Studies on Pyrazines. 17. [1]. An Efficient Synthesis of Pteridine-6-carboxylic Acids

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2,4-Diaminopteridine-6-carboxylic acid (**1**) and pterin-6-carboxylic acid (**2**) were prepared by permanganate oxidation of the corresponding 6-(2-furyl)-substituted pteridines under much milder conditions. Several attempts to cleave the furan ring with other oxidizing agents are also described.

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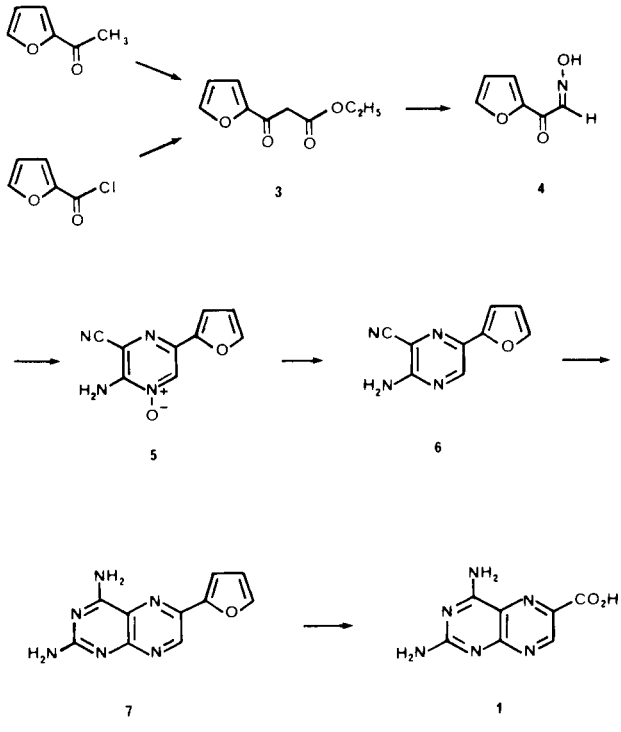
The furan nucleus is particularly susceptible to oxidation, whose reactions yield a wide variety of synthetically valuable intermediates [2-4]. Permanganate oxidation of 2-substituted furans results in destruction of the ring, the carbon atom of which at the position 2 remains in the form of a carboxy group [5]. Earlier work in our laboratory [6] also demonstrated the utility of the furan ring as a latent carboxylic functionality in the synthesis of 5-chloropyrazinecarboxylic acid from 2-chloro-5-furylpyrazine. The oxidation reaction proved to complete under much milder conditions compared with that of an aromatic alkyl side chain, the most frequently employed synthetic method for aromatic carboxylic acids. This higher susceptibility of furans strongly suggests effectiveness for synthesis of functional carboxylic acids labile to drastic oxidative conditions. In this paper, we focus on the development of this methodology in the synthesis of pteridine-6-carboxylic acids. One of them is 2,4-diaminopteridine-6-carboxylic acid (**1**), the amino group of which at C-4 is subject to base-catalyzed hydrolysis even at moderate steam-bath temperatures. A few esters of **1** have attracted interest because of their significant diuretic activity [7]. The other target is 2-amino-4(3*H*)-pteridinone-6-carboxylic acid (pterin-6-carboxylic acid, **2**) which is an important naturally occurring pteridine compound [8].

