An Alternate Synthesis of 6-Substituted-5-deazapteridines

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Received May 24, 1982

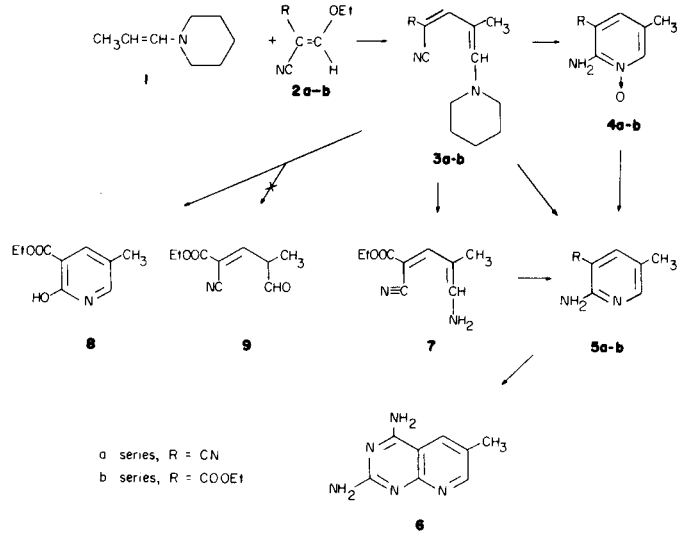
A procedure for synthesis of 2,4-diamino-6-substituted-5-deazapteridines (pyrido[2,3-*d*]pyrimidines) is described. Condensation of 1-piperidino-1-propene with ethoxymethylenemalononitrile afforded an enamino malononitrile adduct, which when treated with ammonia yielded 2-amino-3-cyano-5-methylpyridine. Cyclization to 2,4-diamino-6-methyl-5-deazapteridine could be effected with guanidine. Similar condensation of piperidinopropene with ethyl methoxymethylenecyanoacetate followed by cyclization with hydroxylamine gave 2-amino-3-carbethoxy-6-methylpyridine 1-oxide. Reduction with phosphorus trichloride afforded the pyridine base, however, attempts to cyclize the amino ester to 2-amino-4-hydroxy-6-methyl-5-deazapteridine were unusccessful.

J. Heterocyclic Chem., **19**, 1461 (1982).

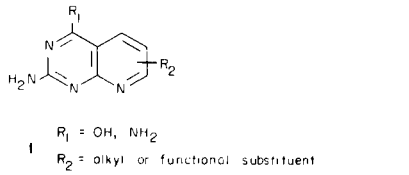
Previous approaches to the synthesis of 2,4-diamino- or 2-amino-4-hydroxy-5-deazapteridines (pyrido[2,3-*d*]pyrimidines) (I) have depended on condensation of a 2,4,6-substituted pyrimidine with an appropriately substituted β-dicarbonyl reagent or derivative thereof. For example Robins and Hitchings (2) condensed 2,4-diamino-6-hydroxypyrimidine with β-diketones to obtain 2-amino-4-hydroxy-5,7-dialkyl-5-deazapteridines. Bernetti, *et al.*, (3) prepared 2-amino-4-hydroxy-6-carbethoxy-5-deazapteridine by reaction of 2,4-diamino-6-hydroxypyrimidine with carbethoxymalonaldehyde, while Stark and Breitmeier (4) produced 2-amino-4-hydroxy-6-alkyl and 5,6-dialkyl analogs by condensation of 2,4-diamino-6-hydroxypyrimidine and β-aminovinyl ketones or aldehydes. Hurlbert and Valenti (5) could obtain 2,4-diamino-6-alkyl-5-deazapteridines by treatment of 2,4,6-triaminopyrimidine with dimethylaminoacrolein compounds. We sought to develop a procedure that did not begin with a pyrimidine reactant and could be adapted for incorporation at C-6 of complex side chains, such as those pertinent to folic acid analogs. An alternate method suitable for this purpose is described herein.

