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The Preparation of 2-Substituted Benzimidazole Derivatives Containing the Ferroin Group (1)

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The preparation of 2-substituted benzimidazoles from the action of *o*-phenylenediamine with esters, amides, acids, or nitriles (but chiefly acids) in presence of polyphosphoric acid at 250° has been described by Hein, Alheim and Leavitt (2).

In this laboratory substituted 2-cyanopyridines (3), 6-cyano-2,2'-bipyridine (4) and 2-cyano-1,10-phenanthroline (5) have been condensed with *o*-phenylenediamine, 7,8-diaminoquinoline (6), 3,4-diaminopyridine (7,8), 3,4-diaminobiphenyl (9) and 5,6-diamino-4,7-phenanthroline, respectively, to yield compounds containing one or more ferroin [=N-C(=)-C(=)-N=] groups and hence potentially capable of chelating metal ions. It has been found that most of the compounds prepared in this way retain water and must be carefully dried for analysis.

Preparations of 2-(2-pyridyl)- and 2-(2-quinolyl)-benzimidazoles, involving the action of the 2-aldehyde with *o*-phenylenediamine in the presence of platinum in a current of air, have already been described (10).

Although 5,6-diamino-4,7-phenanthroline is mentioned in the literature (11), its preparation is not recorded. It has been made in this laboratory by tosylation of 5-amino-4,7-phenanthroline (12) followed by nitration, hydrolysis, and reduction.

This diamine was condensed with 4,7-phenanthroline-5,6-dione to yield tetrapyrido(2,3-*a*:3',2'-*c*:2'',3''-*h*:3''',2'''-*j*)phenazine which was previously prepared in a hydrated form in this laboratory using an entirely different method (13).

EXPERIMENTAL

General Procedure for Preparation of Substituted Benzimidazoles.

Equimolecular amounts of nitrile and diamine (not to exceed 0.01 mole of each) were mixed with 20 g. of polyphosphoric acid and the mixture maintained at 250° for 4 hours. It was then poured into water and neutralized with ammonium hydroxide. The resulting precipitate was dried and crystallized from the solvent indicated in the tables.

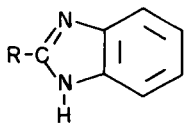
5-(*p*-Toluenesulfonamido)-4,7-phenanthroline.

A mixture of 18 g. each of 5-amino-4,7-phenanthroline and *p*-toluenesulfonyl chloride and 180 ml. of pyridine was heated for 2 hours on a steam bath. It was then poured on ice, and the separated solid crystallized from ethanol. The yield was 19.5 g. (59.3%). An analytical sample melted at 192-193°.

Anal. Calcd. for $C_{19}H_{15}N_3O_2S$: C, 65.31; H, 4.33; N, 12.03. Found: C, 65.23; H, 4.30; N, 12.28.

TABLE I

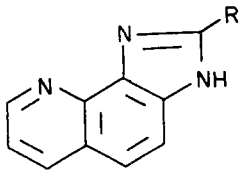
2-Substituted Benzimidazoles



R	Yield %	M.P. (°C)	Crystallization Solvent	Formula	Analysis Calcd. % C	Calcd. % H	Found % C	Found % H
4-Methyl-2-pyridyl	38.7	224-225	Benzene	$C_{13}H_{11}N_3$	74.61	5.30	74.65	5.28
4-Phenyl-2-pyridyl	53.3	209-210	Benzene	$C_{18}H_{13}N_3$	79.68	4.83	79.57	4.84
2-Quinolyl	44.9	220-221	Benzene	$C_{16}H_{11}N_3$	78.34	4.52	78.06	4.53
2,2'-Bipyridin-6-yl	22.1	221-222	Benzene	$C_{17}H_{12}N_4$	74.97	4.44	75.13	4.58
2-Phenanthrolyl	60.0	271-272	Benzene	$C_{19}H_{12}N_4 \cdot H_2O$	72.61	4.46	73.05	4.51

TABLE II

2-Substituted 3*H*-Imidazo[4, 5-*h*]quinolines

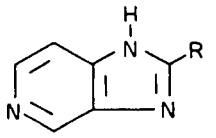


R	Yield %	M.P. (°C)	Crystallization Solvent	Formula	Analysis Calcd. % C	H	Found % C	H
2-Pyridyl	78.9	235	Ethanol	$C_{15}H_{10}N_4$	73.15	4.09	73.29	4.10
4-Methyl-2-pyridyl	22.7	173-174	Benzene	$C_{16}H_{12}N_4$	73.82	4.65	74.10	4.67
4-Ethyl-2-pyridyl	38.7	103-104	Benzene-Petroleum ether	$C_{17}H_{14}N_4$	74.43	5.14	74.53	5.41
4-Phenyl-2-pyridyl	44.0	110-111	Benzene	$C_{21}H_{14}N_4$	78.24	4.37	78.27	4.43
2,2'-Bipyridin-6-yl	55.6	179-180	Benzene	$C_{20}H_{13}N_5$	74.20	4.05	74.38	3.92
2-Phenanthrolyl	19.9	269-270	Benzene	$C_{22}H_{13}N_5 \cdot \frac{1}{2}H_2O$	74.13	3.96(a)	74.30	4.16

(a) *Anal.* Calcd.: N, 19.67. Found: N, 19.97.

