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Synthesis of Piperidine Derivatives Fused to a Tetrahydrofuran Ring

A. I. Moskalenko[a] and V. I. Boev[b]

[a] *Lipetsk State Pedagogical University, ul. Lenina 42, Lipetsk, 398020 Russia*
e-mail: kaf_himii@lspu.lipetsk.ru

[b] *Timiryazev Russian State Agrarian University, Moscow, Russia*

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Abstract—Intramolecular nucleophilic opening of the oxirane ring in *tert*-butyl 6-(2-hydroxyethyl)-7-oxa-3-azabicyclo[4.1.0]heptane-3-carboxylate by the action of excess potassium hydroxide in 75% aqueous dimethyl sulfoxide at 110–120°C gave *tert*-butyl (3a*R*,7a*S*)-3a-hydroxyhexahydrofuro[2,3-*c*]pyridine-6(2*H*)-carboxylate whose treatment with $POCl_3$ resulted in elimination of water molecule and *tert*-butoxycarbonyl group with formation of 2,3,4,5,6,7-hexahydrofuro[2,3-*c*]pyridine hydrochloride. The latter reacted with electrophiles (acetic anhydride, methanesulfonyl chloride, and benzaldehyde in combination with sodium triacetoxyhydridoborate) in the presence of triethylamine, yielding the corresponding N-substituted 2,3,4,5,6,7-hexahydrofuro[2,3-*c*]pyridine derivatives.

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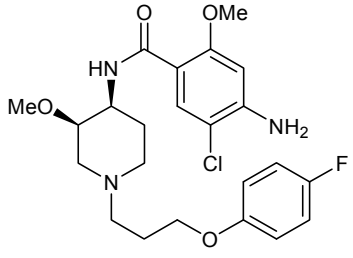
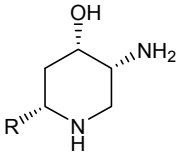
Many oxygen-containing piperidine derivatives exhibit high biological activity; in particular, they act as strong inhibitors toward some glucosidases and related enzymes [1, 2]. An example is Cisapride (**I**), an efficient serotonin 5-HT_4 receptor agonist, which is used to enhance gastrointestinal motility with no any undesirable side effect [3, 4]. Diastereoisomeric amino hydroxy piperidine alkaloids **II**–**IV** isolated from marine organisms have attracted much attention due to their anticancer activity [5–8]. Therefore, synthesis of new oxygen-containing piperidine derivatives seems to be promising from the viewpoint of design of efficient biologically active compounds and building blocks for fine organic synthesis.

While developing general procedures for the preparation of piperidine derivatives containing a tetrahydrofuran fragment [9], we have synthesized new compounds in which piperidine ring is fused to a tetrahydrofuran ring. As starting compound we used accessible 1-Boc-piperidin-4-one (**V**) which was brought into the Wittig–Horner reaction [10–12] with phosphonate **VI**. Depending on the conditions, unsaturated ester **VII** was formed as the major product or a mixture of esters **VII** and **VIII** was obtained. When the reaction was carried out in the presence of sodium hydride as deprotonating agent at room temperature (reaction time 12 h), the conversion of ketone **V** was as low as ~30%, and ester **VII** was the only product. Under more severe conditions, by heating equimolar amounts of the reactants in boiling tetrahydrofuran in the presence of potassium *tert*-butoxide for 4 h, we obtained a mixture of esters **VII** and **VIII**, the conversion of **V** being complete (Scheme 1).

Isomerization of ester **VII** by the action of lithium diisopropylamide (LDA) in THF also afforded compound **VIII**. Ester **VIII** was then reduced with lithium



I



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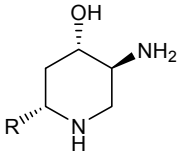
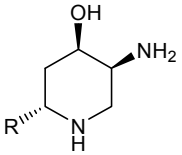
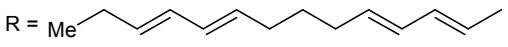


