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# TETRAHEDRON REPORT NUMBER 122

# HETARYNES

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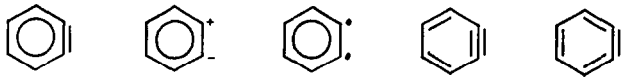
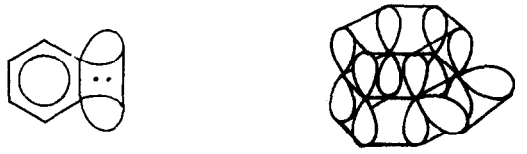
## I. INTRODUCTION

Benzyne (1) is the prototype of a well-known[1] kind of bidentate reactive intermediate, also known as an aryne, a dehydrobenzene or a didehydrobenzene, which can be *formally* generated by removing two



1a 1b 1c 1d 1e

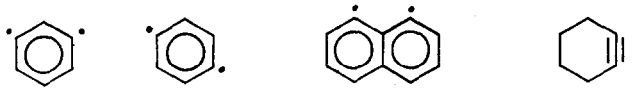
vicinal hydrogen atoms from a parent aromatic molecule. The resulting species can be represented by several structural formulae (**1a–1e**) or by the molecular orbital representations **1f** and **1g** which better



1f 1g

illustrate that these intermediates possess two orbitals containing two electrons coplanar with the sigma-framework of the aromatic ring and orthogonal to its pi-system.

Related but less well-known intermediates are those in which the reactive orbitals are not vicinal (**2–4**)[2], in which the parent molecule is not aromatic (**5**)[3], or in which the parent molecule is heterocyclic.[4]



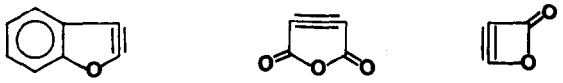
2 3 4 5

It is this last category of reactive intermediates, referred to as hetarynes,[5] dehydroheterocycles,[4] or didehydroheterocycles,[6] which will be reviewed in this Report.

Except for contemporaneous ones restricted to 5-[7] and 6-membered[7a] hetarynes, all prior reviews on this topic are over ten years old.[4,6,8–10] Although hetarynes are mentioned in more recent reviews on arynes in general,[11–13] the considerable activity in this field in the last decade warrants this separate Report which will discuss much of this older work in the light of all published and unpublished results available to the author as of December 1981.

## II. HISTORICAL PERSPECTIVE

The first structural formula for a didehydro aromatic intermediate to appear in the literature was for the 5-membered hetaryne, 2,3-didehydrobenzofuran (**6**).[14] Although a few other didehydroheterocycles (**7** and **8**)[15] as well as diradical (**1c**)[16] and dipolar (**1b**)[17] formulations for benzyne were suggested in the next half-century, the definitive evidence for such intermediates is due to the investigations of Roberts,[18] Huisgen[19] and Wittig[20] which thoroughly examined the symmetry and reactivity of such species.[1]



6 7 8

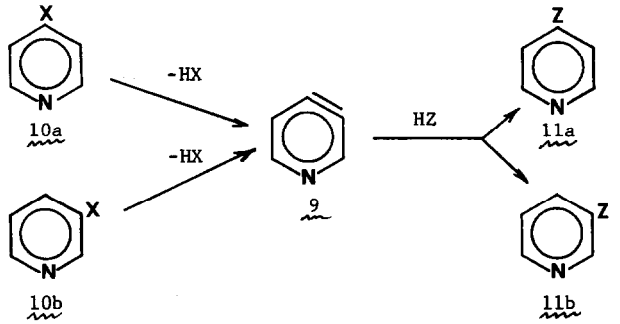
Subsequent spectroscopic examination in the gas-phase[21] and in an argon matrix[22] have established beyond a shadow of a doubt that benzyne (**1**) is a true reactive intermediate, not just a transition state, and that it can exist free of solvent or residual fragments of its precursor.[23]

Not surprisingly the rigor with which the case for benzyne had been assembled was often abandoned as analogous didehydroaromatic intermediates were sought. The observation of typical aryne reactivity such as cine-substitution[24] or cycloaddition[25] often was taken as presumptive evidence for aryne intermediates without the time-consuming experimental elimination of alternative nonaryne pathways as had been done with benzyne itself.[26-28] In some cases arynes were proposed with no more support than the author's ability to include them in a mechanistic rationale of the reaction. While these "short cuts" probably led to few erroneous claims of carbocyclic arynes, some rather serious detours resulted with proposed hetarynes. Consequently a major emphasis of this report will be to examine and evaluate the evidence on which the claimed existence of a hetaryne is based.

## III. SPECIAL PROBLEMS IN HETARYNE DETECTION

### A. *Cine-substitution*

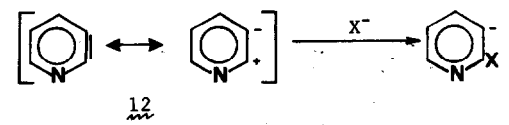
With one possible exception[29] this evidence is of an indirect chemical nature based on trapping experiments. The first known and most characteristic of these is the addition of polar species, especially nucleophiles, to the "triple bond" of the hetaryne.[24] Since arynes are bidentate intermediates, such additions may lead to two different products in the case of unsymmetrical hetarynes such as 3, 4-didehydropyridine (**9**). If, as is often the case for such polar additions, the aryne was generated by elimination of HX from a




monosubstituted heterocycle **10a**, then the product (**11a**) with addend Z in the same position as the leaving group X is called the product of normal substitution while the rearranged product (**11b**) is referred to as that of cine-substitution. If the hetaryne is generated from the isomeric precursor **10b**, then designation of normal and cine-substitution products is of course reversed.

Although it was observation of such cine-substitution in the reactions of aryl halides with strong bases which led to the first postulates of aryne intermediates,[13,18,19] by what is known as the elimination-addition (EA) mechanism of nucleophilic aromatic substitution,[8] it is now clear that without additional information cine-substitution is neither a necessary nor a sufficient criterion for the existence of aryne intermediates. This is especially true with heterocycles where nucleophilic substitution via hetarynes might occur without cine-substitution and cine-substitution is known to occur without hetarynes.

1. *Normal substitution via arynes.* This possibility can occur if the addition of the nucleophile to the aryne is regiospecific and gives only the normal substitution product, i.e. **10a**→**9**→**11a**. Such regiospecificity is known in the benzene series[27,31] and can be rationalized either on the basis of polarization of the aryne[24] or by the relative stabilization of the first-formed anion by the substituent.[31,32] Either explanation would predict that 2, 3-didehydropyridine (**12**) might selectively add nucleophiles at the 2-position and 2, 3-didehydrothiophene (**13**) at the 3-position based on the known effects of a pyridine

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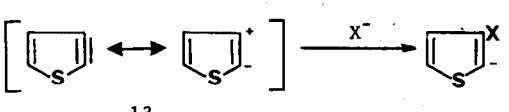


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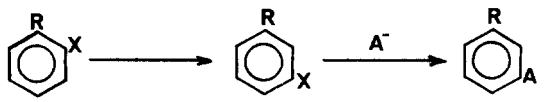
nitrogen[33] and a thiophene sulfur atom[34] on the destabilization and stabilization, respectively, of an adjacent carbanion. Consequently the absence of cine-substitution products in reactions of such heterocycles cannot be taken as evidence against a hetaryne intermediate.

2. *Cine-substitution via transhalogenation (BCHD).* In his classic paper on the mechanism of amination of halobenzenes[26] Roberts convincingly demonstrated that the cine-substitution product **14** did not arise via a prior rearrangement of the starting aryl halide. Halogen rearrangements under aryne-



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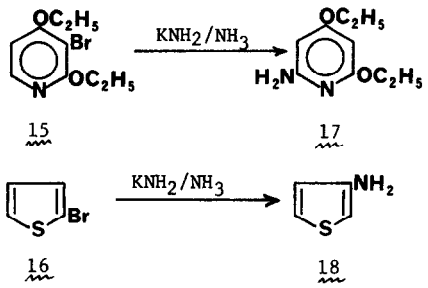
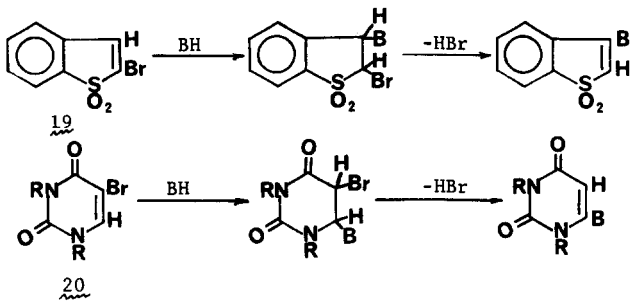
forming conditions have subsequently been recognized for *poly*halobenzenes[35] and a variety of *mono*heterocycles.[36-45] This reaction has been labelled the "base-catalyzed halogen dance" (BCHD) and shown to proceed by a series of positive halogen transfers involving stable aryl anions.[46] At least two examples are known, one with a 6- (**15**)[36] and one with a 5-membered heterocyclic halide (**16**),[37,39,45] where rearranged substitution products (**17** and **18**, respectively) arise *via* the BCHD rather than the EA mechanism. It will therefore always be necessary to consider this alternative mechanism for cine-substitution of heterocyclic halides before a hetaryne intermediate is claimed.



15 17

16 18

3. *Cine-substitution via abnormal addition elimination (AEa).* This mechanism, involving addition of a nucleophile ortho to a leaving group which is subsequently eliminated, was suggested,[47] considered, and rejected[26] as an explanation for the cine-amination of halobenzenes. The opinion[48] has been voiced, however, that the AEa mechanism should not be *generally* excluded as a possible explanation for cine-substitution, and it has in fact now been recognized[49] as being operative for several 5- (**19**)[50] and 6-membered heterocycles (**20**)[51] as well as carbocycles containing electron-withdrawing substituents.[52]



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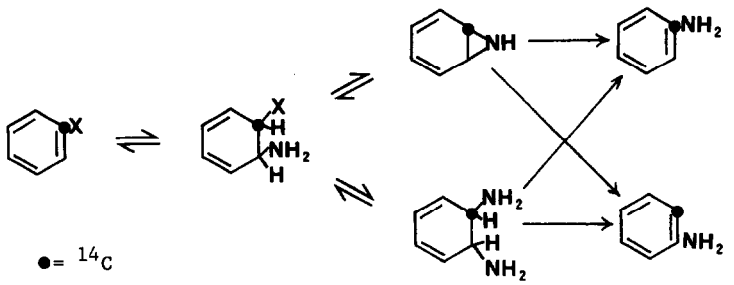
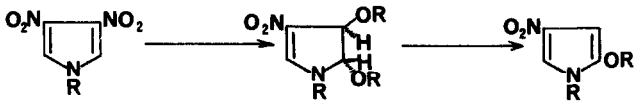
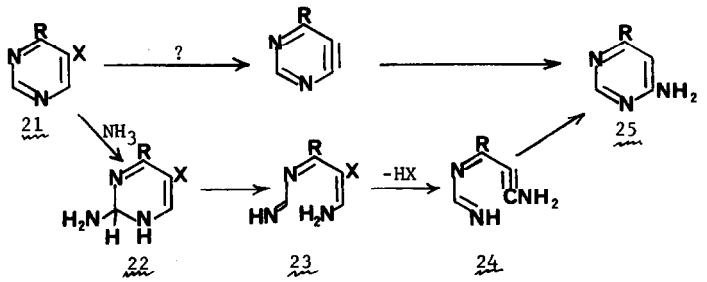
4. *Cine-substitution via addition-substitution-elimination (ASE).* Roberts[26] considered this mechanism unlikely for the amination of halobenzenes since the observed ortho-hydrogen isotope effect would require the probably exothermic last step to be rate-determining and the probably endothermic preceeding steps to be rapid equilibria. Although these arguments were substantiated for halobenzenes by an elegant double labelling experiment,[27] it has now been demonstrated that many heterocycles do react with ammonia,[53] amide ion,[54,55] and other nucleophiles[56,57] rapidly and reversibly to give covalent addition products. Furthermore, such addition compounds have been shown to undergo substitution by a second molecule of nucleophile at positions which are at,[58] adjacent to,[59,60] or remote from[61] the point of attachment of the first molecule of nucleophile. A recent example of this mechanism which leads to overall



cine-substitution of a 5-membered heterocycle[62,63] emphasizes the necessity of considering the possibility of the ASE process in the heterocyclic series. In some quarters[64] it is still considered possible for halobenzenes.



5. *Cine-substitution via addition-ring-opening-elimination-ring-closure* (*ANRORC cine*). The final nonaryne mechanism of cine-substitution to be discussed also begins with addition of a nucleophile to the heterocycle (**21**). Instead of elimination (AEa-mechanism) or substitution (ASE-mechanism) the addition product (**22**) undergoes a sequence of ring-opening to **23**, elimination of HX to **24** and ring-closure to the cine-substitution product (**25**). This variation of the ANRORC-mechanism[65] was



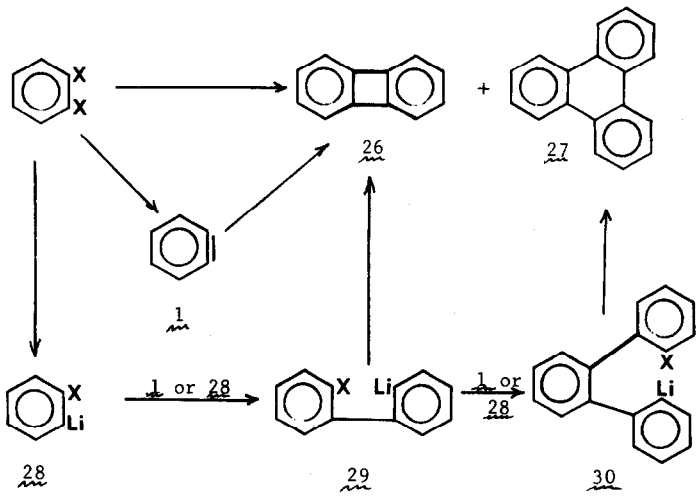
recently proposed[66] to explain at least part of the cine-amination of certain 5-halopyrimidines previously[67] thought to react via didehydropyrimidine (Section V.B.6.c).

6. *Precautions.* The above five examples amply illustrate the prior assertion that cine-substitution is neither a necessary nor a sufficient criterion for claiming a hetaryne intermediate. It has been suggested[4] that such sufficiency can be achieved "only if the nucleophile adds to *both* ends of the dehydro bond and the resulting isomer ratio turns out to be independent of the nature of the leaving group." In practice the acquisition of this information may be complicated first by the simultaneous operation of several of the mechanisms described above and second by the regiospecific addition of the nucleophile to the aryne bond as described in Section III. A. 1. The "base competition method" has been proposed to detect an EA process in the presence of normal (AEn) and/or abnormal (AEa) mechanisms of nucleophilic aromatic substitution and even for cases where only a single substitution product is formed.[10,68] These complications also can be overcome by intercepting the aryne intermediate with traps which can be shown not to react with the aryne precursor. Weakly basic amines,[68a] mercaptides,[69] and dienes (Section III. B. 2) have been used for this purpose.

## B. *Cycloaddition*

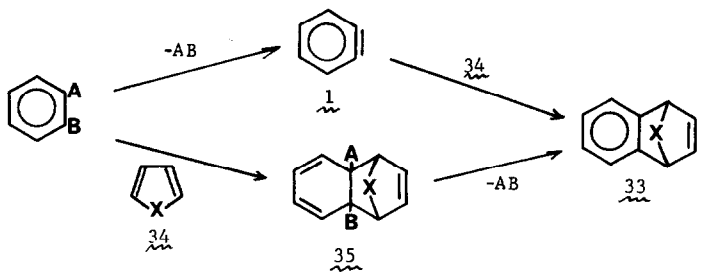
Their bidentate character leads to the second typical reaction of arynes, cycloaddition with themselves and other reactants.[25]

1. *Dimerization and trimerization.* This property was first recognized by Wittig who found that generation of arynes from o-dihalobenzenes and lithium amalgam leads to the formation of biphenylene (**26**) and triphenylene (**27**).[20] Although the actual dimerization of arynes[27,70] has been demonstrated in the gas-phase, a stepwise Wurtz-type coupling via biphenyls (**29**) and *o*-terphenyls (**30**) must be considered a possible[20] source of the dimers **26** and a probable[24] source of the trimers **27** in solution, particularly in,



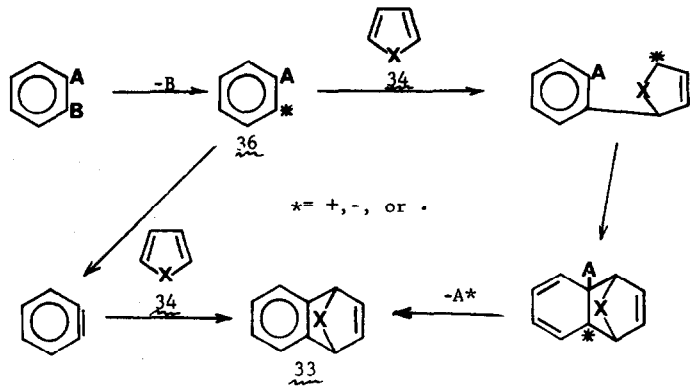

but not restricted to,[71] the presence of organometallic species. While this stepwise coupling reaction probably does involve arynes in the benzene series (i.e. **28** + **1** → **29** → **26**) it need not (i.e. **28** + **28** → **29** → **26**), especially with those heterocycles which react readily with organometallic species.[72] This fact, in conjunction with the expected instability of 5-membered heterocyclic analogues of biphenylene such as **31**[73,74] but not necessarily **32**,[73,75] compromises the value of observing such dimers as evidence for the presence of hetaryne intermediates.


2. *Diels–Alder reactions.* The formation of Diels–Alder adducts **33** with various conjugated dienes **34**[20] has become the second major indirect method for detecting aryne intermediates.[25] In spite of the

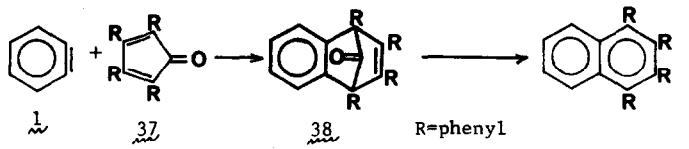



general acceptance of this method, it suffers the same limitation as the cine-substitution criterion (Sec. III A), i.e. the adduct **33** might arise by a nonaryne mechanism such as the addition-elimination process *via* **35** in which the diene **34** adds to the aryne precursor *prior* to elimination of the vicinal leaving groups A and B.

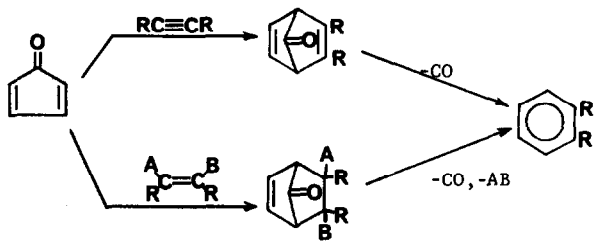
The tendency for such addition-elimination reactions to occur depends on the nature of both the aryne precursor and the diene trapping agent. Because of their lower resonance energy[76] heterocycles in general will be more prone to undergo addition reactions than the analogous aryne precursors in the benzene series. Furthermore, virtually all aryne precursors under certain conditions decompose in a stepwise manner via anionic, radical or cationic intermediates (**36**)[7,77] which may also be able to react with the dienes **34** to form adducts **33**. Such reactions would be particularly likely to occur if the aryne formation was inhibited since the intermediate **36** would then have a longer lifetime. Finally, there are certain dienes which have been shown to be especially prone to participate in addition-elimination reactions and must therefore be used with caution in claiming the presence of an aryne intermediate.




The most prominent among this latter category is tetraphenylcyclopentadienone **37** whose initial adduct (**38**) with benzyne is readily decarbonylated to give the very stable and easily detected tetra-

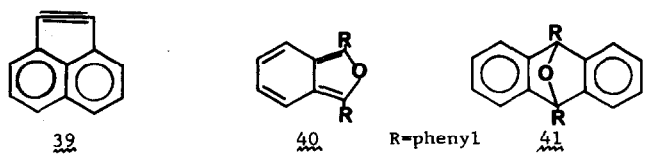



phenylnaphthalene.[78] Many examples are also known, however, of addition of cyclopentadienones to alkenes and alkynes *followed* by loss of CO and aromatization to give "aryne" adducts.[79] Although none of

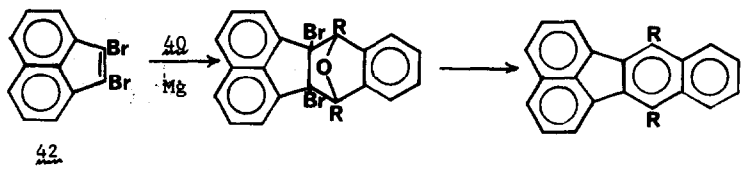


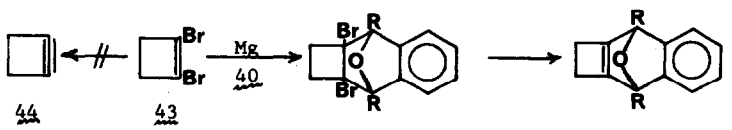

these examples involve addition to a benzene ring, several potential precursors of acenaphthyne (**39**) have been shown to undergo this reaction.[80]

A second ambiguous aryne trap is 1,3-diphenylisobenzofuran (**40**). With benzyne precursors the expected adduct forms by an elimination-addition mechanism,[81] but with the dibromoacenaphthene (**42**)[80]

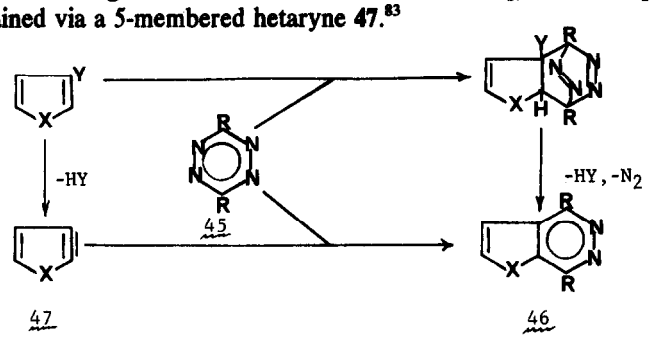



and the dibromocyclobutene (**43**)[82] the corresponding adducts arise primarily by an addition-elimination process which avoids the apparently high-energy acenaphthyne (**39**) and cyclobutyne (**44**).

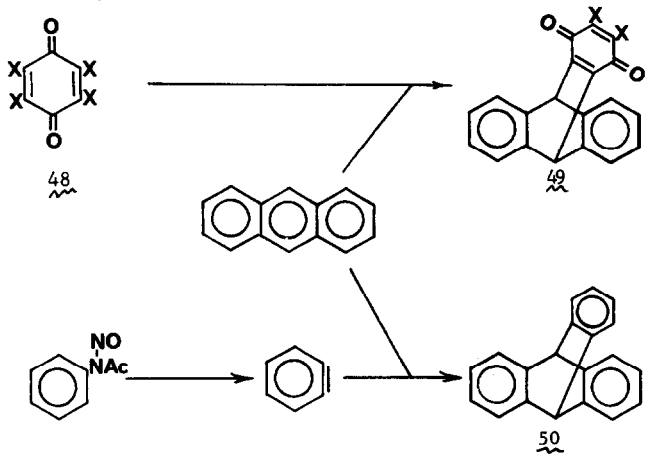


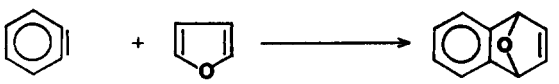
With electron-rich precursors such as 5-membered heterocycles, electron deficient dienes such as 1,2,4,5-tetrazines (**45**), react to give after elimination of HY and $N_2$, the same pyridazine (**46**) which would have been obtained via a 5-membered hetaryne **47**.[83]




While the above examples all involve very reactive diene traps, if the precursor is a powerful dienophile such as a tetrahalo-p-benzoquinone (**48**) then even a relatively "normal" diene such as anthracene can react by an addition-elimination mechanism to give an apparent aryne adduct **49**.[84] A similar process was once considered for the formation of triptycene **50** from N-nitrosoacetanilide[85] until the intermediacy of benzyne was established.[86]



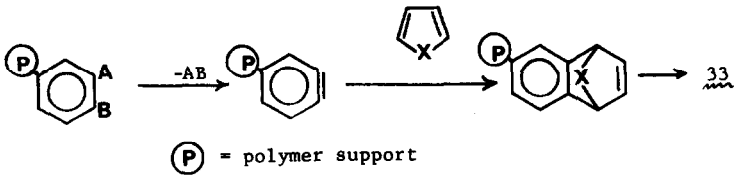

Even the status of furan as an unambiguous trap for aryne intermediates has been questioned,[87] although without firm evidence.[4,10,64,88,89] On the contrary, cogent arguments *against* an addition-elimination mechanism have been presented,[90] and the direct reaction of matrix-isolated benzyne with furan to give the adduct **51** has been demonstrated.[22]




3. *Precautions.* The above examples support the well-advised precaution[4,10] that before the observation of a Diels–Alder adduct **33** can be taken as conclusive evidence for an aryne intermediate, addition-elimination mechanisms via **35** or **36** must be excluded. Possible approaches include isolating intermediates such as **35** and determining if they are precursors of the aryne adducts **33**.[80,82,91,92] If they can not be isolated or detected spectroscopically the adducts **35** can be tested for kinetically by determining the effect of trap concentration on the rate of decomposition of the putative aryne precursor. With an elimination-addition mechanism there is no effect, of course.[88,93]

Intermediates such as **36** can be rendered unlikely if a variety of potential aryne precursors, which could not all give the same species **36**, give the same aryne adducts **33**. This strategy is the basis of the competition method using mixtures of dienes or dienes with several reactive sites as traps.[28,94] The constancy of product ratio with different precursors signals the presence of a common intermediate unencumbered by residual fragments of the precursor molecules.

An alternative method for demonstrating the presence of such a "free" aryne is a techniques known as pseudodilution[95] in which the aryne precursor and hence also the aryne is immobilized on a polymer. Since the trapping agent is not added until the precursor has completely reacted, the formation of the




adduct **33** (which is subsequently removed from the polymer) demonstrates that an elimination-addition, not an addition-elimination, mechanisms is involved.

In the absence of such confirmatory experiments claims for hetarynes based on isolation of Diels–Alder adducts from single precursors and single diene traps (particularly the ambiguous ones cited above) must be regarded as tentative.

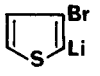
## IV. SPECIAL PROBLEMS IN HETARYNE GENERATION

An analysis of the difficulties associated with the generation of hetarynes as compared to carbocyclic arynes[4,7] reveals the existence of two interrelated problems. Potential precursors of hetarynes are either more labile toward nonaryne reactions or more stable toward aryne formation. As the latter property becomes more pronounced the former is naturally also exacerbated.

Many examples of nonaryne reactions of potential hetaryne precursors have already been given in the previous section. Foremost among these are reactions (Section II: A.3, A.4, A.5, B.1, B.2) which involve addition to the heteroaromatic ring, whose lower resonance energy compared to benzene doubtless facilitates the process.[76] To this category one must also add several reactions which, although they do not give aryne-type products as in Section II, do consume the aryne precursor. These include normal nucleophilic substitution of halogen atoms $\alpha$ or $\gamma$ to a pyridine-type nitrogen atom, which proceeds with much greater facility than in the benzene series,[96] and the ANRORC mechanism which leads not only to cine-substitution (Section II A.5) but also to ring-opening,[97] ring contraction,[98] and ring-transformation products.[99]

A second property of hetaryne precursors, the ease with which particularly sulfur heterocycles form carbanions,[34] is responsible not only for cine-substitution by the BCHD mechanism (Section II A.2) but also halogen disproportionation[37–44] and ring-opened products.[100] Several additional, less general nonaryne reactions of potential precursors will be discussed under the specific hetarynes (Section V).

The stability of certain precursors to hetaryne formation is best illustrated by the remarkable stability[101] of the 3-bromo-2-lithiothiophene (**52**) at 100° whereas the benzene analogue **53** decomposes to benzyne at −100°. Attempts to increase the severity of the reaction conditions often leads to a general breakdown of the molecule or the intervention of the nonaryne reactions discussed above. Even if a

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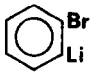



53

precursor undergoes reaction the lifetimes of the intermediates leading to the aryne[7,77] might be sufficiently prolonged that nonaryne reactions could compete more effectively.

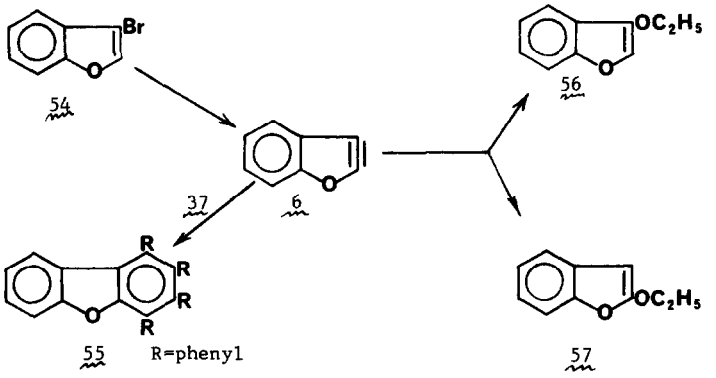
The above considerations dictate that considerably more care must be exercised in selecting the precursors and conditions for generating hetarynes than benzynes. On the other hand it is just this uniqueness as well as that of the detection methods discussed in Section II which give hetaryne chemistry its special character and interest as will be shown in the following survey.

