Synthesis of Bridgehead Nitrogen Heterocycles

John P. Scovill (1)

Division of Experimental Therapeutics, Walter Reed Army Institute of Research
Washington, DC 20012

and

Joseph H. Burckhalter

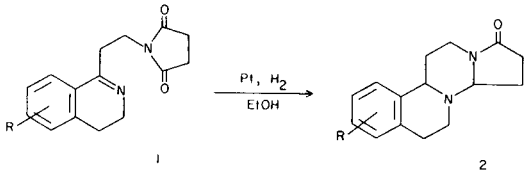
Interdepartmental Program in Medicinal Chemistry, The University of Michigan,
Ann Arbor, Michigan 48104

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-tetrahydroquinolyl stage. Controlled reduction of the tetrahydroquinolyl imides with sodium borohydride gave amido alcohols which afforded bridgehead nitrogen heterocycles upon cyclodehydration.

J. Heterocyclic Chem., **17**, 23 (1980).

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.



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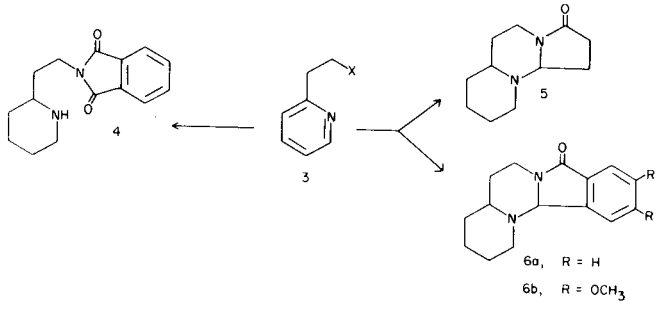
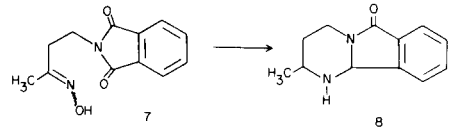


4 3 5 6a, R = H 6b, R = OCH_3



7 8

3a, X = succinimido
3b, X = phthalimido
3c, X = 4,5-dimethoxyphthalimido

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 platinium oxide lead 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

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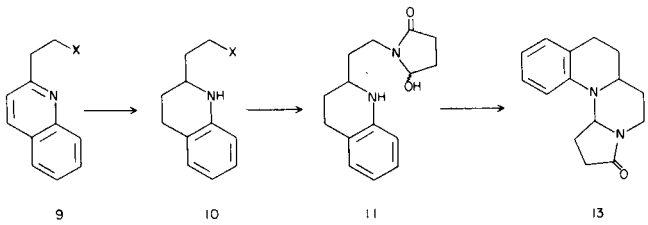
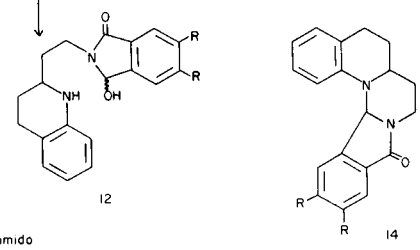


9 10 11 13



12 14

9a, 10a, X = succinimido
9b, 10b, X = phthalimido
9c, 10c, X = 4,5-dimethoxyphthalimido
9d, 10d, X = NH_2
12a, 14a, R = H
12b, 14b, R = OCH_3

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-carbomethoxypropionaldehyde 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 Laboratories, Eagle Harbor, MI.

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

To a solution of 2.44 g. (0.02 mole) of 2-(2-aminoethyl)-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), 313 (11), 312 (72, m^+), 221 (6), 220 (44), 208 (7), 207 (100), 106 (12), and 79 (5).

Anal. Calcd. for $C_{17}H_{16}N_2O_4$: C, 65.37; H, 5.16; N, 8.97. Found: C, 65.38; H, 5.17; N, 8.95.

N-[2-(2-Piperidyl)ethyl]phthalimide (4) Hydrochloride.

A solution of 1 g. (4 mmoles) of *N*-[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. Calcd. for $C_{15}H_{18}N_2O_2$.HCl: C, 61.11; H, 6.50; N, 9.50. Found: C, 61.10; H, 6.50; N, 9.49.

Octahydro-5*H*-pyrido[1,2-*c*]pyrrolo[1,2-*a*]pyrimidin-3(2*H*)one (**5**).

