Pyrrolopyridazines. 1. Synthesis and Reactivity of Pyrrolo[2,3-*d*]pyridazine 5-Oxides (1)

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Received April 4, 1973

Reaction of ethyl 4-ethoxymethyleneamino-3-methoxy-5-pyridazinylpyruvate 1-oxide (**8**) under various conditions constitutes a new approach to substituted pyrrolo[2,3-*d*]pyridazines. The resulting substituted pyrrolo[2,3-*d*]pyridazine 5-oxides were allowed to react further to provide a number of new compounds in this ring system.

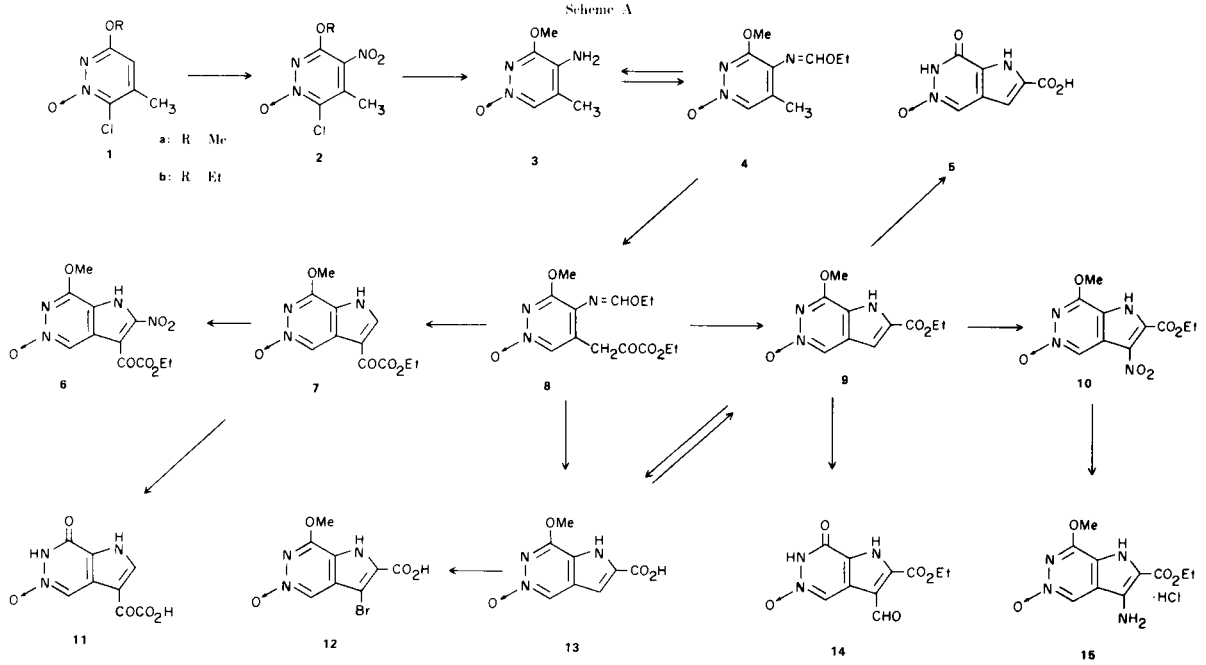
The first reported pyrrolo[2,3-*d*]pyridazines (5,6-diazaindoles) were obtained by Fischer, *et al.*, during early porphyrin syntheses (2a-e). More recently, several pyrrolo[2,3-*d*]pyridazines have been prepared as potential antineoplastic agents (3a-c). 4-Benzylamino-1-benzylpyrrolo[2,3-*d*]pyridazine possessed activity against human KB cancer cells *in vitro* (3b) and antimitotic activity in hamster cells (3a). The more recent papers describe the preparation of a number of derivatives (3a,b); however, their preparation as well as the position and type of substituent do not contribute greatly to the chemistry of the ring system. We, therefore, began a study of this ring system, first, to explore the fundamental chemistry and second, because of its structure relationship to the biologically important purines and indoles. Furthermore, we wished to devise a synthetic sequence which would lead not only to pyrrolo[2,3-*d*]pyridazines, but also to the isomeric pyrrolo[3,2-*c*]- and pyrrolo[2,3-*c*]pyridazines.

