SYNTHESIS OF 3-ARYL-2-(2-ARYL-2-OXOETHYL)PYRIDO[2,3-*d*]-4(3H)PYRIMIDONES AND 3-ARYL-2-(2-ARYLETHENYL)PYRIDO[2,3-*d*]-4(3H)PYRIMIDONES AS POTENTIAL ANTIEPILEPTIC DRUGS

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(ABSTRACT)

A series of 2-alkyl-3-arylpyrido[2,3-*d*]-4(3H)pyrimidones were synthesized for testing as potential antiepileptic drugs. The goal was to achieve better neurological activity and/or lower toxicity than displayed by a series of 2-alkyl-3-aryl-4(3H)quinazolinones prepared previously in our research group. From the pharmacological testing data of these target compounds, we have found that the additional nitrogen at the C-8 position of the quinazolinone framework increased the anticonvulsant activity. However, the neruological toxicity increased as well. The anticonvulsant and neurotoxic activity seen in the various 2-alkyl side chains and 3-aryl substituents incorporated into these new pyridopyrimidones was consistent with the activity observed with the same substituents on the 4(3H)-quinazolinones. The 3-aryl group consists of various *ortho*-substituted phenyl rings, while the 2-alkyl chain consists of a 2-(2-aryl-2-oxo)ethyl or 2-arylethenyl group.

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Table of Contents

List of Tables

List of Schemes

SYNTHESIS OF 3-ARYL-2-(2-ARYL-2-OXOETHYL)PYRIDO[2,3-*d*]-4(3H)PYRIMIDONES AND 3-ARYL-2-(2-ARYLETHENYL)PYRIDO[2,3-*d*]-4(3H)PYRIMIDONES AS POTENTIAL ANTIEPILEPTIC DRUGS

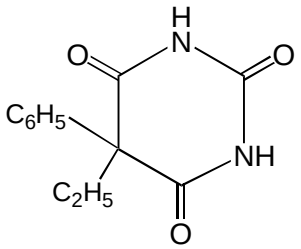
I. Background

Epilepsy is a condition that effects, at a conservative estimate, nearly fifty million people throughout the world. In general, most seizures are due to electrical disturbances in the brain caused by abnormal neuronal discharges. The increased electrical activity causes symptoms in sufferers that range from momentary lapses of attention, to partial motor and sensory abnormalities, to extended loss of consciousness associated with complete convulsive activity.[1] The seizures of many patients can be "satisfactorily controlled" by antiepileptic drug (AED) therapy. By "satisfactorily controlled," it is meant that the balance between the adverse side effects caused by the AED therapy and the lowered incidence of seizures is at a level acceptable to the patient.[2] Since many patients require polytherapy, where two or more drugs are used simultaneously in an attempt to minimize side effects and provide optimal seizure control, there remains an enormous need for new anticonvulsant drugs.

Compounds exhibiting protection of test mice from seizures induced by subcutaneous injection of the convulsant drug, pentylenetetrazole (PTZ), have been shown to be beneficial in controlling petit mal seizures, while those that offer protection in test mice from maximal electroshock (MES) induced seizures, often give protection to patients who suffer from grand mal seizures.[8] Episodes of petit mal epilepsy (or absense seizures) are usually found in children. The disorder manifests itself as either brief myoclonic jerks that last for merely a few seconds or as "daydreaming". Brief eyelid fluttering, drooping of the head and slight blanching of the skin are all characteristics of absense seizures, but there is no loss of muscle tone, so the child does not fall[9]. With grand mal epilepsy (tonic-clonic seizures), "disordered contraction of all muscles is

[its] hallmark."[9] First, the tonic phase of the seizure occurs with loss of normal coordinated posture, increased rigidity of muscles, increased respiratory contractions resulting in expulsion of air from the lungs, and hueing of skin color to a dusky blue, due to oxygen deprevation.[9] Several minutes after onset, the seizure concludes with the clonic stage. This phase is the convulsive stage when muscles alternatively relax and spasm.

The development of antiepileptic drugs began in 1857 when Sir Charles Locock used potassium bromide in patients suffering from epilepsy and reported a reduction in seizure frequency.[3] Even though patients often exhibited severe toxic side-effects such as skin eruptions and psychosis[4], this mode of AED therapy was utilized for the next fifty years until 1912 when phenobarbital (**1**), a synthetic sedative-hypnotic, was developed. The side-effects of phenobarbital were less than with potassium bromide and seizure control was better. However, when 5,5-diphenylhydantoin (**2**), also known generically as phenytoin, was introduced in 1937, it provided good seizure control without the sedative properties of phenobarbital.[4]



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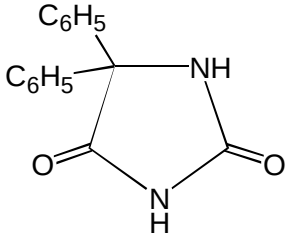
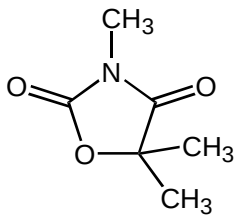


2

A tremendous surge in AED research occurred between the years of 1937-1960, when most AED development focused on simple heterocyclic ring structures. A number of drugs were developed

and approved during this period for use against absense seizures including: trimethadione (**3**), phensuximide (**4**), methsuximide (**5**) and ethosuximide(**6**).



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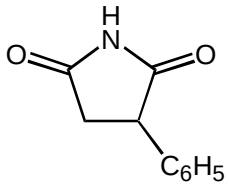

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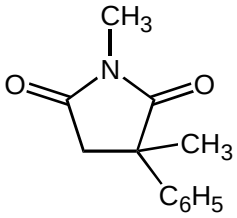

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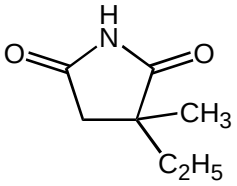
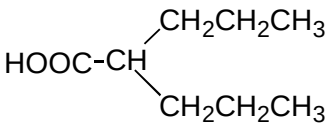


6

In the early 1970s, research into new AEDs shifted to novel structures, which led to the development and commercialization of valproic acid (**7**), clonazepam (**8**) and carbamazepine (**9**).



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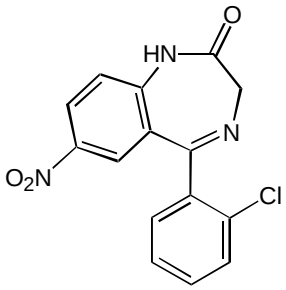

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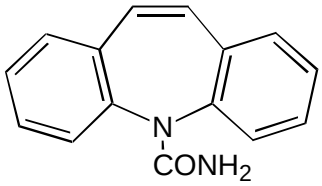
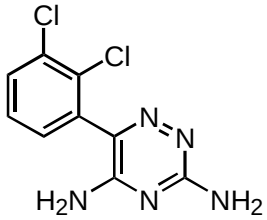


9

The need for even more research in this area led the Epilepsy Branch of the National Institute of Neurological and Communicative Disorders and Stroke to establish the Antiepileptic Drug Development (ADD) Program in 1972. The ADD program has helped AED research by conducting and/or funding screening programs for new compounds, toxicity testing for advanced and promising preclinical compounds, and clinical trials.[4] However, during the years 1978 through 1993, no new anticonvulsant drugs were approved by the U.S. Food and Drug Administration (FDA).[5] In 1993 the FDA approved the three new compounds known generically

as lamotrigine (**10**), gabapentin (**11**), and felbamate (**12**). In August 1994, felbamate came under severe scrutiny for potentially causing the serious side-effect of aplastic



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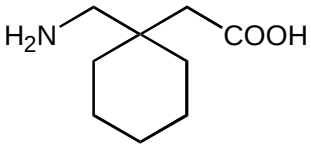

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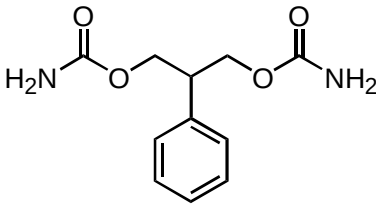
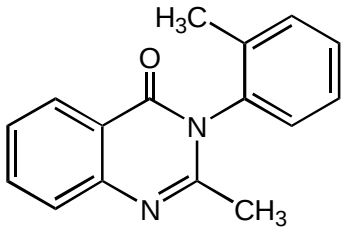


12

anemia, a bone-marrow disease.[5] A hundred times higher frequency of aplastic anemia was found in patients undergoing felbamate treatment than in the general population.[27] Felbamate was subsequently removed from the AED market. Currently, there are less than two dozen antiepileptic compounds that have been approved by the U.S. FDA for use in battling epileptic seizures. In 1995, of the newly diagnosed cases of epilepsy, approximately 70% were treated with either carbamazepine, phenytoin, valproic acid, or phenobarbital.[5] Even though there is continued progress in synthesizing and testing of new AEDs, there still exists an enormous need for further exploration.

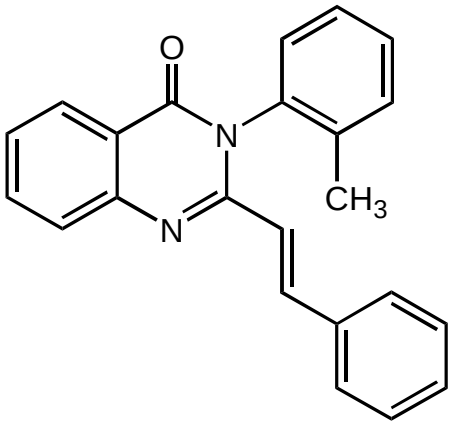
An important compound that achieved FDA approval in 1961 as a sedative-hypnotic was 2-methyl-3-(2-methylphenyl)-4(3H)quinazolinone (**13**), known generically as methaqualone.[10]



13

Originally designed as a potential analgesic,[6] it is currently registered as a sedative-hypnotic under several proprietary names, including Quaalude®. The emergence of newer and more efficacious sedative-hypnotics and the abuse potential of methaqualone has led to the decline of it being prescribed. Since derivatives of **13** should have the potential for Central Nervous System (CNS) activity, literally hundreds of quinazolinones related to **13** have been synthesized and their CNS activity studied.[6, 13-24] Several of these compounds have shown some potential antiepileptic activity, however, none of the AEDs currently on the world market contain the 4(3H)-quinazolinone ring system.[25]

In 1963, a study by Boltze[6] and coworkers led to several conclusions about substituent effects on the CNS activity of certain methaqualone derivatives. They reported that 2-(2-arylethenyl)-3-*o*-tolyl-4(3H)quinazolinones **14** and **15** afforded some protection against MES induced seizures.



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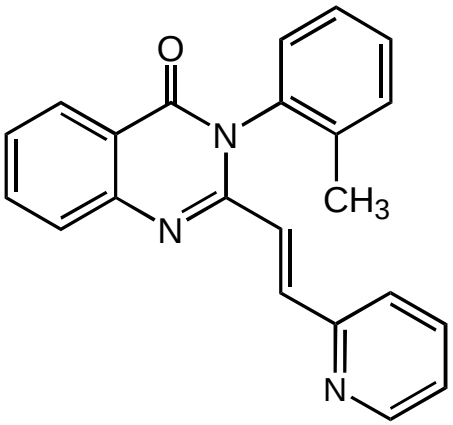

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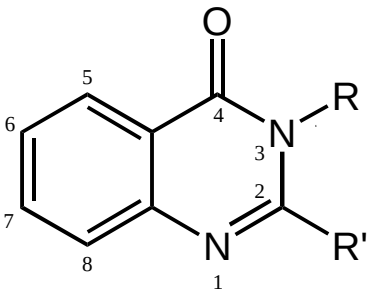
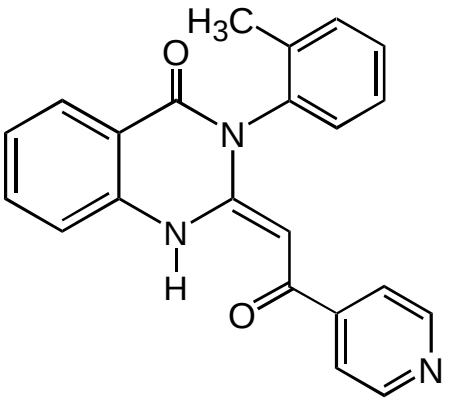
Research performed at Virginia Tech by Rathman[7] in 1972 led to some additional discoveries about how substituents effect the CNS activity of on 2-alkyl-3-aryl-4(3H)quinazolinones **16**.



