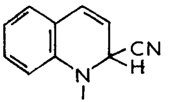
328. *Reissert Compound Studies. Part V.* Nature of the Acid Chloride.*

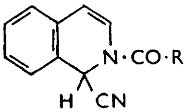
By Frank D. Popp and Aida Soto.

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. Acid-catalyzed hydrolysis of the Reissert compounds gave the expected aldehydes.

Reissert compounds[1] (I and II) result from the addition of an acyl and a cyano-group to a wide variety of quinolines[2] 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]



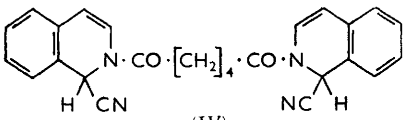
(I)



(II)

R·CO·O·CR(CN)$_2$

(III)



(IV)

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; $\mathrm{R} = \mathrm{Bu}^{t}$) 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 reported[9] 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.

[2] Popp, Blount, and Melvin, *J. Org. Chem.*, 1961, **26**, 4930.

[3] 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 earlier work of McEwen and his co-workers.

[8] Popp and Blount, *Chem. and Ind.*, 1961, 550.

[9] Buchanan, Cook, and Loudon, *J.*, 1944, 325.

TABLE 1.

Formation of Reissert compounds.

R in R·COCl (or R·CO)	Base *	Yield (%)	M. p.†	Reported m. p.‡	Found (%)			Formula	Required (%)		
					C	H	N		C	H	N
Me	Q	50	92—93°	96—97°							
Me	I	87	119—120	119—121							
Et	Q	12	46—48	49—50							
Et	I	49	115—117		73·55	5·6	13·1	$C_{13}H_{12}N_2O$	73·5	5·7	13·2
Pr^n	Q	25	97—98	97—98							
Pr^n	I	64	87—88		74·6	6·1	12·3	$C_{14}H_{14}N_2O$	74·3	6·2	12·4
Pr^i	Q	18	126—127	129—130							
Pr^i	I	11	87—88		74·3	6·4	12·4	$C_{14}H_{14}N_2O$	74·3	6·2	12·4
Bu^n	I	35	88—89		75·1	6·8	11·7	$C_{15}H_{16}N_2O$	75·0	6·7	11·7
C_9H_{19}	I	Trace	53—55		77·2	8·2	9·2	$C_{20}H_{26}N_2O$	77·4	8·4	9·0
(Cinnamoyl)	Q	43	149—150	149—150							
(Cinnamoyl)	I	64	164—165	160—162							
Ph	Q	70	154—155	154—155							
Ph	I	69	124—125	124—126							
Ph	P	71	140—142	140—142							
p-C_6H_4Cl	Q	20	145—147	143—144							
p-C_6H_4Cl	I	30	150—151	155—156	69·35	4·0	9·7	$C_{17}H_{11}ClN_2O$	69·3	3·8	9·5
m-C_6H_4Cl	I	17	185—187		69·1	3·9	9·4	$C_{17}H_{11}ClN_2O$	69·3	3·8	9·5
p-C_6H_4F	Q	50	112—114		73·1	3·7	9·8	$C_{17}H_{11}FN_2O$	73·4	4·0	10·1
p-C_6H_4F	I	37	178—179		73·4	4·3	10·15	$C_{17}H_{11}FN_2O$	73·4	4·0	10·1
(2-Furoyl)	I	63	110—111		71·9	3·75	11·4	$C_{15}H_{10}N_2O_2$	72·0	4·0	11·2
p-MeO·C_6H_4	Q	80	119—120	120							
p-MeO·C_6H_4	I	72	173—174		74·2	4·7	9·7	$C_{18}H_{14}N_2O_2$	74·5	4·9	9·65
p-MeO·C_6H_4	P	60	153—154		77·8	4·75	8·2	$C_{22}H_{16}N_2O_2$	77·6	4·9	8·2
1-$C_{10}H_7$	Q	63	193—195 § 202—204		81·0 81·1	4·9 4·6	9·0 9·0	$C_{21}H_{14}N_2O$	81·3	4·5	9·0
1-$C_{10}H_7$	I	11	198—200		81·2	4·55	8·9	$C_{21}H_{14}N_2O$	81·3	4·5	9·0
2-$C_{10}H_7$	I	12	165—167		81·1	4·8	9·1	$C_{21}H_{14}N_2O$	81·3	4·5	9·0
m-NO_2·C_6H_4	Q	12	165—166	171							
m-NO_2·C_6H_4	I	12	183—184		66·95	3·4	13·5	$C_{17}H_{11}N_3O_3$	66·9	3·6	13·8
p-NO_2·C_6H_4	Q	3	166—167		66·55	3·75	13·8	$C_{17}H_{11}N_3O_3$	66·9	3·6	13·8
p-NO_2·C_6H_4	I	3	177—178		66·8	3·6	13·9	$C_{17}H_{11}N_3O_3$	66·9	3·6	13·8
p-CF_3·C_6H_4	I	5	159—160		65·6	3·6	8·3	$C_{18}H_{11}F_3N_2O$	65·85	3·4	8·5
3,4,5-$(MeO)_3C_6H_2$	Q	65	174—175	176—177							
Cyclopropane	Q	77	131—132		74·7	5·3	12·6	$C_{14}H_{12}N_2O$	75·0	5·4	12·5
Cyclopropane	I	52	109—111		75·0	5·2	12·6	$C_{14}H_{12}N_2O$	75·0	5·4	12·5
Cyclopentane	Q	33	117—118		76·0	6·4	11·1	$C_{16}H_{16}N_2O$	76·2	6·4	11·1
Cyclopentane	I	10	87—88		76·3	6·2	10·9	$C_{16}H_{16}N_2O$	76·2	6·4	11·1
Cyclohexane	I	Trace	127—128		76·95	6·6	10·75	$C_{17}H_{18}N_2O$	76·7	6·8	10·5
(Adipoyl)	Q	Trace	178—179		73·45	5·15	13·3	$C_{26}H_{22}N_4O_2$	73·9	5·2	13·3
(Adipoyl)	I	6	189—190 ¶		73·8	5·4	13·5	$C_{26}H_{22}N_4O_2$	73·9	5·2	13·3
(Phthaloyl)	Q	Trace	234—235 ¶		75·7	4·15	12·9	$C_{28}H_{18}N_4O_2$	76·0	4·1	12·7
(Phthaloyl)	I	Trace	197—199		75·75	4·3	12·4	$C_{28}H_{18}N_4O_2$	76·0	4·1	12·7

