

## The Preparation of 1,2,4-Triazines and 1,2,4-Triazolines from Substituted Carboxamide Hydrazones

Francis H. Case

Department of Chemistry, Temple University

Substituted carboxamide hydrazones have been condensed with 2,3-butanedione and with glyoxal to form 1,2,4-triazines; with benzaldehyde and pyridine-2-carboxaldehyde to yield 1,2,4-triazolines.

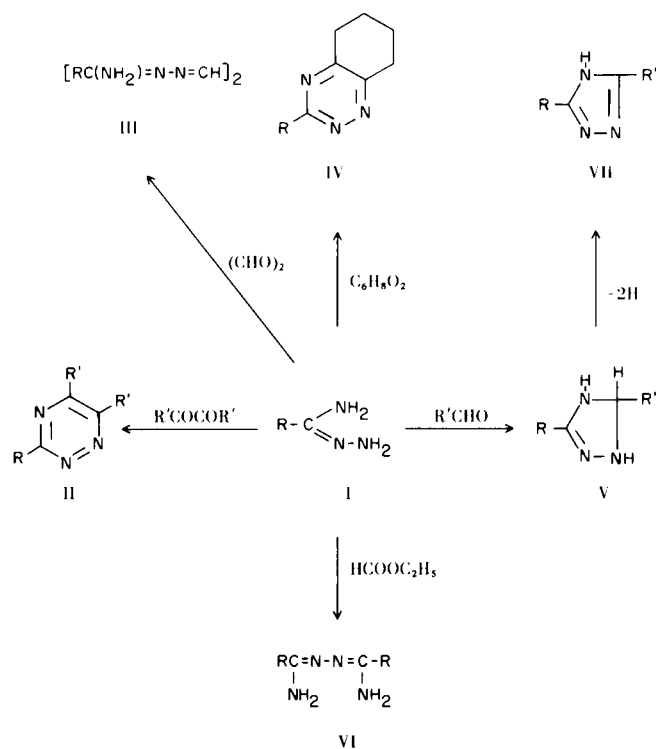
In a previous communication (1) dealing with a search for new chelating agents for Fe(II) and Cu(I) was described the preparation of 3-substituted-5,6-diphenyl and 5,6-bis(2-pyridyl)-1,2,4-triazines from the action of substituted carboxamide hydrazones (amidrazones) (I) with benzil and  $\alpha$ -pyridil, respectively. Of these 3-(2-pyridyl)-5,6-diphenyl-1,2,4-triazine has been found to be outstanding (2).

In the present work 2,3-butanedione as the diketone has been condensed with picolinamide hydrazone and its 4-methyl and 4-phenyl derivatives as well as thiazole-2-carboxamide hydrazone and 1,10-phenanthroline-2-carboxamide hydrazone to yield 3-substituted-5,6-dimethyl-1,2,4-triazines (II:  $R' = CH_3$ ).

3-Substituted-1,2,4-triazines (II:  $R' = H$ ) have also been prepared from the action of glyoxal with picoline- and 4-methyl picolinamide hydrazones and thiazole-2-carboxamide hydrazone. However, in the case of 4-phenylpicolinamide hydrazone, two moles react with one of glyoxal to form "4,4'-diphenylpicolinamide diazine with glyoxal" (III:  $R = 4-C_6H_5C_5H_3N$ ).

Condensation of picolinamide hydrazone with cyclohexan-1,2-dione, which was successful only if water was removed as formed, yielded 5,6,7,8-tetrahydro-3-(2-pyridyl)-1,2,4-benzotriazine (IV:  $R = 2-C_5H_4N$ ). Dehydrogenation of this compound afforded 2-(2-pyridyl)-benzimidazole instead of the expected benzotriazine. Attempts to effect the above condensation with 4-methyl- and 4-phenylpicolinamide hydrazones were unsuccessful.

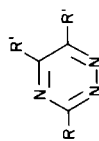
In condensation of the hydrazones of the three picolinamides, thiazole-2-carboxamide, and 1,10-phenanthroline-2-carboxamide with benzaldehyde and 2-pyridinecarboxaldehyde (two moles), only one mole of aldehyde reacted,



yielding 3-substituted-5-phenyl and -5-(2-pyridyl)-1,2,4-triazolines (V). Of these the 5-pyridyl derivatives gave a more intense red color with Fe(II) than the 5-phenyl compounds. From salicylaldehyde and picolinamide hydrazone, 3-(2-pyridyl)-5-(2-hydroxyphenyl)-1,2,4-triazoline was prepared. Several of the above triazolines were dehydrogenated to the corresponding triazoles (VII) with resulting loss of chelating ability.