All of the previously reported syntheses of pyrrolo[2,3-*d*]pyridazines have used pyrroles substituted in the 2- and 3-positions with acyl and/or carbalkoxyl groups (2a-e,3a,b,4a,b). It appeared that an approach which utilizes properly substituted pyridazines would be more versatile. Subsequent work indicated that ethyl 4-ethoxymethyleneamino-3-methoxy-5-pyridazinylpyruvate 1-oxide (**8**, Scheme A) might serve as an immediate precursor to the pyrrolo[2,3-*d*]pyridazine ring. It was envisaged that acid hydrolysis of the formimidate function of **8** and subsequent cyclodehydration, parallel to the latter stage of the Reissert indole cyclization (5a,6a,b), would afford ethyl 7-methoxypyrrolo[2,3-*d*]pyridazine-2-carboxylate 5-oxide (**9**).

Treatment of ethyl 4-ethoxymethyleneamino-3-methoxy-5-methylpyridazine 1-oxide (**4**, obtained in a straightforward manner in 67% overall yield as shown in Scheme A) with diethyl oxalate and potassium ethoxide in ether afforded a bright yellow-orange precipitate characteristic of previously prepared heterocyclic pyruvate enolates (7a-c). However, tlc of the acidified product indicated a major component with a low Rf value and two minor components with relatively higher Rf values. The crude yellow solid changed to a white solid at 168-170° followed by decomposition at 275-276°. Refluxing the yellow material in ethanol or chloroform converted the major component of low Rf value into approximately equal amounts of the two compounds of higher Rf values. Recrystallization or column chromatography of this mixture afforded two, tlc pure, white crystalline products. The component with the higher Rf value was ethanol soluble, chloroform insoluble and decomposed at 197-198°. The component with the intermediate Rf value was chloroform soluble, ethanol insoluble and decomposed at 275-276°. The structures of these compounds were assigned as ethyl 7-methoxypyrrolo[2,3-*d*]pyridazine-3-glyoxalate 5-oxide (**7**, 275-276° dec.) and ethyl 7-methoxypyrrolo[2,3-*d*]pyridazine-2-carboxylate 5-oxide (**9**, 197-198° dec.) on the basis of elemental analysis, spectroscopic data (ir and pmr), and further chemical transformations.

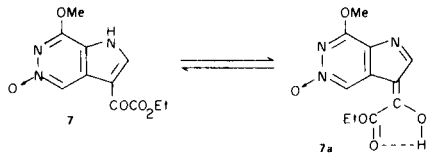
No pmr data has been reported for the pyrrolo[2,3-*d*]-pyridazines; however, the spectra for this system appears to follow closely related systems such as the indoles (8a), pyrrolopyrimidines (8b), pyrrolo[2,3-*c*]pyridazines (8c), and monoazaindoles (5b). The pmr spectra (TFA) of the compounds assigned to structures **7** and **9** were superimposable except for the aromatic protons in the 2-, 3-, and 4-positions. In **9**, a doublet at 7.9 δ, which intergrated for one proton, was assigned to the 3-proton. Another one proton doublet appearing at 12.1 δ was assigned to the proton on the pyrrole ring nitrogen. The coupling constant between the 1- and 3-protons was 2 Hz

Scheme A



and is in accordance with the related systems previously mentioned (5b,8a-c). Analogously, the 1- and 2-protons in **7** are coupled (J = 2 Hz) and exhibit doublets at 12.1 δ and 9.28 δ, respectively. One proton singlets at 9.4 δ and 9.84 δ are assigned to the 4-proton of structures **9** and **7**, respectively.

The significant absorptions in the ir spectrum of **9** are: a weak broad band, centered at 2650 cm^{-1}, intramolecular hydrogen bonding of the pyrrole NH to the ester carbonyl; a strong absorption at 1730 cm^{-1}, the carbonyl of the ester; a medium absorption at 1620 cm^{-1}, intramolecular hydrogen bonded carbonyl of the ester. The ir spectrum of compound **7** indicates an keto-enol tautomerism between **7** and **7a**. The significant absorptions in this case are: a weak broad band at 2550 cm^{-1}, chelated hydroxyl of **7a**; a strong absorption at 1730 cm^{-1}, free ester carbonyl in **7**; a strong absorption at 1665 cm^{-1}, ketone carbonyl in **7** and free ester carbonyl in **7a**; a strong absorption at 1625 cm^{-1}, nitrogen-carbon and carbon-carbon double bond in **7a**. No tautomerism between **7** and **7a** was observed in the pmr spectrum of **7**.



