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Radical Chain Reductive Dehalogenation of Hetaryl Halides Promoted by Methoxide Ion

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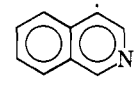
Abstract: 3-Iodopyridine and 4-bromoisoquinoline rapidly react with $NaOCH_3$ at 165° to give mixtures consisting of pyridine and isoquinoline, respectively, as the major products along with the substitution products 3-methoxypyridine and 4-methoxyisoquinoline. Reduction of 3-iodopyridine in $NaOCH_3$–CH_3OD takes place without the incorporation of a significant amount of deuterium at the 3 position of pyridine. Reduction of both the iodo and bromo compounds is inhibited by nitrobenzene, azoxybenzene, and 1,1-diphenylethylene but not by oxygen and is believed to take place by a radical chain process which involves the formation of 3-pyridyl and 4-isoquinolyl radical intermediates. Low concentrations of copper(II) chloride accelerate the methoxydehalogenation of both hetaryl halides so that substitution becomes the major reaction. In the presence of the radical initiator azobisisobutyronitrile (AIBN) and $NaOCH_3$, the two halogenated reactants as well as 2- and 4-iodopyridines undergo at 100° rapid reductive dehalogenation. Kinetic studies carried out with the three isomeric iodopyridines show that the rate of the reduction reaction is limited by the decomposition of AIBN and is independent of the identity of the iodide. In the presence of AIBN–$NaOCH_3$–CH_3OD 3-iodopyridine gives pyridine largely free of deuterium at position 3, indicating the formation of the 3-pyridyl radical intermediate. Reactions involving $NaOCH_3$ and AIBN–$NaOCH_3$ represent new ways to generate hetaryl radicals.

We wish to report that 3-iodopyridine and 4-bromoisoquinoline react with methoxide ion in methanol to give the dehalogenated compounds pyridine and isoquinoline as major products. These reactions are shown to be radical chain processes. Reduction may be initiated by the radical initiator azobisisobutyronitrile (AIBN) acting in the presence of $NaOCH_3$ and inhibited by various radical and electron trapping agents. 3-Pyridyl (I) and 4-isoquinolyl (II) radicals are intermediates. Our results show that hetaryl halides are a new source of hetaryl free radicals, especially under highly basic conditions. We previously have shown that radical II may be trapped by thiophenoxide ion in methanol to give 4-phenylthioisoquinoline substitution product by a new route.[1] Others have demonstrated that aryl and hetaryl radicals may be trapped by a variety of nucleophiles, giving rise to new and useful routes to aromatic substitution products.[2-6] Indeed, trapping of radicals under basic conditions represents a promising new method of nucleophilic aliphatic and aromatic substitution.[7-9]

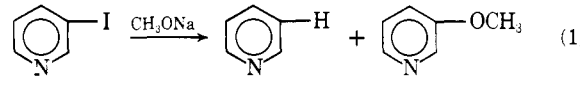
I



II

Results

Iodopyridines. The results of ten experiments involving 3-iodopyridine and $NaOCH_3$ in methanol are summarized in Table I. Pyridine is the major product; yields range from 73 to 90% when the reaction is complete. Other heterocyclic products include 3-methoxypyridine and the anion of 3-hydroxypyridine. The hydroxy compound is produced from the 3-methoxy compound in an ether cleavage reaction with methoxide ion, $k = 4.7 \times 10^{-5}\ M^{-1}\ \text{sec}^{-1}$ at 165°,[10] eq 1

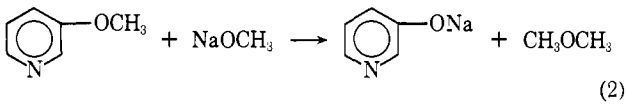


(1)

Table I. Formation of Pyridine in the Reaction of 3-Iodopyridine with Sodium Methoxide

Conditions	$[NaOCH_3]_0$, M	Time, min	% pyridine[a]
Degassed, 165°[b]	0.95	7[c]	9
Air, 165°[b]	0.95	7[c]	10
Air, 165°[b]	0.95	32[c]	46
O_2, 165°[b]	0.74	15[c]	10
N_2, 165°[d]	0.95	37[e]	86[f]
Air, 165°[d]	1.5	21[e]	82[f]
O_2, 165°[d]	1.5	19[e]	84[f]
N_2, 165°[d]	1.9	18[e]	73[f]
N_2, 191°[d]	1.0	5[e]	88[f]
N_2, 100°[d]	1.2	8200[e]	90[f]

[a] Other products included 3-methoxypyridine and the anion of 3-hydroxypyridine. [b] 0.011 M substrate. [c] Total reaction time. [d] 0.24 M substrate. [e] Time for the first half-life. [f] Yield at completion.



(2)

and 2. The reduction of 3-iodopyridine stands in marked contrast with the substitution reactions of 3-chloro- and 3-bromopyridines, which are converted completely to 3-methoxypyridine by methoxide ion.[10]

Experiments were carried out generally at 165° to determine the influence of oxygen, substrate, and base concentrations on the rate of the reduction reaction. The first four entries in Table I represent determinations by GLC of the composition of mixtures at low (0.011 M) substrate concentration at a single point in a reaction interrupted prior to complete disappearance of substrate. The remaining six entries refer to mixtures analyzed by NMR as a function of time at higher (0.24 M) substrate concentration; the yield of pyridine at complete conversion of the substrate is indicated.

Oxygen does not influence the rate of reduction. Degassing by means of four freeze–thaw cycles in order to remove dissolved oxygen did not change the rate relative to an identical sample prepared under air. About the same amount of pyridine formed in both cases in these interrupted reactions. The presence of a large excess of oxygen (13 ml of gas over 2 ml of reaction mixture, entry 4, Table I) did not give rise to a significant retardation in rate. When the substrate concentration was increased 22-fold and mixtures were analyzed periodically, no induction period could be detected, even at 100° where the reaction is very slow. The 22-fold variation in substrate concentration does not appear to influence initial rates appreciably.

No reaction rakes place in the absence of $NaOCH_3$. A sample of 3-iodopyridine heated at 165° for 5300 min in methanol free of added methoxide ion remained unchanged. High concentrations of $NaOCH_3$ are required for rapid reduction (Table I).

