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1,6-Dihydro-3(2*H*)-pyridinones. I. Facile Synthesis of *N*-Substituted 1,6-Dihydro-3(2*H*)-pyridinones[1)]

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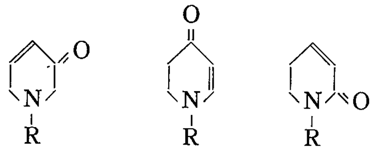
The first synthesis of the *N*-substituted 1,6-dihydro-3(2*H*)-pyridinones (**4** and **16**) is described. 1-Benzyl-1,2,3,6-tetrahydropyridine (**9**) was treated with ethyl chloroformate to give the urethane (**6**), which was oxidized to the epoxide (**10**) with perbenzoic acid. Regioselective hydrobromination of **10** afforded the 4-bromo-3-hydroxypiperidine (**11**). Acetylation of **11** followed by dehydrobromination with DBU yielded the 5-acetoxy-Δ^3-piperideine (**13**), which was hydrolyzed to the alcohol (**15**). Basic hydrolysis of **15** and subsequent condensation with methanesulfonyl chloride gave the sulfonamide analogue (**22**). The allylic alcohols (**15** and **22**) were oxidized to give the 1,6-dihydro-3(2*H*)-pyridinones (**4** and **16**), respectively.

Keywords——dihydropyridinone; α,β-unsaturated ketone; synthon; regioselective bond cleavage of oxirane; hydrolysis of urethane; tetrahydropyridine

There are many kinds of alkaloids possessing piperidine rings with a variety of substituents at any position of the ring, *e.g.* some indole alkaloids, monoterpene alkaloids, and simple piperidine alkaloids. In order to synthesize these alkaloids, it would be of great value to develop general methods for the formation of new carbon–carbon bonds from simple piperidine compounds. Of three isomeric dihydropyridinones (**1**, **2**, and **3**) bearing an enone structure, the *N*-protected 1,6-dihydro-3(2*H*)-pyridinone (**1**), which consists of the simplest azacyclic enone structure lacking conjugation with the ring nitrogen atom, is an attractive synthon for these alkaloids because of its potential for new carbon–carbon bond formations at any desired position of the ring. Although a few reports on C_5-substituted 1,6-dihydro-3-(2*H*)-pyridinones have appeared,[2)] the *C*-unsubstituted 1,6-dihydro-3(2*H*)-pyridinone (**1**) has not so far been described in the literature.[3)]

As an approach to systematic studies on many kinds of alkaloid syntheses using 1,6-dihydro-3(2*H*)-pyridinones as a common synthon, we first wish to report herein the efficient synthesis of *N*-substituted 1,6-dihydro-3(2*H*)-pyridinones from easily available starting materials using a sequence of simple operations.



1 **2** **3**

Chart 1

Synthesis of Ethyl 1,6-Dihydro-3(2*H*)-pyridinone-1-carboxylate (4)

Recently, Berti and his co-workers found that 3,4-epoxytetrahydropyran undergoes a highly regioselective hydrobromination to give 4-bromo-3-hydroxytetrahydropyran along with its regioisomer in a ratio of 92:8 upon treatment with hydrobromic acid owing to the inductive effect of the ring oxygen atom.[4)] A modification of this method seems to be applicable to the piperidine system.

1,2,3,6-Tetrahydropyridine (**5**) was treated with ethyl chloroformate in water in the presence of potassium carbonate to give the urethane (**6**)[5)] in quantitative yield; this product was also obtained by the following two alternative methods. The tosylhydrazone (**7**), prepared in a usual manner from ethyl 4-oxopiperidine-1-carboxylate (**8**),[6] was treated with potassium *tert*-butoxide in refluxing xylene to afford **6** in 57% yield. On the other hand, the most inexpensive method is the route from 1-benzyl-1,2,3,6-tetrahydropyridine (**9**),[7] which was obtained by the sodium borohydride reduction of 1-benzylpyridinium chloride. Treatment of **9** with a small excess of ethyl chloroformate in boiling benzene for 2 h afforded **6** contaminated with a small amount of benzyl chloride. Removal of the impurity was easily achieved in the next step.

