Popp and Soto:

328. Reissert Compound Studies. Part V.* Nature of the Acid Chloride.

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Reaction of a wide variety of aromatic, aliphatic, cyclic, and di-acid chlorides with potassium cyanide and quinoline or isoquinoline in methylene chloride-water has given the appropriate Reissert compounds. The acid bromide or anhydride may be used in place of the acid chloride. Acidcatalyzed hydrolysis of the Reissert compounds gave the expected aldehydes.

REISSERT compounds¹ (I and II) result from the addition of an acyl and a cyano-group to a wide variety of quinolines² and isoquinolines.³ The initial interest in Reissert compounds was concerned with the nature of the acyl group since this could be hydrolyzed 4.5 to an aldehyde, so that the sequence presented a useful method for the preparation of aldehydes from acids. It might be noted that this method is still used ⁶ despite the various newer methods for aldehyde synthesis. More recent interest, however, has been in the use of Reissert compounds in the synthesis of various heterocyclic compounds.^{1,7}



Since a number of these synthetic sequences involve the migration of the acyl group to the carbon which had been bonded to the cyano-group to form quinolyl and isoquinolyl ketones and alcohols, it is of particular interest to know what acid chlorides may be used to form Reissert compounds and what are the most convenient conditions for their use.

We recently reported ^{2,3,8} that methylene chloride-water was the solvent of choice for formation of Reissert compounds from a variety of quinolines or isoquinolines and benzoyl chloride. Despite the presence of water this solvent system can also be used for the preparation of Reissert compounds from quinoline, isoquinoline, or phenanthridine and a wide variety of acid chlorides. The results obtained from the use of a variety of acid chlorides are presented in Table 1.

With the aliphatic acid chlorides Reissert compounds were obtained in all cases tried, with the exception of pyruvoyl chloride. In this case, with quinoline or isoquinoline, the " dimer" (III; $R = Bu^t$) was obtained. This type of product has been previously reported in studies of Reissert compounds.¹ The failure of pyruvoyl chloride to give a Reissert compound can probably be attributed to steric factors. All aromatic acid chlorides subjected to this reaction gave Reissert compounds including p-nitrobenzoyl chloride which had been reported⁹ as failing to do so. The use of cyclopropane-, cyclopentane-, and cyclohexane-carbonyl chloride resulted in the formation of Reissert compounds in yields decreasing with increasing ring size. This is the first report of the use of this type of acid chloride in this reaction. Also reported for the first time is the use of two diacid chlorides which led to "bis-Reissert compounds" such as (IV).

- * Part IV, Popp, Blount, and Soto, Chem. and Ind., 1962, 1022.
- ¹ McEwen and Cobb, Chem. Rev., 1955, 55, 511.

- ^a Notwert and Cool, Chem. Rev., 1939, 33, 311.
 ^a Popp, Blount, and Melvin, J. Org. Chem., 1961, 26, 4930.
 ^a Popp and Blount, J. Org. Chem., 1962, 27, 297.
 ⁴ Cobb and McEwen, J. Amer. Chem. Soc., 1955, 77, 5042.
 ⁵ Davis, Jr., J. Org. Chem., 1960, 25, 376.
 ⁶ Shirai and Oda, Chem. and Pharm. Bull., 1960, 8, 744.
 ⁷ Walters, Podrebarac, and McEwen, J. Org. Chem., 1961, 26, 1161, and references cited therein to jer work of McEwen and bis converters. earlier work of McEwen and his co-workers.
 - Popp and Blount, Chem. and Ind., 1961, 550.
 - ⁹ Buchanan, Cook, and Loudon, J., 1944, 325.

R in R·COCl

(or R·CO)

Reissert Compound Studies. Part V. TABLE 1.

Formation of Reissert compounds.

С

Reported

m. p.‡

92-93° 96-97°

Found (%)

Н

N

12.4

11.7

 $9 \cdot 2$

9.7

 $8 \cdot 2$

 $9 \cdot 0$

 $9 \cdot 0$

8.9 9·1

13.5

13.8

13.9

8.3

13.3

13.5

12.9

12.4

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Required (%)

H

5.7 13.2

6.2 12.4

6.2 12.4

6.7 11.7

8.4 9.0

3.8 9.53.8 9.5 4.0 10.1 4.0 10.1

4·9

4.9

4.5

4.5

4.5

3.6 13.8 3.6 13.8

3.6 13.8 $3 \cdot 4$

5.4 12.5

5.4 12.5

6.4 11.1

6.4 11.1 $\begin{array}{cccc} 6{\cdot}8 & 10{\cdot}5 \\ 5{\cdot}2 & 13{\cdot}3 \end{array}$

