The Chemistry of 3-Azaisotoic Anhydrides. Synthesis and Reactions of Polyaza Heterocycles

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The preparation of a variety of N-substituted 3-azaisatoic anhydrides **3** and **8** is described. These anhydrides reacted with thiopseudoureas to give interesting bicyclic, tricyclic, and tetracyclic heterocycles many of which are new ring systems. One such heterocycle, the imidazo[1,2-*a*]pyrido[2,3-*d*]pyrimidine ring system, was studied further with respect to alkylation and reduction reactions. Alkylation of **12h** occurred on the nitrogen in the central B ring, whereas, in the reduced species **33**, alkylation took place in the C ring.

The reaction of 3-azaisatoic anhydrides with carbanions was also investigated. Reactions occur with anions generated from nitromethane, diethylmalonate, ethyl nitroacetate, ethyl isocyanate, and ethyl *o*-fluorobenzoylacetate.

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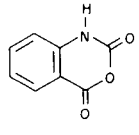
The chemistry of 2*H*-3,1-benzoxazine-2,4(1*H*)-dione (isatoic anhydride) (**1**) and its derivatives has provided the synthetic chemist with a rich source of chemical transformations which generate useful synthetic intermediates as well as a wide variety of interesting heterocyclic ring systems and natural products [1,2].

Although isatoic anhydride has been known for nearly a century, its 3-aza analog **2** [3] has only been prepared within the last fifteen years [4-7]. In comparison with **1**, reactions of **2** have received little attention [8-12] but we feel that **2** and its derivatives will be useful in the convergent construction of a variety of polyaza heterocyclic compounds.



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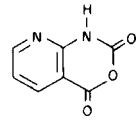

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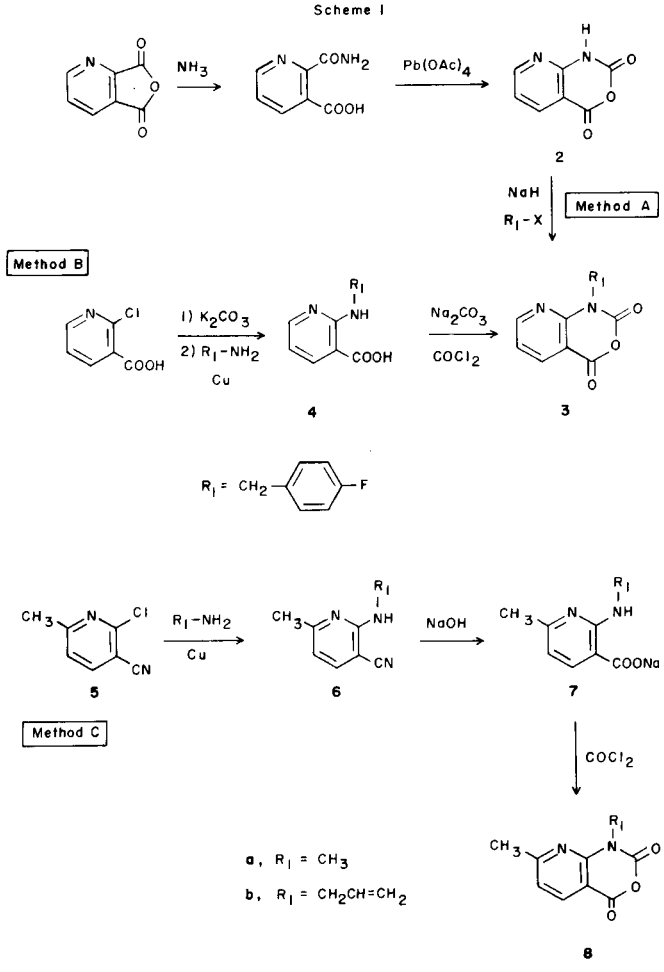
In this publication we wish to report the preparation of *N*-substituted-3-azaisatoic anhydrides (**3** and **8**) and their subsequent reactions with nucleophiles (such as thiopseudoureas and carbanions) which ultimately result in the formation of several new ring systems.

N-Alkyl-3-Azaisatoic Anhydrides.

3-Azaisatoic anhydride (**2**) is prepared in two steps (Scheme 1) from 2,3-pyridinedicarboxylic anhydride by treatment with ammonia [13] then subsequent oxidation of the 2-carbamylnicotinic acid with lead tetraacetate [5]. This procedure lends itself to large scale preparations with 400 g quantities of **2** easily attainable.

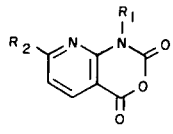
In the isatoic anhydride series, the best method for directly obtaining compounds of type **1** where the nitrogen is substituted, is the treatment of **1** with sodium hydride followed by the desired alkylating agent [14]. We found

Scheme I



that this method is also amenable to the direct alkylation of **2** [11] (Method A, Scheme 1) and serves as a convenient route for the preparation of *N*-substituted-3-azaisatoic anhydrides **3** (Table 1), although the yields are somewhat lower than in the alkylation of **1**.

Table 1



Compound No.	R_1	R_2	Method	Yield, %	MP, °C	Crystallization Solvent	Molecular Formula	Analysis Calcd. (Found) C	H	N
3a	CH_3	H	A	75	169-172	Dichloromethane/ ethanol	$C_8H_6N_2O_3$	53.9 (54.0)	3.4 (3.3)	15.7 (15.3)
3b	CH_2CH_3	H	A	67	151-154	Dichloromethane/ ethanol	$C_9H_8N_2O_3$	56.3 (56.1)	4.2 (4.3)	14.6 (14.6)
3c	$CH_2C_6H_5$	H	A	63	152-158	Dichloromethane/ ether	$C_{14}H_{10}N_2O_3$	66.1 (66.1)	4.0 (3.7)	11.0 (10.8)
3d	$CH_2C_6H_4F(p)$	H	A B	82 62	148-151	Dichloromethane/ ether	$C_{14}H_9FN_2O_3$	61.8 (61.9)	3.3 (3.6)	10.3 (10.0)
3e	Cyclopropylmethyl	H	A	72	129-132	Dichloromethane/ ethanol	$C_{11}H_{10}N_2O_3$	60.5 (60.5)	4.6 (4.7)	12.8 (12.4)
3f	$CH_2CH=CH_2$	H	A	41	114-117	Dichloromethane/ ethanol	$C_{10}H_8N_2O_3$	58.8 (58.8)	4.0 (3.9)	13.7 (14.0)
3g	$CH_2C\equiv CH$	H	A	20	126-129	Dichloromethane/ ethanol	$C_{10}H_6N_2O_3$	59.4 (59.0)	3.0 (2.7)	13.9 (14.1)
3h	$CH_2C\equiv CCH_3$	H	A	14	139-141	Dichloromethane/ ether	$C_{11}H_8N_2O_3$	61.1 (61.1)	3.7 (3.7)	13.0 (12.8)
3i	$(CH_2)_6CH=CH_2$	H	A	27	77-80	Benzene/ether/ petroleum ether	$C_{15}H_{18}N_2O_3$	65.7 (65.8)	6.6 (6.5)	10.2 (10.2)
3j	$CH_2CH=CHCH=CH\text{-}CH_3$	H	A	17	120-123	Dichloromethane/ ether	$C_{13}H_{12}N_2O_3$	63.9 (63.2)	5.0 (5.0)	11.5 (11.4)
3k	2-Furylmethyl	H	A	25	127-129	Dichloromethane/ ether	$C_{12}H_8N_2O_4$	59.0 (59.0)	3.3 (3.4)	11.5 (11.4)
3l	$CH_2COOCH_2CH_3$	H	A	23	112-115	Dichloromethane/ ether	$C_{11}H_{10}N_2O_5$	52.8 (52.7)	4.0 (4.5)	11.2 (11.1)
8a	CH_3	CH_3	C	51	138-141	Dichloromethane/ ether	$C_9H_8N_2O_3$	56.3 (56.0)	4.2 (4.1)	14.6 (14.6)
8b	$CH_2CH=CH_2$	CH_3	C	25	122-125	Dichloromethane/ ether	$C_{11}H_{10}N_2O_3$	60.5 (60.3)	4.6 (5.0)	12.8 (12.8)

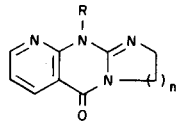
Systems of this type (*e.g.* **3d**) can be alternately synthesized by a shorter route starting from 2-chloronicotinic acid (Method B, Scheme 1). After preforming the potassium salt of the nicotinic acid, reaction with *p*-fluorobenzylamine in the presence of copper powder (Ullmann reaction) in refluxing dimethylformamide affords the amino-acid **4** in 38% yield. Treatment of **4** with sodium carbonate followed by phosgene results in the formation of **3d** in 62% yield (29% overall from 2-chloronicotinic acid). This method is especially advantageous with high boiling amines and although the overall yield is lower than the direct alkylation of **2** with *p*-fluorobenzyl bromide, the sequence requires one less step than Method A and employs less expensive, readily available [15] starting materials.

The synthesis of an *N*-alkyl-3-azaisatoic anhydride with a substituent in the pyridine ring (*e.g.* CH_3) requires a somewhat more laborious procedure, because the requisite starting materials for Methods A and B are not readily available. This third approach (Method C, Scheme 1) starts with 2-chloro-6-methylnicotinonitrile (**5**). Its reaction with either methylamine (60° in a steel vessel) or allylamine (53°, used as the solvent) furnishes the corresponding 2-amino-6-methylnicotinonitrile (**6a** or **6b**) in good yields. Hydrolysis of **6** with sodium hydroxide gives the sodium salt of the 2-aminonicotinic acid (**7**) which is then treated directly with phosgene to yield the *N*-alkyl-4-methyl-3-azaisatoic anhydride **8a** or **8b** (Table 1).

Reactions with Thiopseudoureas.

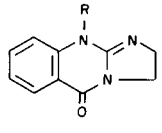
Previously it has been found that imidazoquinazolines of general structure **9** exhibit broncholytic activity [16], and tetracyclic pyridoimidazoquinazolines of general structure **10** provide a profile of CNS-depressant activity [17]. Since **9** and **10** are readily prepared from the reaction of an appropriately functionalized isatoic anhydride with a 2-alkylmercaptoimidazoline [16-19], we felt that analogs of these systems in which the benzene ring is replaced by a pyridine ring could easily be assembled using the azaisato-

Table 2



Compound No.	n	R	Method Yield, %	MP, °C	Crystallization Solvent	Molecular Formula	Analysis Calcd. (Found) C	H	N	F
12a	1	H [21]	D, 61	308-311	Dimethylacetamide	$C_9H_8N_4O$	57.4 (57.0)	4.3 (4.3)	29.8 (30.2)	
12b	1	CH_3	D, 51	168-171	Dichloromethane/ ether	$C_{10}H_{10}N_4O$	59.4 (59.4)	5.0 (5.2)	27.7 (27.8)	
12c	1	CH_2CH_3	D, 39	184-186	Dichloromethane/ ether	$C_{11}H_{12}N_4O$	61.1 (61.0)	5.6 (5.6)	25.9 (25.8)	
12d	1	Cyclopropylmethyl	D, 42	139-142	Dichloromethane/ ether	$C_{13}H_{14}N_4O$	64.4 (64.5)	5.8 (6.0)	23.1 (22.9)	
12e	1	$CH_2C_6H_5$	E, 49	203-205	Dichloromethane/ ethanol	$C_{16}H_{14}N_4O$	69.1 (69.0)	5.1 (5.0)	20.1 (20.2)	
12f	1	$CH_2C_6H_4F(p)$	D, 61	202-205	Chloroform/ ethanol	$C_{16}H_{13}N_4OF$	64.8 (65.0)	4.4 (4.7)	18.9 (18.8)	6.4 (6.4)
12g	1	$CH_2C\equiv CH$	D, 36	206-209	Dichloromethane/ ether	$C_{12}H_{10}N_4O$	63.7 (63.5)	4.5 (4.1)	24.8 (25.1)	
12h	2	H [21]	D, 57	316-320	Dimethylacetamide	$C_{10}H_{10}N_4O$	59.4 (59.6)	5.0 (5.2)	27.7 (27.7)	
12i	2	CH_2CH_3	D, 35	96-100	Ether	$C_{12}H_{14}N_4O$	62.6 (62.8)	6.1 (6.4)	24.3 (24.5)	
12j	2	$CH_2C_6H_4F(p)$	D, 35	182-184	Dichloromethane/ ether	$C_{17}H_{15}N_4OF$	65.8 (65.9)	4.9 (4.8)	18.1 (18.2)	6.1 (6.0)

ic anhydrides **2** or **3**. These novel heterocycles can then be compared to **9** and **10** to investigate what effect the introduction of the nitrogen has on their properties.



