Synthesis of Bridgehead Nitrogen Heterocycles

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Received June 11, 1979

Reductive cyclizations of N-[2-(2-pyridyl)ethyl]imides were accomplished by employing a palladium on carbon catalyst in ethanolic acetic acid as the hydrogenation medium. Reduction of the corresponding N-[2-(2-quinolyl)ethyl]imides ceased at the 1,2,3,4-tetrahydroquinolinyl stage. Controlled reduction of the tetrahydroquinolinyl imides with sodium borohydride gave amido alcohols which afforded bridgehead nitrogen heterocycles upon cyclodehydration.


Our interest in the reductive cyclization of N-[2-(3,4-dihydro-1-isoquinolyl)ethyl]succinimides (1) (2-4) to the corresponding 8,13-diazasteroids (2) prompted us to consider the application of this procedure to the preparation of other heterocyclic systems containing multiple bridgehead nitrogen atoms. Of particular interest was the replacement of the 3,4-dihydro-1-isoquinolyl moiety of 1 with either 2-pyridyl or 2-quinolyl groups as these substitutions would maintain the same geometric relationship between the heterocyclic nitrogen atom and the imide carbonyl group.

The N-[2-(2-pyridyl)ethyl]succinimide (3a) (5) required for this study was prepared by reaction of 2-(2-hydroxyethyl)pyridine and succinimide. N-[2-(2-Pyridyl)ethyl]phthalimide (3b) (6) was prepared by base catalyzed Michael addition of phthalimide to 2-vinylpyridine. Dimethoxyphthalimido derivative 3c was prepared by condensation of 4,5-dimethoxyphthalic acid (7) and 2-(2-aminoethyl)pyridine in glacial acetic acid.

The attempted reduction of 3b in absolute ethanol over platinum oxide led to the recovery of starting material, while the reduction of the hydrochloride of 3b gave the hydrochloride of 4. However, the reduction of 3a-c over 10% palladium on carbon in ethanol containing 1 equivalent of acetic acid yielded the desired heterocycles 5, 6a and 6b, respectively. Reduction of the oxime of 4-phthalimidobutan-2-one (7) under these conditions gave 8.

Preparation of a series of quinolines analogous to 3 allowed the investigation of the behavior of a secondary aromatic amine. Thus condensation of succinimide with 2(2-hydroxyethyl)quinoline (9) gave N-[2-(2-succinimido)-ethyl]quinoline (9a). Analogous 9b was prepared similarly. Hydrolysis of 9a yielded 2-(2-aminoethyl)quinoline (9d). Condensation of 9d with 4,5-dimethoxyphthalic acid afforded 9c.

Reduction of these imides in absolute ethanol over platinum oxide gave the 1,2,3,4-tetrahydro-2-quinolyl derivatives 10a-c. These imides could be reduced to the amido alcohols 11 and 12a,b by sodium borohydride, employing the procedure developed by Hubert et al., (10). Cyclization of the amido-alcohols was accomplished by heating in refluxing benzene or xylene containing
toluenesulfonic acid as a catalyst. Thus, elimination of water from 11 could be accomplished in benzene, affording 13. However, 12a and 12b required refluxing in xylene containing acid in order to cause formation of 14a and 14b, respectively.

An alternative synthesis of 13 involved the hydrolysis of succinimide 10a to diamine 10d. Condensation of 10d with β-carbethoxymethylaldehyde afforded 13.

**EXPERIMENTAL**

Melting points were observed with a Mel-Temp apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 337 spectrophotometer. Nuclear magnetic resonance spectra were obtained by using a Varian A-60A spectrometer with tetramethylsilane as internal standard. Mass spectra were recorded on an AEI MS 30 mass spectrometer. Chemical ionization spectra (CI) were obtained on a Finnigan 3100D mass spectrometer. Analyses were performed by Spang Microanalytical Laboratorics, Eagle Harbor, MI.

4,5-Dimethoxy-N-[2-(2-pyridyl)ethyl] phthalimide (3b).

To a solution of 2.44 g. (0.02 mole) of 2-(2-aminothethyl)-pyridine (Aldrich) in 100 mL of xylene was added 4.52 g. (0.02 mole) of 4,5-dimethoxyphthalic acid (9). The solution was refluxed for 4 hours under a Dean Stark trap, after which time the theoretical amount of water had collected (0.36 mL). Cooling the solution in ice afforded 5.3 g. (86%) of faintly yellow needles, m.p. 196-199°; ir (potassium bromide): 1750 and 1700 cm⁻¹; nmr (deuteriochloroform): δ 8.00-7.00 (m, 6H), 4.2-3.95 (t, 2H, J = 7 Hz), 4.00 (s, 6H) and 3.20 (t, 2H, J = 7 Hz); ms: (24 eV) m/e (relative intensity) 314 (1), 315 (1), 312 (72, m²), 221 (6), 220 (44), 208 (7), 207 (100), 106 (12), and 79 (5).

