Pyrrolopyridazines. II. Synthesis of the Novel Pyrrolo[3,2-*c*]pyridazine Ring System (1)

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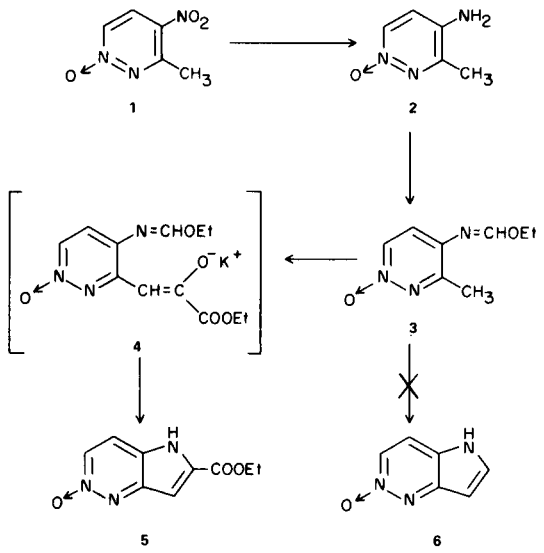
The first derivatives of the pyrrolo[3,2-*c*]pyridazine ring system, ethyl pyrrolo[3,2-*c*]-pyridazine-6-carboxylate 2-oxide (**5**) and ethyl 3-chloro-6-methylpyrrolo[3,2-*c*]pyridazine-7-glyoxalate 1-oxide (**12**), were obtained in good yields from the cyclization of 4-ethoxymethyl-eneamino-3-methylpyridazine 1-oxide (3) and 3-chloro-5-(α-ethoxyethylideneamino)-6-methyl-pyridazine 1-oxide (**14**, R = Cl, R_1 = OMe), respectively, with diethyl oxalate and potassium ethoxide in ether.

Pyrrolo[2,3-*d*]pyridazine, pyrrolo[3,2-*c*]pyridazine, and pyrrolo[2,3-*c*]pyridazine are members of a relatively unknown class of heterocyclic compounds (2). Indeed, the pyrrolo[3,2-*c*]pyridazine (4,5-diazaindole) ring system has not yet been described in the literature (2). Only three pyrrolo[2,3-*c*]pyridazines (6,7-diazaindoles) have been reported (3). A number of pyrrolo[2,3-*d*]pyridazines (5,6-diazaindoles) have been prepared as potential anti-metabolites of purine bases (4,5). Because of the structural resemblance of these pyrrolopyridazines to the biologically important purines and indoles, a synthetic program was initiated (6) with an objective of devising a synthetic approach which could be applied to the preparation of all three ring systems. This communication describes the cyclization of 4-ethoxymethyleneamino-3-methylpyridazine 1-oxide (**3**) and 3-chloro-5-(α-ethoxyethylideneamino)-6-methylpyridazine 1-oxide (**14**, R = Cl, R_1 = Me) *via* their potassium enolates (**4** and **13**, respectively) to ethyl pyrrolo[3,2-*c*]pyridazine-6-carboxylate 2-oxide (**5**) and ethyl 3-chloro-6-methylpyrrolo[3,2-*c*]pyridazine-7-glyoxalate 1-oxide (**12**). This cyclization method was previously developed for the synthesis of pyrrolo[2,3-*d*]pyridazines (6).

4-Amino-3-methylpyridazine 1-oxide (**2**, Scheme I), obtained in an 85% yield from the palladium catalyzed reduction of 3-methyl-4-nitropyridazine 1-oxide (**1**), was treated with triethyl orthoformate and a catalytic amount of anhydrous hydrogen chloride in DMF to afford an 85% yield of 4-ethoxymethyleneamino-3-methylpyridazine 1-oxide (**3**). Compound **3** is stable; however, Lorenz *et al.*, report that structurally similar picolylformimidates (without an *N*-oxide) are unstable (7). Also, none of the

