7.5 Hz), 7.38-7.46 (m, 6H), 7.67-7.70 (m, 4H). IR (neat) 3400, 3050, 2950 cm^{-1}, $[\alpha]_D^{25}=+8.0$ (*c* 0.15, $CHCl_3$). MS (m/e) 325 (M-*t*Bu), 269, 247, 199 (base peak), 181, 139, 135, 109, 57. **6**: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.85 (t, 3H), 0.95 (d, 2H), 1.25-1.34 (m, 6H), 2.05 (m, 1H), 3.50 (m, 1H), 3.65 (m, 1H), 4.22 (m, 1H), 5.40 (dd, 1H), 5.65 (m, 1H). IR (neat) 3300, 2950 cm^{-1}, $[\alpha]_D^{25}=+1.82$ (*c* 0.17, $CHCl_3$). **10**: TLC; SiO_2, EtOAc/hexane 1 : 5, $R_f=0.33$, ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.86 (t, 3H, *J*=7.5 Hz), 0.97 (d, 3H, *J*=6.9 Hz), 1.27-1.37(m, 1H), 3.57 (dd, 1H, *J*=11.4, 7.8 Hz), 3.69 (dd, 1H, *J*=10, 3.6 Hz), 4.22 (m, 1H), 4.58 (s, 2H), 5.38 (ddd, 1H, *J*=15.5, 6.6, 1 Hz), 5.65 (ddd, 1H, *J*=15.5, 6.6, 1 Hz), 7.35 (s, 5H). **11**: $[\alpha]_D^{24}=-39.8$ (*c* 3.0, $CHCl_3$).

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Synthesis of Steroidal Cyclophosphamide, 2-Bis (2-chloroethyl)amino-2-oxo-6-(5α-cholestanyl)-1, 3,2-oxazaphosphorinane

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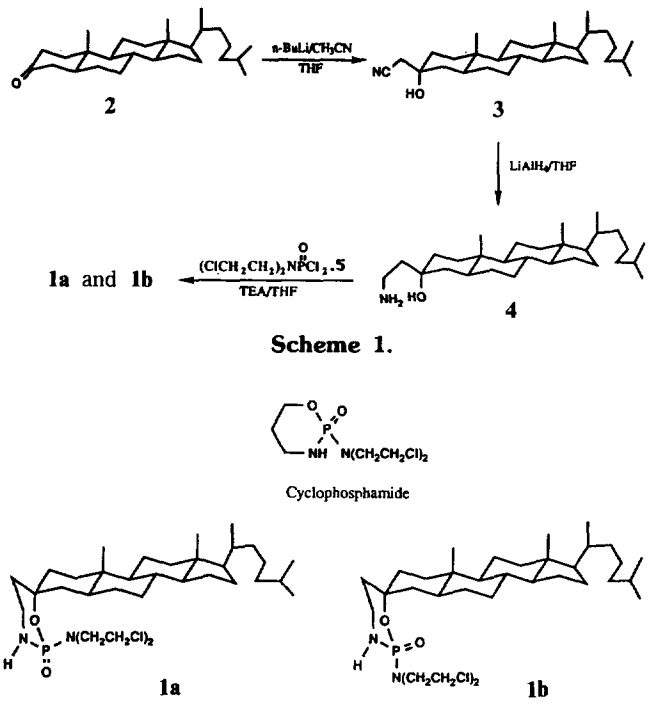
Received January 8, 1993

Cyclophosphamide and its analogues are important clinical agents in the treatment of cancer.[1] We have prepared steroidal cyclophosphamides (**1a** and **1b**). The approach used for the synthesis of **1a** and **1b** is outlined in Scheme 1. Treatment of cholestanone (**2**) with *n*-butyllithium and acetonitrile gave a 72.5% yield of β-hydroxynitrile derivative **3**[2], which was subsequently reacted with $LiAlH_4$ to give aminoethyl derivative **4**.[3] Cyclization of **4** with bis(2-chloroethyl)phosphoramidic dichloride (**5**) in the presence of 2 equiv. of Et_3N afforded crude mixtures of **1a** and **1b**, which were chromatographed on silica gel with EtOAc : CH_2Cl_2 : hexane = 2 : 2 : 1 to give analytically pure crystals of the faster (mp. 192-194℃) and slower (mp. 178-180℃) eluting diastereomers of **1a** and **1b** in 58% yield. Assignment of cyclophosphamide structures to the faster and slower eluting diastereomeric cyclization products has been suggested by the IR, ^{1}H-NMR, ^{31}P-NMR[4], and ^{13}C-NMR.

