Synthesis of 2-Amino-4-hydroxy-1,3,5-triazanaphthalenes

J. I. DeGraw and V. H. Brown

Department of Pharmaceutical Chemistry, SRI, Menlo Park, California 94025

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The synthesis of 2-amino-4-hydroxy-6-amyl-1,3,5-triazanaphthalene (**8**) is described as a model sequence pertinent to preparation of 8-deazafolic acid and its analogs. Condensation of 2-acetamido-4-hydroxy-6-pyrimidinealdehyde (**3**) with dimethyl 2-oxoheptylphosphonate afforded 1-(2′-acetamido4′-hydroxy-6′-pyrimidinyl)-1-octene-3-one (**4**) as a key intermediate. Conversion of **4** to 1-(2′-amino-4′-hydroxy-5′-phenylazo-6′pyrimidinyl)-3-octanone (**7**) followed by reductive cyclization yielded **8** or its tetrahydro derivative (**9**).

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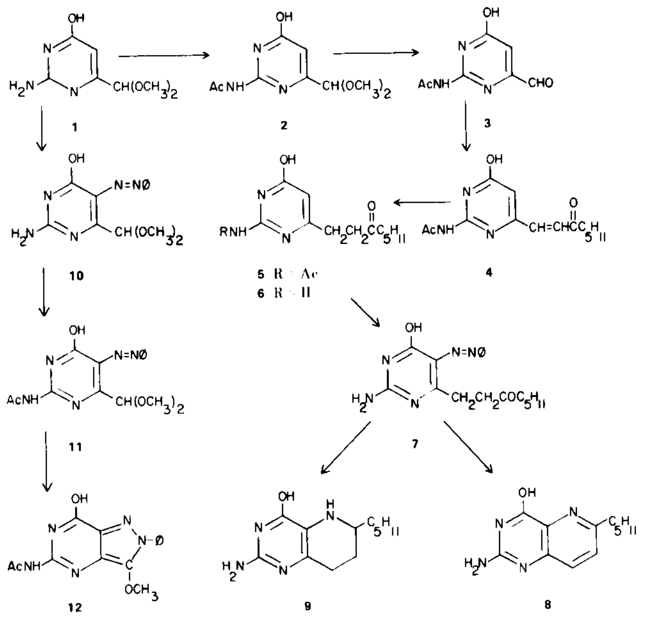
In a recent communication (1), we reported on the synthesis of 8-deazafolic acid and the antibacterial activity of the compound and its reduced forms in certain folate dependent bacteria. The interesting spectrum of activity has encouraged further exploration of structure-activity parameters in this new series of antifolate compounds. However, methods suitable for the preparation of 2-amino-4-hydroxy-1,3,5-triazanaphthalenes containing a variety of side chains at position 6 were not available. We report herein the development of a convenient synthetic sequence, amenable to complex folate side chains. The process was applied to the preparation of a model compound, 2-amino-4-hydroxy-6-amyl-1,3,5-triazanaphthalene (**8**).

The synthetic route, which centers around 2-acetamido-4-hydroxy-6-formylpyrimidine (**3**) as the key intermediate, is outlined in Scheme 1. Condensation of ethyl dimethoxyacetoacetate with guanidine afforded 2-amino-4-hydroxy-6-dimethoxymethylpyrimidine (**1**). Acetylation of **1** by acetic anhydride gave the 2-acetamido acetal (**2**). Selective hydrolysis of the acetal function was accomplished in 94% yield by the action of 88% formic acid at 90-100°. When this hydrolysis was carried out at room temperature, the starting acetal (**2**) was recovered unchanged. The temperature requirement for hydrolysis in this case is in contrast to some other examples (2,3) of selective acetal hydrolysis with 90% formic acid at ordinary temperatures.

