

RING ANNELATIONS VIA REISSERT COMPOUNDS

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Abstract - Conversion of isoquinoline and related heterocycles to the corresponding Reissert compound provides a starting point for the annelation of an additional ring. This has proved an attractive route to a wide range of ring systems. The review discusses the versatility of such procedures which include cycloaddition of cyclic Reissert salts with alkynes, addition of Reissert compound conjugate bases to suitable Michael acceptors, intramolecular cyclisations of Reissert compounds derived from chloroalkyl-substituted acid chlorides, the reaction of conjugate bases of chloroformate derived Reissert compound analogs with suitable electrophiles including heterocumulenes, and other methods. Annelations are exemplified with a variety of heterocycles in addition to isoquinoline and quinoline, including phthalazine, phenanthridine and 3,4-dihydro- β -carboline.

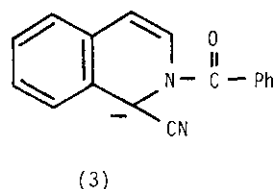
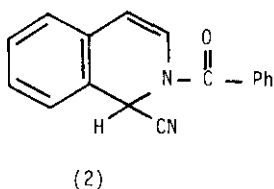
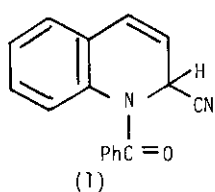
In 1905 Reissert reported¹ the formation of 1-benzoyl-1,2-dihydroquinolone nitrile (1) from the reaction of benzoyl chloride with quinoline in aqueous potassium cyanide solution. Such compounds, derived from the reaction of aromatic nitrogen heterocyclic compounds, cyanide and acyl halides have been designated as Reissert compounds and have been the subject of a number of comprehensive reviews²⁻⁵ as well as some more specialized reviews.⁶⁻¹⁰ After a brief introduction to Reissert compound chemistry, this review concentrates on the application of Reissert compounds to ring annelation reactions of the parent heterocycle.

Reissert compounds have been prepared from quinolines,^{2-5, 9} isoquinolines,^{2-5, 10} phenanthridines,^{2,11} phthalazine,^{3,4,7} several naphthyridines,^{4,7} several of the phenanthrolines,^{3,4,7} [1]-benzothieno[2,3-d]pyridazine,^{4,7} thieno[2,3-c]pyridine,¹² quinazoline,^{7,13,14} cinnoline,⁷ ellipticine,^{4,7} 3,4-dihydro- β -carboline,¹⁵ pyrimidine,¹⁶ pyridazine,¹⁶ pyrrolo[1,2-a]quinoxaline¹⁷ and pyrido[2,3-b]pyrazine.¹⁸ The chemistry of Reissert compounds is thus applicable to a wide variety of heterocyclic bases. Analogs of Reissert compounds have also been prepared when the

acyl halide is replaced by sulphonyl halides,^{2,3} N-phenylbenzimidyl chloride,² carbamoyl chlorides,^{2,3} chloroformates^{2,3} and dialkylphosphates.^{2,3}

The most general and most frequently used method of Reissert compound formation involves adding the acyl halide, neat or in methylene chloride to a mixture of the heterocyclic compound in methylene chloride and potassium cyanide in a minimum of water.^{2,3,19} In cases where competition with pseudo base formation is a problem a phase transfer agent³ or crown ether²⁰ is used. The use of trimethylsilyl cyanide as the cyanide source has been reported.²¹ Generally this reagent offers no advantage with quinolines and isoquinoline, but it appears to be essential for positive results with many of the diaza systems.⁷