A solution of 17.4 g. (72 mmoles) of *N*-[2-(2-pyridyl)ethyl]-succinimide (**3a**) and 8 ml. of glacial acetic acid in 100 ml. of ethanol was hydrogenated over 1.4 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 10 g. (67%) of lactam **5**, b.p. 108-110° (0.1 mm), m.p. 59.5-60.5° (hydrate); ms: (70 eV) m/e (relative intensity) 195 (8), 194 (80, m^+), 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. Calcd. for $C_{11}H_{18}N_2O$·HCl: C, 57.26; H, 7.86; N, 12.14; Cl, 15.36. Found: C, 56.97; H, 8.07; N, 12.02; Cl, 15.49.

2,3,4,4a,5,6-Hexahydro-10,11-dimethoxy-1*H*-pyrido[1′,2′:3,4]-pyrimido[2,1-*a*]isoindol-8(12b*H*)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, m^+), 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 (8), 77 (8), 55 (29), and 54 (12).

Anal. Calcd. for $C_{17}H_{22}N_2O_3$: 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(2*H*)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 azeotropic distillation of 150 ml. portions of the following solvents from the residue: ethyl acetate, toluene, and ethanol. Rubbing under acetone gave a white solid. Crystallization 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

bromide): 1695 cm^{-1}; nmr (deuterium oxide): δ 7.75 (m, 4H), 5.75 (s, 1H) and 0.5 (d, 3H, J = 7 Hz); ms: (70 eV) m/e (relative intensity) 202 (16, m-HCl), 201 (100), 200 (8), 185 (11), 159 (43), 158 (10), 132 (5), 131 (10), 130 (31), 104 (13), 76 (85) and 44 (5).

Anal. Calcd. for $C_{12}H_{14}N_2O$·HCl: C, 60.38; H, 6.33; N, 11.73; Cl, 14.85. Found: C, 60.68; H, 6.55; N, 11.57; Cl, 14.59.

N-[2-(2-Quinolyl)ethyl]succinimide (**9a**).

A solution consisting of 36 g. (0.2 mole) of 2-(2-hydroxyethyl)quinoline (10), 21 g. (0.2 mole) of succinimide, 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 four 300 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°. Crystallization from methanol gave hexagonal plates, m.p. 115-116°. An analytical sample was prepared by sublimation (90°, 1 mm Hg); ir (potassium bromide): 1775, 1700, 1400, 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) 256 (2), 255 (18), 254 (96, m^+), 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), 56 (10), and 55 (29).

Anal. Calcd. for $C_{15}H_{14}N_2O_2$: C, 70.84; H, 5.54; N, 11.01. Found: C, 70.86; H, 5.63; N, 11.02.

N-[2-(2-Quinolyl)ethyl]phthalimide (**9b**).

A solution of 8.75 g. (50 mmoles) fo 2-(2-hydroxyethyl)-quinoline (10), 7.35 g. (50 mmoles) of phthalimide, and 3 ml. of 40% Triton B in methanol in 100 ml. of xylene was refluxed with separation of water for 18 hours. The solution was allowed to cool, was treated with charcoal, and was filtered. The solution was diluted with 100 ml. of chloroform and then extracted with four 250 ml. portions of water. The chloroform solution was dried (potassium carbonate), and solvent was removed under reduced pressure. Rubbing under ether caused solidification of the dark oil. After recrystallization from ethanol, 7.5 g. (53% yield) of **9b** was obtained, m.p. 127-129°; ir (potassium bromide): 1771, 1700, 1400 and 718 cm^{-1}; nmr (deuteriochloroform): δ 8.25-7.2 (m, 10H), 4.25 (t, 2H, J = 7 Hz), and 3.4 (t, 2H, J = 7 Hz); ms: (24 (eV) m/e (relative intensity) 304 (2), 303 (15), 302 (71, m^+), 301 (11), 273 (5), 231 (6), 169 (6), 160 (38), 157 (12), 156 (100), 154 (14), 147 (6), 146 (6), 143 (14), 130 (9), 129 (38), 128 (12), 115 (6), 105 (10), 104 (15), 89 (7), 77 (26), and 76 (19).

Anal. Clacd. for $C_{19}H_{14}N_2O_2$: C, 75.48; H, 4.67; N, 9.29. Found: C, 75.62; H, 4.59; N, 9.00.

4,5-Dimethoxy-*N*-[2-(2-quinolyl)ethyl]phthalimide (**9c**).