Scheme I



When the blocked aldehyde (**3**) was condensed with the anion of dimethyl 2-oxoheptylphosphonate (**4**), the pyrimidinyl enone (**4**) was obtained in 87% yield in an optimal run. The reaction was carried out by the slow addition of a hexamethylphosphoramide solution of the sodium salt (from sodium hydride) of **3** to a solution of the phosphonate anion (also from sodium hydride) in the same solvent. However, the yield could be quite variable depending on the quantity of sodium hydride used to form the phosphonate anion. In practice the yield was stabilized (70-80%) by using slightly less than a stoichiometric quantity of hydride to form the reactant anions.

Attempts to directly couple the acetamido enone (**4**) with benzene diazonium chloride were unsuccessful. Hydrolytic removal of the acetyl group followed by diazonium coupling gave an uncharacterizable product which failed to yield a triazanaphthalene upon reduction. To obtain stable intermediates capable of reductive cyclization, it was necessary to reduce the olefinic moiety. The saturated ketone (**5**) was prepared by hydrogenation of **4** over a rhodium catalyst and deacetylated by mild alkaline hydrolysis. The amino hydroxy product (**6**) was coupled with diazonium reagent to afford the 5-phenylazo intermediate (**7**).

It was expected that reductive cyclization of **7** would yield a 7,8-dihydro product by analogy with the pteridine series (3,5). However, treatment of **7** with either hydrogen (5% palladium-on-carbon) or sodium dithionite gave the fully aromatic product (**8**). Catalytic reduction of the hydrochloride salt of **8** yielded the 5,6,7,8-tetrahydro derivative (**9**). The structures of **8** and **9** were confirmed by ^{13}C-nmr spectroscopy. In the decoupled spectrum of **8**, five signals were observed in the saturated carbon region corresponding to the *n*-amyl group. The spectrum of **9** revealed eight signals in this region, one of which appeared at 50.61 ppm, characteristic of the 2-carbon in 2-methylpiperidine (6). The proton nmr of **8** was also consistent with the assigned structure, showing two *ortho* coupled aromatic protons.

The mechanism by which the fully aromatic compound was obtained from the reductive closures has not been investigated, although it is suspected that air oxidation is responsible for this transformation. Ultraviolet spectra of the crude reduction products were very similar to the purified products which would not suggest the presence of a variety of reduced states. It was noted that the tetrahydro compound (**9**) was unaffected by prolonged exposure to air or dilute aqueous hydrogen peroxide.

To reduce the number of synthetic steps required to introduce new side chains, it was considered desirable to prepare 2-acetamido-4-hydroxy-5-phenylazo-6-formylpyrimidine as the key common intermediate. The amino acetal (**1**) was accordingly coupled with benzene diazonium chloride and the phenylazo product (**10**) was subsequently treated with acetic anhydride. However, the reaction produced a crystalline product identified as the heteropurine (**12**) (pmr spectrum and elemental analysis) rather than the expected 2-acetamidophenylazo acetal (**11**). Acetylation of **10** under milder conditions (acetic anhydride-pyridine) appeared to give **11**, but attempted hydrolysis with 88% formic acid yielded **12** as the only isolable product.

The application of the model synthetic methods toward the synthesis of 8-deazafolic acid analogs will be the subject of a future communication.

EXPERIMENTAL

2-Amino-4-hydroxy-6-dimethoxymethylpyrimidine (**1**).

A mixture of 26 g. (13.7 mmoles) of ethyl dimethoxyacetoacetate (7), 24.9 g. (13.7 mmoles) of guanidine carbonate and 680 ml. of absolute ethanol was stirred at reflux for 48 hours, then concentrated *in vacuo*. The residue was suspended in ether and the solid collected by filtration to give 26.0 g. of crude product. Recrystallization from absolute ethanol afforded 18.6 g. (73%) of white crystals, m.p. 202-206°.

Anal. Calcd. for $C_7H_{11}N_3O_3$: C, 45.4; H, 5.99; N, 22.7. Found: C, 45.4; H, 6.02; N, 22.7.

2-Acetamido-4-hydroxy-6-dimethoxymethylpyrimidine (**2**).

