Electrochemical versus Anionic Oxygenation of Azathymine Derivatives

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Electrochemical versus Anionic Oxygenation of Azathymine Derivatives

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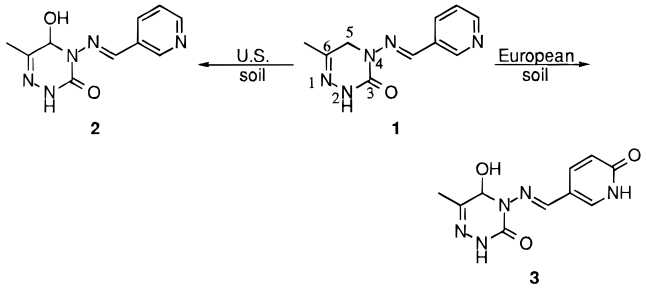
Abstract: Pymetrozine (**1**) was converted to hemiaminal **2** in low to moderate yield by trapping its dianion with oxygen followed by reduction with ferrous salts. Pymetrozines **18** and **19** failed to undergo this type of oxygenation. All three pymetrozines were oxidized electrochemically at C5 to methyl hemiaminals **20**, **21**, and **22**, respectively. Hydrolysis of **20** to **2** was accomplished under either acid- or base-catalyzed conditions in excellent yields, whereas the hydrolysis of methyl hemiaminals **21** and **22** was best performed under basic conditions. Soil metabolites of pymetrozine **1**, hemiaminals **2** and **3**, were prepared on a medium scale and in excellent yields. Linear sweep voltammetry data and conditions for preparative-scale electrochemistry are furnished for the precursory pymetrozines. Complete experimental and spectral data are provided for all new compounds, and the relative merits of anionic versus electrochemical oxidations for alkyl amides are discussed. A cautionary note is provided with the description of the conditions for large-scale anionic oxygenation because of potential explosive hazards.

Introduction

Pymetrozine (**1**), 2,3,4,5-tetrahydro-3-oxo-4-[(pyridin-3-yl-methylene)amino]-6-methyl-1,2,4-triazine, represents a novel type of insecticide with a new mode of action currently being developed by Novartis Crop Protection, Inc., for the control of aphids and white flies in vegetables, ornamentals, cotton, field crops, hops, deciduous fruit, and citrus.[1] This compound exhibits a high degree of selectivity for plant-sucking insects; it acts by blocking feeding behavior, which leads to starvation and death within several days.

Investigations of the environmental fate and effects of this new insecticide in both the United States and Switzerland have revealed the presence of several interesting metabolites. One of these compounds was found in greater than 30% of the applied dosage rate (1.5−2.0 ppm of **1** in the soil) in the soil photolysis studies, greater than 20% of applied dosage in aerobic soil studies, and greater than 10% of applied dosage in aged leaching studies.[2] On the basis of HPLC−mass spectral analysis data and limited ^{1}H-NMR evidence, this metabolite was tentatively assigned the structure **2**. Pyridone **3**, isolated only from experiments performed on European soils, has been similarly assigned.

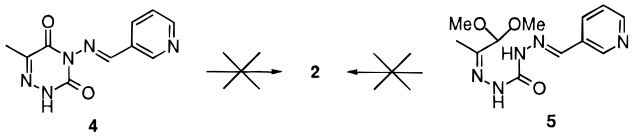


2 **1** **3**

Verification of the structure of metabolites **2** and **3** required independent medium-scale syntheses of these compounds, which were to be compared to the soil isolates and evaluated for biological activities. In this paper we report efficient syntheses of **2** and **3** along with a detailed discussion of the interesting chemistry associated with the preparation of these compounds by anionic versus electrochemical oxidation.

Results and Discussion

Condensation Approaches. Our initial strategy for the preparation of **2** and **3** relied on reductive or condensation techniques. 5-Oxopymetrozine (**4**) was easily prepared from carbohydrazide, pyruvic acid, and 3-pyridinecarboxaldehyde.[2] However, all attempts at selective reduction (hydrogenation, Meerwein−Ponndorf reduction, lithium aluminum hydride, Superhydride, sodium borohydride, etc.) of amide **4** to 5-hydroxypymetrozine (**2**) failed to yield the desired compound and resulted mostly in the reduction of the aldimine moiety. The acid-catalyzed deprotection and subsequent closure of **5**, prepared from pyruvaldehyde dimethyl acetal, carbohydrazide, and 3-pyridinecarboxaldehyde, also failed. The latter route resulted in complex mixtures composed chiefly of nicotinaldehyde and symmetrical hydrazones derived from carbohydrazide and pyruvate.



4 **5**

Anionic Oxidation of Pymetrozine (1). As the construction of the triazine with the required oxidation state *via* condensation chemistry and/or selective reductions of 5-oxopymetrozine was unsuccessful, we turned our focus to oxidation at position 5 in the parent pymetrozine (**1**).[3]

Introduction of oxygen functionality into carbanions derived from hydrocarbon acids is well established.[4] In a preliminary experiment, a suspension of pymetrozine in THF/TMEDA at −78 °C was treated with *sec*-butyllithium (2.2 equiv) followed

† Novartis Crop Protection, Inc., Greensboro, NC 27409.

⊗ Abstract published in *Advance ACS Abstracts,* August 1, 1997.

(1) (a) Kristinsson, H. U.S. Patent 4 931 439, 1990. (b) Kristinsson, H. U.S. Patent 4 996 325, 1991.

(2) Unpublished observation, Novartis group.

(3) Although the *E* vs *Z* geometry of the Schiff base was not determined for **1**, it is drawn throughout this paper as the *E* form.

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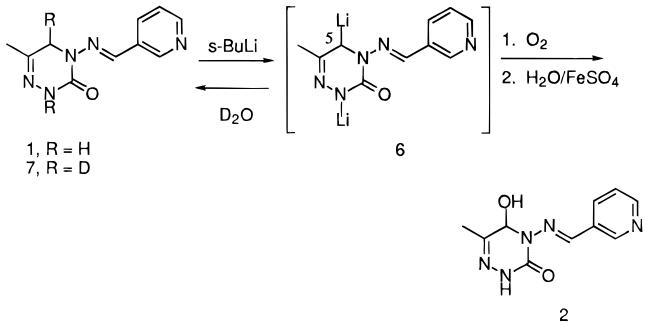
Scheme 1. Anionic Oxidation of **1**



by a D_2O quench (Scheme 1). ^{1}H-NMR analysis of the isolated pymetrozine, assigned as **7**, indeed indicated the incorporation of deuterium at the 5 position of the triazine ring, as evidenced by the decrease in the intensity of the signal at 4.35 ppm (DMSO-d_6 (1H)), as well as the exchange of the amide proton.

In agreement with the results of the deuterium quench experiments, hemiaminal **2** was successfully prepared on a small scale and in 10−35% yield by oxygenation of the lithium dianion **6**.[4] The anion was generated by treating a suspension of **1** in THF containing TMEDA at −78 °C with *sec*-butyllithium (5 equiv). A slow stream of oxygen was passed through the reaction mixture, while the temperature was allowed to warm to 20 °C over 8 h. Following the quench of all peroxides by aqueous ferrous ammonium sulfate[5] and subsequent extraction, compound **2** was isolated by crystallization from methanol (large scale) or column chromatography (small scale) from a mixture of at least 20 compounds. The reaction of **1** was eventually scaled up to 10 g, yielding approximately 1−3 g of hemiaminal **2** per run after crystallization from methanol. The precise regime of oxygen concentration or the concentration of peroxides derived from unreduced peroxides of **2** was not accurately determined, but positive qualitative peroxide tests were observed at all stages of the reaction until the iron(II) quench. On two occasions the larger scale runs flashed and exploded during the warming phase of the experiment (first at −16 °C, second at 12 °C). A 20 g reaction performed in a 12 L flask exploded and burned with complete destruction of the fume hood. (See the cautionary note in the Experimental Section.)