## V. SURVEY OF HETARYNES

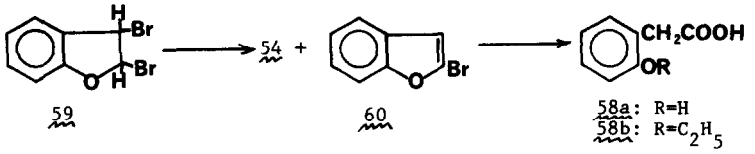
In this section the attempted and claimed generation of didehydroheterocycles will be critically examined in light of the *caveats* discussed in Section III. The organization, first by ring size and then by kind and number of heteroatoms, is based on the expectation[4,6–10] that these features will contribute significantly and perhaps uniquely to the chemistry of hetarynes as they do to that of the parent heterocycles.[76]

### A. *Five-membered hetarynes*[7]

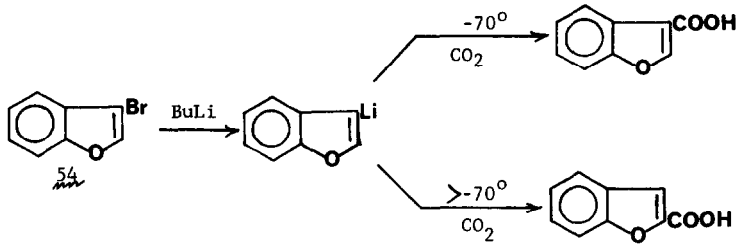
1. 2,3-*Didehydrobenzofuran* (**6**). This historically important hetaryne (Section II) was postulated to rationalize the apparent cine-substitution of 3-bromobenzofuran (**54**) with ethoxide[14] and seemed to be subsequently substantiated by the isolation of the adduct **55** when this reaction was carried out in the presence of tetracyclone (**37**).[103] Both of these criteria are at best ambiguous, however.[7]



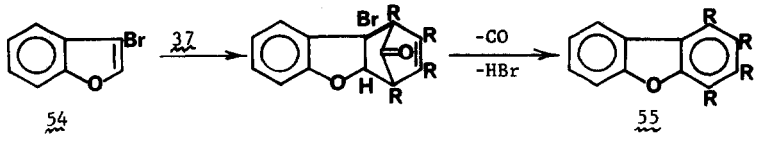

The first is compromised by the failure to actually isolate either of the substitution products **56** or **57** (the only pure compounds adequately characterized were *o*-hydroxyphenylacetic acid **58a** and its ethyl ether **58b** presumably formed from **57** on workup) as well as by the possibility[104] that the mode of preparation of **54** (from the dibromo compound **59**) might lead to the presence of the 2-bromo isomer **60** which would give **58a** in quantitative yield under the reaction conditions.[14] Although precautions were



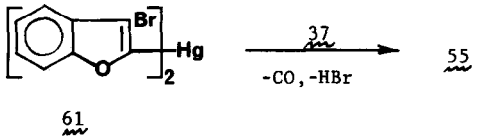

taken to avoid this possibility,[14] because of just such an occurrence with the corrsesponding chlorine compounds,[105] the intervention of other cine-substitution mechanisms (Section III. A) was not eliminated. A presumably BCHD rearrangement (Section III. A.2) in precisely the required direction is observed during the reaction of 3-bromobenzofuran (**54**) with BuLi if the temperature is allowed to exceed $-70°$.[106]



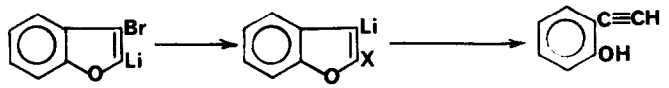

The formation of adduct **55** probably does not involve the aryne **6** since the rate of the reaction of **54** is nearly doubled in the presence of tetracyclone **37**[107] and the reaction occurs even in the absence of base.[101] Both observations suggest an addition-elimination mechanism (Section III. B.2). A similar rate enhancement in the decomposition of the mercury compound **61** in the presence of tetracyclone (**37**) is




ascribed to a similar mechanism,[107] and not the intermediacy of the aryne **6** as originally suggested.[108]



Attempts to generate the aryne **6** from the very stable[109] bromolithium derivative **62** gave only ring-opening to the *o*-hydroxyphenylacetylene **63**[109] even in the presence of furan as a trap.[101] Presumably a BCHD mechanism intervenes[101,107] to give a 3-lithiobenzofuran which under the relatively severe

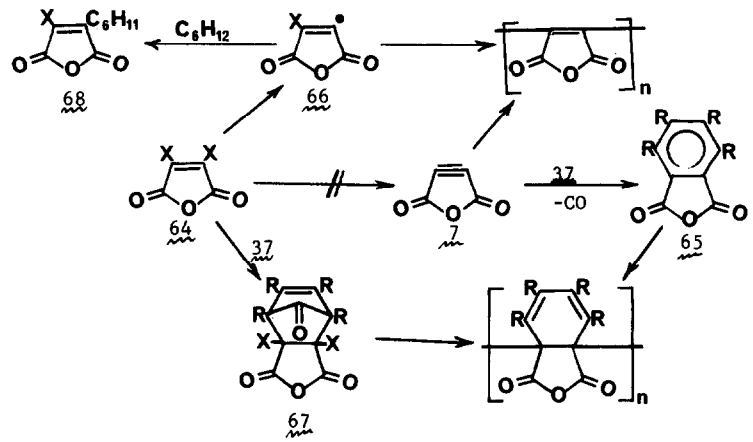



62 X=H,Br,Li 63

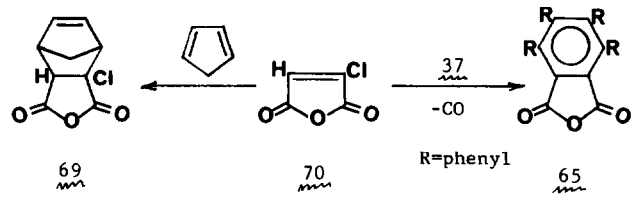
reaction conditions can undergo ring-opening to **63**.[110] The sodium analogue of **62** shows similar thermal stability.[101]

2. *Didehydrofurans.* Neither claims nor attempts to generate these arynes have been made although the chemistry of several potential precursors has been examined.[7]

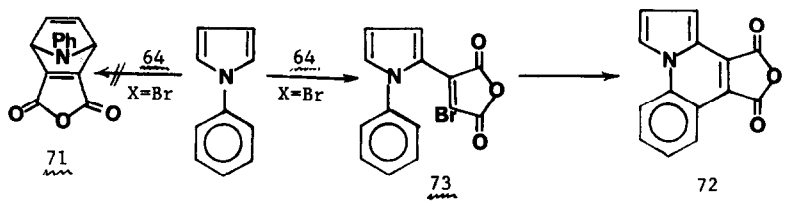
3. *Didehydromaleic Anhydride* (**7**). Both early[111] and more recent[112] attempts to generate **7** by the thermolysis of dihalomaleic anhydrides **64** ended in failure. Only apparent polymers of the intermediate **7** or its tetracyclone adduct **65** were obtained, probably by an addition-elimination process via intermediate radicals **66** or Diels–Alder adducts **67**. Support for the intervention of **66** comes from the




photolysis of **64** (X = Cl) which in the solid state gives the same polymer as with thermolysis but in cyclohexane solution gives the substitution product **68**.[113] Similarly, Diels–Alder adducts (**69**) of chloromaleic anhydride (**70**) are obtained with unambiguous dienes such as cyclopentadiene, but, as emphasized in Section III. B.2, apparent adducts (**65**) of **7** are found when tetracyclone (**37**) is used.[114]

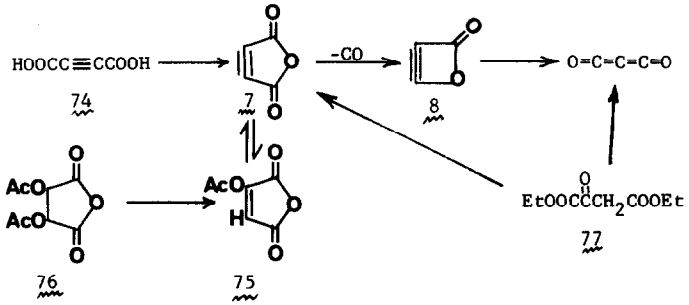



Photolysis of **64** (X = Br) in the presence of the relatively "safe" aryne trap N-phenylpyrrole[115,116] gave, instead of an aryne adduct **71**, the double substitution product **72** which was shown to arise via **73**.[117]



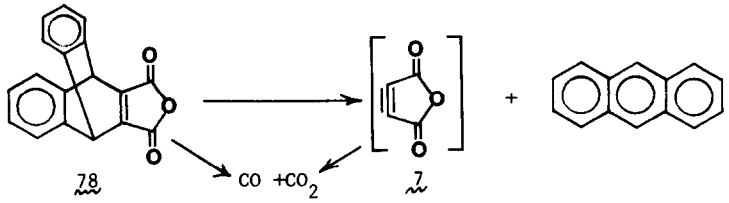

Treatment of acetylene dicarboxylic acid (**74**) with acetic anhydride gives acetoxymaleic anhydride **75**[118] postulated as arising from the addition of acetic acid to **7**.[15,119] The possibility that addition

preceded cyclization was not excluded and seems more reasonable. Pyrolysis of **75** or of diacetyltartaric acid anhydride (**76**) also was claimed to regenerate **7** which ultimately decomposed via the unlikely cyclobutyne species **8** to carbon suboxide, $C_3O_2$.[15] More recent isotope studies of the formation of $C_3O_2$ from the reaction of the diester **77** with acetic anhydride, while initially supporting the

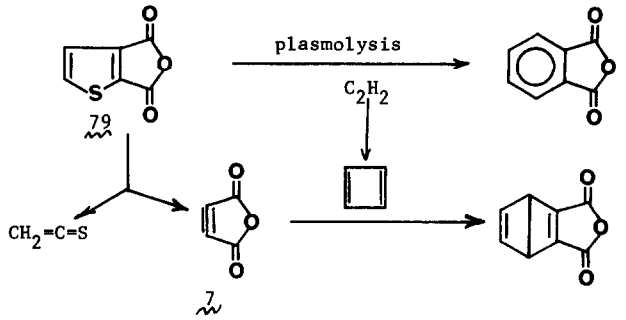



intermediacy of **7**,[120] ultimately eliminated this possibility.[121]

Although flash vacuum thermolysis of the anthracene adduct **78** of **7** (prepared by another method) led to a quantitative yield of anthracene by an apparent retro-Diels–Alder reaction, no evidence for the generation of **7** could be obtained from trapping experiments.[122] The only other products, CO and $CO_2$, could have arisen by thermal fragmentation of the anhydride moiety[123] of the adduct prior to the retro-Diels–Alder reaction.



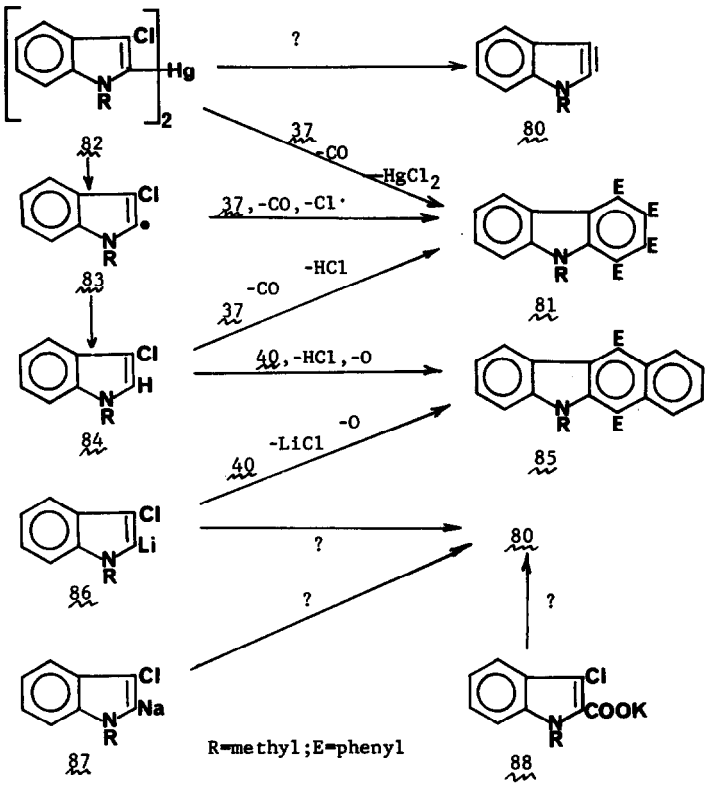

A retro 1,3-dipolar addition[124] of the thiophene anhydride **79** to thioketene and **7** was postulated to explain the formation of phthalic anhydride from plasmolysis in the presence of acetylene as shown.[125] Except for the demonstrated presence of cyclobutadiene in the plasmolysis of acetylene,[126] no evidence to support this speculation was obtained.



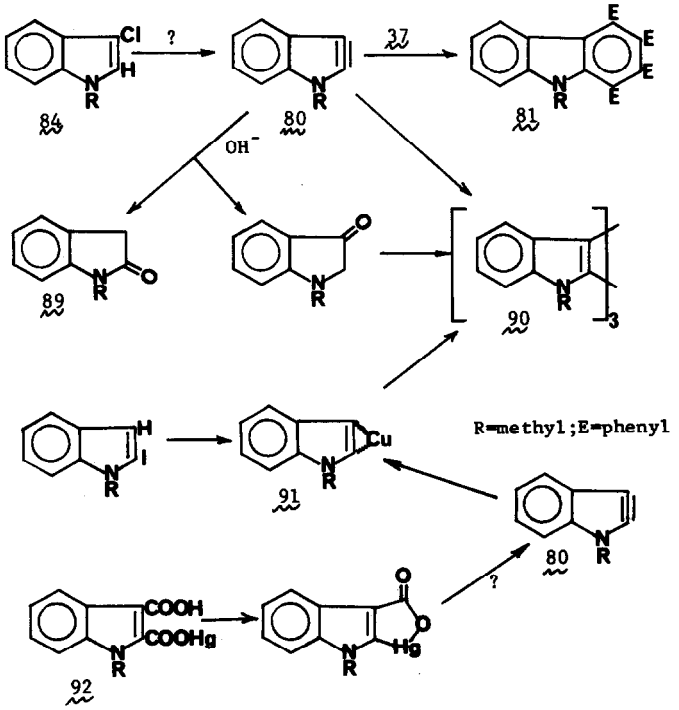

4. 2,3-*Didehydro-N-methylindole* (**80**). Even initially the isolation of the tetracyclone adduct **81** from the decomposition of the mercury compound **82** was considered as insufficient evidence for claiming the intermediacy of the aryne **80**.[103] An addition-elimination process involving either the precursor **82**, the radical **83**, or the 3-chloro-compound **84** was considered and supported by the isolation of the latter compound from the reaction[103] and the demonstration of its efficient conversion to the adduct **81** under nonbasic conditions.[127] The 3-chloro compound **84** also forms an "aryne" adduct **85** with the isobenzofuran **40**, thereby compromising the significance of finding **85** in the reaction of the lithium derivative **86** as evidence for the intermediacy of the aryne **80**. An addition-elimination mechanism is further indicated by the increased rate of decomposition of **86** in the presence of the trapping agent **40**[127].

While neither the sodium derivative **87**[101] nor the halocarboxylate **88**[127] give any identication of aryne

formation, treatment of **84** with NaOH at 200° in the presence of tetracylone **37** leads to the "aryne" adduct **81**, the oxindole cine-substitution product **89**, and a cyclic "aryne" trimer **90**[127]. No definitive claim for the aryne **80** can be made, however, since, as stated above, **84** gives **81** even under nonaryne forming conditions, since the oxindole **89** could arise by other mechanisms of cine-substitution (Section III.A), and since the trimer **90** might be formed by either Wurtz coupling (Section III. B.1) or aldol condensation of N-methylindoxyl, the product of normal substitution. The recent demonstration that the

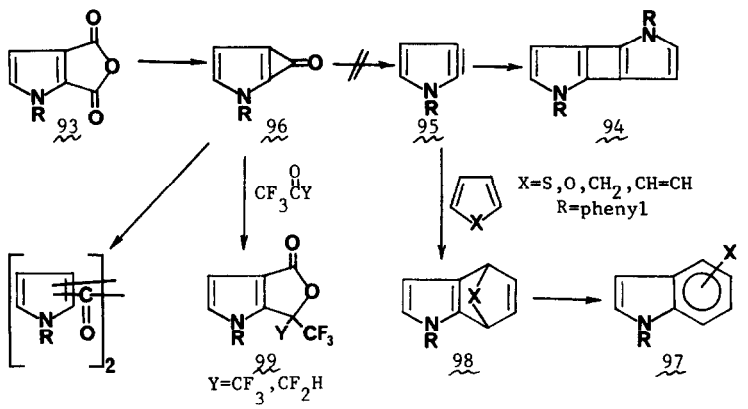



trimer has the symmetrical structure **90**[128] rather than an unsymmetrical[129] one has been suggested as supporting a nonaryne mechanism[4] although the reasoning lacks rigor.[7]



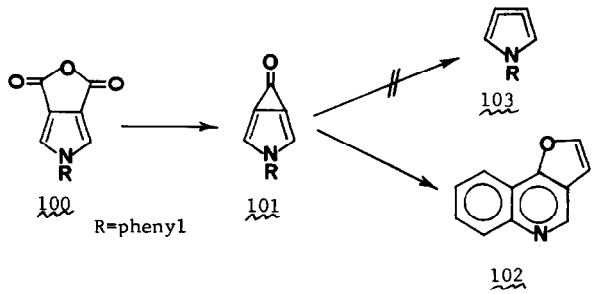
The preparation of the trimer **90** from 2-iodo-N-methylindole has been proposed to involve a stepwise trimerization of a hetaryne-Cu complex (**91**) since biindolyl species do not appear to be intermediates.[128] While the evidence is consistent with a copper-containing intermediate, an oligomeric structure such as that proposed for N-methyl-2-indolyl copper[128] or *o*-phenylenemercury[130] rather than **91** cannot be excluded. Decomposition of the mercury carboxylate **92** in the presence of copper–bronze also gives trimer **90**, suggesting the intermediacy of the complex **91**, or its oligomer, presumably[128] formed by trapping of the hetaryne **80**. Since the only independent evidence for the hetaryne **80** in this reaction is the formation of the ambiguous tetracyclone adduct **81**, however, reaction of the copper–bronze with some mercury-containing precursor of **80** is more likely.

5. *Didehydropyrroles.* In contrast to phthalic anhydride,[131] pyrolysis of the pyrrole anhydride **93** gave no biphenylene type compounds **94** which might indicate the generation of the aryne **95**. Instead, several quinones, postulated to be dimers of the cyclopropenone **96**, were the only products.[132] Because the possible instability of **94**[73,74] might prevent its surviving the pyrolysis conditions, the decomposition of the anhydride **93** was examined[133] in the presence of several dienes which, based on results in the thiophene series (Section V.A.7), should give stable N-phenylindoles **97** by aromatization of the initially formed Diels–Alder adducts **98** of the aryne **95**. The absence of indoles **97**

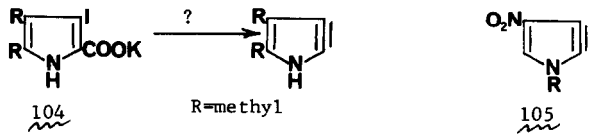



and detection of the lactone **99** when the pyrolysis is conducted in the presence of fluorinated ketones[134] supports the original claim[132] that the cyclopropenone **96**, but not the *aryne* **95** is an intermediate in the pyrolysis of anhydride **93**.

The same conclusion can be drawn for the isomeric anhydride **100** where the intermediate cyclopropenone **101** rearranges to the furoquinoline **102** rather than eliminates CO to the 3,4-didehydropyrrole **103**.[132]

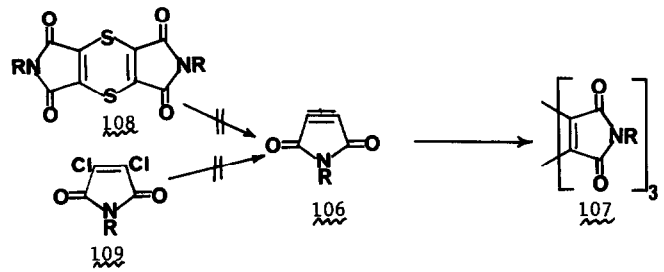



One other attempt to prepare a didehydropyrrole[135] from the iodocarboxylate **104**[136] was inconclusive[7] and as already discussed (Section III.A.4) the cine-substitution of the nitropyrrole proceeds by an ASE mechanism, not the aryne **105**.[62,63]

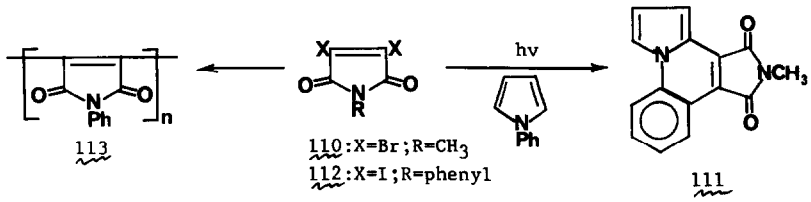



6. *Didehydromaleimide* (**106**). The formation of the triphenylene analogue **107** during the decomposition of the dithiin **108** was suggested[137] to indicate the intermediacy of the didehydro species **106** in

spite of the failure of several dienes such as cyclopentadiene, butadiene and anthracene[138] to give the appropriate adducts. In contrast to the statement in a recent review,[139] therefore, the species **106** has not been trapped, and only **107** has been obtained for which a stepwise mechanism of formation can be



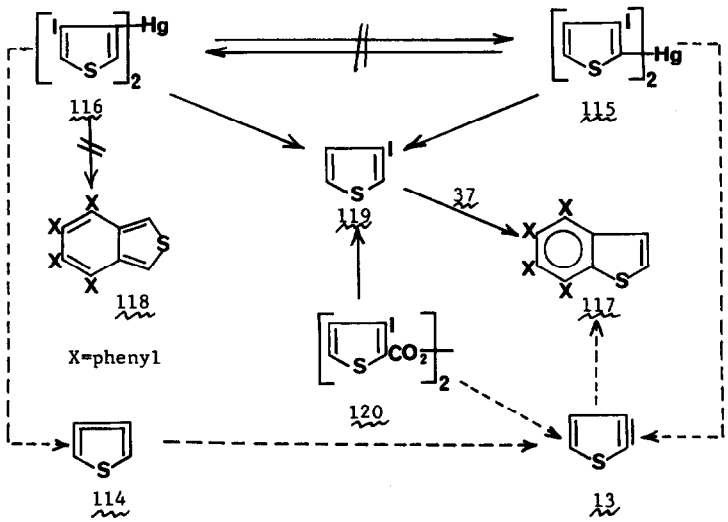
written[7] conceptually similar to that discussed in Section III. B.1. A stepwise mechanism probably is also responsible for trimer (**107**) formation during the preparation of the dithiin (**108**) from dichloromaleimide **109**.[137] Photolysis of the dibromo compound **110** in the presence of N-phenylpyrrole[140] to give **111** and thermolysis of the diiodo compound **112** to an "aryne" polymer **113**[112] parallels results in the maleic



anhydride series (Section IV.A.3) and probably has a similar nonaryne interpretation.

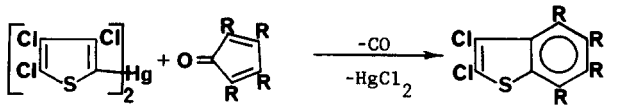
7. *Didehydrothiophenes.* The discussion of these, the most studied of the 5-membered hetarynes,[7] is divided according to the contribution a reaction makes toward supporting the existence of didehydrothiophenes.

(a) *Reactions which give typical aryne products by nonaryne mechanisms.* Both 2,3-didehydrothiophene (**13**)[141] and its 3,4-isomer (**114**)[108] were originally suggested as intermediates in the thermolysis of the mercury compounds **115** and **116**, respectively, based on the isolation of the same tetracyclone adduct **117**. Since the mercury compounds did not isomerize under the reaction conditions,[101] the isolation of **117** rather than the expected adduct **118** from **115** was ascribed[108] to an unprecedented aryne isomerization of **114** to **13** in contrast to the calculated relative stabilities of these intermediates.[142] The validity of this interpretation was questioned almost immediately,[103] and it was soon shown that the common



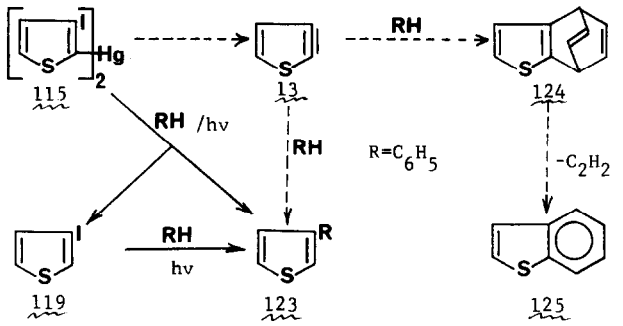
intermediate from the decomposition of the two mercury compounds **115** and **116** was not the aryne **13** but 3-iodothiophene (**119**) which reacts with tetracyclone (**37**) by an addition-elimination mechanism

(Section III. B.2) to give the adduct **117**.[101] A similar conclusion is probable[101] for the iodoperoxide **120** and for the formation of the adduct **121** from the perchloromercury compound **122**.[143] Although the



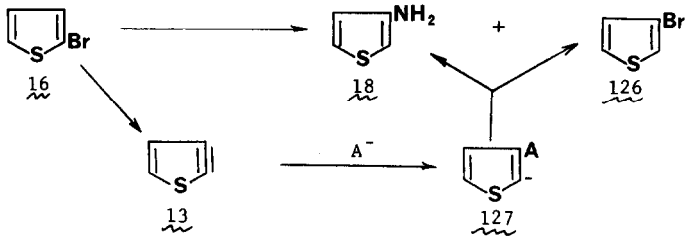

122 37 121

3-phenylthiophene (**123**) formed from the photolysis of **115** in benzene might arise by an insertion reaction of the aryne **13**, the presence of 3-iodothiophene (**119**) as a coproduct which can also yield **123** by a straightforward substitution reaction argues against this interpretation[101] as does the absence of the expected[144] Diels–Alder adduct (**124**) or products obviously derived therefrom such as thianaphthene (**125**).



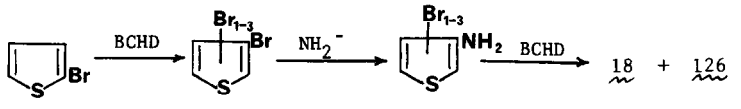

115 13 124 119 123 125

Cine-substitution (Section III.A) as well as cycloaddition (Section III.B) has proven ambiguous in the didehydrothiophene series. Treatment of 2-bromothiophene (**16**) with $KNH_2$ under the precise conditions used by Roberts in his classic studies establishing the intermediacy of benzyne in the amination of chlorobenzene,[18] led to the formation of 3-amino- (**18**) and 3-bromothiophene (**126**).[37] This result, and several supporting observations[7,37] are apparently consistent with the regiospecific addition of $NH_2^-$ and




16 18 126 13 127

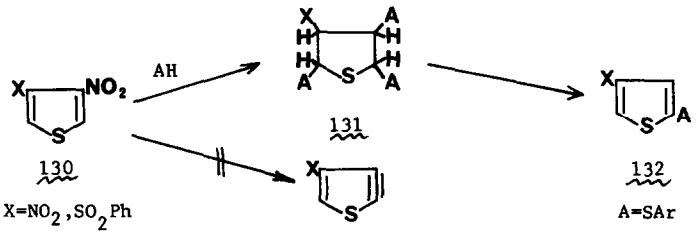
$Br^-$ to the intermediate aryne **13** to give the expected,[31] more stable anion (**127**) with the negative charge adjacent to sulfur.[34] When it was revealed, however, that any change in reaction conditions resulted in the formation of polybromo- (**129**) and/or aminobromothiophenes (**129**),[7] and that these compounds were converted to **18** and **126** under the original reaction conditions,[7,37] it was concluded that a BCHD mechanism of cine-substitution (Section III. A.2) was operative.[37,39,45] The possibility that the actual




16 128 129

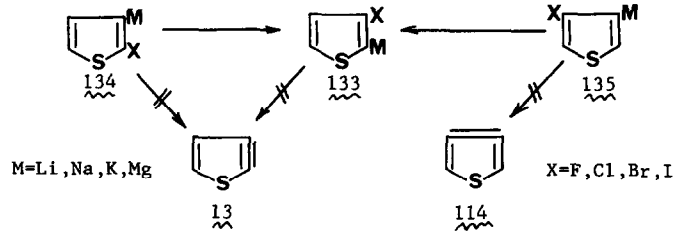
substitution step (**128**→**129**) involves an aryne was rendered unlikely by the blocking of this reaction by remote methyl groups[41] and the failure to detect an aryne adduct in the presence of tetracyclone (**37**).[7] Either a normal addition-elimination[7] or an $S_{RN}1$ mechanism[145] seems a more likely explanation.

The other known examples of cine-substitution in the thiophene series involve the replacement of a nitro group in **130** by an arylthio substituent.[146] An ASE mechanism (Section III.A.4), rather than aryne



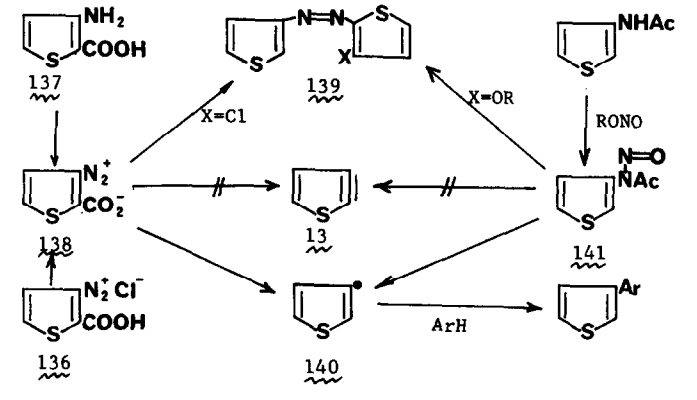

mechanism, is suggested by the recent isolation of **131** from this reaction and its subsequent conversion to the product **132**.[147]

(b) *Reactions which failed to give aryne products.* The extensively studied chemistry of the *o*-halo group IA and group IIA metal derivatives of thiophene has given neither claim nor evidence of aryne formation.[7] In part this is due to the previously mentioned stability (Sec. IV) of 2-metallo-3-halothiophenes (**133**) and the resulting tendency of the isomers **134** and **135** to rearrange to **133**[148–151] rather than form arynes **13** or **114**. Under more severe conditions, or with isomerization blocked, dispor-

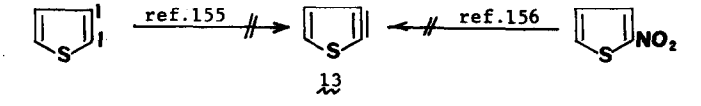



portionation[101] and ring-opening[100,101] are observed, but no products which might arise from trapping the arynes **13** or **114** by a variety of dienes.[101,149]

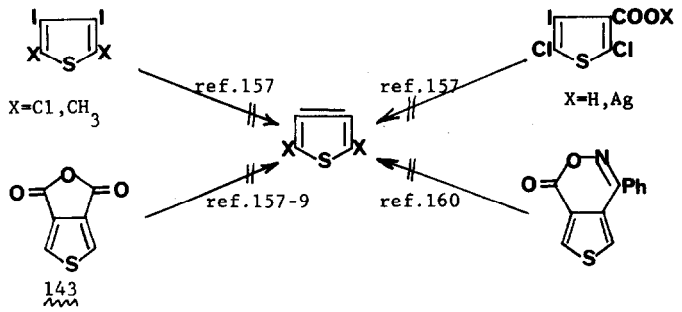
The diazonium carboxylate **138** has been isolated[152] as well as generated *in situ* from its hydrochloride salt (**136**) or the corresponding amino acid (**13**) and its chemistry with various aryne traps studied.[153] The only reactions observed where self-coupling to azo compounds such as **139**[154] and arylation probably via the 3-thienyl radical **140**.[7,153] Decomposition of the N-nitroso compound **141** generated *in situ* gave an identical result.[153]



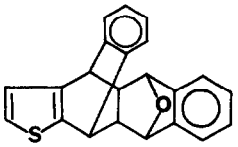

Several other potential aryne precursors have been examined under thermolysis conditions as shown




below, but fail to give any evidence of aryne formation even in the presence of various aryne traps.[7]




(c) *Reactions which are speculated without evidence to give arynes.* Didehydrothiophenes have been speculated to be intermediates in a variety of complicated reactions including the pyrolysis of thiophene, alone[161] and in the presence of phthalic anhydrides,[162] the pyrolysis of thianaphthene, alone[163] or in the presence of phthalic anhydride,[162] the acid hydrolysis of the adduct **142**,[7,164] the plasmolysis of the anhydride **143**,[125] and the reaction of the dilithiocompound **144** with $Me_2SO_4$ and air.[157] Although the data, invariably just product analysis, is permissive of an aryne interpretation, it is certainly not conclusive, since no *characteristic* aryne reactions (Section III) were observed and alternative non-aryne mechanisms are often possible.[7]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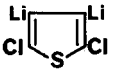
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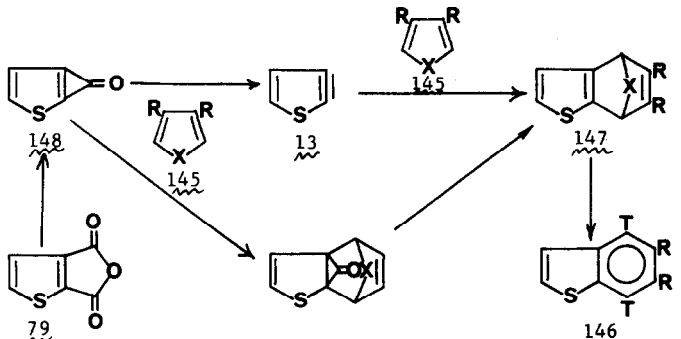
(d) *Reactions which give aryne products probably via arynes.* The best evidence to date for the existence of 2,3-didehydrothiophene (**13**) or for that matter any 5-membered hetaryne, comes from the flow vacuum thermolysis of the anhydride (**79**) in the presence of a variety of diene traps (**145**).[158,159] The major products were substituted thianaphthenes **146** whose formation could be most easily rationalized by known aromatization reactions of initially formed Diels–Alder adducts **147** of the aryne **13**. The




| | X= | R= | T= |
|---|---|---|---|
| a: | $CH_2CH_2$ | H | H |
| b: | S | H | H |
| c: | CH=CH | H | H |
| d: | $CH_2$ | H | H,$CH_3$ |
| e: | H,H | $CH_3$ | H |
| f: | O | H | H,OH |

possibility that the adducts **147** arose by an addition-elimination process (Section III. A.2) was considered highly unlikely because of the variety and apparent nonambiguity as aryne traps of the dienes (**145**) used and the demonstrated lack of dienophilic reactivity of the anhydride **79**.