Epoxidation of **6** with perbenzoic acid in chloroform at room temperature yielded quantitatively the epoxide (**10**), which was reacted with 47% hydrobromic acid in chloroform at −50°C. A highly regioselective cleavage of the C_4–O bond of the oxirane ring occurred to give the desired product (**11**) as a sole detectable isomer. The stereochemistry of **11** was confirmed by the fact that the treatment of **11** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) afforded **10** exclusively. The acetate (**12**), obtained from **11** by acetylation in a usual way,

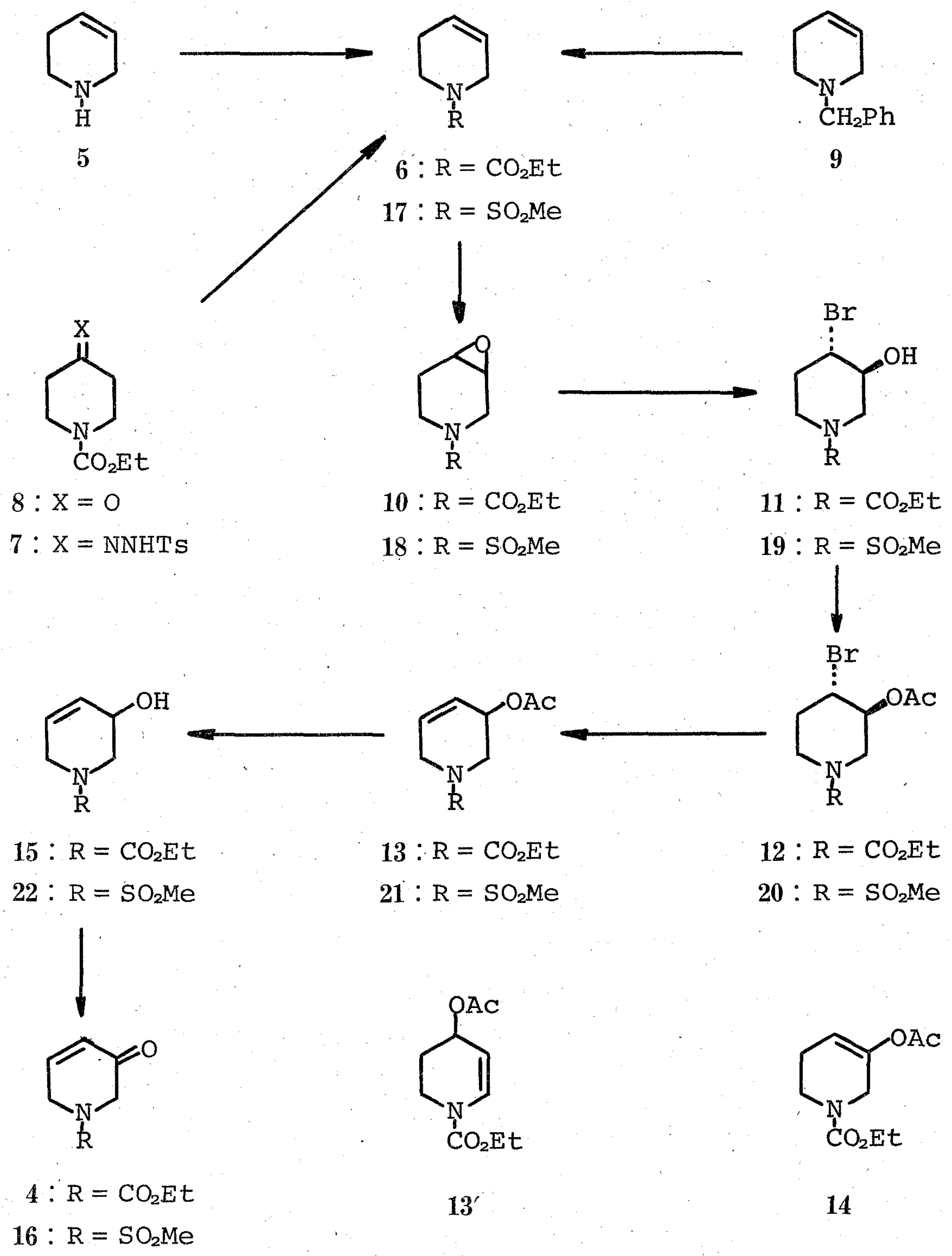


Chart 2

was dehydrobrominated with DBU to give the allylic acetate (**13**) in 83% yield.[8] None of the enol acetate (**14**) was formed because of the *cis* relationship between the C_4–Br and C_3–H. The proton nuclear magnetic resonance (^{1}H-NMR) spectrum of **13** exhibited a two-proton signal in the region of 5.63—6.08 ppm due to the C_4- and C_5-protons and no signals due to ring protons in the region above 3.2 ppm, indicating that the structure was as depicted in **13** rather than **13′**. Thus, the regioselectivity in the reaction of **10** with the acid was finally confirmed. Mild hydrolysis of **13** with sodium hydroxide in ethanol under ice cooling gave the allylic alcohol (**15**) in 72% overall yield from the tetrahydropyridine or 42% yield from 1-benzyl-1,2,3,6-tetrahydropyridine.[9] Finally, oxidation of **15** with the Jones reagent in acetone under ice cooling furnished the dihydropyridinone (**4**) in 87% yield. Its infrared (IR) spectrum showed a carbonyl band at 1690 cm^{-1} and a carbon-carbon double bond band at 1630 cm^{-1}, and the ^{1}H-NMR spectrum exhibited a singlet at 4.17 ppm due to the C_2-protons, a doublet of doublets at 4.30 ppm ($J=3$, 2.5 Hz) due to the C_6-protons, and two doublets of triplets at 6.20 ($J=10.5$, 2.5 Hz) and 7.03 ppm ($J=10.5$, 3 Hz) due to the C_4- and C_5-protons, respectively. The ultraviolet (UV) spectrum showed an absorption maximum at 218 nm (log $\varepsilon=3.96$) characteristic of an α,β-unsaturated ketone chromophore. On standing at room temperature, **4** decomposed slowly (almost complete decomposition within a week), while the allylic alcohol (**15**) remained unchanged after standing in a refrigerator for three months.

