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Formation of a Novel Ring System : An Unexpected Intermolecular Cyclization.

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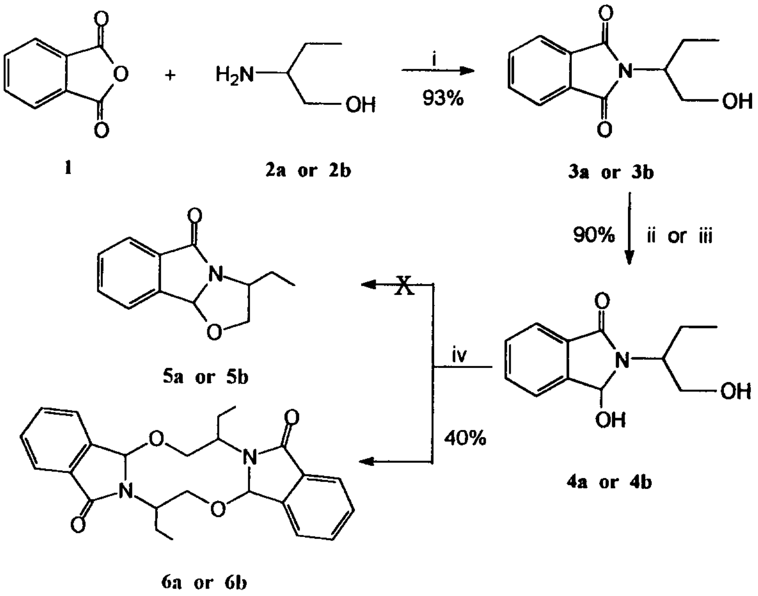
Abstract : A novel chiral ten membered heterocyclic ring is synthesised in two steps from phthalimide derivatives of *(R)* and *(S)* -2-amino-1-butanol. The structures have been unambiguously established by single crystal X-ray diffraction of one of the compounds. © 1997 Published by Elsevier Science Ltd.

A number of synthetic routes are known for the preparation of chiral quarternary carbon compounds from bicyclic lactams.[1] Several natural products have been reported to be prepared, using this methodology in high enantiomeric purity.[2] The bicyclic lactams were inturn prepared by either cyclodehydration of chiral aminoalcohols with γ and δ ketoacids[3] or via the intermediate acyl iminium ions, which were easily derived from 2-alkoxyamines which can be obtained by the sodium borohydride reduction of imides.[4]

We applied the same methodology for the preparation of a tricyclic lactam. The phthalimides **3a** and **3b**[5] were derived from phthalic anhydride **1** and ***(R)*** -(-)-2-amino-1-butanol **2a** or ***(S)*** -(+)-2-amino-1-butanol **2b**. The phthalimides **3a** and **3b** were reduced with sodium borohydride in methanol or methanolic HCl. The compounds obtained were not the methoxyderivatives but hydroxy derivatives **4a** and **4b**[6]. **4a** and **4b** were subjected to acid catalyzed cyclization with an expectation that they would undergo an intramolecular cyclization to furnish **5a** and **5b** instead they undergo an intermolecular cyclization to yield **6a** and **6b**,[7] which was found to be a hitherto unknown ten membered heterocyclic ring system with four chiral centres (Scheme-I). **6a** was subjected to single crystal X-ray diffraction,[8] and its structure solved by SIR 92[9] and refined by SHELX 93[10] (Fig.1).



Scheme I. Reagents and Conditions (i) Neat, 140°C (ii) $NaBH_4$, MeOH (iii) $NaBH_4$, Methanolic HCl (1N) (iv) CF_3COOH, CH_2Cl_2, 16 hrs, N_2 atmos, RT.

The absolute configuration of **6a** was found to be ***(2S, 11R, 14S, 23R)***, which was assigned according to the chirality of carbon atoms C-11 and C-23, known from the reagent.

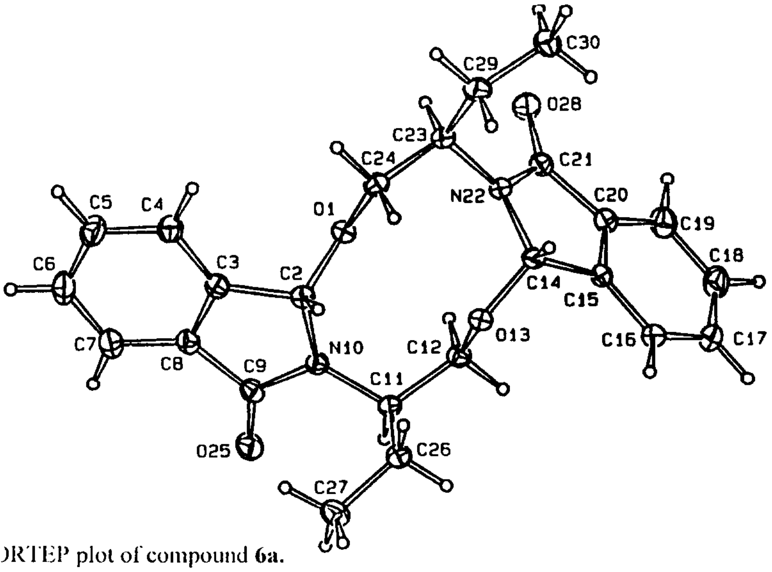


Figure 1. ORTEP plot of compound **6a**.
Displacement parameters of non-hydrogen atoms are drawn at 20% probability level.

