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Nucleophilic Reaction upon Electron-Deficient Pyridone Derivatives. XIII.[1) Regioselective Synthesis of 2-Substituted 3-Nitropyridines by One-Pot Reaction of Either 4- or 6-Substituted 1-Methyl-3,5-dinitro-2-pyridones with Ketones and Ammonia

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A one-pot synthesis of 2-substituted 3-nitropyridines was developed by a ring transformation of 6- or 4-substituted 1-methyl-3,5-dinitro-2-pyridones (**2** or **3**) with ammonia and enamines derived from ketones. Some intermediates having a 2,6-diazabicyclo[3.3.1]nonane skeleton were isolated from reactions of **3**. The ring transformation proceeds via an addition-addition-elimination-elimination mechanism. Few competitive isomeric by-products, 4-substituted 3-nitropyridines and 4-nitroanilines, were formed. All the **2** substrates showed good reactivity, but the **3** substrates having electron-withdrawing substituents were less reactive and selective. 1,4,6-Trimethyl-3,5-dinitro-2-pyridone did not gave any products. The selectivity is interpreted in terms of differences of thermodynamic (main selection rule B) and kinetic stability (minor selection rule A) between the possible bicyclic intermediates which are expected to be formed via the mechanism.

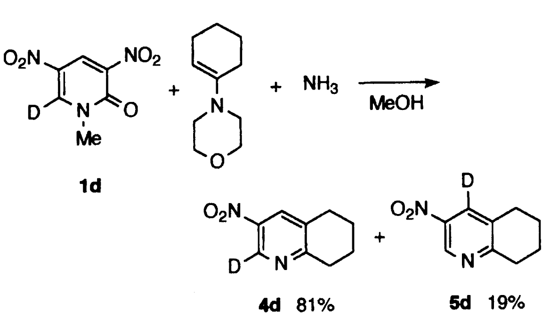
Nitropyridines are important intermediates in syntheses of heterocyclic compounds, dyes and pharmaceutical products.[2) Whereas 4-nitropyridines can be easily obtained by nitration of the N-oxides and subsequent reduction, 3-nitro derivatives are difficult to obtain by nitration of the parent pyridines.[3)

Recently we reported a novel one-pot synthesis of 5-, 6-, and 5,6-disubstituted 3-nitropyridines by ring transformation of 1-methyl-3,5-dinitro-2-pyridone (**1**) with aldehydes, methyl ketones, and ketones having α-methylene group in the presence of ammonia.[4) In this reaction, **1** provides the C(2)–C(4) moiety of the 3-nitropyridine and the ketones or the aldehydes provide the C(5)–C(6) one.

A similar synthesis of 3-nitropyridine was reported using nitromalonaldehyde as the corresponding three carbon building block.[5) The two reagents are just complementary to each other in the synthesis of 3-nitropyridines. Thus nitromalonaldehyde reacts with only β-diketones[5a) or β-keto esters,[5b) while **1** reacts with only simple ketones or aldehydes. In the efforts to prepare 2- and/or 4-substituted 3-nitropyridines, Zaichenko reported a reaction of 2-nitro-3-oxobutanal with ethyl acetoacetate and ammonia to give a 2-methyl-3-nitropyridine derivative.[6) However, 2-nitro-3-oxobutanal does not react with simple ketones or aldehydes as well as nitromalonaldehyde.

The following facts suggested that 6- and 4-substituted 1-methyl-3,5-dinitro-2-pyridones (**2** and **3**) might be good reagents for the synthesis of 2- and 4-substituted 3-nitropyridines, because **2** and **3** were stable and easily prepared by nitration of the corresponding 1-methyl-2-pyridones which were readily available via various routes.[7) Previously we had found that 6-deuterio-1-methyl-3,5-dinitro-2-pyridone (**1d**) gave 2-deuterio-3-nitropyridine (**4d**) as a main product and its 4-deuterio isomer **5d** as a by-product (Eq. 1).[4) Obviously, the 3-nitropyridines **4d** and **5d** are formed via two different reaction courses. The main course is that the ammonia nitrogen and the enamine α-carbon attack at the C_6 and the C_4 positions of the dinitropyridone **1**, respectively, to give **4d**. The minor course is that the nucleophiles attack the alternative electrophilic sites to give **5d**. We call the fact that the former course is preferred over the latter one selection rule A. If such a selection rule would also work with 6-substituted 1-methyl-3,5-dinitro-2-pyridone (**2**) and 4-substituted one (**3**), **2** and **3** would selectively give 2-substituted 3-nitropyridines (**4**) and 4-substituted ones (**5**), respectively.

Now, we wish to report unexpected selective formation of 2-substituted 3-nitropyridines (**4**) by reactions of both **2** and **3** with ketones and ammonia. Scope and limitation of the 3-nitropyridine synthesis and mechanism of the selectivity are also described.



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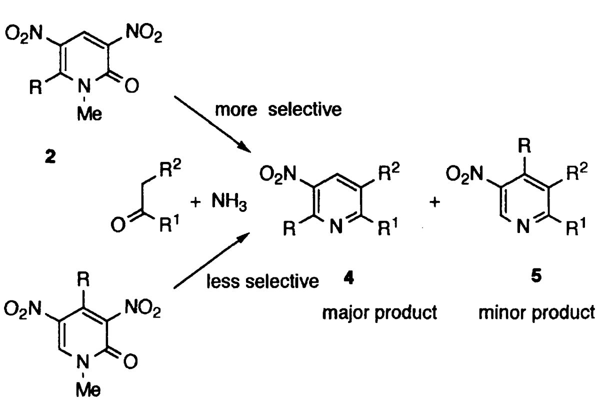
Results and Discussion

Several 6- and 4-substituted 1-methyl-3,5-dinitro-2-pyridones (**2** and **3**) were prepared and tested as the substrates of the pyridine synthesis. Because 1-aryl-3,5-dinitro-2-pyridones gave no 3-nitropyridines,[4) their 6- and 4-substituted derivatives were not tried. All substrates are quite stable except for 6-methoxy derivative **2f**, which could not be obtained because of failure of nitration of its precursor.[8] When **2** or **3** were treated with ketones or the corresponding enamines derived from morpholine in the presence of ammonia in methanol, unexpected results were obtained, which are summarized in Scheme 1, Tables 1 and 2. In contrast with our prediction based on selection rule A, not only **2** but also **3** gave 2-substituted 3-nitropyridines **4** with high regio-selectivity. In many cases, the 4-substituted isomer **5** could not be detected at all. The structures of the products were identified unequivocally by ^{1}H NMR spectra.

These facts are interpreted by another "selection rule B" which should be applied to the 6- or 4-substituted 3,5-dinitro-2-pyridones **2** or **3** but not to **1** or **1d**. The rule is that the predominant reaction course involves nucleophilic attacks of the ammonia and the enamine (or the corresponding ketone) to the substituted carbon and the unsubstituted carbon of the dinitropyridone ring, respectively.

The regioselectivity of the reaction of **2** is higher than that of **3**, as shown in Tables 1 and 2. This fact indicates that both rules, A and B, control the reaction, but rule B is far more significant than rule A. Thus the difference of the selectivities between **2** and **3** is interpreted as follows: In the case of the reactions of **2**, both rule A and rule B indicate that **4** is the major product, whereas in the case of the reactions of **3**, rule A reduces the predominant formation of **4**.

With respect to reactivity of the reagents, enamines derived from the ketones and morpholine are more reactive than the original ketones. The reactivity of the reagents are the same as in the case of the reaction of **1**.[4] It is worth mentioning that ketones having α-methylene carbon are more reactive and selective to give **4** than are methyl ketones. Unfortunately no aldehydes and their enamine derivatives gave either **4** or **5**. One of the possible side reactions may be a reverse electron-demand Diels–Alder reaction of the pyridone with the enamines.[1] β-Keto esters, β-diketones, and their enamines did not react with **2** or **3** as well as with **1**.[4] By using 2-acetylpyridine as the ketone, an unsymmetrical 2,2'-bipyridine was prepared (Entry 35). Such compounds are difficult to prepare and so are of interest in coordination chemisty.[9]

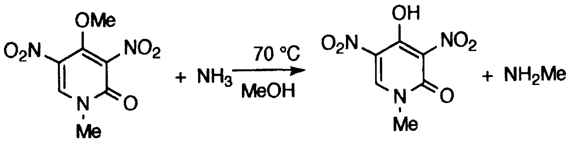


Scheme 1. Selective formation of **4** from **2** and **3**. **a**: R=Me, **b**: R=CO$_2$Me, **c**: R=C$_6$H$_4$NO$_2$-*p*, **e**: R=4-pyridyl, **f**: R=OMe, R^1=alkyl or aryl, R^2=H, alkyl, or aryl.

