The Synthesis of Some Pyrrolo[1,5-*b*:2,3-*c*']dipyridazines

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A facile method for the preparation of the aromatic pyrrolo[1,5-*b*:2,3-*c*']dipyridazine ring system is reported. A number of compounds have been prepared and the biological screening data reported.

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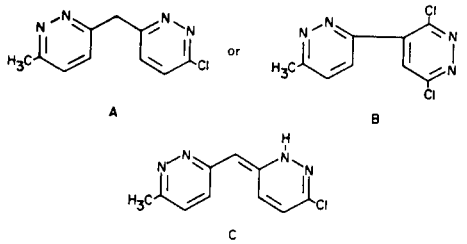
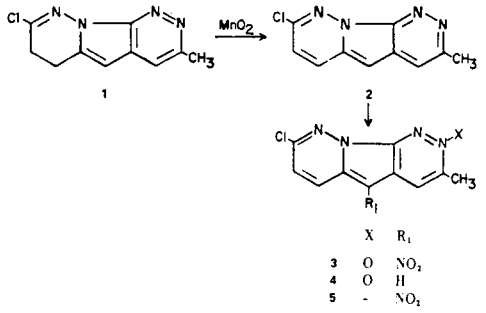
The pyrrolo[1,5-*b*:2,3-*c*']dipyridazine ring system has not been extensively investigated. Kumagai (2) isolated a condensation product, $C_{10}H_9ClN_4$ from the reaction of phosphoryl chloride and 3-methyl-6-pyridazinone. He proposed structures **A** or **B** which were later shown to be incorrect. Basu and Rose (3) prepared the same compound without referring to the earlier report of Kumagai (2) and proposed two possible structures, **C** and **1**. Basu and Rose indicated a preference for **1** which was shown to be correct from pmr and chemical data by Lund and Gruhn (4) and later confirmed by the x-ray crystallography data of Lehmann and Rasmussen (5). Furthermore, Lund and Gruhn (4) prepared several compounds in the 6,7-dihydropyrrolo[1,5-*b*:2,3-*c*']dipyridazine series as well as a few examples in the aromatized ring system.



We have prepared a number of compounds in the aromatized pyrrolo[1,5-*b*:2,3-*c*']dipyridazine ring system in order to make these compounds available for biological screening.

8-Chloro-3-methyl-6,7-dihydropyrrolo[1,5-*b*:2,3-*c*']-dipyridazine (**1**) (4) was readily aromatized by heating with manganese dioxide in ethyl acetate (or in benzene) solution producing 8-chloro-3-methylpyrrolo[1,5-*b*:2,3-*c*']-dipyridazine (**2**) in 90% yield. Compound **2** was allowed to react with *m*-chloroperbenzoic acid giving 8-chloro-3-methylpyrrolo[1,5-*b*:2,3-*c*']dipyridazine 2-oxide (**4**) (6a,b) in 61% yield. Compound **4** was smoothly nitrated to give 8-chloro-3-methyl-5-nitropyrrolo[1,5-*b*:2,3-*c*']dipyridazine 2-oxide (**3**) in quantitative yield. Compound **2** was also nitrated easily producing 8-chloro-3-methyl-5-nitropyrrolo[1,5-*b*:2,3-*c*']dipyridazine (**5**) in 67% yield. These transformations are shown in Scheme I.

Scheme I

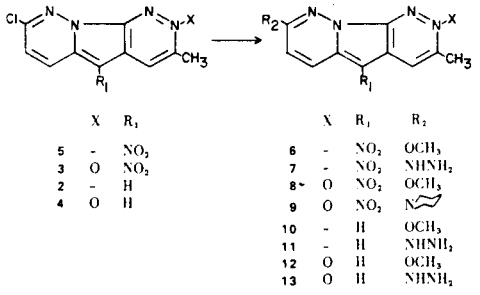


	X	R_1
3	O	NO_2
4	O	H
5	-	NO_2

The chloro compounds (**2**, **3**, **4**, **5**) reacted readily with nucleophiles. When **5** was allowed to react with sodium methoxide in methanol, 8-methoxy-3-methyl-5-nitro-

pyrrolo[1,5-*b*:2,3-*c*']dipyridazine (**6**) was obtained in 85% yield. Furthermore, the following were obtained in like manner: 8-methoxy-3methylpyrrolo[1,5-*b*:2,3-*c*']dipyridazine (**10**), 76% yield from **2** and 8-methoxy-3-methylpyrrolo[1,5-*b*:2,3-*c*']dipyridazine 2-oxide (**12**), 88% yield from **4**. However, 8-methoxy-3-methyl-5-nitropyrrolo[1,5-*b*:2,3-*c*']dipyridazine 2-oxide (**8**) was obtained from **12** by direct nitration. The hydrazino compounds were prepared by allowing the corresponding 8-chloro compounds to react briefly with anhydrous hydrazine in DMSO at 130°, thus from **5**, 8-hydrazino-3-methyl-5-nitropyrrolo[1,5-*b*:2,3-*c*']dipyridazine (**7**) was obtained in 66% yield. From **2**, 8-hydrazino-3-methylpyrrolo[1,5-*b*:2,3-*c*']dipyridazine (**11**) (65% yield) and from **4**, 8-hydrazino-3-methylpyrrolo[1,5-*b*:2,3-*c*']dipyridazine 2-oxide (**13**) (63% yield) were both obtained. When an attempt was made to condense the 3-methyl group of 8-chloro-3-methyl-5-nitropyrrolo[1,5-*b*:2,3-*c*']-dipyridazine 2-oxide (**3**) with benzaldehyde in DMF solution to which piperidine had been added, the product isolated was 3-methyl-5-nitro-8-piperidinopyrrolo[1,5-*b*:-2,3-*c*']dipyridazine 2-oxide (**9**) in 85% yield. No styryl derivative was detected. These transformations are illustrated in Scheme II.

