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AN EFFICIENT CONSTRUCTION OF 4-OXO-1,3-DIAZABICYCLO[3.3.0]OCTANES VIA THIOHYDANTOINS

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ABSTRACT: New stereoisomeric *N*-bridged heterocycles, 4-oxo-1,3-diazabicyclo-[3.3.0]octanes(**4**) were synthesized from *trans*-4-hydroxy-L-proline(**1**). Thiohydantoins **3** as the key intermediates were prepared by nucleophilic addition of **1** to isothiocyanates, and subsequent cyclization. These thiohydantoins **3** were readily desulfurized to provide **4**.

As a part of our investigations of medicinal chemistry we became interested in the synthesis of some 4-oxo-1,3-diazabicyclo[3.3.0]octanes. This fused bicyclic skeleton containing bridgehead nitrogen has hitherto been reported very rarely.[1] For the same purpose (6*S*,8*R*)-8-hydroxy-5-oxo-1,4-diaza-*bicyclo[4.3.0]nonanes* having structural similarity had already synthesized in our laboratory.[2]

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We now wish to describe our results on the efficient construction of 7-hydroxy-4-oxo-1,3-diazabicyclo[3.3.0]octanes(**4**) with bridgehead nitrogen. The title compounds are expected as the convenient intermediates to a variety of organic syntheses due to their amide and hydroxy groups which can be readily functionalized to other chemical transformations.

trans-4-Hydroxy-L-proline(**1**) was *N*-alkylated by alkyl or aryl isothiocyanates under basic condition, leading to thiocarbamoylpyrrolidic acids **2**. They were *in situ* refluxed for 2hrs with 2*N*-HCl to give thiohydantoins **3** in 90–97% yield(Table 1).[3] Thiohydantoins **3** were obtained as a mixture of two stereoisomers. It is thought that the epimerization of acidic α-hydrogen adjacent to carbonyl of **2** under basic condition was to afford the mixture. **3** were rendered to next step without separation of mixture. Reductive desulfurization of **3** with Raney-Ni(*W*-2)[4] was readily proceeded to afford 7-hydroxy-4-oxo-1,3-diazabicyclo[3.3.0]octanes(**4**), which are the stereoisomeric mixture of $\mathbf{4}_1$ and $\mathbf{4}_2$ in 43-55% yield(Scheme 1). Structure elucidation of the stereoisomers was established by Nuclear Overhauser Effect(NOE) in AMX 400 Brucker spectrometer. In the case of $\mathbf{4c}_2$ the irradiation of H_{6a} at C-6 position led to a 5% increase in the intensity of signal for H_5 while no such effect was observed in the case of $\mathbf{4c}_1$(Fig. 1). A speculation on coupling constant also shows the consistence between calculated and experimental values.[5]

Several results obtained under the standard condition were summarized in Table 2.

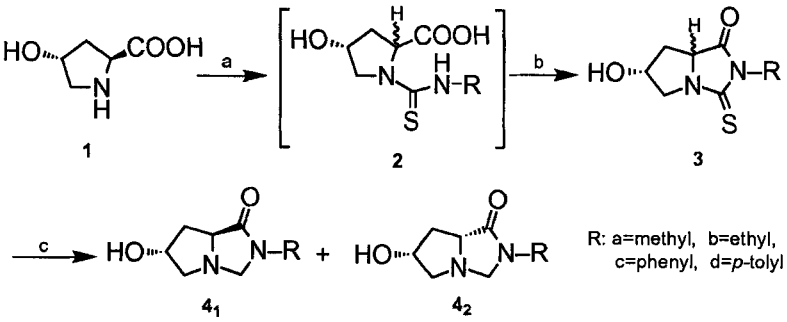
EXPERIMENTAL

All melting points were determined on a Thomas-Hoover capillary melting point apparatus and were uncorrected. IR spectra were recorded on a Perkin-Elmer 16F PC FT-IR spectrophotometer. NMR spectra were obtained on a

Table 1. Preparation of Thiohydantoins **3**.

