Advances in HETEROCYCLIC CHEMISTRY

A. R. KATRITZKY

A. J. BOULTON

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Volume 9

Academic Press · New York and London · 1968

ACADEMIC PRESS INC.
111 Fifth Avenue, New York, New York 10003

United Kingdom Edition published by
ACADEMIC PRESS INC. (LONDON) LTD.
Berkeley Square House, London W.1

LIBRARY OF CONGRESS CATALOG CARD NUMBER: 62-13037

PRINTED IN THE UNITED STATES OF AMERICA

Preface

The ninth volume of *Advances in Heterocyclic Chemistry* includes surveys of the chemistry of the following groups of heterocyclic compounds: 1,2,5-thiadiazoles (L. M. Weinstock and P. I. Pollack); 1,3,4-thiadiazoles (J. Sandström); pyridazines (M. Tišler and B. Stanovnik); Reissert compounds (F. D. Popp); phenothiazines (C. Bodea and I. Silberg); and pyrrolopyridines (R. E. Willette).

Suggestions are welcomed for contributions to future volumes; they should be in the form of short synopses.

Thanks are due to the Editorial Board, the publisher, and the authors for their cooperation.

A. R. Katritzky
A. J. Boulton

Norwich, England
February, 1968

Contents

Recent Advances in the Chemistry of 1,3,4-Thiadiazoles

JAN SANDSTRÖM

Pyridazines

M. TIŠLER AND B. STANOVNIK

Recent Advances in the Chemistry of Phenothiazines

CORNEL BODEA AND IOAN SILBERG

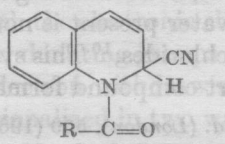
Reissert Compounds

F. D. POPP

Clarkson College of Technology, Potsdam, New York

I. Introduction

The chemistry of *N*-acyldihydroquinaldonitriles (1) and *N*-acyldihydroisoquinaldonitriles (2) (Reissert compounds) was the subject of an excellent review in 1955.[1] The purpose of the present



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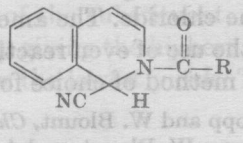

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review is to summarize the results since that date. The same general format that was followed in the previous review[1] will be used, as far as possible, in the present one. The literature is covered from the previous review up to August 1967.

[1] W. E. McEwen and R. L. Cobb, *Chem. Rev.* 55, 511 (1955).

II. Preparation

A valuable dimension was added to Reissert compound chemistry with the discovery of the methylene chloride–water solvent system for their preparation.[2, 3]

A. Preparation in Aqueous Media

Although several new[4, 5] Reissert compounds were prepared by this method[1] it has been largely displaced by the methylene chloride–water system. The disadvantages of the aqueous method have been discussed.[4]

B. Preparation in Nonaqueous Media

Although solvents such as dimethylformamide[5] have been tried, the use of anhydrous benzene and anhydrous hydrogen cyanide[1] appears to remain as the most general nonaqueous solvent system and several new Reissert compounds have been prepared by this method.[6–8] With the use of anhydrous hydrogen cyanide this method suffers from an obvious disadvantage.

C. Preparation in Methylene Chloride–Water

An extremely convenient and general[2–4, 9–11] method of Reissert compound formation has been developed. This involves the addition of the acid halide (or less frequently anhydride) neat or in methylene chloride to a mixture of the heterocyclic base in methylene chloride and potassium cyanide in a minimum of water. Although the methylene chloride–water system is heterogeneous it has the advantage over the aqueous system that all the reactants and products are soluble in one phase or the other. Also water is slightly soluble in methylene chloride. The amount of water present is not sufficient to prevent the use of even reactive acid chlorides.[10] This system appears to be the method of choice for Reissert compound formation.

