Synthesis of Substituted Dihydrobenzo[*f*]pyrimido[4,5-*b*]-quinolines as Tetracyclic 5-Deaza Nonclassical Folates

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Cyclocondensation of 2,4,6-triaminopyrimidine (**10**) with chlorovinyl aldehyde **7** afforded the linear regioisomer 9,11-diamino-5,6-dihydrobenzo[*f*]pyrimido[4,5-*c*]quinoline (**1**) while the cyclocondensation of 2,6-diamino-4-hydroxypyrimidine (**11**) or 6-amino-2,4-dihydroxypyrimidine (**12**) with chlorovinyl aldehyde **7** was regiospecific affording the linear regioisomers 9-amino-11-oxo-5,6-dihydrobenzo[*f*]pyrimido[4,5-*c*]quinoline (**2**) and 9,11-dioxo-5,6-dihydrobenzo[*f*]pyrimido[4,5-*c*]quinoline (**3**) respectively. The linear structures of these compounds were established by ^{1}H nmr and ^{13}C nmr spectral data.

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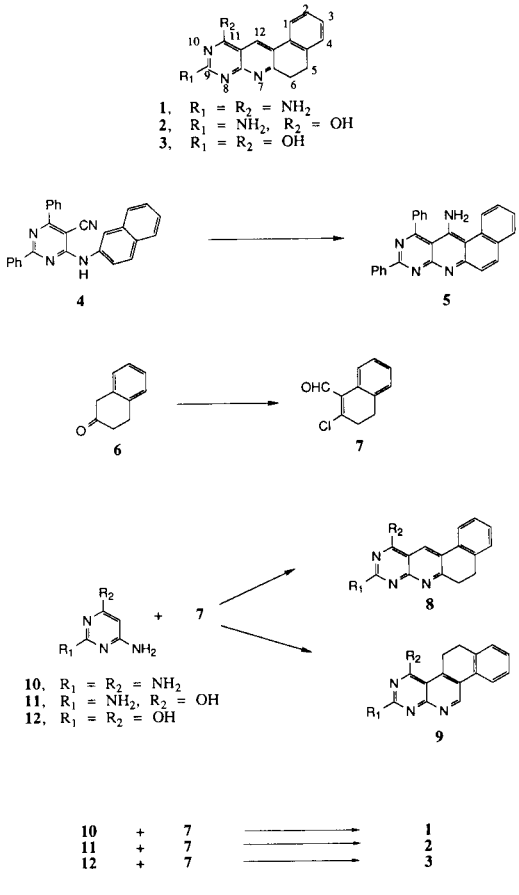
Compounds possessing the pyrimidine ring or the pyrido[2,3-*d*]pyrimidine ring as part of their ring system have shown significant antitumor activity [1-6]. Our interest in the development of novel nonclassical antifolates directed us toward the synthesis of three new tetracyclic 5-deaza nonclassical folates **1-3** possessing the pyrido-[2,3-*d*]pyrimidine ring as part of their ring systems.

Synthesis of the parent benzo[*f*]pyrimido[4,5-*b*]quinoline ring has been reported by Robev [7]. The synthetic route he employed involved reacting *N*-naphthylbenzamidine with 1-phenyl-2,2-dicyanoethylene to give nitrile **4** which was cyclized with polyphosphoric acid or aluminum chloride to give amine **5**. This procedure was however not suitable for our purpose so an alternative route to the dihydrobenzo[*f*]pyrimido[4,5-*b*]quinoline ring was sort. It was envisioned that a single step facile entry into the dihydrobenzo[*f*]pyrimido[4,5-*b*]quinoline ring could be achieved *via* the cyclocondensation of an appropriately substituted 6-aminopyrimidine and a biselectrophile derived from 2-tetralone (**6**). Gangjee *et al.* [8,9] and Taylor and Warner [10] have reported the cyclocondensation of cyclic chlorovinyl aldehydes and vinyl aldehydes with substituted 6-aminopyrimidines and have indicated that the direction of ring closure in such cyclocondensation reactions is influenced by the nature of the biselectrophile, the pyrimidine, and the solvent. Thus, condensation of 2-chloro-3,4-dihydronaphthyl-1-carboxaldehyde (**7**) with a substituted 6-aminopyrimidine can afford either 5,6-dihydrobenzo[*f*]pyrimido[4,5-*b*]quinoline (**8**) and/or its angular isomer 5,6-dihydrobenzo[*h*]pyrimido[4,5-*c*]isoquinoline (**9**).

Chlorovinyl aldehyde **7** was synthesized from **6** by Vilsmeier chloroformylation with dimethylformamide and phosphorus oxychloride following a modification of the procedure of Benson and Pohland [11]. The 1-formyl isomer was obtained exclusively as established by homogeneity on silica gel in two different solvent systems and by ^{1}H nmr analysis. Both the ir and ^{1}H nmr spectra of the pro-



duct were as expected. The compound was purified by flash chromatography on silica gel with methylene chloride-methanol (20:1) as eluant.