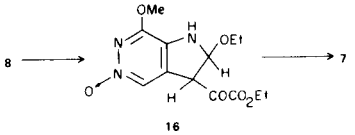
Ethyl 4-ethoxymethyleneamino-3-methoxy-5-pyridazinylpyruvate 1-oxide (**8**), the apparent precursor to **7** and **9** was difficult to obtain analytically pure due to its reactive nature. However, by allowing **4** and diethyl oxalate to react at -10° for a shorter period of time and subjecting the acidified product to a washing procedure in lieu of recrystallization, a pure sample of **8** could be obtained. A pmr spectrum of this material in TFA indicated 3 one-proton singlets at 7.88 δ, 8.30 δ, and 9.38 δ assigned as the methine proton in position 5 (enol structure), methine proton in position 4 and the aromatic proton in the 6 position, respectively; two almost superimposable ethoxyl group absorptions at 1.5 δ and 4.61 δ assigned to the ester and formimidate groups; a methoxyl group singlet at 4.45 δ and a broad singlet at 12.1 δ assigned to the chelated hydroxyl group (enol). The pmr spectrum of the potassium salt of **8** (potassium enolate) in hexadeuteriodimethylsulfoxide indicated the same ethoxyl and methoxyl group absorptions as well as 3 one-proton singlets at 5.6 δ, 7.96 δ, and 9.62 δ assigned to the methine proton in the 5-position, methine proton in the 4-position and the aromatic proton in the 6-position, respectively. The significant absorptions in the ir spectrum of **8** are: a weak broad band centered at 2560 cm^{-1}, chelated hydroxyl group; a strong absorption at 1720 cm^{-1}, free ester carbonyl; two strong absorptions at 1645 cm^{-1} and 1635 cm^{-1}, intramolecular hydrogen bonding of the ester carbonyl and nitrogen-carbon double bond.

The relatively unreactive acetimidate (9a) analog of **4** and **8** was desired for reactivity studies. However, attempts to prepare the required 4-(α-ethoxyethylideneamino)-3-methoxy-5-methylpyridazine 1-oxide in a sufficient yield failed. The inactiveness of the amino group of **3** was also indicated by the difficulty in obtaining its acetyl derivative,

4-acetamido-3-methoxy-5-methylpyridazine 1-oxide, in a practical yield. 4-Acetamido-3-methoxy-5-methylpyridazine 1-oxide was desired because it is the easiest obtainable pyridazine which possesses the necessary structural features required for the Madelung indole cyclization (5c). The inertness of the amino group is attributed to steric hindrance (9b) and the facile formation of the 1-acetoxyammonium salt of **3** by use of acetic acid derivatives (10a).

A preponderance of either **7** or **9** can be readily obtained by allowing **8** to react under various conditions. Thus, heating anhydrous **8** at 170-175° for a short time or heating the potassium salt of **8** (potassium enolate) in DMF at 100° followed by acidification provided **7** in 75% and 90% yields, respectively. A 60% yield of **9** could be obtained by heating wet **8** at 75° for a few hours. Also, **9** could be obtained in 85% yield by the action of dilute hydrochloric acid on **8**. Refluxing **8** in concentrated hydrobromic or hydrochloric acid provided 7-methoxypyrrolo[2,3-*d*]pyridazine-2-carboxylic acid 5-oxide (**13**) in good yield. Esterification of **13** also provided **9**. Treatment of **8** with ammonia, methylamine, or hydrazine in ethanol at room temperature provided mixtures of **7** and **9**.

Some tentative suggestions as to the mechanism of the formation of the pyrrolopyridazines **7** and **9** can be made. The formation of the pyrrolopyridazine **9** by refluxing **8** in ethanol or chloroform can be envisaged as a cyclodehydration between the 4-amino group derived from prior hydrolysis of the formimidate group of **8** and the ketone carbonyl of the pyruvate of **8**. The suggested hydrolysis of the formimidate (**8**) is supported by the fact that the pyridazinylformimidate **4** is completely converted to the aminopyridazine **3** by four hours of refluxing in commercial absolute ethanol. The same conversion is one-half completed by 24 hours of refluxing in technical grade chloroform. The cyclodehydration step is the same as the last step of the Reissert indole cyclization which is well documented (5a,6a,b). The formation of **7** by refluxing **8** in ethanol, chloroform or heating at 170-175° can be envisaged as intermolecular prototropic rearrangement among molecules of **8** to form a diazaindolene (**16**) from which a molecule of ethanol is pyrolytically eliminated.



