Reissert Compounds and Their Open-Chain Analogs in Organic Synthesis

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Reactions of major synthetic interest employing Reissert compounds (1,2-dihydro-1-acyl-2-cyanoquinolines and 1,2-dihydro-2-acyl-1-cyanoisoquinolines) and related heterocyclic species are surveyed. The chemistry of open-chain analogs of Reissert compounds (*i.e.*, derivatives of *N*-acyl-α-aminoacetonitriles) is described and compared with conventional Reissert compounds.

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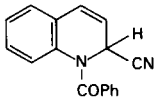
I. Introduction.

In 1905, while studying the benzoylation of cyclic tertiary amines, Arnold Reissert discovered that quinoline and benzoyl chloride reacted in the presence of aqueous potassium cyanide to form crystalline compound, 1,2-dihydro-1-benzoyl-2-cyanoquinoline, **1** [1]. It was soon discovered that isoquinoline gave an analogous compound under the same conditions, the product being 1,2-dihydro-2-benzoyl-1-cyanoisoquinoline, **2** [2]. Compounds **1** and **2** have come to be known as "Reissert compounds", and have been developed into useful intermediates for a variety of synthetic applications [3].



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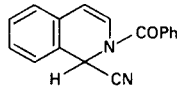

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The present review is concerned with providing synthetic chemists with a critical survey which may facilitate the application of Reissert compound chemistry in a variety of synthetic schemes. As a class, Reissert compounds are generally simple to prepare, easily handled, yet quite reactive when subjected to acidic or basic conditions. This review covers the literature through September 1982 [4]. Topics not covered by this article include reductions, photochemical reactions, and the Reissert-Henze procedure [5,6].

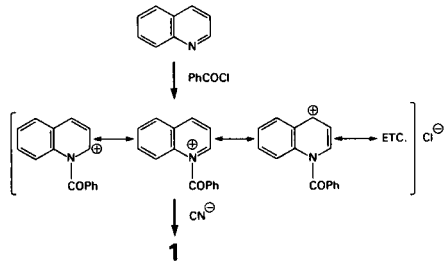
II. Preparation of Reissert Compounds.

Reissert compounds have been prepared in aqueous, non-aqueous, and mixed solvent systems.

Preparation in Aqueous Media.

In the original synthesis of 1,2-dihydro-1-benzoyl-2-cyanoquinoline, a nearly quantitative yield of the Reissert compound was obtained by the gradual addition of benzoyl chloride (2 equivalents) to a suspension of quinoline in aqueous potassium cyanide. A likely mechanism for the reaction involves the formation of benzoylquinolinium chloride as an intermediate, as proposed by McEwen and Cobb [3a]. Subsequent addition of cyanide ion occurs preferentially at the 2-position of the quinoline ring to afford **1** (Scheme 1).

SCHEME 1



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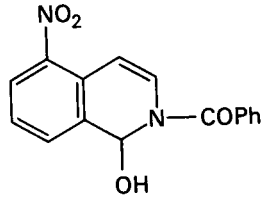
Although a variety of Reissert compounds has been synthesized by this method, it remains a method with several implicit drawbacks [7]. One shortcoming is the fact that both the starting quinoline and the product are insoluble in water, the product often being a gum. Another is the problem of hydrolysis for reactive acid halides; though this can be minimized by using cold, saturated aqueous potassium cyanide, and by adding the acid halide to the quinoline suspension dropwise. A third difficulty which may arise in the presence of water (or an alcohol) involves a competing reaction which results in the formation of a "pseudo-base" (such as **3**) in addition to or instead of the desired Reissert compound [8]. Thus, it has been found that yields of desired Reissert compounds can often be increased by changing to non-aqueous or mixed solvent systems.

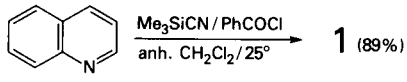


3 (ref. 8a)

Preparation in Non-Aqueous Media.

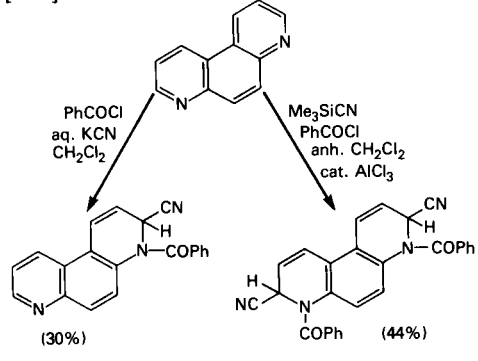
Since reactive acid halides may hydrolyze appreciably in the presence of water, non-aqueous media have been investigated as solvents for Reissert compound synthesis. The use of such solvents has met with varying degrees of success. For example, Woodward found that quinoline, benzoyl chloride, and potassium cyanide did not form **1** in such common organic solvents as acetonitrile, acetone, benzonitrile, chloroform, dioxane, and ether; although success was obtained with liquid sulfur dioxide [9].

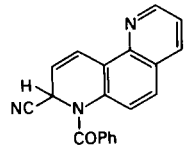
Probably the most general non-aqueous medium for Reissert compound synthesis remains the use of anhydrous benzene with anhydrous hydrogen cyanide [10]. This method may soon be surpassed, however, by a newer scheme employing trimethylsilyl cyanide in anhydrous methylene chloride [11]. For example:



It has been found that the addition of a catalytic amount of aluminum chloride often increases the yield of the desired product in this procedure [12].

The trimethylsilyl cyanide route to Reissert compounds may prove to be of value in the formation of Reissert compounds which are difficult to form by conventional means. For example, while 4,7-phenanthroline can be made to form a Reissert compound by conventional means, the use of trimethylsilyl cyanide affords a "di-Reissert compound", **4** [12b]. In a similar manner, a Reissert compound (**5**) derived from 1,7-phenanthroline can be synthesized in 39% yield by the use of trimethylsilyl cyanide, while none of the Reissert compound is formed in aqueous medium [12b].



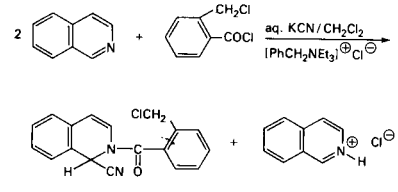


Silver cyanide, benzoyl chloride, and chloroform have been used to generate a Reissert compound from 1,6-naphthyridine [6b]; however, this method of Reissert compound synthesis may not be general [8g].

Preparation in Mixed-Solvent Systems.

For the formation of Reissert compounds involving acid halides of intermediate reactivity towards water, a mixed solvent system often provides the most convenient alternative [7]. Generally, the acid chloride is added (neat or in methylene chloride solution) to a mixture of the nitrogen heterocycle, methylene chloride, potassium cyanide and a minimal amount of water. This procedure has been used to synthesize a wide variety of Reissert compounds with good success, and has the advantage that all the reactants and products are soluble in one or the other solvent. A complication which occurs on occasion is formation of the pseudo-base, as mentioned earlier.

