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A series of structurally novel 7,8,9,10-tetrahydropyrido[3′,4′:4,5]pyrrolo[2,3-*c*]quinolines, **4a-c**, were synthesized *via* a facile Fischer indole cyclization from the appropriately substituted hydrazinoquinolines **2a-c**. Acetamides **4a,c** were hydrolyzed to **5a,b** and further converted to tertiary amines **6a-c**. Potent antihypertensive activity has been observed with a number of the title compounds as well as the intermediate **3a**.

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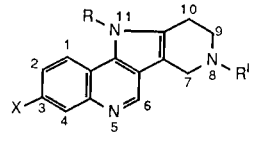
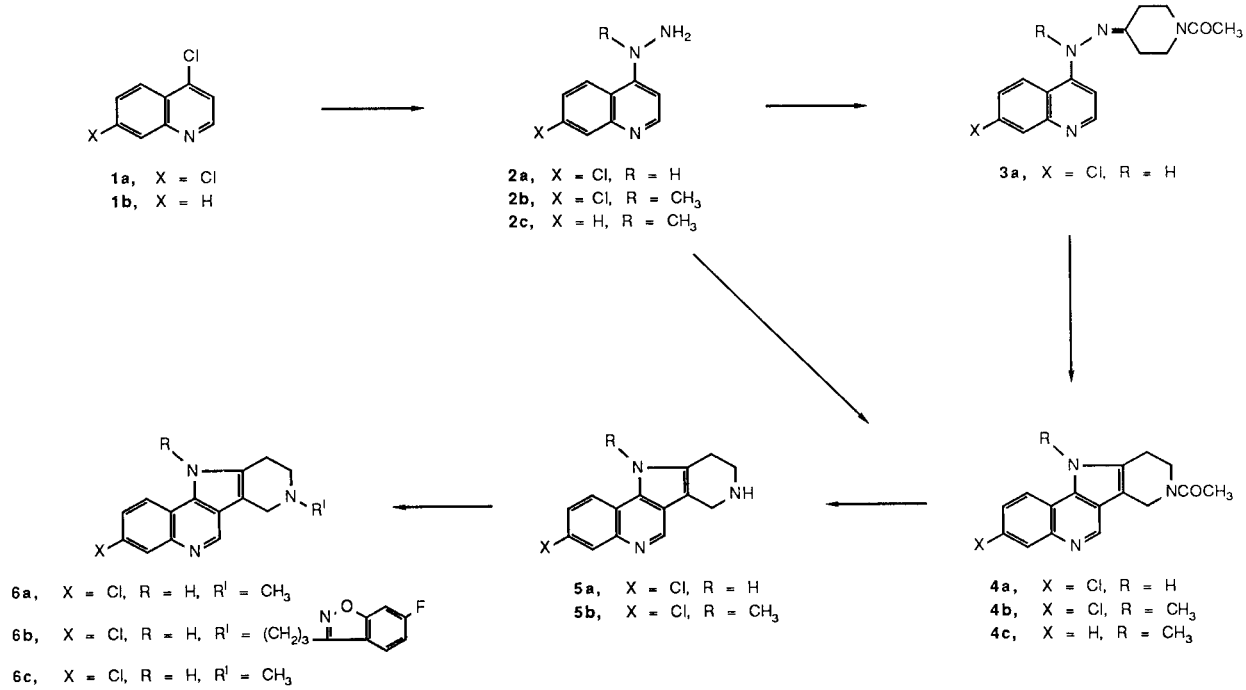
Our long-standing interest in the biological activity of fused polycyclic structures, in particular those incorporating a pyridine, pyrrole, or one of their reduced forms [1-3], has led us to prepare derivatives of pyrido[3′,4′:4,5]pyrrolo[2,3-*c*]quinolines, a hitherto unknown heterocyclic system. This paper discribes the syntheses of a number of 7,8,9,10-tetrahydropyrido[3′,4′:4,5]pyrrolo[2,3-*c*]quinolines (**I**), some with nuclear C(3) or N(11) substituents, by a facile Fischer indole synthesis from readily accessible intermediates.