**Anal.** Caled. for C₁₄H₁₄N₂O₄: C, 65.37; H, 5.17; N, 8.97. Found: C, 65.38; H, 5.17; N, 8.95.


A solution of 1 g. (4 mmoles) of N₂[2-(2-pyridyl)ethyl]-phthalimide (3b) in 75 mL of ethanolic hydrogen chloride was hydrogenated over 50 mg of platinum oxide at an initial pressure of 55 psi for 18 hours. The solution was filtered, and the solvent was removed under reduced pressure. The white residue was recrystallized from acetone-chloroform and again from methanol-chloroform. This procedure afforded 1 g. (85%) of white solid, m.p. 242-244°, ir (potassium bromide): 1750 and 1700 cm⁻¹; ms: (70 eV) m/e 258 (m-HCl).

**Anal.** Caled. for C₁₄H₁₇NO₄Cl: C, 51.76; H, 5.60; N, 9.76. Found: C, 51.10; H, 5.60; N, 9.49.

Octahydro5H-pyrrolo[1,2-e]pyrrolo[1,2-e]pyrimidin-3(2H)one (5).

A solution of 17.4 g. (72 mmoles) of N₂[2-(2-pyridyl)ethyl]-succinimide (3a) and 8 mL of glacial acetic acid in 100 mL of ethanol was hydrogenated over 3.4 g. of 10% Pd on carbon at an initial pressure of 54 psi and a temperature of ca. 80°. Catalyst was removed by filtration and the solvent was evaporated under reduced pressure. The residue was neutralized with potassium carbonate solution and the alkaline liquid was extracted with four 50-mL portions of dichloromethanol. The combined extracts were dried (potassium carbonate) and concentrated. Distillation gave 1 g. (67%) of lactum 5, b.p. 108-110° (0.1 mm), m.p. 59.5-60.5° (hydrate); ms: (70 eV) m/e (relative intensity) 195 (9), 194 (80, m²), 193 (94), 139 (5), 138 (42), 137 (100), 112 (6), 111 (38), 110 (27), 85 (6), 84 (94), 83 (44), 69 (8), 68 (17), 56 (21), 55 (35) and 54 (15).

The hydrochloride salt of 5 had m.p. 260° dec.; ir (potassium bromide): 1700 cm⁻¹.

**Anal.** Cooled. for C₁₄H₁₇NO₄ClH₂O: C, 57.26; H, 7.86; N, 12.14; Cl, 15.36. Found: C, 56.97; H, 7.80; N, 12.02; Cl, 15.49.

2,3,4,5,6,7-Hexahydro-10,11-dimethoxy-1H-5-pyrrolo[1',2',3':4,5',6'-|isoindol-2]b(2H)one (6).

A solution of 2 g. (6.4 mmoles) of 3c in 100 mL of ethanol was hydrogenated over 1 g. of 10% Pd on carbon for 72 hours at 80° and 60 psi. The catalyst was removed by filtration and the solvent evaporated under reduced pressure. The residue solidified after rubbing with boiling ether.

This yielded 1 g. (52%) of a white solid, m.p. 158-163°. Four crystallizations from acetone gave the pure product, m.p. 177-178°; ir (potassium bromide): 1680 cm⁻¹; nmr (deuteriochloroform): δ 7.35 (s, 1H), 7.05 (s, 1H), 4.7 (s, 1H), and 3.97 (s, 6H); ms: (70 eV) m/e (relative intensity) 304 (0.3), 303 (7), 302 (45, m²), 301 (100), 285 (5), 273 (6), 220 (12), 219 (64), 192 (7), 191 (56), 190 (5), 164 (16), 137 (5), 136 (9), 110 (16), 84 (10); 82 (6), 77 (8), 55 (29), and 54 (12).

**Anal.** Cooled. for C₁₆H₁₄N₂O₄Cl: C, 67.52; H, 7.34; N, 9.27. Found: C, 67.79; H, 7.36; N, 9.31.

1,3,4,10b-Tetrahydro-2-methylpyrimido[2,1-a]isoindol-6(2H)one (8) Hydrochloride.

