Synthesis of Some Substituted Tetrahydropyrimido[4,5-*b*][1,6]naphthyridines as Potential Antitumor Agents [1]

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Received July 1, 1986

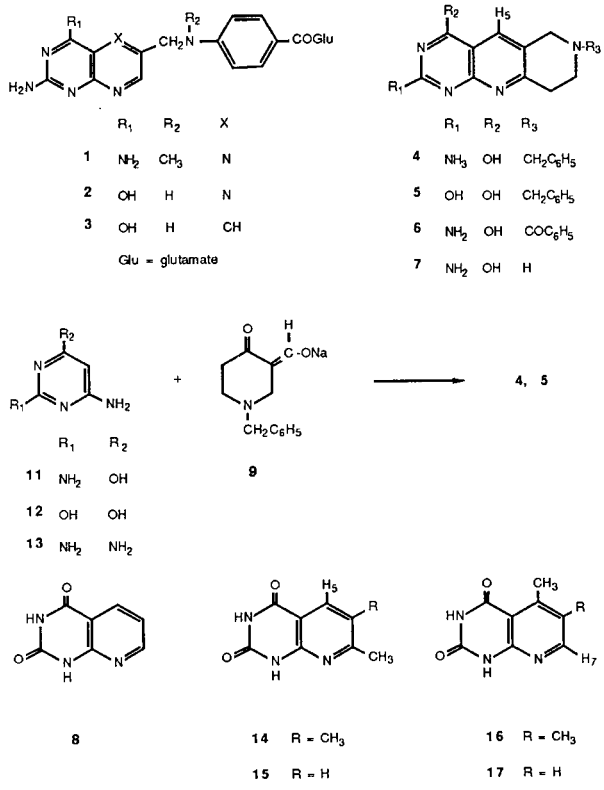
Cyclocondensation of two disubstituted 6-aminopyrimidines **11** and **12** with 1-benzyl-3-hydroxymethylene-4-piperidone afforded new tricyclic, linear disubstituted 6,7,8,9-tetrahydropyrimido[4,5-*b*][1,6]naphthyridines **4** and **5** respectively. Similar cyclocondensation of **11** with 1-benzoyl-1,2,3,6-tetrahydropyridine-5-carboxaldehyde gave the corresponding benzoylated tetrahydropyrimido[4,5-*b*][1,6]naphthyridine **6**. Debenzoylation of **6** afforded **7**. 1-Benzyl-3-aminomethylene-4-piperidone when cyclocondensed with **11** also afforded **4**. The linear structures were established by ^{1}H nmr and ^{13}C nmr. The growth of leukemia L1210 cells in culture was inhibited about 50% by **4**,**5**,**6** and **7** at 100 μM.

J. Heterocyclic Chem., **24**, 123 (1987).

Methotrexate (MTX) (**1**) is a dihydrofolate reductase inhibitor and a clinically useful antitumor agent. All of the potent antifolate, dihydrofolate reductase inhibitors reported thus far have been 2,4-diamino substituted classical and nonclassical analogues of folic acid (**2**) [3]. However, recently, Stone *et al.*, [4] have reported that 5-deazafolic acid (**3**), a 2-amino-4-oxo substituted analogue, possess significant inhibitory activity against dihydrofolate reductases. As part of our interest in tricyclic, 5-deaza, folate analogues and homologues as potential antitumor agents [1,5,6] we have synthesized three new pyrimido[4,5-*b*][1,6]naphthyridines **4-6**. The 2-amino-4-oxo substituted compounds **4** and **6** are nonclassical tricyclic analogues of **3**, while compound **5** is a pyridine annulated analogue of 2,4-dioxopyrido[2,3-*d*]-pyrimidine (**8**) which has been reported to possess antitumor activity [7].

Based on our previous report [6] that cyclic ketoaldehydes, when cyclocondensed in acid with substituted 6-aminopyrimidines, afford regiospecifically the linear rather than the angular isomers, we proposed that 1-benzyl-3-hydroxymethylene-4-piperidone as its sodium salt **9** should serve as the ketoaldehyde for the syntheses of compounds **4** and **5**. The synthesis of **9** was accomplished by formylation of 1-benzyl-4-piperidone (**10**) with ethyl formate in the presence of sodium metal and a catalytic amount of ethanol according to a literature procedure [8]. The ^{1}H nmr spectrum of **9** was as anticipated and the ir spectrum compared favorably with that reported in the literature [8].