In order to determine whether the hydrogen atom which is incorporated into the product comes from a carbon or oxygen center of the solvent a reaction was carried out in $NaOCH_3$–CH_3OD at 165°. An NMR spectrum of the reaction mixture indicated that hydrogen rather than deuterium is added to position 3 of pyridine. Because there is signal overlap which makes accurate analysis difficult, some deuterium may have been introduced into position 3. A generous estimate of the maximum amount of deuterium possibly introduced is about 15%. Two conclusions may be drawn from this result. (a) The hydrogen which is incorporated into the major product comes from a methyl rather than from a hydroxyl group of the solvent.[11] (b) The heterocyclic intermediate must be a radical rather than an ion. A 3-pyridyl radical is expected to remove a hydrogen atom from a methyl group but a 3-pyridyl anion[12] should remove a proton from a hydroxyl group of solvent.

Table II. Effect of Additives on the Product Distribution from the Reaction of 0.24 M 3-Iodopyridine and 1.9 M Sodium Methoxide at 165° for 30 Min[a]

	Yield, %		
$[Additive]_0$	3-Iodopyridine	3-Methoxypyridine	Pyridine
	26 ± 2[b]	7 ± 1[b]	67 ± 2[b]
0.50 M pyrazine	3	7	90
0.71 M pyrazine		5	95
0.87 M naphthalene	13	5	82
0.079 M azoxybenzene	39	13	48
0.30 M azobenzene	44	9	47
0.049 M 1,1-diphenylethylene	62	9	29
0.11 M 1,1-diphenylethylene	78	13	9
4.4×10^{-3} M $CuCl_2$[c,d]		>95	<5
4.4×10^{-4} M $CuCl_2$[c]	~3	93	~4
4.4×10^{-5} M $CuCl_2$[c]	41	42	17
0.055 M 1,1-diphenylethylene + 4.4×10^{-2} M $CuCl_2$		>95	<5

[a] Results of single experiments, except where indicated. [b] Average of three runs. [c] Heated for 10 min. [d] Heterogeneous.

The results in Table II indicate how organic and inorganic additives influence the rate and composition of reaction mixtures. All reactions were carried out with the same concentrations of substrate and $NaOCH_3$ heated usually for 30 min at 165°. Under these conditions the reaction is incomplete in the absence of additives and so changes in the amount of reactant and products provide a sensitive measure of the effects of these additives. All mixtures were analyzed by GLC.

Three experiments conducted in the absence of additives show that these results are highly reproducible; 26% of the reactant remains and 7% of 3-methoxypyridine and 67% of pyridine form after 30 min. Interestingly, both pyrazine and naphthalene accelerate the disappearance of 3-iodopyridine by promoting the formation of pyridine. It is not clear how these additives operate. By contrast, azoxybenzene, azobenzene, and 1,1-diphenylethylene retard the reaction. For example, in the presence of 0.11 M diphenylethylene, 78% of 3-iodopyridine remains after 30 min. Increasing the concentration of diphenylethylene, the most effective inhibitor, increases the extent of retardation by inhibiting the formation of pyridine. Because the three benzene derivatives are known to be effective in breaking radical chain reactions,[7,8,13] it seems likely that pyridine is being formed by a radical chain process.

The effect of copper(II) chloride on the reaction is different from the effects of the promoters and the inhibitors (Table II). Very low levels, as little as 4.4×10^{-5} M, accelerate the reaction of 3-iodopyridine to give 3-methoxypyridine. Conversion to 3-methoxypyridine is nearly complete after just 10 min in the presence of 4.4×10^{-4} M copper salt. 1,1-Diphenylethylene does not suppress the extraordinary catalytic effect of the copper salt. Note that a mixture of 3-chloropyridine (0.63 M), copper(II) chloride (0.03 M), and $NaOCH_3$ (1.6 M) when heated at 165° for 90 min gave starting material and only a trace of 3-methoxypyridine. Clearly, the identity of the halogen of the hetaryl halide is important in the copper-catalyzed reactions.

The radical initiator azobisisobutyronitrile (AIBN) was used to promote reductive deiodination of 3- as well as 2- and 4-iodopyridines in $NaOCH_3$–CH_3OH. Results are summarized in Table III. We were led to try this initiator by a report that AIBN–$NaOCH_3$ brings about the reductive deiodination of *m*-chloroiodobenzene.[14]

When 3-iodopyridine was heated at 165° for 10 min in

Table III. Composition of Reaction Mixtures from the Reductive Deiodination of 2-, 3-, and 4-Iodopyridines Promoted by AIBN[a] in $NaOCH_3$–CH_3OH.

[Compd]$_0$, M	[NaO-CH_3]$_0$, M	[AIBN]$_0$, M	Temp, °C	Time, min	Yield, % Iodo	Methoxy	Pyridine
3-I, 0.32	1.04	0.16	165	3	~5		~95
3-I, 0.50	1.19[b]	0.26	165	3	~10		~90
3-I, 0.37	1.19	0.19	100	50	12		88
2-I, 0.26	0.97	0.16	165	4		31	69
2-I, 0.30	1.11	0.18	100	50	35	5	60
4-I, 0.28	0.97	0.16	165	4		10	90
4-I, 0.33	1.11	0.19	100	50	2	10	88

[a] Azobisisobutyronitrile. [b] Methanol-*O*-*d* is the solvent.

methanol containing AIBN but not methoxide ion, the iodo compound did not react. The initiator decomposed completely under these conditions.[15] In another experiment involving AIBN at 165° (this time 1.04 M $NaOCH_3$ was present), the 3-iodo compound was converted to pyridine in greater than 90% yield in 3 min. Clearly, reduction is promoted by the radical initiator AIBN in a reaction which requires $NaOCH_3$. An experiment with AIBN–$NaOCH_3$ was carried out at 165° in methanol-*O*-d. Again, pyridine was formed in at least 90% yield; NMR analysis indicated that no more than about 15% of deuterium was incorporated into position 3. Therefore, a 3-pyridyl radical intermediate is likely to occur in these reactions too.

Experiments with 3-iodopyridine and AIBN–$NaOCH_3$ also were carried out at 100° where reductive dehalogenation is slower. The disappearance of reactant and the appearance of product followed smooth concentration–time curves which showed no evidence of an induction period, the first measurement being made at 5 min. The formation of pyridine was judged to be complete at 50 min.