The substituents R on the pyridone ring affect the reactivity of **2** and **3**. The pyridones having more electron-donating groups are more reactive, the order of the reactivity being **2a** (R=Me)>**2c** (R=C$_6$H$_4$NO$_2$−*p*)>**2b** (R=CO$_2$Me), and **3a** (R=Me)>**3e** (R=4−Py)≫**3b** (R=CO$_2$Me). Although **2b** gave methyl 3-nitro-2-pyridinecarboxylates **4b** in sufficient yields, **3b** showed poor reactivity. Thus, the 6-substituted dinitriopyridones **2** are generally better reagents than the corresponding 4-substituted isomers **3** for the synthesis of 2-substituted 3-nitropyridines **4** when the substituent R is electron-withdrawing. On the other hand, for the synthesis of 2-substituted 3-nitropyridines **4** of which the 2-substituent R is electon-donating, both **2** and **3** are suitable substrates.

It is obvious from the results of Tables 1 and 2 that **2a** and **3a** (R=Me) are more reactive than **1** (R=H) or **1d** (R=D). In spite of these substituent effects on the reactivity of the pyridone, 1,4,6-trimethyl-3,5-dinitro-2-pyridone (**7**) did not react with any ketones or enamines at all.

The substrate **3f** showed special results. When **3f** was treated with the reagents, neither **4f** nor **5f** was obtained, but an ammonium salt of 4-hydroxy-1-methyl-3,5-dinitro-2-pyridone **8** was afforded in ca 90% yield (Entries 21 and 37). The product **8** was also yielded from a reaction of **3f** with morpholine. These reactions are an S$_\text{N}$2 reaction at the methoxyl carbon of **3f** as shown in Eq. 2. A similar reaction of picryl ethers had been reported by Strauss.[10]



3f **8** (2)

Since methoxyl group is an electron-donating group, **3f** is expected from the above results to be a reactive substrate. Thus **3f** was treated with the enamines and ammonia at ambient temperature for 24 h and then heated at 70 °C for 3 h. Then, only the expected products **4** (**Af**: R=OMe, R^1 and R^2=(CH$_2$)$_4$) and **4** (**Bf**: R=OMe, R^1=Ph, and R^2=H) were obtained in reasonable yields of 45 and 76%, respectively (Entries 23 and 38).

In order to obtain product **4** more selectively, another effort was tried. Previously we have found that a strongly basic amine accelerates a similar ring trans-

Table 1. Regioselective Formation of 2-Substituted 3-Nitropyridines **4**

Entry	Substrate[a]		Reagent[a]			Conditions		Yields		Regioselectivity
		R	Type	R^1	R^2	Temp	Time	**4**	**5**	
						°C	h	%	%	**4**/**4**+**5**/%
	(6-Substituted dinitropyridones)									
			(Ketones having α-methylene carbon)							
1[b]	**1d**	6-D	**A**	$-(CH_2)_4-$		70	3	46[c]	44[c]	58
2[b]	**1d**	6-D	**A′**	$-(CH_2)_4-$		70	3	66[c]	16[c]	81
3	**2a**	Me	**A**	$-(CH_2)_4-$		70	3	88	0	100
4	**2b**	CO_2Me	**A′**	$-(CH_2)_4-$		70	3	90	0	100
5	**2b**	CO_2Me	**A′**	$-(CH_2)_4-$		100	5	28	0	100
6	**2c**	$C_6H_4NO_2$-*p*	**A′**	$-(CH_2)_4-$		70	3	78	0	100
			(Methyl ketones)							
7	**2a**	Me	**B′**	Ph	H	r.t.	24	88	0	100
8	**2a**	Me	**B**	Ph	H	70	3	40	0	100
9	**2b**	CO_2Me	**B′**	Ph	H	70	3	68[c]	7.4[c]	90
10	**2b**	CO_2Me	**B′**	Ph	H	100	5	46[c]	7.6[c]	86
11	**2c**	$C_6H_4NO_2$-*p*	**B′**	Ph	H	100	3	34	0	100
	(4-Substituted dinitropyridones)									
			(Ketones having α-methylene carbon)							
12	**3a**	Me	**A**	$-(CH_2)_4-$		70	3	90	0	100
13	**3b**	CO_2Me	**A′**	$-(CH_2)_4-$		100	5	27	0	100
14	**3b**	CO_2Me	**C′**	$-(CH_2)_3-$		100	5	6.8	trace[c]	100
15	**3b**	CO_2Me	**D′**	Ph	Me	100	5	17[c]	0.7[c]	97
16	**3e**	4-Py	**A′**	$-(CH_2)_4-$		70	3	81	0	100
17	**3e**	4-Py	**C′**	$-(CH_2)_3-$		70	3	30	0	100
18	**3e**	4-Py	**D′**	Ph	Me	100	3	49	0	100
19	**3e**	4-Py	**E′**	Ph	Et	100	3	49	0	100
20	**3e**	4-Py	**F**	$-o-C_6H_4(CH_2)_2-$		100	3	25	0	100
21[d]	**3f**	OMe	**A′**	$-(CH_2)_4-$		70	3	0	0	—
22	**3f**	OMe	**A′**	$-(CH_2)_4-$		r.t.	96	30	0	100
23	**3f**	OMe	**A′**	$-(CH_2)_4-$		1) r.t.	24			
						2) 70	3	45	0	100
24	**3f**	OMe	**C′**	$-(CH_2)_3-$		r.t.	96	24	0	100
			(Methyl ketones)							
25	**3a**	Me	**B**	Ph	H	70	3	0	0	—
26	**3a**	Me	**B**	Ph	H	100	3	27	0	100
27	**3a**	Me	**B′**	Ph	H	r.t.	48	77	0	100
28	**3b**	CO_2Me	**B′**	Ph	H	100	5	6.0[c]	20[c]	23
29	**9Bb**	CO_2Me	—	(Ph	H)	100	5	7.0[c]	17[c]	33
30	**3e**	4-Py	**B**	Ph	H	100	3	12[c]	9[c]	57
31	**3e**	4-Py	**B′**	Ph	H	80	5	7.3[c]	3.2[c]	70
32	**3e**	4-Py	**B′**	Ph	H	100	3	29[c]	14[c]	67
33	**3e**	4-Py	**B′** +KOH	Ph	H	100	3	66	0	100
34	**3e**	4-Py	**G**	*t*-Bu	H	100	3	14	0	100
35	**3e**	4-Py	**H**	2-Py	H	100	3	36[c]	5.0[c]	88
36[e]	**3f**	OMe	**B′**	Ph	H	70	3	0	0	—
37[f]	**3f**	OMe	**B′**	Ph	H	r.t.	96	2.7	0	100
38	**3f**	OMe	**B′**	Ph	H	1) r.t.	24			
						2) 70	3	76	0	100
39	**9Bf**	OMe	—	(Ph	H)	70	3	86	0	100

a) Notation of the substrates and the reagents are as follows: **2**=6-Substituted 1-methyl-3,5-dinitro-2-pyridones, **3**=4-substituted 1-methyl-3,5-dinitro-2-pyridones, **A**—**H** are ketones and **A′**—**D′** are enamine derivative from morpholine and the corresponding ketones. Notations, R, R^1, and R^2 are shown in Scheme 1. b) These data are adopted from Ref. 4. c) Yields were determined by ^{1}H NMR spectra of the reaction mixtures. Other yields were isolated ones. d) Ammonium salt of 4-hydroxy-1-methyl-3,5-dinitro-2-pyridone **8** was obtained in 86% yield. e) Ammonium salt of 4-hydroxy-1-methyl-3,5-dinitro-2-pyridone **8** was obtained in 90% yield. f) A bicyclo-type intermediate **9Bf** was isolated in 76% yield.

formation of **1** with acetone and morpholine into a 4-nitroaniline derivative **6**.[11] When potassium hydroxide was added in the reaction mixture of **3e**, both the yield and the regioselectivity of **4e** were extremely improved

Table 2. Product- and Regio-Selective Reactions of 4- and 6-Substituted 1-Methyl-3,5-dinitro-2-pyridones, **2** and **3**

Entry	Substrates		Ketones^a)^			Conditions		Yields/%			Selectivities^b)^/%	
		R	Type	R^1	R^2	Temp °C	Time h	**4**	**5**	**6**	Regio-	Product-
40[c)]	**1**	H	**J**	Et	Me	70	3	34		47	—	42
41	**2a**	Me	**J**	Et	Me	70	3	34	0	0	100	100
42	**2b**	CO_2Me	**J**	Et	Me	100	3	46	0	4.2	100	92
43	**3a**	Me	**J**	Et	Me	70	3	32	0	0	100	100
44	**3b**	CO_2Me	**J**	Et	Me	100	5	4.9	0	9.5	100	34
45	**3e**	4-Py	**J**	Et	Me	100	3	62	0	0	100	100
46[c)]	**1**	H	**K**	Me	H	70	3	17		34	—	23
47	**2a**	Me	**K**	Me	H	70	3	59	0	0	100	100
48	**2b**	CO_2Me	**K**	Me	H	70	3	54[d)]	1.2[d)]	11	98	83
49	**3a**	Me	**K**	Me	H	70	3	48	0	0	100	100
50	**3b**	CO_2Me	**K**	Me	H	100	5	1.3[d)]	1.1[d)]	4.1	54	37
51	**3e**	4-Py	**K**	Me	H	100	3	20[d)]	4.0[d)]	0	83	100
52[c)]	**1**	H	**L**	Me	Me	70	3	23[d)]		43	—	41
			L′	Et	H			7[d)]			—	
53	**2a**	Me	**L**	Et	Me	70	3	51[d)]	0	0	100	100
			L′	Et	H			26[d)]	0		100	
54	**3a**	Me	**L**	Me	H	70	3	37[d)]	0	0	100	100
			L′	Et	H			29[d)]	0		100	
55	**3b**	CO_2Me	**L**	Et	H	120	5	4.0	0	15	100	21
56	**3e**	4-Py	**L**	Et	H	100	3	46[d)]	0	0	100	100
			L′	Et	H			1.1[d)]	0		100	