5.2 13.3

4.1 12.7

4.1 12.7

4·0 11·2

9.65

 $8 \cdot 2$

9.0

9.0

9·0

8.5

N

С

73.5

74.3

74.3

75.0

77.4

72.0

74.5

77.6

81.3

81.3

81.3

66.9

66.9

66·9

65.85

75.0

75.0

 $76 \cdot 2$

76.2

76.7

73·9

7**3**·9

76.0

76.0

Formula

 $13.1 C_{13}H_{12}N_2O$

 $12.3 \quad C_{14}H_{14}N_2O$

 $\substack{ C_{14}H_{14}N_2O\\ C_{15}H_{16}N_2O\\ C_{20}H_{26}N_2O}$

 $\begin{array}{ccccccc} 9.7 & C_{17}H_{11}ClN_2O & 69\cdot3\\ 9\cdot4 & C_{17}H_{11}ClN_2O & 69\cdot3\\ 9\cdot8 & C_{17}H_{11}FN_2O & 73\cdot4\\ 10\cdot15 & C_{17}H_{11}FN_2O & 73\cdot4\\ 11\cdot4 & C & H & N & O \end{array}$

 $\substack{ \mathrm{C_{18}H_{14}N_2O_2}\\ \mathrm{C_{22}H_{16}N_2O_2} }$

 $C_{21}H_{14}N_2O$

 $\substack{ C_{21}H_{14}N_2O\\ C_{21}H_{14}N_2O}$

 $\begin{array}{c} C_{17}H_{11}N_{3}O_{3}\\ C_{17}H_{11}N_{3}O_{3}\\ C_{17}H_{11}N_{3}O_{3}\\ C_{17}H_{11}N_{3}O_{3}\\ \end{array}$

 $C_{18}H_{11}F_{3}N_{2}O$

 $\begin{array}{c} C_{26}H_{22}N_4O_2\\ C_{26}H_{22}N_4O_2\\ C_{28}H_{18}N_4O_2\\ \end{array}$

 $C_{28}H_{18}N_4O_2$

 $11.4 C_{15}H_{10}N_2O_2$

Me	Q	50	9293°	$96 - 97^{\circ}$		
Me	ĩ	87	119-120	119-121		
Et	Q	12	46 - 48	49 - 50		
Et	Ĩ	49	115 - 117		7 3 ·55	5.6
Pr ⁿ	Q	25	97 - 98	9798		
Pr ^a	Ĩ	64	87-88		74.6	6.1
Pr ⁱ	Q	18	126 - 127	129-130		
Pr^i	ĩ	11	87		74.3	$6 \cdot 4$
Bu ⁿ	Ι	35	8889		75.1	6.8
$C_{9}H_{19}$	I	Trace	53 - 55		$77 \cdot 2$	$8 \cdot 2$
(Cinnamoyl)	Q	43	149 - 150	149-150		
(Cinnamoyl)	Ĩ	64	164 - 165	160 - 162		
Ph	Q	70	154 - 155	154-155		
Ph	Ĩ	69	124 - 125	124 - 126		
Ph	\mathbf{P}	71	140 - 142	140 - 142		
p-C ₆ H ₄ Cl	Q	20	145 - 147	143-144		
$p - C_6 H_4 Cl$	Ĩ	30	150 - 151	155 - 156	69.35	4.0
$m - \tilde{C}_{B}H_{A}Cl$	I	17	185 - 187		69·1	$3 \cdot 9$
p-C ₆ H ₄ F	Q	50	112 - 114		$73 \cdot 1$	3.7
$p - C_{6} H_{4} F$	Ĩ	37	178 - 179		73.4	4.3
(2-Furoyl)	I	63	110-111		71.9	3.75
p-MeO·C ₆ H ₄	Q	80	119-120	120		
p-MeO·C ₆ H ₄	Ĩ	72	173 - 174		74.2	4.7
p-MeO·C ₆ H ₄	Ρ	60	153 - 154		77.8	4.75
	0	69 5	193-195	\$ ſ	81 ·0	4.9
1-(v ₁₀ f1 ₇	\mathcal{Q}	03 Y	202-204	ં રે	81.1	4 ·6
1-C ₁₀ H ₇	Ι	11	198-200		81.2	4.55
2-C ₁₀ H ₇	I	12	165 - 167		81.1	4 ·8
$m - NO_2 \cdot C_6 H_4 \dots$	Q	12	165 - 166	171		
$m \cdot NO_2 \cdot C_6 H_4 \dots$	ľ	12	183 - 184		66.95	$3 \cdot 4$
p-NO ₂ ·C ₆ H ₄	Q	3	166 - 167		66.55	3.75
p-NO ₂ ·C ₆ H ₄	I	3	177 - 178		66.8	$3 \cdot 6$
<i>p</i> -CF ₃ ·C ₆ H ₄	I	5	159 - 160		65.6	3.6
$3,4,5-(MeO)_{3}C_{6}H_{2}$	Q	65	174 - 175	176 - 177		
Cyclopropane	Q	77	131 - 132		74.7	$5 \cdot 3$
Cyclopropane	I	52	109-111		75.0	$5 \cdot 2$
Cyclopentane	Q	33	117 - 118		76.0	6·4
Cyclopentane	I	10	87		76.3	$6 \cdot 2$
Cyclohexane	Ι	Trace	127 - 128		76.95	6.6
(Adipoyl)	Q	Trace	178 - 179		73.45	5.15
(Adipoyl)	I	6	189-190	T	73.8	5.4
(Phthaloyl)	Q	Trace	234 - 235	T	75.7	4.12
(Phthaloyl)	Ι	Trace	197 - 199		75.75	$4 \cdot 3$