A solution of 1.1 g. (4.9 mmoles) of fused 4,5-dimethoxyphthalic acid, 1.2 g. (4.9 mmoles) of 2-(2-aminoethyl)quinoline (**9d**) hydrochloride, and 0.82 g. (10 mmoles) of fused sodium acetate in 20 ml. of glacial acetic acid was refluxed for 30 minutes. The solvent was removed under reduced pressure and the residue was neutralized with dilute sodium bicarbonate solution. Crystallization of the product from chloroform-ethanol afforded 1 g. (56%) of white needles, m.p. 248-251°. An analytical sample was crystallized from dichloromethane-ether, m.p. 251-253°. An additional crystallization from the same solvent gave pure product, m.p. 248-249° (sealed tube, stage preheated to 240°); ir (potassium bromide): 1770 and 1710 cm^{-1}; nmr (deuteriochloroform): δ 8.2-7.3 (m, 6H), 7.25 (s, 2H), 4.2 (t, 2H, J = 7 Hz), 3.94 (s, 6H), and 3.4 (t, 2H, J = 7 Hz); ms: (24 eV) m/e (relative intensity) 364 (3), 373 (20), 362 (89, m^+), 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. Calcd. for $C_{21}H_{18}N_2O_4$: C, 69.60; H, 5.01; N, 7.73. Found: C, 69.44; H, 5.21; N, 7.60.

2-(2-Aminoethyl)quinoline (**9d**) Dihydrochloride.

A solution of 2.54 g. (10 mmoles) of **9a** in 20 ml. of 6*N* hydrochloric acid was heated at 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° dec.; nmr (deuterium oxide): δ 9.05 (d, 1H, J = 9 Hz), 8.5-7.8 (m, 5H), and 3.8 (s, 4H).

Anal. Calcd. for $C_{11}H_{12}N_2$·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 55 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°; 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 (m, 1H), 2.85-2.32 (t, 2H, J = 7 Hz), 2.65 (s, 4H), 1.92-1.32 (m, 4H); (70 eV) m/e (relative intensity) 259 (3), 258 (16, m^+), 156 (9), 133 (14), 132 (100), 130 (10), 117 (12), and 77 (6).

Anal. Calcd. for $C_{15}H_{18}N_2O_2$: 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 5 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 light yellow solution was filtered and was concentrated to one quarter of its original volume. Cooling gave 3.65 g. (72%) of a yellow solid, m.p. 137-145°. An analytical sample was prepared by two crystallizations from ethanol, m.p. 156-158°. This compound showed a single spot, R_f = .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, m^+), 133 (13), and 132 (100).

Anal. Calcd. for $C_{19}H_{18}N_2O_2$: 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° 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°: 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),

2.75 (t, 2H), 2.2-1.5 (m, 4H); ms: (70 eV) m/e (relative intensity) 368 (0.2), 367 (1.5), 366 (8, m^+), 158 (5), 133 (9), 132 (100), 130 (5), and 117 (6).

Anal. Calcd. for $C_{21}H_{11}N_2O_4$: C, 68.83; H, 6.05; H, 7.65. Found: C, 68.54; H, 6.14; N, 7.62.

2(2-Aminoethyl)-1,2,3,4-tetrahydroquinoline (**10d**) Dihydrochloride

A solution of 2.58 g. (10 mmoles) of imide **10a** in 25 ml. of 6*N* hydrochloric acid was refluxed for 18 hours. The solution was evaporated to dryness under reduced pressure, and the residue was extracted with several large portions of boiling acetone in order to remove succinic acid. Crystallization from absolute ethanol-acetone gave 2.3 g. (92%) of white needles, m.p. 205° dec. An analytical sample was prepared by two additional crystallizations from the same solvents: nmr (deuterium oxide): δ 7.49 (s, 4H), 4.1-3.6 (m, 1H), 3.55-2.85 (m, 2H), 2.6-1.8 (m, 4H).

The free base of **10d** was obtained by stirring a suspension of 5 g. (16 mmoles) of the dihydrochloride in dichloromethane saturated with anhydrous ammonia. Ammonium chloride was removed by filtration and the solvent was evaporated under reduced pressure, distillation [b.p. 115°, 0.15 mm; lit. (11) b.p. 45°, 1 mm] afforded the amine in 85% yield; nmr (deuteriochloroform): 7.0-6.1 (m, 4H), 3.8-2.9 (m, 2H), 2.9-2.3 (m, 3H), 2.1-1.2 (m, 4H).

Anal. Calcd. for $C_{11}H_{16}N_2 \cdot 2HCl$: C, 53.02; H, 7.28; N, 11.24. Found: C, 53.06; H, 7.26; N, 11.22.

3-Hydroxy-2-[2-(1,2,3,4-tetrahydro-2-quinolyl)ethyl]-2,3-dihydro-1*H*-isoindol-1-one (**12a**).

