

Fused *s*-Triazino Heterocycles. II. 1,3,4,6,9b-Pentaazaphenalenes and 1,3,4,6,7,9b-Hexaazaphenalene (1)

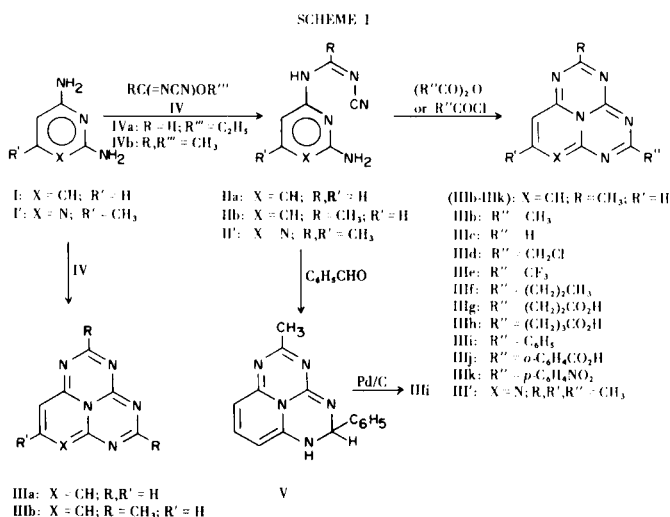
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As part of a continuing program for the preparation of fused *s*-triazino heterocycles, the reaction of substituted  $\alpha$ -aminopyridines with *N*-cyanoimidates has been under investigation in our laboratories. Recently in a preliminary communication (3) we reported how refluxing a solution of ethyl *N*-cyanoformimidate (IVa) or methyl *N*-cyanoacetimidate (IVb) with 2,6-diaminopyridine (I) gave the symmetrically substituted 1,3,4,6,9b-pentaazaphenalene (IIIa) and 2,5-dimethyl-1,3,4,6,9b-pentaazaphenalene (IIIb), respectively; if these reactions were carried out at room temperature, then *N*-cyano, *N'*-(6-amino-2-pyridyl)-formamidine (IIa) and *N*-cyano, *N'*-(6-amino-2-pyridyl)-acetamidine (IIb) were obtained, respectively.

In the present paper we describe: (a) attempts to extend these reactions to certain diaminopyrimidine derivatives; and (b) additional related work involving 2,6-diaminopyridine. These transformations are outlined in Scheme I.



Refluxing 2,4-diamino-6-methylpyrimidine (I') with IVb in dry glyme (using the same molar concentrations that gave IIIb from I) gave a 73% crude yield of *N*-cyano-*N'*-(2-amino-4-methyl-6-pyrimidyl)acetamidine (II') (4) rather than the expected 2,5,8-trimethyl-1,3,4,6,7,9b-hexaazaphenalene (III'). Many attempts to prepare

either 2,5-dimethyl-1,3,4,6,7,9b-hexaazaphenalene, or *N*-cyano-*N'*-(2-amino-6-pyrimidyl)acetamidine from 2,4-diaminopyrimidine and IVb gave only tarry decomposition products. The success with I' may be due to the methyl group at position-6 on the pyrimidine ring preventing undesired reactions of the nitrogen at position 1 with IVb. Conversion of II' to III' was accomplished using a method of synthesis previously disclosed: The reaction of anhydrides with type II compounds (3). Thus refluxing II' with acetic anhydride gave the new ring system III', in 53% yield; analytical and spectral data to support the structure of III' are given in the experimental section.

This alternative mode of synthesis of type III compounds was further explored using other anhydrides (Method A), acid chlorides (with pyridine present) (Method B), *N*-cyanoimidates, esters, and isocyanates. Only the first three of these proved useful and the results are summarized in Scheme I and Table I.