The recently reported procedures of Taylor, *et al.*, (6) for synthesis of 2,4-diamino-6-substituted-pteridines served as a guideline for our approach. The Taylor process entails condensation of aminomalononitrile with an α-keto oxime to afford a 2-amino-3-cyano-5-substituted-pyrazine 1-oxide which is reduced and cyclized with guanidine to the desired 2,4-diamino-6-substituted-pteridine. We reasoned that reaction of an enamine (II) of an appropriate aldehyde with ethoxymethylenemalononitrile (III) would yield an aldehydo ylidinemalononitrile (IV). Ring closure with ammonia or hydroxylamine could be expected to give a 2-amino-3-cyanopyridine compound substituted at position 5 and capable of further elaboration to a 2,4-diamino-6-substituted-5-deazapteridine.

When 1-piperidino-1-propene (**1**, Scheme 1) was allowed to react with an equivalent of ethoxymethylenemalononitrile (**2a**) in benzene at 25° the 2-cyano-4-methyl-5-piperidino-2,4-pentadiene (**3a**) was obtained in low yield (14%). The enamino compound (**3a**) could be cyclized with hydroxylaminehydrochloride in ethanol to yield 2-amino-3-cyano-5-methylpyridine 1-oxide (**4a**) in 65% yield. The *N*-oxide function was readily reduced by treatment of **4a** with excess phosphorus trichloride at room temperature to afford 2-amino-3-cyano-5-methylpyridine (**5a**) in 70% yield. It was also found that direct treatment of the enamino compound (**3a**) with ammonium hydroxide in ethanol at room temperature gave the amino cyano pyridine (**5a**) in 60% yield. When **5a** was treated with guanidine free base in boiling methanol (22 hours) cyclization to 2,4-diamino-6-methylpyrido[2,3-*d*]pyrimidine (**6**) was accomplished in 56% yield. While the overall reaction scheme was successful for preparation of the target 5-deazapteridine (**6**) the low yield obtained in the first step appears to limit the utility of the process. We were unable to improve upon the low yield despite variation in time, temperature, solvent medium, etc.



A parallel sequence was conducted with the condensation of 1-piperidinopropene (**1**) and ethyl ethoxymethylenecyanoacetate (**2b**). The piperidino cyano dienoate (**3b**)



R_1 = OH, NH_2

R_2 = alkyl or functional substituent

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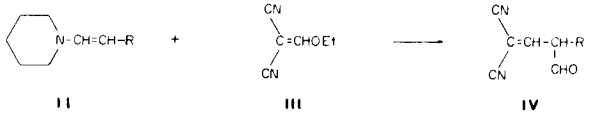

II III IV

was obtained in a 40% yield. Cyclization of **3b** with hydroxylamine hydrochloride afforded 2-amino-3-carbethoxy-5-methylpyridine 1-oxide (**4b**) in 83% yield, while reduction with phosphorus trichloride at room temperature yielded 2-amino-3-carbethoxy-5-methylpyridine (**5b**, 70%). If **3b** was treated wtih ethanolic ammonium hydroxide at room temperature the piperidine was displaced by amino, but no pyridine compound was observed. The intermediate ethyl 5-amino-3-cyano-4-methyl-2,3-pentadienoate (**7**) was obtained in 95% yield. This compound was exceptionally stable, requiring heating at 150° in ethanolic solution to undergo cyclization to the pyridine (**5b**). In contrast to the nitrile case described earlier we were unable to effect ring closure of **5b** to the 2-amino-4-hydroxy-5-deazapterin by treatment with guanidine at room temperatures up to 190° in ethanol.

The reaction of **3b** with an acidic medium was also studied. Exposure of the enamino cyano ester to hot 50% acetic acid caused formation of 2-hydroxy-3-cyano-5-methylpyridine (**8**) in 41% yield. The ultra-violet and proton resonance spectrum indicated **8** to be the product rather than the aldehyde (**9**).

