The S_N(ANRORC) Mechanism: A New Mechanism for Nucleophilic Substitution

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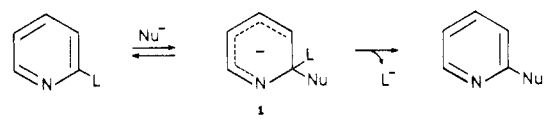
Nucleophilic substitution in pyridine, in diazines (e.g., pyrimidine), and in triazines and tetrazines has attracted organic chemists for decades. Numerous product and kinetic studies have been made with attention to features such as leaving group mobilities, aza activation, solvent effects, and the influence of hydrogen bonding between nucleophiles and substrates. Excellent reviews[1-3] have appeared.

One well-recognized substitution mechanism, one that is also very important in carbocyclic aromatic systems, is the S_NAr or S_N(AE) mechanism,[4] the central feature



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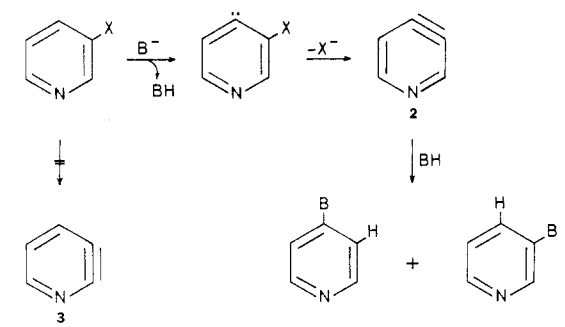
S_NAr or S_N(AE) mechanism

of which is initial **A**ddition of the nucleophile Nu^- to the substrate to form a 1:1 σ adduct (**1**). Next follows **E**limination of the nucleofugic or leaving group L^- in a step that is often but not always very fast.

Although σ adducts of a nucleophile to a carbon atom in an azine carrying also a nucleofugic substituent have never been isolated, there is overwhelming evidence, mainly from NMR and UV spectroscopic studies, that 1:1 σ adducts from azines and nucleophiles really exist.

In the mid-1950s, evidence for the existence of benzyne (didehydrobenzene) and 3,4-pyridyne (3,4-didehydropyridine, **2**) was obtained. The intermediary



S_N(EA) mechanism

existence of **2** was unequivocally proved in reactions of 3-X- and 4-X-pyridine (X = Cl, Br, or I) with KNH_2 in ammonia.[5] In all six reactions a mixture of 3- and 4-aminopyridine was found, the ratio being independent of the *nature* and *position* of the halogen atom. The initial step is **E**limination of a proton from position 4 with concerted or subsequent loss of halide ion. By **A**ddition of the amide ion or ammonia to 3,4-pyridyne (**2**) a mixture of 3- and 4-aminopyridine is obtained. This process is sometimes called an S_N(EA) process.[4] Analogous results were obtained in reactions of 3-chloro- and 3-bromopyridine with lithium piperidide in piperidine.[6]

Remarkably, 2,3-pyridyne (**3**) is not formed in these reactions, as evidenced by the complete absence of 2-aminopyridine or 2-piperidinopyridine as products. This is in agreement with the relatively low acidity of the hydrogen atom at position 2 of the pyridine ring compared to that of positions 3 and 4.[7,8]

This hetaryne mechanism stimulated great interest in reactions of heteroaryl halides with strong basic reagents and in the development of new methods for the generation of hetarynes.[7-11] In the decade of the 1960s many chemists were infected by the disease "hetarynitis". It became popular to explain every substitution reaction performed with strong basic nucleophiles—and even weak nucleophiles (!)—via the intermediacy of a hetaryne. However, we found that one has to proceed with caution before reaching a conclusion about the occurrence or nonoccurrence of a hetaryne as an intermediate.

The discovery of 3,4-pyridyne induced us to study the generation and reactivity of 4,5(5,6)-pyrimidyne [4,5-(5,6)-didehydropyrimidine, **5**] by a reaction of 5-bromo-4-R-pyrimidine **4** (R = *t*-C_4H_9, C_6H_5, CH_3, OCH_3, OH, or NH_2) with KNH_2 in ammonia[12,13] at −33 °C. In all these reactions the 6-amino-4-R-pyrimidines **6** were formed in reasonable to good yields, and no trace of a 5-amino product could be detected.[14] The pyrimidyne

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(1) R. G. Shepherd and A. L. Fredrick, *Adv. Heterocycl. Chem.*, **4**, 145 (1965).
(2) G. Illuminati, *Adv. Heterocycl. Chem.*, **3**, 285 (1964).
(3) J. Miller in "Aromatic Nucleophilic Substitution", Elsevier, Amsterdam, 1968, Chapter 7, p 234.
(4) The term S_N(AE) was first introduced by Th. Kauffmann, A. Risberg, J. Schulz, and R. Weber, *Tetrahedron Lett.*, 3563 (1964), as a counterpart to the hetaryne mechanism S_N(EA).
(5) (a) R. Levine and W. W. Leake, *Science*, **121**, 780 (1955); (b) M. J. Pieterse and H. J. den Hertog, *Recl. Trav. Chim. Pays-Bas*, **80**, 1376 (1961).
(6) Th. Kauffmann and F.-P. Boettcher, *Chem. Ber.*, **95**, 1528 (1962).
(7) H. J. den Hertog and H. C. van der Plas, *Adv. Heterocycl. Chem.*, **4**, 121 (1965).
(8) Th. Kauffmann, *Angew. Chem., Int. Ed. Engl.*, **4**, 543 (1965).
(9) R. W. Hoffmann, "Dehydrobenzene and Cycloalkenes", Academic Press, New York, N.Y., 1967, pp 273–309.
(10) H. J. den Hertog and H. C. van der Plas in "Chemistry of Acetylenes", H. G. Viehe, Ed., Marcel Dekker, New York, N.Y., 1969, Chapter 17.
(11) Th. Kauffmann and R. Wirthwein, *Angew. Chem., Int. Ed. Engl.*, **10**, 20 (1971).
(12) H. C. van der Plas and G. Geurtsen, *Tetrahedron Lett.*, 2093 (1964).
(13) H. C. van der Plas, *Tetrahedron Lett.*, 555 (1965).