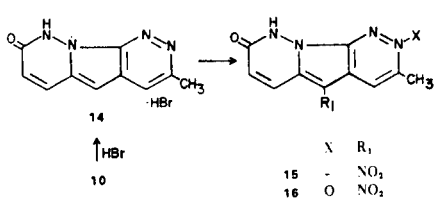
Scheme II



	X	R_1		X	R_1	R_2
5	-	NO_2	6	-	NO_2	OCH_3
3	O	NO_2	7	-	NO_2	$NHNH_2$
2	-	H	8	O	NO_2	OCH_3
4	O	H	9	O	NO_2	N≈
			10	-	H	OCH_3
			11	-	H	$NHNH_2$
			12	O	H	OCH_3
			13	O	H	$NHNH_2$

8-Methoxy-3-methylpyrrolo[1,5-*b*:2,3-*c*']dipyridazine (**10**) was allowed to reflux in 48% hydrobromic acid solution. The product was 3-methyl-9*H*-pyrrolo[1,5-*b*:-2,3-*c*']dipyridazin-8-one hydrobromide (**14**) (70% yield). Compound **14** was readily nitrated to give 3-methyl-5-nitro-9*H*-pyrrolo[1,5-*b*:2,3-*c*']dipyridazin-8-one (**15**) in 64% yield. The nitro compound **15** was *N*-oxidized with *m*-chloroperbenzoic acid giving 3-methyl-5-nitropyrrolo-[1,5-*b*:2,3-*c*']dipyridazine 2-oxide (**16**) in 49% yield. These transformations are shown in Scheme III.

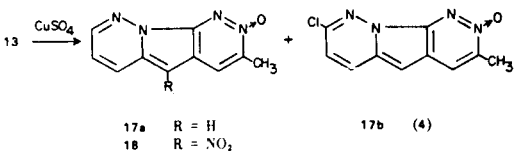
Scheme III



	X	R_1
15	-	NO_2
16	O	NO_2

8-Hydrazino-3-methylpyrrolo[1,5-*b*:2,3-*c*']dipyridazine 2-oxide (**13**) was allowed to react with cupric sulfate in very dilute hydrochloric acid solution. Chromatography on alumina (chloroform as eluent) gave 3-methylpyrrolo-[1,5-*b*:2,3-*c*']dipyridazine 2-oxide (**17a**) and **17b** in nearly equal amounts. The structure of **17b** was not readily apparent. The pmr spectrum of **17b** indicates that the H atoms at C3, C4, C5, C6 and C7 have not been disturbed compared with the pmr spectra of other compounds in this series. When the ir spectra of **17a** and **17b** were compared, the most noticeable difference was the increased intensity of the absorbance at 1523 and 1505 cm^{-1} in **17b**. A mass spectrum of **17b** revealed a peak at m/e 234 with a relative intensity of 100 and another peak at m/e 236 with a relative intensity of 34 which immediately indicated the presence of a chlorine atom in **17b**. A comparison of **4** and **17b** established the identity of these two compounds. Compound **17b** obviously arose from the unexpected nucleophilic displacement of the hydrazino group by the chloride anion in the very dilute aqueous hydrochloric acid solution. Treatment of **17a** with fuming nitric acid gave 3-methyl-5-nitropyrrolo-[1,5-*b*:2,3-*c*']dipyridazine 2-oxide (**18**) in 75% yield. These transformations are outlined in Scheme IV.