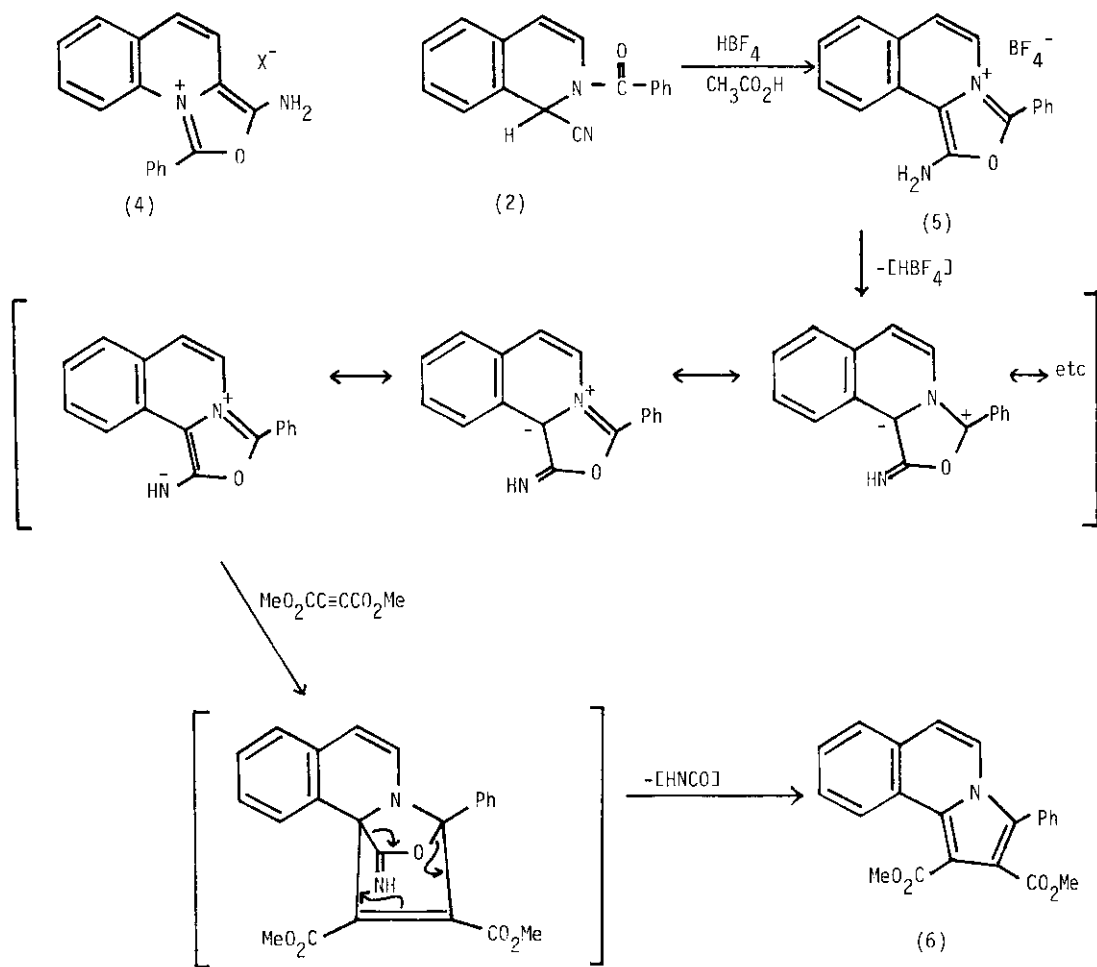
Early interest in Reissert compounds as synthetic tools centered on the acid-catalysed hydrolysis to aldehydes and a heterocyclic carboxylic acid.¹ This is in fact a useful route for the conversion of a carboxylic acid, via its acid chloride and then Reissert compound, to an aldehyde. Through actual isolation of the so-called "Reissert salt" McEwen's group has extended this area of Reissert compound chemistry and examples will be cited later in this review. Treatment of a Reissert compound, with a base, preferably sodium hydride in dimethylformamide gives rise to the carbanion, for example (3), generated from (2).¹⁻³ The Reissert anion has proven to be a very valuable synthetic intermediate. A major area of this usefulness has been in the synthesis of many of the isoquinoline alkaloids and related compounds.⁶ Many examples of reactions of these Reissert anions are cited later in this review.