Isothiocyanates	Products	Yield(%)[a,b]
CH_3NCS	**3a**	90
C_2H_5NCS	**3b**	97
C_6H_5NCS	**3c**	91
4'-$CH_3C_6H_4NCS$	**3d**	96

[a]Isolated yields. [b]These yields are overall yields based on **1**.



Reagents and conditions; a: alkyl or aryl isothiocyanate/ pyridine:H_2O=1:1/ 1*N*-NaOH, 40°C; b: 1*N*-HCl, reflux; c: Raney-Ni(W-2)/ EtOH, refux

Scheme 1

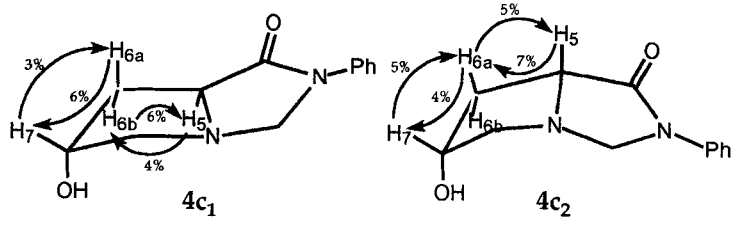


Fig. 1

Table 2. Yield and mixture ratio of **4**.

Products	Yield(%)[a]	Ratio[b]	
4a	49	**4a**$_1$: **4a**$_2$	61: 39
4b	43	**4b**$_1$: **4b**$_2$	56: 44
4c	55	**4c**$_1$: **4c**$_2$	55: 45
4d	52	**4d**$_1$: **4d**$_2$	56: 44

[a]Isolated yield. [b]Ratio of each compound isolated by column chromatography.

Varian Gemini 300 or an AMX 400 Brucker spectrometer. All chemical shift values were reported in the δ scale from internal tetramethylsilane. Mass spectra were recorded on a Hewlett-Packard Model 5985B spectrometer.

General Procedure for the Preparation of Thiohydantoins(3). *trans*-4-Hydroxy-L-proline(**1**, 76.3 mmol) was dissolved in a mixture of 70 ml of water and 70 ml of pyridine. The solution was heated to 40°C and kept at that temperature during the reaction. 1.1–1.5eq. of alkyl or aryl isothiocyanates were added with vigorous stirring. 1*N*-NaOH was added to keep the pH at about 9. After the reaction was completed, the reaction mixture was stirred additionally for 2hr. Pyridine and excess isothiocyanate were removed by repeated extractions with benzene. Then, the pH of solution was adjusted to about 2 by addition of 1*N*-HCl. The solution was refluxed for 2hr. After cooling of the reaction mixture, the precipitate was filtered and washed with water several times.

7-Hydroxy-3-methyl-4-oxo-2-thioxo-1,3-diazabicyclo[3.3.0]octanes(3a$_1$ and 3a$_2$): Yellow oil; IR(thin film) 3440, 1748, 1436, 1330, 1086 and 1002cm^{-1}; ^{1}H NMR ($CDCl_3$, 300MHz) δ 4.60-4.57(1H, m, -OH), 4.45-4.39(1H, m, C_7-H), 4.45-4.39 and

4.19-4.13(1H, m, C_5-H of mixture, respectively), 3.92-3.85 and 3.40-3.27(2H, m, C_8-H of mixture, respectively), 3.00 and 2.98(3H, s, CH_3 of mixture, respectively), 2.12–2.05 and 1.88–1.80(2H, m, C_6-H of mixture, respectively); ^{13}C NMR($CDCl_3$, 75.5MHz) δ 189.90, 186.60, 174.89, 173.75, 72.34, 71.81, 63.30, 62.34, 57.78, 57.06, 35.31, 34.42, 28.02 and 27.69; MS *m/z* 186(M^+, $C_7H_{10}N_2O_2S$).