Yield Base * (%)

M. p.†

* Q = quinoline, I = isoquinoline, P = phenanthridine. † Recryst. from 95% ethanol except where noted. ‡ See ref. 1. § Dimorphic forms. ¶ Recryst. from dioxan.

TABLE 2.

Comparison	of	methods	of	formation	of	Reissert	compounds
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			Yields (%	6) †			•	Yields (%	5) †
R in R·COCl (or R·CO)	Base *	In H.O	In HCN– C.H.	In CH ₂ Cl ₂ -	R in R·COCl	Base *	In H O	In HCN-	In CH ₂ Cl ₂ -
Me Me	Q I	****	74 85	50 87	p-C ₆ H ₄ Cl p-C ₆ H ₄ Cl	Q I	$\frac{11_20}{26}$	77	$ \begin{array}{c} 20 \\ 30 \end{array} $
Et Pr ⁿ	Q	+++++++++++++++++++++++++++++++++++++++	10 64	12 25	p-MeO-C ₆ H ₄ m-NO ₂ ·C ₆ H ₄	Q Q	51	88 Low	80 12
(Cinnamoyl) (Cinnamoyl)	Õ Ĩ	$\mathbf{\overset{I}{34}}$	28 91 91	18 43 64	p-NO ₂ ·C ₆ H ₄ 3,4,5-(MeO) ₃ C ₆ H ₂	Q Q	Low	0 Low	3 65
Ph Ph	Q I	87 58	96	70 58					
Pn	P		94	71					

* Q = Quinoline, I = isoquinoline, P = phenanthridine. \dagger Yields for the first two methods are taken from ref. 1. ‡ Aliphatic acid chlorides cannot be used in this method. 3 L

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The yields obtained by use of the methylene chloride-water system, the aqueous system,¹ and the anhydrous hydrogen cyanide method ¹⁰ are compared in Table 2. Although yields are generally higher by the anhydrous hydrogen cyanide method, the convenience and generality of the methylene chloride-water method make it the best.

Although no systematic attempt was made to isolate the dimer (III), its presence was noted in a few cases in addition to that of pyruvoyl chloride. These are shown in Table 3. Reported preparations of Reissert compounds have involved the use of the acid

TABLE 3.

"Dimeric " products R·CO·O·CR(CN)₂.

		F	ound (%	6)		Re	quired (%)
R	М. р.	ć	н	Ň	Formula	Ċ	н	N
Et	$65-67^{\circ}$	57.8	6·0	16.9	$C_8H_{10}N_2O_2$	57.8	6.0	16.9
Cyclohexyl	54 - 55	70.3	$8 \cdot 2$	10.25	C ₁₆ H, N ₂ O ₂	70·1	8.0	10.2
Bu ^t	55 - 57	64.8	7.8	12.9	$C_{1,2}H_{1,8}N_{2}O_{2}$	64.8	8.2	12.6
<i>p</i> -C ₆ H ₄ Cl	161 - 162	58.0	$2 \cdot 4$	•	$C_{16}H_8Cl_2N_2O_2$	58.2	$2 \cdot 4$	

TABLE 4.

Formation of Reissert compounds from acid bromides and acid anhydrides.