2 F. D. Popp and W. Blount, *Chem. & Ind.* (*London*), 550 (1961).
3 F. D. Popp, W. Blount, and A. Soto, *Chem. & Ind.* (*London*), 1022 (1962).
4 F. D. Popp, W. Blount, and P. Melvin, *J. Org. Chem.* **26**, 4930 (1961).
5 I. W. Elliott, Jr., *J. Am. Chem. Soc.* **77**, 4408 (1955).
6 H. Shirai and N. Oda, *Chem. & Pharm. Bull.* (*Tokyo*) **8**, 744 (1960).
7 E. Cuingnet and M. Adalberon, *Compt. Rend.* **258**, 3053 (1964).
8 F. D. Popp and W. E. McEwen, *J. Am. Chem. Soc.* **79**, 3773 (1957).
9 F. D. Popp and W. Blount, *J. Org. Chem.* **27**, 297 (1962).
10 F. D. Popp and A. Soto, *J. Chem. Soc.*, 1760 (1963).
11 F. D. Popp and J. Wefer, *Chem. Commun.*, 59 (1967).

D. Effect of Structure on Reactivity of the Heterocyclic Amine

The failure of pyridine and acridine to yield Reissert compounds has already been discussed.[1] Although many of the arguments advanced[1] for the failure of pyridine to yield a Reissert compound suffer from the fact that analogous compounds have been prepared from pyridine, no one yet appears to have found the proper conditions for formation of a pyridine Reissert compound.

1. *Quinolines*

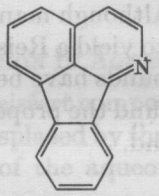
The previous review[1] noted the formation of Reissert compounds from less than half the quinolines investigated and stated that "... the ease of formation of Reissert compounds is dependent upon steric as well as electronic factors, since the presence of substituents in the 2- and 8-positions of quinoline inhibits the formation of ..." Reissert compounds. That a steric factor does indeed exist is evidenced by the fact that from a total of seven 2-substituted and nine 8-substituted quinolines subjected to the reaction none has yielded a Reissert compound.[1,4] Using the methylene chloride–water solvent system, however, Reissert compounds have been prepared from 3-, 4-, 5-, 6-, and 7-substituted quinolines and from disubstituted quinolines.[4] Quinolines having various substituents in these positions, including all those previously reported as not giving Reissert compounds, gave positive results in this solvent system.[4] In addition to Reissert compound formation, hydroxyquinolines were esterified and aminoquinolines were converted to the amides.

The yields of Reissert compounds with substituents on the quinoline ring vary with the electronic character of the substituent, quinolines with electron-donating groups generally giving the highest yields and those with electron-withdrawing groups the lowest yields. This result has been rationalized in two ways.[4]

2. *Isoquinolines*

Although the number and variety of isoquinolines investigated does not approach that of the quinoline series, it would appear that the synthesis of isoquinoline Reissert compounds is general when the methylene chloride–water solvent system is used.[9] A possible exception is 1-substituted isoquinolines where a steric effect, similar to that

in the quinoline series, may exist. 1-Methylisoquinoline failed to give a Reissert compound although 2-azafluoranthene (**3**), benzoyl chloride, and potassium cyanide gave a material which had the correct



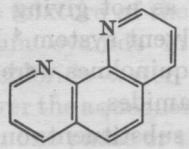
(3)

elemental analysis for a Reissert compound.[9] It should be noted, however, that the compound derived from **3** did not give benzaldehyde on acid-catalyzed hydrolysis.[12] Such a reaction is generally typical for a Reissert compound.[1]

3. *Diazaheterocyclic Compounds*

Except for the formation of a mono Reissert compound from 2,3′-biquinoline and a di-Reissert compound from 6,6′-biquinoline[1] relatively little had been done on diaza systems until recent years.

o-Phenanthroline (**4**) does not give a Reissert compound[13, 14] while *m*-phenanthroline gives the mono-Reissert compound (**5**).[13] Neither



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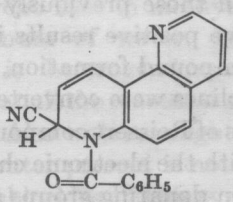


(5)

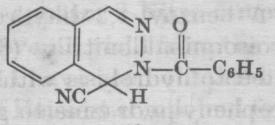
of these results is surprising if one considers that 8-substituted quinolines do not form Reissert compounds.