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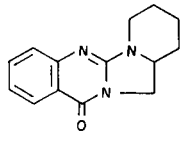

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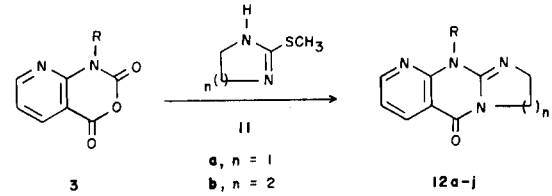
The azaisatoic anhydrides in Table 1 were allowed to react with a variety of thiopseudoureas and the results are summarized in Scheme 2 and Table 2. The reaction is performed by refluxing a mixture of **3** and the free base of the thiopseudourea in an inert solvent with a catalytic amount of base (Method D). An alternate method involves essentially the same procedure as above except the hydroiodide salt of the thiopseudourea is employed. In this case the free base is generated *in situ* with an excess of potassium or sodium carbonate (Method E). When monocyclic thiopseudoureas **11a** or **11b** are allowed to react with **3** in the above manner, the novel tricyclic systems **12** are readily obtained (Table 2). Analogous reactions using hexahydro-3-methylthioimidazole[1,5-*a*]pyridine (**20**) and hexahydro-2-methylthio-1*H*-benzimidazole (**21**) afford tetracycles **16**, **17**, **18** and **19** each of which represents a new ring system.

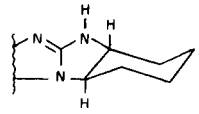


3 **11** **a**, n = 1 **b**, n = 2 **12a-j**

Reactions which employ **21** produce a mixture of *trans* and *cis* isomers (*e.g.* **17** and **18**) due to the fact that **21** itself is not isomerically pure (*trans:cis* ratio of 66:34). The isomeric mixture of **17** and **18**, formed in 60% yield, possesses approximately the same *trans:cis* ratio as that of **21**. Isomer **17** is easier to crystallize that *cis* isomer **18** and its purification is readily accomplished by fractional crystallization from ethanol. Isomer **18**, however, could not be isolated totally free of **17**. Analogously, the reaction of **3a** with **21** produces **19** in 48% yield (*trans:cis* ratio of 65:35). The oily mixture **19** is readily converted to a crystalline maleic acid salt but fractional crystallization does not result in the separation of isomers.

The stereochemical assignment of isomers **17** and **18** is based upon consideration of the 200 MHz proton nmr data and carbon-13 shift data. Isomer **17** exhibits two low-field aliphatic protons (adjacent to nitrogen) at δ 3.7 and 3.35, each as a triplet of doublets with a coupling constant of 13.5 Hz. This observation reflects a diaxial relationship

between these two protons and full proton-proton decoupling confirms this hypothesis.

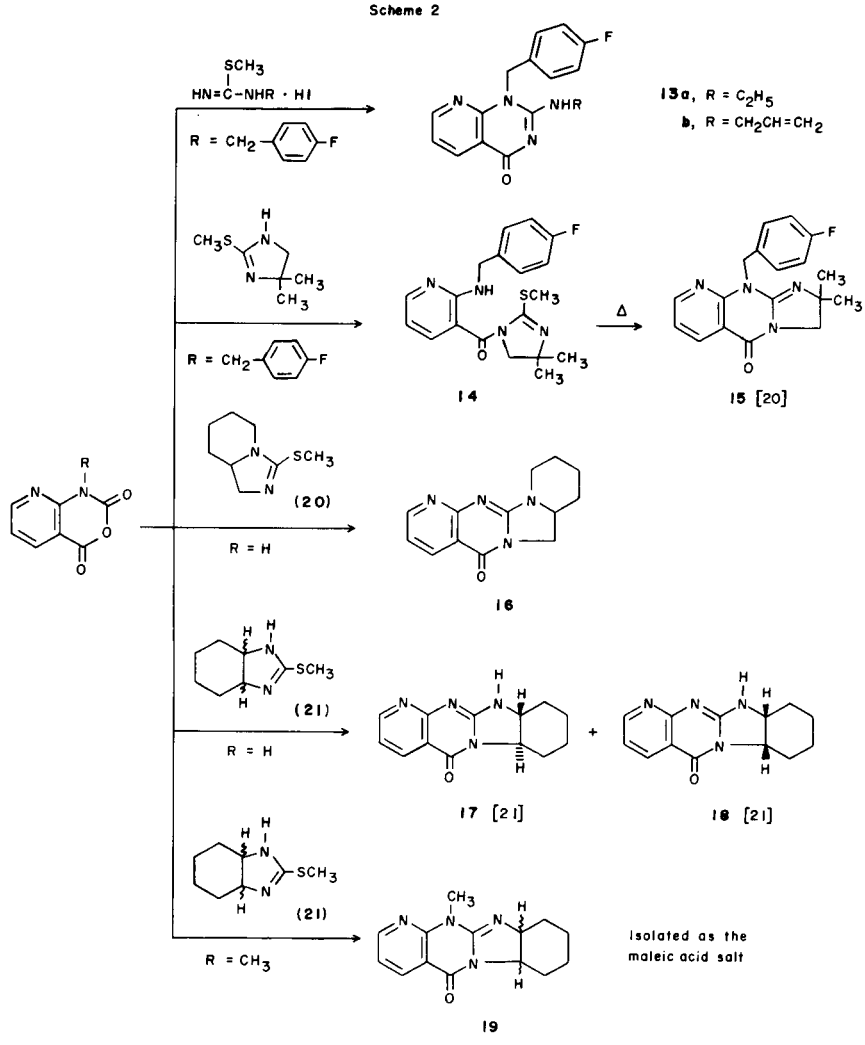


The corresponding protons for the *cis* isomer **18** are observed at δ 4.65 and 4.23 with the lowerfield proton resonance split by 12 Hz and 6 Hz. The higherfield signal exhibits only small long range couplings indicative of a structure containing one axial and one equatorial proton.

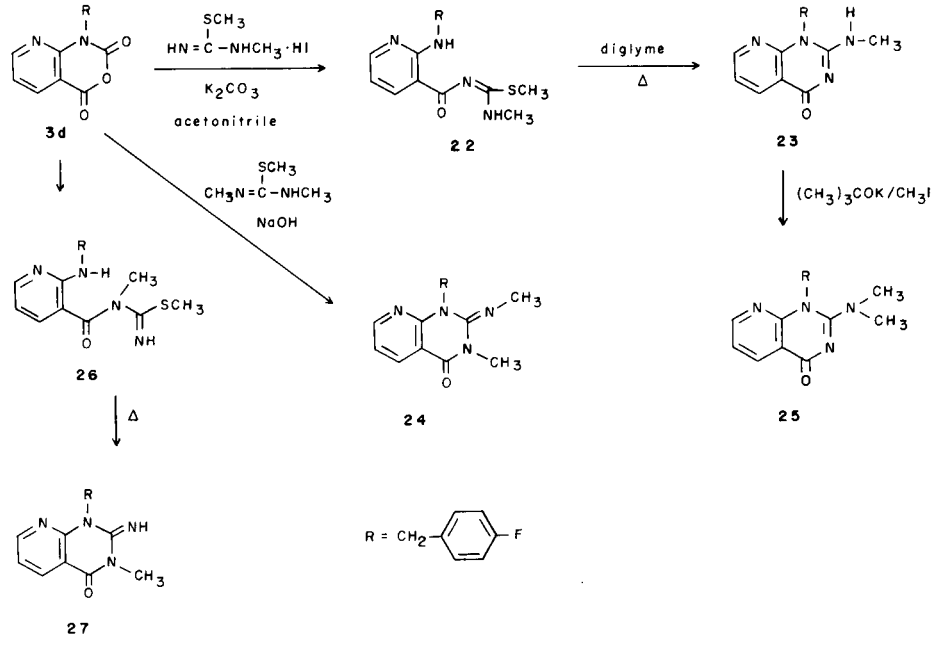
Additional support for the stereochemistry of isomers **17** and **18** is obtained from the analysis of their carbon-13 chemical shifts. It would be expected that all carbon shifts should be observed at higher field for *cis* isomer **18** than for *trans* isomer **17** [22]. The data shown in Figure 1 indicate that this indeed is the case.

In the reaction of **3** with unsymmetrical thiopseudoureas, two regioisomeric products are possible (*e.g* **23** or **27**, Scheme 3). Nucleophilic attack of the more substituted nitrogen atom of the thiopseudourea on the anhydride would give intermediate **26** which would then cyclize to the 3-methylpyrimidine **27**, whereas attack of the unsubstituted nitrogen atom should furnish **23**. When a mixture of **3d**, 2,3-dimethyl-2-thiopseudourea hydroiodide, and potassium carbonate are refluxed in toluene for 9 hours a single product is isolated in 51% yield. Its nmr spectrum reveals that an SCH_3 group is still present (singlet, δ 2.37) while an NCH_3 signal falls at δ 2.95 (doublet, J = 10 Hz) with the methylene of the *p*-fluorobenzyl group also seen as a doublet at 4.73 (J = 10 Hz). In addition, the presence of N-H absorptions at 3310 and 3200 cm^{-1} in its ir spectrum indicates that cyclization did not occur and an acyclic compound (**22** or **26**) is actually the product. The splitting of the *N*-methyl signal strongly suggests structure **22**. Although the methylated nitrogen of the thiopseudourea might be the more basic of the two, steric considerations may favor the unsubstituted nitrogen in the initial attack on the anhydride **3d** therefore causing the reaction to pro-

Scheme 2



Scheme 3



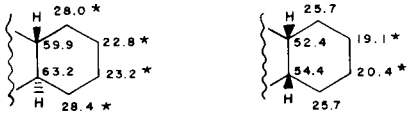


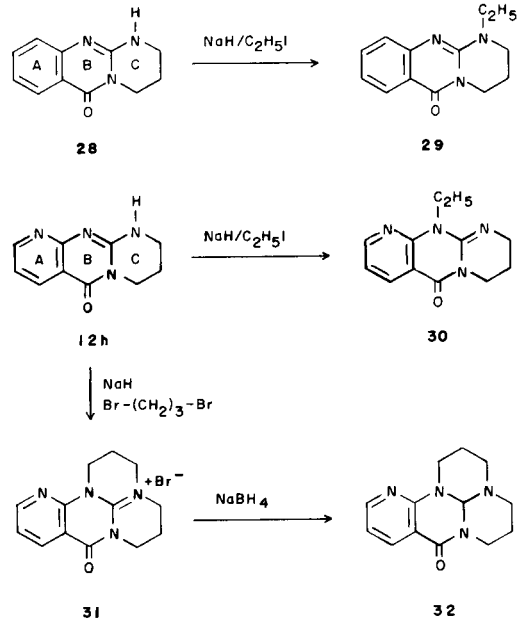
Figure 1. Carbon-13 data for the D ring of isomers **17** and **18**.

ceed to compound **22** rather than **26**.