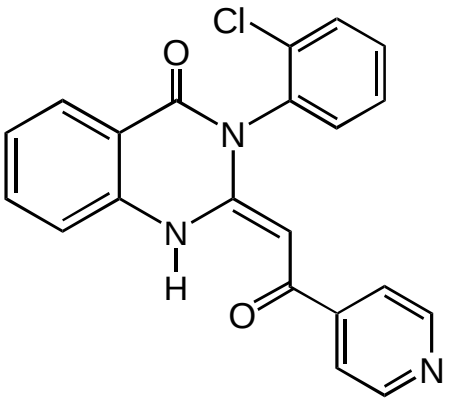
R = aryl
R' = alkyl

16

After pharmacological testing of twenty-nine unique analogs of type **16**, it was concluded that when the group at the C-2 position was a 2-oxo-2-(4-pyridyl)ethyl group and the 3-substituent consisted of an aryl group containing either an *ortho*-methyl (**16b**) or an *ortho*-chloro (**16c**) group, the anti-PTZ activity increased at the expense of undesirable sedative-hypnotic effects.



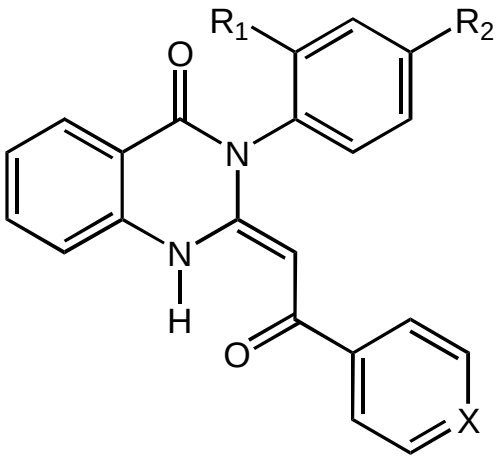
16b



16c

The separation of sedative-hypnotic side-effects and anticonvulsant activity in the analogs that Rathman synthesized was significant, but the compounds lacked the efficacy to be used as marketable AEDs because of poor absorption from the gut following oral administration to rats.[25]

X-ray structural studies and molecular modeling calculations were performed by Duke and Codding[43] on five quinazolinone analogs, **16a-e**, synthesized by Rathman. This study led to the proposal that the activity of the quinazolinone derivatives arises from the presence of an



16a, R_1 = H, R_2 = H, X = N

16b, R_1 = CH_3, R_2 = H, X = N

16c, R_1 = Cl, R_2 = H, X = N

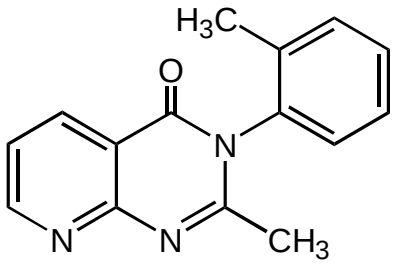
16d, R_1 = Cl, R_2 = H, X = CH

16e, R_1 = H, R_2 = Cl, X =N

ortho-substituted phenyl ring in a perpendicular conformation with respect to the quinazolinone framework, while an unsubstituted (**16a**) or a *para*-substituted (**16e**) phenyl ring provides little activity. The structure activity relationship (SAR) data for these compounds indicate that the type of substituent in the *ortho*-position has little effect on activity.[43] The study also reported, with X-ray crystallography data, that compounds **16a-e**, in the solid state, exist as the enamine tautomer.[43] A strong hydrogen bond exists between the hydrogen of the enamine group and the carbonyl oxygen of the ethanone group of the 2-alkyl chain. This hydrogen bond establishes planarity of the quinazolinone framework and the 2-(2-aryl-2-oxo)ethyl side chain. The 3-aryl group resides in a perpendicular orientation to the established planar framework. These proposals

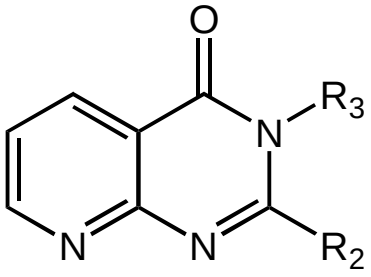
were consistent with the findings of Lloyd,[44] that a common structural feature of many CNS-active drugs was the topographical arrangement of an aromatic ring perpendicular to a planar base framework.

Numerous reports indicate that nitrogen moieties may be responsible for CNS activity because of their ability to act as primary binding groups.[44] Thus, the present study was initiated on the hypothesis that incorporating a nitrogen into the 4(3H)-quinazolinone ring system at the C-8 position, to produce a series of pyrido[2,3-*d*]-4(3H)pyrimidone analogs, might enhance CNS efficacy and hopefully show some selectivity for anticonvulsant activity with less sedative-hypnotic action. Several studies on the synthesis of pyrido[2,3-*d*]-4(3H)pyrimidones have appeared, but little is known of their CNS activity. Vaidya[19] has shown that 2-methyl-3-*o*-tolylpyrido[2,3-*d*]-4(3H)pyrimidone (**17b**) exhibits activity comparable to methaqualone in the scPTZ test, but unlike methaqualone, activity in the MES test only occurs at anesthetic doses.



17b

Combining the above information on substituent effects, we set out to synthesize a series of 2-alkyl-3-arylpyrido[2,3-*d*]-4(3H)pyrimidones (**18**) for CNS activity studies. The C-2

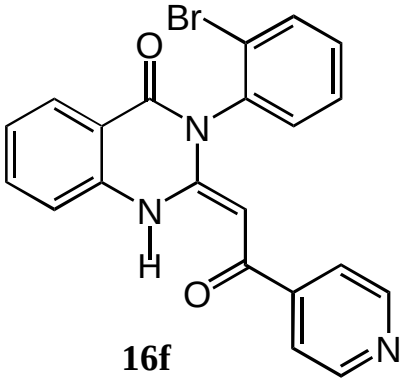


R_2 = alkyl

R_3 = aryl

18

substituents chosen were the 2-(2-oxo-2-phenyl)ethyl group and the 2-[2-oxo-2-(4-pyridyl)]ethyl group, which were analogs of substituents used by Rathman,[7] and the styryl and 2-(4-pyridyl)ethenyl groups derived from the work of Boltze.[6] In the series of pyridopyrimidones to be synthesized, the 3-aryl group would consist of an unsubstituted phenyl ring, an *ortho*-methyl, an *ortho*-chloro, and an *ortho*-bromo substituted phenyl ring. The idea of adding the *ortho*-bromo substituted phenyl ring into the series of target compounds came from Phase II anticonvulsant testing data on quinazolinone analog **16f** synthesized by Rathman.[25] Compound **16f** showed no



16f

MES ED_{50} = 136 mg/kg

scMET ED_{50} = 19 mg/kg

TD_{50} = >2000 mg/kg

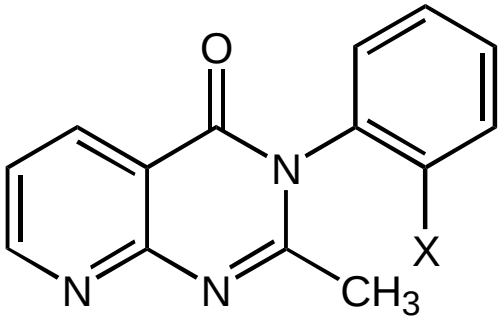
PI = $>14.7_{MES}$, $>105_{scMET}$

significant improvement in anticonvulsant activity over **14b** or **14c**; however, the reported median neurotoxic dose (TD_{50}) value indicated that the *ortho*-bromo substituent on the 3-phenyl ring might be responsible for lowering the sedative-hypnotic properties of the compound. The

hypothesis used in this study was that incorporation of the *ortho*-bromo substituted phenyl ring into the pyridopyrimidone analogs may produce the same effect. The goal was to integrate both variations of substituents in the hopes of achieving better neurological activity and/or lower neurotoxicity than displayed by the quinazolinone analogs.

II. Results and Discussion

Based on previous pharmacological studies of methaqualone derivatives, it seemed possible to improve the anticonvulsant activity of the pyridopyrimidones by varying the substituents attached to the C-2 and C-3 carbons of the heterocyclic framework. Rathman concluded that the anticonvulsant activity increased when the 3-aryl group was an *ortho*-substituted phenyl ring. Furthermore, the activity was highest when the *ortho*-substituent was either a methyl or a chloro group. Therefore, we set out to employ a synthetic process that would allow for the facile variation of the *ortho*-substituent of the 3-aryl group of a series of 3-aryl-2-methylpyrido[2,3-*d*]-4(3H)pyrimidones **17a-d**. By synthesizing this series of compounds, we hoped

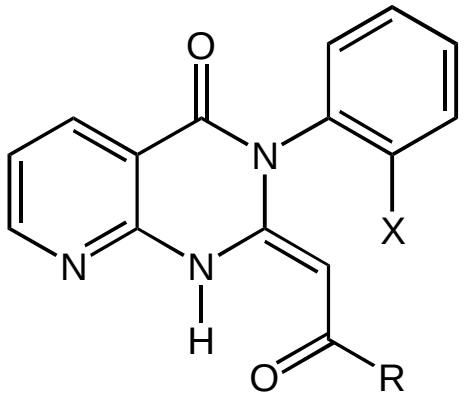


17a, X = H
17b, X = CH_3
17c, X = Cl
17d, X = Br

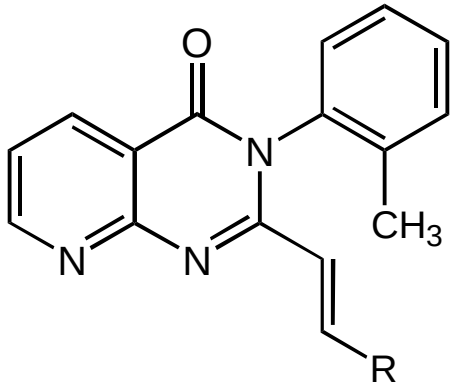
to be able to easily incorporate new alkyl side-chains through the 2-methyl group of **17a-d**. These compounds also provided an interesting new set of molecules for anticonvulsant screening in the ADD program.

We then proceeded to incorporate into **17a-d** the 2-(2-oxo-2-phenyl)ethyl group and the 2-[2-oxo-2-(4-pyridyl)]ethyl group to give target compounds **18a-d** and **19**. 2-Methyl-3-(2-

methylphenyl)pyrido[2,3-*d*]-4(3H)pyrimidone **17b** was converted to styryl and 2-(4-pyridyl)ethenyl target compounds **20** and **21**, respectively.