Cyclocondensation of 2,6-diamino-4-hydroxypyrimidine (**11**) with **9** in phosphoric acid (generating the aldehyde from **9** *in situ*) afforded regiospecifically 2-amino-7-benzyl-4-oxo-6,7,8,9-tetrahydro-3*H*-pyrimido[4,5-*b*][1,6]naphthyridine (**4**). Similarly, 2,4-dioxo-6-aminopyrimidine (**12**) when condensed with **9** yielded 7-benzyl-2,4-dioxo-6,7,8,9-tetrahydro-1*H*,3*H*-pyrimido[4,5-*b*][1,6]naphthyridine (**5**).

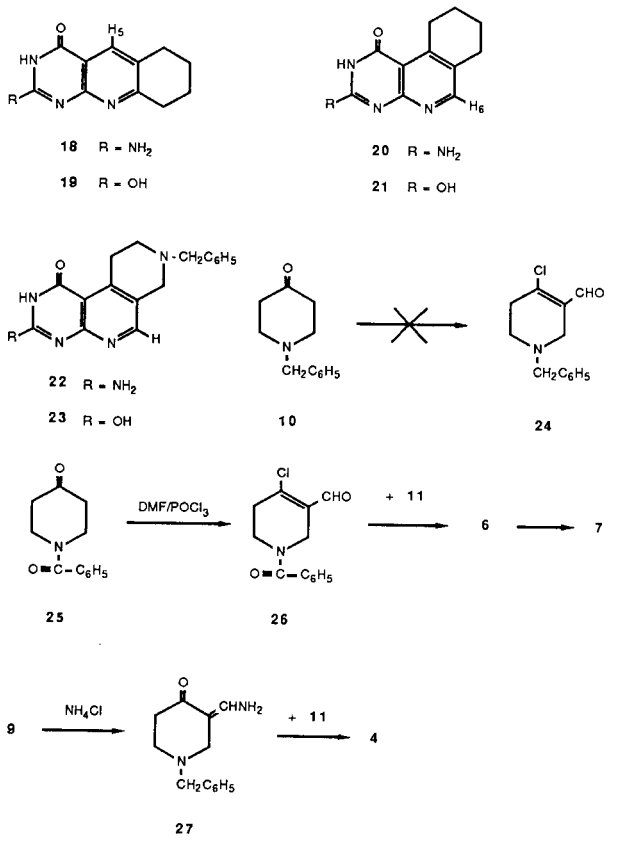


Assignment of the linear structures to compounds **4** and **5** was based in part on the report of Robins and Hitchings [9]. These workers had reported that aminopyrimidines such as **12** when cyclocondensed with simple 3-ketoaldehydes such as 2-methyl-3-oxobutanal afforded regiospecifically the 6,7-dimethylpyrido[2,3-*d*]pyrimidine **14** rather than the 5,6-dimethyl isomer **16**. Robins and Hitchings [9] unambiguously assigned the structures of their products based on a comparison with products synthesized from independent routes. The direction of such ring closures using aminopyrimidines and 3-ketoaldehydes has since been confirmed by Wood *et al.*, [10] in their resynthesis of **14**

and by us [6] in our synthesis of linear pyrimido[4,5-*b*]quinolines **18** and **19** using appropriate aminopyrimidines and a 3-ketoaldehyde derived from cyclohexanone. It is known that in each of the reported cases [6,9,10] the most nucleophillic position in the pyrimidine, which is the C_5 carbon, attacks the aldehyde carbonyl of the ketoaldehyde while the 6-amino group of the pyrimidine condenses with the ketone carbonyl.