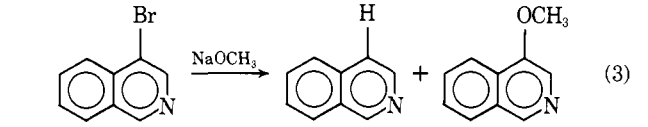
Similar experiments were conducted with 2- and 4-iodopyridines and AIBN–$NaOCH_3$ at 165 and 100°. Again, pyridine is the major product but some 2- and 4-methoxypyridines are formed as well (Table III). No induction period could be detected. Again, the formation of pyridine appears to be complete after 50 min at 100°. When iodopyridine remains after the destruction of the initiator, additional heating does not give rise to more pyridine. Instead, iodo compound is converted to methoxypyridine.

Control runs suggest that the formation of 2- and 4-methoxypyridines is likely to result chiefly from methoxydeiodination, an ionic side reaction. In these experiments the concentrations of iodopyridines and $NaOCH_3$ are the same as those in runs with AIBN but initiator was not present. Thus, after 3–4 min at 165° conversion to methoxypyridine is essentially complete. After 50 min at 100° 23% of 2- and 45% of 4-methoxypyridine are formed. Pyridine was not detected.

When the rate of disappearance of 2-, 3-, or 4-iodopyridine in the AIBN–$NaOCH_3$ reactions at 100° was corrected for the presence of unreacted iodide, linear first-order plots were obtained. The three substrates all reacted with the same half-life, 6–7 min. Since the half-life of AIBN in various solvents at 100° is about 6 min and the decomposition of AIBN is known to be first order,[15] it is likely that the rate of disappearance of the iodopyridines measures the rate of decomposition of AIBN. This new finding shows that the thermolysis of AIBN to radical intermediates is rate determining and slower than reductive dehalogenation. Sodium methoxide plays a role in product-determining steps but not in initiator decomposition. Perhaps these conclusions apply to the reductive deiodination of *m*-chloroiodobenzene as well.[14]

4-Bromoisoquinoline. In the presence of $NaOCH_3$ at 235° 4-bromoisoquinoline is known to be converted to isoquinoline.[16] We have found that product forms in greater than 90% yield at temperatures ranging from 143 to 165°. At 165° in the presence of 0.79 M $NaOCH_3$ the reaction is complete after 1 hr. By contrast, in the absence of $NaOCH_3$ no noticeable reaction occurred after 1146 min heating at 165°. Clearly, $NaOCH_3$ is required.

Two other products containing the isoquinoline ring are formed as well. They are 4-methoxy- and 4-hydroxyisoquinolines, eq 3 and 4. Reaction mixtures heated for long



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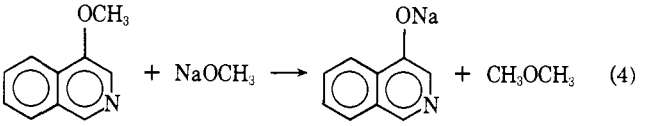


(4)

periods of time showed a decrease in the amount of 4-methoxyisoquinoline product while the amount of 4-hydroxyisoquinoline, present in its ionized form, increased. The conversion of 4-methoxyisoquinoline to 4-hydroxyisoquinoline was confirmed in separate experiments. Authentic 4-methoxyisoquinoline was converted to 4-hydroxyisoquinoline in methanol–sodium methoxide solution at 165°; this reaction has a rate constant of 9.7×10^{-5} M^{-1} sec^{-1}. It is assumed that methyl ether is the other product of the cleavage reaction.

The combined yields of substitution products were less than 10%. Hence, the reduction to substitution product ratio is greater than 10. Results are highly reproducible in that ten runs in which the ratio of $NaOCH_3$ to 4-bromoisoquinoline varied from 2.2 to 5.7 gave similar product ratios. No change in the product ratio or rate of conversion was detected when the reaction was carried out in an amber tube, and therefore photocatalysis[17] is not essential to the reaction. The product ratio and the rate of reduction were the same when either an oxygen or a nitrogen atmosphere was employed. A short induction period may have been present in these reactions followed as a function of time.

Sodium formate, a solvent-derived oxidation product, is present as well. Identification rests on the observed chemical shift (τ 1.30) and reports that sodium formate forms when redox reactions are carried out in methanol–sodium methoxide solution.[18] The isoquinoline to formate ion ratio in a typical reaction mixture was estimated by NMR analysis to be 2.

Because sodium formate may result from the hydrolysis of methyl formate, an oxidation product produced from the solvent, a control experiment was carried out to verify the presence of water and to determine the water content of the methanol solvent used in the kinetic studies. To a known sample of methyl formate in methanol was added $NaOCH_3$; sodium formate immediately precipitated from the mixture. From the amount of ester remaining in solution (NMR analysis) it was calculated that the solvent was 0.33 M in water. This is sufficient water to give rise to the quantities of sodium formate observed in the kinetic studies. (It was not clear whether sodium formate appeared in the reactions involving 3-iodopyridine. This substrate and also pyridine have signals in the same region as sodium formate and make accurate analysis difficult.)

Two attempts to initiate the reduction of 4-bromoisoquinoline were made using AIBN–$NaOCH_3$ at 100°. A 0.32 M solution of this substrate containing 0.30 M $NaOCH_3$ and 0.63 M AIBN was heated for 90 min with little notice-

Table IV. Influence of Additives on the Yields of Reduction and Substitution Products Formed from 4-Bromoisoquinoline and Sodium Methoxide[a]

$[4\text{-Bromo}]_0$, M	$[NaOCH_3]_0$, M	Temp, °C	Additive	% methoxy[b]	% isoquinoline
0.66	1.6	165	N_2 saturated	<10	>90
0.66	1.6	165	O_2 saturated	<10	>90
0.58	1.3	165	0.01 M $CuCl_2$[c]	20	80
0.38	0.8	165	0.05 M $CuCl_2$[c]	80	20
0.44	2.5	143	0.05 M azoxybenzene	17	83
0.50	3.3	143	~0.6 M azoxybenzene	50	50
0.44	2.5	143	0.05 M nitrobenzene	19	81
0.66	1.6	147	~0.6 M 1,1-diphenylethylene[c]	18	82
0.66	1.6	147	0.3 M 2,2'-dinitrobiphenyl	~50	~50

[a] Product yields were determined when the reactions were approximately complete. Results of single experiments. [b] Includes the ether cleavage product 4-hydroxyisoquinoline. [c] Heterogeneous mixture.

able reaction of the halide. A second, more basic, solution was prepared. It consisted of 0.15 M substrate, 1.5 M $NaOCH_3$, and 0.30 M AIBN. After heating for 30 min a 30% conversion to isoquinoline resulted. This conversion is not solely due to $NaOCH_3$ because no reaction occurred over 3 hr under the same conditions in the absence of AIBN. Therefore, high concentrations of $NaOCH_3$ are an essential requirement of the AIBN-induced reaction. The ability of AIBN to induce reductive dehalogenation is not limited to iodides.