A third route to a pentaazaphenalene derivative involved first the preparation of 2-methyl-5-phenyl-5,6-dihydro-1,3,4,6,9b-pentaazaphenalene (V) by reaction of benzaldehyde with IIb in refluxing glyme. Dehydrogenation of V to 2-methyl-5-phenyl-1,3,4,6,9b-pentaazaphenalene (IIIi) was effected by heating V with palladium on carbon in boiling diglyme. The reactions of IIb with acetophenone or *n*-butyraldehyde to yield the corresponding dihydro-pentaazaphenalenes were not successful.

The pathway whereby symmetrically substituted type III compounds are formed directly from I and *N*-cyanoimidates is intriguing. One possible route, using IIIb as an example, would be the following. Some support for this mode of reaction is provided by the following

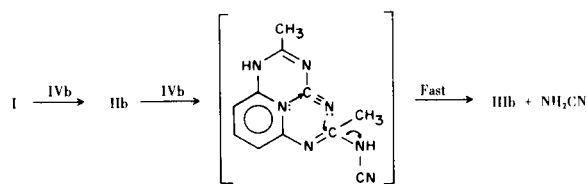
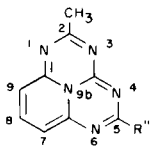


FIGURE 1

TABLE I  
Pentaazaphenalenes



Formula Number	R	Method (a)	Yield, % (b)	M.p. °C (c)	Molecular Formula	Analysis (%)		
						C Found	H Found	N Found
IIIc	H	A (d)	48 (e)	249-251	C <sub>9</sub> H <sub>7</sub> N <sub>5</sub>	58.37 (f) 58.16	3.81 3.78	37.81 38.00
IIIb	CH <sub>3</sub>	A (g)	62					
IIIb	CH <sub>3</sub>	B (h)	44					
IIIb	CH <sub>3</sub>	A (i)	29					
IIIe	CF <sub>3</sub>	A (j)	36	238-240	C <sub>10</sub> H <sub>6</sub> F <sub>3</sub> N <sub>5</sub>	47.43 47.71	2.39 2.64	27.66 27.49
IIIg	(CH <sub>2</sub> ) <sub>2</sub> CO <sub>2</sub> H (k)	A (l)	94	243-244	C <sub>12</sub> H <sub>11</sub> N <sub>5</sub> O <sub>2</sub>	56.03 55.95	4.31 4.56	27.23 27.39
IIIh	(CH <sub>2</sub> ) <sub>3</sub> CO <sub>2</sub> H (m)	A (l)	89	227-229	C <sub>13</sub> H <sub>13</sub> N <sub>5</sub> O <sub>2</sub>	57.56 57.44	4.83 4.68	25.81 25.57
IIIi	C <sub>6</sub> H <sub>5</sub> (n)	A	74	245-246	C <sub>15</sub> H <sub>11</sub> N <sub>5</sub>	68.95 69.11	4.24 4.21	26.80 26.64
IIIj	<i>o</i> -C <sub>6</sub> H <sub>4</sub> CO <sub>2</sub> H (o)	A (l)	83	243-244 dec.	C <sub>16</sub> H <sub>11</sub> N <sub>5</sub> O <sub>2</sub>	62.92 62.60	3.63 3.77	22.94 23.07
IIIk	<i>p</i> -C <sub>6</sub> H <sub>4</sub> NO <sub>2</sub> (p)	B (q)	94	313-314 dec.	C <sub>15</sub> H <sub>10</sub> N <sub>6</sub> O <sub>2</sub>	58.82 59.02	3.29 3.73	27.44 27.58