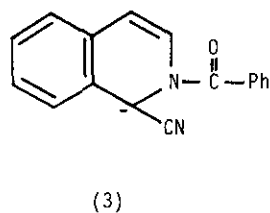
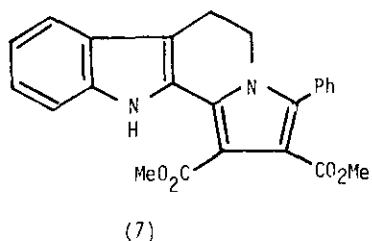
Perhaps the first example of ring annelation goes back to Reissert's original observation¹ that (1) gave benzaldehyde on acid-catalyzed hydrolysis. The mechanism of this reaction as proposed by McEwen and Cobb^{2,22} requires an interaction of the cyano and carbonyl groups to give a cyclic intermediate. It is frequently possible to isolate and study the chemistry of these cyclic Reissert salts^{3,4,11,15,16,23-38} and a variety of acids have been used to generate the Reissert salt although the fluoroborate counterion is the one most frequently encountered. These salts, which have been studied largely by McEwen and coworkers, can be exemplified by the aminooxazolo[3,4-a]quinolinium salt (4)³² derived from (1). In addition to quinoline and isoquinoline such salts have been obtained from phthalazine,^{35,37} ellipticine,³⁸ pyridazine,¹⁶

phenanthridine,¹¹ and 3,4-dihydro- β -carboline.¹⁵

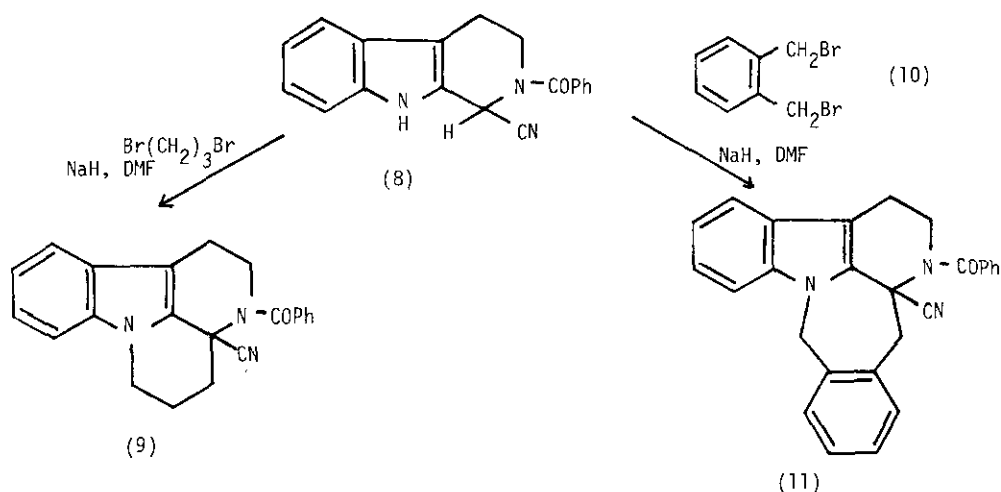
Not only are these Reissert salts themselves ring annelation products of quinoline and the other heterocyclic bases noted but they are, as demonstrated by McEwen and coworkers, valuable intermediates in the formation of other cyclic structures. The Reissert salts undergo cycloaddition reactions with alkynes to yield a pyrrolo-fused heterocycle. The proposed mechanism^{33,36-7} involves a mesoionic 1,3-dipolar compound which is formed by deprotonation of the Reissert salt as shown in Scheme I for the reaction of the oxazolo[4,3-*a*]isoquinolinium fluoroborate salt (5) of the isoquinoline Reissert compound with dimethyl acetylenedicarboxylate to give the 3-phenylpyrrolo[2,1-*a*]isoquinoline (6). Other alkynes have also been used. In addition to isoquinoline and quinoline this ring annelation technique has been applied to phenanthridine,¹¹ phthalazine,^{35,37} pyridazine,¹⁶ and 3,4-dihydro- β -carboline,¹⁵ giving in the last case (7).



