Synthesis of Pyrido[4,3,2-*de*]quinazolines *via* Nitro-Substituted Tetrahydroquinolines

Alan R. Katritzky*, Sonja Strah and Dmytro O. Tymoshenko

Center for Heterocyclic Compounds, University of Florida, Department of Chemistry, Gainesville, FL 32611-7200, USA

Graham Johnson

Bristol-Myers Squibb Co., Pharmaceutical Research Institute, 5 Research Parkway, Wallingford, CT 06492-7660, USA

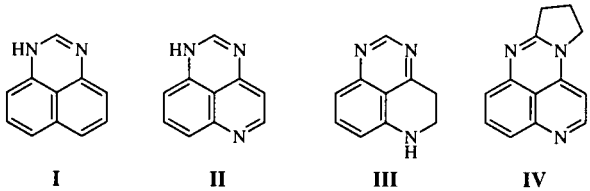
Received November 27, 1998

The simple and efficient synthesis of novel dihydropyrido[4,3,2-*de*]quinazolines in four steps from *m*-nitroaniline is described.

J. Heterocyclic Chem., **36**, 755 (1999).

Introduction.

Quinazolines show activity as antitumor drugs [1], tyrosine kinase [2a,b], phosphodiesterase [3], and thymidylate synthase [4] inhibitors. Such activity is enhanced by introducing amino substituents into the phenyl ring of the quinazoline system [2b] or by the annelation of another ring to the quinazoline system. Syntheses of imidazo-, dihydropyrimido- [5], triazino- [6], pyrazolo- [7], pyrrolo- [8] and pyrido- [2b, 9] quinazolin(on)es were reported recently. Perimidine (**I**) shows intercalative binding to DNA and antitumor activity [10]. Modification of the structure **I** afforded the more electron-deficient pyrido[4,3,2-*de*]quinazoline (**II**) [11]; some 1,3-dihydro derivatives of **II** exhibit *in vitro* activity as aldose reductase inhibitors [12].



I **II** **III** **IV**

Figure 1.

Usually, heteroannelated quinazolines are obtained by constructing an additional ring onto an appropriate quinazoline derivative, for example a 4-thione [5]. However, the only previously reported synthesis of the pyrido[4,3,2-*de*]quinazoline ring system utilized a multistep procedure starting from quinoline and adding the pyrimidine ring [11]. We recently reported convergent routes to functionalized tetrahydroquinolines by the addition of 1-(α-aminoalkyl)benzotriazoles to enamines, enamides and vinyl ethers [13-15]. Application of this methodology to nitro-substituted 1,2,3,4-tetrahydroquinolines **9** has now enabled the preparation of dihydropyrido[4,3,2-*de*]quinazolines **III** and **IV** (Figure 1).

Results and Discussion.

α-Aminoalkylbenzotriazoles **4** (Scheme 1) were readily prepared by reactions of *m*-nitroaniline (**1**) with benzotriazole (**2**) and alkylaldehydes **3** in methanol at room temperature in good yields (76-80%). Adducts **4** undergo partial ionization in solution to form benzotriazolyl anion **5** and the corresponding iminium cations **6** [16], which were trapped with electron-rich enamides **7** in the presence of Lewis acid. As previously reported [13, 14] this reaction involves double addition to form intermediate *N*-(β-amidopropyl)-substituted anilines **8**, which cyclized *in situ*, upon intramolecular electrophilic attack of the corresponding iminium cation on an electron rich *ortho* carbon of the aniline ring to form 5-nitro-substituted 1,2,3,4-tetrahydroquinolines **9** in moderate to good yields (62-78%) (Scheme 1, Table 1). One would expect the formation of two regio isomers due to two nonequivalent *ortho* positions, but electronic effects evidently favor cyclization exclusively at the C-atom between the nitro and amino groups of the aniline ring, as shown by nmr data of the crude cyclic product. Additionally, reactions of compounds **4** with 1-vinyl-2-pyrrolidinone (**7a**) resulted in the exclusive formation of only one diastereoisomer of **9a-c**. Their stereochemistry was assigned by NOE difference which showed *cis* relationship between protons at C-2 and C-4 in the tetrahydroquinoline ring which is consistent with literature data [14]. However, mixtures of *cis* and *trans* isomers in an approximate ratio of 4:1, according to nmr spectra, were isolated in the case of formamido substituent at C-4 in the tetrahydroquinoline ring. Subsequent catalytic hydrogenation of the nitro group over palladium on carbon led to amino derivatives **10** in nearly quantitative yields (91-98%). Compounds **10** are prone to air oxidation which at times precluded elemental analysis (Scheme 1, Table 1).