Synthesis of 1-Methanesulfonyl-1,6-dihydro-3(2*H*)-pyridinone (16)

The 1-methanesulfonyl analogue (**16**) was also synthesized (Chart 2) according to the above method for the preparation of **4**. Namely, reaction of **5** with 3 equivalents of methanesulfonyl chloride in dichloromethane–water in the presence of potassium carbonate gave the sulfonamide (**17**), mp 63—64°C, in 90% yield, and this was oxidized with perbenzoic acid to yield the epoxide (**18**), mp 78—79°C, in 97% yield. On treatment with 47% hydrobromic acid, **18** gave the sole product (**19**), mp 125—126°C, in 76% yield, and this was acetylated with acetic anhydride in pyridine for 1 h to afford **20** (88% yield, mp 96—97°C). On dehydrobromination followed by hydrolysis **20** gave the allylic alcohol (**22**), mp 57—58°C, in 71% yield. Oxidation of **22** with the Jones oxidant afforded 1-methanesulfonyl-1,6-dihydro-3(2*H*)-pyridinone (**16**), mp 70—71°C, in 75% yield. This route for the preparation of **16**, however, was found to be unsuitable for large-scale operation (more than 10 g) because of the low solubility of this series of compound in the solvents used in operations. For large-scale synthesis, the next route is preferable.

The urethane (**15**) was treated with potassium hydroxide in boiling aqueous ethanol for 12 h and then with methanesulfonyl chloride in dichloromethane to afford the sulfonamide (**22**) in 71% yield. The title compound (**16**) was also obtained from the *N*-ethoxycarbonyl analogue (**4**) in an another reaction sequence. Ketalization of **4** with ethylene glycol in a usual manner gave the ketal (**24**) in 60% yield. The position of the double bond was confirmed by the ^{1}H-NMR spectrum, which exhibited two olefinic proton signals at 5.58 (doublet of triplets, $J=10$, 1.5 Hz) and 5.85 ppm (doublet of triplets, $J=10$, 2 Hz). On reaction with

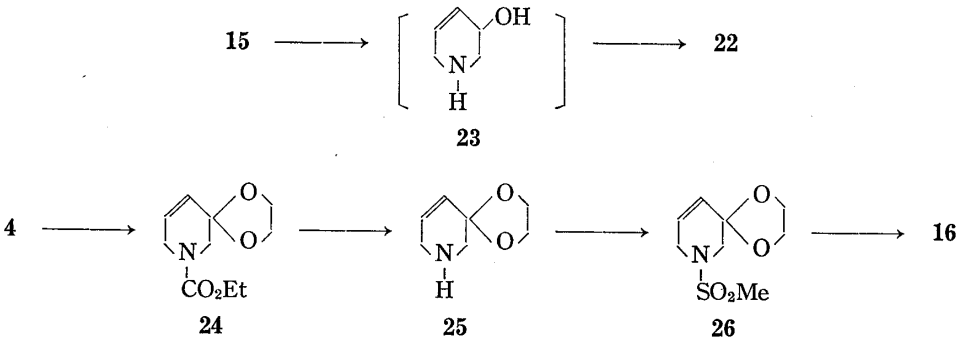


Chart 3

potassium hydroxide in boiling aqueous ethanol **24** afforded the amine (**25**) in 95% yield, and this was condensed with methanesulfonyl chloride to yield **26**, mp 111—112°C, in 68% yield. Finally, acidic hydrolysis of **26** furnished **16** in 69% yield. The last two methods for **16** might well be applicable to the preparations of other *N*-substituted 1,6-dihydro-3(2*H*)-pyridinones.

Thus, the first synthesis of *N*-substituted 1,6-dihydro-3(2*H*)-pyridinones has been achieved, and by an efficient method. Various alkaloid syntheses using the dihydropyridinones as common synthons are in progress.