Scheme IV

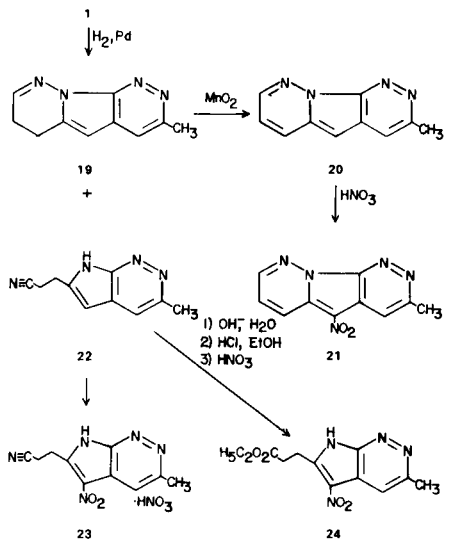


17a R = H **17b** (4)
18 R = NO_2

The ring cleavage and dehalogenation of 8-chloro-3-methyl-6,7-dihydropyrrolo[1,5-*b*:2,3-*c*']dipyridazine (**1**) with hydrogen and palladium has been previously reported (4). The products were 3-methyl-6,7-dihydropyrrolo[1,5-*b*:2,3-*c*']dipyridazine (**19**) and 6-(β-cyanoethyl)-3-methyl-7*H*-pyrrolo[2,3-*c*]pyridazine (**22**). Manganese dioxide oxidation of **19** gave 3-methylpyrrolo-[1,5-*b*:2,3-*c*']dipyridazine (**20**) in 95% yield. Compound **20** was smoothly nitrated providing an 81% yield of 3-methyl-5-nitropyrrolo[1,5-*b*:2,3-*c*']dipyridazine (**21**). Nitration of **22** gave 6-(β-cyanoethyl)-3-methyl-5-nitro-7*H*-pyrrolo[2,3-*c*]pyridazine (**23**) in 82% yield. Nitrile **22** was hydrolyzed with aqueous base followed by esterification with ethanol and this previously reported ester (4) was nitrated with fuming nitric acid to give 6-(β-carbethoxyethyl)-3-methyl-5-nitro-7*H*-pyrrolo[2,3-*c*]-pyridazine (**24**) in 87% yield. These transformations are shown in Scheme V.

Some of the pyrrolo[1,5-*b*:2,3-*c*']dipyridazines demonstrated good inhibitory activity against c-AMP-phosphodiesterase (PDE) (7). Evaluation procedures of the inhibitory activity against the rabbit lung and beef heart

Scheme V



PDE activity have been previously described (8,9). 3-Methyl-5-nitropyrrolo[1,5-*b*:2,3-*c*']dipyridazine (**21**) and 8-chloro-3-methyl-5-nitropyrrolo[1,5-*b*:2,3-*c*']dipyridazine (**3**) showed considerable activity when compared with theophylline. The α values of **21** and **3** for the rabbit lung enzyme were 3.6 and 3.2, respectively, and 1.0 for **3** in the beef heart screen (**21** was too insoluble for evaluation in the beef heart screen). 8-Chloro-3-methyl-6,7-dihydropyrrolo[1,5-*b*:2,3-*c*']dipyridazine (**1**) showed α values of 0.9 and 0.3 against the rabbit lung and beef heart enzymes, respectively. 6-(β-Carbethoxyethyl)-3-methyl-5-nitro-7*H*-pyrrolo[2,3-c]pyridazine (**24**) possessed α values of 1.5 (rabbit lung) and 0.5 (beef heart). In general, only those compounds possessing the nitro group in a position analagous to the 7-position in the purine ring have consistently demonstrated significant PDE inhibitory activity against the rabbit lung enzyme.

8-Chloro-3-methylpyrrolo[1,5-*b*:2,3-*c*']dipyridazine 2-oxide (**4**) possessed moderate antiviral activity (VR of 0.8 against type 13 rhinovirus) (12,13).

Antimicrobial evaluation demonstrated that 8-hydrazino-3-methyl-5-nitropyrrolo[1,5-*b*:2,3-*c*']dipyridazine (**7**) possessed significant activity against *Staphylococcus aureus* (14) (MIC/MLC, 0.0025/0.005 μmoles/ml.) (15).

Significant antiparasitic activity against *Schistosoma mansoni* (SM), *Trypanosoma cruzi* (TC), and *Tritrichomonas foetus* (TF) was shown by 8-chloro-3-methyl-5-nitropyrrolo[1,5-*b*:2,3-*c*']dipyridazine 2-oxide (**3**) and 8-chloro-3-methyl-6,7-dihydropyrrolo[1,5-*b*:2,3-*c*']dipyridazine (**1**). The MAC/MLC (15) against SM was >1.0/3.2 for **3** and 3.2/10 for **1**; the MIC/MLC against TC was 100/>100 for **3** and >10/100 for **1**; MIC against TF was 100 for **3** and **1** was inactive. The above concentrations are expressed μg./ml.

EXPERIMENTAL

Melting points were recorded on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The pmr spectra were recorded on a Varian A-60A or EM-390 instrument and compared with tetramethylsilane as an internal standard. The ir spectra were recorded in potassium bromide discs with a Perkin-Elmer 457 spectrophotometer. The mass spectrum was determined using a LKB-9000-S spectrophotometer.

8-Chloro-3-methylpyrrolo[1,5-*b*:2,3-*c*']dipyridazine (**2**).

Compound **1** (4a,b) (10.0 g., 45.4 mmoles) and 100 g. of manganese dioxide (activated) suspended in ethyl acetate (500 ml.) were refluxed with stirring for 24 hours. Upon filtration and cooling 2.5 g. (25%) of bright yellow needles crystallized. An additional 6.5 g. of product (65%) was obtained from continuously extracting the manganese dioxide with ethyl acetate. Recrystallization from ethyl acetate provided **2** as bright yellow needles, m.p. 204-205°; pmr (TFA): δ 3.13 (methyl, singlet), 7.22 (C5-H, singlet), 7.63 (C7-H, doublet), 8.35 (C6-H, doublet), 8.55 (C4-H, singlet), $J_{6,7}$ = 10 Hz; ir: 3100(w), 1605(w), 1575, 1520(s), 1480, 1405, 1330, 1270(s), 1192(w), 1158(w), 1147, 1100(s).