18a, X = H, R = 4-pyridyl
18b, X = CH_3 R = 4-pyridyl
18c, X = Cl, R = 4-pyridyl
18d, X = Br, R = 4-pyridyl
19, X = CH_3 R = phenyl



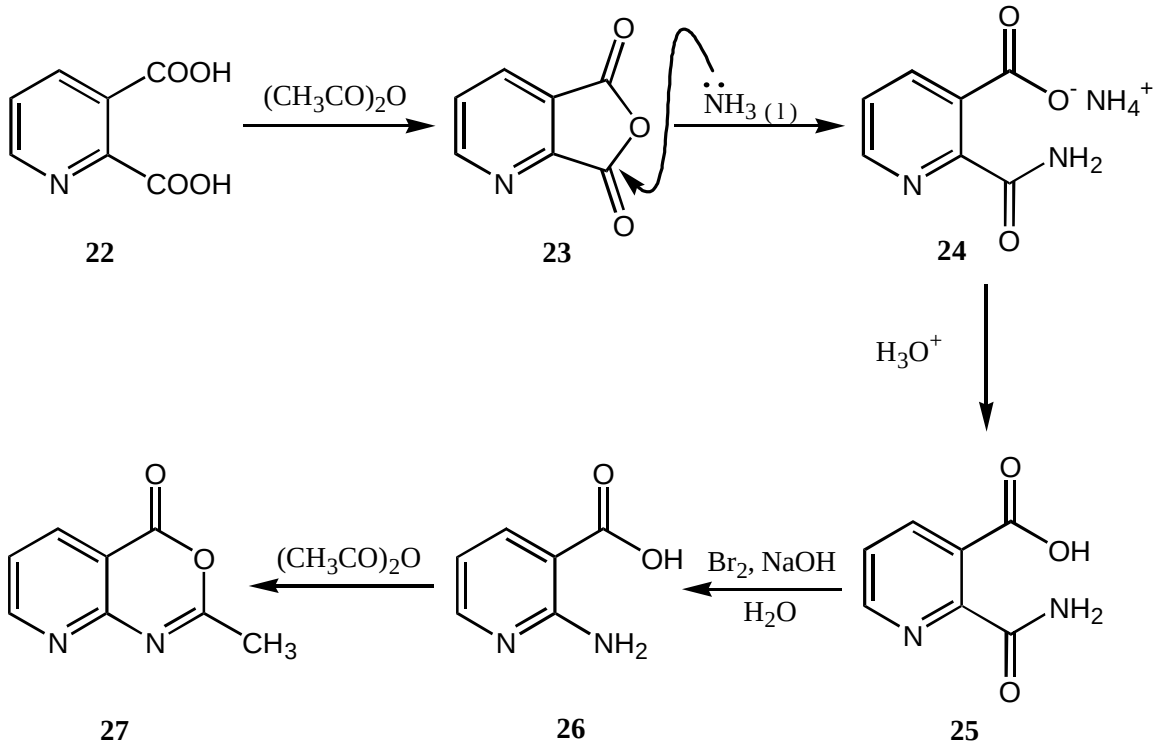
20, R = phenyl
21, R = 4-pyridyl

A. <u>Synthesis of 3-Aryl-2-methylpyrido[2,3-*d*]-4(3H)pyrimidones 17a-d.</u>

The method employed for the synthesis of this series of compounds is based on the initial synthesis of the key intermediate 2-methylpyrido[2,3-*d*][1,3]-4(H)-one (**27**). The synthesis of **27** is outlined in Scheme I and starts with the commercially available 2,3-pyridinedicarboxylic acid or quinolinic acid (**22**). Cyclization of **22** by refluxing in acetic anhydride afforded 2,3-pyridinedicarboxylic anhydride or quinolinic anhydride (**23**). Anhydride **23** was then allowed to

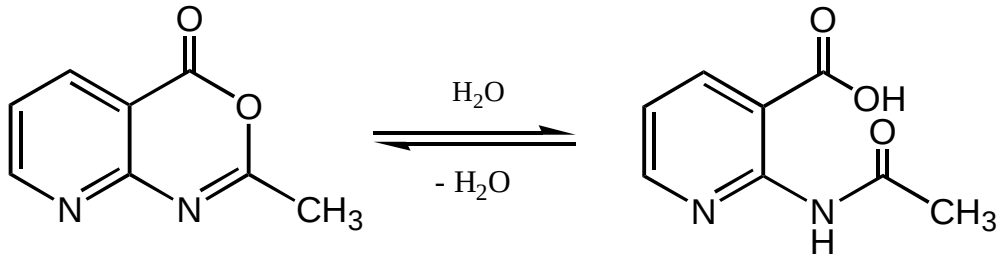
Scheme I

Synthesis of 2-Methylpyrido[2,3-*d*][1,3]oxazin-4(H)-one (27)



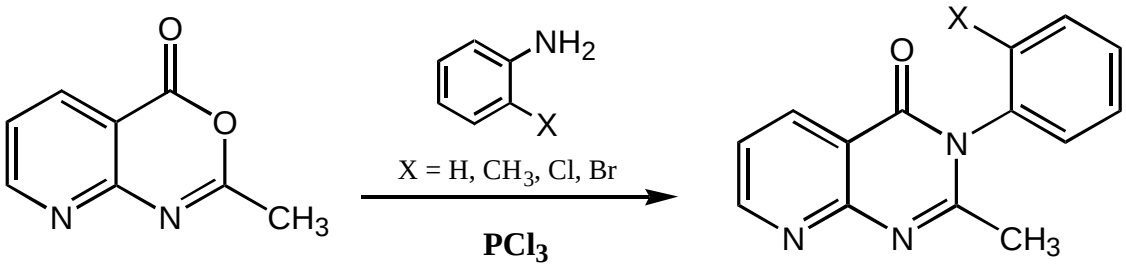
react with liquid ammonia to open the anhydride ring and form ammonium quinolinamate (**24**), which was then acidified to afford quinolinamic acid (**25**). The carbonyl group of anhydride **23** closest to the nitrogen of the pyridine ring acts as the more electrophilic center for attack by ammonia because of the electronegativity of the ring nitrogen. Next, acid **25** was treated with bromine in aqueous sodium hydroxide. The resulting Hoffman rearrangement, where the carbonyl group in the amide functional group was eliminated, afforded 2-aminonicotinic acid (**26**). Treatment of **26** with refluxing acetic anhydride produced 2-methylpyrido[2,3-*d*][1,3]oxazin-4(H)-one (**27**). Since **27** readily undergoes hydrolytic ring opening to **27a,** which reacts poorly in

subsequent steps, it was important to eliminate all water from solvents and keep the product away from the moisture in the air.



27 **27a**

The synthesis of the target compounds **17a-d** (listed in Table I) was then completed by subjecting **27** to treatment with phosphorus trichloride (PCl_3) and selected *ortho*-substituted anilines, as shown below.

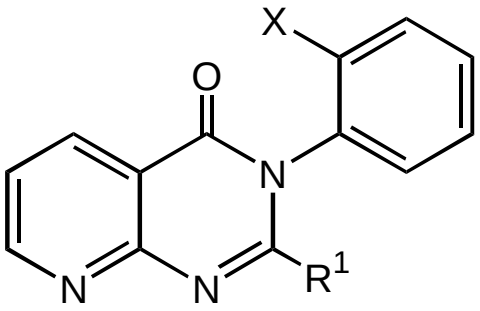


27 **17a-d**

Compounds **17a-d** were characterized by ^1H NMR spectroscopy and elemental analyses, all of which were consistent with the assigned structures.

Table 1

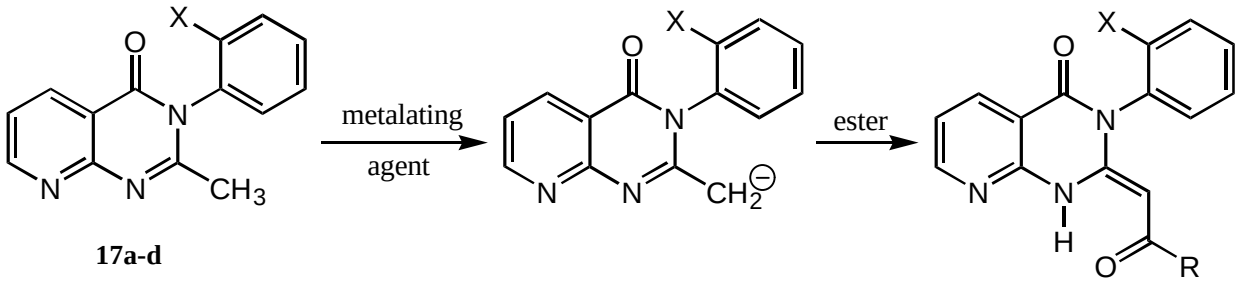
2-Alkyl-3-arylpyrido[2,3-*d*]-4(3H)pyrimidones



Cmpd	R^1	X	mp, °C	recryst solv	yield
17a	-CH_3	H	203.0-203.8	CH_2Cl_2 / Hexane	52%
17b	-CH_3	CH_3	178.6-178.9	CH_2Cl_2 / Hexane	52%
17c	-CH_3	Cl	192.4-192.9	CH_2Cl_2 / Hexane	73%
17d	-CH_3	Br	172.5-173.0	CH_2Cl_2 / Hexane	45%
18a	=CHCO-4-pyridyl	H	204.0-204.8	CH_2Cl_2 / Hexane	55%
18b	=CHCO-4-pyridyl	CH_3	225.5-226.0	CH_2Cl_2 / Hexane	77%
18c	=CHCO-4-pyridyl	Cl	216.0-216.6	CH_2Cl_2 / Hexane	46%
18d	=CHCO-4-pyridyl	Br	218.0-218.5	CH_2Cl_2 / Hexane	32%
19	=CHCO-C_6H_5	CH_3	216.5-217.0	CH_2Cl_2 / Hexane	60%
20	-CH=CH-C_6H_5	CH_3	188.0-188.5	CH_3OH (aq)	94%
21	-CH=CH-4-pyridyl	CH_3	205.0-206.0	CH_3OH (aq)	97%

B. <u>Acylation of 17a-d to Produce 3-Aryl-2-(2-aryl-2-oxoethyl)pyrido[2,3-*d*]-4(3H)pyrimidones 18a-d and 19.</u>

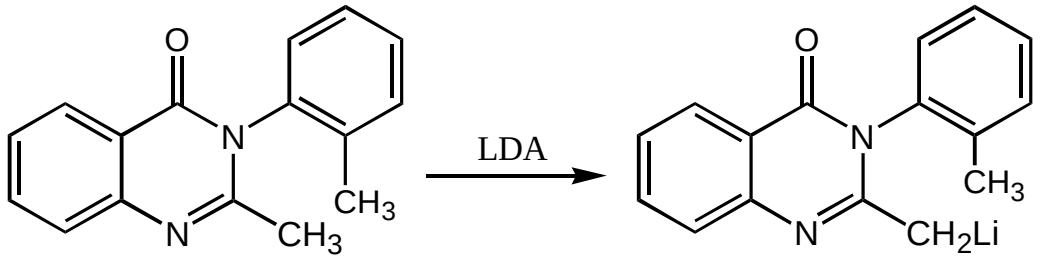
Once compounds **17a-d** were synthesized, elaboration of the 2-methyl group to produce the target compounds **18a-d** and **19** could be addressed. Both lithium diisopropylamide (LDA) and sodium hydride (NaH) were used as metalating agents with **17a-d**, along with the acylating esters, ethyl isonicotinate and methyl benzoate.



17a-d

18a-d, **19**
R = aryl

Rathman successfully used LDA for the metalation and subsequent elaboration of the lateral 2-methyl group on **13** as shown below.[7] So, for the extraction of a proton from the 2-methyl group of **17a**, we initially used LDA as the metalating reagent.



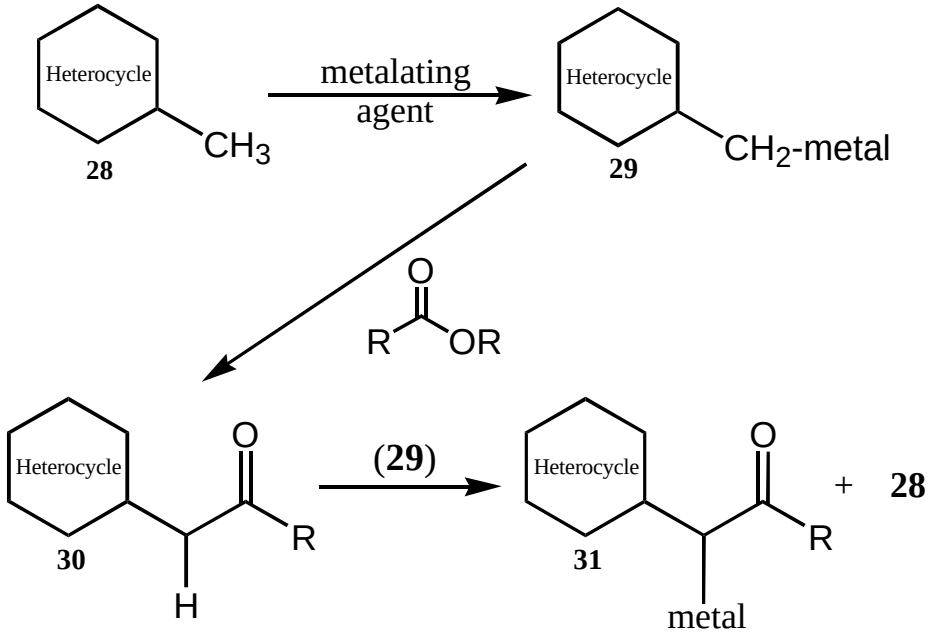
13

The process indeed afforded the desired product, 2-[2-oxo-2-(4-pyridyl)ethyl]-3-phenylpyrido[2,3-*d*]-4(3H)pyrimidone (**18a**) upon treatment of the intermediate 2-lithomethyl derivative with ethyl isonicotinate. However, the yield based on **17a** was only 27%. Attempts to increase this yield were unsuccessful.