Scheme I

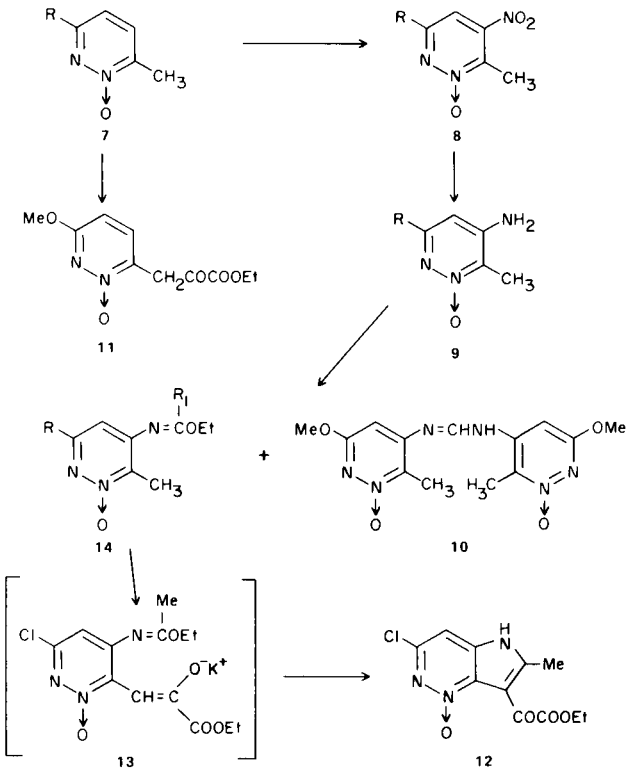


corresponding *N,N'*-bis(3-methyl-1-oxido-4-pyridazinyl)-formamidine was detected in the preparation and storage of **3**. Thus, it appears that the electron-releasing nature of the *N*-oxide function (8) has stablized the *p*-formimidate group since aromatic amines (9) and pyridylamines (10) possessing electron-withdrawing substituents form formamidines more readily than do those with electron-releasing substituents. Treatment of **3** with diethyl oxalate and potassium ethoxide in ether (room temperature, 24 hours) afforded an apparent quantitative yield of the potassium salt (potassium enolate) of ethyl 4-ethoxymethyleneamino-3-pyridazinylpyruvate 1-oxide (**4**).

No evidence of any cyclized products was apparent in the pmr spectrum of **4** in DMSO-d_6. This is further evidence of the stability of the formimidate group in this series. Compound **4** was dissolved in a hydrochloric acid solution (*ca.* 0.01 *M* in 2% aqueous DMF) and stirred at room temperature for 18 hours to afford a 77% yield of the Reissert indole cyclization type product (**1**), ethyl pyrrolo-[3,2-*c*]pyridazine-6-carboxylate 2-oxide (**5**). The pmr spectrum of **5** in DMSO-d_6 indicated a pair of distorted doublets (J = 7 Hz) at 8.42 δ and 8.04 δ representing the C_3 and C_4 protons, respectively. The C_7-proton, appearing at 7.30 δ was not coupled to the proton on the pyrrole nitrogen. This lack of coupling was also observed between the pyrrole nitrogen proton and the ring protons of the pyrrole moiety of pyrrolo[2,3-*d*]pyridazines (**11**) and pyrrolo[2,3-*c*]pyridazines (**11**) when their pmr spectra were recorded in DMSO-d_6 and pyrrolo[2,3-*b*]pyridines in deuteriochloroform (**12**). No pyrrole nitrogen proton could be observed above the base line noise in the pmr (DMSO-d_6) of **5**; however, addition of deuterium oxide caused the appearance of a DHO peak at 4.0 δ. This is in accordance with the pmr spectra of pyrrolo[2,3-*d*]pyridazines in DMSO-d_6 (**11**).