A suspension of 7.5 g. (25 mmoles) of **10b** in 175 ml. of THF containing 10 ml. of water was cooled to 0°. Sodium borohydride was added portion wise to the rapidly stirred mixture, which was maintained at 0-5°. The *p*H was kept between 8-10 by dropwise addition of 4*N* hydrochloric acid. Addition of approximately 3 g. of sodium borohydride over a 2 hour period was required to dispel the yellow color of the starting imide. The reaction mixture was diluted with 700 ml. of water (hydrogen evolution) and the oily product extracted into 300 ml. of ether. The ether solution was washed with three 200 ml. portions of water, and the solvent removed under reduced pressure. The residue was dissolved in 10 ml. of acetonitrile and chilled overnight; 5.4 g. (72%) of white needles were collected, m.p. 118-125°. An analytical sample was prepared by two additional crystallizations from acetonitrile, m.p. 118-125°; ir (potassium bromide): 3300, 2940, 1696, 1625, 1595, 1325, 1055, 805, 750 and 700 cm^{-1}; ms: (CH_4 CI) m/e (relative intensity) 309 (M+1, 38), 308 (55), 291 (65), 186 (33), 159 (36), 158 (100), and 132 (70).

Anal. Calcd. for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.08. Found: C, 73.91; H, 6.55; N, 9.20.

1,6,6a,7,8,13a-Hexahydro-5*H*-pyrrolo[2',1':2,3]pyrimido[1,6-*a*]-quinolin-3(2*H*)one (**13**). Method A.

A solution of 1 g. (3.9 mmoles) of imide **10a** in 100 ml. of 90% ethanol was treated with 1 g. of sodium borohydride at 0°, the temperature being maintained at 0-5° and the *p*H between 8 and 10 by addition of 6*N* hydrochloric acid. It was stirred for 1 hour at 0-5°, an additional 1 g. portion of sodium borohydride was added while the *p*H was maintained between 8 and 10. The temperature was allowed to rise to 25°. Solvent was removed by distillation at reduced pressure and the residue was extracted with four 50-ml. portions of chloroform. The solution was dried (potassium carbonate) and solvent was removed under reduced pressure. The oily residue was dissolved in 100 ml. of benzene and the solution was refluxed for 45 minutes. Evaporation of solvent under reduced pressure and crystallization of the residue 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, R_f = 0.43: ir (potassium bromide): 1675 cm^{-1}; nmr (deuteriochloroform): δ 7.3-6.3 (m, 4H), 5.4-1.4 (m, 14H); ms: (70 eV) m/e (relative intensity) 243 (12), 242 (75, m^+), 241 (16), 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. Calcd. for $C_{15}H_{18}N_2O$: 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-Aminoethyl)-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 refluxed under nitrogen for 6 hours, filtered, and the solvent removed under reduced pressure. The residue was rubbed with a mixture of ether and hexane and allowed to stand in the cold for 4 days; redundant 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-5*H*-isoindolo[1',2':2,3]pyrimido[1,6-*a*]quinolin-10(14b*H*)one (**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, 1497, 1420, 787, 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), 3.2-2.4 (m, 4H) and 2.05-1.44 (m, 4H); ms: (70 eV) m/e (relative intensity) 291 (17), 290 (86, m^+), 289 (31), 160 (27), 159 (100), 158 (39), 156 (23), 132 (34), 131 (27), 130 (98), 117 (21), 104 (36), 103 (22), and 102 (6); ms: (CH_4 CI) m/e (relative intensity) 292 (29), 291 (M+1, 100), 290 (54), 143 (30), 153 (50), and 130 (25).

Anal. Calcd. for $C_{19}H_{18}N_2O$: C, 78.59; H, 6.25; N, 9.65. Found: C, 78.32; H, 6.43; N, 9.54.

6,6a,7,8-Tetrahydro-12,13-dimethoxy-5*H*-isoindolo[1',2':2,3]pyrido[1,6-*a*]quinolin-10(14b*H*)one (**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 *p*H 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 150 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°; R_f = 0.59 (chloroform-alumina); ir (potassium bromide): 1680 cm^{-1}; nmr (deuteriochloroform): δ 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); ms: (70 eV) m/e (relative intensity) 352 (2), 351 (14), 350 (78, m^+), 349 (38), 220 (10), 219 (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), 158 (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 $C_{21}H_{22}N_2O_3$: C, 71.98; H, 6.33; N, 8.00. Found: C, 71.78; H, 6.42; N, 8.03.

REFERENCES AND NOTES

(1) Contribution No. 1545 to the U.S. Army Research Program in Malaria. Taken from the Ph.D. thesis presented by J. P. S. to the Horace H. Rackham School of Graduate Studies of the University 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. 5-PO1-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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