

Department of Chemistry, Clarkson College of Technology

## Reisert Compound Studies. XV.

## Preparation and Reaction of the Reisert Anion at Room Temperature (1)

Frank D. Popp and John M. Wefer (2)

The anions (I and II) have been conveniently generated from the parent Reisert compounds in dimethylformamide using sodium hydride. Rearrangements to ketones, alkylations, and participation of I and II in other nucleophilic displacements have been investigated.

In an earlier communication (3) we reported that the anions (I and II) of the corresponding Reisert compounds (III and IV) may be conveniently generated and allowed to react at room temperature in dimethylformamide using sodium hydride as the base. Previous systems for the generation of these anions have involved high (for example, refluxing xylene) or low (for example,  $-10^{\circ}$ ) temperatures (4).

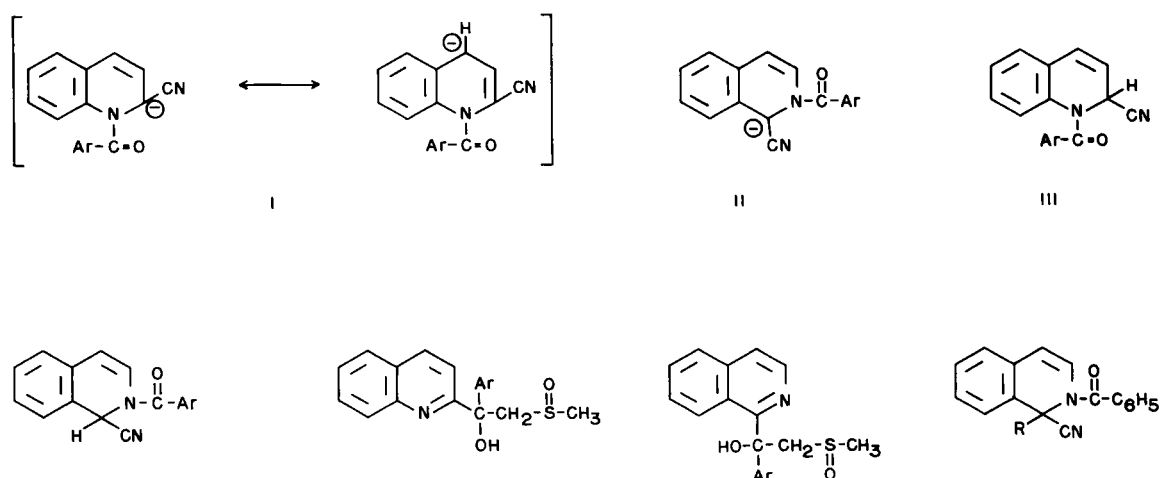
Treatment of a dimethylformamide solution of III or IV with sodium hydride caused the immediate appearance of a red color (the anion) accompanied by vigorous evolution of hydrogen. After treatment with ice the corresponding aryl-2-quinolyl or aryl-1-isoquinolyl ketones were isolated as summarized in Table I. This method greatly increases the generality of this previously reported (5) rearrangement.

The anion could also be generated in dimethylsulfoxide but the initially formed ketones reacted further with the solvent anion to give products of the type V and VI. That this was the case was demonstrated by the reaction of aryl-1-isoquinolyl

ketones with dimethylsulfoxide and sodium hydride to give VI. When a solution of IV ( $\text{Ar} = \text{C}_6\text{H}_5$ ) in dimethylformamide containing two equivalents of dimethylsulfoxide was treated with sodium hydride, 1-benzoylisoquinoline was obtained rather than VI. Compound VI ( $\text{Ar} = \text{C}_6\text{H}_5$ ) was unchanged upon further treatment with sodium hydride in dimethylformamide.

The presence of an alkyl halide prevented rearrangement of II ( $\text{Ar} = \text{C}_6\text{H}_5$ ) to 1-benzoylisoquinoline and 1-alkyl-2-benzoyl-1,2-dihydroisoquinolondinitriles (VII) were isolated in excellent yield as shown in Table III. In all cases tried, basic hydrolysis conveniently gave the desired 1-alkylisoquinoline. Use of 1,6-dibromohexane led to the formation of compound VIII which was hydrolyzed to 1,1'-bis(hexamethylene)isoquinoline (IX). Although several alkylations of IV have been previously reported using phenyllithium in ether-dioxane at  $-10^{\circ}$ , this low temperature procedure is less convenient than that described herein and gives generally lower yields.