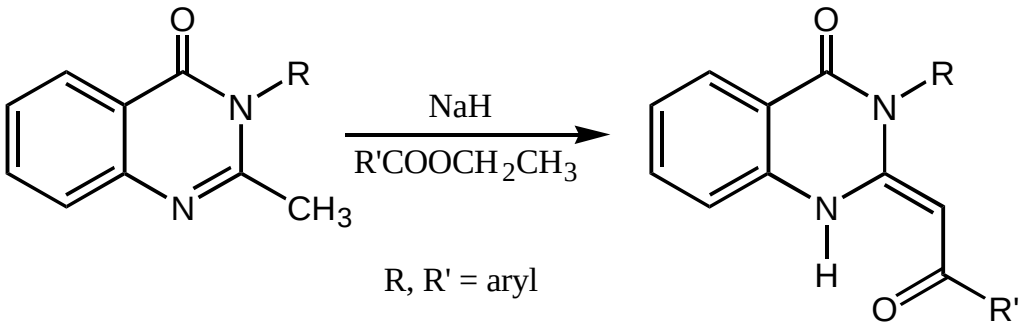
The use of organolithium reagents as metalating agents with methylated heterocycles, such as **17a**, has been previously demonstrated; however, the efficacy of this process can be jeopardized by side reactions, such as the addition of the metalating agent to carbonyl groups contained in the heterocycle framework.[38, 39] Alkali metal amides or alkali salts of certain dialkylamines, such as LDA, are often more satisfactory metalating agents than organolithium reagents since they are weaker nucleophiles.[41] However, even with these bases the overall stoichiometry is often unfavorable, as shown in Scheme II, for the hypothetical reaction of a 2-methyl heterocycle **28** with an ester.[7, 34-36] The yield of the acylation product **30** is limited to 50%, based on starting material, since the initially formed carbanionic intermediate **29** can abstract an acidic methylene proton from **30** to form the less basic carbanion **31** faster than **29** undergoes condensation with the ester. So, when the stoichiometry of the heterocycle, the base and the ester is 1:1:1, only half of the heterocycle and ester are consumed. If the molar ratio is increased to 2:2:1, utilization of the ester is improved, but an equivalent of the heterocycle remains unreacted and must be separated from the product. A 1:2:1 ratio of reactants increases the possibility of base cleavage of the ester function by LDA. Since the 2-methylated starting materials used in this research are synthesized from a mutli-step process, these potential losses of starting material were judged to be unacceptable.

Scheme II

General Mechanism for the Metalation and Acylation of Methylated Heterocycles



To eliminate the above problem, it seemed possible that the non-nucleophilic, insoluble base, sodium hydride could be used as the basic reagent with nonenolizable acylating esters.[37] Two equivalents of sodium hydride are needed for the reaction, one to deprotonate the methylated heterocycle and a second to deprotonate the acylated product. Rathman, utilizing sodium hydride as the basic reagent, showed that even if the acylated product **30** were deprotonated by the metalated substarte **29**, a second equivalent of NaH would be present to regenerate **29**. The reaction of 3-aryl-2-methyl-4(3H)-quinazolinones **32** with various benzoate esters produced 3-aryl-2-(2-aryl-2-oxo)ethyl-4(3H)quinazolinones **33** in good yields.[7]

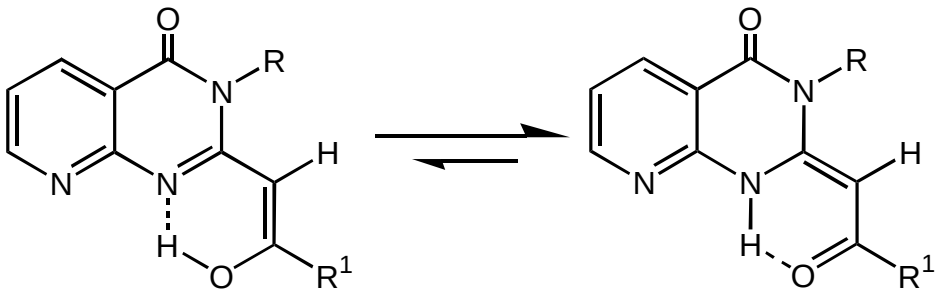


32 **33**

In attempts to maximize the yield in conversion of **17a-d** to **18a-d** and **19**, optimum conditions for the NaH promoted acylation reaction were investigated. The best conditions involved dissolving the ester in THF in the presence of eight equivalents of NaH in the reaction vessel, which was heated almost to reflux, and the ester, as a solution in THF. During refluxing of the reaction, thin layer chromatography (TLC) plates were spotted with aliquots of the reaction mixture and aliquots of the starting materials. An increase of product concentration and decrease in starting material concentration was seen in the TLC plates until approximately 4 h after the reaction was started, so the reactions were stopped there. Hydrogen gas evolution (2 equivalents) also ceased after 4 h of reflux indicating termination of the reaction.

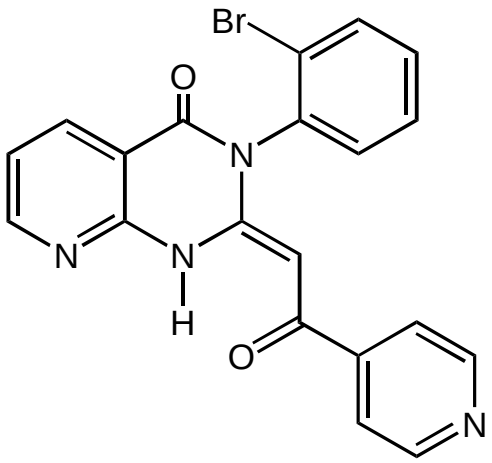
When **17a-d** were treated with NaH and either ethyl isonicotinate or methyl benzoate, the acylation of the 2-methyl group was achieved, producing **18a-d** and **19** in yields of 36-77%. ^{1}H NMR spectroscopy, melting point determination, elemental analysis and mass spectrometry were all used to establish structures and purity. Data on compounds **18a-d** and **19** are listed in Table 1.From ^{1}H NMR data, we propose that the 3-aryl-2-(2-aryl-2-oxo)ethylpyrido[2,3-*d*]-

4(3H)pyrimidones **18a-d** and **19** exist in an enamine tautomeric form. The ^{1}H NMR spectra of these compounds, showed a broad singlet (N-H of enamine) in the range of δ 14.87-15.00 and a



sharp singlet, corresponding to the side chain vinyl proton, in the range of δ 5.05-5.17. These spectral data on **18a-d** and **19** were consistent with the tautomerism previously observed with Rathman's quinazolinone analogs and in a variety of heterocyclic systems containing exocyclic β-carbonyl substituents.[7, 42]

In the initial preparation of 3-(2-bromophenyl)-2-[2-oxo-2-(4-pyridyl)ethyl]pyrido[2,3-*d*]-4(3H)pyrimidone (**18d**), two unique melting points (142-143°C and 216-217°C) were observed. The solid melted slowly, resolidified, then melted again. The results of elemental analysis were consistent with the hypothesis that **18d** existed as a dihydrate.



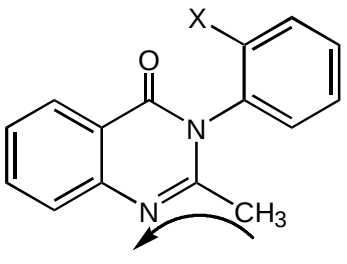
18d

High resolution mass spectroscopy showed that the compound was indeed **18d**. The rapid heating of the mass spectroscopy process made it difficult to quantify the water present in the sample. The H^1 NMR spectral characteristics of the sample gave some evidence that water was present in the compound. A single peak at δ 1.87 was observed in the spectrum, which led to the conclusion that two water molecules were present in the sample. When the sample was dried, under vacuum in a drying pistol heated with refluxing xylene and a melting point then determined for the newly dried material, the original lower melting point was absent and a single melting point was observed at 218-218.5°C. In subsequent experiments when **18d** was resynthesized, the dihydrate phenomenon was not observed and material melting sharply at 218-218.5°C was obtained.

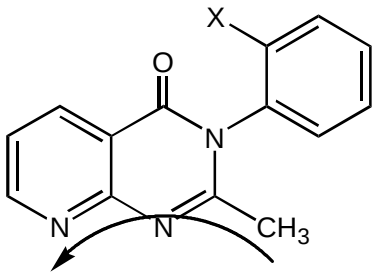
C. Mechanistic Study of NaH Promoted Acylations

As mentioned earlier, two equivalents of NaH are needed for these acylation reactions. One equivalent is needed for the removal of a proton from the 2-methyl group of the heterocycle to produce carbanion intermediate **29** (from Scheme II), while the other equivalent is used to effect the ionization of the methylene proton of the acylated product **30**. Therefore, evolution of hydrogen gas from the reaction can assist in determining how the reaction is proceeding. For the 3-aryl-2-methyl-4(3H)-quinazolinones, it has been observed that partial ionization occurred when they were subjected to treatment with NaH, in the absence of the any ester, since a small amount of hydrogen gas was evolved. However, these substrates were not fully ionized by NaH even after prolonged reflux. When the acylating ester was added, hydrogen evolution began again and continued until two equivalents had been produced.

Since, the 3-aryl-2-methylpyrido[2,3-*d*]-4(3H)pyrimidones, **17a-d**, used in this study contain a second nitrogen, it seemed possible that the acidity of the C-2 methyl hydrogens might be increased to the point where the complete ionization may occur without the need for the ester being present.

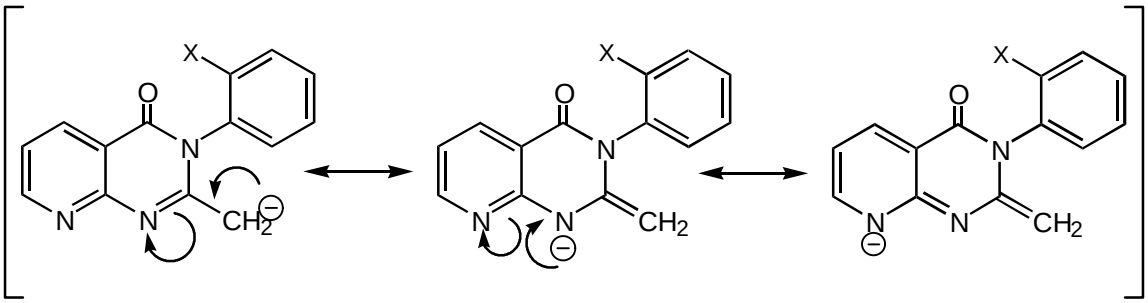


3-Aryl-2-methyl-4(3H)-quinazolinones

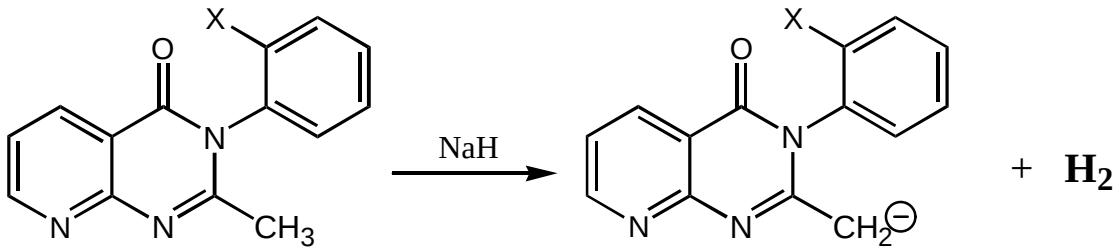


3-Aryl-2-methylpyrido[2,3-*d*]-4(3H)pyrimidones

The proposed resonance effects, shown below, along with inductive effects of the ring nitrogen at position 8, may help to stabilize the carbanion formed when the 2-methyl group is deprotonated with NaH.