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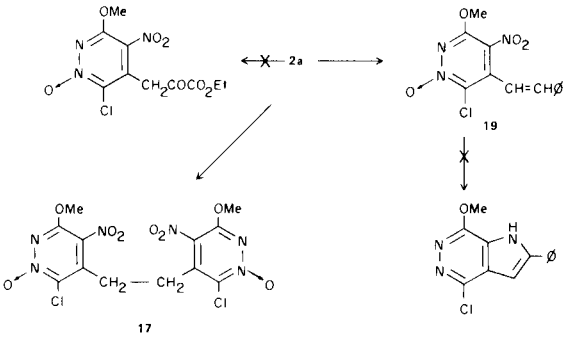
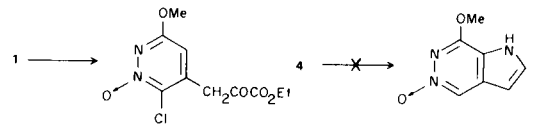
The powerful electron-withdrawing or π-deficient pyridazine ring fused to the electron-releasing or π-excessive pyrrole ring does not appear to affect electrophilic substitution of the 3-position of **9** since nitration (nitric acid, d. 1.56, 0°) and formylation (phosphorus oxychloride-DMF, 50°) of **9** afforded ethyl 7-methoxy-3-nitropyrrolo[2,3-*d*]pyridazine-2-carboxylate 5-oxide (**10**) and ethyl 3-formylpyrrolo[2,3-*d*]pyridazin-7(6*H*)one-2-carboxylate 5-oxide (**14**) in 89% and 60% yields, respectively. Also, bromination (bromine, acetic acid 25°) of **13** provides 3-bromo-7-methoxypyrrolo[2,3-*d*]pyridazine-2-carboxylic acid 5-oxide (**12**) in 73% yield. Nitration (nitric acid, d. 1.56, 25°) of the 2-position of **7** readily affords ethyl 7-methoxy-2-nitropyrrolo[2,3-*d*]pyridazine-3-glyoxalate (**6**) in 71% yield. On the other hand, the electron release of the pyrrole ring to the pyridazine ring has rendered the 7-methoxyl group in **9** resistant to boiling, concentrated hydrobromic acid. Hydrolysis of the 7-methoxyl group of **9** to pyrrolo[2,3-*d*]pyridazin-7(6*H*)one-2-carboxylic acid 5-oxide (**5**) was finally obtained by a boiling sodium hydroxide solution (25%, 2 hours). An electron-withdrawing group in the 3-position of the fused pyrrole ring appears to activate the 7-methoxyl group to hydrolysis since the dilute sodium hydroxide solution used to hydrolyze the Vilsmeier adduct of **9** also hydrolyzed the 7-methoxyl group providing **14** and boiling, concentrated hydrobromic acid cleaves the 7-methoxyl group of **7** providing pyrrolo[2,3-*d*]pyridazin-7(6*H*)one-3-glyoxalic acid 5-oxide (**11**) in 79% yield. Later, it was found that an ethoxyl group in the 3-position of pyridazines similar to **2** was more susceptible to nucleophilic substitution than a methoxyl group (11). Thus, preparation of the ethoxy analogs of this series was begun (preparation of **1b** and **2b**) but not completed.

Reduction of the 3-nitro group in **10** was resistant to palladium catalyst but was readily reduced with Raney nickel to ethyl 3-amino-7-methoxypyrrolo[2,3-*d*]pyridazine-2-carboxylate 5-oxide. The resulting 3-amino compound was subsequently acidified and isolated as the hydrochloride salt (**15**) because of the instability of the free base.