One of the most efficient synthetic routes to 6-substituted pteridines is the Taylor synthesis [9] which involves the preparation of 2-amino-3-cyano-5-substituted pyrazines *via* their 1-oxides which were accessible by condensation of α-ketoaldoximes with aminomalononitrile tosylate. Subsequent manipulation of these pyrazine intermediates and final annulation of the pyrimidine ring then led to 6-substituted pteridines. This synthetic strategy was also found to be applicable to synthesis of our desired 2,4-diamino-6-(2-furyl)pteridine (**7**) as outlined in Scheme 1. The requisite β-ketoester **3** was prepared in 79% yield by base-catalyzed condensation of diethyl carbonate and 2-acetylfuran with sodium hydride in refluxing benzene, or in 67% yield by that of 2-furoyl chloride and diethyl malonate in a two phase system of hexane and aqueous sodium hydroxide followed by decarboxylation. Alkaline hydrolysis of the ester **3** with aqueous potassium hydroxide overnight at room temperature furnished the β-carboxylic acid, which was treated *in situ* with sodium nitrite and successively acidified leading with decarboxylation to oximinoketone **4** in 86% yield. Condensation of **4** with aminomalononitrile tosylate in 2-propanol overnight at room temperature gave the pyrazine *N*-oxide **5** in approximately 50% yield. The pyrazine construction was optimized to 68% yield by prolonging the reaction time to 88 hours. Deoxygenation of the *N*-oxide **5** was readily accomplished by treating with phosphorus trichloride in THF giving aminocyanopyrazine **6** in 57% yield. This pyrazine intermediate **6** cyclized readily with guanidine in methanol/sodium methoxide under reflux to give the 2,4-diaminopteridine **7** in 88% yield.

Scheme 1

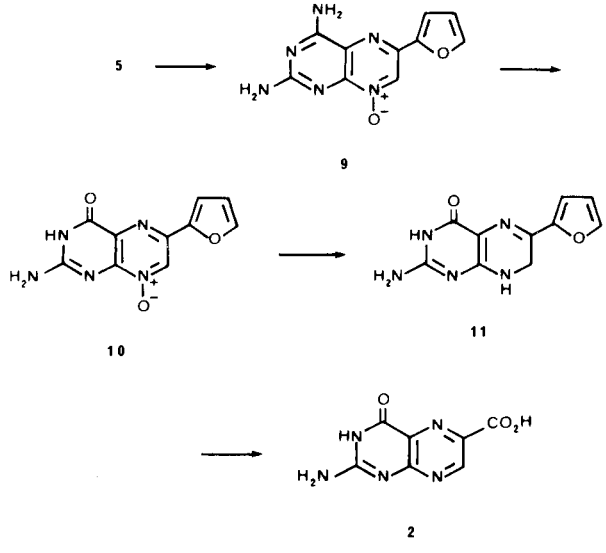


Previously, the 2,4-diaminopteridine-6-carboxylic acid (**1**) has been made in 43% yield by permanganate oxidation of 2,4-diamino-6-methylpteridine (**8**) at temperatures

above 75° for several hours [10]. Additionally, the oxidation reaction was carried out at approximately *p*H 8 to avoid hydrolysis of the 4-amino group forming the pterin. By contrast, however, we have now found that treatment of 6-furylpteridine **7** with potassium permanganate in 0.5*N* sodium hydroxide at 50-55° for 30 minutes affords a 73% yield of the desired carboxylic acid **1** without hydrolytic deamination at C-4. Under the same conditions, the methylpteridine **8** was entirely inert to the alkaline permanganate oxidation resulting in no formation of any carboxylic acid nor pterin compound. It was noteworthy that despite the liability to hydrolysis the 4-amino group could survive even on exposure to a strong basic solution under the predescribed conditions feasible for the progress in the destruction of furan ring to carboxylic functionality.

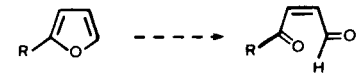
Alkaline hydrolysis of 2,4-diaminocarboxylic acid **1** by heating at 65-68° in a 1*N* sodium hydroxide gave a 79% yield of pterin-6-carboxylic acid **2**, which was alternatively prepared by four-step sequence of reactions starting from the pyrazine *N*-oxide **5** as outlined in Scheme 2. Pyrimidine ring annulation to the pteridine *N*-oxide **9** was accomplished in 88% yield from **8** by the same manner as the synthesis of 2,4-diaminopteridine **7**. Hydrolysis of the *N*-oxide **9** by heating under reflux in 1*N* sodium hydroxide produced quantitatively the pterin *N*-oxide **10**. This compound **10** could be reduced with sodium dithionite in refluxing 0.5*N* sodium hydroxide to form the 7,8-dihydropterin **11** in 89% yield. In the case of pterins possessing aromatic substituent at C-6 or its *N*-oxides, the dithionite reduction to the 7,8-dihydropterins was only effected on refluxing in diluted alkaline solution [11]. Permanganate oxidation of the dihydropterin **11** under the same conditions as that to **1** resulted in dehydration to pterin as well as oxidative cleavage of furan nucleus to carboxylic functionality giving a 73% yield of pterin-6-carboxylic acid **2**.

