Synthesis of 1,2,5,6-/1,2,3,6-Tetrahydropyridinyl-tetrahydro-cyclopentaisoxazole Derivatives

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Fused tetrahydrocyclopenta-isoxazoles were synthesized by 1,3-dipolar cycloaddition reactions with pyridinealdoxime or tetrahydropyridinealdoxime and cycloalkenes.

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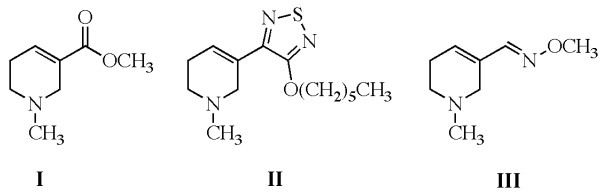
Recent research effort on Alzheimer's Disease (AD) has focused on the development of muscarinic M_1 agonists [1]. M_1 agonists are expected to bind selectivity to M_1 muscarinic receptors and stimulate phosphoinositide (PI) turnover in the hippocamus [2]. Arecoline (**I**, Figure 1), a naturally occurring alkaloid, is one of the first clinical drugs used for AD [3]. Despite being an M_1 agonist, however, its lack of subtype selectivity and poor metabolic stability caused by the ester moiety, has hindered its use as a therapeutic agent.

To improve the duration of action and pharmacological profile (potency and efficacy), the ester moiety had to be replaced. Continuing efforts to synthesize derivatives of this lead compound have brought about xanomeline (**II**) [4] and milameline (**III**) [5]. Chemically, they possess a 1,2,5,6-tetrahydropyridine ring while the unstable ester moiety of arecoline has been replaced with its bioisosteres alkoxythiadiazole and alkoxyimino groups, respectively. The structure of xanomeline (**II**) shows a resemblance to that of tetrahydropyridinylbenzoxazoles (**IV**) [6] and tetrahydropyrimidinylbenzoxazoles (**V**) [7] previously prepared in our laboratory (Figure 2). Compounds IV and V, which possess a benzoxazole ring, exhibited interesting biological activity as potential agrochemicals as well as clinical drugs. SAR studies have revealed that pharmacological activity may be maintained if the ester in arecoline is exchanged with a heterocyclic ring. Therefore, a series of tetrahydrocyclopenta-isoxazole system as an ester bioisostere seemed like an attractive target.

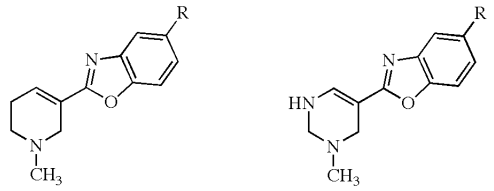
The isoxazoles belong to an important structural group found in a variety of anticonvulsants [8], antivirals [9], and analgesics [10]. Many papers have been published describing the synthesis of isoxazole derivatives [11]. In our continuous research program on the synthesis of isoxazole derivatives as possible M_1 agonists, we describe in this report the synthesis of 1-methyl-1,2,5,6-tetrahydropyridin-3-yl-tetrahydrocyclopenta/furoisoxazoles **5a-c** and 1-methyl-1,2,3,6-tetrahydropyridin-4-yl-tetrahydrocyclopenta/furoisoxazoles **8a-c** as shown is Schemes 1 and 2.

The starting material 3-pyridinealdoxime **1** was prepared from 3-pyridinealdehyde and hydroxylamine hydrochloride according to a known procedure [12]. Treatment of`3-pyridinealdoxime **1** and cycloalkenes **2** with sodium hypochlorite in dichloromethane solution at 0 °C gave the bicyclic compounds **3a-c** in moderate to good yields by 1,3-dipolar cycloaddition reaction. The expected *cis*-ring junction stereochemistry of **3a-c** was confirmed



