Preparation of Benzo[*c*][2,7]naphthyridin-5(1*H*)-ones as Analogs of Benzopyrano[3,4-*c*]pyridin-5-one Bronchodilators

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A series of 2,3,4,6-tetrahydro-8,9-dimethoxybenzo[*c*][2,7]naphthyridin-5(1*H*)-ones was prepared as potential anticholinergic bronchodilators. The naphthyridine ring system was constructed by cyclization of a 3-amido-4-piperidone. Alkylation with alkylaminoethyl chlorides or reductive amination of an intermediate methyl ketone yielded the final target compounds.

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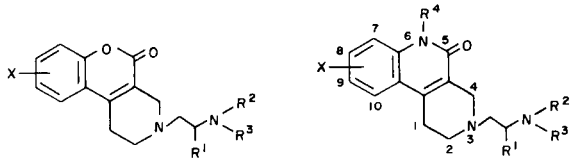
We recently described [1] the synthesis of a series of 1,2,3,4-tetrahydro-5*H*-[1]-benzopyrano[3,4-*c*]pyridin-5-ones **1** as potential bronchodilators. The preparation of the related benzo[*c*][2,7]naphthyridin-5(1*H*)-one ring system **2** thus became of interest as an analog of **1**.



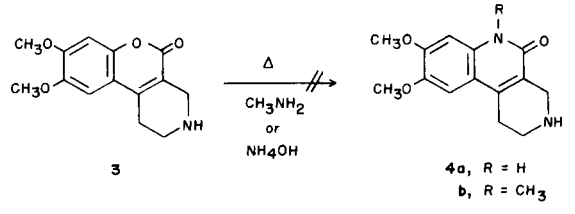
1 **2**

R^1–R^4 = H, alkyl

The basic tricyclic ring system **2** has been reported [2] in the synthesis of perlolidine, a minor alkaloid found in ryegrass. We required a synthetic procedure that permitted incorporation of the 5-position carbonyl and the aminoalkyl side chain on the naphthyridine sub-structure.

Direct lactone to lactam conversion by aminolysis at elevated temperature has been employed in the preparation of certain phenanthridinones from coumarins [3] and other benzopyrones [4]. However, when we attempted aminolysis (Scheme I) of lactone **3** [1] with methylamine or ammonium hydroxide under similar conditions, no lactam **4a,b** could be isolated from the complex reaction mixture.

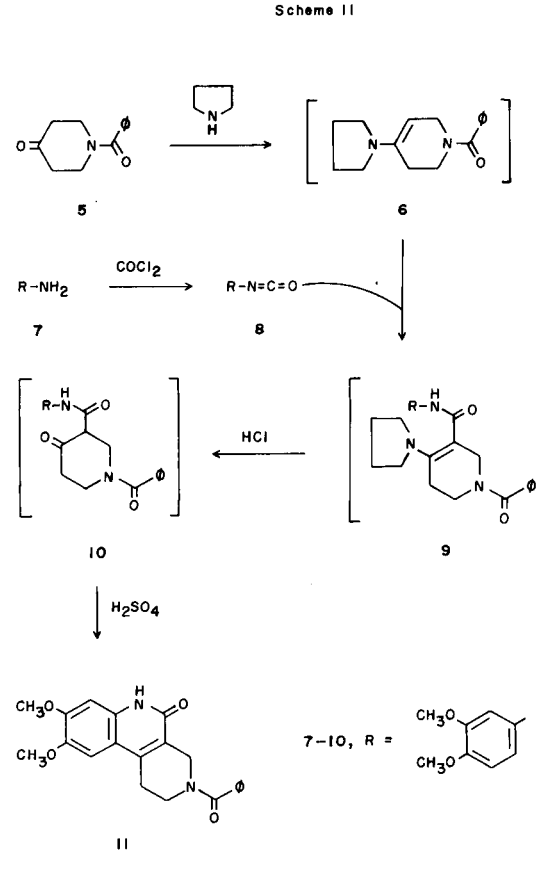
Scheme I



3 **4a**, R = H; **b**, R = CH_3

As an alternate route to compounds of type **2**, the desired benzo[*c*][2,7]naphthyridin ring system was prepared (Scheme II) by cyclization of a suitably substituted 4-piperidone.

