Pteridines. III. Unexpected Facile Ring Closure of 2-Amino-6-phenethylpteridin-4(3*H*)-one in the Presence of Fluorosulfonic acid[1,2]

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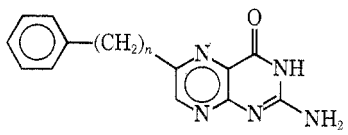
2-Amino-6-phenethylpteridin-4(3*H*)-one (1) underwent a novel ring closure to 10-amino-5,6-dihydronaphtho[2,1-*g*]pteridin-8(9*H*)-one (3) in 74% yield on mild treatment with a 1:4 mixture of fluorosulfonic acid and trifluoroacetic acid. The structure of 3 was deduced on the basis of uv and nmr spectral data and supported chemically by aromatization to 10-aminonaphtho[2,1-*g*]pteridin-8(9*H*)-one (5) with selenium dioxide. A mechanism is proposed involving an unusual pteridine carbonium ion with the positive charge at C-7 delocalized anchimerically by the 6-phenethyl substituent.

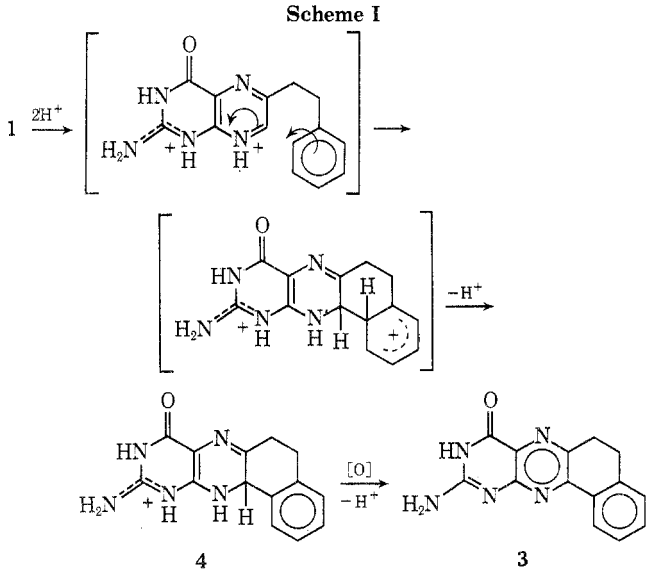
2-Amino-6-phenethylpteridin-4(3*H*)-one (1) and 2-amino-6-(3-phenylpropyl)pteridin-4(3*H*)-one (2) were prepared recently in this laboratory from 2,4,5-triamino-6-hydroxypyrimidine *via* a novel unidirectional pteridine synthesis involving the use of 1-methylsulfinyl-4-phenyl-2-butanone and 1-methylsulfinyl-5-phenyl-2-pentanone, respectively, as "latent" α-keto aldehydes.[3] This method of synthesis was superior to earlier procedures[4,5] in a number of respects. In the course of our characterization of 1 and 2 by nmr spectrometry an unusual event was observed which forms the subject of this report.



1, $n = 2$
2, $n = 3$

When the nmr spectrum of 1 was determined in trifluoroacetic acid solution, the CH_2CH_2 protons were observed as a multiplet at δ 3.2 and the C-7 proton on the pteridine ring was discerned as a sharp singlet at δ 8.53.[3] Upon addition of fluorosulfonic acid to a final concentration of 20%,[3,6] the solution became warm and the color changed from amber to deep red. At the same time a pronounced change occurred in the nmr spectrum, including most notably the replacement of the original CH_2CH_2 multiplet at δ 3.2 by a singlet at δ 3.43. In addition, broad absorption at δ 7.85–8.65 and a new singlet at δ 6.50 became evident. Contrastingly, nmr spectra of the 6-(3-phenylpropyl) homolog 2 showed persistence of the $CH_2CH_2CH_2$ signal as a multiplet even in the presence of fluorosulfonic acid. The change in nmr spectrum of 1 was suggestive of a specific chemical reaction in which the 6-phenethyl group was probably an important requisite. We considered the possibility of a cyclization process as depicted in Scheme I.