Scheme 2



The possibility of oxidative cleavage unaccompanied carbon-carbon degradation in the furan ring was investigated because the pteridines carrying multifunctional carbon side chains at position 6 are of current interest as the intermediate for the synthesis of a vast variety of biologically significant naturally occurring pterins and chemotherapeutically useful pteridine derivatives. A great number of oxidation procedures have been available for conversion of the parent and substituted furans into 2-butene-1,4-dicarbonyl compounds [2-4]. Unfortunately, however, all attempts to cleave the furan ring attached to the pyrazine or pteridine nucleus in such fashion (see Scheme 3) was unsuccessful. For example, photooxidation of the furylpyrazine *N*-oxide **5** [12] catalyzed with tetraphenylporphine (TPP) in dichloromethane at temperatures below -20° followed by treating with dimethyl sulfide gave only the unchanged starting material. At higher temperatures, the compound **5** provided a complex

Scheme 3



R= Pyrazinyl or Pteridinyl

mixture of unidentified products. The Clauson-Kaas reaction [13] of **5** with bromine in methanol containing potassium acetate or sodium carbonate led to partial formation of the desired 1,4-dimethoxy adducts, which was isolated with difficulty because of its propensity to revert to the starting material during chromatography. Varying the reaction temperatures and the amount of the reagents had no effect on the improvement in yield and proportion of the product. Lead tetraacetate [14] and pyridinium chlorochromate [15] also brought about no reaction on **5** at all. The 7,8-dihydropterin **11** was mostly recovered on treating with bromine in diluted sodium hydroxide/tetrachloromethane or with ruthenium oxide/sodium periodate in the same two phase system. In general, oxidation of furan involves an initial 1,4-addition of the oxidant to the diene system [2]. Probably, an electron-withdrawing pyrazinyl or pteridinyl substituent reduced the electron density of the diene in the furan ring resulting in a remarkable suppression of the addition reaction of the oxidizing agent. Nevertheless, the much greater electrophilicity of the permanganate anion is sufficient to promote the oxidative destruction.

EXPERIMENTAL

All melting points were determined in capillary tubes on a Büchi 535 or a Laboratory Devices Mel-Temp apparatus and are uncorrected. The infrared spectra were recorded on a Hitachi 260-10 or a JASCO IR-810 spectrometer as potassium bromide pellets unless otherwise stated, ^{1}H nmr spectra on a JEOL JNM-MH-100 instrument with tetramethylsilane as the internal standard, and exact mass spectra on a Hitachi M-82B mass spectrometer.

Ethyl 3-(2-Furyl)-2-oxopropionate (**3**).

Method A.

A solution of 2-acetylfuran (52.5 g, 0.477 mole) in dry benzene (100 ml) was added dropwise to a stirred and refluxed mixture of diethyl carbonate (112.6 g, 0.953 mole) and sodium hydride (55.4 g of 60% dispersion in mineral oil, 1.39 moles, the mineral oil was removed by washing with four 80-ml portions of dry benzene) in dry benzene (500 ml) over a period of 3 hours. The resulting solution was refluxed until no more evolution of gas was observed (approximately 1 hour). After cooling to 10°, the reaction mixture was neutralized with acetic acid (95 ml), and then ice-water (about 200 ml) was added to dissolve the pasty solid which formed. The benzene layer was separated, and the aqueous layer was extracted with benzene (3 x 100 ml). The combined organic layer was washed with water and dried over magnesium sulfate. Evaporation *in vacuo* gave a deep amber oil which was distilled at 111-120° (2 mm) to give 68.2 (79%) of pale yellow oil. An analytical sample was obtained by further distillation, bp 115-116° (5 mm); ir (neat): 3130, 2975, 2935, 1735, 1675, 1463, 1023 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.22 (t, 3H, J = 7.0 Hz), 3.84 (s, 2H), 4.18 (q, 2H, J = 7.0 Hz), 6.58 (dd, 1H, J = 3.4, 1.8 Hz), 7.29 (dd, 1H, J = 3.5, 0.8 Hz), 7.66 (dd, 1H, J = 1.8, 0.8 Hz).