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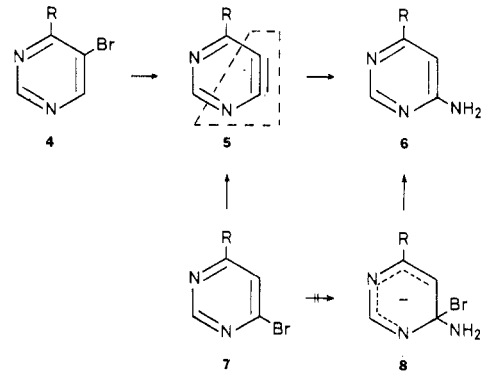
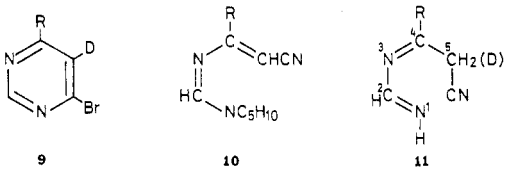


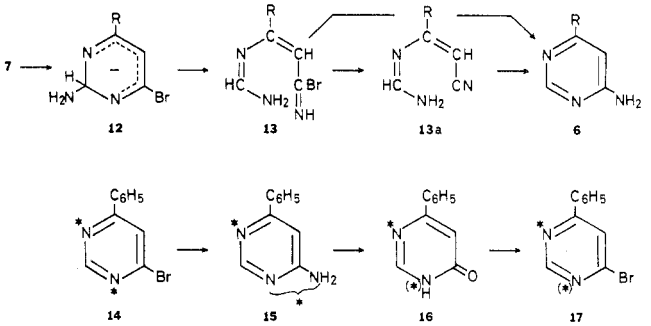
5 was proposed[15] as an intermediate in this cine substitution since **5** features, like 2,3-pyridyne, an ynamine structure[10,16] and, therefore, can be expected to undergo addition of the nucleophile only to the carbon atom adjacent to the nitrogen, i.e., to C-6 in **5**.

The 6-bromo-4-R-pyrimidines **7** (R = t-C_4H_9 or C_6H_5) were found to give exclusively the 6-amino compounds **6**[17] in fast reactions at −75 °C. Although an addition–elimination process via intermediate **8** seemed to be a reasonable pathway, a possible alternative S_N(EA) process via **5** cannot be excluded, since the hydrogen at C-5 in **7** is more acidic[18] than the hydrogen at C-6 in **4**. In order to test this hypothesis, we prepared the 5-deuteriopyrimidine **9** (R = t-C_4H_9) and found that,



after reaction with KNH_2 in ammonia, the 6-amino product does *not* contain deuterium. Since under these reaction conditions **9** only gave little D/H exchange and 6-amino-5-deuterio-4-*tert*-butylpyrimidine no D/H exchange at all, the conclusion seemed justified that the didehydropyrimidine **5** is an intermediate in the conversion **7** → **6**. This seemed a surprising result, inasmuch as a halogen atom at position 6 of the pyrimidine ring is usually reactive in an S_N(AE) process.

In order to find out whether reactions with other strong basic reagents would behave similarly, we investigated the reaction of **7** (R = t-C_4H_9 or C_6H_5) with lithium piperidide in piperidine/ether.[19] From the reaction mixture no trace of a 6-piperidino-4-R-pyrimidine was isolated but instead 2-aza-4-cyano-1-piperidino-1,3-butadiene (**10**), which, in the case of R = C_6H_5, was proved to be a Z/E mixture. Thus no replacement of the bromine atom had taken place in the usual manner. Instead, the lithium piperidide had attacked position 2 of the pyrimidine ring, followed by ring opening with loss of bromide ion. Since it seemed inconsistent that KNH_2 should react with **7** by an initial *deprotonation* at C-5 and lithium piperidide by *addition* at C-2, we wondered whether in the reaction with KNH_2 an initial attack at C-2 also occurred. It would form σ complex **12** from which, after ring opening by



fission of the N-1 to C-2 bond, the highly reactive imidoyl bromide **13** would be formed. **13** might easily cyclize into the 6-amino compound **6** or lose hydrogen bromide in an exceedingly rapid step yielding **13a**. This aminocyano compound might also undergo ring closure to **6**.

In order to prove whether this hypothesis were correct, we synthesized monolabeled 6-bromo-4-phenyl[1(3)-^{15}N]pyrimidine (**14**); it contained 6.0% of ^{15}N excess,[20–22] which is scrambled over both nitrogen atoms. If the mechanism via **13** were correct, the 6-amino product should have the same percentage of excess of ^{15}N as in **14**. Treatment of the 6-amino product **15** by acid would give 4-phenylpyrimidin-6-one (**16**) from which **17** could be obtained by treatment with phosphoryl bromide.

We found that in **15** 6.0% of ^{15}N excess and in **17** 3.5% of ^{15}N excess were present,[20–22] indicating that in **15** 2.5% of ^{15}N excess is present in the exocyclic nitrogen. Since under these conditions no ring nitrogen–exocyclic nitrogen exchange occurs in the 6-amino compound, our conclusion was that in the "simple" amino debromination of **7** (R = C_6H_5) 2.5/3.0 or 83%[23] of the 6-bromo compound reacts via a series of reaction steps, involving an **A**ddition of the **N**ucleophile, **R**ing **O**pening, and **R**ing **C**losure. We refer to this as the S_N(ANRORC) mechanism.

The loss of deuterium in the amination of **9** can also be explained by this mechanism. Since no D/H exchange occurs in the starting material or product, the fast D/H exchange in this reaction can only take place

(14) Only in the reaction of 5-bromo-4-*tert*-butylpyrimidine could a very small amount of 5-amino-4-*tert*-butylpyrimidine be detected by GLC.

(15) There is one earlier report in the literature on the formation of a 2-methyl-4,5-didehydropyrimidine. This was proposed to explain the formation of 4-amino-2-methylpyrimidine in the reaction of 2-methyl-5-chloropyrimidine with sodamide. See Th. J. Schwan and H. Tieckelmann, *J. Org. Chem.*, **29**, 941 (1964).

(16) For a review, see H. G. Viehe in "Chemistry of Acetylenes", H. G. Viehe, Ed., Marcel Dekker, New York, N.Y., 1969, Chapter 12, pp 861–912.

(17) H. C. van der Plas, P. Smit, and A. Koudijs, *Tetrahedron Lett.*, 9 (1968).