EXPERIMENTAL

2-Cyano-4-methyl-5-piperidino-1,3-pentadienylnitrile (**3a**).

To a chilled (6°) solution of 1.25 g (0.01 mole) of 1-piperidinopropene (**1**) (7) in 5 ml of benzene was added 1.34 g (0.011 mole) of ethoxymethylenemalononitrile. The mixture was stirred at 0-5° for 1 hour then kept at room temperature for another 17 hours. After evaporation of solvent the residue was chromatographed on silica gel with elution by chloroform. The product was crystallized from benzene-ether to afford 276 mg (14%) of yellow needles, mp 133-134°; ir (Nujol): cm^{-1} 2200, 2180 (-C≡N); nmr (deuteriochloroform): δ 1.73 (6 H, m, piperidine -$(CH_2)_3$), 2.20 (3 H, s, CH_3), 3.60 (4 H, m, piperidine -CH_2NCH_2-), 6.89 (2 H, s, olefins); uv (ethanol): λ nm 383.

Anal. Calcd. for $C_{12}H_{15}N_3$: C, 71.6; H, 7.51; N, 20.9. Found: C, 71.4; H, 7.33; N, 21.1.

2-Amino-3-cyano-5-methylpyridine 1-Oxide (**4a**).

A solution of **3a** (121 mg, 0.0006 mole) in 5 ml of ethanol was treated with 70 mg (0.001 mole) of hydroxylamine hydrochloride and the mixture was stirred at room temperature for 2 hours, followed by heating at reflux for another hour. The solvent was evaporated *in vacuo* and the residue partitioned between water and chloroform. The chloroform extract was dried (sodium sulfate) and evaporated *in vacuo*. The residue was crystallized from benzene to give 58 mg (65%) of yellow crystals, mp 180-182°; ir (Nujol): cm^{-1} 2240 (C≡N); nmr (deuteriochloroform): δ 2.26 (3 H, s, CH_3), 6.47 (2 H, broad s, NH_2), 7.22 (1 H, s, C_4-H), 8.16 (1 H, s, C_5-H); uv (ethanol): λ nm 243, 368.

Anal. Calcd. for $C_7H_7N_3O$: C, 56.4; H, 4.73; N, 28.2. Found: C, 56.2; H, 4.78; N, 28.3.

2-Amino-3-cyano-5-methylpyridine (**5a**).

Method A.

A mixture of **3a** (403 mg, 0.002 mole) and 0.3 ml of concentrated ammonium hydroxide in 30 ml of ethanol was stirred at ambient temperature for 40 hours. Solvent was removed *in vacuo* and the residue was chromatographed on silica gel (chloroform). Crystallization from benzene afforded 159 mg (60%) of product, mp 169-170°; ir (Nujol): cm^{-1} 3410, 3330 (NH_2), 2220 (C≡N); nmr (deuteriochloroform): δ 2.21 (3 H, s, CH_3), 7.55 (1 H, d, J = 2 Hz, C_4-H), 8.12 (1 H, d, J = 2 Hz, C_6-H); uv (ethanol): λ max nm 251, 343.

Anal. Calcd. for $C_7H_7N_3$: C, 63.1; H, 5.30; N, 31.6. Found: C, 62.9; H, 5.28; N, 31.8.

Method B.

A solution of **4a** (31 mg, 0.0002 mole) in 3 ml of tetrahydrofuran was cooled to 0-5° and treated slowly with 2 ml of phosphorus trichloride. The reaction mixture was stirred at room temperature for 40 minutes, concentrated *in vacuo* to a volume of about 2 ml and then poured into 10 ml of ice water. The resulting solution was adjusted to *p*H 8 with 1 *N* sodium hydroxide and thrice extracted with 5 ml portions of chloroform. The chloroform extract was washed with 5 ml of water, dried over sodium sulfate and evaporated. The residue was chromatograhed on silica gel (chloroform) and the product crystallized from benzene to give 20 mg (70%) of material identical to that produced by Method A above.