(a) Compound IIIc was prepared from IIa, all others were prepared from IIb; all compounds were recrystallized from 2-methoxyethanol unless otherwise noted. (b) Crude yield. (c) The melting points reported were taken on recrystallized products. (d) A mixture of 0.1 mole of acetic anhydride and 0.01 mole of IIa in 10 ml. of glyme was used; crude product purified by column chromatography (alumina/chloroform) before recrystallization from butyronitrile. (e) Repeating this reaction without using glyme as solvent gave a lower yield. (f) The upper line in each pair of values is the calculated value. (g) Acetic anhydride served as reactant and solvent (0.1 mole anhydride/0.01 mole IIb). (h) An amount of 0.06 mole of pyridine/0.025 mole of IIb was used; mixture was refluxed for 17 hours. (i) "Method A" was followed except that 0.014 mole of IVb and 2.5 ml. of glyme were used in place of 0.05 mole of butyric anhydride and 10 ml. of glyme, respectively. (j) A mixture of 0.02 mole of trifluoroacetic anhydride, 0.03 mole of pyridine, 0.01 mole of IIb and 14 ml. of glyme was used; addition of anhydride was very exothermic (addition temperature < 18°); the mixture was refluxed for 18 hours. (k) Succinic anhydride was used. (l) A mixture of 0.03 mole of anhydride and 0.01 mole of IIb in 25 ml. of glyme was used; recrystallization from 2-ethoxyethanol. (m) Glutaric anhydride was used. (n) Benzoic anhydride was used. (o) Phthalic anhydride was used. (p) *p*-Nitrobenzoyl chloride was used. (q) An amount of 70 ml. of glyme/0.0025 mole of IIb was used and the mixture was refluxed for 18 hours; neutralization of the crude hydrochloride was done in water with 5% sodium hydroxide and the insoluble material was recrystallized from a large volume of 2-ethoxyethanol.

facts: (a) I does react with IVb to give IIb and IIb reacts with IVb to form IIIb (5); (b) the reaction appears to occur stepwise since after refluxing I and IVb in glyme for four hours, only IIb could be isolated while after 8 hours the formation of IIIb was evident. However, attempts to isolate VI have not been successful. Another point of interest is that previous ring closure reactions of I with reagents like ethyl ethoxymethylene malonate (6) or ethyl malonate (7) have not resulted in attack by these reagents on the amino nitrogen and position-1 of pyridine (as in the present case). Instead, attack occurred at the amino nitrogen and position-3 of pyridine leading to 1,3-naphthyridine derivatives.

Reactions of type III compounds will be discussed in a future paper.

#### EXPERIMENTAL

Melting points were determined in open capillaries on a Thomas-Hoover melting-point bath and are uncorrected. Infrared spectra were recorded using a Perkin-Elmer Infracord Model 137. Nmr spectra were obtained on Varian A-60 and Varian HA-100 spectrophotometers using TMS as an internal reference. The mass spectra were determined on a Varian CH7 spectrometer. Analyses were performed by Micro-Analyses, Inc., Marshallton, Del. and Crobaugh Laboratories, Cleveland, Ohio.

All of the *N*-cyanoimidates used in this paper were prepared by the method of Huffman and Schaefer (8). Glyme, 1,2-

dimethoxyethane, was dried over calcium hydride and stored over molecular sieves. 2,6-Diaminopyridine and 2,4-dichloro-6-methylpyrimidine were obtained from Aldrich Chemical Company.

#### 1,3,4,6,9b-Pentaazaphenalene (IIIa).

A solution of 14.5 g. (0.133 mole) of 2,6-diaminopyridine (I) and 26.1 g. (0.266 mole) of ethyl *N*-cyanoformimidate (IVa) in 160 ml. of dry glyme was refluxed and stirred for 18 hours. The solid which formed was filtered at room temperature and washed with ether: 17.6 g. (77%), m.p. 247-255°. Two recrystallizations from 2-methoxyethanol gave lavender crystals, m.p. 258-260° dec.;  $\text{ir } \lambda$  (Nujol): 12.13  $\mu$  (all of the pentaazaphenalenes had a moderate to strong band around 12.1  $\mu$ ), no significant absorption 2.75-3.2 or 4-5  $\mu$ ; nmr (deuteriochloroform):  $\delta$  6.09 (d, J  $\sim$  8 Hz, 2H, H<sub>7</sub> and H<sub>9</sub>),  $\delta$  7.26 (t, J  $\sim$  8 Hz, 1H, H<sub>8</sub>),  $\delta$  7.29 (s, 2H H<sub>2</sub> and H<sub>5</sub> molecular ion peak at 171.