(18) Based on H/D exchange studies the following relative rates of exchange were found in pyrimidine: H(1):H(4,6):H(5) = 1:3,2:48 [see J. A. Zoltewicz, G. Grahe, and C. L. Smith, *J. Am. Chem. Soc.*, **91**, 5503 (1969)]. Possibly the exchange occurs by an addition–elimination mechanism. See, for an example, C. Weiss, *Tetrahedron*, **22**, 145 (1966).

(19) H. C. van der Plas and A. Koudijs, *Recl. Trav. Chim. Pays-Bas*, **89**, 129 (1970).

(20) J. de Valk and H. C. van der Plas, *Recl. Trav. Chim. Pays-Bas*, **90**, 1239 (1971).

(21) J. de Valk and H. C. van der Plas, *Recl. Trav. Chim. Pays-Bas*, **91**, 1414 (1972).

(22) The ^{15}N enrichment in compound **14** and in all the compounds which are monolabeled with ^{15}N was simply calculated from the ratio of the (M + 1)/M peak, with adjustment for the natural abundances of nuclides of the several atoms present [Δ(M + 1)/M].

(23) A more elaborate calculation leads to 80% instead of 83%. This calculation is performed as follows: 6.0% of ^{15}N excess means that on 100 molecules with the mass M, six molecules with the mass M + 1 are present. Thus in the mixture 100/106 × 100% 94.36% of the molecules is *un*labeled and 5.64% is *mono*labeled. After the reaction, 3.5% of ^{15}N excess is present in **17**, which means that 96.63% of the molecules has the mass M—and is thus unlabeled—and 3.37% of the molecules is monolabeled. Thus 2.27% of the molecules being originally monolabeled is now unlabeled. So 2.27/3.37 × 100% = 80% has reacted according to the S_N(ANRORC) mechanism.

Table I
Percentage of ^{15}N Excess in Compounds 18a-f, 19a-f and 20a-f [Calculated from $\Delta(M + 1)/M$] and the Percentage of These Compounds[a] Which React with KNH_2 According to the S_N(ANRORC) Mechanism

	compd 18, %	compd 19, %	compd 20, %	% S_N(ANRORC) mechanism
a	7.4	7.4	4.7	70
b	6.0	6.1	3.2	90
c	6.0	6.0	3.5	80
d	7.4	7.4	6.9	13
e	8.2	8.0	8.0	0
f	7.4	7.4	3.7	100

[a] See ref 23 and 25.

in a reaction intermediate. We think that 11—being in tautomeric equilibrium with **13a**—is the appropriate intermediate for exchange at C-5 under these basic conditions.

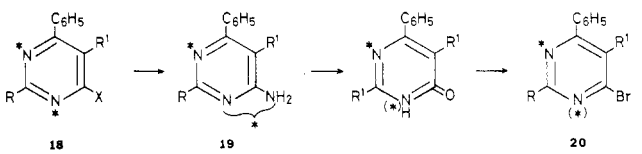
Although in both substrate and product a pyrimidine ring is present, in this S_N(ANRORC) reaction a *ring transformation* has taken place, since the nitrogen at position 1 in substrate and in product is *not* the same. These ring transformations form a special class among the many ring transformations[24] which heterocycles can undergo. One can refer to these reactions as *degenerate* (or *ipso*) ring transformations.

Studies were undertaken to investigate the scope of the S_N(ANRORC) mechanism. Problems studied were (1) which heterocyclic systems are able to react according to this mechanism, (2) what are the necessary electronic requirements of the leaving group, (3) can intermediates be identified, and (4) which nucleophiles, other than amide ions, are able to react to this S_N(ANRORC) mechanism.

In this Account only the basic principles of the S_N(ANRORC) mechanism are discussed, with attention especially to the results obtained with *pyrimidine* derivatives, since this group of compounds has been investigated in more detail than for any of the other azines.

Pyrimidines

6-Halogeno-4-phenylpyrimidines. The discovery that amination of the 6-bromo compound **7** (R = C_6H_5) occurred about 80% by an S_N(ANRORC) mechanism induced us to investigate the influence of other halogen atoms at position 6. Therefore the monolabeled 6-fluoro-, 6-chloro-, and 6-iodo-4-phenyl[1(3)-^{15}N]pyrimidines (**18a**, **18b**, and **18d**, respectively, with ^{15}N



18 **19** **20**

a) R = R¹ = H, X = F ; b) R = R¹ = H, X = Cl ; c) R = R¹ = H, X = Br
d) R = R¹ = H, X = I ; e) R = C_6H_5, R¹ = H, X = Br ; f) R = H, R¹ = CN, X = Cl

scrambled over both positions) were prepared and subjected to a treatment with KNH_2 in ammonia. The 6-amino compound **19** obtained was in each case hydrolyzed with acid, and the corresponding 4-phenylpyrimidin-6-one was converted into the 6-bromo compound **20**. Measurements of the ^{15}N excess in compounds **18a–f**, **19a–f**, and **20a–f** are summarized in Table I. The fluoro and chloro compounds behave just as the bromo compound; they react for the greater part according to this ring-opening/ring-closure mechanism. In the amino deiodination only, to a small percentage ring opening is involved.

By which mechanism does the remaining 87% of the 6-iodo compound react? The S_N(AE) and S_N(EA) processes are alternative substitution mechanisms. Amination of 5-deuterio-6-iodo-4-phenylpyrimidine gave[21] a 6-amino compound in which *no* deuterium was present; it excludes the S_N(AE) mechanism and suggests the occurrence of an S_N(EA) mechanism. Although convincing arguments for explaining the difference between the 6-iodo compound **18d** and the 6-fluoro compound **18a**—to take the two extremes—cannot be given, there are some relevant facts. (1) The amide ion has both nucleophilic and basic properties, always in competition. (2) Deprotonation at C-5 takes place more easily with the 6-fluoro compound than with the 6-iodo compound, but iodine is more nucleofugic than fluorine. A priori it would not be evident which of these opposing effects should control the reaction. Apparently the loss of the halide ion yielding 5,6-pyrimidyne is favored with the 6-iodo compound **18d**. (3) There is sound ^1H NMR evidence[25] that addition of the amide ion to pyrimidine occurs exclusively at C-4 with almost no indication of addition at position 2.[26] This means that the introductory step for the S_N(ANRORC) mechanism, i.e., addition at C-2, is not in general a favored reaction. The 6-fluoro compound will promote addition at C-2 more effectively—because of its stronger $-I$ effect—than the 6-iodo compound.