Anal. Calcd. for $C_9H_{10}O_4$: C, 59.34; H, 5.53. Found: C, 59.66; H, 5.50.

Method B.

A 33% aqueous sodium hydroxide (3.0 ml) was added dropwise to a stirred mixture of ethyl acetoacetate (9.2 g, 0.071 mole) in hexane-water (12 ml + 25 ml) below 5°. With vigorous stirring, 2-furoyl chloride (10.2 g, 0.078 mole) and 33% aqueous sodium hydroxide (12.8 ml) were simultaneously added to the above mixture below 10°. After the mixture was stirred at room temperature for 1 hour, the hexane layer was removed, and ammonium chloride (3.8 g) was added to the aqueous solution. The resulting mixture was stirred at room temperature for 23 hours, then saturated with sodium chloride (4.5 g) and extracted with benzene (3 x 50 ml). The extract was worked up in the same manner as described above to give 8.6 g (67%) of a yellow oil, bp 126-130° (3 mm).

2-(2-Furyl)glyoxal 1-Oxime (**4**).

A mixture of the ketoester **3** (20.0 g, 0.11 mole) in aqueous potassium hydroxide solution (10.2 g/275 ml of water) was stirred at room temperature overnight, and to the homogenous solution was added a solution of sodium nitrite (9.1 g, 0.13 mole) in water (30 ml). The resulting solution was cooled to 0°, and 6*N* sulfuric acid (48 ml) was added dropwise to it at the same temperature. The precipitated solid was extracted with ether (3 x 100 ml), and the extract was washed with water, dried over magnesium sulfate, and evaporated to dryness *in vacuo*. The residue was redissolved in ether, and an insoluble matter was removed by filtration. Evaporation of the solvent *in vacuo* gave a waxy tan solid which was recrystallized from dichloromethane to give 13.1 g (86%) of tan tiny prisms, mp 110-111°. The analytical sample was prepared by further recrystallization, mp 116-117°; ir: 3180, 1630, 1605, 1456, 1014 cm^{-1}; ^1H nmr (deuteriochloroform): δ 6.55 (dd, 1H, J = 3.7, 1.9 Hz), 7.23 (s, 1H), 7.49 (dd, 1H, J = 3.7, 0.9 Hz), 7.66 (dd, 1H, J = 1.9, 0.9 Hz), 7.93 (s, 1H).

Anal. Calcd. for $C_6H_5NO_3$: C, 51.80; H, 3.62; N, 10.07. Found: C, 51.60; H, 3.61; N, 10.06.

2-Amino-3-cyano-5-(2-furyl)pyrazine 1-Oxide (**5**).

A mixture of the oximinoketone **4** (2.11 g, 15.2 mmoles) and aminomalononitrile tosylate (3.55 g, 14.0 mmoles) in 2-propanol (23 ml) was stirred at room temperature for 88 hours. Then the mixture was evaporated to dryness *in vacuo*, and the residue was washed with water, dried, and recrystallized from ethyl acetate to give 1.92 g (68%) of a yellow solid, mp 240-241° dec. The analytical sample was obtained by recrystallization from ethanol as long yellow needles, mp 245° dec; ir: 3340, 3110, 2240, 1638, 1603, 1504, 1481, 1178 cm^{-1}; ^1H nmr (DMSO-d_6): δ 6.64 (dd, 1H, J = 3.4, 1.9 Hz), 7.09 (dd, 1H, J = 3.4, 0.7 Hz), 7.82 (dd, 1H, J = 1.9, 0.7 Hz), 8.07 (s, 2H), 8.85 (s, 1H).