Scheme I



Addition of the foregoing 1:4 fluorosulfonic–trifluoroacetic acid solution of compound 1 to a large volume of 95% ethanol caused instantaneous discharge of the dark red color and evolution of an unpleasant odor suggestive of sulfinic acid. At the same time a pale yellow solid appeared, which on isolation proved to be distinctly different (ir, uv, nmr) from 1. The yield was nearly quantitative and remained in excess of 75% even on a 2-g scale. The product was homogeneous by tlc analysis and could be recrystallized unchanged and in excellent recovery from 80% formic acid.

The uv spectrum of the product in 0.1 *N* sodium hydroxide showed maxima at 240, 273, and 387 nm, whereas the spectrum of compound 1 contained maximum absorption only at 254 and 363 nm.[3] The significant bathochromic shift manifested in the spectrum of this new compound indicated the likelihood that the action of fluorosulfonic acid had given rise to an extension of conjugation as a consequence of a rearrangement.

The nmr spectrum of the material recovered after dilution of the 1:4 fluorosulfonic–trifluoroacetic acid mixture with ethanol and recrystallization from 80% formic acid was different from the spectrum prior to quenching. When the product was redissolved in 1:4 fluorosulfonic–trifluoroacetic acid, the previously observed singlet at δ 3.43 (*vide supra*) now was replaced by a multiplet at δ 3.80 and the singlet at δ 6.50 was no longer discernible. In trifluoroacetic acid alone, the nmr spectrum revealed a complex pattern of aromatic proton absorption in the δ 7.2–8.6 region and a broad singlet with poorly resolved fine structure at δ 3.30. This spectrum contrasted sharply with that of 1 in trifluoroacetic acid alone,[3] which contained a prominent C-7 pteridine proton singlet at δ 8.53, a single strong peak at δ 7.13 corresponding to five aromatic protons in a freely rotating phenyl group, and a well-defined CH_2CH_2 multiplet centered at δ 3.20. Thus, nmr evidence indicated that, in the presence of a very strong acid such as fluorosulfonic acid, a transient intermediate 4 (Scheme I) was generated from 1 which underwent immediate conversion into a new species (3) upon quenching with ethanol. That the latter transformation probably entailed an

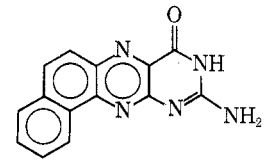
oxidative step was consistent with the very pronounced odor of sulfinic acid, which could be assumed to arise from fluorosulfonic acid or its ethanolysis product, ethyl sulfate, as part of a redox reaction.

Microchemical analysis established the empirical formula of the product to be $C_{14}H_{11}N_5O$, whereas the starting material 1 had the composition $C_{14}H_{13}N_5O$. Thus, fluorosulfonic acid treatment of 1 appeared to have effected an oxidative change involving the loss of two hydrogens. On the basis of the microanalytical results as well as uv and nmr spectral evidence cited above, the rearrangement product was assigned structure 3. This is a new example of the heretofore only sparsely studied naphtho[2,1-*g*]pteridine ring system.[7] Structure 3 satisfactorily accommodated the extended conjugation shown by the uv spectrum and was consistent with the absence of a C-7 pteridine proton in the nmr spectrum. Moreover, a plausible mechanism could be deduced for the cyclization of 1 to 3 as shown in Scheme I.

Protonation of N-8 in pteridines by very strong acids has been postulated previously[6] in order to explain the effectiveness of fluorosulfonic acid as an nmr solvent permitting a clear distinction between isomeric 6- and 7-substituted pteridines.[3,6] It was therefore reasoned that protonation at N-8 might also impart some positive character to the adjacent C-7 position, especially if additional charge delocalization could be provided *via* participation of a suitably placed phenyl group. A 6-phenethyl derivative would be especially appropriate in this regard, since formation of a resonance-stabilized species (see Scheme I) would occur *via* closure of a six-membered ring. Expulsion of a bridgehead proton (providing steric relief) would lead to an intermediate 4 having, in essence, a 7,8-dihydropteridine structure. Analogously to other known oxidations of condensed 7,8-dihydropteridines to pteridines,[8] further transformation of 4 into 3 would be expected to take place rapidly under oxidizing conditions.