Several comments are in order regarding the possible mechanism of the oxygenation. Although more direct evidence is not available, it is interesting to note that product **2** did not appear in the reaction mixtures during the oxygen sparge. No product or unreacted starting material **1** was observed (*vide* TLC analysis) until the reaction mixture had been stirred at room temperature for 8−12 h following the completion of the oxygen sparge. The fact that **2** was present before reduction but not immediately after the reaction reached ambient temperature suggests the possibility of an *intramolecular oxygenation* of dianion **6** by peroxides such as **8** derived from excess *sec*-butyllithium.[6] Thus, as the reaction mixture warms, some of the proposed intermediates (**9**, **10a**, **10b**, or **11**, for example) that would ultimately lead to the product may be generated as suggested in Figure 1. The presence of hemiaminal **2** before the addition of ferrous salts may be rationalized by invoking the path **6** → **9** → **11**, for which no external reducing agent is necessary. Furthermore, the presence of cyclic peroxides such as **10b** cannot be excluded. The cyclic peroxide **10b** could generate the product reductively as well as by a reaction with anion **6**.[6e] Finally, the presence of unreacted starting material at the time of quench, but not at the end of oxygen sparge, can be explained by protonation and slow elimination of the species derived from **9**. Such a pathway, involving intermediates derived from *sec*-butyl peroxides, would also explain the need for 5 equiv of *sec*-butyllithium.[7]

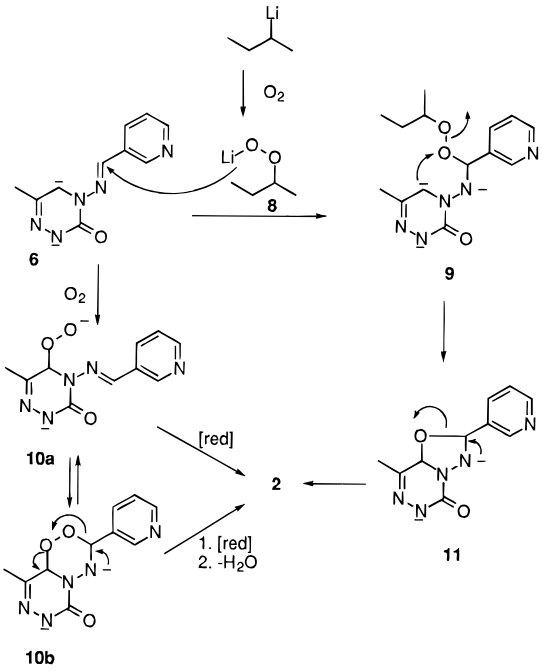


Figure 1. Suggested mechanism for oxygenation of **1**.

Attempted Anionic Oxygenation of Pymetrozines 18 and 19. The starting materials for the synthesis of **3** were prepared as shown in Scheme 2. 2,5-Dibromopyridine (**12**) was converted, via 2-methoxy-5-bromopyridine (**13**), to 6-methoxynicotinaldehyde (**14**) by adapting Comins's procedure for the metal−halogen exchange in **13** and the addition of the organolithium species to DMF.[8] This material was converted to pyridone **16** by treatment with aqueous HBr. The literature conditions for HBr demethylations of **14** to **16**[9] have been improved for large-scale preparation by careful optimization of the temperature regime and the workup of the reaction (see the

(4) (a) Kim, M. Y.; Starrett, J. E.; Weinreb, S. M. *J. Org. Chem.* **1981**, *46*, 5383. (b) Wasserman, H. H.; Lipshutz, B. H. *Tetrahedron Lett.* **1975**, 1731. (c) Williams, R. M. *Tetrahedron Lett.* **1981**, *22*, 2341. (d) Vedejs, E.; Engler, D. A.; Telshow, J. E. *J. Org. Chem.* **1978**, *43*, 188. (e) Ohta, T.; Hosoi, A.; Nozoe, S. *Tetrahedron Lett.* **1988**, *29*, 329. (f) Davis, F. A.; Vishwakarma, L. *Tetrahedron Lett.* **1985**, *26*, 3539.

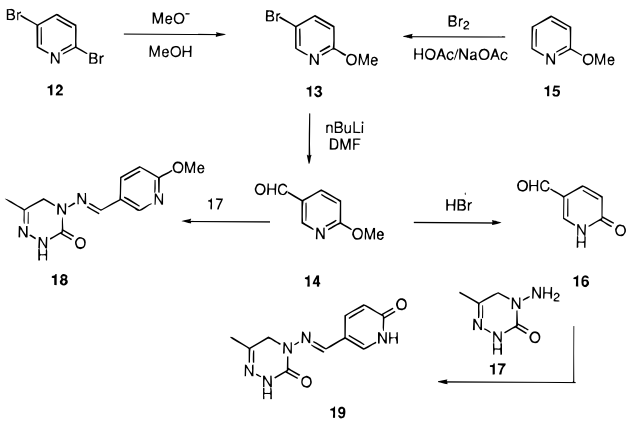
(5) For qualitative determination of peroxides see: Gordon, A. J.; Ford, R. A. *The Chemist's Companion*; Wiley-Interscience: New York, 1972; p 437. Prior to the addition of the Fe(II) salts, the presence of the peroxides was monitored by means of sodium ferrothiocyanate solution, prepared as follows: $FeSO_4 \cdot 7\ H_2O$ (9 g) was dissolved in aqueous HCl (50 mL, 18%), and a small amount granular Zn was added. Sodium thiocyanate (5 g) was added, and after the transient color faded, additional sodium thiocyanate (12 g) was added. The solution was decanted from the unused Zn, and stored in a clean reagent bottle. Upon mixing the colorless reagent with the tested solution, the appearance of deep red color indicates peroxide presence. Since the presence of ferrous salts, used to decompose the peroxides, can lead to a false negative result with the sodium ferrothiocyanate reagent, standard potassium iodide/starch test paper was used to follow the peroxide presence after the quench.

(6) (a) Boche, G.; Mobus, K.; Harms, K.; Marsch, M. *J. Am. Chem. Soc.* **1996**, *118*, 2770. (b) Boche, G.; Bosold, F.; Lohrenz, J. C. W. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1161. (c) Boche, G.; Mobus, K.; Harms, K.; Lohrenz, J. C. W.; Marsch, M. *Chem. Eur. J.* **1996**, *2*, 604. (d) For a comprehensive review see: Criegee, R. Herstellung und Umwandlung von Peroxiden. *Methoden der Organischen Chemie. (Houben-Weyl). Band VIII SauerstoffVerbindungen III*; Georg Thieme Verlag: Stuttgart, 1970; p 3. (e) Schollkopf, U. Metalorganische Verbindungen. *Methoden der Organischen Chemie. (Houben-Weyl). Band XIII/1*; Georg Thieme Verlag: Stuttgart, 1970; p 171.

(7) We thank the reviewers of this paper for helpful comments on this topic.

(8) Comins, D. L.; Killpack, M. O. *J. Org. Chem.* **1990**, *55*, 69−73.

Scheme 2. Synthesis of Pyridone **19**

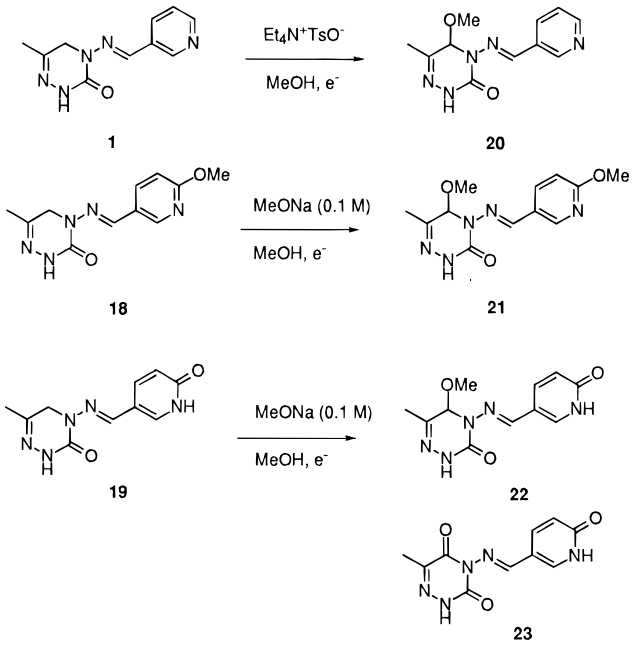


Experimental Section). An alternative and a more cost-effective preparation of **16** (also included in the Experimental Section) was realized via bromination[10] of 2-methoxypyridine **(15)**, replacing the more expensive 2,5-dibromo derivative **12**.