	Yield	Yield (%)	Acyl		Yield	Yield (%)
Base	(%)	from R•COCl	compound	Base	(%)	from R·COCl
Q	8	50	Isobutyryl bromide	Q	3	18
Î	63	87	Isobutyryl bromide	Ĩ	6	11
I	24	87	Benzoyl bromide	Q	32	70
I	25	49	Benzoyl bromide	I	25	58
I	21	64	Benzoic anhydride	I	34	58
	Base Q I I I I I	Yield Base (%) Q 8 I 63 I 24 I 25 I 21	Yield Yield (%) Base (%) from R*COCI Q 8 50 I 63 87 I 24 87 I 25 49 I 21 64	YieldYield (%)AcylBase(%)from R•COClcompoundQ850Isobutyryl bromideI6387Isobutyryl bromideI2487Benzoyl bromideI2549Benzoyl bromideI2164Benzoic anhydride	YieldYield (%)AcylBase(%)from R·COClcompoundBaseQ850Isobutyryl bromideQI6387Isobutyryl bromideII2487Benzoyl bromideQ12549Benzoyl bromideI2164Benzoic anhydrideI	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$

TABLE 5.

Acid-catalyzed hydrolysis of Reissert compounds.

	Yield (%) of aldehyde *							
Acid chloride	Base	Method A	Method B	M. p.†				
Butyryl	I		57	119°				
m-Chlorobenzoyl	I	75		252				
p-Chlorobenzoyl	I	92		258				
Cyclohexanecarbonyl	I	76		168				
Cyclopentanecarbonyl	Q		84	154				
Decanoyl	ĩ		46	102				
p-Fluorobenzoyl	Q	97		274				
Furoyl	Ĩ	51		198				
Isobutyryl	Q		80	178				
p-Methoxybenzoyl	Q	96		248				
p-Methoxybenzoyl	Ĩ	90		247				
p-Methoxybenzoyl	Р	99		249				
1-Naphthoyl	Q	99		252				
2-Naphthoyl	Ĩ	90		266				
m-Nitrobenzoyl	Q	97		287				
m-Nitrobenzoyl	Ĩ	92		287				
Propionyl	1		75	152				
p-Trifluoromethylbenzoyl	I	60		$257 \ddagger$				
3,4,5-Trimethoxybenzoyl	Q	95		239 §				
Valeryl	ĩ		53	93				
* As 2 4-dinitrophenylhydrazone † M	n agrees	within 5° with	that reported	† Found				

* As 2,4-dinitrophenylhydrazone. † M. p. agrees within 5° with that reported. ‡ Found: C, 47.6; H, 2.6. $C_{14}H_9N_4O_4F_3$ requires C, 47.6; H, 2.2%. § Found: C, 50.9; H, 4.1. $C_{16}H_{16}N_4O_7$ requires C, 51.1; H, 4.3%.

chloride. As shown in Table 4 the acid bromide or anhydride can also be used but yields are then lower.

We also studied the acid-catalyzed hydrolysis of some of the compounds. As shown in Table 5 the aldehydes were obtained, as their 2,4-dinitrophenylhydrazones, in good yield.

¹⁰ Groscheintz and Fisher, J. Amer. Chem. Soc., 1941, 63, 2021.

EXPERIMENTAL

Recrystallizations were from 95% ethanol unless otherwise stated. Reagent-grade methylene chloride and potassium cyanide were used. Quinoline (synthetic), isoquinoline, phenanthridine, and acid bromides and anhydrides were used as obtained commercially. The acid chlorides were used as obtained commercially or were prepared by reaction of the acid and thionyl chloride.

Formation of Reissert Compounds.—The acid chloride (or acid bromide or anhydride) (0.031 mole) was added (aromatic acid chlorides in 2 hr., aliphatic acid chlorides in 30 min.; if solid, the minimum amount of methylene chloride) to a stirred mixture of quinoline (or isoquinoline or phenanthridine) (0.016 mole) in methylene chloride (20 ml.) and potassium cyanide (0.048 mole) in water (8 ml.). After an additional 6—8 hours' stirring, the layers were separated and the water layer was washed with methylene chloride (10 ml.). The combined methylene chloride solutions were washed with water (2×10 ml., 5% hydrochloric acid, water, 5% aqueous sodium hydroxide, and water, dried (MgSO₄), and evaporated, to give the Reissert compound which was crystallized from an appropriate solvent. In a few cases the dimer (III) was obtained during recrystallization. The results are shown in Tables 1—4.

Acid-catalyzed Hydrolysis of Reissert Compounds.—(A; ref. 11). Concentrated hydrochloric acid (11 ml. per 0.5 g. of Reissert compound) was added to an equimolar mixture of Reissert compound and 2,4-dinitrophenylhydrazine, and the mixture was heated for 30 min., then left at room temperature for 2 days. The quantity of aldehyde 2,4-dinitrophenylhydrazone was determined as shown in Table 5.

(B) In a few cases where method (A) gave impure or tarry products, hydrochloric acid (6 ml.) and water (5 ml.) were used in place of hydrochloric acid (11 ml.).

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¹¹ McEwen, Terss, and Elliott, J. Amer. Chem. Soc., 1952, 74, 3605.