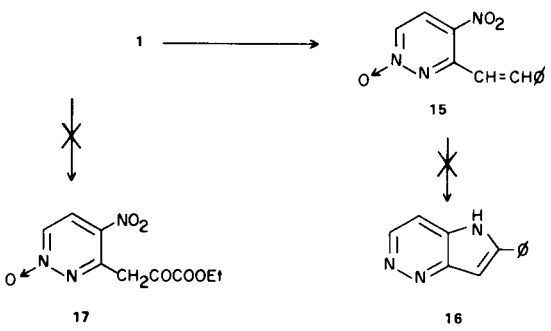
Although the *o*-ethoxymethyleneaminomethylpyridazine 1-oxide (**3**) successfully led to a pyrrolo[3,2-*c*]-pyridazine, it appeared that a more appropriately substituted and accessible *o*-ethoxymethyleneaminomethylpyridazine 1-oxide could be obtained. Thus, nitration of 3-methoxy-6-methylpyridazine 1-oxide (**7**, R = OMe, Scheme II) with benzoyl nitrate (prepared *in situ* from benzoyl chloride and silver or potassium nitrate) according to the procedure of Itai and Natsume (13) provided a 43% yield of 3-methoxy-6-methyl-5-nitropyridazine 1-oxide (**8**, R = OMe). The possibility that nitration occurred in the 4-position of **7** (R = OMe) was ruled out on the basis of the dissimilarity of the ir spectra and melting points of **8** (R = OMe) and authentic 3-methoxy-6-methyl-4-nitropyridazine 1-oxide (14). 5-Amino-3-methoxy-6-methylpyridazine 1-oxide (**9**, R = OMe), obtained in an 86% yield from the palladium catalyzed reduction of **8** (R = OMe), was treated with triethyl orthoformate and a catalytic amount of hydrogen chloride in DMF to furnish a 61% yield of 5-ethoxymethyleneamino-3-methoxy-6-methylpyridazine 1-oxide (**14**, R = OMe, R_1 = H) and a 29% yield of *N,N'*-bis(3-methoxy-6-methyl-1-oxido-5-pyridazinyl)formamidine (**10**). The instability of **14** (R = OMe, R_1 = H) (*e.g.* facile hydrolysis to **9** (R = OMe) and formation of **10**) is attributed to its lack of an *N*-oxide function *para* to the formimidate group. Furthermore, the 5-position of pyridazine 1-oxides is particularly electron-deficient (15) which would tend to destabilize a 5-formimidate group. Unfortunately, compound **14** (R = OMe, R_1 = H) did not form the pyruvate derivative under the usual conditions of diethyl oxalate and potassium ethoxide in ether. The relatively stable 5-(α-ethoxyethylideneamino)-3-methoxy-6-methylpyridazine 1-oxide (**14**, R = OMe, R_1 = Me), obtained in 72% yield from **9** (R = OMe) and triethyl orthoacetate, also failed to form the pyruvate with diethyl oxalate and potassium ethoxide in refluxing ethanol. Initially, the unexpected failure of **14** (R = OMe, R_1 = H or Me) to form a pyruvate derivative was attributed to steric hindrance since other heterocyclic methyl groups which have condensed with diethyl oxalate have had at least one position adjacent to the methyl group unsubstituted except 5-phenylmethyleneamino-1,3,6-trimethyluracil (16). This conclusion was supported by the fact that **7** (R = OMe) which is unsubstituted in the 5-position readily condensed with diethyl oxalate affording a quantitative yield of the potassium salt (potassium enolate) of ethyl 3-methoxy-6-pyridazinylpyruvate 1-oxide (**11**). However, mesomeric factors are also important since 3-chloro-5-(α-ethoxyethylideneamino)-6-methylpyridazine 1-oxide (**14**, R = Cl, R_1 = Me) readily reacted with diethyl oxalate and potassium ethoxide in ether (24 hours) to provide after acidification, the Madelung indole cyclization type product (**1**), ethyl 3-chloro-6-methylpyrrolo[3,2-*c*]pyridazine-7-glyoxalate 1-oxide (**12**) in 72% yield. The stable acetimidate intermediate, **14** (R = Cl, R_1 = Me), was obtained in a manner analogous to the preparation of the methoxy analog **14** (R = OMe, R_1 = Me, Scheme II)

Scheme II



except with the following changes: i) nitration of 3-chloro-6-methylpyridazine 1-oxide (**7**, R = Cl) failed when the benzoyl nitrate was prepared *in situ* with potassium nitrate (instead of silver nitrate) and benzoyl chloride; ii) the reduction of 3-chloro-6-methyl-5-nitropyridazine 1-oxide (**8**, R = Cl) to 5-amino-3-chloro-6-methylpyridazine 1-oxide (**9**, R = Cl) (92%) was catalyzed with Raney nickel. The pmr spectrum (DMSO-d_6) of **12** exhibits a one proton singlet at 7.72 δ (C_4-H), a three proton singlet at 2.65 δ (C_6-methyl) and a low, broad peak at 6.35-7.43 δ (NH) which disappears on the addition of deuterium oxide. The usual carbethoxy group absorptions were present.

Several other cyclization reactions failed to provide pyrrolo[3,2-*c*]pyridazines. These same reactions previously failed to produce pyrrolo[2,3-*d*]pyridazines (6). Thus, treatment of **3** with potassium ethoxide in ether, refluxing ethanol, or refluxing DMF failed to provide the desired pyrrolo[3,2-*c*]pyridazine 2-oxide (**6**). This modification of the Madelung indole cyclization reaction (17) produced **2** as the major product. The Reissert indole cyclization method (18) was also attempted; however, the necessary pyruvate derivative of **1** (**17**) could not be obtained. The major product identified in this reaction was the corresponding bispyridazinylethane. Reductive cyclization of 4-nitro-3-styrylpyridazine 1-oxide (**15**) (obtained from **1**, benzaldehyde, and piperidine in 59% yield) with triethyl phosphite according to a recent procedure (19) has only produced complex mixtures.