7-Hydroxy-3-ethyl-4-oxo-2-thioxo-1,3-diazabicyclo[3.3.0]octanes($3b_1$ and $3b_2$): mp 61-63°C as the white needles; IR(KBr) 3488, 1732, 1434, 1350, 1264 and 1064 cm^{-1}; ^1H NMR($CDCl_3$, 300MHz) δ 4.73-4.70(1H, m, -OH), 4.53-4.48(1H, m, C_7-H), 4.53-4.48 and 4.24-4.18(1H, m, C_5-H of mixture, respectively), 4.08-4.02 and 3.49-3.41(2H, m, C_8-H of mixture, respectively), 3.78-3.70(2H, m, CH_2), 2.26–2.19 and 1.76–1.66(2H, m, C_6-H of mixture, respectively), 1.17-1.12(3H, m, CH_3 of mixture, respectively); ^{13}C NMR($CDCl_3$, 75.5MHz) δ 190.15, 186.19, 174.65, 173.37, 72.51, 71.96, 63.14, 62.17, 58.08, 57.22, 36.72, 36.44, 35.64, 34.60, 12.31 and 12.10; MS *m/z* 200(M^+, $C_8H_{12}N_2O_2S$).

7-Hydroxy-3-phenyl-4-oxo-2-thioxo-1,3-diazabicyclo[3.3.0]octanes($3c_1$ and $3c_2$): mp 157-158°C as the white needles; IR(KBr) 3486, 1756, 1720, 1500, 1432, 1272 and 1090cm^{-1}; ^1H NMR(DMSO-d_6, 300MHz) δ 7.52-7.40(3H, m, aromatic-H), 7.35-7.26(2H, m, aromatic-H), 5.46 and 5.31(1H, d, J=3.3 and 3.6, -OH of mixture, respectively), 4.81 and 4.67(1H, t, J=8.8 and 6.6, C_7-H of mixture, respectively), 4.67-4.64 and 4.49-4.45(1H, m, C_5-H of mixture, respectively), 4.05-3.95, 3.62-3.57 and 3.40-3.36(2H, m, C_8-H of mixture, respectively), 2.51-2.38, 2.12–2.09 and 2.01–1.91(2H, m, C_6-H of mixture, respectively); ^{13}C NMR(DMSO-d_6, 75.5MHz) δ 188.40, 185.85, 174.43, 173.34, 128.76, 128.69, 128.53, 128.47, 71.75, 71.25, 64.00, 63.00, 57.96, 57.88, 35.29 and 35.00; MS *m/z* 248(M^+, $C_{12}H_{12}N_2O_2S$).

7-Hydroxy-3-(4'-methylphenyl)-4-oxo-2-thioxo-1,3-diazabicyclo[3.3.0]octanes ($3d_1$ and $3d_2$): mp 184-186°C as the white needles; IR(KBr) 3480, 1754, 1720, 1518,

1430, 1320, 1720 and 1090cm^{-1}; ^{1}H NMR(DMSO-d_6, 300MHz) δ 7.30-7.27(2H, m, aromatic-H), 7.20-7.13(2H, m, aromatic-H), 5.44 and 5.29(1H, d, J=3.5 and 3.6, -OH of mixture, respectively), 4.79 and 4.65(1H, t, J=9.1 and 6.6, C_7-H of mixture, respectively), 4.65-4.45 and 4.47-4.45(1H, m, C_5-H of mixture, respectively), 4.04-3.93, 3.61-3.56 and 3.38-3.34(2H, m, C_8-H of mixture, respectively), 2.35(3H, s, CH_3), 2.49-2.42, 2.11–2.08 and 1.97–1.89(2H, m, C $_6$-H of mixture, respectively); ^{13}C NMR(DMSO-d_6, 75.5MHz) δ 188.15, 186.08, 174.10, 173.40, 129.25, 129.19, 128.26, 128.20, 71.72, 71.24, 63.90, 62.93, 57.95, 57.88, 35.31, 35.00 and 20.73; MS *m/z* 262(M^+, $C_{13}H_{14}N_2O_2S$).