I **II** **III**

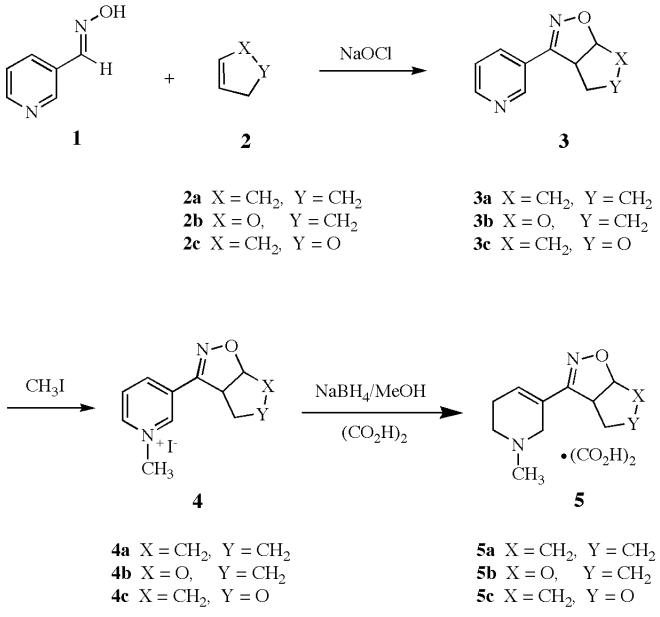
Figure 1. Muscanimic agonists



IV **V**

Figure 2. Structures of tetrahydropyridinylbenzoxazoles (**IV**) and tetrahydropyrimidinylbenzoxazoles (**V**).

Scheme 1



1 **2** **3**

2a X = CH_2, Y = CH_2
2b X = O, Y = CH_2
2c X = CH_2, Y = O

3a X = CH_2, Y = CH_2
3b X = O, Y = CH_2
3c X = CH_2, Y = O

4 **5**

4a X = CH_2, Y = CH_2
4b X = O, Y = CH_2
4c X = CH_2, Y = O

5a X = CH_2, Y = CH_2
5b X = O, Y = CH_2
5c X = CH_2, Y = O

by X-ray crystallography [13] and result of **3b** is shown in Figure 3. Compounds **3a-c** were further treated with the conventional method of methyl iodide in acetone to afford 1-methylpyridinium iodides **4a-c** in good yields.

Treatment of 1-methylpyridinium salts **4a-c** with sodium borohydride in cold (-20 °C) methanol yielded tetrahydropyridinyl-cyclopenta/furoisoxazole derivatives as the sole product. For enhanced purity and stability, the obtained derivatives were further treated with oxalic acid to afford the oxalate salts **5a-c**.

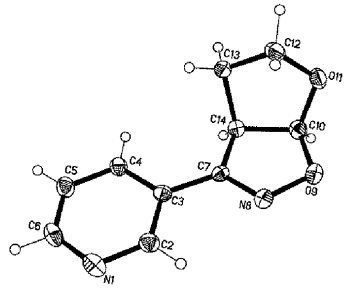
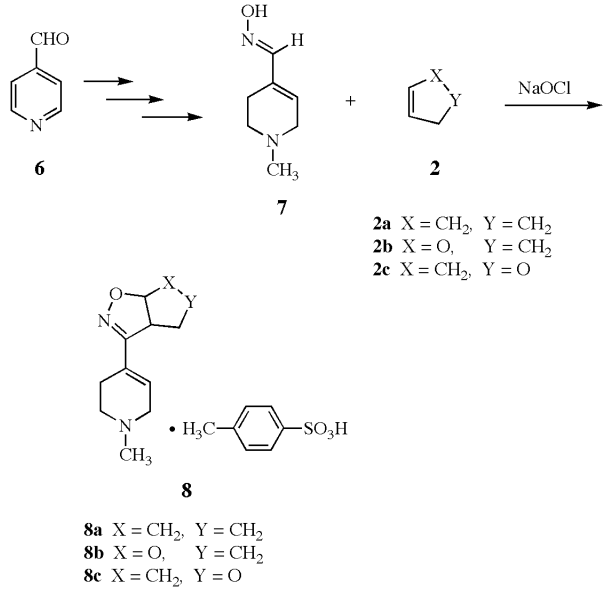


Figure 3. X-Ray Crystallography of **3b** (arbitrary numbering system).

Compounds **8a-c** were synthesized as positional isomers of compounds **5a-c** for a structure-activity relationship study. Synthesis of compounds **8a-c** is shown in Scheme 2. Similar to the previous experiment, starting from 4-pyridinealdehyde **6**, we obtained 4-pyridinealdoxime [12]. Before the cycloaddition reaction, methylation of 4-pyridinealdoxime led to the corresponding pyridinium salts which underwent hydride reduction with sodium borohydride to produce compound **7** as starting material. The bicyclic tosylate salts **8a-c** were prepared from compound **7** and the corresponding cycloalkenes **2** by 1,3-dipolar cycloaddition. Better purity was obtained for compounds **8a-c** when prepared as tosylate salts instead of the oxalate salts.