Upon heating of 2-methyl- (**10c**) and 2-*n*-propyl-5-amino-4-formamido-1,2,3,4-tetrahydroquinoline (**10d**)

Scheme 1

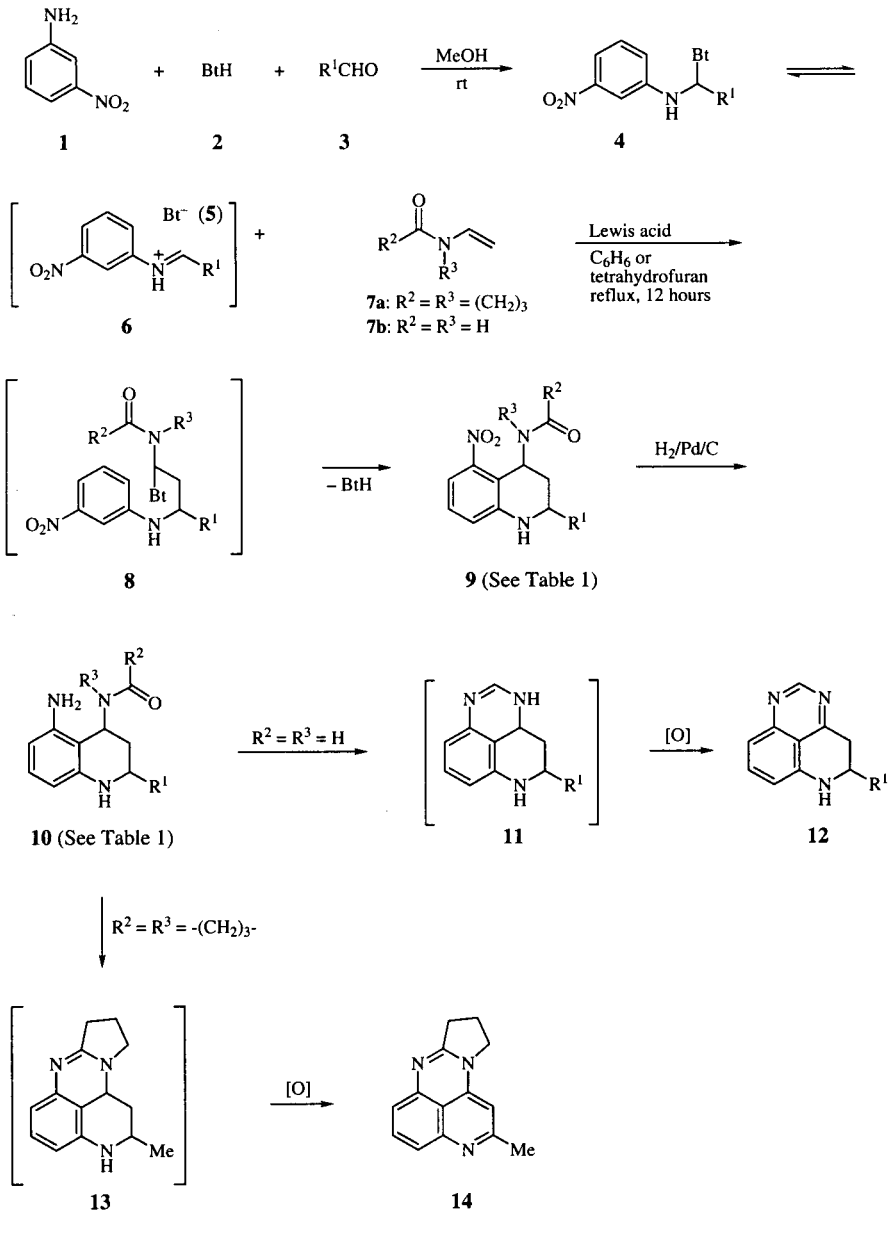


Table 1

The Preparation of 2,4,5-Trisubstituted 1,2,3,4-tetrahydroquinolines **9** and **10**