General Procedure for the Preparation of 7-Hydroxy-4-oxo-1,3-diazabicyclo[3.3.0]octane(4). Raney-Ni(W-2) was added to the solution of thiohydantoin(**3**, 20–40 mmol) in EtOH(50–150 ml). The reaction mixture was refluxed for 2h. After removal of Raney-Ni(W-2) with celite, the filtrate was evaporated on vacuo. Careful column chromatography(ethyl acetate:MeOH=2:1) of the crude material afforded $\mathbf{4}_1$ and $\mathbf{4}_2$.

(5*S*,7*R*)-7-Hydroxy-3-methyl-4-oxo-1,3-diazabicyclo[3.3.0]octane($\mathbf{4a}_1$): Yield 30%; mp 58-60°C as the colorless plates; IR(thin film) 3393, 1680, 1447, 1328, 1087 and 971cm^{-1}; ^{1}H NMR(DMSO-d_6, 300MHz) δ 4.75(1H, br-s, -OH), 4.33(1H, d, J=8.0Hz, C_2-H), 4.15(1H, br-s, C_7-H), 4.01(1H, d, J=8.0Hz, C_2-H), 3.63(1H, dd, J=4.6 and 8.5Hz, C_5-H), 2.95(1H, br-s, J=10.0Hz, C_8-H), 2.68(3H, s, CH_3), 2.62(1H, dd, J=4.9 and 10.0Hz, C_8-H), 2.02–1.94(1H, m, C $_6$-H) and 1.88–1.80(1H, m, C $_6$-H); ^{13}C NMR ($CDCl_3$, 75.5MHz) δ 174.50, 71.79, 70.87, 63.47, 62.64, 36.92 and 27.93; MS *m/z* 156(M^+, $C_7H_{12}N_2O_2$).

(5*R*,7*R*)-7-Hydroxy-3-methyl-4-oxo-1,3-diazabicyclo[3.3.0]octane($\mathbf{4a}_2$): Yield19%; colorless oil; IR(thin film) 3379, 1680, 1445, 1407, 1335, 1125 and 1050cm^{-1}; ^{1}H NMR(DMSO-d_6, 300MHz) δ 4.69(1H, d, J=2.8Hz, -OH), 4.37(1H, d, J=7.4Hz, C_2-

H), 4.12(each 1H, d, J=7.4Hz, C_2- and C_7-H), 3.48(1H, br-d, J=9.5Hz, C_5-H), 3.06 (1H, dd, J=4.1 and 11.0Hz, C_8-H), 2.68(3H, s, CH_3), 2.62(1H, dd, J=3.6 and 11.0Hz, C_8-H), 2.04–1.96(1H, m, C_6-H) and 1.79(1H, d, J=13.1Hz, C_6-H); ^{13}C NMR($CDCl_3$, 75.5MHz) δ 174.54, 74.43, 71.23, 64.82, 64.64, 37.62 and 27.68; MS *m/z* 156(M^+, $C_7H_{12}N_2O_2$).

(5*S*,7*R*)-3-Ethyl-7-hydroxy-4-oxo-1,3-diazabicyclo[3.3.0]octane(4b_1): Yield 24%; colorless oil; IR(thin film) 3400, 1678, 1458, 1325 and 1093cm^{-1}; ^1H NMR(DMSO-d_6, 300MHz) δ 4.81(1H, br-s, -OH), 4.36(1H, d, J=8.0Hz, C_2-H), 4.14(1H, br-s, C_7-H), 4.04(1H, d, J=8.0Hz, C_2-H), 3.63(1H, dd, J=4.7 and 8.4Hz, C_5-H), 3.30–3.19 (1H, m, -$\underline{CH_2}CH_3$), 3.13–3.01(1H, m, - $\underline{CH_2}CH_3$), 2.95(1H, d, J=10.2Hz, C_8-H), 2.57(1H, dd, J=4.5 and 10.2Hz, C_8-H), 2.04– 1.96(1H, m, C_6-H), 1.87–1.80(1H, m, C_6-H) and 1.01(3H, t, J=7.1Hz, CH_3); ^{13}C NMR($CDCl_3$, 75.5MHz) δ 173.76, 71.20, 68.23, 63.76, 62.37, 36.63, 35.69 and12.35; MS *m/z* 170(M^+, $C_8H_{14}N_2O_2$).