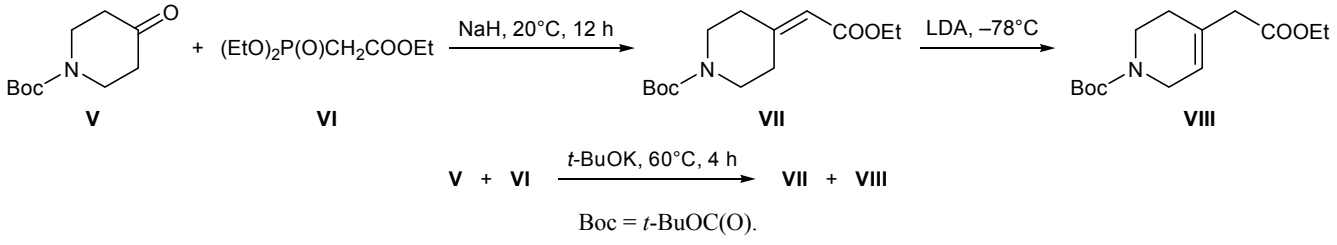
III



IV

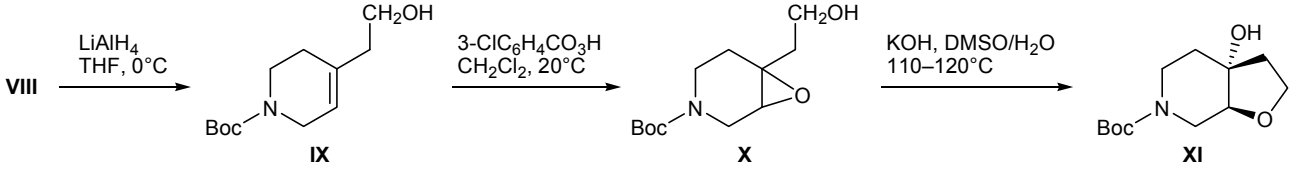


Scheme 1.

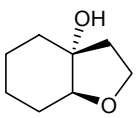


Boc = *t*-BuOC(O).

Scheme 2.



tetrahydridoaluminate to unsaturated alcohol **IX** in 71% yield. The oxidation of the double bond in **IX** with 3-chloroperoxybenzoic acid in methylene chloride gave 63% of epoxy derivative **X** as a 1:1 mixture of diastereoisomers (according to the GC/MS and ^{1}H NMR data). With account taken of published data [13, 14], the final step in the synthesis of target compound **XI** was intramolecular nucleophilic opening of the oxirane ring in **X** by the action of excess potassium hydroxide in 75% aqueous dimethyl sulfoxide at 110–120°C. As a result, we isolated 54% of new piperidine derivative **XI** with a fused tetrahydrofuran ring (Scheme 2). The product was a single stereoisomer analogous to benzofuran derivative **XII** described in [14]. We can conclude that intramolecular oxirane ring opening in **X** is also stereospecific.



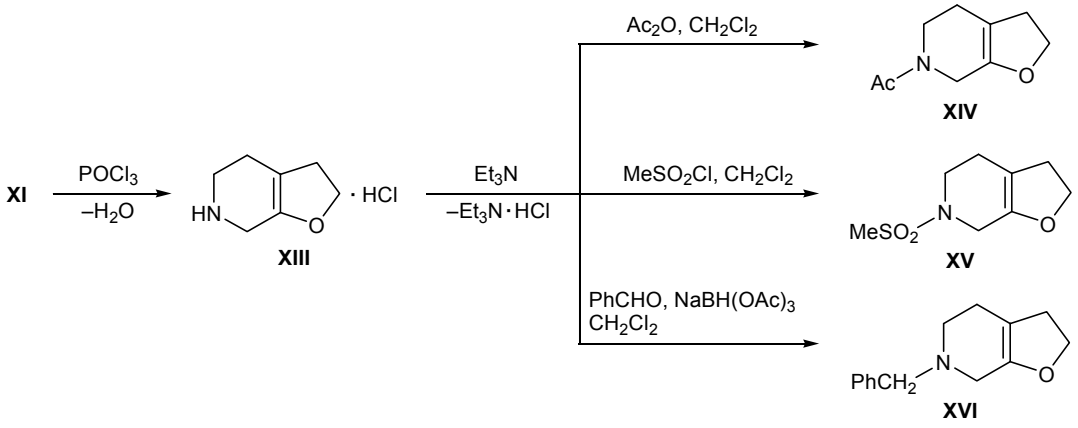
XII

Treatment of tertiary alcohol **XI** with $POCl_3$ according to the procedure described in [15] led to elimination of water molecule with simultaneous loss of the Boc protecting group to produce unsaturated *N*-unsubstituted secondary amine **XIII** which was isolated as hydrochloride. The NH hydrogen atom in **XIII** was replaced by acetyl, methanesulfonyl, and benzyl groups by reactions with the corresponding electrophiles according to [16, 17]. The structure of compounds **VII**–**XI** and **XIII**–**XVI** was determined on the basis of their elemental compositions, IR and ^{1}H NMR spectra, and GC/MS data.