Entry	R^1	R^2		R^3	Yield (%)
9a	Me		$(CH_2)_3$		65
9b	*n*-Pr		$(CH_2)_3$		78
9c	*i*-Pr		$(CH_2)_3$		61
9d	Me	H		H	62
9e	*n*-Pr	H		H	69
9f	*i*-Pr	H		H	67
10a	Me		$(CH_2)_3$		98
10b	*n*-Pr		$(CH_2)_3$		94
10c	Me	H		H	91
10d	*n*-Pr	H		H	92

at 105-110° (neat) for 12 hours and further purification by column chromatography, cyclizations of the 4-formamido and 5-amino groups formed 5-methyl- (**12a**) and 5-*n*-propyl-5,6-dihydro[4,3,2-*de*]quinazoline (**12b**) which were isolated in 63% and 67% yields, respectively. Similarly, 2-methyl-5-amino-4-(pyrrolidin-2-on-1-yl)-1,2,3,4-tetrahydroquinoline (**10a**) was transformed to the corresponding dihydropyrido-[4,3,2-*de*]pyrrolo[2,1-*b*]quinazoline **14** in 61% yield (Scheme 1).

In conclusion, a simple and efficient synthesis of novel dihydropyrido[4,3,2-*de*]quinazolines *via* nitro-substituted tetrahydroquinolines is reported.

EXPERIMENTAL

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. The ^1H and ^{13}C nmr spectra were recorded on a Varian VXR-300 spectrometer at 300 MHz and 75 MHz respectively, with tetramethylsilane for ^1H and chloroform-*d* or dimethyl-d_6 sulfoxide for ^{13}C as internal references. Microanalyses were performed on a Carlo Erba 1106 elemental analyzer. High resolution mass spectra were recorded on an AEI-30 mass spectrometer. Tetrahydrofuran was distilled from sodium/benzophenone prior to use.

General Procedure for the Preparation of Substituted *N*-(Benzotriazol-1-yl)methyl-3-nitroanilines **4**.

The mixture of 3-nitroaniline (**1**, 1.38 g, 0.01 mole), 1*H*-benzotriazole (**2**, 1.19 g, 0.01 mole) and the corresponding aldehyde (**3**, 0.01 mole) in methanol (100 ml) was stirred at room temperature overnight. The precipitate formed was collected by filtration and washed with methanol to give product **4**.

N-(Benzotriazol-1-yl)ethyl-3-nitroaniline (**4a**).

This compound was obtained as yellow microcrystals, mp 128-130°; ^1H nmr (deuteriochloroform with dimethyl-d_6 sulfoxide): δ 1.99 (d, J = 6.5 Hz, 3H), 6.63-6.75 (m, 1H), 7.07 (d, J = 8.0 Hz, 1H), 7.23 (t, J = 8.2 Hz, 1H), 7.32-7.50 (m, 3H), 7.60 (s, 1H), 7.82 (d, J = 7.9 Hz, 1H), 7.96 (d, J = 8.2 Hz, 1H), 8.08 (d, J = 8.5 Hz, 1H); ^{13}C nmr: δ 20.7, 65.8, 106.8, 110.6, 111.9, 118.2, 119.0, 123.4, 126.7, 129.4, 130.3, 145.7, 146.1, 148.3.

Anal. Calcd. for $C_{14}H_{13}N_5O_2$: C, 59.36; H, 4.62; N, 24.72. Found: C, 59.63; H, 4.83; N, 24.95.

N-(α-Benzotriazol-1-yl)butyl-3-nitroaniline (**4b**).

This compound was obtained as yellow microcrystals, mp 130-131°; ^1H nmr (deuteriochloroform): δ 0.98 (t, J = 7.2 Hz, 3H), 1.25-1.32 (m, 1H), 1.45-1.52 (m, 1H), 2.39 (q, J = 7.5 Hz, 2H), 5.56 (d, J = 8.0 Hz, 1H), 6.41-6.49 (m, 1H), 7.10 (d, J = 7.9 Hz, 1H), 7.22 (t, J = 8.2 Hz, 1H), 7.35 (t, J = 7.4 Hz, 1H), 7.46-7.56 (m, 2H), 7.65 (s, 1H), 7.79 (d, J = 8.3 Hz, 1H), 7.07 (d, J = 8.2 Hz, 1H); ^{13}C nmr: δ 13.4, 18.7, 37.6, 69.8, 108.4, 109.8, 114.1, 119.0, 120.3, 124.3, 127.7, 130.2, 131.6, 145.6, 146.5, 149.1.