Condensation of both aldehydes **14** and **16** with hydrazine **17**[11] furnished the requisite pymetrozines **18** and **19**, respectively. Both pymetrozines were subjected to the anionic oxygenation conditions described above for **1**, but in both cases no oxygenated products were detected in the complex reaction mixtures (*vide* NMR, expected signals for the hemiaminal CH at 6.0 ± 0.4 ppm). The anionic oxygenation protocol was abandoned for safety considerations and the general unpredictability of the hazards, as well as the complexity of the reaction mixture.[12]

Electrochemical Oxidation of Pymetrozines 1, 18, and 19. Given the experience with hazardous anionic oxygenation, we turned to alternative methods of introducing the C5 hydroxyl. The most convenient approach was found in the electrochemical removal of an electron from an alkyl amide in the presence of an oxygen nucleophile (such as lower alcohols). The electrochemically generated radical cation is rapidly quenched, ultimately yielding an *O*-alkyl *N*-acylhemiaminal.[13] This reaction seems to be generally applicable for the α-alkoxylation of amides[13a] and carbamates.[13d] Since the procedure is typically not complicated by overoxidation,[13g] large quantities of otherwise inaccessible *O*-alkyl *N*-acylhemiaminals can be synthesized by galvanostatic oxidation, requiring only simple equipment and inexpensive reagents. Many examples of successful electrochemical alkoxylations of amides are known and are listed, along with their applications to synthesis, in an excellent review.[13h]

Scheme 3. Electrochemical Oxidation of Pymetrozines **1**, **18**, and **19**



When a methanolic solution of **1** was subjected to direct current electrolysis under galvanostatic conditions (100 mA, initial 6 V, graphite electrodes, undivided cell, tetraethylammonium *p*-toluenesulfonate), methyl hemiaminal **20** was isolated in essentially quantitative yield, Scheme 3. The oxidation was found to be surprisingly tolerant of a wide range of applied potentials, required no cooling, and was successfully scaled up to 20 g with the added advantage that the completion of the reaction was indicated by the dissolution of all solid starting material in methanol. Unexpectedly, electrooxidation of both **18** and **19** under the conditions where pymetrozine (**1**) was cleanly converted to 5-methoxypymetrozine (**20**) resulted in complex mixtures, and we initially attributed these problems to extended reaction times dictated by the low solubility of both **18** and **19** in methanol.

Because the solubility of both **18** and **19** could be improved dramatically at pH >10, sodium methoxide (0.1 M) in methanol was used as the electrolyte. Under these conditions, galvanostatic runs clearly afforded the required methyl hemiaminals **21** and **22** from pymetrozines **18** and **19**, respectively, Scheme 3. In the electrolysis of pyridone **19**, substantial overoxidation to 5-oxopymetrozinone **23** was observed and complicated scale-up and isolation. Eventually it proved possible to separate the overoxidized 5-oxopymetrozinone (**23**) from 5-methoxypymetrozinone (**22**) during workup, and pure **22** was obtained by crystallizations from methanol. Because the starting material **19** could not be separated from the product in this fashion, the electrooxidations were continued until the starting material completely disappeared. This practice resulted in approximately 25% overoxidation to **23** and a decrease in the yields of **22** to 45−50% on larger scales (10−15 g of **19**).

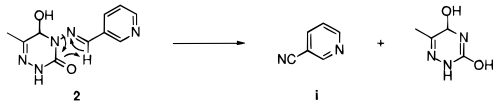
Linear Sweep Voltammetry Measurements[14a] **and the Controlled Potential**[14b] **Electrolysis of 19.** In order to understand the process of electrooxidations of these pymetrozines with the hope that the overoxidation of **22** to **23** could ultimately be curtailed, we performed the cyclic (CV) and the linear sweep (LSV) voltammetry analyses of pymetrozines **18**, **19**, **21**, and **22.** These measurements were hampered by adsorption to the electrode and were characterized by broad irreversible oxidation waves that shifted to more positive potentials with increasing sweep rates (0.01−1.0 V/s). LSV analysis of **19** (0.1 V/s)

(9) Ross, S. T.; Kruse, L. I.; Ohlstein, E. H.; Erickson, R. W.; Ezekiel, M.; Flaim, K. E.; Sawyer, J. L.; Berkowitz, B. A. *J. Med. Chem.* **1987**, *30*, 1309−1313.

(10) Windscheif, P. M.; Vogtle, F. *Synthesis* **1994**, 87.

(11) Gold, H. In *Methoden der Organischen Chemie. (Houben-Weyl). Band VII 2b. Ketone II., 1976*; Muller, E., Ed.; Georg Thieme Verlag: Stuttgart, 1954.

(12) Among the various byproducts of the reaction **i** was identified by isolation and matching.



(13) (a) Nyberg, K.; Servin, R. *Acta Chem. Scand.* **1976**, *30*, 640. (b) Eberson, L.; Hlavaty, J.; Jönsson, L.; Nyberg, K.; Servin, R.; Sternerup, H.; Wistrand, L.-G. *Acta Chem. Scand.* **1979**, *33*, 113. (c) Rudd, E. J.; Finkelstein, M.; Ross, S. D. *J. Org. Chem.* **1972**, *37*, 1763. (d) Shono, T.; Hamaguchi, H.; Matsumura, Y. *J. Am. Chem. Soc.* **1975**, *97*, 4264. (e) Ross, S. D.; Finkelstein, M.; Petersen. R. *J. Am. Chem. Soc.* **1966**, *88*, 4657. (f) Okita, M.; Wakamatsu, T.; Ban, Y. *J. Chem. Soc., Chem. Commun.* **1979**, 749. (g) Mitzlaff, M.; Warning, K.; Jensen, H. *Liebigs Ann. Chem.* **1978**, 1713. (h) Shono, T. *Tetrahedron* **1984**, *40*, 811.

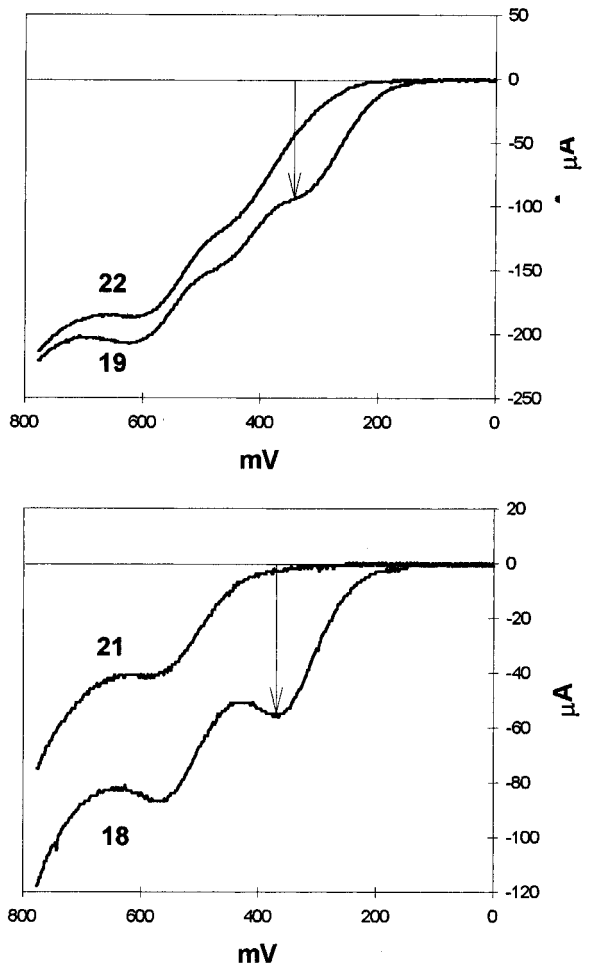


Figure 2. Linear sweep voltammetry comparison of compounds **19** and **22** and compounds **18** and **21** (0.1 V/s): methanol solvent; 0.5 mol dm^{-3} NaOMe; GCE and 0.1 mol dm^{-3} Ag^+/Ag as working and reference electrodes, respectively.

revealed the presence of three oxidation waves at $E_1 = 344$ mV, $E_2 = 484$ mV, and $E_3 = 612$ mV versus the Ag/Ag^+ (0.1 M, acetonitrile) electrode, Figure 2. The half-peak potential[15] could only be determined for E_1 and was found to be 88 mV. The peak width remained relatively constant from 0.01 to 1 V/s at a value of 93 ± 13 mV. Oxidation peaks shifted with increasing sweep rate on the order of 36 ± 5 mV/decade.

LSV analysis of **22** (0.1 V/s) revealed the presence of only two oxidation waves at $E_1 = 468$ mV and $E_2 = 614$ mV versus the Ag/Ag^+ (0.1 M, acetonitrile) electrode, Figure 2. The oxidation potentials shifted with increasing sweep rate (0.01−1 V/s) on the order of 31 ± 1 mV/decade. Because of the difficulty in precisely determining the oxidation potential E_1, peak width analysis could not be conducted.