Phase-transfer catalysts have been used in the methylene chloride-water medium, and have been found to be helpful in increasing the yield of Reissert compound obtained [8e-g,13]. Catalytic amounts of benzyltrialkylammonium chloride are usually employed as phase transfer agent. It has been suggested that catalysis is due to an enhanced transfer of cyanide ion to the methylene chloride phase by the phase transfer agent [3c]. In a typical application, Tyrell and McEwen recently reported a yield enhancement of from 20% to 80% for compound **6** when a catalytic amount of benzyltriethylammonium chloride was added to the two-phase medium [13e]. The use of phase transfer catalysts may also help suppress pseudo-base formation [8f].



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A one phase, mixed solvent system employing dimethylformamide in water has been reported, but it has not been widely used, and would appear to have few if any advantages over the other methods of Reissert compound synthesis that have been developed.

III. Analogs of Reissert Compounds.

Reissert Compounds Derived from Heterocycles Other Than Quinoline and Isoquinoline.

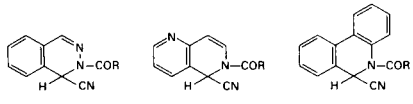
In a strict sense, the term "Reissert compound" applies only to those species derived from quinoline or isoquinoline (*i.e.*, 1,2-dihydro-1-acyl-2-cyanoquinoline and 1,2-dihydro-2-acyl-1-cyanoisoquinoline); although the term is generally applied today so as to include species derived

from a variety of heterocyclic bases. The characteristic features of Reissert compounds are: (a) a tertiary amide group in which the nitrogen is part of a heterocyclic ring, and (b) a hydrogen atom and a cyanide group bonded to a ring carbon atom adjacent to the ring nitrogen. Thus, a generalized Reissert compound can be represented as **7**.

7

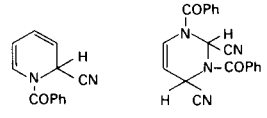
Although most of the early work with Reissert compounds involved the study of the quinoline derived species [3a,d], the study of isoquinoline Reissert compounds has been expanding steadily, primarily because of the pharmacologically useful nature of the isoquinoline alkaloids [14].

A particularly active field of research recently has been the study of the Reissert compounds derived from phthalazine (**8**), also of potential medical interest [8e,f,h,12a,15]. Reissert compounds have been formed from a variety of other heterocyclic nitrogen compounds including 1,7-phenanthroline (**5**), 4,6-phenanthroline, 4,7-phenanthroline, 1,6-naphthyridine (**9**), 1,7-naphthyridine, phenanthridine (**10**), ellipticine, and quinine [16].



8 **9** **10**

To date, Reissert compounds have not been synthesized from pyridine, acridine, and 1,10-phenanthroline. This situation may be remedied through improvements in Reissert compound synthesis. Popp and co-workers recently attempted to synthesize the elusive pyridine Reissert compound (**11**) through the use of trimethylsilyl cyanide, however this effort met with failure [12d]. They were, however, successful in synthesizing Reissert compounds from pyrimidine and 3-methylpyridazine (**12** and **13**, respectively) by this method. These represent the first monocyclic Reissert compounds which have been synthesized. An analog of the pyridine Reissert compound has been made wherein a carbethoxy group is present on the 1-position (**14**); however, the yield was low [17].



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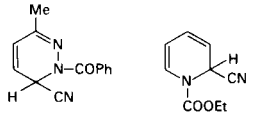
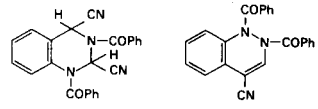
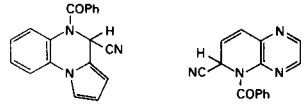


13 **14**

Recent attempts to form Reissert compounds from quinazoline and cinnoline have met with mixed success; quinazoline forming a di-Reissert compound, and cinnoline forming a cyano-diamide when treated with trimethylsilyl cyanide (**15** and **16** [12b]). Earlier attempts to form a Reissert compound from quinazoline had been entirely unsuccessful, with ring opening to give *N*-benzoylanthranilaldehyde being reported [8c]. Similarly, quinoxaline has been reported to give a ring opened product, 1,2-di(*N*-benzoylamino)benzene, rather than a Reissert compound [12b]. Yet, pyrrolo[1,2-*a*]quinoxaline does form a Reissert compound [13d], **17**, and pyrido[2,3-*b*]pyrazine reacts to form **18** [18].



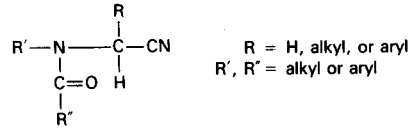
15 **16**



17 **18**

Open-Chain Analogs of Reissert Compounds.

Compounds which are related to Reissert compounds have been prepared in which the acylated nitrogen is not a member of a heterocyclic ring [19]. Such compounds are termed "open-chain Reissert analogs", and are represented by structure **19**.



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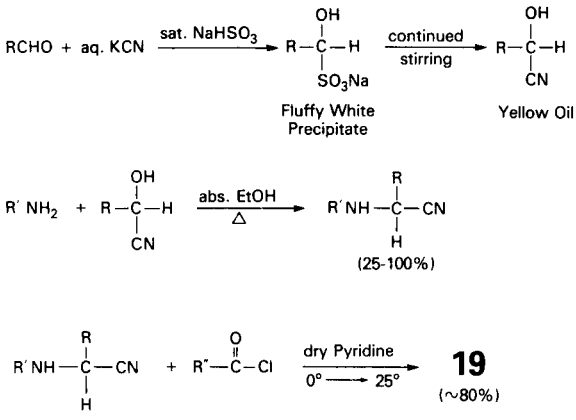
Open-chain Reissert analogs are readily available in good yields from inexpensive starting materials. Scheme 2 summarizes a general procedure for the synthesis of this class of compounds, which has been developed by McEwen and co-workers [19c]. The procedure involves condensation of a cyanohydrin with a primary amine to form an α-aminonitrile, which is then acylated in the presence of pyridine. For open-chain Reissert analogs with R = Phenyl, commercial mandelonitrile may be employed with good results [20]. Yields of the final acylation step may occasionally be improved by a change in reaction medium; for example, a satisfactory alternative appears to be to run the reaction in refluxing anhydrous benzene in the presence of one equivalent of triethylamine [21].

The reaction of benzoyl cyanide with Schiff bases (in anhydrous ether at room temperature) provides an alterna-

SCHEME 2

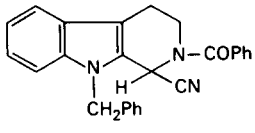


tive route to the synthesis of open-chain Reissert analogs. However, the generality of this procedure has not been fully determined [22]. Treatment of Schiff bases with benzoyl chloride and potassium cyanide (conditions used to synthesize Reissert compounds) results only in amide formation [22b]. However, when imines are allowed to react with sodium cyanide in glacial acetic acid, *in situ* hydrocyanation occurs which leads to the formation of the desired α-aminonitriles [23]. An open-chain Reissert analog has also been prepared from an isoquinoline Reissert compound (by treatment with hypochlorous acid), but this preparation was found to be unreproducible [24].

Open-chain Reissert analogs are generally stable, crystalline species which are easily purified [25]. Infrared spectra fail to show the presence of an absorption due to the cyano group (2200-2400 cm^{-1}); this is also the situation for Reissert compounds [3a]. In the proton nmr spectrum, the hydrogen atom present on the carbon which bears the cyano group appears in the aromatic region at approximately δ = 7.0.