A solution of 2 g. (8.62 mmoles) of the oxime of 4-phthalimido-butan-2-one (7) in 50 mL of ethanol was hydrogenated over 1 g. of 10% Pd on carbon at 80° and 60 psi. Catalyst was removed by filtration and solvent was evaporated under reduced pressure. The residue was dissolved in a mixture of chloroform and ether and was treated with anhydrous hydrogen chloride. A thick syrup separated. The syrup was caused to solidify by acetone or ether and washed with dilute ethereal. A solution from a mixture of methanol, ethanol, acetone and ether afforded 1 g. (49%) of a white melting solid, m.p. 310° dec. The analytical sample was prepared by sublimation at 180°, 0.08 mm: ir (potassium...
A solution consisting of 36 g. (0.2 mole) of 2(2-hydroxyethyl)quinoline (10), 21 g. (0.2 mole) of sucinnic acid, 150 ml. of xylene and 50 ml of DMF in a flask attached to a Dean-Stark trap was refluxed for 20 hours. The reaction mixture was washed with 500 ml portions of water. The organic layer was dried (sodium carbonate). The solution was diluted with 300 ml of ether. The crystals were collected, yielding 29 g (55%) of 9a, m.p. 110-111°C. Crystallization from methanol gave hexagonal plates, m.p. 115-116°C. An analytical sample was prepared by simultaneous 90°, 1 mm Hg; ir (potassium bromide): 1775, 1700, 1410, 1160 and 840 cm⁻¹, nmr (deuteriochloroform): δ 8.23-7.19 (m, 6H), 4.02 (t, 2H, J = 7 Hz), 3.25 (t, 2H, J = 7 Hz); ms: (70 eV) m/e (relative intensity) 252 (2), 255 (18), 258 (96, m²), 253 (11), 157 (19), 156 (100), 155 (36), 154 (16), 144 (8), 143 (47), 142 (7), 130 (9), 129 (47), 128 (16), 116 (7), 115 (12), 102 (6), 50 (10), and 55 (29).

Anal. Caled. for C₁₃H₁₄N₂O₂: C, 70.84; H, 5.54; N, 11.01.
Found: C, 70.86; H, 5.63; N, 11.02.

2-(2-Aminoethyl)quinoline (9b) Dihydrochloride.

A solution of 2.54 g. (10 mmole) of 9a in 20 ml of 6N hydrochloric acid was allowed to reflux for 16 hours. The acid was removed under reduced pressure and the residue was washed thoroughly with boiling acetone in order to remove succinic acid. The residue was crystallized from methanol-ethyl acetate, affording 2.3 g. (94%) of white needles, m.p. 190°C; nmr (deuteriochloroform): δ 9.05 (d, 1H, J = 9 Hz), 8.5-7.8 (m, 3H), and 3.8 (s, 4H).

Anal. Caled. for C₁₃H₁₄N₂O₂·2HCl: C, 53.87; H, 5.76; N, 11.43; Cl, 28.92.
Found: C, 53.97; H, 6.00; N, 11.70; Cl, 28.86.

N-[2(1,2,3,4-Tetrahydro-2-quinolyl)ethyl]succinimide (10a).

A solution of 5 g. (0.02 mole) of N-[2(2-quinolyl)ethyl]succinimide (9a) in 75 ml of absolute ethanol was hydrogenated over 300 mg of platinum oxide for 18 hours at an initial pressure of 35 psi. The solution was filtered, was concentrated, and was diluted with hexane. Cooling in ice yielded 3.2 g (62%) of white plates, m.p. 107-109°C; ir (potassium bromide): 3405, 1765, 1700, 1610, 1595, 1485, 1410, 1200, 1167, 760 and 680 cm⁻¹, nmr (deuteriochloroform): δ 7.2-6.4 (m, 4H), 3.70 (t, 2H, J = 7 Hz), 2.85-2.32 (2H, J = 7 Hz), 2.65 (s, 4H), 1.92-1.32 (m, 4H), (70 eV) m/e (relative intensity) 259 (3), 258 (16, m²), 156 (9), 133 (14), 132 (100), 130 (10), 117 (12), and 77 (6).

Anal. Caled. for C₁₃H₁₄N₂O₂: C, 69.74; H, 7.02; N, 10.84.
Found: C, 69.65; H, 6.95; N, 10.78.

N-[2(1,2,3,4-Tetrahydro-2-quinolyl)ethyl]phthalimide (10b).

