

Synthesis of the 1,8-Diazaspiro[4.5]decane System

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Several years ago we described the preparation of 1-veratrylcarbonyl-1-azaspiro[4.5]decane (**2**) by the acid-catalyzed spiroamidation of *N*-[3-(1-cyclohexen-1-yl)propyl]-2-(3,4-dimethoxyphenyl)acetamide (**1**) (2). We have utilized this process for the synthesis of the hitherto unreported 1,8-diazaspiro[4.5]decane system, which is the subject of this Note.

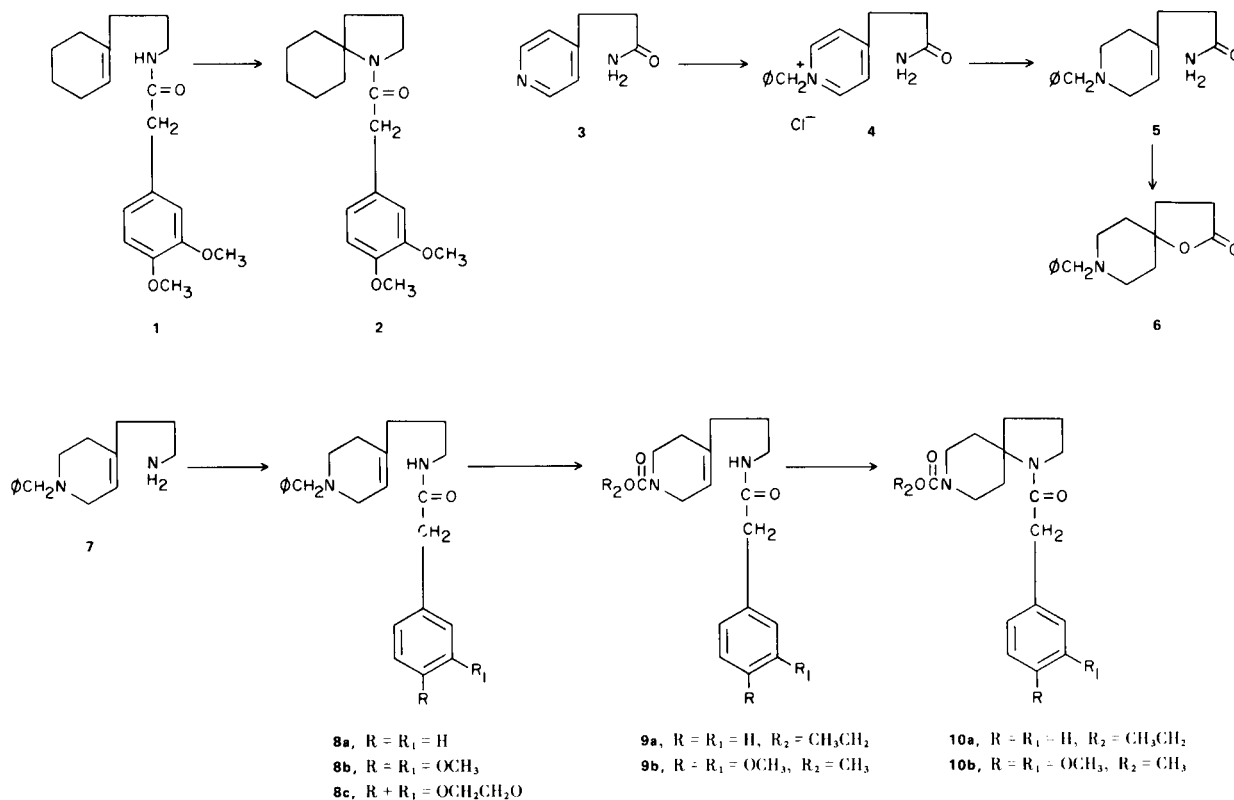
Treatment of 4-(2-carbamoyl-ethyl)pyridine (**3**) with benzyl chloride gave quaternary salt **4** which was reduced with sodium borohydride to tetrahydropyridine **5** (4). Reduction of **5** with lithium aluminum hydride afforded amine **7** which was converted to amides **8a**, **8b** and **8c**.

Unlike neutral amide **1**, which was cyclized readily to **2** by polyphosphoric acid at 25°, basic amides **8a**, **8b** and

8c were stable in this medium to 150°; at higher temperatures **8a**, **8b** and **8c** were converted slowly to complex mixtures according to thin-layer chromatography. Like **1**, neutral amides **9a** and **9b**, prepared by treatment of **8a** and **8b** with ethyl and methyl chloroformate (5), respectively, were cyclized smoothly to spiro[4.5]decanes **10a** and **10b**.

