SYNTHESIS OF ETHYL 7,10-ETHANO-4-AMINO-4-DEOXYPTEROATE[1]

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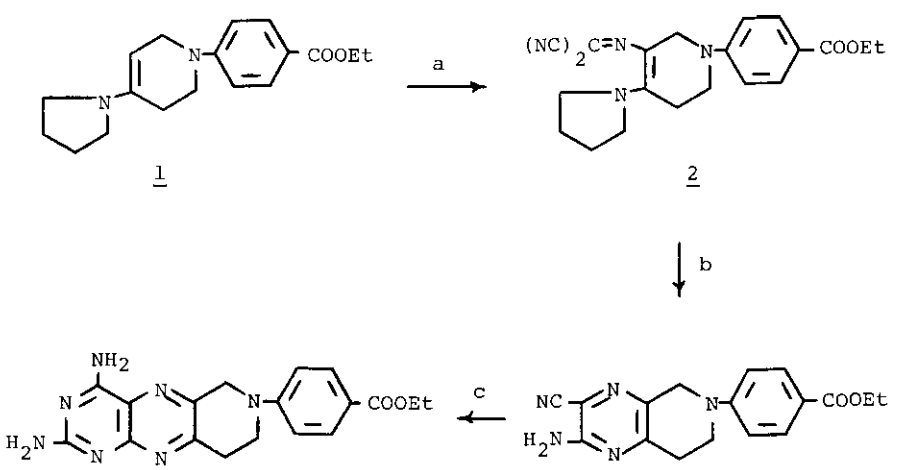
Abstract - Ethyl 7,10-ethano-4-amino-4-deoxypteroate (4) was prepared in three steps from 1-(4-carbethoxyphenyl)-4-pyrrolidino-1,2,5,6-tetrahydropyridine (1).

As a part of our program directed towards the preparation of selective inhibitors of dihydrofolate reductase as antitumor agents, we have explored the synthesis of a variety of C-6, C-7 annulated pteridine derivatives suitably functionalized for elaboration to analogs of the clinically important chemotherapeutic agent methotrexate.[3,4] The rationale for the design of these compounds has been detailed elsewhere.[3,5] Herein we report a short synthesis of one member of this series, ethyl 7,10-ethano-4-amino-4-deoxypteroate (4).

Treatment of enamine 1[3] with 0.5 equiv of O-(p-tosyl)isonitrosomalonitrile[6,7] in THF gave 1-(4-carbethoxyphenyl)-3-(2,2-dicyanomethyleneimino)-4-(1-pyrrolidino)-1,2,5,6-tetrahydropyridine



1 2 3 4

a) $(NC)_2C{=}NOTs$ b) NH_3 c) $(CH_3)_2NC(=NH)NH_2$

(2) in 26% yield. The use of pyridine rather than an extra equivalent of the enamine 1 as a scavenger for p-toluenesulfonic acid in the above reaction did not improve the yield or the purity of the condensation product 2. Reaction of the latter with an excess of saturated methanolic ammonia then gave 2-amino-6-(4-carbethoxyphenyl)-3-cyano-5,6,7,8-tetrahydropyrido[4,3-b]pyrazine (3) in 99% yield. Some improvement in the overall yield of 3 was observed when the azadiene 2 was treated directly without isolation with alcoholic ammonia.

Cyclization of 3 to 4 was best carried out with 1,1-dimethylguanidine in anhydrous DMF at 100°C (71% yield). The more conventional method of using guanidine for this pyrimidine ring annulation was less satisfactory (55% yield after refluxing in absolute ethanol for 2 days).

The above sequence of reactions thus provides a straightforward route to 7-aryl-2,4-diamino-6,7,8,9-tetrahydropyrido[3,4-g]pteridines suitable for elaboration to "tied-back" congeners of aminopterin and methotrexate.