(5*R*,7*R*)-3-Ethyl-7-hydroxy-4-oxo-1,3-diazabicyclo[3.3.0]octane(4b_2): Yield 19%; colorless oil; IR(thin film) 3381, 1678, 1458, 1300 and 1128 cm^{-1}; ^1H NMR(DMSO-d_6, 300MHz) δ 4.69(1H, d, J=3.2Hz, -OH), 4.40(1H, d, J=7.4 Hz, C_2-H), 4.16(1H, d, J=7.4Hz, C_2-H), 4.15–4.09(1H, m, C_7-H), 3.50(1H, dd, J=2.6 and 9.5Hz, C_5-H), 3.29–3.16(1H, m, - $\underline{CH_2}CH_3$), 3.12–3.02(each 1H, m, - $\underline{CH_2}CH_3$ and C_8-H), 2.59(1H, dd, J=3.8 and 11.0Hz, C_8-H), 2.06–1.97(1H, m, C_5-H) and 1.78(1H, dt, J=3.3 and 13.1Hz, C_6-H); ^{13}C NMR($CDCl_3$, 75.5 MHz) δ 173.95, 71.99, 71.18, 65.01, 64.75, 37.56, 35.72, 12.17; MS *m/z* 170(M^+, $C_8H_{14}N_2O_2$).

(5*S*,7*R*)-7-Hydroxy-4-oxo-3-phenyl-1,3-diazabicyclo[3.3.0]octane(4c_1): Yield 30%; mp 72–74°C as the white powder; IR(KBr) 3440, 1672, 1596, 1497, 1320, 1202, 1083, 960, 851 and 789cm^{-1}; ^1H NMR(DMSO-d_6+D_2O, 300 MHz) δ 7.56(2H, d, J=7.5Hz, aromatic-H), 7.37(2H, t, J=7.5Hz, aromatic-H), 7.15(1H, t, J=7.5Hz, aromatic-H), 4.86(1H, d, J=8.4Hz, C_2-H), 4.59(1H, d, J=8.4Hz, C_2-H), 4.21(1H,

br-s, C_7-H), 3.90(1H, dd, J=4.8 and 9.2Hz, C_5-H), 3.04(1H, d, J=10.5Hz, C_8-H), 2.69(1H, dd, J=4.8 and 10.5Hz, C_8-H), 2.20(1H, ddd, J=4.8, 5.8 and 13.6Hz, C_6-H) and 2.00–1.93(1H, m, C_6-H); ^{13}C NMR($CDCl_3$, 75.5MHz) δ 173.97, 138.22, 128.88, 124.24, 118.87, 69.95, 69.80, 65.09, 62.50 and 37.13; MS *m/z* 218(M^+, $C_{12}H_{14}N_2O_2$).

(5*R*,7*R*)-7-Hydroxy-4-oxo-3-phenyl-1,3-diazabicyclo[3.3.0]octane(4c$_2$): Yield25%; mp 137–139°C as the white powder; IR(KBr) 3244, 1689, 1599, 1465, 1325, 1242, 1063, 976 and 757cm^{-1}; ^{1}H NMR(DMSO-d_6, 300MHz) δ 7.63(2H, d, J=7.5Hz, aromatic-H), 7.38(2H, t, J=7.5Hz, aromatic-H), 4.93 (1H, d, J=7.7Hz, C_2-H), 4.76(1H, d, J=2.9Hz, -OH), 4.69(1H, d, J=7.7Hz, C_2-H), 4.16(1H, br-s, C_7-H), 3.77 (1H, dd, J=2.0 and 8.9Hz, C_5-H), 3.21(1H, dd, J=4.0 and 11.3Hz, C_8-H), 2.75(1H, dd, J=2.2 and 11.3Hz, C_8-H), 2.16– 2.07(1H, m, C_6-H) and 1.99(1H, d, J=13.2Hz, C_6-H); ^{13}C NMR(DMSO-d_6, 75.5MHz) δ 173.83, 138.34, 128.83, 123.98, 118.63, 71.92, 69.85, 65.36, 64.21 and 37.32; MS *m/z* 218(M^+, $C_{12}H_{14}N_2O_2$).