Scheme II



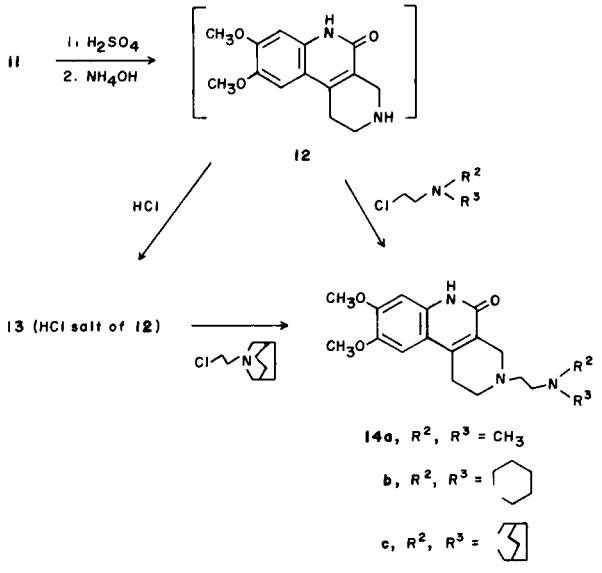
5 **6** **7** **8** **9** **10** **11**

7–10, R =

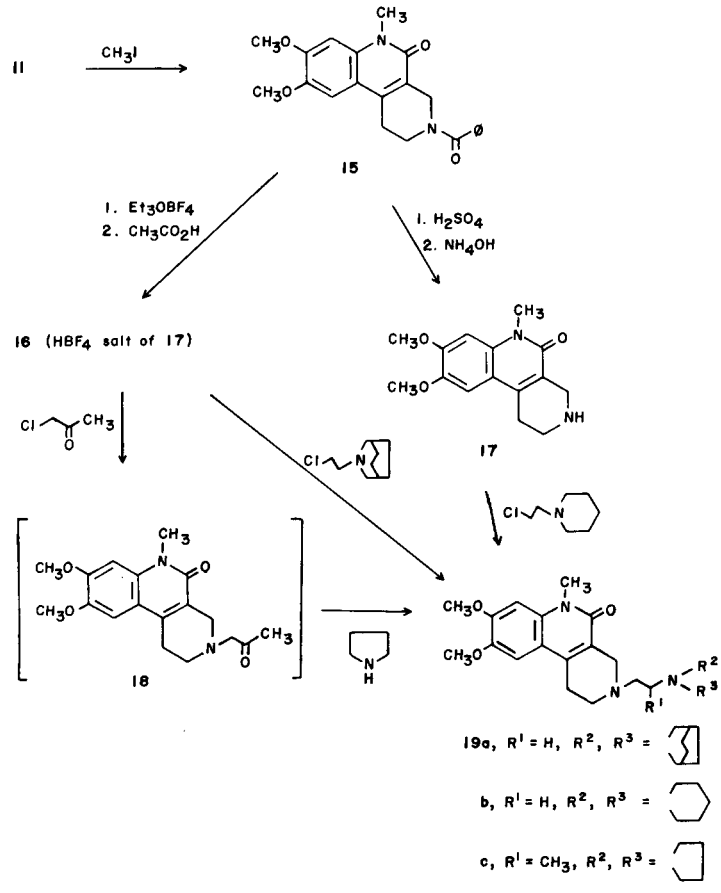
Isocyanate **8** [5] was prepared from 3,4-dimethoxybenzenamine **7** by treatment with phosgene in chlorobenzene. The pyrrolidine enamine **6**, generated from 1-benzoyl-4-piperidone **5**, was acylated with isocyanate **8** to yield the piperidine diamide **9**. Acidic hydrolysis of **9** at 25° yielded the β-keto-amide **10**, which was cyclized under strongly acidic conditions to the desired benzonaphthyridine intermediate **11**. Compounds **6**, **9**, and **10** were employed as crude intermediates without extensive purification.