A mixture of 5.0 g. of the aminopyrimidine (**1**) and 50 ml. of acetic anhydride was heated on a steam bath for 4 hours, then concentrated under reduced pressure. The residual amber syrup was treated with 10 ml. of 2-propanol, and the pale yellow solid was collected by filtration and dried to leave 5.95 g. (97%). Two crystallizations from 2-propanol afforded an analytical sample, m.p. 163-166°.

Anal. Calcd. for $C_9H_{13}N_3O_4$: C, 47.6; H, 5.77; N, 18.5. Found: C, 47.3; H, 5.92; N, 18.4.

2-Acetamido-4-hydroxy-6-formylpyrimidine (**3**).

A mixture of 1.6 g. of 2-acetamido-4-hydroxy-6-dimethoxymethylpyrimidine (**2**) and 14 ml. of 88% formic acid was heated on a steam bath for 70 minutes then concentrated *in vacuo*. The residue was suspended in warm 2-propanol then filtered and the cake dried to afford 1.2 g. (94%). Material from another run was recrystallized from DMF to give an analytical sample, m.p. >300°; nmr δ (ppm) (DMSO-d_6) 12.19 (2H, NH, OH), 9.72 (1H, s, $C\mathit{H}O$), 6.63 (1H, s, Ar-H), 2.20 (3H, s, CH_3).

Anal. Calcd. for $C_7H_7N_3O_3$: C, 46.4; H, 3.90; N, 23.2. Found: C, 46.5; H, 4.12; N, 23.4.

1-(2′-Acetamido-4′-hydroxy-6′-pyrimidinyl)-1-octene-3-one (**4**).

To a stirred solution of 13.8 g. (61 mmoles) of dimethyl 2-oxoheptyl phosphonate in 100 ml. of hexamethylphosphoramide was added 2.7 g. (61 mmoles) of sodium hydride (55% dispersion in mineral oil). The mixture was stirred at room temperature for 45 minutes then warmed briefly on a steam bath. The amber mixture was cooled in a cold water bath and treated dropwise with a solution prepared by the reaction of 11.2 g. (61 mmoles) of **3** and 2.43 g. (56 mmoles) of sodium hydride in 100 ml. of hexamethylphosphoramide. After standing in the cold water bath for 3 hours, the mixture was acidified to *p*H 5-6 with glacial acetic acid and poured into 1500 ml. of cold water. The cream colored precipitate was collected by filtration and washed well with water and cyclohexane to afford 15.0 g. (87%). Two crystallizations from methanol afforded an analytical sample, m.p. 223-225.5°; uv λ (*p*H 13): 258 nm (ϵ, 9,500), 328 (2,580); nmr (DMSO-d_6): 11.90 (2H, NH, OH), 7.20 (2H, q, olefin, J_{AB} = 16 Hz), 6.43 (1H, s, ArH), 2.72 (2H, t, $\overset{\overset{O}{\|}}{C}C\mathit{H}_2C_4H_9$), 2.23 (3H, s, $COCH_3$), 0.90 (3H, t, $(CH_2)_4$-CH_3).

Anal. Calcd. for $C_{14}H_{19}N_3O_3$: C, 60.6; H, 6.91; N, 15.2. Found: C, 60.3; H, 6.75; N, 15.0.

1-(2′-Acetamido-4′-hydroxy-6′-pyrimidinyl)-3-octanone (**5**).

A mixture of 0.26 g. of the pyrimidine olefin (**4**), 50 mg. of 5% rhodium-on-carbon catalyst and 20 ml. of methanol was stirred under one atmosphere of hydrogen for 2 hours, taking up the theoretical amount. The mixture was filtered through Celite and the filtrate was evaporated *in vacuo* to leave 0.25 g. (95%). Recrystallization from benzene afforded an analytical sample, m.p. 121-127°; uv λ (*p*H 13): 239 nm (ϵ, 4,520), 272 (3,110); nmr showed loss of vinyl protons.