Anal. Calcd for $C_{16}H_{17}N_5O_2$: C, 61.72; H, 5.50; N, 22.49. Found: C, 62.08; H, 5.56; N, 22.72.

N-[(α-Benzotriazol-1-yl)-2-methyl]propyl-3-nitroaniline (**4c**).

This compound was obtained as yellow microcrystals, mp 132-134°; ^1H nmr (dimethyl-d_6 sulfoxide with deuteriochloroform): δ 0.68 (d, J = 6.4 Hz, 3H), 1.30 (d, J = 6.6 Hz, 3H), 2.65-2.78 (m, 1H), 6.10 (t, J = 8.8 Hz, 1H), 7.06 (d, J = 8.0 Hz, 1H), 7.19 (t, J = 8.0 Hz, 1H), 7.30-7.48 (m, 3H), 7.62 (s, 1H), 7.80 (d, J = 8.4 Hz, 1H), 7.96 (d, J = 8.3 Hz, 1H), 8.05 (d, J = 8.5 Hz, 1H); ^{13}C nmr: δ 18.2, 19.3, 32.5, 74.7, 106.7, 110.9, 111.8, 118.6, 119.2, 123.7, 127.1, 129.8, 131.1, 145.7, 146.9, 148.5.

Anal. Calcd. for $C_{16}H_{17}N_5O_2$: C, 61.72; H, 5.50; N, 22.49. Found: C, 61.73; H, 5.55; N, 22.60.

General Procedure for the Preparation of 5-Nitro-substituted 1,2,3,4-Tetrahydroquinolines **9**.

To a mixture of Bt-derivative **4** (3 mmoles) and the corresponding vinylamide **7** (3.6 mmoles) in dry tetrahydrofuran (50 ml) 5 drops of boron trifluoride etherate were added at room temperature. The reaction mixture was heated at reflux temperature for 12 hours, cooled, washed with water, aqueous sodium hydroxide (1*M*) and water again. The organic layer was separated and dried over anhydrous magnesium sulfate. The solvent was removed *in vacuo* to give an oily residue, which was triturated with ethyl acetate and hexanes. On cooling, the precipitate formed was collected by filtration and rinsed with ethyl acetate to give a pure product **9**.

2-Methyl-5-nitro-4-(pyrrolidin-2-on-1-yl)-1,2,3,4-tetrahydroquinoline (**9a**).

This compound was obtained as yellow microcrystals, mp 226-228°; ^1H nmr (deuteriochloroform): δ 1.25 (d, J = 6.1 Hz, 3H); 1.63 (q, J = 11.8 Hz, 1H), 1.88-1.96 (m, 2H), 2.04-2.11 (m, 1H), 2.23-2.43 (m, 2H), 2.93 (q, J = 7.3 Hz, 1H), 3.14 (q, J = 7.5 Hz, 1H), 3.45-3.53 (m, 1H), 5.74 (dd, J = 10.8 Hz and 7.5 Hz, 1H), 6.70 (d, J = 5.8 Hz, 1H), 6.88 (d, J = 7.7 Hz, 1H), 7.10 (t, J = 8.0 Hz, 1H); ^{13}C nmr: δ 17.9, 21.5, 30.6, 33.4, 42.7, 45.8, 46.1, 110.9, 112.7, 118.1, 128.4, 137.7, 147.8, 174.8.

Anal. Calcd. for $C_{14}H_{17}N_3O_3$: C, 61.08; H, 6.22; N, 15.26. Found: C, 61.24; H, 6.41; N, 15.34.

5-Nitro-2-*n*-propyl-4-(pyrrolidin-2-on-1-yl)-1,2,3,4-tetrahydroquinoline (**9b**).