Initially, considerable effort was expended towards adapting the Reissert and Madelung indole cyclization methods to the synthesis of pyrrolo[2,3-*d*]pyridazines since these methods have been successful in the closely related monoazaindoles (5a,c). 6-Chloro-3-methoxy-5-methyl-4-nitropyridazine 1-oxide (**2a**), the easiest obtainable pyridazine which possesses the structural features required by the Reissert indole cyclization (5a), failed to form the necessary pyruvate derivative by condensing with diethyl oxalate. Heterocyclic pyruvates are obtained from the condensation of heteroaromatic methyl groups and diethyl oxalate in the presence of potassium or sodium ethoxide (7a-d). These same conditions applied to **2a** afforded the 1,2-bis(6-chloro-3-methoxy-4-nitro-1-oxido-5-pyridazinyl)ethane (**17**) (12).



A recent modification of the Madelung indole cyclization which employed formimidates and formamidines of *o*-aminopicolines at 200° in the presence of sodium *N*-methylanilide (14) was considered. In this case the easiest obtainable pyridazine which had the necessary structural features for this modified Madelung indole cyclization was ethyl 4-ethoxymethyleneamino-3-methoxy-5-methylpyridazine 1-oxide (**4**). It appeared that because of the added activating effect the *N*-oxidized ring nitrogen in **4** (10b,c) compared with a picolylformimidate, milder reaction conditions could be employed. For example, the reaction of **1a** with diethyl oxalate in the presence of ether and potassium ethoxide immediately forms the potassium enolate of ethyl 6-chloro-3-methoxy-5-pyridazinylpyruvate 1-oxide (**18**) in quantitative yield. However, treatment of **4** with potas-



sium ethoxide in ethyl ether, refluxing ethanol, or refluxing dimethylformamide provided in each case starting material, appearance of ring opening, and mainly the parent aminopyridazine **3**. Thus, it was concluded that the more strenuous conditions previously mentioned for picolylformimidates would also fail (14).

One other recently developed indole cyclization method (15) that has been applied to the synthesis of 5- and 6-azaindoles (16) and 5,7-diazaindole (17) was attempted. In this case, reductive cyclization of *o*-nitrostyrylpyridines (16) and pyrimidines (17) with triethyl phosphite was obtained. However, reaction of 6-chloro-3-methoxy-4-nitro-5-styrylpyridazine 1-oxide (**19**, obtained from **2a** and benzaldehyde) and triethyl phosphite has only produced complex mixtures.

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 tetramethylsilane as an internal standard. The ir spectra were recorded in potassium bromide discs with a Perkin-Elmer 457 spectrophotometer.

6-Chloro-3-methoxy-5-methyl-4-nitropyridazine 1-Oxide (**2a**).

6-Chloro-3-methoxy-5-methylpyridazine 1-oxide (**1a**) (18) (1.54 g., 0.00883 mole) was dissolved with stirring in 7 ml. of concentrated sulfuric acid (temperature less than 40°). Red fuming nitric acid (3 ml., d. 1.56) was added dropwise (temperature less than 40°). After addition of the nitric acid and cessation of cooling, the temperature of the solution rose to *ca.* 40-45° for a short time. The solution was allowed to stand for 24 hours, poured over crushed ice and the light yellow precipitate filtered and washed with water to give 1.6 g. of the fairly pure **2a**. Another 0.3 g. of product was obtained by extracting the filtrate with chloroform, drying the extracts with magnesium sulfate, and removing the solvent under reduced pressure. A total yield of 1.7 g. (88%) of the light yellow **2a** was obtained after recrystallization from ethanol, m.p. 136-137°; pmr (deuteriochloroform): 2.47 δ (methyl, singlet), 4.12 δ (methoxy, singlet). Compound **2a** is light sensitive, turning a reddish color on exposure to light for a short time.

Anal. Calcd. for $C_6H_6ClN_3O_4$: C, 32.8; H, 2.8; N, 19.2. Found: C, 32.6; H, 2.5; N, 19.0.

6-Chloro-3-ethoxy-5-methyl-4-nitropyridazine 1-Oxide (**2b**).

The same procedure as for the preparation of 6-chloro-3-methoxy-5-methyl-4-nitropyridazine 1-oxide (**2a**) was employed. A mixture of 6-chloro-3-ethoxy-4-methylpyridazine 1-oxide and 6-chloro-3-ethoxy-5-methylpyridazine 1-oxide (19) was used as starting material. The reaction was poured over crushed ice causing **2b** to precipitate. Recrystallization from ethanol afforded an 85% yield of light yellow crystals, m.p. 111-112°; pmr (deuteriochloroform): 1.45 δ (ethyl-CH_3, triplet), 2.50 δ (methyl, singlet), 4.54 δ (ethyl-CH_2, quartet).