In an attempt to further substantiate the linear structures of **4** and **5** we turned to the ^1H nmr spectral data of the compounds and in particular to the chemical shift position of the aromatic H_5 proton in each case. Evidence from the literature of the aromatic proton position of similar compounds were compared with those of **4** and **5**. The 2,4-dioxopyrido[2,3-*d*]pyrimidine **15** and related compounds [10] and the substituted pyrimido[4,5-*b*]quinolines **18** and **19** [6] consistently had their H_5 aromatic protons at about δ 9.00 in deuterated trifluoroacetic acid. This resonance position is about 0.5 ppm downfield compared to the corresponding aromatic proton H_7 of the 5,6-dimethyl and 5-methyl substituted isomers **16** and **17** respectively in the pyrido[2,3-*d*]pyrimidine series, which occurred at about δ 8.5 [10]. This was also true for the aromatic protons H_6 of the substituted, angular pyrimido-[4,5-*c*]isoquinolines **20** and **21** [11]. Compounds **4** and **5** had aromatic proton signals in their ^1H nmr spectra at δ 8.66 and 8.73 respectively. These chemical shifts are not in the δ 9.00, range indicating that perhaps the angular isomers **22** and **23** may have been formed. This appeared to be inconsistent with the established direction of ring closure [6,9,10] of similar cyclocondensations. An alternate explanation of the upfield shift of the H_5 aromatic proton, from about δ 9.00 could be a long range shielding effect attributable to the 7-benzyl moiety in both **4** and **5**. If this were indeed true, then the *N*-debenzylated product should have its H_5 proton near δ 9.00. Thus **4** was *N*-debenzylated using catalytic hydrogenation to afford 2-amino-4-oxo-6,7,8,9-tetrahydro-3*H*-pyrimido[4,5-*b*][1,6]naphthyridine (**7**) [12]. The ^1H nmr spectrum of compound **7**, in deuterated trifluoroacetic acid, showed an aromatic proton signal at δ 8.93. This chemical shift position, obtained after debenzylation, confirmed that the 7-benzyl group was involved in shielding of the H_5 proton and that indeed the cyclocondensation had afforded the linear isomer as depicted in **4**.

Further evidence for the linear structures of **4** and **5** were obtained from the ^{13}C nmr spectra, in particular from the one bond coupling constant $^1J_{C\text{-}H}$ and the chemical shift of the γ-carbon. It has been reported [13,14] that the carbon γ to the nitrogen atom of the pyridine ring in pyrido[2,3-*d*]pyrimidines and pyridine like heteroaromatic systems has a chemical shift position in the range of 134-137 ppm which is at a higher field than the α carbon.



Further the $^1J_{C_\gamma\text{-}H}$ is in the range of 164-166 Hz which is about 15 Hz less than the $^1J_{C_\alpha\text{-}H}$ coupling constant. The carbon-13 resonances which were doublets in the aromatic region for the proton coupled spectra of **4** and **5** occurred at δ 133.84 and 134.07 respectively which was in the range of carbons γ to the nitrogen. In addition the one bond coupling constants for **4** and **5** $J^{13}{}_{C\text{-}}{}^1{}_H$ were 163.50 Hz and 163.58 Hz respectively. Both the chemical shift position and the $J^{13}{}_{C\text{-}}{}^1{}_H$ coupling constants confirmed that the carbon involved in coupling to the hydrogen in each case was the C_5 carbon and consequently that **4** and **5** have linear structures as shown.

Having established the structures for two of the target compounds **4** and **5** we were interested in extending our recently reported method of cyclocondensation of aminopyrimidines with chlorovinyl aldehydes which in the case of the 2-amino-4-oxo and 2,4-dioxo-6-aminopyrimidines had afforded the linear tricyclic isomers **18** and **19** in excellent yields [6]. Modification of this cyclocondensation for the synthesis of pyrimido[4,5-*b*][1,6]naphthyridines required the synthesis of 1-benzyl-4-chloro-1,2,3,6-tetrahydropyridine-5-carboxaldehyde (**24**). The synthesis of **24** from 1-benzyl-4-piperidone involved a modification of the Vilsmier chloroformylation with dimethylformamide and phosphorous oxychloride as we have reported for cyclohexanone [6]. Several attempts at the chloroformylation of

1-benzyl-4-piperidone with a variety of time, temperature, and solvent modifications, were unsuccessful and the expected product **24** could not be obtained. It was suspected that the basicity of the piperidone nitrogen caused its protonation and that perhaps an intermediate hydrochloride salt was precipitating out as a yellow crystalline material, effectively inhibiting the reaction. In an attempt to circumvent this problem by reducing the basicity of the pyridine nitrogen, 1-benzoyl-4-piperidone (**25**) was chloroformylated to afford 1-benzoyl-4-chloro-1,2,5,6-tetrahydropyridine-5-carboxaldehyde (**26**) [12]. Condensation of **11** with **26** yielded 2-amino-7-benzoyl-4-oxo-6,7,8,9-tetrahydro-3*H*-pyrimido[4,5-*b*][1,6]naphthyridine (**6**) in 62% yield. The elemental analysis and spectral data (^{1}H nmr, ir) for **6** were as anticipated. Since the compound was insoluble in trifluoroacetic acid a comparison of the chemical shift of its H_5 aromatic proton with that of **4** and **5** was not possible. However, acid hydrolysis of **6** afforded the *N*-debenzoylated product which was identical to **7** in all respects (tlc, ^{1}H nmr, ir). Compound **7** has been recently reported by us [12] and was obtained from the catalytic *N*-debenzylation of **4** as described earlier.

