Synthesis of a Pyrrolo Annulated Pyrido[2,3-*d*]pyrimidine As a Potential Nonclassical Antifolate

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Cyclocondensation of 2,4,6-triaminopyrimidine (**4**) with ethyl *N*-benzyl-4-oxo-3-pyrrolidine carboxylate (**5**) in diphenyl ether regiospecifically afforded a new tricyclic, angular 1,3,8-trisubstituted pyrrolo[3',4':4,5]-pyrido[2,3-*d*]pyrimidine-6-one **1** in excellent yield. The ketoester **5** was prepared by a literature method. Compound **1** in addition to being a new heterocyclic system is an important key precursor to a variety of classical and nonclassical tricyclic, 5-deaza analogues of the folate cofactor 5,10-methylenetetrahydrofolate **3**.

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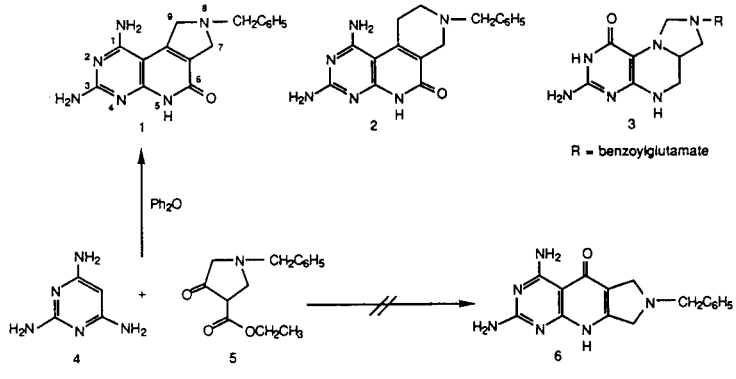
We wish to report the synthesis of 8-benzyl-1,3-diamino-5,7,8,9-tetrahydro-1*H*-pyrrolo[3',4':4,5]pyrido[2,3-*d*]pyrimidine-6-one (**1**), a new heterocyclic ring system, which we have synthesized as part of our efforts towards the synthesis of tricyclic-5-deazafolates as potential antitumor agents [1-3]. The synthesis of a homologue of **1**, 8-benzyl-1,3-diamino-7,8,9,10-tetrahydropyrimido[4,5-*c*][2,7]naphthyridin-6-(5*H*,8*H*)-one (**2**) was reported by our group in 1984 [1]. This compound had shown 50% inhibition of the growth of leukemia L1210 cells in culture at 2 x 10^{-6} *M*. We were interested in the synthesis of compound **1** to investigate the effect of a pyrrolo annulated ring on biological activity in the leukemia L1210 system and more importantly as a key precursor to classical and nonclassical tricyclic-5-deaza-analogues of the folate cofactor 5,10-methylenetetrahydrofolate (**3**).

The synthesis of angular compound **2** was reported by our group [1] *via* the regiospecific cyclocondensation of 2,4,6-triaminopyrimidine (**4**) with methyl *N*-benzyl-4-oxo-3-piperidine carboxylate in glacial acetic acid. We anticipated that a similar cyclocondensation of ethyl *N*-benzyl-4-oxo-3-pyrrolidinecarboxylate (**5**) with **4** in glacial acetic acid should afford **1**. Accordingly, compound **5** was synthesized based on the method of Jaeger and Biel [4]. This method involved the synthesis of ethyl *N*-benzyl-*N*-(β-carbethoxyethyl)glycinate which upon Dieckmann cyclization affords **5**. Condensation of **4** with **5** in glacial acetic acid at reflux for 12-18 hours did not afford any product. Prolonged heating for up to 48 hours in glacial acetic acid gave the starting pyrimidine and unidentifiable product as indicated on tlc.

In an attempt to avoid a multistep synthetic sequence to the heterocyclic ring system which would build the tricyclic system stepwise from appropriately substituted pyrimidines, pyridines or pyrrolidines we sought a different solvent system that would allow the cyclocondensation of **4** and **5** to afford the desired tricyclic compound **1** in one step.

Hurlbert and co-workers [7] had reported that cyclocondensations of 1,2-disubstituted β-ketoesters with aminopyrimidines in diphenyl ether, as solvent, also afforded regiospecifically the 5,6-disubstituted pyrido-[2,3-*d*]pyrimidines and not the 6,7-disubstituted isomers. These workers had confirmed their structure by independent synthetic routes. Diphenyl ether was also utilized as a solvent by Grivsky *et al.* [8] in an extension of the work reported by



Hurlbert *et al.* to afford other 5,6-disubstituted pyrido-[2,3-*d*]pyrimidines. Thus diphenyl ether was a logical choice in our one step cyclocondensation. We were initially concerned about using different solvent systems, in view of the fact that the direction of ring closure dictates the structure (angular **1** and/or linear **6**) of the product [5,6] and that the solvent, among other factors, does influence the direction of ring closure and hence the regiospecificity of the reaction [6].