A solution of 3 g. (16.5 mmoles) of N-[2(2-quinolyl)ethyl]phthalimide (9b) in 200 ml of absolute ethanol was hydrogenated over 100 mg of platinum oxide at an initial pressure of 60 psi. After 24 hours the yellow solution was filtered and was concentrated to one quart of its original volume. Cooling gave 3.65 g (72%) of a yellow solid, m.p. 157-157°C. An analytical sample was prepared by two crystallizations from ethanol, m.p. 156-156°C. This compound showed a single spot, Rf = .78 in a chloroform-alumina tlc system: ir (potassium bromide): 3400, 1760, 1745, 1710, 1405 and 721 cm⁻¹; nmr (deuteriochloroform): δ 7.45 (m, 4H), 7.2-6.2 (m, 4H), 4.5-3.9 (br s, 1H, N-H), 3.9-3.6 (t, 2H), 3.5-2.9 (m, 1H), 2.9-2.6 (t, 2H), 2.25-1.1 (m, 4H); ms: (70 eV) m/e (relative intensity), 308 (5), 307 (5), 306 (22, m²), 133 (13), and 132 (100).

Anal. Caled. for C₁₃H₁₄N₂O₂: C, 74.49; H, 5.92; N, 9.15.
Found: C, 74.20; H, 6.15; N, 9.09.

4,5-Dimethoxy-N-[2(1,2,3,4-tetrahydro-2-quinolyl)ethyl]phthalimide (10c).

A solution of 0.5 g. (1.38 mmoles) of 9c in 60 ml of chloroform and 100 mg of ethanol was hydrogenated over 100 mg of platinum oxide at 60 psi and 80°C for 20 hours. The solution was cooled, was filtered, and was evaporated to dryness under a stream of nitrogen. The residue was dissolved in dichloromethane, concentrated and cooled to give 250 mg (50%) of a yellow solid, m.p. 175°C; ir (potassium bromide): 3350, 1750 and 1700 cm⁻¹; nmr (deuteriochloroform): δ 7.3 (s, 2H), 7.1-6.4 (m, 4H), 4.35 (br s, 1H), 3.95 (s, 6H), 3.85 (t, 2H, J = 7 Hz), 3.3 (m, 1H), 3.94 (s, 6H), and 3.4 (t, 2H, J = 7 Hz); ms: (24 eV) m/e (relative intensity) 364 (3), 372 (30), 362 (89, m²), 221 (7), 220 (56), 208 (11), 207 (100), 205 (6), 192 (8), 165 (11), 164 (5), 157 (7), 156 (62), 155 (92), 154 (18), 143 (13), 136 (10), 129 (33), 128 (13), 122 (14), 102 (6), 93 (10), 78 (7), 77 (15), 75 (10), and 63 (7).

Anal. Caled. for C₁₃H₁₄N₂O₂: C, 69.60; H, 5.01; N, 7.73.
Found: C, 69.44; H, 5.21; N, 7.60.
from benzene-hexane afforded 600 mg (64%) of white product, m.p. 111-114°. Two additional crystallizations yielded white needles (dichloromethane-ether), m.p. 113-115°. The product displayed a single spot in the tlc system chloroform-alumina, Rf 0.43: ir (potassium bromide): 1675 cm⁻¹; nmr (deuteriochloroform): δ 7.3-7.6 (m, 4H), 5.4-5.1 (4H, m), 7.0 (v, 2H), 187 (6), 186 (29), 185 (38), 158 (14), 156 (9), 133 (11), 132 (100), 131 (12), 130 (28), 117 (8), 111 (34), 83 (23), 77 (7), 69 (10), 48 (5), 56 (14), and 55 (15).

Anal. Caled. for C₁₃H₁₄N₂O: C, 74.34%; H, 7.48; N, 11.56.
Found: C, 74.02; H, 7.49; N, 11.27.
Preparation of 13 from 2-(2-Aminomethyl)-1,2,3,4-tetrahydroquinoline (10d) and 2-Carbomethoxypropionaldehyde. Method B.

A solution of 2.8 g (0.016 mole) of 2-(2-aminoethyl)-1,2,3,4-tetrahydroquinoline (10d) in benzene was added to a solution of 3 g (0.026 mole) of 2-carbomethoxypropionaldehyde in 150 ml of benzene. The solution was filtered under nitrogen for 6 hours, filtered, and the solvent removed under reduced pressure. The residue was rubber with a mixture of ether and was extracted with a mixture of ether and allowed to stand in the cold for 4 days: residual 200 mg, (5%) of a white solid was collected, m.p. 112-114°. The ir and mass spectrum of this compound was identical to that of 13 prepared by Method A.