Other Analogs of Reissert Compounds.

Analogs of Reissert compounds may be formed from dihydro heterocyclic precursors [26]. For example, the dihydro-β-carboline Reissert compound **20** [27] and the dihydroisoquinoline derived compound **21** [28] have recently been synthesized by use of trimethylsilyl cyanide. It is interesting to note that β-carboline itself failed to form a Reissert compound under a variety of conditions [29].



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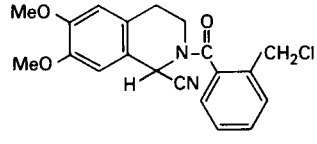

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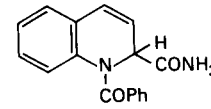

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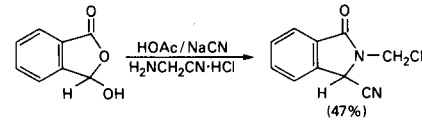
Compounds which are related to Reissert compounds have been prepared wherein both the cyano and acyl groups have been replaced by other moieties. Such changes in the structure of the molecule often alter the chemical properties. For example, when 1-benzoyl-1,2-dihydroquinaldamide (**22**) is treated with hydrochloric acid, the production of benzaldehyde is not observed; 1,2-dihydro-1-benzoyl-2-cyanoquinoline (**1**) is observed to yield benzaldehyde under identical conditions [30]. The cyano group has also been replaced by such groups as -COOH [31], -C≡C-Ph [32], -OH [8], -P(O)(OMe)$_2$ [33], and 3-indolyl [34]. Phosphonate analogs of Reissert compounds may prove useful in Wittig-Horner type olefinations [33].

Reissert analogs in which the acyl group has been replaced by alkyl and arylsulfonyl (-SO_2R, [35]), alkoxycarbonyl (-COOR, [15b,36]), and phenylbenzimidyl (-CPh=NPh, [37]) have been prepared and studied in some detail [3b,c]. Other similar analogs which have been synthesized include species with -CH_2OR [38], -C(O)NR_2 [8b], -P(O)(OR)$_2$ [13b,39], and -C(S)OR [40] groups bonded to the nitrogen atom of the heterocyclic ring. One interesting Reissert analog which has been recently prepared is 2-(cyanomethyl)-1,3-dihydro-3-oxo-1*H*-isoindole-1-carbonitrile (**23**), in which the heterocyclic nitrogen is bonded to an acyl moiety that is a member of the ring [41].



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In all, the literature contains a great number of compounds which can be thought of as being structurally related to Reissert compounds. However, the majority of these have been examined in limited detail with regard to chemistry. Thus, it might prove to be an unrealistic assumption that a given Reissert "analog" will behave in a reaction scheme in a similar manner to that expected for the true Reissert compound. In light of the above disclaimer, attention is now directed towards the synthetic utility of Reissert compounds [42].

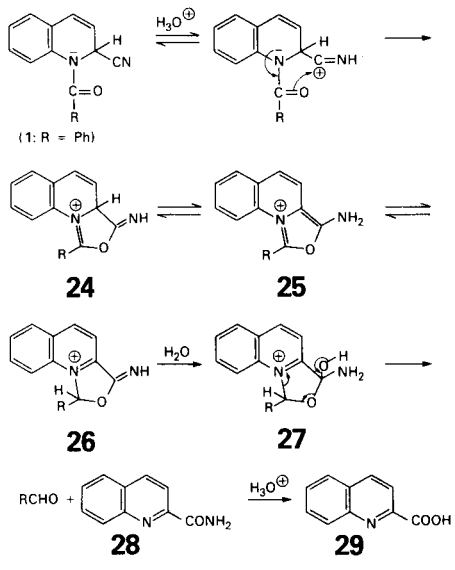
IV. Acid-Catalyzed Reactions of Reissert Compounds.

Synthesis of Aldehydes.

Acid-catalyzed hydrolysis of Reissert compounds to aldehydes, a procedure known as the "Reissert Aldehyde Synthesis", remains one of the best known synthetic uses

of these compounds [3a,b,43]. The hydrolysis was first observed by Reissert when he determined that treatment of 1,2-dihydro-1-benzoyl-2-cyanoquinoline with hydrochloric acid resulted in quantitative formation of benzaldehyde, along with various quinoline derivatives [1]. The mechanism of the hydrolysis, as proposed by McEwen and Cobb [3a], appears in Scheme 3.

SCHEME 3



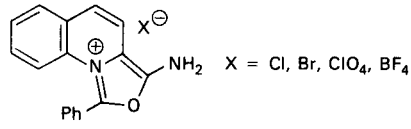
In this scheme, protonation of the cyano nitrogen is followed by intramolecular cyclization to form **24**, which is in tautomeric equilibrium with forms **25** and **26** (the predominant tautomer being **25** [44]). Addition of water across the carbon-nitrogen double bond to form **27** is then followed by a general base assisted ring opening to generate benzaldehyde (when R is phenyl) and quinaldamide **28**. The quinaldamide is isolated only in trace quantities, however, as most of it is further hydrolyzed under the reaction conditions to quinaldic acid (**29**).

Thus, the Reissert Aldehyde Synthesis achieves the conversion RCOCl → RCHO. As such, it represents an alternative to the more commonly used Rosenmund and lithium tri-*t*-butoxyaluminum hydride methods of reduction [45]. The use of deuterated hydrolytic media permits the synthesis of aldehydes which are deuterium labelled in the aldehyde group [46]. An advantage of the Reissert method is that it is specific for the acid halide group, so that other easily reducible groups present in the molecule remain unaffected.

Upon acid-catalyzed hydrolysis, open-chain Reissert analogs have been observed to form mainly carboxylic acids (by conventional amide hydrolysis) rather than aldehydes [19a-c]. It appears that for the aldehyde synthesis reaction to occur in high yield, it may be necessary for the nitrogen to be a member of a heterocyclic ring. Furthermore, since Reissert analogs derived from dihydro heterocyclic precursors also fail to form significant quantities of the desired aldehyde upon acid hydrolysis, it is possible that the re-aromatization step (**27**→**28**) as shown in Scheme 3 may provide the necessary driving force for the formation of RCHO [3a,b].

Reactions of Reissert Salts.

When Reissert compounds are treated with a suitable acid, it is frequently possible to isolate "Reissert salts" [15f,43d,44,47]. These salts form by way of the same cyclization which was postulated for the mechanism of the Reissert Aldehyde Synthesis (*i.e.*, **24-26**). A variety of acids has been used to form the Reissert salts; these can be generalized by structure **30** (derived from **1**). This is believed to be the predominant tautomer, and its "*cis*-diene" configuration plays a role in the synthetic utility of these salts.