Anal. Calcd. for $C_9H_6N_4O_2$: C, 53.47; H, 2.99; N, 27.71. Found: C, 53.88; H, 3.02; N, 28.03.

2-Amino-3-cyano-5-(2-furyl)pyrazine (**6**).

Phosphorus trichloride (1.0 ml) was added dropwise to an ice-cold and stirred suspension of the *N*-oxide **5** (1.012 g, 5.0 mmoles) in dry tetrahydrofuran (40 ml) over a period of 5 minutes, and then the mixture was stirred for 30 minutes at room temperature. The resulting dark red solution was evaporated to dryness *in vacuo*, and residue was triturated with ice-water. The dark solid which separated was collected by filtration, dried, and extracted with hot benzene (80 ml). The extract was evaporated *in vacuo* to give 0.534 g (57%) of a yellow solid, mp 215-216°. Sublimation (~170°) *in vacuo* and recrystallization from benzene yielded the analytical sample as bright yellow tiny needles, mp 216-217° dec; ir: 3400, 3340, 3250, 2240, 1650, 1503 cm^{-1}; ^1H nmr (DMSO-d_6): δ 6.63 (dd, 1H, J = 3.4, 1.8 Hz), 6.98 (dd, 1H, J = 3.4, 0.9 Hz), 7.47 (s, 2H), 7.79 (dd, 1H, J = 1.8, 0.9 Hz), 8.70 (s, 1H).

Anal. Calcd. for $C_9H_6N_4O$: C, 58.06; H, 3.25; N, 30.09. Found: C, 57.84; H, 3.25; N, 29.86.

2,4-Diamino-6-(2-furyl)pteridine (**7**).

Sodium (0.20 g, 8.7 mmoles) was dissolved in dry methanol (20 ml), and to this solution was added guanidine hydrochloride (0.322 g, 3.37 moles). After an insoluble material which formed was removed by filtration, the aminonitrile **7** (0.474 g, 2.55 mmoles) was added to the filtrate, and the solution was stirred under reflux for 20 hours. A yellow precipitate started to separate from the yellow solution after refluxing for approximately 1 hour. The mixture was cooled to room temperature and then filtered. The collected solid was washed successively with water, methanol, and ether to give 0.517 g (88%) of a yellow powder. The analytical sample was obtained by recrystallization from DMF as golden microcrystals, mp 230° dec; ir: 3410, 3320, 3150, 1640, 1530, 1456, 1088 cm^{-1}; ^1H nmr (trifluoroacetic acid): δ 6.74 (dd, 1H, J = 3.5, 1.7 Hz), 7.49 (dd, 1H, J = 3.5, 0.7 Hz), 7.76 (dd, 1H, J = 1.7, 0.7 Hz), 9.30 (s, 1H).

Anal. Calcd. for $C_{10}H_8N_6O \cdot 1/5H_2O$: C, 51.81; H, 3.65; N, 36.25. Found: C, 52.23; H, 3.74; N, 36.03.

2,4-Diaminopteridine-6-carboxylic Acid (**1**).