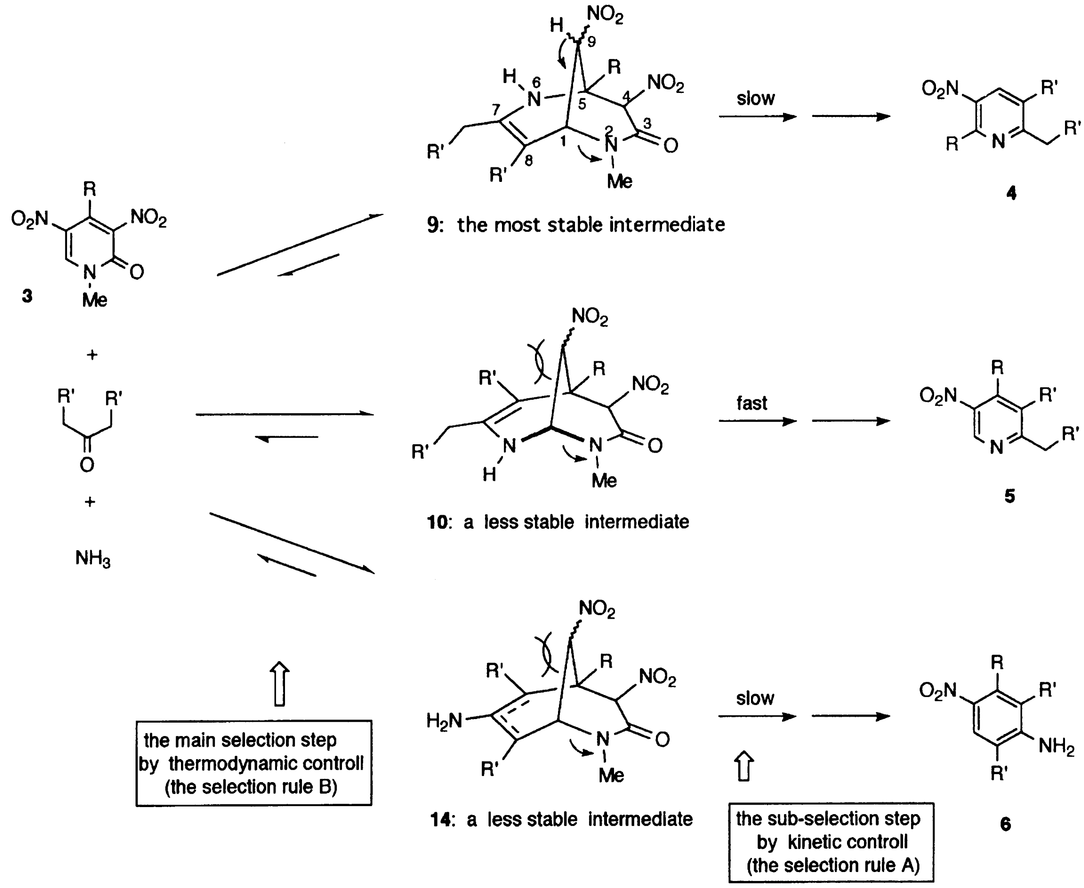
a) Reagent: **J**=3-pentanone, **K**=acetone, **L**=2-butanone acting as a ketone having α-methylene carbon, **L′**=2-butanone acting as a methyl ketone. b) Regioselectivity and product-selectivity are represented by **4**/**4**+**5** and **4**+**5**/**4**+**5**+**6**. c) The data are adopted from the Ref. 4. d) Yields were determined by ^{1}H NMR spectra of the reaction mixtures. Other yields were isolated ones.

(Entry 33). The effect of the additive may be acceleration of decomposition of a bicyclic intermediate **9** (vide infra). The improvement of the additive was effective only in the reaction of **3e**. In the case of the other substrate, the additive causes unfavorable side reactions, such as hydrolysis of the ester in **2b** and **3b** and proton abstraction from methyl group of **2a** and **3a**, to defeat the positive effect.

When ketones of the type $R'-CH_2-CO-CH_2-R'$ were used as the reagent, competitive formation of 3-nitropyridines (**4** and **5**) and their isomeric 4-nitroanilines **6** was expected.[4)] In the case of the unsubstituted substrate **1**, 3-nitropyridines had been a minor product and 4-nitroanilines **6** had been a major product. In contrast with these results, both the substituted substrates **2** and **3** gave 2-substituted 3-nitropyridines **4** predominantly. In this competition reaction, reactions of higher product-selectivity, which is presented by the molar ratio of **4**+**5**/**4**+**5**+**6**, are generally ones of the higher regioselectivity shown by the molar ratio of **4**/**4**+**5** (Table 2).

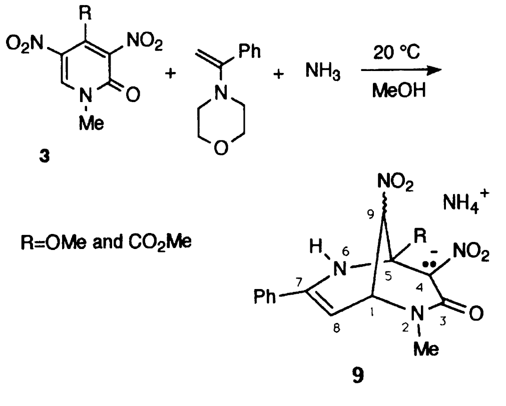
In the case of reactions of **2** and **3** using 2-butanone as the reagent, two isomeric **4** products were yielded. One is product **4L** that is formed from the ketone acting as one having α-methylene hydrogens (**L**: R^1=Me and R^2=Me) and another is product **4L′** that is formed from the ketone acting as a methyl ketone (**L′**: R^1=Et and R^2=H). The former is usually the major product as in the case of the reaction of **1**.[4)] Furthermore, two isomeric 4-nitroaniline products were expected to form but only one isomer, methyl 5-amino-4-methyl-2-nitrobenzoate **6Lb** was afforded when the yields of the 3-nitropyridines were low (Entry 55).

Bicyclic intermediates **9Bb** and **9Bf** were isolated in 92 and 76% yields as precipitates from reactions of **3b** and **3f** with α-morpholinostyrene (**B′**) and ammonia at room temperature. (Eq. 3) Such intermediates were not isolated from **3a** nor from all the **2**, but they gave the final products under the similar conditions. Structures of these compounds were determined by elemental analyses, IR, and NMR spectra. The elemental analyses show the neutral intermediate **9Bf** is formally composed of **3** and an enamine derived from ammonia and the corresponding ketone and **9Bb** is composed of them and ammonia. The IR spectra show strong N–H, C=O, and C=C stretching bands at about 3300, 1660, and 1630 cm^{-1}, respectively. The proton NMR spectra of **9B** show a vicinal coupling between the enamine vinyl proton (H-8) and the bridge head proton (H-1). These spectra show that the compounds **9** are the precursors of **4** but not the isomeric precursors **10** which lead to the products **5**. (see Scheme 2) The ^{13}C NMR spectra



Scheme 2. The product selective reaction of 3 to give 4.

of these intermediates indicate that they consist of only one diastereomer.