Anal. Calcd. for $C_{14}H_{21}N_3O_3$: C, 60.2; H, 7.58; N, 15.0. Found: C, 59.8; H, 7.42; N, 15.0.

1-(2'-Amino-4'-hydroxy-6'-pyrimidinyl)-3-octanone (**6**).

A mixture of 1.76 g. of the acetamido pyrimidine (**5**) and 20 ml. of 1*N* sodium hydroxide was heated on a steam bath for ½ hour, then cooled and adjusted to *p*H 7 with glacial acetic acid. The white precipitate was collected by filtration and washed well with water to leave 1.42 g. (95%). Two crystallizations from methanol afforded an analytical sample, m.p. 156.5-158°; uv λ (*p*H 13): 230 nm (ε, 3,700), 275 (3,210).

Anal. Calcd. for $C_{12}H_{19}N_3O_2$: C, 60.7; H, 8.07; N, 17.7. Found: C, 60.4; H, 8.14; N, 17.4.

1-(2'-Amino-4'-hydroxy-5'-phenylazo-6'-pyrimidinyl)-3-octanone (**7**).

To a cold (2°), stirred mixture of 0.17 ml. (1.8 mmoles) of aniline, 1.1 ml. (6.9 mmoles) of 6*N* hydrochloric acid and 2.5 ml. of water was added dropwise a solution of 0.13 g. (1.8 mmoles) of sodium nitrite in 1 ml. of water. The solution was stirred at 0-3° for 15 minutes then added dropwise to a cold (0°), stirred solution of 0.44 g. (1.8 mmoles) of **6** in 9 ml. of water containing 2.2 ml. (2.2 mmoles) of 1*N* sodium hydroxide and 0.37 g. (3.5 mmoles) of sodium carbonate. The mixture was stirred at 0-4° for 30 minutes, then at ambient temperature for 3.5 hours. The *p*H of the mixture was adjusted to 7 with 1*N* hydrochloric acid and the red-orange solid was collected by filtration. The filter cake was washed well with water and ether to leave 0.46 g. (73%). A small amount was recrystallized from 2-propanol to give red crystals, m.p. 137-140°; ir: 13.0, 14.5 μ (φ); uv λ (*p*H 13): 366 nm.

Anal. Calcd. for $C_{18}H_{23}N_5O_2\cdot\frac{1}{4}H_2O$: C, 62.6; H, 6.87; N, 20.3. Found: C, 62.4; H, 6.94; N, 20.0.

2-Amino-4-hydroxy-6-*n*-amyl-1,3,5-triazanaphthalene (**8**).

A mixture of 0.50 g. of the phenylazo pyrimidine (**7**), 50 mg. of 10% palladium-on-carbon catalyst and 15 ml. of methanol was stirred under one atmosphere of hydrogen for 24 hours, taking up 86% of the theoretical amount of hydrogen. The mixture was filtered through a Celite pad and the filtrate was evaporated *in vacuo*. The residue was triturated with a little methanol and the tan solid was collected by filtration to afford 0.10 g. (29%), m.p. 284-289°: uv λ (*p*H 13): 238 nm (ε, 19,400), 271 (ε, 8,270), 335 (ε, 4,350); nmr (proton, DMSO-d_6 + deuterium oxide): 7.50 (2H, q, Ar-H, J = 9 Hz), 2.78 (2H, t, Ar-CH_2), 0.90 (3H, t, CH_3); nmr-^{13}C: ppm 13.72 (CH_3), 21.82; 28.82, 30.86, 37.04 (amyl CH_2), 127.58, 131.98 (C-7,8), 133.18 (C-6), 145.73 (C-2), 151.36, 156.05 (C-4a, 8a), 160.66 (C-4).

Anal. Calcd. for $C_{12}H_{16}N_4O\cdot\frac{1}{4}H_2O$: C, 60.9: H, 7.02; N, 23.7. Found: C, 61.2; H, 6.97; N, 23.5.