Potassium permanganate (0.980 g, 6.20 mmoles) was added in one portion to a suspension of **7** (0.232 g, 1.0 mmole) in 0.5*N* sodium hydroxide (20 ml), and the mixture was vigorously stirred and warmed at 50-55° on a preheated steam bath. After 30 minutes, the excess of oxidizing agents was decomposed by addition of 2-propanol, and then the mixture was cooled to 0° and filtered. The filter cake was washed well with 0.1*N* sodium hydroxide (40 ml). The filtrate and washings were combined and adjusted to *p*H 2 with 2*N* hydrochloric acid. A creamed-colored fluffy precipitate separated immediately. The mixture was digested at 50-60° for 10 minutes, refrigerated for several hours, and centrifuged. The precipitate was collected by filtration, and washed well with water, and dried at 100° *in vacuo* for 3 hours to give 0.148 g (72%) of a pale yellow solid. The crude product was redissolved in 0.5*N* sodium hydroxide, and an insoluble material was removed by filtration. Precipitation with 2*N* hydrochloric acid, digestion, centrifugation, filtration, and finally drying at 100° *in vacuo* for 5 hours gave 0.138 g (67%) of creamed-colored crystals which was identical in all respects with the authentic material [10], mp >300°; ir: 3330, 3190, 3040, 1638, 1610, 1366 cm^{-1}; ^1H nmr (trifluoroacetic acid): δ 9.63 (s, 1H).

Anal. Calcd. for $C_7H_6N_6O_2$: C, 40.78; H, 2.93; N, 40.76. Found: C, 41.17; H, 2.94; N, 41.10.

2,4-Diamino-6-(2-furyl)pteridine 8-Oxide (**9**).

A mixture of the *N*-oxide **5** (1.010 g, 5.0 mmoles) and methanolic guanidine, which was prepared by treatment of guanidine hydrochloride (0.621 g, 6.5 mmoles) with dry methanol (35 ml) containing sodium (0.37 g, 16 mmoles) as described above, was stirred under reflux for 18 hours. During this period, all of starting materials passed into solution, and a yellow precipitate was again separated from the solution. The mixture

was cooled to room temperature and then filtered. The collected precipitate was washed successively with water, methanol, and ether to give 1.107 g (88%) of a yellow powder. Recrystallization from DMF gave a yellow microcrystalline solid which proved by nmr spectrum to have residual DMF (1:1), and an analytical sample was obtained by drying at 100° *in vacuo* overnight, mp 230° dec; ir: 3470, 3110, 1637, 1540, 1460, 1191 cm^{-1}; ^1H nmr (trifluoroacetic acid): δ 6.74 (dd, 1H, J = 3.5, 1.6 Hz), 7.51 (dd, 1H, J = 3.5, 0.9 Hz), 7.73 (dd, 1H, J = 1.6, 0.9 Hz), 9.20 (s, 1H).

Anal. Calcd. for $C_{10}H_8N_6O_2 \cdot \frac{1}{2}H_2O$: C, 47.43; H, 3.58; N, 33.19. Found: C, 47.34; H, 3.73; N, 33.50.

2-Amino-6-(2-furyl)-4(3*H*)pteridinone 8-Oxide (6-(2-Furyl)pterin 8-Oxide, **10**).

A suspension of the *N*-oxide **9** (0.461 g, 1.82 mmoles) in 1*N* sodium hydroxide (20 ml) was stirred under reflux for 2 hours. All of the starting materials passed into solution, and a light yellow precipitate started to separate from yellow solution after approximately 1 hour. The mixture was cooled to room temperature, and the precipitated material was redissolved by dropwise addition of 1*N* sodium hydroxide. The solution was acidified to *p*H 2 with 2*N* hydrochloric acid, and the precipitated solid was collected by filtration, washed with water, and dried to give a yellow solid which was purified by dissolvation in 1*N* sodium hydroxide followed by precipitation with 2*N* hydrochloric acid as described above yielding 0.481 g (99%) of a yellow microcrystalline solid after drying at 100° *in vacuo* for 4 hours, mp 330°; ir: 3320, 3130, 1691, 1660, 1502, 1472 cm^{-1}; ^1H nmr (trifluoroacetic acid): δ 6.76 (dd, 1H, J = 3.4, 1.8 Hz), 7.53 (dd, 1H, J = 3.4, 0.6 Hz), 7.74 (dd, 1H, J = 1.8, 0.6 Hz), 9.20 (s, 1H).