As shown in Scheme 1, 4,7-dichloroquinoline (**1a**) [4] was treated with hydrazine hydrate in refluxing ethanol to give 7-chloro-4-hydrazinoquinoline (**2a**) in 80% yield. For the condensation of **1a** with *N*-methylhydrazine, it was, however, necessary to maintain the temperature below 25° in order that 7-chloro-4-(1-methylhydrazino)quinoline (**2b**) be formed as the exclusive product. At higher temperatures, increased amounts of the isomeric 7-chloro-4-(2-methylhydrazino)quinoline could be detected. Similarly, **2c** was obtained from 4-chloroquinoline (**1b**) which was prepared by reacting 4-hydroxyquinoline with phosphorus oxychloride at 80-90°.

Compound **2a** reacted readily with *N*-acetyl-4-piperidone at room temperature to afford hydrazone **3a**, which upon heating at 220° [5] underwent Fischer indole cycliza-

Scheme 1



tion to give the desired 8-acetyl-3-chloro-7,8,9,10-tetrahydro-11*H*-pyrido[3',4':4,5]pyrrolo[2,3-*c*]quinoline (**4a**) in good yield. It was further discovered that the tetracyclic target structures could be constructed without isolation of the hydrazone intermediate, or they could be prepared by a one-pot procedure as demonstrated by the syntheses of **4b** and **4c**, respectively. It is also noteworthy that the overall yields of **4a-c** by the direct approach were generally better than those obtained by a two-step process. For reasons not clearly understood, hydrazones prepared from *N*-methyl-4-piperidone and analogous to **3a** gave much lower yields of the cyclization products.

Acetamides **4a-c** were thus subjected to hydrolysis with concentrated hydrochloric acid to secondary amines **5a** and **5b** without appreciable destruction of the pyrrole incorporated heterocycle. Further derivatization of **5a,b** to *N*-methyl analogues **6a** and **6c** could be effected with a mixture of formaldehyde and formic acid, while the 1,2-benzisoxazole derivative **6b** was readily prepared from 3-(3-chloropropyl)-6-fluoro-1,2-benzisoxazole according to the reported procedure by Strupczewski and co-workers [6].

Many of the target 7,8,9,10-tetrahydro-11*H*-pyrido[3',4':-4,5]pyrido[2,3-*c*]quinolines as well as the precursory hydrazones (*e.g.*, **4b** and **3a**) displayed potent antihypertensive activity in the spontaneously hypertensive rat. Details of their biological properties will be published elsewhere.

EXPERIMENTAL

Melting points were determined on a Thomas Hoover Capillary apparatus and are uncorrected. The structures of all compounds are supported by their ir (Pye Unicam SP3-300), ^{1}H nmr (Varian XL 200; chemical shift values are reported in δ units downfield relative to tetramethylsilane as internal standard), and ms (Finnigan 4023) spectra. Preparative hplc separations were performed on silica gel with a Waters Associates Prep LC/System 500 equipped with a Gow Mac Model 80-800 uv detector. Microanalyses were performed by Micro Tech Laboratories, Skokie, IL and Baron Associates, Milford, CT.

7-Chloro-4-hydrazinoquinoline (**2a**).

A mixture of 9.9 g (0.05 mole) of 4,7-dichloroquinoline, 5 g (0.1 mole) of hydrazine hydrate in 30 ml of ethoxyethanol was stirred at 110° for 2 hours. The cooled solution was poured onto ice-water (200 ml), and the precipitated solid was filtered and dried. Recrystallization from 2-propanol afforded 7.6 g (80%) of colorless prisms, mp 218-221° (lit [7] 212-214°).

7-Chloro-4-(methylhydrazino)quinoline (**2b**).

A solution of 30 g (0.151 mole) of 4,7-dichloroquinoline and 30.6 g (0.644 mole) of methylhydrazine in 350 ml of methanol was stirred at room temperature for 2 days. The reaction mixture was poured onto 800 ml of ice water and the solid was filtered after stirring for 30 minutes. The filtrate was extracted with dichloromethane (3 x 400 ml), the combined filtrate was washed (water), dried over magnesium sulfate and thin layer chromatography (silica gel, 10% methanol in dichloromethane) showed the two crops to be identical. The combined product was thus recrystallized from isopropanol to give 20.0 g (64%) of **2b** as colorless prisms, mp 94-97° (lit [8] 95-97°).

4-(1-Methylhydrazino)quinoline (**2c**).