* 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.

R in R·COCl (or R·CO)	Base *	Yields (%) † In H_2O	Yields (%) † In HCN–C_6H_6	Yields (%) † In CH_2Cl_2–H_2O
Me	Q	‡	74	50
Me	I	‡	85	87
Et	Q	‡	10	12
Pr^n	Q	‡	64	25
Pr^i	Q	‡	28	18
(Cinnamoyl)	Q	34	91	43
(Cinnamoyl)	I		91	64
Ph	Q	87	96	70
Ph	I	58		58
Ph	P		94	71
p-C_6H_4Cl	Q	26	77	20
p-C_6H_4Cl	I	11		30
p-MeO-C_6H_4	Q	51	88	80
m-NO_2·C_6H_4	Q		Low	12
p-NO_2·C_6H_4	Q		0	3
3,4,5-$(MeO)_3C_6H_2$	Q	Low	Low	65

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

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

TABLE 3.

" Dimeric " products $R{\cdot}CO{\cdot}O{\cdot}CR(CN)_2$.

R	M. p.	Found (%) C	H	N	Formula	Required (%) C	H	N
Et	65—67°	57·8	6·0	16·9	$C_8H_{10}N_2O_2$	57·8	6·0	16·9
Cyclohexyl	54—55	70·3	8·2	10·25	$C_{16}H_{22}N_2O_2$	70·1	8·0	10·2
Bu^t	55—57	64·8	7·8	12·9	$C_{12}H_{18}N_2O_2$	64·8	8·2	12·6
p-C_6H_4Cl	161—162	58·0	2·4	—	$C_{16}H_8Cl_2N_2O_2$	58·2	2·4	—

TABLE 4.

Formation of Reissert compounds from acid bromides and acid anhydrides.

Acyl compound	Base	Yield (%)	Yield (%) from R·COCl	Acyl compound	Base	Yield (%)	Yield (%) from R·COCl
Acetyl bromide	Q	8	50	Isobutyryl bromide	Q	3	18
Acetyl bromide	I	63	87	Isobutyryl bromide	I	6	11
Acetic anhydride	I	24	87	Benzoyl bromide	Q	32	70
Propionic anhydride	I	25	49	Benzoyl bromide	I	25	58
Butyric anhydride	I	21	64	Benzoic anhydride	I	34	58

TABLE 5.

Acid-catalyzed hydrolysis of Reissert compounds.

Acid chloride	Base	Yield (%) of aldehyde * 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	I		46	102
p-Fluorobenzoyl	Q	97		274
Furoyl	I	51		198
Isobutyryl	Q		80	178
p-Methoxybenzoyl	Q	96		248
p-Methoxybenzoyl	I	90		247
p-Methoxybenzoyl	P	99		249
1-Naphthoyl	Q	99		252
2-Naphthoyl	I	90		266
m-Nitrobenzoyl	Q	97		287
m-Nitrobenzoyl	I	92		287
Propionyl	I		75	152
p-Trifluoromethylbenzoyl	I	60		257 ‡
3,4,5-Trimethoxybenzoyl	Q	95		239 §
Valeryl	I		53	93

* 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%.

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 ($MgSO_4$), 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.).

We express our appreciation to the Research Corporation for a grant which supported this work. A portion of this material was presented at the 142nd National Meeting of the American Chemical Society, September 1962.

DEPARTMENTS OF CHEMISTRY, UNIVERSITY OF MIAMI, CORAL GABLES, FLORIDA, U.S.A.,
AND CLARKSON COLLEGE OF TECHNOLOGY,
POTSDAM, NEW YORK, U.S.A.

[*Received, October 11th*, 1962.]

---

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