

The Vilsmeier-Haack Reaction. IV.  
Reaction of Phosphorus Oxychloride-Dimethylformamide With Semicarbazones

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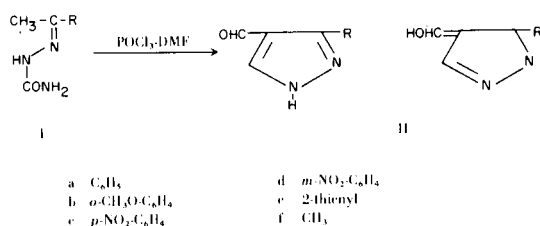
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Ketone semicarbazones react with two moles of phosphorus oxychloride-dimethylformamide with the formation of 3-substituted pyrazole-4-carboxaldehydes. Aldehyde semicarbazones give, with one mole of phosphorus oxychloride-dimethylformamide, amidazines.

In continuation to previous work (1) on the cyclization of ketone phenylhydrazones to 1-substituted pyrazole-4-carboxaldehydes, the reaction of phosphorus oxychloride-dimethylformamide (2) with ketone and with aldehyde semicarbazones has now been investigated.

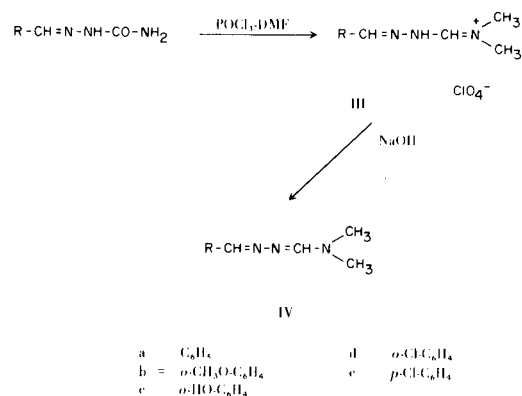
Acetophenone semicarbazone (Ia) reacted with two moles of phosphorus oxychloride-dimethylformamide with the formation of 3-phenylpyrazole-4-carboxaldehyde (IIa), in 85% yield. The structure assigned to this compound was established from its IR and NMR spectra. The IR spectrum showed absorption bands at  $3250\text{ cm}^{-1}$  (NH) and at  $1630\text{ cm}^{-1}$  (CHO). The NMR spectrum (3) (deuteriochloroform) showed signals at  $2.4\ \tau$  (five phenyl protons),  $1.85\ \tau$  (5-H proton),  $1.32\ \tau$  (NH proton) and at  $-0.45\ \tau$  (CHO proton). The NMR spectrum showed no change upon the addition of deuterium oxide. The IR absorption at  $1630\text{ cm}^{-1}$  and the low field absorption of the aldehydic proton in the NMR (4) may well be attributed to the enolic nature of IIa. Compounds IIa-e dissolve in dilute alkali and are precipitated by mineral acids.

Similarly the pyrazole aldehydes IIb-f were prepared. They all afforded 2,4-dinitrophenylhydrazone and semicarbazone derivatives. Their physical properties are listed in Table I.



No cyclized products could be obtained from the reaction of acetaldehyde and cyclohexanone semicarbazones under similar conditions. This might be due to a steric configuration (5) which does not favour cyclization.

On the other hand, benzaldehyde semicarbazone gave with one mole of phosphorus oxychloride-dimethylformamide, in 57% yield, 1-benzylidene-2-dimethylamino-methylenehydrazine (IVa), isolated as its perchlorate salt (IIIa).



The structure of the bases IVb-c was supported by NMR spectra. Compound IVb showed the following signals:  $7\ \tau$  (six protons;  $\text{N}(\text{CH}_3)_2$ ),  $6.17\ \tau$  (three protons;  $\text{OCH}_3$ ),  $3.05$  and  $2.3$  (two protons each, *ortho* and other phenyl protons), and two signals at  $\tau = 1.82$  and  $1.62$  ( $-\text{CH}=\text{N}$  and  $\text{R}-\text{CH}=\text{N}-$ , respectively). The NMR spectrum of IIIc is of special interest. Besides the absorption bands at  $7\ \tau$  (six protons),  $3$  and  $2.8\ \tau$  (four protons),  $2$  and  $1.54\ \tau$  (one proton each), a broad band at  $-2.01\ \tau$  was also recorded. The OH of the *o*-hydroxyphenyl group is therefore bonded to the unshared electron pair of the nitrogen atom in  $o\text{-HO-C}_6\text{H}_4-\text{CH}=\text{N}$ , thus indicating its configuration (6,7).