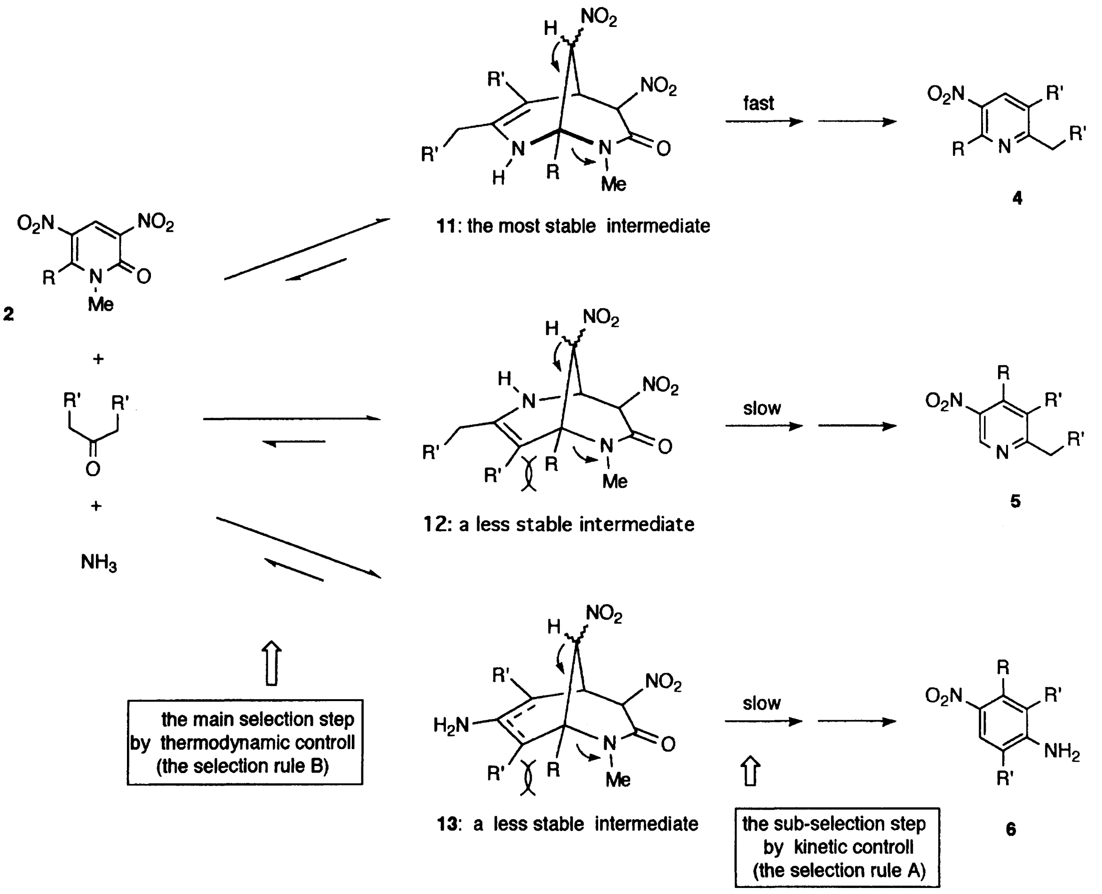


(3)

In order to demonstrate that **9** are the intermediates, they were treated with ammonia in the absence of ketones. On treatment of **9Bf** with ammonia at 70°C, the expected product **4Bf** was obtained in 86% yield (Entry 39). On the other hand, **9Bb** gave a mixture of **4Bb** and **5Bb** as **3b** did (Entry 29). The unexpected results indicate following matters. In the first place, both intermediates, **9** and **10**, are reversibly formed from **3**, but **9** is thermodynamically more stable than **10**. In the second place, the decomposition of **9** to **4** is slower than that of **10** to **5**.

Based on these results, a reaction course from **3** to **4** and **5** is proposed, as shown in Scheme 2. It is clear that the bicyclic intermediates **9** are formed by consecutive addition of the two nucleophiles, ammonia and a ketonic α-carbon, to the 2-pyridone ring, although the order of the additions of the two nucleophiles and the timing of cyclization between the ketone and the ammonia are not known. The final product **4** is formed by cleavage of C(1)–N(2) and C(4)–C(5) bonds of **9**. Thus the present ring transformation proceeds via an addition-addition-elimination-elimination mechanism (AAEE mechanism), which is characteristic for the reactions of 3,5-dinitro-2-pyridones.[4,11—13] By a similar mechanism, some ring transformations of 3,5-dinitro-4-pyridones[14] and 3-nitropyridinium salts[15] were interpreted. Such bicyclo[3.3.1]nonane derivatives were well studied in reactions of 1,3,5-trinitrobenzene derivatives with ketonic nucleophiles,[10,16] although little further bond cleavage occurred in the benzene system.[17] On the other hand, in the case of similar ring transformations of electron-deficient six-membered heterocyclic compounds such as 1,3,5-triazines[18] and uraciles[19] to other six-membered aromatic compounds, an addition-elimination-addition-elimination mechanism (AEAE mechanism) was proposed which involves open-chain intermediates instead of the bicyclic ones.

The reason why **10** is less stable than **9** is as follows.



Scheme 3. The product selective reaction of **2** to give **4**.

Among the two nucleophiles, ketone α-carbon and ammonia, the former is more bulky than the latter. On the other hand, the pyridone CR moiety is larger than the pyridone CH one. So the bicyclic intermediate **10** has steric hindrance between the large moieties CR^2 (CR′ in Scheme 2) and CR but **9** has no such hindrance.

The fact that ketones having α-methylene carbon gave **4** more regioselectively than methyl ketones also agrees with the above interpretation, because the former are more hindered carbon nucleophiles than the latter. Thus selection rule B can be interpreted by differences of thermodynamic stability between the two possible intermediates **9** and **10**. The present selective transformation of **2** and **3** to **4** may be also explained by the soft-hard principle;[12] i.e., as the nucleophile, the ketone is softer than ammonia, while the pyridone carbon having no substituent is softer than those having the substituents as the electrophilic center. However, the steric factor is more reasonable in this reaction.

The fact that 1,4,6-trimethyl-3,5-dinitro-2-pyridone (**7**) does not give any products is also interpreted as due to the same steric hindrance. Thus the bulky ketonic nucleophiles can not attack either of the two bulky electrophilic centers of the pyridone **7**.

We also propose a reason why the conversion of **10** to **3** is faster than that of **9** to **4**. It is the difference of the cleaving C–N bond strengths. Thus the C–N bond in **10** is a weak acetal type and the C–N bond in **9** is a normal amine type. Selection rule A can be recognized by differences of kinetic stability between the alternative bicyclic intermediates.

Evidently the kinetic stability of the bicyclic intermediate **9** depends upon the electronic character of the substituent R at the C-5 atom; the intermediate in which R is methyl is labile enough to be isolated, while the one in which R is methoxycarbonyl is very stable (Entry 29). The substituent effect may be explained as follows: Since decomposition of **9** to **4** is promoted by a base, the reaction begins by proton abstraction at C-9 position. The substituent R at C-5 position may affect the acidity of the hydrogen at C-9 position.

The transformation from **2** to **4** or **5** must proceed via a similar AAEE mechanism (Scheme 3), although the corresponding bicyclic intermediates **11** and **12** were not isolated. The higher regio-selectivity of **2** compared to that of **3** can be recognized by the chemical interpretations for rules A and B. The intermediate **11** is sterically more stable than **12** (selection by rule B). And the acetal type C–N bond in **11** must be cleaved faster to give **4** than the amine type C–N bond of **12** is cleaved to give **5** (selection by rule A).

The product selectivity of the pyridines over the 4-nitroanilines are also interpreted by the same chemical reasons. The formation of the 4-nitroanilines **5** must proceed via the AAEE mechanism which involves the 2-azabicyclo[3.3.1]nonane **13** (from **2**) or **14** (from **3**) because the similar intermediates had been isolated in the reaction of **1**,[11,13] **2**,[12] or **3**[12] with ketones. These intermediates **13** and **14** are more unstable than the diazabicyclo[3.3.1]nonane intermediates **9** and **11**, because the former involve a sterically unfavorable interaction between CR–CR^2 (or CR–CR$'$) as in the case of the intermediates **10** and **12**. So preferential formation of **9** and **11** over **13** and **14** as well as **10** and **12** is one of the major reasons of the product selectivity (Schemes 2 and 3). By the same steric control, the reason why the alternative 4-nitroaniline product, 3-substituted 2-methyl-4-nitroaniline, was not formed in the reaction of 2-butanone (Entry 55) can be explained. Furthermore, decomposition of these intermediates **13** and **14** to the corresponding anilines must be slower than that of the intermediates **10** and **11** because of lack of the acetal type C–N bonds in the former intermediates.

Conclusion

The reaction of 6- and 4-substituted 3,5-dinitro-2-pyridones, **2** and **3**, with simple ketones and ammonia is a good synthetic method for preparation of 2-substituted 3-nitropyridines **4**. The 6-substituted pyridones **2** are always better substrates than the 4-substituted ones. The reaction proceeds via an AAEE mechanism which is characteristic for the pyridones. Each of two possible [3.3.1]bicyclic intermediates (**9** and **10** from **3**, **11** and **12** from **2**) is reversibly formed by consecutive nucleophilic addition of ammonia nitrogen and α-carbon of the ketones to the substrates. The less crowded intermediates (**9** and **11**) which are precursors of the 2-substituted 3-nitropyridines **4** are more selectively formed by thermodynamic control than the more crowded ones (**10** and **12**). This is the primary reason why **2** or **3** give **4** selectively (selection rule B). The intermediates which have acetal type C–N bonds (**10** and **11**) are kinetically labile compared with ones which have normal amine type C–N bonds (**9** and **12**). This is the reason why **2** gives **4** more selectively than **3** does (selection rule A).

Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus. Elemental analyses were carried out using a Yanagimoto MT-3 CHN-corder. ^{1}H NMR spectra were obtained on a Hitachi R-20B (60 MHz) spectrometer and ^{13}C NMR spectra were on a Brucker-MW 360 (360 MHz) instrument. IR spectra were collected with a Hitachi model 260-10 spectrophotometer.