The extremely mild conditions and good yields in which the pyrrolo[3,2-*c*]pyridazines **5** and **12** and pyrrolo-[2,3-*d*]pyridazines (1,6) were formed by this cyclization method suggests that its application to the synthesis of other aza- and polyazaindoles would be feasible. In particular, its successful application to the synthesis of various substituted pyrrolopyridines (monoazaindoles) would be of value since the scope of the Reissert (17) and Madelung (18) indole cyclization methods in the synthesis of these type compounds is limited.

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 instrument and compared with TMS as an internal standard. The ir spectra were recorded in potassium bromide discs with a Perkin-Elmer 457 spectrophotometer. Uv spectra were determined with a Cary 15 spectrophotometer.

4-Amino-3-methylpyridazine 1-Oxide (2).

A solution of 4-nitro-3-methylpyridazine 1-oxide (**1**) (20) (8.5 g., 0.0548 mole), 400 ml. of ethanol, and 4 g. of 5% palladium on charcoal was stirred under an atmosphere of hydrogen until 3 equivalents were absorbed. The catalyst was removed and the filtrate evaporated *in vacuo* to provide an off-white foam which was dissolved in warm ethanol. Ether was added until the cloud point appeared. White micro crystals (5.0 g.) were obtained by cooling at 0° overnight. Another crop was obtained by taking the filtrate back to a foam and repeating the recrystallization procedure. Total yield of **2** was 5.8 g. (85%) after recrystallization, m.p. 251-253° dec.; ir cm^{-1}: 3380 (s), 3170 (s), and 1660 (s) (NH_2): pmr (DMSO-d_6): 2.25 δ (methyl, singlet), 6.05 δ (NH_2, broad singlet), 6.90 δ (C_5-H, doublet), 7.88 δ (C_6-H, doublet), $J_{5,6}$ = 7 Hz.

Anal. Calcd. for $C_5H_7N_3O$: C, 48.0; H, 5.6; N, 33.6. Found: C, 48.0; H, 5.7; N, 33.7.

4-Ethoxymethyleneamino-3-methylpyridazine 1-Oxide (3).

A mixture of **2** (2 g., 0.016 mole), triethyl orthoformate (10 ml.), DMF (20 ml.), and 10 drops of absolute ethanol that had been adjusted to *ca.* *p*H 1 with gaseous hydrogen chloride, was heated at 120-125° under an 11 cm. Vigreux column and distilling head until *ca.* 3 ml. of ethanol was collected. Tlc indicated complete consumption of starting material. The solvents were removed under reduced pressure (1 torr, 50-60°) providing a yellow oil which solidified on cooling to room temperature. The yellow material was washed with 30-60° ligroin and recrystallized from benzene-isopropyl ether (norite) providing light yellow needle crystals (2.3 g., 80%), m.p. 99-100°; ir cm^{-1}: 1625 (s) (N=C); pmr (deuteriochloroform): 1.40 δ (ethyl-CH_3, triplet), 2.45 δ (methyl, singlet), 4.40 δ (ethyl-CH_2, quartet); 7.10 δ (C_5-H, doublet); 7.86 δ (methine, broadened singlet); 8.02 δ (C_6-H, doublet), $J_{5,6}$ = 6 Hz.

Anal. Calcd. for $C_8H_{11}N_3O_2$: C, 53.1; H, 6.1; N, 23.2. Found: C, 53.0; H, 6.3; N, 23.4.

Ethyl 4-Ethoxymethyleneamino-3-pyridazinylpyruvate 1-Oxide Potassium Enolate (4).

A 1 l. three-neck flask equipped with mechanical stirrer, reflux condenser, and nitrogen inlet tube was flamed while purging with dry nitrogen. After allowing the flask to cool to room temperature, a potassium ethoxide solution was prepared by adding portionwise potassium metal (2.15 g., 0.055 g.-atom) to absolute ethanol (15 ml.) with stirring. After dissolution was complete, absolute ether (800 ml.) was added to the potassium enolate solution, followed by additions of diethyl oxalate (14.6 g., 0.1 mole). After 5 minutes of stirring, **3** (18.1 g., 0.05 mole) was added. Only partial solution was obtained. The suspension gradually became a dark orange color (3-4 hours). Stirring was continued at room temperature for 20 hours. The potassium enolate was filtered, washed thoroughly with ether and air-dried to provide a quantitative yield of **4**. This material was stable and pure enough for further reactions.