Anal. Calcd. for $C_{10}H_7ClN_4$: C, 54.9; H, 3.2; N, 25.6. Found: C, 54.9; H, 3.2; N, 25.9.

8-Chloro-3-methylpyrrolo[1,5-*b*:2,3-*c*']dipyridazine 2-Oxide (**4**).

Compound **2** (1 g., 4.5 mmoles) was dissolved in 15 ml. of chloroform and 1.1 g. (6.5 mmoles) of *m*-chloroperbenzoic acid was then added and stirred until dissolved. The solution was allowed to stand overnight. The solvent was removed under reduced pressure and the residue washed with sodium hydroxide solution (1.0 *M*), then with water to provide 650 mg. (61%) of a bright yellow solid. Recrystallization from chloroform-benzene provided orange crystals, m.p. 247-248° dec.; pmr (TFA): δ 3.14 (methyl, singlet), 7.24 (C5-H, singlet), 7.50 (C7-H, doublet), 8.30 (C6-H, doublet), 8.67 (C4-H, singlet), $J_{6,7}$ = 10 Hz; ir: 3110(w), 3065(w), 1620(w), 1520(w), 1500(w), 1345(s), 1315, 1170(w), 1120(w), 1090(w), 1033(w).

Anal. Calcd. for $C_{10}H_7ClN_4O$: C, 51.1; H, 3.0; N, 23.9. Found: C, 51.2; H, 2.9; N, 23.8.

8-Chloro-3-methyl-5-nitropyrrolo[1,5-*b*:2,3-*c*']dipyridazine 2-Oxide (**3**).

Method A.

Compound **4** (1 g., 3.6 mmoles) was added portionwise to 7 ml. of red fuming nitric acid (d = 1.56) at 0° with stirring. The solution was maintained at 0° for 1 hour then poured over crushed ice whereupon a yellow precipitate formed, providing a quantitative yield of the crude product. Recrystallization of a small amount of the yellow powder from DMF-water provided a red powder, dec., > 270° (losses on purification were large, however, the crude product was satisfactory for all reactions); pmr (TFA): δ 3.20 (methyl, singlet), 8.06 (C7-H, doublet), 9.10 (C6-H, doublet), 9.32 (C4-H, singlet), $J_{6,7}$ = 10 Hz; ir: 3095(w), 3080(w), 1527, 1505(w), 1473, 1460(w), 1410(s), 1360(s), 1305(s), 1224, 1176, 1145, 1127, 1012(w).

Anal. Calcd. for $C_{10}H_6ClN_5O_3$: C, 42.9; H, 2.4; N, 25.0. Found: C, 42.6; H, 2.5; N, 24.8.

Method B.

8-Chloro-3-methyl-6,7-dihydropyrrolo[1,5-*b*:2,3-*c*']dipyridazine 2-oxide (**4**) was treated in the same manner as in method A except that after addition of the dihydro compound to the nitric

acid, the reaction mixture was then warmed to 50° and maintained at this temperature for 30 minutes. This method provided a 50% yield of crude III.

8-Chloro-3-methyl-5-nitropyrrolo[1,5-*b*:2,3-*c*']dipyridazine (**5**).

Compound **2** (1.0 g., 4.6 mmoles) was treated with nitric acid in the same manner as **4** (method A). Eight hundred mg. (67%) of **5** was obtained as green crystals upon recrystallization from 2-methoxyethanol, dec., > 250°; pmr (TFA): δ 3.30 (methyl, singlet), 8.18 (C7-H, doublet), 9.22 (C6-H, doublet), 9.22 (C4-H, singlet), $J_{6,7}$ = 10 Hz; ir: 3042(w), 3020(w), 1593, 1537, 1483(s), 1447(b), 1399(s), 1347(s), 1320, 1300, 1277, 1232, 1182(w), 1132(s).

Anal. Calcd. for $C_{10}H_6ClN_5O_2$: C, 45.5; H, 2.3; N, 26.6. Found: C, 45.4; H, 2.2; N, 26.5.

Method of Preparation of Hydrazino Derivatives.

The hydrazino derivatives, **7**, **11** and **13**, were prepared as follows: 1.0 g. of the corresponding chloro compound was dissolved in a minimal amount of DMSO at 130°. A slight excess of hydrazine (anhydrous, 97%) was added dropwise with stirring while the temperature was maintained at 130° for 1-2 minutes. The hot solution was filtered and the product allowed to crystallize.

8-Hydrazino-3-methyl-5-nitropyrrolo[1,5-*b*:2,3-*c*']dipyridazine (**7**).