Scheme 2



EXPERIMENTAL

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Infrared spectra were recorded on a Mattson Genesis II FTIR. Nuclear magnetic resonance spectra were measured on a Brucker AM-300 spectrometer. For single crystal X-ray diffractometry, the intensity data were collected at room temperature on a Siemens P4 four-circle X-ray diffractometer with graphite-monochromated Mo Kα radiation (λ = 0.71073 Å). All calculation in the structural solution and refinement was performed using the Siemens SHELXTL crystallographic software package on a Silicon Graphics system. All the non-hydrogen atoms were refined anisotropically; all the hydrogen atoms fixed at the calculated positions with the isotropic thermal parameters were included in the final structure factor calculations.

General Procedure for Preparation of 3-Pyridin-3-yl-tetrahydrocyclopenta/furoisoxazoles (**3a-c**).

To a stirred solution of pyridine-3-carboxaldehyde oxime **1** (10.0 mmol) in dichloromethane (100 ml) was added cycloalkene **2** (5.0 mmol). The mixture was stirred at 0 °C, after NaOCl (20.50 mmol) was added over a 30 min. period. After 4 h stirring at room temperature, the organic layer was separated, and the aqueous layer was extracted with dichloromethane, combined to the organic layer, dried over anhydrous $MgSO_4$, and then evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (*n*-hexane:acetone=2:1) to give the title compounds **3a-c**.

3-Pyridin-3-yl-4,5,6,6a-tetrahydro-3a*H*-cyclopenta[*d*]isoxazole (**3a**).

This compound was obtained as yellow oil, yield 58 %, ir (neat): 3030 (CH), 1590 cm^{-1}; ^1H nmr ($CDCl_3$): δ 8.84 (dd, 1H, C2'-H), 8.59 (dd, 1H, C6'-H), 8.05 (dt, 1H, C4'-H), 7.31 (ddd, 1H, C5'-H), 5.25 (dd, 1H, C6a-H), 4.04 (m, 1H, C3a-H), 2.17, 1.77 (m, 2H, C5-H), 1.89 (m, 2H, C4-H), 1.75, 1.53 (m, 2H, C6-H); ^{13}C nmr ($CDCl_3$): δ 156.1 (C-3), 150.4 (C-6'), 147.8 (C-2'), 133.9 (C-4'), 125.5 (C-3'), 123.5 (C-5'), 88.1 (C-6a), 51.4 (C-3a), 35.6 (C-5), 31.3 (C-4), 23.3 (C-6)

Anal. Calcd. for $C_{11}H_{12}N_2O$•HCl: C, 58.80; H, 5.83; N, 12.47. Found: C, 58.92; H, 5.85; N, 12.43.

3-Pyridin-3-yl-3a,4,5,6a-tetrahydrofuro[3,2-*d*]isoxazole (**3b**).

This compound was obtained as white powder, yield 35 %, mp 82-83°; ir (potassium bromide): 3050 (CH), 1595, 1090 cm^{-1}; ^1H nmr ($CDCl_3$): δ 8.83 (d, 1H, C2'-H), 8.62 (dd, 1H, C6'-H), 8.05 (dt, 1H, C4'-H), 7.34 (dd, 1H, C5'-H), 6.33 (d, 1H, C6a-H), 4.17 (dd, 1H, C3a-H), 4.07, 3.58 (m, 2H, C5-H), 2.27, 2.09 (m, 2H, C4-H); ^{13}C nmr ($CDCl_3$): δ 155.2 (C-3), 151.2 (C-6'), 147.8 (C-2'), 134.0 (C-4'), 124.8 (C-3'), 123.8 (C-5'), 109.5 (C-6a), 66.5 (C-5), 50.9 (C-3a), 30.2 (C-4). Crystal data for compound **3b** are found in Table.

Anal. Calcd. for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.52; H, 5.49; N, 14.92.

3-Pyridin-3-yl-3a,4,6,6a-tetrahydrofuro[3,4-*d*]isoxazole (**3c**).