Experimental

All boiling points and melting points are uncorrected. IR spectra were measured with a Hitachi IR-G and a JASCO A-102 spectrometer. Mass spectra (MS) were taken with a Hitachi M-80 mass spectrometer (direct inlet, at 70 eV). ^{1}H-NMR spectra were recorded with a JEOL PMX-60 and FX-100 spectrometer using tetramethylsilane as an internal standard. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets. All organic extracts were dried over anhydrous sodium sulfate. Column chromatography was carried out with Kieselgel 60 (70—230 mesh, Merck) and Aluminiumoxid 90 (Aktivitätsstufe II–III, 70—230 mesh, Merck).

Ethyl 1,2,3,6-Tetrahydropyridine-1-carboxylate (6)——a) From 1,2,3,6-Tetrahydropyridine (**5**): Ethyl chloroformate (15 ml) was added dropwise to a stirred solution of **5** (9.6 g) in water (20 ml) under ice cooling. Immediately, a solution of K_2CO_3 (18 g) in water (20 ml) was added to the above mixture, and stirring was continued for 30 min, then the reaction mixture was extracted with ether (50 ml × 3). The extracts were washed with brine, dried, and concentrated to give 18.8 g (quantitative yield) of **6** as a colorless oil, which was used for the next step without further purification. The sample for spectroscopy was obtained by distillation under reduced pressure, bp 120—125°C (25 mmHg) [lit.[8] bp 93°C (12 mmHg)]. IR $\nu_{\max}^{\mathrm{CHCl_3}}$ cm^{-1}: 1685 (CO), 1665 (C=C). ^{1}H-NMR (CCl_4) δ: 1.25 (3H, t, $J=7$ Hz, $OCH_2C\underline{H}_3$), 1.95—2.30 (2H, m, C_5–H), 3.48 (2H, t, $J=6$ Hz, C_6–H), 3.81—4.00 (2H, m, C_2–H), 4.08 (2H, q, $J=7$ Hz, $OC\underline{H}_2CH_3$), 5.45—6.00 (2H, m, C_3– and C_4–H).

b) From Ethyl 4-Oxopiperidine-1-carboxylate (**8**): A mixture of **8**[6] (5.2 g), *p*-toluenesulfonylhydrazine (6.2 g), and abs. EtOH (50 ml) was stirred at room temperature for 15 min, then allowed to stand for 3 h. The precipitate formed was collected by filtration and recrystallized from isopropyl ether to give the tosylhydrazone (**7**) (9.5 g; 92%) as colorless needles, mp 149—151°C. IR $\nu_{\max}^{\mathrm{KCl}}$ cm^{-1}: 3250 (NH), 1685 (CO). *Anal.* Calcd for $C_{15}H_{21}N_3O_4S$: C, 53.09; H, 6.24; N, 12.38. Found: C, 53.06; H, 6.23; N, 12.43. A solution of **7** (6.0 g) in dry xylene (10 ml) was added to a stirred solution of *tert*-BuOK, prepared from potassium (0.76 g) and *tert*-BuOH, in dry xylene (140 ml) all at once, and the resulting mixture was heated under reflux for 6 h. The cooled mixture was filtered and the solid was washed with C_6H_6. The combined organic solution was concentrated *in vacuo* and the residue was distilled under reduced pressure to give 1.6 g (57%) of **6**, bp 120—122°C (25 mmHg).

Ethyl 3,4-Epoxypiperidine-1-carboxylate (10)——a) From Pure Ethyl 1,2,3,6-Tetrahydropyridine-1-carboxylate (**6**): A mixture of the olefin (**6**; 18.8 g), perbenzoic acid (prepared from 50 g of benzoyl peroxide according to the method in the literature[10]), and $CHCl_3$ (300 ml) was allowed to stand overnight at room temperature. The mixture was washed with sat. $NaHCO_3$ containing $Na_2S_2O_3$ and brine. The dried extract was concentrated and the residue was distilled to afford 19.7 g (quantitative yield) of **10** as a colorless oil, bp 120—123°C (7 mmHg). IR $\nu_{\max}^{\mathrm{film}}$ cm^{-1}: 1695 (CO). ^{1}H-NMR ($CDCl_3$) δ: 1.24 (3H, t, $J=7$ Hz, $OCH_2C\underline{H}_3$), 1.84—2.20 (2H, m, C_5–H), 3.00—3.66 (4H, m, C_3–, C_4– and C_6–H), 3.70—3.90 (2H, m, C_2–H), 4.12 (2H, q, $J=7$ Hz, $OC\underline{H}_2CH_3$). *Anal.* Calcd for $C_8H_{13}NO_3$: C, 56.12, H, 7.65; N, 8.18. Found: C, 56.45; H, 7.66; N, 8.02.

b) From 1-Benzyl-1,2,3,6-tetrahydropyridine (**9**): A solution of $ClCO_2Et$ (80 ml) in C_6H_6 (100 ml) was added over a period of 30 min to a stirred solution of the tetrahydropyridine (**9**; 115 g), prepared from pyridine (86 g) according to the literature,[7] in C_6H_6 (300 ml). The resulting mixture was heated under reflux in a stream of N_2 for 1 h, then washed with water, and dried. Evaporation of the solvent followed by distillation of the residue afforded 80 g of **6** contaminated with benzyl chloride, bp 105—120°C (30 mmHg). The product was treated with perbenzoic acid (prepared from 150 g of benzoyl peroxide) in the same manner as described above. Work-up as usual gave 66 g (58% from **9**; 38% from pyridine) of pure **10**, bp 102—105°C (1.7 mmHg).