2,4-Diamino-6-methylpyrido[2,3-*d*]pyrimidine (**6**).

To a solution of sodium (138 mg, 0.006 g-atom) in 5 ml of methanol was added 573 mg (0.006 mole) of guanidine hydrochloride and the mixture was stirred at reflux for 30 minutes. The precipitated salt was removed by filtration and the filtrate was treated with 133 mg (0.001 mole) of **5a**. The reaction mixture was heated at reflux for 22 hours and chilled in an ice bath. The precipitate was collected, washed successively with water (1 ml), dimethylformamide (2 ml) and methanol (2 ml). The material was recrystallized from dimethylformamide to give 100 mg (56%) of pale yellow crystals, mp >300°; nmr (trifluoroacetic acid): δ 2.66 (3 H, s, CH_3), 8.63 (1 H, s, C_5-H), 9.16 (1 H, s, C_7-H); uv (ethanol): λ max nm 249, 353.

Anal. Calcd. for $C_8H_9N_5 \cdot 1/9H_2O$: C, 54.2; H, 5.25; N, 39.5. Found: C, 54.4; H, 5.47; N, 39.5.

Ethyl 2-Cyano-4-methyl-5-piperidino-2,4-pentadienoate (**3b**).

To a solution of 1.25 g (0.01 mole) of 1-piperidino-1-propene (**1**) in 15 ml of benzene was added 1.86 g (0.011 mole) of ethyl ethoxymethylenecyanoacetate and the mixture was stirred at ambient temperature for 1 hour. The mixture was heated at reflux for an additional hour and evaporated *in vacuo*. Following chromatography on silica gel, the product was crystallized from benzene-ether to afford 999 mg (40%) of yellow needles, mp 99-100°; ir (Nujol): cm^{-1} 2200 (C≡N), 1680 (C=O); nmr (deuteriochloroform): δ 1.30 (3 H, t, ester CH_3), 1.71 (6 H, m, -$(CH_2)_3$-), 2.24 (3 H, s, CH_3), 3.52 (4 H, m, -CH_2NCH_2-), 4.27 (2 H, q, -OCH_2-), 6.83 (1 H, s, =CHN-), 7.57 (1 H, s, =CH-); uv (ethanol): λ max nm 386.

Anal. Calcd. for $C_{15}H_{20}N_2O_2$: C, 67.7; H, 8.12; N, 11.3. Found: C, 67.7; H, 7.91; N, 11.3.

2-Amino-3-carbethoxy-5-methylpyridine 1-Oxide (**4b**).

A mixture of 124 mg (0.005 mole) of **3b**, 125 mg (0.0018 mole) of hydroxylamine hydrochloride and 5 ml of ethanol was stirred at room temperature for 40 hours. Solvent was removed *in vacuo* and the residue partitioned between water and chloroform. The chloroform extract was

washed with water, dried over sodium sulfate and evaporated *in vacuo*. Crystallization of the residue from benzene afforded 81 mg (83%) of yellow crystals, mp 163-165°; ir (Nujol): cm^{-1} 3380, 3260 (NH_2), 1695 (COOEt); nmr (deuteriochloroform): δ 1.40 (3 H, t, ester CH_3), 2.16 (3 H, s, CH_3), 4.40 (2 H, q, -OCH_2-), 7.30 (2 H, broad s, NH_2), 7.70 (1 H, s, C_4-H), 8.15 (1 H, s, C_6-H); uv (ethanol): λ max nm 243, 371.

Anal. Calcd. for $C_9H_{12}N_2O_3$: C, 55.1; H, 6.16; N, 14.3. Found: C, 55.2; H, 6.16; N, 14.3.

Ethyl 2-Cyano-4-methyl-5-amino-2,4-pentadienoate (**7**).