However, we were aware that the structure of the product **1** and/or **6** could be identified based on the chemical shift position of the carbonyl carbon of the lactam. The linear isomer **6** would be a γ-pyridone and the angular isomer **1** would be an α-pyridone. According to literature precedent [6] γ-pyridones have their carbonyl carbon chemical shift positions in the ^{13}C nmr spectra in the range of δ 177.9-178.5, while α-pyridones have their carbonyl carbons at about 10 ppm higher field than α-pyridones. Compound **2** an α-pyridone had its lactam carbonyl at δ 166.03 [1].

Using a modification of the method described by Grivsky *et al.* [8] **4** was cyclocondensed with **5** in diphenyl ether at 190-200° with continuous removal of ethanol and water *via* a Dean-Stark attachment to afford an 87% yield of a single product. This product was homogeneous on tlc in three different solvent systems and its decoupled ^{13}C nmr showed fourteen signals indicating that the cyclocondensation was indeed regiospecific and that a single product had formed. Evidence for the angular structure for compound **1** (an α-pyridone) was provided by the chemical shift position of the lactam carbonyl which occurred at δ 170.90. This position agrees well with the carbonyl position obtained for compound **2** (δ 166.03) and is about 8 ppm higher field than the range for γ-pyridones [6]. This along with the established direction of ring closure in similar cyclocondensation reactions using diphenyl ether as solvent [7,8] confirms the angular structure as shown as **1**. The ^1H nmr spectra of **1** was consistent with its structure; in particular the lactam proton which occurs at δ 8.97 in the free base. This lactam proton exchanges on addition of deuterium oxide. The 2- and 4-amino protons occur at δ 5.60 and δ 6.00 and also exchange on addition of deuterium oxide.

We are currently utilizing **1** in the synthesis of classical and nonclassical 5-deaza analogues of **3** which will be the topic of future communications.

EXPERIMENTAL

Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared spectra (ir) were recorded with a Perkin Elmer Model 1430, in Nujol mulls. Nuclear magentic resonance spectra for proton (^1H nmr) were recorded on a Varian EM-360 and for carbon-13 (^{13}C nmr) 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, m = multiplet. Thin layer chromatography (tlc) was performed on silica gel plates and cellulose plates with fluorescent indicator or as otherwise indicated and were visualized with light at 254 nm and 366 nm. Elemental analysis was performed by Galbraith Laboratories, Inc., Knoxville, Tennessee.

8-Benzyl-1,3-diamino-5,7,8,9-tetrahydro-1*H*-pyrrolo[3',4':4,5]pyrido-[2,3-*d*]pyrimidine-6-one (**1**).

In a flask equipped with a Dean-Stark trap, a mixture of 5.6 g (0.045 mole) of 2,4,6-triaminopyrimidine (**4**) and 11.1 g (0.045 mole) of the keto-ester **5** (hydrochloride salt, mp 126-127°; lit mp 127-129° [4]) in 60 ml of diphenyl ether was heated rapidly with vigorous stirring to a temperature of 190-200°. The reaction mixture was then maintained at 190-200° until no additional ethanol-water mixture distilled off (4.5 hours). The mixture was then allowed to cool to room temperature, treated with 50 ml of methanol and the product collected by filtration. The product was washed with ether (200 ml) and air dried to afford 6.2 g of a yellow powder. The filtrate was treated with excess ether (450 ml) to yield a precipitate that was filtered, washed with ether and air dried to yield a further 5.8 g of a yellow powder identical to that obtained earlier (tlc). The total yield of the product was 87%. The compound was homogeneous on tlc: a. silica gel; chloroform-methanol (4:1 v/v) R_f = 0.54; b. silica gel; ethanol-water-pyridine (16:4:3 v/v) R_f = 0.81; c. cellulose; butanol-acetic acid-water (3:1:3 v/v) R_f = 0.95; mp 216-220° dec; ir (nujol): 3440, 3340 cm^{-1} (NH_2), 3155 cm^{-1} (NH), 1650 cm^{-1} (broad, C=O); ^1H nmr (DMSO-d_6): (free base) δ 3.13 (s, 2H, CH_2N), 3.73 (s, 2H, CH_2N), 4.47 (s, 2H, $CH_2C_6H_5$), 5.60 (s, 2H, NH_2), 6.00 (s, 2H, NH_2), 7.30 (s, 5H, C_6H_5), 8.97 (s, 1H, NHCO); ^{13}C nmr (DMSO-d_6): 170.90 ppm (free base). An analytical sample was prepared as a pale yellow hydrochloride salt by recrystallization from ethanol-ethyl acetate-hydrochloric acid (6:1:1 v/v).

Anal. Calcd. for $C_{16}H_{16}N_6O \cdot HCl \cdot 0.25H_2O$: C, 55.02; H, 5.05; N, 24.06; Cl, 10.15. Found: C, 54.72; H, 4.96; N, 23.71; Cl, 9.97.

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