Me), 8·6 (br s, 19-Me), and 7·93 (s,5-*N*-Ac). Oxidation of (IX) with Jones reagent (ice-bath, 2 hr.) led to smooth oxidation of the hydroxyls at C-2 and C-17 to

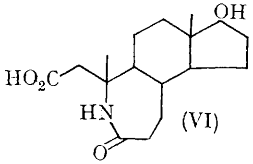

(I)

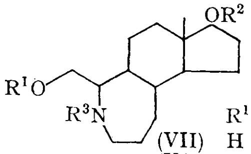


| | R |
|---|---|
| (II) | H |
| (III) | Ac |

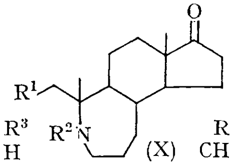


| | R |
|---|---|
| (IV) | O |
| (V) | NOH |

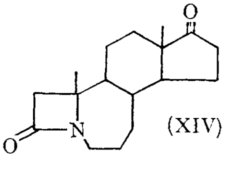

(VI)



| | R¹ | R² | R³ |
|---|---|---|---|
| (VII) | H | H | H |
| (VIII) | Ac | Ac | Ac |
| (XI) | H | H | Ac |



| | R² | R¹ |
|---|---|---|
| (X) | CHO | Ac |
| (XI) | $CO_2H$ | Ac |
| (XII) | $CO_2Me$ | Ac |
| (XIII) | $CO_2H$ | H |


(XIV)

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† Satisfactory analyses were obtained for all new crystalline compounds. Optical rotations were determined in 95% ethanol on a Perkin–Elmer 411 polarimeter and have been approximated to the nearest degree, i.r. spectra on a Perkin–Elmer 21 spectrometer in pressed potassium bromide pellets unless otherwise indicated, and n.m.r. spectra on a Varian A-60 in $CDCl_3$ with $Me_4Si$ as internal standard. Melting points were taken on a Fisher–Johns apparatus and are uncorrected.

give the *N*-acetyl aldehyde (X) (m.p. 172–173°; $[\alpha]_D$ + 60°; λ 3·55, 3·68, 5·75, 5·84 and 6·07 μ; τ 9·12 (s,18-Me), 8·54 (s,19-Me), 7·92 (s,5-*N*-Ac), and 0· 28 (t,*J* 1·8 c./sec., 2-CHO). Treatment of (X) with silver oxide in the dark at room temperature for 4 hours afforded the *N*-acetyl amino-acid (XI) (m.p. 180·5—181·5°; $[\alpha]_D$ − 2°; λ 2·8—3·2(b), 5·78, and 6·28 μ; τ 9·12 (s,18-Me), 8·44 (s,19-Me) and 7·91 (s,5-*N*-Ac). Diazomethane treatment of the mother-liquor afforded the methyl ester (XII) (m.p. 131·5—132·5°; λ 5·79 and 6·15 μ; τ 9·12 (s,18-Me), 8·46 (s,19-Me), 7·94 (s,5-*N*-Ac), and 6·41 (s,2-$CO_2Me$). The free acid (XI) was refluxed in dioxan containing concentrated hydrochloric acid to give a hygroscopic material, the i.r. spectrum of which was consistent with the amino-acid (XIII) [λ($CHCl_3$) 2·9, 3·2—4·9, 5·87 and 6·22 μ]. The amino-acid (XIII) was cyclized at room temperature for 21 hr. in nitromethane using dicyclohexylcarbodi-imide to give the steroidal β-lactam (XIV) (m.p. 158—159°; $[\alpha]_D$ + 117°; λ 5·70, 5·75 μ; τ 9·09 (s,18-Me), 8·56 (s,19-Me) and 6·66 (m,6-$CH_2$).

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[1] T. Kikuchi and S. Uyeo, *Chem. and Pharm. Bull. Japan*, **1967**, **15**, 549.

[2] A ring-A γ-lactam was an intermediate in the synthesis of A-nor-B-homo-5-azacholestane (W. J. Rodewald and J. Wicha, *Roczniki Chem.*, 1966, **40**, 837).

[3] S. D. Levine, *J. Medicin. Chem.*, 1965, **8**, 537.