Selective hydrolysis (Scheme III) of the 3-benzoyl substituent of **11** with sulfuric acid in aqueous propanol, followed by treatment with base, yielded the free base

Scheme III



Scheme IV



naphthyridine **12** as a crude intermediate. Alkylation of **12** with alkylaminoethyl chlorides was employed to prepare target compounds **14a,b**. Conversion of **12** to the hydrochloride salt **13**, followed by similar alkylation, yielded target **14c**.

The *N*-methyl lactam **15** was prepared by methylation of **11** with sodium hydride and iodomethane (Scheme IV). Subsequent hydrolysis of **15** yielded the free base intermediate **17**. Hydrolysis of **15** was also effected [6] by initial conversion of the 3-benzamide function to an imidate with triethyloxonium fluoroborate (Meerwein's Reagent), followed by mild acid hydrolysis. The resulting fluroborate salt **16** and free base **17** were alkylated as previously described to yield diamino target compounds **19a,b**.

Fluoroborate salt **16** was also alkylated with chloro-2-propanone in dimethyl sulfoxide to obtain the methyl ketone **18** as a crude intermediate. Reductive amination of **18** with pyrrolidine then yielded the target α-methyl diamine **19c**.

Table 1 describes the analytical and spectral data for the benzo[*c*][2,7]naphthyridin-5(1*H*)-ones prepared.

Target compounds **14a-c** and **19a-c** did not demonstrate anticholinergic bronchodilator activity in contrast to the related benzopyrano[3,4-*c*]pyridin-5-ones **1**.

EXPERIMENTAL

Melting points were determined in a Mel-Temp capillary apparatus and are uncorrected. The nmr spectra were recorded at 90 MHz on a Varian EM-390 spectrometer or at 200 MHz on a Varian XL-200 spectrometer. All nmr spectra were recorded with tetramethylsilane as an internal standard. Infrared spectra were recorded as potassium bromide disks on a Digilab FTS-14 pulsed Fourier-transform spectrophotometer.

3,4-Dimethoxyphenylisocyanate (**8**).

A solution of 25.0 g (0.16 mole) of 3,4-dimethoxybenzenamine in 250 ml of chlorobenzene was stirred and treated with excess hydrogen chloride gas, resulting in a heavy precipitate of the hydrochloride salt. The mixture was heated at reflux while a stream of phosgene gas (50 g, 0.51 mole) was introduced over 30 minutes. After heating at reflux for an additional 30 minutes, the mixture was cooled and the solvent evaporated (vacuum). Distillation of the residue yielded 23 g (79%) of the isocyanate **8**, bp 145-150° (18 mm), lit [5] bp 90° (2.0 mm).

Anal. Calcd. for $C_9H_9NO_3$: C, 60.33; H, 5.06; N, 7.82. Found: C, 60.63; H, 5.12; N, 7.55.

3-Benzoyl-2,3,4,6-tetrahydro-8,9-dimethoxybenzo[*c*][2-7]naphthyridine-5-(1*H*)-one (**11**).

A mixture of 53.0 g (0.26 mole) of 1-benzoyl-4-piperidone **5** and 42 ml (35.8 g, 0.50 mole) of pyrrolidine in 250 ml of benzene was stirred at reflux for 90 minutes, employing a Dean-Stark trap. An additional 15.0 ml (12.8 g, 0.18 mole) of pyrrolidine was added, and heating was continued for one hour. The mixture was cooled and evaporated (vacuum). The resulting residue was dissolved in ethanol and evaporated, then dissolved in benzene and evaporated again.

The resulting crude enamine oil **6** from the above procedure was dissolved in 250 ml of dichloromethane and treated over 15 minutes with a solution of 47.0 g (0.26 mole) of isocyanate **8** in 50 ml of dichloromethane. An additional 400 ml of dichloromethane was added to aid in stirring, and the new mixture was stirred at room temperature for 16 hours. Evaporation of the solvent (vacuum) yielded the crude amide **9** residue.