Syntheses of Substituted Dinitro-2-pyridones 2, 3, and 7. Methyl 1-Methyl-3,5-dinitro-6-oxo-1,6-dihydro-2-pyridinecarboxylate (2b). Methyl 2-pyridinecarboxylate (13.7 g, 0.1 mol) was heated with dimethyl sulfate (18.9 g, 0.15 mol) at 100 °C for 2 h. Two sorts of solutions, sodium hydroxide (48 g, 0.2 mol) in water (40 ml) and potassium hexacyanoferrate(III) (66 g, 0.2 mol) in water (140 ml) were added to the mixture at −10 °C over 30 min. The mixture was allowed to stand for 12 h at room temperature. Methanol (100 ml) was added to the mixture and precipitates were filtered off. The filtrate was acidified with conc HCl to pH 3. The solvent was removed in vacuo and the residual solid was extracted with methanol. The extract was dried with sodium sulfate and condensed to ca. 200 ml. Sulfuric acid (22 ml) was added and the solution was refluxed for 3 h. Aqueous sodium carbonate (5%, 400 ml) was added and then the solutions was extracted with chloroform. The extract was washed with water and dried with sodium sulfate. After the solvent was removed, residual oil was treated with nitric acid (d=1.42, 12 g) and sulfuric acid (22 ml) at 100 °C for 2 h. The mixture was poured on ice (150 g) and precipitates were washed with water and then methanol. The solid (1.6 g) was column-chromatographed on silica gel. The first eluate (ethyl acetate–benzene 1 : 20) gave 0.47 g (3.4%) of **2b**. Mp 184.5—185 °C, pale yellow needles (methanol). IR (Nujol), 1760 (CO_2Me), 1713 (pyridone CO), 1586, 1530 (NO_2), 1348, 1320 (NO_2), 1268 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ=3.54 (s, 3 H), 4.08 (s, 3 H), 9.03 (s, 1 H). Found: C, 37.34; H, 2.78; N, 16.44%. Calcd for $C_8H_7N_3O_7$: C, 37.36; H, 2.74; N, 16.34%. The second eluate gave 1.0 g of 1-methyl-3,5-dinitro-2-pyridone (**1**).

Similarly, **3b** was obtained in 43% yield by nitration of methyl 1-methyl-2-oxo-1,2-dihydro-4-pyridinecarboxylate. Methyl 1-methyl-3,5-dinitro-2-oxo-1,2-dihydro-4-pyridinecarboxylate (**3b**): Mp 206—208 °C, pale yellow needles. IR (Nujol), 1760 (CO_2Me), 1696 (pyridone CO), 1630, 1555 (NO_2), 1330 (NO_2), 1293, 1248, 1035 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ=3.68 (s, 3 H), 3.92 (s, 3 H), 9.62 (s, 1 H). Found: C, 37.39; H, 2.72; N, 16.49%. Calcd for $C_8H_7N_3O_7$: C, 37.36; H, 2.74; N, 16.34%.

1-Methyl-6-(4-nitrophenyl)-3,5-dinitro-2-pyridone (2c). A mixture of 2-phenylpyridine (3.10 g, 20 mmol) and dimethyl sulfate (3.78 g, 30 mmol) was heated at 100 °C for 2 h. After cooling, water (4 ml) was added to the mixture and it was cooled with ice-salt bath. To the aqueous solution cooled at −10 °C, sodium hydroxide (4.80 g, 120 mmol) in water (15 ml) was added over 1 h, while potassium hexacyanoferrate(III) (19.76 g, 60 mmol) in water (75 ml) was added for 2 h. The mixture was kept at room temperature for 12 h and then extracted with chloroform. After removal of the solvent, crude 1-methyl-6-phenyl-2-pyridone was obtained as black oil (2.55 g, 70%). Mp 84—87 °C, colorless needles (hexane). IR (Nujol), 1650 (CO), 1580 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ=3.34 (s, 3 H), 6.06 (dd, J=6.0, 1.4 Hz, 1 H), 6.53 (dd, J=8.2, 1.4 Hz, 1 H), 7.1—7.5 (m, 6 H). The crude pyridone (2.55 g, 14 mmol) was treated with sulfuric acid (28 ml) and fuming nitric acid (d 1.52, 8.82 g, 140 mmol) at 100 °C for 2 h. After cooling, the mixture was poured onto ice (150 g). Precipitates were collected by filtration and washed with water. Crude products (2.30 g, mp 70—80 °C) were treated with column-chromatography on silica gel. A benzene–ethyl acetate (5 : 1) eluate gave 0.25 g 5.6% of **2c**. Mp 245—250 °C, pale yellow needles (AcOEt). IR (Nujol), 1690 (CO), 1600, 1575, 1520 (NO_2), 1350, 1330 (NO_2), 870, 860 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ=3.19 (s, 3 H), 7.84 (d, J=9.0 Hz, 2 H), 8.46 (d, J=9.0 Hz, 2 H), 9.14 (s, 1 H). Found: C, 45.08; H, 2.58; N, 17.44%. Calcd for $C_{12}H_8N_4O_7$: C, 45.01; H, 2.52; N, 17.50%.

1-Methyl-3,5-dinitro-(4-pyridyl)-2-pyridone (3e).

To a stirred solution of 4,4′-bipyridine (4.68 g, 30 mmol) in benzene (60 ml), dimethyl sulfate (3.78 g, 30 mmol) was added at 0 °C. The mixture was stirred at room temperature for 1 h and then refluxed for 2 h. After removal of the solvent, water (15 ml) was added to the mixture. The solution was cooled at −10 °C and sodium hydroxide (4.80 g, 120 mmol) in water (15 ml) was added over 1 h, while potassium hexacyanoferrate(III) (19.76 g, 60 mmol) in water (75 ml) was added over 2h. The mixture was kept at room temperature for 12 h. Yielded precipitates were collected by filtration, washed with water, and dried. Crude 1-methyl-4-(4-pyridyl)-2-pyridone (3.87 g, 69%, mp 109—110 °C) was obtained. Mp 118 °C, colorless needles (benzene–hexane). IR (Nujol), 1660 (CO), 1580 cm^{-1}. ^{1}H NMR (CDCl$_3$) δ=3.60 (s, 3 H), 6.41 (dd, J=7.0, 1.9 Hz, 1 H), 6.84 (d, J=1.9 Hz, 2 H), 7.43 (m, 3 H), 8.70 (d, J=6.1 Hz, 2 H). Found: C, 70.45; H, 5.43; N, 15.04%. Calcd for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.05%.

The crude pyridone (5.58 g, 30 mmol) was treated with sulfuric acid (30 ml) and fuming nitric acid (d 1.52, 18.9 g, 300 mmol) at 130 °C for 4 h. After cooling, the mixture was poured onto ice (300 g) and the solution was neutralized with sodium carbonate to pH 4. Precipitates were filtered and washed with water. Crude dinitro compound (2.39 g, 29%) was obtained. Mp 208—210 °C, pale yellow plates (ethyl acetate–methanol 1 : 20). IR (Nujol), 1695 (CO), 1615, 1600, 1520, (NO$_2$), 1370, 1335 (NO$_2$), 1160, 900 cm^{-1}. ^{1}H NMR (CDCl$_3$–DMSO-d$_6$ 1 : 1) δ=3.84 (s, 3 H), 7.33 (d, J=5.8 Hz, 2 H), 8.76 (d, J=5.8 Hz, 2 H), 9.58 (s, 1 H). Found: C, 48.07; H, 2.94; N, 20.35%. Calcd for $C_{11}H_8N_4O_5$: C, 47.83; H, 2.92; N, 20.29%.

1,4,6-Trimethyl-3,5-dinitro-2-pyridone (7). A solution of 4,6-dimethyl-2-pyridone[20] (11.9 g, 97 mmol), sodium methoxide (prepared from 2.65 g of sodium) and methyl iodide (18.4 g, 128 mmol) in methanol (60 ml) was refluxed for 12 h. After removal of the solvent, water was added and the mixture was extracted with chloroform. The extract was dried with sodium sulfate and distilled at 130—150 °C/70 Pa to give 1,4,6-trimethyl-2-pyridone (8.47 g, 64%). ^{1}H NMR (CCl$_4$) δ=2.05 (s, 3 H), 2.30 (s, 3 H), 3.35 (s, 3 H), 5.7 (broad s, 1 H), 6.0 (broad s, 1 H). To acetic anhydride (85 ml), fuming nitric acid (d=1.52, 7.2 g) and then 3.90 g (28.5 mmol) of 1,4,6-trimethyl-2-pyridone were added by portions at 0 °C. The solution was allowed to stand at room temperature for 2 d. The mixture was poured onto ice (200 g) and the solvents were removed in vacuo. Yellow residual oil was washed with water and crystallized from ethanol to give 1.85 g (8.15 mmol, 29%) of 1,4,6-trimethyl-3,5-dinitro-2-pyridone (**7**). Yellow needles, mp 157—159 °C (methanol). IR (Nujol), 1683 (CO), 1620 (C=C), 1530 (NO$_2$), 1350 (NO$_2$), 1203, 877, 695 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ=2.17 (s, 3 H), 2.24 (s, 3 H), 3.57 (s, 3 H). Found: C, 42.11; H, 3.78; N, 18.36%. Calcd for $C_8H_9N_3O_5$: C, 42.29; H, 3.99; N, 18.50%.