LSV analysis of **18** (0.1 V/s) also revealed the presence of two oxidation waves at $E_1 = 366$ mV and $E_2 = 566$ mV versus the Ag/Ag^+ (0.1 M, acetonitrile) electrode, Figure 2. The half-peak potential could be determined for E_1 and was found to be 72 mV. The oxidation potentials shifted to more positive potentials with increasing sweep rate at 31 ± 1 mV/decade between sweep rates of 0.01−1 V/s. The peak width remained relatively constant at values of 79 ± 11 mV.

LSV analysis of **21** (0.1 V/s) revealed the presence of only one oxidation peak at $E_1 = 580$ mV versus the Ag/Ag^+ (0.1 M, acetonitrile) electrode, Figure 2. The half-peak potential was found to be 88 mV. Peak potentials shifted at 31 ± 1 mV/decade to more positive potentials with increasing sweep rate. Peak widths remained relatively constant from 0.01 to 1 V/s at 92 ± 10 mV.

The similarity in the voltammograms of **19** and **22**, Figure 2, clearly indicates that the first oxidation wave can be attributed to the removal of one electron from **19** followed by methanol quench in an EC type mechanism, whereas the second and third oxidations are associated with the oxidation of the produced methyl hemiaminal **22** to the 5-oxopymetrozinone (**23**). A similar conclusion can be inferred from the voltammograms of **18** and **21**, Figure 2. Again, the first oxidation wave at $E_1 = 366$ mV (Ag/Ag^+, 0.1 M, acetonitrile) can be attributed to the one electron oxidation of **18** followed by methanol quench, resulting in **21**, while the second wave corresponds to the further oxidation of methyl hemiaminal **21**. Potentiostatic runs on **19** confirmed the first of these hypotheses since extended electrolysis at potentials above 160 mV (Ag/Ag^+, 0.1 M, acetonitrile) resulted in full oxidation of **19** to **23** while TLC analysis confirmed the transitory presence of **22**.

The strikingly different electrochemical behavior of **1** when compared to **18** and **19**, especially with regard to their propensity toward overoxidation, seems to reflect the ease by which electrons are removed from the charged versus the neutral triazine ring. Galvanostatic oxidation of pymetrozine (**1**), performed in a neutral medium, afforded the methyl hemiaminal **20** in high yield without the formation of 5-oxopymetrozine. On the other hand, fixed-potential oxidation of both **18** and **19**, performed in a strongly basic medium, in which the sodium salt of **18** and disodium salt of **19** were the active species, resulted in substantial overoxidation.

In principle, two electrochemical events can be separated, provided that the gap between them is at least 200 mV.[16] Indeed in potentiostatic small-scale preparative runs performed at a fixed potential of +63 mV (Ag/Ag^+, 0.1 M, acetonitrile), the overoxidation could be largely suppressed, resulting in a clean formation of the desired methyl hemiaminal **22** in 90% isolated yield, with small amounts of starting material still remaining in the reaction mixture.

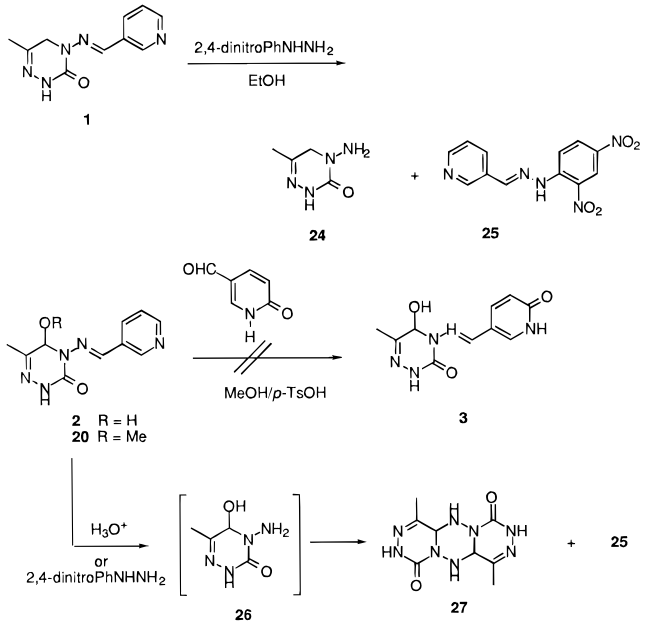
Exchange experiments. Prior to the success in the potentiostatic oxidations of pyridone **19**, attempts were made to prepare 5-hydroxypymetrozinone (**3**) by subjecting either the simpler analog **2** (prepared by the oxygenation process) or the methyl hemiaminals **20** and **21** to the conditions of Schiff base exchange, Scheme 4. Whereas pymetrozine (**1**) yielded upon treatment with dinitrophenylhydrazine in ethanol the parent aminotriazine **24** and the expected hydrazone **25**, the same conditions failed with hemiaminal **2** and methyl hemiaminal

(14) (a) **Cyclic and Linear Sweep Voltammetry**. Electrochemical measurements were conducted on a Princeton Applied Research EG&G Model 263A potentiostat/galvanostat interfaced to a HP PC running M270 electrochemical analysis software. All measurements were performed on 0.5 M solutions of sodium methoxide in methanol. Substrate concentrations were adjusted to maintain a 50-fold excess of electolyte to substrate concentration. Voltammograms were acquired with a 2 mm planar button glassy carbon electrode versus 0.1 M Ag/Ag^+ in CH_3CN. A platinum rod was utilized as the auxiliary electrode. Cell resistance was corrected utilizing positive feedback IR compensation incorporated in the M270 software. Typical measurements were conducted in the following manner. The sodium methoxide solution was placed in the voltammetry cell and degassed with argon for 30 min. At this point background voltammograms were taken at all sweep rates to be investigated. An amount of the electroactive substrate needed to bring the concentration to 0.01 M was then added to the voltammetry cell and the solution stirred until the substrate was completely dissolved. At this point voltammatry measurements were begun. After each voltammetric run the solution was stirred and the working electrode polished to remove material adsorbed to the working electrode surface. (b) Preparative potentiostatic electrooxidations were performed on a Princeton Applied Research EG&G Model 263A potentiostat, equipped with a modified power amplifier with a current output capability of 2 A.

(15) A potential at which the current is half of its maximum value. For an electrochemically reversible system $E_p - E_{p/2} = 59.2/n$ mV/decade.

(16) Fry, A. J.; Mitnick, M.; Reed, R. G, *J. Org. Chem.* **1970**, *35*, 1232.

Scheme 4. Attempted Schiff-Base Exchange Experiments



20. Under the conditions of acid catalysis only the dimer **27** was produced, presumably because of the inherent instability of the intermediate hydroxyaminotriazine **26**, generated upon the liberation of the aldehyde and the free hydrazine from the corresponding Schiff base. Attempted *in situ* exchange of the nicotinaldehyde unit in **2** or **20** for 6-oxo-pyridine-3-carbaldehyde (**16**), performed in MeOH with a catalytic amount of pTsOH, failed also. These conditions yielded, in the case of **2**, only the methyl hemiaminal **20**, indicating the lability of the C5 substituents, and therefore the potential for replacing groups at this position.

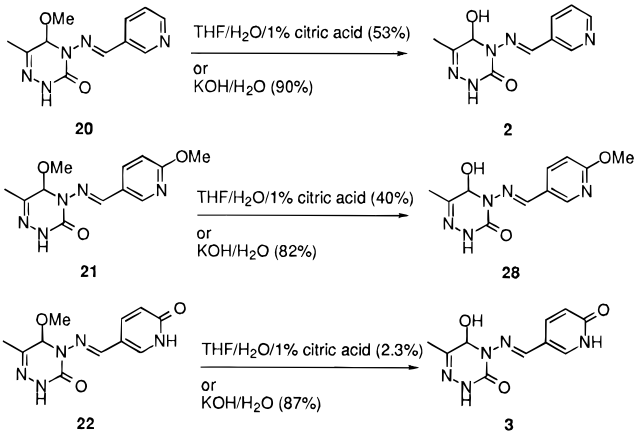
Hydrolysis of Methyl Hemiaminals 20 and 22. Analytically pure **20** was hydrolyzed to **2** under acidic conditions. The acidic hydrolysis was best performed by suspending solid **20** in THF/1% aqueous citric acid (2:1) and letting this mixture stir overnight. The suspension cleared after 2 h, and **2** began precipitating from solution. Reduction of the volume by 50% and cooling provided essentially pure **2**. Alternatively, **20** was suspended in 1% aqueous citric acid and brought to reflux until dissolved, whereupon **2** began to precipitate. With either procedure, the final crude product contained 2−6% of dimer **27** and was purified further by recrystallization from methanol and water. The presence of this material in the final product was completely avoided by eliminating heating during the volume reduction or by recrystallization. Recrystallization of mixtures containing this compound from methanol−water (1:2) gave analytically pure **2**, Scheme 5. Similar hydrolysis furnished hemiaminal **28** from **21**.