Ethyl Pyrrolo[3,2-c]pyridazine-6-carboxylate 2-Oxide (**5**).

A suspension of **4** (1 g., 0.00314 mole), 75 ml. of DMF, 1 ml. of concentrated hydrochloric acid, and 1 ml. of water was stirred at room temperature for 18 hours. The light yellow suspension was filtered to remove *ca.* 0.2 g. of yellow solid, m.p. > 320° (potassium chloride). The filtrate was taken to dryness under reduced pressure (1 torr, 60-70°) and the yellow residue was placed into solution with a mixture of chloroform and methanol (1:1) and placed on a column of silica gel (50 g.). The first long running yellow band was taken off with chloroform. Removal of the solvents under reduced pressure afforded 0.5 g. (77%) of **5**. Recrystallization from ethyl acetate-methanol provided light yellow needles, m.p. 252-253° dec.; ir cm^{-1}: 3200 (m) (NH), 1723 (s) (C=O); uv (ethanol): λ max (*p*H 1) 215 (s) nm (ε, 13,800), 254 nm (ε, 26,500), 348 nm (ε, 13,200); λ max (*p*H 7) 255 nm (ε, 27,000), 348 nm (ε, 12,600); λ max (*p*H 11) 263 nm (ε, 30,400), 345 nm (ε, 14,200), pmr (DMSO-d_6): 1.47 δ (ethyl-CH_3, triplet), 4.57 δ (ethyl-CH_2, quartet), 7.30 δ (C_7-H, singlet), 8.04 δ (C_4-H, distorted doublet), 8.42 δ (C_3-H, distorted doublet), $J_{3,4}$ = 7 Hz. The NH was not visible above the base line noise; however, addition of deuterium oxide caused a DHO peak to appear at 4.0 δ.

Anal. Calcd. for $C_9H_9N_3O_3$: C, 52.3; H, 4.4; N, 20.3. Found: C, 52.2; H, 4.4; N, 20.4.

3-Methoxy-6-methyl-5-nitropyridazine 1-Oxide (**8**, R = OMe).

Benzoyl chloride (28 g., 0.2 mole) was added to a cold solution of 3-methoxy-6-methylpyridazine 1-oxide (**7**, R = OMe) (14,21) (28 g., 0.2 mole) in chloroform (200 ml.). Finely powdered silver nitrate (34 g., 0.2 mole) (potassium nitrate can be used with the same results) was added with stirring and keeping the temperature below -10°. Stirring was continued for 4 hours at the same temperature and then allowed to stand 4 days at room temperature. The silver chloride which had precipitated, was filtered, washed with hot chloroform, and the filtrate was combined with the washings. The chloroform solution was extracted 4 times with dilute hydrochloric acid, the hydrochloric acid layer was evaporated *in vacuo* below 50°, made alkaline with sodium bicarbonate, and extracted with chloroform. The chloroform extracts contained 8.4 g. (30%) of starting material (**7**, R = OMe) and a small amount of the desired product. Next, the initial chloroform solution was extracted with saturated sodium bicarbonate solution. The sodium bicarbonate solution was neutralized with hydrochloric acid and extracted successively with ether and chloroform. The chloroform extracts contained a small amount of the desired product. Finally, the chloroform solution was dried (magnesium sulfate) and evaporated *in vacuo* to afford the majority of the desired product. Recrystallization of the combined fractions from isopropyl ether or ethanol afforded 16 g. (43%) of bright yellow **8** (R = OMe), m.p. 105-106°; ir cm^{-1}: 1555 (s) and 1335 (s) (NO_2); pmr (deuteriochloroform): 2.55 δ (methyl, singlet), 4.07 δ (methoxy, singlet), 7.02 δ (C_4-H, singlet).

Anal. Calcd. for $C_6H_7N_3O_4$: C, 38.9; H, 3.8; N, 22.6. Found: C, 38.8; H, 4.0; N, 22.6.

3-Chloro-6-methyl-5-nitropyridazine 1-Oxide (**8**, R = Cl).