Since the first step in the S_N(ANRORC) mechanism is addition of the nucleophile at C-2, this mechanism can be expected to be hampered by large substituents at C-2. This has indeed been found[27] experimentally. Treatment of 2,4-diphenyl-6-bromo[1(3)-^{15}N]pyrimidine (**18e**) with KNH_2 gives the 6-amino compound **19e**, in which ^{15}N is present only in the *ring* nitrogen atoms. The same results were found with the fluorine and iodine analogues of **18e**.

All attempts to isolate an intermediate from the reaction of 4-phenyl-6-bromopyrimidine (**7**, R = C_6H_5) with KNH_2 were unsuccessful. Therefore, we tried to obtain *indirect* evidence for the existence of **13** (R = C_6H_5) or **13a** (R = C_6H_5). We prepared the labeled compound, 4-chloro-5-cyano-6-phenyl[1(3)-^{15}N]pyrimidine (**18f**), and established[28] by the method described above that it reacts with KNH_2 entirely via a ring-opening/ring-closure sequence (see Table I).

This result poses a new question. The same reaction with carbon-labeled **21** conceivably might involve ring closure via intramolecular amino group attack either in the imidoyl chloride (**25**) or in 1-amino-4,4′-dicyano-2-azabutadiene (**22**).[29] Since both cyano groups of the

(24) See H. C. van der Plas, "Ring Transformations of Three-, Four-, Five-, Six- and Seven-membered Heterocycles", Vol. I and II, Academic Press, New York and London, 1973.

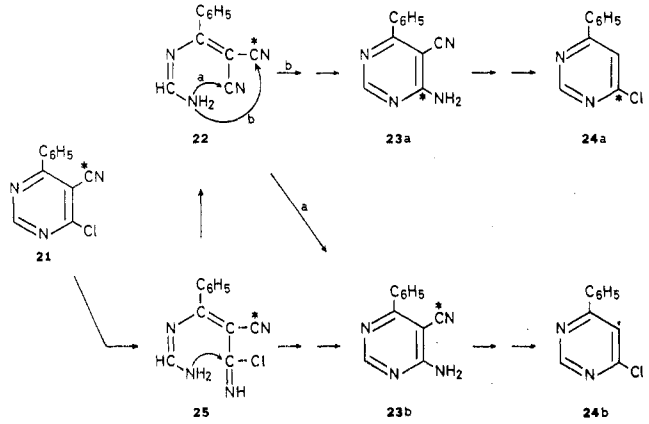
(25) J. A. Zoltewicz and L. S. Helmick, *J. Am. Chem. Soc.*, **94**, 682 (1972).

(26) Very recently it was observed that 4,6-diphenylpyrimidine with KNH_2 in ammonia gives a σ adduct at C-2: J. P. Geerts and H. C. van der Plas, unpublished results.

(27) J. de Valk and H. C. van der Plas, *Recl. Trav. Chim. Pays-Bas*, **92**, 145 (1973); J. de Valk, H. C. van der Plas, and J. W. A. de Bode, *ibid.*, **92**, 442 (1973).

(28) J. de Valk and H. C. van der Plas, *Recl. Trav. Chim. Pays-Bas*, **92**, 471 (1973).

(29) In the original literature for the 2-fluoro compound **18a**, 73% is mentioned, for the 2-chloro compound **18b**, 93%, and for the 2-iodo compound **18d**, 13%. See remark in ref 23.

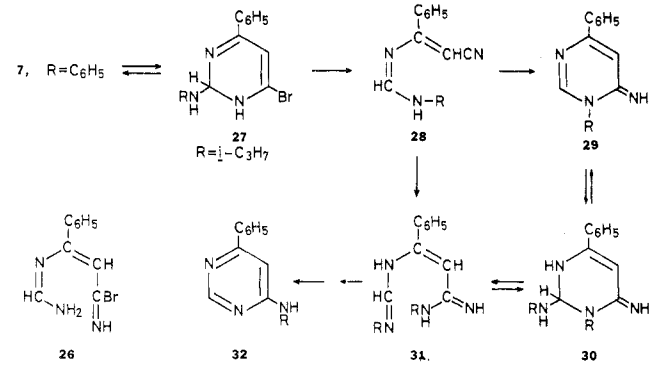


latter may have about the same reactivity, cyclization might take place according to pathway a or b, yielding a mixture of **23a** and **23b** and thus effecting partial incorporation of carbon-14 in the pyrimidine ring.

This, however, is not found. After a series of reactions involving acid hydrolysis, decarboxylation, and treatment with $POCl_3$, 6-amino-5-cyano-4-phenylpyrimidine (**23**) was converted into 6-chloro-4-phenylpyrimidine (**24**), and this compound was found to have only a very small specific ^{14}C radioactivity. Apparently only **24b** is formed. This suggests[28] that not **22** but imidoyl chloride **25** undergoes cyclization into **23b**.

An alternative explanation for the failure of the ^{14}C incorporation experiment may lie in the stereochemical stability of the conjugate base of intermediate **22**. Rotation around the pertinent C–C bond of this species may be so slow that the carbon-labeled cyano group is not brought cis to the formamidine moiety fast enough to compete with direct ring closure onto the unlabeled cyano group.

It is thus firmly proved that 4-phenyl-6-bromopyrimidine (**7**, R = C_6H_5) reacts with the potassium salt of ammonia to form the highly reactive **13** (R = C_6H_5) or its precursor, the imidoyl bromide **26** (=**13**, R =



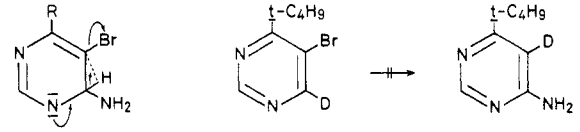
C_6H_5), and with the lithium salt of the secondary amine, piperidine, to form the stable open-chain product **10** (R = C_6H_5).

We therefore investigated the reaction of **7** (R = C_6H_5) with the lithium salt of a primary amine. On reaction of **7** (R = C_6H_5) with lithium isopropylamide in isopropylamine[30] at 20 °C, 4-phenyl-6-(isopropylamino)pyrimidine (**32**) was formed in 70% yield. However, when the reaction was carried out at −75 °C, we could only isolate a product which, according to IR and ^1H NMR spectra, was a mixture of the open-chain compound **28** and its isomeric 6-imino-4-phenyl-1-isopropyl-1,6-dihydropyrimidine (**29**): ratio **28**:**29** = 10:1. On standing, **28** gradually changes into **29**. Since this iminopyrimidine **29** gives a very fast Dimroth rearrangement[31] into **32** by treatment with lithium isopropylamide at 20 °C, it is clear that the seemingly simple conversion of **7** (R = C_6H_5) into **32** actually occurs by a complicated series of steps, three being involved in the S_N(ANRORC) mechanism (**7** → **27** → **28** → **29**) and three in the Dimroth rearrangement (**29** → **30** → **31** → **32**).