Table 1

Microanalytical and Spectral Data for Benzo[*c*][2,7]naphthyridin-5(1*H*)-ones

Compound No.	Molecular Formula	Analyses % Calcd. (Found) C	H	N	IR (KBr) ν cm−1	^{1}H-NMR [a] δ ppm
11	$C_{21}H_{20}N_2O_4$	69.21 (69.12	5.53 5.47	7.69 7.52)	3215, 1655, 1523, 1432, 1271	(DMSO-d_6): 11.67 (s, 1H, N*H*), 7.50 (s, 5H, Ar*H*), 7.10 (s, 1H, Ar*H*), 6.87 (s, 1H, Ar*H*), 4.45 (m, 2H, 4CH_2), 3.82 (s, 6H, OCH_3)
13	$C_{14}H_{16}N_2O_3$ ·HCl [b]	55.00 (55.35	5.93 5.96	9.16 9.14)	2960, 1647, 1518, 1428, 1266	(DMSO-d_6): 11.85 (s, 1H, N*H*), 9.75 (s, 2H, NH_2+), 7.09 (s, 1H, Ar*H*), 6.94 (s, 1H, Ar*H*), 3.93 (s, 2H, 4CH_2), 3.83 (s, 6H, OCH_3)
14a	$C_{18}H_{25}N_3O_3$	65.23 (65.44	7.60 7.64	12.68 12.92)	2948, 1652, 1520, 1428, 1267	(deuteriochloroform): 12.17 (broad s, 1H, N*H*), 6.90 (s, 1H, Ar*H*), 6.87 (s, 1H, Ar*H*), 4.05 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 3.62 (s, 2H, 4CH_2), 2.30 (s, 6H, NCH_3)
14b	$C_{21}H_{29}N_3O_3$	67.90 (67.86	7.87 7.73	11.31 11.28)	2936, 1655, 1517, 1428, 1165	(deuteriochloroform): 12.41 (s, 1H, N*H*), 6.85 (s, 1H, Ar*H*), 6.83 (s, 1H, Ar*H*), 3.97 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.61 (s, 2, 4CH_2)
14c	$C_{24}H_{33}N_3O_3$ ·2HCl [c]	56.36 (56.24	7.49 7.48	8.22 7.97)	2950, 1650, 1520, 1430, 1268	(deuterium oxide): 6.72 (s, 1H, Ar*H*), 6.19 (s, 1H, Ar*H*), 4.25 (s, 2H, 4CH_2), 3.84 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3)
15	$C_{22}H_{22}N_2O_4$	69.82 (69.57	5.86 5.89	7.40 7.25)	1645, 1597, 1528, 1430, 1263	(deuteriochloroform): 7.39 (s, 5H, Ar*H*), 7.00 (s, 1H, Ar*H*), 6.78 (s, 1H, Ar*H*), 4.56 (s, 2H, 4CH_2), 4.03 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 3.68 (s, 3H, NCH_3)
16	$C_{15}H_{18}N_2O_3$ ·HBF_4	49.75 (49.56	5.29 5.15	7.74 7.71)	3046, 1592, 1383, 1205, 1020 (broad	(DMSO-d_6): 9.00 (s, 2H, NH_2+), 7.21 (s, 1H, Ar*H*), 7.06 (s, 1H, Ar*H*), 4.03 (s, 2H, 4CH_2), 3.96 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 3.70 (s, 3H, NCH_3)
17	$C_{15}H_{18}N_2O_3$	65.67 (65.47	6.61 6.63	10.21 9.92)	1660, 1595, 1531, 1430, 1258	(deuteriochloroform): 8.29 (s, 1H, N*H*), 7.05 (s, 1H, Ar*H*), 6.82 (s, 1H, Ar*H*), 4.45 (s, 2H, 4CH_2), 4.02 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 3.76 (s, 3H, NCH_3)
19a	$C_{25}H_{35}N_3O_3$ ·HCl·HBF_4 [c]	52.05 (51.70	6.99 6.65	7.28 7.17)	2950, 1642, 1577, 1259 1060 (broad)	(deuterium oxide): 6.83 (s, 1H, Ar*H*), 6.27 (s, 1H, Ar*H*), 4.25 (s, 2H, 4CH_2), 3.82 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3), 3.39 (s, 3H, NCH_3)
19b	$C_{22}H_{31}N_3O_3$ ·2HCl [b]	56.53 (56.51	7.33 7.25	8.99 8.97)	2950, 1642, 1594, 1431, 1259	(deuterium oxide): 6.97 (s, 1H, Ar*H*), 6.43 (s, 1H, Ar*H*), 4.22 (s, 2H, 4CH_2), 3.89 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.47 (s, 3H, NCH_3)
19c	$C_{22}H_{31}N_3O_3$ ·2HCl [d]	55.46 (55.68	7.40 7.50	8.82 8.70)	2961, 1650, 1581, 1439, 1268	(deuterium oxide): 6.93 (s, 1H, Ar*H*), 6.41 (s, 1H, Ar*H*), 4.28 (s, 2H, 4CH_2), 3.85 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.48 (s, 3H, NCH_3), 1.67 (d, 3H, CH_3)