In view of our interest in the direction of ring closure and our previous report that aminomethylene ketones when condensed with aminopyrimidines afford the linear rather than the angular isomers [6] it was of interest to extend the aminomethylene ketone biselectrophile to the synthesis of pyrimido[4,5-*b*][1,6]naphthyridines. Accordingly 1-benzyl-3-aminomethylene-4-piperidone (**27**) was synthesized by the aminolysis of **9** according to a modification of a literature report [15]. Cyclocondensation of **11** with **27** afforded regiospecifically a product identical to **4** in all respects (tlc, ^{1}H nmr, ir). This further substantiates the linear structure of **4** and reconfirms our earlier report [6] that aminomethylene ketones do indeed afford the linear tricyclic isomers.

The growth of leukemia L1210 cells in culture [17] was inhibited 45% by **4** at 100 μM, 57% by **5** at 100 μM, 42% by **6** at 100 μM and 47% by **7** at 100 μM. We are currently in the process of synthesizing the 2,4-diamino analogues derived from **13** and **9** and variously substituted nonclassical folate analogues of **7**.

EXPERIMENTAL

Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Infrared (ir) spectra were recorded with a Perkin-Elmer Model 337 in Nujol mulls. Nuclear magnetic resonance spectra for proton (^{1}H 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 μseconds. 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 and m = multiplet. Thin layer chromatography (tlc) was performed on cellulose plates with fluorescent indicator or as otherwise indicated and were visualized with light at 254 nm. The elemental analyses were performed by Atlantic Microlabs, Inc. Atlanta, Georgia.

Sodium Salt of 1-Benzyl-3-hydroxymethylene-4-piperidone (**9**).

Into a three-necked flask fitted with a drying tube containing 65 ml of anhydrous ether was added 0.74 g (0.03 mole) of sodium metal which had been cut into small pieces (about 1 cm^3). To the mixture was added 3.6 g (0.05 mole) of ethyl formate (dried with potassium carbonate) and 6.12 g (0.03 mole) of 1-benzyl-4-piperidone **10**. The reaction was initiated by the addition of 0.15 ml of absolute ethanol to the mixture which was cooled in an ice bath to 5°. The reaction was allowed to proceed for 6 hours with continuous stirring then stirring was discontinued and the mixture left to stand for 6 hours. The reaction was completed by the addition of 0.2 ml of absolute ethanol, and stirred for an additional hour. The yellow precipitate thus formed was filtered, washed with anhydrous ether and dried under reduced pressure with phosphorus pentoxide for 4 hours to give 6.2 g (86%) of **9**. Owing to the nature of the product, further purification was not possible. Tlc (silica gel, methanol-chloroform, 3:17) R_f 0.82; ir (nujol): 1643 cm^{-1} (C=O), 1560 (C=C); (lit [8] 1643 cm^{-1}, 1560); ^{1}H nmr (deuterium oxide): δ 2.45 (t, 2H, C-CH_2-N), 2.60 (t, 2H, CH_2-C=O), 3.25 (s, 2H, C=C-CH_2), 3.60 (s, 2H, CH_2C$_6$H$_5$), 7.40 (s, 5H, C$_6$H$_5$), 9.12 (s, 1H, HC-ONa).

1-Benzyl-3-aminomethylene-4-piperidone (**27**).