Methyl hemiaminal **22** was also subjected to the conditions of acid catalysis, but the yields of pyridone **3** were low because of its instability to prolonged exposure to acidic pH.

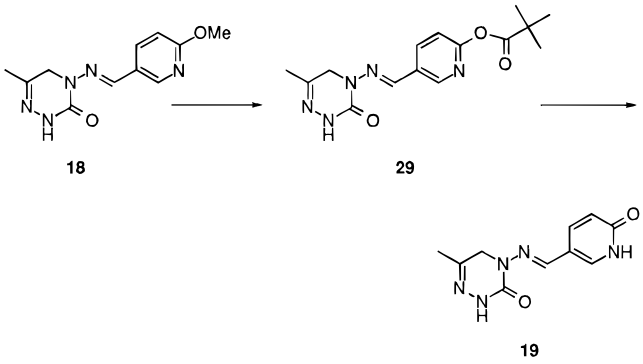
The content of dimer **27** in reactions attempted with **20**, **21**, and **22** was ∼5%, ∼45%, and >90% resectively. We rationalized these differences in increased lability of the methoxypyridine and pyridone moieties toward hydrolysis under acidic conditions, thereby generating increased concentrations of the free hemiaminal hydrazine for the irreversible dimerization.

A method that would simultaneously replace both methoxy groups with hydroxyls in dimethoxypymetrozine **21**, under mild, neutral, or basic conditions, was therefore sought. A suitable protocol for this cleavage appeared to be that developed by Oku[17] (NaI/pivaloyl chloride). This sequence was first tested

Scheme 5. Hydrolysis of Methyl Hemiaminals

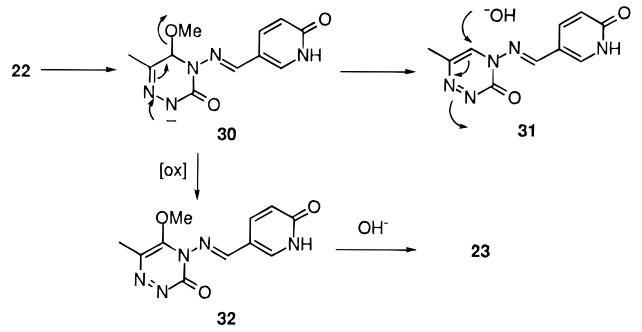


Scheme 6. Generation of Pyridone by Cleavage of Pivaloyl Ester



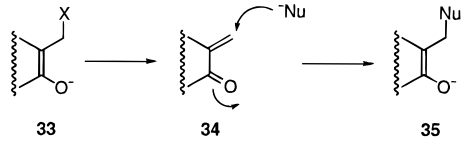
with pymetrozine derivative **18** which was, under somewhat forcing conditions, converted *via* **29** to the pyridone **19** in 95% yield as shown in Scheme 6. In contrast, these conditions did not provide **3** from dimethoxypymetrozine **21** and led only to complex mixtures, but the application of this protocol to methyl hemiaminal **20** provided the expected hemiaminal **2** in essentially quantitative yield. Careful examination of the reaction progress for the cleavage of **20** to **2** revealed that the exchange of a methoxy group for hydroxyl was a result of base-catalyzed hydrolysis of methyl hemiaminal **20**, rather than the cleavage of the ether bond. This observation had a positive impact on the final solution to the preparation of **3** on a large scale under the conditions of base-catalyzed hydrolysis.

Both methyl hemiaminals **20** and **22** were cleanly hydrolyzed to **2** and **3**, respectively, without formation of **27** by exposure to aqueous KOH. The hydrolysis under basic conditions (which emerged as a result of the above-mentioned pivaloate experiment) furnished pure **3** in a process that might involve the vinylogous hemiaminal functionality in the amide anion **30** to generate the azadiene **31** (or its oxidized analog **32**) as shown.



(17) Oku, A.; Harada, T.; Kita, K. *Tetrahedron Lett.* **1982**, *23*, 681.

The only analogy to this process we are aware of is the nucleophilic alkylative saturation of isatin ketals reported by Wenkert.[18] Presumably this procedure is general for vinylogous systems of the type **33**, provided that the final double bond



33 **34** **35**

created by the nucleophilic addition leads to the formation of a stable chromophore. This certainly is the case with both hemiaminals **2** and **3**.

The best overall route to 5-hydroxypymetrozine (**2**) involved galvanostatic electrooxidation of the parent pymetrozine (**1**) at neutral pH (62%), followed by a base-catalyzed hydrolysis of the methyl hemiaminal **20** (90%). On the other hand, the best route to **3** required a controlled potential electrooxidation of **19**, performed at strongly basic conditions (91%) followed by a base-catalyzed hydrolysis (87%) to **3**. Only the 5-hydroxypymetrozine (**2**) could be obtained by an acid-catalyzed hydrolysis of the corresponding *O*-methyl hemiaminal **20**, in 53% yield.

Conclusions. Even though the acquired experimental data do not allow for quantitative assessment of the pertinent mechanistic pathways, it seems unlikely that the commonly accepted mechanism[13d] (i.e., cation radical) for amide oxidation can operate in the reaction medium containing anionic species (as for **18** and **19**). We propose that the initial removal of an electron from the anions of **18** and **19** is followed either by the removal of the second electron and loss of a proton or by a loss of hydrogen atom induced by electrochemically generated radicals. Although the evidence for a two-electron oxidation is not directly available from the voltammetry experiments, it might be the more probable path. The intermediate **31**, generated by one of the above paths, is rapidly substituted by MeOH (MeO^-) to furnish the methyl hemiaminal **30**. The overoxidation to **23** may follow the same course to the stage of dienol ether **32** which furnished **23** either hydrolytically or by S_N2-like cleavage of the methyl enol ether. In the case of pymetrozine (**1**) the normal cation radical pathway may be considered, since the substrate is not negatively charged under the conditions of electrolysis.

The proposed azadienes of types **31** and **32** may be the likely intermediates in all hydrolyses of the methyl hemiaminals, and their reactivity might have contributed to the solution of the hydrolysis problem. The chemistry associated with these compounds offers some interesting possibilities with regard to further exploitation in the realm of cycloaddition chemistry, for example.

In summary, the preparation of hemiaminals **2** and **3** *via* electrochemically generated methyl hemiaminals **20** and **22** has been accomplished in excellent yields and on a medium scale (75 g of each). A comparison between the anionic and electrochemical methods is available and shows the superiority of the mild electrochemical protocol over the more traditional (and hazardous) technique. The chemistry of the triazine moiety contained within the pymetrozines is also interesting, as demonstrated with both electrochemical oxidations and the base-catalyzed hydrolyses of the methyl hemiaminals. Future endeavors will likely exploit some of these features and will be reported in due course.

Experimental Section[19]

5-Hydroxy-6-methyl-3-oxo-4-[(pyridin-3-ylmethylene)amino]-2,3,4,5-tetrahydro-1,2,4-triazine (**2**). **Method A.** An oven-dry 5-L round-bottomed flask (RBF) was charged with the 6-methyl-3-oxo-4-[(pyridin-3-ylmethylene)amino]-2,3,4,5-tetrahydro-1,2,4-triazine (**1**; 20.00 g, 92.07 mmol) and set under a static Ar atmosphere. Dry tetrahydrofuran (3.5 L, Aldrich) was added (*via* steel capillary), followed by *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (70 mL, 446 mmol, distilled from CaH_2), *via* syringe. The assembly was cooled to −78 °C, and cyclohexane solution of *sec*-butyllithium (360 mL, 468 mmol, 1.3 M, Aldrich) was added dropwise, over 90 min, and the reaction mixture was stirred for an additional 60 min. A slow stream of oxygen was passed through the reaction mixture while the temperature was allowed rise to 25 °C over 8 h. The oxygen stream was disconnected, and the reaction mixture was stirred at room temperature overnight. The reaction mixture was degassed a with stream of argon, and quenched with 800 mL of water. The aqueous phase was separated and extracted with ethyl acetate (1 × 800 mL). The water layer was treated with solid ferrous ammonium sulfate hexahydrate (40 g, 102 mmol), and the suspension was stirred until the starch/potassium iodide test for peroxides was negative. The mixture was placed into a continuous extractor, and extracted with chloroform overnight. The crude extract was filtered through Celite, and the solvent was removed under reduced pressure. The remaining semisolid was triturated with methanol (50 mL), and the separated product was filtered off. Drying on high vacuum yielded 2.61 g (12%) of pure product as an off-white powder. *CAUTION: Following the passage of oxygen into the reaction mixture extreme caution should be exercised. The solution is rich in peroxides and is saturated with oxygen. On two occasions while being warmed from −78 °C the mixture flashed (10 g scale) or exploded (20 g scale). We recommend against performing this type of reaction on higher than a 2 mmolar scale*.