This compound was obtained as yellow microcrystals, mp, 107-109°; ^1H nmr (deuteriochloroform): δ 0.97 (t, J = 6.6 Hz, 3H); 1.41-1.66 (m, 5H), 1.88-1.96 (m, 2H), 2.08-2.14 (m, 1H), 2.26-2.43 (m, 2H), 2.90-2.98 (m, 1H), 3.10-3.15 (m, 1H), 3.31-3.40 (m, 1H), 4.16 (br s, 1H), 5.74 (dd, J = 10.7 Hz and 7.7 Hz, 1H), 6.70 (d, J = 8.0 Hz, 1H), 6.88 (d, J = 7.7 Hz, 1H), 7.10 (t, J = 7.0 Hz, 1H); ^{13}C nmr: δ 14.0, 17.9, 18.4, 30.7, 31.5, 37.9, 42.7, 45.8, 50.1, 111.9, 112.6, 118.2, 128.3, 147.9, 151.1, 174.8; hrms (EI): m/z Calcd. for $C_{16}H_{22}N_3O_3$: 304.1661 (M+1). Found: 304.1648 (M+1).

5-Nitro-2-*i*-propyl-4-(pyrrolidin-2-on-1-yl)-1,2,3,4-tetrahydroquinoline (**9c**).

This compound was obtained as yellow microcrystals, mp 96-98°; ^1H nmr (deuteriochloroform): δ 1.01 (t, J = 6.6 Hz, 6H); 1.57-1.83 (m, 2H), 1.87-1.97 (m, 2H), 2.03-2.10 (m, 1H), 2.25-2.44 (m, 2H), 2.91-2.98 (m, 1H), 3.11-3.22 (m, 2H), 4.12 (br s, 1H), 5.75 (dd, J = 11.3 Hz and 7.4 Hz, 1H), 6.73 (d, J = 5.8 Hz, 1H), 6.88 (d, J = 7.7 Hz, 1H), 7.11 (t, J = 8.0 Hz, 1H); ^{13}C nmr: δ 17.8, 17.9, 18.3, 28.0, 30.7, 32.1, 42.7, 46.1, 55.8, 111.9, 112.6, 118.3, 128.4, 148.2, 151.1, 174.8.

Anal. Calcd. for $C_{16}H_{21}N_3O_3$: N, 13.85. Found: N, 14.13.

4-Formamido-2-methyl-5-nitro-1,2,3,4-tetrahydroquinoline (**9d**).

This compound was obtained as yellow microcrystals, mp 194-196°; ^1H nmr (deuteriochloroform with dimethyl-d_6 sulfoxide): δ 1.20 (d, J = 6.0 Hz, 3H); 1.47 (1.64) (q, J = 11.3 Hz, 1H), 2.13-2.20 (m, 1H), 3.65 (br s, 1H), 5.43 (5.02) (q, J = 8.9 Hz, 1H), 6.79-6.84 (m, 2H); 7.07 (t, J = 7.8 Hz, 1H), 7.90 (8.02) (s, 1H), 8.21 (d, J = 8.3 Hz, 1H); ^{13}C nmr: δ 20.9, 37.0, 41.4, 44.8, 111.0, 112.1, 117.7, 127.5, 148.0, 150.7, 159.9.

Anal. Calcd. for $C_{11}H_{13}N_3O_3$: C, 56.16; H, 5.57; N, 17.86. Found: C, 55.79; H, 5.60; N, 17.68.

4-Formamido-5-nitro-2-*n*-propyl-1,2,3,4-tetrahydroquinoline (**9e**).

This compound was obtained as yellow microcrystals, mp 183-185°; ^1H nmr (deuteriochloroform): δ 0.96 (t, J = 6.6 Hz,

3H), 1.46-1.61 (m, 5H), 2.13-2.29 (m, 1H), 3.29-3.34 (m, 1H), 5.52-5.60 (m, 2H), 6.86 (t, J = 12.3 Hz, 1H), 7.11 (t, J = 8.0 Hz, 1H), 7.96 (s, 1H), 8.06 (d, J = 8.0 Hz, 1H); ^{13}C nmr: δ 13.1, 17.4, 34.2, 36.6, 48.5, 110.7, 111.9, 117.4, 126.9, 147.1, 150.1, 159.6.

Anal. Calcd. for $C_{13}H_{17}N_3O_3$: C, 59.30; H, 6.51; N, 15.96. Found: C, 59.30; H, 6.63; N, 15.96.

4-Formamido-5-nitro-2-*i*-propyl-1,2,3,4-tetrahydroquinoline (**9f**).

