[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF TEMPLE UNIVERSITY[1]]

The Synthesis of Certain Substituted 1,3,5-Triazines Containing the Ferroin Group

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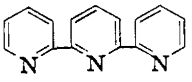
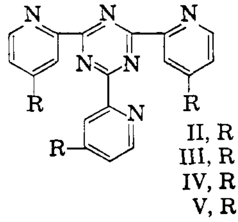
A series of trisubstituted 1,3,5-triazines has been prepared by the trimerization of the corresponding nitriles. These nitriles, treated with dicyandiamide, yield diamino-monopyridyl triazines. When treated with guanidine, monoamino-dipyridyltriazines result. The synthesis of 2,5-bis-(2-pyridyl)-pyrazine is described. All the above compounds contain the ferroin group, —N=C—C=N—.

The chelating ability of 2,6-bis-(2-pyridyl)-pyridine (I) for Fe(II) and Cu(I) is well known. The structural similarity of 2,4,6-tris-(2-pyridyl)-1,3,5-triazine (II) to it has suggested the synthesis of the latter compound and several of its derivatives.

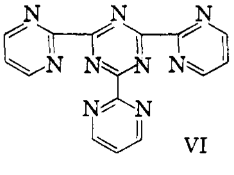

I


II, R = H
III, R = CH_3
IV, R = C_2H_5
V, R = C_6H_5

For this the trimerization of the corresponding 2-cyanopyridine appeared to be the most convenient approach. For the trimerization of benzonitrile to 2,4,6-triphenyl-1,3,5-triazine many methods are available. However, the only one which was found to be successful in this connection was heating of the nitrile with catalytic amounts of sodium hydride.[2] We have applied this successfully to 2-cyanopyridine and its 4-methyl-, 4-ethyl- and 4-phenyl- derivatives,[3] to yield the corresponding trisubstituted triazines II, III, IV and V, respectively, and also to 2-cyanoquinoline.

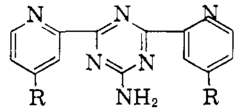
It is of interest that these triazines crystallize with varying amounts of water, depending on the substituents present. Thus II forms a trihydrate and IVa dihydrate, while III and the trimer of 2-cyanoquinoline form sesquihydrates; V is not hydrated.

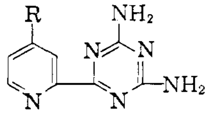
Another compound which appeared to be of special interest is tris-2,4,6-(2-pyrimidyl)-1,3,5-triazine (VI), which should result from trimerization of 2-cyanopyrimidine, the preparation of which was effected by the method of Klötzer[4] from 2-chloropyrimidine. In this case trimerization could not be achieved by the usual method, but a small amount of the product was found to be formed after several month's standing of 2-cyanopyrimidine.[5]


VI

It already has been found that compounds II, III and IV chelate with Fe(II) to yield deep-blue complexes.

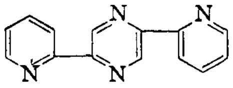
The synthesis of 2-amino-4,6-bis-(3-pyridyl)-1,3,5-triazine by the action of guanidine with 3-cyanopyridine already has been described.[6] Application of a similar procedure to 2-cyanopyridine and its 4-ethyl and 4-phenyl derivatives yielded the corresponding 2-amino-4,6-dipyridyl-1,3,5-triazines, VII, VIII and IX, respectively. From 2-cyanoquinoline was obtained 2-amino-4,6-bis-(2-quinolyl-1,3,5-triazine. Compounds VII and VIII have been found to yield violet-colored complexes with Fe(II).


VII, R = H
VIII, R = C_2H_5
IX, R = C_6H_5


X, R = H
XI, R = C_2H_5
XII, R = C_6H_5

The synthesis of 2,4-diamino-6-phenyltriazine has been accomplished by the action of benzonitrile and dicyandiamide in presence of potassium hydroxide.[7] Using a similar procedure, 2-cyanopyridine and its 4-ethyl and 4-phenyl derivatives yielded the corresponding 2,4-diamino-6-pyridyl-1,3,5-triazines, X, XI and XII, respectively.

In addition to the foregoing triazines 2,5-bis-(2-pyridyl)-pyrazine (XIII) was synthesized by the self-condensation of 2-pyridylaminomethyl ketone,[8] followed by dehydrogenation.


XIII

Experimental Part

Synthesis of 2,4-Diamino-6-pyridyl-1,3,5-triazines.—A mixture of one molar proportion of 2-cyanopyridine derivative, 1.25 of dicyandiamide, 0.2 of potassium hydroxide and 6.2 of methyl Cellosolve was refluxed for 4 hr. After cooling, the contents of the flask were poured in water, the precipitate collected by filtration, dried and crystallized. In the case of 2-cyanopyridine only, the reaction proceeded rather violently and cooling was necessary in the early stages.