Support for the mechanism outlined in Scheme I was derived from the nmr spectrum of the dark red 1:4 fluorosulfonic–trifluoroacetic acid mixture prior to quenching with ethanol. As stated above, a singlet was observed at δ 6.50 prior to quenching which was absent in the spectrum of the eventual product and was likewise not seen in the spectrum of homolog 2 under the same conditions. The origin of this signal, apparently unique in the spectrum of the 6-phenethyl derivative, is believed to be the newly formed benzylic bridgehead proton occupying what was once the C-7 position of the pteridine moiety. The disappearance of this signal on quenching is consistent with instantaneous oxidation of the 7,8-dihydropteridine intermediate 4 to the pteridine 3.

Direct chemical evidence for the tetracyclic nature of compound 3 was also obtained *via* selenium dioxide dehydrogenation experiments,[9] which gave a 75% yield of a new bright-yellow substance having the composition $C_{14}H_9N_5O$. The uv spectrum of this dehydrogenation product in 0.1 *N* sodium hydroxide contained maxima at 232, 285, and 428 nm. Since these values were consistent with a fully aromatized chromophore, the dehydrogenation product was formulated as structure 5. An isomeric tetracyclic 2-aminopteridin-4(3*H*)-one, compound 6, was obtained in 1954 by Timmis and coworkers by acid hydrolysis of the 2,4-diaminopteridine derivative.[10] The latter was formed on thermal condensation of 2-naphthol and 2,4,6-triamino-5-nitrosopyrimidine at 150°.[11] A sample of compound 6 was synthesized *via* this route and found to absorb at 254, 291, and 420 nm in 0.1 *N* sodium hydroxide. Additionally, compounds 5 and 6 both showed a characteristic bright blue uv fluorescence on tlc, possessed similar ir spectra, and resembled each other closely in their ready recrystallizability from 80% formic acid.



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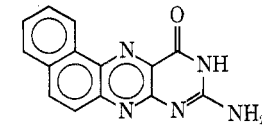

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It is interesting to consider possible reasons for the singular behavior of compound 1 in the presence of very strong acid. A likely explanation for the fact that ring closure of 1 is so facile is that formation of a resonance-stabilized positively charged intermediate (Scheme I) is energetically favorable in this particular instance because the five carbon atoms among which the positive charge is distributed can exist in a planar configuration. Such a configuration is readily achieved when the newly created ring is six membered and thus relatively strain-free. When cyclization involves formation of a seven-membered ring, as in the 6-(3-phenylpropyl)homolog 2, unfavorable ring distortion forces and eclipsing phenomena conspire to block this pathway. In preference to cyclization, therefore, simple substitution at the para position takes place,[3] presumably as a consequence of electrophilic attack by fluorosulfonic acid itself or the known mixed anhydride $CF_3C(O)OSO_2F$. The existence of this alternative pathway is supported by nmr evidence indicating gradual change of the aromatic proton signal in the 6-(3-phenylpropyl) compound 2 from a singlet to a typical AB quartet.[3,12]

The present serendipitous discovery of a reaction wherein the C-7 position of a pteridine functions as an electrophile because of protonation at N-8 represents a novel observation in pteridine chemistry.[13]

Experimental Section

Ir spectra were taken with a Perkin-Elmer Model 137B double-beam recording spectrophotometer and quantitative uv spectra were measured on Cary Model 11 and 15 spectrophotometers. Nmr spectra were determined on a Varian A-60 instrument with Me_4Si as the reference. When FSO_3H was present in the solvent mixture a sealed capillary containing Me_4Si was placed in the nmr sample tube. Melting point determinations were performed in Pyrex capillary tubes in a Mel-Temp apparatus (Laboratory Devices, Inc., Cambridge, Mass.). Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