This compound was obtained as white crystal, yield 20 %, mp 113-114°; ir (potassium bromide): 3060 (CH), 1588, 1090 cm^{-1}; ^1H nmr ($CDCl_3$): δ 8.75 (dd, 1H, C2'-H), 8.61 (dd, 1H, C6'-H), 8.02 (dt, 1H, C4'-H), 7.32 (2xdd, 1H, C5'-H), 5.39 (dd, 1H, C6a-H), 4.30 (d, 1H, C6-H), 4.26 (m, 1H, C3a-H), 4.10 (d, 1H, C4-H), 3.84 (dd, 1H, C4-H), 3.74 (dd, 1H, C6-H); ^{13}C nmr ($CDCl_3$): δ 154.2 (C-3), 151.0 (C-6'), 147.6 (C-2'), 134.0 (C-4'), 124.8 (C-3'), 123.8 (C-5'), 86.6 (C-6a), 76.2 (C-6), 71.4 (C-4), 53.2 (C-3a).

Anal. Calcd. for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 62.81; H, 5.29; N, 14.71.

General Procedure for Preparation of Pyridinium Salts (**4a-c).**

To a stirred solution of **3a-c** (5.0 mmol) in acetone (30 ml) was added a solution of iodomethane (50.0 mmol) in acetone (10 ml). The mixture was stirred at room temperature for 17 h. The precipitate was collected by filtration, the filter cake washed with ethyl ether, and dried under reduced pressure to give **4a-c**.

3-(1-Methyl-pyridin-3-yl)-4,5,6,6a-tetrahydro-3a*H*-cyclopenta-[*d*]isoxazole Iodide (**4a**).

This compound was obtained as yellow powder, yield 97 %, mp 162-163°; ir (potassium bromide): 3060 (CH), 1640 cm^{-1}; ^1H nmr (DMSO-d_6): δ 9.33 (s, 1H, C2'-H), 9.01 (d, 1H, C6'-H), 8.78 (d, 1H, C4'-H), 8.18 (dd, 1H, C5'-H), 5.33 (dd, 1H, C6a-H), 4.40 (s, 3H, N^+CH_3), 4.27 (dt, 1H, C3a-H), 1.99, 1.74 (m, 2H, C5-H), 1.80 (m, 2H, C4-H), 1.68, 1.25 (m, 2H, C6-H); ^{13}C nmr (DMSO-d_6): δ 154.8 (C-3), 145.8 (C-6'), 143.7 (C-2'), 141.8 (C-4'), 129.2 (C-3'), 128.0 (C-5'), 89.3 (C-6a), 50.7 (C-3a), 48.5 (N^+CH_3), 35.4 (C-5), 30.9 (C-4), 23.8 (C-6).

Anal. Calcd. for $C_{12}H_{15}IN_2O$: C, 43.65; H, 4.58; N, 8.48. Found: C, 43.94; H, 4.56; N, 8.55.

3-(1-Methyl-pyridin-3-yl)-3a,4,5,6a-tetrahydrofuro[3,2-*d*]isoxazole Iodide (**4b**).

This compound was obtained as yellow powder, yield 97 %, mp 205-206°; ir (potassium bromide): 3070 (CH), 1638, 1100 cm^{-1}; ^1H nmr (DMSO-d_6): δ 9.39 (s, 1H, C2'-H), 9.04 (d, 1H, C6'-H), 8.82 (d, 1H, C4'-H), 8.21 (dd, 1H, C5'-H), 6.45 (d, 1H, C6a-H), 4.52 (dt, 1H, C3a-H), 4.40 (s. 3H, N^+CH_3), 4.05, 3.39 (m, 2H, C5-H), 2.15 (m, 2H, C4-H); ^{13}C nmr (DMSO-d_6): δ 154.4 (C-3), 146.2 (C-6'), 144.1 (C-2'), 142.2 (C-4'), 128.7 (C-3'), 128.1 (C-5'), 110.4 (C-6a), 66.6 (C-5), 50.6 (C-3a), 48.5 (N^+CH_3), 29.8 (C-4).

Anal. Calcd. for $C_{11}H_{13}IN_2O_2$: C, 39.78; H, 3.95; N, 8.43. Found: C, 40.01; H, 4.05; N, 8.63.

3-(1-Methyl-pyridin-3-yl)-3a,4,6,6a-tetrahydrofuro[3,4-*d*]isoxazole Iodide (**4c**).