[a] Omitted from the table are complex, overlapping multiplets representing the 1 and 2 methylene protons plus any side chain methylene protons. [b] Calculated as the molecular formula +0.50 water. [c] Calculated as the molecular formula +1.50 water. [d] Calculated as the molecular formula +1.0 water.

A solution of amide **9** in 200 ml of methanol was treated with 60 ml of concentrated hydrochloric acid, and the mixture was stirred at room temperature for 5 hours. The new mixture was diluted with water to 1000 ml and extracted with chloroform (4 x 150 ml). The combined organic layers were back-washed several times with water, dried (anhydrous sodium sulfate), and evaporated (vacuum) to yield the crude β-ketoamide **10** as a gummy residue.

The crude amide residue **10** was treated with 100 ml of concentrated sulfuric acid and warmed momentarily on the steam bath. After the initial exothermic reaction had subsided, heating on the steam bath was continued for 10 minutes. The cooled reaction mixture was added to 800 g of ice/water, and the precipitated crude product **11** (55.0 g, 58%) was filtered and washed with water. A sample recrystallized from *N,N*-dimethylformamide yielded the analytically pure naphthyridine **11**, mp 296-300°.

2,3,4,6-Tetrahydro-8,9-dimethoxybenzo[*c*][2,7]naphthyridin-5(1*H*)-one hydrochloride (**13**).

A mixture of 14.2 g (0.039 mole) of the benzoylnaphthyridine **11**, 60 ml of water, 25 ml of 2-propanol, and 25 ml of concentrated sulfuric acid was stirred at reflux for 20 hours. The reaction mixture was cooled in ice and made basic by the addition of concentrated ammonia hydroxide. The resulting solid was filtered, washed with water, then digested on the steam bath with 75 ml of acetonitrile. Filtration yielded 9.0 g (89%) of the crude naphthyridine **12**. This material was employed in further syntheses without additional purification. A sample of **12** was recrystallized from 3.0 *N* hydrochloric acid to yield the analytically pure hydrochloride salt **13**, mp 250-255°.

3-[2-(Dimethylamino)ethyl]-2,3,4,6-tetrahydro-8,9-dimethoxybenzo[*c*][2,7]-naphthyridin-5(1*H*)-one (**14a**).

A mixture of 5.2 g (0.020 mole) of crude naphthyridine **12**, 3.5 g (0.024 mole) of 2-dimethylaminoethyl chloride hydrochloride, and 7.0 ml (5.1 g, 0.050 mole) of triethylamine in 125 ml of methanol was stirred at reflux for 24 hours. The mixture was filtered hot, then cooled and evaporated (vacuum). The residue was dissolved in 100 ml of water and made strongly basic with concentrated ammonium hydroxide. The product was extracted with chloroform (3 x 50 ml), and the combined extracts were

washed with water (1 x 75 ml), dried (anhydrous sodium sulfate) and evaporated (vacuum). The residue was triturated with petroleum ether to yield 2.0 g (30%) of the dimethylamino naphthyridine **14a**. A sample of **14a** recrystallized several times from acetonitrile was analytically pure, mp 160-165°.

2,3,4,6-Tetrahydro-8,9-dimethoxy-3-[2-(1-piperidinyl)ethyl]benzo[*c*][2,7]-naphthyridin-5(1*H*)-one (**14b**).