Phthalazine has been reported to give the compound **6** which, as noted in subsequent sections, behaves as a normal Reissert compound on acid-catalyzed hydrolysis and alkylation.[11]

[12] W. Blount, J. Wefer, and F. D. Popp, unpublished observations (1961, 1966).

[13] F. D. Popp, unpublished results (1962–1963) (presented at *19th Intern. Congr. Pure Appl. Chem., London*, 1963).

[14] E. J. Corey, A. L. Borror, and T. Foglia, *J. Org. Chem.* **30**, 288 (1965).



(6)

Much further study is needed on the extension of this class of compounds to the diazaheterocyclic area.

E. Reactivity of the Acid Chloride

Until the advent of the methylene chloride–water solvent system the less reactive acid chlorides could be used in the aqueous method but the more reactive acid chlorides required the anhydrous hydrogen cyanide method.[1] This latter method is still sometimes used[6, 8] and in fact has been used with quinoline and the 2- and 3-carboxylic acid chlorides of methylcyclopentadienyl manganese tricarbonyl.[7]

The methylene chloride–water method[3] has demonstrated a wide range of utility and aromatic, aliphatic, cyclic, and diacid chlorides have been used to give the appropriate Reissert compound.[10] It is of interest to note that despite the presence of water in the system it can be used successfully with even aliphatic acid chlorides.

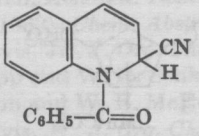
The acid bromide or acid anhydride may be used in place of the acid chloride but the yields of Reissert compounds are generally not as satisfactory with these reagents.[10]

III. Chemical Properties and Reactions

A. Acid-Catalyzed Hydrolysis

In the early work on Reissert compounds[1] the reaction that attracted the greatest attention was the acid-catalyzed hydrolysis to aldehydes plus the corresponding heterocyclic carboxylic acid or acid derivative.

1. *Scope*



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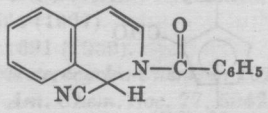
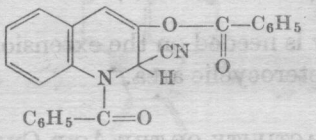


(8)

A wide variety of *N*-benzoyl-1,2-dihydroquinaldonitriles (**7**) and *N*-benzoyl-1,2-dihydroisoquinaldonitriles (**8**) with various ring substituents were subjected to hydrolysis with hydrochloric acid in the presence of 2,4-dinitrophenylhydrazine to give, with the exceptions



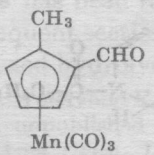
(**9**)

noted below, high yields of benzaldehyde-2,4-dinitrophenylhydrazone.[4, 9] The Reissert compound (**9**) from 3-hydroxyquinoline failed to yield benzaldehyde.[4] The proximity of the carbonyl function in the 3-position of the Reissert compound (**9**) to the cyano group may interfere with the interaction of the cyano group and the carbonyl function in the 1-position which is necessary, as indicated in the next section, for the hydrolysis to an aldehyde. The nitro-substituted Reissert compounds such as those from 5-, 6-, and 7-nitroquinoline and from 5- and 8-nitroisoquinoline gave very low yields of benzaldehyde on acid-catalyzed hydrolysis.[4, 9] A somewhat higher yield was obtained from 5- and 8-nitro-3-methylisoquinoline[9] indicating a possible electronic effect. For unexplained reasons the Reissert compounds derived from disubstituted quinolines generally gave lower yields of benzaldehyde than those from monosubstituted quinolines.[4]

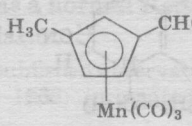
Under similar conditions of hydrolysis the phthalazine Reissert compound (**6**) gave a near quantitative yield of benzaldehyde-2,4-dinitrophenylhydrazone.[11]

A group of Reissert compounds containing various *N*-acyl groups were subjected to hydrolysis under similar conditions to give the aldehyde-2-,4-dinitrophenylhydrazone.[8, 10]