Ethyl 4-Bromo-3-hydroxypiperidine-1-carboxylate (11)——Aqueous HBr (47%; 100 ml) was added dropwise to a vigorously stirred solution of **10** (19.7 g) in $CHCl_3$ (200 ml) at -50—-60°C over a period of 30 min and stirring was continued at the same temperature for another 2 h. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (100 ml). The combined organic layers were washed with sat. $NaHCO_3$ and brine, and dried. Evaporation of the solvent left 30.5 g (quantitative yield) of the crude bromohydrin (**11**), which was used for the next step without further purification. An analytical sample was obtained by distillation under reduced pressure, bp 132—133°C (0.9 mmHg). IR $\nu_{\max}^{\text{film}}$ cm^{-1}: 3350 (OH), 1675 (CO). *Anal.* Calcd for $C_8H_{14}BrNO_3$: C, 38.11; H, 5.60; N, 5.56. Found: C, 37.98; H, 5.55; N, 5.23.

Treatment of 11 with DBU——A mixture of **11** (55 mg), DBU (0.10 ml), and toluene (1.5 ml) was heated under reflux for 1 h. The reaction mixture was diluted with toluene (2 ml) and washed with 0.5 N HCl and water. The dried solution was concentrated to leave 29 mg (78%) of a colorless oil, which was indistinguishable from authentic **10** by means of IR spectral comparison.

Ethyl 3-Acetoxy-4-bromopiperidine-1-carboxylate (**12**)——A mixture of the alcohol (**11**; 30.5 g), acetic anhydride (33 ml), and dry pyridine (54 ml) was allowed to stand overnight at room temperature and then the solvent was removed *in vacuo*. The residue was diluted with water and made alkaline with K_2CO_3. Extraction of the resulting mixture with $CHCl_3$ (100 ml × 3) was followed by washing of the extract with water and drying. Evaporation of the solvent gave 31.2 g (96%) of **12** as a colorless oil, which was used for the next step without further purification. An analytical sample was prepared by distillation of the crude product under reduced pressure, bp 129—130°C (0.9 mmHg). IR $\nu_{\max}^{\text{film}}$ cm^{-1}: 1740, 1695 (CO). ^{1}H-NMR ($CDCl_3$) δ: 2.04 (3H, s, $COCH_3$). *Anal.* Calcd for $C_{10}H_{16}BrNO_4$: C, 40.83; H, 5.48; N, 4.76. Found: C, 40.81; H, 5.39; N, 4.58.

Ethyl 3-Acetoxy-1,2,3,6-tetrahydropyridine-1-carboxylate (**13**)——A mixture of **12** (31.2 g) and DBU (30 g) was stirred at 90°C for 2 h. After cooling, the mixture was diluted with C_6H_6 (250 ml) and the resulting precipitate was filtered off. The filtrate was washed with dil. HCl and water, and dried. Evaporation of the solvent gave an oily residue, which was distilled under reduced pressure to afford 17.5 g (72%) of **13** as a colorless oil, bp 115—118°C (0.8 mmHg). IR $\nu_{\max}^{\text{film}}$ cm^{-1}: 1740, 1705 (CO), 1655 (C=C). ^{1}H-NMR ($CDCl_3$) δ: 1.27 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 2.04 (3H, s, $COCH_3$), 3.40—4.10 (4H, m, C_2– and C_6–H), 4.18 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 5.09—5.30 (1H, m, C_3–H), 5.63—6.08 (2H, m, C_4– and C_5–H). *Anal.* Calcd for $C_{10}H_{15}NO_4$: C, 56.32; H, 7.09; N, 6.57. Found: C, 55.76; H, 7.07; N, 6.70.