The temperature requirements for the conversion of **22** to **23** are somewhat higher than allowed by the toluene used in the initial reaction of **3d** with the thiopseudourea. Cyclization can be effected (58% yield) by refluxing **22** in diglyme for 6 hours. Alternately, **23** can be obtained directly from **3d** by using diglyme as the solvent in the initial reaction instead of toluene. After 4 hours the product is isolated in higher overall yield (60%) and the reaction mixture tends to be cleaner than in the two step procedure.

In an alkylation reaction, compound **23** possesses two possible sites for substitution; the ring nitrogen in the 3-position of the pyridopyrimidine or the methylamino nitrogen attached to the 2-position. When **23** is allowed to react with methyl iodide in the presence of potassium *t*-butoxide (in tetrahydrofuran) alkylation occurs predominantly on the exocyclic nitrogen to furnish **25**, although minor amounts of **24** can also be detected. Compound **24** can be synthesized unambiguously by the reaction of **3d** with the symmetrically *N*-substituted thiopseudourea in the presence of sodium hydroxide. As expected, in the nmr spectrum the *N*-methyl groups of **25** appear as a singlet at δ 3.12 whereas those of **24** appear as two distinct singlets at δ 3.47 and 3.35, respectively.

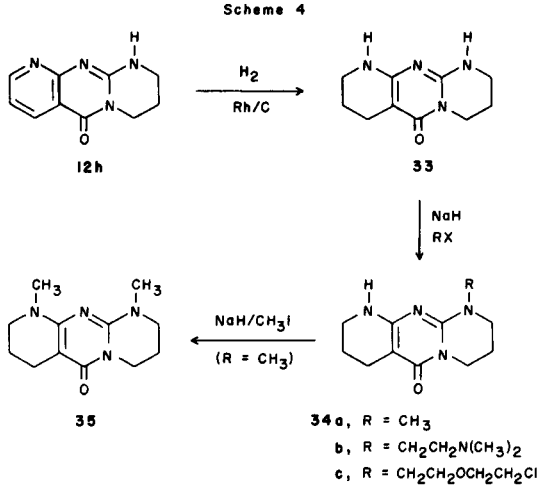
Alkylation reactions were also performed on the *N*-unsubstituted tricycle **12h** (Table 2). An interesting difference in the regiochemical outcome is observed when compared to the analogous alkylation of pyrimidoquinazoline **28**, derived from isatoic anhydride. Previously [16] it was shown that alkylation of **28** occurs exclusively on the nitrogen of the C ring to produce **29**. When the analogous



aza analog **12h** is alkylated under the same conditions, product **30** is isolated resulting from alkylation of the nitrogen of the B ring. All spectral data of **30** are identical to **12i** (Table 2) which is prepared unambiguously from the *N*-alkylated azaisatoic anhydride **3b**. The novel tetracyclic system **32** can readily be prepared by di-alkylation of **12h** with 1,3-dibromopropane followed by reduction of the resulting salt **31** with sodium borohydride.

Reduction of the pyridine A ring of **12h** is readily accomplished by catalytic hydrogenation over rhodium and the resulting saturated tricycle **33** is isolated in 76% yield (Scheme 4). The monoalkylation of **33** presents interesting regiochemical possibilities. In view of the results obtained with alkylations of compounds **28** and **12h**, and with an additional reaction site generated in ring A by reduction of **12h**, substitution in either the A, B, or C ring cannot easily be predicted. The monoanion of **33** is readily generated by the addition of one equivalent of sodium hydride. Subsequent addition of methyl iodide furnishes a monomethylated derivative as the only isolable product.

Scheme 4

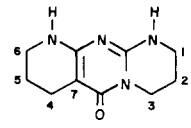


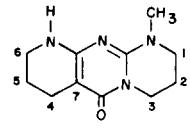
In order to solve the regiochemical outcome of the reaction, a detailed analysis of the proton and carbon nmr spectra of **33** was undertaken (see Table 3). The proton nmr spectrum (200 MHz) gives rise to individual multiplets for all protons in the molecule. The lowest field protons are assigned to those on C_3 (δ 3.9, triplet) due to the deshielding effect of both the nitrogen and carbonyl groups. Irradiation of these protons results in the simplification of the protons at δ 2.0 thus allowing their assignment. Irradiation at δ 2.0 then assigns the protons at C_1. Analogous assignments of the protons at C_6, C_5, and C_4 can be made by similar treatment. The aliphatic carbon assignments (Table 3) can readily be made by single frequency low power decoupling.

The proton nmr spectrum of the alkylated product **34a** has the same general appearance as that of **33**. Proton decouplings lead readily to their assignments. Single frequency proton decoupling then gives the corresponding carbon assignments. While in principle the assignment of the methylation position can be accomplished by substituent effects, the use of deuterium isotope shifts appears to be more reliable. This method allows facile determination of the position of exchangeable protons (in this instance the N-H group). The adjacent carbons in this experiment are split into doublets and this conclusively assigns the overall structure. In this particular case it is the carbon at δ 41.1 which splits and since it is assigned to C_6 by the single frequency decoupling method, methylation therefore occured on the nitrogen in the C ring.

Table 3

Proton and Carbon Chemical Shifts for Compounds **33** and **34a**.





	δ C	δ H		δ C	δ H
C_1	39.6	3.4		47.6	3.38
C_2	21.1	2.0		20.7*	2.03
C_3	40.0	3.9		38.7	3.96
C_4	20.4	2.45		19.6	2.50
C_5	22.1	1.8		21.5*	1.85
C_6	41.5	3.3		41.1	3.30
C_7	84.9			84.3	
			N-CH_3	36.7	3.08

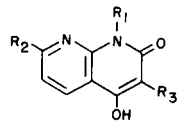
Spectra were taken in deuteriochloroform

Analogous alkylations of **33** with 2-chloro-*N,N*-dimethyl-1-ethylamine and 2-chloroethyl ether afford **34b** and **34c**. Compound **34a** can be additionally alkylated in the A ring in low yield by treatment with sodium hydride followed by methyl iodide. By this method **35** can be prepared in 19% yield. Several attempts to effect the intramolecular alkylation of **34c** resulted in the decomposition of the starting material.

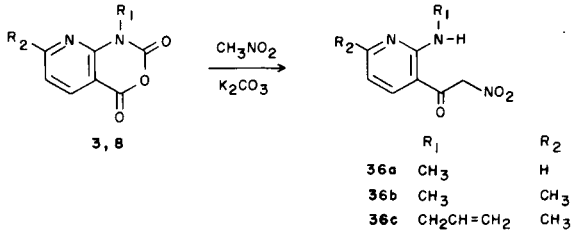
Reactions with Carbanions.

Isatoic anhydrides are readily attacked at the C-4 carbonyl in the hetero ring of the benzoxazine by carbanions to give a wide range of interesting products [1,2]. Several analogous representative experiments were performed with selected 3-azaisatoic anhydrides to generate the corresponding aza derivative of the products and to investigate the effect of the additional nitrogen on the course of the reaction. The initial substrate chosen was nitromethane. Its anion is easily generated with potassium carbonate in dimethylsulfoxide and reaction with either **3** or **8** occurs readily at room temperature to give the intensely yellow colored pyridylethanones **36** in moderate yields.

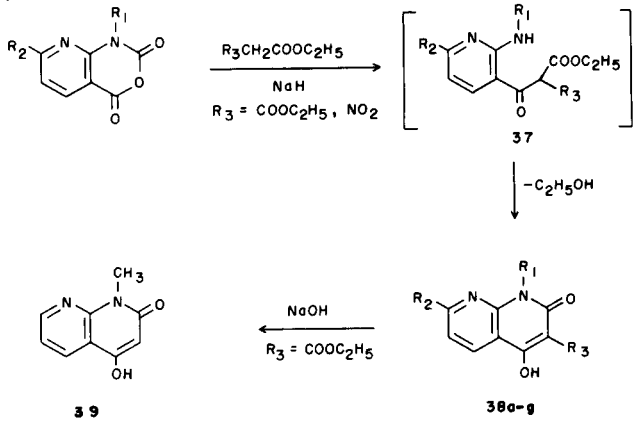
Table 4



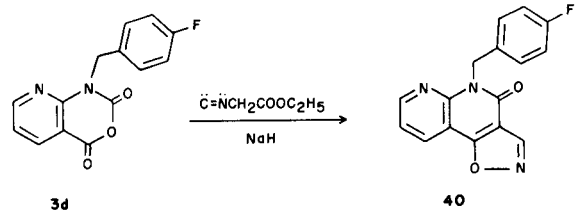
Compound No.	R_1	R_2	R_3	Yield, %	MP, °C	Crystallization Solvent	Molecular Formula	Analysis Calcd. (Found) C	H	N
38a	CH_3	H	$COOCH_2CH_3$	60	163-166	Dichloromethane/ether	$C_{12}H_{12}N_2O_4$	58.1 (57.9)	4.9 (4.8)	11.3 (11.3)
38b	CH_2CH_3	H	$COOCH_2CH_3$	46	124-127	Dichloromethane/ether/petroleum ether	$C_{13}H_{14}N_2O_4$	59.5 (59.0)	5.4 (5.1)	10.7 (10.7)
38c	CH_3	CH_3	$COOCH_2CH_3$	35	148-151	Dichloromethane/ether	$C_{13}H_{14}N_2O_4$	59.5 (59.2)	5.4 (5.8)	10.7 (10.8)
38d	$CH_2CH=CH_2$	CH_3	$COOCH_2CH_3$	43	122-125	Dichloromethane/ether/pentane	$C_{15}H_{16}N_2O_4$	62.5 (62.1)	5.6 (5.7)	9.7 (9.8)
38e	CH_3	H	NO_2	22	156-158	Ethyl Acetate	$C_9H_7N_3O_4$	48.9 (48.4)	3.2 (3.5)	19.0 (18.8)
38f	$CH_2CH=CH_2$	H	NO_2	29	115-118	Dichloromethane/ether	$C_{11}H_9N_3O_4$	53.4 (53.0)	3.8 (3.7)	17.0 (16.7)
38g	CH_3	CH_3	NO_2	26	159-161	Dichloromethane/ether	$C_{10}H_9N_3O_4$	51.1 (51.4)	3.9 (4.1)	17.9 (18.2)



When the carbanion is flanked by a group capable of cyclization (*e.g.* ester) with the liberated nitrogen (**37**) [23], naphthyridine derivatives **38** (Table 4) are formed. A compound such as **38a** (R_3 = $COOC_2H_5$) is susceptible to decarboxylative hydrolysis when subjected to strong aqueous base and **39** is isolated in nearly quantitative yield.

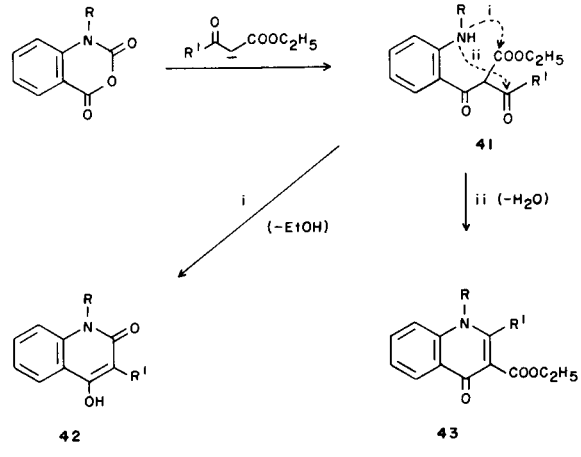


The introduction of an isocyano group (*e.g.* R_3 = $\ddot{N}=\ddot{C}$) into a system such as **38** provides the capability of an additional mode of cyclization with the adjacent hydroxyl function. When **3d** is treated with metallated ethyl isocyanoacetate, tricycle **40** is isolated directly from the reaction mixture.