Copper(II) chloride had a dramatic effect on the product distribution (Table IV). Solutions were heterogeneous, owing to the poor solubility of copper salts employed in high concentration. Indicated concentrations reflect the amount of material which would have been present in solution if the salts were soluble. With 0.01 M copper(II) chloride the amount of isoquinoline formed decreased to 80% while the yield of substitution products increased to 20%. In the presence of 0.05 M copper salt reduction decreased to only 20% and substitution increased to 80%. The run having the lower concentration of the copper salt was examined as a function of time. The first determination was made after heating the sample for 6 min, approximately the first half-life at 165°. The formation of the substitution product was complete; additional heating only served to produce reduction product. A control reaction involving only $NaOCH_3$ and copper(II) chloride showed that rapid reduction to elemental copper occurred when the sample was heated at 165°. Hence the limited catalytic effect of the copper salt on the substitution reaction. 4-Methoxyisoquinoline was isolated in 47% yield from a reaction between 4-bromoisoquinoline and $NaOCH_3$ on a preparative scale in the presence of copper(II) chloride.

Several experiments were conducted to investigate the effects of potential inhibitors on the course of the reaction. Initial experiments focused on the effects the additives had on the reduction to substitution product ratio when the reaction was complete. Organic compounds which brought about a decrease in the yield of isoquinoline and an increase in the yield of 4-methoxyisoquinoline included azoxybenzene, nitrobenzene, 1,1-diphenylethylene, and 2,2'-dinitrobiphenyl. Results are summarized in Table IV. Azoxybenzene and nitrobenzene present in low concentrations (0.05 M) caused the yield of isoquinoline to decrease to about 83%. Increasing the concentration of azoxybenzene to about

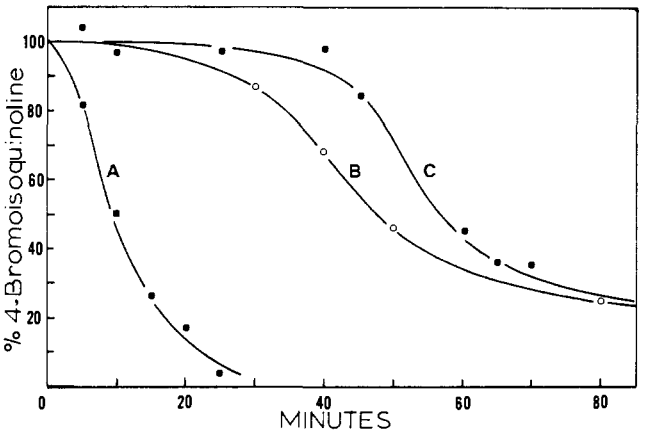


Figure 1. Rates of disappearance of 0.44 M 4-bromoisoquinoline in 2.5 M sodium methoxide solution at 143°, curve A. Curves B and C show the inhibitory effects of 0.05 M azoxybenzene and 0.05 M nitrobenzene, respectively, on the reaction.

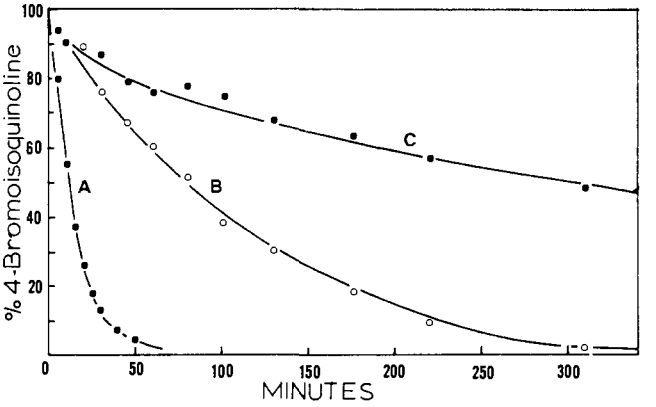


Figure 2. Rates of disappearance of 0.66 M 4-bromoisoquinoline in 1.6 M sodium methoxide solution at 147°, curve A. Curves B and C show the inhibitory effects of approximately 0.6 M 1,1-diphenylethylene and 0.3 M 2,2'-dinitrobiphenyl, respectively, on the reaction.

0.6 M resulted in a further reduction in the yield of isoquinoline to 50%. In the presence of 1,1-diphenylethylene, only partially miscible, 82% of isoquinoline was formed. When 0.3 M 2,2'-dinitrobiphenyl was present, about 50% of the bromo compound was converted to isoquinoline.

In order to obtain more information about the effects of the organic additives, the disappearance of 4-bromoisoquinoline was followed as a function of time. Figure 1 shows three curves referring to three separate experiments in which the initial concentrations of substrate and $NaOCH_3$ are the same. Curve A shows the rate of disappearance of 4-bromoisoquinoline in the presence of 2.5 M $NaOCH_3$ at 143° containing no additive. Curves B and C show the substantial rate-retarding effects of 0.05 M azoxybenzene and 0.05 M nitrobenzene, respectively, on the rate of the reaction. Both inhibitors give rise to long induction periods, lasting for about 40 min in the case of nitrobenzene and slightly less for azoxybenzene.

Figure 2 shows the inhibitory effects of 1,1-diphenylethylene and of 0.3 M 2,2'-dinitrobiphenyl, respectively, on the rate of reaction of 4-bromoisoquinoline at 147° in 1.6 M $NaOCH_3$. Note that inhibition persists for long periods of time. For example, in the absence of additive the conversion of 4-bromoisoquinoline to products is complete in about 50 min. However, in the presence of the ethylene derivative about 300 min are required for completion. The true concentration of the ethylene inhibitor in solution is not known

owing to its limited solubility. The sample was prepared so that the concentration would be 0.6 *M* if it were completely soluble. Curve C, Figure 2, shows the substantial rate retardation by 2,2′-dinitrobiphenyl. After 300 min the reaction is only about 50% complete.

In all these experiments showing inhibition, 4-methoxyisoquinoline is slowly being formed at the expense of isoquinoline. Such results are strongly suggestive of a radical chain process for the formation of isoquinoline.