EXPERIMENTAL

The IR spectra were recorded in KBr on a Specord 75IR spectrometer. The ^{1}H NMR spectra were measured on a Varian Mercury Plus 400 instrument (400 MHz) using hexamethyldisiloxane as internal reference. The mass spectra (atmospheric pressure chemical ionization) were obtained on a Thermo Finnigan Surveyor MSQ mass spectrometer (USA). The purity of the isolated compounds was checked by

Scheme 3.



TLC on Silufol UV-254 plates using hexane–ethyl acetate (1:1 by volume); spots were developed by treatment with a solution of ninhydrin in isopropyl alcohol on heating. Silica gel 60 (Merck) was used for column chromatography.

***tert*-Butyl 4-(2-ethoxy-2-oxoethylidene)piperidine-1-carboxylate (VII).** *a*. Phosphonate **VI**, 5.66 g (25 mmol), was dissolved in 40 mL of anhydrous THF, 0.96 g (25 mmol) of a 60% suspension of sodium hydride in mineral oil was added in portions under stirring and cooling with cold water, the mixture was stirred for 0.5 h, 4.0 g (20 mmol) of ketone **V** in 40 mL of THF was added, and the mixture was stirred for 20 h at room temperature. The mixture was treated with 150 mL of water and 70 mL of ethyl acetate and shaken, the organic layer was separated, and the aqueous layer was extracted with ethyl acetate (2×70 mL). The extracts were combined with the organic phase, washed with water and brine, and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the residue (6.81 g) was subjected to chromatography on silica gel. Elution with ethyl acetate–hexane (1:3) gave 2.41 g of compound **VII**, and with ethyl acetate–hexane (1:1), 3.18 g of unreacted ketone **V**. Yield of **VII** 100% (on the reacted ketone **V**), mp 85–86°C [10]. IR spectrum, ν, cm^{-1}: 1706, 1684 (C=O), 1643 (C=C). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.28 t (3H, Me), 1.47 s (9H, CMe_3), 2.25 t (2H, CH_2), 2.98 t (2H, CH_2), 3.49 m (4H, NCH_2), 4.16 q (2H, CH_2O), 5.73 s (1H, HC=C). Mass spectrum, *m*/*z* (I_{rel}, %): 170.22 (100) $[M - 101 + 2H]^+$. Found, %: C 62.18; H 8.43; N 5.31. $C_{14}H_{23}NO_4$. Calculated, %: C 62.45; H 8.55; N 5.20. *M* 269.28.

b. Potassium *tert*-butoxide, 11.20 g (100 mmol), was added in portions under stirring and cooling with ice water to a mixture of 19.90 g (100 mmol) of ketone **V** and 22.40 g (100 mmol) of phosphonate **VI** in 200 mL of anhydrous THF, and the mixture was heated for 4 h under reflux in an argon atmosphere. The solvent was distilled off under reduced pressure, 250 mL of ethyl acetate and 150 mL of 5% aqueous HCl were added to the residue, the mixture was shaken, and the organic layer was separated, washed with brine, and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the residue (34.21 g) was subjected to chromatography on silica gel. Elution with ethyl acetate–hexane (1:3) gave in succession 21.0 g (78%) of **VII** (mp 84–85°C) and 1.32 g (4.9%) of **VIII** as a light yellow thick material which crystallized on storage.

***tert*-Butyl 4-(2-ethoxy-2-oxoethyl)-1,2,3,6-tetrahydropyridine-1-carboxylate (VIII).** A solution of 2.37 g (8.8 mmol) of compound **VII** in 200 mL of anhydrous THF was cooled to –78°C, a solution of 15.4 mmol of lithium diisopropylamide in 15 mL of THF was added under stirring in an argon atmosphere, the mixture was stirred for 30 min at –78°C, 1.2 mL of glacial acetic acid in 10 mL of THF was added, and the mixture was stirred for 20 min at that temperature. The mixture was then allowed to warm up to room temperature, 200 mL of a saturated aqueous solution of sodium hydrogen carbonate and 70 mL of ethyl acetate were added, the mixture was shaken, the organic layer was separated, and the aqueous layer was extracted with 100 mL of ethyl acetate. The extract was combined with the organic phase, washed with brine, and dried over anhydrous sodium sulfate. Removal of the solvent under reduced pressure left 2.36 g (99.9%) of compound **VIII** as a light yellow thick oily material. IR spectrum, ν, cm^{-1}: 1718, 1685 (C=O), 1628 (C=C). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.27 t (3H, Me), 1.48 s (9H, CMe_3), 2.13 s (2H, CH_2), 3.03 s (2H, CH_2O), 3.51 t (2H, CH_2N), 3.88 s (2H, CH_2N), 4.15 q (2H, CH_2O), 5.53 s (1H, HC=C). Mass spectrum, *m*/*z* (I_{rel}, %): 170.24 (100) $[M - 101 + 2H]^+$. Found, %: C 62.03; H 8.41; N 5.16. $C_{14}H_{23}NO_4$. Calculated, %: C 62.45; H 8.55; N 5.20. *M* 269.28.