This compound was obtained as yellow powder, yield 96 %, mp 179-180°; ir (potassium bromide): 3060(CH), 1636, 1070 cm^{-1}; ^1H nmr (DMSO-d_6): δ 9.35 (s, 1H, C2'-H), 9.02 (d, 1H, C6'-H), 8.81 (d, 1H, C4'-H), 8.18 (dd, 1H, C5'-H), 5.56 (dd, 1H, C6a-H), 4.58 (dt, 1H, C3a-H), 4.38 (s, 3H, N^+CH_3), 4.15 (d, 1H, C6-H), 4.07, 3.72 (2xd, 2H, C4-H), 3.68 (dd, 1H, C6-H); ^{13}C nmr (DMSO-d_6): δ 153.3 (C-3), 146.1 (C-6'), 143.9 (C-2'), 141.9 (C-4'), 128.7 (C-3'), 128.1 (C-5'), 88.1 (C-6a), 75.7 (C-6), 71.1 (C-4), 52.4 (C-3a), 48.5 (N^+CH_3).

Anal. Calcd. for $C_{11}H_{13}IN_2O_2$: C, 39.78; H, 3.95; N, 8.43. Found: C, 39.85; H, 4.06; N, 8.58.

General Procedure for Preparation of 1-Methyl-1,2,5,6-tetrahydropyridin-3-yl-tetrahydrocyclopenta/furoisoxazole Oxalates (**5a-c**).

To a cooled (-20 °C) and stirred suspension of **4a-c** (4.0 mmol) in methanol (40 ml) was added portion-wise sodium borohydride (4.5 mmol). After stirring for 5 h at room temperature, the solvent was evaporated. The residue was dissolved in ethyl acetate and washed with aqueous $NaHCO_3$ solution. The organic layer was washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo* and the residue was purified by flash column chromatography on silica gel (methylene chloride: methanol) to give the reductive compounds. To a stirred solution of above mentioned reductive compounds in 10 ml acetone was added oxalic acid (1.0 eq). After 2 h stirring at room temperature, the precipitates were collected by filtration and washed with a small amount of ethyl ether, then dried under vacuum to give the title compounds **5a-c**.

3-(1-Methyl-1,2,5,6-tetrahydropyridin-3-yl)-4,5,6,6a-tetrahydro-3a*H*-cyclopenta[*d*]isoxazole Oxalate (**5a**).

This compound was obtained as white powder, yield 55 %, mp 138-139°; ir (potassium bromide): 3460 (COOH), 2970 (CH), 1732 (CO), 1660 cm^{-1}; ^1H nmr (DMSO-d_6): δ 6.32 (m, 1H, C4'-H), 5.04 (dd, 1H, C6a-H), 4.68 (br s, COOH), 3.94-3.79 (m, 3H, C2'-H, C3a-H), 3.25 (m, 2H, C6'-H), 2.82 (s, 3H, NCH_3), 2.53 (m, 2H, C5'-H), 1.90, 1.78 (m, 2H, C5-H), 1.75 (m, 2H, C4-H), 1.70, 1.26 (m, 2H, C6-H); ^{13}C nmr (CD_3OD): δ 165.4 (COOH), 159.3 (C-3), 129.7 (C-4'), 124.3 (C-3'), 89.8 (C-6a), 52.6, 52.4, 51.4 (C-2', C-6', C-3a), 43.5 (NCH_3), 36.8 (C-5), 33.1 (C-4), 24.7, 24.3 (C-5', C-6).

Anal. Calcd. for $C_{14}H_{20}N_2O_5$: C, 56.75; H, 6.80; N, 9.45. Found: C, 56.72; H, 6.90; N, 9.38.

3-(1-Methyl-1,2,5,6-tetrahydropyridin-3-yl)-3a,4,5,6a-tetrahydrofuro[3,2-*d*]isoxazole Oxalate (**5b**).

This compound was obtained as white powder, yield 46 %, mp 151-152°; ir (potassium bromide): 3440 (COOH), 1757 (CO), 1650 cm^{-1}; ^1H nmr (CD_3OD): δ 6.50 (br s, 1H, C4'-H), 6.24 (d, 1H, C6a-H), 4.05 (m, 4H, C3a-H, C5-H, C2'-H), 3.46 (m, 3H, C5-H, C6'-H), 3.03 (s, 3H, NCH_3), 2.75 (br s, 2H, C5'-H), 2.24 (m, 2H, C4-H); ^{13}C nmr (CD_3OD): δ 166.9 (COOH), 158.4 (C-3), 131.2 (C-4'), 124.2 (C-3'), 111.2 (C-6a), 67.9 (C-5), 52.3, 52.0, 51.3 (C-2', C-6', C-3a), 43.5 (NCH_3), 32.0 (C-4), 24.4 (C-5').