TABLE I

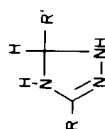
## 3-Substituted-1,2,4-Triazines



	R	R'	Yield %	M.p. °C	Crystallization Solvent	Formula	Analysis					
							Calcd. % C	Calcd. % H	Calcd. % N	Found % C	Found % H	Found % N
VIII	2-Pyridyl	H	15.9	86-87	benzene- petroleum ether	C <sub>8</sub> H <sub>6</sub> N <sub>4</sub>	60.75	3.82	35.42	60.62	3.74	35.63
IX		CH <sub>3</sub>	36.5	92-93	benzene	C <sub>10</sub> H <sub>10</sub> N <sub>4</sub>	64.50	5.41	30.09	64.88	5.46	30.25
X	4-Methyl-2-pyridyl	H	50.0	106-107	benzene	C <sub>9</sub> H <sub>8</sub> N <sub>4</sub>	62.78	4.68	32.54	62.89	4.67	32.55
XI		CH <sub>3</sub>	34.4	147-148	benzene	C <sub>11</sub> H <sub>12</sub> N <sub>4</sub>	65.98	6.04	27.98	66.14	6.03	27.93
XII	4-Phenyl-2-pyridyl	CH <sub>3</sub>	12.0	112-113	benzene	C <sub>16</sub> H <sub>14</sub> N <sub>4</sub>	73.26	5.38	21.36	73.64	5.52	21.44
XIII	2-Thiazolyl	H	42.9	170-171	petroleum ether	C <sub>6</sub> H <sub>4</sub> N <sub>4</sub> S	43.89	2.46	34.12	44.14	2.41	34.42
XIIIa		CH <sub>3</sub>	26.3	140-141	ethanol	C <sub>8</sub> H <sub>8</sub> N <sub>4</sub> S	50.00	4.20	29.15	50.21	4.28	29.21
XIV	2-(1,10-Phenanthrolyl)	CH <sub>3</sub>	32.3	210-211	ethanol	C <sub>17</sub> H <sub>13</sub> N <sub>5</sub> ·H <sub>2</sub> O	66.87	4.95	22.94	67.08	4.92	23.16

TABLE II

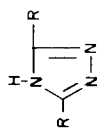
## 3,5-Disubstituted-1,2,4-Triazolines



	R	R'	Yield %	M.p. °C	Crystallization Solvent	Formula	Analysis				
							Calcd. %	Found %	C	H	N
XV	2-Pyridyl	CH <sub>3</sub>	81.0	50	ether-petroleum ether	C <sub>8</sub> H <sub>10</sub> N <sub>4</sub>	6.21	6.10	59.09	34.54	34.77
XVI		C <sub>6</sub> H <sub>5</sub>	81.6	111	ethanol	C <sub>13</sub> H <sub>12</sub> N <sub>4</sub>	5.39	5.40	69.68	24.98	25.10
XVII		2-HOC <sub>6</sub> H <sub>4</sub>	85.4	127	ethanol	C <sub>13</sub> H <sub>12</sub> N <sub>4</sub> O	5.03	5.06	65.05	23.32	23.53
XVIII		2-C <sub>5</sub> H <sub>4</sub> N	70.0	139	ethanol	C <sub>12</sub> H <sub>11</sub> N <sub>5</sub>	4.92	4.92	63.53	31.09	31.30
XIX	4-Methyl-2-pyridyl	C <sub>6</sub> H <sub>5</sub>	79.2	115	ethanol	C <sub>14</sub> H <sub>14</sub> N <sub>4</sub>	5.92	5.84	70.24	23.51	23.67
XX		2-C <sub>5</sub> H <sub>4</sub> N	72.9	152-153	ethanol	C <sub>13</sub> H <sub>13</sub> N <sub>5</sub>	5.48	5.36	64.88	29.27	29.62
XXI	4-Phenyl-2-pyridyl	C <sub>6</sub> H <sub>5</sub>	88.6	149-150	benzene	C <sub>19</sub> H <sub>16</sub> N <sub>4</sub>	5.37	5.35	75.64	18.65	18.61
XXII		2-C <sub>5</sub> H <sub>4</sub> N	70.4	148	benzene	C <sub>18</sub> H <sub>15</sub> N <sub>5</sub>	5.02	4.98	71.76	23.24	23.37
XXIII	2-Thiazolyl	C <sub>6</sub> H <sub>5</sub>	87.0	146-147	ethanol	C <sub>11</sub> H <sub>10</sub> N <sub>4</sub> S	4.38	4.47	57.05	24.33	23.85
XXIV		2-C <sub>5</sub> H <sub>4</sub> N	69.6	180-181	ethanol	C <sub>10</sub> H <sub>9</sub> N <sub>5</sub> S	3.91	3.98	52.33	30.28	30.49
XXV	2-(1,10-Phenanthrolyl)	C <sub>6</sub> H <sub>5</sub>	60.0	135-136	ethanol	C <sub>20</sub> H <sub>15</sub> N <sub>5</sub> ·H <sub>2</sub> O	4.99	4.94	69.82	20.39	20.35
XXVI		2-C <sub>5</sub> H <sub>4</sub> N	92.6	151-152	ethanol	C <sub>19</sub> H <sub>14</sub> N <sub>6</sub> ·2H <sub>2</sub> O	5.01	5.06	63.19	23.19	23.42