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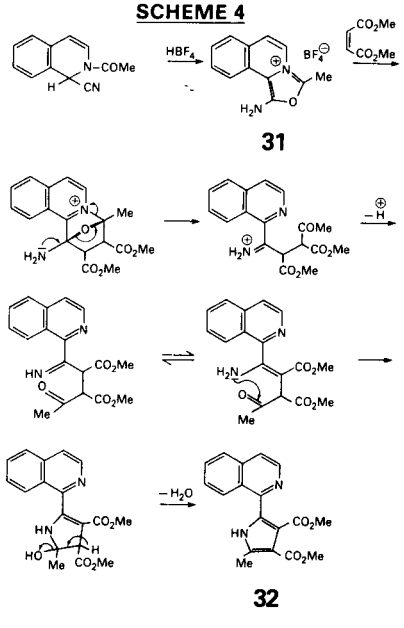
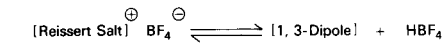
In particular, it has been found that Reissert salts will react with a variety of alkenes to form products which can be regarded as having been formed from an initial Diels-Alder type cycloaddition reaction [47k,l]. For example, the hydrofluoroborate salt of 1,2-dihydro-2-acetyl-1-cyanoisoquinoline (**31**) was condensed with dimethylmaleate to form a substituted pyrrole (**32**) in 76% yield [47i]. The presumed mechanism appears in Scheme 4.

SCHEME 4

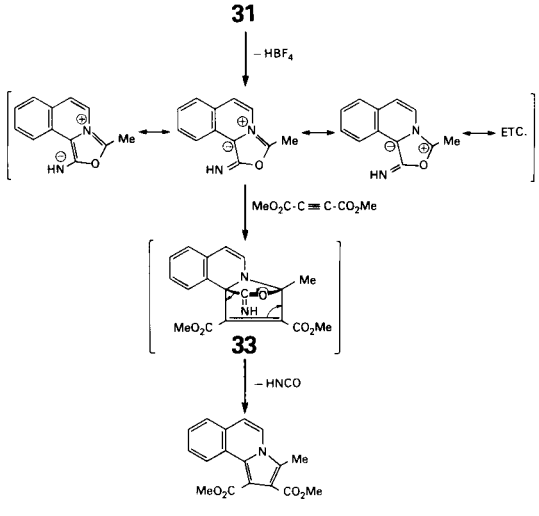


Reissert salts can also be made to undergo cycloaddition with alkynes, with the product being a pyrrolo-fused heterocycle. The postulated mechanism involves a mesoionic 1,3-dipolar compound, which is formed by deprotonation of the Reissert salt [47i,k]. Presumably an equilibrium exists between the 1,3-dipolar compound and the Reissert salt:



Thus, heating a mixture of 1,2-dihydro-2-acetyl-1-cyanoisoquinoline hydrofluoroborate (**31**) and dimethyl acetylenedicarboxylate in anhydrous dimethylformamide resulted in the formation of 3-methylpyrrolo[2,1-*a*]isoquinoline in 64% yield [47i]. The mechanism appears to involve the formation of a bridged intermediate (**33**), which can then lose isocyanic acid by a retro Diels-Alder reaction (Scheme 5). Through careful control of reaction conditions, it is possible to isolate the bridged intermediate in certain instances [47c,e].

SCHEME 5

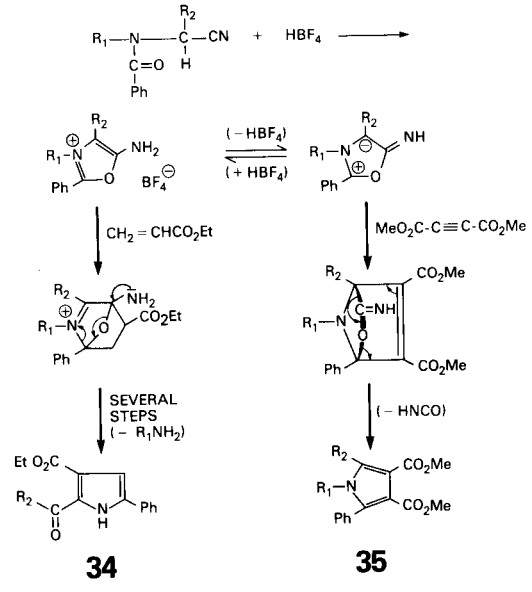


Kinetic rate and orientation data for condensation reactions of Reissert hydrofluoroborate salts with various alkenes and alkynes have indicated that these reactions may be better understood if the cycloadditions are regarded as occurring in stepwise fashion through merostabilized biradicaloid intermediates, rather than through the more conventional concerted cycloaddition mechanism [47l].

It has been found that certain Reissert analogs may also undergo acid-catalyzed intramolecular cyclization to form related salts. For example, the hydrofluoroborate salt of 1,2-dihydro-2-benzoyl-1-cyanophthalazine has been prepared, and has been made to react with alkenes and alkynes (the products are 2-(1-phthalazyl)pyrroles and pyrrolo[2,1-*a*]phthalazines, respectively [15f,47l]). Similarly, the hydrochloride salts of the pyridazine and 3-methylpyridazine Reissert analogs have been formed [12d].

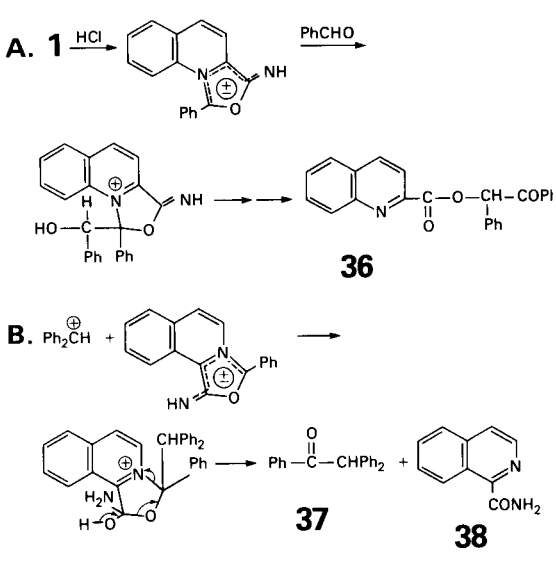
McEwen and co-workers have shown that open-chain Reissert analogs give isolable salts with hydrofluoroboric acid [19c,48,49]. These salts were made to condense with ethyl acrylate and dimethyl acetylenedicarboxylate to form products resulting from Diels-Alder and 1,3-dipolar cycloadditions, **34** and **35**, respectively (Scheme 6). It appears that chemistry involved in the condensation of Reissert analog salts with alkenes and alkynes parallels that observed with the quinoline and isoquinoline derived Reissert salts.

SCHEME 6



The condensation of Reissert salts with carbocations has been demonstrated [50]. The proposed mechanisms involve addition of the positive species to one of the charge-

SCHEME 7

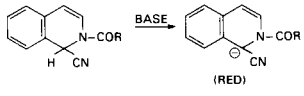


bearing positions in the 1,3-dipolar Reissert compound. Thus, when 1,2-dihydro-1-benzoyl-2-cyanoquinoline (**1**) was treated with benzaldehyde in the presence of hydrochloric acid, **36** was produced (Scheme 7A). Similarly, the benzhydryl cation has been made to react with the 1,3-dipolar compound derived from **2** to form **37** and **38** (Scheme 7B [51]).