It has been reported that 4-bromoisoquinoline reacts with potassium *tert*-butoxide in *tert*-butyl alcohol to give isoquinoline.[16] We have verified the formation of isoquinoline in this solvent at 140° but there was extensive degradation as evidenced by discoloration and a loss of resolution in the NMR spectrum. It appears that 0.04 *M* azoxybenzene and approximately 0.1 *M* 1,1-diphenylethylene inhibit the formation of isoquinoline. Although these results are interesting because the solvent is known to be a very poor hydrogen atom donor by comparison with methanol,[19] studies were discontinued owing to the severe decomposition.

Other Hetaryl Halides. 4-Chloroisoquinoline also reacts with $NaOCH_3$ at 165° to give isoquinoline as the major product, but 4-methoxyisoquinoline formation is more extensive than in the case of the bromo compound. Clearly, reduction is not limited to iodides and bromides.

3-Bromoquinoline reacts with $NaOCH_3$ at 165° to give quinoline, 71% being isolated on a preparative scale. The reductive debromination of 3-bromopyridine could not be initiated with AIBN–$NaOCH_3$. Thus, heating 0.32 *M* 3-bromopyridine, 0.24 *M* AIBN, and 0.97 *M* $NaOCH_3$ at 165° for 10 min left the bromopyridine unchanged.

Discussion

The evidence clearly indicates that 3-iodopyridine and 4-bromoisoquinoline give rise to their respective dehalogenation products pyridine and isoquinoline by a radical chain process. (1) The pyridine which is formed in methanol-*O*-*d* contains little deuterium at position 3. (2) The formation of both reduction products is inhibited by substances known to trap electrons and radicals. (3) Reductive dehalogenation is promoted by the radical initiator AIBN. The pyridine formed in this reaction shows little incorporation of deuterium at position 3 when methanol-*O*-*d* serves as the solvent.

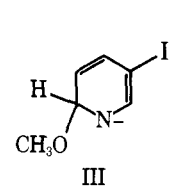
Methoxydehalogenated products formed from halogenated pyridines and isoquinolines do not arise primarily by a reaction involving trapping of an intermediate hetaryl radical by methoxide ion. These substitution products must arise largely by an SNAr pathway involving the formation of an anionic σ complex. This conclusion follows from the observations that (1) the reduction to substitution product ratio decreases in the presence of inhibitors and (2) the radical initiator AIBN promotes the formation of the reduction but not the substitution product. The variable affinity of alkoxide ions for aliphatic radicals has been noted.[9]

We can only speculate about the detailed nature of the radical chain reductive dehalogenation reaction involving $NaOCH_3$. It does seem very likely that σ radicals I and II form during the reaction. However, the nature of the initiation process is unclear. The most direct pathway involves the donation of an electron from methoxide ion[20] to a hetaryl halide to give radical anion C–X·$^-$ which then is converted to σ radical C· on elimination of halide ion, eq 5 and 6.

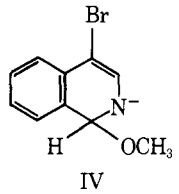
$$CH_3O{:}^- + C{-}X \longrightarrow CH_3O\cdot + C{-}X\cdot^- \quad (5)$$

$$C{-}X\cdot^- \longrightarrow C\cdot + X^- \quad (6)$$

A less direct pathway for initiation proceeds through an anionic σ complex. Perhaps methoxide ion reversibly adds to a hetaryl halide to give a π-delocalized σ complex such as III or IV which then donates an electron to uncomplexed halide



III



IV

to give a radical anion. Related σ complexes are known to exist.[21] Moreover, π-delocalized anions can be good electron donors.[22]

The propagation steps may very well involve the radical anion of formaldehyde, $\cdot CH_2O^-$, as the chain carrier.[14] This reducing agent forms when a σ radical abstracts a hydrogen atom from the methyl group of either methanol or methoxide ion, eq 7–9. Donation of an electron from the reducing agent to the hetaryl halide continues the chain by giving more radical anion of the halide and formaldehyde, eq 10. Formaldehyde may be converted to formate ion, an

$$C\cdot + CH_3OH \longrightarrow CH + \dot{C}H_2OH \quad (7)$$

$$\dot{C}H_2OH + CH_3O^- \longrightarrow \dot{C}H_2O^- + CH_3OH \quad (8)$$

$$C\cdot + CH_3O^- \longrightarrow CH + \dot{C}H_2O^- \quad (9)$$

$$C{-}X + \dot{C}H_2O^- \longrightarrow C{-}X\cdot^- + CH_2{=}O \quad (10)$$

observed product, in two ways. The aldehyde may react with hydroxide ion to give the product directly or it may first be converted to methyl formate which then hydrolyzes by reacting with the residual water in the solvent.

Radical propagation steps 6–8 and 10 have been proposed to account for the reductive deiodination of *m*-chloroiodobenzene by methoxide ion.[14] There is considerable precedent for the formation of hetaryl radicals from hetaryl halides and electrons generated by chemical and electrochemical methods.[23]

Inhibitors function by breaking radical chains. They serve as electron acceptors and/or radical trapping reagents.[7,8,13] Although the nitrated inhibitors are known to react with methoxide ion,[18] the rate retardations observed with these additives must largely be the result of inhibition and not of methoxide ion consumption. From the known stoichiometry of nitro group reduction[18,24] and the low levels of inhibitor employed, it can be concluded that changes in the concentration of methoxide ion are much too small to result in the observed rate changes. Moreover, molecules such as azoxybenzene and 1,1-diphenylethylene do not react with methoxide ion,[13,24] yet they retard reductive dehalogenation. True radical chain breaking is being observed.

No inhibition by added oxygen was observed in spite of a careful search. We have no explanation for its absence. However, the failure of oxygen to serve as an inhibitor of a radical chain reaction is not unprecedented.[20,25] Chain reactions also are known where oxygen may promote or inhibit the same reaction depending on its concentration.[26] Oxygen may even exert a beneficial effect.[20]

The ability of organic additives to inhibit reduction reactions while oxygen fails is not unexpected. Consider, for example, several reported competition reactions involving aryl radicals. When aryl radicals are allowed to compete for oxygen and unsaturated organic additives, preferential reaction between either trapping reagent may be observed as radical structure is varied. The more nucleophilic the radical, the more readily will it react with oxygen.[27] However, these interesting and related observations provide no explanation for the lack of an oxygen effect in our reduction reactions.