TABLE III

3,5-Disubstituted 1,2,4-Triazolones



	R	R'	Yield %	M.p. °C	Crystallization Solvent	Formula	Analysis			
							Calcd. %	Found %	C	N
XXXVII	2-Pyridyl	C <sub>6</sub> H <sub>5</sub>	46.7	212-213	benzene	C <sub>13</sub> H <sub>10</sub> N <sub>4</sub>	4.54	4.58	70.03	25.62
XXXVIII		2-C <sub>5</sub> H <sub>4</sub> N	25.0	208-209	water	C <sub>12</sub> H <sub>9</sub> N <sub>5</sub>	4.06	4.12	64.35	31.84
XXXIX	4-Methyl-2-pyridyl	C <sub>6</sub> H <sub>5</sub>	35.0	221-222	ethanol	C <sub>14</sub> H <sub>12</sub> N <sub>4</sub>	5.12	5.00	71.11	24.11
XXX	4-Phenyl-2-pyridyl	C <sub>6</sub> H <sub>5</sub>	61.5	236-237	ethanol	C <sub>19</sub> H <sub>14</sub> N <sub>4</sub>	4.73	4.84	76.22	18.81
XXXI	2-Pyridyl	CH <sub>3</sub>	28.0	165	benzene	C <sub>8</sub> H <sub>8</sub> N <sub>4</sub>	5.03	5.12	60.05	34.97

With acetaldehyde, picolinamide hydrazone yielded 5-methyl-3-(2-pyridyl)-1,2,4-triazoline, which on dehydrogenation afforded 5-methyl-3-(2-pyridyl)-1,2,4-triazole, identical with the product obtained by treating the same amidrazone with acetic anhydride.

An attempt to bring about a reaction between picolinamide hydrazone and ethyl formate resulted in the formation of picolinamide azine (VI: R = 2-C<sub>5</sub>H<sub>4</sub>N-) identical with the product described by Ried and Schomann (3) as resulting from the action of ethyl malonate on the above amidrazone.

These compounds will be tested for chelating properties toward Fe(II) and Cu(I) by Dr. Alfred Schilt.

## EXPERIMENTAL

## Preparation of 3-Substituted-1,2,4-triazines.

To a suspension of 0.0125 mole of the appropriate carboxamide hydrazone in 20 ml. of water was added a solution of 3.4 g. (0.0129 mole) of glyoxal sodium bisulfite in 20 ml. of water at 80°. The mixture was stirred at 70° for 15 minutes. It was then cooled, made alkaline with sodium hydroxide solution, and extracted with ether. Evaporation of the dried ether solution yielded crude crystals which were then crystallized from the solvents mentioned in Table I. In the case of the thiazolyl derivative, the precipitate resulting on basification was extracted with ethanol, the solution evaporated and the residue crystallized from ethanol.

## 4,4'-Diphenyl Picolinamide Diazine with Glyoxal (III).

When the above procedure was applied to 4-phenylpicolinamide hydrazone, a precipitate formed on addition of sodium hydroxide. This was removed by filtration, dried and crystallized from dimethyl formamide. The yield of pure product, melting at 259-260° was 1.0 g. (37.0%).

*Anal.* Calcd. for C<sub>26</sub>H<sub>22</sub>N<sub>8</sub>: C, 69.94; H, 4.97; N, 25.09. Found: C, 69.71; H, 4.94; N, 25.02. Mol. wt. by mass spectrograph: 446.

## Preparation of 3-Substituted-5,6-dimethyl-1,2,4-triazines.

A mixture of 0.015 mole of the appropriate carboxamide hydrazone, 0.017 mole of 2,3-butanedione and 20 ml. of benzene was heated at reflux for 2.5 hours. The benzene was then removed by evaporation, and the residue crystallized from the solvent indicated in Table I.

