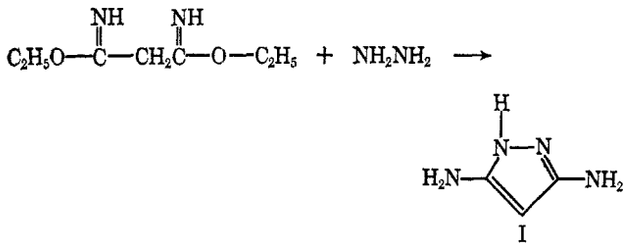
# Heterocyclic Amines. II. Synthesis of 3,5-Diaminopyrazole[1]

JOSEPH A. SETTEPANI AND JERRY B. STOKES

*Entomology Research Division, Agricultural Research Service U. S. Department of Agriculture, Beltsville, Maryland 20705*

*Received February 26, 1968*

A number of unsuccessful attempts to prepare 3,5-diaminopyrazole (I) have appeared in the literature. The reaction of hydrazine with malononitrile, originally reported as a route to I,[2] has been shown by Taylor and



Hartke[3] to lead instead to 3-cyanomethyl-4-cyano-5-aminopyrazole. In another approach, an attempted Curtius reaction starting with diethyl pyrazole-3,5-dicarboxylate, provided a syrup that was incompletely characterized.[4] Finally, phenylhydrazine and phenethylhydrazine were recently reported to react with ethyl 2-cyanoacetimidate hydrochloride to form corresponding 1-substituted 3,5-diaminopyrazoles in yields of 22 and 9%, respectively.[5] However, attempts to extend this reaction to hydrazine itself were unsuccessful.[5]

Our attention was drawn to this work by a continuing interest in heterocyclic amines as potential insect-sterilizing agents.[1,6] It occurred to us that reaction of hydrazines with a suitable diimidic ester, under the mild conditions of Pinner's synthesis of amidines,[7] could lead to formation of 3,5-diaminopyrazoles.

When equimolar amounts of hydrazine and diethyl malonimidate were dissolved in warm ethanol and combined, an immediate exothermic reaction occurred. Subsequent chilling of the reaction mixture caused 3,5-diaminopyrazole (I) to precipitate in 78% yield. Analogous reactions with methylhydrazine and, utilizing a somewhat longer reaction time, with phenylhydrazine, provided the 1-methyl and 1-phenyl derivatives of I. Ultraviolet spectra of the basic and protonated forms of the products, as well as infrared and nmr spectra were consistent with pyrazole structures.

The predominant tautomeric form of various aminopyrazoles has been the subject of a number of recent publications.[8] Although we have not undertaken a similar determination in the present study, an nmr spectrum of I recorded in $D_6$-methyl sulfoxide solution [$\tau$ 4.70 (5 H), 5.42 (1 H)] is clearly inconsistent with any tautomer that does not possess an $sp^2$ carbon atom at position 4.

Electrophilic substitution of I occurred quite readily in aqueous bromine to provide a sample of 3,5-diamino-4-bromopyrazole.

## Experimental Section

**3,5-Diaminopyrazole (I).**—A solution of 95% hydrazine hydrate (0.1 mol) in 50 ml of ethanol was warmed to boiling before adding 15.8 g (0.1 mol) of diethyl malonimidate[9] at such a rate that the mixture continued to reflux without external heating. Five minutes after the addition of the ester, the reaction mixture was chilled causing precipitation of 7.6 g (78%) of I. On recrystallization from isopropyl alcohol an analyical sample was obtained: mp 110°; ir (KBr), 3350, 3250, 1560, 1470, 1040, 970, and 720 $cm^{-1}$; uv max (95% EtOH), 217 m$\mu$ ($\epsilon$ 9400), cation 237 m$\mu$ ($\epsilon$ 18,500).

*Anal.* Calcd for $C_3H_6N_4$: C, 36.73; H, 6.16; N, 57.11. Found: C, 36.89; H, 6.30; N, 57.06.