(5*S*,7*R*)-7-Hydroxy-3-(4'-methylphenyl)-4-oxo-1,3-diazabicyclo[3.3.0]octane(4d$_1$) : Yield 29%; mp 149–150°C as the colorless needles; IR(thin film) 3392, 1692, 1516, 1406, 1336, 1206, 1083, 966, 816 and 754cm^{-1}; ^{1}H NMR (DMSO-d_6+D_2O, 300MHz) δ 7.46(2H, d, J=8.3Hz, aromatic-H), 7.18(2H, d, J=8.3Hz, aromatic-H), 4.84(1H, d, J=8.5Hz, C_2-H), 4.56(1H, d, J=8.5Hz, C_2-H), 4.21(1H, br-s, C_7-H), 3.88(1H, dd, J=4.2 and 9.0Hz, C_5-H), 3.03(1H, d, J=10.4Hz, C_8-H), 2.69(1H, dd, J=4.7 and 10.4Hz, C_8-H), 2.26– 2.14(4H, m, CH_3 and C_6-H) and 1.98–1.91(1H, m, C_6-H); ^{13}C NMR(DMSO-d_6, 75.5Hz) δ 173.67, 135.73, 133.37, 129.26, 118.93, 69.95, 69.92, 65.03, 62.53, 37.10 and 20.46; MS *m/z* 232(M^+, $C_{13}H_{16}N_2O_2$).

(5*R*,7*R*)-7-Hydroxy-3-(4'-methylphenyl)-4-oxo-1,3-diazabicyclo[3.3.0]octane(4d$_2$) : Yield 23%; mp 175.5–176.5°C as the colorless needles; IR(KBr) 3419, 1666, 1514, 1432, 1332, 1190, 1133, 1091, 867, 822, 623 and 506cm^{-1}; ^{1}H NMR(DMSO-d_6+D_2O, 300MHz) δ 7.46(2H, d, J=8.5Hz, aromatic-H), 7.16 (2H, d, J=8.5Hz, aromatic-H),

4.87(1H, d, J=8.0Hz, C_2-H), 4.63(1H, d, J=8.0 Hz, C_2-H), 4.14(1H, br-s, C_7-H), 3.75–3.72(1H, m, C_5-H), 3.18(1H, dd, J=4.0 and 11.3Hz, C_8-H), 2.72(1H, dd, J=2.2 and11.3Hz, C_8-H), 2.25(3H, s, CH_3), 2.14–2.05(1H, m, C_6-H) and 1.96(1H, d, J=13.2Hz, C_6-H); ^{13}C NMR(DMSO-d_6, 75.5MHz) δ 173.51, 135.87, 133.07, 129.21, 118.70, 71.97, 69.88, 65.30, 64.11, 37.23 and 20.45; MS *m/z* 232(M^+, $C_{13}H_{16}N_2O_2$).

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   Vicinal coupling constants were theoretically predicted by Karplus-Conrey equation for the dependence of vicinal H-H coupling on the dihedral angle ø, although they are less well defined for cyclopentane derivatives.

   $^3J = A + B\cos\phi + C\cos 2\phi$ (the empirical constants A=7, B=-1, and C=5)

   For **4c$_1$**:

   Calculated value; $J_{5a,6a}$=7-cos120°+5cos240°=5.0Hz

   $J_{5b,6b}$=7-cos0°+5cos0°=11.0Hz

   Experimental value; $J_{5a,6a}$=4.8Hz, $J_{5b,6b}$=9.2Hz

For **4c**$_2$:

Calculated value; $J_{5a,6a}$=7-cos30°+5cos60°=8.6Hz

$J_{5b,6b}$=7-cos90°+5cos180°=2.0Hz

Experimental value; $J_{5a,6a}$=8.9Hz, $J_{5b,6b}$=2.0Hz

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