Ethyl 3-Hydroxy-1,2,3,6-tetrahydropyridine-1-carboxylate (**15**)——An alcoholic NaOH solution (0.2 N; 100 ml) was added over a period of 1 h to a stirred solution of **13** (17.5 g) in EtOH (50 ml) under ice cooling. The resulting mixture was neutralized with AcOH, concentrated *in vacuo*, and extracted with $CHCl_3$ (150 ml). After washing and drying of the extract, evaporation of the solvent gave 14.2 g (quantitative yield) of **15** as a colorless viscous oil. IR $\nu_{\max}^{\text{film}}$ cm^{-1}: 3350 (OH), 1675 (CO), 1655 (C=C). ^{1}H-NMR ($CDCl_3$) δ: 1.23 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 2.10 (1H, b, disappeared with D_2O, OH), 3.50—3.72 (2H, m, C_2–H), 3.80—3.95 (2H, m, C_6–H), 4.12 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 4.00—4.20 (1H, m, C_3–H), 5.73 (2H, m, C_4– and C_5–H). High resolution MS *m/e*: Calcd for $C_8H_{13}NO_3$: 171.0894. Found: 171.0886.

Ethyl 1,6-Dihydro-3(2*H*)-pyridinone-1-carboxylate (**4**)——The Jones oxidant[11] (8 N; 2.2 ml) was added dropwise to a stirred solution of **15** (1.0 g) in purified acetone (10 ml) over a period of 25 min under ice cooling. After decomposition of the excess oxidant by addition of MeOH, the mixture was diluted with water and extracted with $CHCl_3$ (20 ml × 3). The extracts were washed with brine, dried, and concentrated at room temperature *in vacuo* to afford 850 mg (87%) of **4** as a colorless oil. IR $\nu_{\max}^{\text{film}}$ cm^{-1}: 1690 (CO), 1630 (C=C). ^{1}H-NMR ($CDCl_3$) δ: 1.30 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 4.17 (2H, s, C_2–H), 4.21 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 4.30 (2H, dd, J=3, 2.5 Hz, C_6–H), 6.20 (1H, dt, J=10.5, 2.5 Hz, C_4–H), 7.03 (1H, dt, J=10.5, 3 Hz, C_5–H). MS *m/e* 169 (M^+, 9%), 140 (11%), 68 (100%), 29 (18%). UV $\lambda_{\max}^{\text{EtOH}}$ nm (log ε): 218 (3.96). The semicarbazone: mp 209—210°C (EtOH). *Anal.* Calcd for $C_9H_{14}N_4O_3$: C, 47.73; H, 6.24; N, 24.77. Found: C, 47.54; H, 6.41; N, 24.73.

1-Methanesulfonyl-1,2,3,6-tetrahydropyridine (**17**)——Methanesulfonyl chloride (3.0 ml) and a solution of K_2CO_3 (3.6 g) in water (5 ml) were added successively to a stirred solution of 1,2,3,6-tetrahydropyridine (**5**; 1.02 g) in CH_2Cl_2 (10 ml). Vigorous stirring was continued at room temperature for 9 h. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (15 ml × 2). The combined organic layers were washed with brine, dried, and concentrated to leave a solid, which was recrystallized from ethanol to afford 1.8 g (90%) of **17** as colorless plates, mp 63—64°C. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1650 (C=C), 1310, 1145 (SO_2). ^{1}H-NMR ($CDCl_3$) δ: 2.26 (2H, m, C_3–H), 2.77 (3H, s, SCH_3), 3.33 (2H, t, J=6 Hz, C_2–H), 3.72 (2H, m, C_6–H), 5.70 (2H, m, C_4– and C_5–H). *Anal.* Calcd for $C_6H_{11}NO_2S$: C, 44.71; H, 6.88; N, 8.69. Found: C, 44.59; H, 6.93; N, 8.57.

3,4-Epoxy-1-methanesulfonylpiperidine (**18**)——A mixture of **17** (1.12 g), *m*-chloroperbenzoic acid (80%; 2.0 g), and $CHCl_3$ (20 ml) was allowed to stand at room temperature overnight. Work-up as usual afforded a crude product, which was recrystallized from ethanol to give 1.2 g (97%) of **18** as colorless leaflets, mp 78—79°C. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1315, 1160 (SO_2). ^{1}H-NMR ($CDCl_3$) δ: 2.10 (2H, dt, J=6, 1.5 Hz, C_5–H), 2.79 (3H, s, SCH_3). *Anal.* Calcd for $C_6H_{11}NO_3S$: C, 40.68; H, 6.26; N, 7.91. Found: C, 40.81; H, 6.13; N, 7.99.

4-Bromo-1-methanesulfonylpiperidin-3-ol (**19**)——Aqueous HBr (47%; 20 ml) was added dropwise to a stirred solution of **18** (1.2 g) in $CHCl_3$ (150 ml) at −60°C over a period of 10 min, and vigorous stirring was continued at the same temperature for another 2 h. Work-up as usual afforded a crystalline residue, which was recrystallized from $CHCl_3$ to give 1.3 g (76%) of **19** as colorless needles, mp 125—126°C. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3450 (OH), 1320, 1135 (SO_2). ^{1}H-NMR (DMSO-d_6) δ: 2.87 (3H, s, SCH_3). *Anal.* Calcd for $C_6H_{12}BrNO_3S$: C, 27.92; H, 4.69; N, 5.43. Found: C, 27.92; H, 4.63; N, 5.69.