The title compound was prepared by the same procedure employed in the preparation of **14a**. From 5.2 g (0.020 mole) of **12** and 4.1 g (0.022 mole) of 1-(2-chloroethyl)piperidine hydrochloride, there was obtained 3.3 g (45%) of the piperidinyl naphthyridine **14b** after recrystallization from acetonitrile. An additional recrystallization from 2-propanol yielded analytically pure **14b**, mp 185-188°.

3-[2-(3-Azabicyclo[3.2.2]non-3-yl)ethyl]-2,3,4,6-tetrahydro-8,9-dimethoxybenzo[*c*][2,7]naphthyridin-5(1*H*)-one Dihydrochloride (**14c**).

A mixture of 10.0 g (0.034 mole) of the naphthyridine hydrochloride **13**, 8.3 g (0.037 mole) of 3-(2-chloroethyl)-3-(2-azabicyclo[3.2.2]nonane) hydrochloride [7] and 10.5 ml (7.6 g, 0.075 mole) of triethylamine in 200 ml of ethanol was stirred at reflux for 55 hours. The mixture was filtered hot, and the filtrate was treated with excess gaseous hydrogen chloride while still warm. The precipitated solid was filtered and recrystallized from ethanol to yield 6.5 g (40%) of the purified hydrochloride product **14c**. An additional recrystallization from methanol yielded analytically pure **14c**, mp 237-241°.

3-Benzoyl-2,3,4,6-tetrahydro-8,9-dimethoxy-6-methylbenzo[*c*][2,7]naphthyridin-5(1*H*)-one (**15**).

A stirred suspension of 0.82 g (0.017 mole) of 50% sodium hydride/mineral oil in 50 ml of *N,N*-dimethylformamide under a nitrogen atmosphere was cooled in ice while 5.0 g (0.014 mole) of the benzoyl naphthyridine **11** was added in portions over 15 minutes. The mixture was stirred an additional 15 minutes, and then 2.2 ml (5.0 g, 0.035 mole) of iodomethane was added in one portion. The ice bath was removed, and the mixture was stirred for an additional 2 hours, then added to 200 g of ice/water. The precipitated solid was filtered, washed with water, and recrystallized from 2-methoxyethanol to yield 4.0 g (77%) of the analytically pure product **15**, mp 243-245°.

2,3,4,6-Tetrahydro-8,9-dimethoxy-6-methyl-benzo[*c*][2,7]naphthyridin-5-(1*H*)-one tetrafluorohydrogenborate (**16**).

A solution of 10.0 g (0.053 mole) of triethyloxonium tetrafluoroborate in 150 ml of dichloromethane under a nitrogen atmosphere was treated with 10.0 g (0.026 mole) of the benzoylnaphthyridine **15**. The new mixture was stirred at reflux for 2 hours, then cooled, and the solvent was evaporated (vacuum). The residue was dissolved in 200 ml of 25% aqueous methanol plus 5.0 ml of glacial acetic acid. After stirring at room temperature for 18 hours, the precipitated fluoroborate salt **16** was removed by filtering (6.6 g, 69%). A sample recrystallized from aqueous methanol yielded the analytically pure salt **16**, mp 300° dec.

2,3,4,6-Tetrahydro-8,9-dimethoxy-6-methylbenzo[*c*][2,7]naphthyridin-5-(1*H*)-one (**17**).

The title compound was prepared by the same procedure employed in the preparation of **12**. From 1.2 g (0.0032 mole) of the benzoylnaphthyridine **15**, there was obtained by hydrolysis 0.7 g (80%) of the crude product **17**. A sample recrystallized from acetonitrile yielded analytically pure **17**, mp 178-179°.

3-[2-(3-Azabicyclo[3.2.2]non-3-yl)ethyl]-2,3,4,6-tetrahydro-8,9-dimethoxy-6-methylbenzo[*c*][2,7]naphthyridin-5(1*H*)-one Monohydrochloride Tetrafluorohydrogen Borate (**19a**).