EXPERIMENTAL

1-(4-Carbethoxyphenyl)-3-(2,2-dicyanomethyleneimino)-4-(1-pyrrolidino)-1,2,5,6-tetrahydropyridine (2). To a magnetically stirred solution of 1.0 g (0.004 mol) of O-(p-tosyl)isonitrosomalononitrile in 10 mL of anhydrous THF cooled to -25°C under nitrogen was added dropwise a solution of 2.5 g (0.0083 mol) of the enamine 1 in 50 mL of THF. The reaction mixture was stirred for 2 h, allowed to warm to 0°C for 30 min, diluted with water, and extracted with 3 x 200 mL-portions of diethyl ether. The combined organic extracts were washed with 5% HCl, 1 N NaOH, and brine, dried over anhydrous sodium sulfate, and the filtrate evaporated under reduced pressure. The residual reddish brown paste was triturated with ethanol/diethyl ether to give 0.26 g of 2 as a reddish brown solid, mp 175-177°C. Concentration of the mother liquors and chromatography of the residual oil over silica gel, using diethyl ether followed by acetone as eluants, provided an additional 0.13 g (total yield 26%) of 2. The analytical sample was obtained in the form of dark red reddish brown crystals, mp 178-179°C, by recrystallization from ethanol. ^{1}H NMR ($CDCl_3$) δ 7.98 and 6.90 (ABq, 4H, J=9 Hz), 4.52 (br s, 2H), 4.37 (q, 2H, J=7 Hz), 4.25-3.90 (m, 2H), 3.80-3.48 (m, 4H), 3.02-2.73 (m, 2H), 2.20-1.88 (m, 4H), 1.38 (t, 3H, J=7 Hz).

Anal. Calcd for $C_{21}H_{23}N_5O_2$: C, 66.82; H, 6.14; N, 18.50. Found: C, 67.10; H, 6.12; N, 18.23.

2-Amino-6-(4-carbethoxyphenyl)-3-cyano-5,6,7,8-tetrahydropyrido[4,3-b]pyrazine (3). A mixture of 1.0 g (0.0026 mol) of the azadiene 2 and 25 mL of saturated methanolic ammonia was stirred magnetically under nitrogen overnight at room temperature. Filtration then gave 0.845 g (99%) of 3 as a pale yellow solid, mp 177-178°C. ^{1}H NMR (100 MHz/$CDCl_3$) δ 7.95 and 6.91 (ABq, 4H, J=9 Hz), 5.09 (br s, 2H), 4.47 (s, 2H), 4.40 (q, 2H, J=7 Hz), 3.76 (t, 2H, J=6 Hz), 3.02 (t, 2H, J=6 Hz), 1.36 (t, 3H, J=7 Hz). HRMS calcd 323.1382; found 323.1376.

Anal. Calcd for $C_{17}H_{17}N_5O_2$: C, 63.14; H, 5.30; N, 21.66. Found: C, 62.83; H, 5.16; N, 21.76.

Ethyl 7,10-Ethano-4-amino-4-deoxypteroate (4). A mixture of 0.96 g (0.0078 mol) of freshly dried (100°C/0.1 mm) 1,1-dimethylguanidine hydrochloride, 0.6 g (0.0088 mol) of sodium ethoxide and 10 mL of anhydrous DMF was stirred magnetically under nitrogen at room temperature for 1 h. To this reaction mixture was then added in one portion a solution of 0.5 g (0.0015 mol) of the pyrazine 3 in 25 mL of DMF. The reaction mixture was heated to 100°C for 2 h, filtered hot, and the collected yellow solid washed successively with DMF, water, diethyl ether, and acetone to give 0.39 g (71%) of 4 as a microcrystalline yellow powder, mp > 300°C. ^{1}H NMR (100 MHz/DMSO-d_6) δ 7.82 and 7.04 (ABq, 4H, J=9 Hz), 7.48 (br s, 2H), 6.48 (br s, 2H), 4.62 (s, 2H), 4.23 (q, 2H, J=7 Hz), 3.84 (t, 2H, J=6 Hz), 3.20-3.0 (m, 2H), 1.27 (t, 3H, J=7 Hz). HRMS calcd 365.1600; found 365.1603.

Anal. Calcd for $C_{18}H_{19}N_7O_2$: C, 59.16; H, 5.24; N, 26.84. Found: C, 58.46; H, 5.04; N, 26.38.

REFERENCES AND NOTES

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2. Recipient of the Cyanamid Education Award, 1977-1979.

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