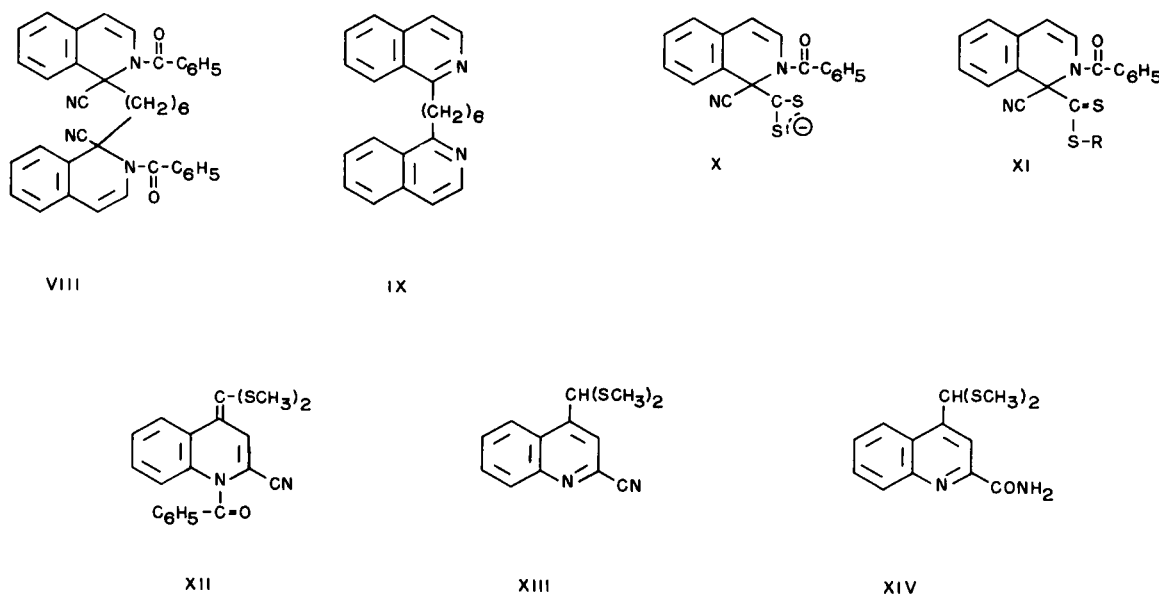
Addition of sodium hydride to a dimethylformamide



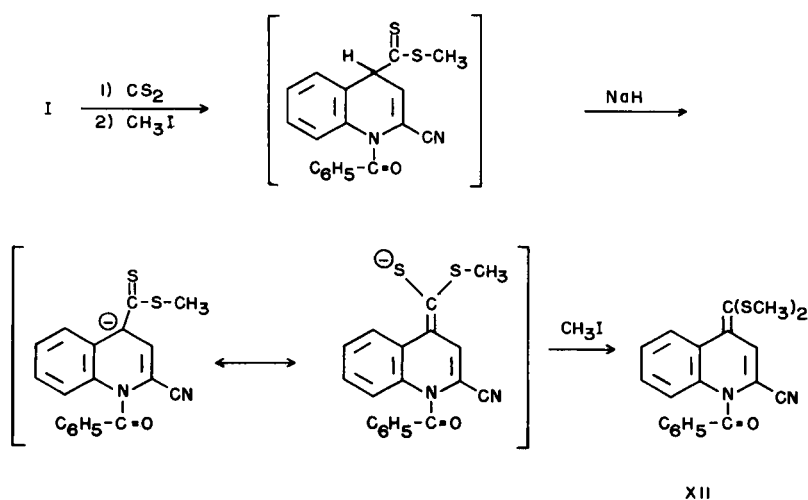
solution of IV (Ar = C<sub>6</sub>H<sub>5</sub>) containing excess carbon disulfide caused the appearance of a brilliant yellow color. After treatment with ice, IV was recovered unchanged (not rearranged) indicating that an adduct of the type X was probably formed and decomposed upon attempted isolation. Addition of an alkyl halide two to five minutes after the start of the reaction permitted the isolation of 1-cyano-2-benzoyl-1,2-dihydrodithioisoquinaldic acid alkyl esters (XI). The n.m.r. spectrum of XI (R = CH<sub>3</sub>) exhibits a 3 proton singlet at  $\delta = 2.60$  corresponding to one methyl group and two signals each of area 1 at  $\delta = 5.72$  and  $\delta = 6.80$  corresponding to the vinylic protons

on carbons 3 and 4 ( $J = 8.2$  cps). The aromatic protons appear as a multiplet of area 9 at  $\delta = 7.52$ .

