SYNTHESIS OF 13-AZA-16-OXA-, 13-AZA-16-THIA- AND 13,16-DIAZASTEROIDAL COMPOUNDS THROUGH CYCLIZATION OF N-ACYL-IMINIUM ION INTERMEDIATES

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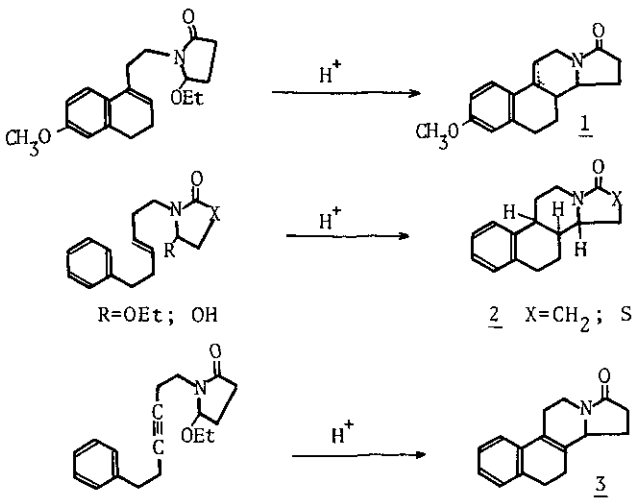
Abstract —— 5,5-Dimethyl-2,4-oxazolidinedione, 2,4-thiazolidinedione and 5,5-dimethylhydantoin were coupled with 2-(3,4-dihydro-1-naphthyl)ethyl alcohol by an application of Mitsunobu's method to give the corresponding N-substituted products (5)-(7), respectively. Reduction of 5-7 with diisobutylaluminium hydride, followed by cyclization of the reduction products with formic acid yielded the 13-aza-16-oxa- (11), 13-aza-16-thia- (12) and 13,16-diaza-1,3,5(10),9(11)-estratetraen-17-one (13), respectively.

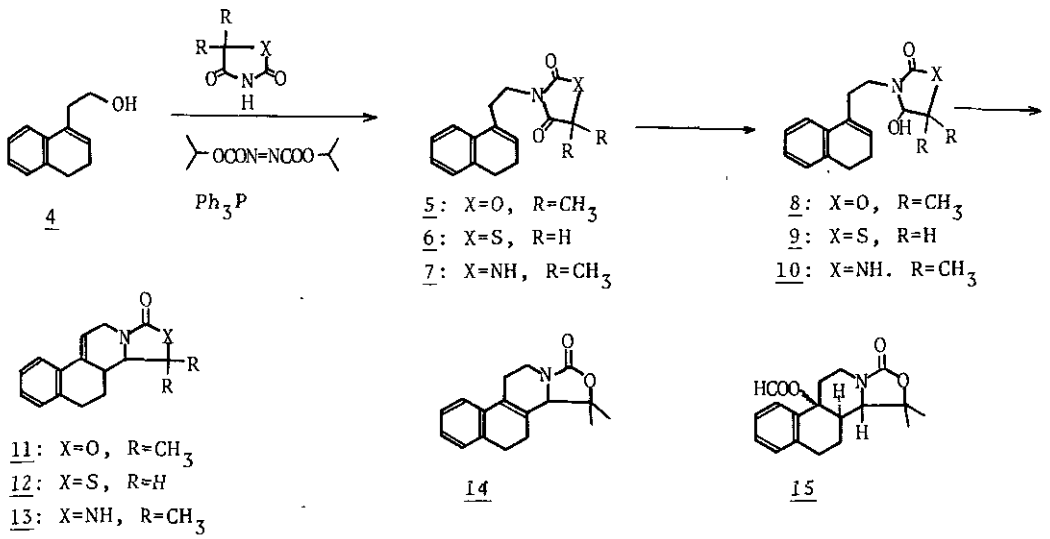
A great deal of synthetic efforts to synthesize heterocyclic steroidal compounds have been made from chemical and biological points of view[1]. Much attention has been devoted to a synthesis of a number of azasteroids[1a,2]. 13-Azasteroids (1)-(3) were prepared via N-acyliminium-induced C-C bond formation[3] (Chart 1).