To 116 ml of phosphorus oxychloride was added, portionwise, 29.0 g (0.2 mole) of 4-hydroxyquinoline. The mixture was vigorously stirred and slowly warmed to 80° to form a clear solution. After stirring for 2 hours at this temperature, the solution was cooled and poured onto 1 l of ice-water. Basification at 0° with 25% sodium hydroxide liberated an oil which was extracted into dichloromethane (3 x 600 ml). The organic solution was dried over magnesium sulfate and concentrated to give 20 g of a thick oil.

The crude 4-chloroquinoline thus prepared was dissolved in 285 ml of methanol and to it was added 23 ml of methylhydrazine. Stirring was continued at room temperature for 2 days. The clear solution was poured into ice water (800 ml), extracted with dichloromethane (2 x 800 ml) and the combined organic solution was dried over magnesium sulfate. Removal of solvent *in vacuo* left a brownish oil which was purified by column chromatography over silica. Elution with 10% methanol in dichloromethane, followed by evaporation of the appropriate fractions, yielded 10.0 g (47%) of **2c** as a pale yellowish oil; ^{1}H nmr (deuteriochloroform): δ 3.24 (s, 3H), 3.90 (broad s, 2H), 6.90 (d, 1H), 7.50-7.70 (m, 2H), 8.24-8.48 (m, 2H), 9.00 (d, 1H); ms: m/e 173 (M^+).

Anal. Calcd. for $C_{10}H_{11}N_3$: C, 69.34; H, 5.77. Found: C, 69.01; H, 6.01.

N-Acetyl-4-[*N'*-[(7-chloroquinolin-4-yl)amino]imino]piperidine (**3a**).

A solution of 46 g (0.238 mole) of **2a** and 33.6 g (0.238 moles) of *N*-acetyl-4-piperidone in 200 ml of ethanol was stirred at room temperature for 2 days and then diluted with 500 ml of water. The solid precipitate was filtered, dried and recrystallized from 95% ethanol to give 55.0 g (73%) of **3a** as tan-colored crystals, mp 153-154°; ir (chloroform): 3010, 1630 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 2.18 (s, 3H), 2.80-3.00 (m, 4H), 3.60-3.82 (m, 4H), 6.80-7.80 (m, 4H), 8.20 (d, 1H), ms: m/e 317 (M^+).

Anal. Calcd. for $C_{16}H_{17}ClN_4O$: C, 60.66; H, 5.41; N, 17.69. Found: C, 60.51; H, 5.25; N, 17.39.

8-Acetyl-3-chloro-7,8,9,10-tetrahydro-11*H*-pyrido[3',4':4,5]pyrrolo[2,3-*c*]-quinoline (**4a**).

A solution of **3a** (10.0 g, 0.0316 mole) in 20 ml of diethylene glycol was heated at 220° under gentle reflux for 1 hour. The cooled mixture was diluted with water (200 ml) and stirred for 2 hours. The solid precipitate was filtered, washed with water and recrystallized from ethanol to give 5.02 g (53%) of **4a** as colorless prisms, mp 235-237°; ir (chloroform): 3080, 3050, 1640 cm^{-1}; ^{1}H nmr (dimethylsulfoxide-d_6): δ 2.2 (s, 3H), 2.82-3.10 (m, 2H), 3.82 (m, 2H), 7.66 (q, 1H), 8.10 (d, 1H), 8.40 (d, 1H), 9.12 (s, 1H); ms: m/e 299 (M^+).

Anal. Calcd. for $C_{16}H_{14}ClN_3O$: C, 64.11; H, 4.67; N, 14.02. Found: C, 64.08; H, 4.79; N, 14.03.

8-Acetyl-3-chloro-11-methyl-7,8,9,10-tetrahydropyrido[3$_9$,4$_9$:4,5]pyrrolo-[2,3-*c*]quinoline (**4b**).

A mixture of **2b** (6.02 g, 0.029 mole), *N*-acetyl-4-piperidone (4.1 g, 0.03 mole) and sodium carbonate (3 g, 0.03 mole) in 50 ml of methanol was heated at reflux for 30 minutes. After cooling, the solution was concentrated to a syrup and to it was added 30 ml of diethylene glycol with good stirring. The homogeneous solution was heated at 180° for 30 minutes and cooled slowly to room temperature. The mixture was then poured onto 200 ml of ice-water and the solid was filtered after stirring for 30 minutes. The crude product was recrystallized from ethanol to give 3.5 g (39%) of **4b** as white prisms, mp 299-301° dec; ir (chloroform): 3000, 1640 cm^{-1}; ^{1}H nmr (dimethylsulfoxide-d_6): δ 2.20 (s, 3H), 2.80-3.08 (m, 2H), 3.84-4.10 (m, 2H), 4.04 (s, 3H), 7.60 (q, 1H), 8.12 (d, 1H), 8.52 (d, 1H), 9.12 (s, 1H); ms: m/e 313 (M^+).