Substitution of III (Ar = C<sub>6</sub>H<sub>5</sub>) in the reaction with carbon disulfide and methyl iodide did not lead to a product analogous to XI but rather to compound XII. The n.m.r. spectrum of XII displays only two proton signals: an aromatic multiplet at  $\delta = 7.0$  and a singlet at  $\delta = 2.10$  corresponding to methyl protons. The relative area of aromatic to methyl protons is  $> 1.6:1$ , confirming the presence of two equivalent methyl groups. The signal from the proton on carbon 3 is masked within the aromatic multiplet due to the high deshielding effect of two powerfully electron



Scheme 1



withdrawing groups.

It should be noted that methylation of III (Ar = C<sub>6</sub>H<sub>5</sub>) has been reported (5) to occur at the 4 position indicating that the charge on I is considerably delocalized to carbon 4. The formation of XII may be rationalized by the stepwise removal of two protons from the Reissert compound as illustrated in scheme 1. Alumina chromatography of pure XII gave compounds XIII and XIV. Acidic hydrolysis of either XIII or XIV gave 4-formylquinaldamide.

The infrared spectra of XIII and XIV are consistent with the structures shown, but additional evidence was obtained from the n.m.r. spectrum of

XIII. This spectrum displays a 6 proton singlet at  $\delta = 2.1$  and a signal corresponding to the dithioacetal CH group at  $\delta = 5.5$ . All the other proton signals appear in a complex multiplet at about  $\delta = 8$ .

In addition to the reactions discussed above, condensation of several other electrophiles with II (Ar = C<sub>6</sub>H<sub>5</sub>) were attempted, as summarized in Table V. The isolation of 1-benzoylisoquinoline indicates that rearrangement took place in preference to nucleophilic displacement. The recovery of unchanged Reissert compound would seem to indicate that displacement took place but that the reaction was reversible during work-up.

TABLE I

Rearrangement of III and IV to Ketones (a)

Ketone	Yield	M. p. (b)	Analyses					
			Calcd.			Found		
			C	H	N	C	H	N
1-Benzoylisoquinoline	56	75-76	reported (c) m. p. 76-77°					
1-( <i>p</i> -Chlorobenzoyl)isoquinoline	24	97-100	71.78	3.77	5.23	71.65	3.68	5.09
1-( <i>p</i> -Bromobenzoyl)isoquinoline	21	95-98	reported (d) m. p. 100-101°					
2-Benzoylquinoline	92	105-107	reported (c) m. p. 109-110°					
2-( <i>p</i> -Fluorobenzoyl)quinoline	99	129-130	76.48	4.01	5.58	76.33	4.07	5.59
2-( <i>p</i> -Methoxybenzoyl)quinoline	83	82-83	77.55	4.98	5.32	77.36	5.16	5.22
2-(3,4,5-Trimethoxybenzoyl)-quinoline	53	159-160 (e)	70.57	5.30	4.33	70.71	5.41	4.36

(a) In dimethylformamide at room temperature, see experimental. Reissert compounds (III and IV) prepared according to ref. 6. (b) Recrystallization from hexane unless otherwise noted. (c) Ref. 5. (d) Ref. 7. (e) Recrystallized from hexane-ethyl acetate.

TABLE II

Preparation of Compounds of Types V and VI

Ar	Type	Yield	M. p. (a)	Analyses					
				Calcd.			Found		
				C	H	N	C	H	N
C <sub>6</sub> H <sub>5</sub>	V	32	153-157	69.42	5.50	4.50	69.21	5.59	4.54
C <sub>6</sub> H <sub>5</sub>	VI	83	250-251 (b)	69.42	5.50	4.50	69.36	5.55	4.43 (c)
<i>p</i> -CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub>	VI	65	155-156	66.84	5.61	4.10	66.62	5.75	4.16

(a) Recrystallized from hexane-ethyl acetate unless otherwise noted. (b) Recrystallized from 95% ethanol. (c) *Anal.* Calcd.: S, 10.29. Found: S, 10.38.