By measuring the hydrogen gas evolved when **17d** was treated with sodium hydride, without the ester present, it was possible to observe the extent of deprotonation of the methyl group. Thus, when **17d** was refluxed with eight equivalents of NaH in THF for 4 h, without an acylating ester present, only 0.3 equivalents of hydrogen were produced. Then ethyl isonicotinate was added and the reaction mixture refluxed for 4 h. Hydrogen gas evolution measurements showed that ionization of the methyl group occurred only after the ester was added. The reaction evolved 1.7 equivalents of hydrogen gas.



17a-d

The theoretical volume of hydrogen gas that should be evolved from the reaction was calculated from the following equation:

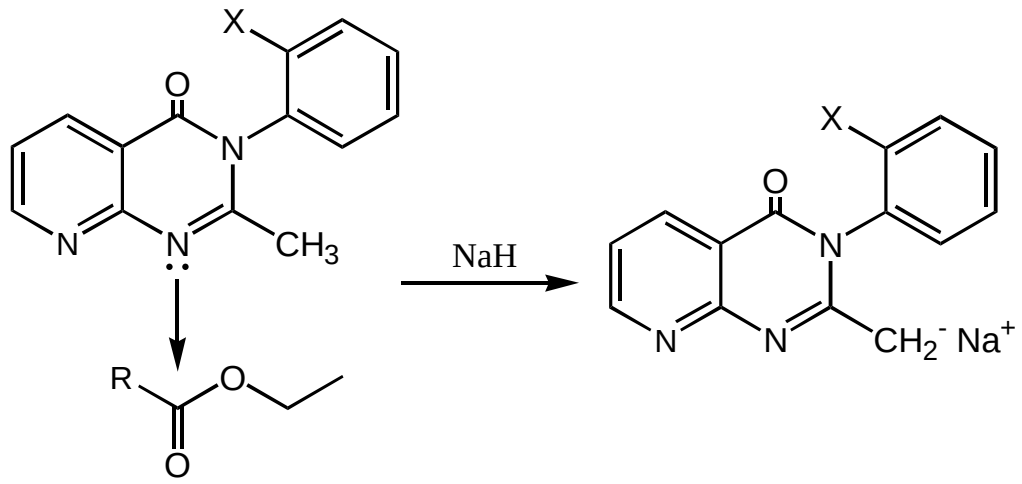
$$V = T_E / T_{STP} \times P_{STP} / (P_E - P°_{H2O}) \quad x \quad n \quad x \quad 10^3 \quad x \quad 22.4$$

The subscript E represents conditions when measurements were taken, the subscript STP represents standard conditions, n represents the theoretical number of moles of hydrogen to be produced by the reaction and $P°_{H2O}$ represents the vapor pressure of water at the given temperature.

It was apparent that the ester assists in the removal of the proton from the 2-methyl group of **17d**. This phenomenon is consistent with previous research on the quinazolinones, which demonstrated that the ester must be present with the methylated heterocycle and NaH for removal of a proton from the methyl group to occur.[37] We propose that the ester helps in increasing the acidity of the 2-methyl hydrogens in the 3-aryl-2-methylpyrido[2,3-*d*]-4(3H)pyrimidones as shown in Scheme III. The partial positive charge located on the carbon of the ester carbonyl group could interact with the lone pair of electrons on nitrogen. The ester, along with the

Scheme III

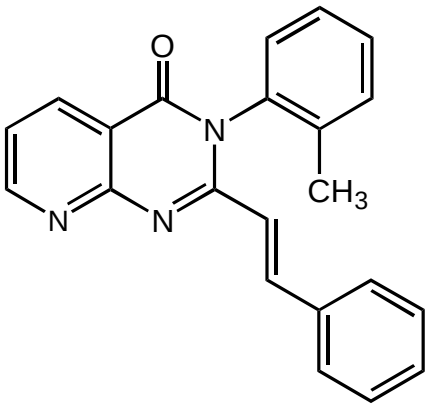
Electrophilic Assistance of Ester on NaH Promoted Acylation



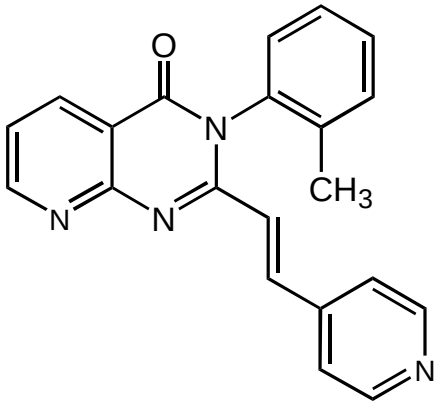
nitrogen, may act as an electron withdrawing group on the 2-methyl group. With the ester interacting in this way, the acidity of the methyl hydrogens would be increased, which would allow for a more facile removal of the proton by NaH.

D. Incorporation of Styryl and Arylethenyl Groups as the 2-Alkyl Chain of 17b.

Boltze[6] observed increased anticonvulsant activity in quinazolinone derivatives **14** and **15**, which contain 2-arylethenyl substituents at the C-2 carbon. Utilizing compound **17b**, we investigated incorporation of an arylethenyl group into the pyridopyrimidone framework in hopes of increasing the anticonvulsant activity and/or decreasing neurotoxicity. An attempt was made to produce **20**, by using **17b**, NaH and benzaldehyde, but the procedure proved ineffective.



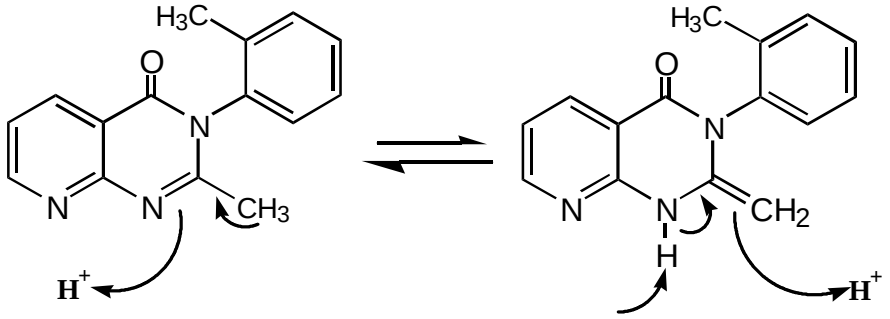
20



21

To produce the target compounds **20** and **21**, a procedure analogous to that of Kassem and Soliman[33] was employed. Addition of benzaldehyde or 4-pyridinecarboxaldehyde to a refluxing solution of **17b** in glacial acetic acid, in the presence of a catalytic amount of concentrated sulfuric acid, afforded the target compounds **20** and **21** in yields of 94% and 97%, respectively.

We propose when the starting material 2-methyl-3-(2-methylphenyl)pyrido[2,3-*d*]-4(3H)pyrimidone (**17b**) is introduced to the acidic reaction environment, two tautomeric forms exist, as shown below.

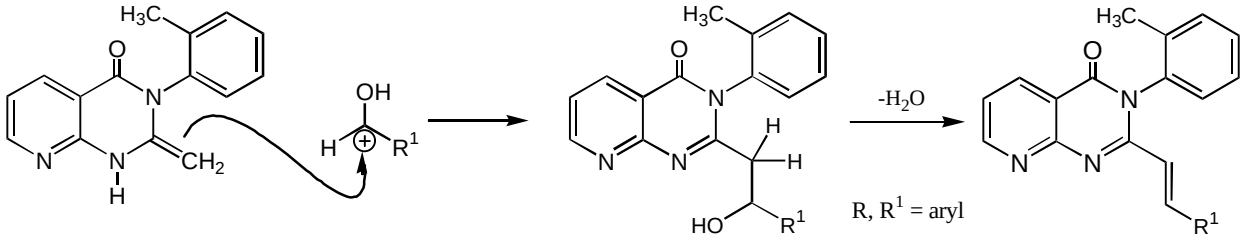


17b

The 2-methylenyl tautomeric form, depicted on the right, acts as the nucleophilic agent, in a reaction with the protonated aldehyde. The resulting alcohol undergoes dehydration to form the unsaturated product, as shown in Scheme IV.

Scheme IV

Synthesis of 2-Arylethenyl Derivatives 20 and 21



Products **20** and **21**, listed in Table 1, were characterized by ^{1}H NMR spectroscopy and elemental analyses, all of which are consistent with the assigned structures.

III. Pharmacological Test Results of Various 2-Alkyl-3-arylpyrido[2,3-*d*]-4(3H)pyrimidones

All compounds prepared in this study and screened for anticonvulsant activity were tested through the Antiepileptic Drug Development (ADD) Program of the National Institute of Neurological Disorders and Stroke (NINDS) with the cooperation of James P. Stables, Assistant Chief, Preclinical Pharmacology Section, Epilepsy Branch, Division of Convulsive, Developmental and Neuromuscular Disorders.

A. NINDS Identification of Anticonvulsant Activity.

Pharmacological evaluations of the candidate compounds, **17a-d**, **18a-d**, **19**, **20** and **21**, were performed by the Epilepsy Branch of NINDS using established protocols.[44] Tests were conducted with either Carworth Farms No. 1 mice or Sprague-Dawley rats. Solutions of the test compounds were prepared in 30% polyethylene glycol 400 and were administered intraperitoneally (ip) or orally (po) in a volume of 0.01 ml/g body weight for mice and 0.004 ml/g body weight for rats.

In Phase I screening each compound was administered as an ip injection at four dose levels (30, 100 and 300 mg/kg) with anticonvulsant activity and neurotoxicity assessed at 30 min and 4 h intervals after administration. Anticonvulsant efficacy was measured by the maximal electroshock (MES) test and the subcutaneous pentylenetetrazol (PTZ) test. In the MES test, seizures were elicited with a 60-Hz alternating current of 50 mA intensity in mice and 150 mA intensity in rats. The current was applied via corneal electrodes for 0.2 s. Abolition of the hind-

leg tonic-extensor component of the seizure indicated protection against the spread of MES-induced seizures. The PTZ test involved subcutaneous injection of a convulsive dose (CD_{97}) of pentylenetetrazol (85 mg/kg in mice, 70 mg/kg in rats). Elevation of the pentylenetetrazol-induced seizure threshold was indicated by the absence of clonic spasms for at least a 5 s duration over a 30 min period following administration of the test compound. Anticonvulsant drug-induced neurologic deficit (neurotoxicity) was detected in mice by the rotorod ataxia test and in rats by the positional sense, gait and stance tests.

The pharmacological parameters estimated in Phase I screening were quantified for several compounds in Phase II screening (Table 3). Anticonvulsant activity was expressed in terms of the median effective dose (ED_{50}) and neurotoxicity was expressed as the median neurotoxic dose (TD_{50}). For the determination of the ED_{50} and TD_{50}, groups of 6-12 mice were given a range of ip doses of the test drug until at least three points were established in the range of 10-90% seizure protection or minimal observed neurotoxicity. From the plot of this data, the respective ED_{50}, TD_{50}, 95% confidence intervals, slope of the regression line and the standard error of the slope were calculated by means of a computer program written at NINDS. The ED_{50} and TD_{50} values are given in units of mg of compound per kg of body weight of test subject. The protective index value (PI) of the compound is the ED_{50} divided by the TD_{50}. PI values are given for both MES-induced seizure protection and scPTZ-induced seizure protection.

B. Anticonvulsant Testing Results.

Primary (Phase I) anticonvulsant testing data obtained from NINDS for the target compounds **17a-d**, **18a-d**, **19**, **20** and **21** is reported in Table 2. The results of the Phase I screening indicate the relative activity of the compound for providing protection from either the MES-induced and scPTZ-induced seizures and indicate the neurotoxicity of the compound.