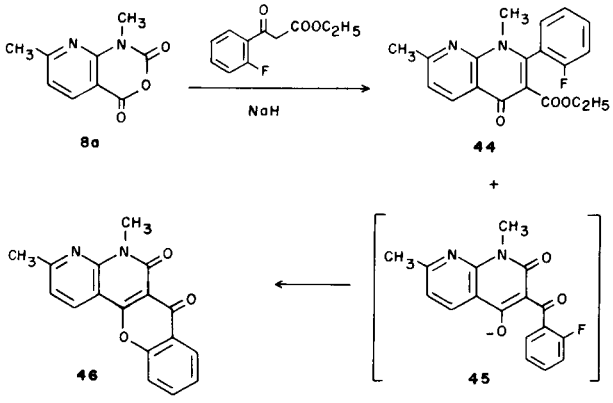
In reactions of isatoic anhydride with a carbanion containing two α substituents capable of condensation with the unmasked aromatic amino function (**41**), two modes of cyclization are possible (Scheme 5). If the reaction follows path **i** by amide formation the 2-quinolone **42** would be

Scheme 5



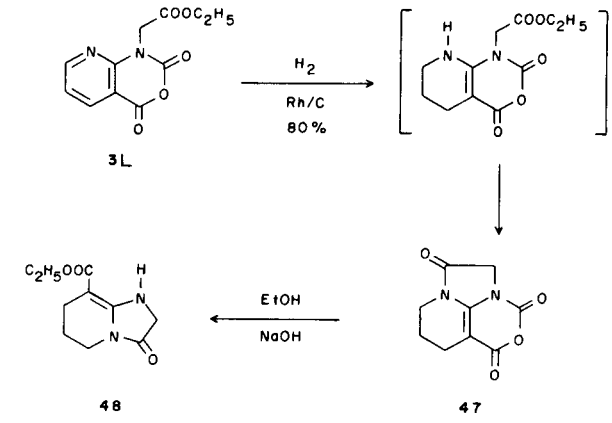
the expected product whereas dehydration as a result of cyclization by path **ii** would form the 4-quinolone **43**. In practice, when isatoic anhydrides are treated with metallated-ketoesters, both products **42** and **43** are isolated from the reaction with **43** being the major component [24].

The reaction of azaisatoic anhydride **8a** with the metallated ethyl *o*-fluorobenzoylacetate proceeds similarly to the illustrated sequence in Scheme 5 and produces products derived from each mode of cyclization. Compound **44**, isolated in 31% yield, results from a dehydrative cyclization corresponding to path **ii** whereas **46** is formed *via* path **i** which initially generates intermediate **45**. Displacement of the activated fluorine by the enolate produces the observed product **46**, isolated in 18% yield [25].

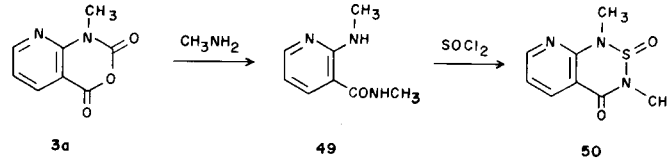


Miscellaneous Reactions.

The reduction of the pyridine ring in systems such as **12h** occurs readily as discussed earlier in this report. It was of interest to us to investigate whether such reduction can be applied to the azaisatoic anhydride system itself. When **31** is catalytically hydrogenated at 3.5 atmospheres over rhodium on carbon, reduction occurs smoothly and the reaction is complete in 2.5 hours. Analysis of the product indicates that the saturation of the pyridine ring happens as expected but that additional cyclization with the ester function occurs and what actually is isolated is the interesting tricycle **47**. Treatment of **47** with ethanol in the presence of sodium hydroxide furnishes **48** as the result of a nucleophilic attack of ethoxide at the C-4 carbonyl of the oxazine ring. It is gratifying to observe in this initial experiment the similarity of chemical reactivity of **47** as compared with *N*-substituted isatoic anhydrides or azaisatoic anhydrides, since this opens up the potential for its further elaboration into a variety of interesting products and ring systems. Investigations are presently underway to explore this territory.



The oxazine ring of *N*-methyl-3-azaisatoic anhydride (**3a**) is susceptible to attack with amines. The introduction of gaseous methylamine into a mixture of **3a** in dioxane results in the quantitative formation of the aminonicotinamide derivative **49**. Treatment of **49** with an excess of thionyl chloride produces **50**, the novel pyrido[2,3-*c*][1,2,6]-thiadiazine ring system, in 56% yield. Since half of the starting amide is used to scavenge the hydrogen chloride generated in the reaction, the yield is based on only the amount of **49** consumed. The unreacted portion of **49** is isolated from the mixture as its hydrochloride simply by filtration. The free base can be regenerated by treatment with aqueous bicarbonate.



EXPERIMENTAL

Melting points were determined on a Thomas-Hoover unimelt apparatus and are uncorrected. The infrared spectra were recorded on Perkin-Elmer Model 257 and 457 spectrophotometers. Absorption frequencies are quoted in reciprocal centimeters. Nuclear magnetic resonance spectra were determined on Varian T-60, EM-360 and Jeol FX-200 spectrometers using tetramethylsilane as an internal reference. Chemical shifts are quoted in parts per million (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet). Proton nmr spectra were taken under the following conditions; 4000 Hz sweep width, 32k data points, and 20° tip angle with a one sec. pulse delay. The mass spectra were determined on a LKB 9000 spectrometer. Carbon-13 nmr data were obtained on a Jeol FX-200 using a 10k sweep width, 16k data points, 45° tip angle, and a one second pulse delay. All samples were in 5 mm tubes at room temperature and were referenced to tetramethylsilane.

Unless otherwise stated, all solutions of organic compounds were washed with saturated sodium chloride solution and dried over sodium sulfate. No attempt has been made to optimize the yields of the described reactions.

General Procedure for the Preparation of *N*-Alkyl-3-azaisatoic Anhydrides **3** (Table 1).

Method A.

To a suspension of 0.30 mole of **2** [5] in 1ℓ of dimethylacetamide (cooled in an ice bath), under a blanket of nitrogen, was added 0.32 mole of sodium hydride (57% in mineral oil, ether washed) in portions. The mixture was allowed to warm to room temperature, stirred 1 hour, then heated at 60° for 30 minutes. After cooling to room temperature 0.34 mole of the appropriate alkyl bromide or alkyl iodide was added dropwise and the mixture was stirred at room temperature for 4 hours. The solvent was concentrated to 300 ml under reduced pressure and then poured into 500 ml of ice/water. The resulting precipitate was filtered, washed with water and dried. Analytical samples were crystallized from the solvents listed in Table 1.

Method B. 2-[4-Fluorophenyl)methylamino]-3-pyridinecarboxylic Acid (**4**).

To a stirred solution of 100 g (0.79 mole) of anhydrous potassium carbonate in 500 ml water was added 60 g (0.38 mole) of 2-chloronicotinic acid. The mixture was stirred at room temperature until a solution formed, then the water was removed under reduced pressure. A suspension of the resulting solid, 75 g (0.60 mole) of *p*-fluorobenzylamine and 5 g of copper powder in 1 ℓ of dimethylformamide was refluxed for 8 hours. The solvent was removed under reduced pressure and the residue was dissolved in water containing a small amount of 2*N* sodium hydroxide. The solution was then brought to *p*H = 7 with 2*N* hydrochloric acid. The resulting precipitate was filtered, washed successively with water, then ethanol/ether (1:1) and dried to give 35.5 g (38%) of **4**. An analytical sample was crystallized from ethanol, mp 228-231°; ir (nujol): 1635, 770 cm^{-1}; nmr (DMSO-d_6): δ 8.5 (broad, 1H, NH), 8.3-7.95 (m, 2H), 7.55-6.85 (m, 4H), 6.6 (dd, 1H), 4.65 (s, broad, 2H), COOH proton is seen as a broadening of the baseline.

Anal. Calcd. for $C_{13}H_{11}FN_2$: C, 63.4; H, 4.5; N, 11.4. Found: C, 63.3; H, 4.7; N, 11.8.

1-[(4-Fluorophenyl)methyl]-2*H*-pyrido[2,3-*d*][1,3]oxazine-2,4-(1*H*)-dione (**3d**).

To a solution of 32 g (0.30 mole) of anhydrous sodium carbonate in 600 ml water was added 21 g (0.085 mole) of **4**. The mixture was stirred at room temperature for approximately 10 minutes (until a solution formed) and then 185 ml of 12.5% phosgene in benzene (0.23 mole) was added dropwise. The mixture was stirred vigorously with a mechanical stirrer for 18 hours at room temperature. Anhydrous sodium carbonate (60 g) and additional cold water was added to the mixture to bring the *p*H to approximately 9. The resulting precipitate was filtered, washed with water and dried to give 11.2 g of **3d**. The filtrate was extracted with ethyl acetate to obtain an additional 5.2 g of crude product which was crystallized from ethanol to give 3.3 g of product (total = 14.5 g (62%)], mp 148-151°; ir (chloroform): 1790, 1740 cm^{-1}; nmr (DMSO-d_6): δ 8.8 (dd, 1H), 8.45 (dd, 1H), 7.7-6.8 (m, 5H), 5.45 (s, 2H); uv (methanol): λ max (logε) 254 (4.18), 345 (3.57).

Method C. 6-Methyl-2-methylamino-3-pyridinecarbonitrile (**6a**).

A mixture of 75 g (0.49 mole) of 2-chloro-6-methylnicotinonitrile (**5**) [26] and 200 ml of methylamine was heated in a steel vessel at 60° for 5 hours. After cooling to -65° the vessel was opened and the excess methylamine was allowed to slowly evaporate. Water and methylene chloride were added to the residue. The methylene chloride layer was separated, washed with water and dried over sodium sulfate. The solvent was concentrated on a steam bath, then ether/petroleum ether was added to furnish 50.5 g (70%) of **6a**, mp 103-106°; ir (chloroform): 3480, 2210 cm^{-1}; nmr (deuteriochloroform): δ 7.45 (d, 1H, J = 8 Hz), 6.4 (d, 1H, J = 8 Hz), 5.45-5.05 (broad, 1H, NH), 3.0 (d, 3H, J = 5 Hz), 2.4 (s, 3H).

Anal. Calcd. for $C_8H_9N_3$: C, 65.3; H, 6.2; N, 28.6. Found: C, 65.2; H, 6.2; N, 29.0.

2-Allylamino-6-methyl-3-pyridinecarbonitrile (**6b**).

A mixture of 70 g (0.46 mole) of 2-chloro-6-methylnicotinonitrile (**5**) and 150 ml of allylamine was refluxed for 4 hours, then stirred at room temperature for 18 hours. The excess allylamine was removed under reduced presure. Then 2*N* sodium hydroxide and ethyl acetate were added to the residue. The organic phase was separated and was washed with water, then saturated sodium chloride. After drying over sodium sulfate, the solvent was removed under reduced pressure to give 70 g (88%) of **6b**. An analytical sample was crystallized from methylene chloride/ether/-petroleum ether, mp 76-78°; ir (chloroform): 3440, 2220 cm^{-1}; nmr (deuteriochloroform): δ 7.5 (d, 1H, J = 8 Hz), 6.45 (d, 1H, J = 8 Hz), 6.35-5.65 (m, 1H), 5.45-5.0 (m, 3H), 4.3-4.0 (m, 2H), 2.4 (s, 3H).

Anal. Calcd. for $C_{10}H_{11}N_3$: C, 69.3; H, 6.4; N, 24.3. Found: C, 68.9; H, 6.7; N, 24.1.