TABLE III

## Preparation of VII (a)

R (b)	Yield	M. p. (c)	Analyses					
			Calcd.			Found		
			C	H	N	C	H	N
CH <sub>3</sub>	98	120-121	reported (d) m. p. 119-121°					
<i>n</i> -C <sub>3</sub> H <sub>7</sub>	99	119-121	79.44	6.00	9.27	79.20	6.13	9.29
<i>i</i> -C <sub>3</sub> H <sub>7</sub>	91	128-130	79.44	6.00	9.27	79.40	6.10	9.20
<i>n</i> -C <sub>4</sub> H <sub>9</sub>	98	106-107 (e, f)	79.72	6.37	8.86	79.65	6.38	8.78
C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> (g)	99	gum (e, h)						
<i>o</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> CH <sub>2</sub> (i)	99	145-147 (j)	82.39	5.53	7.69	82.17	5.44	7.63
CH <sub>2</sub> CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub> (k)	94	129-131	72.82	5.24	8.09	72.75	5.16	8.08

(a) In dimethylformamide at room temperature, see experimental. (b) Alkyl iodide used unless otherwise noted. (c) Recrystallized from 95% ethanol. (d) Ref. 5. (e) Reported as oil (ref. 5). (f) Hydrolyzed to 1-(*n*-butyl)isoquinoline, picrate m.p. 185-186°; reported (5) m.p. 185.5°. (g) Benzyl chloride used. (h) Hydrolyzed to 1-benzylisoquinoline, picrate m.p. 182-184°; reported (5) m.p. 184°. (i) *o*-Methylbenzyl bromide used. (j) Hydrolyzed to 1-(*o*-methylbenzyl)isoquinoline, m.p. 44-45° from hexane; reported m.p. 60-62° (9). *Anal.* Calcd. for C<sub>17</sub>H<sub>15</sub>N: C, 87.52; H, 6.48; N, 6.00. Found: C, 87.44; H, 6.36; N, 5.96. Picrate m.p. 183-184° from ethanol; reported (9) m.p. 180-181°. (k) Ethyl chloroacetate used.

TABLE IV

## Preparation of XI

R	Yield	M. p. (a)	Analyses							
			Calcd.				Found			
			C	H	N	S	C	H	N	S
Methyl	99	174-176	65.11	4.03	7.99	18.30	65.12	4.11	8.07	18.24
Benzyl	99	139-141	70.39	4.25	6.57	15.04	70.54	4.26	6.64	15.16

(a) Recrystallized from 95% ethanol.

TABLE V

Miscellaneous Reactions of the Anion (II, Ar = C<sub>6</sub>H<sub>5</sub>) (a)

Reactant	Product	Yield	M. p.
Benzaldehyde	Phenyl-1-isoquinolyl carbinyl benzoate	65	165-166 (b)
Acrylonitrile	2-Formamido-3-phenyl-7, 8-benzopyrrocoline	98	160-165 (c)
Ethylene oxide	1-Benzoylisoquinoline	31	75-77 (d)
Vinyl ferrocene	1-Benzoylisoquinoline	low	76-77 (d)
Epichlorohydrin	1-Benzoylisoquinoline	30	75-76 (d)
$\delta$ -Valerolactam	1-Benzoylisoquinoline	12	75-76 (d)
Phenylisocyanate	unchanged IV (Ar = C <sub>6</sub> H <sub>5</sub> )	99	120-124 (d)
Ethyl chloroformate	unchanged IV (Ar = C <sub>6</sub> H <sub>5</sub> )	99	124-126 (d)
Acetophenone	solid (e)	low	141-142

(a) Reactions were carried out as described in the experimental section for alkylation of IV (Ar = C<sub>6</sub>H<sub>5</sub>) substituting the above reactants for the alkyl halide. (b) Reported (10) m.p. 166.6-167.6°. (c) Reported (11) m.p. 168-169°. (d) Mixed m.p. and infrared spectrum identical with authentic sample. (e) Yellow crystals from ethanol. *Anal.* Found: C, 81.34, 81.38; H, 4.90, 4.96; N, 4.13, 4.16.

## EXPERIMENTAL

Ketones from III and IV.

Compound III or IV (6) (0.01 mole) was dissolved in 40 ml. of dimethylformamide and 30% sodium hydride in oil (0.01 mole) was added to the stirred solution. A red color formed which faded in several minutes. After stirring for 1.5 hours the mixture was poured onto ice (500 g.) and the products described in Table I were isolated.

Formation of Compounds V and VI.

Substitution of dimethylsulfoxide for dimethylformamide in the above procedure permitted the isolation of the products described in Table II.

Alkylation of IV.