Table 2

Phase I Anticonvulsant Screening Results of Target Pyridopyrimidones

	MES[a]		scPTZ[a]		toxcity[a]	
Compd	0.5 h	4.0 h	0.5 h	4.0 h	0.5 h	4.0 h
17a	-	-	-	-	++	+
17b	++	+	++	+	+++	+
17c	++	++	++	++	++	++
17d	++	-[b]	+++	++	++	-
18a	++	++	++	++	++	++
18b	+++++	+++	+++++	+++	++++	+++
18c	+++++	+++	+++++	+++	++++	+++
18d	++++	+++	+	++++	++++	+++
19	-	+	-	+	++	++
20	+	-	-	+	+	+
21	+	++	+	-	++	++

[a] Activity and toxicity at 3, 10, 30, 100, 300 mg/kg are represented by +++++, ++++, +++, ++, and +, respectively. Activity at a given dosage level is indicated if at least one test animal exhibited protection; - denotes no activity observed at 300 mg/kg

[b] At 0.5 h, 2/3 animals were protected at 30 mg/kg

The ED_{50} and TD_{50} values for compounds **17b** and **18c**, which showed the greatest activity in the Phase I testing, were quantified in Phase II testing and are reported in Table 3, along with several additional compounds for comparison. The results are promising; however, the protective indices of **17b** and **18c** are not sufficient for further testing.

Table 3

Phase II Anticonvulsant Screening Results of Several Pyridopyrimidones, Quinazolinones and Currently Marketed Antiepileptic Drugs (AEDs)

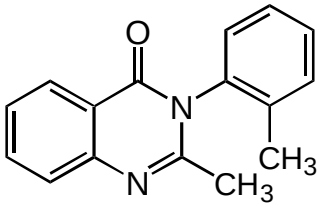
Compd	MES ED_{50} mg/kg	scPTZ ED_{50} mg/kg	TD_{50} mg/kg
17b	<100	40	137
18c	2.49	>31	<62.5
13[19]	52	33.5	55
14[6]	19	>2500	110
15[6]	14.5	145	120
16b[7]	148	100	561
16c[7]	196	14.5	262
phenytoin[46]	9.5	>300	65
phenobarbital[46]	22	13	69
valproate[46]	272	14	426
ethosuximide[46]	>1000	130	441

References refer to the source for the Phase II anticonvulsant screening data

C. Conclusions On Pyridopyrimidone Antiepileptic Activity.

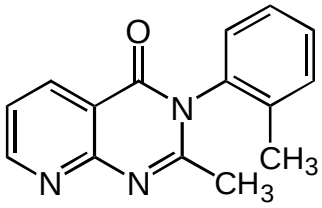
Results of anticonvulsant screening of the 2-methylated pyridopyrimidones **17a-d** support the proposal that the perpendicular element that most CNS-active drug contain must consist of an *ortho*-substituted phenyl ring. Compound **17a**, which contains an unsubstituted phenyl ring,

exhibits no protection from either the MES-induced or scPTZ-induced seizures. While compounds **17b-d** show protection, in dosage levels of 100-300 mg/kg, for both types of induced seizures. A comparison of **17b** and **13** (methaqualone) gives some information on the activity differences between the 2-methyl-3-(2-methylphenyl) heterocyclic compounds, where the only difference between **17b** and



MES ED_{50} = 52 mg/kg
scMET ED_{50} = 33.5 mg/kg
TD_{50} = 55 mg/kg
PI = 1.1_{MES}, 1.6_{scMET}

13

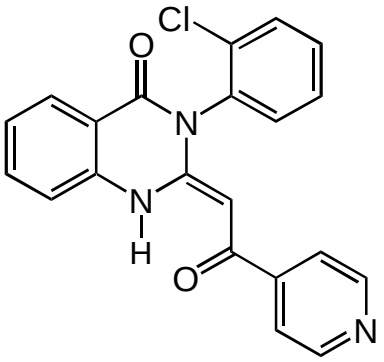


MES ED_{50} = <100 mg/kg
scMET ED_{50} = 40 mg/kg
TD_{50} = 137 mg/kg
PI = $>1.4_{MES}$, 3.4_{scMET}

17b

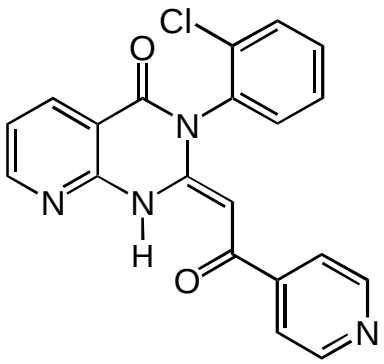
13 is the nitrogen located at C-8 position in **17b**. The anticonvulsant activity of the pyridopyrimidone derivative **17b** is similar to **13**, however, the neurotoxicity is lower giving compound **17b** a better protective index against both the MES-induced and scPTZ-induced seizures.

The Phase II test results of **16c** and **18c** nicely illustrates the difference between the pyridopyrimidones and the quinazolinones which contain an *ortho*-substituted phenyl ring as the 3-aryl group and a 2-oxo-2-(4-pyridyl)ethyl group as the 2-alkyl side chain. Both of these substituents have been shown to be effective for increasing the anticonvulsant activity of a compound.[7] Compounds **16c** and **18c** each contain an *ortho*-chloro substituted phenyl ring, so



MES ED_{50} = 196 mg/kg
scMET ED_{50} = 14.5 mg/kg
TD_{50} = 262 mg/kg
PI = 1.3_{MES}, 18_{scMET}

16c

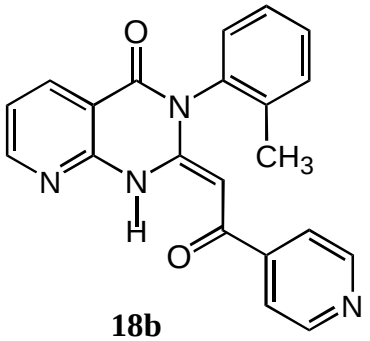


MES ED_{50} = 2.49 mg/kg
scMET ED_{50} = >31 mg/kg
TD_{50} = <62.5 mg/kg
PI = $<25_{MES}$, $<2_{scMET}$

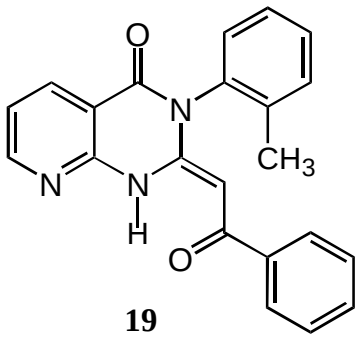
18c

the sole difference between the two compounds is the nitrogen atom found at the C-8 position in the fused ring system of the pyridopyrimidones. The test results show nearly an eighty-fold increase in the protection against MES-induced seizures in **18c** relative to **16c**, with only a slight decrease in the protection against scPTZ-induced seizures, however, the toxicity of **18c** increased significantly from that of **16c**.

The 2-oxo-2-(4-pyridyl)ethyl group is an important substituent in the quinazolinones for increasing the anticonvulsant activity, but we wanted to determine if it has the same pharmacological effects on pyridopyrimidone derivatives. Comparison of the screening results of compounds **18b** and **19** shows that the 2-oxo-2-(4-pyridyl)ethyl group does indeed have a similar effect on the anticonvulsant activity of pyridopyrimidones. Removal of the ring nitrogen in the 2-



18b



19

alkyl chain of **18b** to render **19** resulted in a tremendous drop in the anticonvulsant activity of the compound (Table 2). As stated earlier, nitrogen moieties may be responsible for CNS activity because of their ability to act as primary binding groups.[44] The large difference between the anticonvulsant activity of **18b** and **19** may be due to the nitrogen of the pyridyl group in the 2-alkyl chain being essential at the binding site for the compound.

Based on the anticonvulsant screening results, we conclude that the replacement of the carbon atom at the C-8 position in the fused ring system of the quinazolinone framework with a nitrogen atom increases the overall anticonvulsant activity, especially with MES-induced seizures, but the neurotoxicity is increased as well. It appears that the *ortho*-bromo substituted phenyl ring as the 3-aryl group in the pyridopyrimidones does not give us the desired separation of anticonvulsant activity and toxicity seen in the quinazolinone **16f**. However, the need for an *ortho*-substituted phenyl ring was evident. The various substituents incorporated into our target analogs had the same pharmacological effects as they did with the quinazolinone derivatives. The 2-oxo-2-(4-pyridyl)ethyl group was observed to have the greatest pharmacological effects on the pyridopyrimidones that we tested. Even though the separation of activity and toxicity was not accomplished in the target compounds of this study, the increased anticonvulsant activity in the

pyridopyrimidones may be an important discovery. By varying the substituents, it may be possible to achieve the separation in other pyridopyrimidone derivatives.

IV. Experimental

A. General

Proton magnetic resonance (^{1}H NMR) spectra were taken on either a Bruker WP200, WP270 or AM360 MHz instruments. Reported chemical shifts are given in units of δ, which represents parts per million (ppm) downfield from the standard tetramethylsilane (TMS) found in the NMR solvent. Splitting patterns have been abbreviated as follows: s = singlet, d = doublet, m = multiplet, and dd = double of doublets.

Melting points of compounds were determined on a Thomas Hoover Uni-melt melting point apparatus, in open capillary tubes, and are reported in degrees Celsius (°C). Elemental analyses were performed by Atlantic Microlab Inc., Norcross, GA.

Tetrahydrofuran (THF) was dried with potassium (K), using benzophenone as a indicator. It was collected and used immediately. The sodium hydride, a 60% oil dispersion, was washed with several aliquots of hexane, then immediately covered by dry THF. The lithium diisopropylamide (LDA) used was obtained from Aldrich®. The acetic acid used for acidifications was 80% reagent grade, unless otherwise mentioned. All other chemicals used throughout the research were commercial reagent grade and, unless otherwise noted, were not further purified.

Analytical thin layer chromatography (TLC) was performed on Whatman Thin Layer Chromatography plates made of silica gel impregnated with fluorescent indicator. The solvent used for the development of the plates is indicated for specific reactions. The detection of the component spots was accomplished with ultraviolet (UV) illumination and iodine chamber

development. The pH of solutions was determined by color comparison on Hydroin Paper. After all extractions, the organic layer was dried with magnesium sulfate ($MgSO_4$) and filtered.

Some units of measure have been abbreviated throughout this thesis and are as follows: grams (g), moles (mol), millimoles (mmol), milliliters (mL), hours (h), minutes (min), degrees Celsius (°C).

B. Preparation of 3-Aryl-2-methylpyrido[2,3-*d*]-4(3H)pyrimidones 17a-d.

The method used for the synthesis of 3-aryl-2-methylpyrido[2,3-*d*]-4(3H)pyrimidones **17a-d** is a procedure patterned after that of Preuss and Hoffmann,[30] which in turn was developed from experiments conducted by Philips.[45] An additional method for generating 2-methyl-3-(2-methylphenyl)pyrido[2,3-*d*]-4(3H)pyrimidone (**17b**), a compound similar in structure to methaqualone (**13**), was reported by Kretzchmar,[28] however this method was not utilized in this research. All procedures were first run on a microscale to determine whether the reaction scheme yielded the desired product, as determined by ^{1}H NMR. The reactions were then scaled up as reported below. Many of the reactions were repeated to increase the amount of compound available for later steps. Such reactions are not reported, but are similar in method and yield to those appearing here.

Preparation of Quinolinic Anhydride (23).

A magnetically stirred solution of 31.31 g (0.18 mol) of quinolinic acid (**22**) and 80 mL of acetic anhydride was refluxed in a round bottom flask for 1 h. The resulting crystals were collected, once the solution had cooled to room temperature. The product was recrystallized using a mixture of methylene chloride and hexane to yield 27.8 g (99%) of quinolinic anhydride (**23**), mp 137-138°C (lit.[26] mp 137-139°C).

Preparation of Quinolinamic Acid (25).

In a 1000 mL three-neck round bottom flask, approximately 500 mL of liquid ammonia (NH_3, l) was collected by condensing the gas with a dry ice/acetone cooled condenser. To the stirred solution, 27.28 g (0.18 mol) of quinolinic anhydride (**23**) was added in small portions as a solid. Since the ammonia gas above the condensed ammonia reacts with the quinolinic anhydride, the addition must be made in small portions, but done as quickly as possible. The flask was allowed to warm to room temperature and stand overnight during which time the NH_3 evaporated. The resulting ammonium quinolinamate (**24**) was dissolved in water and acidified with acetic acid to pH of ~5 to precipitate the quinolinamic acid (**25**). The acid was subsequently filtered and washed with hexane to afford 12.9 g (43%) of **25**, mp 129-130°C.