Scheme I

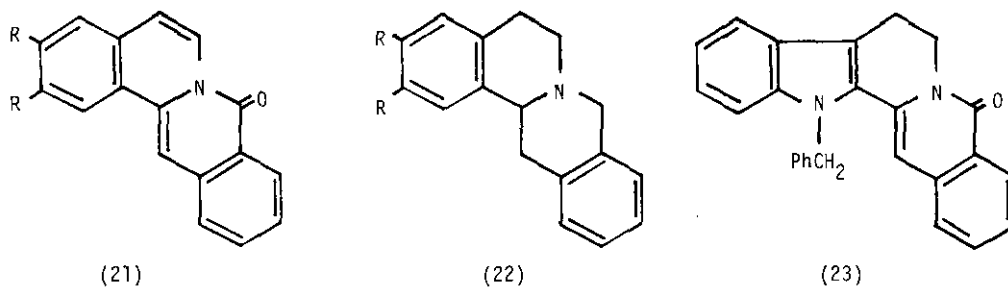
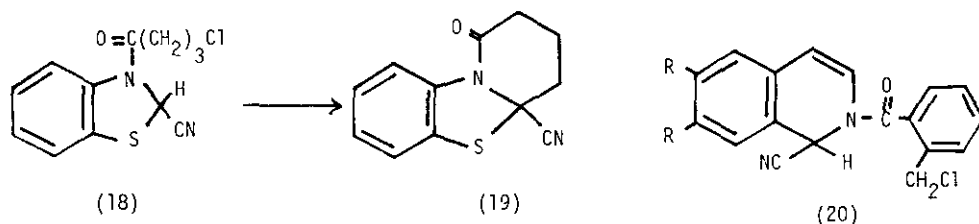
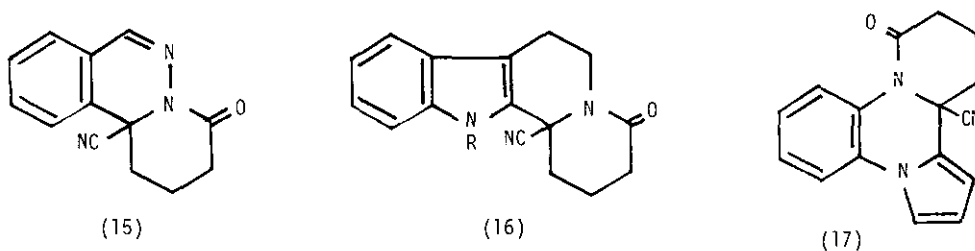
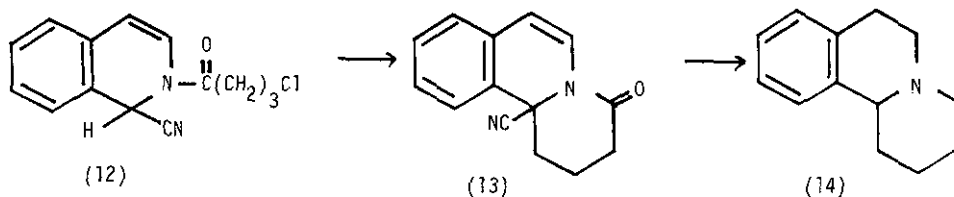


Much of the recent chemistry of Reissert compounds has involved the conjugate base. Thus, as mentioned above, treatment of (2) with sodium hydride in dimethylformamide^{3,4} gives rise to (3). Alkylation reactions of anions of this type have proved to be an important route to isoquinoline alkaloids.⁶ In the case of the Reissert compound (8) alkylation can take place both at the C-1 position and at the indole nitrogen to give ring annelation products: 1,3-dibromopropane gives the 1H-indolo[3,2,1-d] [1,5]naphthyridine system (9) and use of the dibromoxylene (10) gives the [2]benzazepino[2,3,4-*l*m]- β -carboline system (11).¹⁵



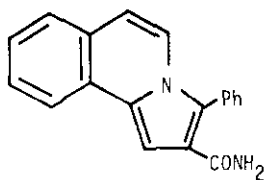
Suitably substituted Reissert compounds can undergo intramolecular alkylation via the conjugate base. Thus, reaction of (12) with sodium hydride in dimethylformamide affords (13) which has subsequently been converted to the hexahydro-11*b*-H-benzo[*a*]quinolizine (14).³⁹ In a similar manner other Reissert compounds derived from 4-chlorobutyryl chloride and quinoline,³⁹ phenanthridine,¹¹ phthalazine,⁴⁰ 3,4-dihydro- β -carboline,¹⁵ and pyrrolo[1,2-*a*]quinoxaline,¹⁷ have been shown to undergo intramolecular alkylation, the products in the last three cases being (15)-(17). Most recently, Reissert compound formation has been achieved with 5-membered ring heterocycles, benzothiazole, for example, giving (18): generation of the conjugate base of (18) then leads in high yield to tricyclic system (19).⁴¹ The Reissert compound formed from

isoquinoline and 5-chloropentanoic acid chloride undergoes cyclization in a similar manner to form a 7-membered annelated ring.³⁹