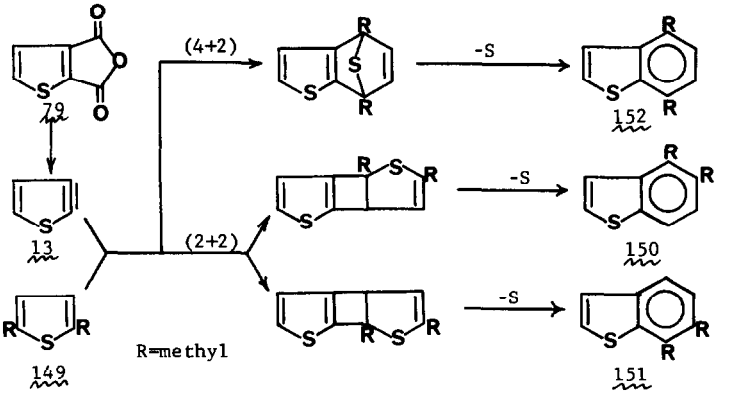
The validity of this argument must be reexamined, however, in light of the recent detection of the cyclopropenone **148** in the FVT of the anhydride **79**.[134,165] Somewhat strained analogies can be cited which permit, but do not require, the involvement of such an intermediate in the formation of the adduct **147** by an addition-elimination mechanism which avoids the aryne **13**.[7] The best evidence against this hypothesis at the present time[7] is that the related cyclopropenone **96** in the pyrrole series (Section V.

A.5), shows no tendency to undergo such an addition-elimination reaction.[133] Definitive rejection of this possibility, however, will require generation of aryne **13** from a precursor which cannot yield the cyclopropenone **148**. In the meanwhile the intermediacy of the aryne **13** offers the best rationalization for the chemistry observed during the FVT of the anhydride **79**.

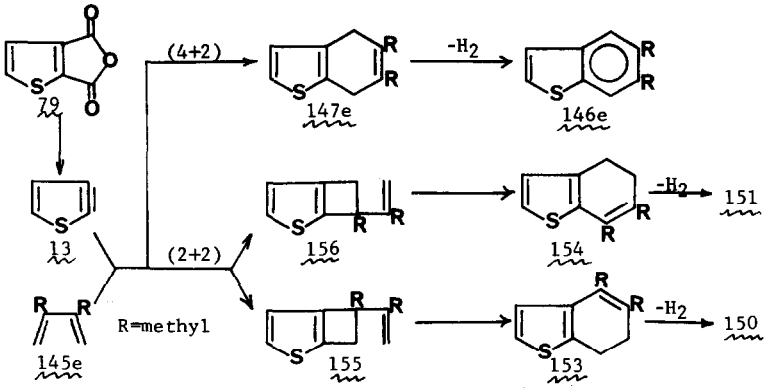
The ubiquity of the cycloaddition of 2,3-didehydrothiophene (**13**) and dienes **145** as outlined above makes this reaction virtually diagnostic for the presence of this aryne. Thus, when **13** is generated with benzene (**145c**) available as a trap, thianaphthene (**125** ≡ **146a, b, c**) is formed by a retro-Diels–Alder loss of acetylene[144] from the adduct **147c**. This supports the contention (Section V. A.7(a)) that the absence of thianaphthene (**125**) in the photolysis of a benzene solution of the mercury compound **115**[101] indicates the absence of the aryne **13** in this reaction.

Although the above cycloaddition reactions of the aryne **13** have been formulated as proceeding in a (4+2) manner,[158,159] the participation of a (2+2) pathway was revealed by the use of substituted thiophenes as traps.[166] Thus with 2,5-dimethylthiophene (**149**) both of the (2+2) cycloaddition products **150** and **151** were produced as well as the (4+2) product **152** in a ratio of 5:2:3. No other thianaphthenes could be detected and no interconversion of the products under FVT conditions was observed.

Because of the tendency of 2,3-dimethylbutadiene (**145e**) to react in a (2+2) manner with benzyne to give benzcyclobutenes[167], analogous products were sought without success from the FVT of the



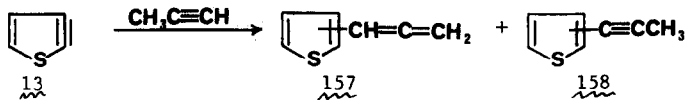

anhydride **79** in the presence of this diene trap. In addition to the major product **146e**, which arises by the (4+2) path, a small amount of a dihydrodimethylthianaphthene (**153** or **154**) and its aromatization product (**150** or **151**) were isolated. These products could derive from the well-known vinylcyclobutane-




cyclohexene rearrangement[168] of the (2+2)-adduct (**155** or **156**) followed by dehydrogenation.

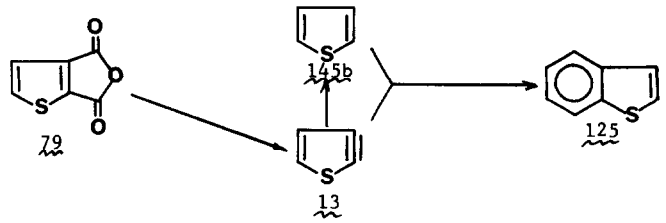
The significance of these examples of (2+2) reactivity of 2,3-didehydrothiophene (**13**) as a probe of aryne structure (i.e. possible diradical or dipolar character analogous to **1b** and **1c**) must await an evaluation of the role of the nature of the diene trap[169] and the concertedness[170] of the reaction path. It has, for example, recently been demonstrated that thiophenes can react as dienes with benzyne in both a (4+2)[171] and a (2+2)[172] manner.

The ene reaction often competes effectively with cycloaddition when the diene used to trap an aryne contains allylic hydrogen atoms.[167–169] No ene products were observed with any of the above dienes (**145, 149**) although in the presence of propyne as a trap, a mixture of thienylallenes (**157**) and thienylmethyl-

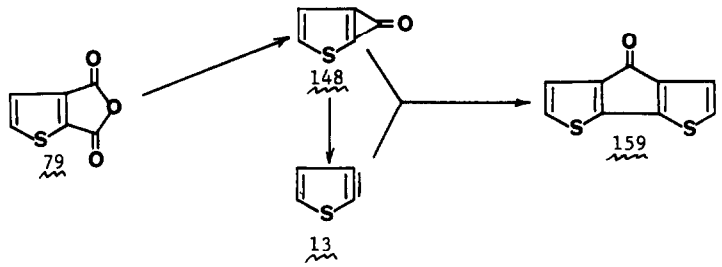



acetylenes (**158**) was obtained.[159] The former is the expected[173] ene product with the aryne **13** and the latter the result of an allene-acetylene rearrangement.[174]

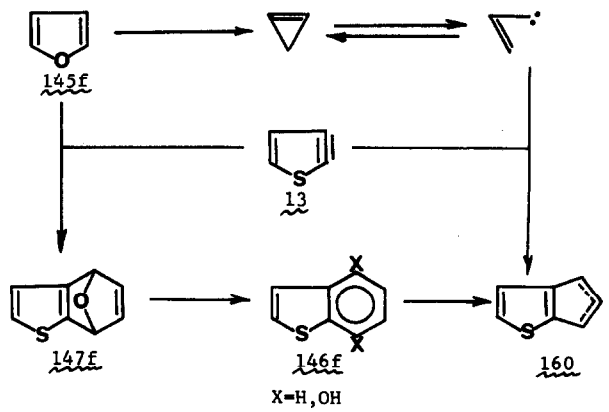
FVT of the anhydride **79** in the presence of hydrogen gave thiophene and thianaphthene (**125**) as the only products[165] presumably by hydrogenation of the aryne **13** and cycloaddition of the resulting




thiophene, respectively. All attempts to determine the direction of addition of nucleophiles to the aryne **13** have thus far run afoul of their reactivities with the anhydride precursor **79** or the cyclopropenone **148**.[165] Finally, reaction of the cyclopropenone **148** with the aryne **13** might account for the formation of the fluorenone analogue (**159**)[159] although other explanations must be considered.[165]

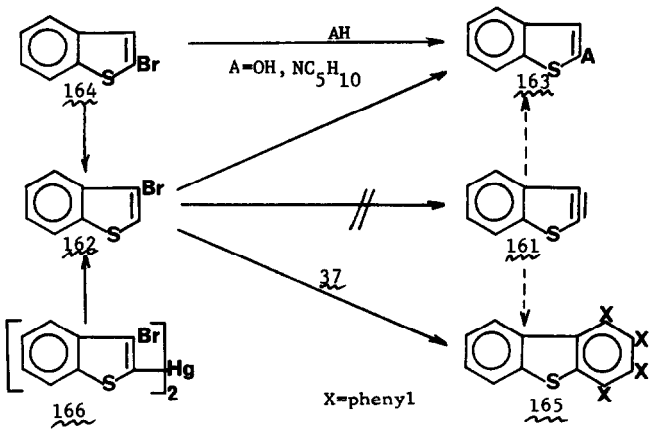



In contrast to the FVT studies of the anhydride **79**, no evidence of aryne formation was obtained from thermolysis in the condensed phase.[159] Plasmolysis experiments, however, were once again indicative of the generation of 2,3-didehydrothiophene (**13**), particularly when carried out in the presence of furan (**145f**) as a trap.[125] The product consisted of a mixture of cyclopentenothiophenes (**160**) proposed to arise by the reaction of the aryne **13** with some unspecified $C_3H_4$ species (probably cyclopropene[175]) known to be formed during the plasmolysis of furan.[125] The same products have been obtained in the FVT of the anhydride **79** with a furan trap and rationalized[159] as arising either by thermolysis of the oxygen bridge of the aryne adduct **147f** followed by decarbonylation of the resulting thianaphthol **146f**[176] or by an electrocyclic reaction[177] of the aryne **13** with the "vinyl carbene" known[178] to be in equilibrium with cyclopropene. The former interpretation is supported by the isolation of the adduct **146f** in the FVT studies[159] but not the plasmolysis experiments. Regardless of which mechanism



is correct, the aryne **13** is clearly implicated. An aryne interpretation is permitted but not required for the plasmolysis of the anhydride **79** with hydrogen or acetylene as traps,[125] since reasonable nonaryne processes can also be postulated[7] to account for the products.

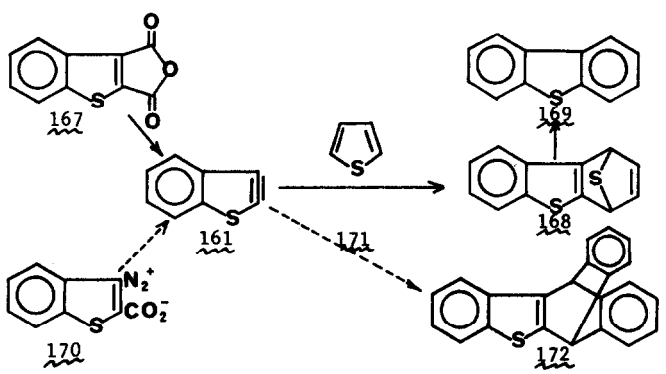
8. *Didehydrothianaphthenes.* The bicyclic hetaryne, 2,3-didehydrothianaphthene (**161**) was first suggested[179] as an intermediate to explain the cine-substitution of 3-bromothianaphthene (**162**) with KOH[180] and slightly later[8] with piperidine.[181] The latter reaction was subsequently reinvestigated [182] and the major portion of the cine-substitution product (**163**) shown to arise from the 2-bromo isomer (**164**) present as a contaminant in the method utilized[183] for preparing the reactant (**162**). The small amount of cine-substitution which persists when pure 3-bromothianaphthene (**162**) is used [182] probably is formed by variations[7] of the BCHD mechanism (Section III. A.2) which is also observed in the rearrangement of 2- to 3-bromothianaphthene (**164**→**162**) in the presence of metal amides[43].



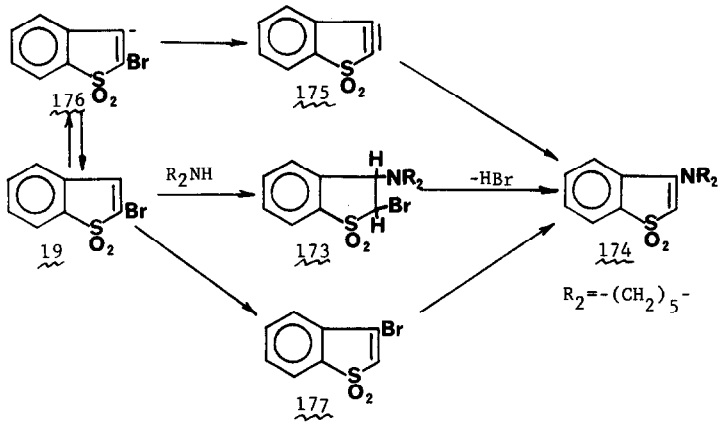

As in the benzofuran (Section V. A.1) and indole series (Section V. A.4), the formation of the adduct **165** from tetracyclone (**37**) and the mercury compound **166** does not involve the aryne **161** but rather an addition-elimination mechanism (Section III. B.2) via 3-bromothianaphthene (**162**).[101] A mechanism involving the aryne **161** can be written to explain some minor products detected during the pyrolysis of thianaphthene (**125**) alone and in the presence of phthalic anhydride.[162,163] This claim must be regarded[7] as highly speculative especially since the structure assignments of the products are quite tenuous.

The best evidence for the generation of the aryne **161** comes from FVT of the anhydride **167** in the presence of thiophene.[159] Desulfurization of the initially formed Diels–Alder adduct **168** accounts for the only isolated product, dibenzothiophene (**169**). The actual isolation of a *primary* adduct of the aryne **161**, or for that matter any 5-membered hetaryne, has recently been reported from the decomposition of the diazonium carboxylate **170** in the presence of various anthracenes **171**.[184] A firm claim that the resulting heterotriptycenes (**172**) in fact arise from the aryne **161** must await the results of competition studies.[28,94]

Because of the reduced aromaticity of the 5-membered ring,[185] the 2,3-double bond of thianaphthene dioxides would be expected to display an increased tendency to undergo both Michael and Diels–Alder additions.[186] Thus the cine-substitution of the bromo derivative **19** by amines in ethanol as solvent[50] represents the prototypical example of the AEa mechanism (Section III. A.3) since the intermediate



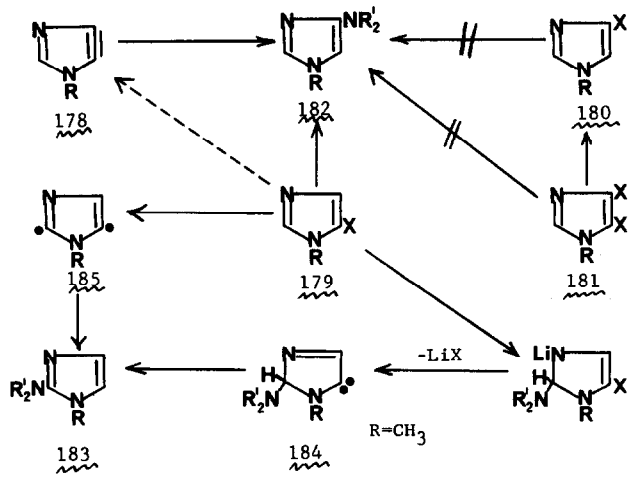
addition product **173** was actually isolated and shown to go on to the product **174** under the reaction conditions. With benzene as the solvent, however, the addition compound **173** was not an intermediate[50] and an elimination-addition mechanism via the didehydro species **175** was postulated.[187] The role of solvent was explained[8] by assuming a rapid reprotonation of the initially formed carbanion **176** in ethanol, but not in benzene, thereby preventing bromide ion loss to the aryne **175**. Additional evidence




either supporting or refuting this hypothesis is lacking, although a transhalogenation mechanism (Section III. A.2) *via* the 3-bromo compound **177** has been considered[7] based on the known rearrangement of **19** to **177** with $KNH_2$ at $-70°$,[44] and the facile conversion of the latter compound to the cine-substitution product **174**.

9. *Didehydroselenophenes.* Although the chemistry of several potential precursors has been examined, neither claims of nor attempts to prepare these arynes have been reported.[7]

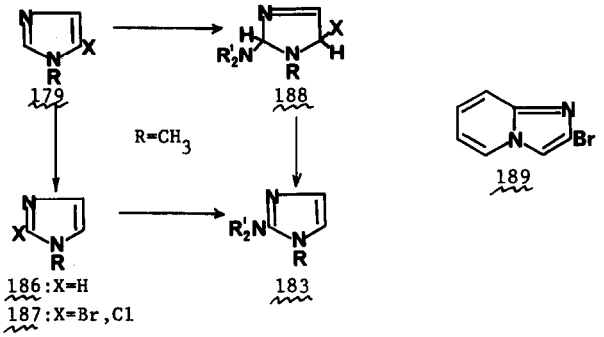
10. *Didehydroimidazoles.* This hetaryne (**178**) was proposed to explain the apparent cine-substitution of 5-haloimidazoles (**179**) with lithium amides.[189] Appropriate control experiments[10] eliminated the intermediacy of either 4-halo (**180**) or 4,5-dihaloimidazoles (**181**), which could possibly form by a transhalogenation mechanism,[40] and competition studies[189] seemed to require that the rearranged product was formed by a single mechanism involving a halogen-free intermediate in the product-determining step. The discovery that it was not the cine (**182**) but tele-substitution product (**183**) which was formed in this reaction effectively eliminated the aryne **178** as a possible intermediate and led to the suggestion of a tentative mechanism via the carbene **184**.[190] The unlikelihood of this mechanism has already been noted,[191] and an alternative[7] via the meta aryne, 2,5-didehydroimidazole (**185**) lacks sufficient precedence



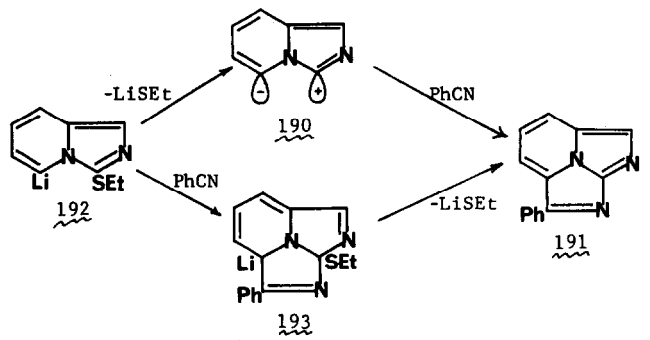

(Section V. B.5) to warrant serious consideration without confirmatory evidence. The formation of **183** from either N-methylimidazole (**186**) or its 2-halo derivative (**187**), possibly obtained by a trans-halogenation reaction of the starting halide **179**, was eliminated experimentally.[190] A proposed[7] AEa mechanism (Section III. A3) *via* the addition compound **188** is possible only if, in contrast to

cine-substitution,[49,68] such a tele-substitution process would not display an element effect so as to be consistent with the competition studies.[189] A rate-determining addition of amine to **179** followed by a rapid 1,4-elimination of HX might meet this requirement.

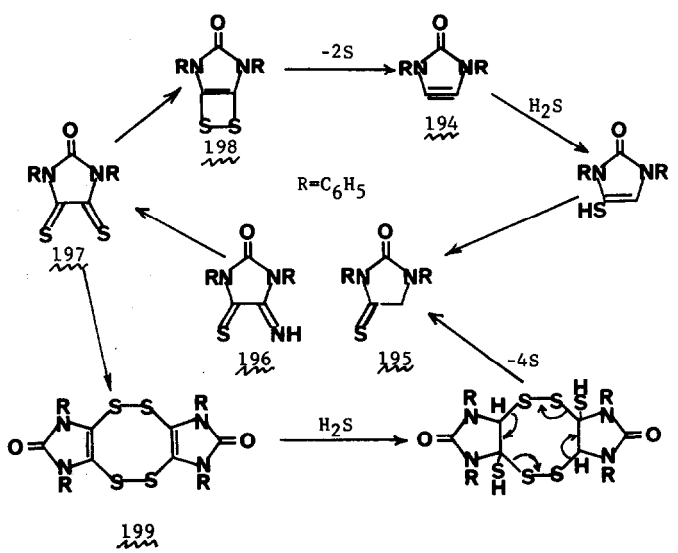
The teleamination of 3-bromoimidazol(1,2-a)pyridine (**189**) has also been rationalized by an AEa




mechanism,[192] although a bicyclic didehydro species **190** related to 1,8-didehydronaphthalene (**4**)[193] recently has been considered to explain the formation of the cyclazine (**191**) from the lithium compound **192** and benzonitrile.[194] An alternative addition-elimination process via **193** has ample precedent in the closely related pyrrocoline ring system[195] and has not yet been disproven.

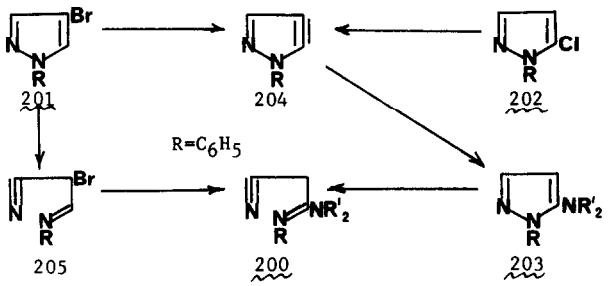



A didehydroimidazolinone (**194**) has recently been considered to explain the formation of the monothione **195** from the iminothione **196** as shown.[196] This mechanism has been questioned[7] since known dithione (**197**)-dithiete (**198**) isomerizations are predicted[197] and observed[198] to occur photochemically, not thermally. The product expected from the dithione **197** is the dimer **199**[198] from which several mechanisms leading to the monothione **195**, but not involving the aryne **194**, can be written.[7]

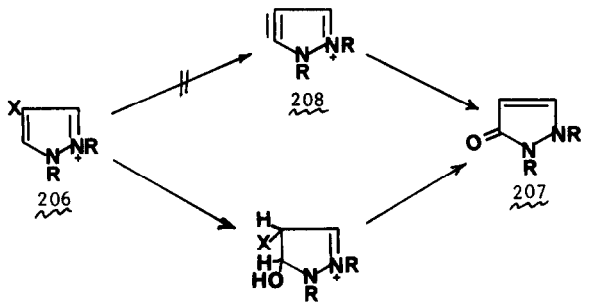


These alternative mechanisms must be eliminated before the intermediacy of **194** can be regarded as other than speculation.

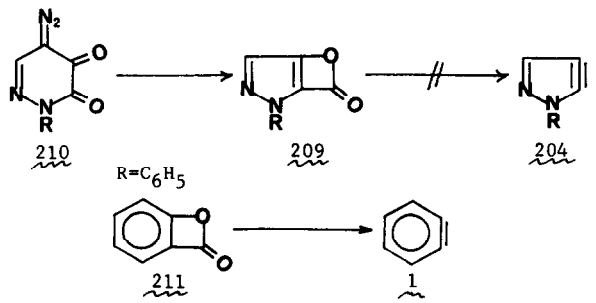
11. *Didehydropyrazoles.* These arynes have been considered but never claimed as intermediates in reactions of strong bases with halopyrazoles and pyrazolium salts. For example, the formation of the cyanoamidine **200** from the halo compounds **201** or **202** and lithium dimethylamide was speculated to involve ring-opening of the aminopyrazole **203** produced by addition of amine to the aryne **204**.[199] Although this mechanism could not be ruled out, the nonaryne alternative via the bromonitrile **205** was shown to be possible as well.



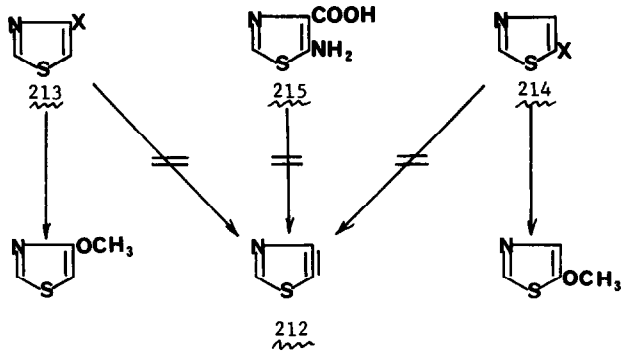

Although no cine-substitution is obtained from the reaction of bromopyrazoles with $KNH_2$,[44] it has been observed in the reaction of 4-halopyrazolium salts **206** with hydroxide ion.[200] The pyrazolone **207** was concluded, however, to arise primarily by an AEa mechanism (Section III. A3) and not via the aryne **208** which could not be trapped in cycloaddition reactions.




The apparent difficulty of forming the didehydropyrazole **204** is demonstrated by the remarkable isolation of the lactone **209** from the thermolysis of the diazocompound **210**.[201] In contrast to the benzene analogue **211** which is detectable only in an argon matrix at 8°K[202] and loses $CO_2$ to give benzyne on photolysis,[22] **209** is stable at room temperature in the absence of nucleophiles.

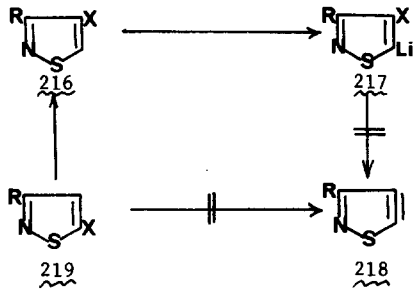



12. *Didehydrothiazole.* The intermediacy of 4,5-didehydrothiazole (**212**) was convincingly ruled out in the nucleophilic substitution of both 4-halo (**213**)[203] and 5-halothiazoles (**214**),[204] based on kinetic and substituent effects and the absence of either cine-substitution or cycloaddition products. *In situ* diazo-

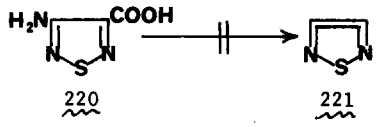


tization[205] of the amino acid **215** in the presence of various diene traps also failed to yield any aryne adducts.[206]

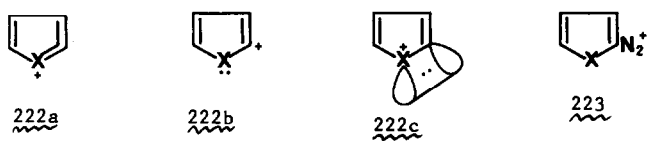
13. *Didehydroisothiazoles.* 4-Haloisothiazoles (**216**) are metallated to give lithium compounds (**217**) which show no tendency to lose LiX and give the aryne **218**. Reaction of 5-haloisothiazoles (**219**) with $KNH_2/NH_3$ similarly results in transhalogenation and normal, but not cine-substitution.[38]



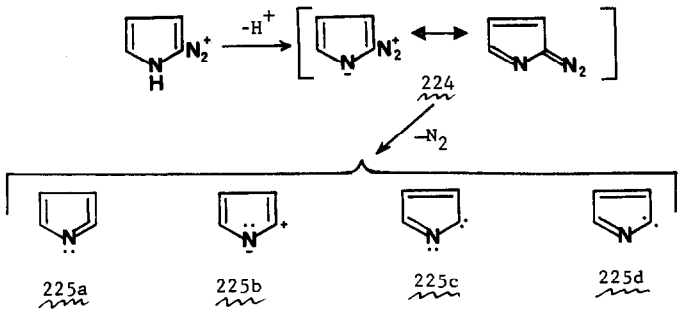
14. *Didehydro-1,2,5-thiadiazole.* The *in situ*[205] diazotization of the amino acid **220** in the presence of anthracene gives no adduct of the aryne **221** but only products resulting from apparent fragmentation of the thiadiazole ring.[208]



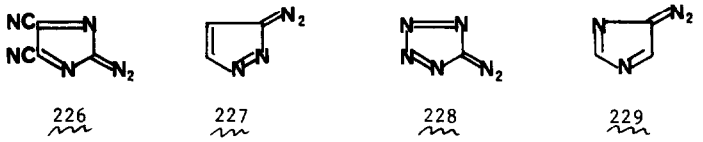
15. *1,2-Didehydroazoles.* Didehydroheterocycles in which one end of the didehydro bond is to a heteroatom may[179] or may not[4] be considered true hetarynes. With a divalent heteroatom these species (**222**) would have to be cationic in order to be isoelectronic with benzyne (**1f**) and hence are referred to as hetarynium ions.[4,7,179]



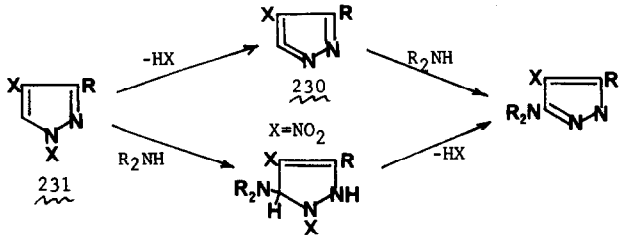
No evidence that such species have been generated by the most likely method,[209] loss of $N_2$ from the diazonium salts **223**,[210] is available. If X = NH, however, the corresponding diazonium salt is readily deprotonated to give a neutral diazo compound **224**[211] which upon loss of nitrogen would lead to a neutral intermediate which could display arynic (**225a**), dipolar (**225b**) or carbenic character, the latter in either singlet (**225c**) or triplet (**225d**) states.[209,211]



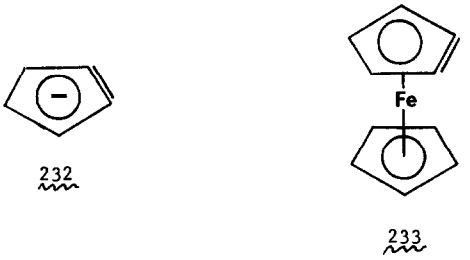

The decompositions of four such diazo compounds have been studied. Dicyanodiazoimidazole (**226**)[213] and the diazopyrazole (**227**)[214] undergo thermolytic loss of nitrogen with substitution in such a way that the intermediacy of a species with dual dipolar and carbenic character is suggested. No evidence for arynic properties was observed. The thermolysis of the diazotetrazole **228**[215] and the photolysis of the 4-diazoimidazole (**229**)[216] are less well studied but appear to proceed by carbenic and radical paths, respectively.




The one example of a reaction in which an intermediate (**230**) with aryne character in principle could be involved is the cine-substitution of the dinitropyrazole **231**.[217] An AEa mechanism (Section III. A.3) is preferred, however, and adequately explains all the data.




16. *Five-membered carbocyclic arynes.* Although outside the scope of this review, two carbocyclic arynes isoelectronic with 5-membered hetarynes have been claimed in the literature, the didehydrocyclopentadiene anion **232**[218] and didehydroferrocene **233**.[219] As discussed elsewhere,[7] the evidence for the former species is based on the use of ambiguous dienes as traps (Section III. B.2) and that for the latter species on the unlikelihood of nonaryne alternatives. Considering the difficulties which have been encountered in proving the existence of other 5-membered arynes discussed in this Report, further evidence for the existence of **232** and **233** is desirable.

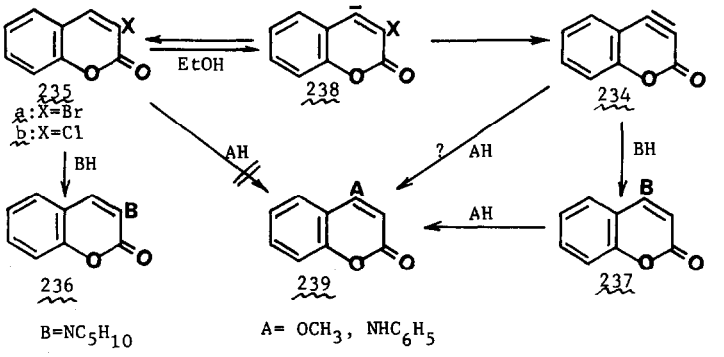



B. *Six-membered hetarynes*

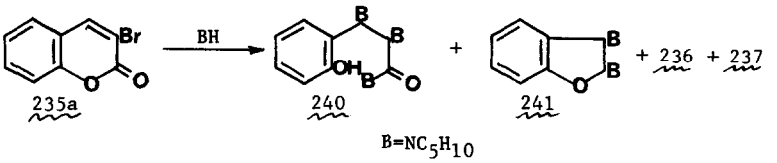
To the extent that their ring size contributes to the problem of generating 5-membered hetarynes,[7] the 6-membered homologues[7a] ought to be more readily available. On the other hand, 6-membered heterocycles also exhibit a lowered resonance energy compared to benzyne[76] and have the consequent

tendency to undergo addition-elimination processes (Section III. A.3–5).[4] Therefore, although this part of the Report will emphasize findings since the last reviews,[6,10] the data upon which the claims for a particular 6-membered hetaryne are based will be evaluated in the light of current knowledge.