Hoffman Rearrangement of 25 to Prepare 2-Aminonicotinic Acid (26).

In a round bottom flask, 13.0 mL (0.25 mol) of bromine, 53.65 g (1.34 mol) of solid sodium hydroxide and 420 mL of water were combined. The flask was placed into an ice bath.

After 5-10 min, 30.64 g (0.18 mol) of **25** was added to the stirred solution. The solution was warmed to room temperature and allowed to react for 15 min, then warmed to 75°C for an additional 75 min. The reaction mixture was acidified with acetic acid to pH ~6, which precipitated the product, 2-aminonicotinic acid (**26**). The product was collected and washed with hexane to yield 10.6 g (42%) of **26**, mp 296-297°C (lit.[31] mp 297-299°C).

Cyclization of 2-Aminonicotinic Acid (26) with Acetic Anhydride to Form 2-Methylpyrido[2,3-*d*][1,3]oxazin-4(H)-one (27).

In a round bottom flask, a solution of 150 mL of acetic anhydride and 10.87 g (0.079 mol) of 2-aminonicotinic acid (**26**) was refluxed for 1 h. Upon cooling, the precipitated product was collected and rinsed with hexane, yielding 12.2 g (95%) of 2-methylpyrido[2,3-*d*][1,3]oxazin-4(H)-one (**27**), mp 176-177°C (lit.[32] mp 164-165°C); ^{1}H NMR (270 Mhz, DMSO) δ 8.96 (d, 1H), 8.50 (d, 1H), 7.45-7.50 (dd, 1H), 2.55 (s, 3H).

Preparation of 2-Methyl-3-phenylpyrido[2,3-*d*]-4(3H)pyrimidone (17a) from 27.

A 500 mL three-neck round bottom flask, fitted with a mechanical stirrer, a condenser and an addition funnel, was placed into a heating mantle. A solution of 14.23 g (0.088 mol) of **27**, 8.15 g (0.088 mol) of aniline and 285 mL of toluene was placed into the flask. Next, 6.05 g (0.044 mol) of phosphorus trichloride (PCl_3), dissolved into 16.5 mL of toluene, was placed into the addition funnel. After several minutes of stirring, the heating mantle was turned on and the PCl_3/toluene solution was added over approximately 10 min. After the addition was completed,

the reaction mixture was refluxed for 4 h, then cooled to room temperature. The toluene was removed by decantation and nitrogen gas was blown over the remaining solid to evaporate any residual toluene. When the solid was void of toluene, approximately 50 mL of water was slowly added. The solution was stirred, as a solution of sodium bicarbonate was slowly added until all bubbling ceased. Next, the solution was extracted with methylene chloride, and the product collected by evaporation of the solvent under vacuum. The product was recrystallized from methylene chloride and hexane, yielding 10.9 g (52%) of 2-methyl-3-phenylpyrido[2,3-*d*]-4(3H)pyrimidone (**17a**), mp 203-203.8°C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.97 (d, 1H), 8.55 (d, 1H), 7.56 (dd, 1H), 7.24-7.54 (m, 5H), 2.31 (s, 3H). Anal. Calcd for $C_{14}H_{11}N_3O$: C, 70.87; H, 4.67; N, 17.71. Found: C, 70.15; H, 4.74; N, 17.53.

Preparation of 2-Methyl-3-(2-methylphenyl)pyrido[2,3-*d*]-4(3H)pyrimidone (17b) from 27.

A reaction mixture of 9.42 g (0.058 mol) of **27**, 7.10 g (0.066 mol) of *o*-toluidine, 3.94 g of PCl_3 and 250 mL of toluene was refluxed for 1 h. The solution was condensed by evaporation under vacuum in a rotary evaporator. The resulting solid was collected and recrystallized from methylene chloride and hexane, yielding 7.60 g (52%) of 2-methyl-3-(2-methylphenyl)pyrido[2,3-*d*]-4(3H)pyrimidone (**17b**), mp 178.6-178.9°C (lit.[32] mp 109-110°C, lit.[30] mp 176-177°C, lit.[31] mp 178-179°C); ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.98 (d, 1H), 8.59 (d, 1H), 7.52 (dd, 1H), 7.13-7.41 (m, 4H), 2.25 (s, 3H), 2.12 (s, 3H). Anal. Calcd for $C_{15}H_{13}N_3O$: C, 71.70; H, 5.21; N, 16.72. Found: C, 71.47; H, 5.29; N, 16.58.

Preparation of 3-(2-Chlorophenyl)-2-methylpyrido[2,3-*d*]-4(3H)pyrimidone (17c) from 27.

A reaction mixture of 8.79 g (0.054 mol) of **27**, 7.02 g (0.055 mol) of 2-chloroaniline, 3.94 g of PCl_3 and 230 mL of toluene was refluxed for 2 h. The solution was condensed by evaporation under vacuum. The resulting solid was collected and recrystallized from methylene chloride and hexane, yielding 10.8 g (73%) of 3-(2-chlorophenyl)-2-methylpyrido[2,3-*d*]-4(3H)pyrimidone (**17c**), mp 192.4-192.9°C (lit.[31] mp 194-195°C); ^{1}H NMR (270 MHz, $CDCl_3$) δ 9.00 (d, 1H), 8.60 (d, 1H), 7.62 (dd, 1H), 7.26-7.50 (m, 4H), 2.31 (s, 3H). Anal. Calcd for $C_{14}H_{10}N_3OCl$: C, 61.89; H, 3.71; N, 15.47. Found: C, 61.88; H, 3.74; N, 15.45.

Preparation of 3-(2-Bromophenyl)-2-methylpyrido[2,3-*d*]-4(3H)pyrimidone (17d) from 27.

Reaction of 3.97 g (0.024 mol) of **27**, 5.91 g (0.034 mol) of 2-bromoaniline, 2.04 g of PCl_3 and 150 mL of toluene was refluxed for 2 h. The solution was condensed by evaporation under vacuum. The resulting solid was collected and recrystallized from methylene chloride and hexane, yielding 3.50 g (45%) of 3-(2-bromophenyl)-2-methylpyrido[2,3-*d*]-4(3H)pyrimidone (**17d**), mp 172.5-173°C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 9.01 (d, 1H), 8.61 (d, 1H), 7.82 (dd, 1H), 7.34-7.55 (m, 4H), 2.31 (s, 3H). Anal. Calcd for $C_{14}H_{10}N_3OBr$: C, 53.19; H, 3.19; N, 13.29. Found: C, 53.01; H, 3.38; N, 13.26.

C. Elaboration of the 2-Methyl Group of 3-Aryl-2-methylpyrido[2,3-*d*]-4(3H)pyrimidones to Give 2-[2-Oxo-2-(4-pyridyl)ethyl]pyrido[2,3-*d*]-4(3H)pyrimidones by LDA and NaH Promoted Acylations

The reaction apparatus used for the following experiments consisted of a 500 mL three-necked round bottom flask containing a magnetic stirring bar, which was placed in a heating mantle. If the reaction used NaH, the flask was fitted with a condenser, a pressure-equalizing addition funnel and an inlet for nitrogen gas flow with a back pressure bubbler. However, if the reaction used LDA, the flask was fitted with a condenser, a pressure-equalizing addition funnel and a rubber septum. The inlet for nitrogen gas was on the top of the condenser, while the LDA was added by syringe through the septum. Several different methods were attempted to elaborate the 2-methyl group of **17a** using LDA and ethyl isonicotinate to give 2-[2-oxo-2-(4-pyridyl)ethyl]-3-phenylpyrido[2,3-*d*]-4(3H)pyrimidone (**18a**). The temperatures and the sequence of additions were varied in the different methods. However, the additional trials gave poorer yields than those described below.

Two Different Preparations of 2-[2-Oxo-2-(4-pyridyl)ethyl]-3-phenylpyrido[2,3-*d*]-4(3H)pyrimidone (18a) from 17a utilizing LDA.

To a stirred solution of 1.18 g (5.0 mmol) of **17a** and 50 mL of THF at 0°C, 8.4 mL of commercial LDA was added by syringe. After the 30 min of stirring, 0.87 g (5.8 mmol) of ethyl isonicotinate, dissolved in 30 mL of THF, was added dropwise by addition funnel over a period of

15 min. The solution turned to a dark reddish, black color and remained that throughout the addition of the ester. The reaction was allowed to warm to room temperature after 1 h, then allowed to stand for 20 h. The reaction mixture was concentrated by evaporation under vacuum. The resulting oil was dissolved in water and quenched with aqueous ammonium chloride to pH ~5.5, then extracted with methylene chloride. The organic layer was separated and evaporated under vacuum, leaving a reddish, yellow solid. The solid was recrystallized from 2-propanol, yielding 0.47 g (27%) of 2-[2-oxo-2-(4-pyridyl)ethyl]-3-phenylpyrido[2,3-*d*]-4(3H)pyrimidone (**18a**), mp 204.3-204.8°C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 15.00 (s, 1H), 8.73 (d, 1H), 8.62 (d, 1H), 8.43 (dd, 1H), 7.24-7.65 (m, 9H), 5.17 (s, 1H). Anal. Calcd for $C_{20}H_{14}N_4O_2$: C, 70.17; H, 4.12; N, 16.37. Found: C, 70.09; H, 4.10; N, 16.25.

Another reaction used 1.18 g (5.0 mmol) of **17a** and 6.8 mL of LDA, at an initial temperature of -78°C. After the addition of 0.91 g (6.0 mmol) of ethyl isonicotinate, the reaction mixture was allowed to warm to room temperature and then stand for 17 h. The solution was condensed by evaporation under vacuum. The solid collected, after a methylene chloride extraction, was passed through a column of silica gel with ethyl acetate as the eluting solvent. The reaction yielded 0.36 g (21%) of 2-[2-oxo-2-(4-pyridyl)ethyl]-3-phenylpyrido[2,3-*d*]-4(3H)pyrimidone (**18a**), mp 204-204.5°C.

Preparation of 2-[2-Oxo-2-(4-pyridyl)ethyl]-3-phenylpyrido[2,3-*d*]-4(3H)pyrimidone (18a) utilizing NaH.

A stirred mixture of 1.25 g (0.052 mol) of NaH from 2.08 g of a 60% oil dispersion of NaH, 1.66 g (0.011 mol) of ethyl isonicotinate and 100 mL of THF was heated to near reflux. A solution of 2.31 g (9.7 mmol) of **17a** dissolved in 100 mL of THF was added by addition funnel to the NaH and ester solution over 15 min. The mixture was refluxed for 4 h, then allowed to cool and then stand overnight. The THF was evaporated under vacuum, then the resulting solid was quenched with acetic acid until all gas evolution ceased. A methylene chloride extraction was performed and the solvent removed by evaporation. The collected product was recrystallized from methylene chloride and hexane. The reaction yielded 1.83 g (55%) of 2-[2-oxo-2-(4-pyridyl)ethyl]-3-phenylpyrido[2,3-*d*]-4(3H)pyrimidone (**18a**), mp 204-204.8°C

Preparation of 3-(2-Methylphenyl)-2-[2-oxo-2-(4-pyridyl)ethyl]pyrido[2,3-*d*]-4(3H)pyrimidone (18b) utilizing NaH.

To a solution of 2.06 g (0.086 mol) of NaH from 3.44 g of a 60% oil dispersion of NaH, 2.41 g (0.016 mol) of ethyl isonicotinate and 100 mL of THF, near reflux, a solution of 3.02 g (0.012 mol) of **17b** and 150 mL of THF was added dropwise over 15 min. The mixture was refluxed for 4 h. After removing the THF by evaporation, quenching with acetic acid, extracting with methylene chloride and recrystallizing from methylene chloride and hexane, 3.29 g (77%) of 3-(2-methylphenyl)-2-[2-oxo-2-(4-pyridyl)ethyl]pyrido[2,3-*d*]-4(3H)pyrimidone (**18b**) was collected, mp 225.5-226°C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 14.97 (s, 1H), 8.71 (d, 1H), 8.61 (d,

1H), 8.42 (dd, 1H), 7.20-7.51 (m, 8H), 5.10 (s, 1H), 2.19 (s, 3H). Anal. Calcd for $C_{21}H_{16}N_4O_2$: C, 70.78; H, 4.53; N, 15.72. Found: C, 70.64; H, 4.61; N, 15.74.