Anal. Calcd. for $C_7H_8ClN_3O_4$: C, 36.1; H, 3.5; N, 18.0. Found: C, 36.0; H, 3.4; N, 17.9.

Most of the 6-chloro-3-ethoxy-4-methylpyridazine 1-oxide was recovered by extraction of the neutralized filtrate with chloroform.

4-Amino-3-methoxy-5-methylpyridazine 1-Oxide (**3**).

A mixture of **2a** (10.97 g., 0.05 mole), 5% palladium on charcoal (1 g.), ethanol (300 ml.) and water (30 ml.) was hydrogenated at atmospheric pressure and room temperature. The reaction was stopped after the uptake of 4 equivalents of hydrogen and the catalyst was removed by filtration and washed with boiling ethanol. The combined filtrates were concentrated to a small volume under reduced pressure and extracted one time with chloroform to remove a small amount of starting material. The aqueous solution was adjusted to *ca.* *p*H 7 by addition of 10% sodium hydroxide solution and concentrated to *ca.* 50 ml. under reduced pressure. Compound **3** (5.9 g.) was obtained by filtration of the white precipitate. Additional product (1 g.) was obtained by evaporating the filtrate to dryness under reduced pressure and washing the residue with absolute ethanol. A total yield of 6.7 g. (86%) of **3** was obtained after recrystallization from ethanol-ethyl acetate, m.p. 203-204° dec.; ir cm^{-1}: 3460 (s), 3300 (s), and 1640 (s) (NH_2); pmr (DMSO-d_6): 2.05 δ (methyl, singlet), 3.92 δ (methoxy, singlet), 5.68 δ (NH_2, broadened singlet), 7.78 δ (C_6-H, singlet).

Anal. Calcd. for $C_6H_9N_3O_2$: C, 46.4; H, 5.9; N, 27.1. Found: C, 46.4; H, 6.1; N, 27.4.

4-Ethoxymethyleneamino-3-methoxy-5-methylpyridazine 1-Oxide (4).

A mixture of **3** (15.5 g., 0.1 mole), ethyl orthoformate (44.4 g., 0.3 mole), 90 ml. of DMF and absolute ethanol (2 ml.) that had been adjusted to *ca.* *p*H 1 with anhydrous hydrogen chloride was heated in an oil bath (150-160°) under a Vigreux distilling column (10 cm) for *ca.* 90 minutes during which time 13 ml. of ethanol was collected (tlc indicates all of 3 consumed). The solvents were removed under reduced pressure (1 torr, 50-60°). The residual light yellow oil solidified after cooling to room temperature and was washed with pentane. Recrystallization from chloroform-isopropyl ether (norite) gave 19 g. (90%) of faint yellow **4**, m.p. 131-132°; ir cm^{-1}: 1645 (s) (N=C); pmr (deuteriochloroform): 1.38 δ (ethyl-CH_3, triplet), 2.16 δ (methyl, singlet), 4.0 δ (methoxyl, singlet), 4.36 δ (ethyl-CH_2, quartet), 7.87 δ (C_6-H, singlet), 8.0 δ (methine, broadened singlet).

Anal. Calcd. for $C_9H_{13}N_3O_3$: C, 51.3; H, 6.2; N, 19.9. Found: C, 51.3; H, 6.1; N, 20.2.

Ethyl 4-Ethoxymethyleneamino-3-methoxypyridazinylpyruvate 1-Oxide (8).