1. 3,4-*Didehydrocoumarin* (**234**). This is the only 6-membered hetaryne to be proposed which does not contain nitrogen. The claim is based on the partial cine-substitution of 3- (but not 4-) halocoumarins (**235**) with piperidine.[187] A change in product ratio with the nature of the halogen indicates that at least two mechanisms must be involved, and the fact that the relative amount of the normal substitution product **236** increases when the solvent is changed from benzene to ethanol suggests that the rearranged product **237** arises *via* an anionic species such as **238** which is competitively protonated to **235** or converted to **237**, presumably *via* the aryne **234**. The presence of this intermediate is apparently supported by the report that 3-bromocoumarin (**235a**) is stable to methanol or aniline under the reaction conditions (3 hr, 80°) but gives rearranged substitution products **239** when piperidine is present.[220]

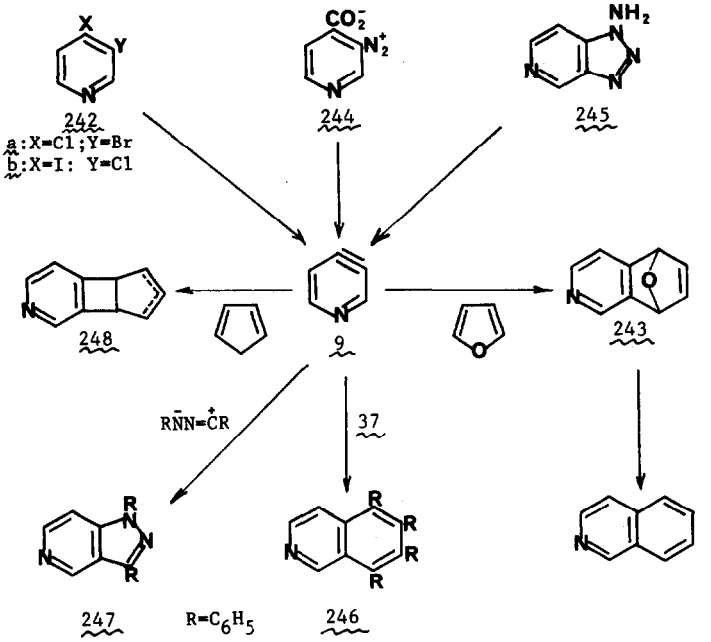



The value of this last observation is diminished by the fact that **239** (A = NHPh) has been shown to arise from **237** under conditions only slightly more severe (3 hr, 100°) than the original reaction.[221] Furthermore, under these original conditions the Russian workers isolated from **235a** not only **236** and **237** (in a different ratio as before[187]—1:9 as compared to 1:2) but also products such as **240** and **241** which indicate that ANRORC and abnormal addition processes (Section III. A.3, 4, 5) are occurring.[221] Clearly the role that these compounds and reactions play in the cine-substitution of 3-halocoumarins **235** must be established before the intermediacy of the aryne **234** can be considered as certain.




2. 3,4-*Didehydropyridines.* The parent species **9** was the first hetaryne to be proposed[222] in modern times (Sec. II), and the evidence supporting its existence is acknowledged to be the most convincing of any hetaryne.[4,6,7a,8–10] Not only has 3,4-didehydropyridine (**9**) been obtained from several different precursors and been detected with both nucleophilic and diene traps, it also has been generated in the gas phase in a time-of-flight mass spectrometer[29] analogous to benzyne.[223] Consistent with this ubiquity, all calculations except one[224] indicate that **9** would be the most stable of the didehydropyridines.[142,225,226]

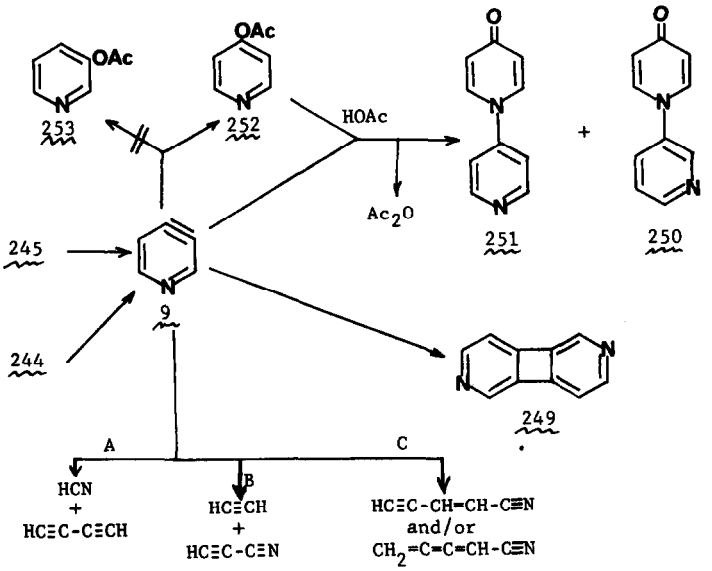
(a) *Bidentate precursors.* Three bidentate precursors of 3,4-didehydropyridine (**9**) have been examined. The earliest[227] of these was the bromochloropyridine **242a** which on treatment with lithium amalgam in the presence of furan gave isoquinoline, presumably by reduction of the intermediate Diels–Alder adduct **243**.[179] This adduct actually can be isolated from the chloroiodopyridine **242b** and BuLi at −78°,[228] from the decomposition of the diazonium carboxylate **244**,[5,8,179] or from the oxidation of the aminotriazole **245** in the presence of furan.[229] The latter precursor also gives the [4+2] adduct **246** with



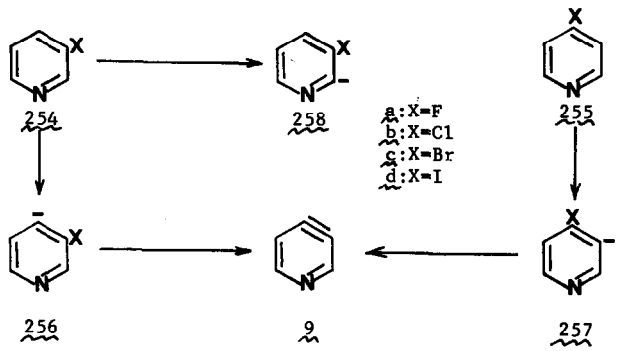

tetracyclone (**37**)[230] as well as [3 + 2] cycloadducts such as **247** with some but not all 1, 3-dipoles.[229] While this last reaction is typical of arynes,[25] the reported formation of the [2 + 2] adduct **248** from **244** and cyclopentadiene[8,220] is unusual since the [4 + 2] adduct (**243** $CH_2$ for O) would be expected.[25] The failure to obtain any adducts with such common[25] aryne traps as anthracene,[8] dimethylfulvene,[229] and norbornadiene[8,229] also lacks an explanation.

In contrast to its benzene analogue,[231] the aminotriazole **245** does not give any aryne dimers **249** when oxidized in the absence of trapping agents.[232] The only products detected are acetic anhydride and a 45:55 mixture of the 3'- and 4'-pyridyl-4-pyridones, **250** and **251**, respectively, probably arising from reaction of the aryne **9** with 4-acetoxypyridine **252**. The observed product ratio is consistent with that from other nucleophilic additions to 3, 4-pyridyne (**9**) (*vide infra*). If the addition of acetic acid to **9** similarly accounts for the origin of **252**, then the absence of 3-acetoxypyridine (**253**), or products derived therefrom, requires explanation. At least part of the rationale offered, [232] greater specificity in the addition to unsymmetrical arynes of carboxylic acids compared to other nucleophiles, appears to be contradicted by the cited reference.[233]

When generated in the gas phase from the diazonium carboxylate **244**, the aryne **9** does dimerize to the diazabiphenylene **249**,[29] although to a lesser extent than in the benzene series.[223] The reason for this difference is that the observed unimolecular ring-openings A, B and C of 3, 4-pyridyne (**9**) are calculated to be about 39 kcal/mol more favorable than comparable reactions with benzyne **1**.[29]

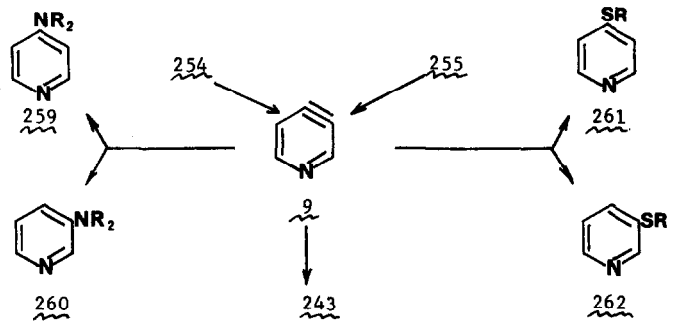


(b) *Monodentate precursors.* The most extensively studied and reviewed[4,6,7a,8-10,12] of these precursors are the 3- (**254**) and 4-halopyridines (**255**). As with benzyne[77] the elimination of HX with base is stepwise *via* the *o*-haloanions (or organometallic derivatives) **256** and **257** which at low temperatures often can be trapped with appropriate electrophiles.[228,234] The formation of the 2-anion **258** is kinetically disfavored[235] due to the theoretically supported[225] repulsion between the N and C-2 nonbonded electron pairs.[33] The stability of these anions to loss of halide ion to give the aryne **9** (F > Cl > Br > I)[228] is similar to that in the benzyne series.[77]




254 258 255 256 9 257

The presence of the aryne intermediate (**9**) from the halopyridines **254** and **255** is indicated by isolation of the Diels–Alder adduct **243** in the presence of furan,[234,236-238] by the constancy of the ratio of the isomeric amines **259** and **260** obtained from isomeric precursors **254** and **255**,[8,239,240] and by the formation of thioethers **261** and **262** in the presence of the corresponding mercaptides (section III. A.6).[69,236] In those cases where one or both of the isomeric halides **254** or **255** react totally or partially by a normal addition-elimination mechanism (AEn) the base-competition method (Section II. A.6) can detect EA-mechanism participation *via* the aryne **9**.



259 254 255 261 9 260 243 262

The extent of 3,4-didehydropyridine (**9**) formation from various halopyridine and base combinations as summarized in Table 1 reveals several generalizations.[4,10] Aryne (**9**) formation is favored by: (i) the heavier halogen (I > Br > Cl > F), (ii) the less reactive isomer to reaction *via* AEn (**254** > **255**), and (iii) the bulkier base ($LiNiPr_2$ > $LiNEt_2$ > LiPip). These trends, as well as the failure of weaker bases such as piperidine[8] and sodium methoxide[249] to generate arynes, run parallel to those observed with benzyne.[77]

In agreement with theoretical calculations[225] nucleophiles add preferentially to the 4-position of 3,4-pyridyne (**9**). As might be expected[24] the product ratio is closer to 1:1 for very reactive nucleophiles such as mercaptides[69,236] and lithium dialkylamides[242,243,245] than for the less reactive[250] $KNH_2$ (2:1).[239,240] The benzophenone dianion,[248] KOH,[244] $NaNHNH_2$[8] and acetophenone enolate[6,222] also favor addition to the 4-position of **9** as does lowering the temperature.[8]

The selectivity of arynes in discriminating between two offered nucleophiles can be taken as a measure of their relative stability.[25] Although the application of this competition method to 3,4-pyridyne **9** with the base pair piperidine-diethylamine (or the respective lithium amides) seemed to indicate that this intermediate was more selective and hence more stable than benzyne (**1**),[8] subsequent studies revealed the experimental ambiguity of this particular base pair[246,247] and led to the use of the diethylamine-diisopropylamine system.[252] The derived competition constants showed that 3,4-pyridyne (**9**) is *less* selective than benzyne (**1**) in keeping with the greater stability of the latter expected from

Table 1. Extent[a] of formation of 3,4-didehydropyridine **9** from halopyridines **254** and **255**

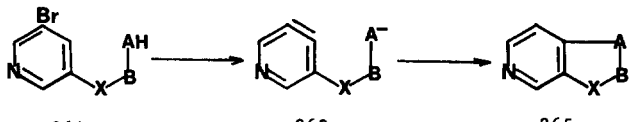
| Precursor \ Base | $KNH_2$ | | LiPip | | $LiNEt_2$ | | $LiNiPr_2$ | | KOtBu | | KOH | | Other | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | % | Ref. | % | Ref. | % | Ref. | % | Ref. | % | Ref. | % | Ref. | % | Ref. |
| 3-F (254a) | N | 6 241 | 8 | 8 68 179 242 | 56 | 68 | 100 | 68 | N | 6 236 | | | BuLi Y | 234 |
| | | | 60 | 243* | | | | | | | | | | |
| 4-F (255a) | N | 6 | N | 8 | | | | | N | 236 | | | | |
| 3-Cl (254b) | 100 | 8 239 | 100 | 8 68 227 242 243 | 100 | 8 68 | | | Y | 6 | Y | 244 | $NaNHNH_2$ Y | 4,8 |
| 4-Cl (255b) | 100 | 8 69 239 | 3 | 8 227 242 243 245 | 81 | 8 68 244 | 100 | 245 | | | | | LiPy <3 | 4 |
| 3-Br (254c) | 100 | 6 69 222 236 237 240 | 100 | 242 243 244 245 | 100 | 246 247 | 100 | 246 247 | Y | 6 236 | Y | 244 | $Ph_2CO^{=}$ Y BuLi Y | 248 238 |
| 4-Br (255c) | 100 | 240 | 90 | 245 | 100 | 245 | 100 | 245 | Y | 236 | | | | |
| 3-I (254d) | 100 | 239 | | | | | | | y | 6 236 | Y | 244 | | |
| 4-I (255d) | 100 | 239 | 96 | 245 | | | | | Y | 236 | | | | |

[a] % of substitution products formed via **9**; N=no evidence for **9**; Y=**9** formed but % unreliable or undetermined; *in the absence of piperidine

Pip=piperidine; Py=pyrrolidine; Et=ethyl; iPr=isopropyl

better overlap of the aryne orbitals[8] and the respective calculated heats of formation (**1** = 114.3[253] and **9** = 131 kcal/mole[226]).

Intramolecular addition of nucleophiles to arynes is a useful synthetic tool for annelating aromatic rings.[13,24] The most examples involving hetarynes to date utilize 5-substituted-3,4-didehydropyridines (**263**) prepared from the corresponding 3-bromo compounds (**264**). Nitrogen (**a** series)[254] and carbon (**b** series)[255] nucleophiles give better yields of products **265** than oxygen (c series).[254] As in intermolecular



**264** **263** **265**

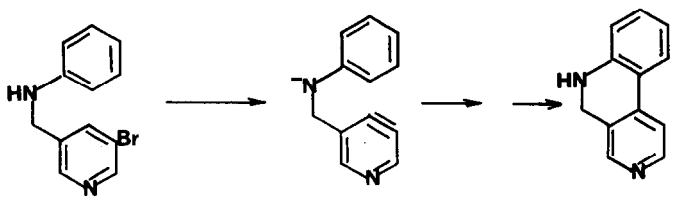
X B A

a: $CH_2$—$CH_2$—NH

b: $CH_2$—$NCH_3$—CHZ (Z=CN, $COOC_2H_5$, $COC_6H_5$)

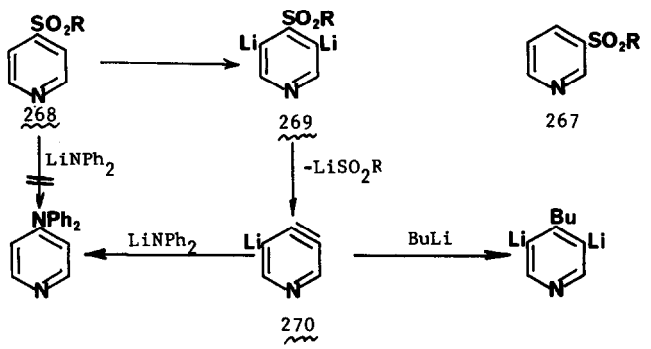
c: N = $CC_6H_5$—O (**264** = amide tautomer)

additions of enolate ions,[6,222,256] competitive amination (and ammonolysis) can occur when $KNH_2$ is used as the aryne generating base.[255] An interesting variation in which an electron-rich benzene ring adds to the hetaryne has been used for the preparation of the alkaloid perlolidine (**266**).[257]



**266**

Apparently the only nonhalogen monodentate precursors of 3,4-didehydropyridines to be studied are the tert-butylsulfones **267** and **268**.[258] Although the former gave no meaningful results when treated with strong base, the 4-isomer (**268**) behaved similar to benzene analogues[259] and formed on *o*-dilithio species **269** which eliminated lithium tert-butylsulfinate to give 5-lithio-3,4-didehydropyridine (**270**). This aryne was trapped by the regiospecific addition of BuLi or $LiNPh_2$ which significantly does not react with **268** in the absence of the stronger base lithium diisopropylamide.



**268** **269** **267**

$LiNPh_2$ $-LiSO_2R$

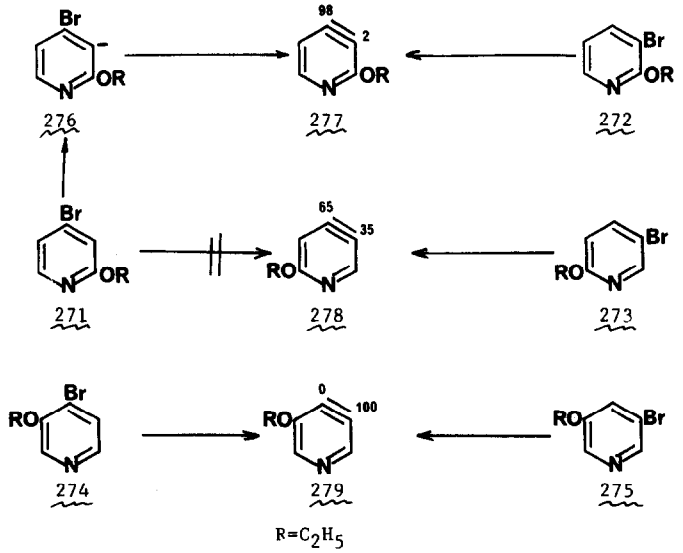
$LiNPh_2$ BuLi

**270**

(c) *Substituted 3,4-didehydropyridines.* The presence of a substituent can affect the chemistry of 3,4-didehydropyridines in three ways. It may vary the proportion of a substitution reaction proceeding by an EA mechanism, it may alter the direction of elimination of HX from monodentate precursors, and it may change the orientation of addition to the aryne. An example of this last phenomenon already cited would be the regiospecific addition of nucleophiles to the 4-position of the lithioaryne **270**.

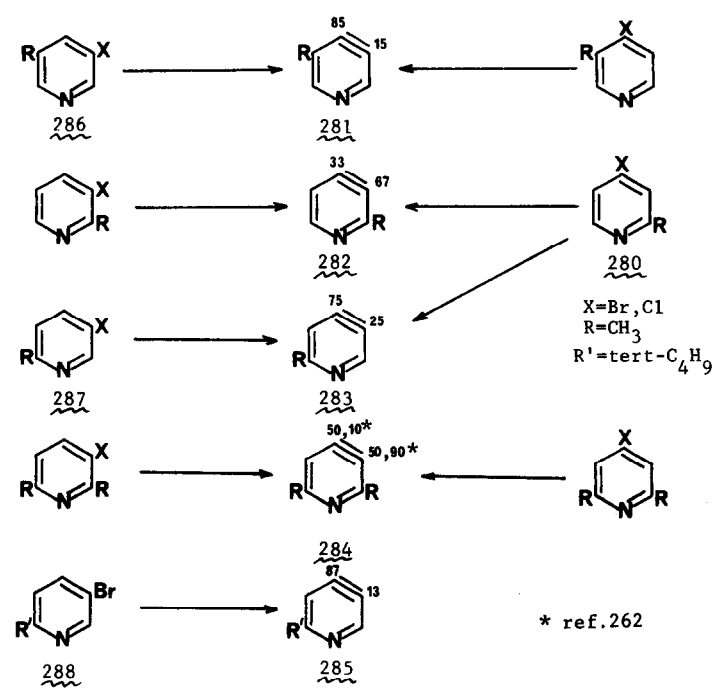
An EA mechanism is indicated in the reactions of bromoethoxypyridines **271–275** with $KNH_2$–$NH_3$ by

the constancy of the ratio of aminoethoxypyridines formed from isomeric precursors.[239,260] Studies of other base-nucleophile systems have been carried out but details are not yet reported.[7a,261] The elimination step avoids a 2,3-didehydropyridine as in the parent series and in the case where isomeric 3,4-arynes could be formed (**271**) prefers the one (**277**) arising from the more stable anion **276** (two ortho − I substituents). As expected[24] the addition of $NH_3$ to the arynes (**277–279**) proceeds via the

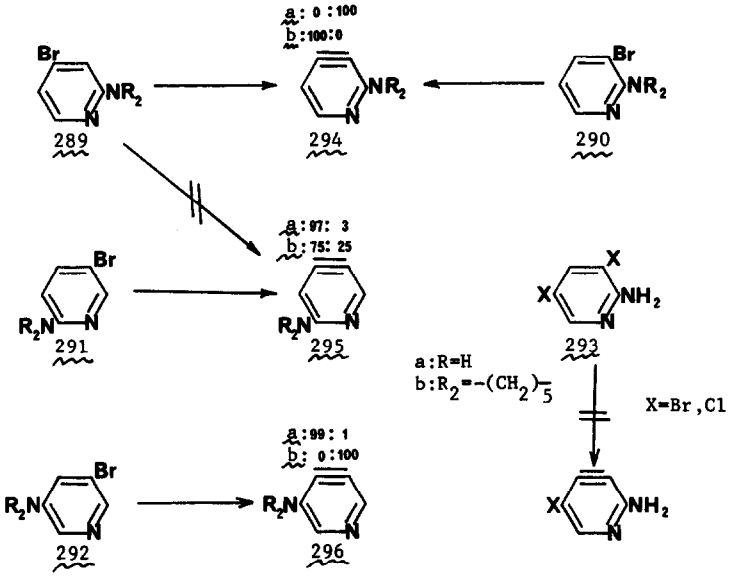



transition state leading to the most stable anion (**276** $NH_2$ for Br) as indicated by the ratios shown on the formulae.[260] Apparently due to its − I character the ethoxy substituent can either reinforce (**277**), have no effect (**278**), or totally reverse (**279**) the orientation observed with the parent aryne **9** depending on its location.

Alkylhalopyridines also react primarily *via* an EA mechanism with $KNH_2$–$NH_3$ by the same criteria cited above.[262,263,311] Once again other base-nucleophile systems apparently have been studied but no details are available.[7a,261] The elimination of HX is regiospecific except for the 4-halo-2-methylpyridines (**280**) which give both 3,4-didehydropyridines (**282**) and (**283**) in varying proportions depending on the halogen[263] much as in the benzene series.[31] The generation of 2,3-didehydropyridines from (**286–288**) is avoided as before. The noted[263] isomer ratios for $NH_3$ addition to the arynes (**281–285**) are consistent with the + I effect of alkyl groups but also may reflect inductive and resonance contributions[31,233,265] from the corresponding picolyl anions (**281–284** R = $CH_2^-$) likely to be present under the strongly basic conditions.[263]

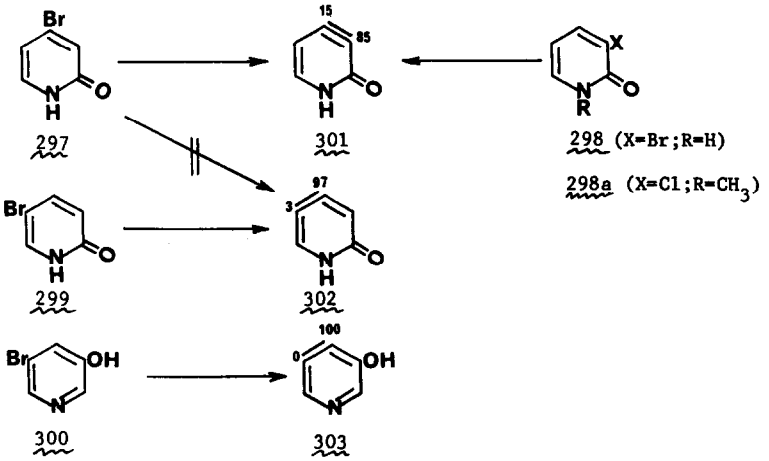


Amino (a series)[265] and piperidino (b series)[266] substituted 3- and 4-bromopyridines (**289–292**) appear to react with $KNH_2$ and lithium piperidide, respectively, according to an EA mechanism, although the possible intervention of some AE processes is acknowledged.[266] Dihaloaminopyridines (**293**) and metal hydroxides,[267] in contrast to simple halopyridines,[244] react by a nonaryne path. The elimination of HBr



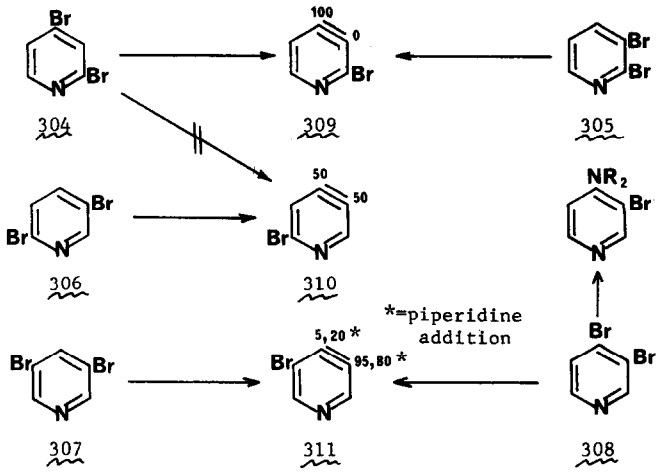

proceeds regiospecifically to avoid the 2,3-aryne in the case of **291** and **292** and by way of the more stable anion (**276** $NR_2$ for OR) for **289**. The striking divergence in behavior in the direction of addition of the amine to the arynes **294–296** indicates that while the piperidino group (b series) is a typical −I substituent (see **277–279**), the amino group (a series) is more electron donating than even alkyl substituents (see **281–285**) which suggests that it is present as the anion $NH^-$.[6,264]

It has been claimed[268] that the three bromo-2-pyridones (**297–299**) and 3-bromo-5-hydroxypyridine (**300**) react with $KNH_2$ by an EA mechanism. The partial intervention of an AEa process (Section III. A.3) with **297** and **298** is an open question pending publication of the detailed results.[7a] The orientation of HBr elimination appears to be governed by the same factors as with the previously discussed substituents, and the direction of $NH_3$ addition to the arynes (**301–303**)[6,268,269] parallels that found for (**294a–296a**) once again suggesting that the oxygen is anionic.[6] Cine-substitutions of 3-chloro-N-methyl-2-



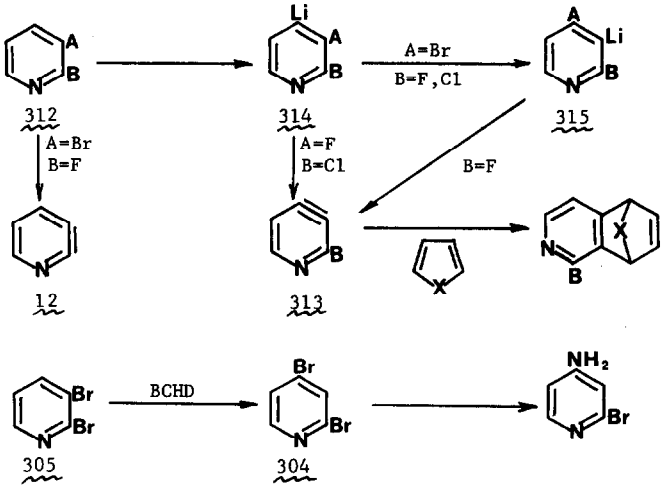

pyridone (**298a**) have also been studied, but no details are available.[10]

The reactions of dibromopyridines **304–308** with $KNH_2$ are consistent with the intermediacy of the bromoarynes **309–311** with respect to constancy of isomer ratios, direction of HBr elimination (*via*




most stable anion for **304** and no 2,3-pyridyne with **306–308**), and orientation of addition (−I effect of Br).[265] With lithium piperidide as base the situation is complicated by extensive tar formation and substantial involvement of a normal AE mechanism for **308**.[266] Only **307** seems to give an aryne (**311**) exclusively, and as previously noted for the unsubstituted aryne **9**, piperidine adds to it less selectively than does $NH_3$.

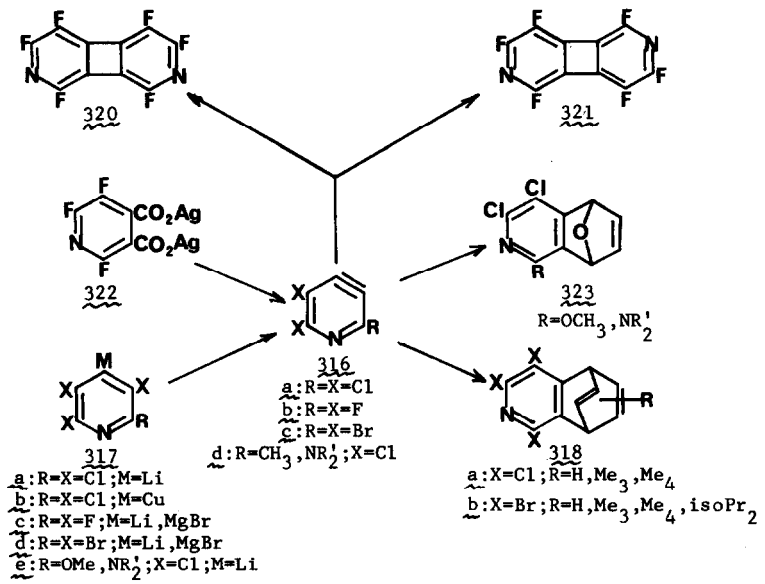
The reactions of 2,3-dihalopyridines **312** with BuLi are diverse and very dependent on reaction conditions. Either 2,3-didehydropyridine (**12**)[270] or a 2-halo-3,4-didehydropyridine (**313**)[234,270] are formed as detected with several furans or N-methylpyrrole. In the case where A = F[234] the




4-lithio compound **314** is probably the immediate precursor of **313**, but if A = Br[270] a prior rearrangement *via* a BCHD mechanism (Section III.A.2) to the more stable lithium compound **315** has been demonstrated.[238,271] In view of this discovery and that BCHD mechanisms occur with $KNH_2$–$NH_3$ as well as BuLi,[37,45] the possibility should be considered that the regiospecific addition of $NH_3$ to the 4-position of **309**[265] might simply reflect a prior rearrangement of **305** via the very stable 3-anion of **304**.