10-Amino-5,6-dihydronaphtho[2,1-*g*]pteridin-8(9*H*)-one (3). A stirred solution of compound 1 (3.5 g, 0.013 mol)[3] in trifluoroacetic acid (35 ml) was treated dropwise with flurorsulfonic acid (8.75 ml). After being allowed to stand at room temperature for 30 min the dark red mixture was poured into 95% ethanol (875 ml). The initial pink color was rapidly discharged from the malodorous mixture and a yellowish solid deposited in the flask. The solid was filtered, washed with 95% ethanol and ether, and recrystallized (charcoal) from 80% formic acid (180 ml) to yield 3 as a pale yellow powder weighing 1.8 g (74%): mp >360°; nmr (CF_3CO_2H) δ 7.2–8.6 (m, aromatic protons), 3.3 (broad singlet with fine structure, CH_2CH_2); nmr (1:4 FSO_3H–CF_3CO_2H) δ 7.6–8.2 (m, aromatic protons), 3.8 (m, CH_2CH_2); uv (0.1 *N* NaOH) 240 nm (ϵ 21,590), 273 (18,830), 387 (15,290).

Anal. Calcd for $C_{14}H_{11}N_5O \cdot 0.5H_2O$: C, 61.30; H, 4.41; N, 25.53. Found: C, 61.55; H, 4.14; N, 25.55.

10-Aminonaphtho[2,1-*g*]pteridin-8(9*H*)-one (5). A mixture of compound 3 (0.5 g, 0.0018 mol) and powdered selenium dioxide (0.2 g, 0.0018 mol) in glacial AcOH (40 ml) was stirred under reflux for 4 hr. The hot mixture was then suction filtered and the filtrate was evaporated to dryness under reduced pressure. The filtered solid and the residue from evaporation were combined and redissolved in hot 80% formic acid (30 ml). Treatment with decolorizing carbon, dilution with a small volume of water, and slow cooling gave several crops totaling 0.36 g (77% yield), mp >360°. A sample recrystallized for microanalysis was washed

thoroughly with water and then dried at 100° (0.1 mm) in a drying pistol containing powdered KOH in order to remove the last traces of formic acid, uv (0.1 *N* NaOH) 232 nm (ε 31,820), 285 (38,340), 428 (13,530).

Anal. Calcd for $C_{14}H_9N_5O \cdot 0.25H_2O$: C, 62.79; H, 3.57; N, 26.15. Found: C, 62.80; H, 3.37; N, 26.08.

Registry No.—**1**, 4215-03-6; **3**, 50803-83-3; **5**, 50803-84-4.

References and Notes

(1) This investigation was supported in part by Research Contract DADA-17-71-C-1001 from the U. S. Army Research and Development Command, Office of the Surgeon General, and by Research Grant C6516 from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service. This is publication no. 1198 from the U.S. Army Research Program on Malaria.
(2) Paper II: A. Rosowsky, M. Chaykovsky, M. Lin, and E. J. Modest, *J. Med. Chem.*, **16**, 869 (1973).
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(8) *Cf.* E. C. Taylor and F. Yoneda, *J. Org. Chem.*, **37**, 4464 (1972), for a somewhat related *in situ* oxidation of a condensed 7,8-dihydropteridine to a pteridine.
(9) A. Rosowsky, K. K. N. Chen, M. E. Nadel, N. Papathanasopoulos, and E. J. Modest, *J. Heterocycl. Chem.*, **9**, 275 (1972).
(10) D. G. I. Felton, T. S. Osdene, and G. M. Timmis, *J. Chem. Soc.*, 2895 (1954).
(11) D. G. I. Felton and G. M. Timmis, *J. Chem. Soc.*, 2881 (1954).
(12) The similar gradual appearance of an AB pattern indicative of para substitution was noted previously[3] with 2-amino-7-phenethylpteridin-4(3*H*)-one and 2-amino-7-(3-phenylpropyl)pteridin-4(3*H*)-one, neither of which would be anticipated to undergo cyclization if the mechanism in Scheme I is valid.
(13) We are grateful to one of the referees for pointing out that the creation of an electrophilic center at C-7 on protonation is akin to the effect of an *N*-oxide. A convenient method has been reported recently for the direct synthesis of pteridine 8-oxides: H. Yamamoto, W. Hutzenlaub, and W. Pfleiderer, *Chem. Ber.*, **106**, 3175 (1973).