Benzoyl chloride (14.0 g., 0.1 mole) was added to a cold solution of 3-chloro-6-methylpyridazine 1-oxide (**7**, R = Cl) (20) (14.4 g., 0.1 mole) in 200 ml. of chloroform. Finely powdered silver nitrate (17.0 g., 0.1 mole) (potassium nitrate does not provide nitrated products) was added with stirring (temperature below -10°). Stirring was continued for 4 hours at the same temperature and then allowed to stand 4 days at room temperature. The silver chloride which had precipitated was filtered, washed with hot chloroform, and the filtrate was combined with the washings. Extraction of the chloroform solution failed to remove any of the unreacted starting material as in the preparation of **8** (R = OMe). However, extraction of the chloroform solution with saturated sodium bicarbonate solution removed a near quantitative yield of sodium benzoate. The resulting chloroform solution was dried (magnesium sulfate) and evaporated *in vacuo* to afford a mixture of **7** (R = Cl) and **8** (R = Cl). Recrystallization of this mixture from benzene afforded 5 g. of **7** (R = Cl). The residue obtained after evaporating the mother liquor to dryness *in vacuo* was dissolved in benzene and placed on a column of silica gel (65 g.). The first long running yellow band was eluted with benzene and evaporated *in vacuo* to provide 6 g. (32%) of fairly pure **8** (R = Cl) as a bright yellow oil which solidified on standing. Elution of the column with chloroform provided additional **7** (R = Cl). The total recovery of **7** (R = Cl) was 7.2 g. (50%). Recrystallization of the product from ethanol provided bright yellow microcrystals, m.p. 81-82°; ir cm^{-1}: 1545 (s) and 1348 (s) (NO_2); pmr (deuteriochloroform): 2.63 δ (methyl, singlet), 7.52 δ (C_4-H, singlet). 3-Chloro-6-methyl-4-nitropyridazine 1-oxide melts at 103° (22).

Anal. Calcd. for $C_5H_4ClN_3O_3$: C, 31.8; H, 2.1; N, 22.2. Found: C, 31.9; H, 2.0; N, 22.2.

5-Amino-3-methoxy-6-methylpyridazine 1-Oxide (**9**, R = OMe).

A solution of **8** (R = OMe) (5 g., 0.027 mole) in 300 ml. of ethanol and 2.5 g. of 10% palladium on charcoal was stirred under an atmosphere of hydrogen until the uptake of hydrogen ceased. The catalyst was filtered and washed with hot ethanol and the filtrates were evaporated *in vacuo* yielding a light yellow glass. Dissolution and evaporation *in vacuo* (1 torr, 60-70°) successively with absolute ethanol and ethyl acetate provided a tan crystalline residue. Recrystallization from ethanol-ethyl acetate (norite) afforded 3.6 g. (86%) of off-white crystals, m.p. 180-181°; ir cm^{-1}: 3380 (s), 3350 (s), and 3205 (s) (NH_2); pmr (DMSO-d_6): 2.28 δ (methyl, singlet), 3.82 δ (methoxy, singlet), 6.00 δ (C_4-H, singlet), 6.55 δ (amino, broadened singlet).

Anal. Calcd. for $C_6H_9N_3O_2$: C, 46.4; H, 5.8; N, 27.1. Found: C, 46.5; H, 6.0; N, 26.9.

5-Amino-3-chloro-6-methylpyridazine 1-Oxide (**9**, R = Cl).

Compound **8** (R = Cl) (4.25 g., 0.0225 mole) in 300 ml. of absolute ethanol was hydrogenated over 10 g. of Raney nickel (23) at atmospheric pressure and room temperature until absorption became slow (*ca.* one hour) then at 45-50° until a total of three equivalents of hydrogen had been absorbed (*ca.* one hour). Removal of the Raney nickel and evaporation of the filtrate under reduced pressure (1 torr, 70-80°) gave 3.3 g. (92%) of fairly pure **9**, (R = Cl). Recrystallization from ethyl acetate provided white crystals, m.p. 210-212° dec.; ir cm^{-1}: 3340 (m) and 3210 (m) (NH_2); pmr (DMSO-d_6): 2.23 δ (methyl, singlet), 6.54 δ (C_4-H, singlet), 6.95 δ (amino, broadened singlet).

Anal. Calcd. for $C_5H_6ClN_3O$: C, 37.6; H, 4.0; N, 26.4. Found: C, 37.5; H, 4.2; N, 26.2.

5-Ethoxymethyleneamino-3-methoxy-6-methylpyridazine 1-Oxide (**14**, R = OMe, R_1 = H), and *N,N'*-Bis(3-methoxy-6-methyl-1-oxido-5-pyridazinyl)formamidine (**10**).