Selective Formation of 2-Substituted 3-Nitropyridine 4. Typical procedures are as follows:

(1) A Reaction at 70 °C under Atmospheric Pressure. A solution of **2b** (0.129 g, 0.5 mmol), α-morpholinostyrene (**B′**) (0.19 g, 1 mmol), and ammonia (5 mmol, provided by 5 mol dm^{-3} methanol solution) in 10 ml of dry methanol was heated at 70 °C. After 3 h, the solvent was removed in vacuo and residual oil was column-chromatographed on silicagel. A benzene eluate gave a mixture of **4Bb** and **5Bb** (0.085 g). The mixture was crystallized from hexane to give methyl 3-nitro-6-phenyl-2-pyridinecarboxylate (**4Bb**, 0.056 g, 0.25 mmol). Colorless needles, mp 83—85 °C. ^{1}H NMR (CDCl$_3$) δ=4.05 (s, 3 H), 7.4—7.5 (m, 3 H), 7.94 (d, J=9.1 Hz, H-5), 8.0—8.2 (m, 2 H), 8.46 (d, J=9.1 Hz, H-4), The solvent of the hexane solution was removed in vacuo and an ^{1}H NMR spectrum of the residual mixture showed that total yields of **4Bb** and **5Bb** are 68 and 7.4%, respectively. An ^{1}H NMR spectrum of methyl 3-nitro-6-phenyl-4-pyridinecarboxylate (**5Bb**) was assigned as follows: (CDCl$_3$) δ=4.00 (s, 3 H), 7.4—7.5 (m, 3 H), 7.93 (s, H-5), 8.0—8.2 (m, 2 H), 9.27 (s, H-2). When ketones were used instead of the enamine, a significant amount of an ammonium salt of N-methyl-2-nitroacetamide was isolated as chloroform-insoluble precipitate.[4]

(2) A Reaction at 100 °C in a Sealed Tube. In a 100 ml autoclave, a mixture of **2b** (0.257 g, 1 mmol), acetone (**K**, 0.290 g, 5 mmol), ammonia (5 mmol), and methanol (20 ml) was heated at 100 °C for 5 h. After removal of the solvent, the residue was column-chromatographed on silica gel. The first benzene–chloroform (1 : 1) eluate gave methyl 6-methyl-3-nitro-2-pyridinecarboxylate (**4Kb**) as a colorless oil (0.080 g, 0.41 mmol). ^{1}H NMR (CDCl$_3$) δ=2.71 (s, 3 H), 4.02 (s, 3 H), 7.46 (d, J=8.5 Hz, H-5), 8.30 (d, J=8.5 Hz, H-4). The second chloroform eluate gave a mixture of **4Kb** and methyl 6-methyl-3-nitro-4-pyridinecarboxylate (**5Kb**, 0.028 g). From an spectrum of the mixture, the identified ^{1}H NMR spectrum of **5Kb** was as follows: (CDCl$_3$) δ=2.71 (s, 3 H), 3.96 (s, 3 H), 7.39 (s, H-5), 9.12 (s, H-2). Total yields of **4Kb** and **5Kb** were 54 and 1.2%, respectively. The third acetone–chloroform (1 : 50) gave methyl 5-amino-2-nitrobenzoate (**6Kb**) as a yellow oil (0.018 g, 11%). ^{1}H NMR (CDCl$_3$) δ=3.91 (s, 3 H), 4.6 (m, 2 H), 6.7 (m, 2 H), 7.93 (d, J=9.9 Hz, 1 H).

Similarly, the following compounds were isolated and identified. ^{1}H NMR spectral data of the compounds in CDCl$_3$ are shown. Elemental analyses, melting points, and IR spectral data of these products are summarized in Table 3.

2-Methyl-3-nitro-5,6,7,8-tetrahydroquinoline (4Aa): δ=1.9 (m, 4 H), 2.80 (s, 7 H), 8.00 (s, H-4).

Methyl 3-Nitro-5,6,7,8-tetrahydroquinoline-2-carboxylate (4Ab): δ=1.9 (m, 4 H), 3.0 (m, 4 H), 4.00 (s, 3 H), 8.05 (s, H-4).

3-Nitro-2-(4-nitrophenyl)-5,6,7,8-tetrahydroquinoline (4Ac): δ=1.9—2.1 (m, 4 H), 2.9—3.1 (m, 4 H), 7.65 (d, J=8.5 Hz, 2 H), 7.98 (s, H-4), 8.29 (d, J=8.5 Hz, 2 H)

3-Nitro-2-(4-pyridyl)-5,6,7,8-tetrahydroquinoline (4Ae): δ=1.5—2.1 (m, 4 H), 2.8—3.2 (m, 4 H), 7.39 (d, J=6 Hz, 2 H), 7.93 (s, H-4), 8.68 (d, J=6 Hz, 2 H).

2-Methoxy-3-nitro-5,6,7,8-tetrahydroquinoline (4Af): δ=1.7—2.0 (m, 4 H), 2.7—3.0 (s, 4 H), 4.07 (s, 3 H), 8.06 (s, H-4).

2-Methyl-3-nitro-6-phenylpyridine (4Ba): δ=2.95 (s, 3 H), 7.4—7.6 (m, 3 H), 7.71 (d, J=8.6 Hz, H-5), 8.0—8.2 (m, 2 H), 8.36 (d, J=8.6 Hz, H-4).

3-Nitro-2-(4-nitrophenyl)-6-phenylpyridine (4Bc): δ=7.79 (d, J=8.7 Hz, 2 H), 7.94 (d, J=9.1 Hz, H-5), 8.0—8.2 (m, 2 H), 8.34 (d, J=9.1 Hz, H-4), 8.38 (d, J=8.7 Hz, 2 H).

Table 3. Elemental Analyses and IR Spectra of the Products **4** and **5**

Compound				Melting point	Found/%			Calcd/%			IR/cm^{-1}		
	R	R^1	R^2	θ_m/°C	C	H	N	C	H	N	NO$_2$		CO
4Aa	Me	$-(CH_2)_4-$		58—59	62.59	6.47	14.26	62.48	6.29	14.58	1514	1338	—
4Ab	CO$_2$Me	$-(CH_2)_4-$		76	56.16	5.14	11.66	55.93	5.12	11.86	1520	1350	1750
4Ac	C$_6$H$_4$NO$_2$-*p*	$-(CH_2)_4-$		129—130	60.24	4.47	13.86	60.19	4.38	14.04	1510	1355	—
4Ae	4-Py	$-(CH_2)_4-$		116	65.83	5.13	16.31	65.87	5.13	16.46	1510	1360	—
4Af	OMe	$-(CH_2)_4-$		64—66	57.58	5.76	13.45	57.68	5.81	13.46	1518	1340	—
4Ba	Me	Ph	H	120—121	67.52	4.69	13.22	67.28	4.71	13.08	1510	1340	—
4Bb	CO$_2$Me	Ph	H	83—85	60.53	3.97	10.78	60.46	3.90	10.85	1520	1350	1750
4Bc	C$_6$H$_4$NO$_2$-*p*	Ph	H	149—151	63.83	3.55	12.99	63.55	3.45	13.08	1520	1350	—
4Be	4-Py	Ph	H	208—210	69.47	4.10	14.92	69.30	4.00	15.16	1520	1345	—
4Bf	OMe	Ph	H	89—90	62.67	4.43	12.01	62.60	4.38	12.17	1514	1355	—
4Cb	CO$_2$Me	$-(CH_2)_3-$		87—88	54.08	4.56	12.55	54.05	4.54	12.61	1525	1350	1745
4Ce	4-Py	$-(CH_2)_3-$		86—87	64.79	4.69	17.23	67.72	4.60	17.42	1510	1350	—
4Cf	OMe	$-(CH_2)_3-$		53—55	55.79	5.21	14.33	55.66	5.19	14.43	1510	1355	—
4Db	CO$_2$Me	Ph	Me	122—124	61.85	4.53	10.26	61.76	4.44	10.29	1530	1350	1745
4De	4-Py	Ph	Me	129—131	70.38	4.59	14.39	70.09	4.50	14.43	1510	1350	—
4Ee	4-Py	Ph	Et	72	70.95	4.98	13.71	70.80	4.95	13.76	1515	1355	—
4Fe	4-Py	$-o-C_6H_4(CH_2)_2-$		246—247	71.56	4.44	13.42	71.27	4.32	13.86	1510	1340	—
4Ge	4-Py	*t*-Bu	H	125	65.57	5.91	16.14	65.35	5.88	16.33	1530	1370	—
4He	4-Py	2-Py	H	187—188	64.80	3.00	20.05	64.74	3.62	20.14	1520	1360	—
4Ja	Me	Et	Me	36—38	60.26	6.80	15.30	59.98	6.71	15.55	1520	1338	—
4Jb	CO$_2$Me	Et	Me	46—48	53.45	5.41	12.41	53.57	5.39	12.50	1530	1355	1750
4Je	4-Py	Et	Me	112—113	64.48	5.36	17.43	64.18	5.39	17.28	1510	1350	—
4Ka	Me	Me	H	27—29	54.95	5.24	18.21	55.25	5.30	18.41	1520	1340	—
4Kb	CO$_2$Me	Me	H	Oil	49.37	4.43	13.95	48.98	4.11	14.28	1530	1350	1745
4Ke	4-Py	Me	H	142—143	61.77	4.26	19.50	61.39	4.22	19.53	1510	1350	—
4La	Me	Me	Me	39—42	57.71	6.05	16.65	57.82	6.02	16.86	1518	1340	—
4Lb	CO$_2$Me	Me	Me	56—58	51.25	4.93	13.39	51.42	4.80	13.33	1520	1350	1740
4Le	4-Py	Me	Me	125—126	63.33	4.84	18.36	62.87	4.84	18.33	1510	1350	—
5Bb	CO$_2$Me	Ph	H	106—108	60.69	3.92	10.97	60.46	3.90	10.85	1517	1340	1740
5He	4-Py	2-Py	H	173—175	64.55	3.87	19.87	64.74	3.62	20.14	1510	1360	—
6Jb	CO$_2$Me	—	—	153	53.67	5.40	12.60	53.57	5.39	12.50	1570	1330	1720
6Kb	CO$_2$Me	—	—	Oil	49.26	4.33	14.04	48.98	4.11	14.28	1510	1320	1730
6Lb	CO$_2$Me	—	—	132—135	51.64	4.78	13.39	51.42	4.80	13.33	1570	1310	1730