Synthesis of 2-Amino-4,6-dipyridyl-1,3,5-triazines.—To a cooled solution of 0.024 mole of guanidine hydrochloride in 20 ml. of absolute ethanol was added 0.024 g. atom of

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(1) This work was supported by a grant (G2162) from the National Science Foundation.

(2) U. S. Patent 2,598,811 (*C. A.*, **46**, 10212 (1952)).

(3) F. H. Case and T. J. Kasper, THIS JOURNAL, **78**, 5842 (1956).

(4) W. Klötzer, *Monatsh.*, **87**, 526 (1956).

(5) The preparation of 2-cyanopyrimidine from the corresponding sulfonate has been reported by E. Ochiai and H. Yamanaka, *Pharm. Bull. (Japan)*, **3**, 173 (1955); *C. A.*, **50**, 7810^e (1956).

(6) P. B. Russel and G. H. Hitchings, THIS JOURNAL, **72**, 4922 (1950).

(7) J. K. Simons and M. R. Saxton, *Org. Syntheses*, **33**, 13 (1953).

(8) G. R. Clemo, T. Holmes and G. Leitch, *J. Chem. Soc.*, 753 (1938).

TABLE I

2,4-DIAMINO-6-SUBSTITUTED-1,3,5-TRIAZINES

Substituent	M.p., °C.	Crystn. solvent	Yield, %	Molecular formula	Carbon, % Calcd. Found	Hydrogen, % Calcd. Found
2-Pyridyl	297–298	Water	73.8	$C_8H_8N_6$	51.05	4.28
					50.97	4.37
4-Ethyl-2-pyridyl	246–247	Water	71.0	$C_{10}H_{12}N_6$	55.54	5.59
					55.09	5.63[a]
4-Phenyl-2-pyridyl	265–266	Ethyl Cellosolve–water	78.9	$C_{14}H_{12}N_6$	63.62	4.58
					63.19	4.45[a]

[a] Analyses were on samples dried at 110° *in vacuo;* loss of weight indicated monohydrates.

sodium. After solution was complete the precipitated sodium chloride was removed by filtration and washed with 7 ml. of absolute ethanol. The nitrile (0.04 mole) was then added and the mixture refluxed for 15 hr. After cooling, the precipitate was collected and purified by crystallization.

TABLE II

2-AMINO-4,6-DIPYRIDYL-1,3,5-TRIAZINES

Substituent	M.p., °C.	Crystn. solvent	Yield, %	Molecular formula	Carbon, % Calcd. Found	Hydrogen, % Calcd. Found
2-Pyridyl	306–308	Methyl Cellosolve	31.6	$C_{13}H_{10}N_6$	62.39	4.03
					62.61	3.83
4-Ethyl-2-pyridyl	334–336 dec.	Ethyl Cellosolve	17.9	$C_{17}H_{18}N_6$	66.64	5.92
					66.34	5.89
4-Phenyl-2-pyridyl	376–378 dec.	Dimethylformamide	45.0	$C_{25}H_{18}N_6$	74.61	4.51
					74.25	4.42
2-Quinolyl	355–356	Dimethylformamide	38.3	$C_{21}H_{14}N_6$	71.98	4.03
					72.35	4.27

2-Cyanopyrimidine.—A solution of 17.6 g. of 2-chloropyrimidine and 20 g. of trimethylamine in 120 ml. of dry benzene was allowed to stand for 5 days. The resulting 2-pyrimidyltrimethylammonium chloride (26 g.) was collected by filtration and dried in a vacuum desiccator. To a mixture of 24.5 g. of potassium cyanide and 42.9 g. of acetamide heated to 80–90° was added gradually 21 g. of the above quaternary salt. Heating was continued at this temperature until no further evolution of gas was observed. The cooled melt then was dissolved in 156 ml. of water, and extracted with ether. After drying and removal of solvent the residue was distilled *in vacuo*, yielding 6.8 g. of a liquid, b.p. 105–112 (7 mm.), which solidified on standing. A sample, crystallized from petroleum ether, melted at 41–42°.

Anal. Calcd. for $C_5H_3N_3$: C, 57.14; H, 2.88. Found: C, 57.18; H, 2.82.

2,4,6-Tris-(2-pyrimidyl)-1,3,5-triazine.—On standing for 3 months, 13.8 g. of 2-cyanopyrimidine deposited 0.8 g. of a solid which on crystallization from water yielded white crystals melting at 450–455°.

Anal. Calcd. for $C_{15}H_9N_9$: C, 57.14; H, 2.88. Found: C, 56.99; H, 2.82.