The isolation of **28** and **29** provides further important evidence for the S_N(ANRORC) mechanism.

4-*tert*-Butyl-5-bromopyrimidine. As already discussed, the reactions of 5-bromo-4-R-pyrimidines with KNH_2 yield cine substitution products **6**. The intermediacy of pyrimidyne **5** was suggested.[12,13] The reactions were slow; even after 24 h at −33 °C, starting material could still be recovered. We obtained further insight by application of a technique developed in our laboratory, which permitted us to measure ^1H and ^{13}C NMR spectra in liquid ammonia solutions containing KNH_2.[32]

When the ^1H NMR spectra of solutions of 5-bromo-4-R-pyrimidines **4** (R = *t*-C_4H_9, C_6H_5, C_6H_5N-CH_3, OCH_3, or CH_3) in ammonia containing 2 equiv of KNH_2 were measured after 5–10 min, no signals of unreacted **4** but only those of the 1:1 σ adduct **33** were observed.[32d] The formation of **33** raised doubts as to the validity of the "hetaryne" mechanism. A possible alternative pathway for the formation of the 6-amino compounds, i.e., the stereoelectronically unfavorable internal hydride shift in the σ adduct **33**, could be



rejected;[33] from 5-bromo-4-*tert*-butyl-6-deuteriopyrimidine (**34**) no 6-amino-5-deuterio-4-*tert*-butylpyrimidine (**35**) was obtained.[17]

The fact that in the potassium amide/ammonia system we deal with adduct **33**, combined with the new concept of nucleophilic substitution by ring opening/ring closure as found with the 6-halogeno-4-phenylpyrimidines, made us reinvestigate the cine amination of 5-bromo-4-R-pyrimidines **4**. Therefore we prepared monolabeled 5-bromo-4-*tert*-butyl[1(3)-^{15}N]pyrimidine (**36**) (with ^{15}N scrambled over both positions).

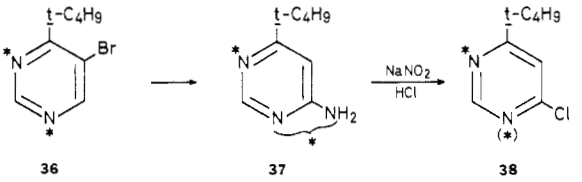
Reaction of **36** with KNH_2 gave, besides recovered starting material, the 6-amino compound **37** which

(30) H. C. van der Plas and A. Koudijs, *Recl. Trav. Chim. Pays-Bas*, **92**, 711 (1973).

(31) D. J. Brown, "Mechanisms in Molecular Migrations", Vol. 1, B. S. Thyagarajan, Ed., Interscience, New York, N.Y., 1968, p 209.

(32) For the 1:1 anionic σ-adduct formation between halodiazines and amide ions, see (a) J. P. Geerts, A. Nagel, and H. C. van der Plas, *Org. Magn. Reson.*, **8**, 607 (1976); (b) J. P. Geerts, H. C. van der Plas, and A. van Veldhuizen, *ibid.*, **7**, 86 (1975); (c) A. P. Kroon, H. C. van der Plas, and G. van Garderen, *Recl. Trav. Chim. Pays-Bas*, **93**, 325 (1974); (d) J. P. Geerts, C. A. H. Rasmussen, H. C. van der Plas, and A. van Veldhuizen, *ibid.*, **93**, 231 (1974); (e) P. J. Lont, H. C. van der Plas, and A. van Veldhuizen, *ibid.*, **92**, 708 (1973); (f) J. P. Geerts, H. C. van der Plas, and A. van Veldhuizen, *ibid.*, **92**, 1232 (1973).

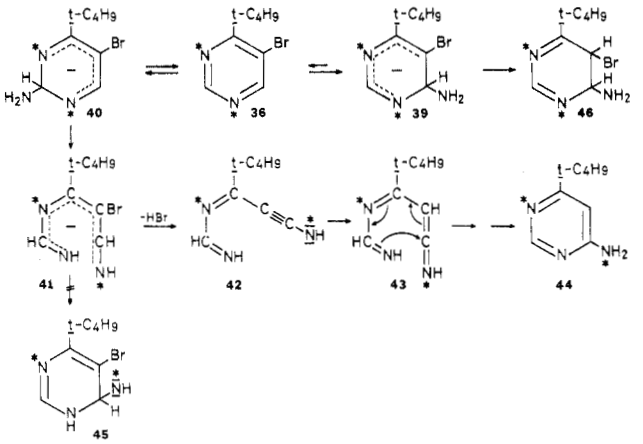
(33) A similar mechanism was suggested by Benkeser and Schroll to explain the exclusive formation of *m*-aminomethoxybenzene from *o*-bromoethoxybenzene by KNH_2 in ammonia [R. A. Benkeser and G. Schroll, *J. Am. Chem. Soc.*, **75**, 3196 (1953)]. However, this proposal was superseded by the benzyne mechanism.



36 37 38

could be converted into the 6-chloro derivative **38** by diazotization in hydrochloric acid. By measuring the excess of ^{15}N in the starting material **36**, in the recovered material **36**, in **37**, and in **38**, we found 7.3, 7.3, 7.25, and 5.45%, respectively. It irresistibly led to the conclusion that the conversion of **36** into **37** occurs about 50% according to the S_N(ANRORC) mechanism.[34]

The results obtained by ^1H NMR spectroscopy and by ^{15}N labeling seem to be in conflict, since a reaction via the σ adduct **39** could never lead to the distribution



of ^{15}N over the ring nitrogen atom and the exocyclic amino function. We concluded that not **39** but the 1:1 σ adduct at C-2, i.e., **40**, plays the key role in the mechanism; however, by ^1H NMR spectroscopy *no* indication for its existence is found. It appears that the favored σ adduct, **39**, is rather unreactive while the isomeric σ adduct,[35] **40**, as formed, quickly reacts to form the resonance-stabilized open-chain intermediate **41**.