3-Nitro-2-(4-pyridyl)-6-phenylpyridine (4Be): δ=7.2—7.5 (m, 5 H), 7.88 (d, J=8.4 Hz, H-5), 8.0—8.2 (m, 2 H), 8.31 (d, J=8.4 Hz, H-4), 8.73 (broad d, J=6 Hz, 2 H).

2-Methoxy-3-nitro-6-phenylpyridine (4Bf): (CCl$_4$) δ=4.21 (s, 3 H), 7.3—7.6 (m, 4 H), 7.9—8.1 (m, 2 H), 8.3 (d, J=9.1 Hz, H-4).

Methyl 6-Nitro-4-azaindan-5-carboxylate (4Cb): δ=2.2—2.4 (m, 2 H), 3.0—3.3 (m, 4 H), 4.03 (s, 3 H), 8.11 (s, H-7).

6-Nitro-5-(4-pyridyl)-4-azaindan (4Ce): δ=2.27 (broad quintet, J=7 Hz, 2 H), 3.15 (m, 4 H), 7.41 (d, J=6 Hz, 2 H), 8.02 (s, H-7), 8.70 (d, J=6 Hz, 2 H).

5-Methoxy-6-nitro-4-azaindan (4Cf): δ=2.1—2.4 (m, 2 H), 2.9—3.1 (m, 4 H), 4.08 (s, 3 H), 8.06 (s, H-7).

Methyl 5-Methyl-3-nitro-6-phenyl-2-pyridinecarboxylaye (4Db): δ=2.53 (s, 3 H), 4.02 (s, 3 H), 7.5 (m, 5 H), 8.30 (s, H-4).

5-Methyl-3-nitro-6-phenyl-2-(4-pyridyl)pyridine (4De): δ=2.53 (s, 3 H), 7.4—7.5 (m, 7 H), 8.16 (s, H-4), 8.7 (m, 2 H).

5-Ethyl-3-nitro-6-phenyl-2-(4-pyridyl)pyridine (4Ee): δ=1.28 (t, J=7.5 Hz, 3 H), 2.87 (q, J=7.5 Hz, 2 H), 7.4—7.7 (m, 7 H), 8.21 (s, H-4), 8.71 (d, J=6 Hz, 2 H).

3-Nitro-2-(4-pyridyl)-5,6-dihydrobenzo[*h*]quinoline (4Fe): δ=3.06 (s, 4 H), 7.2—7.5 (m, 5 H), 8.06 (s, H-4), 8.3—8.4 (m, 1 H), 8.71 (d, J=5 Hz, 2 H).

6-*t*-Butyl-3-nitro-2-(4-pyridyl)pyridine (4Ge): δ=1.43 (s, 9 H), 7.5 (m, 2 H), 7.51 (d, J=8.7 Hz, H-5), 8.17 (d, J=8.7 Hz, H-4), 8.7 (m, 2 H).

3-Nitro-6-(2-pyridyl)-2-(4-pyridyl)pyridine (4He): δ=7.3—7.5 (m, 1 H), 7. 53 (d, J=6 Hz, 2 H), 7.86 (td, J=7.8, 1.9 Hz, 1 H), 8.33 (d, J=8.6 Hz, H-5), 8.5—8.9 (m, 2 H), 8.67 (d, J=8.6 Hz, H-4), 8.76 (d, J=6 Hz, 2 H).

5-Ethyl-2,6-dimethyl-3-nitropyridine (4Ja): δ=1.29 (t, J=7.5 Hz, 3 H), 2.38 (s, 3 H), 2.81 (s, 3 H), 2.86 (q, J=7.5 Hz, 2 H), 8.02 (s, H-4).

Methyl 5-Ethyl-6-methyl-3-nitro-2-pyridinecarboxylate (4Jb): δ=1.31 (t, J=7.4 Hz, 3 H), 2.47 (s, 3 H), 2.92 (q, J=7.4 Hz, 2 H), 4.00 (s, 3 H), 8.10 (s, H-4).

5-Ethyl-6-methyl-3-nitro-2-(4-pyridyl)pyridine (4Je): δ=1.33 (t, J=7.4 Hz, 3 H), 2.45 (s, 3 H), 2.93 (q, J=7.4 Hz, 2 H), 7.43 (d, J=6 Hz, 2 H), 7.97 (s, H-4), 8.68 (d, J=6 Hz, 2 H).

2,6-Dimethyl-3-nitropyridine (4Ka): δ=2.63 (s, 3 H), 2.85 (s, 3 H), 7.17 (d, J=8.5 Hz, H-5), 8.20 (d, J=8.5 Hz, H-4).

6-Methyl-2-(4-pyridyl)-3-nitropyridine (4Ke): δ=2.71 (s, 3 H), 7.35 (d, J=8.2 Hz, H-5), 7.42 (d, J=6 Hz, 2 H), 8.17 (d, J=8.2 Hz, H-4), 8.72 (d, J=6 Hz, 2 H).

2,5,6-Trimethyl-3-nitropyridine (4La): δ=2.36 (s, 3 H), 2.57 (s, 3 H), 2.77 (s, 3 H), 8.03 (s, H-4).

Methyl 5,6-Dimethyl-3-nitro-2-pyridinecarboxylate (4Lb): δ=2.43 (s, 3 H), 2.63 (s, 3 H), 4.00 (s, 3 H), 8.04 (s, H-4).

5,6-Dimethyl-2-(4-pyridyl)-3-nitropyridine (4Le): δ=2.45 (s, 3 H), 2.65 (s, 3 H), 7.39 (d, J=6 Hz, 2 H), 7.97 (s, H-4), 8.69 (d, J=6 Hz, 2 H).

3-Nitro-6-(2-pyridyl)-4-(4-pyridyl)pyridine (5He): δ=7.34 (d, J=6 Hz, 2 H), 7.4—7.6 (m, 1 H), 7.91 (td, J=7.8, 1.8 Hz, 1 H), 8.5—8.8 (m, 2 H), 8.56 (s, H-5), 8.76 (d, J=6 Hz, 2 H), 9.27 (s, H-2).

Methyl 3-Amino-2,4-dimethyl-6-nitrobenzoate (6Jb): δ=2.12 (s, 3 H), 2.24 (s, 3 H), 3.97 (s, 3 H), 4.4 (m, 2 H), 7.90 (s, 1 H).

Methyl 4-Amino-3-methyl-2-nitrobenzoate (6Lb): δ=2.19 (s, 3 H), 3.88(s, 3 H), 4.3 (m, 2 H), 6.66 (s, 1 H), 7.82 (s, 1 H).

Similarly, the following compounds **4**, **5**, and **6** were not isolated but were identified by ^{1}H NMR spectra of mixtures with the above isomers in $CDCl_3$.

6-Ethyl-2-methyl-3-nitropyridine (4La′): δ=1.33 (t, J=7.9 Hz, 3 H), 2.83 (s, 3 H), 2.89 (q, J=7.9, 2 H), 7.20 (d, J=8.6 Hz, H-5), 8.22 (d, J=8.6 Hz, H-4).