The spectral properties (see Experimental) of spiro[4.5]decanes **10a** and **10b** were consistent with the structures assigned to these compounds by analogy with the transformation of **1** to **2**.

Cyclization of amide **5** with polyphosphoric acid at 145° afforded 1-oxa-8-azaspiro[4.5]decane (**6**), the infrared spectrum of which exhibited an intense absorption band at 1770 cm⁻¹, characteristic of a γ -lactone (7).



EXPERIMENTAL (8)

1-Benzyl-4-(2-carbamoylethyl)pyridinium Chloride Hemihydrate (4).

A solution of 4-(2-carbamoylethyl)pyridine (3) (25 g., 0.17 mole), benzyl chloride (23 g., 0.19 mole) and acetone (1 l.) was heated under reflux for 4 days and then cooled in an ice-bath. The precipitate was collected and recrystallized from 2-propanol-anhydrous ether; yield 24 g., (49%) of pyridinium chloride hemihydrate 4, m.p. 206-207° dec.; ν max (nujol) 3350 (NH₂), 1667 (C=O) cm⁻¹; λ max 251 m μ (ϵ , 5,590); δ (deuterium oxide) 3.00 (A₂B₂, 4H, -CH₂CH₂-), 4.61 (singlet, 2H, NH₂-), 5.65 (singlet, 2H, -CH₂-), 7.31 (singlet, 5H, benzene), 7.78, 8.61 (AB, J = 6 c.p.s., 4H, pyridinium) ppm.

Anal. Calcd. for C₁₅H₁₇ClN₂O·½H₂O: C, 63.05; H, 6.35; Cl, 12.41; N, 9.80; O, 8.40. Found: C, 63.21; H, 6.49; Cl, 12.15; N, 9.90; O, 8.65.

1-Benzyl-1,2,3,6-tetrahydro-4-pyridinepropionamide (5).

Sodium borohydride (14.1 g., 0.373 mole) was added, in small portions, to a stirred solution of pyridinium chloride 4 (61.5 g., 0.223 mole) and 95% ethanol (1.2 l.), cooled in an ice-bath. After the addition was complete, the reaction mixture was stirred at 0° for 2 hours and at room temperature for 5 days. The precipitate was collected. Water was added to the filtrate and the mixture was extracted with methylene chloride. The organic extract was washed with saturated sodium chloride solution, dried (sodium sulfate), filtered and evaporated. Recrystallization of the residue from 2-propanol and from benzene gave 28 g. (52%) of tetrahydropyridine 5, m.p. 97-98°; ν max (dichloromethane) 3400, 3375 (NH₂), 1670 (C=O, C=C), 1590, 1490 (aromatic) cm⁻¹; λ max 250 m μ (ϵ , 195), 257 (220), 263 (156); δ (deuteriochloroform) 1.8-3.0 (multiplet, 10H, -CH₂-), 3.44 (singlet, 2H, ϕ CH₂-), 5.20 (broad singlet, 1H, vinyl proton), 5.9 (deuterium oxide-exchangeable broad multiplet, 2H, NH₂-), 7.05 (broad singlet, 5H, aromatic) ppm.

Anal. Calcd. for C₁₅H₂₀N₂O: C, 73.73; H, 8.25; N, 11.47; O, 6.55; mol. wt., 244. Found: C, 73.75; H, 8.43; N, 11.64. O, 6.57; mol. wt., 244 (mass spectrometry).

1-Benzyl-4-(3-aminopropyl)-1,2,3,6-tetrahydropyridine (7).

A solution of amide 5 (20 g., 0.084 mole) and tetrahydrofuran (300 ml.) was added dropwise, with stirring, to a slurry of lithium aluminum hydride (18 g., 0.045 mole) and tetrahydrofuran (150 ml.). After the addition was complete, the reaction mixture was heated under reflux for 60 hours. Water (80 ml.) was added and, after 2 hours, the solid was collected and washed with ether. The filtrate was dried (sodium sulfate) and evaporated. Distillation of the residue at 0.5 mm. gave 12.5 g. (65%) of the amine 7, b.p. 151-153°; ν max (dichloromethane) 1600 (C=C), 1590, 1500 (aromatic) cm⁻¹.