The reduction reactions promoted by AIBN probably do not take place by a reaction involving a radical from the ini-

tiator and the hetaryl halide, e.g., by halogen atom abstraction.[28] According to this route it is not apparent why methoxide ion is required for reductive dehalogenation. Instead, it is likely that a radical produced from the initiator reacts with either methanol or methoxide ion to generate the reducing agent which, in turn, reacts with hetaryl halide according to eq 10 by electron transfer. Moreover, AIBN–$NaOCH_3$ promotes the reductive dehalogenation of 4-bromoisoquinoline and not 3-bromopyridine. The difference in reactivity between these two bromo compounds can be rationalized in terms of the electron acceptor properties of the two heterocycles. 3-Bromopyridine is less reactive than 4-bromoisoquinoline primarily because it is a poorer electron acceptor.[29]

Copper salts have long been known to catalyze substitution reactions at an aromatic carbon atom,[30] but the mechanism of catalysis continues to remain obscure. It has been speculated recently that ether formation from copper(I) alkoxides and aryl iodides in the presence of pyridine may take place by a radical chain (SRN1) pathway.[31] Our results clearly demonstrate that if such a route does operate, substitution product cannot form by a reaction between a σ radical and methoxide ion because these reactants give rise to reduction product instead.

There is a ready explanation for the observed differences in the reaction of 3-chloro- and 3-bromopyridine with $NaOCH_3$[10] and in the reaction of 3-iodopyridine with the same reagent. Iodo compounds often undergo aromatic nucleophilic substitution more slowly than the corresponding chloro and bromo compounds.[32] However, iodo compounds in their radical anion form usually revert to σ radicals much faster than the radical anions of bromides. Radical anions of bromides, in turn, are more reactive than chlorides.[33] Hence, the radical anion route is favored for 3-iodopyridine but the substitution pathway predominates for the other 3-halopyridines. In the case of 4-haloisoquinolines, the isoquinoline ring is sufficiently better at accepting electrons than the pyridine ring so that the electron transfer process predominates for the bromide and even the chloride.

The reductive dehalogenation reactions reported here provide convenient ways to generate hetaryl radicals from readily available materials. Iodides, bromides, and even chlorides may react. Even those compounds which undergo rapid methoxydehalogenation may be made to yield radical intermediates by using a radical initiator such as AIBN. It is likely that other initiators may be employed as well.

Other hetaryl halides are likely to undergo reductive dehalogenation in the presence of alkoxide ions. The halogen atom need not be bonded to the ring containing a heteroatom. For example, 6- and 8-bromoquinolines gave good yields of quinoline when heated with $NaOCH_3$.[34] An obscure ionic mechanism was suggested for these transformations. More likely, these are radical chain reactions in which the halogen atom is removed from the carbocyclic portion of the heterocycle.

We are beginning to recognize when reductive dehalogenation is going to predominate over nucleophilic substitution. Reductive dehalogenation is favorable when SNAr substitution is difficult. For example, in contrast with the reductive dehalogenation of 6- and 8-bromoquinolines, 7-bromoquinoline reacts with methoxide ion to give 7-methoxyquinoline.[35] In the case of the 6- and 8-bromo compounds the negative charge present on the ionic σ complex leading to substitution product is only slightly stabilized by the annular nitrogen atom, but the nitrogen atom provides considerably more stabilization in the case of the 7-bromo isomer because the charge is resonance delocalized onto this atom in a σ complex. No doubt, many other examples of reductive dehalogenation at an aromatic carbon atom will be reported. It seems likely that the intermediate free radicals will be trapped in reactions with nucleophiles to effect new routes to substitution products.

Experimental Section

2-Iodopyridine, prepared from 2-bromopyridine and HI,[36] is contaminated with a small amount of starting material; this is inconsequential because the impurity gives rise to substitution and not to reduction product. 4-Iodopyridine was prepared using 2-aminopyridine;[37] 3-[38] and 4-methoxypyridines[39] were prepared by known methods. 4-Chloroisoquinoline[40] was prepared in 13% yield from isoquinoline by a modification of the procedure used for the preparation of 4-bromoisoquinoline,[41] chlorine being substituted for bromine. Other chemicals were commercially available. Reagent grade methanol was used. Solutions were protected from air by serum stoppers; transfers were made by syringe.

Spectra were obtained with a Varian A-60A spectrometer; *tert*-butyl alcohol often served as an internal standard. A Varian 1400 instrument with flame ionization detector was used for GLC analyses; the recorder had a Disc integrator.

Pyridines were analyzed by GLC using a 2 m × 0.125 in. copper column packed with Chromosorb W HDMS 60/80 coated either with 17% Carbowax 20M or 10% sodium carbonate and 20% Versamid 900. Response factors for the Carbowax column are 1.00, pyrazine; 0.670, pyridine; 0.680, 3-methoxypyridine; and 0.812, 3-iodopyridine. Response factors for the Versamid column are 1.00, naphthalene, 2.47, pyridine; 2.29, 3-methoxypyridine; and 2.56, 3-iodopyridine. Isoquinolines were analyzed using a 40-cm copper column packed with Chromosorb W HMDS 60/80 coated with 10% Na_2CO_3 and 20% Versamid 900. Response factors are 1.00, 7,8-benzoquinoline; 1.51, isoquinoline; 1.39, 4-bromoisoquinoline; and 1.51, 4-methoxyisoquinoline. Peaks for 4-bromo- and 4-methoxyisoquinolines overlap.

Constant temperatures were maintained using a steam cone (100°) or vapor baths consisting of mesitylene (165°) or benzonitrile (191°). All other temperatures were obtained using an electronically regulated oil bath; temperatures were checked with an NBS certified thermometer. Concentrations indicated throughout this article are corrected for the thermal expansion of methanol using known densities.[42]

Rates of Reductive Deiodination of Iodopyridines Using Azobisisobutyronitrile and Methoxide Ion. 2-, 3-, or 4-iodopyridine (~0.15 g, 0.73 mmol) and azobisisobutyronitrile (AIBN, 0.068 g, 0.41 mmol) were weighed into a 2-ml volumetric flask and 0.618 ml of 3.94 *M* $NaOCH_3$ was added by syringe. Following dilution to the mark with methanol an aliquot was transferred to an NMR tube and the tube was sealed. A spectrum was taken before heating and then intermittently after heating the sample in a steam cone. Concentrations of iodopyridine, pyridine, and 2- and 4-methoxypyridine were obtained as a function of time by integrating the following signals: 2-iodopyridine, H-6 (τ 1.66), pyridine, H-2,6 (τ 1.46), and 2-methoxypyridine, H-3,5 (τ 3.16); 3-iodopyridine, H-2 (τ 1.21) and H-6 (τ 1.46), and pyridine, H-2,6; 4-iodopyridine, H-2,6 (τ 1.78), pyridine, H-3,5 (τ 2.56), and 4-methoxypyridine, H-2,6 (τ 1.66) and H-3,5 (τ 3.03). The amount of 4-iodopyridine was determined by subtracting from the combined areas for H-2,6 of iodo- and methoxypyridines the area of H-3,5 of the methoxy compound. The approximate center of a multiplet is indicated.