3-Acetoxy-4-bromo-1-methanesulfonylpiperidine (**20**)——A mixture of **19** (1.1 g), acetic anhydride

(1.0 ml), and dry pyridine (2 ml) was allowed to stand at room temperature for 1 h. Work-up as usual afforded a crystalline residue, which was recrystallized from ethanol to give 1.1 g (88%) of **20** as colorless plates, mp 96—97°C. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1730 (CO), 1325, 1150 (SO_2). ^{1}H-NMR ($CDCl_3$) δ: 2.10 (3H, s, $COCH_3$), 2.80 (3H, s, SCH_3). *Anal.* Calcd for $C_8H_{14}BrNO_4S$: C, 32.01; H, 4.70; N, 4.67. Found: C, 32.16; H, 4.56; N, 4.84.

3-Acetoxy-1-methanesulfonyl-1,2,3,6-tetrahydropyridine (**21**)——A mixture of **20** (0.90 g) and DBU (1.0 g) was stirred at 90°C for 4 h. Work-up as usual gave a crystalline residue, which was recrystallized from ethanol to give 0.58 g (90%) of **20** as colorless plates, mp 104—105°C. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1715 (CO), 1660 (C=C), 1320, 1150 (SO_2). ^{1}H-NMR ($CDCl_3$) δ: 2.03 (3H, s, $COCH_3$), 2.87 (3H, s, SCH_3), 3.50 (2H, t, J=4 Hz, C_2–H), 3.78 (2H, m, C_6–H), 5.17 (1H, m, C_3–H), 5.92 (2H, m, C_4– and C_5–H). *Anal.* Calcd for $C_8H_{13}NO_4S$: C, 43.83; H, 5.98; N, 6.39. Found: C, 44.01; H, 6.07; N, 6.42.

1-Methanesulfonyl-1,2,3,6-tetrahydropyridin-3-ol (**22**)——a) From Ethyl 3-Hydroxy-1,2,3,6-tetrahydropyridine-1-carboxylate (**15**): A mixture of **15** (5.0 g), 5 N KOH solution (20 ml), and ethanol (20 ml) was heated under reflux for 19 h. After removal of ethanol *in vacuo*, a solution of methanesulfonyl chloride (5.0 g) in CH_2Cl_2 (10 ml) was added to the resulting aqueous solution and the whole was stirred at room temperature for 5 h. The CH_2Cl_2 layer was separated and the aqueous layer was extracted thoroughly with $CHCl_3$. The combined organic layers were washed with brine and dried. Evaporation of the solvent afforded an oily residue, which was chromatographed on silica gel with $CHCl_3$ to give 4.1 g (79%) of **22** as a colorless oil. On standing at room temperature, **22** solidified and recrystallization from ether afforded colorless plates, mp 57—58°C. IR $\nu_{\max}^{\text{film}}$ cm^{-1}: 3470 (OH), 1325, 1155 (SO_2). ^{1}H-NMR ($CDCl_3$) δ: 2.85 (3H, s, SCH_3), 3.33 (2H, d, J=4 Hz, C_2–H), 3.73 (2H, m, C_6–H), 4.20 (1H, m, C_3–H), 5.82 (2H, m, C_4– and C_5–H). *Anal.* Calcd for $C_6H_{11}NO_3S$: C, 40.68; H, 6.26; N, 7.91. Found: C, 40.42; H, 6.04; N, 7.85.

b) From 3-Acetoxy-1-methanesulfonyl-1,2,3,6-tetrahydropyridine (**21**): An alcoholic NaOH solution (0.2 N; 3 ml) was added dropwise to a stirred suspension of **21** (430 mg) in ethanol (10 ml) under ice cooling. The resulting mixture was further stirred for 1 h and neutralized with AcOH. Removal of ethanol *in vacuo* followed by extraction of the residue with $CHCl_3$ (20 ml × 2) and work-up as usual afforded an oily residue, which was chromatographed on silica gel with $CHCl_3$ to give 258 mg (71%) of **22** as an oil.

Ethyl 1,4-Dioxa-7-azaspiro[4.5]dec-9-ene-7-carboxylate (**24**)——A mixture of the dihydropyridinone (**4**; 1.05 g), ethylene glycol (1.0 ml), *p*-TsOH (20 mg), and C_6H_6 (40 ml) was heated under reflux for 2 h while water was azeotropically removed with a Dean-Stark apparatus. The cooled mixture was washed with sat. $NaHCO_3$ and water, and dried. Evaporation of the solvent left an oily residue, which was chromatographed on alumina with an 1 : 1 mixture of $CHCl_3$ and C_6H_6 to give 790 mg (60%) of **24** as a colorless oil. IR $\nu_{\max}^{\text{CHCl}_3}$ cm^{-1}: 1685 (CO), 1655 (C=C). ^{1}H-NMR ($CDCl_3$) δ: 1.31 (3H, t, J=7 Hz, $OCH_2\underline{CH_3}$), 3.49 (2H, s, C_6–H), 3.94 (4H, s, C_2– and C_3–H), 4.10 (2H, q, J=7 Hz, $O\underline{CH_2}CH_3$), 5.58 (1H, dt, J=10, 1.5 Hz, C_{10}–H), 5.85 (1H, dt, J=10, 2 Hz, C_9–H).