Rapid carbonation precluded satisfactory characterization of 7.

The hydrobromide of 7 had m.p. 133-135°; γ max (chloroform) 2800-3400 (NH₃), 1600, 1495 (aromatic) cm⁻¹; δ (deuterium oxide) 1.5-3.3 (multiplet, 12H, -CH₂-), 3.67 (singlet, 2H, ϕ CH₂-), 5.49 (broad singlet, 1H, vinyl proton), 7.38 (singlet, 5H, aromatic) ppm.

Anal. Calcd. for C₁₅H₂₃BrN₂: C, 57.89; H, 7.45; Br, 25.67; N, 9.00. Found: C, 58.11; H, 7.51; Br, 25.88; N, 8.90.

N-[3-(1-Benzyl-1,2,3,6-tetrahydro-4-pyridyl)propyl]phenylacetamide (8a).

A solution of amine 7 (13.8 g., 0.0591 mole), phenylacetic acid (9.0 g., 0.066 mole) and xylene (100 ml.) was heated under reflux with continuous water separation (Dean-Stark trap) for 48 hours. The reaction mixture was washed with 5% sodium hydroxide solution and 1N hydrochloric acid. The acidic extract was cooled in an ice-bath, basified with 5% sodium hydroxide solution and extracted with benzene. The organic phase was washed with saturated sodium chloride solution, dried (sodium sulfate), filtered and evaporated. Trituration of the residue with ether followed by recrystallization from ether gave 13.5 g. (66%) of amide 8a, m.p. 86-87°; ν max (dichloromethane) 3450 (NH), 1668 (C=O), 1600, 1515 (aromatic) cm⁻¹; λ max 251 m μ (ϵ , 348), 257 (383), 263 (313); δ (deuteriochloroform) 1.2-2.7 (multiplet, 12H, -CH₂-), 3.46, 3.54 (doublet, 4H, ϕ CH₂-), 5.29 (multiplet, 1H, vinyl proton), 5.95 (deuterium oxide-exchangeable broad singlet, 1H, -NH-), 7.29 (broad singlet, 10H, aromatic) ppm.

Anal. Calcd. for C₂₃H₂₈N₂O: C, 79.27; H, 8.10; N, 8.04; O, 4.59. Found: C, 79.45; H, 7.93; N, 8.02; O, 4.84.

N-[3-(1-Benzyl-1,2,3,6-tetrahydro-4-pyridyl)propyl]-3,4-dimethoxyphenylacetamide (8b).

Amide 8b was prepared by the procedure described for 8a. From amine 7 (3.90 g., 0.0169 mole), 3,4-dimethoxyphenylacetic acid (3.65 g., 0.0186 mole) and xylene (50 ml.), there was obtained 4.83 g. (70%) of amide 8b, m.p. 79-81°; ν max (dichloromethane) 3410 (NH), 1665 (C=O), 1605, 1590 (aromatic) cm⁻¹; λ max 231 m μ (ϵ , 8,300), 280 (3,060); δ (deuteriochloroform) 1.3-3.3 (multiplet, 12H, -CH₂-), 3.48, 3.55 (doublet, 4H, -COCH₂-), 3.86 (singlet, 6H, CH₃O-), 5.1-5.8 (multiplet, 2H, -NH-, vinyl proton), 6.81 (singlet, 3H, aromatic), 7.30 (singlet, 5H, aromatic) ppm.

Anal. Calcd. for C₂₅H₃₂N₂O₃: C, 73.49; H, 7.90; N, 6.86; O, 11.75. Found: C, 73.46; H, 7.97; N, 6.93; O, 11.97.

N-[3-(1-Benzyl-1,2,3,6-tetrahydro-4-pyridyl)propyl]-3,4-methylenedioxyphenylacetamide (8c).

Amide 8c was also prepared by the procedure described for 8a. From amine 7 (5.47 g., 0.0237 mole), 3,4-methylenedioxyphenylacetic acid (4.6 g., 0.026 mole) and xylene (50 ml.), there was obtained 4.3 g., (65%) of amide 8c, m.p. 86-87°; ν max (dichloromethane) 3440 (NH), 1665 (C=O), 1610, 1505 (aromatic) cm⁻¹; λ max 237 m μ (ϵ , 4,510), 287 (3,920); δ (deuteriochloroform) 1.3-3.6 (multiplet, 12H, -CH₂-), 3.44, 3.56 (doublet, 4H, ϕ CH₂-), 5.32 (multiplet, 1H, vinyl proton), 5.68 (deuterium oxide-exchangeable multiplet, 1H, -NH-), 5.97 (singlet, 2H, -OCH₂O-), 6.79 (singlet, 3H, aromatic), 7.30 (singlet, 5H, aromatic) ppm.