## Preparation of 3-Substituted-5-phenyl or -(2-pyridyl)-1,2,4-triazolines.

A mixture of 0.015 mole of the requisite carboxamide hydrazone, 0.030 mole of benzaldehyde or pyridine-2-carboxaldehyde, and 20 ml. of ethanol was heated at reflux 2.5 hours. The solvent was then removed and the triazole crystallized from the solvent mentioned in Table II. When acetaldehyde and picolinamide hydrazone were condensed in the above manner, 2-methyl-5-(2-pyridyl)-1,2,4-triazoline resulted.

## Preparation of 3-Substituted-5-phenyl or -(2-pyridyl)-1,2,4-triazoles.

A mixture of 0.007 mole of the corresponding triazolone, 15 ml. of decahydronaphthalene and 0.6 g. of 10% palladium on carbon was heated for 4 hours at 210°. After cooling and filtering, the precipitate was extracted with ethanol. After removal of

ethanol, the residue was crystallized from the solvent indicated in Table III.

#### 2-Methyl-5-(2-pyridyl)-1,2,4-triazole.

A solution of 2 g. of picolinamide hydrazone in 5 ml. of acetic anhydride was heated at 100-105° for 40 minutes. The cooled mixture was then poured into water, made alkaline with sodium carbonate solution and extracted with ether. Removal of ether, and crystallization of the residue from benzene yielded 0.5 g. (20.9%) of pure product, melting at 167-168°.

*Anal.* Calcd. for C<sub>8</sub>H<sub>8</sub>N<sub>4</sub>: C, 59.99; H, 5.03; N, 34.98. Found: C, 60.06; H, 5.12; N, 34.97.

This compound was found to be identical (by mixed melting point) with the product (XXXI) obtained by dehydrogenating 2-methyl 5-(2-pyridyl)-1,2,4-triazoline (XV) by the standard procedure.

#### 5,6,7,8-Tetrahydro-3-(2-pyridyl)-1,2,4-benzotriazine (IV).

A mixture of 4.5 g. of picolinamide hydrazone, 3.7 g. of cyclohexane-1,2-dione and 50 ml. of benzene was heated at reflux for 3 hours, using a Dean-Stark tube for removal of water, of which 1 ml. was collected. After treatment with decolorizing carbon and removal of benzene, the residue was crystallized from benzene, yielding 1.7 g. (24.3%) of crystals melting at 119-120°.

*Anal.* Calcd. for C<sub>12</sub>H<sub>12</sub>N<sub>4</sub>: C, 67.91; H, 5.70; N, 26.40. Found: C, 67.93; H, 5.77; N, 26.47.

On dehydrogenation with decahydronaphthalene in the manner described above, IV yielded 2-(2-pyridyl)benzimidazole, whose melting point (221-222°) was unchanged when mixed with a sample prepared by heating  $\alpha$ -picolinic acid with *o*-phenylenediamine (4).

#### Picolinamide Azine (VI: R = 2-C<sub>5</sub>H<sub>4</sub>N-).

A solution of 1.3 g. of ethyl formate and 2.72 g. of picolinamide hydrazone in 30 ml. of benzene was heated under reflux for 3 hours. After removal of the solvent the residue was extracted with benzene and the insoluble part crystallized from ethanol, yielding 0.8 g. (69.6%) melting at 210-211°.

*Anal.* Calcd. for C<sub>12</sub>H<sub>12</sub>N<sub>6</sub>: C, 59.99; H, 5.03; N, 34.98. Found: C, 59.84; H, 5.09; N, 35.17. Mol. wt. (mass spectrograph) 240.

This compound proved to be identical (mixed melting point) with that prepared by Ried and Schomann (3) by treating picolinamide hydrazone with ethyl malonate.

#### Acknowledgment.

The author acknowledges the helpful suggestions of Drs. David Dalton, Alfred Schilt, and Francis Pfeiffer.

#### REFERENCES

- (1) F. H. Case, *J. Org. Chem.*, **30**, 931 (1965).
- (2) A. A. Schilt and P. J. Taylor, *Anal. Chem.*, **42**, 220 (1970).
- (3) W. Ried and P. Schomann, *Ann. Chem.*, **714**, 122 (1968).
- (4) J. L. Walter and H. Freiser, *Anal. Chem.*, **26**, 218 (1954).

Received June 8, 1970

Philadelphia, Pa., 19122