*Anal.* Calcd. for C<sub>8</sub>H<sub>5</sub>N<sub>5</sub>: C, 56.13; H, 2.94; N, 40.91. Found: C, 56.03; H, 3.12; N, 40.62.

#### 2,5-Dimethyl-1,3,4,6,9b-pentaazaphenalene (IIIb).

The reaction conditions for preparing IIIa were followed except 16.4 g. (0.15 mole) of I, 35.3 g. (0.36 mole) of methyl *N*-cyanoacetimidate (IVb) and 38 ml. of dry glyme were used. The crude product weighed 11.9 g. (40%), m.p. 264-268°. Two recrystallizations from 2-methoxyethanol gave burgundy crystals, m.p. 275-277°;  $\text{ir } \lambda$  (Nujol): 12.1  $\mu$ , no significant absorption 2.5-3.2 or 4-5  $\mu$ ; nmr (deuteriochloroform):  $\delta$  2.02 (s, 6H, 2CH<sub>3</sub>),  $\delta$  6.10 (d, J = 8 Hz, 2H, H<sub>7</sub> and H<sub>9</sub>),  $\delta$  7.28 (t, J = 8 Hz, 1H, H<sub>8</sub>); molecular ion peak at 199.

*Anal.* Calcd. for C<sub>10</sub>H<sub>9</sub>N<sub>5</sub>: C, 60.29; H, 4.55; N, 35.16. Found: C, 60.41; H, 4.30; N, 35.42.

Using the same volume of 95% ethanol or DMF at (80°) in the place of glyme above gave 28 and 37% crude yields respectively of IIIb. Also, it should be noted that a 20% crude yield of IIIb was obtained even when the ratio IVb/I was lowered from 2.4 (this experiment) to 0.9.

#### *N*-Cyano-*N'*-(6-amino-2-pyridyl)acetamidine (IIb).

The preparation just given for IIIb was followed exactly except that the reaction mixture was stirred at room temperature for 24 hours: 13.5 g. (51%) m.p. 174-176°. Several recrystallizations from 95% ethanol gave an analytical sample, off-white crystals, m.p. 179-181°;  $\text{ir } \lambda$  (Nujol): 2.92 and 3.05  $\mu$  (NH), 4.57  $\mu$  (C $\equiv$ N).

*Anal.* Calcd. for C<sub>8</sub>H<sub>9</sub>N<sub>5</sub>: C, 54.84; H, 5.18; N, 39.97. Found: C, 54.73; H, 5.08; N, 39.79.

Efforts to isolate 2,6-bis(*N*-cyano-*N'*-acetamidino)pyridine (VI) in this experiment and other experiments where the ratio of IVb/I was at least 2 were unsuccessful. Lowering the ratio of IVb/I from 2.4 (this experiment) to 1.5 and 0.9 gave 45% and 37% crude yields respectively. Reaction times longer than 24 hours did not improve yields.

#### *N*-Cyano-*N'*-(6-amino-2-pyridyl)formamidine (IIa).

An amount of 10.9 g. (0.1 mole) of I was heated to boiling with 80 ml. of glyme, filtered (to remove a trace of precipitate, allowed to cool to room temperature and treated dropwise with 9.0 g. (0.092 mole) of ethyl *N*-cyanoformimidate and stirred for 2 hours at room temperature. The precipitate was filtered and washed with ether; 6.65 g. (41%), m.p. 168-169°. An off-white analytical sample was obtained by stirring 1.0 g. of crude product with 20 ml. of glyme for 24 hours: 0.67 g., m.p. 170-171°,  $\text{ir } \lambda$  (Nujol): 2.80, 2.90 and 3.1  $\mu$  (NH), 4.52  $\mu$  (C $\equiv$ N).

*Anal.* Calcd. for C<sub>7</sub>H<sub>7</sub>N<sub>5</sub>: C, 52.16; H, 4.38; N, 43.45.

Found: C, 52.38; H, 4.55; N, 43.41.

Attempts to prepare either *N*-Cyano-*N'*-(6-amino-2-pyridyl)benzamidine or 2,5-diphenyl-1,3,4,6,9b-pentaazaphenalene by methods similar to those presented were unsuccessful.

