Studies on Pyrazines. 26 [1]. Synthesis of 2,4-Diamino-6-methylpteridine 5-Oxide and the Inertness of the 6-Methyl-group Functionalization

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Synthesis of 2,4-diamino-6-methylpteridine 5-oxide was achieved in a five-step sequence of reaction starting from 5-methylpyrazinecarboxamide. Several attempts to introduce functionality into the 6-methyl group are described.

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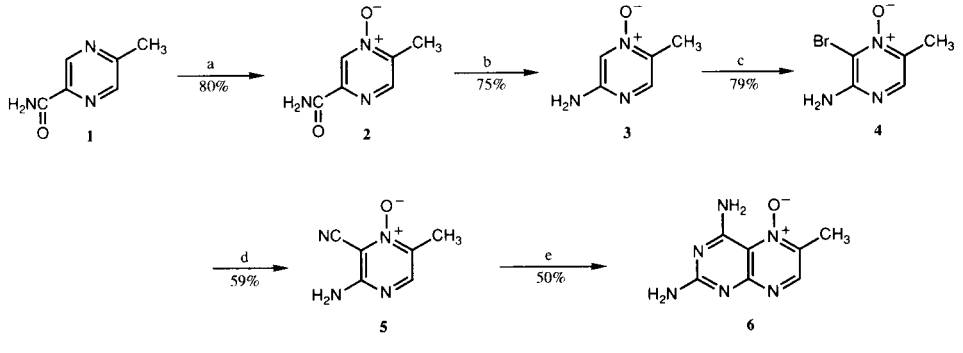
6-Halomethyl and 6-hydroxymethyl substituted 2,4-diaminopteridines are of great interest because they are precursors for methotrexate which is one of the most widely used chemotherapeutic agents for the treatment of some forms of leukemia, carcinoma and sarcoma [2]. Several excellent methods are available for synthesis of those compounds [3,4]. Recently we had an opportunity to obtain 5-methylpyrazinecarboxamide (**1**) which was easily prepared by technical ammoxidation of 2,5-dimethylpyrazine [5] followed by hydrolysis. This led us to consider a divergent synthetic route which involved functionalizing the methyl group of 2,4-diamino-6-methylpteridine *via* the 5-oxide. We wish here to present results of some attempts as well as the synthesis of the pteridine *N*-oxide **6**.

We previously developed the methodology for synthesis of 2-amino-3-cyanopyrazines from 2-aminopyrazines [6], which could be also successfully applied to that of 3-amino-2-cyano-6-methylpyrazine 1-oxide (**5**). The starting material **1** was converted into 5-amino-2-methylpyrazine 1-oxide (**3**) by treatment with formic peracid followed by Hoffman degradation of the resulting *N*-oxide **2**. Bromination of **3** by bromine in chloroform containing pyridine furnished 3-amino-2-bromo-6-methylpyrazine 1-oxide (**4**), but this method resulted in a yield less than 60% and particularly the unsatisfied combustion analysis. Instead of the above reagents, treatment with *N*-bromosuccinimide in aqueous dimethyl sulfoxide increased the yield of **4** as the succinimide salt to 79%. Transformation of **4** into **5** was accomplished by nucleophilic replacement of the bromo substituent with sodium dicyanocuprate in dimethylformamide. The best yield of 59% was obtained when the cyanation was refluxed for 4 hours. Prolonged heating reduced the yield due to deoxygenation of the *N*-oxide **5**. Annulation of **5** to the pteridine ring was frustrated on treating with guanidine prepared from the hydrochloride salt with methanolic sodium methoxide to recover the starting *N*-oxide. Ultimately, the desired product **6** was obtained in 50% yield by using guanidine carbonate in dimethylacetamide at 130-135° for 2 hours. The yield was optimized by shortening the reaction period and somewhat lower temperatures to avoid the deoxygenation.