A mixture of 13.1 g, (0.06 mole) of the sodium salt of 1-benzyl-3-hydroxymethylene-4-piperidone **9**, and 4.4 g (0.08 mole) of ammonium chloride in 50 ml of absolute ethanol was stirred for 12 hours in a three-necked flask fitted with a drying tube. A mixture of 100 ml of chloroform and 50 ml of water was then added to the reaction. The chloroform layer was separated and the aqueous layer extracted twice with 20 ml of chloroform. The combined chloroform fractions were dried with anhydrous magnesium sulfate, filtered and evaporated to dryness under reduced pressure (water aspirator) to give 8.7 g (70%) of (**27**), as a thick red syrup. Tlc (silica gel, methanol-chloroform, 9:1) two spots R_f 0.82 and 0.78 (considered to be the two tautomeric forms [16]; ir (neat): 1650 cm^{-1} (C=N); ^{1}H nmr (DMSO-d$_6$): δ 6.60 (broad s, 2H, NH and OH, exchanges with deuterium oxide), 7.33 (s, 5H, C$_6$H$_5$), 8.44 (s, 1H, HC=N); (deuterated chloroform): δ 2.5-4.0 (m, 8H, C-CH_2-N, CH_2-C=O, C=C-CH_2 and C$_6$H$_5$-CH_2), 5.65 (broad s, 2H, NH$_2$, exchanges with deuterium oxide), 7.25 (s, 6H, H-C=C and C$_6$H$_5$).

2-Amino-7-benzyl-4-oxo-6,7,8,9-tetrahydro-3*H*-pyrimido[4,5-*b*][1,6]-naphthyridine (**4**). Method A.

Finely powdered 4.0 g (0.02 mole) of the sodium salt of 1-benzyl-3-hydroxymethylene-4-piperidone **9**, was added to a solution of 2.2 g (0.02 mole) of 2,6-diamino-4-hydroxypyrimidine **11** in 30 ml of 85% phosphoric acid. The solution was heated at 100° for 3 hours and poured into 180 ml of water, cooled to 5° and neutralized to *p*H 7 with concentrated ammonium hydroxide solution (with the temperature maintained below 15°). The white precipitate thus formed was filtered, washed with water and dried under reduced pressure with phosphorous pentoxide for 24 hours to give 4.2 g (68%) of **4**. Tlc (cellulose; butanol-acetic acid-water, 3:1:3) R_f 0.88. An analytical sample was prepared as the hydrochloride salt by suspending the compound in water then heating to boil followed by the addition of drops of concentrated hydrochloric acid (12*N*) till a solution was obtained. The solution was treated with charcoal, filtered hot and left at 10° to deposit 5.5 g of the hydrochloride salt (75%); mp >300°; ir (Nujol): 3325 cm^{-1} (NH$_2$), 3228 (NH), 1667 (C=O); ^{1}H nmr (deuteriotrifluoroacetic acid): δ 3.4-5.1 (m, 8H, 6-, 8-, 9-CH$_2$ and -CH_2C$_6$H$_5$), 7.43 (s, 5H, C$_6$H$_5$), 8.66 (s, 1H, 5CH).

Anal. Calcd. for C$_{17}$H$_{17}$N$_5$O·2HCl: C, 53.69; H, 5.04; N, 18.42. Found: C, 53.84; H, 5.05; N, 18.41.

Method B.

A solution of 1.0 g (0.005 mole) of 1-benzyl-2-aminomethylene-4-piperidone **27** and 0.02 g of piperidine acetate catalyst in 5 ml of acetic acid was added to a solution of 0.6 g (0.005 mole) of 2,6-diamino-4-hydroxypyrimidine **11** in 20 ml of acetic acid-water mixture (2:1) at 25°. The mixture was refluxed for 4 hours, filtered hot, the filtrate cooled to 15° and made basic with concentrated ammonium hydroxide solution

with the temperature maintained below 20°. The precipitate formed was filtered, washed with water and air dried to give 0.4 g (28%) of **4**. The hydrochloride salt was prepared as in Method A which afforded a compound that was identical to **4** (tlc, ir, ^{1}H nmr and ^{13}C nmr).

7-Benzyl-2,4-dioxo-6,7,8,9-tetrahydro-1*H*,3*H*-pyrimido[4,5-*b*][1,6]naphthyridine (**5**).