Our measurements of **1a** and **1b** indicated the ^{1}H-NMR chemical-shift difference between the NH resonances at 2.73 and 2.50 ppm for the faster and slower eluting diastereomers of **1a** and **1b**, respectively. The substantial deshielding (0.23 ppm) of N-H proton thus exhibited by the faster moving



Scheme 1.

compound **1a**, suggests more efficient intramolecular H-bonding to the adjacent P=O functionality. This difference in H-bonding was also founded in ^{13}C-NMR by the deshielding of chemical shift[41.9 ppm (-NH-CH_2-)] in the proposed **1a**, as opposed by the shielding of chemical shift [36.0 ppm (-NH-CH_2-)] in the proposed **1b**. These compounds may have a greater impact as anticancer agents by their lipophilicity. Compounds **1a** and **1b** were found no activity against Hepatoma cells[5].

Experimental

3-Cyanomethyl-5α-cholestan-3-ol (3). To a stirred solution of 1.6 M *n*-butyllithium in 9.5 m*l* (15 mmol) hexane, at −80℃ under nitrogen, was rapidly added a solution of 0.82 m*l* (15 mmol) of acetonitrile in 30 m*l* of anhydrous THF. After stirring for 1 hr, the resulting white suspension was treated with a solution of 3.0 g (7.5 mmol) **2** in 10 m*l* of THF. The cold-ice bath was removed and stirred for additional 10 min before it was poured into ice-water hydrochloric acid. The aqueous layer was extracted with three 50 m*l* portions of Et_2O. The combined ether extracts were dried($MgSO_4$) and evaporated in vaccuo, and the residual crude product was chromatographed on silica gel with CH_2Cl_2 as an eluent, and obtained 2.4 g (73% yield) of white solids. mp. 158-159 ℃; ^{1}H-NMR ($CDCl_3$) δ 2.6 (s, 2H, -CH_2CN), 0.6-2.0 (m, H steroid); IR (KBr) 3480 (-OH), 2930, 2255 (-CN), 1460, 1370, 1080, 1050 cm^{-1}.

3β-Aminoethylene-5α-cholestan-3-ol (4). To a stirred solution of 1.7 g (3.9 mmol) of **3** in 150 m*l* of anhydrous THF was added in small portions, 0.75 g (19.5 mmol) of lithium aluminum hydride. The mixture was refluxed with stirring for 17 hrs. After decomposing excess lithium aluminum hydride with 0.75 m*l* water and 2.3 m*l* of 20% NaOH, the mixture was filtered and filtrate was evaporated in vaccuo to obtain yellow oily residues (45% yield). All attempts

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to obtain crystallization was unsuccessful. IR (KBr) 3330 (NH_2), 1560 (NH), 1470, 1380, 1150, 1020 cm^{-1}.