Chart 1



In a similar way, synthesis of some 13-azasteroids with a modification of the A- or B-ring have been reported[4]. In view of the current interest in an effecient synthesis of heterocyclic steroidal systems with a modification of the D-ring, we examined the synthesis of 13-azasteroids through ring closure of N-acyliminium ion intermediates[3,4]. The results of our studies will be described in this paper. N-[2-(3,4-Dihydro-1-naphthyl)ethyl]-2,4-oxazolidinedione, 2,4-thiazolidinedione and hydantoin derivatives were used as the starting materials for this purpose because of easy handling and ready conversion to the desired N-acyliminium ions. *2-(3,4-Dihydro-1-naphthyl)ethyl alcohol* (4)[5] *was coupled with* 5,5-dimethyl-2,4-oxazolidinedione, 2,4-thiazolidinedione, and 5,5-dimethylhydantoin by the modified Mitsunobu's method[6] using diisopropyl azodicarboxylate instead of diethyl azodicarboxylate to give the corresponding N-substituted products (5), (6) and (7), respectively. Reduction of 5 with diisobutylaluminium hydride, followed by treatment of the resulting 5-hydroxy derivative (8) with formic acid at room temperature for 1 h gave 3-deoxy-18-nor-15,15-dimethyl-13-aza-16-oxa-1,3,5(10),9(11)-estratetraen-17-one (11) in 65 % yield, mp 114-115°C, the structure of which was confirmed by the spectroscopic method together with decoupling technique in its ^{1}H NMR spectra. In this reaction, neither the $\Delta^{8,9}$-isomer (14) nor the 9-oxygenated product (15) was obtained (Chart 2). In a similar fashion, 13-aza-16-thia (12) and 13,16-diaza derivatives (13) were easily obtained from 9 and 10,

Chart 2



which were derived from 6 and 7, respectively. Thus, the synthesis of heterocyclic steroidal systems with D-ring modification was achieved by Speckamp's method[3].

EXPERIMENTAL

All melting points are not corrected. ^{1}H NMR spectra were determined on a Varian EM-390 spectrometer operating at 90 MHz by using $CDCl_3$ as a solvent and tetramethylsilane as an internal standard. Mass spectra were taken with a Hitachi RMU-7L instrument.

N-[2-(3,4-Dihydro-1-naphthyl)ethyl]-5,5-dimethyl-2,4-oxazolidinedione (5) To a stirred mixture of 4 (3.48 g, 20 mmol), triphenylphosphine (6.29 g, 24 mmol), 5,5-dimethyl-2,4-oxazolidinedione (3.10 g, 24 mmol) and THF (30 ml) was added a solution of diisopropyl azodicarboxylate (4.85 g, 24 mmol) in THF (20 ml) under ice-cooling. After the stirring had been continued for 14 h at room temperature, the solvent was evaporated. The remaining residue was chromatographed on silica gel (25 g) by using benzene-hexane (1:2) as an eluent. Evaporation of the solvent (80-100 ml) gave 5 (3.71 g, 65 % yield) as an oil; ^{1}H NMR ($CDCl_3$) δ 1.47 (6H, s), 1.73-2.72 (4H, m), 2.80 (2H, t, J=8 Hz), 3.70 (2H, t, J=8 Hz), 5.94 (1H, t, J=5 Hz), 7.03-7.20 (4H, m); Mass spectrum m/e 285.1366 (M^+, calcd. for $C_{17}H_{19}NO_3$ m/e 285.1364)

N-[2-(3,4-Dihydro-1-naphthyl)ethyl]-2,4-thiazolidinedione (6) This compound was obtained by the same procedure as above except the use of 2,4-thiazolidinedione (2.81 g, 24 mmol) instead of 5,5-dimethyl-2,4-oxazolidinedione (3.10 g) in 75 % yield (4.1 g) as an oil; ^{1}H NMR ($CDCl_3$) δ 1.77-2.33 (4H, m), 2.71 (2H, t, J=8 Hz), 3.77 (2H, s), 3.80 (2H, t, J=8 Hz), 5.60 (1H, t, J=5 Hz), 7.04-7.29 (4H, m); Mass spectrum m/e 273.0819 (M^+, calcd. for $C_{15}H_{15}NO_2S$ m/e 273.0822).