Method B. The crystalline methyl aminal **20** (5.0 g, 20.22 mmol) was placed in a 50 mL RBF, and tetrahydrofuran (50 M) was added, followed by an aqueous solution of citric acid (1%, 100 mL). After overnight stirring at room temperature, the precipitated product was filtered off, washed with methanol (20 mL) and diethyl ether (50 mL), and dried under high vacuum to yield 2.5 g (53%) of pure product as a white crystalline material.

The spectral and physical characteristics were found to be identical to those of the oxygenation product. $R_f = 0.53$ (ethyl acetate/ethanol, 7:3), $R_f = 0.32$ (chloroform/methanol, 85:15). Mp: 208−210 °C (THF/H_2O). ^{1}H NMR (400 MHz, CD_3OD, drop of D_2O): δ 8.91 (s, 1H), 8.58 (br d, $J = 3.81$ Hz, 1H), 8.51 (s, 1H), 8.38 (ddd, $J = 7.9$, 2, 2 Hz, 1H), 7.54 (dd, $J = 8.4$, 4.9 Hz, 1H), 5.95 (s, 1H), 2.16 (s, 3H). ^{1}H NMR (500 MHz, $(CD_3)_2SO$): δ 10.52 (s, 1H), 8.86 (d, $J = 1.5$ Hz, 1H), 8.60 (dd, $J = 4.9$, 1.5 Hz, 1H), 8.58 (s, 1H), 8.12 (dt, $J = 8.3$, 2.0 Hz, 1H), 7.48 (dd, $J = 7.8$, 4.9 Hz, 1H), 7.02 (d, 8.3 Hz, 1H), 5.79 (d, $J = 8.3$ Hz, 1H), 2.03 (s, 3H). ^{13}C NMR (400 MHz, CD_3OD, drop of D_2O, apt): δ 151.2 (CH), 150.4 (C), 149.7 (CH), 147.6 (C), 145.3 (CH), 136.6 (CH), 132.5 (C), 125.7 (CH), 76.3 (CH), 19.2 (CH_3). IR (KBr, 2%): 3200, 2950, 1690, 1650, 1590 cm^{-1}. MS (EI): *m/z* (rel intens) 233 (M^+, 3), 114 (28), 105 (42), 66 (100). For $C_{10}H_{11}N_5O_2$ (233.23) Calcd: 51.50% C, 4.75% H, 30.03% N. Found: 51.34% C, 4.88% H, 29.82% N.

2-Methoxy-5-bromopyridine (13). Method A.[8] A solution of 2,5-dibromopyridine (20 g, 0.084 mol) in methanol (150 mL) containing sodium methoxide (22.8 g, 0.42 mol) was stirred at reflux for 16 h. After cooling to room temperature, the reaction mixture was poured into an aqueous saturated solution of sodium bicarbonate. The product was extracted with diethyl ether (4 × 250 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. Distillation initially at atmospheric pressure (to remove MeOH) and then under vacuum (47−50 °C, 0.5 mmHg) gave 2-methoxy-5-bromopyridine (12.65 g, 80%).

Method B.[10] A solution of bromine (372 g, 2.3 mol) in glacial acetic acid (400 mL) was added dropwise into a mechanically stirred suspension of 2-methoxypyridine (180 g, 1.65 mol) and sodium acetate (144 g, 1.75 mol) in glacial acetic acid (800 mL) at 10 °C. The suspension was stirred at room temperature for 12 h and then

(18) Wenkert, E.; Hudlicky, T. *Synth. Commun.* **1977**, *7*, 541.

(19) All nonhydrolytic reactions were performed in solvents either dried according to standard procedures or purchased from Aldrich. Analytical TLC was performed on silica gel 60F-254 plates (Whatman). Flash chromatography was performed with Fisher silica gel (grade 60, 200−425 mesh).

concentrated to 1/3 of its original volume, poured onto ice, and made basic (pH *ca.* 8) with NaOH before extraction with ether (4×). The combined organic extracts were dried ($MgSO_4$), and the solvent was removed at reduced pressure. The crude product was distilled under reduced pressure (47−50°C, 0.5 mmHg) to give 212 g (68%) of 2-methoxy-5-bromopyridine as a colorless liquid, with spectral characteristics identical to those published in the literature.[10]

6-Methoxy-3-pyridinecarboxaldehyde (14).[8] Butyllithium (27.9 mL, 10 M solution in hexanes, 0.279 mol) was added dropwise to a solution of 2-methoxy-5-bromopyridine (**13**; 50 g, 0.266 mol) in dry tetrahydrofuran (500 mL) at −78 °C and the suspension stirred at −78 °C for 90 min. *N*,*N*-Dimethylformamide (39 mL, 0.532 mol) was then added, dropwise, and stirring continued for a further 90 min. The mixture was allowed to warm to room temperature and then it was poured into $NaHCO_3$ (aqueous saturated) and extracted with ether (3×). The combined organic extracts were dried ($MgSO_4$), and the solvent was removed at reduced pressure to give 6-methoxy-3-pyridinecarboxaldehyde (36.4 g, quantitative) as a pale yellow solid. The physical and spectral data were found to be identical to those published in the literature.[8]

6-Oxopyridine-3-carboxaldehyde (16).[9] A solution of 6-methoxy-3-pyridinecarboxaldehyde (**14**; 36.4 g, 0.266 mol) was dissolved in HBr (48% aqueous, 500 mL), and the temperature of the heating bath was gradually raised to 150 °C over a period of 1 h. Gas evolution was observed at 90−110 °C. The dark red-brown solution was allowed to cool and concentrated to a light brown solid. MeOH (100 mL) and acetone (50 mL) were added, and the solution was washed with ether (3 × 500 mL). Water (100 mL) was then added and the pH adjusted to *ca.* 7 with $NaHCO_3$ (aqueous saturated). A small amount of brown solid was removed by filtration and the filtrate concentrated to a tan solid. This was taken into $CHCl_3$/MeOH (7:3) and filtered through a silica plug. Removal of the solvent at reduced pressure gave 6-oxopyridine-3-carboxaldehyde (32 g, 98%). The physical and spectral data were found to be identical to those published in the literature.[9]

6-Methyl-3-oxo-4-[[(6-methoxypyridin-3-yl)methylene]amino]-2,3,4,5-tetrahydro-1,2,4-triazine (18). A solution of the 4-amino-6-methyl-3-oxo-1,2,3,4-tetrahydro-1,2,4-triazine (**17**; 3.84 g, 30 mmol, as free base) and 6-methoxypyridine-3-carbaldehyde (**14**; 4.11 g, 30 mmol) in methanol (150 mL) was stirred at reflux overnight. The solvent was removed at reduced pressure, and the remaining solid was triturated with water (100 mL). The insoluble organic product was filtered, washed with acetone (2 × 20 mL), and dried under vacuum to yield 5.01 g (68%) of pure product as a white, crystalline material. R_f = 0.7 (chloroform/methanol, 7:3). Mp: 189−190 °C (precipitated from MeOH). ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.05 (s, 1H), 8.40 (d, J = 1.7 Hz, 1H), 8.06 (dd, J = 8.5, 2.2 Hz, 1H), 7.85 (s, 1H), 6.88 (d, J = 8.8 Hz, 1H), 4.33 (s, 2H), 3.88 (s, 3H), 1.93 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 164.2, 147.1, 147.0, 143.9, 138.4, 135.9, 124.9, 111.2, 53.5, 47.6, 20.2. IR (KBr, 3%): 3289, 3118, 2995, 1685 cm^{-1}. MS (EI): *m*/*z* (rel intens) 247 (27), 135 (34), 113 (67), 98 (100). HRMS for $C_{11}H_{13}N_5O_2$: calcd 247.1069, found 247.1063 (δ = 0.7). For $C_{11}H_{13}N_5O_2$ Calcd: 53.43% C, 5.30% H, 28.33% N. Found: 54.24% C, 5.57% H, 28.21% N.