Treatment of **5** with hydrazine as described above provided 650 mg. (66%) of **7**. Recrystallization from DMSO gave fine yellow needles, dec., > 255°; pmr (TFA): δ 3.26 (methyl, singlet), 8.03 (C7-H, doublet), 9.15 (C4-H, singlet), 9.18 (C6-H, doublet), $J_{6,7}$ = 10 Hz; ir: 3500-3200, 1595(w), 1565(w), 1545(w), 1495, 1397(s), 1345(w), 1320, 1272, 1236, 1213.

Anal. Calcd. for $C_{10}H_9N_7O_2$: C, 46.3; H, 3.5; N, 37.8. Found: C, 46.4; H, 3.5; N, 37.6.

8-Hydrazino-3-methylpyrrolo[1,5-*b*:2,3-*c*']dipyridazine 2-Oxide (**13**).

Treatment of **4** with hydrazine as described above provided 630 mg. (63%) of **13**. Recrystallization from DMSO gave yellow needles, m.p. 229-230°; pmr (TFA): δ 3.07 (methyl, singlet), 7.13 (C5-H, singlet), 7.28 (C7-H, doublet), 8.22 (C6-H, doublet), 8.53 (C4-H, singlet), $J_{6,7}$ = 10 Hz; ir: 3500-3200, 1648, 1600(w), 1595, 1565(w), 1348(s), 1315(b), 1260, 1180.

Anal. Calcd. for $C_{10}H_{10}N_6O$: C, 52.2; H, 4.4; N, 36.5. Found: C, 52.0; H, 4.2; N, 36.6.

8-Hydrazino-3-methylpyrrolo[1,5-*b*:2,3-*c*']dipyridazine (**11**).

Treatment of **2** with hydrazine as described above provided 650 mg. (65%) of **11**. Recrystallization of **11** from DMSO gave fine yellow needles, m.p. 236-237°; pmr (TFA): δ 3.08 (methyl, singlet), 7.14 (C5-H, singlet), 7.43 (C7-H, doublet), 8.27 (C6-H, doublet), 8.44 (C4-H, singlet), $J_{6,7}$ = 10 Hz; ir: 3500-3200, 1633(b), 1520(s), 1421(w), 1355(w), 1265(s), 1190.

Anal. Calcd. for $C_{10}H_{10}N_6$: C, 56.1; H, 4.7; N, 39.3. Found: C, 56.0; H, 4.6; N, 39.5.

8-Methoxy-3-methyl-5-nitropyrrolo[1,5-*b*:2,3-*c*']dipyridazine (**6**).

Sodium (0.19 g., 0.825 g.-atom) was dissolved in 45 ml. of methanol and 1.0 g. of **5** was added. The suspension was refluxed with stirring for two hours then cooled and filtered. Compound **6** was taken up with hot 2-methoxyethanol, the salt removed by filtration and **6** allowed to crystallize to provide 850 mg. (85%) of yellow needles, dec., > 245°; pmr (TFA): δ 3.27 (methyl, singlet), 4.40 (methoxy, singlet), 7.88 (C7-H, doublet), 9.12 (C6-H, doublet), 9.14 (C4-H, singlet), $J_{6,7}$ = 10 Hz; ir: 3110(w), 3070(w), 3045(w), 1587, 1540, 1504(s), 1475, 1447, 1389(s), 1363(s), 1337(s), 1317, 1300, 1278, 1224(s), 1210(s), 1173, 1147(w), 1118, 1063.

Anal. Calcd. for $C_{10}H_9N_5O_3$: C, 51.0; H, 3.5; N, 27.0. Found: C, 51.5; H, 3.4; N, 27.3.

8-Methoxy-3-methyl-5-nitropyrrolo[1,5-*b*:2,3-*c*']dipyridazine 2-Oxide (**8**).

Compound **8** was obtained from **12** in the same manner as described for **3** (method A) except that the reaction time was only 30 minutes. Fine yellow floculant needles (540 mg., 72%) were obtained upon recrystallization from DMSO, m.p. 285-286° dec.; pmr (TFA): δ 3.10 (methyl, singlet), 4.31 (methoxy, singlet), 7.68 (C7-H, doublet), 9.00 (C6-H, doublet), 9.15 (C4-H, singlet), $J_{6,7}$ = 10 Hz; ir: 3119(w), 3107(w), 1540, 1500(s), 1443(w), 1407, 1360(s), 1328, 1287, 1210(s), 1168, 1135(w).

Anal. Calcd. for $C_{11}H_9N_5O_4$: C, 48.0; H, 3.3; N, 25.5. Found: C, 47.8; H, 3.5; N, 25.4.

8-Methoxy-3-methylpyrrolo[1,5-*b*:2,3-*c*']dipyridazine (**10**).