6-Ethyl-2-(4-pyridyl)-3-nitropyridine (4Le′): δ=1.38 (t, J=7.6 Hz, 3 H), 2.99 (q, J=7.6, 2 H), 7.4 (m, 3 H), 8.18 (d, J=8.6 Hz, H-4), 8.7 (m, 2 H).

5-Nitro-4-(4-pyridyl)-2-phenylpyridine (5Be): δ=7.2—7.5 (m, 5 H), 7.79 (s, H-5), 8.0—8.2 (m, 2 H), 8.73 (broad d, J=6 Hz, 2 H), 9.28 (s, H-6).

Methyl 6-Nitro-4-azaindan-7-carboxylate (5Cb): δ=2.3 (m, 2 H), 3.1 (m, 4 H), 3.97 (s, 3 H), 9.08 (s, H-5).

Methyl 3-Methyl-5-nitro-2-phenyl-4-pyridinecarboxylate (5Db): δ=2.36 (s, 3 H), 3.89 (s, 3 H), 7.5 (m, 5 H), 9.28 (s, H-2).

2-Methyl-4-(4-pyridyl)-5-nitropyridine (5Ke): δ=2.71 (s, 3 H), 7.19 (s, H-5), 7.42 (d, J=6 Hz, 2 H), 8.72 (d, J=6 Hz, 2 H), 9.13 (s, H-2).

Isolation of the Bicyclic Intermediates 9. 5-Methoxy-2-methyl-4,9-dinitro-7-phenyl-2,6-diazabicyclo[3.3.1]non-7-en-3-one (9Bf): A solution of **3f** (0.229 g, 1 mmol), α-morpholinostyrene (0.38 g, 2 mmol), and ammonia (5 mmol) in methanol (10 ml) was allowed to stand at room temperature for 4 d. The solvent was removed in vacuo and residual oil was crystallized from chloroform to give 0.153 g (67%) of **9Bf**. Mp (decomp) 174—180 °C, colorless prisms. IR (Nujol), 3100 (NH), 3070, 1665 (CO), 1634 (C=C–N), 1565 (NO_2), 1380 (NO_2), 1350 (NO_2), 1305, 1245, 1133, 778, 698 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ=3—4 (broad, NH, 1 H), 3.21 (s, NCH_3), 3.55 (s, OCH_3), 4.44 (t, J=2.5 Hz, H-1), 5.08 (d, J=2.5 Hz, H-9), 5.67 (s, H-4), 5.71 (d, J=2.1 Hz, H-8), 7.4—7.6 (m, 5 H). ^{13}C NMR (DMSO-d_6) δ=33.19, 35.60, 50.16, 53.96, 79.64, 85.33, 89.81, 127.33, 128.60, 131.90, 136.39, 158.54, 169.03. Found: C, 51.61; H, 4.64; N, 16.17%. Calcd for $C_{15}H_{16}N_4O_6$: C, 51.72; H, 4.63; N, 16.09%.

Ammonium 5-Methoxycarbonyl-2-methyl-4,9-dinitro-3-oxo-7-phenyl-2,6-diazabicyclo[3.3.1]non-7-en-4-ide (9Bb): A solution of **3b** (0.514 g, 2 mmol), α-morpholinostyrene (0.57 g, 3 mmol), and ammonia (10 mmol) in methanol (20 ml) was allowed to stand at room temperature. After 2 h precipitates began to form and after 4 d the precipitates were collected by filtration and washed with methanol. The compound was analytically pure **9Bb** (0.720 g, 92%). The compound was also isolated in 45% yield along with **4Bb** (13%) by a reaction of **3b** (1 mmol), α-morpholinostyrene (2 mmol), and ammonia (10 mmol) in methanol (10 ml) at 70 °C for 2 h. Mp (decomp) 146—152 °C; IR (Nujol), 3330, 3260 (NH), 3150, 1750 (ester CO), 1630 (C=C–N), 1613 (amide CO), 1555 (NO_2), 1370 (NO_2), 1320, 1275, 1250, 1170, 1137, 775, 690 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ=2.92 (s, NCH_3), 3.69 (s, OCH_3), 4.21 (dd, J=4.5 and 2.0 Hz, H-1), 5.19 (d, J=4.5 Hz, H-9), 5.24 (s, 1 H, NH), 5.50 (broad s, H-8), 6.9 (m, NH_4^+), 7.3—7.9 (m, 5 H, ph). ^{13}C NMR (DMSO-d_6) δ=33.09, 50.87, 52.21, 63.1, 81.20, 93.62, 112.34, 124.65, 126.43, 128.06, 128.43, 128.56, 136.37, 141.37, 161.99. Found: C, 48.94; H, 4.84; N, 17.81%. Calcd for $C_{16}H_{19}N_5O_7$: C, 48.85; H, 4.87; N, 17.81%.

Similarly, the following intermediates **9** were isolated as precipitates by reactions of **3**, an enamine, and ammonia in methanol at room temperature.

Ammonium 5-Methoxycarbonyl-2,8-dimethyl-4,9-dinitro-3-oxo-7-phenyl-2,6-diazabicyclo[3.3.1]non-7-en-4-ide (9Db): 90% yield. Pale yellow powder. Mp (decomp) 148—156 °C; IR (Nujol), 3330, 3260 (NH), 3200—2800 (NH_4^+), 1750 (ester CO), 1640 (C=C–N), 1620 (amide CO), 1555 (NO_2), 1372 (NO_2), 1300, 1247, 1160, 1062, 925, 770, 705 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ=1.68 (s, CCH_3), 3.04 (s, NCH_3), 3.66 (s, OCH_3), 4.03 (d, J=2.0 Hz, H-1), 4.96 (broad s, NH), 5.21 (broad d, J=2 Hz, H-9), 7—7.5 (m, NH_4^+), 7.1 (m, 2 H, Ph), 7.4 (m, 3 H, Ph). ^{13}C NMR (DMSO-d_6) δ=16.73, 35.53, 52.26, 56.12, 63.38, 82.31, 101.13, 112.59, 127.90, 128.06, 128.33, 128.49, 136.95, 137.54, 161.94. Found: C, 50.62; H, 5.34; N, 16.64%. Calcd for $C_{17}H_{21}N_5O_7$: C, 50.12; H, 5.20; N, 17.19%.

Ammonium 7,8-Butano-5-methoxycarbonyl-2-methyl-4,9-dinitro-3-oxo-2,6-diazabicyclo[3.3.1]non-7-en-4-ide (9Ab): 94% yield. Pale yellow powder. Mp (decomp) 137—149 °C, IR (Nujol), 3320 (NH), 3200—3250 (NH_4^+), 1750 (ester CO), 1680 (C=C–N), 1613 (amide CO), 1553 (NO_2), 1375 (NO_2), 1270, 1158, 1044, 930, 690 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ=1.5—2.1 (m, 8 H), 3.02 (s, NCH_3), 3.68 (s, OCH_3), 3.79 (s, NH), 4.80 (broad s, H-1), 5.08 (s, H_9), 7.2 (m, NH_4^+). ^{13}C NMR (DMSO-d_6) δ=21.97, 22.55, 26.49, 26.58, 35.17, 51.86, 55.01, 55.09, 63.00, 81.93, 100.72, 113.04, 134.28, 161.61. Found: C, 45.24; H, 5.58; N, 19.10%. Calcd for $C_{14}H_{21}N_5O_7$: C, 45.28; H, 5.70; N, 18.86%.

Reaction of 3f with Ammonia. A solution of **3f** (0.229 g, 1 mmol), cyclohexanone (0.29 g, 3 mmol), and ammonia (5 mmol) in methanol (10 ml) was heated at 70°C for 3 h. After removal of the solvent, residual oil was column-chromatographed on silica-gel. An ethanol eluate gave the ammonium salt of 4-hydroxy-1-methyl-3,5-dinitro-2-pyridone (**8**) (0.112 g, 48%) Decomp 234—245 °C (ivory powder from chloroform). IR (Nujol), 3300—3200 (NH_4^+), 1650 (CO), 1578, 1518 (NO_2), 1320 (NO_2), cm^{-1}. ^{1}H NMR (DMSO-d_6) δ=3.37 (s, 3 H), 7.18 (m, 4 H), 8.69 (s, 1 H). Found: C, 31.15; H, 3.42; N, 23.61%. Calcd for $C_6H_8N_4O_6$: C, 31.04; H, 3.47; N, 24.14%. The salt was heated in vacuo (0.1 mmHg, 1 mmHg=133.322 Pa) at 150 °C for 2 h to give free 4-hydroxy-1-methyl-3,5-dinitro-2-pyridone (**8**). Mp 212—216 °C. IR (Nujol), 3100 (OH), 1700 (CO), 1670 (CO), 1560, 1518 (NO_2), 1320 (NO_2) cm^{-1}. ^{1}H NMR (DMSO-d_6) δ=3.52 (s, 3 H), 8.85 (s, 1 H), 9.07 (s, 1 H). Found: C, 31.15; H, 3.42; N, 23.61%. Calcd for $C_6H_5N_3O_6$: C, 33.50; H, 2.34; N, 19.54%.

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