Although the synthetic utility of this as a method of aldehyde synthesis has been largely displaced by new techniques, some reports



(**10**)



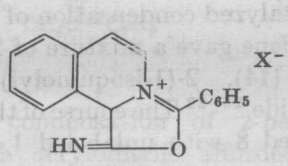
(**11**)

of its use continue to appear. 2-Nitro-5-methoxybenzaldehyde has been prepared in 62% overall yield from the corresponding acid[6] and the aldehydes **10** and **11** have been obtained from the corresponding acids[7] by making use of Reissert compound formation and hydrolysis. The acid hydrolysis of Reissert compounds has been utilized for the preparation of deuterium-labeled aldehydes.[14a]

The acid-catalyzed hydrolysis continues to be used as a highly satisfactory method for the synthesis of quinaldic acids. The reaction of Reissert compound (**7**) with hydrobromic acid in acetic acid gave near quantitative yields of quinaldic acid hydrobromide with no contamination from other acid derivatives[15] and would appear to be the method of choice for this conversion. This method has subsequently been used to produce high yields of benzo(*f*)quinoline-3-carboxylic acid[16] and phthalazine-1-carboxylic acid.[11]

2. *Studies of the Mechanism*

A reasonable mechanism has been proposed for this somewhat unusual hydrolysis[1, 17] and the isolation of a hydrobromide analog of one of the proposed cyclic intermediates[17] has been reported.[18] This



(**12**)

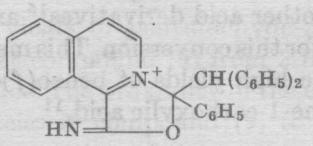
intermediate (**12**) may be crystallized from hot alcohol and does not decompose on treatment with hot or cold water. Upon decomposition it gives benzaldehyde, isoquinaldamide hydrobromide, and isoquinaldic acid hydrobromide.[18] An impure intermediate had previously been isolated from the acid hydrolysis of another Reissert compound.[8] The reduction of **12** which is discussed in Section III, C confirms structure **12**.[19]

[14a] M. Wahren, *Abhandl. Deut. Akad. Wiss. Berlin, Kl. Chem., Geol. Biol.* **1964** (7), 687 (1963); *Chem. Abstr.* **66**, 3564 (1967).
[15] J. W. Davis, Jr., *J. Org. Chem.* **24**, 1691 (1959).
[16] F. D. Popp and W. R. Schleigh, *J. Heterocyclic Chem.* **1**, 107 (1964).
[17] R. L. Cobb and W. E. McEwen, *J. Am. Chem. Soc.* **77**, 5042 (1955).
[18] J. W. Davis, Jr., *J. Org. Chem.* **25**, 376 (1960).
[19] I. W. Elliott and J. O. Leflore, *J. Org. Chem.* **28**, 3181 (1963).

3. *Acid-Catalyzed Condensations*

On the basis of the mechanism for the acid-catalyzed hydrolysis of Reissert compounds[1, 17] it can be reasoned that such compounds might function as acylating agents towards carbonium ions. Studies toward this end have been reported.[20–23]

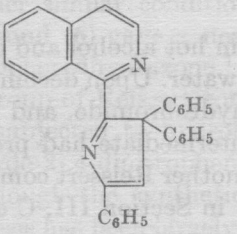
Treatment of 2-benzoyl-1,2-dihydroisoquinaldonitrile (**8**) with benzhydrol and concentrated sulfuric acid in dioxan solution gave isoquinaldamide bisulfate and α,α-diphenylacetophenone.[20] These results can be explained by the acid-catalyzed conversion of **8** to **12**



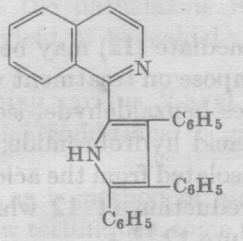
(**13**)

followed by deprotonation of **12** and condensation with the benzhydryl cation to give **13**. Addition of water to **13** affords an intermediate which can rearrange to give the observed products.[20]