Compound **2** (1.0 g., 4.5 mmoles) was refluxed with stirring in 20 ml. of 0.5 *M* solution of sodium methoxide in methanol for 1 hour. The hot solution was then filtered and the solvent removed under reduced pressure. The residue was dissolved in water and then neutralized with concentrated hydrochloric acid whereupon 760 mg. (76%) fine yellow needles formed. Recrystallization from benzene provided brownish yellow crystals, m.p. 191-192°; pmr (TFA): δ 3.10 (methyl, singlet), 4.28 (methoxy, singlet), 7.10 (C5-H, singlet), 7.37 (C7-H, doublet), 8.20 (C6-H, doublet), 8.40 (C4-H, singlet), $J_{6,7}$ = 10 Hz; ir: 3098, 3070(w), 3022(w), 2950(w), 1628, 1587, 1418(s) borad, 1463, 1442(s), 1420(w), 1390(w), 1380(w), 1350, 1287(s), 1270(s), 1203, 1196, 1175(w), 1154, 1117.

Anal. Calcd. for $C_{11}H_{10}N_4O$: C, 61.7; H, 4.7; N, 26.2. Found: C, 61.5; H, 4.7; N, 26.4.

8-Methoxy-3-methylpyrrolo[1,5-*b*:2,3-*c*']dipyridazine 2-Oxide (**12**).

Compound **4** (1.0 g., 4.3 mmoles) was refluxed with stirring for 3 hours in 50 ml. of a 0.5 *M* solution of sodium methoxide in methanol. The hot solution was filtered and 880 mg. (88%) of fine yellow needles was allowed to precipitate. Compound **12** was recrystallized from methanol, m.p. 218-219°; pmr (TFA): δ 3.08 (methyl, singlet), 4.28 (methoxy, singlet), 7.06 (C5-H, singlet), 7.23 (C7-H, doublet), 8.13 (C6-H, doublet), 8.50 (C4-H, singlet), $J_{6,7}$ = 10 Hz; ir: 3130(w), 3066, 3018(w), 2990(w), 2940(w), 2930(w), 1630, 1600, 1533(s), 1509, 1442, 1394(s), 1373(s), 1350(s), 1330(s), 1290(s) broad, 1207, 1170(s), 1120, 1110.

Anal. Calcd. for $C_{11}H_{10}N_4O_2$: C, 57.4; H, 4.4; N, 24.4. Found: C, 57.2; H, 4.4; N, 24.2.

3-Methyl-5-nitro-8-piperidinopyrrolo[1,5-*b*:2,3-*c*']dipyridazine 2-Oxide (**9**).

Compound **3** (2 g., 7.17 mmoles), piperidine (12.2 g., 143.4 mmoles) and DMF (100 ml.) were refluxed for 2 hours. The brown solution was evaporated to a small volume under reduced pressure and treated with water. The brown residue was collected and recrystallized from ethanol-chloroform providing 2.0 g. (85%) of **9** as brown needles, m.p. 253-254° dec.; pmr (TFA): δ 1.80 (β and γ methylenes of piperidino group, broadened singlet), 3.16 (methyl, singlet), 3.97 (α methylenes of piperidino group,

broadened singlet), 8.14 (C7-H, doublet), 8.97 (C6-H, doublet), 9.15 (C4-H, singlet), $J_{6,7}$ = 10 Hz.

Anal. Calcd. for $C_{15}H_{16}N_6O_3$: C, 54.9; H, 4.9; N, 25.6. Found: C, 55.0; H, 5.2; N, 25.6.

3-Methyl-9*H*-pyrrolo[1,5-*b*:2,3-*c'*]dipyridazin-8-one Hydrobromide (**14**).

Compound **10** (2.5 g., 1.17 mmoles) was gently refluxed in 50 ml. of hydrobromic acid (48%) for 14 hours with stirring. The solution which was initially homogenous contained a precipitate toward the end of the 14 hour period. The solution was then cooled and the red precipitate filtered and air dried providing 2.3 g. (70%) of red powder. Recrystallization from 2-methoxyethanol-water gave red crystals, m.p. 345-346° dec.; pmr (TFA): δ 3.14 (methyl, singlet), 7.17 (C5-H, singlet), 7.44 (C7-H, doublet), 8.34 (C6-H, doublet), 8.46 (C4-H, singlet), $J_{6,7}$ = 10 Hz; ir: 3100-2800, 1640(w), 1613(w), 1587, 1534(s), 1425(w), 1395(w), 1380, 1370, 1348(s), 1290(s), 1216(w).

Anal. Calcd. for $C_{10}H_8N_4O \cdot HBr$: C, 42.7; H, 3.2; N, 19.9. Found: C, 42.7; H, 3.4; N, 19.6.

3-Methyl-5-nitro-9*H*-pyrrolo[1,5-*b*:2,3-*c'*]dipyridazin-8-one (**15**).

Compound **15** (560 mg., 64%) was obtained from **14** in the same manner as **3** (method A) as fine green needles upon recrystallization from DMSO, dec., > 300°; pmr (TFA): δ 3.27 (methyl, singlet), 7.90 (C7-H, doublet), 9.13 (C4-H, singlet), 9.16 (C6-H, doublet), $J_{6,7}$ = 10 Hz; ir: 3500(b), 3080(w), 1600, 1545, 1505, 1395(s), 1320, 1270, 1208(s).

Anal. Calcd. for $C_{10}H_7N_5O_3$: C, 49.0; H, 2.9; N, 28.6. Found: C, 48.8; H, 3.0; N, 28.5.