From plots of time vs. the concentrations of reactants and products obtained from runs at 100° an "infinity" value for the disappearance of iodopyridine was estimated. A first-order kinetic plot was constructed with the aid of eq 11. All plots were linear for 4 half-lives; half-lives for the three substrates at 100° were 6–7 min. "Infinity" values are those given in Table III after 50 min of reaction.

$$\ln \frac{[\text{Iodo}]_0 - [\text{Iodo}]_\infty}{[\text{Iodo}] - [\text{Iodo}]_\infty} = kt \qquad (11)$$

Reactions of 3-Iodopyridine with Sodium Methoxide. Mixtures were prepared as indicated above except that AIBN was not added; several stock solutions of standardized sodium methoxide were employed. In some cases a blanket of nitrogen or oxygen was added before sealing the NMR tube. Samples were heated intermittently and concentration-time curves were constructed by inte-

grating the multiplets indicated above. Random samples were analyzed by GLC in order to check concentration ratios. A mass balance was obtained using an internal GLC standard. The agreement between the two analytical methods is good. For example, by NMR analysis it was concluded that a sample consisted of 75% pyridine, 25% 3-methoxypyridine, and a trace of 3-iodopyridine; by GLC analysis the values were 73, 25, and 2%, respectively.

A sample of 3-iodopyridine was heated at 165° for 30 min with 1.7 M $NaOCH_3$ in methanol-*O-d*. Analysis by NMR indicated that position 4 of the iodopyridine had undergone extensive hydrogen-deuterium exchange prior to reduction as expected.[43] Pyridine was the major product and the H-3,5 to H-2,6 ratio was 0.85. Pyridine does not undergo extensive H–D exchange under these conditions.[12]

For reactions involving the additives listed in Table III, stock solutions of 3-iodopyridine and sodium methoxide were added to a volumetric flask by syringe. A 0.500-ml aliquot then was transferred to an NMR tube which contained a weighed amount of inhibitor. In the case of copper(II) chloride reactions a sample of 0.0275 M stock solution prepared from the anhydrous salt and methanol was added to the volumetric flask prior to dilution to the mark.

Isolation of Pyridine from the Reaction of 3-Iodopyridine with Sodium Methoxide. A mixture of 4.1 g (0.020 mol) of 3-iodopyridine and sodium methoxide made from 3.2 g (0.14 mol) of sodium and 30 ml of methanol was heated in a bomb at 165° for 12.5 hr. The cooled solution was diluted with water and the mixture was extracted with methylene chloride ($MgSO_4$). Distillation afforded 0.50 g (6.3 mmol) of pyridine (33%) which was identified by NMR and by GLC. Under these conditions 3-methoxypyridine is cleaved to 3-hydroxypyridine, which is soluble in aqueous alkali.[10]

4-Methoxyisoquinoline. A solution of 3.5 g (0.026 mol) anhydrous copper(II) chloride in 50 ml of methanol was added to 5.0 g (0.024 mol) of 4-bromoisoquinoline in 15 ml of absolute methanol. The resulting light green precipitate was removed by filtration and placed in a Monel bomb with 23 ml of 4.30 M sodium methoxide. The bomb was heated at 165° for 30 min. After cooling to room temperature, the reaction mixture was filtered and the filtrate was diluted with 20 ml of water and extracted three times with 20-ml portions of ether. The ether layer, dried over calcium chloride, was concentrated. The concentrate was recrystallized from ether using a Dry Ice–acetone bath to induce crystallization; 1.8 g (0.011 mol) of white crystals was obtained, mp 71–75°, for a yield of 47%.

Anal. Calcd for $C_{10}H_9NO$: C, 75.42; H, 5.70; N, 8.81. Found: C, 75.56; H, 5.75; N, 8.74.

NMR (CCl_4) τ 5.99 (s, 3), 1.90–2.60 (m, 5), 0.70–1.78 [s (broad), 1]. The absorption between 0.70 and 1.78 ppm becomes a singlet in methanol. The absence of any resolution in carbon tetrachloride is most likely the result of relaxation.

Reactions of 4-Bromoisoquinolines with Sodium Methoxide. 4-Bromoisoquinoline was weighed into a volumetric flask (1–5 ml), *tert*-butyl alcohol and standardized sodium methoxide were added by syringe, and the mixture was diluted to the mark with methanol. Aliquots were transferred to NMR tubes which then were sealed. For runs involving inhibitors (Table IV), the inhibitor was weighed into an NMR tube prior to the addition of the aliquot. The maximum volume change resulting from the addition of inhibitor is estimated to be 5%.

Periodically the NMR tube was removed from the bath and quenched in cold water and the NMR spectrum of the solution was recorded. Peak areas were determined by repeated integrations in both directions, and the average value was calculated. Reactions were followed by measuring the change in the integrated areas of the protons of interest with respect to the area of the protons of internal standard.

The doublet at τ 1.62 for H-3 of isoquinoline was used to measure the amount of this material. The amount of 4-bromoisoquinoline was determined from the sum of the combined areas of H-1 (τ 0.92) of the bromo compound and isoquinoline (τ 0.85) minus the area of H-3 of isoquinoline. The singlet at τ 1.22 of H-1 of 4-methoxyisoquinoline was used to determine the amount of this material. Random samples were analyzed by GLC and found to be in good agreement.