1,4-Dioxa-7-azaspiro[4.5]dec-9-ene (**25**)——A mixture of **24** (870 mg), KOH (1.4 g), water (5 ml), and ethanol (10 ml) was heated under reflux for 11 h. After removal of ethanol *in vacuo* the residue was extracted with $CHCl_3$ (20 ml × 4). Concentration of the dried extract gave an oily residue, which was chromatographed on alumina with $CHCl_3$ to afford 550 mg (95%) of the amine (**25**) as a colorless oil. IR $\nu_{\max}^{\text{CHCl}_3}$ cm^{-1}: 3320 (NH), 1638 (C=C). ^{1}H-NMR ($CDCl_3$) δ: 2.85 (2H, s, C_6–H), 3.21 (2H, dd, J=2.5, 2 Hz, C_8–H), 3.90 (4H, s, C_2– and C_3–H), 3.93 (1H, s, NH), 5.62 (1H, br d, J=10 Hz, C_{10}–H), 5.92 (1H, dt, J=10, 2.5 Hz, C_9–H). The picrate of **24**: mp 171°C (dec.) (isopropyl ether–methanol). *Anal.* Calcd for $C_7H_{11}NO_2 \cdot C_6H_3N_3O_7$: C, 42.17; H, 3.81; N, 15.13. Found: C, 42.16; H, 3.67; N, 15.27.

7-Methanesulfonyl-1,4-dioxa-7-azaspiro[4.5]dec-9-ene (**26**)——Methanesulfonyl chloride (0.06 ml) and a solution of K_2CO_3 (360 mg) in water (2 ml) were added successively to a stirred solution of **25** (70 mg) in CH_2Cl_2 (10 ml) under ice cooling. Stirring was continued for 30 min, then the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (10 ml × 2) and the combined organic layers were washed with brine and dried. Evaporation of the solvent gave a crystalline mass, which was recrystallized from C_6H_6 to afford 74 mg (68%) of **26** as colorless leaflets, mp 111—112°C. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1655 (C=C), 1315, 1140 (SO_2). ^{1}H-NMR ($CDCl_3$) δ: 2.90 (3H, s, SCH_3), 3.46 (2H, s, C_6–H), 3.82 (2H, t, J=2 Hz, C_8–H), 3.96 (4H, s, C_2– and C_3–H), 5.60 (1H, dt, J=10, 2 Hz, C_{10}–H), 5.98 (1H, dt, J=10, 2 Hz, C_9–H). *Anal.* Calcd for $C_8H_{13}NO_4S$: C, 43.83; H, 5.98; N, 6.36. Found: C, 43.82; H, 6.05; N, 6.45.

1-Methanesulfonyl-1,6-dihydro-3(2*H*)-pyridinone (**16**)——a) From **22**: The Jones oxidant (8 N; 0.6 ml) was added dropwise to a stirred solution of **22** (223 mg) in purified acetone (5 ml) over a period of 30 min under ice cooling. Work-up as usual and recrystallization of the crude product gave 165 mg (75%) of **16** as colorless plates, mp 70—71°C. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1667 (CO), 1318, 1150 (SO_2). ^{1}H-NMR ($CDCl_3$) δ: 2.80 (3H, s, SCH_3), 3.92 (2H, s, C_2–H), 4.08 (2H, t, J=2 Hz, C_6–H), 6.10 (1H, dt, J=11, 2 Hz, C_4–H), 6.93 (1H, dt, J=11, 2 Hz, C_5–H). *Anal.* Calcd for $C_6H_9NO_3S$: C, 41.14; H, 5.18; N, 8.00. Found: C, 41.29; H, 5.09; N, 8.02.

b) From **26**: A mixture of **26** (60 mg), 10% HCl (2 ml), and acetone (2 ml) was stirred at room temperature for 2 h. After removal of acetone *in vacuo*, the residue was extracted with $CHCl_3$ (10 ml × 2) and the extract was washed with sat. $NaHCO_3$ and brine. The dried extract was concentrated and the crude product was recrystallized from C_6H_6 to afford 33 mg (69%) of **16**, which was found to be identical with the sample obtained from **22** by means of ^{1}H-NMR spectral comparison.

References and Notes

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