The title compound was prepared by the same procedure employed in the preparation of **14c**. From 6.0 g (0.017 mole) of the fluoroborate salt **16** and 4.3 g (0.019 mole) of 3-(2-chloroethyl)-3-(2-azabicyclo[3.2.2]-nonane)hydrochloride [7] there was obtained 2.9 g (30%) of the mixed 50/50 fluoroborohydrogen borate/monohydrochloride salt **19a** after recrystallization from methanol. An additional recrystallization as above yielded analytically pure **19a**, mp 231-236°.

2,3,4,6-Tetrahydro-8,9-dimethoxy-6-methyl-3-[2-(1-piperidinyl)ethyl]-benzo[*c*][2,7]naphthyridin-5(1*H*)-one Dihydrochloride (**19b**).

The title compound was prepared by the same procedure employed in the preparation of **14c**, except that the heating time was reduced to 16 hours. From 2.2 g (0.008 mole) of the free base naphthyridine **19** and 1.84 (0.010 mole) of 1-(2-chloroethyl)piperidine hydrochloride, there was obtained 1.7 g (46%) of the piperidinylnaphthyridine **19b**, after recrystallization from 2-propanol/methanol. The analytically pure dihydrochloride had mp 234-240°.

2,3,4,6-Tetrahydro-8,9-dimethoxy-6-methyl-3-[2-(1-pyrrolidinyl)propyl]-benzo[*c*][2,7]naphthyridin-5(1*H*)-one Dihydrochloride (**19c**).

A mixture of 14.5 g (0.040 mole) of the flouroborate salt **16**, 7.4 g (0.077 mole) of ammonium carbonate, and 15.0 ml (17.4 g, 0.19 mole) of chloro-2-propanone in 75 ml of dimethyl sulfoxide was stirred at room temperature for 18 hours. The mixture was added to 800 g of ice/water and the crude ketone product **18** was extracted with dichloromethane (3 x 275 ml). The combined organic layers were back-washed with water (2 x 300 ml), dried (anhydrous sodium sulfate) and evaporated (vacuum). The residue was digested on the steam bath with 100 ml of ethyl acetate, then filtered and washed with hexane. There was obtained 9.0 g (68%) of the crude ketone intermediate **18**, mp 155°-dec, suitable for further synthesis.

The crude ketone intermediate **18** from the above procedure (9.0 g, 0.027 mole) was placed in a stirred stainless-steel autoclave and treated with 10.0 ml (8.5 g, 0.12 mole) of pyrrolidine, 0.5 ml (0.53 g, 0.0088 mole) of glacial acetic acid and 0.5 g of 10% palladium on carbon catalyst, all in 100 ml of 2-methoxyethanol. The reactor was pressurized with hydrogen (400 psig), heated to 90° for 5 hours, then allowed to cool while stirring continued for an additional 12 hours. The catalyst was removed by filtration, and the filtrate was evaporated (vacuum). The residue was dissolved hot in ethanol, filtered, and the filtrate was treated with excess gaseous hydrogen chloride, followed by diethyl ether. Cooling yielded 3.6 g (28%) of the purified dihydrochloride **19c**. A sample recrystallized again from ethanol-water-water-ether yielded analytically pure pyrrolidine naphthyridine **19c**, mp 210° dec.

Acknowledgement.

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REFERENCES AND NOTES

[1] D. T. Connor, P. C. Unangst, C. F. Schwender, R. J. Sorenson, M. E. Carethers, C. Puchalski, and R. E. Brown, *J. Heterocyclic Chem.*, **21**, 1561 (1984).

[2] R. N. Seelye and D. W. Stanton, *Tetrahedron Letters*, 2633 (1966).

[3] U. Kraatz and F. Korte, *Chem. Ber.*, **106**, 62 (1973).

[4] J. F. Hoops, H. Bader, and J. H. Biel, *J. Org. Chem.*, **33**, 2995 (1968).

[5] Z. Budesinsky and P. Lederer, *Collect. Czech. Chem. Commun.*, **37**, 2779 (1972).

[6] H. Muxfeldt and W. Rogalski, *J. Am. Chem. Soc.*, **87**, 933 (1965).

[7] P. P. Karkhanis and W. L. Nobles, *J. Pharm. Sci.*, **56**, 265 (1967).