TABLE III

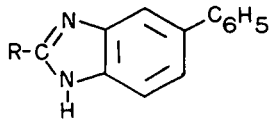
2-Substituted 1*H*-Imidazo[4, 5-*c*]pyridines



R	Yield %	M.P. (°C)	Crystallization Solvent	Formula	Analysis Calcd. % C	H	Found % C	H
2-Pyridyl	28.6	234-235	Benzene	$C_{11}H_8N_4$	67.33	4.11	67.18	4.10
4-Methyl-2-pyridyl	18.7	289-290	Ethanol	$C_{12}H_{10}N_4$	68.55	4.79	68.09	4.94
4-Phenyl-2-pyridyl	22.1	253-254	Ethanol	$C_{17}H_{12}N_4$	74.98	4.44	74.82	4.50
2,2'-Bipyridin-6-yl	47.6	241-242	Ethanol-water	$C_{16}H_{11}N_5$	70.31	4.06	70.25	4.18

TABLE IV

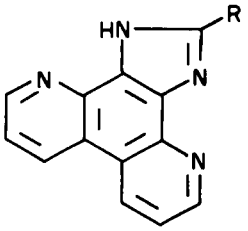
2-Substituted 5(6)-Phenylbenzimidazoles



R	Yield %	M.P. (°C)	Crystallization Solvent	Formula	Analysis Calcd. % C	H	Found % C	H
2-Pyridyl	50.0	150-151	Benzene-Petroleum ether	$C_{18}H_{13}N_3$	79.68	4.83	79.21	4.85
4-Methyl-2-pyridyl	41.4	171-172	Benzene	$C_{19}H_{15}N_3$	79.98	5.30	79.54	5.30
4-Phenyl-2-pyridyl	35.7	252-253	Benzene	$C_{24}H_{17}N_3$	82.97	4.93	83.15	5.07
2,2'-Bipyridin-6-yl	26.3	170-171	Benzene	$C_{23}H_{16}N_4$	79.29	4.63	79.25	4.61

TABLE V

2-Substituted 1*H*-Imidazo[4,5-*f*][4,7]phenanthrolines



R	Yield %	M. P. (°C)	Crystallization Solvent	Formula	Analysis Calcd. % C	H	Found % C	H
2-Pyridyl	90.9	248-249	Benzene	$C_{18}H_{11}N_5$	72.72	3.73	72.23	3.95
4-Methyl-2-pyridyl	50.6	251-252	Ethanol	$C_{19}H_{13}N_5$	73.30	4.21	73.05	4.43
4-Phenyl-2-pyridyl	42.3	167-168	Benzene	$C_{24}H_{15}N_5$	77.20	4.05	77.32	4.35
2,2'-Bipyridin-6-yl	69.0	315-316	Ethanol	$C_{23}H_{14}N_6$	73.76	3.77	73.47	4.06

5-Nitro-6-(*p*-toluenesulfonamido)-4,7-phenanthroline.

To a suspension of 8.8 g. of 5-*p*-toluenesulfonamido-4,7-phenanthroline in 20 ml. of glacial acetic acid was added a solution of 2.2 ml. of nitric acid (s.g., 1.5) in 4 ml. of acetic acid at a temperature of 80°. The mixture was then kept at this temperature for a further 0.5 hour during which time a precipitate settled. After pouring on ice and filtration the resulting solid was crystallized from aqueous dimethyl formamide. The yield of pure product, melting at 253-254°, was 5.5 g. (55.6%). A qualitative test for sulfur was obtained.

Anal. Calcd. for $C_{19}H_{14}N_4O_4S$: C, 57.87; H, 3.58. Found: C, 57.72; H, 3.76.

5-Amino-6-nitro-4,7-phenanthroline.

A suspension of 5.5 g. of 5-nitro-6-(*p*-toluenesulfonamido)-4,7-phenanthroline in 75 ml. of concentrated sulfuric acid was heated 1.5 hours on a steam bath, and then poured in ice-water. The crude base was precipitated by adding ammonium hydroxide and crystallized from methyl cellosolve. The yield of pure base was 3.5 g. (87.5%) melting at 219-220°.

Anal. Calcd. for $C_{12}H_8N_4O_2$: C, 60.00; H, 3.36. Found: C, 59.77; H, 3.44.

5,6-Diamino-4,7-phenanthroline.

To a suspension of 4.1 g. of 5-amino-6-nitro-4,7-phenanthroline in 13 ml. of concentrated hydrochloric acid was added a solution of 13 g. of stannous chloride dihydrate in 6 ml. of concentrated hydrochloric acid at such a rate that the temperature did not exceed 45°. After standing for one hour at this temperature the mixture was made strongly alkaline with sodium hydroxide, the precipitate removed by filtration, dried, and extracted with benzene. Evaporation of solvent, followed by crystallization of the residue from benzene, yielded 2.0 g. (55.6%) of product melting at 218°. An analytical sample melted at 223-224°.

Anal. Calcd. for $C_{12}H_{10}N_4$: C, 68.56; H, 4.79; N, 26.65. Found: C, 68.11; H, 4.70; N, 26.78.

Tetrapyrido(2,3-*a*:3',2'-*c*:2'',3''-*h*:3''',2'''-*j*)phenazine.

A suspension of 0.5 g. of 5,6-diamino-4,7-phenanthroline and 0.5 g. of 4,7-phenanthroline-5,6-dione in 80 ml. of ethanol was heated at reflux for 17 hours. The ethanol was then removed by distillation, the residue poured into water, and the precipitate crystallized from dimethyl sulfoxide. The yield of product melting over 450° was 0.54 g. (59.3%).

Anal. Calcd. for $C_{24}H_{12}N_6$: C, 74.99; H, 3.15. Found: C, 74.56; H, 3.37.

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