1,7-Dimethyl-2*H*-pyrido[2,3-*d*][1,3]oxazine-2,4(1*H*)-dione (**8a**) (3-Aza-N,4-dimethylisatoic anhydride).

A mixture of 43 g (0.292 mole) of **6a**, 200 ml of 25% sodium hydroxide and 200 ml of ethanol was refluxed for 18 hours. The solvent was partially removed under reduced pressure until **7a** precipitated as a white solid. The crude sodium salt was not isolated and 500 ml of water was added to form a solution. After cooling in an ice bath, 800 ml of 12.5% phosgene in benzene was added dropwise while stirring vigorously with a mechanical stirrer. After addition, the ice bath was removed and the mixture stirred for 2 hours. The benzene was removed under reduced pressure and the resulting precipitate was filtered, washed with water, dried and recrystallized from methylene chloride/ether to yield 28.5 g (51%) of **8a**. An analytical sample was prepared by a second recrystallization using methylene chloride/ethanol, mp 138-141°; ir (chloroform): 1790, 1740 cm^{-1}; nmr (deuteriochloroform): δ 8.2 (d, 1H, J = 8 Hz), 7.1 (d, 1H, J = 8 Hz), 3.65 (s, 3H), 2.65 (s, 3H).

1-Allyl-7-methyl-2*H*-pyrido[2,3-*d*][1,3]oxazine-2,4(1*H*)-dione (**8b**).

A mixture of 33.8 g (0.195 mole) of **6b**, 150 ml of 25% sodium hydroxide and 150 ml of ethanol was refluxed for 5 days. The crude sodium salt (**7b**) was dissolved in 400 ml water and the solution was washed with methylene chloride. Phosgene gas was then introduced into the aqueous solution through a gas dispersion tube for 30 minutes. The resulting precipitate was filtered, washed with water, dried, and then recrystallized from methylene chloride/ether to give 10.9 g (25%) of **8b**, mp 123-125°; ir (chloroform): 1800, 1740 cm^{-1}; nmr (deuteriochloroform): δ 8.25 (d, 1H, J = 8 Hz), 7.15 (d, 1H, J = 8 Hz), 6.35-5.65 (m, 1H), 5.5-5.05 (m, 2H), 4.95-4.75(m, 2H), 2.6 (s, 3H).

General Procedure for the Preparation of Tricyclic Pyridopyrimidine Systems (**12**) (Table 2). Method D.

A mixture of 0.052 mole of **3** (Table 1), 0.058 mole of thiopseudourea **11a** [15] or **11b** [27] and 2 pellets of sodium hydroxide in 350 ml of dioxane was refluxed for 8 hours. The solvent was removed under reduced pressure and the residue dissolved in methylene chloride. The organic solution was washed with water, then extracted twice with 2*N* hydrochloric acid. The combined acid phases were washed with methylene chloride, treated with charcoal and filtered through celite. The filtrate was then made basic with cold 2*N* sodium hydroxide. The resulting precipitate was filtered, washed with water and dried. Analytical samples were crystallized from the solvents listed in Table 2. The more insoluble unsubstituted products **12a** and **12h** crystallized directly out of the cooled reaction mixture.

Method E. 2,3-Dihydro-10-phenylmethylimidazo[1,2-*a*]pyrido[2,3-*d*]pyrimidin-5(10*H*)-one (**12e**).

A suspension of 22 g (0.092 mole) of **3c**, 25 g (0.102 mole) of 2-methylthio-2-imidazoline hydroiodide and 15 g (0.108 mole) of powdered anhydrous potassium carbonate in 500 ml of toluene was refluxed for 3.5 hours. The insoluble salts were filtered off and washed twice with methylene chloride. The organic filtrate was evaporated to dryness under reduced pressure. The resulting residue was dissolved in methylene chloride, washed with water, then extracted twice with 2*N* hydrochloric acid. The combined acid phases were washed with methylene chloride, treated with charcoal, and filtered through celite. The filtrate was then made basic with cold 2*N* sodium hydroxide. The aqueous mixture was extracted with methylene chloride, washed with water, and dried over sodium sulfate.

The solvent was removed under reduced pressure to give 12.5 g (49%) of **12e**. An analytical sample was crystallized from methylene chloride/ethanol, mp 203-205°; ir (chloroform): 1680, 1640 cm^{-1}; nmr (deuteriochloroform): δ 8.5-8.05 (m, 2H), 7.55-7.1 (m, 5H), 6.9 (dd, 1H), 5.4 (s, 2H), 4.15-3.85 (m, 4H).

2-Ethylamino-1-[(4-fluorophenyl)methyl]pyrido[2,3-*d*]pyrimidin-4(1*H*)-one (**13a**).

A suspension of 15 g (0.055 mole) of **3d**, 15 g (0.061 mole) of 3-ethyl-2-methyl-2-thiopseudourea hydroiodide and 9 g (0.065 mole) of powdered anhydrous potassium carbonate in 150 ml of diglyme was refluxed for 3.5 hours. The reaction mixture was filtered while hot and the filtrate was concentrated under reduced pressure until crystallization occurred giving 6.8 g (42%) of **13a**. An analytical sample was crystallized from methanol/methylene chloride/ether, mp 249-253°; ir (nujol): 3240, 1630 cm^{-1}; nmr (DMSO-d_6): δ 8.70-8.25 (m, 2H), 7.75-7.1 (m, 6H), 5.65 (s, 2H), 3.55-3.2 (m, 2H), 1.1 (t, 3H, J = 7 Hz).

Anal. Calcd. for $C_{16}H_{15}FN_4O$: C, 64.4; H, 5.1; N, 18.8; F, 6.4. Found: C, 64.1; H, 5.2; N, 19.0; F, 6.1.

2-Allylamino-1-[(4-fluorophenyl)methyl]pyrido[2,3-*d*]pyrimidin-4(1*H*)-one (**13b**).

A suspension of 27 g (0.099 mole) of **3d**, 27.5 g (0.11 mole) of 3-allyl-2-methyl-2-thiopseudourea hydroiodide [28] and 12 g (0.11 mole) of anhydrous sodium carbonate in 250 ml acetonitrile was refluxed for 1 hour. The solvent was removed under reduced pressure and the resulting residue was suspended in methylene chloride. The insoluble material was filtered off and the filtrate was evaporated under reduced pressure. The resulting residue was dissolved in 150 ml diglyme and refluxed for 1.5 hours. Upon cooling the product crystallized giving 17.3 g (56%) of **13b**. An analytical sample was crystallized from methylene chloride/methanol/ether, mp 192-195°; ir (nujol): 3230, 1624 cm^{-1}; nmr (DMSO-d_6): δ 8.6 (dd, 1H), 8.35 (dd, 1H), 7.8 (s, broad, 1H, NH), 7.5-6.95 (m, 5H), 6.15-5.6 (m, 3H), 5.2-5.05 (m, 1H), 5.0-4.75 (m, 1H), 4.2-3.95 (m, 2H).

Anal. Calcd. for $C_{17}H_{15}FN_4O$: C, 65.8; H, 4.9; N, 18.1. Found: C, 65.9; H, 5.0; N, 18.0.

1-[[2-(4-Fluorophenyl)methylamino-3-pyridinyl]carbonyl]-4,5-dihydro-4,4-dimethyl-2-methylthio-1*H*-imidazole (**14**).

A mixture of 20 g (0.073 mole) of **3d**, 12.5 g (0.087 mole) of 2-methylthio-4,4 dimethyl-2-imidazoline [16] and 2 pellets of sodium hydroxide in 300 ml of dioxane was refluxed for 1.5 hours. The solvent was removed under reduced pressure and the residue dissolved in methylene chloride. The organic solution was washed with water, then extracted twice with 2*N* hydrochloric acid. The combined acid phases were washed with methylene chloride and then made basic with cold 2*N* sodium hydroxide. The aqueous mixture was extracted with methylene chloride. The organic phase was washed with water, treated with charcoal, dried over sodium sulfate and filtered through celite. The filtrate was concentrated on a steam bath, ethanol added, and upon cooling the product crystallized giving 13.4 g (49%) of **14**, mp 152-154°; ir (chloroform): 3415, 1650 cm^{-1}; nmr (deuteriochloroform): δ 8.15 (dd, 1H), 7.55-6.4 (m, 7H), 4.65 (d, 2H, J = 6 Hz), 3.7 (s, 2H), 2.4 (s, 3H), 1.3 (s, 6 H).

Anal. Calcd. for $C_{19}H_{21}FN_4OS$: C, 61.3; H, 5.7; N, 15.0; S, 8.6. Found: C, 60.9; H, 5.6; N, 15.1; S, 8.5.

10-[(4-Fluorophenyl)methyl]-2,3-dihydro-2,2-dimethylimidazo[1,2-*a*]pyrido[2,3-*d*]pyrimidin-5(10*H*)-one (**15**).

A mixture of 12 g (0.032 mole) of **14**, and 2 pellets of sodium hydroxide in 200 ml of diglyme was refluxed for 3 hours. The solvent was removed under reduced pressure and the residue chromatographed on a column of silica gel using chloroform to elute the product, 7 g (67%) of **15**. An analytical sample was crystallized from methylene chloride/ether/petroleum ether, mp 115-117°; ir (chloroform): 1685, 1640 cm^{-1}; nmr (deuteriochloroform): δ 8.55-8.15 (m, 2H), 7.75-7.45 (m, 2H), 7.1-6.8 (m, 3H), 5.4 (s, 2H), 3.8 (s, 2H), 1.35 (s, 6H).

Anal. Calcd. for $C_{18}H_{17}FN_4O$: C, 66.6; H, 5.3; N, 17.3; F, 5.9. Found: C, 66.5; H, 5.0; N, 17.5; F, 5.9.

7,7a,8,9,10,11-Hexahydro-5*H*-pyrido[2,3-*d*]pyrido[1′,2′-3,4]imidazo[1,2-*a*]-pyrimidin-5-one (**16**).

A mixture of 6.5 g (0.039 mole) of 3-azaisatoic anhydride (**2**), 7.0 g (0.041 mole) of 1,5,6,7,8,8a-hexahydro-3-methylthioimidazo[1,5-*a*]pyridine (**20**) [17] and 1 pellet of sodium hydroxide in 100 ml dioxane/diglyme (1:1) was refluxed for 4 hours. The reflux condenser was removed allowing the dioxane to evaporate until only diglyme remained and this mixture was refluxed an additional 0.5 hours. The reaction was then worked up in the same manner as the procedure for **14**. Crystallization of the product from methylene chloride/ether gave 1.1 g (12%) of **16**, mp 149-152°; ir (chloroform): 1680, 1620, 1595 cm^{-1}; nmr (deuteriochloroform): δ 8.7 (dd, 1H), 8.35 (dd, 1H), 7.05 (dd, 1H), 4.6-3.5 (m, 4H), 3.3-2.7 (m, 1H), 2.25-1.1 (m, 6H).

Anal. Calcd. for $C_{13}H_{14}N_4O$: C, 64.4; H, 5.8; N, 23.1. Found: C, 64.3; H, 5.6; N, 23.2.

6a,7,8,9,10,10a-Hexahydrobenzimidazo[1,2-*a*]pyrido[2,3-*d*]pyrimidin-5-(11*H*)-one (6a-*trans*) (**17**) and 6a,7,8,9,10,10a-Hexahydrobenzimidazo-[1,2-*a*]pyrido[2,3-*d*]pyrimidin-5(11*H*)-one (6a-*cis*) (**18**).