Another important conclusion is that the loss of the bromide ion must *precede* cyclization; thus, **41** → **42** and not **41** → **45**. The reasoning is that σ adduct **45** is the conjugate base of **33** (R = t-C_4H_9) which can revert to **4** and amide ion. After the 24-h reaction, a decrease of ^{15}N excess ought to be found in the recovered starting material if reaction occurred via **45**. This was not the case; recovered material **36** contained the *same* excess of ^{15}N as the starting material (7.3%).

The ynamine anion **42** is postulated to be the intermediate which undergoes protonation by ammonia into the ketenimine **43**; cyclization gives the 6-amino compound **44**, which is labeled on the ring nitrogen *and* the exocyclic nitrogen.

Since in the mechanism an hydrogen bromide elimination is involved, we tried to establish whether the overall reaction displays a kinetic isotope effect. We observed indeed that deuterium-labeled compound **34**

(34) C. A. H. Rasmussen and H. C. van der Plas, *Recl. Trav. Chim. Pays-Bas*, **96**, 101 (1977).

(35) Concerning the formation of isomeric ("Jackson–Meisenheimer") σ complexes from highly deficient aromatics and nucleophiles, see M. J. Strauss, *Chem. Rev.*, **70**, 667 (1970), and M. R. Crampton, *Adv. Phys. Org. Chem.*, **7**, 211 (1969).

Table II
Percentage of ^{15}N Excess in Compounds 51 and 53 [Calculated from $\Delta(M + 2)/M$] and the Percentage of These Compounds Which React According to the S_N(ANRORC) Mechanism

X	compd 51, %	compd 53, %	% S_N(ANRORC) mechanism[a]
F	6.0	1.1	92
Cl	6.0	0.7	100
Br	6.0	0.7	100
I	6.0	1.6	83
SCH_3	6.0	0.5	100
SO_2CH_3	6.0	1.6	83
SCN	6.0	0.6	100
CN	6.0	5.7	6
$^+N(CH_3)_3$	6.0	5.4	11

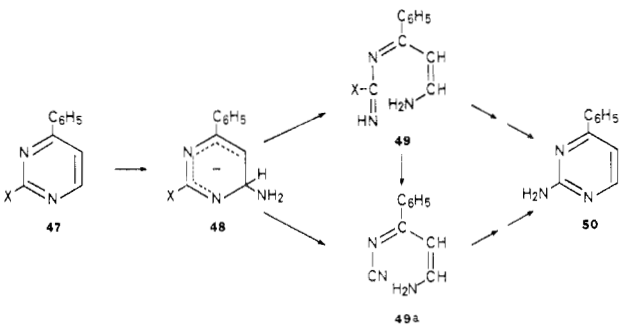
[a] See ref 37.

undergoes amination at a slower rate than its protium analogue **4** (R = t-C_4H_9). An isotope effect of ~2 was found. Thus it is evident that in the rate-determining step the abstraction of protium from C-6 is preferred to the abstraction of deuterium. The conversion of **41** to **42** can be considered to be the rate-determining step.

By which mechanism is the 6-amino compound formed with ^{15}N remaining in the pyrimidine ring? The most plausible pathway seems to be that the σ adduct **39** undergoes protonation to form 6-amino-5-bromo-5,6-dihydro-4-*tert*-butylpyrimidine (**46**) from which hydrogen bromide is then eliminated. If this elimination is rate determining, it must exhibit a kinetic isotope effect.

One final remark has to be made. The S_N(ANRORC) process which takes place with 5-bromo-4-*tert*-butylpyrimidine is different in principle from that found with the 6-halogeno-4-phenylpyrimidines. In those amino dehalogenations, the ANRORC process occurs in such a way that the newly formed amino group is attached to the *same* carbon from which the leaving group departed. This behavior is thus different from the cine substitutions described in this section, and we suggest, therefore, to use the term S_N(ANRORC)^{cine} for the conversion of **36** into **44**.[34] In order to differentiate the S_N(ANRORC)^{cine} from the "normal" S_N(ANRORC) mechanism, we suggest the use of the index n, thus S_N(ANRORC)^n.[36]

4-Phenyl-2-substituted Pyrimidines. The high reactivity of position 4(6) in the pyrimidine ring for addition of amide ions induced us to investigate reactions of 4-phenyl-2-substituted pyrimidines **47**. If

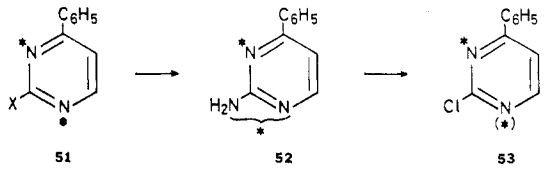


47 48 49 49a 50

addition at C-6 would take place, the pyrimidinide ion

(36) For reference, S_N(ANRORC)^n symbolizes a process in which the new amino group appears at the *same* position vacated by the halogen, S_N(ANRORC)^{cine} is one in which it appears adjacent to that position, and S_N(ANRORC)^{tele} is one in which it appears even farther away.

48 would be ideally suited for undergoing ring opening into 49 which then should cyclize to 2-amino compound 50 in a subsequent ring closure. Seeking evidence of this S_N(ANRORC) mechanism, we synthesized a series of double-labeled 4-phenyl[1,3-^{15}N]pyrimidines 51,



51 52 53

containing at position 2 substituents of different nucleofugicity. Thus, compounds 51 have, in contrast to the monolabeled compounds 18 and 36, in the mass spectrum an M + 2 peak. The ratio (M + 2)/M, with adjustment for the natural abundances of the nuclides of the several atoms present, indicates the ^{15}N content on both positions. After the reaction of 51 with KNH_2 in ammonia at −33 °C, the 2-amino compound 52 was isolated and converted into the 2-chloro compound 53. The results of the mass spectrometric measurements of the ^{15}N excess and the percentages of the compounds 51 that react according to the S_N(ANRORC) mechanism[32c,36-38] are summarized in Table II.