#### 2,4-Diamino-6-methylpyrimidine (I').

The preparation of I' was patterned after a known synthesis of 2,4-diaminopyrimidine (9).

Ammonia gas was bubbled through a mixture of 25 g. (0.153 mole) of 2,4-dichloro-6-methylpyrimidine, 121 g. of phenol and 0.5 g. of anhydrous copper sulfate. The mixture was heated to reflux and the ammonia addition was continued for four hours; the cooled reaction mixture was acidified to Congo Red and steam distilled to remove the phenol. The residue was treated with 32 g. of ammonium nitrate and refrigerated overnight. The precipitate was collected by filtration, neutralized with 40% sodium hydroxide (~40 ml.) and evaporated to dryness *in vacuo*; Soxhlet extraction of the residue with ethyl acetate gave 11 g. (58%) of crude I', m.p. 181-184° (Lit., 183-185°, (10). Recrystallization from acetone raised the melting point to 184-186°.

#### *N*-Cyano-*N'*-(2-amino-4-methyl-6-pyrimidyl)acetamidine (II') (4).

A mixture of 3.72 g. (0.03 mole) of I' and 7.06 g. (0.072 mole) of methyl *N*-cyanoacetimidate in 7.15 ml. of glyme was refluxed and stirred for 3 hours. The precipitate was collected by filtration and washed with ether: 4.16 g. (73%), m.p. 246-249°. Two recrystallizations from 2-methoxyethanol gave yellow crystals, m.p. 253-255°;  $\text{ir } \lambda$  (Nujol): 2.92, 3.15  $\mu$  (NH), 4.5  $\mu$  (C $\equiv$ N). increasing the reaction time to 18 hours gave II' as the only product and no improvement in yield.

*Anal.* Calcd. for C<sub>8</sub>H<sub>10</sub>N<sub>6</sub>: C, 50.52; H, 5.30; N, 44.18. Found: C, 50.63; H, 5.25; N, 43.95.

#### 2,5,8-Trimethyl-1,3,4,6,7,9b-hexaazaphenalene (III').

A mixture of 2 g. (0.0105 mole) of II' and 21.6 g. (0.212 mole) of acetic anhydride was refluxed and stirred for 5 hours, then filtered at room temperature; the ether-washed precipitate weighed 1.19 g. (53%) m.p. 250-253°. Two recrystallizations from ethyl butyrate gave burnt-orange crystals, m.p. 255-256°;  $\text{ir } \lambda$  (Nujol): 12.18  $\mu$ , no significant absorption 2.75-3.2 or 4-5  $\mu$ ; nmr (DMSO-d<sub>6</sub>):  $\delta$  2.07 (s, 3H, CH<sub>3</sub>),  $\delta$  2.09 (s, 3H, CH<sub>3</sub>),  $\delta$  2.14 (s, 3H, CH<sub>3</sub>),  $\delta$  6.16 (s, 1H, H<sub>9</sub>); molecular weight 215 (vapor-phase osmometry).

*Anal.* Calcd. for C<sub>10</sub>H<sub>10</sub>N<sub>6</sub>: C, 56.06; H, 4.71; N, 39.24. Found: C, 56.26; H, 4.98; N, 39.14.

The following examples are illustrative of the methods used to prepare the compounds listed in Table I.

#### Method A (Using Anhydrides).

##### 2-Methyl-5-*n*-propyl-1,3,4,6,9b-pentaazaphenalene (IIIf).

A solution of 1.75 g. (0.01 mole) of IIb and 7.91 g. (0.05 mole) of butyric anhydride in 10 ml. of glyme was refluxed for 18 hours. The solid was filtered at room temperature and washed with (30-60°) petroleum ether: 1.50 g. (66%), m.p. 171-172°. Two recrystallizations from petroleum ether (110-120°) did not alter the melting point of the pink solid;  $\text{ir } \lambda$  (Nujol): 12.18  $\mu$ .