Compound IV (0.01 mole) was dissolved in 40 ml of dimethylformamide and an alkyl halide (0.01 mole to 0.02 mole for more volatile halides) was added to the stirred solution followed by the addition of 30% sodium hydride in oil (0.01 mole). Stirring was continued for 1.5 hours and the reaction mixture was poured onto cracked ice. Products of the type VII were obtained as summarized in Table III.

Use of 1,6-dibromohexane permitted the isolation of VIII, m.p. 190-193° from ethanol, in 99% yield.

*Anal.* Calcd. for  $C_{10}H_{14}N_2O_2$ : C, 79.71; H, 5.69; N, 9.30. Found: C, 79.68; H, 5.74; N, 9.22.

Hydrolysis of VIII with alcoholic potassium hydroxide (5) gave IX as an oil in 85% yield. Dipicrate, m.p. 249-250° from ethanol-dimethylformamide.

*Anal.* Calcd. for  $C_{18}H_{20}N_2O_4$ : C, 54.14; H, 3.79; N, 14.03. Found: C, 54.15; H, 3.85; N, 14.00.

Formation of XI and XII.

These preparations were carried out in dimethylformamide as described above except that 0.04 mole of carbon disulfide were added prior to addition of sodium hydride and 0.01-0.02 mole of benzyl bromide or methyl iodide were added 2-5 minutes after the addition of the base. Use of IV (Ar =  $C_6H_5$ ) gave the dithioesters XI described in Table IV.

Use of III (Ar =  $C_6H_5$ ) and methyl iodide gave compound XII in nearly quantitative yield, orange needles, m.p. 155-157° from ethanol.

*Anal.* Calcd. for  $C_{20}H_{18}N_2OS_2$ : C, 65.90; H, 4.42; N, 7.69; S, 17.60. Found: C, 65.92; H, 4.43; N, 7.47; S, 17.57.

Formation of XIII and XIV.

Purified XII was dissolved in benzene and chromatographed on Merck alumina (not acid washed). Elution with benzene gave a yellowish solid, m.p. 138-140° from ethanol, in 83% yield.

*Anal.* Calcd. for  $C_{13}H_{12}N_2S_2$ : C, 59.96; H, 4.65; N, 10.76; S, 24.51. Found: C, 59.65; H, 4.89; N, 10.74; S, 24.51.

Gradual change of eluting solvent to chloroform brought down XIV, m.p. 180-181° from ethanol, in 8.5% yield.

*Anal.* Calcd. for  $C_{13}H_{14}N_2OS_2$ : C, 56.08; H, 5.07; N, 10.06; S, 23.04. Found: C, 55.85; H, 5.03; N, 10.15; S, 23.15.

Acid Hydrolysis of XIII and XIV.

Treatment of XIII or XIV with refluxing concentrated hydrochloric acid for 30 minutes in the presence of 2,4-dinitrophenylhydrazine gave 4-formylquinaldamide-2,4-dinitrophenylhydrazone, m.p. 350°.

*Anal.* Calcd. for  $C_{17}H_{12}N_6O_5$ : C, 53.69; H, 3.18; N, 22.10. Found: C, 53.56; H, 3.39; N, 21.96.

## REFERENCES

- (1) Part XIV, F. D. Popp and J. M. Wefer, *Chem. Commun.*, 59 (1967).
- (2) U.S.P.H.S. Predoctoral Fellow 1-F1-GM-25,896 from Institute of General Medical Sciences.
- (3) F. D. Popp and J. M. Wefer, *Chem. Commun.*, 207 (1966).
- (4) W. E. McEwen and R. L. Cobb, *Chem. Rev.*, 55, 511 (1955).
- (5) V. Boekelheide and J. Weinstock, *J. Am. Chem. Soc.*, 74, 660 (1952).
- (6) F. D. Popp and A. Soto, *J. Chem. Soc.*, 1760 (1963).
- (7) H. W. Gibson and F. D. Popp, *ibid.*, 1860 (1966).
- (8) W. E. McEwen, R. H. Terss and I. W. Elliott, *J. Am. Chem. Soc.*, 74, 3605 (1952).
- (9) J. v. Braun and J. Nelles, *Ber.*, 70, 1767 (1937).
- (10) L. R. Walters, N. T. Iyer, and W. E. McEwen, *J. Am. Chem. Soc.*, 80, 1177 (1958).
- (11) V. Boekelheide and J. C. Godfrey, *ibid.*, 75, 3679 (1953).

Received December 28, 1966

Potsdam, N. Y. 13676