

Reisert Compound Studies. XVII.  
Phosphorus-containing Reisert Compound Analogues (1)

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The reaction of isoquinoline, potassium cyanide, and chlorophosphates or chlorothiophosphates leads to the formation of phosphorus containing analogues of Reisert compounds. These analogues can be converted by base to an anion which undergoes elimination to isoquinaldonitrile or which can be alkylated. Acid-catalysed hydrolysis of the analogues leads to isoquinoline.

As part of our study of the chemistry of Reisert compounds (1,3) we have been investigating the effect of replacing the acyl group of a normal Reisert compound (I and II) by other groupings. Thus we have prepared and have studied the chemistry of III (4), IV (5), and V (6). We now wish to report on the preparation of Reisert compound analogues of the type VI from chlorophosphates and chlorothiophosphates.

A number of arylchlorophosphates, alkylchlorophosphates, and alkylchlorothiophosphates were allowed to react with isoquinoline and potassium cyanide in methylene chloride-water to give compounds of the type VI. The compounds that were prepared in this manner are included

in Table I. As is characteristic of Reisert compounds and the analogues III and IV, the infrared spectrum of these phosphorus analogues did not exhibit any nitrile absorption. The P-O-C stretching vibration was present at about 1040 and 780  $\text{cm}^{-1}$  in the alkyl esters and at 1190 and 970  $\text{cm}^{-1}$  in the aryl esters. The phosphorus oxygen and phosphorus sulfur stretching vibrations were present at 1290 and 675-700  $\text{cm}^{-1}$  respectively. The N.M.R. spectra of VI ( $Z = S$ ,  $R = \text{CH}_3$ ) showed methyl peaks at 3.66 and 3.92  $\delta$ , aromatic peaks centered at 7.45  $\delta$ , and the protons on carbons one, three, and four at 6.30, 6.90, and 6.17  $\delta$  respectively. The protons on carbons one and three and the methyl protons were split by the phosphorus.

The anion of the phosphorus Reisert compound analogues could be generated with sodium hydride in dimethylformamide and was deep red-brown in solution. Treatment of the anion from VI ( $Z = S$ ,  $R = \text{C}_2\text{H}_5$ ) with methyl iodide yielded the alkylated compound VII, which was hydrolyzed by base to isoquinaldine. In the absence of methyl iodide the anion (from VI,  $R = \text{C}_2\text{H}_5$ ,  $Z = S$  or O) underwent elimination to give isoquinaldonitrile. This latter compound was also obtained when the anion, generated by *n*-butyllithium at  $-30^\circ$ , was treated with benzaldehyde. The anion thus appears to lie somewhere between those of I and III in stability and reactivity.

Acid hydrolysis of VI ( $R = \text{C}_2\text{H}_5$ ,  $Z = \text{O}$  or S) produced isoquinoline with hydrogen sulfide being released in the reaction where Z is S. This behavior on acid-catalyzed hydrolysis is typical of that of Reisert compound analogues III and V.

The substitution of quinoline for isoquinoline in the preparation of the above compounds led always to the recovery of quinoline. It should be noted that a Reisert compound analogue of the types III and IV also could not be isolated in the quinoline series although the evidence indicated that an unstable quinoline analogue of III did form (4).

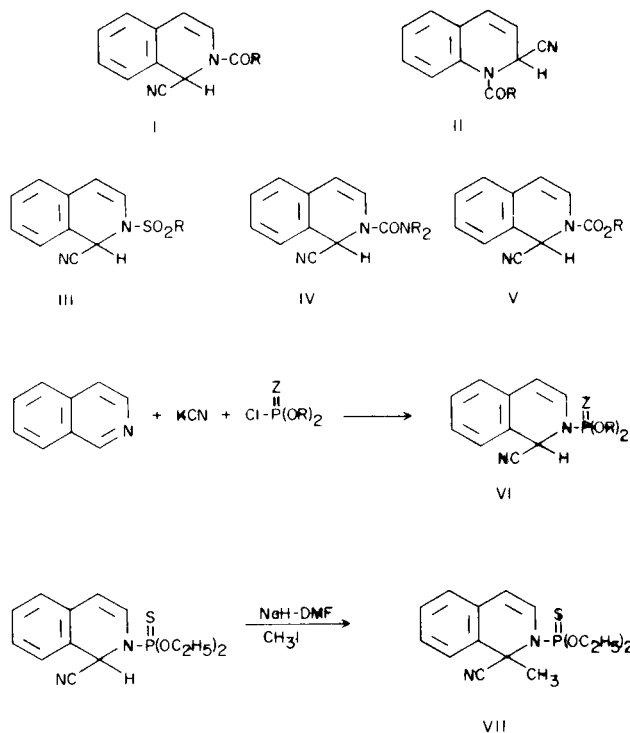
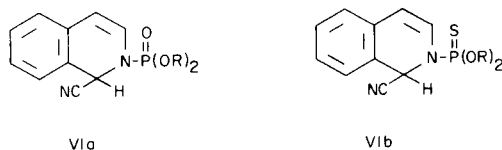


TABLE I



Type	R	Yield	M.p. (a)	Analyses							
				Calcd.				Found			
				C	H	N	P	C	H	N	P
VIa	C <sub>2</sub> H <sub>5</sub>	30	60-61	57.53	5.86	9.59	10.60	57.43	5.77	9.57	10.51
VIa	C <sub>6</sub> H <sub>5</sub>	21	111-113	68.04	4.41	7.21		67.90	4.43	7.16	
VIa	<i>p</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	38	134-135	69.22	5.21	6.73	7.44	69.22	5.12	6.66	7.32
VIb	CH <sub>3</sub>	85	78-80	51.42	4.67	10.00		51.53	4.72	10.09	
VIb	C <sub>2</sub> H <sub>5</sub> (b)	62	66-67	54.53	5.56	9.09	10.05	54.56	5.56	9.12	10.17

(a) Recrystallized from 95% ethanol. (b) See R. W. Young and E. Gelblum, U. S. Patent 3,249,614 (1966) for a previous report of this compound.