The data show that a series of substituents which vary extensively in their electronic effects (F, Cl, Br, I, SCH_3, SO_2CH_3, and SCN) is able to take part in this ring-opening/ring-closure mechanism. Of interest is the great contrast between the high percentage (83%) of 2-iodo-4-phenylpyrimidine (51, X = I) which reacts according to the S_N(ANRORC) mechanism and the low percentage (13%) found for 4-iodo-6-phenylpyrimidine (18d) (Table I). The facts that (1) with 51 (X = I) no competitive pyrimidyne formation can take place and (2) addition of the amide ion to C-6 in 51 (X = I) is more favored than addition at C-2 in 18d explain the difference. It has been suggested[38] that groups with high nucleofugicity are more inclined to undergo an S_N(AE) process. This suggestion seems to be in conflict with the observations that the methanesulfonyl group—which has a higher nucleofugicity than the methylthio group—gives such a high percentage. ^{1}H NMR spectroscopic evidence indicates, however, that 51 (X = SO_2CH_3), when dissolved in liquid ammonia containing KNH_2, undergoes deprotonation of the methanesulfonyl group into the conjugate base, almost preventing addition of the amide ion to C-2 because of steric and coulombic repulsions; it makes the competitive addition to C-6 more favorable.

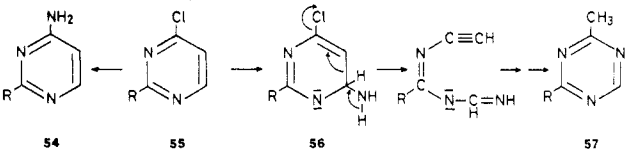
Strong support for the intermediacy of the σ adduct 48 (X = SCH_3) was obtained by ^{1}H NMR spectroscopy.[38] The chemical shifts of the pyrimidine ring protons of a solution of 47 (X = SCH_3) in $CDCl_3$ were completely different from those measured in a solution of 47 (X = SCH_3) in liquid ammonia containing 2 equiv of KNH_2.

(37) The values reported in Table II are obtained by the same type of calculations, being described in ref 23 for the monolabeled compounds. They differ about 10% from those reported in the literature, being obtained by simply comparing the increase of the (M + 1)/M peak and the decrease of the (M + 2)/M peak. By this method the following values are found:[32c,38] 2-F = 82%, 2-Cl = 89%, 2-Br = 89%, 2-I = 73%, 2-SCH_3 = 91%, 2-SO_2CH_3 = 73%, 2-SCN = 90%, 2-CN = 5%, 2-$N^+(CH_3)_3Cl^-$ = 10%. It is evident that the general conclusions are not influenced by the method of calculation which is used.

(38) A. P. Kroon and H. C. van der Plas, *Recl. Trav. Chim. Pays-Bas*, 93, 325 (1974).

A further point in support of the S_N(ANRORC) mechanism is the fact that we could isolate from the reaction mixture from the 2-bromo compound 47 (X = Br) a small amount of (3-amino-1-phenylallylidene)-cyanamide (49a).[38] Thus, study of reactions of the 2-substituted 4-phenylpyrimidines with amide ions provided us with unique examples of substitutions in which both the addition product, i.e., 48 (X = SCH_3), and the open-chain intermediate, i.e., 49a, could be established as intermediates.

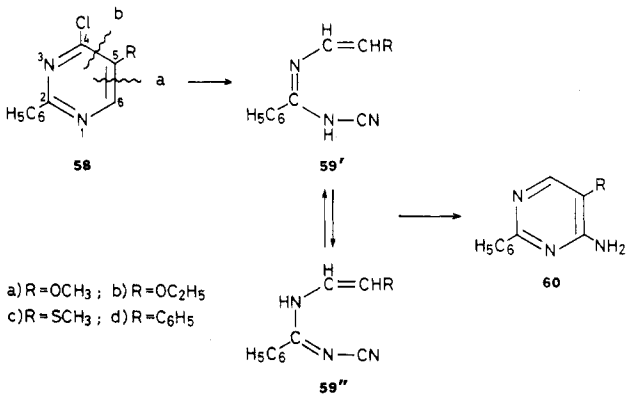
4-Chloro-5-methoxy-2-phenylpyrimidine (58). In the reactions of the 4-chloro-2-R-pyrimidines 55 [R =



54 55 56 57

CH_3, C_2H_5, C_6H_5, β-$C_{10}H_7$, $N(CH_3)_2$, c-NC_5H_{10}, c-$N(CH_2CH_2)_2O$, or $N(CH_3)C_6H_5$] with KNH_2 in ammonia, the 4-amino compound 54 is formed in only a small yield;[39] the main product is 4-methyl-2-R-1,3,5-triazine (57). This carbon–nitrogen skeleton rearrangement provides us with a good synthesis of 2,4-disubstituted 1,3,5-triazines 57 containing at positions 2 and 4 different substituents. Although a discussion on the conversion of 55 → 57 is beyond the scope of this Account, the transformation clearly shows that 55 preferably forms the anionic 1:1 σ adduct 56 and that addition to C-4, the carbon atom to which the halogen atom is attached, is less favored. By ^{1}H and ^{13}C NMR spectroscopy it is proved that in this KNH_2/NH_3 system 56 is indeed formed.[32b,32f]

Extending these studies to 5-substituted 4-chloro-2-phenylpyrimidines, we found[40] that if 4-chloro-5-methoxy-2-phenylpyrimidine (58) reacts with KNH_2 in



58 59′ 59″ 60

a) R = OCH_3; b) R = OC_2H_5
c) R = SCH_3; d) R = C_6H_5

ammonia and the reaction products are isolated by preparative GLC, no evidence of a 1,3,5-triazine derivative was found, only-4-amino-5-methoxy-2-phenylpyrimidine (60a). Surprisingly, when the reaction mixture was worked up under more carefully controlled conditions at low temperature, only the 1,3-diazapentadienes (59′ ⇄ 59″) were isolated. On heating, the azadienes 59 easily underwent ring closure

(39) H. C. van der Plas, B. Haase, B. Zuurdeeg, and M. C. Vollering, *Recl. Trav. Chim. Pays-Bas*, 85, 1101 (1966); H. C. van der Plas and B. Zuurdeeg, *ibid.*, 88, 426 (1969); H. C. van der Plas, B. Zuurdeeg, and H. W. van Meeteren *ibid.*, 88, 1156 (1969).

(40) H. W. van Meeteren and H. C. van der Plas, *Recl. Trav. Chim. Pays-Bas*, 90, 105 (1971); H. W. van Meeteren and H. C. van der Plas, *Tetrahedron Lett.*, 4517 (1966).