Rate of Conversion of 4-Methoxyisoquinoline to 4-Hydroxyisoquinoline by Sodium Methoxide. Method A. A solution of 4-methoxyisoquinoline (0.71 M) and sodium methoxide (1.1 M) containing a drop of *tert*-butyl alcohol as an internal area standard was sealed in an NMR tube. This sample was heated at 165° in a constant-temperature bath, removed periodically and immediately quenched to room temperature, and analyzed by NMR using singlet peaks at τ 1.22 and 1.66 to measure 4-methoxy- and 4-hydroxyisoquinoline, respectively. The hydroxy compound is present as an anion. A second-order plot was constructed, assuming the reaction to be first order in methoxide ion; the plot was linear over 78% conversion and gave a rate constant 9.7×10^{-5} M^{-1} sec^{-1}, after correcting concentrations for the thermal expansion of methanol.

Method B. The rate at which the cleavage of 4-methoxyisoquinoline occurs under conditions which are zero order in sodium methoxide was determined by GLC analysis. Aliquots (4 ml) of 0.020 M 4-methoxyisoquinoline, 0.017 M 7,8-benzoquinoline (internal area standard), and 0.91 M sodium methoxide solution were sealed in tubes and heated at 165°. The tubes were periodically removed, thermally quenched, and analyzed by GLC. First-order plots were linear over 4 half-lives. The rate constant is 9.4×10^{-5} M^{-1} sec^{-1}, a value in good agreement with that obtained by method A.

Conversion of 3-Bromoquinoline to Quinoline by Sodium Methoxide. A mixture of 5.2 g (0.025 mol) of 3-bromoquinoline and 30 ml of 3.5 M sodium methoxide in methanol was heated in a metal bomb at 165° for 11 hr under a blanket of nitrogen. Following removal of the solvent, water was added to the residue and the mixture was extracted with methylene chloride and dried over $MgSO_4$. Distillation afforded 2.3 g (0.018 mol, 71%) of quinoline which was identified by its NMR spectrum.

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Formycin Anhydronucleosides. Conformation of Formycin and Conformational Specificity of Adenosine Deaminase[1]

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Abstract: The synthesis and CD spectra of 2,5′-anhydroformycin (**6**), 2,5′-anhydroformycin B (**9**), and 4,5′-anhydroformycin (**14**) are described. Treatment of formycin (**1**) with dimethylformamide dineopentyl acetal at 130° for 14 hr gave, depending on the work-up of the reaction mixture, compound **6**, *N*-dimethylaminomethylene derivative **7**, or 2′,3′-*O*-dimethylaminomethylene derivative **5**. Similarly, formycin B (**8**) afforded 2,5′-anhydroformycin B (**9**). The reaction of **1** with dimethylformamide dimethyl acetal gave selectively, after ammonolysis, 1-methylformycin (**10**). The reaction of 2′,3′-*O*-isopropylideneformycin (**13**) with *p*-toluenesulfonyl chloride in pyridine gave, after deblocking with 90% CF_3COOH, compounds **6** and **14**. The CD spectra of **6** and **9** in water and 0.01 *N* HCl show a negative Cotton effect at ca. 300 nm whereas that of **14** exhibits in water a positive Cotton effect of low intensity at ca. 280 nm which is considerably enhanced in 0.01 *N* HCl (at ca. 300 nm). Formycin (**1**) and formycin B (**8**) have a negative Cotton effect in water at ca. 290 and 270 nm, respectively. The magnitude of the Cotton effect of **1** in 0.01 *N* HCl is markedly decreased whereas that of **8** remains essentially unchanged. The results can be interpreted by assuming that the anti conformation of **1** and **8** is preponderant in water and that there is a higher proportion of **1** in the syn form in 0.01 *N* HCl. Compound **6** is deaminated by calf intestine adenosine deaminase to give **9** whereas **14** is completely resistant. This indicates that the substrate must be in (or approximately in) an anti conformation. The diastereoisomeric composition of **2, 4, 5, 12a,** and **12b** was determined by NMR spectroscopy.

Formycin (**1**) is a pyrazolopyrimidine C-nucleoside antibiotic which exhibits distinct cancerostatic activity.[2] X-Ray studies of formycin dihydrobromide hydrate have shown that **1** has a β configuration and a syn conformation.[3] More recent studies using formycin hydrate have suggested[4] a conformation intermediate between syn and anti.[5] A syn conformation of formycin units in the corresponding polynucleotide (poly F) has also been postulated[5a,6a] to explain the anomalous behavior of this polymer toward nucleases.[5a,6] It was, therefore, of interest to study some formycin derivatives fixed in either a syn or anti conformation or some approximation thereof. The present work presents the results of the synthesis and CD studies of both possible 5′-anhydronucleosides of **1**—2,5′-anhydroformycin (**6**) and 4,5′-anhydroformycin (**14**)—derived from anti and syn conformations of **1**. A method of preparation of 2,5′-anhydroformycin B (**9**) and selective N-1 methylation of **1** are also reported.

Results and Discussion

The interaction of **1** and excess dimethylformamide dineopentyl acetal in dimethylformamide (DMF) at 130° for 14 hr gave the anhydronucleoside **6** in almost 80% yield. Although intermediate **3** was not isolated,[7] *N*-dimethylaminomethylene-2,5′-anhydroformycin (**7**) was obtained merely by hydrolysis of **4** with water, and the product **7** was characterized by uv and NMR spectra. Previous studies[8,9] have indicated that a mixed dimethylformamide acetal of an aliphatic alcohol and nucleoside hydroxyl function can serve as an effective leaving group. It is, therefore, likely that intermediate **3** gives **4** via intramolecular nucleophilic attack at C-5′ by N-2 which is presumably ionized under the reaction conditions (Scheme I). Similarly, when formycin B (**8**) was heated with dimethylformamide dineopentyl acetal in DMF for 5 hr at 130°, the corresponding anhydro derivative **9** was obtained in 78% yield after briefly heating the crude reaction product (presumably the 2′,3′-*O*-dimethylaminomethylene derivative of **9**) in water (Scheme II). The formation of 3,5′-anhydroxanthosine from xanthosine and dimethylformamide dineopentyl acetal has been similarly explained.[8] The pK_a of the pyrazole portion of **1** (9.5)[10] is reasonably close to those compounds that undergo smooth N-alkylation with dimethylformamide dialkyl acetals.[7a,11] The reason for using dimethylformamide dineopentyl acetal was to suppress intermolecular alkylation.[7a,11] Thus, when **1** was treated with excess dimethylformamide dimethyl acetal a nearly quantitative yield of 1-methylformycin (**10**) was obtained and **6** could not be detected (Scheme III). By contrast, both intra- and intermolecular alkylation were observed on treatment of xanthosine with