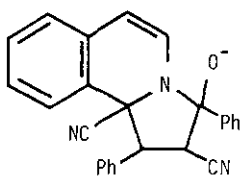


The intramolecular cyclization of the Reissert compounds (20) prepared from 2-chloromethylbenzoyl chloride, by treatment with base, is accompanied by elimination of hydrogen cyanide to give (21).^{42,43} These dehydro-8-oxoberbines (21) have been converted to the berbines (22).⁴³ This same type of cyclization has been applied to Reissert compounds derived from 2-chloromethylbenzoyl chloride and phthalazine,⁴³ phenanthridine,¹¹ ellipticine,⁴³ pyrrolo[1,2-a]quinoxaline,¹⁷ and *N*-benzyl-3,4-dihydro- β -carboline.^{15,44} The structure of the product (23) from the last compound is of potential interest for further work^{15,44} in the indole alkaloid area.

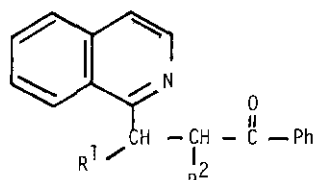
The anion of the Reissert compound (2) has been used with unsaturated electrophiles to give Michael-type products.^{2,4} Reaction of (3) with acrylonitrile thus leads to the pyrrolo[2,1-*a*]isoquinoline (24).⁴⁵ Use of Reissert compounds formed from substituted benzoyl chlorides leads to the replacement of the 3-phenyl group in (24) by substituted phenyl groups.⁴⁶ A similar compound is also obtained when cinnamionitrile is used in the condensation.^{27,28} This reaction probably proceeds through an intermediate of the type (25). Use of compounds such as ethyl acrylate,⁴⁵ 2-vinylpyridine,⁴⁵ and ethyl cinnamate^{27,28} leads to ketones such as (26) probably through an alternative pathway of decomposition of (25). These ketones can, however, be cyclized to pyrrolo[2,1-*a*]isoquinolines.⁴⁵ Similar ring annelations with acrylonitrile and the anions of Reissert compounds of 4-substituted quinolines,⁴⁶ thieno[2,3-*c*]pyridine,¹² phthalazine,⁴⁷ and phenanthridine,¹¹ have been observed. The products in the latter two cases, were the pyrrolo[2,1-*a*]phthalazine (27) and pyrrolo[1,2-*f*]phenanthridine (28).