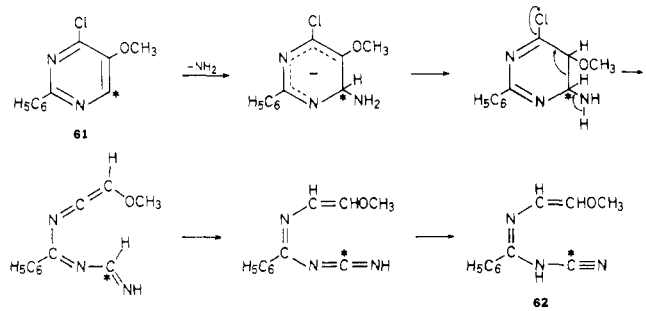
Table III
Products Formed on Amination of Azines, Diazines, Triazines, and Some Benzo Derivatives with Potassium Amide and the Percentage of S_N(ANRORC) Mechanism in These Aminations

entry	azines	product	% S_N(ANRORC) mechanism	ref
1	2-bromopyridine	2-aminopyridine	0	41
2	3-bromoisoquinoline	3-aminoisoquinoline	55	42
3	chloropyrazine	aminopyrazine	100	43
4	2-chloroquinoxaline	2-aminoquinoxaline	0	44
5	4-chloroquinazoline	4-aminoquinazoline	53	45
6	2-chloro-4-phenylquinazoline	2-amino-4-phenylquinazoline	70	46
7	3-thiomethyl-1,2,4-triazine	3-amino-1,2,4-triazine	92	47
8	2-chloro-4,6-diphenyl-1,3,5-triazine	2-amino-4,6-diphenyl-1,3,5-triazine	80	48
9	2-thiomethyl-4,6-diphenyl-1,3,5-triazine	2-amino-4,6-diphenyl-1,3,5-triazine	100	48
10	2,4-diphenyl-1,3,5-triazine	2-amino-4,6-diphenyl-1,3,5-triazine	0	48
11	phenyl-1,3,5-triazine[a]	aminophenyl-1,3,5-triazine	50	49
12	2-chloropurine[a]	2-aminopurine	100	50
13	purine[a]	adenine	0	50
14	2-thiomethyl-4,6,7-triphenylpteridine[a]	2-amino-4,6,7-triphenylpteridine	85[b]	51

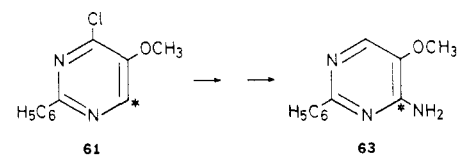
[a] This reaction was performed with unlabeled azines with labeled potassium [^{15}N]amide. [b] This percentage is found to be dependent upon the potassium amide concentration.

into **60**. The 5-ethoxy- (**58b**), the 5-thiomethyl- (**58c**), and the 5-phenylpyrimidine derivatives (**58d**) showed the same behavior.[40] These results show that the overall amino dechlorination, **58** → **60**, occurs by an S_N(ANRORC) mechanism involving the intermediacy of **59**, which apparently is stable enough to be isolated.

In order to establish whether in the ring opening of **58** a carbon–carbon fission between C-5 and C-6 (fission a) or between C-4 and C-5 (fission b) is involved—both possibilities lead to the same product, **59**—4-chloro-5-methoxy-2-phenyl[6-^{14}C]pyrimidine (**61**) was prepared. We could prove[40] that in the open-chain compound all the ^{14}C radioactivity was present on the carbon of the cyano group of the cyanoaminoazabutadiene **62**. It follows that the initial addition of the amide ion must have taken place at C-6.



Furthermore, the 4-amino product ultimately obtained on heating has its amino group *not* present on the same carbon atom which originally carried the chlorine atom, but on a position meta to that chlorine atom. The overall amination process **61** → **63** is thus a tele-substitution reaction. Although some tele-substitutions in heterocycles have been reported, the conversion of **61** → **63** is the first example of a tele-substitution reaction involving ring opening. We refer to this mechanism[34,36] as an S_N(ANRORC)^{tele}.



Other Azines

In Table III[41–51] are summarized results of ^{15}N studies of the reactions of ten different azines and their benzo derivatives with KNH_2. Nearly all compounds are characterized by the presence of a leaving group with high nucleofugicity (bromo, chloro, or thiomethyl group) at a position adjacent to the ring nitrogen. Exceptions are 2,4-diphenyl-1,3,5-triazine, phenyl-1,3,5-triazine, and purine (entries 10, 11, and 13), which underwent amination by replacement of a hydride ion by an amide ion (Chichibabin reaction).

Of considerable interest is the fact that aminophenyl-1,3,5-triazine (entry 11), obtained by a Chichibabin reaction from phenyl-1,3,5-triazine, is formed in 50% yield by a ring-opening/ring-closure sequence. This reaction shows for the first time that a Chichibabin-type amination can take place via an S_N(ANRORC) mechanism. Another conclusion from these studies is that the blocking effect of a phenyl group on the initial addition of an amide ion is, in general, not very severe (entries 6, 8, 9, and 14). Apparently the reactivity of those positions toward the amide ion is so high that addition occurs despite the presence of a phenyl group.

(41) H. J. den Hertog, H. Boer, J. W. Streef, F. C. A. Vekemans, and W. J. van Zoest, *Recl. Trav. Chim. Pays-Bas*, **93**, 195 (1974).
(42) G. M. Sanders, M. van Dijk, and H. J. den Hertog, *Recl. Trav. Chim. Pays-Bas*, **93**, 198 (1974).
(43) P. J. Lont, H. C. van der Plas, and A. J. Verbeek, *Recl. Trav. Chim. Pays-Bas*, **91**, 949 (1972).
(44) P. J. Lont and H. C. van der Plas, *Recl. Trav. Chim. Pays-Bas*, **91**, 851 (1972).
(45) J. de Valk, H. C. van der Plas, F. Jansen, and A. Koudijs, *Recl. Trav. Chim. Pays-Bas*, **92**, 460 (1973).
(46) A. P. Kroon and H. C. van der Plas, *Recl. Trav. Chim. Pays-Bas*, **93**, 227 (1973).
(47) A. Rykowski and H. C. van der Plas, *Recl. Trav. Chim. Pays-Bas*, **94**, 204 (1974).
(48) G. Simig, H. C van der Plas, and C. A. Landheer, *Recl. Trav. Chim. Pays-Bas*, **95**, 113 (1976).
(49) G. Simig and H. C. van der Plas, *Recl. Trav. Chim. Pays-Bas*, **96**, 125 (1976).
(50) N. Kos and H. C. van der Plas, unpublished results.
(51) A. Nagel and H. C. van der Plas, *Heterocycles*, **7**, 205 (1977).