**3,5-Diamino-1-methylpyrazole.**—To a stirred refluxing solution of 1.84 g (0.04 mol) of methylhydrazine in 50 ml of ethanol was added, under nitrogen, 6.3 g (0.04 mol) of diethyl maloimidate. Warming was continued for 5 min after the addition, and the mixture was then concentrated *in vacuo* to an oil. Crystallization from acetonitrile–ether provided 4.5 g (80%) of colorless plates, mp 51–53°. Purification was accomplished by sublimation: 75° (0.5 mm); mp 54°; ir (KBr), 3280, 3150, 1620, 1560, 1490, 1440, 1270, and 1000 $cm^{-1}$; uv (95% EtOH), 220 m$\mu$ ($\epsilon$ 10,500), cation 241 m$\mu$ ($\epsilon$ 18,200).

*Anal.* Calcd for $C_4H_8N_4$: C, 42.85; H, 7.19; N, 49.96. Found: C, 42.85; H, 7.20; N, 49.78.

**3,5-Diamino-1-phenylpyrazole.**—A solution of phenylhydrazine (1.08 g, 0.01 mol) and diethyl malonimidate (1.58 g, 0.01 mol) in 75 ml of methanol was refluxed under nitrogen for 12 hr. The chilled reaction mixture was acidified with 1 ml of concentrated HCl and concentrated to dryness. Three recrystallizations of the residue from ethanol–ether provided 1.3 g (62%) of 3,5-diamino-1-phenylpyrazole hydrochloride, mp 229–230° dec (mmp 229–230° dec with an authentic specimen).[5]

**3,5-Diamino-4-bromopyrazole.**—A solution of 1.6 g (0.01 mol) of bromine in 150 ml of water was added dropwise with stirring to 0.98 g (0.01 mol) of 3,5-diaminopyrazole dissolved in 50 ml of water. The dark reaction mixture was then warmed to 80°, treated with activated charcoal, and filtered. The pale yellow filtrate was neutralized ($Na_2CO_3$) and concentrated *in vacuo* to dryness. Extraction of the residue with absolute ethanol, followed by concentration and chilling afforded 1.2 g (68%) of 3,5-diamino-4-bromopyrazole, mp 133–134° dec. An analytical sample was recrystallized from ethanol–ether: mp 135–136° dec; ir, 3410, 3370, 3280, 3140, 1610, 1490, 1440, 1345, and 1020 $cm^{-1}$; uv (95% EtOH), 222 m$\mu$ ($\epsilon$ 9200) cation 244 m$\mu$ ($\epsilon$ 14,200).

*Anal.* Calcd for $C_3H_5BrN_4$: C, 20.36; H, 2.85; Br, 45.14; N, 31.65. Found: C, 20.61; H, 2.79; Br, 44.94; N, 31.70.

**Registry No.**—I, 16082-33-0; 3,5-diamino-1-methylpyrazole, 16675-35-7; 3,5-diamino-4-bromopyrazole, 16675-36-8.

(1) Part I: J. A. Settepani and A. B. Borkovec, *J. Heterocycl. Chem.*, **3**, 188 (1966).

(2) R. von Rothenburg, *Ber.*, **27**, 685 (1894).

(3) E. C. Taylor and K. S. Hartke, *J. Amer. Chem. Soc.*, **81**, 2452 (1959).

(4) L. Knorr, *Ber.*, **37**, 3520 (1904).

(5) W. J. Fanshawe, V. J. Bauer, and S. R. Safir, *J. Org. Chem.*, **29**, 942 (1964).

(6) A. B. Borkovec and A. B. DeMilo, *J. Med. Chem.*, **10**, 457 (1967). For a recent review of this subject, see A. B. Borkovec, "Insect Chemosterilants," Interscience Publishers, New York, N. Y., 1966.

(7) R. L. Shriner and F. W. Newmann, *Chem. Rev.*, **35**, 351 (1944).

(8) V. G. Vinokurov, V. S. Troitskaya, and I. I. Grandberg, *Zh. Obshch. Khim.*, **34**, 654 (1964); V. G. Vinokurov, V. S. Troitskaya, and I. I. Grandberg, *ibid.*, **35**, 1288 (1965); H. Dorn and H. Dilcher, *Ann. Chem.*, **707**, 141 (1967).

(9) S. M. McElvain and J. P. Schroeder, *J. Amer. Chem. Soc.*, **71**, 40 (1949).