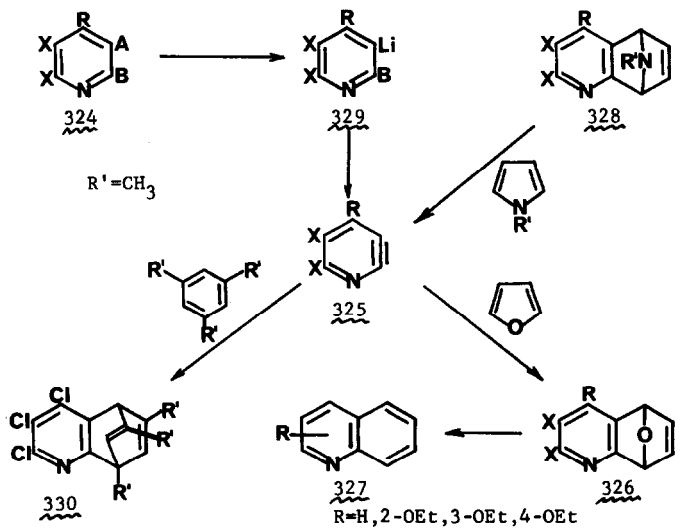
Several trihalo-3,4-didehydropyridines (**316**) have been postulated. The chloro intermediate **316a** is generated from the 4-lithio compound **317a**[272] as deduced by the formation of Diels–Alder adducts (**318a**) with several benzene derivatives[273] and diphenylisobenzofuran (**40**)[274] but not furan itself.[273,274] By similar criteria the aryne **316a** is *not* involved in the reactions of the pyridyl copper compound **317b**.[275] The failure to observe a furan adduct from either the lithium or Grignard derivative **317c** indicated that the fluoroaryne **316b** had not been formed,[276] although this species was suggested to explain the formation of the diazabiphenylenes **320** and **321** from the pyrolysis of the silver salt **322**.[277] The bromoaryne **316d** generated from the lithium or Grignard derivative **317d** also gave Diels–Alder adducts (**318d**) with benzene derivatives but not with furan.[278] The sole example of a furan adduct **323** is with the 2-substituted chloroaryne **316d** generated from the lithium compound **317e**.[279] The unique failure of furan

to give aryne adducts has been observed before[85] and demonstrated to be due to its ability to induce competitive nonaryne reactions.[86]



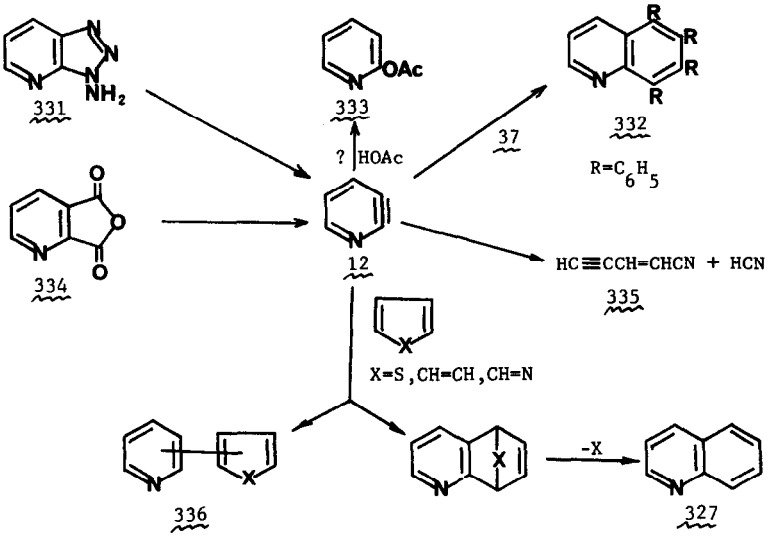

3. 2,3-*Didehydropyridine* (**12**). With one exception[224] M.O. calculations predict that 2,3-didehydropyridine (**12**) would be less stable than its 3,4-isomer **9**.[142,225,226] It is therefore perhaps not surprising that the evidence supporting the generation of **12** is neither as extensive nor as compelling as with **9** (Section V. B.2).

(a) *Bidentate Precursors.* Halogen-metal exchange of 2,3-dihalopyridines (**324**) has provided the most evidence for the generation of 2,3-didehydropyridines (**325**). With lithium amalgam the furan adducts (**326**), while sometimes isolated,[237] are usually reduced to the quinolines (**327**) in low overall yields[280,281] compared to the 3,4-series (Section V. B.2.(a)). The use of organolithium reagents permits the isolation of both furan (**326**) and N-methylpyrrole adducts (**328**)[270] in markedly improved yields especially for polyhalopyridines containing a 4-methoxy (X=Cl, Br)[279,282] or a 4-dialkylamino group (X=Cl).[89,283] Presumably these substituents aid in the formation of the respective 3-lithio intermediates (**329**), an effect well-known in the benzene series.[284] Although 4-aryl groups (X=Cl) seem to be just as effective in this regard, no intramolecular[285] and only traces of the intermolecular adduct **326** were found, apparently due, in the latter case, to transmetallation between furan and the intermediate **329** prior to elimination of LiCl to give the aryne **325**.[286] The fully chlorinated aryne **326** (R=X=Cl) appears to be formed in low yield from the analogous lithium species **329**[274] as shown by isolation of the adduct **330**[278] from mesitylene but no other traps.[273,274] As already discussed (Section III. B.2) the ambiguity ascribed to the isolation of the furan adduct **326** as evidence for the intermediacy of the 2,3-didehydropyridines **325**[10,89] is probably unnecessary.

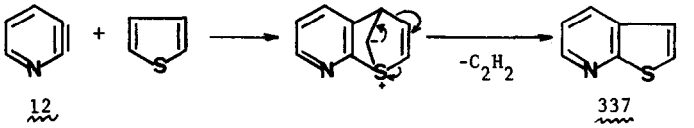


Oxidation of the N-aminotriazolopyridine **331** in the presence of tetracyclone **37** gives the expected adduct **332** in low yield if $CH_2Cl_2$ is the solvent,[230] but only 2-acetoxypyridine (**333**) in acetic acid.[232] As in the 3,4-series (Section V.B.2(a)) no azabiphenylenes were formed. This apparent preferential reaction of 2,3-pyridyne (**12**) with acetic acid rather than tetracyclone **37** is reversed from the behavior of the 3,4-aryne **9** and was rationalized[232] by the lower stability and selectivity of **12** and/or by its greater polarization[142] (Section III.A.1). Further evidence that the arynes **9** and **12** are in fact involved in the formation of the acetoxypyridines **252** and **333** is desirable, however.

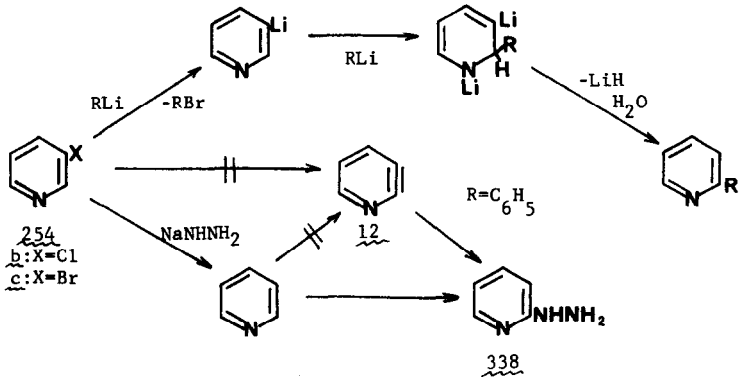
Thermolysis of the anhydride **334** gives HCN and the unsaturated nitrile (**335**), presumably *via* 2,3-pyridyne (**12**).[287] In contrast to benzyne (**1**)[287] and 3,4-pyridyne (**9**), which also decomposes to the




nitrile **335** (Section V.B.2(a)),[29] no aryne dimers were found. However, pyrolysis of **334** in the presence of benzene, pyridine,[288] or thiophene[162] led to products claimed to arise by insertion (**336**) and cycloaddition-aromatization (**327**) of 2,3-didehydropyridine (**12**). The thiophene reaction also gave a pyridothiophene **337**, probably not by the suggested [2+2]-cycloaddition of **12** to the C–S bond,[162] but rather by the recently discovered [3+2] cycloaddition of **12** to the S and beta-carbon of the thiophene ring.[289]



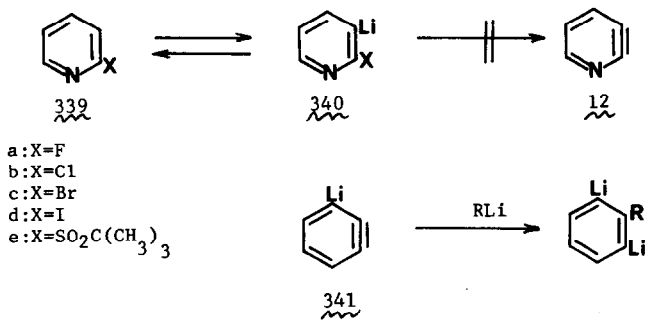

(b) *Monodentate Precursors.* As discussed in Section V.B.2(b), 3-halopyridines (**254**) do not form 2,3-didehydropyridines **12** under aryne-producing conditions. Reports of cine-substitution to the 2-position, as would be expected for the addition of nucleophiles to the aryne **12**,[142,224,225] either have appeared only in preliminary form[290,291] or been rationalized by nonaryne mechanisms. For example, 2-phenylpyridine appears to arise from 3-bromopyridine (**254c**) and PhLi by halogen-metal interchange followed by addition as shown.[292] A similar sequence of reductive dehalogenation and a Chichibabin



reaction with $NaNHNH_2$ explains the formation of 2-hydrazinopyridine **338** from **254b**.[8] The suggestion that the Chichibabin reaction itself proceeds *via* 2,3-pyridyne **12**[29] has been widely criticized,[293] disproven,[294] and generally,[295] but not uniformly,[296] rejected.

Since 2-halopyridines (**339**) are more reactive than the 3-isomers (**254**) to nucleophilic substitution by a normal AE mechanism[76,297] the intervention of an EA process via the aryne **12** is rather unlikely.[4] Trapping[228,238,298] and exchange experiments[299] demonstrate that the 3-anion or lithio species **340** is formed, but the absence of any cine-substitution products from the halides **339a–d**[6,8,227,242,260,300] or the sulfone **339e**[258] fails to provide evidence for the intermediacy of the aryne **12**. That "absence of evidence is not evidence of absence"[301] was recognized[9] even before MO calculations[142,224,225] provided the theoretical justification for the expected regioselective 2-addition of nucleophiles to the aryne **12** (Section III.A.1). Subsequent attempts to obtain evidence for 2,3-didehydropyridine **12** by trapping with mercaptides[69] or furan[229], by the competition method[68], or by isotopic labelling[299] all failed. Only a fragmentary report[68] of some incomplete competition studies suggests that 2-halopyridines (**339**) may give the aryne **12**. The fact that the isoelectronic 2-lithiobenzyne (**341**) can be generated[259] and add nucleophiles[302] as predicted[303] probably reflects the suppression of the unfavorable effect of the ortho-situated nonbonded electron pair[142,224,225] by the lithium atom (see Section V.B.4).

The generation of a 2,3-didehydropyridine (**342**) should be more favorable from a 4-substituted-3-halopyridine **343** which can not give a 3,4-aryne **9** and which would be unlikely[76] to undergo normal nucleophilic substitution. Initial results with 4-ethoxy-3-bromopyridine (**343a**)[36,239,260] and its 6-ethoxy derivative (**343b**)[36,280] seemed promising since the corresponding 2-amino compounds **344a** and **344b**

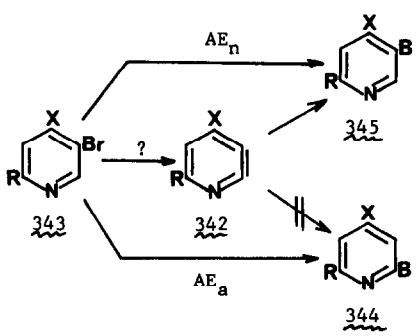



were obtained with $KNH_2$. With lithium piperidide as a base both a 4-ethoxy (**343a**)[304] or a 4-bromo (**343c**)[266] substituent are first displaced to give 4-piperidino-3-bromopyridine (**343d**) which reacts further to give 2,4-dipiperidinopyridine **344d**, presumably via the 2,3-aryne **342d**. The same aryne is probably not involved, however, in the substantial formation of the unrearranged product **345e** from **343d** and $KNH_2$.[6] Amination of the 4-methyl (**343f**)[9] and 4-amino (**343g**)[305] derivatives proceeds very slowly but gives the respective cine-substitution products **344f** and **344g**, while the 4-isopropylpyridine **343h** once again gives some unrearranged product **345h**.[6]

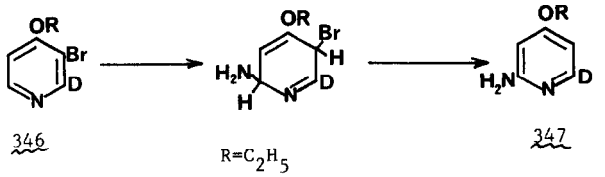
Although the possibility that the cine-amination products **344** might arise from the products of the observed[36,260] BCHD side reaction (Section III. A.2) had been examined and eliminated early on,[36] the suggestion[8] of an AEa pathway (Section III.A.3) was considered only later.[6,266] The inability to trap the aryne **342a** with either furan[237] or thiophenoxide[306] led to the conclusion that the evidence for the

| | R | X | B |
|---|---|---|---|
| a: | H | OEt | $NH_2$ |
| b: | OEt | OEt | $NH_2$ |
| c: | H | Br | - |
| d: | H | Pip | Pip |
| e: | H | Pip | $NH_2$ |
| f: | H | $CH_3$ | $NH_2$ |
| g: | H | $NH_2$ | $NH_2$ |
| h: | H | isoPr | $NH_2$ |

Pip=piperidyl
Et=ethyl
isoPr= isopropyl

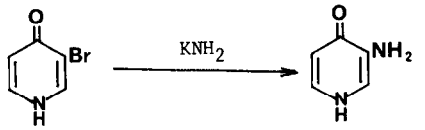


generation of 2,3-didehydropyridines **342** was poor.[306] The intermediacy of the aryne **342a** was finally rejected[307] and an AEa mechanism proposed based on the retention of the deuterium during the reaction **346**→**347**.[308] A similar claim,[268] without supporting data,[7a] has been made to explain the exclusive[6]



346 R=$C_2H_5$ 347

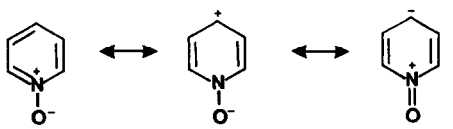
cine-amination of 3-bromo-4-pyridone (**348**). In light of the above remarks any new or continuing claims



348

for the preparation of a 2,3-didehydropyridine **12** or **342** from a monodentate precursor must be accompanied by substantial proof.

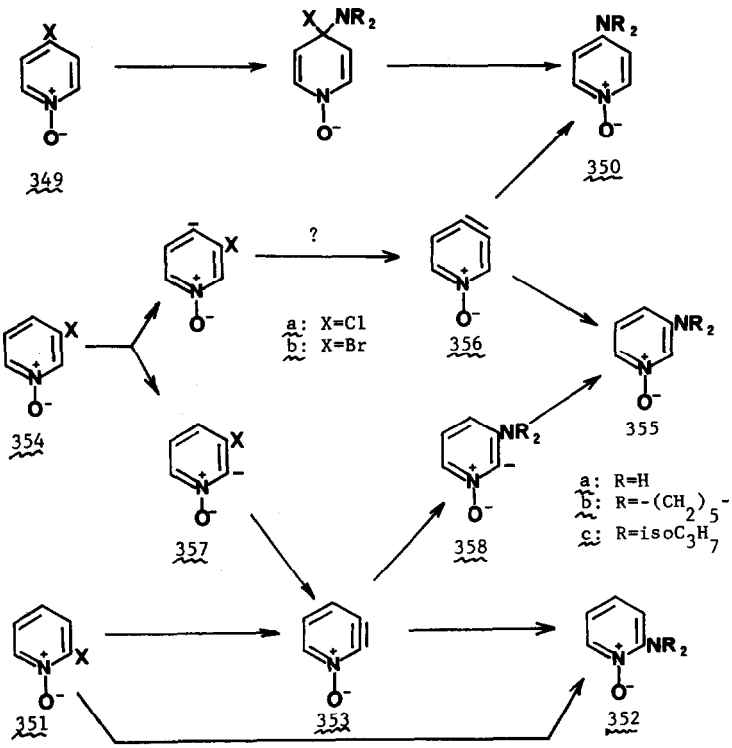
4. *Didehydropyridine-N-oxides.* Blocking the free nitrogen electron pair of pyridine as an N-oxide function can have a pronounced effect on the mechanism of nucleophilic substitution of halogen. First of all the balance of electron donation and withdrawal by the oxygen in either the reactant, as shown, or in possible transition states may play an important, if unpredictable, role on the proportion of EA vs AE or



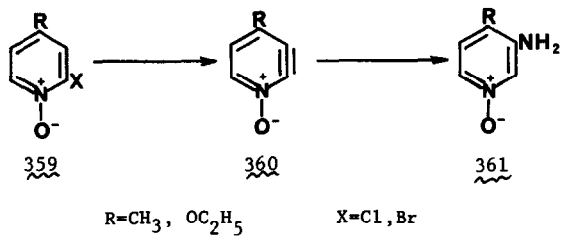
other mechanisms. Secondly, if the former mechanism is followed, the regiochemistry of HX elimination and of nucleophile addition to the aryne will be directed toward, not away from, the 2-anion as in the case of pyridine itself (Sec. V. B.2(b)),[225,235] since base-catalyzed exchange experiments[33,309] predict an order of anion stabilities for 3-halopyridine-N-oxides (2 > 6 > 4 > 5) opposite from those of the corresponding pyridines (4 > 2).

To illustrate the first generalization, it is the 4-halopyridine-N-oxides (**349**) which react with $KNH_2$ without rearrangement to give **350a** by an AE mechanism and the 2-isomers **351** that give cine-substitution products **352a** *via* 2,3-didehydropyridine-N-oxide (**353**).[281,310,311] Compared to pyridine (Section V. B.2b,3b), therefore, the N-oxide function activities a 4-halo and deactivates a 2-halo substituent to nucleophilic substitution by an AE mechanism. The nature of the nucleophile also plays a role, however, since with the less basic piperidine, both isomers **349a** and **351a** give **350b** and **352b**, respectively, by an AE mechanism.[312] The 3-halopyridine-N-oxides (**354**), initially claimed to react with $KNH_2$ by an AE mechanism since only ipso substitution to **355a** was observed (Section III.A.1)[310], are now believed to react by an EA mechanism, not only with piperidine which gives cine-substitution to **305b**,[312] but also with $KNH_2$.[262,281] This last claim is based on the lack of reactivity of the fluoroanalogue of **354**,[311] which should be the most reactive by an AE mechanism,[30a,313] and on trapping the aryne **353** as **355c** with isopropylamine, which was shown neither to react directly with **354b** nor form the more nucleophilic potassium isopropylamide under the reaction conditions.[314]

The second generalization is illustrated by the predicted[336] preferential formation of the 2,3-aryne **353** rather than the 3,4- aryne **356** from 3-halopyridine-N-oxides **354** and $KNH_2$, presumably *via* the kinetically favored 2-anion **357**.[281,311,314] Piperidine is once again anomalous, giving rise to the 3-(**355b**) and 4-substituted products **350b** in low yield but none of the 2-isomer **352b**.[312] In view of the exceptional nature of this result the conclusion that 3,4-didehydropyridine-N-oxide **356** is involved is best regarded as tentative until the AEa mechanism (Section III. A.3) especially is eliminated. The highly regioselective addition of nucleophiles to the 3-position of the 2,3-aryne **353**[281,310,311,314] probably reflects the 2-carbanion character (**358**) of the transition state and/or instability of the 2-amino compounds **352a**.[311]

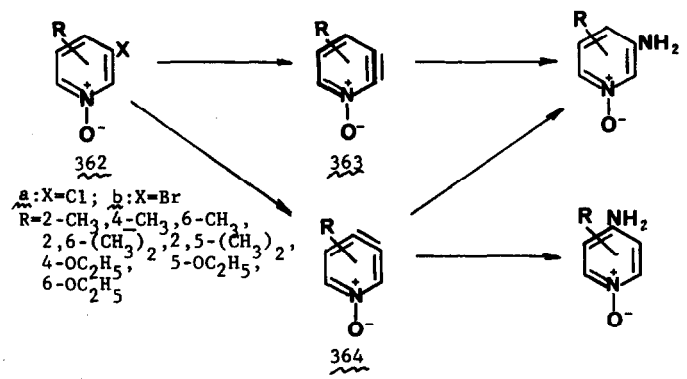



As with pyridine itself, substituents on the pyridine-N-oxide ring can alter the mechanism of nucleophilic substitution of halogen, the regiochemistry of aryne formation, and the regiochemistry of nucleophilic addition to the aryne. The reactions of 2-halopyridine-N-oxides **359** are largely unchanged by 4-substituents, still proceeding *via* the corresponding 2,3-aryne **360** to give primarily the cine-substitution product **361**.[281,311,315] No amination products were observed from the 6-methyl analogue of

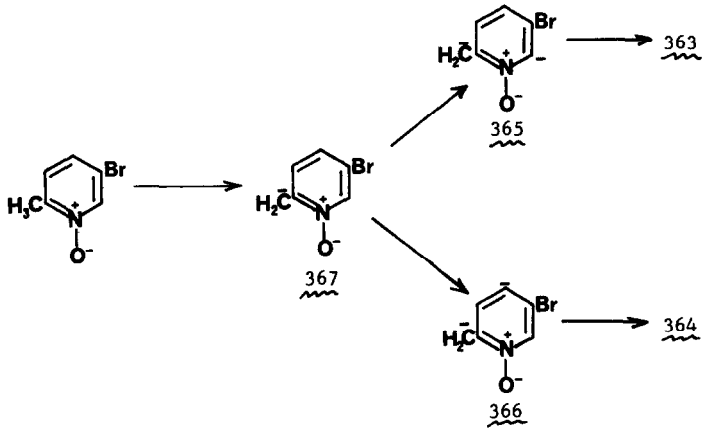



**359**, however.[315]

Substituted 3-halopyridine-N-oxides **362** also still prefer to react by an EA mechanism via the 2,3-aryne **363** if the substituent is at the 4-position[281,311,315] or the 3,4-aryne **364** if it is at the 2-position.[262,311,315] The former arynes add ammonia at the 3-position for reasons given above,[281,311,315] and the latter arynes prefer[263] attack at the 4-position in ratios of 4:1 or more.[262,311,315] Only if the substituent is at the 5- or 6-position is the formation of both arynes possible, of course, and this is observed for the 5-ethoxy[311] and 6-methyl derivatives[314] of **362b** which preferentially give the 2,3-aryne

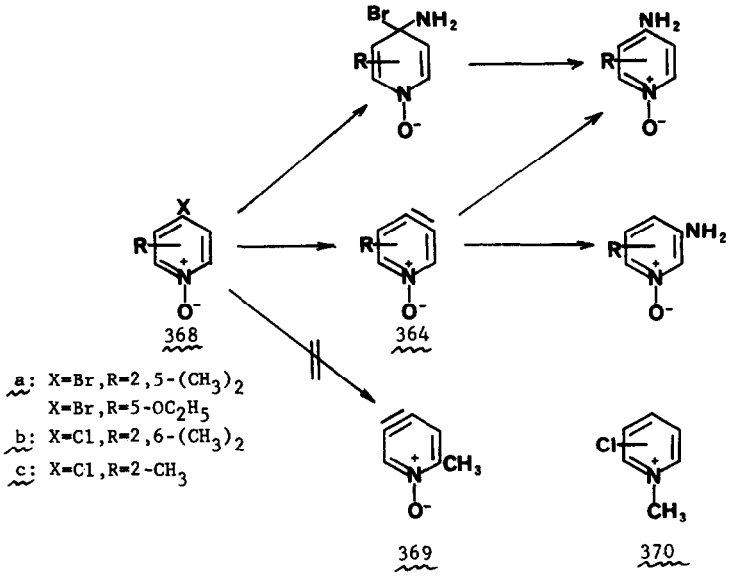


363 and the 3,4-aryne 364, respectively. The generation of some 3,4-aryne 364 from the 5-ethoxy[311] but not the 6-ethoxy[314] derivative of 362b reflects the ability of the former substituent to stabilize the intermediate 4-anion. Similarly the suppression, by a 6-methyl group, of the natural tendency toward 2,3-aryne formation appears to be due to a relative decrease in the rate of 2-(365) vs 4-anion (366) formation compared to the unsubstituted 3-halopyridine-N-oxide (354) which in turn is ascribed to



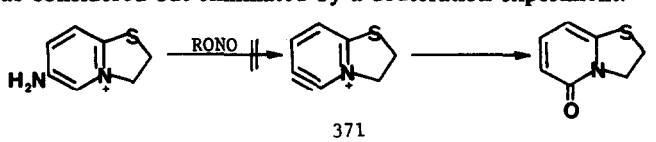
picolyl anion (367) formation.[314] This latter phenomenon is also held responsible for the lower regiospecificity of $NH_3$ addition to that aryne (363, R = 6-methyl) which is generated.[314] Interestingly, the chlorine analogue of 367 gives no indication of 2,3-aryne formation[315] suggesting additional relative stabilization of the 4-anion (366, Br=Cl) in this case by the chlorine.

Substituted 4-bromopyridine-N-oxides (368a) react predominantly, but not exclusively, by an AE



mechanism,[311] while the chloro analogues 368b,c in contrast also to the unsubstituted compound (349a) undergo nucleophilic substitution largely by an EA mechanism.[262,315] These interesting differences, as well as the observed[315] regiospecificity of HCl elimination from 368c to give only the 3,4-aryne 364c and none of the 4,5-aryne 369, may be rationalized by the +I effect of the methyl groups and by the appropriate choice of rate-determining steps in the two mechanisms (Sec. V. B.2(c)).[263]

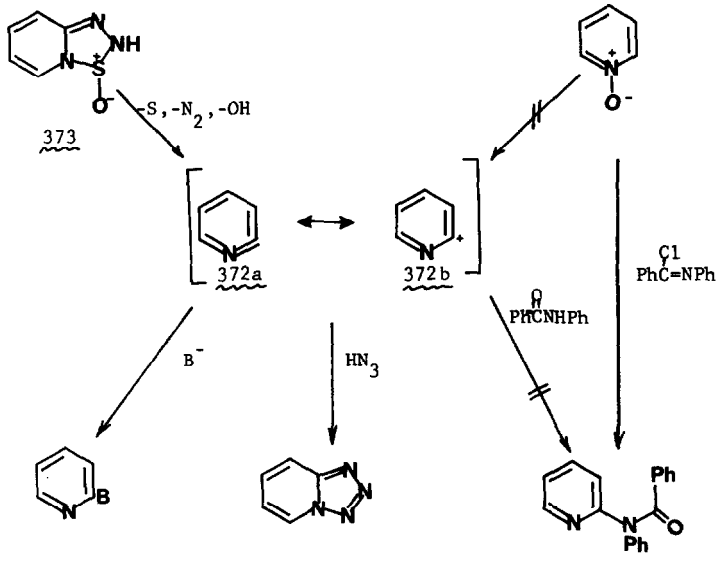
No evidence for other didehydropyridines with the free electron pair on nitrogen blocked has been obtained. The N-methylchloropyridinium salts 370 react with piperidine either by an AE-mechanism (2- and 4-isomers) or not at all (3-isomer).[8] The possibility of a didehydropyridinium intermediate 371 in the following reaction was considered but eliminated by a deuteration experiment.[316]



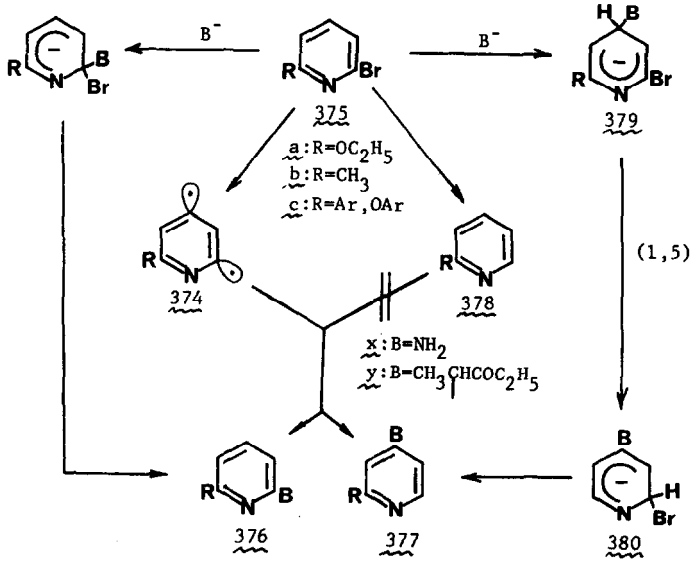
5. *Other didehydropyridines.*

The remaining ortho-didehydropyridine is the hetarynium ion **372**[179] (Section V.A.15) which is claimed to be an intermediate in the thermolysis of the thiatriazolopyridine **373** on the basis of trapping with nucleophiles or hydrazoic acid,[317] but not in the acylamination of pyridine-N-oxides.[318] Whether **372** is best represented as an aryne **372a**[8] or a pyridyl cation structure **372b**[4] is debatable.[318a]

According to MO calculations[225,226] the second most stable didehydropyridine is actually the 2, 4-isomer **374**. This intermediate was cautiously considered[256,306] and then firmly claimed[299,319] to explain the tele-substitution of 6-substituted-2-bromopyridines (**375**→**377**) with $KNH_2$[9,99,239,256,260,319-321]

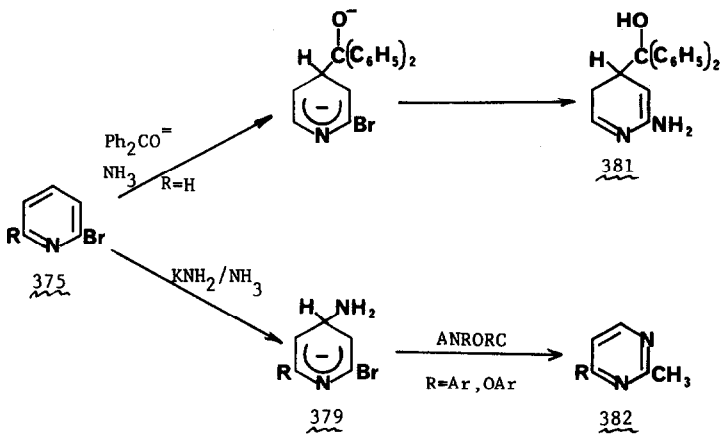



but not lithium piperidide.[304] Although the basis for this more definitive claim has not yet been published,[7a] it is supported by (i) the tele-substitution of **375a** with the enolate of 3-pentanone *only* if $KNH_2$ is present,[256] (ii) the independence of the product ratio **376bx/377bx** from the nature of the halogen in **375b**,[320] and (iii) the exclusion of an alternative mechanism involving dehalogenation to **378** followed by a Chichibabin reaction to **376** and **377**.[239]

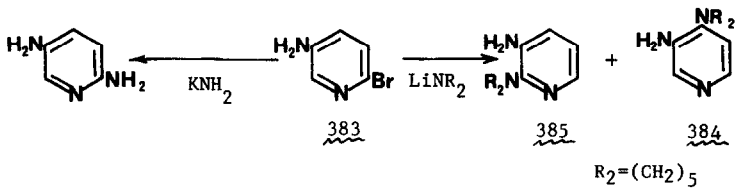



What has not yet been excluded is the suggested[10] AEa mechanism (Section III. A.3) via the adduct **379**. While no details of the transformation of **379** into the tele-substitution product **377** were given (the normal substitution product **376** can always arise by a normal AE mechanism) a 1, 5-prototropic shift[322] to **380** can be envisioned, and ample evidence for the attack of nucleophiles at the 4-position of

2-bromopyridines **375** is available. For example, the adduct **381** has been isolated using the benzophenone dianion[248] and **379** has been proposed[99] as an intermediate in the accompanying ANRORC rearrangement of **375c** to pyrimidines **382**.[99,321] The necessity for the presence of $KNH_2$ for the



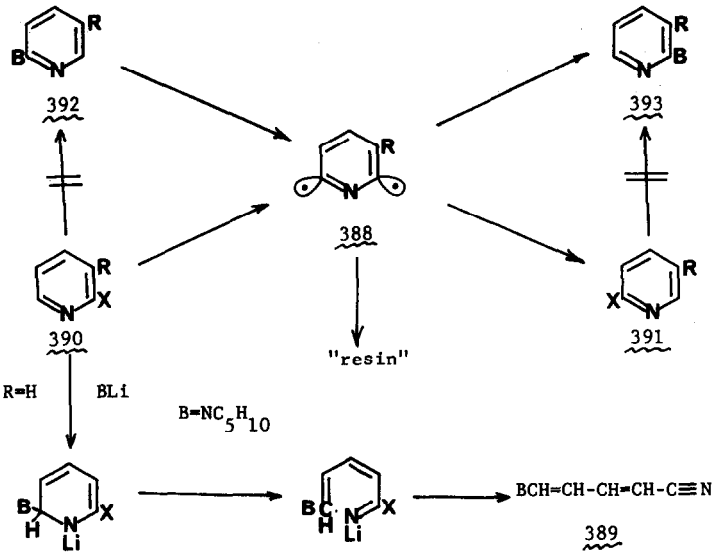

formation of **377ay** (item i above) would require an unspecified catalysis[10] perhaps involving a variation of the ASE mechanism (Section III. A.4) or modification of the attacking enolate. The apparent lack of an element effect on the product ratio (item ii above) may be an experimental artifact of the low yields (20–25%)[99] and high ratio of **376ax**:**377ax** (60:1),[320] or it might be related to a similar absence of an element effect for tele-substitution in the imidazole series (Section V. A.10). The nature of the halogen atom in **375a** does affect the partition between substitution (Br and I) and ANRORC processes (Cl), however.[319] Substituent type and position may have a similar influence[99] and even reverse the previously mentioned[304] effect of the attacking nucleophile so that with **383** it is $KNH_2$ which gives the normal and lithium piperidide which gives only the tele-substitution products **384** and **385**.[97] On the other hand, the



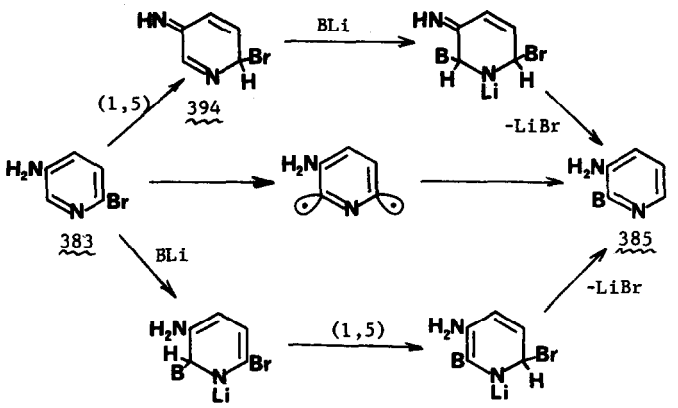

3-ethoxy compound **386** is also claimed to give a 2, 4-didehydropyridine **387** with $KNH_2$.[299] Clearly, more


information is necessary before the existence of these species can be considered to be as certain as that of the 3, 4-isomer **9**.