N-[2-(3,4-Dihydro-1-naphthyl)ethyl]-5,5-dimethylhydantoin (7) This compound was obtained by the same procedure as above except the use of 5,5-dimethylhydantoin (3.07 g, 24 mmol) instead of 5,5-dimethyl-2,4-oxazolidinedione (3.10 g) in 72 % yield (4.09 g) as an oil; ^{1}H NMR ($CDCl_3$) δ 1.34 (6H, s), 1.70-2.33 (2H, m), 2.63-2.87 (4H, m), 3.70 (2H, t, J=8 Hz), 5.96 (1H, t, J=5 Hz), 7.03-7.20 (4H, m); Mass spectrum m/e 284.1521 (M^+, calcd. for $C_{17}H_{20}N_2O_2$ m/e 284.1523).

Preparation of 11 To a stirred solution of 5 (1.5 g, 5.26 mmol) in toluene (30 ml) was added diisobutylaluminium hydride (1.49 g, 6.87 ml of 25 % toluene solution: 10.52 mmol) at -78°C. After the stirring had been continued for 1 h at the same temperature, the mixture was decomposed with 5 % H_2SO_4 (60 ml) and

extracted with $CHCl_3$. The extract was washed with water, dried (Na_2SO_4) and evaporated. The resulting residue was mixed with formic acid (20 ml) under stirring at room temperature. After the stirring had been continued for 1 h, the mixture was made basic with 28 % ammonia and extracted with $CHCl_3$. The extract was washed with water, dried (Na_2SO_4) and evaporated to give 11 (0.92 g, 65 % yield), mp 114-115°C (methanol-ether); ^1H NMR ($CDCl_3$) δ 1.47 (3H, s), 1.64 (3H, s), 3.26 (1H, d, J=10 Hz), 3.89 (1H, t, J=2 and 18 Hz), 4.28 (1H, t,d, J=2 and 18 Hz), 6.33-6.44 (1H, m), 7.16-7.33 (3H, m), 7.61-7.84 (1H, m); Mass spectrum m/e 269 (M^+). Anal. Calcd for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.60; H, 7.10; N, 5.16.

Preparation of 12 The compound (6) (1.5 g, 5.49 mmol) was reduced with diisobutylaluminum hydride (1.56 g, 7.17 ml of 25 % toluene solution: 10.98 mmol) by the same procedure as above and resulting reduction product was mixed with formic acid (20 ml) and worked up as above to yield 12 (1.2 g, 85 % yield), mp 181-182°C (methanol-ether); ^1H NMR ($CDCl_3$) δ 3.82 (1H, t,d, J=2 and 18 Hz), 4.45 (1H, t,d, J=2 and 18 Hz), 6.26-6.37 (1H, m), 7.12-7.26 (3H, m), 7.53-7.68 (1H, m); Mass spectrum m/e 257 (M^+). Anal. Calcd for $C_{15}H_{15}NOS$: C, 70.01; H, 5.88; N, 5.44. Found: C, 69.88; H, 5.84; N, 5.27.

Preparation of 13 The compound (7) (1.5 g, 5.28 mmol) was reduced with diisobutylaluminium hydride (1.50 g, 6.90 ml of 25 % toluene solution: 10.56 mmol) by the same procedure as above and resulting reduction product was mixed with formic acid (20 ml) and worked up as above to yield 13 (1.25 g, 88 % yield), mp 80-83°C (methanol-ether); ^1H NMR ($CDCl_3$) δ 1.30 (3H, s), 1.44 (3H, s), 3.77 (1H, t,d, J=2 and 18 Hz), 4.26 (1H, t,d, J=2 and 18 Hz), 6.37-6.48 (1H, m), 7.20-7.33 (3H, m), 7.63-7.86 (1H, m); Mass spectrum m/e 268 (M^+). Anal. Calcd for $C_{17}H_{20}N_2O$: C, 76.08; H, 7.51; N, 10.44. Found: C, 75.80; H, 7.29; N, 10.16.

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