Nucleotides. II. Syntheses and Deblocking of 1-Oxido-2-pyridylmethyl Protected Nucleosides and Nucleotides[1,2]

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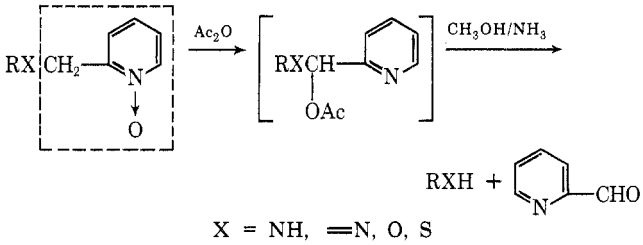
1-Oxido-2-pyridylmethyl group (op group) was found to be useful for protection of amino or hydroxyl groups of adenine, nucleosides (cytidine and adenosine), or phosphate functions of nucleotides (uridine 5′-phosphate and adenosine 5′-phosphate). N^6-(1-Oxido-2-pyridylmethyl)adenine (**1**) was prepared by the reaction of 1-oxido-2-pyridylmethylamine (**9**) and 6-methylsulfonylpurine (**11**). N^4-(1-Oxido-2-pyridylmethyl)cytidine (**2**) and N^6-(1-oxido-2-pyridylmethyl)adenosine (**3**) were also prepared by the reactions of **9** and appropriate sulfonate or sulfone derivatives of nucleosides **8** and **13**. 1-Oxido-2-pyridylmethyl nucleoside 5′-phosphates (**4**, **5**, and **6**) were prepared in excellent yields by the reactions of the nucleotides with 1-oxido-2-pyridyldiazomethane (**15**), a water-soluble alkylating agent newly developed for the present investigation. By the use of **15** op protection could be introduced into phosphate functions of nucleotides in aqueous solution in excellent yields. Deblocking of these op-protected nucleoside (**2**) and nucleotides (**4** and **6**) could be achieved in satisfactory yields (86–96%) by treatment with acetic anhydride, followed by methanolic ammonia.

In the past few years, the development of procedures for the chemical synthesis of oligonucleotides has depended to a significant extent on the design of a new protecting group with specific properties.[3]

In the preceding paper it was shown that 1-oxido-2-pyridylmethyl group (op group)[4] was useful as an easily removable blocking group for amino, imino, and hydroxyl functions[5] (Chart I).

Chart I



X = NH, =N, O, S

The present paper deals firstly with the preparation of 1-oxido-2-pyridylmethyl protected nucleosides **2** and **3** (Chart II) as well as 1-oxido-2-pyridylmethyl protected adenine (**1**), secondly with the preparation of the nucleotide derivatives **4**, **5**, and **6** by the use of 1-oxido-2-pyridyl diazomethane (**15**), and finally with the deblocking of these compounds (**2**, **5**, and **6**) with acetic anhydride treatment and subsequent hydrolysis.

Although two op-protected nucleosides (**2** and **3**) might be prepared by Dimroth rearrangement[6] of the respective 1- or 3-op-substituted nucleosides, we have adopted alternative routes (see Chart III).

Oxidation of 4-thiouridine (**7**)[7] with potassium permanganate (at 0° for 15 min) afforded the corresponding 4-sulfonate (**8**).[8] Without isolation, the reaction mixture was treated with 1-oxido-2-pyridylmethylamine (**9**) at room temperature for 25 hr to give the expected N^4-(1-oxido-2-pyridylmethyl)cytidine (**2**) (crude yield was almost quantitative) which was purified by charcoal treatment. The product was homogeneous on tlc and paper chromatography.

The structural confirmation of **2** rests upon the elemental analysis and spectral data (uv, ir, and nmr). Although the isolated yield was rather poor (34.7%), the possibility of optimizing isolation (charcoal treatment) conditions could improve the yield.

N^6-(1-Oxido-2-pyridylmethyl)adenine (**1**) was prepared according to a route shown in Chart IV. The synthetic sequence starts with 6-methylthiopurine (**10**),[9] which on oxidation with aqueous bromine solution afforded the corresponding 6-methylsulfonylpurine (**11**), contaminated with a small amount of 6-methylsulfinylpurine. Without purification, the mixture was treated with 1 equiv of 1-oxido-2-pyridylmethylamine (**9**) to yield **1** in 20% yield. The structure was confirmed by elemental analyses as well as spectral data.