2,5-Bis-(2-pyridyl)-pyrazine.—A solution of 12 g. of crude 2-pyridylaminomethyl ketone (prepared by the method of Clemo, Holmes and Leitch[8]), in 42 ml. of water, was made alkaline with sodium hydroxide and extracted with ether. The residue, after removal of ether, was dissolved in 70 ml. of methanol, cooled to 0° and, after addition of 7 ml. of 30% hydrogen peroxide, allowed to stand 4 hr. The solution was then treated with 0.5 g. of 5% palladium-on-carbon, and allowed to stand overnight. After filtration and removal of methanol, the residue was extracted with chloroform, and the chloroform-soluble residue crystallized from benzene. The resulting solid (0.5 g.) melted at 226–227°.

Anal. Calcd. for $C_{14}H_{10}N_4$: C, 71.78; H, 4.30. Found: C, 72.26; H, 4.37.

2,4,6-Tris-(2-pyridyl)-1,3,5-triazine.—2-Cyanopyridine (6 g.) and 0.1 g. of sodium hydride were heated at 160–165° for 5 hr. in an atmosphere of nitrogen. The solid reaction mixture was extracted with hot benzene and crystallized from ethanol–water. The yield of trihydrate was 3.9 g. (55.7%), m.p. 244–245°.

Anal. Calcd. for $C_{18}H_{12}N_6\cdot 3H_2O$: C, 59.01; H, 4.95; N, 22.94. Found: C, 58.97; H, 4.60; N, 23.17.

Dehydration was effected by heating for 80 hours at 140° (25 mm.) plus 8 hours at 190° (0.25 mm.)

Anal. Calcd. for $C_{18}H_{12}N_6$: C, 69.22; H, 3.87. Found: C, 69.32; H, 3.79.

2,4,6-Tris-(2-quinolyl)-1,3,5-triazine.—From 8 g. of 2-cyanoquinoline, treated with 0.1 g. of sodium hydride as before, with subsequent benzene extraction and crystallization from ethanol–water, was obtained 1.9 g. of trimer sesquihydrate, m.p. 270–271°, yield 22.4%.

Anal. Calcd. for $C_{30}H_{18}N_6\cdot 1^1/_2H_2O$: C, 73.60; H, 4.32. Found: C, 73.79; H, 3.97.

The hydrate then was dried to constant weight at 120° *in vacuo.*

Anal. Calcd. for $C_{30}H_{18}N_6$: C, 77.90; H, 3.92. Found: C, 77.72; H, 3.87.

2,4,6-Tris-(4-ethyl-2-pyridyl)-1,3,5-triazine.—Six grams of 4-ethyl-2-cyanopyridine was heated with 0.1 g. of sodium hydride at 120–130° for 23 hours. The solid residue, after extraction with petroleum ether (60–70°) to remove unchanged material, was dissolved in chloroform and eluted through alumina. The oily residue, after removal of chloroform, solidified after several days standing exposed to air. Crystallization from benzene–petroleum ether yielded 1 g. of product melting at 98–104° (15.1%) or 0.3 g., m.p. 105–106°.

Anal. Calcd. for $C_{24}H_{24}N_6\cdot 2H_2O$: C, 66.67; H, 6.48. Found: C, 66.78; H, 6.51.

The hydrate, after drying to constant weight at 110° *in vacuo*, melted at 136–137°.

Anal. Calcd. for $C_{24}H_{24}N_6$: C, 72.70; H, 6.10. Found: C, 73.11; H, 5.78.

2,4,6-Tris-(4-methyl-2-pyridyl)-1,3,5-triazine.—Six grams of 4-methyl-2-cyanopyridine was heated with 0.1 g. of sodium hydride at 120–130° for 6 hours. The residue, after extraction with petroleum ether, was dissolved in chloroform and eluted through alumina. Removal of chloroform yielded a crystalline residue which after one crystallization from benzene–petroleum ether, and one from ethanol–water yielded 0.8 g. of hydrate melting at 213–214°, yield 12.3%.

Anal. Calcd. for $C_{21}H_{18}N_6\cdot 1^1/_2H_2O$: C, 66.12; H, 5.55; N, 22.04. Found: C, 65.82; H, 5.47; N, 21.85.

The hydrate was heated at 120° *in vacuo* to constant weight.

Anal. Calcd. for $C_{21}H_{18}N_6$: C, 71.16; H, 5.12. Found: C, 70.94; H, 5.17.

2,4,6-Tris-(4-phenyl-2-pyridyl)-1,3,5-triazine.—A mixture of 4.2 g. of 4-phenyl-2-cyanopyridine and 0.1 g. of sodium hydride was heated at 120–130° for 6 hours. The residue, after extraction with petroleum ether, was dissolved in chloroform and eluted through alumina. Removal of chloroform and crystallization of the residue from benzene yielded 1.7 g. (40.5%) of product melting at 244–245°.

Anal. Calcd. for $C_{36}H_{24}N_6$: C, 79.98; H, 4.48. Found: C, 80.18; H, 4.50.

PHILADELPHIA 22, PENNA.