#### EXPERIMENTAL (7)

##### Phosphorus Reissert Compound Analogues (VI).

To a mixture of 4 g. (0.031 mole) of isoquinoline in 40 ml. of methylene chloride and 7.2 g. (0.11 mole) of potassium cyanide in 16 ml. of water was added the alkyl or aryl chlorophosphates (0.062 mole) or the alkyl chlorothiophosphates (0.062 mole) dropwise with stirring over a 2 hour period. Solid chlorophosphates were dissolved in a minimum amount of methylene chloride for the addition. After stirring an additional 2 hours the layers were separated and the aqueous layer washed with methylene chloride. The combined methylene chloride layers were washed with water, 10% hydrochloric acid, water, 5% sodium hydroxide and water and dried over magnesium sulfate. Concentration of the methylene chloride gave compounds of the type VI as indicated in Table I. Typical infrared (potassium bromide pellets) and N.M.R. (carbon tetrachloride) data are included in the discussion.

##### Methylation of VI.

To a solution of 0.01 mole of VI (Z = S, R = C<sub>2</sub>H<sub>5</sub>) in 40 ml. of dimethylformamide was added 0.02 mole of methyl iodide. To this solution was added 0.01 mole of sodium hydride (30% in oil). After 2 hours of stirring the reaction mixture was poured onto 500 g. of ice and filtered to give a 99% yield of VII, m.p. 66-68°.

*Anal.* Calcd. for C<sub>15</sub>H<sub>19</sub>N<sub>2</sub>O<sub>2</sub>PS: C, 55.89; H, 5.94; N, 8.69; S, 9.95. Found: C, 56.09; H, 6.02; N, 8.61; S, 10.08.

##### Base Hydrolysis of VII.

To 0.003 mole of VII in 20 ml. of ethanol and 8 ml. of water

was added 3 g. of sodium hydroxide and the mixture was refluxed with stirring for 12 hours. Concentration of the ethanol, extraction of the aqueous phase with ether and concentration of the ether gave a 96% yield of 1-methylisoquinoline identified as its picrate, m.p. 235-236° alone and on mixing with 1-methylisoquinoline picrate.

##### Reaction of VI with Sodium Hydride.

To 0.005 mole of VI (R = C<sub>2</sub>H<sub>5</sub>, Z = O or S) in 40 ml. of dimethylformamide was added 0.005 mole of sodium hydride (30% in oil) with continuous stirring. After 2 hours the mixture was poured onto ice and extracted with ether. Concentration of the ether gave a 90-95% yield of isoquinaldonitrile, m.p. 86-88° alone and on mixing with isoquinaldonitrile. The infrared spectra showed a strong nitrile absorption at 2235 cm<sup>-1</sup>.

##### Attempted Condensation of VI with Benzaldehyde.

To a solution of 0.005 mole of VI (R = C<sub>2</sub>H<sub>5</sub>, Z = O or S) in 50 ml. of anhydrous dioxane and 100 ml. of anhydrous ether maintained at -30° under a nitrogen atmosphere was added 0.005 mole of *n*-butyllithium. To the resulting anion was added 0.005 mole of benzaldehyde in ether. After 2 hours in the cold the mixture was allowed to stir for 10 hours at room temperature. Isoquinaldonitrile was the only identifiable product from this reaction.

##### Acid Hydrolysis of VI.

A mixture of 0.008 mole of VI (R = C<sub>2</sub>H<sub>5</sub>, Z = O or S), 2.1 ml. of glacial acetic acid, and 2.1 ml. of fuming hydrobromic acid was refluxed for 1.5 hours. (After 5 minutes of heating evolution of hydrogen sulfide was observed when Z = S). The

mixture was cooled, diluted with water, made alkaline, and extracted with ether to give a 60% yield of isoquinoline. The picrate had m.p. 222-225<sup>o</sup> and was undepressed when mixed with isoquinoline picrate.

## REFERENCES

- (1) Part XVI: J. M. Wefer and F. D. Popp, *J. Org. Chem.*, **32**, 1999 (1967).
- (2) N.S.F., Undergraduate Research Participant.
- (3) F. D. Popp, *Adv. Heterocyclic Chem.*, **9**, 1 (1968).
- (4) J. M. Wefer, A. Catala, and F. D. Popp, *J. Org. Chem.*, **30**, 3075 (1965).
- (5) F. D. Popp, J. M. Wefer, and A. Catala, *J. Heterocyclic Chem.*, **2**, 317 (1965).
- (6) J. M. Wefer, L. E. Katz, C. W. Klinowski, and F. D. Popp, unpublished results reported in part at the First International Congress of Heterocyclic Chemistry, Albuquerque, N. M., June 12-15, 1967 and at the 155th National American Chemical Society Meeting.
- (7) Analyses by Spang Microanalytical Lab., Ann Arbor, Mich. All melting points are in capillaries and are corrected.

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