Reduction of **7** with 2 equivalents of sodium dithionite in 0.1*N* sodium hydroxide solution at 100° also afforded **8** in 47% yield. When conducted at room temperature for 18 hours, only starting phenylazo compound was recovered.

2-Amino-4-hydroxy-6-*n*-amyl-5,6,7,8-tetrahydro-1,3,5-triazanaphthalene Hydrochloride (**9**).

A mixture of 0.84 g. (2.48 mmoles) of the phenylazo pyrimidine (**7**), 100 ml. of methanol, 2.5 ml. of 1*N* hydrochloric acid and 50 mg. of 10% palladium-on-carbon catalyst was stirred under one atmosphere of hydrogen for 64 hours, taking up 65% of the theoretical amount of hydrogen. The catalyst was removed by filtration through Celite and the filtrate was concentrated *in vacuo* to afford a brown solid. A small portion of this solid was recrystallized from methanol to leave white crystals, m.p. 179-182°; uv λ (*p*H 13): 252 nm (ε, 8,200), 305 (ε, 5,810); nmr-^{13}C (DMSO-d_6) ppm: 13.75 (CH_3), 21.89, 23.21, 24.44, 24.81 (amyl CH_2), 31.13, 33.45 (C-7,8), 50.67 (C-6), 102.36, 118.88 (C-4a, 8a), 148.59 (C-2), 156.54 (C-4).

Anal. Calcd. for $C_{12}H_{20}N_4O\cdot HCl$: C, 52.8; H, 7.76; N, 20.5; Cl^-, 13.0. Found: C, 52.8; H, 7.86; N, 20.4; Cl^-, 13.0.

2-Amino-4-hydroxy-5-phenylazo-6-dimethoxymethylpyrimidine (**10**).

To a cold (0-2°), stirred mixture of 0.17 ml. (1.8 mmoles) of aniline in 1.15 ml. (6.9 mmoles) of 6*N* hydrochloric acid and 2.5 ml. of water was added dropwise a mixture of 0.13 g. (1.8 mmoles) of sodium nitrite in 1 ml. of water, maintaining a temperature of 0-2° during the addition. The mixture was stirred at this temperature for 15 minutes then added dropwise to a cold (0-2°), stirred mixture of 0.18 g. (1.0 mmoles) of 2-amino-4-hydroxy-6-dimethoxymethylpyrimidine (**1**) in 2.2 ml. of 1*N* sodium hydroxide, 0.37 g. (3.5 mmoles) of sodium carbonate and 9 ml. of water. The dark red mixture was stirred in the cold for 30 minutes, then at room temperature for 3.5 hours. The red-brown solid was collected by filtration and washed well with water and ether to afford 0.27 g. (95%). A small sample was recrystallized from methanol to leave rust colored crystals, m.p. 200-202°; ir λ (Nujol): 13.0, 14.4 μ (φ): uv: λ (*p*H 13): 232, 367 nm; nmr (DMSO-d_6): 7.60 (8H, m, Ar-H, NH_2, OH), 6.04 (1H, s, C-6H), 3.40 (6*H*, s, OCH_3).

2-Acetamido-6-hydroxy-8-phenyl-9-methoxyheteropurine (**12**).

A mixture of 0.65 g. of the phenylazopyrimidine (**10**) and 15 ml. of acetic anhydride was heated on a steam bath for 2.5 hours. The solvent was removed under reduced pressure and the residue was suspended in acetone and the solid collected by filtration to leave 0.17 g. (26%). A sample from another run was recrystallized twice from 2-methoxyethanol to afford a cream colored solid, m.p. 269-271°; uv λ (*p*H 13): 241 nm (ε, 13,330), 317 (3,740); nmr: 11.95 (1H, s, NH), 11.25 (1H, s, OH), 7.55 (5H, m, Ar-H), 4.30 (3H, s, OCH_3), 2.15 (3H, s, $COCH_3$).

Anal. Calcd. for $C_{14}H_{13}N_5O_3$: C, 56.2; H, 4.38; N, 23.4. Found: C, 56.3; H, 4.59. N, 23.0.

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