A mixture of **9** (R = OMe) (3 g., 0.0194 mole), 10 ml. of triethyl orthoformate, 10 ml. of DMF, and 5 drops of ethanol that had been adjusted to *ca.* *p*H 1 with gaseous hydrogen chloride was heated in an oil bath (120-125°) for 35 minutes. Tlc indicated complete consumption of starting material. The

solvents were removed *in vacuo* (1 torr, 50-60°) yielding a yellowish crystalline residue which was dissolved in chloroform and placed on a column of silica gel (60 g.). Elution with chloroform provided the formimidate (**14**, R = OMe, R_1 = H). Recrystallization from isopropyl ether-chloroform afforded 215 g. (61%) of **14** (R = OMe, R_1 = H) as light yellow crystals, m.p. 142-143°; ir cm^{-1}: 1645 (s) (N=C); pmr (deuteriochloroform): 1.40 δ (ethyl-CH_3, triplet), 2.37 δ (methyl, singlet), 3.96 δ (methoxy, singlet), 4.39 δ (ethyl-CH_2, quartet), 6.15 δ (C_4-H, singlet), 7.78 δ (methine, singlet).

Anal. Calcd. for $C_9H_{13}N_3O_3$: C, 51.2; H, 6.2; N, 20.0. Found: C, 51.4; H, 5.9; N, 20.3.

Elution of the column with methanol provided the formamidine (**10**) which after recrystallization from DMF yielded faint yellow crystals (0.9 g., 29%), m.p. 250° dec.

Anal. Calcd. for $C_{13}H_{18}N_6O_4$: C, 48.2; H, 5.6; N, 25.9. Found: C, 48.4; H, 5.3; N, 26.2.

5-(α-Ethoxyethylideneamino)-3-methoxy-6-methylpyridazine 1-Oxide (**14**, R = OMe, R_1 = Me).

The pyridazinylacetimidate (**14**, R = OMe, R_1 = Me) was prepared in essentially the same manner as the pyridazinylformimidate (**14**, R = OMe, R_1 = H). No formamidine was detected and starting material was completely consumed. A 72% yield of the desired product was obtained after column chromatography. Pmr indicated pure material; pmr (deuteriochloroform): 1.37 δ (ethyl-CH_3, triplet), 1.88 δ (C_5-methyl, singlet), 2.28 δ (C_6-methyl, singlet), 3.97 δ (methoxy, singlet), 4.28 δ (ethyl-CH_2, quartet), 6.05 δ (C_4-H, singlet). This material was stable and sufficiently pure for further reactions.

3-Chloro-5-(α-ethoxyethylideneamino)-6-methylpyridazine 1-Oxide (**14**, R = Cl, R_1 = Me).

A mixture of 5-amino-3-chloro-6-methylpyridazine 1-oxide (**9**, R = Cl) (2.8 g., 0.0176 mole), triethyl orthoacetate (15 ml.), DMF (6 ml.), and 5 drops of anhydrous ethanol that had been adjusted to *ca.* *p*H 1 with gaseous hydrogen chloride was heated in an open flask (oil bath 110-120°) for 4 hours. The solvents were removed *in vacuo* (1 torr, 90°) providing a dark brown residue which was placed into solution with benzene-chloroform (1:1) and placed on a column of silica gel (75 g.). The first light yellow band was eluted with benzene. Removal of the solvent *in vacuo* and recrystallization of the residue from isopropyl ether provided 3.23 g. (80%) of **14** (R = Cl, R_1 = Me) as long white needles, m.p. 114-115°; ir cm^{-1}: 1670 (s) (C=N); pmr (deuteriochloroform): 1.37 δ (ethyl-CH_3, triplet), 1.97 δ (C_5-methyl, singlet), 2.32 δ (C_6-methyl, singlet), 4.30 δ (ethyl-CH_2, quartet), 6.62 δ (C_4-H, singlet).

Anal. Calcd. for $C_9H_{12}ClN_3O_2$: C, 47.2; H, 5.3; N, 18.3. Found: C, 47.0; H, 5.0; N, 18.1.

Ethyl 3-Chloro-6-methylpyrrolo[3,2-*c*]pyridazine-7-glyoxalate 1-Oxide (**12**).