Cyclocondensation of chlorovinyl aldehyde **7** with 2,4,6-triaminopyrimidine (**10**) in glacial acetic acid afforded the linear regioisomer 9,11-diamino-5,6-dihydrobenzo[*f*]pyrimido[4,5-*b*]quinoline (**1**) and an unidentified yellow solid. Condensation of chlorovinyl aldehyde **7** with either 2,6-diamino-4-hydroxypyrimidine (**11**) or 6-amino-2,4-dihydroxypyrimidine (**12**) in glacial acetic acid was regiospecific and gave the linear regioisomers 9-amino-11-oxo-5,6-dihydrobenzo[*f*]pyrimido[4,5-*b*]quinoline (**2**) and 9,11-dioxo-5,6-dihydrobenzo[*f*]pyrimido[4,5-*b*]quinoline (**3**) respectively.

Assignment of linear structures to these compounds was based on ^{1}H nmr and ^{13}C nmr spectral data. Literature evidence [12-16] indicate that in compounds in which the pyrido[2,3-*d*]pyrimidine ring forms part of the heterocycle, the aromatic proton *gamma* to the nitrogen atom of the pyridine ring always occurs close to δ 9.00 while the aromatic proton *alpha* to the nitrogen atom of the pyridine ring resonates about 0.50 ppm upfield from δ 9.00 in deuteriotrifluoroacetic acid. Compounds **1**, **2**, and **3** had their pyridine-like aromatic protons (*i.e.* H_{12}) resonating at δ 9.22, 9.40 and 9.44 respectively in deuteriotrifluoroacetic acid and hence establishes their linear structures as designated.

Further evidence for the linear structure of these compounds were furnished by the ^{13}C nmr spectral data since it has been established that the aromatic carbon *gamma* to the nitrogen atom of the pyridine ring in pyrido[2,3-*d*]-pyrimidines and pyridine-like heterocycles resonate between 134-137 ppm with a one bond coupling constant $^1J_{C_{\gamma}\text{-}H}$ of 164-166 Hz while the aromatic carbon *alpha* to the nitrogen atom of the pyridine ring in such ring systems resonate around 155 ppm with a one bond coupling constant $^1J_{C_{\alpha}\text{-}H}$ of 177-180 Hz [16-18]. Thus, there is a distinct difference in the chemical shift positions as well as the coupling constants of these aromatic carbons in the ^{13}C nmr. The C_{12} carbons of compounds **1**, **2** and **3** resonated at 141.21 ppm, 140.17 ppm, and 141.26 ppm respectively with a one bond coupling constant $^1J_{C_{\gamma}\text{-}H}$ of 190 Hz, 169.7 Hz, and 170.5 Hz respectively. Though the coupling constant ($^1J_{C_{\gamma}\text{-}H}$) of compound **1** (190 Hz) is large compared to literature values (164-166 Hz) for compounds of this system with an aromatic carbon *gamma* to the nitrogen atom of the pyridine ring, the resonance position of the C_{12} carbon (141.21 Hz) in the ^{13}C nmr as well as the resonance position of the C_{12} proton (δ 9.22) in the ^{1}H nmr strongly support the linear structure of compound **1** as designated rather than an angular structure.

Due to solubility problems, biological testing of compounds **1-3** could not be performed. We are currently in the process of synthesizing other soluble tetracyclic non-classical folates.

EXPERIMENTAL

Melting points were determined on a Mel-Temp melting point apparatus and are uncorrected. Infrared spectra (ir) were recorded with a Perkin-Elmer 1320 Infrared Spectrophotometer in nujol mulls. Nuclear magnetic resonance spectra for proton (^{1}H nmr) were run on a Varian EM 390 nmr spectrometer and for carbon-13 (^{13}C) on a Brucker WH-300 at 75.46 MHz, 90° pulse, 14 μsec. The data was accumulated by 16K size with 0.5 second delay time and 70° tip angle with internal standard TMS; s = singlet, d = doublet, t = triplet, m = multiplet. Thin layer chromatography (tlc) was performed on cellulose or silica gel plates with fluorescent indicator and were visualized with light at 254 nm. Elemental analysis were performed by Atlantic Microlabs Inc., Atlanta Georgia.

2-Chloro-3,4-dihydronaphthyl-1-carboxaldehyde (**7**).