References and Notes

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5. **3a** : $[\alpha]_D$ at 20°C - -11.0° (*c*1.0 in MeOH); δppm ($CDCl_3$)- 0.9 (3H,t, $-CH_3$), 1.9 (2H, m, - CH_2), 3.8 (3H, m, $-CH-CH_2-0$), 5.3 (1H, s, -OH), 7.5 (4H, s, $-C_6H_4$); υmax (Neat)/cm^{-1} - 3500, 2950, 1710, 1610, 1470, 1370, 1230; CHN Found (calculated) - C- 65.89 (65.75), H-5.74 (5.93), N-6.50 (6.39).

   3b : $[\alpha]_D$ at 20°C - 21.0° (*c*1.0 in MeOH); δppm ($CDCl_3$)- 0.9 (3H,t, $-CH_3$), 1.9 (2H, m, - CH_2), 3.9 (3H, m, $-CH-CH_2-0$), 5.3 (1H, s, -OH), 7.5 (4H, s, $-C_6H_4$); υmax (Neat)/cm^{-1} - 3500, 2950, 1700, 1610, 1470, 1360, 1230; CHN Found (calculated) - C -65.70 (65.75) H-5.89 (5.93), N-6.30 (6.39).

6. **4a** : $[\alpha]_D$ at 20°C - -7.0° (*c*1.0 in MeOH); δppm ($CDCl_3$)- 0.9 (3H,t, $-CH_3$), 1.7 (2H, m, - CH_2), 4.2 (3H, m, $-CH-CH_2-0$), 5.8 (1H, d, -CH on the 5 membered ring), 7.4 (4H, m, $-C_6H_4$); υmax (Neat)/cm^{-1} - 3450, 2950, 1680, 1610, 1460, 1360, 1240; CHN Found (Calculated) - C- 65.26 (65.15), H-6.91 (6.78), N-6.49 (6.33).

   4b : $[\alpha]_D$ at 20°C - 25.0° (*c*1.0 in MeOH); δppm ($CDCl_3$)- 0.9 (3H,t, $-CH_3$), 1.7 (2H, m, - CH_2), 4.2 (3H, m, $-CH-CH_2-0$), 5.7 (1H, d, -CH on the 5 membered ring), 7.5 (4H, m, $-C_6H_4$); υmax (Neat)/cm^{-1} - 3500, 2950, 1680, 1470, 1360, 1220; CHN Found (calculated) - C -65.82 (65.75), H-5.72 (5.93), N-6.52 (6.33).

7. **6a** : $[\alpha]_D$ at 20°C - 14.0° (*c*0.5 in $CHCl_3$); δppm ($CDCl_3$)- 0.9 (6H,t, $2-CH_3$), 1.8 (4H, m, $2-CH_2$), 3.5 (4H, t, $2-CH_2-0$), 4.2 (2H, s, 2-CH), 6.0 (2H,s, 2-CH on the 5 membered ring), 7.7 (8H, m, $2-C_6H_4$); υmax (KBr)/cm^{-1} - 2950, 1700, 1510, 1470, 1360; CHN Found (Calculated) - C-70.76 (70.93), H-6.52 (6.40), N-6.93 (6.89).

   6b : $[\alpha]_D$ at 20°C - 134.0° (*c*0.5 in $CHCl_3$); δppm ($CDCl_3$)- 0.9 (6H,m, $2-CH_3$), 1.7 (4H, m, $2-CH_2$), 3.6 (4H, m, $2-CH_2-0$), 4.5 (2H, m, 2-CH) 6.0 (2H, d, 2-CH on the 5 membered ring), 7.8 (8H, m, $2-C_6H_4$); υmax (KBr)/cm^{-1} - 2950, 1710, 1510, 1470, 1350; CHN Found (Calculated) - C- 71.01 (70.93) H-6.46 (6.40), N-6.74 (6.89).

8. Crystal data of Compound **6a** : $C_{24}H_{26}N_2O_4$,M_r=406.47, orthorhombic, space group $P2_12_12_1$, a=9.747(1), b=9.824(1), c=21.978(2) Å, V=2104.5(4) $Å^3$, Z=4, D_c=1.283 gcm^{-3}, $F(000)$=864, Mo-K_α radiation λ=0.71073 Å. Intensity data were collected with Siemens P4 diffractometer. 4154 reflections collected in the range $4.5 < 2\theta < 50°$, h 0 to 11, k 0 to 11, l -26 to 26; 3701 independent ($R_{merging}$ = 0.0128), 3192 observed [$I > 2\sigma\ (I)$]. Anisotropic displacement parameters were used for nonhydrogen atoms. The hydrogen atoms were located by difference Fourier map and refined

isotropically. Final $R=0.0266$, R_w (on F^2)$=0.0604$ [with $w^{-1} = \sigma^2 (Fo^2) + (0.0366P)^2$, where $P=(F_o^2+2F_o^2)/3$}.

Lists of fractional atomic coordinates, atomic displacement parameters, bond lengths and angles have been deposited with the Cambridge Crystallographic Date Centre, U.K. as supplementary materials.

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