V. Base-Catalyzed Reactions of Reissert Compounds.

Formation of the "Reissert Anion".

Treatment of a Reissert compound with a suitable base results in the formation of the highly colored "Reissert anion", **39**.

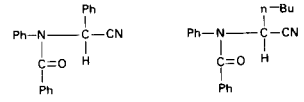


39

The anion is most conveniently prepared through the use of sodium hydride in dimethylformamide or tetrahydrofuran [3b, 52]. Other bases which have been used include phenyllithium, Grignard reagents, metallic sodium, lithium diisopropylamide, sodium amide, and even aqueous sodium or potassium hydroxide (with a phase transfer catalyst). A wide variety of organic solvents has been employed as the medium for the reaction.

The apparent ease of deprotonation of Reissert compounds is a reflection of the stability of the conjugate base. Thus, for **39**, the negative charge is stabilized through resonance with the cyano group and with the heterocyclic ring.

In a similar manner, analogs of Reissert compounds may be converted to their conjugate bases upon treatment with strong base. Thus, while open-chain Reissert analog **40** can be readily deprotonated at room temperature with sodium hydride in dimethylformamide, **41** cannot be converted to its conjugate base under identical conditions [19c,53]. The loss in resonance stabilization of the resulting anion which occurs when the phenyl ring is replaced with an alkyl group (*n*-butyl) renders the proton of interest less acidic. A stronger base, lithium diisopropylamide, will effect the deprotonation of **41**. An analogous situation exists for Reissert analogs derived from dihydro heterocyclic precursors, which are less acidic than their "normal" counterparts [26d].



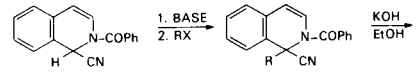
40 **41**

Once prepared, Reissert anions are reactive species which can be used in a variety of synthetic schemes. Four categories of Reissert anion reactions have received the greatest attention:

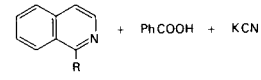
a. Alkylation
b. Condensation with Aldehydes and Ketones
c. Rearrangement Reactions
d. Conjugate Addition Reactions

Base-Catalyzed Alkylation of Reissert Compounds.

The reactions of Reissert anions with alkyl halides have provided a useful method for synthesizing 1-alkylisoquinolines and 4-alkylquinolines. In this two-step procedure, a typical Reissert anion is first alkylated to form **42** (which can be isolated), which is subsequently hydrolyzed under basic conditions to form **43** [3,54].



42



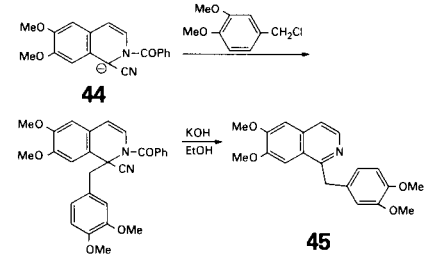
43

The use of crown ether and phase transfer catalysis of the alkylation step has proven fruitful in cases where hydroxide ion was employed as the base [13a,55]. In addition to hot ethanolic potassium hydroxide treatment for the hydrolysis of **42**, such systems as sodium methoxide-methanol [56], sodium borohydride-ethanol [57], and Triton B-dimethylformamide [58] have been used successfully.

It has been suggested that the driving force for the hydrolysis step may be the aromatization of the heterocyclic ring [59].

The principal application of the base-catalyzed alkylation reaction of Reissert compounds (with subsequent hydrolysis) has been in the area of natural product synthesis. Several isoquinoline alkaloids have been synthesized in this way [3b,c,14,56,58,60]. For example, Popp and McEwen alkylated a Reissert compound (**44**) and then hydrolyzed the adduct formed to afford papaverine (**45**) in 22% overall yield (Scheme 8 [10a]).

SCHEME 8



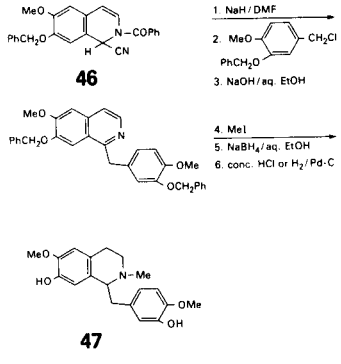
44 **45**

Using an analogous scheme, 3-azapapaverine has been synthesized from 6,7-dimethoxyphthalazine [15d].

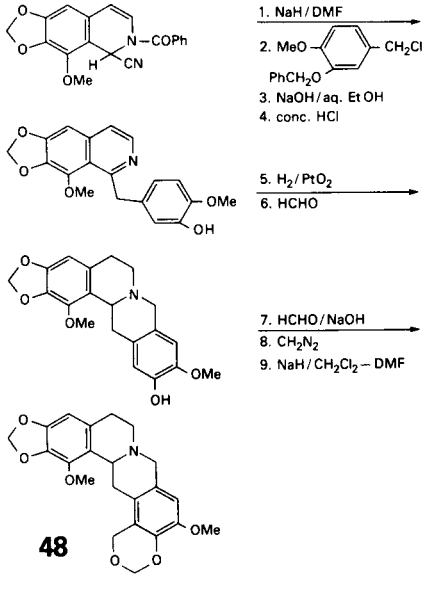
Kerekes and co-workers have used the alkylation of the

Reissert anion resulting from **46** as a route to (±)-reticuline (**47**), an important intermediate in the biosynthesis of isoquinoline alkaloids (Scheme 9 [60e]). Similarly, (±)-mecambridine (**48**) has been produced by a path which implicates a key Mannich reaction in the formation of the tetracyclic skeleton (Scheme 10 [60f]).

SCHEME 9

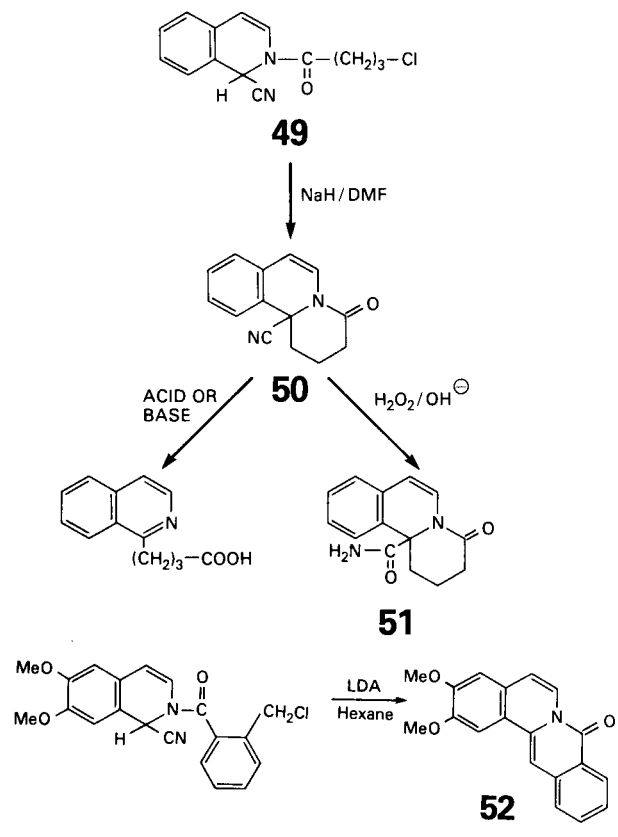


SCHEME 10

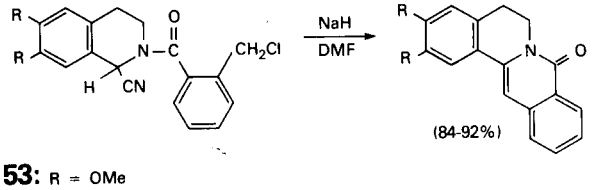


Suitably substituted Reissert compounds have been made to undergo intramolecular alkylation and cyclization upon treatment with strong base. Thus, treatment of **49** with sodium hydride affords **50**. This can subsequently be converted into either 4-(1-isoquinolyl)butyric acid or an amide, **51** [61].