The IR spectrum of IIIa (Nujol) showed bands at  $3200\text{ cm}^{-1}$  (NH) and a broad band at  $1100\text{ cm}^{-1}$  ( $\text{ClO}_4^-$ ). It showed, however, an intense band at  $1715\text{ cm}^{-1}$  which is of  $\text{C}=\overset{\oplus}{\text{N}}$  (8). This band is absent in the spectrum of the bases IIIa-c.

Amidrazones (2) and amidazines (6) which are analogous to III have been recently reported.

Compounds IVa-c gave the phenylhydrazones (2,4-dinitrophenylhydrazones) of the corresponding aldehydes when treated with phenylhydrazine (2,4-dinitrophenylhydrazine). They also gave stable picrate salts.

The physical properties of compounds III-IV are listed in Table II.

TABLE I

Comp. No. II	M.p. <sup>o</sup>	Yield %	M.p. of semicarb.	IR cm <sup>-1</sup>	Formula	Calculated			Found		
						C	H	N	C	H	N
a	143 <sup>o</sup>	85	210 <sup>o</sup>	3250; 1630	C <sub>10</sub> H <sub>8</sub> N <sub>2</sub> O	69.76	4.65	16.26	69.57	4.71	16.1
b	154 <sup>o</sup>	95	246 <sup>o</sup>	3225; 1630	C <sub>11</sub> H <sub>10</sub> N <sub>2</sub> O <sub>2</sub>	65.34	4.95	13.86	65.5	5.18	13.78
c	200 <sup>o</sup>	63	224 <sup>o</sup>	3225; 1660	C <sub>10</sub> H <sub>7</sub> N <sub>3</sub> O <sub>3</sub>	55.29	3.22	19.35	55.37	3.28	19.71
d	156 <sup>o</sup>	54	223 <sup>o</sup>	3255; 1665	C <sub>10</sub> H <sub>7</sub> N <sub>3</sub> O <sub>3</sub>	55.29	3.22	19.35	55.26	3.39	19.53
e	64 <sup>o</sup>	83	210 <sup>o</sup>		C <sub>8</sub> H <sub>6</sub> N <sub>2</sub> OS	53.9	3.37	15.73	53.81	3.35	18.01
f (a)											

(a) See experimental.

TABLE II

Comp. No.	M.p.	Yield %	M.p. of picrate	Formula	Calculated			Found		
					C	H	N	C	H	N
IIIa	150 <sup>o</sup>	57		C <sub>10</sub> H <sub>14</sub> N <sub>3</sub> ClO <sub>4</sub>	43.55	5.08	15.24	43.35	5.14	15.31
b	200 <sup>o</sup>	86		C <sub>11</sub> H <sub>16</sub> N <sub>3</sub> ClO <sub>5</sub>	43.20	5.23	13.74	43.10	5.31	13.55
c	213 <sup>o</sup>	57		C <sub>10</sub> H <sub>14</sub> N <sub>3</sub> ClO <sub>5</sub>	41.16	4.8	14.40	41.88	4.37	14.13
d	231 <sup>o</sup>	93		C <sub>10</sub> H <sub>13</sub> N <sub>3</sub> Cl <sub>2</sub> O <sub>4</sub>	38.70	4.19	13.54	38.91	4.39	13.24
e	216 <sup>o</sup>	76		C <sub>10</sub> H <sub>13</sub> N <sub>3</sub> Cl <sub>2</sub> O <sub>4</sub>	38.70	4.19	13.54	38.73	4.34	13.38
IVa	47 <sup>o</sup>	70	211 <sup>o</sup>	C <sub>10</sub> H <sub>13</sub> N <sub>3</sub>	68.56	7.42	24.0	68.84	7.15	24.23
b	86 <sup>o</sup>	85	192 <sup>o</sup>	C <sub>11</sub> H <sub>15</sub> N <sub>3</sub> O	64.39	7.32	20.48	64.32	7.41	20.19
c	108 <sup>o</sup>	81	221 <sup>o</sup>	C <sub>10</sub> H <sub>13</sub> N <sub>3</sub> O	62.82	6.8	21.98	62.93	6.85	21.82
d	42 <sup>o</sup>	74	235 <sup>o</sup>	C <sub>10</sub> H <sub>12</sub> N <sub>3</sub> Cl	57.27	5.72	20.04	57.20	5.61	20.36
e	54 <sup>o</sup>	67	220 <sup>o</sup>	C <sub>10</sub> H <sub>12</sub> N <sub>3</sub> Cl	57.27	5.72	20.04	57.25	5.65	20.00