The apparatus and procedure described for the preparation of **4** was employed. Complete dissolution was immediately obtained on adding **14** (R = Cl, R_1 = Me) (0.9 g., 0.00393 mole) to the reaction medium followed by a heavy yellow-orange precipitate within 30 seconds. Starting material was completely consumed within 3 hours (tlc). Stirring was continued for 24 hours. The precipitate was filtered, washed thoroughly with ether, air-dried (1.35 g.), and dissolved in a minimum amount of water. Complete dissolution was obtained followed by precipitation of an orange material within 30 seconds which was removed by filtration (0.18 g.), m.p. > 310°. The filtrate was adjusted to *ca.* *p*H 4 by acetic acid causing a yellow material to precipitate. This material was filtered, washed thoroughly with water and recrystallized from ethyl acetate-ethanol to afford 0.6 g. of **12** as light yellow crystals, m.p. 256-257° dec. An additional 0.2 g. of **12** was obtained from the filtrate. Total yield of **12** is 0.8 g. (72%); ir cm^{-1}: 1740 (s) (C=O); uv (ethanol): λ max (*p*H 1) 234 nm (ε, 36,500), 353 nm (ε, 10,300); λ max (*p*H 7) 236 nm (ε, 34,400), 298 nm (ε, 7,350), 364 nm (ε, 9,420); λ max (*p*H 11) 238 nm (ε, 33,800), 298 nm (ε, 10,300), 323 nm (ε, 8,550), 376 nm (ε, 11,200); pmr (DMSO-d_6): 1.32 δ (ethyl-CH_3, triplet), 2.68 δ (methyl, singlet), 4.35 δ (ethyl-CH_2, quartet), 6.35 δ - 7.43 δ (NH and ½H_2O, broadened singlet), 7.72 δ (C_4-H, singlet). Addition of deuterium oxide causes the broad peak at 6.35 δ - 7.43 δ to disappear and a DHO peak appears at 4.1 δ.

Anal. Calcd. for $C_{11}H_{10}ClN_3O_4 \cdot ½H_2O$: C, 45.2; H, 3.8; N, 14.4. Found: C, 45.5; H, 3.6; N, 14.4.

Stopping the reaction after 3 hours stirring at room temperature reduced the yield of **12** to 35% and the orange material to 0.1 g. A water soluble material (0.6 g.) was obtained from the acidified aqueous filtrate which may be ethyl 3-chloro-5-(α-ethoxyethylideneamino)-6-pyridazinylpyruvate 1-oxide.

Ethyl 3-Methoxy-6-pyridazinylpyruvate 1-Oxide (**11**).

The apparatus and procedure described for the preparation of **4** was employed. 3-Methoxy-6-methylpyridazine 1-oxide (**7**, R = OMe) (21) immediately dissolved in the reaction medium followed by precipitation of the potassium enolate. The crude product obtained from acidification of the potassium enolate was recrystallized from 65-110° ligroin-chloroform to afford pale yellow crystals of **11** (90%), m.p. 144-146°; ir cm^{-1}: 1720 (s) (C=O); pmr (deuteriochloroform): 1.38 δ (ethyl-CH_3, triplet), 4.04 δ (methoxy, singlet), 4.18 δ (C_6-methylene, singlet, *ca.* 0.6 proton), 4.37 δ (ethyl-CH_2, quartet), 6.65 δ (C_6-methine, singlet, *ca.* 0.7 proton), 6.81 δ (C_4-H, doublet), 7.85 δ (C_5-H, doublet), $J_{4,5}$ = 9 Hz. Pmr of **11** in DMSO-d_6 indicated only the enol tautomer.

Anal. Calcd. for $C_{10}H_{12}N_2O_5$: C, 50.0; H, 5.0; N, 11.6. Found: C, 50.1; H, 5.0; N, 11.5.

4-Nitro-3-styrylpyridazine 1-Oxide (**15**).

A solution of 3-methyl-4-nitropyridazine 1-oxide (**1**) (20) (1.3 g., 0.0084 mole), 15 ml. of methanol, piperidine (0.5 ml.), and benzaldehyde (1.78 g., 0.0168 mole) was refluxed 20 hours. The brown solution was cooled at 0° overnight causing precipitation of a brown solid which was collected, washed successively with water and methanol, and recrystallized from chloroform (norite) to give 1.2 g. (59%) of bright yellow **15**, m.p. 209-210°; ir cm^{-1}: 1625 (m) (C=C), 1565 (s) and 1325 (s) (NO_2); pmr (deuteriochloroform): 7.20 δ - 7.80 δ (vinyl and phenyl, multiplet), 7.98 δ (C_5-H, distorted doublet), 8.28 δ (C_6-H, distorted doublet), $J_{5,6}$ = 7 Hz.

Anal. Calcd. for $C_{12}H_9N_3O_3$: C, 59.3; H, 3.7; N, 17.3. Found: C, 59.4; H, 3.9; N, 17.3.

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