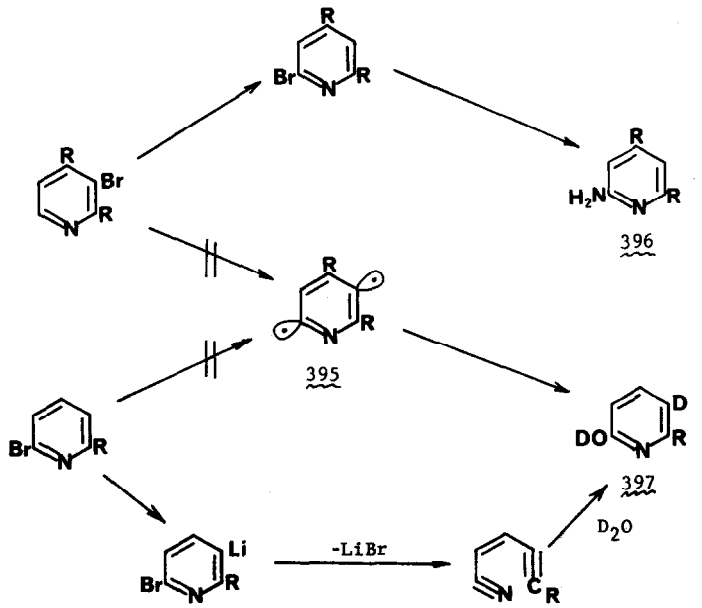
Although originally claimed to be the most stable of the didehydropyridines,[224] subsequent MO calculations predict that the 2, 6-isomer **388** would have much lower[226] or even the lowest stability.[225] Similarly, the suggestion that this species is an intermediate in the Chichibabin reaction of 3-substituted pyridines[224] has been effectively refuted.[294] Speculation that the resin formation observed when 2-halopyridines with, but not without, a 6-hydrogen atom are treated with lithium piperidide is due to the intervention of 2, 6-didehydropyridine (**388**)[8] led to the consideration of this intermediate in other reactions as well[266,274] but without supporting evidence.[306] A reinvestigation of this reaction at lower temperature revealed that ring-opening to **389** occurred[97] presumably by initial addition to the 6-position analogous to the behavior of halopyrimidines.[323,324] Secondary reactions of **389** are probably responsible for the resin formation observed at higher temperatures.[8] This observation, along with the failure to observe tele-substitution products from some $\beta$-substituted pyridines (**390**→**392** and **391**→**393**),[10] supports the improbability[299] of the 2, 6-aryne **388** being involved in the reactions of 2-halopyridines with




base. The only evidence for the contrary view might be the tele-substitution **383**→**385**[97] which could proceed, however, by an AEa mechanism (Section III. A.3) involving a 1,5-prototropic shift[322] similar to **379**→**380** or *via* the imino form **394** . If the latter possibility is correct then a dialkylamino analogue of **383** would not give the tele-substitution to **385**. Additional evidence on this point is desirable.




Of the remaining didehydropyridines the 2,5-isomer (**395**) is calculated to be the most stable, immediately below the 2,4-isomer **374**.[225,226] Two reactions which might be cited as supporting the



intermediacy of **395** instead appear to give the observed products **396** and **397** by a transhalogenation mechanism (Section III. A.2)[6] and an unusual ring-opening-cyclization process,[325] respectively.

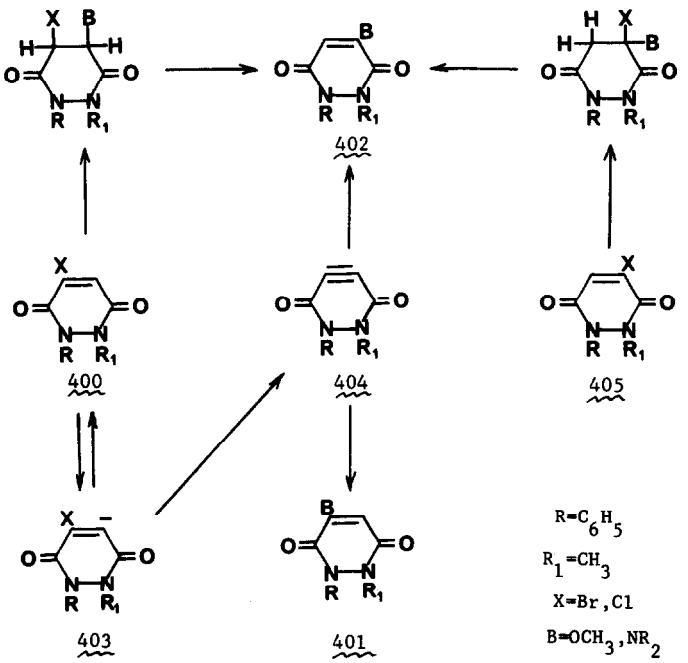
6. *Didehydrodiazines.* The presence of a second nitrogen atom in a six membered ring increase its susceptibility to nucleophilic addition[326] and hence nonaryne mechanisms of substitution (Section III.A) are likely to be more prevalent than with pyridine. Nevertheless claims of didehydrodiazine intermediates abound.

(a) *Didehydropyridiazines.* The 4, 5-didehydropyridazine **398** is calculated [225] to be more stable than the

398

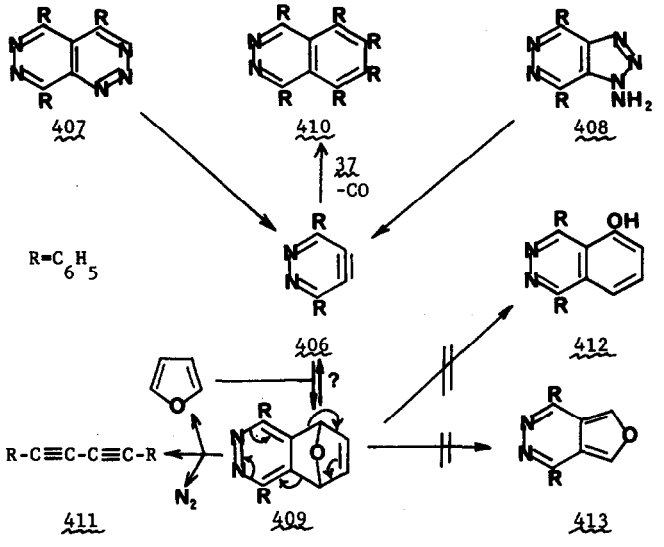
399

3, 4-isomer **399** and was first proposed[327] to rationalize the cine-substitution of halopyridazinediones **400** with sodium methoxide[328] and various amines.[329] Although an AEa mechanism[330, 331] was originally[328] considered for this reaction, the EA mechanism is supported by the following results: (i) weak bases such as aniline and methanol react with **400** only if the strong base piperidine is present,[327] (ii) the ratio of normal (**401**) to cine-substitution products (**402**) is independent of the nature of the halogen atom in the reactant **400**,[187] and (iii) the proportion of rearranged product (**402**) is diminished when ethanol is present, presumably due to reprotonation of the anion **403** before the aryne **404** can be formed.[187] A more cautious interpretation is suggested, however, by the failure to trap **404** with furan[327] or phenyl azide[8] and by the complete, [328, 329] or predominant;[187, 327] preference for the product **402** regardless if the reactant is **400** or **405**. A rationalization of this high regioselectivity of nucleophilic attack on the aryne **404** based on the additivity of the directive effects of the nitrogen substituents[327] does not agree with the cited analogy[332] which would predict a 1:1 ratio of the products **401** and **402**. An AEa mechanism[330] could be consistent with the observed regioselectivity, however, if it is assumed that the phenyl-nitrogen resonance increases the ketonic character, and hence Michael-acceptor properties, of the adjacent carbonyl group. Further studies on this system therefore appear warranted.[10, 332a]

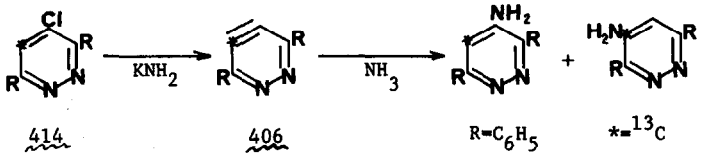



The 4, 5-didehydropyridazine **406** has been generated by thermolysis of the triazine **407** or oxidation of the aminotriazole **408** and trapped as Diels–Alder adducts **409** with furan[333] and **410** with tetracyclone.[334] In the absence of a trap the aryne **406** apparently fragments to diphenylbutadiyne **411** (see Section V. B.2(a)) which is also obtained upon thermolysis of the adduct **409**. The formulation of the latter reaction as a retro-Diels–Alder process which regenerates the aryne **406**[333, 334] would be unique[335]

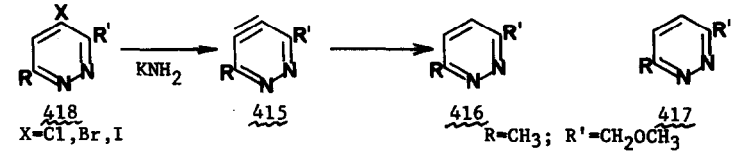
since thermolysis of aryne adducts usually leads to aromatization[158,159,336] (→**412**) or to the alternate retro-Diels–Alder reaction (→**413**) giving an isobenzo derivative.[337] A concerted loss of $N_2$ and furan from the adduct **409** is an alternative path to **411**.[7]



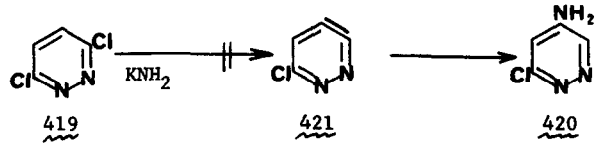

The intermediacy of the aryne **406** was also proven in the amination of the chloro compound **414** by means of a classical[18] labelling experiment with $^{13}C$, [338] while the related 4,5-didehydropyridazine **415**



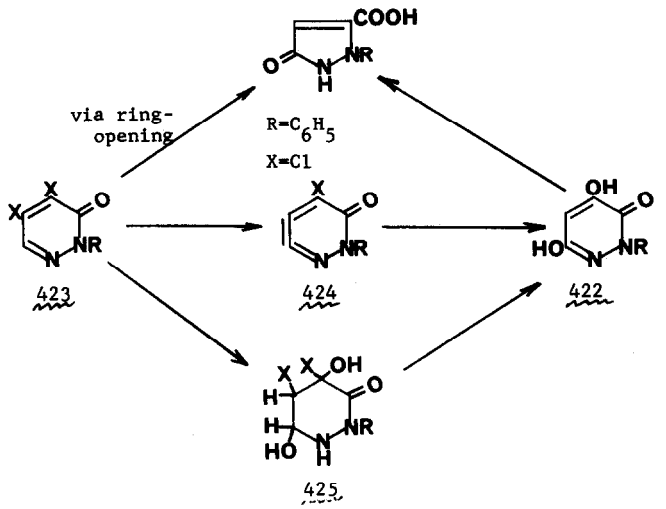

was implicated by the invariance of the product ratio **416**:**417** with the identity of the halogen atom in the reactant **418**.[339]



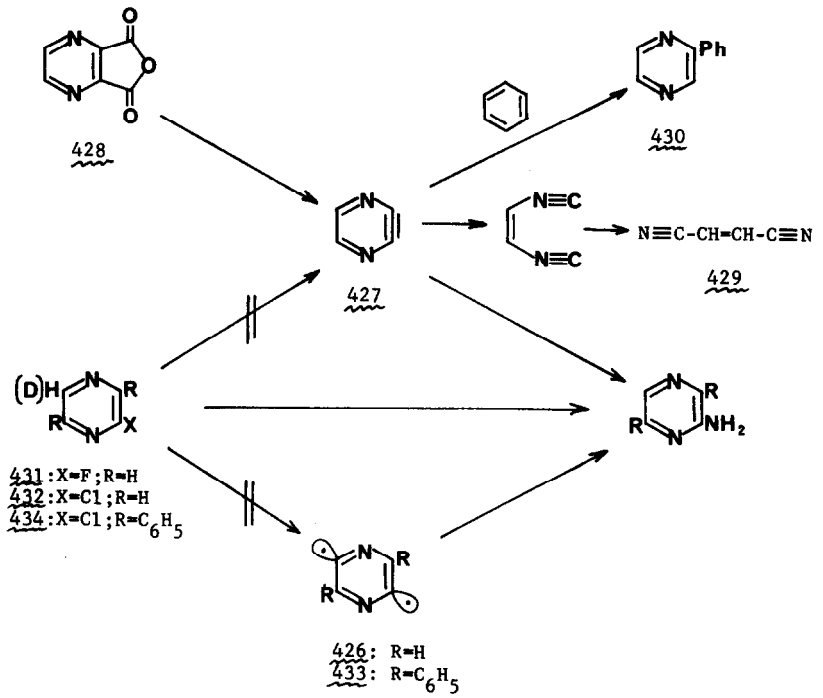

A report of cine-substitution (**419**→**420**)[340] which might have indicated the presence of the less stable[225] 3,4-didehydropyridazine **421** was shown to be in error.[341] A cine-substitution product **422** was



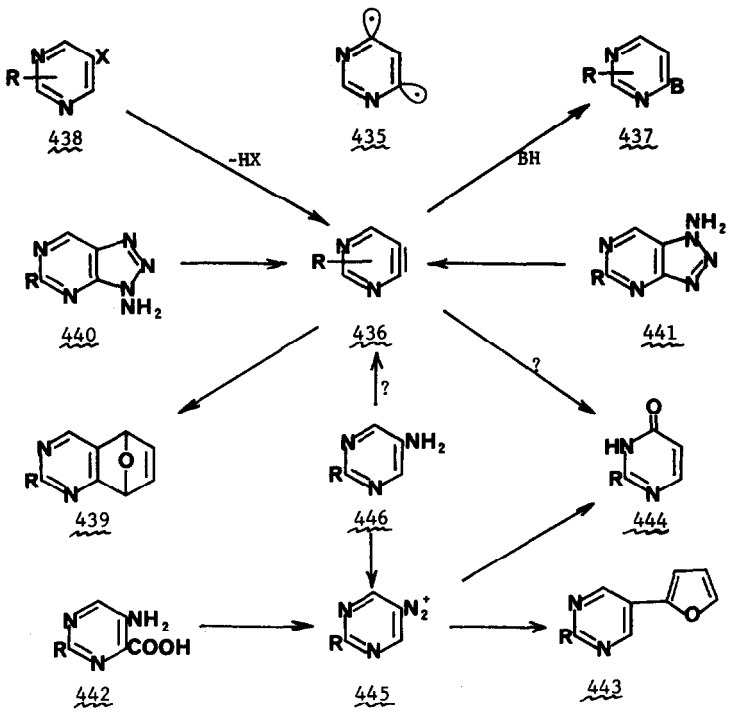

also postulated to be involved in the ring-contraction of the chloropyridazinone **423** with hydroxide[342] (but not methoxide)[343] ion and has been rationalized by an EA-mechanism via the aryne **424**. Until ring-opening processes which avoid **422**[342] and/or AEa-mechanisms involving tetrahydropyridazines such as **425** can be eliminated, however, the evidence for a 3,4-didehydropyridazine intermediate **424** must remain speculative.



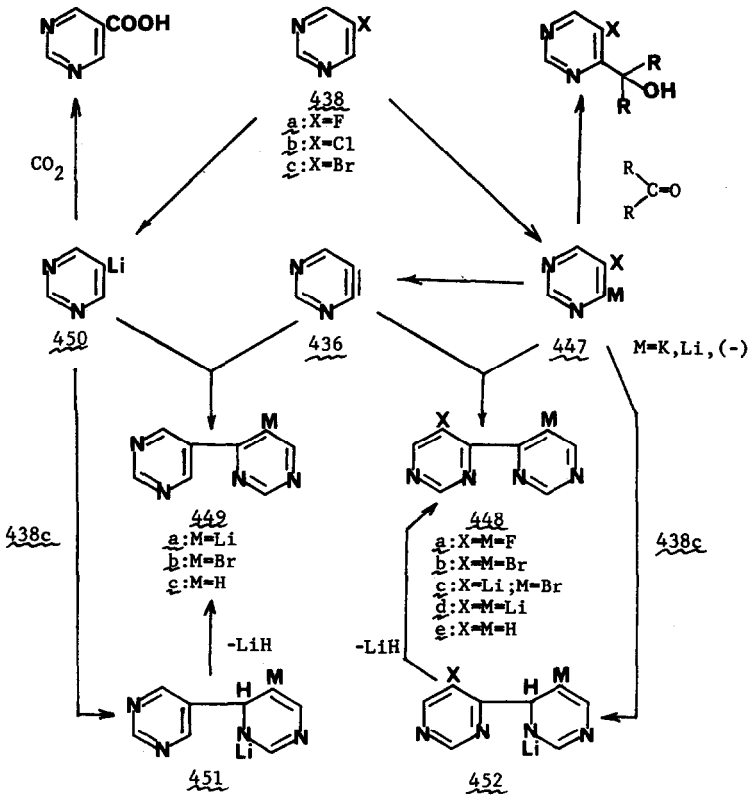

(b) *Didehydropyrazines.* Although the most stable didehydropyrazine is calculated[225] to be the 2,5-isomer **426**, it is the least stable 2,3-isomer **427** which has been postulated as an intermediate in the pyrolysis of the anhydride **428** based on the formation of the unsaturated nitriles **429**.[344] No aryne derived products were observed in the presence of pyridine, but with benzene a small amount of the formal insertion product, phenylpyrazine **430**, was identified.[288] An EA-mechanism was not considered likely in the amination of 2-fluoropyrazine (**431**)[345] and the 2-chloro compound **432** was shown to react exclusively by an ANRORC-mechanism (Section III. A.5).[346] The possibility that the 2,5-aryne **433** is involved in the amination of the diphenylpyrazine **434** was eliminated by the complete retention of a 6-deuterium atom during the process.[347] It therefore appears that the existence of didehydropyrazines must still be considered problematical.




(c) *Didehydropyrimidines.* Of the four possible didehydropyrimidines the 4,6-isomer (**435**) is the most stable[225] and the sole ortho-isomer (**436**) the most studied. The latter was first claimed to explain the predominant formation of cine-substitution products (**437**) from the reaction of 5-halopyrimidines (**438**) with $NaNH_2$,[348] $KNH_2$,[349] and piperidine,[187,220] but, as will be discussed below, alternative, nonaryne mechanisms are now favored. The best evidence for the generation of 4,5-didehydropyrimidine (**436**) is its trapping as the furan adduct **439** from isomeric aminotriazoles **440** and **441**.[350] However, from



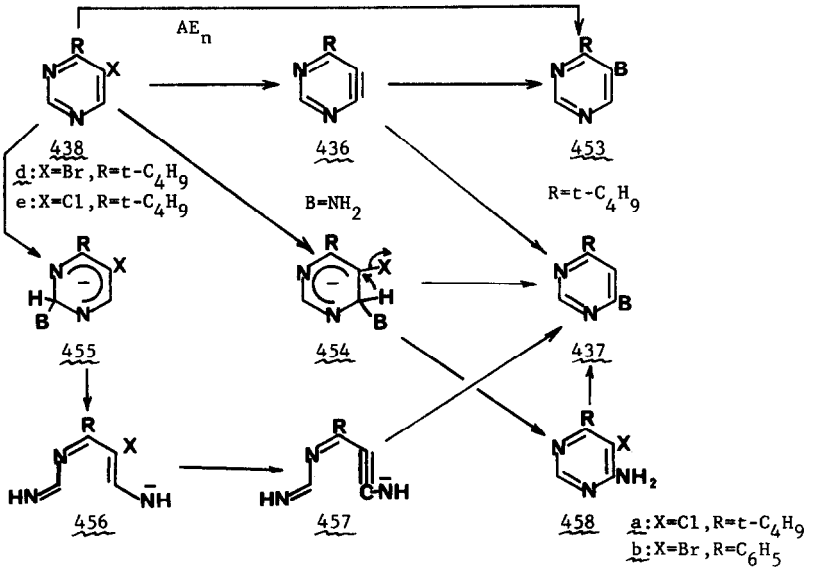

diazotization of the aminoacid **442**, only the arylation product **443**[351] or the cine-substitution product **444**[352] was obtained. The former product probably[351] arises by a Gomberg-type reaction (Section V.A.7(b)) and the latter was assumed[352] to involve an AEa-mechanism (Section III.A.3) of the intermediate diazonium salt **445**, since **444** was also formed when the amino compound **446** was diazotized. An EA mechanism via the aryne **436** cannot be excluded as an explanation for the conversion **446**→**444**, however, since diazonium salts can give rise to arynes[86] and the observed regiochemistry is that predicted for nucleophilic addition to the 4, 5-didehydropyrimidine (**436**).[142,225]



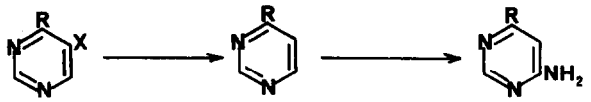
This same argument could be used to support the aryne explanation for the cine-substitution **438**→**437**, as can the relatively low reactivity of 5-halopyrimidines (**438**) to nucleophilic substitution by an AEn-mechanism compared to their 2- and 4-isomers.[96] On the other hand 5-halopyrimidines **438** are more reactive than phenyl or 3-pyridyl halides **254**,[96] and the anion (**447**) which would lead to the aryne **436** is predicted [225] and observed[33] to be relatively difficult to form, similar to the 2-pyridyl anion **258** (Section V.B.2(b)). Nevertheless, the anion **447** has been trapped with ketones in the reaction of 5-bromopyrimidine (**438c**) with lithium diisopropylamide (LDA)[353] and also implicated in the formation of 4, 4′-(**448**) and 4, 5′-bipyrimidines (**449**) from 5-fluoropyrimidine (**438c**) with LDA[353] or butyllithium.[354-357] Whether or not the anion **447** in fact gives the aryne **436** as claimed for some of these reactions[354-357] is far from certain, however. Thus, in the presence of furan no adduct **439** could be found from **438c** and LDA,[353] and even at 35° only starting material was recovered from reaction of **438c** with lithium piperidide.[8]

The claim or aryne intermediates (**436**) is restricted to 5-bromopyrimidines containing a 4-methoxy or 4-thiomethoxy substituent and is based on the formation of the lithiobipyrimidines **448c** and **449a**, presumably by the regioselective[142,225] addition of the anions **447** and **450** to **436**.[354-357] If the above 4-substituents are absent the halobipyrimidines **448a**,[6] **448b**,[353] and **449b**[357] still form but *via* the addition of anions **447** or **450** to the C=N of the halopyrimidine **438** followed by oxidation or loss of LiH. Evidence for such addition–aromatization reactions includes trapping of the anion **450**[354,358] and isolation of the dihydro adducts **451**[358] and **452**.[353] This same process offers a nonaryne rationalization for the production of **448c** and **449a** by simply appending the appropriate halogen-metal interchange reactions, i.e. **452**→**448b**→**448c** or **451**→**449b**→**449a**, which are known to occur readily with butyllithium in these systems (**438**→**450** and **448c**→**448d**).[354-358] The role of the 4-substituents may now be explained as facilitating the halogen–metal interchange of the halobipyrimidines (**448b** and **449b**) rather than aryne formation from the halopyrimidines (**438**). This hypothesis is supported by the fact that **449b** with 2- and 2′-methoxy substituents apparently does not undergo halogen–metal interchange to the corresponding derivative of **449a** under the reaction conditions.[357]

The presence of a variety of substituents at the 4-position[349,359] also markedly improves the low yields[6,8,348] of cine-amination products (**437**) obtained from 5-halopyrimidines (**438**) and metal amides thereby permitting a more thorough study of this reaction. Although originally interpreted as proceeding by an EA-mechanism through the 4,5-didehydropyrimidine (**436**),[348,349,359] the remarkable regiospecificity of this reaction (only for the 4-tert-butyl analogue **438d** is any normal substitution product **453** formed)[359] led to considerations of an AEa-mechanism (Section III.A.3) *via* the adduct **454**.[8,67] One variation of this mechanism involving an *intramolecular* transfer of hydride ion[47] from C–6 to C–5 was eliminated by the demonstration that a 6-deuterium atom in reactant **438d** did not appear in the product **437**.[67] The more significant result of this experiment, however, is the surprising stability of **438d** to base-catalyzed exchange at the 6-position in view of the probable intermediacy of the anion **447** in the reaction of **438d** with LDA[353] and butyllithium[354-357] discussed previously. The suggestion[55] that this resistance of **438d** to exchange was due to formation of the anionic sigma complex (**454**) was supported by the detection of this species by NMR spectroscopy.[360] This observation in turn prompted a $^{15}N$–isotope study[66] which conclusively demonstrated



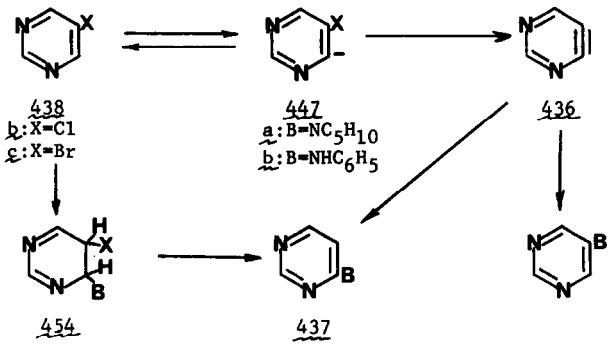
that *half* of the observed cine-amination of **438d** proceeds *via* an ANRORC-mechanism (Section III.A.5),[65] probably involving the undetected C–2 sigma adduct **455** as shown. The mechanism by which the remaining half of the cine-amination occurs has not been proven, although an AEa-mechanism involving protonation of **454** and elimination of HBr has been considered[66] the most plausible in view of the high concentration of this species present in the reaction medium.[360] The demonstration of an isotope effect for removal of the 6-proton in the overall conversion of **438d** to **437**[66] provides little information on this second mechanism, since any of the steps **438**→**436**, **454**→**437**, or **456**→**457** might be responsible and hence an EA-mechanism via the aryne **436** cannot be eliminated rigorously. What has been eliminated is a mechanism involving a Chichibabin reaction followed by dehalogenation (Section III.A.2). The first step of this reaction has been observed for the chloropyrimidine **438e**→**458a**,[361] but the dehalogenation step **458**→**437** fails, not only for the chloro compound **458a**[361] as expected[46] but also for the bromopyrimidine **458b**.[362] A mechanism utilizing the same steps but in reversed order, i.e. dehalogenation followed by a Chichibabin reaction (**438**→**459**→**437**), has some precedence in both the pyrimidine[363] and pyridine series (Section V.B.3(b)) and has not yet




438 459 437

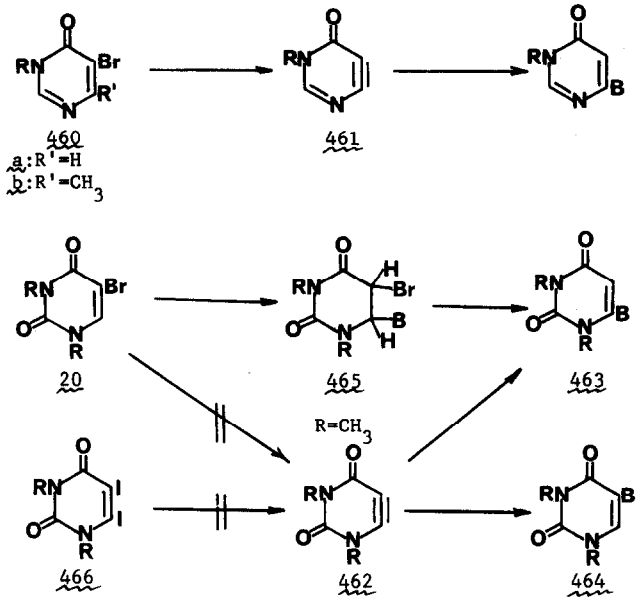
been ruled out. Finally, it should be emphasized that changing the nature of either the halogen or the substituent can markedly affect the extent and mechanism of the cine-amination of 5-halopyrimidines (**438**) with $KNH_2$,[361,362] so conclusions derived from a well-investigated compound such as **438d** may not be generally valid.

The same comment is warranted regarding the nature of the base. The predominant cine-substitution of 5-bromopyrimidine (**438c**) with piperidine[220] is inhibited in favor of normal substitution in the presence of ethanol[187] or aniline[8] suggesting protonation of the precursor of the aryne **436**, the anion **447**. The intermediacy of **436** is further supported by trapping with aniline to give **437b**, but only in the presence of a more basic amine.[99,68a] That an EA-mechanism *via* the aryne **436** is also involved in the cine-substitution of the chloro compound **438b** is indicated by a similar trapping with aniline, although the absence of an inhibiting effect by ethanol as well as competition studies[68] with piperidine and diethylamine require that a second mechanism of cine-substitution, presumably the AEa-mechanism (Section III.A.3) via **454** is operative as well.[49,68a] What remains unexplained is how ethanol fails to inhibit the overall cine-substitution of **438b** while apparently blocking that part proceeding *via* **447** and **436**. The postulated promotion of the AEa-mechanism[10] remains unspecified and requires further investigation.