A mixture of 25 g (0.152 mole) of 3-azaisatoic anhydride (**2**), 28 g (0.164 mole) of hexahydro-2-methylthio-1*H*-benzimidazole (**21**) (*trans:cis* ratio of 66:34) [16] and 2 pellets of sodium hydroxide in 200 ml dioxane/diglyme (3:1) was refluxed for 2.5 hours. The reflux condenser was removed allowing the solvent to concentrate to approximately one-half volume. After cooling, the resulting precipitate was filtered, washed with diglyme, then ether and dried to give 22 g (60%) of a mixture of isomers **17** and **18**. Successive recrystallization from methylene chloride/ethanol and then from chloroform/ethanol yielded an analytically pure sample of the less soluble *trans* isomer **17**, mp 327-332°; ir (nujol): 1460, 1375 cm^{-1}; nmr (DMSO-d_6 + deuteriochloroform): (120°) δ 8.6 (dd, 1H), 8.25 (dd, 1H), 7.85 (s, broad, NH, 1H), 7.1 (dd, 1H), 3.7 (td, 1H), 3.3 (td, 1H), 3.15-2.8 (m, 1H), 2.25-1.25 (m, 7H).

Anal. Calcd. for $C_{13}H_{14}N_4O$: C, 64.4; H, 5.8; N, 23.1. Found: C, 64.4; H, 6.0; N, 23.2.

Further crystallization from the methylene chloride/ethanol mother liquid provided a sample of the *cis* isomer **18** (containing approximately 15% *trans* isomer **17**), mp 235-245°; nmr (deuteriochloroform): δ 9.95 (s, 1H), 8.7 (dd, 1H), 8.4 (dd, 1H), 7.1 (dd, 1H), 4.7-4.55 (m, 1H), 4.35-4.2 (m, 1H), 2.65-2.3 (m, 2H), 2.0-1.15 (m, 6H).

Anal. Calcd. for $C_{13}H_{14}N_4O$: C, 64.4; H, 5.8; N, 23.1. Found: C, 64.4; H, 5.9; N, 23.3.

6a,7,8,9,10,10a-Hexahydro-12-methylbenzimidazo[1,2-*a*]pyrido[2,3-*d*]pyrimidin-5(12*H*)-one (**19**).

A mixture of 10 g (0.056 mole) of **3a**, 10 g (0.058 mole) of **21** [16] and 1 pellet of sodium hydroxide in 100 ml diglyme was refluxed for 1 hour. The reaction was worked up in the same manner as **14** giving 12.2 of a crude yellow oil. This was chromatographed on a column of silica gel using chloroform as the eluent to afford 6.8 g (48%) of **19**. The maleate salt of **19** was formed with maleic acid in ether and was then recrystallized from methylene chloride/ether, mp 158-162°; *trans:cis* ratio of 65:35); ir (chloroform): 1715, 1650 cm^{-1}; nmr (deuteriochloroform): δ 15.3 (s, broad, 2H), 8.7 (m, 1H), 8.4 (m, 1H), 7.5 (m, 1H), 6.2 (s, 2H), 4.85 (m, *cis* isomer, 0.35H), 4.5 (m, *cis* isomer, 0.35H), 3.97 (s, *N*-methyl, *cis* isomer, 1.05 H), 3.95 (s, *N*-methyl, *trans* isomer, 1.95H), 3.93 (m, *trans* isomer, 0.65H), 3.7 (m, *trans* isomer, 0.65H), 3.1 (d, *trans* isomer, 0.65H), 2.45 (d, *cis* isomer, 0.35H), 2.35-1.3 (m, 7H).

Anal. Calcd. for $C_{18}H_{20}N_4O_5$: C, 58.1; H, 5.4; N, 15.1. Found: C, 58.2; H, 5.7; N, 15.0.

2-(4-Fluorophenyl)methylamino-*N*-(methylamino)(methylthio)methylene-3-pyridinecarboxamide (**22**).

A suspension of 5.0 g (0.0183 mole) of **3d**, 4.4 g (0.0189 mole) of 2,3-dimethyl-2-thiopseudourea hydroiodide and 2.1 g (0.0198 mole) of anhydrous sodium carbonate in 75 ml of acetonitrile was refluxed for 1 hour. The solvent was removed under reduced pressure and the resulting

residue was suspended in methylene chloride. The insoluble salts were filtered off through celite. The filtrate was concentrated under reduced pressure and methanol was added. Upon cooling in a dry ice/acetone bath the product crystallized to give 4.3 g (75%) of **22**, mp 84-86°; ir (chloroform): 3310, 3200, 1600 cm^{-1}; nmr (deuteriochloroform): δ 10.9 (broad, 1H, NH), 9.15 (broad, 1H, NH), 8.6 (dd, 1H), 8.25 (dd, 1H), 7.5-6.8 (m, 4H), 6.55 (dd, 1H), 4.73 (d, 2H, J = 5 Hz), 2.95 (d, 3H, J = 5 Hz), 2.37 (s, 3H).

Anal. Calcd. for $C_{16}H_{17}FN_4OS$: C, 57.8; H, 5.2; N, 16.9; S, 9.6. Found: C, 57.7; H, 5.2; N, 16.8; S, 9.5.

1-[(4-Fluorophenyl)methyl]-2-methylaminopyrido[2,3-*d*]pyrimidin-4-(1*H*)-one (**23**).

A solution of 32 g (0.096 mole) of **22** in 150 ml diglyme was refluxed for 2.5 hours. The reaction mixture was cooled in an ice bath and the resulting precipitate was filtered, washed with diglyme, then ether and dried to give 19.2 g (70%) of **23**. An analytical sample was crystallized from methanol/methylene chloride/ether, mp 242-246°; ir (nujol): 3240, 1630 cm^{-1}; nmr (DMSO-d_6): δ 8.5 (dd, 1H), 8.3 (dd, 1H), 7.6-7.0 (m, 6H), 5.55 (s, 2H), 2.85 (s, 3H).

Anal. Calcd. for $C_{15}H_{13}FN_4O$: C, 63.4; H, 4.6; N, 19.7; F, 6.7. Found: C, 63.6; H, 4.7; N, 19.7; F, 6.3.

1-[(4-Fluorophenyl)methyl]-2,3-dihydro-3-methyl-2-methyliminopyrido[2,3-*d*]pyrimidin-4-(1*H*)-one (**24**).

A mixture of 6.8 g (0.025 mole) of **3d**, 3.4 g (0.032 mole) of 1,2,3-trimethyl-2-thiopseudourea and 2 pellets of sodium hydroxide in 100 ml dioxane were refluxed for 6 hours. The reaction was worked up in the same manner as in the procedure for **14** giving 2.5 g of crude product which was crystallized from ethanol to yield 1.3 (18%) [29] of **24**, mp 112-114°; ir (chloroform): 1695, 1655, 1610 cm^{-1}; nmr (deuteriochloroform): δ 8.4-8.05 (m, 2H), 7.3-6.65 (m, 5H), 5.45 (s, 2H), 3.42 (s, 3H), 3.3 (s, 3H); uv (methanol): λ max (log ε) 246 (4.19), 329 (3.60).

Anal. Calcd. for $C_{16}H_{15}FN_4O$: C, 64.4; H, 5.1; N, 18.8; F, 6.4. Found: C, 64.1; H, 5.2; N, 18.7; F, 6.2.

2-Dimethylamino-1-[(4-fluorophenyl)methyl]pyrido[2,3-*d*]pyrimidin-4-(1*H*)-one (**25**).

To a suspension of 10.0 g (0.035 mole) of **24** in 300 ml tetrahydrofuran was added 4.3 g (0.038 mole) of potassium *t*-butoxide in portions. The mixture was stirred at room temperature for 45 minutes, then 6.0 g (0.042 mole) of methyl iodide was added and the reaction was stirred for 24 hours. The precipitated potassium iodide was filtered off and the filtrate was evaporated to dryness under reduced pressure. The resulting residue was dissolved in methylene chloride and washed with water. The organic phase was dried over sodium sulfate, then chromatographed on a column of silica gel using chloroform to elute the product, 6.8 g (65%) of **25**. An analytical sample was crystallized from methylene chloride/ether, mp 170-172°; ir (chloroform): 1640, 1595 cm^{-1}, nmr (deuteriochloroform): δ 8.7-8.38 (m, 2H), 7.44-6.76 (m, 5H), 5.55 (s, 2H), 3.12 (s, 6H); uv (methanol): λ max (log ε) 246 (4.26), 273 (3.93), 278 (3.94), 308 (4.00).

Anal. Calcd. for $C_{16}H_{15}FN_4O$: C, 64.4; H, 5.1; N, 18.8; F. 6.4. Found: C, 64.5; H, 5.2; N, 19.3; F, 6.3.

11-Ethyl-2,3,4,11-tetrahydro-6*H*-pyrido[2,3-*d*]pyrimido[1,2-*a*]pyrimidin-6-one (**30**).

To a suspension of 12 g (0.059 mole) of **12h** in 250 ml dimethylacetamide, under a blanket of nitrogen, was added 3 g (0.071 mole) of sodium hydride (57% in mineral oil, ether washed) in portions. The mixture was stirred at room temperature for 1 hour during which time a brown solution formed. Then 11.5 g (0.074 mole) of ethyl iodide was added dropwise and the mixture was stirred at room temperature for 18 hours. The reaction was poured into 250 ml ice/water and then extracted three times with ethyl acetate. The combined organic phases were washed with water and dried over sodium sulfate. The solvent was removed under reduced pressure and the residue was chromatographed on a column of silica gel using chloroform as eluent to obtain 3.6 g (26%) of **30**. An analytical sample was crystallized from methylene chloride/ether, mp 98-101°; ir (chloroform): 1680, 1630 cm^{-1}; nmr (deuteriochloroform): δ 8.52 (dd, 1H), 8.28 (dd, 1H), 6.95 (dd, 1H), 4.35 (q, 2H, J = 7 Hz), 3.98 (t, 2H, J = 6 Hz), 3.6 (t, 2H, J = 6 Hz), 2.04-1.76 (m, 2H), 1.25 (t, 3H, J = 7 Hz); uv (methanol): λ max (log ε) 213 (4.29), 221 (4.27), 249 (4.06).

Anal. Calcd. for $C_{12}H_{14}N_4O$: C, 62.6; H, 6.1; N, 24.3. Found: C, 62.4; H, 6.4; N, 24.1

2,3,6,7-Tetrahydro-9-oxo-1*H*,5*H*,9*H*-pyrido[2,3-*d*]pyrimido[1,2,3-*ij*]-pyrimido[1,2-*a*]pyrimidin-4-ium Bromide (**31**).

To a suspension of 2.1 g (0.0498 mole) of sodium hydride (57% in mineral oil, ether washed) in 200 ml dimethylacetamide, under a blanket of nitrogen, was added 9 g (0.0445 mole) of **12h** in portions. The mixture was stirred at room temperature for 15 minutes, then heated at 60° for 1 hour. Next, 18 g (0.0895 mole) of 1,3-dibromopropane was added. Then the temperature was raised to 70° for 1 hour. A precipitate formed, which, after cooling, was filtered, washed with ether and dried to give 7.3 g (50%) of crude **31** [30], mp 247-252° dec; ir (nujol): 1705, 1635 cm^{-1}; nmr (deuterium oxide): δ 8.65 (dd, 1H), 8.4 (dd, 1H), 7.4 (dd, 1H), 4.65-3.55 (m, 6H), 2.5-1.95 (m, 4H).

2,3,6,7-Tetrahydro-1*H*,5*H*,9*H*,14a*H*-pyrido[2,3-*d*]pyrimido[1,2,3-*ij*]pyrimido[1,2-*a*]pyrimidin-9-one (**32**).