***tert*-Butyl 4-(2-hydroxyethyl)-1,2,3,6-tetrahydropyridine-1-carboxylate (IX).** A solution of 2.58 g (9.6 mmol) of compound **VIII** in 80 mL of anhydrous THF was cooled to 0°C, 0.63 g (16.6 mmol) of $LiAlH_4$ was added in portions under stirring, and the mixture was stirred for 3 h at room temperature. The mixture was then cooled to 0°C, 1.8 mL of water and 10 mL of 10% H_2SO_4 were added dropwise, the mixture was stirred for 0.5 h, 70 mL of ethyl acetate was added, and the mixture was filtered through a thin layer of celite. The precipitate was washed with 80 mL of ethyl acetate, and the organic layer was separated from the filtrate, washed with brine, and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure to isolate 1.54 g (71%) of compound **IX** as a light yellow thick oily substance. IR spectrum, ν, cm^{-1}: 3242 (OH), 1684 (C=O), 1625 (C=C). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.48 s (9H, CMe_3), 2.12 s (2H, CH_2), 2.58 t (2H, CH_2C=C), 3.51 t (2H, CH_2N), 3.48 t (2H, CH_2N), 3.71 t (2H, CH_2O), 3.83 s (2H, CH_2N), 5.47 s (1H, HC=C). Mass spectrum, *m*/*z* (I_{rel}, %): 227.67 (22.4) $[M + H]^+$, 128.36 (100) $[M - 101 + 2H]^+$. Found, %: C 63.18; H 9.13; N 5.98. $C_{12}H_{21}NO_3$. Calculated, %: C 63.44; H 9.25; N 6.17. *M* 227.30.

***tert*-Butyl 6-(2-hydroxyethyl)-7-oxa-3-azabicyclo-[4.1.0]heptane-3-carboxylate (X).** 3-Chloroperoxybenzoic acid, 1.70 g (9.91 mmol), was added under stirring to a solution of 1.50 g (6.61 mmol) of compound **IX** in 15 mL of anhydrous methylene chloride. After 18 h, the precipitate of 3-chlorobenzoic acid was filtered off, and the filtrate was diluted with 40 mL of methylene chloride, washed with three portions of 7% aqueous potassium hydroxide and with water, and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to obtain 1.02 g (63%) of compound **X** as a colorless thick oily substance. IR spectrum, ν, cm^{-1}: 3238 (OH), 1685 (C=O), 868 (oxirane) [18]. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.48 s (9H, CMe_3), 1.78 m (2H, CH_2C), 1.82 m (2H, CH_2C), 1.97 m (2H, CH_2CN), 2.01 m (2H, CH_2CN), 2.12 br.s (1H, OH), 2.98 m (2H, CH_2N), 3.04 m (2H, CH_2N), 3.31 m (2H, CH_2N), 3.56 m (2H, CH_2N), 3.68 t (1H, 5-H), 3.72 t (1H, 5-H), 3.76 t (2H, CH_2O), 3.81 t (2H, CH_2O). Mass spectrum, *m*/*z* (I_{rel}, %): 144.32 (100), 144.26 (78) $[M - 101 + 2H]^+$. Found, %: C 59.03; H 8.53; N 5.64. $C_{12}H_{21}NO_4$. Calculated, %: C 59.26; H 8.64; N 5.76. *M* 243.32.