Anal. Calcd. for $C_{13}H_{18}N_2O_6$: C, 52.34; H, 6.08; N, 9.39. Found: C, 52.60; H, 6.16; N, 9.30.

3-(1-Methyl-1,2,5,6-tetrahydropyridin-3-yl)-3a,4,6,6a-tetrahydrofuro[3,4-*d*]isoxazole Oxalate (**5c**).

This compound was obtained as white powder, yield 47 %, mp 143-144°; ir (potassium bromide): 3470 (COOH), 1726 (CO), 1630 cm^{-1}; ^1H nmr (CD_3OD): δ 6.38 (br s, 1H, C4'-H), 5.32 (dd, 1H, C6a-H), 4.24 (br t, 1H, C3a-H), 4.19 (br d, 1H, C6-H), 4.12 (br d, 1H, C4-H), 4.05 (br s, 2H, C2'-H), 3.80 (dd, 1H, C4-H), 3.72 (dd, 1H, C6-H), 3.45 (br s, 2H, C6'-H), 3.02 (s, 3H, NCH_3), 2.73 (br s, 2H, C5'-H); ^{13}C nmr (CD_3OD): δ 166.9 (COOH), 157.5 (C-3), 130.4 (C-4'), 124.0 (C-3'), 88.3 (C-6a), 77.4 (C-6), 73.3 (C-4), 54.1, 52.4, 51.3 (C-2', C-6', C-3a), 43.5 (NCH_3), 24.4 (C-5').

Anal. Calcd. for $C_{13}H_{18}N_2O_6$: C, 52.34; H, 6.08; N, 9.39. Found: C, 52.25; H, 6.13; N, 9.28.

General Procedure for Preparation of 1-Methyl-1,2,3,6-tetrahydropyridin-4-yl-tetrahydrocyclopenta/furoisoxazole Tosylates (**8a-c**).

Compounds **8a-c** were prepared in three steps without isolation of the pyridinium salts from 1-methyl-1,2,3,6-tetrahydropyridin-4-aldoxime **7** according to general procedures **3a-c** to **5a-c**, using *p*-toluene sulfonic acid instead of oxalic acid to form the salt.

3-(1-Methyl-1,2,3,6-tetrahydropyridin-4-yl)-4,5,6,6a-tetrahydro-3a*H*-cyclopenta[*d*]isoxazole Tosylate (**8a**).

This compound was obtained as white powder, yield 36 %, mp 134-135°; ir (potassium bromide): 3470 (SO_3H), 3040 (CH), 1230 cm^{-1}; ^1H nmr (CD_3OD): δ 7.73, 7.28 (ABq, 4H, arom. H), 6.13 (m, 1H, C3'-H), 5.15 (dd, 1H, C6a-H), 4.19, 3.70, 3.28, 2.75 (m, 6H, C2'-H, C6'-H, C5'-H), 3.88 (m, 1H, C3a-H), 3.01 (s, 3H, NCH_3), 2.41 (s, 3H, CH_3), 2.07, 1.90 (m, 2H, C5-H), 1.85 (m, 2H, C4-H), 1.80, 1.43 (m, 2H, C6-H); ^{13}C nmr (CD_3OD): δ 160.3 (C-3), 143.8, 142.1, 130.2, 127.2 (arom. C), 128.4 (C-4'), 124.0 (C-3'), 90.2 (C-6a), 53.4 (C-2'), 52.2, 51.7 (C-6', C-3a), 43.4 (NCH_3), 36.8 (C-5), 33.1 (C-4), 24.7 (C-5'), 23.9 (C-6), 21.6 (CH_3).

Anal. Calcd. for $C_{19}H_{26}N_2O_4S$: C, 60.29; H, 6.92; N, 7.40; S, 8.47. Found: C, 59.93; H, 6.97; N, 7.34; S, 8.42.

3-(1-Methyl-1,2,3,6-tetrahydropyridin-4-yl)-3a,4,5,6a-tetrahydrofuro[3,2-*d*]isoxazole Tosylate (**8b**).