Anal. Calcd. for C₂₄H₂₈N₂O₃: C, 73.44; H, 7.19; N, 7.19; O, 12.23. Found: C, 73.60; H, 7.19; N, 7.24; O, 12.08.

Ethyl 1,2,3,6-Tetrahydro-4-[[3-[2-phenylacetamido]propyl]-1-pyridinecarboxylate (9a).

A mixture of amide 8a (2.5 g., 7.2 millimoles), ethyl chloroformate (3.2 g., 29.4 millimoles), potassium carbonate (3.2 g.) and methylene chloride (125 ml.) was stirred at room temperature for 24 hours. The solid was collected. The filtrate was washed with 5% sodium hydroxide solution, 1N hydrochloric acid and water, dried (sodium sulfate), filtered and evaporated. Repeated trituration of the residue with pentane afforded 1.4 g. (57%) of carbamate 9a, m.p. 43-45°; ν max (chloroform) 3450 (NH), 1690 (carbamate C=O), 1670 (amide C=O), 1605, 1518 (aromatic) cm⁻¹; δ (deuteriochloroform), 1.23 (triplet, J = 6 c.p.s., 3H, CH₃-), 1.5-2.2 (multiplet, 6H, -CH₂-), 3.53 (singlet, 2H, ϕ CH₂-),

4.13 (quartet, $J = 6$ c.p.s., 2H, $-\text{CH}_2\text{O}$), 3.0-4.0 (multiplet, 6H, $-\text{CH}_2\text{N}$), 5.29 (broad multiplet, 1H, vinyl proton), 5.83 (deuterium oxide-exchangeable broad signal, 1H, $-\text{CONH}$), 7.28 (singlet, 5H, aromatic) ppm.

Anal. Calcd. for $\text{C}_{19}\text{H}_{26}\text{N}_2\text{O}_3$: C, 69.06; H, 7.93; N, 8.48. Found: C, 68.76; H, 7.89; N, 8.15.

Methyl 1,2,3,6-Tetrahydro-4-[[3-[2-(3,4-dimethoxyphenyl)acetamido]propyl]-1-pyridinecarboxylate (**9b**).

A mixture of amide **8b** (3.5 g., 8.4 millimoles), methyl chloroformate 2.4 g., 25 millimoles), potassium carbonate (2.5 g.) and methylene chloride (125 ml.) was stirred at room temperature for 3 hours. The reaction mixture was worked-up by the procedure described for **9a**. Recrystallization from ether gave 1.9 g. (60%) of carbamate **9b**, m.p. 79-81°; ν max (chloroform) 3420 (NH), 1690 (carbamate C=O), 1665, 1690 (amide C=O), 1610, 1510 (aromatic) cm^{-1} ; λ max 232 $\text{m}\mu$ (ϵ , 6,450), 280 (2,440); δ (deuteriochloroform) 1.5-2.2 (multiplet, 6H, $-\text{CH}_2-$), 3.55 (singlet, 2H, ϕCH_2-), 3.75 (singlet, 3H, CH_3OCO), 3.92 (singlet, 6H, CH_3O), 3.2-4.1 (multiplet, 6H, $-\text{CH}_2\text{N}$), 5.34 (multiplet, 1H, vinyl proton), 5.7 (deuterium oxide-exchangeable broad signal, 1H, $-\text{CONH}$), 6.88 (singlet, 3H, aromatic) ppm.

Anal. Calcd. for $\text{C}_{20}\text{H}_{28}\text{N}_2\text{O}_5$: C, 63.81; H, 7.50; N, 7.44; O, 21.25. Found: C, 64.01; H, 7.54; N, 7.42; O, 21.08.

Ethyl 1-(Benzylcarbonyl)-1,8-diazaspiro[4.5]decanecarboxylate (**10a**).