This compound was obtained as yellow microcrystals, mp 133-135°; ^{1}H nmr (deuteriochloroform): δ 1.01 (t, J = 6.7 Hz, 6H), 1.49-1.84 (m, 2H), 2.36-2.42 (m, 1H), 3.16-3.21 (m, 1H), 5.52 (d, J = 6.4 Hz, 1H), 5.69-5.75 (m, 1H), 6.73 (d, J = 8.0 Hz, 1H), 7.01 (d, J = 7.8 Hz, 1H), 7.13 (t, J = 7.8 Hz, 1H), 7.28 (s, 1H), 8.11 (s, 1H); ^{13}C nmr: δ 19.5 (20.0), 33.6 (33.8), 37.0, 44.7, 57.3, 62.0, 112.8, 114.7, 115.4, 120.2, 130.2, 149.4, 161.9 (162.0).

Anal. Calcd. for $C_{13}H_{17}N_3O_3$: C, 59.30; H, 6.51; N, 15.96. Found: C, 59.12; H, 6.61; N, 15.86.

General Procedure for the Preparation of 5-Amino-Substituted 1,2,3,4-Tetrahydroquinolines **10**.

A mixture of the corresponding 5-nitro-substituted 1,2,3,4-tetrahydroquinoline **9** (1 mmole) and palladium on activated carbon in methanol (50 ml) was placed in a steel hydrogenator and subjected to hydrogenation at p = 300 psi and at room temperature overnight. Catalyst was filtered before removing the solvent *in vacuo* to give the desired product **10** which is prone to air oxidation and was subjected to cyclization without additional purification.

5-Amino-2-methyl-4-(pyrrolidin-2-on-1-yl)-1,2,3,4-tetrahydroquinoline (**10a**).

This compound was obtained as an oil; ^{1}H nmr (deuteriochloroform): δ 1.19 (d, J = 6.1 Hz, 3H), 1.67 (q, J = 11.8 Hz, 1H), 1.92-1.99 (m, 2H), 2.17 (t, J = 7.7 Hz, 1H), 2.41-2.46 (m, 2H), 2.89 (q, J = 7.7 Hz, 1H), 3.21-3.34 (m, 2H), 3.62 (br s, 1H), 3.70 (br s, 2H), 5.42 (t, J = 9.5 Hz, 1H), 5.99 (d, J = 8.0 Hz, 1H), 6.04 (d, J = 7.9 Hz, 1H), 6.84 (t, J = 7.7 Hz, 1H); ^{13}C nmr: δ 17.9, 21.8, 31.2, 35.7, 42.1, 45.0, 47.1, 104.6, 105.1, 106.0, 128.7, 146.3, 148.8, 175.7.

Anal. Calcd. for $C_{14}H_{19}N_3O_1$: C, 68.54; H, 7.81; N, 17.13. Found: C, 68.19; H, 8.24; N, 17.08.

5-Amino-2-*n*-propyl-4-(pyrrolidin-2-on-1-yl)-1,2,3,4-tetrahydroquinoline (**10b**).

This compound was obtained as an oil; ^{1}H nmr (deuteriochloroform): δ 0.97 (t, J = 6.8 Hz, 3H), 1.37-1.46 (m, 4H), 1.67 (q, J = 12.1 Hz, 1H), 1.92-1.99 (m, 2H), 2.21 (dd, J = 8.0 Hz and 10.7, 1H), 2.38-2.50 (m, 2H), 2.90 (q, J = 7.7 Hz, 1H), 3.16-3.29 (m, 2H), 3.65 (br s, 1H), 3.70 (br s, 2H), 5.43 (t, J = 9.6 Hz, 1H), 6.03 (t, J = 8.7 Hz, 2H), 6.85 (t, J = 7.8 Hz, 1H); ^{13}C nmr: δ 14.1, 17.9, 18.6, 31.2, 33.9, 38.2, 42.1, 45.0, 51.2, 104.9, 105.2, 105.9, 128.7, 146.3, 148.8, 175.7; hrms (FAB): m/z Calcd. for $C_{16}H_{24}N_3O_1$: 274.1919 (M+1). Found: 274.1932 (M+1).

5-Amino-4-formamido-2-methyl-1,2,3,4-tetrahydroquinoline (**10c**).