Preparation of 3-(2-Chlorophenyl)-2-[2-oxo-2-(4-pyridyl)ethyl]pyrido[2,3-*d*]-4(3H)pyrimidone (18c) utilizing NaH.

To a solution of 1.22 g (0.051 mol) of NaH from 2.03 g of a 60% oil dispersion of NaH, 1.24 g (0.008 mol) of ethyl isonicotinate and 100 mL of THF, near reflux, a solution of 1.83 g (0.007 mol) of **17c** and 150 mL of THF was added dropwise over 15 min. The mixture was refluxed for 4 h. After removing the THF by evaporation, quenching with acetic acid, extracting with methylene chloride and recrystallizing from methylene chloride and hexane, 1.17 g (46%) of 3-(2-chlorophenyl)-2-[2-oxo-2-(4-pyridyl)ethyl]pyrido[2,3-*d*]-4(3H)pyrimidone (**18c**) was collected, mp 216-216.5°C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 14.87 (s, 1H), 8.72 (d, 1H), 8.62 (d, 1H), 8.42 (dd, 1H), 7.24-7.70 (m, 8H), 5.06 (s, 1H). Anal. Calcd for $C_{20}H_{13}N_4O_2Cl$: C, 63.75; H, 3.48; N, 14.87. Found: C, 63.90; H, 3.53; N, 14.66.

Preparation of 3-(2-Bromophenyl)-2-[2-oxo-2-(4-pyridyl)ethyl]pyrido[2,3-*d*]-4(3H)pyrimidone (18d) utilizing NaH.

To a solution of 1.51 g (0.063 mol) of NaH from 2.51 g of a 60% oil dispersion of NaH, 1.40 g (9.0 mmol) of ethyl isonicotinate and 100 mL of THF, near reflux, a solution of 2.43 g (8.0 mmol) of **17d** and 150 mL of THF was added dropwise over 15 min. The mixture was refluxed

for 4 h. After removing the THF by evaporation, quenching with acetic acid, extracting with methylene chloride and recrystallizing from ethyl acetate, 1.17 g (36%) of 3-(2-bromophenyl)-2-[2-oxo-2-(4-pyridyl)ethyl]pyrido[2,3-*d*]-4(3H)pyrimidone (**18d**), was collected. Elemental analysis showed that the product was impure, so the product was extracted with ethyl ether and recrystallized from methylene chloride and hexane. Two distinct melting points were observed for the resulting solid; the first at 142-143°C and after resolidification, a second at 216-217°C, which are believed to represent the behavior of a dihydrate form of the solid (further discussion in Chapter III). The product was dried under vacuum in a drying pistol heated with refluxing xylene. After drying, the lower melting point was no longer present. The final yield of **18d** was 1.02 g (32%), mp 218-218.5°C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 14.91 (s, 1H), 8.73 (d, 1H), 8.63 (d, 1H), 8.43 (dd, 1H), 7.26-7.89 (m, 8H), 5.05 (s, 1H). Anal. Calcd for $C_{20}H_{13}N_4O_2Br$: C, 57.03; H, 3.11; N, 13.30. Found: C, 57.23; H, 3.17; N, 13.35.

D. Elaboration of the 2-Methyl Group of 3-(2-Methylphenyl)-2-methylpyrido[2,3-*d*]-4(3H)pyrimidone (17b) to Give 2-(2-Oxo-2-phenylethyl)pyrido[2,3-*d*]-4(3H)pyrimidone by NaH Promoted Acylation.

The apparatus used for the elaboration of the 2-methyl group of **17b** to 2-(2-Oxo-2-phenylethyl) was identical to the apparatus used for the elaboration of the 2-methyl group of 3-

aryl-2-methylpyrido[2,3-*d*]-4(3H)pyrimidones (**17a-d**) to 2-[2-oxo-2-(4-pyridyl)ethyl] in the previous section.

Preparation of 3-(2-Methylphenyl)-2-(2-oxo-2-phenylethyl)pyrido[2,3-*d*]-4(3H)pyrimidone (19).

A solution of 2.83 g (0.021 mol) of methyl benzoate, 2.30 g (0.096 mol) of NaH recovered from 3.83 g of a 60% oil dispersion of NaH and 150 mL of THF was heated to near reflux. A solution of 3.20 g (0.012 mol) of **17b** dissolved in 120 mL of THF was added over a period of 15 min, then the mixture was refluxed for 8 h. After the THF was removed by evaporation under vacuum, acetic acid was added to quench the excess NaH. The solution was extracted with methylene chloride and the product was collected by evaporating the solvent under vacuum. The product was chromatographed on silica gel column using a 1:1 mixture of ethyl acetate and hexane for the eluting solvent. The product was collected and recrystallized from ethyl acetate yielding 2.72 g (60%) of 3-(2-methylphenyl)-2-(2-oxo-2-phenylethyl)pyrido[2,3-*d*]-4(3H)pyrimidone (**19**), mp 216.5-217°C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 14.92 (s, 1H), 8.69 (d, 1H), 8.58 (d, 1H), 8.41 (dd, 1H), 7.20-7.52 (m, 9H), 5.09 (s, 1H), 2.18 (s, 3H). Anal. Calcd for $C_{22}H_{17}N_3O_2$: C, 74.35; H, 4.82; N, 11.82. Found: C, 74.43; H, 4.89; N, 11.87.

E. Elaboration of the 2-Methyl Group of 3-(2-Methylphenyl)-2-methylpyrido[2,3-*d*]-4(3H)pyrimidone (17b) to Give 2-Styryl and 2-[2-(4-Pyridyl)]ethenylpyrido[2,3-*d*]-4(3H)pyrimidone.

For the incorporation of the styryl substituent, a procedure analogous to that of Kassem and Soliman[33] was used for the condensation of 3-aryl-2-methylpyrido[2,3-*d*]-4(3H)pyrimidone (**17b**) with benzaldehyde. The method used refluxing glacial acetic acid in the presence of concentrated sulfuric acid, which afforded good yields. The apparatus used was a single-neck round bottom flask, containing a magnetic stirrer, which was placed in a heating mantle. The flask was fitted with a condenser connected to a nitrogen inlet with a back pressure outlet.

Attempted Preparation of 3-(2-Methylphenyl)-2-styrylpyrido[2,3-*d*]-4(3H)pyrimidone (20) Using NaH.

A stirred solution of 0.98 g (9 mmol) of benzaldehyde and 1.14 g (0.05 mol) of NaH recovered from 1.90 g of a 60% oil dispersion of NaH was dissolved in 100 mL of THF and heated to near reflux. After the flask was heated, a solution of 1.58 g (6 mmol) of **17b** dissolved in 100 mL of THF was slowly added. The reaction mixture was heated to reflux and allowed to stand for 2 h. The mixture was condensed by evaporation under vacuum and quenched with acetic acid to eliminate excess NaH. The solution was extracted with methylene chloride. TLC performed on the resulting solid showed primarily unreacted starting material. This method was abandoned.

Condensation of 17b to Form 3-(2-Methylphenyl)-2-styrylpyrido[2,3-*d*]-4(3H)pyrimidone (20) with Acetic and Sulfuric Acids.

A solution of 0.47 g (1.9 mmol) of **17b**, 0.22 g (2.1 mmol) of benzaldehyde, 50 mL of glacial acetic acid and 10 drops of sulfuric acid was refluxed for 4 h. The solution was condensed by evaporation under vacuum and then neutralized with sodium carbonate. The solution was extracted with ethyl acetate and then condensed by evaporation. The resulting solid was recrystallized from aqueous methanol, yielding 0.59 g (94%) of 3-(2-methylphenyl)-2-styrylpyrido[2,3-*d*]-4(3H)pyrimidone (**20**), mp 188-188.5°C (lit.[33] mp 187-188°C); ^{1}H NMR (360 MHz, $CDCl_3$) δ 9.05 (d, 1H), 8.67 (d, 1H), 8.37 (dd, 1H), 7.23-7.51 (m, 9H), 6.39 (s, 1H), 6.33 (s, 1H), 2.14 (s, 3H). Anal. Calcd for $C_{22}H_{17}N_3O$: C, 77.86; H, 5.05; N, 12.38. Found: C, 77.71; H, 5.00; N, 12.16.

Condensation of 17b to Form 3-(2-Methylphenyl)-2-[2-(4-pyridyl)]ethenylpyrido[2,3-*d*]-4(3H)pyrimidone (21) with Acetic and Sulfuric Acids.

A solution of 1.43 g (6 mmol) of **17b**, 1.01 g (9 mmol) of 4-pyridinecarboxaldehyde, 80 mL of acetic acid and 10 drops of sulfuric acid was refluxed for 4 h. The solution was condensed by evaporation under vacuum, neutralized with sodium carbonate and extracted with ethyl acetate. After removing the solvent by evaporation, the resulting solid was recrystallized from aqueous methanol to yield 1.88 g (97 %) of 3-(2-Methylphenyl)-2-[2-(4-pyridyl)]ethenylpyrido[2,3-*d*]-4(3H)pyrimidone (**21**), mp 205-206°C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 9.02 (d, 1H), 8.61 (d, 1H), 8.33 (dd, 1H), 7.23-7.49 (m, 8H), 6.38 (s, 1H), 6.32 (s,

1H), 2.14 (s, 3H). Anal. Calcd for $C_{21}H_{16}N_4O$: C, 74.10; H, 4.74; N, 16.46. Found: C, 74.40; H, 4.79; N, 16.29.

F. Hydrogen Gas Evolution Experiments During NaH Acylation of 3-(2-Bromophenyl)-2-methylpyrido[2,3-*d*]-4(3H)pyrimidone (17d).

Two separate experiments were performed for measuring the hydrogen gas evolution from the reaction of **17d** with ethyl isonicotinate to form **18d**. The apparatus consisted of a three-neck round bottom flask containing a magnetic stirring bar. The flask was fitted with a condenser, a pressure-equalizing funnel and a gas line connector. The flask was placed in a heating mantle. Initially, the gas line was for nitrogen pressure flow with a back pressure bubbler. The gas line was converted to an outflow line connected to a drying tube, filled with Drierite, which was then connected to a 1000 mL water trap for collection of released hydrogen gas. The gas line was switched once the solution was at a temperature just below reflux, but before any additions were made.

Measurements of Hydrogen Gas Evolution in the Reaction of 17d with NaH without Ester Present.

A solution of 0.71 g (0.030 mol) of NaH removed from 1.18 g of a 60% oil dispersion of NaH and 100 mL of THF was heated in the flask to just below reflux. After the nitrogen line was switched to the collection line and equilibrated, a solution of 1.02 g (3.2 mmol) of **17d** dissolved

in 50 mL of THF was added. After 4 h of refluxing, only 45 mL (26%) of hydrogen gas was evolved.

A solution of 1.28 g (8.5 mmol) of ethyl isonicotinate dissolved in 10 mL of THF was added and the evolution of gas measured. An additional 90 mL of hydrogen gas was evolved from the solution. After 8 h, the reaction yielded 135 mL of hydrogen gas, which was 79% of the calculated theoretical amount.

Measurements of Hydrogen Gas Evolution of the Reaction of 17d with NaH and the Ester Present.

A solution of 0.98 g (0.041 mol) of NaH removed from 1.64 g of NaH in 60% oil dispersion, 0.84 g (5.6 mmol) of ethyl isonicotinate and 100 mL of THF was heated in the flask to just below reflux. After the nitrogen line was switched to the collection line and equilibrated, a solution of 1.46 g (4.6 mmol) of **17d** dissolved in THF was added. After 4 h of refluxing, approximately 205 mL of hydrogen gas was collected from the reaction, which was 83% of the calculated theoretical amount.

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