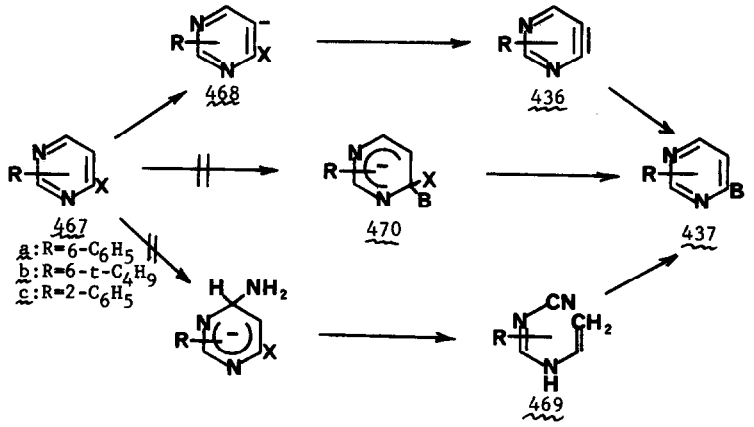

438 b:X=Cl c:X=Br
447 a:B=NC5H10 b:B=NHC6H5
436
454
437

Although 5-halo-4-pyrimidones (**460**) and 5-halouracils (**20**) might be expected to be especially susceptible to cine-substitution by an AEa-mechanism, the corresponding arynes **461** and **462** have been considered as intermediates with a variety of bases including $KNH_2$,[349,359] piperidine,[10,351] $NH_3$,[8] potassium *t*-butoxide,[364] and NaCN.[51,365] The only evidence supporting this hypothesis rather than an AEa-mechanism is the inertness of the 6-methyl compound **460b**[351] and the inhibition of the cine-(**20**→**463**) (R=H, B=$NH_2$) but not the normal substitution (**20**→**464**) by ethanol.[8] This interpretation has been questioned and further research called for.[10,66] Evidence supporting the AEa-mechanism includes the detection and rearomatization of adducts **465**[57,59,60,366] and the *failure* of water to inhibit the reaction **20**→**463** (R=$CH_3$, B=CN).[51] The difference in response to an added proton donor with the nature of R in **20** and B in **463** once again illustrates the dangers of generalizing in these systems. The 4,5-



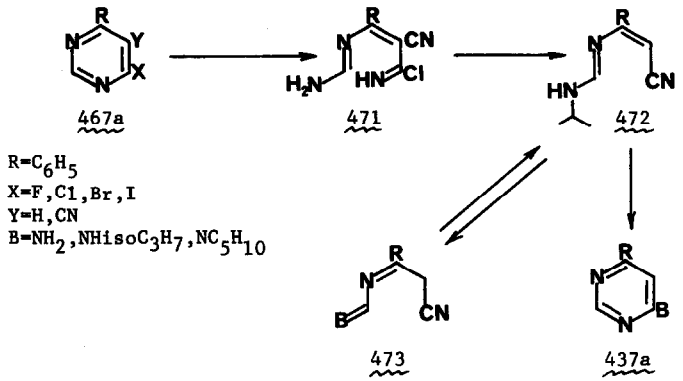
didehydrouracil **462** was also considered and rejected as an intermediate in the photolysis of the diiodocompound **466** which gives products derived from loss of only one iodine atom.[367]

The predicted[142,225] regiospecific attack of nucleophiles at the 4-position of 4,5-didehydropyrimidine **436** requires that this intermediate also be at least considered for the observed exclusive normal substitution of 4-halopyrimidines **467** with piperidine[220] and $KNH_2$.[368] The precursor of the aryne **436**, the anion **468**, would be expected[33,225] to form more readily than that (**447**) from 5-halopyrimidines **438** thereby supporting the aryne intervention. On the other hand 4-halopyrimidines (**467**) are more reactive to nucleophilic substitution by an AEn-mechanism than the 5-isomers **438**.[96] Such an AEn process is supported by the failure of a 5-substituent to inhibit 4-substitution,[368,369] as would have been expected for an EA-mechanism via **436**, and also by a $^{14}C$-labeling experiment which eliminates an ANRORC mechanism via **469c** involving nucleophilic attack at C-6.[370] The AEn-mechanism via **470** was also



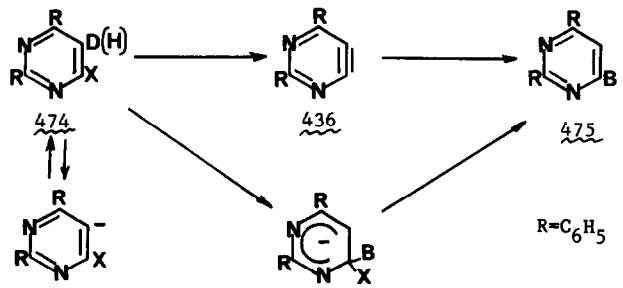
effectively eliminated for the 6-phenyl (**a**) and 6-t-butyl (**b**) derivatives of **467**, however, by the finding that a 5-deuterium atom was completely lost during the substitution reaction **467ab**→**437ab**.[67,323] Although an EA-mechanism *via* **436** therefore provides the most obvious rationale for this observation,[6] further proof was called for[306] and an AEn-mechanism continued to be considered for 2-substituted-4-halopyrimidines.[371,372] A series of $^{15}N$-labeling experiments revealed that, depending on the halogen atom, varying proportions (F = 73%, Cl = 93%, Br = 83%, I = 13%) of 6-phenyl-4-halopyrimidines **467a** reacted by an ANRORC mechanism initiated by nucleophilic attack at C-2.[324,373] With lithium piperidide[323] or lithium isopropylamide[374] as nucleophiles, or with a 5-cyano substituent in **467a**,[375] intermediate ring-opened compounds **471** and **472** could be isolated. That portion of the substitution product **437a** which arose by an ANRORC mechanism was assumed to have undergone exchange at the

5-position via **473**,[324] and the remainder was assumed to have been formed by an EA-mechanism.[373] With 2,6-diphenyl-4-halopyrimidines (**474**) the proportion of substitution by an ANRORC-mechanism



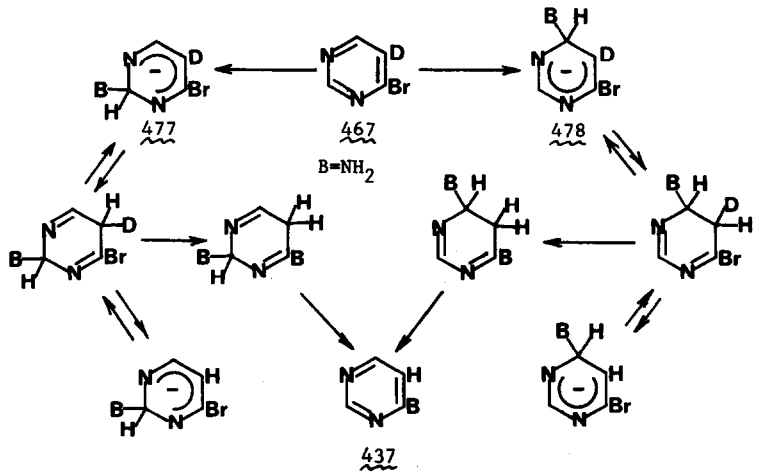

467a 471 472 473 437a

decreased markedly,[363,376] presumably due to steric hinderance to nucleophile attack at C-2, and either EA or AEn-mechanisms or both were *assumed*. The basis for including an EA-mechanism is somewhat equivocal, however, since, in contrast to the monosubstituted-4-bromopyrimidines **467**,[67,323] substantial exchange at the 5-position of the reactant **474** was observed,[363] thereby decreasing the value of observing D-loss in the product **475** as a means of ruling out an AEn-mechanism *via* **476**. In fact, the recent



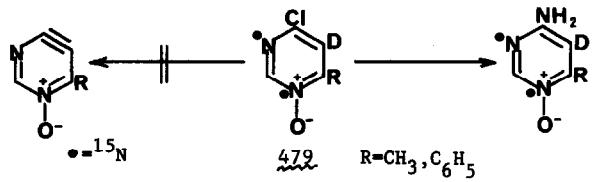

474 436 475 476

observation of an increase in the proportion of substitution **467b**→**437b** by an ANRORC-mechanism with decreasing temperature has led to questioning of the intermediacy of the arynes **436** in the reactions of halopyrimidines with strong bases *in general*.[377] Such a total abandonment of the aryne hypothesis would require an explanation for (or revision of) the observation of 5-proton exchange in non-ANRORC substitutions of 4-halopyrimidines (**467ab**). Possibilities include solubility considerations[363] or the intervention of still other substitution processes such as the ASE mechanism (Section III. A.4). For example, fast prototropy of an irreversibly formed C-2 (**477**) or C-6 (**478**) adduct followed by substitution and irreversible elimination of $NH_3$ would account for the observed exchange results and conform to the known tendency of some, but not all substituted pyrimidines to form anionic adducts.[54,360,361,378] As was

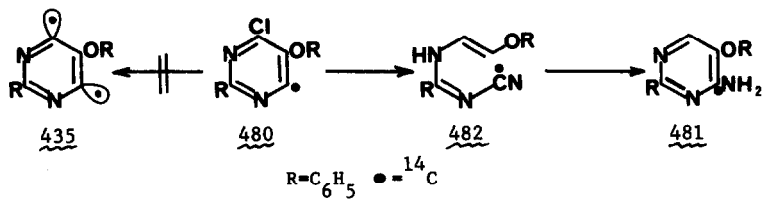



477 467 478 437

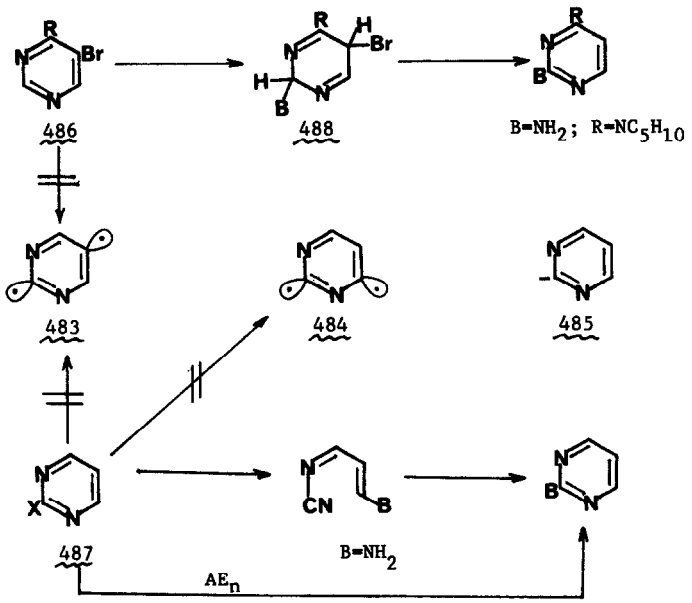
emphasized in the reactions of the 5-halo isomers **436**, the marked effect of substituents on the products and mechanisms of base attack on 4-halo-pyrimidines **467** cannot be neglected. It will therefore be necessary to do both the $^{15}N$-scrambling and the 5-proton exchange experiments on the same molecule under the same conditions before conclusions on mechanism are valid. Such precautions have been taken for the 4-bromo derivatives of **467a**,[323,324,379] the bromo compound **467b**,[67,377] the iodo compound **467a**,[373] and the N-oxide **479**.[380] Based on these experimental results the intervention of a 4,5-didehydropyrimidine **436** may be considered as probable,[373] possible as a minor pathway,[67,323,324,377] or disproven.[379,380]




No evidence for any of the other didehydropyrimidines has been obtained. The most stable[225] 4,6-isomer (**435**) is not an intermediate in the reaction **480**→**481** since the ANRORC intermediate **482** can be isolated and recyclized to **481**, and $^{14}C$-labeling studies show that the substitution is exclusively *tele* in

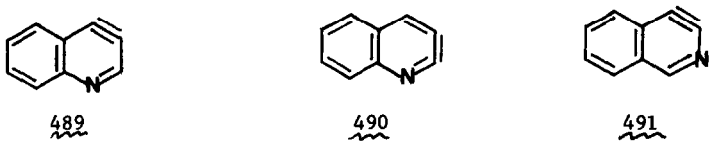



contrast to the 1:1 mixture predicted for the symmetrical aryne intermediate **435**.[369] The remaining possible didehydropyrimidines **483** and **484** are calculated to be the least stable[225] and would probably add nucleophiles exclusively at the 2-position to avoid the relatively high energy[33,225] 2-anion **485**. This agrees with the tele-substitution of the 5-halopyrimidine **486**[362] and the normal substitution of a variety of 2-halopyrimidines **487** with available 5- and 6-protons.[381–383] The first reaction probably proceeds by an AEa-mechanism (Section III.A.3) via **488**,[362] however, and the latter ones by a combination of AEn and ANRORC processes as shown.[381–383]



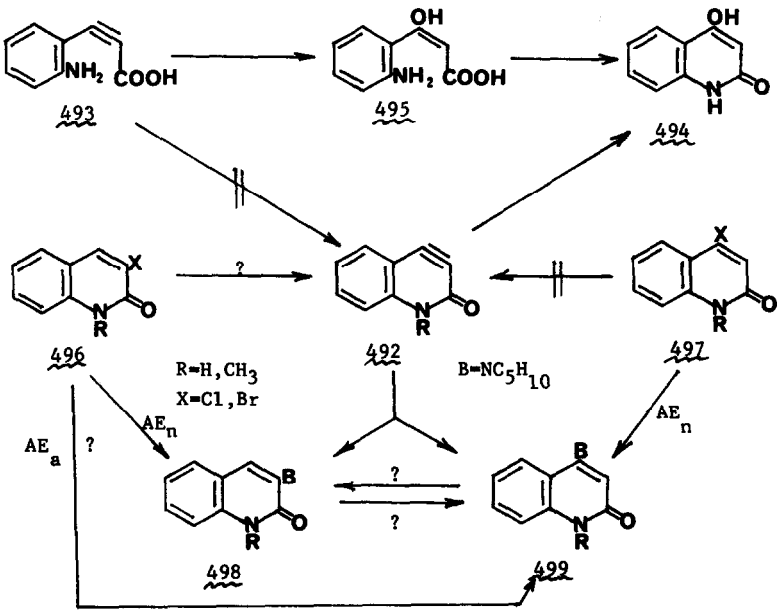

7. *Multicyclic Didehydropyridines.* Fusion of an aromatic ring on to the pyridine nucleus probably will not alter significantly the predicted[225] and observed (Section V.B. 2,3) relative stability of the

corresponding arynes or anions. The latter hypothesis is confirmed for the base-catalyzed H–D exchange of quinoline which proceeds in the order 4 > 3 > 2, 8,[384] while the former suggestion is supported by the relative quality and quantity of evidence, to be discussed below, favoring the existence of 3,4-didehydroquinoline (**489**) compared to its 2,3-isomer (**490**), or 3,4-didehydroisoquinoline (**491**). The major difference to be anticipated between the mono- and bicyclic systems is the much greater tendency of the latter to undergo nucleophilic addition reactions, a property well-demonstrated with amide ion and both quinoline and isoquinoline.[55]

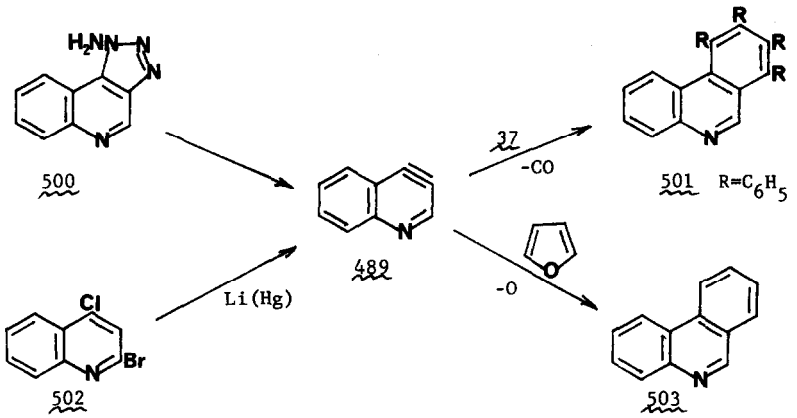


489 490 491

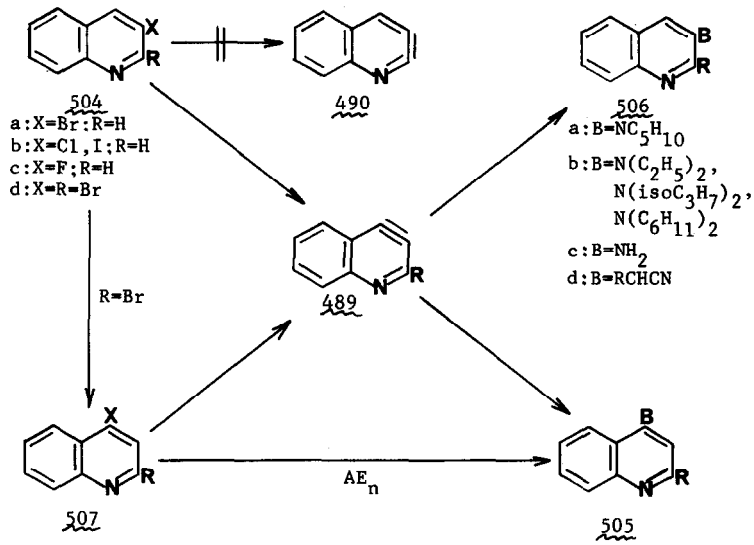
(a) 3,4-*Didehydroquinolines.* The 3,4-didehydro-2-quinolone (**492**) was apparently the first aryne to be the goal of a synthetic effort.[385] It was concluded, however, that the cyclization of the o-aminophenylpropiolic acid **493** to **494** probably proceeds by an addition-cyclization sequence *via* **495** and not *via* **492**. Over eighty years later this aryne was claimed[187, 220, 386] to rationalize the cine-substitution of 3- (**496**) but not 4-halo-2-quinolones (**497**) with piperidine. The EA-mechanism is supported by the constancy of the isomer ratio **498:499** with different halogens in the reactant **496** and by the partial suppression by ethanol of all or just the cine-component of the substitution reaction.[386] In view of the questions raised for related molecules such as **235** (Section V.B.1) and **400** (Section V.B.6(a)), however, the possibility of AEa-type mechanisms[330, 331] and/or product isomerization (**498**⇄**499**) under the reaction conditions[221] should be eliminated before the intermediacy of **492** is considered certain.




The case for the parent 3,4-didehydroquinoline **489** is more convincing. Oxidation of the aminotriazole **500** in the presence of tetracyclone **37** gave the excepted adduct **501** in good yield,[230] and treatment of the chlorobromoquinoline **502** with lithium amalgam in the presence of furan yielded phenanthridine **503**.[5, 387] Reaction of 3-haloquinolines (**504a, b**) with lithium piperidide[5, 387] gave a characteristic ratio (1:1) of cine (**505a**) and normal (**506a**) substitution products independent of halogen. As in

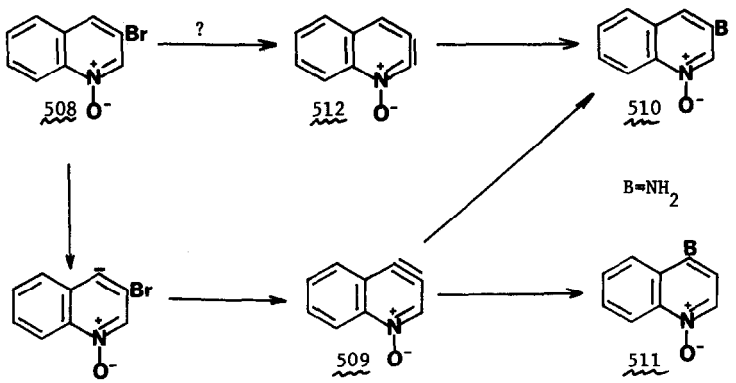



the pyridine series (Section V. B.2(b)) no evidence for the generation of the corresponding 2,3-aryne (**490**) was obtained, while the 4-halo (**507**)[8,10] and 3-fluoro (**504c**) compounds[387] react predominantly by an AEn mechanism. Increasing either the bulk of the halogen or the bulk of the amine increases the proportion of EA mechanism in the substitution,[10] once again similar to the findings with didehydropyridine and benzyne.[77] Bulkier amines also give proportionally greater amounts of the cine-substitution product (**505b**)[10,68] presumably due to unfavorable peri interactions in **506b**. Competition studies with the base pair diethylamine/diisopropylamine confirmed the EA mechanism, compared the selectivity of **489** with other arynes, and quantified the selectivity differences between the 3- and 4-positions.[10,68,246,247,252]

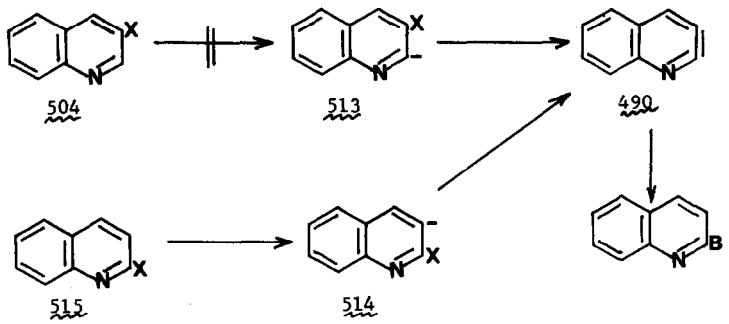



The reactions of a variety of 2-R, 3-(**504**) and 2-R, 4-bromoquinolines (**507**) with $KNH_2$ also appear to involve the aryne **489**. In the case where R=H,[388] R=$NH_2$,[389] and R=Br[390] both isomers give the same mixture of substitution products **505c** and **506c**. Only the 3-isomer **504a** was studied for R=$OC_2H_5$[391] and for R=H with $NaNH_2$ and substituted acetonitriles,[392] but cine-substitution to **505c** and **505d**, respectively, was the major reaction. The 4-amino compounds **505** were also favored slightly for R=H[388] and strongly for R=Br,[390] but the 3-amino compound **506** was much preferred for R=$NH_2$,[389] consistent with the expected[24,264] effect of substituents on the direction of addition to the 3,4-didehydroquinoline **489** (Section V. B. 2(c)). Although the interpretation of these results in terms of an EA-mechanism is therefore reasonable, it should be pointed out that for R=Br a transhalogenation (Section III. A.2) of 2,3- to 2,4-dibromoquinoline (**504d** → **507d**) has been demonstrated[390] so the possibility of a subsequent AEn substitution to **505** would also explain the data. The reaction of 3-bromoquinoline-N-oxide (**508**) with piperidine[312] and $KNH_2$[314] also appears to go through the corresponding aryne (**509**) since both normal (**510**) and cine-substitution products (**511**) were obtained. In contrast to the pyridine analogues (Section V. B.4) no evidence for the intervention of the 2,3-aryne (**512**) was noted which may either be due to the

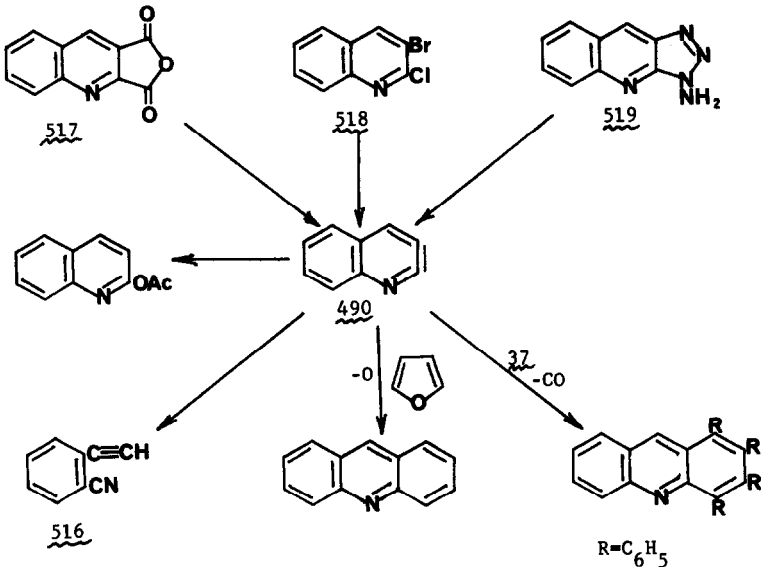
expected very regioselective addition of nucleophiles (**512** → **510**)[6] or to the more favorable abstraction of the 4-proton in **508** than in 3-bromopyridine-N-oxide (**354b**).[314]



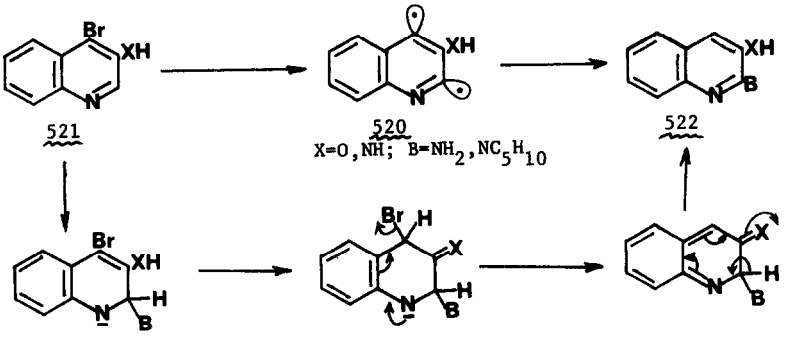

(b) 2,3-*Didehydroquinoline.* While, as stated above, the absence of products from substitution at the 2-position does not eliminate a 2,3-aryne intermediate (**512**) in the reactions of 3-bromoquinoline-N-oxide (**508**),[312] the same observation with 3-haloquinolines (**504**) themselves appears to do so with respect to **490**.[387,388] This conclusion is consistent with the expected[225,384] difficulty in generating the anion (**513**), the precursor to **490**. The isomeric anion **514** should be more easily produced from the 2-haloquinolines **515**, but because of the probable[142,224,225] preferential addition of nucleophiles at the 2-position of the aryne **490**, cine-substitution will not be a useful criterion for establishing the EA-mechanism. Competition studies have led to the suggestion, but not conclusive proof, that 2,3-didehydroquinoline **490** is partially involved in some,[10,68] but not all,[6] substitutions of 2-haloquinolines (**515**) with amines. The




suggested involvement of the aryne **490** in the Chichibabin reaction[224,393] is subject to the same criticisms cited[293–295] for 2,3-didehydropyridine (**12**) (Sec. V. B.3(b)), and the formation of ring-opened product **516** from the pyrolysis of the anhydride **517**,[394] while explicable by a mechanism involving the aryne **490** analogous to that postulated in the pyridine[287] (Section V. B.3(a)) and pyrazine[344] (Section V. B.6(b)) series, does not provide conclusive evidence. The best indication that 2,3-didehydroquinoline (**490**) has in fact been generated comes from trapping experiments with furan and tetracyclone (**37**) during the reaction of the bromochloroquinoline **518** with lithium amalgam[395] and oxidation of the aminotriazole **519**,[230] respectively. Even here the yields of the adducts are much lower than in the analogous reactions leading to the 3,4-aryne **489** (Section V. B.7(a)) and caution has been expressed.[10] The apparent tendency of **490** to react preferentially with acetic acid rather than tetracyclone (**37**)[232] parallels the behavior of 2,3-pyridyne **12** and the same question of interpretation (Section V. B.3(a)) can be raised.

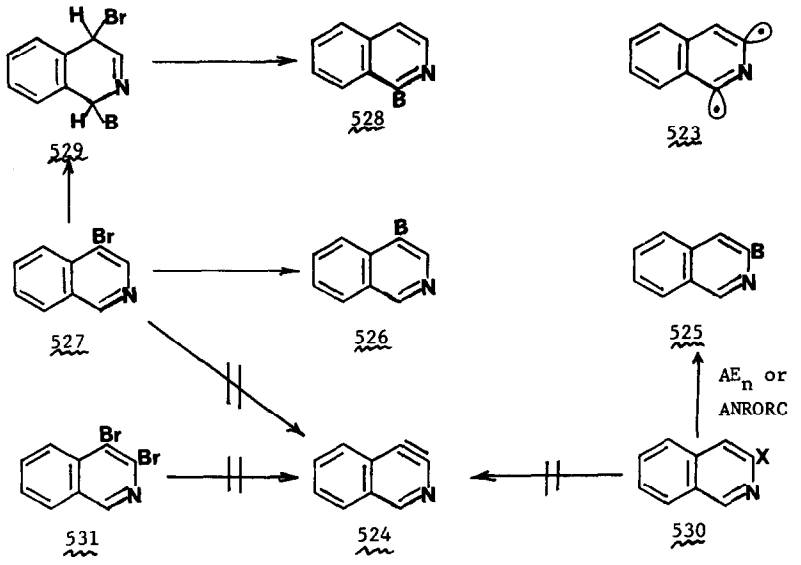



(c) 2,4-*Didehydroquinoline.* By analogy with the corresponding pyridine species **374** (Section V. B.5), 2,4-didehydroquinoline **520** might be expected to have substantial stability.[225,226] Although this intermediate could explain the observed tele-substitutions **521**→**522**, especially since alternatives involving transhalogenation/AEn and Chichibabin/dehalogenation sequences were eliminated,[389] the suggested AEa process is at least as attractive[389] and is supported by the fact that for X = O the weaker base



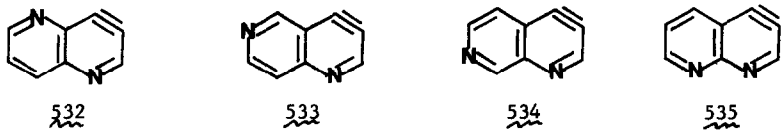

piperidine gives tele-substitution but the stronger base lithium piperidide gives normal substitution.[268]

(d) *Didehydroisoquinolines.* Except for the highly criticized[293–295] (Section. V. B.3(b)) suggestion[224] that 1,3-didehydroisoquinoline (**523**) is an intermediate in the Chichibabin reaction, and those arynes solely in the carbocyclic ring (Section V.D), the only other didehydroisoquinoline mentioned in the literature is the 3,4-isomer **524**. A claim[327] that this species had been generated was based on the apparent isolation of the cine- (**525**) as well as the normal substitution product **526** from the reaction of 4-bromoisoquinoline (**527**) with piperidine.[8] This result could not be reproduced[396] and subsequent studies on all four of the 4-haloisoquinolines revealed that it was the tele (**528**) and not the cine-substitution (**525**) product which was produced, presumably by AEa mechanism *via* the NMR detectable adduct **529**.[191] The trace (< 0.5%) of **525** probably detected from the reaction of only **527** is insufficient evidence to support a claim of aryne intermediacy.

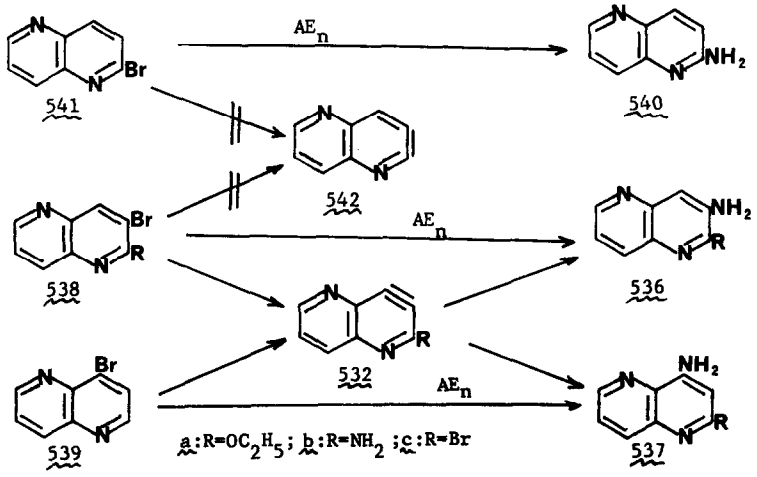



Reaction of **527** with stronger bases such as lithium piperidide[8] or $KNH_2$[191] leads, respectively, either to recovery of **527** or to complex mixtures of normal and telesubstitution, dehalogenation, Chichibabin amination, and coupling products. No cine-substitution products (**525**) were detected, and hence no aryne **524** is implicated. Neither blocking of the 1-position by substituents,[397] nor utilizing 3-haloisoquinolines (**539**) as precursors,[396] gave any indication that 3, 4-didehydroisoquinoline (**524**) had been generated. The former precursors led to reduction and normal substitution to **525**, but to the extent of 55% via an ANRORC mechanism. An attempt to generate **524** by dehalogenation of the dibromo compound **531** with lithium amalgam gave no trapping products in the presence of furan.[396] It therefore seems valid to conclude that no compelling evidence for 3, 4-didehydroisoquinoline **524** is as yet available.

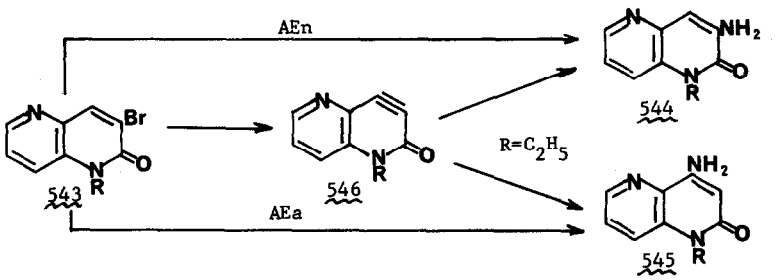
(e) *Didehydronaphthyridines.* Based on the greater stability of 3, 4-compared to 2, 3-didehydropyridines (Section V. B.2, 3) the most stable and hence most readily generated didehydronaphthyridines would be expected to be the four isomers **532–535**. Each of these, and only these, have been claimed in the reactions of the corresponding halogen compounds with $KNH_2$.