This compound was obtained as an oil; ^{1}H nmr (deuteriochloroform with dimethyl-d_6 sulfoxide): δ 1.16 (d, J = 6.3 Hz, 3H), 1.60-1.67 (m, 1H), 2.16-2.23 (m, 1H), 3.20-3.29 (m, 1H), 4.39 (br s, 2H), 4.99 (br s, 1H), 5.05 (q, J = 8.1 Hz, 1H), 5.88 (d, J = 7.9 Hz, 1H), 5.94 (d, J = 7.7 Hz, 1H), 6.68 (t, J = 7.8 Hz, 1H), 8.05 (s, 1H), 8.13 (d, J = 9.1 Hz, 1H); ^{13}C nmr: δ 21.5, 38.5, 40.3, 45.5, 103.6, 104.0, 104.6, 127.9, 146.8, 147.6, 160.7; hrms (FAB): m/z Calcd. for $C_{11}H_{16}N_3O_1$: 206.1293 (M+1). Found: 206.1227 (M+1).

5-Amino-4-formamido-2-*n*-propyl-1,2,3,4-tetrahydroquinoline (**10d**).

This compound was obtained as an oil; ^{1}H nmr (deuteriochloroform): δ 0.95 (t, J = 7.0 Hz, 3H), 1.24-1.46 (m, 4H), 1.62-1.75 (m, 1H), 2.40-2.46 (m, 1H), 3.15-3.27 (m, 1H), 3.78 (br s, 1H), 3.87 (br s, 2H), 5.25-5.33 (m, 1H), 5.85 (d, J = 7.3 Hz, 1H), 5.97 (d, J = 7.9 Hz, 1H), 6.04 (d, J = 7.9 Hz, 1H), 6.85 (t, J = 7.9 Hz, 1H), 8.17 (s, 1H); ^{13}C nmr: δ 14.0, 19.1, 37.1, 38.2, 41.2, 50.5, 105.1, 105.6, 105.7, 129.2, 146.3, 147.3, 161.1; hrms (FAB): m/z Calcd. for $C_{13}H_{19}N_1O_3$: 233.1528 (M^+). Found: 233.1531 (M^+).

General Procedure for the Preparation of 5,6-Dihydropyrido[4,3,2-*de*]quinazolines **12**.

The corresponding 5-aminosubstituted 1,2,3,4-tetrahydroquinoline **10** (0.10 g) was heated at 105-110° neat, under nitrogen, for 12 hours to give a crude product which was purified by column chromatography on silica gel (eluent: chloroform/methanol 50:1) to give the product **12**.

5-Methyl-5,6-dihydro-4*H*-pyrido[4,3,2-*de*]quinazoline (**12a**).

This compound was obtained as yellow microcrystals, mp 136-138°; ^{1}H nmr (deuteriochloroform): δ 1.44 (d, J = 6.1 Hz, 3H), 2.97-3.24 (m, 2H), 3.80-3.86 (m, 1H), 4.52 (br s, 1H), 6.68 (d, J = 7.5 Hz, 1H), 7.28 (d, J = 8.7 Hz, 1H), 7.64 (t, J = 8.5 Hz, 1H), 9.09 (s, 1H); ^{13}C nmr: δ 21.7, 40.6, 48.1, 107.8, 113.0, 115.7, 135.4, 145.7, 149.8, 155.2, 165.9.

Anal. Calcd. for $C_{11}H_{11}N_3$: C, 71.33; H, 5.99; N, 22.69. Found: C, 71.07; H, 6.31; N, 22.31.

5-*n*-Propyl-5,6-dihydro-4*H*-pyrido[4,3,2-*de*]quinazoline (**12b**).

This compound was obtained as yellow microcrystals, mp 127-129°; ^{1}H nmr (deuteriochloroform): δ 1.02 (t, J = 7.3 Hz, 3H), 1.47-1.59 (m, 2H), 1.67-1.75 (m, 2H), 2.97-3.06 (m, 1H), 3.25 (dd, J = 3.6 Hz and 16.7 Hz, 1H), 3.67-3.72 (m, 1H), 4.61 (br s, 1H), 6.69 (d, J = 7.7 Hz, 1H), 7.28 (d, J = 8.2 Hz, 1H), 7.64 (t, J = 8.0 Hz, 1H), 9.09 (s, 1H); ^{13}C nmr: δ 14.0, 18.6, 37.7, 38.2, 52.1, 107.7, 111.2, 115.6, 135.4, 145.6, 155.3; hrms (FAB): m/z Calcd. for $C_{13}H_{16}N_3$: 214.1344 (M+1). Found: 214.1328 (M+1).