This compound was obtained as white powder, yield 33 %, mp 137-138°; ir (potassium bromide): 3460 (SO_3H), 3040 (CH), 1235 cm^{-1}; ^1H nmr (CD_3OD): δ 7.73, 7.28 (ABq, 4H, arom. H), 6.24 (d, 1H, C6a-H), 6.23 (m, 1H, C3'-H), 4.10 (m, 3H, C3a-H, C2'-H), 3.88, 3.66 (m, 2H, C5-H), 3.47, 3.28 (m, 2H, C6'-H), 3.02 (s, 3H, NCH_3), 2.79 (m, 2H, C5'-H), 2.41 (s, 3H, CH_3), 2.15 (m, 2H, C4-H); ^{13}C nmr (CD_3OD): δ 159.4 (C-3), 143.7, 142.2, 130.2, 127.2 (arom. C), 128.4 (C-4'), 125.3 (C-3'), 111.6 (C-6a), 67.8 (C-5), 53.4, 51.8, 51.6 (C-2', C-6', C-3a), 43.4 (NCH_3), 32.1 (C-4), 23.7 (C-5'), 21.6 (CH_3).

Anal. Calcd. for $C_{18}H_{24}N_2O_5S \cdot H_2O$: C, 54.26; H, 6.58; N, 7.03; S, 8.05. Found: C, 54.64; H, 6.48; N, 7.19; S, 7.93.

3-(1-Methyl-1,2,3,6-tetrahydropyridin-4-yl)-3a,4,6,6a-tetrahydrofuro[3,4-*d*]-isoxazole Tosylate (**8c**).

This compound was obtained as white powder, yield 12 %, mp 144-145°; ir (potassium bromide): 3470 (SO_3H), 3015 (CH), 1220 cm^{-1}; ^1H nmr (CD_3OD): δ 7.73, 7.28 (ABq, 4H, arom. H), 6.11 (m, 1H, C3'-H), 5.33 (dd, 1H, C6a-H), 4.21 (d, 1H, C6-H), 4.18 (br t, 1H, C3a-H), 4.08 (d, 1H, C4-H), 3.97 (br s, 2H, C2'-H), 3.78 (dd, 1H, C4-H), 3.72 (dd, 1H, C6-H), 3.47 (br s, 2H, C6'-H), 3.01 (s, 3H, NCH_3), 2.78 (m, 2H, C5'-H), 2.41 (s, 3H CH_3); ^{13}C nmr (CD_3OD): δ 158.5 (C-3), 143.7, 142.2, 130.2, 127.2 (arom. C), 128.2 (C-4'), 124.5 (C-3'), 88.7 (C-6a), 77.5 (C-6), 73.4 (C-4), 53.9, 53.4, 51.7 (C-2', C-6', C-3a), 43.3 (NCH_3), 23.9 (C-5'), 21.6 (CH_3).

Anal. Calcd. For $C_{18}H_{24}N_2O_5S$: C, 56.82; H, 6.36; N, 7.36; S, 8.43. Found: C, 56.51; H, 6.36; N, 7.34; S, 8.38.

Table

Crystal Data and Structure Refinement for **3b**

Empirical formula	$C_{10}H_{10}N_2O_2$
Formula weight	190.20
Temperature	297(2) K
Wavelength	0.71073 Å
Crystal system, space group	Monoclinic, $P2_1/c$
Unit cell dimensions	a = 9.635(2) Å α = 90°
	b = 11.799(2) Å β = 117.354(15)°
	c = 9.0545(13) Å γ = 90°
Volume, Z	914.3(3) $Å^3$, 4
Calculated density	1.382 Mg/m^3
Absorption coefficient	0.099 mm^{-1}
F(000)	400
Crystal size	0.40 x 0.26 x 0.21 mm
θ range for data collection	2.38 to 26.50°
Limiting indices	$-12 \le h \le 11$, $-1 \le k \le 14$, $-1 \le l \le 11$
Reflections collected	2423
Independent reflections	1868 [R_{int} = 0.0725]
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	1868 / 0 / 128
Goodness-of-fit on F^2	1.094
Final R indices [I>2σ(I)]	R1 = 0.0855, wR2 = 0.2479
R indices (all data)	R1 = 0.1256, wR2 = 0.2988
Extinction coefficient	0.015(10)
Largest diff. peak and hole	0.283 and -0.453 $e.A^{-3}$

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