Deoxydative nucleophilic substitution frequently occurs on a methyl substituent adjacent to the *N*-oxide function [7] although competing with that on the ring carbons. Obviously, 2-methylpyrazine 1-oxides were converted into chloromethyl and acetoxymethyl pyrazines by treatment with phsophoryl chloride [8] and acetic anhydride [9], respectively. Owing to structural features in which both of ring carbons neighboring to the *N*-oxide group are occupied by junction with the pyrimidine ring and by the 6-methyl substituent, pteridine *N*-oxide **6** was expected to undergo the substitution on the methyl group. Treatment of **6** with phosphoryl chloride surprisingly gave not 6-chloromethyl-2,4-diaminopteridine but 7-chloro-6-methyl

Scheme 1



Reagents: a, 30%H_2O_2/HCO_2H; b, NaClO/aq NaOH; c, NBS/aq DMSO; d, $NaCu(CN)_2$/DMF; e, $[NH_2C(=NH)NH_2]_2{\cdot}H_2CO_3$/DMA

isomer in 24% yield, which was confirmed with an authentic sample prepared by chlorination of 2,4-diaminopteridine 8-oxide [10] with the same reagent. On the other hand, acetoxylation did not proceed at all by acetic or trifluoroacetic anhydride itself. An addition of their carboxylic acid or amine such as triethylamine, diethylaniline or DBU effected neither chlorination nor acetoxylation.

Another distinctive reaction of the methyl group next to the *N*-oxide function is the Knoevenagel-type condensation with aromatic aldehyde, *e.g.*, 2-methylpyrazine 1-oxide has been found to react with benzaldehyde forming styrylpyrazine *N*-oxide in excellent yield [11]. However, pteridine *N*-oxide **6** as well as pyrazine *N*-oxide **3** and its dimethylaminomethylene protected compound did not undergo such condensation with 4-formylbenzoic *tert*-butyl ester in the presence of methanolic sodium methoxide or with butyl lithium. Eventually, derivatization from pteridine *N*-oxide **6** was abandoned due to extremely weak acidity of the methyl group.

EXPERIMENTAL

All melting points were determined using a Büchi 535 apparatus and are uncorrected. The ir spectra (potassium bromide) were recorded on a JASCO IR-810 spectrometer. The ^1H and ^{13}C nmr spectra were obtained with a JEOL JNM EX-270 instrument with tetramethylsilane as the internal standard.

5-Methylpyrazinecarboxamide 4-Oxide (**2**).

A solution of 5-methylpyrazinecarboxamide **1** (68.6 g, 0.50 mole) in 90% formic acid (250 ml) and 30% hydrogen peroxide (150 ml) was mechanically stirred and warmed. The temperature was remained between 40-50° by occasional cooling for 4 hours. A colorless solid started to separate from the solution after warming for approximately 30 minutes. The mixture was refrigerated overnight, then filtered, washed well with water and dried in air to give the *N*-oxide **2** (60.9 g, 80%), mp 216-217°. The mother liquor was condensed *in vacuo*, and the pasty residue was triturated with water providing, by filtration, the second crop (5.7 g, total yield 87%), mp 211-213°. This material was used directly successive transformation without purification. The analytical sample was obtained by recrystallization from methanol, mp 217°; ir: 3490, 3460, 1650, 1550, 1370, 1335, 1270, 960, 910 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 2.39 (s, 3H), 7.94 (br s, 1H), 8.26 (br s, 1H), 8.59 (s, 1H), 8.68 (s, 1H); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 14.0, 132.0, 145.6, 146.3, 147.6, 163.5.

Anal. Calcd. for $C_6H_7N_3O_2$: C, 47.06; H, 4.61; N, 27.44. Found: C, 46.85; H, 4.53; N, 27.31.

5-Amino-2-methylpyrazine 1-Oxide (**3**).

Sodium hypochlorite solution (10.4% available chlorine; 120 ml, 0.22 mole) was added dropwise to a mechanically stirred solution of 95% sodium hydroxide (33.9 g, 0.81 mole) in water (500 ml) below 10°. The crude amide **2** (30.63 g, 0.20 mole) was added in small portions to the above solution, and the resulting mixture was heated at 70° with stirring for 1 hour. During this period, the suspension passed into solution. After the solution was cooled below 10°, concentrated hydrochloric acid was added to it until evolution of gas ceased. Then the resulting solution was again basified at *p*H 9-10 with 2*N* aqueous sodium hydroxide and evaporated to dryness *in vacuo*. The residue was extracted with hot ethanol (300 ml + 2 x 200 ml) and the extracts were evaporated to dryness. The residue was again extracted with chloroform by a soxlet extractor for 24 hours to give **3** (18.68 g, 75%), mp 210°. Recrystallization from ethyl acetate-ethanol (1:1) and subsequently ethyl acetate alone afforded the analytical sample as colorless needles, mp 213-214°; ir: 3480, 3390, 3280, 1580, 1480, 1455, 1145, 965 cm^{-1}; ^1H nmr (dimethyl sufoxide-d_6): δ 2.14 (s, 3H), 6.29 (s, 2H), 7.54 (s, 1H), 7.92 (s, 1H); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 12.9, 117.7, 131.6, 144.4, 157.5.