## EXPERIMENTAL

The NMR spectra were measured by a Varian A-60 apparatus. Melting points are uncorrected.

The following illustrates the general procedure: (a) The ketone semicarbazone (0.05 mole) was added, portionwise with stirring, to a mixture of phosphorus oxychloride-dimethylformamide. The latter was prepared by the slow addition of phosphorus oxychloride (10 ml., 0.11 mole) to dimethylformamide (24 g., 0.22 mole), below 5°. The reaction mixture was heated at 60-70° for about four hours, cooled, and poured onto ice (60 g.). It was neutralized with sodium hydroxide (20 g. in 80 ml. of water), heated at 50-60° for five minutes, cooled and acidified with 10 N hydrochloric acid. The precipitated solid was filtered off and recrystallized. Compounds IIa-b were recrystallized from water, IIc-d from ethanol and IIe from benzene. Compound IIf was isolated, as the 2,4-dinitrophenylhydrazone, in the following manner: the reaction mixture was treated with 30 ml. of ethanol followed by the addition of an ethanolic solution containing 2,4-dinitrophenylhydrazine (10 g.) and one ml. of sulfuric acid. The precipitated 2,4-dinitrophenylhydrazone, 8 g., m.p. 281°, was recrystallized from acetic acid.

Anal. Calcd. for C<sub>11</sub>H<sub>10</sub>N<sub>6</sub>O<sub>4</sub>: C, 45.51; H, 3.45; N, 28.96. Found: C, 46.00; H, 3.37; N, 28.73.

(b) The aldehyde semicarbazone was allowed to react with half the amount of phosphorus oxychloride-dimethylformamide, poured onto ice and treated with a solution of perchloric acid

(7.5 ml. of 75% perchloric acid in 20 ml. of water). The precipitated perchlorate salt was filtered off. To liberate the base, the salt was treated with a cold 5% ammonium hydroxide solution. Compounds III and IV were recrystallized from ethanol.

## REFERENCES

- (1) Part III of this series cf. M. A. Kira, M. O. Abdel-Rahman and K. Z. Gadalla, *Tetrahedron Letters*, 109 (1969).
- (2) H. Bredereck, R. Gompper, K. Klemm and H. Rempfer, *Chem. Ber.*, **92**, 837 (1959).
- (3) J. Elguero and R. Jacquier, *Bull. Soc. Chem. France*, 2832 (1966).
- (4) R. M. Silverstein and G. C. Bassler, "Spectrophotometric Identification of Organic Compounds," 2nd Edition, John Wiley and Sons, New York, 1967, p. 88-89 and p. 140.
- (5) G. J. Karabatos, J. D. Graham and F. M. Vanc, *J. Am. Chem. Soc.*, **84**, 753 (1962); P. de Mayo and A. Stoessl, *Can. J. Chem.*, **38**, 950 (1960).
- (6) H. Eilingsfeld, M. Seefelder and H. Weidiger, *Angew. Chem.*, **72**, 836 (1960).
- (7) H. Wolf and O. Westphal, *Ann. Chem.*, **657**, 39, 52, 64 (1962).
- (8) J. Elguero, R. Gil and R. Jacquier, *Spectrochim. Acta*, **23A**, 383 (1967).

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