Intramolecular alkylation of Reissert compounds has provided a useful route to analogs of berbine and berberine [12c,13e,27,28]. Tyrell and McEwen were able to synthesize 2,3-dimethoxy-5,6,13,14-didehydro-8-oxoberbine (**52**) in 74% yield by treating the appropriate Reissert compound with lithium diisopropylamide in hexane [13e].



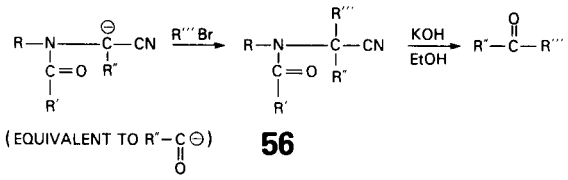
Ruchirawat and co-workers accomplished fundamentally the same transformation, but were able to use the sodium hydride in dimethylformamide system to effect the cyclization with partially reduced Reissert compounds **53-55** [20].



53: R = OMe
54: R = H
55: R = $-OCH_2O-$

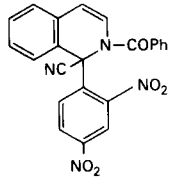
The alkylation of Reissert anions derived from heterocycles other than quinoline and isoquinoline has been amply demonstrated [62], and dihydro Reissert compounds have been alkylated [63]. Some examples of dialkylation have appeared, wherein an active dihalide has been alkylated by two Reissert anions simultaneously [64]. Reissert anions have also been allowed to react with polymers containing pendant benzylic halide groups, and the expected alkylation was observed to occur [65].

Open-chain Reissert analogs may be alkylated *via* their conjugate bases to yield intermediates (**56**) which, when subjected to basic hydrolysis conditions, afford ketones [19c,53,66,67]. In this way, the open-chain Reissert anion serves as an acyl anion equivalent.



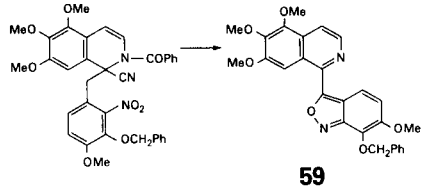
56

Base-catalyzed arylation of isoquinoline Reissert compounds has been accomplished with activated aryl halides [3c]. For example, Piccirilli and Popp discovered that treatment of **39** (R = Ph) with 2,4-dinitrofluorobenzene resulted in the formation of the arylation product **57** [68]. Similarly, alkylation of **39** with *p*-chloronitrobenzene was found to afford 1-(*p*-nitrophenyl)isoquinoline after alkaline hydrolysis [13a,69]. Arylation of a quinoline Reissert compound with 4-nitrofluorobenzene was found to give a product derived from attack at the 4-position of the quinoline ring [68]. Thus, it would appear that the regioselectivities of arylation and alkylation are similar for quinoline Reissert anions.



57

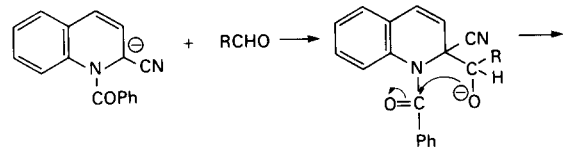
When a Reissert compound is alkylated with an *o*-nitro substituted benzyl halide, the product of what is formally an arylation can be isolated after alkaline hydrolysis [70]. Thus, **59** was formed from **58** upon treatment with ethanolic potassium hydroxide [58].



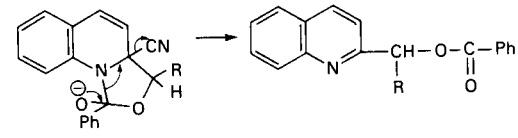
58 59

Base-Catalyzed Reactions of Reissert Compounds With Aldehydes and Ketones.

The condensation of the Reissert anion with aldehydes results in the formation of esters of secondary alcohols (*e.g.*, **62**), in which the carboxylate carbonyl group in the ester is derived from the carbonyl group of the amide of the original Reissert compound [3b]. The presumed mechanism (starting with the conjugate base of **1**) involves an initial condensation of the Reissert anion with the carbonyl of the aldehyde to form an alkoxide intermediate (**60**). The charge-bearing oxygen is now conveniently positioned to attack the amide group, forming a five-membered ring in the process (**61**). Decomposition of **61** occurs with regeneration of the quinoline ring and expulsion of cyanide ion, forming **62** as the product [71].



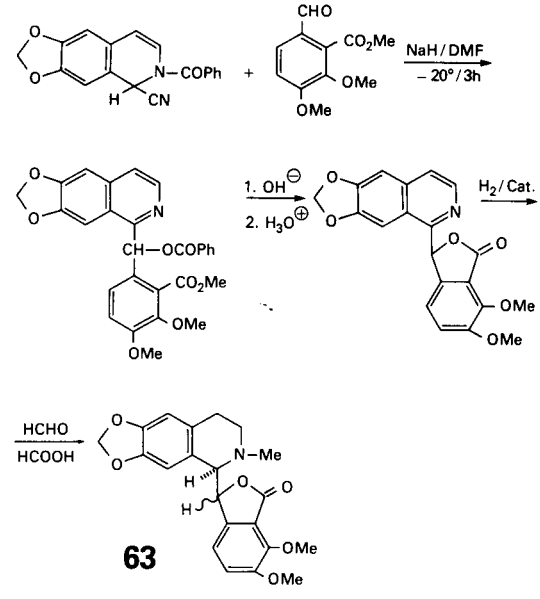
60



61 62

This reaction has been observed to occur for both aliphatic and aromatic aldehyes [72], and has been conducted with Reissert analogs (*e.g.*, the phthalazine Reissert compound [15b,73]). The reaction of the Reissert anion with aldehydes has been employed in the synthesis of a number of natural products [3c]. The recent synthesis of (±)-hydrastine (**63**) by Kerekes and co-workers is illustrative (Scheme 11 [74]).