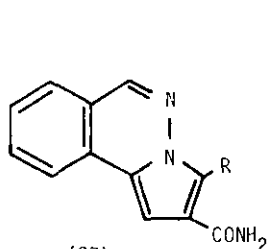
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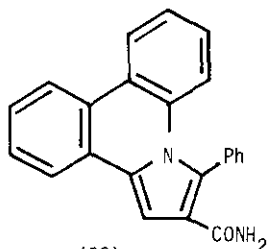
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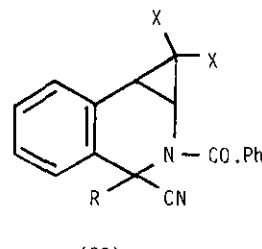
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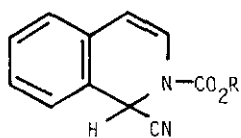
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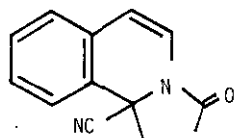
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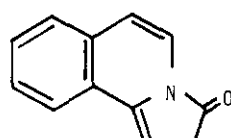
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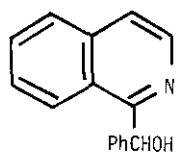
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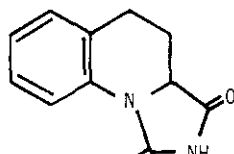
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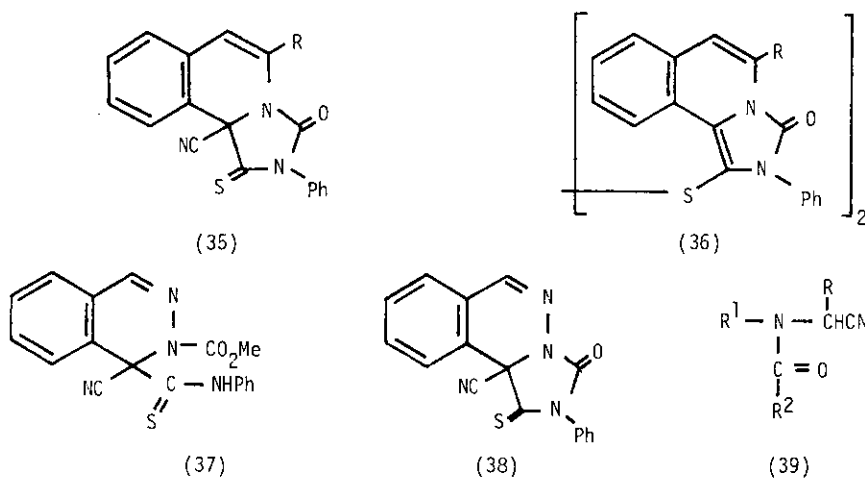


(34)

In a reaction involving the 3,4-double bond of (2), it has been observed that dichloro- or dibromocarbene reacts with 1-alkyl-1-cyano-2-benzoyl-1,2-dihydroisoquinolines to give the cyclopropa[c]isoquinolines (29).⁴⁸

Among the so-called analogs of Reissert compounds^{3,4} those derived from the reaction of the heterocyclic base, cyanide, and chloroformates have proved to be of value in ring annelation reactions. Thus reaction of (30) with benzaldehyde in the presence of n-butyllithium gave (31);⁴⁹ use of sodium hydride in dimethylformamide gave the oxazo[lo[4,3-a]isoquinoline (32) and the carbinol (33).⁴⁹ This latter product is the same as obtained in the reaction of benzaldehyde with (3).³ Reaction of the analog of (30) obtained from 3,4-dihydroisoquinoline with benzaldehyde gave the dihydro analog of (31).⁵⁰ The quinoline analog of (30) has led to the oxazo[lo[3,4-a]quinoline analogs of (31) and (32).⁵¹ At -78°C the chloroformate derived Reissert analog of phenanthridine reacts with benzaldehyde to give the benzo derivative of (31).¹¹ Although the chloroformate derived quinoline analog from 3,4-dihydroquinoline apparently does not react with benzaldehyde, it gives the cyclic product (34) on base hydrolysis.⁵²

Reaction of the chloroformate derived Reissert compound (30) and its 3-methyl analog with phenyl isothiocyanate and sodium hydride in dimethylformamide gives the imidazo[5,1-a]isoquinoline system (35).⁵³ Disulfides of the type (36) have also been obtained as co-products in this synthesis.⁵⁴ Application of this approach to the phthalazine analog of (30) gives the open chain compound (37) which can be cyclized to the imidazo[5,1-a]phthalazine (38) by heating in the presence of molecular sieves.⁵⁴ Attempts to obtain (38) directly by raising the temperature of the original reaction gave the aza analog of (36).⁵⁴



It should be noted that although ring annelations are not involved, the so-called open chain Reissert analogs (39) have been converted into cyclic derivatives.⁵ Reissert compounds have also been indirectly involved in ring annelation sequences. Thus, for example, various benzylisoquinolines and related compounds that were prepared via Reissert compounds have been converted into examples of the cularine, pavinane, isopavine and aporphine alkaloids^{3,4,5,6} the oxazolo[4,3-a]isoquinolines⁵⁵ and the berbines.⁵⁶

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