The sulfuric acid-catalyzed condensation of Reissert compound (**8**) with 1,1-diphenylethylene gave a mixture of 2-(1-isoquinolyl)-3,3,5-triphenylpyrrolenine (**14**), 2-(1-isoquinolyl)-3,4,5-triphenylpyrrole (**15**), and isoquinaldamide.[20–22] The course of this reaction was studied by carbonyl-^{14}C labeled **8** with unlabeled 1,1-diphenylethylene, as



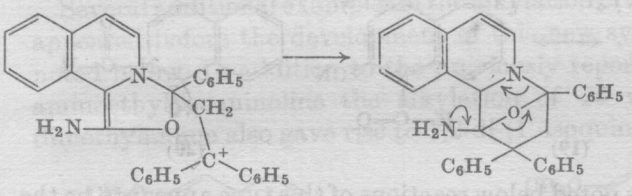
(**14**)



(**15**)

[20] T. K. Liao and W. E. McEwen, *J. Org. Chem.* **26**, 5257 (1961).
[21] T. Y. Yee, W. E. McEwen, and A. P. Wolff, *Tetrahedron Letters*, 3115 (1965).
[22] W. E. McEwen, T. Y. Yee, T. K. Liao, and A. P. Wolff, *J. Org. Chem.* **32**, 1947 (1967).
[23] E. K. Evanguelidou and W. E. McEwen, *J. Org. Chem.* **31**, 4110 (1966).

well as by reaction of unlabeled **8** with methylene-^{14}C labeled 1,1-diphenylethylene.[21, 22] These tracer studies as well as other evidence established the structures. The product **15** arose through a rearrangement of **14** and the formation of **14** can be explained by the attack of the conjugate acid (**12**) on 1,1-diphenylethylene to give **16** which can then proceed as shown to **14**.[21, 22]



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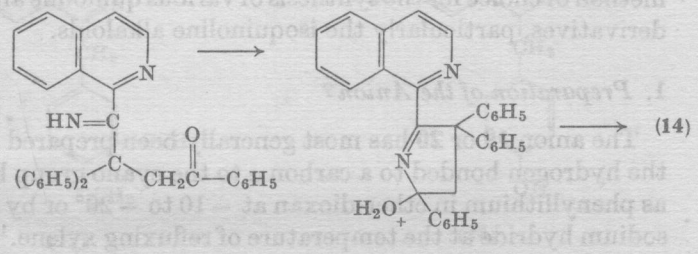
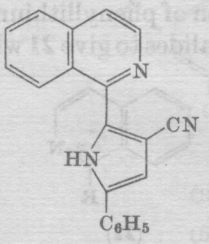


(14)

The acid-catalyzed condensation of 2-benzoyl-1,2-dihydroisoquinaldonitrile (**8**) with acrylonitrile afforded 2-(1-isoquinolyl)-3-cyano-5-phenylpyrrole (**17**),[23] while ethyl 2-(2-quinolyl)-5-phenylpyrrole-3-carboxylate (**18**) is produced by the acid-catalyzed condensation of 1-benzoyl-1,2-dihydroquinaldonitrile (**7**) with ethyl



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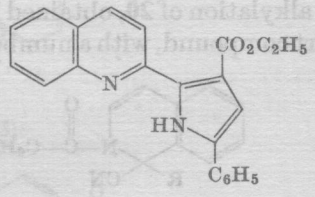


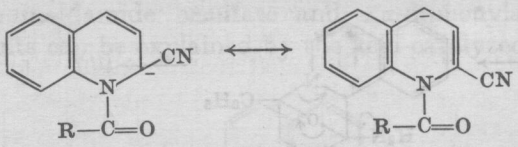
(18)

acrylate.[24] These reactions can also be explained by involving the intermediate originally proposed in the acid-catalyzed hydrolysis of Reissert compounds.

[24] W. E. McEwen, private communication (1966).