To a solution of 0.5 g (13.1 mmoles) of sodium borohydride in 20 ml of ethanol/water (4:1), cooled to -25°, was added dropwise a solution of 1.5 g (4.6 mmoles) of **31** in 30 ml ethanol/water (1:1) at such a rate to keep the temperature between -15° to -20°. After addition was complete the reaction was allowed to warm to room temperature and was stirred for 48 hours. The solvent was removed under reduced pressure and the resulting solid was suspended in methylene chloride. After filtering though celite and drying over sodium sulfate, the methylene chloride solution was concentrated on a steam bath. Ether/petroleum ether was then added to furnish 0.7 g (62%) of **32**, mp 158-160°; ir (chloroform): 1660, 1600 cm^{-1}; nmr (deuteriochloroform): δ 8.32-8.02 (m, 2H), 6.7 (dd, 1H), 5.22-4.62 (m, 3H), 3.15-1.3 (m, 10H).

Anal. Calcd. for $C_{13}H_{16}N_4O$: C, 63.9; H, 6.6; N, 22.9. Found: C, 63.7; H, 6.5; N, 23.0.

1,2,3,4,7,8,9,10-Octahydro-6*H*-pyrido[2,3-*d*]pyrimido[1,2-*a*]pyrimidin-6-one (**33**).

A mixture of 10 g (0.0495 mole) of **12h** and 3 g of 5% rhodium on carbon in 100 ml glacial acetic acid was hydrogenated at room temperature at 3.5 atmospheres for 2 days. The catalyst was filtered off through celite and the solvent was removed under reduced pressure. The resulting residue was chromatographed on a short column of silica gel using chloroform to elute the product, 7.7 g (76%) of **33**. An analytical sample was crystallized from methanol/chloroform, mp 270-276°; nmr (deuteriochloroform/deuteriomethanol): δ 3.9 (t, 2H), 3.4 (t, 2H), 3.3 (t, 2H), 2.45 (t, 2H), 2.0 (m, 2H), 1.8 (m, 2H). (The two exchangeable H's are not visible in deuteriomethanol.) (For ^1H and ^{13}C nmr assignments, see Table 3); uv (methanol): λ max (log ε): 227 (4.44), 283 (4.09).

Anal. Calcd. for $C_{10}H_{14}N_4O$: C, 58.2; H, 6.9; N, 27.2. Found: C, 58.0; H, 7.4; N, 27.1.

1,2,3,4,7,8,9,10-Octahydro-1-methyl-6*H*-pyrido[2,3-*d*]pyrimido[1,2-*a*]-pyrimidin-6-one (**34a**).

To an ice cold suspension of 1.5 g (0.031 mole) sodium hydride (50% in mineral oil, ether washed) in 50 ml dimethylacetamide, under a blanket of nitrogen, was added 6.0 g (0.029 mole) of **33** in portions. The mixture was allowed to warm to room temperature, and stirring was continued for an additional 15 minutes. Then 4.3 g (0.030 mole) of methyl iodide was added dropwise resulting in an exothermic reaction and formation of a precipitate. The mixture was stirred at room temperature for 18 hours then poured into 200 ml ice/water. The resulting precipitate was filtered, washed with water and dried to give 2.0 g (31%) of **34a**. An analytical sample was crystallized from methylene chloride/ether, mp 262-270°; ir (chloroform): 3450, 1640 cm^{-1}; nmr (DMSO-d_6): δ 4.60 (s, 1H, NH), 3.96 (t,

2H), 3.4-3.25 (m, 4H), 3.08 (s, 3H, NCH_3), 2.50 (t, 2H), 2.03 (m, 2H), 1.85 (m, 2H); (for ^1H and ^{13}C nmr assignments, see Table 3); uv (methanol): λ max (log ε): 233 (4.46), 285 (4.10).

Anal. Calcd. for $C_{11}H_{16}N_4O$: C, 60.0; H, 7.3; N, 25.4. Found: C, 60.1; H, 7.6; N, 25.0.

1,2,3,4,7,8,9,10-Octahydro-1-(2-dimethylaminoethyl)-6*H*-pyrido-[2,3-*d*]pyrimido[1,2-*a*]pyrimidin-6-one (**34b**).

Using the procedure for **34a**, 6.0 g (0.029 mole) of **33**, 4.0 g (0.083 mole) of sodium hydride (50% in mineral oil) and 6.0 g (0.042 mole) of 2-chloro-*N*,*N*-dimethylethylamine hydrochloride yielded 3.0 g (37%) of **34b**, mp 178-181°; ir (chloroform): 3480, 1640 cm^{-1}; nmr (deuteriochloroform): δ 4.6 (s, 1H, broad), 4.05-3.1 (m, 9H), 2.5 (t, 3H), 2.3 (s, 6H), 2.15-1.7 (m, 4H).

Anal. Calcd. for $C_{14}H_{23}N_5O$: C, 60.6; H, 8.4; N, 25.3. Found: C, 60.7; H, 8.4; N, 25.1.

1,2,3,4,7,8,9,10-Octahydro-1-[2-(2-chloroethoxyethyl)]-6*H*-pyrido[2,3-*d*]-pyrimido[1,2-*a*]pyrimidin-6-one (**34c**).

Using the procedure for **34a**, 8.0 g (0.039 mole) of **33**, 2.3 g (0.048 mole) of sodium hydride (50% in mineral oil) and 6.0 g (0.042 mole) of 2-chloroethyl ether gave 5.9 g of crude product. Chromatography on a short column of silica gel using chloroform as the eluent yielded 2.5 g (21%) of **34c**, mp 83-90°; ir (chloroform): 3470, 1640 cm^{-1}; nmr (deuteriochloroform): δ 4.65 (s, 1H, NH), 3.95 (t, 2H), 3.75-3.15 (m, 12H), 2.5 (t, 2H), 2.2-1.6 (m, 4H).

Anal. Calcd. for $C_{14}H_{21}ClN_4O_2$: C, 53.7; H, 6.8; N, 17.9. Found: C, 53.4; H, 6.5; N, 17.5.

1,2,3,4,7,8,9,10-Octahydro-1,10-dimethyl-6*H*-pyrido[2,3-*d*]pyrimido[1,2-*a*]-pyrimidin-6-one (**35**).

To a solution of 6 g (0.027 mole) of **34a** in 100 ml dimethylacetamide, under a blanket of nitrogen, was added 2 g (0.041 mole) of sodium hydride (50% in mineral oil, ether washed) in portions. The mixture was stirred at room temperature for 15 minutes, then 5 g (0.035 mole) of methyl iodide was added dropwise and the mixture was stirred at room temperature for 18 hours. The solvent was removed under reduced pressure and ice/water was added to the residue. The aqueous mixture was extracted with ethyl acetate, washed with water and dried over sodium sulfate. The solvent was removed under reduced pressure and the resulting solid was recrystallized from methylene chloride/ether to give 1.2 g (19%) of **35**, mp 163-167°; ir (chloroform): 1640 cm^{-1}; nmr (deuteriochloroform): δ 4.05-3.8 (m, 2H), 3.5-2.95 (m, 4H), 3.1 (s, 3H), 3.05 (s, 3H), 2.5 (t, 2H), 2.2-1.6 (m, 4H).

Anal. Calcd. for $C_{12}H_{18}N_4O$: C, 61.5; H, 7.8; N, 23.9. Found: C, 61.5; H, 7.4; N, 23.9.

1-[(2-Methylamino)-3-pyridinyl]-2-nitroethanone (**36a**).

A mixture of 10.0 g of **3a**, 5.3 g of nitromethane, and 10.6 g of anhydrous potassium carbonate in 150 ml of dimethyl sulfoxide was stirred at room temperature for 5 hours. The reaction was poured into cold water. The mixture was washed with methylene chloride (3x) and the aqueous phase was neutralized with 2*N* hydrochloric acid. The resulting precipitate was filtered and then chromatographed on a column of silica gel using chloroform to elute the product, 4.5 g (41%) of **36a**. An analytical sample was crystallized from methylene chloride/ethanol, mp 156-159°; ir (chloroform): 3370, 1655, 1560 cm^{-1}; nmr (deuteriochloroform): δ 8.7 (s, broad, 1H, NH), 8.45 (dd, 1H), 7.65 (dd, 1H), 6.4 (dd, 1H), 5.85 (s, 2H, CH_2), 3.1 (d, 3H, J = 5 Hz).

Anal. Calcd. for $C_8H_9N_3O_3$: C, 49.2; H, 4.7; N, 21.5. Found: C, 49.3; H, 4.6; N, 21.3.

1-[(6-Methyl-2-methylamino)-3-pyridinyl]-2-nitroethanone (**36b**).

Following the procedure for **36a**, 6.0 g of **8a**, 3.0 g of nitromethane, and 6.1 g of anhydrous potassium carbonate furnished 4.1 g (63%) of essentially pure **36b**. An analytical sample was crystallized from ethyl acetate, mp 209-212° dec; ir (nujol): 3365, 1655, 1590 cm^{-1}; nmr (DMSO-d_6): δ 8.55 (s, broad, 1H, NH), 7.87 (d, 1H, J = 8 Hz), 6.52 (d, 1H, J = 8 Hz), 6.24 (s, 2H), 3.0 (d, 3H, J = 5 Hz), 2.4 (s, 3H).

Anal. Calcd. for $C_9H_{11}N_3O_2$: C, 51.7; H, 5.3; N, 20.1. Found: C, 51.3; H, 5.7; N, 20.4.

1-[(6-Methyl-2-[(2-propenyl)amino]-3-pyridinyl]-2-nitroethanone (**36c**).

Following the procedure for **36a**, 2.4 g of **8b**, 0.8 g of nitromethane, and 1.7 g of anhydrous potassium carbonate were allowed to react for 24 hours to give 0.3 g (12%) of **36c**. An analytical sample was crystallized from methylene chloride/ether/pentane, mp 98-100°; ir (chloroform): 3360, 1660 cm^{-1}; nmr (deuteriochloroform): δ 8.6 (s, broad, 1H, NH), 7.55 (d, 1H, J = 8 Hz), 6.47 (d, 1H, J = 8 Hz), 6.22-5.7 (m, 1H), 5.8 (s, 2H), 5.45-5.01 (m, 2H), 4.4-4.12 (m, 2H), 2.47 (s, 3H).

Anal. Calcd. for $C_{11}H_{13}N_3O_3$: C, 56.2; H, 5.6; N, 17.9. Found: C, 56.5; H, 6.1; N, 17.9.

General Procedure for the Preparation of Compounds **38** (Table 4). Compounds **38a-38d**.

To a solution of 0.051 mole of diethyl malonate in 100 ml of dimethylacetamide was added 0.052 mole of sodium hydride in portions. When the evolution of hydrogen ceased, the mixture was placed in an oil bath at 120°. Then a solution of 0.05 mole of the appropriately substituted **3** or **8** in 80 ml of dimethylacetamide was added dropwise. The mixture was then allowed to stir at 120° for 18 hours. Approximately one-half of the solvent was removed under reduced pressure and the resulting precipitate was filtered. The solid was washed with ether then was dissolved in water. Acidification with 6*N* hydrochloric acid furnished the product which was filtered, washed with water, and recrystallized from the solvents listed in Table 4.

Sample Spectra **38a**; ir (nujol): 1690, 1620 cm^{-1}; nmr (deuteriochloroform): δ 15.5 (s, 1H, OH), 8.5-8.25 (m, 2H), 7.3-7.05 (m, 1H), 4.52 (q, 2H), 3.77 (s, 3H), 1.48 (t, 3H).

Compounds **38e-38g**

To a solution of 0.0255 mole of ethyl nitroacetate in 50 ml of dimethylacetamide was added 0.0256 mole of sodium hydride. After the addition was complete, the mixture was stirred at room temperature for 30 minutes then was placed in an oil bath at 80°. Then a solution of 0.025 mole of **3a**, **3f**, or **8a** in 75 ml of dimethylacetamide was added all at once. The temperature of the oil bath was raised to 120° and the mixture was stirred at that temperature for 18 hours. The reaction was worked-up as described above.