2-Bis(2-chloroethyl)amino-2-oxo-6-(5α-cholestanyl)-1,3,2-oxazaphosphorinane (1a and 1b). A crude 1.7 g (3.9 mmol) of **4** and 1.0 g (3.9 mmol) of bis(2-chloroethyl) phosphoramidic dichloride (**5**) was dissolved in 160 m*l* of anhydrous THF, and added 0.79 m*l* (7.8 mmol) of anhydrous Et_3N. The reaction mixture was vigorously stirried for 24 hrs, and the $Et_3N \cdot HCl$ formed was filtered. The filtrate was evaporated in vaccuo and the residue was chromatographed on silica gel using EtOAc : CH_2Cl_2 : Hexane (2 : 2 : 1) to give fractions containing faster eluting **1a** and slower eluting **1b** (**1a** : **1b**=1 : 1.2; 1.2 g; 58% yield). For **1a**: mp. 192-194℃ ; ^{1}H-NMR ($CDCl_3$) δ 3.61 (t, J=7.40, 4H, 2 x -$NCH_2\underline{CH_2}Cl$), 3.25-3.50 (m, 4H, 2 x -$N\underline{CH_2}CH_2Cl$), 3.19 (m, 2H, -$NH\underline{CH_2}$-CH_2-), 2.73 (br s, 1H, NH), 2.12 (m, 2H, -$NHCH_2\underline{CH_2}$-), 0.6-2.0 (m, H steroid); ^{13}C-NMR ($CDCl_3$) δ 84.9 (d, $J_{C.P.}$=7.8, spiro carbon), 49.3 (d, $J_{C.P.}$=3.0, 2 x -$N\underline{CH_2}CH_2Cl$), 42.5 (2 x -NCH_2-$\underline{CH_2}Cl$), 41.9 (d, $J_{C.P.}$=8.5, -$NH\underline{CH_2}CH_2$-), 36.0 (-$NHCH_2\underline{CH_2}$-), 12.0, 12.1, 18.7, 21.3, 22.5, 22.8, 23.8, 24.2, 28.0, 28.2, 28.5, 31.9, 32.0, 35.5, 35.8, 36.0, 36.2, 38.1, 39.5, 40.0, 42.5, 42.6, 43.7, 54.5, 56.3, and 56.5 (steroid carbons); ^{31}P-NMR ($CDCl_3$) δ 10.25; Mass (FAB) (m/z) 618 (M+1); Anal. Calcd. for $C_{33}H_{59}N_2O_2PCl_2$: C, 64.17; H, 9.62; N, 4.53. Found: C, 64.09; H, 9.79; N, 4.32. For **1b**: mp. 178-180℃ ; ^{1}H-NMR ($CDCl_3$) δ 3.60 (t, J=6.9, 4H, 2 x -$NCH_2\underline{CH_2}Cl$), 3.28-3.54 (m, 4H, 2 x -$N\underline{CH_2}CH_2Cl$), 3.19 (m, 2H, -$NH\underline{CH_2}CH_2$-), 2.50 (br d, 1H, NH), 2.13 (m, 2H, -$NHCH_2$ $\underline{CH_2}$-), 0.6-2.0 (m, H steroid); ^{13}C-NMR ($CDCl_3$) δ 84.7 (d, $J_{C.P.}$= 7.8, spiro carbon), 49.4 (d, $J_{C.P.}$=4.3, 2 x -$N\underline{CH_2}CH_2Cl$), 42.5 (2 x -$NCH_2\underline{CH_2}Cl$), 35.0 (d, $J_{C.P.}$=7.4, -$NH\underline{CH_2}CH_2$-), 35.8 (-NH-$CH_2\underline{CH_2}$-), 12.0, 12.1, 18.7, 21.1, 22.5, 22.8, 23.8, 24.2, 28.0, 28.5, 32.0, 35.4, 35.7, 35.9, 36.2, 38.7, 39.4, 40.0, 42.5, 42.6, 43.9, 54.5, 56.3, and 56.5 (steroid carbons); ^{31}P-NMR ($CDCl_3$) δ 10.48; Mass (FAB) (m/z) 618 (M+1); Anal. Calcd. for C_{33}-$H_{59}N_2O_2PCl_2$: C, 64.17; H, 9.62; N, 4.53. Found: C, 64.32; H, 9.98; N, 4.49.

Acknowledgement. The authers wish to express their appreciation to professor Hae-Young Chung, College of Pharmacy, Pusan National University for the antitumor assay. The present study was supported in part by the Basic Science Research Institude Program, Ministry of Education, 1991 (BSRI-91-308).

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Transformation Mechanism of Bicyclic Ketal Compound to 1,5-Diketone

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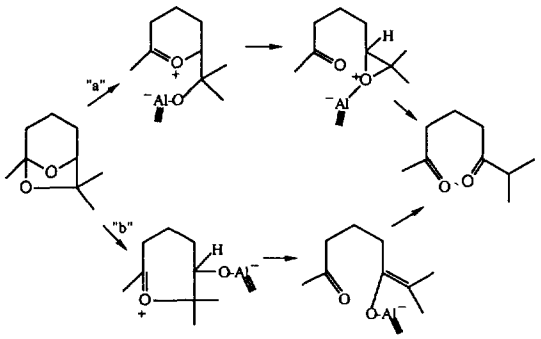
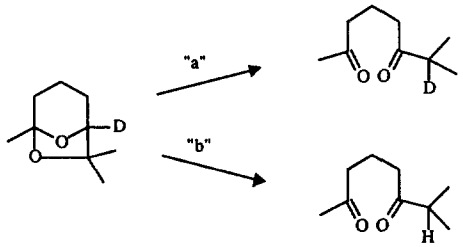
Received January 22, 1993

The chemistry of bicyclic ketals in the 6,8-dioxabicyclo[3.2.1]octane series are very unique and interesting. Our initial success in the preparation of 1,5-diketone from bicyclic ketal[1] expanded the utilities of this bicyclic ketal system to the direct syntheses of 2,6-disubstituted pyridines,[2] 2,3,6-trisubstituted pyridines,[3] cyclohexenones[4] and cyclopentanediol derivatives.[5] The 1,5-diketone is thought to be an active intermediate for these transformation reactions.

We proposed two possible mechanisms for the formation of 1,5-diketone from bicyclic ketal using aluminium chloride-sodium iodide in methylene dichloride.[1] The mechanism "a" in Scheme 1 involves O(6)-C(5) bond cleavage followed by 1,2-hydride shift *via* an epoxide intermediate, whereas the alternative mechanism "b" involves O(8)-C(5) bond cleavage followed by proton abstraction.



Scheme 1.



Scheme 2.