A solution of 2.5 g (0.02 mole) of 6-aminouracil **12**, in 30 ml of 85% phosphoric acid was prepared by heating to 60° and then cooled to 25°. To this cooled solution was added 4.5 g (0.02 mole) of the finely powdered sodium salt of 1-benzyl-3-hydroxymethylene-4-piperidone **9**. The mixture was heated at 100° for 3 hours with stirring and poured into 120 ml of water. The precipitate formed was filtered, washed with warm water and air dried. It was then dissolved in 20 ml of warm 2*N* sodium hydroxide and filtered. The filtrate was neutralized to *p*H 7 with dilute acetic acid. The resulting precipitate was filtered, air dried and recrystallized from dimethylsulfoxide-water (20:1) to afford 4.9 g (80%) of **5**, mp >300°; tlc (cellulose, butanol-acetic acid-water; 3:1:3) R_f 0.92; ir (Nujol): 3154 cm^{-1} (NH) 1724, 1667 (C=O); ^{1}H nmr (DMSO-d_6): δ 2.9 (s, 4H, 8- and 9-CH_2), 3.67 (d, 4H, 6-CH_2 and C_6H_5-CH_2), 7.4 (s, 5H, C_6H_5), 8.0 (s, 1H, 5-CH), 11.48 (s, 1H, 1NH), 11.63 (s, 1H, 3-NH); (deuteriotrifluoroacetic acid): δ 3.2-5.2 (m, 8H, 8-, 9-, 6-CH_2, and C_6H_5-CH_2), 7.67 (s, 5H, C_6H_5), 8.73 (s, 1H, 5-CH).

Anal. Calcd. for $C_{17}H_{16}N_4O_2 \cdot 0.2H_2O$: C, 65.46; H, 5.30; N, 17.96. Found: C, 65.47; H, 5.28; N, 18.10.

2-Amino-7-benzoyl-4-oxo-6,7,8,9-tetrahydro-3*H*-pyrimido[4,5-*b*][1,6]-naphthyridine (**6**).

A solution of 15 g (0.06 mole) of 1-benzoyl-4-chloro-1,2,3,6-tetrahydropyridine-5-carboxaldehyde (**26**) [12] in 20 ml of acetic acid was added dropwise to a stirred solution of 6.3 g (0.05 mole) of 2,6-diamino-4-hydroxypyrimidine (**11**) in 180 ml of acetic acid over a 45-minute period. The mixture was refluxed for 14 hours and poured into 100 ml of water, cooled to 25° and filtered. The filtrate was neutralized to *p*H 7 with concentrated ammonium hydroxide solution at a temperature maintained below 20°. The precipitate formed was filtered, washed with water, air dried and suspended in 150 ml of cold water. The suspension was chilled in an ice bath to 5° and sodium hydroxide pellets added while stirring until all the solid had dissolved. The solution was then filtered and neutralized to *p*H 7 with 10% hydrochloric acid. The resulting precipitate was filtered and recrystallized from ethanol-water-hydrochloric acid (8:2:1) to afford 12.9 g (62%) of **6** as the hydrochloride salt, mp >300°; ir (Nujol): 3300 cm^{-1} (NH_2), 3130 (NH), 1724, 1715, 1667 (C=O), 1610 (C=C); ^{1}H nmr (DMSO-d_6-deuterium oxide 9:1): δ 3.13 (m, 2H, 8-CH_2) 3.83 (m, 2H, 9-CH_2, 4.83 (s, 2H, 6-CH_2), 7.47 (s, 5H, C_6H_5), 8.40 (s, 1H, 5-CH).

Anal. Calcd. for $C_{17}H_{15}N_5O_2 \cdot 0.5HCl \cdot 0.6H_2O$: C, 58.28; H, 4.80; N, 19.99. Found: C, 58.03; H, 5.04; N, 19.87.

2-Amino-4-oxo-6,7,8,9-tetrahydro-3*H*-pyrimido[4,5-*b*][1,6]naphthyridine (**7**).

A solution of 2.3 g (0.006 mole) of **6** in 15 ml of concentrated hydrochloric acid (12*N*) and 4 ml of water was refluxed for 2.5 hours and cooled to deposit a yellowish brown solid which was filtered and the residue stirred in 20 ml of ether filtered and air dried. Recrystallization from ethanol-water-hydrochloric acid (8:2:1) afforded 1.7 g (90%) of **7** as the hydrochloride salt. This product was identical to that previously reported from the *N*-debenzylation of **4** [12].

Acknowledgements.

We thank Dr. Arthur A. Katoh, Department of Pathology, Mercy Hospital, Pittsburgh, PA 15219 for the leukemia L1210 assay and Dr. Fu-Tyan Lin, Department of Chemistry, University of Pittsburgh, Pittsburgh, PA 15260 for the carbon-13 spectra. This investigation was supported in part by a Faculty Development Grant to Aleem Gangjee from Duquesne University and in part by a grant #CH-332 from the American Cancer Society.

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