3-Methyl-5-nitro-9*H*-pyrrolo[1,5-*b*:2,3-*c'*]dipyridazin-8-one 2-Oxide (**16**).

Compound **15** (300 mg., 1.22 mmoles) was suspended in acetone (100 ml.) and 400 mg. (2.41 mmoles) of *m*-chloroperbenzoic acid was added. The suspension was stirred at room temperature for 25 hours. The suspension was filtered and the green solid recrystallized from DMSO providing 155 mg. (49%) of **16** as fine yellow needles, dec., > 320°; pmr (TFA): δ 3.07 (methyl, singlet), 7.72 (C7-H, doublet), 9.06 (C6-H, doublet), 9.13 (C4-H, singlet); ir: 3450(b), 3180(w), 1600(w), 1550, 1495, 1400(s), 1335(s), 1270, 1210(s), 1020(w).

Anal. Calcd. for $C_{10}H_7N_5O_4$: C, 46.0; H, 2.7; N, 26.8. Found: C, 45.8; H, 2.8; N, 26.7.

The Reaction of 8-Hydrazino-3-methylpyrrolo[1,5-*b*:2,3-*c'*]dipyridazine 2-Oxide (**13**) with Cupric Sulfate.

Compound **13** (1.5 g., 3.35 mmoles) was dissolved in 60 ml. of water and 3 ml. of concentrated hydrochloric acid. The solution was heated to 75° and 1.5 g. of cupric sulfate pentahydrate dissolved in 5 ml. of water was added with stirring. The reaction was maintained at 75° for 1 hour during which time a copious evolution of nitrogen was observed. The solution was basified with concentrated ammonium hydroxide, then exhaustively extracted with chloroform. Two compounds were separated by chromatography on alumina using chloroform as the eluent.

The first component, compound **17b** was recrystallized from chloroform-benzene yielding 350 mg. of a yellow solid, m.p. 249-250°; pmr (TFA): δ 3.16 (singlet), 7.20 (singlet), 7.48 (doublet), J = 10 Hz, 8.28 (doublet), J = 10 Hz, 8.65 (singlet); ir: 3115(w), 3075(w), broad, 1625(w), 1587(w), 1523, 1505, 1445(w), 1428(w), 1395, 1347(s), broad, 1320(s), 1290, 1265(w), 1175, 1157(w), 1125(b), 1095, 1040; mass spectrum (70 eV) m/e (relative intensity): 236 (34), 234 (100), 220 (40), 218 (100), 204 (43), 189 (65), 168 (47), 155 (46).

Anal. Calcd. for $C_{10}H_7ClN_4O$: C, 51.2; H, 3.0; N, 24.0. Found: C, 51.5; H, 3.2; N, 24.0.

On the basis of the above data, particularly the mass spectral data and confirming mixed m.p. (249-250°), **17b** was shown to be identical with 8-chloro-3-methylpyrrolo[1,5-*b*:2,3-*c'*]dipyridazine 2-oxide (**4**).

3-Methylpyrrolo[1,5-*b*:2,3-*c'*]dipyridazine 2-Oxide (**17a**).

The second component from the above reaction, compound **17a**, was recrystallized from chloroform-benzene yielding 300 mg. (18%) of a yellow solid m.p. 237-238°; pmr (TFA): δ 3.12 (methyl, singlet), 7.22 (C5-H, singlet), 7.56 (C7-H, doublet of doublet, $J_{6,7}$ = 10 Hz, $J_{7,8}$ = 4.5 Hz), 8.30 (C6-H, doublet, $J_{6,7}$ = 10 Hz), 8.60 (C4-H, singlet), 8.80 (C8-H, doublet, $J_{7,8}$ = 4.5 Hz); ir: 3110(w), 3015(w), 1530(w), 1502(w), 1447(w), 1395(w), 1354, 1340, 1333, 1317, 1307, 1290, 1260, 1190.

Anal. Calcd. for $C_{10}H_8N_4O$: C, 60.0; H, 4.0; N, 28.0. Found: C, 60.0; H, 4.0; N, 28.3.

3-Methyl-5-nitropyrrolo[1,5-*b*:2,3-*c'*]dipyridazine 2-Oxide (**18**).

Compound **17a** (300 mg., 1.5 mmoles) was added portionwise to 3 ml. of red fuming nitric acid (d = 1.56) at 0° with stirring. The solution was maintained at 0° for 40 minutes then poured over crushed ice upon which a brownish yellow precipitate formed and was filtered. The precipitate was recrystallized from DMSO yielding 270 mg. (75%) of fine brownish yellow crystals, m.p. 322-323° dec.; pmr (TFA): δ 3.13 (methyl, singlet), 8.05 (C7-H, doublet of doublet, $J_{6,7}$ = 4.5 Hz, $J_{7,8}$ = 10 Hz), 8.97 (C6-H, doublet of doublet, $J_{6,7}$ = 10 Hz, $J_{6,8}$ = 1.5 Hz), 9.15 (C8-H, doublet of doublet, $J_{7,8}$ = 10 Hz, $J_{6,8}$ = 1.5 Hz), 9.15 (C4-H, singlet); ir: 3100(w), 1600(w), 1532, 1484, 1473, 1425, 1405(s), 1365, 1350, 1340, 1297(s), 1269(s), 1199, 1162.