6-Methyl-3-oxo-4-[[(6-oxopyridin-3-yl)methylene]amino]-2,3,4,5-tetrahydro-1,2,4-triazine (19). Method A. A solution of 6-oxopyridine-3-carbaldehyde (**16**; 1.23 g, 10 mmol) and 4-amino-6-methyl-3-oxo-1,2,3,4-tetrahydro-1,2,4-triazine hydrochloride **17** (1.64, 10 mmol) in methanol (30 mL) was treated with sodium methoxide (0.54 g, 10 mmol) and heated to reflux overnight. The thick suspension was allowed to cool to room temperature, and the solid product was filtered off, washed with water (2 × 10 mL), and dried under vacuum to yield 2.3 g (98%) of the pure product as a white crystalline solid.

Method B. Pivaloyl chloride (60 mg, 0.493 mmol) was added to the solution of 6-methyl-3-oxo-4-[[(6-methoxypyridin-3-yl)methylene]-amino]-2,3,4,5-tetrahydro-1,2,4-triazine (**18**; 111 mg, 0.448 mmol) and sodium iodide (81 mg, 0.538 mmol) in acetonitrile (15 mL), *via* syringe. Stirring at reflux temperature was continued for 12 h, when TLC indicated complete disappearance of the starting material. The reaction mixture was allowed to cool to room temperature. An aqueous solution of sodium hydroxide (6.0 mL, 0.1 M) was added, and stirring was continued for 1 h. The pH was adjusted to neutral with 0.1 M HCl, and the solvent was removed at reduced pressure. The remaining crude product was triturated with methanol (10 mL) and water (10 mL) and dried under vacuum to yield 99 mg (95%) of the desired product as a white crystalline material. R_f = 0.25 (chloroform/methanol, 85:15, dilute solution applied). Mp: over 250 °C (precipitated from H_2O). ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.85 (br s, 1H), 9.98 (s, 1H), 7.86 (dd, J = 9.8, 2.5 Hz, 1H), 7.74 (s, 1H), 6.68 (d, J = 2.5 Hz, 1H), 6.40 (d, J = 9.3 Hz, 1H), 4.25 (s, 2H), 1.91 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6); δ 161.9, 146.8, 143.3, 138.3, 136.7, 136.4, 120.3, 113.9, 47.2, 19.9. IR (KBr, 3%): 3113, 2927, 1690, 1664, 1596. MS (FAB): *m*/*z* (rel intens) $(M + H)^+$ 234 (100), 202 (14), 165 (32). HRMS for $C_{10}H_{12}N_5O_2$: calcd: 234.2320, found 234.0988. For $C_{10}H_{11}N_5O_2$ Calcd: 51.50% C, 4.75% H, 30.03% N. Found: 50.36% C, 4.91% H, 29.26% N.

5-Methoxy-6-methyl-3-oxo-4-[(pyridin-3-ylmethylene)amino]-2,3,4,5-tetrahydro-1,2,4-triazine (20). A 1000-mL beaker was charged with a suspension of 6-methyl-3-oxo-4-[(pyridin-3-ylmethylene)amino]-2,3,4,5-tetrahydro-1,2,4-triazine (**1**; 5.0 g, 23.017 mmol) and tetraethylammonium *p*-toluenesulfonate (0.8 g, 2.65 mmol) in methanol (800 mL). A direct current (6V, 200 mA) was passed through the reaction mixture *via* graphite electrodes (150 × 45 × 9 mm, held parallel at a distance of 30 mm with a Teflon spacer). The oxidation was continued until TLC showed complete disappearance of the starting material, about 24 h. The reaction mixture was treated with charcoal and filtered through a plug of silica gel, and the volume was reduced to approximately 50 mL. The precipitated solid was filtered off and washed with methanol/diethyl ether, 1:3 (2 × 20 mL). Drying under high vacuum yielded 3.5 g (62%) of pure product, as a white crystalline material. Note: In a trial experiment, a methanolic solution of 5-hydroxy-6-methyl-3-oxo-4-[(pyridin-3-ylmethylene)amino]-2,3,4,5-tetrahydro-1,2,4-triazine (**2**) containing a spatula tip of *p*-toluenesulfonic acid was stirred at reflux for 24 h. After chromatographic purification, the *O*-methyl hemiaminal **20** could be obtained in approximately 30% yield. R_f = 0.52 (chloroform/methanol, 85:15). Mp: 167−168 °C (MeOH). ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.7 (s, 1H), 8.88 (d, J = 2.0, 1H), 8.72 (s, 1H), 8.62 (dd, J = 4.4, 1.5, 1H), 8.14 (dt, J = 7.8, 2.0 Hz, 1H), 7.48 (dd, J = 8.3, 4.9 Hz, 1H), 5.95 (s, 1H), 3.14 (s, 3H), 2.02 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 151.0, 149.0, 147.9, 145.8, 142.2, 133.6, 130.3, 124.0, 82.6, 51.8, 18.9. IR (KBr, 3%): 3212, 3093, 2915, 1690, 1653 cm^{-1}. MS (EI): *m*/*z* (rel intens) 280.9824 (16), 248.1133 (32), 180.9888 (34), 130.9920 (41), 118.9920 (38), 68.9952 (100). HRMS (EI) for $C_{11}H_{14}N_5O_2$ $(M + H)^+$: calcd: 248.1147, found 248.1133. For $C_{11}H_{13}N_5O_2$ (247.259) Calcd: 53.43% C, 5.30% H, 28.32% N. Found: 53.10% C, 5.19% H, 28.35% N.

5-Methoxy-6-methyl-3-oxo-4-[[(6-methoxypyridin-3-yl)methylene]-amino]-2,3,4,5-tetrahydro-1,2,4-triazine (21). A 1200-mL beaker was charged with 6-methyl-3-oxo-4-[[(6-methoxypyridin-3-yl)methylene]-amino]-2,3,4,5-tetrahydro-1,2,4-triazine (**18**; 1.4 g, 5.66 mmol) and methanol (900 mL). To this suspension was added sodium methoxide (5.0 g, 92.6 mmol), and a pale yellow solution resulted. A direct current (1.7 V, 100 mA) was passed through the reaction mixture *via* graphite electrodes (150 × 40 × 10 mm, held parallel 30 mm apart with a Teflon spacer). The conversion reached 50% after about 6 h, and was complete after 14 h. The volume of the solvent was reduced to approximately 100 mL (rotavap), and the pH was adjusted with aqueous HCl (1 M) to 7.0. Chloroform (300 mL) was added, and the solvent was distilled off at reduced pressure. The solid residue was triturated with water (20 mL) for 30 min. The undissolved product was filtered off, washed with acetone (4 × 50 mL), and dried under high vacuum to yield 685 mg (44%) of pure product as a white crystalline material. R_f = 0.7 (chloroform/methanol, 85:15). Mp: 162−163 °C (precipitated from MeOH). ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.63 (s, 1H), 8.45 (d, J = 2.0 Hz, 1H), 8.10 (dd, J = 8.8, 2.4 Hz, 1H), 6.91 (d, J = 8.3 Hz, 1H), 5.89 (s, 1H), 3.90 (s, 3H), 3.14 (s, 3H), 2.01 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6, spiked with D_2O): δ 165.1, 148.5, 148.3, 146.6, 142.5, 136.6, 124.5, 111.7, 82.4, 54.0, 52.0, 19.3. MS (FAB) *m*/*z* (rel intens) $(M + H)^+$ 278 (51), 185 (84), 152 (16), 111 (72). HRMS (FAB) for $C_{12}H_{16}N_5O_3$: calcd 278.1250, found 278.1302. IR (KBr, 3%): 3240, 3118, 2954, 1690, 1654 cm^{-1}.