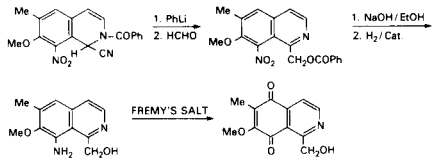
SCHEME 11



63

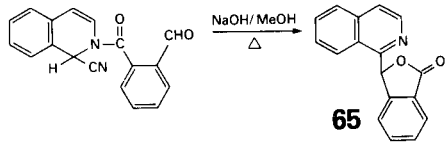
Another example of the utility of this procedure in the synthesis of natural products is provided by a recent synthesis of renierone (**64**), an antimicrobial metabolite isolated from a marine sponge (Scheme 12 [75]).

SCHEME 12



64

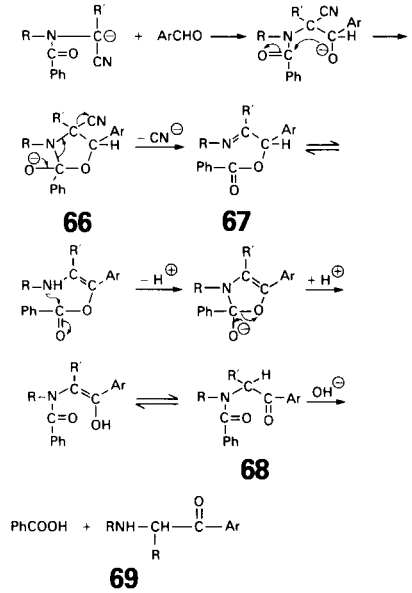
Condensation of the Reissert anion with an aldehyde can occur in an intramolecular sense. Phthalideisoquinoline **65** has been synthesized in 58% yield *via* an intramolecular condensation scheme which employed hydroxide as the base catalyst [13e].



65

Open-chain Reissert analogs have been made to condense with aromatic aldehydes, with α-anilinoketones being isolated after basic hydrolysis [19c,76]. The presumed mechanism for the reaction is similar in its initial stages to that accepted for heterocyclic Reissert compounds. Thus, condensation of an open-chain Reissert anion with an aldehyde leads to the formation, after ring closure, of an unstable five-membered ring (**66**), which decomposes with loss of cyanide ion to form a benzoate ester (**67**). From this stage, a prototropic shift and an N→O acyl migration now occur, with the result that the ketoamide **68** is formed. Some the ketoamide has been isolated from the reaction mixture; however, further hydrolysis to the α-anilinoketone (**69**) eventually occurs under the basic conditions (Scheme 13).

SCHEME 13

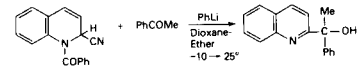


66 **67**

68

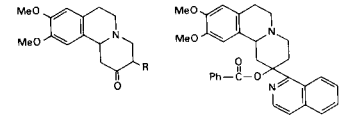
69

The reaction of the Reissert anion with ketones appears to be of more limited value [3b,c]. Unfavorable steric and electronic factors have been blamed for the lack of reactivity of ketones (relative to aldehydes [77]). Thus, Walters, Iyer and McEwen reported that acetophenone reacted with the anion of **1** to form a tertiary alcohol (**70**) in but 31% yield. No product was obtained when acetophenone (or any other ketone tested) was allowed to react with the Reissert anion of **2**. It is interesting to note that the product **70** results from attack at the 2-position on the ring, while alkylation and arylation of the anion of **1** usually occur at the 4-position [59].



1 **70**

Recently, phase transfer catalysis has been applied to the reaction of ketones with isoquinoline Reissert anions with some success [3c]. A variety of *N*-substituted piperidones and isatin have been made to react with isoquinoline Reissert anions which were formed in sodium hydride-dimethylformamide medium; the expected esters were generally produced [78]. However, the process is quite sensitive to steric factors. Thus, while ketone **71** was observed to form benzoate **73** [78c], the related ketone **72** did not undergo reaction with the anion of **2** [78b].

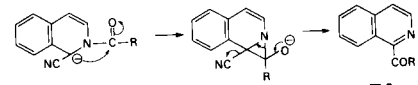


71: R = H
72: R = Et

73

Base-Catalyzed Rearrangements of Reissert Compounds.

If a Reissert anion is generated in the absence of a suitable electrophile, that anion may undergo an intramolecular rearrangement with loss of cyanide ion to form a 1-acyl-isoquinoline or a 2-acyl-quinoline [1,13c,d,47h,52a, 59,60a,b,78b,79]. The presumed mechanism (implied by ^{14}C-labelling studies) is [3a]:

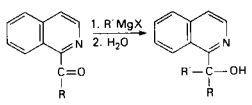


74

Formation of **74** is conveniently accomplished by using sodium hydride in dimethylformamide at room temperature, or in refluxing toluene [3b]. This reaction occurs most readily at elevated temperatures, and can be a principal reaction pathway if condensation of a Reissert anion with a sluggish electrophile is attempted.

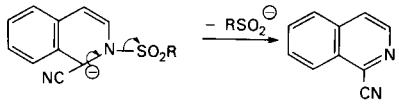
If a Grignard reagent is used to generate the Reissert anion, tertiary alcohols are formed as the principal pro-

duct [3a]. The rearrangement of **2** in phenyllithium has also been reported to give a tertiary alcohol [80]. The product is most likely formed by attack of the organometallic species upon the ketone group in **74** to give **75**.



74 **75**

In the case of *N*-alkyl- or arylsulfonylisoquinoline Reissert analogs, the attempted rearrangement of the Reissert anion is thwarted by a competing elimination to form isoquinaldonitrile (**76**).

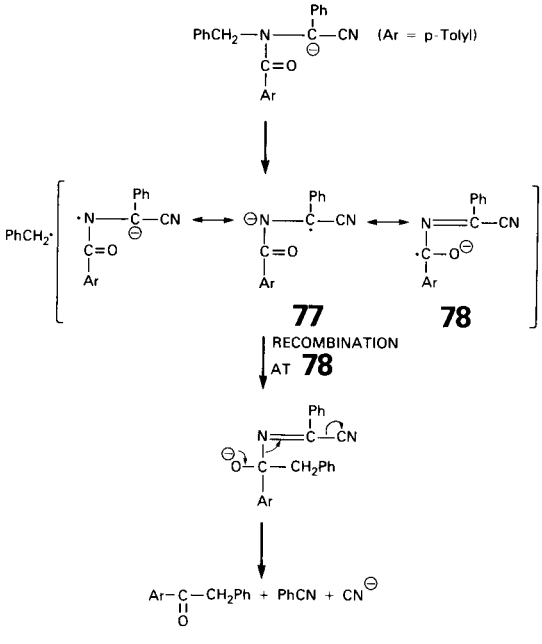


76

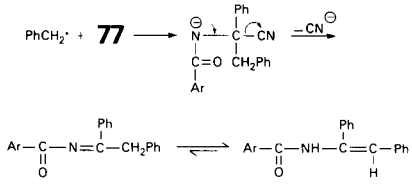
Base-catalyzed rearrangement of isoquinoline Reissert compound chlorohydrins has been examined; treatment with triethylamine in dioxane affords isochromenes [24,81].