Anal. Calcd. for $C_{10}H_7N_5O_3$: C, 49.0; H, 2.9; N, 28.6. Found: C, 49.2; H, 2.7; N, 28.5.

3-Methylpyrrolo[1,5-*b*:2,3-*c'*]dipyridazine (**20**).

A suspension of **19** (2.0 g., 10.76 mmoles), activated manganese dioxide (10 g.) and 50 ml. of benzene was refluxed with stirring for 24 hours. One g. of the aromatized product was obtained after filtration and drying. Continuous extraction of the manganese dioxide with benzene provided an additional 0.9 g. of **20**. Recrystallization from ethyl acetate provided **20** as bright yellow crystals, m.p. 161-162°; pmr (deuteriochloroform): δ 2.90 (methyl, singlet), 6.44 (C5-H, singlet), 7.08 (C7-H, doublet of doublet, $J_{6,7}$ = 10 Hz, $J_{7,8}$ = 2 Hz), 7.68 (C4-H, singlet), 7.96 (C6-H, doublet of doublet, $J_{6,7}$ = 10 Hz, $J_{6,8}$ = 4 Hz), 8.30 (C8-H, doublet of doublet, $J_{7,8}$ = 10 Hz, $J_{6,8}$ = 4 Hz); ir: 3108(w), 3076, 2995(w), 1585(s), 1526, 1505(s), 1445, 1400, 1368, 1340(s), 1265, 1190, 1145, 1119.

Anal. Calcd. for $C_{10}H_8N_4$: C, 65.3; H, 4.3; N, 30.4. Found: C, 65.0; H, 4.5; N, 30.4.

3-Methyl-5-nitropyrrolo[1,5-*b*:2,3-*c'*]dipyridazine (**21**).

Compound **20** (1.0 g., 5.45 mmoles) was allowed to react in the same manner as for **4** (method A). One g. (81%) of **21** was obtained upon recrystallization from DMF-water as yellow crystals, m.p. 308-309° dec.; pmr (TFA): δ 3.3 (methyl, singlet), 8.34 (C7-H, multiplet), 9.28 (C4-H, C6-H, C8-H, multiplet); ir: 3095, 1597(s), 1530, 1500, 1475, 1440, 1405(s), 1363, 1337(s), 1302, 1270, 1206, 1175, 1142, 1110.

Anal. Calcd. for $C_{10}H_7N_5O_2$: C, 52.4; H, 3.1; N, 30.6. Found: C, 52.4; H, 3.3; N, 30.4.

6-(β-Cyanoethyl)-3-methyl-5-nitro-7*H*-pyrrolo[3,2-*c*]pyridazine Nitrate (**23**).

Compound **23** was obtained from **22** in the same manner as **3** (method A). Eight hundred mg. (82%) of **23** was obtained as white needles upon recrystallization from ethyl acetate-benzene, m.p. 158-159°; pmr (DMSO-d_6): δ 2.98 (methyl, singlet), 3.20 (methylene, triplet, J = 6 Hz), 3.74 (methylene, triplet, J = 6 Hz), 8.74 (C4-H, singlet); ir: 3000-2500, 2430(w), 2250(w), 1630, 1560, 1525, 1445, 1420(s), broad, 1383(s), broad, 1360(s), 1260, 1230, 1213, 1178, 1098(w), 1040.

Anal. Calcd. for $C_{10}H_{10}N_6O_5$: C, 40.8; H, 3.4; N, 28.6. Found: C, 40.6; H, 3.5; N, 28.4.

6-(β-Carbethoxyethyl)-3-methyl-5-nitro-7*H*-pyrrolo[2,3-*c*]-pyridazine (**24**).

6-(β-Carbethoxyethyl)-3-methyl-7*H*-pyrrolo[2,3-*c*]pyridazine (4) (1.1 g., 4.75 mmoles) was added portionwise to 7 ml. of red fuming nitric acid (d = 1.56) at 0° with stirring. The mixture was maintained at 0° for 2 hours then poured over crushed ice whereupon a precipitate formed. The solution was neutralized with sodium bicarbonate and the precipitate filtered to provide 1.15 g. (87%) of **24**. Recrystallization from ethyl acetate-benzene provided fine white needles, m.p. 220-222° dec.; pmr (TFA): δ 1.40 (methyl, triplet, J = 8 Hz), 3.20 (C3-methyl, methylene, multiplet), 4.00 (methylene, triplet, J = 6 Hz), 4.41 (methylene, quartet, J = 8 Hz), 9.00 (C3-H, singlet); ir: 3100-2800, 1730(s), 1610(w), 1582(w), 1535, 1495, 1440(s), 1420(s), 1380, 1356(s), 1316, 1280, 1243, 1210, 1197(s).

Anal. Calcd. for $C_{12}H_{14}N_4O_4$: C, 51.8; H, 5.0; N, 20.1. Found: C, 51.6; H, 5.0; N, 19.8.

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