Into a three-necked flask fitted with a drying tube, a thermometer and a nitrogen inlet tube, was placed 1.67 g (22.9 mmoles) dimethylformamide and cooled to 0-5°. To this was added dropwise 2.25 g (14.67 mmoles) phosphorus oxychloride with continuous stirring while maintaining the temperature below 20°. After 30 minutes the reaction mixture became turbid and 10 ml of methylene chloride was added. After the addition was complete, the reaction was continued at 27° for 2 hours. A solution of 1 g (5.68 mmoles) of **6** in 5 ml of methylene chloride was added dropwise to the mixture while maintaining the temperature of the reaction below 30°. After addition was complete, the reaction was continued at 27° for 8 hours. Following this period 20 g of crushed ice was added and the mixture stirred for 15 minutes and the methylene chloride fraction was separated. The aqueous portion was extracted with 10 ml of methylene chloride. The combined methylene chloride extracts were poured into 15 ml of saturated sodium bicarbonate solution and the mixture was stirred vigorously for 15 minutes. The methylene chloride fraction was then separated, washed twice with water (10 ml), dried (magnesium sulfate) and evaporated under reduced pressure (water aspirated). It was purified by flash chromatography on silica gel with methylene chloride-methanol (20:1) as the eluant to give 84% of **7**; tlc (a. silica gel: hexenes-acetone, 2:1, R_f 0.73; b. silica gel: ethyl acetate-methanol-ammonium hydroxide, 8:2:1, R_f 0.85); ir (neat): 1670 cm^{-1} (CHO); ^{1}H nmr (deuteriochloroform): δ 2.80 (m, 4H, CH_2CH_2), 7.10 (m, 2H, aromatic), 7.92 (m, 2H, aromatic), 10.42 (s, 1H, CHO).

9,11-Diamino-5,6-dihydrobenzo[*f*]pyrimido[4,5-*b*]quinoline (**1**).

To a refluxing solution of 4.11 g (0.033 mole) of 2,4,6-triaminopyrimidine (**10**) in 150 ml of glacial acetic acid was added dropwise a solution of 6.4 g (0.033 mole) of chlorovinyl aldehyde **7** in 10 ml glacial acetic acid over a period of 30 minutes and the mixture was refluxed for 18 hours. The reaction mixture was cooled to room temperature and the precipitated yellow solid was filtered. The filtrate was basified (*p*H 9) with ammonium hydroxide while maintaining the temperature below 15° by means of an ice bath. The precipitated solid was filtered, air dried and recrystallized from ethanol-hydrochloric acid mixture to give 41% of **1** as the hydrochloride salt, mp >300°. The compound was homogeneous on tlc in three different solvent systems: a) cellulose: butanol-water-acetic acid, 3:3:1, R_f 0.79; b) silica gel: ethyl

acetate-methanol-ammonium hydroxide, 8:2:1, R_f 0.73, c) silica gel: methylene chloride-methanol, 3:1, R_f 0.65; ir (nujol): 3140 cm^{-1} (NH_2); ^1H nmr (deuteriotrifluoroacetic acid): δ 3.18 (t, 2H, 5-CH_2), 3.72 (t, 2H, 6-CH_2), 7.54 (m, 3H, aromatic protons) 7.82 (br s, 1H, aromatic proton), 9.22 (s, 1H, 12-CH); ^{13}C nmr (deuteriotrifluoroacetic acid): 141.21 ppm (190 Hz) (C_{12} aromatic carbon).

Anal. Calcd. for $C_{15}H_{13}N_5 \cdot 1.1HCl$: C, 59.38; H, 4.68; N, 23.08; Cl, 12.85. Found: C, 59.41; H, 4.73; N, 22.72; Cl, 13.05.

9-Amino-11-oxo-5,6-dihydrobenzo[*f*]pyrimido[4,5-*b*]quinoline (**2**).

To a refluxing solution of 3.24 g (0.026 mole) of 2,6-diamino-4-hydroxypyrimidine (**11**) in 100 ml of glacial acetic acid was added dropwise a solution of 5.0 g (0.026 mole) of chlorovinyl aldehyde **7** in 10 ml of glacial acetic acid during a 20 minute period and refluxing was continued for 18 more hours. Following this period the mixture was cooled to room temperature and the precipitated solid was filtered. It was suspended in 10% ammonium hydroxide, stirred for 15 minutes, filtered and the solid was washed with water until the washings were neutral. It was suspended in ethanol and drops of concentrated hydrochloric acid was added to make it acidic. The mixture was boiled for five minutes, cooled to room temperature and filtered. The filtrate was set aside to deposit 3.8 g (55.8%) of **2**, mp >300° tlc analysis [cellulose: butanol-water-acetic acid (3:3:1), R_f = 0.78] indicated a homogeneous product; ir (nujol): 3100 cm^{-1} (NH_2), 1650 cm^{-1} (C=O); ^1H nmr (deuteriotrifluoroacetic acid): δ 3.30 (t, 2H, 5-CH_2), 3.48 (t, 2H, 6-CH_2), 7.50 (m, 3H, aromatic protons), 7.90 (br s, 1H, aromatic proton), 9.40 (s, 1H, 12-CH); ^{13}C nmr (deuteriotrifluoroacetic acid): 140.17 ppm (169.7 Hz) (C_{12} aromatic carbon).