5-Methoxy-6-methyl-3-oxo-4-[[(6-oxopyridin-3-yl)methylene]amino]-2,3,4,5-tetrahydro-1,2,4-triazine (22). A 1200-mL beaker was charged with 6-methyl-3-oxo-4-[[(6-oxopyridin-3-yl)methylene]amino]-2,3,4,5-tetrahydro-1,2,4-triazine (**19**; 0.7 g, 3.00 mmol) and suspended

in methanol (1000 mL). Sodium methoxide (5.4 g, 100 mmol) was added, and a pale yellow solution resulted. A direct current was passed through the magnetically stirred reaction mixture *via* a rack of alternating stainless steel (five, 150 × 40 × 3 mm) and graphite (four, 150 × 40 × 10 mm) electrodes, separated by 3 mm with Teflon spacers. The potential of the anode (graphite) was set to +63 mV *vs* Ag/Ag^+, 0.1 M, acetonitrile, yielding an approximately 900 mV compliance potential and an initial 100 mA current. TLC indicated 50% conversion after about 3 h, and the oxidation was complete after 7 h. Methanol was distilled off at reduced pressure, and the residue was triturated with a mixture of chloroform and methanol (85:15, 100 mL). The suspension was filtered through a plug of silica gel, and the filtrate was evaporated to dryness. The residual off white solid was triturated with 10 mL of hot chloroform and filtered to afford 721 mg (91%) of pure methyl aminal. R_f = 0.36 (chloroform/methanol/triethylamine, 80:18:2). Mp: 252−255 °C (trituration with $CHCl_3$). ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.9 (s, 1H), 10.56 (s, 1H), 8.50 (s, 1H), 7.87 (dd, J = 9.8, 2.4 Hz, 1H), 7.80 (d, J = 2.0 Hz, 1H), 6.42 (d, J = 9.3 Hz, 1H), 5.74 (s, 1H), 3.13 (s, 3H), 1.99 (s, 3H). ^{13}C NMR (75 MHz, MeOH-d_4): δ 209.8, 146.4, 144.1, 137.1, 118.4, 82.1, 66.89, 66.90, 51.5, 15.4. MS (FAB): *m/z* (rel intens) $(M + H)^+$ 264 (19), 246 (20). HRMS for $C_{11}H_{14}N_5O_3$: calcd 264.2434, found 264.1093. Note: On the scale of 20 g, the yield decreased to approximately 35%.

5-Hydroxy-6-methyl-3-oxo-4-[[(6-methoxypyridin-3-yl)methylene]-amino]-2,3,4,5-tetrahydro-1,2,4-triazine (28). Method A. 5-Methoxy-6-methyl-3-oxo-4-[[(6-methoxypyridin-3-yl)methylene]amino]-2,3,4,5-tetrahydro-1,2,4-triazine (**21**; 100 mg, 0.361 mmol) was dissolved in a mixture of tetrahydrofuran and water (1:1, 6.0 mL), and a spatula tip of citric acid was added. After overnight stirring at room temperature, the volume of the solvent was reduced to approximately 1 mL and the precipitated product was filtered off, washed with acetone (1 × 2 mL) and a methanol/diethyl ether mixture (1:2, 1 × 2 mL), and dried under high vacuum to yield 46 mg of white crystalline material. ^{1}H-NMR analysis confirmed the presence of the desired product; however, it was contaminated with the dimerization product 2,3,4a,6,7,-8a,9,10-octaaza-1,5-dimethyl-4,8-dioxo-3,4,10,10a,7,8,8a,9-octahydroanthracene (**27**), to the tune of 29 mol %.

The reaction mixture and the mother liquor contained a considerable amount of 5-methoxypyridine-3-carbaldehyde and dimer **27**.

2,3,4a,6,7,8a,9,10-Octaaza-1,5-dimethyl-4,8-dioxo-3,4,10,10a,7,8,-8a,9-octahydroanthracene (27). R_f = 0.20 (chloroform/methanol, 85:15). ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.1 (s, 2H), 5.73 (d, J = 10.8 Hz, 2H), 5.01 (d, J = 10.3 Hz, 2H), 1.89 (s, 6H). MS *m/z* (rel intens) 253.1156 (1), 177.0027 (13), 166.9562 (1.5), 152.0001 (30.3), 132.9140 (47). HRMS for $C_8H_{13}N_8O_2$ $(M + H)^+$: calcd 253.1161, found 253.1156.

Method B. A solution of 5-methoxy-6-methyl-3-oxo-4-[([6-methoxypyridin-3-yl)methylene]amino]-2,3,4,5-tetrahydro-1,2,4-triazine (**21**; 329 mg, 1.186 mmol) in aqueous potassium hydroxide (1.0 N, 5.0 mL) was stirred at room temperature for 40 min. The clear reaction mixture was cooled to 0 °C, and the pH was adjusted to 9 (4.4 mL of 1.0 N HCl). The mother liquor was separated via centrifugation, and the remaining solid was stirred with water and centrifuged again (repeated two times). The product was dried on vacuum to obtain 256 mg (82%) of the desired hemiaminal as a white crystalline material. R_f = 0.45 (chloroform/methanol, 85:15). Mp: 175−177 °C (precipitated from H_2O). ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.4 (s, 1H), 8.57 (s, 1H), 8.42 (d, J = 2.0 Hz, 1H), 8.09 (dd, J = 8.7, 2.4, Hz, 1H), 8.98 (d, J = 8.5 Hz, 1H), 8.91 (d, J = 8.7 Hz, 1H), 5.73 (d, J = 8.3 Hz), 3.89 (s, 3H), 2.02 (s, 3H). IR (3%, KBr): 3476, 3127, 2949, 1692 cm^{-1}. ^{13}C NMR (DMSO-d_6, 125 MHz): δ 164.5, 147.8, 147.6, 144.7, 144.3, 136.0, 124.7, 75.7, 53.6, 18.9. MS (EI, 70 eV): *m/z* (rel inten) 263.10095 (16), 135.0626 (100), 129.0696 (31), 114.0285 (38), 86.9699 (28). HRMS for $C_{11}H_{13}N_5O_3$: calcd 263.1018, found 263.1009 (0.9 mmu).

5-Hydroxy-6-methyl-3-oxo-4-[[(6-oxopyridin-3-yl)methylene]amino]-2,3,4,5-tetrahydro-1,2,4-triazine (3). Method A. Crude 5-methoxy-6-methyl-3-oxo-4-[[(6-oxopyridin-3-yl)methylene]amino]-2,3,4,5-tetrahydro-1,2,4-triazine (**22**; 1.624 g, about 80% pure, 1.3 g pure, 4.94 mmol) was dissolved in water (40 mL), and the pH was set to 4 (HCl, 1 M). After 1 h of stirring at room temperature, the pH was readjusted to 7−8, and the solvent was removed by distillation. The solid residue was extracted with a mixture of chloroform and methanol (7:3, 3 × 30 mL), and the mother liquor was separated. The remaining solid (1.48 g) was briefly heated with 8 mL of water, and the undissolved organic material was filtered off after 4 h to yield 337 mg of beige solid. ^{1}H-NMR analysis (500 MHz, DMSO-d_6) indicated the presence of the desired product, contaminated with approximately 10% of starting material and 25% of the product of overoxidation at the triazine ring, the 3,5-dioxo-6-methyl-4-[[(6-oxopyridin-3-yl)methylene]amino]-2,3,4,5-tetrahydro-1,2,4-triazine. The crude product was recrystallized from DMF/diethyl ether (60 mg, 84% pure by ^{1}H-NMR spectroscopy) and once again from a DMF/THF mixture (36 mg) and triturated with water (1 × 3 mL) to yield 28 mg (2.3%) of the pure product as an off white crystalline material.

Method B. A solution of 5-methoxy-6-methyl-3-oxo-4-[[(6-oxopyridin-3-yl)methylene]amino]-2,3,4,5-tetrahydro-1,2,4-triazine (**22**; 89 mg, 0.338 mmol) in aqueous potassium hydroxide (2.0 mL, 1 M) was stirred at room temperature for 10 min. The pH was adjusted with aqueous hydrochloric acid to 8 (1.8 mL, 1 M). After a short induction period, crystallization began and was continued at +5 °C for 6 h. The mother liquor was aspirated through a fritted tube, the remaining solid was washed with water (2 × 2 mL), and the crystalline product was dried under vacuum to yield 73.1 mg (87%) of pure product as an off-white powder. R_f = 0.55 (chloroform/methanol, 7:3, dilute solution of the sample; because of its low solubility, it tends to streak). Mp: 255 °C dec (H_2O). ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.87 (br s, 1H), 10.36 (s, 1H), 8.42 (s, 1H), 7.88 (dd, J = 9.3, 2.4 Hz, 1H), 8.74 (d, J = 2.4 Hz, 1H), 6.88 (br d, J = 5.4 Hz, 1H), 6.42 (d, J = 9.8 Hz, 1H), 5.58 (br d, J = 10 Hz, 1H), 2.00 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ162.4, 147.9, 145.8, 144.5, 138.0, 136.6, 120.7, 113.8, 76.0, 18.9. IR (KBr, 3%): 3022, 2926, 1684, 1654 cm^{-1}. MS (FAB): *m/z* (rel intens) 250.0947 (6), 107.0617 (26). HRMS (FAB) for $C_{10}H_{12}N_5O_3$ $(M + H)^+$: calcd 250.0942, found 250.0947. For $C_{10}H_{11}N_5O_3$ (249.230) Calcd: 48.19% C, 4.45% H, 28.10% N. Found: 48.00% C, 4.59% H, 27.81% N.

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