Anal. Calcd. for $C_{17}H_{16}ClN_3O$: C, 65.07; H, 5.10; N, 13.40. Found: C, 65.03; H, 5.17; N, 13.47.

8-Acetyl-11-methyl-7,8,9,10-tetrahydropyrido[3',4':4,5]pyrrolo[2,3-*c*]quinoline (**4c**).

A mixture of **2c** (10.0 g, 0.058 mole) and *N*-acetyl-4-piperidone (8.15 g, 0.06 mole) in 20 ml of diethylene glycol was stirred at 190-210° for 2 hours or until tlc indicated completion of reaction. The mixture was poured onto 500 ml of ice-water and the organics were extracted into di-

chloromethane (3 x 300 ml). After drying over magnesium sulfate, the organic solution was concentrated *in vacuo* to give a yellowish crystalline solid. Recrystallization from 2-propanol afforded 8.4 g (52%) of **4c** as off-white prisms, mp 218-221°; ir (chloroform): 3000, 1670 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.26 (s, 3H), 2.74-2.90 (m, 2H), 3.80-4.16 (m, 2H), 4.82 (q, 2H), 7.48-7.70 (m, 2H), 8.20-8.40 (m, 2H), 9.0 (s, 1H); ms: m/e 279 (M^+).

Anal. Calcd. for $C_{17}H_{17}N_3O$: C, 73.09; H, 6.14; N, 15.04. Found: C, 73.06; H, 5.98; N, 15.16.

3-Chloro-7,8,9,10-tetrahydro-11*H*-pyrido[3',4':4,5]pyrrolo[2,3-*c*]quinoline (**5a**).

A mixture of **4a** (27.0 g, 0.09 mole) in 200 ml of concentrated hydrochloric acid was heated at reflux for 1 hour, during which a solid gradually deposited. After stirring at room temperature overnight, the mixture was diluted with 200 ml of water and basified with an excess of 25% sodium hydroxide. The free base was filtered, washed with water and recrystallized from ethanol to give 17.2 g (74%) of **5a** as tan-colored crystals, mp 285-287° dec; ^1H nmr (dimethylsulfoxide-d_6): δ 3.04-3.40 (m, 2H), 3.54-3.84 (m, 2H), 4.64 (s, 2H), 7.90 (q, 1H), 8.28 (d, 2H), 8.46 (d, 2H), 9.60 (s, 1H), 9.84 (broad s, 2H); ms: m/e 257 (M^+).

Anal. Calcd. for $C_{14}H_{12}ClN_3$: C, 65.24; H, 4.66; N, 16.31. Found: C, 65.07; H, 4.80; N, 16.20.

3-Chloro-11-methyl-7,8,9,10-tetrahydropyrido[3',4':4,5]pyrrolo[2,3-*c*]quinoline (**5b**).

A suspension of **4b** (17.5 g, 0.056 mole) in 125 ml of concentrated hydrochloric acid was refluxed under nitrogen for 1 hour. The solution was cooled at 0° and the precipitate was filtered. The crude amine hydrochloride was suspended in 500 ml of water and the mixture was basified with an excess of 25% sodium hydroxide. The newly formed precipitate, after stirring for 30 minutes, was filtered and washed exhaustively with water and dried. Recrystallization from isopropanol yielded 11.0 g (72%) of **5b** as a white crystalline solid, mp 209-210°; ^1H nmr (dimethylsulfoxide-d_6): δ 2.70-2.84 (m, 2H), 3.06-3.20 (m, 2H), 4.04 (q, 2H), 4.08 (s, 3H), 7.60 (q, 1H), 8.10 (d, 1H), 8.56 (d, 1H), 9.00 (s, 1H); ms: m/e 271 (M^+).

Anal. Calcd. for $C_{15}H_{14}ClN_3$: C, 66.30; H, 5.19; N, 15.46. Found: C, 66.01; H, 5.07; N, 15.29.