6,6a,7,8-Tetrahydro-5H-isaindolo[1',2',3']pyrimidin-1,6-aquinol-10(1H)none (14a).

A solution of 2.5 g (8.1 mmoles) of 12a in 30 ml of xylene containing a few mg of toluenesulfonic acid was heated on reflux for an hour. Solvent was removed under reduced pressure and the residue extracted twice with 200 ml portions of boiling methanol. The methanol extracts were combined and solvent removed under reduced pressure, yielding 1.3 g (50%) of a white residue, m.p. 180-186°. Crystallization from 25 ml of ethanol afforded 1.02 g (43%) of stout white needles, m.p. 190-191°: ir (potassium bromide): 3080, 2948, 2903, 2870, 1695, 1605, 1479, 1420, 1330, 760, 755, 715 and 692 cm⁻¹; nmr (deuteriochloroform): δ 7.44-6.19 (m, 8H), 5.9 (s, 1H), 4.32-3.92 (m, 1H), 3.22-2.44 (m, 4H) and 2.05-1.44 (m, 4H); ms: (70 eV) m/e (relative intensity) 291 (17), 290 (86, m), 299 (31), 160 (27), 159 (100), 158 (39), 156 (23), 152 (34), 151 (27), 130 (90), 117 (21), 104 (36), 103 (22), and 102 (6); ms: (CH₄Cl) m/e (relative intensity) 292 (29), 291 (M⁺, 100), 290 (54), 143 (40), 153 (50), and 130 (25).

Found: C, 78.32; H, 6.43; N, 9.54.

6,6a,7,8-Tetrahydro-12,13-dimethoxy-5H-isaindolo[1',2',3']pyrimidin-1,6-aquinol-10(1H)none (14b).

A solution of 250 mg of 10c (0.68 mmole) in 20 ml of THF and 30 ml of ethanol was treated with 250 mg. of sodium borohydride. This suspension was kept <5° and the pH was maintained between 8 and 10. It was stirred for 30 minutes while an additional 250 mg. of sodium borohydride was added and conditions were maintained as before for 1 hour. The alkaline solution was then diluted with 10 ml of water and was extracted with four 100-ml portions of dichloromethane. The extracts were combined, and dried (potassium carbonate), and solvent was removed under reduced pressure. The residue was dissolved in 150 ml of xylene. The solution was treated with 10 mg of toluenesulfonic acid, and was refluxed for 5 hours. It was then washed with dilute potassium carbonate, was dried (potassium carbonate), and solvent was removed under reduced pressure. Crystallization from dichloromethane-ether afforded 180 mg.
(74%) of a white solid, m.p. 204-206°C; $R_f = 0.59$ (chloroform-
alkalum); $\pi$ (potassium bromide): 1680 cm$^{-1}$; nmr (deutero-
chloroform): $\delta$ 7.4 (s, 1H), 7.4-6.5 (m, 4H), 6.95 (s, 1H),
6.25 (s, 1H), 4.5-4.1 (m, 1H), 3.95 (s, 3H), 3.85 (s, 3H), 3.4-2.5
(m, 4H), and 2.3-1.5 (m, 4H); $m/e$: (79 eV) m/e (relative
intensity) 352 (2), 351 (14), 350 (78, m$^3$), 349 (38), 345 (38), 341 (4),
319 (75), 206 (24), 205 (11), 193 (8), 192 (9), 191 (70), 190
(10), 176 (6), 175 (6), 164 (26), 163 (7), 162 (6), 159 (15),
159 (100), 157 (8), 156 (21), 144 (6), 143 (6), 136 (20), 134 (6),
133 (7), 132 (52), 131 (15), 130 (73), 117 (14), 104 (6), 103
(8), 91 (9), 78 (6), 77 (19), and 51 (8).

Anal. Calcd. for $C_{21}H_{22}N_{2}O_{3}$: C, 71.98; H, 6.33; N, 8.00.
Found: C, 71.76; H, 6.42; N, 8.03.

REFERENCES AND NOTES

(1) Contribution No. 1545 to the U.S. Army Research Pro-
gram in Malaria. Taken from the Ph.D. thesis presented by J. P. S.
to the Horace H. Rackham School of Graduate Studies of the Univer-
sity of Michigan in partial fulfillment of the requirements for the
degree of Doctor of Philosophy (1975). The authors gratefully
acknowledge the financial support of the National Institutes of
Health (Training Grant No. S-P01-GM02010, to J. P. S.). Part of
this work was conducted by J. P. S. at the Walter Reed Army
Institute of Research, Washington, DC 20012.

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