B. Reactions Involving the Formation of an Anion of the Reissert Compound

A number of alkylation reactions, Michael-type additions, and base-catalyzed rearrangements have been previously reported for Reissert compounds.[1] These reactions appear to proceed through the conjugate



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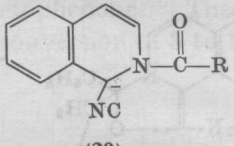


(20)

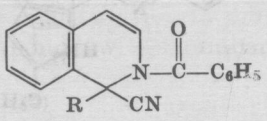
bases **19** and **20**. As noted below reactions of this type appear to be the method of choice for the synthesis of various quinoline and isoquinoline derivatives, particularly the isoquinoline alkaloids.

1. *Preparation of the Anion*

The anion **19** or **20** has most generally been prepared by removal of the hydrogen bonded to a carbon α to the cyano group by a base such as phenyllithium in ether-dioxan at -10 to $-20°$ or by a base such as sodium hydride at the temperature of refluxing xylene.[1] Recent work, however, has shown that these anions can be generated and caused to react at room temperature by use of sodium hydride in dimethylformamide.[25–27]

2. *Reactions with Alkyl Halides*

The alkylation of **20**, obtained by the action of phenyllithium on the Reissert compound, with a number of alkyl halides to give **21** which can



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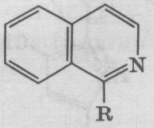


(22)

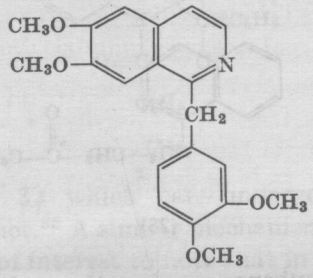
then be hydrolyzed to **22** has been discussed.[1] The use of sodium hydride in dimethylformamide at room temperature[25] greatly

[25] F. D. Popp and J. M. Wefer, *Chem. Commun.*, 207 (1966).
[26] J. R. Kershaw and B. C. Uff, *Chem. Commun.*, 331 (1966).
[27] F. D. Popp and J. M. Wefer, *J. Heterocyclic Chem.* **4**, 183 (1967).

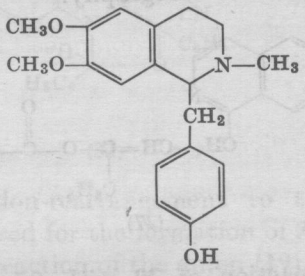
increases the utility of this reaction and it now appears to be the method of choice for the synthesis of 1-alkylisoquinolines.[26, 27]

A new synthesis of aporphines has appeared.[27a] The key step in this synthesis involves the generation of 1-(*o*-nitrobenzyl)isoquinoline by reaction of a Reissert compound with *o*-nitrobenzyl chloride in dimethylformamide in the presence of sodium hydride.

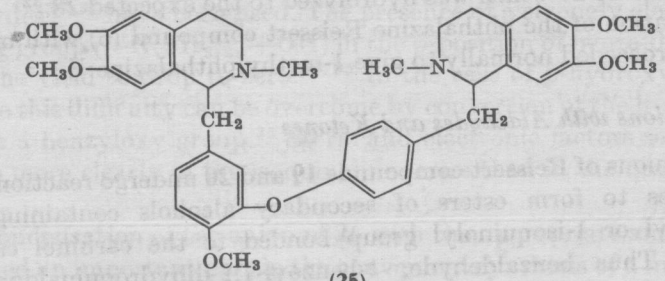
Several additional examples of the alkylation of Reissert compounds appeared before the development of this new system and these are noted below. In addition to the previously reported[1] 1-(β-dimethylaminoethyl)isoquinoline the alkylation of **20** with β-chloroethyldimethylamine also gave rise to 1,2-di-(1′-isoquinolyl)ethane.[28]



(23)



(24)



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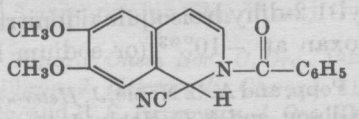

(26)

27a J. L. Neumeyer, B. R. Neustadt, and J. W. Weintraub, *Tetrahedron Letters*, 3107 (1967).

28 V. Boekelheide and A. L. Sieg, *J. Am. Chem. Soc.* **77**, 3128 (1955).