A mixture of amide **9a** (1.00 g., 3.14 millimoles), 85% phosphoric acid (7 g.) and phosphorus pentoxide (7 g.) was stirred at room temperature for 5 days. The reaction mixture was poured onto ice-water and extracted with methylene chloride. The organic extract was washed with 5% sodium hydroxide solution, dried (sodium sulfate), filtered and evaporated. Recrystallization of the residue from cyclohexane gave 0.44 g. (44%) of 1,8-diazaspiro[4.5]decane (**10a**), m.p. 87-89°; ν max (dichloromethane) 1690 (carbamate C=O), 1645 (amide C=O) cm^{-1} ; λ max 252 (ϵ , 234), 258 (260), 264 (204); δ (deuteriochloroform) 1.23 (triplet, $J = 7$ c.p.s., 5H, CH_3 -, $-\text{CH}_2-$), 1.6-2.0 (multiplet, 4H, $-\text{CH}_2-$), 2.7-3.2 (multiplet, 4H, $-\text{CH}_2-$), 3.61 (singlet, 2H, ϕCH_2-), 3.3-3.7 (multiplet, 2H, $-\text{CH}_2-$), 7.29 (singlet, 5H, aromatic) ppm.

Anal. Calcd. for $\text{C}_{19}\text{H}_{26}\text{N}_2\text{O}_3$: C, 69.06; H, 7.93; N, 8.48. Found: C, 68.47; H, 7.79; N, 8.27.

Several constant-melting samples of **10a**, homogeneous according to thin-layer chromatography, gave consistently low (ca. 0.5%) carbon values by combustion analysis even though the hydrogen and nitrogen values fell within the accepted range.

Methyl 1-(Veratrylcarbonyl)-1,8-diazaspiro[4.5]decanecarboxylate (**10b**).

A mixture of amide **9b** (3.00 g., 7.99 millimoles), 85% phosphoric acid (21 g.) and phosphorus pentoxide (21 g.) was stirred at room temperature for 7 days. The reaction mixture was poured onto ice-water, and extracted with methylene chloride. The organic extract was washed with 5% sodium hydroxide solution, water, dried (sodium sulfate), filtered and evaporated. The residue (2.3 g.) was dissolved in benzene and placed on top of a column of silica gel (Grace, grade 923, 450 g.). Elution with ethyl acetate followed by evaporation, trituration of the residue

with cyclohexane and recrystallization from ether gave 0.41 g. (14%) of 1,8-diazaspiro[4.5]decane (**10b**), m.p. 108-109°; ν max (dichloromethane) 1710 (carbamate C=O), 1635 (amide C=O),

1590 (aromatic) cm^{-1} ; λ max 280 $\text{m}\mu$ (ϵ , 3,380); δ (deuteriochloroform), 1.1-2.0 (multiplet, 6H, $-\text{CH}_2-$), 2.5-4.2 (multiplet, 8H, $-\text{CH}_2\text{N}$), 3.59 (singlet, 2H, ϕCH_2-), 3.66 (singlet, 3H, CH_3OCO), 3.66 (singlet, 6H, CH_3O), 6.79 (singlet, 3H, aromatic) ppm.

Anal. Calcd. for $\text{C}_{20}\text{H}_{28}\text{N}_2\text{O}_5$: C, 63.81; H, 7.50; N, 7.44; O, 21.25; mol. wt., 276. Found: C, 64.02; H, 7.53; N, 7.40; O, 21.25; mol. wt., 276 (mass spectrometry).

8-Benzyl-1-oxa-8-azaspiro[4.5]decan-2-one (**6**).

A mixture of propionamide **5** (20 g., 0.082 mole), phosphorus pentoxide (140 g.) and 85% phosphoric acid (140 g.) was heated at 145°, for 24 hours under a nitrogen atmosphere. The reaction mixture was poured into saturated potassium carbonate solution and extracted with methylene chloride. The organic extract was washed with saturated sodium chloride solution, dried (sodium sulfate), filtered and evaporated. Extraction of the residual oil with pentane followed by repeated recrystallization from pentane gave 6.5 g. (32%) of lactone **6**, m.p. 63-64°; ν max (methylene chloride) 1770 (C=O) cm^{-1} ; λ max 246 $\text{m}\mu$ (ϵ , 169), 251 (181), 257 (208), 263 (153); δ (deuteriochloroform), 1.6-2.8 (multiplet, 12H, $-\text{CH}_2-$), 3.51 (singlet, 2H, ϕCH_2-), 7.30 (singlet, 5H, aromatic) ppm.

Anal. Calcd. for $\text{C}_{15}\text{H}_{19}\text{NO}_2$: C, 73.44; H, 7.81; N, 5.71; O, 13.04. Found: C, 73.49; H, 7.76; N, 5.56; O, 13.29.

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