A mixture of 497 mg of **3b**, 0.3 ml of concentrated ammonium hydroxide and 20 ml of ethanol was stirred at room temperature for 14 hours followed by removal of solvent *in vacuo*. The residue was washed with ether and dried to leave 343 mg (95%) of a yellow powder. An analytical sample, mp 165-167°, was crystallized from benzene; ir (Nujol): cm^{-1} 3440, 3340 (NH_2), 2210 (C≡N), 1685 (COOEt); nmr (perdeuteriomethanol): δ 1.30 (3 H, t, ester CH_3), 2.04 (3 H, s, CH_3), 4.21 (2 H, q, -OCH_2), 7.29 (1 H, s, =CH-N), 7.66 (1 H, s, =CH-C); uv (ethanol): λ max nm 370. The uv spectrum was concentration dependent. The recorded maximum was obtained by dilution to a constant wavelength observation.

Anal. Calcd. for $C_9H_{12}N_2O_2$: C, 60.0; H, 6.71; N, 15.6. Found: C, 59.7; H, 6.68; N, 15.4.

2-Amino-3-carbethoxy-5-methylpyridine (**5b**).

Method A.

A solution of 196 mg of **4b** in 14 ml of tetrahydrofuran was cooled to 0-5° and treated dropwise with 2.0 ml of phosphorus trichloride. The mixture was stirred for 40 minutes at room temperature, concentrated *in vacuo* and poured into ice water. After adjustment of the *p*H to 7-8 with 1 *N* sodium hydroxide the product was extracted into chloroform. The extract was washed with water, dried (sodium sulfate) and evaporated. Following chromatography of the residue on silica gel (chloroform) the resulting product was crystallized from ether-hexane to give 125 mg (69%) of yellow crystals, mp 105-108°; ir (Nujol): cm^{-1} 3440, 3280 (NH_2), 1690 (COOEt); nmr (deuteriochloroform): δ 1.38 (3 H, t, ester CH_3), 2.20 (3 H, s, CH_3), 4.39 (2 H, q, OCH_2), 6.34 (2 H, broad s, NH_2), 8.05 (2 H, q, J = 2 Hz, C_4 and C_6-H's); uv (ethanol): λ max nm 250, 344.

Anal. Calcd. for $C_9H_{12}N_2O_2$: C, 60.0; H, 6.71; N, 15.6. Found: C, 59.7; H, 6.55; N, 15.6.

Method B.

A solution of 200 mg of **7** in 10 ml of ethanol was heated at 140-150° for 40 hours. The solvent was evaporated and the residue chromatographed on silica gel (chloroform). Crystallization of the product gave 100 mg (50%) of yellow crystals identical with material prepared by Method A.

In one run the piperidino enamine ester (**3b**) was carried through intermediate **7** on to **5b**, without isolation, in an overall 89% yield.

3-Carbethoxy-5-methyl-3-pyridone (**8**).

A mixture of 500 mg (0.002 mole) of **3a** and 50% acetic acid (30 ml) containing 8 g of sodium acetate was heated at reflux for 30 minutes and evaporated *in vacuo*. The residue was treated with 10 ml of water, adjusted to *p*H 8 with saturated sodium bicarbonate and extracted with two 10-ml portions of ethyl acetate. The extract was washed with 5 ml of water, dried (sodium sulfate) and evaporated to leave a solid residue that afforded 150 mg (41%) of pale yellow crystals, mp 120-122°, after crystallization from ether; ir (Nujol): cm^{-1} 3210 (OH), 1720 (COOEt); nmr (deuteriochloroform): δ 1.38 (3 H, t, ester CH_3), 2.17 (3 H, s, CH_3), 4.38 (2 H, q, OCH_2), 7.66 (1 H, d, C_4-H), 8.15 (1 H, d, C_6-H); uv (ethanol): λ max nm 238, 341.

Anal. Calcd. for $C_9H_{11}NO_3$: C, 59.7; H, 6.12; N, 7.73. Found: C, 59.5; H, 6.06; N, 7.88.

Acknowledgement.

This work was supported in part by a grant, CA-28783, from the National Cancer Institute, National Institutes of Health.

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