***tert*-Butyl (3a*R*,7a*S*)-3a-hydroxyhexahydrofuro-[2,3-*c*]pyridine-6(2*H*)-carboxylate (XI).** Potassium hydroxide, 1.12 g (20 mmol), was added to a solution of 0.486 g (2 mmol) of compound **X** in 45 mL of 75% aqueous dimethyl sulfoxide, and the mixture was heated for 2 h at 110–120°C, cooled, diluted with 100 mL of water, and extracted with ethyl acetate (3×50 mL). The extract was washed with two portions of water and with brine and dried over anhydrous sodium sulfate. The solvent was distilled off under reduced pressure, and the residue (0.45 g) was subjected to chromatography on silica gel using ethyl acetate–hexane (1:1) as eluent. Yield 0.262 g (54%), colorless oily substance. IR spectrum, ν, cm^{-1}: 3248 (OH), 1683 (C=O). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.48 s (9H, CMe_3), 1.68 t (2H, CH_2), 1.86 m (2H, 4-H), 2.42 br.s (1H, OH), 2.84 t (2H, CH_2N), 3.65 m (2H, CH_2N), 3.87 t (2H, CH_2O), 4.02 m (1H, 7a-H). Mass spectrum, *m*/*z* (I_{rel}, %): 226.41 (35) $[M - H_2O + H]^+$, 144.28 (57) $[M - 101 + 2H]^+$, 126.15 (100) $[M - H_2O - 101 + 2H]^+$. Found, %: C 59.18; H 8.41; N 5.63. $C_{12}H_{21}NO_4$. Calculated, %: C 59.26; H 8.64; N 5.76. *M* 243.32.

2,3,4,5,6,7-Hexahydrofuro[2,3-*c*]pyridine hydrochloride (XIII) was synthesized according to the procedure described in [15]. Yield 86%, mp 184–185°C. IR spectrum, ν, cm^{-1}: 3452–3298 (NH_2^+), 1658 (C=C). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 1.68–2.03 m (4H, CH_2), 3.94 s (2H, CH_2N), 4.01 t (2H, OCH_2), 10.63 br.s (2H, NH_2^+). Mass spectrum, *m*/*z* (I_{rel}, %): 126.41 (100) $[M + H]^+$. Found, %: C 51.83; H 7.28; N 8.43. $C_7H_{11}NO \cdot HCl$. Calculated, %: C 52.01; H 7.43; N 8.67. *M* 125.43 (fee base).

1-(3,4,5,7-Tetrahydrofuro[2,3-*c*]pyridin-6(2*H*)-yl)ethanone (XIV) was synthesized according to [17]. Yield 94%. IR spectrum, ν, cm^{-1}: 1668 (C=O), 1645 (C=C). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.71–1.93 m (4H, CH_2), 2.03 s (3H, CH_3), 2.87 t (2H, NCH_2), 3.58 s (2H, NCH_2), 3.89 t (2H, OCH_2). Mass spectrum, *m*/*z* (I_{rel}, %): 168.53 (100) $[M + H]^+$. Found, %: C 64.75; H 7.63; N 8.21. $C_9H_{13}NO_2$. Calculated, %: C 64.67; H 7.78; N 8.38. *M* 167.48.

6-Methylsulfonyl-2,3,4,5,6,7-hexahydrofuro-[2,3-*c*]pyridine (XV) was synthesized according to [17]. Yield 95%. IR spectrum, ν, cm^{-1}: 1648 (C=C); 1322, 1178 (SO_2). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.74–1.98 m (4H, CH_2), 2.89 t (2H, NCH_2), 3.01 s (3H, SO_2CH_3), 3.61 s (2H, NCH_2), 3.98 t (2H, OCH_2). Mass spectrum, *m*/*z* (I_{rel}, %): 204.26 (100) $[M + H]^+$. Found, %: C 47.43; H 6.52; N 7.04. $C_8H_{13}NO_3S$. Calculated, %: C 47.29; H 6.40; N 6.90. *M* 203.56.

6-Benzyl-2,3,4,5,6,7-hexahydrofuro[2,3-*c*]pyridine (XVI) was synthesized according to [16]. Yield 76%. IR spectrum: ν 1638 cm^{-1} (C=C). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.64–1.92 m (4H, CH_2), 2.68 m (2H, NCH_2), 3.54–3.63 m (4H, NCH_2, CH_2Ph), 3.95 t (2H, OCH_2), 7.18–7.32 m (5H, Ph). Mass spectrum, *m*/*z* (I_{rel}, %): 216.31 (100) $[M + H]^+$. Found, %: C 76.83; H 7.98; N 6.34. $C_{14}H_{17}NO$. Calculated, %: C 78.14; H 7.91; N 6.51. *M* 215.42.

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