Sample Spectra **38g**; ir (potassium bromide): 1670, 1600 cm^{-1}; nmr (deuteriochloroform + DMSO-d_6): δ 11.1 (s, 1H, OH), 8.3 (d, 1H, J = 9 Hz), 7.12 (d, 1H, J = 9 Hz), 3.75 (s, 3H), 2.65 (s, 3H).

4-Hydroxy-1-methyl-1,8-naphthyridin-2(1*H*)-one (**39**).

A mixture of 2.8 g of **38a** in 40 ml of 2*N* sodium hydroxide was refluxed for 1 hour. The resulting solution was cooled in an ice bath then was acidified with 2*N* hydrochloric acid. The resulting precipitate was filtered, washed with water, and dried to give 1.9 g (98%) of **39**. An analytical sample was crystallized from methanol, mp 308-310° dec; nmr (DMSO-d_6): δ 11.5 (s, broad, 1H, OH); 8.55 (m, 1H), 8.1 (m, 1H), 7.2 (m, 1H), 5.88 (s, 1H), 3.54 (s, 3H).

Anal. Calcd. for $C_9H_8N_2O_2$: C, 61.4; H, 4.6; N, 15.9. Found: C, 61.8: H, 4.6; N, 16.3.

5-[(4-Fluorophenyl)methyl]isoxazolo[4,5-*c*][1,8]naphthyrimidin-4(5*H*)-one (**40**).

To a solution of 4.5 g (0.039 mole) of ethyl isocyanoacetate in 100 ml of dimethylacetamide was added 1.9 g (0.39 mole) of sodium hydride (50%, pentane washed) in portions. When the evolution of hydrogen ceased a solution of 10 g (0.036 mole) of **3d** in 100 ml dimethylacetamide was added all at once. The mixture was then placed in an oil bath at 50°, and the temperature was raised slowly to 120° over a period of 30 minutes and then kept there for 4 hours. The solvent was removed under reduced pressure and water was added to the residue. The resulting precipitate

was filtered, washed with water, dried, and was crystallized from methylene chloride/ether. The product was further recrystallized from methylene chloride/ethanol to yield 2.7 g (25%) of **40**, mp 177-184°; ir (chloroform): 1680 cm^{-1}; nmr (deuteriochloroform): δ 8.65 (dd, 1H), 8.2 (dd, 1H), 8.15 (s, 1H), 7.7-6.7 (m, 5H), 5.8 (s, 2H).

Anal. Calcd. for $C_{16}H_{10}FN_3O_2$: C, 65.1; H, 3.4; N, 14.2. Found: C, 64.8; H, 3.7; N, 13.9.

3,5-Dimethyl-1-benzopyrano[3,2-*c*][1,8]naphthyridine-6,7(5*H*)-dione (**46**).

To a solution of 11 g (0.052 mole) of ethyl *o*-fluorobenzoylacetate in 100 ml of dimethylacetamide was added 2.5 g (0.052 mole) of sodium hydride (50%, ether washed) in portions. When the evolution of hydrogen ceased, the mixture was placed in an oil bath and the temperature slowly raised to 120°. A solution of 10 g (0.052 mole) of **8a** in 80 ml of dimethylacetamide was then added dropwise and the mixture was stirred at 120° for 8 hours. Upon cooling, the more insoluble product **46** precipitated from the reaction mixture. The solid was filtered, washed with ethanol, then with ether and dried to give 2.7 g (18%) of **46**. An analytical sample was crystallized from methylene chloride/ethanol, mp 286-289°; ir (nujol): 1690, 1635 cm^{-1}; nmr (deuteriochloroform): δ 8.5-8.1 (m, 2H), 7.75-7.0 (m, 4H), 3.75 (s, 3H), 2.65 (s, 3H).

Anal. Calcd. for $C_{17}H_{12}N_2O_2$: C, 69.9; H, 4.1; N, 9.6. Found: C, 69.6; H, 4.6; N, 9.5.

2-(2-Fluorophenyl)-1,4-dihydro-1,7-dimethyl-4-oxo-1,8-naphthyridine-3-carboxylic Acid Ethyl Ester (**44**).

After filtration of the less soluble product **46** from the above reaction mixture, the dimethylacetamide filtrate was evaporated under reduced pressure. The residue was chromatographed on a column of silica gel to obtain 5.5 g (31%) of **44**. An analytical sample was crystallized from methylene chloride/ether, mp 134-137°; ir (chloroform): 1730, 1610 cm^{-1}; nmr (deuteriochloroform): δ 8.55 (d, 1H, J = 8 Hz), 7.6-7.0 (m, 5H), 3.95 (q, 2H), 3.7 (s, 3H), 2.65 (s, 3H), 0.9 (t, 3H).

Anal. Calcd. for $C_{10}H_{17}N_2O_3F$: C, 67.0; H, 5.0; N, 8.2. Found: C, 67.4; H, 5.3; N, 8.2.

7,8-Dihydro-3*H*,5*H*,6*H*-4-oxa-2a,8a-diazaacenaphthylene-1,3,5(2*H*)-trione (**47**).

A mixture of 20 g (0.08 mole) of **31** and 3 g of 5% rhodium on carbon in 200 ml glacial acetic acid was hydrogenated at room temperature at 3.5 atmospheres for 2.5 hours. The catalyst was filtered off through celite and the solvent removed under reduced pressure. The residue was crystallized from methylene chloride/ether to yield 13.3 g (80%) of **47**, mp 233-236°; nmr (DMSO-d_6): δ 4.43 (s, 2H), 3.58 (t, 2H, J = 5 Hz), 2.32 (t, 2H, J = 5 Hz), 2.1-1.6 (m, 2H).

Anal. Calcd. for $C_9H_8N_2O_4$: C, 51.9; H, 3.9; N, 13.5. Found: C, 51.7; H, 4.2; N, 13.4.

1,2,3,5,6,7-Hexahydro-3-oxoimidazo[1,2-*a*]pyridine-8-carboxylic Acid Ethyl Ester (**48**).

A suspension of 2.0 g of **47** and 1 pellet of sodium hydroxide in 30 ml absolute ethanol was refluxed for 1 hour during which time a dark colored solution formed. Upon cooling the resulting precipitate was filtered, washed with ethanol, and recrystallized from methylene chloride/ethanol to yield 1.0 g (50%) of **48**, mp 140-143°; ir (chloroform): 3400, 1740 cm^{-1}; nmr (deuteriochloroform): δ 7.25 (s, broad, 1H, NH), 4.13 (q, 2H), 4.02 (s, 2H), 3.55 (t, 2H), 2.4 (t, 2H), 2.05-1.55 (m, 2H), 1.3 (t, 3H).

Anal. Calcd. for $C_{10}H_{14}N_2O_3$: C, 57.1; H, 6.7; N, 13.3. Found: C, 56.9; H, 6.7; N, 13.0.

N-Methyl-2-methylamino-3-pyridinecarboxamide (**49**).

Into a solution of 10.0 g of **3a** in 300 ml of dioxane was bubbled anhydrous methylamine for 30 minutes. The solvent was removed under reduced pressure and the residue was dissolved in methylene chloride. After treatment with charcoal, the solvent was removed under reduced pressure to give 9.5 g (100%) of **49** as an oil. The material was used in the next step without further purification; ir (chloroform): 3480, 3375, 1655, 1585, 1525 cm^{-1}; nmr (deuteriochloroform): δ 8.2 (dd, 1H), 8.0 (m, broad, 1H, NH), 7.55 (dd, 1H), 6.5 (m, broad, 1H, NH), 6.42 (dd, 1H), 3.02 (d, 3H), 2.92 (d, 3H).

1,2-Dihydro-1,3-dimethylpyrido[2,3-*d*][1,3,2]thiadiazine-4(3*H*)-one (**50**).

A mixture of 10.0 g of **49** and 7.5 g of thionyl chloride in 250 ml of benzene was refluxed for 18 hours. The insoluble material which formed was filtered and the filtrate was washed with saturated sodium chloride. The organic phase was dried over sodium sulfate and the solvent was removed under reduced pressure. The resulting solid was sublimed at 105-110° (0.3 mm) to give 3.6 g (56% based on the amount of **49** consumed) of **50**, mp 107-109°; ir (chloroform): 1678 cm^{-1}; nmr (deuteriochloroform): δ 8.65-8.3 (m, 2H), 7.1 (dd, 1H), 3.53 (s, 3H), 3.4 (s, 3H).

Anal. Calcd. for $C_8H_9H_3O_2S$: C, 45.5; H, 4.3; N, 19.9; S, 15.2. Found: C, 45.5; H, 4.3; N, 20.0; S, 15.6.

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[1] Review: G. M. Coppola, *Synthesis*, 505 (1980).

[2] Review: T. Kappe and W. Stadlbauer, "Advances in Heterocyclic Chemistry", Vol 28, Academic Press, New York, NY, 1981, p 127.

[3] Throughout this paper the name 3-azaisatoic anhydride will be used for compounds of general structure **2**. The chemical abstracts nomenclature for this compound is 2*H*-pyrido[2,3-*d*][1,3]oxazine-2,4(1*H*)-dione.

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[16] G. E. Hardtmann, G. Koletar, O. R. Pfister, J. H. Gogerty and L. C. Iorio, *J. Med. Chem.*, **18**, 447 (1975).

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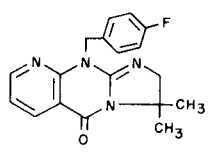
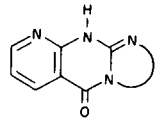
[20] In Structure **15**, the gem-dimethylgroup is shown at position 2. Although the spectrum shows only one isomer, the structure where the methyl groups reside in the 3 position cannot be totally ruled out.

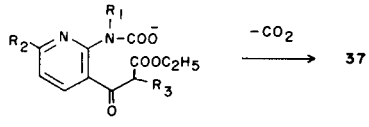


[21] The most likely tautomer for this system is as shown although the surprising results of alkylations of these systems (described in the text) may indicate that the double bond remains in the imidazoline ring (shown below) or is in equilibrium between the two.



[22]D. K. Dalling, D. M. Grant and E. G. Paul, *J. Am. Chem. Soc.*, **95**, 3718 (1973).

[23] The initial intermediate formed from the nucleophilic attack at the C-4 carbonyl of the oxazine ring is an *N*-carboxy-β-ketoester which spontaneously decarboxylates to give **37**.



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[25] Tetracycles similar to **46**, but lacking the nitrogen of the pyridine ring have been synthesized by the reaction of an isatoic anhydride with ethyl *o*-fluorobenzoylacetate (ref [11]). In that series we were only interested in the very insoluble product which crystallized directly from the reaction mixture. No detailed study was made on the remainder of the mixture to determine if the 4-quinolone derived from path **ii** was present.

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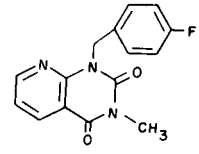
[29] The majority of product **24** hydrolyzed upon workup to the pyridopyrimidinedione (shown below) which was isolated in 30% yield, mp 146-148°; ir (chloroform): 1715, 1670 cm^{-1}; nmr (deuteriochloroform): δ 8.6 (dd, 1H), 8.35 (dd, 1H), 7.6-6.7 (m, 5H), 5.47 (s, 2H), 3.45 (s, 3H).

Anal. Calcd. for $C_{15}H_{12}FN_3O_2$: C, 63.1; H, 4.2; N, 14.7; F, 6.7. Found: C, 63.1; H, 4.4; H, 15.1; F, 6.5.



[30] No attempt was made to further purify **31** which was subsequently reduced to product **32**.