3-Chloro-8-methyl-7,8,9,10-tetrahydro-11*H*-pyrido[3',4':4,5]pyrrolo[2,3-*c*]quinoline (**6a**).

A mixture of **5a** (3.7 g, 0.014 mole) and 0.45 g (0.015 mole) of paraformaldehyde in 10 ml of formic acid was heated at 90° for 1 hour. After quenching with water (100 ml), the solution was made alkaline (*p*H 9) with an excess of 25% sodium hydroxide. The crystalline product was filtered, washed with water, and purified by hplc using 20% methanol in dichloromethane as the eluent. The appropriate fractions which contained a major component of Rf = 0.1 were combined and concentrated to a crystalline residue. Recrystallization from isopropanol afforded 2.1 g (55%) of **6a** as a tan-colored powder, mp 286-288°; ^1H nmr (deuteriochloroform + dimethylsulfoxide-d_6): δ 2.52 (s, 3H), 2.72-2.88 (m, 2H), 2.88-3.00 (m, 2H), 3.72 (s, 2H), 7.44 (q, 1H), 8.00 (d, 1H), 8.30 (d, 1H), 8.92 (s, 1H): ms: m/e 285 (M^+).

Anal. Calcd. for $C_{15}H_{14}ClN_3$: C, 66.30; H, 5.19; N, 15.46. Found: C, 66.28; H, 5.20; N, 15.59.

3-Chloro-8-[3-(6-fluorobenzisoxazol-3-yl)propyl]-7,8,9,10-tetrahydropyrido[3',4':4,5]pyrrolo[2,3-*c*]quinoline (**6b**).

A mixture of **5a** (5.15 g, 0.02 mole), 7.0 g (0.033 mole), 3-(3-chloropropyl)-6-fluoro-1,2-benzisoxazole [6], and 4.0 g (0.029 mole) of finely pulverized potassium carbonate in 30 ml of dimethylsulfoxide was stirred at 100° for 2 hours. After cooling to room temperature, the mixture was diluted with 150 ml of water and the oily precipitate was extracted into dichloromethane (3 x 250 ml). Drying over magnesium sulfate, followed by concentration *in vacuo* yielded a crude product which was purified by hplc using 10% methanol in dichloromethane as the eluent. The appropriate fractions containing a major component of Rf = 0.3 were combined and concentrated to yield 1.2 g (14%) of pure **6b**, mp 221-222°; ^1H nmr (deuteriochloroform + dimethylsulfoxide-d_6): δ 2.10-2.36 (m, 2H), 2.80 (t, 2H), 2.88-3.04 (m, 4H), 3.12 (t, 2H), 3.88 (s, 2H), 7.08-7.16 (m, 1H), 7.26 (q, 1H), 7.44 (q, 1H), 7.64-7.76 (m, 1H), 8.12 (d, 1H), 8.28 (d, 1H), 9.00 (s, 1H); ms: m/e 434 (M^+).

Anal. Calcd. for $C_{24}H_{20}ClFN_4O$: C, 66.28; H, 4.04; N, 12.88. Found: C, 66.36; H, 4.79; N, 12.74.

3-Chloro-8,11-dimethyl-7,8,9,10-tetrahydropyrido[3',4':4,5]pyrrolo[2,3-*c*]-quinoline (**6c**).

A mixture of **5b** (6 g, 0.022 mole) and 0.7 g (0.023 mole) of paraformaldehyde in 16 ml of formic acid was heated at 90° for 1 hour. The mixture was cooled to room temperature, diluted with 50 ml of water and basified with an excess of 25% sodium hydroxide. The solid precipitate was filtered, dried, and purified by hplc using 10% methanol in dichloromethane as the eluent. The appropriate fractions which contained a major component of Rf = 0.13 were combined and evaporated to dryness. Recrystallization from ethyl acetate afforded 1.44 g of **6c** (23%) as a white crystalline solid, mp 188-190°; ^1H nmr (dimethylsulfoxide-d_6): δ 2.48 (s, 3H), 2.72-2.96 (m, 4), 3.68 (s, 2H), 4.08 (s, 3H), 7.60 (q, 1H), 8.10 (d, 1H), 8.56 (d, 1H), 9.00 (s, 1H); ms: m/e 285 (M^+).

Anal. Calcd. for $C_{16}H_{16}ClN_3$: C, 67.24; H, 5.64; N, 14.70. Found: C, 66.97; H, 5.41; N, 14.86.

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