*Anal.* Calcd. for C<sub>12</sub>H<sub>13</sub>N<sub>5</sub>: C, 63.41; H, 5.76; N, 30.81. Found: C, 63.25; H, 5.70; N, 30.98.

#### Method B (Using Acid Chlorides)

##### 2-Methyl-5-chloromethyl-1,3,4,6,9b-pentaazaphenalene (IIIg).

A cold slurry (8°) of 4.38 g. (0.025 mole) of IIb and 1.98 g. (0.025 mole) of dry pyridine in 35 ml. of dry glyme was stirred

and treated in portions with 6.78 g. (0.06 mole) of chloroacetyl chloride; an exothermic reaction brought the temperature to 28°. The mixture was then heated at reflux for 3 hours, cooled to room temperature and filtered. The ether-washed precipitate was stirred with 15 ml. of ice-cooled methanol and neutralized to pH ~ 10 by the slow addition of 1*N* methanolic sodium methoxide. The filtrate from this mixture was evaporated to dryness *in vacuo*, and the residue extracted with 3 x 50 ml. portions of boiling chlorobenzene. Evaporation of the combined extracts *in vacuo* gave a solid, 2.84 g. (49%), m.p. 241-242° dec. Two recrystallizations from chlorobenzene gave pink plates, m.p. 243-244° dec.;  $\text{ir } \lambda$  (Nujol): 12.11  $\mu$ .

*Anal.* Calcd. for  $\text{C}_{10}\text{H}_8\text{ClN}_5$ : C, 51.40; H, 3.45; N, 29.98. Found: C, 51.70; H, 3.51; N, 29.78.

2-Methyl-5-phenyl-5,6-dihydro-1,3,4,6,9b-pentaazaphenalene (V) and 2-Methyl-5-phenyl-1,3,4,6,9b-pentaazaphenalene (IIIi).

A mixture of 1.75 g. (0.01 mole) of IIb and 1.27 g. (0.012 mole) of benzaldehyde in 7.5 ml. of dry glyme was heated to reflux with stirring; the mixture shortly became so thick that an additional 5 ml. of glyme was added. After refluxing for 2 hours, 10 ml. of glyme was added and the mixture was filtered hot; the ether-washed filter cake weighed 1.87 g. (71%), m.p. 220-222°. Two recrystallizations from xylene did not alter the melting point of the yellow solid,  $\text{ir } \lambda$  (Nujol): 5.9  $\mu$  (C=N), 12.85  $\mu$  (11).

*Anal.* Calcd. for  $\text{C}_{15}\text{H}_{13}\text{N}_5$ : C, 68.42; H, 4.98; N, 26.60. Found: C, 68.13; H, 5.12; N, 26.36.

A mixture of 0.50 g. (0.0019 mole) of V and 0.1 g. of 5% palladium on carbon in 10 ml. of diglyme was refluxed for 18 hours. Filtration of the mixture followed by vacuum evaporation of the filtrate gave a gummy material which was chromatographed using chloroform/alumina: 0.1 g. (20%), m.p. 241-243°; recrystallization from 2-methoxyethanol gave purple crystals, m.p. 244-246° identical to IIIi in Table I.

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- (2) Taken in part from the Senior Honors Projects of Mary E. O'Connor, Richard C. Allen, William M. Westler and Bruce D. Stefanko.
- (3) J. T. Shaw, W. M. Westler and B. D. Stefanko, *Chem. Commun.*, 1070 (1972).
- (4) The structure of II' could also be *N*-Cyano-*N'*-(4-amino-6-methyl-2-pyrimidyl)acetamide; either structure would give III' on reaction with acetic anhydride.
- (5) See footnote (i) in Table I; the lack of solubility of IIb in glyme under these reaction conditions may have contributed to the lower yield of IIIb, since use of 2-methoxyethanol (in which IIb is soluble) resulted in a 37% yield of crude IIIb.
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- (11) The lack of an NH band suggest that V may have tautomerized to give a 5,7, or 5,9 dihydropentaazaphenalene derivative. Very low solubility precluded an nmr analysis.