Open-chain Reissert analogs derived from benzylamine have been found to undergo a facile Stevens-type rearrangement to form desoxybenzoins and benzonitriles as the major products [19d,76]. This reaction has been observed to occur in sodium hydride-tetrahydrofuran medium, and proceeds unabated even when a suitable electrophile (*i.e.*, an aldehyde) is present. A radical mechanism has been invoked, based on several lines of evidence [19d]. The major reaction pathway is as follows (Scheme 14):

SCHEME 14



A competing radical recombination pathway (recombination at **77** rather than **78**) affords α-benzamidostilbenes (**79**), the principal side product.

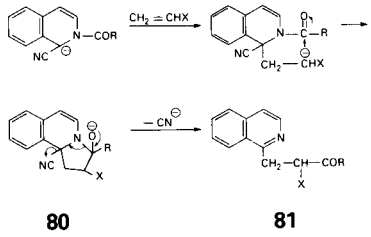


79

For open-chain Reissert analogs derived from benzhydrylamine, the formation of the stilbene-type product is the principal radical recombination pathway [82].

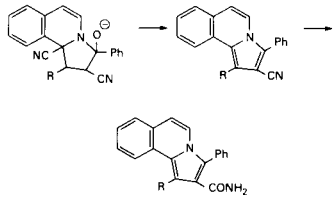
Base-Catalyzed Conjugate Addition Reactions of Reissert Compounds.

Reissert anions react with unsaturated electrophiles (of the type CH_2=CHX, where X is an electron-withdrawing group) to give Michael-type addition products [3a,c]. A generalized scheme for these reactions appears below:



80 **81**

In this manner, **39** has been added to 2-vinylpyridine, 4-vinylpyridine, ethyl acrylate, ethyl cinnamate, and substituted cinnamates to give products of type **81** [47d-f,83]. In contrast, the reaction of **39** (R = Ph) with acrylonitrile has been found to result in the formation of 3-phenyl-2-formamido-7,8-benzopyrrocoline (**82**) in 76% yield [3a,15c, 26c,79e,83]. The formation of **82** represents an alternative pathway of decomposition for the intermediate **80**.



82: R = H
83: R = Ph

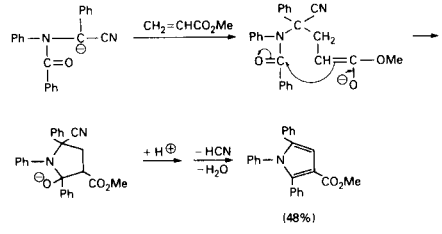
The reaction of **39** with cinnamonitrile also results in a pyrrolo-fused isoquinoline product, **83** [47e,f]. However, reaction of **39** with dimethyl acetylenedicarboxylate gives a product related to **81** [47e].

Although base-catalyzed conjugate addition reactions of quinoline Reissert compounds have received little attention in the literature, it may be possible to form products analogous to those produced *via* **39** [79e]. Phthalazine Re-

issert compounds have been reported to add to acrylonitrile under basic conditions to give pyrrolo-fused products similar to **82** [15c].

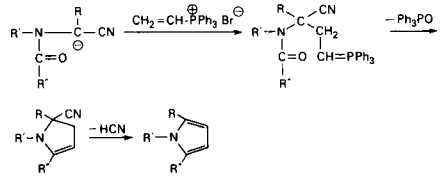
The anion of an open-chain Reissert analog has been added to methyl acrylate to form a substituted pyrrole [19c,66]. For example (Scheme 15):

SCHEME 15



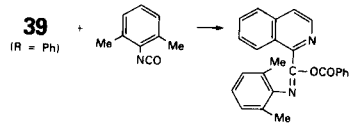
Open-chain Reissert anions react readily with vinyltriphenylphosphonium bromide (Schweizer's reagent) to form 1,2,5-trisubstituted pyrroles in high yields (Scheme 16 [84]). This reaction represents the first known example of a Wittig reaction occurring in an intramolecular sense on the carbonyl group of a tertiary amide [85]. The reaction is general for a variety of open-chain Reissert analogs; however, best results are obtained when the amide functionality is derived from aromatic acid halides rather than aliphatic [86]. Intramolecular attack upon the carbonyl group of the amide is seen to occur exclusively even when the Wittig reagent is generated in the presence of an aldehyde [86]. Attempts to generate 3-phenylpyrrolo[2,1-*a*]isoquinoline by a similar reaction employing **39** (R = Ph) have been unsuccessful [84,86].

SCHEME 16

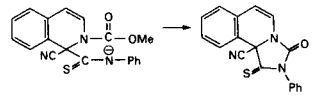


Base-Catalyzed Reactions of Reissert Compounds With Other Electrophiles.

Reissert anions have been made to react with other electrophiles with varying degrees of success [3b]. For example, isocyanates react with the conjugate base of **2** but not with the anion of **1** [87]. Giridhar and McEwen used this reaction in the preparation of lidocaine-type local anesthetics [88].

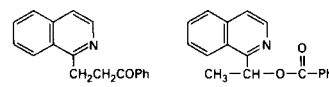


Reaction of isothiocyanates with *N*-methoxycarbonyl Reissert analogs occurs in a different manner; regioselectivity is reversed as the nitrogen atom of the isocyanate (not the sulfur) acts as nucleophile during intramolecular attack upon the *N*-methoxycarbonyl moiety [89]. Compound **84** is isolated as product when phenyl isothiocyanate is used.



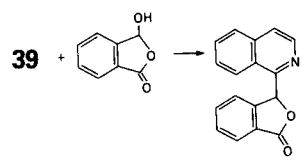
84

Reaction of **39** with lactones has been examined, and also gives varying results. Thus, while **39** (R = Ph) reacts with β-propiolactone to give β-(1-isoquinolyl)ethyl phenyl ketone (**85**), reaction with β-butyrolactone gives methyl-1-isoquinolyl carbinyl benzoate (**86**), and γ-lactones fail to react altogether [90].



85 **86**

Hung and co-workers found that reaction of **39** with a hydroxy lactone (phthalaldehydic acid) occurs in good yield under phase transfer conditions so as to form 1-(3-phthalidyl)isoquinolines (**87**), compounds of medicinal interest [79f].



87

Base-catalyzed reactions of Reissert compounds with carbon disulfide and epoxides have been attempted, but appear to be of little synthetic importance [3b,91].

Reissert compounds have been shown to undergo autoxidation in basic solution [92]. For this reason, it is advisable to conduct most base-catalyzed reactions of Reissert compounds under an inert atmosphere. The products of the oxidation of **1** and **2** are quinaldonitrile and isoquinaldonitrile, respectively. Reissert analogs derived from 3,4-dihydroisoquinoline are readily oxidized to dihydroisocarbostyrils; however, dihydroquinoline Reissert analogs appear to be stable to such oxidation [92c].

VI. Summary.

Since the first review of Reissert compound chemistry appeared in 1955 [3a], over 300 papers have been published in this area. With the advent of new synthetic reagents and of new approaches to using this class of compounds, it

should prove possible to develop more efficient synthetic pathways to a variety of alkaloids and other natural products. Clearly, the continued study of the chemistry of analogs of Reissert compounds will prove useful in the development of analogs of known biologically active molecules. It is hoped that this survey of the chemistry of Reissert compounds and related species has succeeded in its goal of provoking the imagination of the synthetic chemist.

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