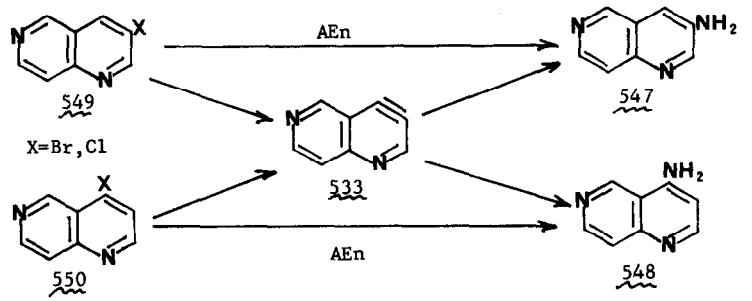

The first such claim, for 3, 4-didehydro-1, 5-naphthyridine **532**, was based on the formation of mixtures of both the 3- (**536**) and 4- amino (**537**) compounds from either the 3-(**538**) or 4-bromo (**539**) precursor.[398] No 2-amino isomer (**540**) was observed from **538** and no 3-amino product **536** was obtained from the 2-bromo precursor **541** thereby providing no evidence for the 2,3-didehydro intermediate **542**. The nonidentity of the product ratios **536**:**537** from the precursors **538** and **539** suggested the involvement



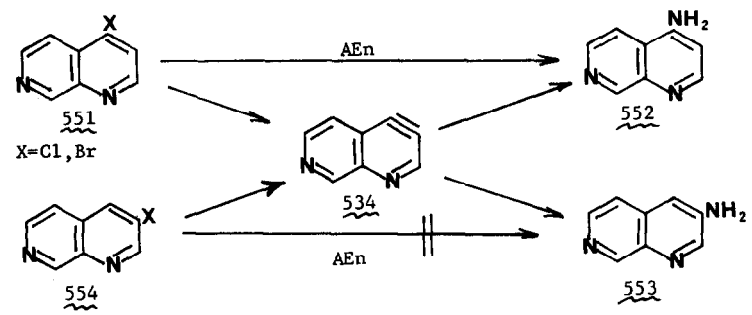
of AEn mechanisms which also were held responsible for the apparently 100% normal substitution of the alleged 3-ethoxy derivative **538a** to **536a**.[9,398] This latter result is surprising in view of the expected (Section V. B.2(c)) effect of a 2-ethoxy group on the formation and reactivity of a 3,4-didehydro species such as **532a** especially since the 2-amino (**538b**) and 2-bromo (**538c**) derivatives give substitution products **536b** and **537c**, respectively, in keeping with the intermediacy of the corresponding arynes **532b** and **532c**.[391] This discrepancy has recently been resolved by the finding that, in fact, *two* reaction products are formed and that the substance thought to be the bromoethoxynaphthyridine **538a** is actually the N-ethylbromonapthyridone **543**.[399] Authentic **538a** was prepared and does give a mixture of **536a** and **537a** in a ratio of 1:4.5 consistent with the intermediacy of aryne **532a**. The two products from **543** were identified as the isomeric substitution products **544** and **545** prompting a claim that the aryne **546** was an intermediate. As mentioned for other such $\alpha,\beta$-unsaturated carbonyl systems (Section V. B., 1, 2(c), 6(a), 6(c), 7(a)) further evidence to eliminate concurrent AEn and AEa processes are necessary to support this claim.




The formation of varying mixtures of 3-(**547**) and 4-amino-1,6-naphthyridines (**548**) from the isomeric bromo and chloro precursors **549** and **550** has led to the postulation of EA-mechanisms via 3,4-didehydro-1,6-naphthyridine (**533**) as well as contributions from AEn processes.[400] A similar mixed mechanism was proposed for the 4-halo-1,7-naphthyridine (**551**) substitution because of the dependence of the product ratio **552**:**553** on the nature of the halogen atom in **551**.[401] By the same token the

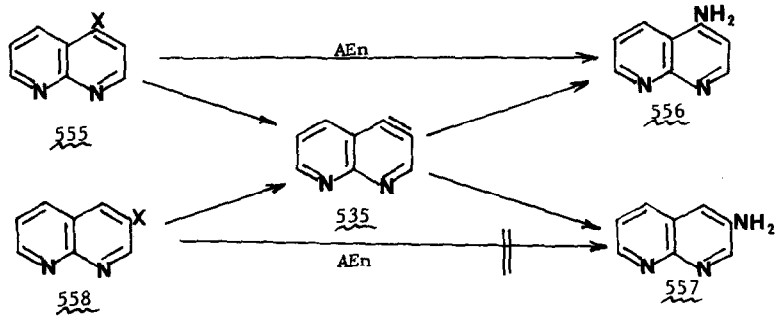



invariance of this ratio led to the conclusion that only an EA-mechanism via 3,4-didehydro-1,7-naphthyridine (**534**) was operative for the 3-halo isomers **554**.[402]

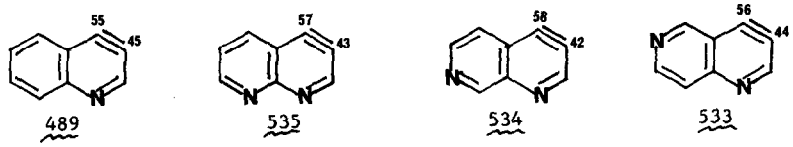



The *same* conclusion has been proposed for the 1,8-naphthyridine series, although in fact it was the 4-isomers **555** which gave identical ratios of **556**:**557** (Br = 69:31; Cl = 70:30) and the 3-isomers (**558**) which gave varying ones (Br = 57:43; Cl = 66:33).[403] The rationale for drawing a conclusion—as to

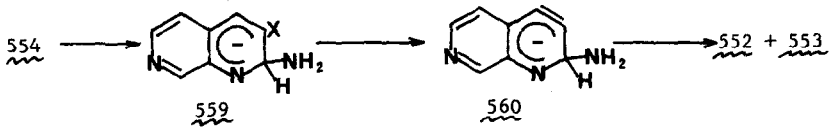
which isomer reacts by a mixed mechanism (**555**) and which reacts by a pure EA mechanism (**558**) via **535**—that is apparently contradicted by the data, is based on expressed doubts as to the accuracy of the




**556**:**557** ratio for **558** X=Cl and the similarity of this ratio for **558** X=Br to that for $NH_3$ addition to other bicyclic 3,4-didehydro species as shown.[403] Further data would be desirable to verify the authors' intuition on this point.

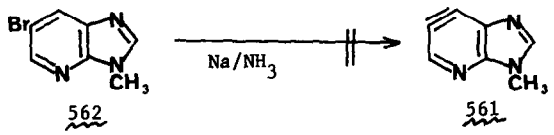



A potential complication of the above explanations for amination of halonaphthyridines by AEn and EA mechanisms is the finding, by NMR, that many of these precursors exist solely as anionic sigma complexes such as **559** under the reaction conditions.[402,403] Similar complexes play an important role in tele-amination reactions,[404,405] and the possibility has been suggested that the observed variations in cine to normal substitution ratios also may depend on the extent of sigma complex involvement, perhaps via didehydro species such as **560**.[402] There is no evidence,[399] however, that sigma complexes are

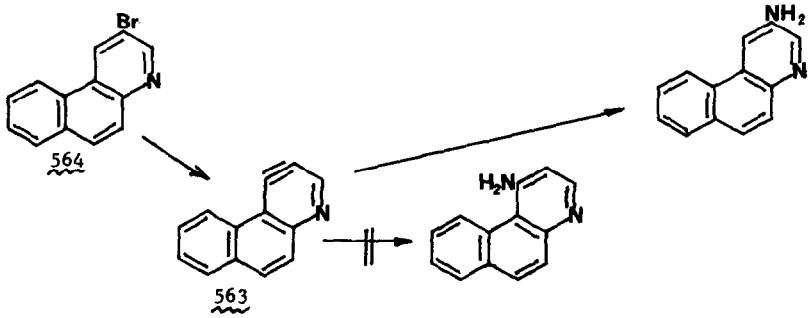



responsible for the unusually high fraction of 3-addition to the arynes **532** and **532a**,[398] a result which perhaps may be explained by either steric[399] or peri[384] effects.

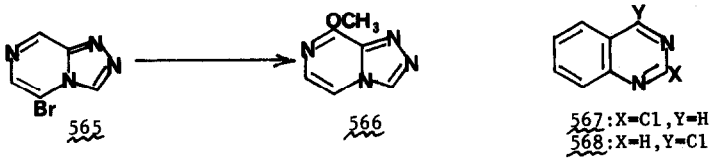
(f) *Other Bicyclic Didehydropyridines.* An attempt to generate the didehydroimidazopyridine **561** from the bromo compound **562** not surprisingly gave only debromination since sodium–liquid $NH_3$ apparently was used instead of sodium amide.[406]



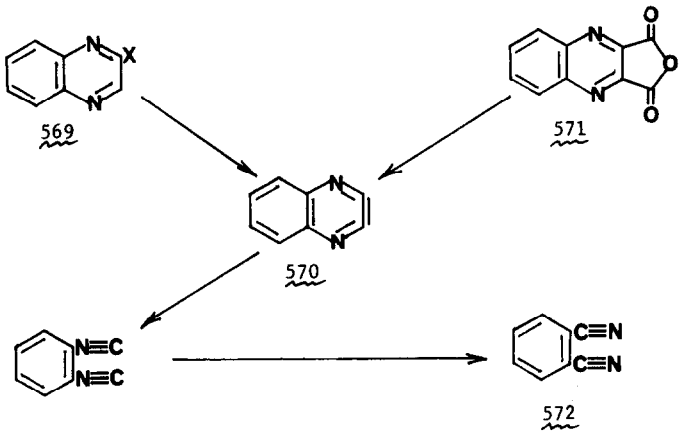

(g) *Tricyclic Didehydropyridines.* Although only normal substitution was observed, the didehydrobenzo-(b)quinoline **563** was postulated as an intermediate in the reaction of the bromo derivative **564** with $KNH_2$.[407] The lack of cine-substitution was attributed to steric interference by the angular ring.



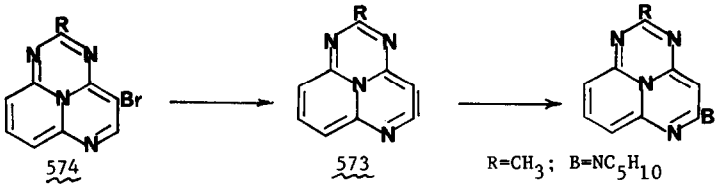
(8). *Multicyclic Didehydrodiazines.* Potential precursors of these arynes will have the combined effect of extra nitrogen atoms and extra rings to increase their susceptability to addition reactions.[56] Consequently, the suggestion that the teleamination **565** → **566** proceeds via an AEa mechanism and not a p-didehydro species is quite reasonable[408] as is the high ANRORC component to the normal substitution of the quinazolines **567** and **568**.[383,409] Contrariwise, isotope experiments have clearly shown that



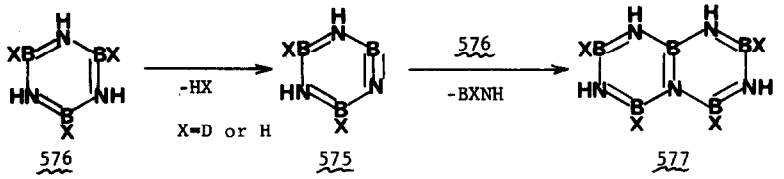

2-haloquinoxalines **569** do not undergo substitution by either ANRORC[346] or EA-mechanisms via 2,3-didehydroquinoxaline **570**.[410] This intermediate is possibly implicated in the pyrolysis of the




anhydride **571** based on the formation of phthalonitrile **572** by a mechanism analogous to that proposed in the quinoline series (Section V. B.7(b)).[394] The only other postulated multicyclic didehydrodiazine (**573**) was suggested to rationalize the cine-substitution of the cyclazine **574** under notably mild conditions.[411] An AEa mechanism has not been excluded, however.




(9) *Didehydroborazine.* This inorganic aryne **575** was proposed as an intermediate in the photolysis of borazine **576** on the basis of D-labeling results which showed that adjacent hydrogen atoms were eliminated by an intramolecular process.[412] The borazanaphthalene (**577**) which was formed presumably

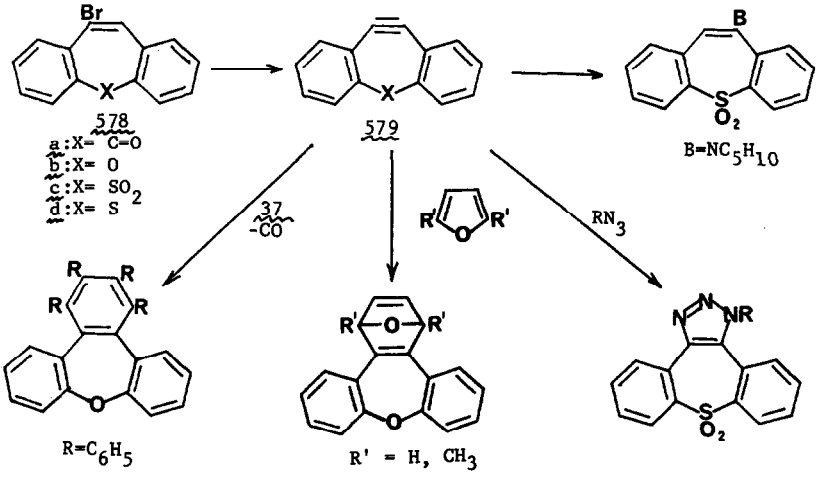



arises by a Diels–Alder reaction of **575** and **576** followed by loss of a XBNH fragment which polymerizes.

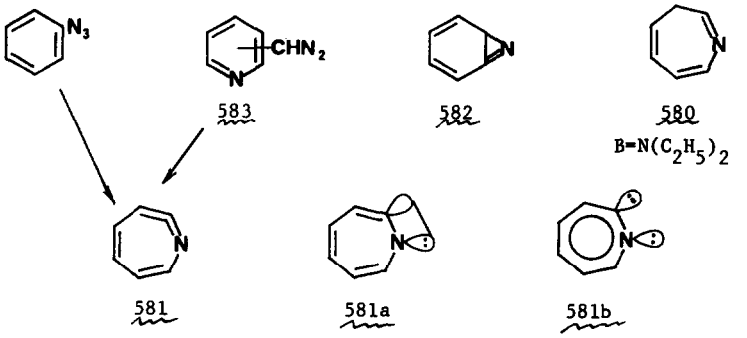
C. *Seven-Membered Hetarynes*

In addition to the obvious difference of ring size the species described in this section are, in contrast to those in Sections V.A and V.B, formally derived (Section I) from nonaromatic heterocycles.[413]

Therefore, while the improved overlap of the aryne orbitals would be expected to make the generation of these didehydro intermediates easier, the lower resonance energy of any precursors would increase the possibility of aryne trapping products being formed by addition elimination pathways (Section III. A.B.). Although this possibility was not as rigorously excluded as in the related carbocyclic series (a),[88] the wide variety of trapping agents used (dienes, nucleophiles, 1, 3-dipoles) and the susceptability of the bromo compounds **578** to HBr loss even in the absence of these traps, strongly suggests that the 4, 5-didehydro derivatives of dibenzooxepin (**579b**) and dibenzothiepindioxide (**579c**) have been generated.[414] The parent 4, 5-didehydrodibenzothiepin (**579d**) has also been reported recently.[414a]



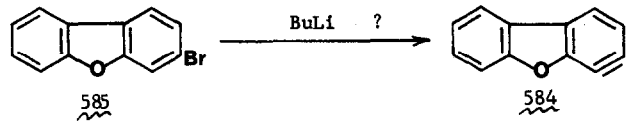

The formation of 2-substituted-3H-azepines (**580**) from the photolysis of phenyl azide in the presence of nucleophiles has been reinterpreted as involving the intermediacy of the azacycloheptatetraene **581** and not the azirene **582** based on its IR detection in an argon matrix at 8 K.[415,416] The same species can be generated from all three diazomethylpyridines **583** by a series of photoisomerizations.[417] The presence of a peak at 1895 $cm^{-1}$ in the infrared spectrum of **581** was used to argue for an electronic structure **581a** with a bonding in-plane interaction similar to that proposed for hetarynium ions (**372**) (Section V.B.5) rather than one with a repulsive in-plane interaction and the more favorable 6-electron pi system (**581b**).[415] Polycyclic analogues of the tetraene **581** are neither necessary nor sufficient to explain the photochemistry of the corresponding azides, the intermediacy of azirines related to **582** being preferred.[418,419] In the napthalene series, however, matrix-isolation experiments suggest that intermediates related to both **581** and **582** are formed.[420]



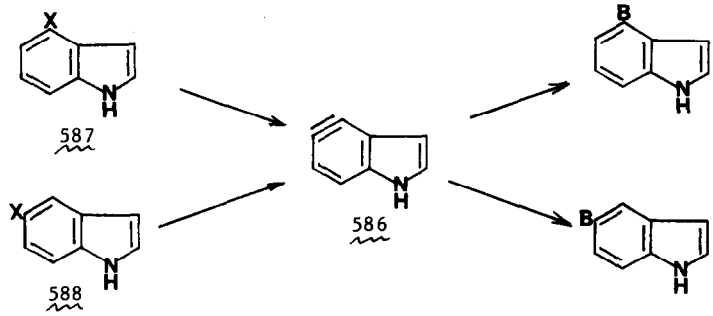

D. *Benzdidehydroheterocycles*

The hetarynes discussed in this section are multicyclic with the aryne bond in a carbocyclic ring. Although these intermediates may therefore be considered as substituted benzynes, to the extent that the fused heterocyclic ring has an effect on the chemistry of the aryne, some justification exists for at least mentioning them in this review.[7,8,10]

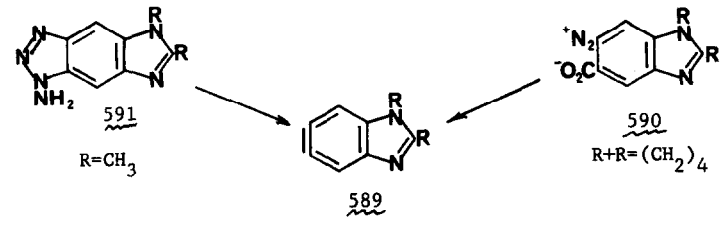
It has been speculated[7] that the didehydrobenzofuran **584** may have been generated from the bromo compound **585** during a series of transmetallation reactions with butyllithium.[421] The 4, 5-didehydroindole



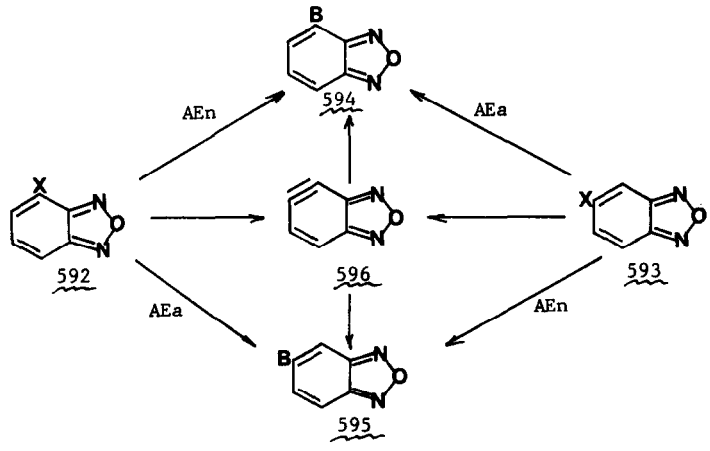

**586** has been generated from both the 4-(**587**) and 5-haloindoles (**588**), as shown by the identity of cine and normal substitution ratios regardless of which reactant was used.[422-424] Application of this reaction to a formal synthesis of d,l-lysergic acid[425] required preliminary reduction of the indole to an indoline, however.[426] Apparently no 5,6-didehydroindole was formed from **588**, but the analogous benzdide-



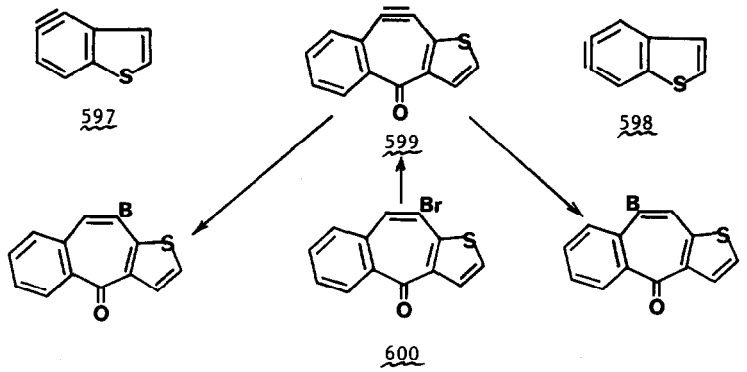

hydroimidazole **589** clearly was generated from both the diazonium carboxylate **590** and the amino-triazole **591** (but not from halobenzimidazoles)[8] based on trapping evidence with a variety of dienes and 1,3-dipoles.[427] With thiomethoxide ion the isomeric halobenzofurazans **592** and **593** give nonidentical



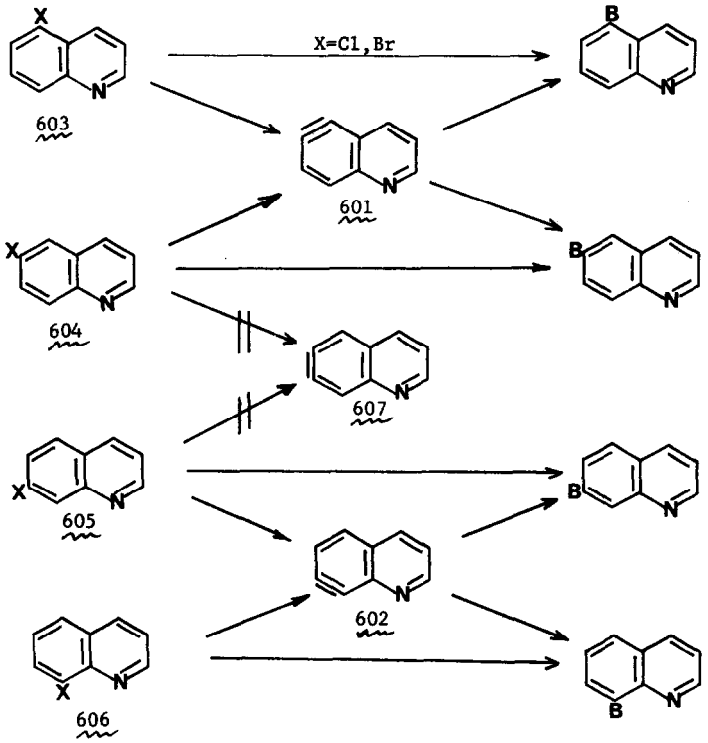

ratios of the substitution products **594** and **595** indicating competing AEn and AEa pathways.[428] With the more basic methoxide ion and the iodo compounds **592** and **593**, identical ratios of **594** and **595** are obtained indicating an EA-mechanism via the aryne **596**.[429] Apparently there have been no attempts to




rationally generate benzdidehydrothianaphthenes,[7] although both the 4,5- (**597**) and 5,6- (**598**) isomers have been speculated to be involved in the thermolysis of phthalic anhydride in the presence of thianaphthene[162] based only on mass spectral evidence.[430] The remaining carbocyclic aryne containing a fused five-membered heterocyclic ring, the didehydrocycloheptenone **599**, was proposed to explain the cine-substitution of the bromo compound **600**[431] but strictly by analogy to **578a** in which competing AEn and AEa mechanisms were rigorously excluded.[88]

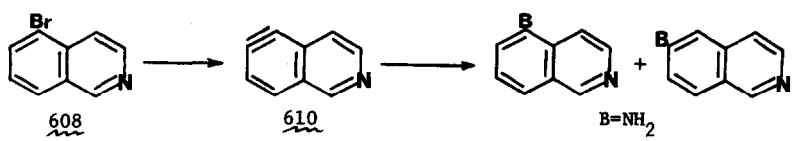



Among the carbocyclic arynes with a fused six-membered heterocyclic ring the 5,6- (**601**) and 7,8-didehydroquinolines (**602**) have been generated from the appropriate halides **603–606** with lithium dialkylamides.[10,252,432] No evidence for the 6,7-aryne **607** was obtained. The extent that substitution by an AEn mechanism competes with the EA mechanism increases with decreasing mass of the halogen[8,10] and decreasing bulk of the base[10] as expected.[77] Specific reaction conditions such as temperature[8] and concentration[252] also effect the proportion of each mechanism as does the location of the halogen (8-haloquinolines (**606**) give a higher proportion of AEn substitution.)[10,432] Competition studies[68,246,247,252] under pure EA conditions (as determined by the independence of product ratios from the nature of the

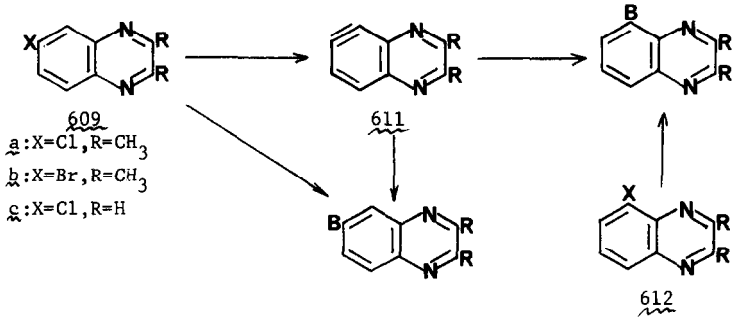



halogen atoms) reveal a greater selectivity of nucleophilic addition to the 5-position of **601** than to the 8-position of **602**. The rationale proposed for this observation is the greater steric interference to the incoming nucleophilie offered by the 4-hydrogen atom than by the nonbonded nitrogen electron pair.[252] It is noteworthy that the opposite rationale was invoked in the reaction of the 3,4-didehydro-1,5-napthyridines **532** and **532a** with $KNH_2$ (Section V. B.7(e)).[399]

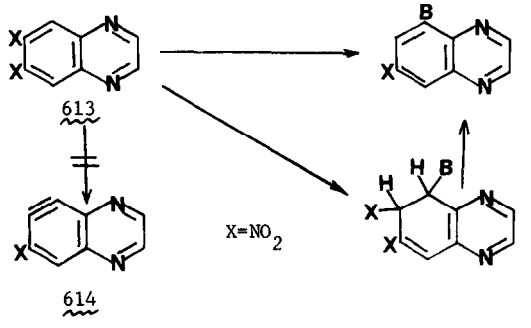
The observation of cine-amination with 5-bromisoquinoline **608**[433] and the 6-haloquinoxalines **609a**



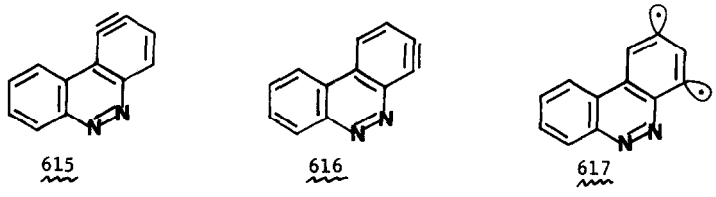
and **609b**[434] points to the intermediacy of the arynes **610** and **611** respectively. In the absence of the two methyl groups (i.e. **609c**) nonaryne side reactions take place,[435] and with lithium piperidide as a base either no reaction (**609c**) or only normal substitution (**609a**) is observed.[8] The 5-chloro compound **612** also



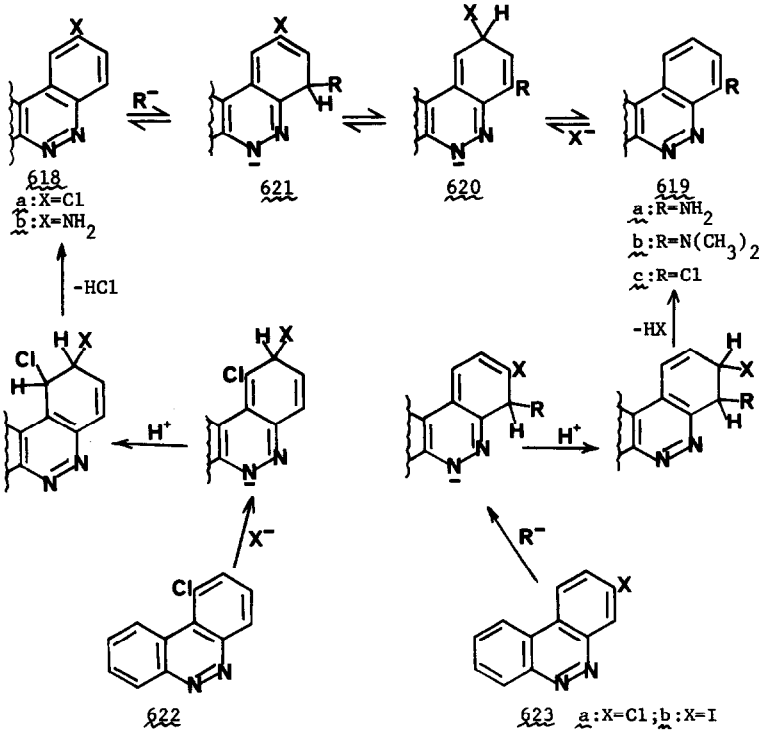

gives only normal substitution with this reagent.[8] Cine-substitution of the dinitroquinoxaline **613** by amines but not methoxide ion[52b] probably does not involve the aryne **614** which ought to be favored with the stronger base. The presence of the extra nitro group makes an AEa mechanism more likely.[52c]



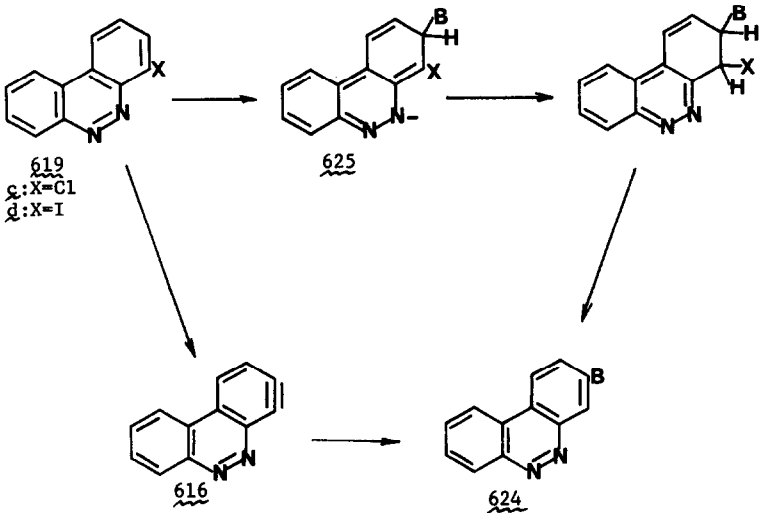

The reaction of halobenzocinnolines with $KNH_2$ gives normal, cine-, and tele-substitution products.[436] With lithium dimethylamide only tele-substitution and Chichibabin-type reactions as well as secondary transformations were observed.[437,438] The three didehydro intermediates **615–617** were postulated to be involved, although it was clear from the inconstancy of the product isomer ratios with varying halogens[436] and reaction conditions[438] that several mechanisms were in competition. One of these, an AEa mechamism with a proton shift (see Section. V. B.5), was suggested as an alternative




explanation to the meta aryne **617** for the tele-substitution reactions **618a—619a**[436] and **618a—619b**.[437,438] The same mechanism can be invoked in the reverse sense to explain the tele-substitution **619c→618b**.[436] The driving force for such a mechanism is the tendency of multicyclic diazines to add nucleophiles (Section V. B.8) and the stabilization of the negative charge on nitrogen for adducts at the 2-(**620**) and the 4-(**621**) position. These same factors should make an AEa mechanism (Sec. III. A.3) a valid alternative to




the arynes **615** and **616** as an explanation for the cine-substitutions **622**→**618b** and **623**→**619a**.[436] Although this possibility does not exclude the participation of arynes in these reactions, the EA mechanism seems most probable for the cine-substitution **619c, d**→**624** since the alternative AEa mechanism would require an intermediate sigma-adduct **625** which would disrupt the aromaticity of all three, rather than just two (**620, 621**) aromatic rings. This hypothesis is supported by the higher proportion of cine-substitution for the




iodo (**619d**) compared to the chloro(**619c**) compound[436] indicative of more reaction by an EA-pathway as expected.[77] A similar trend is *not* observed for the cine-substitution of the 3-halo compounds **623** in keeping with the AEa mechanism described above.

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