Anal. Calcd. for $C_5H_7N_3O$: C, 47.99; H, 5.64; N, 33.58. Found: C, 48.05; H, 5.56; N, 33.72.

3-Amino-2-bromo-6-methylpyrazine 1-Oxide (**4**).

A freshly recrystallized *N*-bromosuccinimide (26.25 g, 0.147 mole) was added in small portions to a stirred solution of **3** (17.57 g, 0.14 mole) in dimethyl sulfoxide (140 ml) containing water (2.7 ml, 0.15 mole) below 15°. The mixture was stirred at room temperature for 4 hours and then evaporated *in vacuo* to dryness. The residue was suspended in refluxing toluene (200 ml), and the supernatant was decanted while it was hot. After cooling in ice bath, the precipitate was collected by filtration. The mother liquor was put back to the residue, and the above process was repeated twice. The final filtrate was evaporated *in vacuo* and the residue was filtered from oily matter. The combined product was dried at 120°/1 mm Hg and then sublimed at 150°/1 mm Hg to give an 1:1 complex of the bromo product with succinimide (33.78 g, 79%), which was used to successive cyanation without further purification. The analytical sample was obtained by recrystallization from toluene as colorless prisms, mp 162°; ir: 3400, 3300, 3200, 3000, 2770, 1700, 1630, 1200 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.40 (s, 3H), 2.77 (s, 4H), 5.09 (s, 2H), 7.83 (s, 1H), 8.86 (br s, 1H); ^{13}C nmr (deuteriochloroform): δ 15.0, 62.0, 62.4, 62.9, 121.6, 126.7, 140.0, 163.1.

Anal. Calcd. for $C_5H_6N_3BrO \cdot C_4H_5NO_2$: C, 35.66; H, 3.66; N, 18.48. Found: C, 35.84; H, 3.61; N, 18.40.

3-Amino-2-cyano-6-methylpyrazine 1-Oxide (**5**).

A mixture of 90% copper(I) cyanide (5.02 g, 50 mmoles) and fresh powdered 95% sodium cyanide (2.66 g, 50 mmoles) in dry DMF (100 ml) was stirred and heated to 110° and to the resulting clear solution was portionwise added the succinimide salt of **4** (7.58 g, 25 mmoles) at that temperature. The mixture was refluxed for 4 hours and then evaporated *in vacuo*. The residue was treated with 10% aqueous sodium cyanide (30 ml) and continuously extracted with chloroform for 24 hours. The extract was evaporated to dryness *in vacuo* and the residue was sublimed at 170°/2 mm Hg and recrystallized from ethanol to give yellow tiny needles (2.06 g, 59%), mp 235°; ir: 3470, 3400, 3210, 2300, 1603, 1560, 1110, 763 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 2.18 (s, 3H), 7.33 (s, 2H), 8.24 (s, 1H); ^{13}C nmr (dimethyl sulfoxide-d_6): δ 12.8, 103.5, 111.8, 132.7, 148.7, 158.7.

Anal. Calcd. for $C_6H_6N_4O$: C, 48.00; H, 4.03; N, 37.32. Found: C, 47.97; H, 3.96; N, 37.29.

2,4-Diamino-6-methylpteridine 5-Oxide (**6**).

A mixture of **5** (0.752 g, 5.0 mmoles) and guanidine carbonate (1.354 g, 7.5 mmoles) in dry dimethylacetamide (10 ml) was stirred and heated at 130-135° for 2 hours. The resulting dark greenish mixture was refrigerated overnight, and the precipitates

which formed were collected by filtration, washed with methanol and dried in air. Recrystallization from DMF (about 200 ml) gave yellow micro crystals (0.478 g, 50%), mp >320°; ir: 3350, 3110, 1670, 1610, 1350, 1180, 1090, 800 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 2.31 (s, 3H), 6.65 (br s, 2H), 8.03 (br s, 1H), 8.61 (s, 1H), 9.39 (br s, 1H).

Anal. Calcd. for $C_7H_8N_6O$: C, 43.75; H, 4.20; N, 43.73. Found: C, 43.82; H, 4.35; N, 43.51.

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