Anal. Calcd. for $C_{10}H_7N_5O_3 \cdot 5/4H_2O$: C, 44.86; H, 3.58; N, 26.16. Found: C, 44.92; H, 3.77; N, 26.02.

2-Amino-7,8-dihydro-6-(2-furyl)-4(3*H*)-pteridinone (7,8-Dihydro-6-(2-furyl)-pterin, **11**).

A slurry of the pterin *N*-oxide **10** (0.437 g, 1.63 mmoles) in 0.5*N* sodium hydroxide (20 ml) containing 80% sodium hydrosulfite (sodium dithionite) (1.55 g, 7.12 mmoles) was refluxed with stirring for 15 minutes. The mixture passed into solution during heating, and an off-white precipitate started to separate after refluxing for 5 minutes. The resulting mixture was cooled to 0°, and the precipitated solid was collected by filtration, washed well with water, and dried in air to give 0.413 g (89%) of a tan powder which proved by nmr spectrum to be the trihydrate of 7,8-dihydropterin **11**. The analytical sample was obtained by drying at 70° *in vacuo* over phosphorus pentoxide for 18 hours, mp >330°; ir: 3380, 3140, 1653, 1600, 1348 cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.33 (s, 3H, 3/2H_2O), 4.22 (s, 2H), 6.49 (s, 2H), 6.60 (dd, 1H, J = 3.6, 1.9 Hz), 6.71 (dd, 1H, J = 3.6, 0.8 Hz), 7.10 (s, 1H), 7.76 (dd, 1H, J = 1.9, 0.8 Hz); ms: m/e Calcd. 231.0758, Found: 231.0751.

Anal. Calcd. for $C_{10}H_9N_5O_2 \cdot 3/2H_2O$: C, 46.51; H, 3.51; N, 27.12. Found: C, 46.34; H, 4.00; N, 26.85.

2-Amino-4(3*H*)-pteridinone-6-carboxylic Acid (Pterin-6-carboxylic Acid, **2**).

Method A.

A slurry of the 7,8-dihydropteridinone **11** (0.412 g, 1.44 mmoles) in 0.5*N* sodium hydroxide (33 ml) was oxidized with potassium permanganate (0.160 g, 10.1 mmoles) in the same manner as the oxidation of **7** to diaminopteridine-6-carboxylic acid **1**, yielding 0.277 g (93%) of a light yellow fluffy solid. Purification of the crude product was achieved sequentially by dissolvation in 0.5*N* sodium hydroxide, precipitation with 2*N* hydrochloric acid, digestion, centrifugation, filtration, and drying *in vacuo* for 5 hours to give 0.217 g (73%) of cream-colored crystals which was identical in all respects with the authentic material [16], mp >300°; ir: 3320, 3070, 1658, 1383, 1162 cm^{-1}; ^1H nmr (trifluoroacetic acid): δ 9.62 (s, 1H).

Anal. Calcd. for $C_7H_5N_5O_3$: C, 40.59; H, 2.43; N, 33.81. Found: C, 40.46; H, 2.27; N, 33.79.

Method B.

A slurry of the carboxylic acid **1** (0.056 g, 0.27 mmole) in 1*N* sodium hydroxide (3 ml) was stirred and heated on a steam bath. The mixture passed into solution immediately, and a light yellow precipitate started to separate after approximately 1 hour. After 2 hours of being stirred at 65-68°, the mixture was cooled to room temperature. The precipitated material was redissolved by dropwise addition of 2*N* sodium hydroxide. Precipitation with 2*N* hydrochloric acid and collection by centrifugation followed by filtration in the same manner as the above gave 0.044 g (79%) of cream-colored fluffy crystals after drying at 100° *in vacuo* for 5 hours.

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[12] The procedure of photooxidation followed that in 2,5-dimethylfuran: W. Adam and K. Takayama, *J. Org. Chem.*, **44**, 1727 (1979); [b] The pyrazine *N*-oxide **5** was used for a more facile function as the substrate for oxidation reactions than pteridines or pterins due to the more solubility in organic solvents.

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