Anal. Calcd. for $C_{15}H_{12}N_4O \cdot 1HCl$: C, 59.90; H, 4.33; N, 18.64; Cl, 11.88. Found: C, 59.86; H, 4.51; N, 18.45; Cl, 11.72.

9,11-Dioxo-5,6-dihydrobenzo[*f*]pyrimido[4,5-*b*]quinoline (**3**).

A mixture of 5.0 g (0.026 mole) of chlorovinyl aldehyde **7** in 10 ml of glacial acetic acid was added dropwise to a refluxing solution of 3.26 g (0.026 mole) of 6-amino-2,4-dihydroxypyrimidine (**12**) in 300 ml of glacial acetic acid and refluxing was continued for a further 12 hours. Following this period the mixture was allowed to cool to room temperature and filtered. The filtrate was basified with ammonium hydroxide at temperatures below 15° to *p*H 8. The precipitated solid was filtered and washed with water until the washings were neutral. The solid was then dried to give 6.4 g (94%) of **3**, mp >300°. The compound was homogeneous on tlc: a). Cellulose: butanol-water-acetic acid, 3:3:1, R_f = 0.82; b). Silica gel: ethyl acetate-methanol-ammonium hydroxide, 8:2:1, R_f = 0.57; ir (nujol): 1670 cm^{-1} (C=O); ^1H nmr (deuteriotrifluoroacetic acid): δ 3.30 (t, 2H, 5-CH_2), 3.48 (t, 2H, 6-CH_2), 7.55 (m, 3H, aromatic protons), 7.98 (d, 1H, aromatic proton), 9.44 (s, 1H, 12-CH); ^{13}C nmr (deuteriotrifluoroacetic acid): 141.26 ppm (170.5 Hz) (C_{12} aromatic carbon).

Anal. Calcd. for $C_{15}H_{11}N_3O_2 \cdot 1H_2O$: C, 63.60; H, 4.63; N, 14.74. Found: C, 63.36; H, 4.64; N, 14.71.

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REFERENCES AND NOTES

[1] B. S. Hurlbert, K. W. Ledig, P. Stenbuck, B. F. Valenti and G. H. Hitchings, *J. Med. Chem.*, **11**, 703 (1968).

[2] A. Rosowsky and N. Papthansopoulos, *ibid*, **17**, 1272 (1974).

[3] E. M. Grivsky, S. Lee, C. W. Sigel, D. S. Duch and C. A. Nichol, *J. Med. Chem.*, **23**, 327 (1980).

[4] S. R. Stone, J. A. Montgomery and J. F. Morrison, *Biochem. Pharmacol.*, **33**, 175 (1984).

[5] L. M. Werbel in Folate Antagonists as Therapeutic Agents, Vol **1**, F. M. Sirotnak, J. J. Burchall, W. B. Ensminger and J. A. Montgomery eds, Academic Press Inc., New York, NY, 1984, p 261.

[6] NSC-112519-Data available from the Drug Development Branch, National Cancer Institute, NIH.

[7] S. Robev, *Dokl. Bolg. Akad. Nauk.*, **33**, 929 (1980).

[8] A. Gangjee, K. A. Ohemeng, J. J. Tulachka, F.-T. Lin and A. A. Katoh, *J. Heterocyclic Chem.*, **22**, 1149 (1985).

[9] A. Gangjee, K. A. Ohemeng, F.-T. Lin and A. Katoh, *ibid*, **23**, 523 (1986).

[10] E. C. Taylor and J. C. Warner, *Heterocycles*, **26**, 2673 (1987).

[11] W. R. Benson and A. E. Pohland, *J. Org. Chem.*, **30**, 1126 (1965).

[12] A. Srinivasan, P. E. Fargerness and A. D. Broom, *J. Org. Chem.*, **43**, 828 (1978).

[13] H. C. S. Wood, R. Wrigglesworth, D. A. Yeowell, F. W. Gurney and B. S. Hurlbert, *J. Chem. Soc., Perkin Trans. 1*, 1225 (1974).

[14] F. Yoneda, M. Koga and T. Nagamatsu, *Synthesis*, 75 (1983).

[15] E. C. Taylor, J. S. Skotnicki and S. R. Fletcher, *J. Org. Chem.*, **50**, 1005 (1985).

[16] A. Gangjee and K. A. Ohemeng, *J. Heterocyclic Chem.*, **24**, 123 (1987).

[17] K. Tori and T. Nakagawa, *J. Phy. Chem.*, **68**, 3163 (1964).

[18] R. T. Pugmire, D. M. Grant, J. J. Robins and R. K. Robins, *J. Am. Chem. Soc.*, **91**, 6381 (1969).