Anal. Calcd. for $C_{13}H_{15}N_3$: C, 73.21; H, 7.09. Found: C, 72.86; H, 7.65.

2-Methyl-9,10-dihydro-8*H*-pyrido[4,3,2-*de*]pyrrolo[2,1-*b*]quinazoline (**14**).

5-Amino-substituted 1,2,3,4-tetrahydroquinoline **10a** (0.10 g) was heated at 135-140° neat under nitrogen for 36 hours to give a crude product which was purified by column chromatography on silica gel (eluent: chloroform/methanol 20:1) to give compound **14** as pale microcrystals, mp 220-222° dec; ^{1}H nmr (deuteriochloroform): δ 2.27-2.34 (m, 2H), 2.53 (s, 3H), 2.90 (t, J = 8.0 Hz, 2H), 3.64 (t, J = 7.4 Hz, 2H), 5.88 (s, 1H), 6.96 (d, J = 7.4 Hz, 1H), 7.42 (d, J = 8.5 Hz, 1H), 7.54 (t, J = 8.0 Hz, 1H); ^{13}C nmr: δ 19.2, 25.7, 31.3, 46.8, 96.2, 114.0, 114.7, 120.5, 131.9, 143.3, 144.4, 148.8, 159.4, 161.1; hrms (EI): m/z Calcd. for $C_{14}H_{14}N_3$: 224.1188 (M+1). Found: 224.1178 (M+1).

Acknowledgment.

Financial support from the Slovenian Science Foundation in the form of a postdoctoral fellowship for S. S. is gratefully acknowledged.

REFERENCES AND NOTES

[1] R. L. Hagan, J. B. Hynes, M. Pimsler, and R. L. Kisliuk, *Biochem. Pharm.*, **50**, 803 (1995).

[2a] B. D. Palmer, S. Trumpp-Kallmeyer, D. W. Fry, J. M. Nelson, H. D. H. Showalter and W. A. Denny, *J. Med. Chem.*, **40**, 1519 (1997); [b] G. W. Rewcastle, B. D. Palmer, A. M. Thompson, A. J. Bridges, D. R. Cody, H. Zhou, D. W. Fry, A. McMichael and W. A. Denny, *J. Med. Chem.*, **39**, 1823 (1996).

[3] Y. Takase, T. Saeki, N. Watanabe, H. Adachi, S. Souda and I. Saito, *J. Med. Chem.*, **37**, 2106 (1994).

[4] J. R. Piper, N. D. Malik, M. S. Rhee, J. Galivan and F. M. Sirotnak, *J. Med. Chem.*, **35**, 332 (1992).

[5] K. Spirkova and S. Stankovsky, *Collect. Czech. Chem. Commun.*, **61**, 957 (1996).

[6] V. G. Reddy and P. S. N. Redy, *Indian J. Chem.*, **31** (B), 764 (1992).

[7] N. P. Peet and E. W. Huber, *Heterocycles*, **35**, 315 (1993).

[8] B. Ojo and B. K. Chowdhury, *Synth. Commun.*, **25**, 569 (1995).

[9] P. Molina, A. Lorenzo and E. Aller, *Tetrahedron*, **48**, 4601 (1992).

[10] J. M. Herbert, P. D. Woodgate and W. A. Denny, *J. Med. Chem.*, **30**, 2081 (1987).

[11] P. D. Woodgate, J. M. Herbert and W. A. Denny, *Heterocycles*, **26**, 1029 (1987).

[12] Japan Kokai Tokkyo Koho, Japan Patent 02,111,762 [90,111,762]; *Chem. Abstr.*, **113**, 172043 (1990).

[13] A. R. Katritzky, B. Rachwal and S. Rachwal, *J. Org. Chem.*, **58**, 812 (1993).

[14] A. R. Katritzky, B.Rachwal and S. Rachwal, *J. Org. Chem.*, **60**, 3993 (1995).

[15] For a recent review on the synthesis and applications of 1,2,3,4-tetrahydroquinolines, see A. R. Katritzky, S. Rachwal and B. Rachwal, *Tetrahedron*, **52**, 15031 (1996).

[16] A. R. Katritzky, K. Yannakopoulou, W. Kuzmierkiewicz, J. M. Aurrecoechea, G. J. Palenik, A. E. Koziol and M. Szczesniak, *J. Chem. Soc., Perkin Trans. 1*, 2673 (1987).