A 1-liter three-neck flask equipped with mechanical stirrer, reflux condenser and nitrogen inlet tube was flamed while purging with dry nitrogen. After allowing 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 ethoxide solution, followed by addition of diethyl oxalate (14.6 g., 0.1 mole). After 5 minutes of stirring, **4** (10.56 g., 0.05 mole) was added. Dissolution was obtained almost immediately, followed by a gradual precipitation of the orange potassium enolate. Stirring under nitrogen was continued for 5 hours. The potassium enolate was filtered, washed thoroughly with absolute ether, air dried (quantitative yield) dissolved in *ca.* 500 ml. of water, and quickly acidified to *ca.* *p*H 4 with acetic acid. The bright yellow pyruvate **8** was immediately filtered, washed with water (3x, 50 ml.) and dried (95°, 0.01 torr, 12 hours) to yield 14.0 g. (90%) of fairly pure **8**; m.p., changes from bright yellow to white between 168-170° and decomposes at 275-276°; ir cm^{-1}: 2560 (m) (chelated hydroxyl), 1720 (s) (free ester carbonyl), 1660 (m) (chelated ester carbonyl), 1645 (s), and 1635 (s) (nitrogen-carbon and carbon-carbon double bonds); pmr (TFA): 1.5 δ (two ethyl-CH_3, multiplet), 4.45 δ (methoxy, singlet), 4.61 δ (two ethyl-CH_2, quartet), 7.88 δ (C_5-methine, singlet), 8.30 δ (C_4-methine, singlet), 9.38 δ (C_6-H singlet), 12.1 δ (chelated hydroxyl, broad singlet); potassium enolate (DMSO-d_6): 1.3 δ (two ethyl-CH_3, multiplet), 3.83 δ (methoxy, singlet), 4.27 δ (two ethyl-CH_2, quartet), 5.60 δ (C_5-methine, singlet), 7.96 δ (C_4-methine, singlet), 9.62 δ (C_6-H, singlet).

Anal. Calcd. for $C_{13}H_{16}KN_3O_6 \cdot 2H_2O$ (potassium enolate): C, 40.5; H, 5.2; N, 11.0. Found: C, 40.5; H, 5.1; N, 11.2.

All attempts to recrystallize **8** resulted in partial to complete conversion to the pyrrolopyridazines **7** and **9**. An analytically pure sample of **8** was obtained by allowing the same reaction to proceed for 3 hours at -10°. The pure potassium enolate was dissolved in water and quickly acidified causing the precipitation of **8** which was washed successively with water and ether and dried *in vacuo* at 95° over phosphorus pentoxide.

Anal. Calcd. for $C_{13}H_{17}N_3O_6$: C, 50.2; H, 5.5; N, 13.5. Found: C, 49.8; H, 5.2; N, 13.6.

Ethyl 7-Methoxypyrrolo[2,3-*d*]pyridazine-3-glyoxalate 5-Oxide (7).

(a) A suspension of the potassium enolate (dihydrate) of **8** (5.0 g., 0.013 mole) and 30 ml. of DMF was heated at 100° for one hour. The reaction solution was evaporated to dryness *in vacuo* yielding a yellow residue which was dissolved in water and adjusted to *ca.* *p*H 4 with acetic acid. The light yellow precipitate was filtered, washed with water, and recrystallized from ethanol to afford 3.1 g. (90%) of white crystals, m.p. 275-276° dec.; ir cm^{-1}: 2550 (m) (broad envelope from chelation of hydroxyl), 1730 (s) (free ester carbonyl), 1665 (s) (N=C, C=C), 1625 (s) (associated ester carbonyl); pmr (TFA): 1.56 δ (ethyl-CH_3, triplet), 4.45 δ (methoxy, singlet), 4.7 δ (ethyl-CH_2, quartet), 9.28 δ (C_2-H, doublet), 9.84 δ (C_4-H, singlet), 12.1 δ (NH, doublet), J_{NH-2} = 2 Hz.

Anal. Calcd. for $C_{11}H_{11}N_3O_5$: C, 49.8; H, 4.2; N, 15.9. Found: C, 50.1; H, 4.1; N, 15.9.

(b) Compound **7** was also obtained in moderate yield by heating anhydrous **8** at 170-175° for a few hours.

Ethyl 7-Methoxypyrrolo[2,3-*d*]pyridazine-2-carboxylate 5-Oxide (9).

(a) A solution of **8** (0.311 g., 0.001 mole), warm DMF (15 ml., 40°), and hydrochloric acid (0.5 ml., 5%) was stirred at room temperature for 17 hours. The reaction solution was evaporated to dryness *in vacuo* yielding a yellow residue which was recrystallized from chloroform (norite). Compound **9** (0.2 g., 84%) was obtained as white crystals, m.p. 197-198° dec.; ir cm^{-1}: 2650 (m) (broad band from hydroxyl group chelation), 1730 (s) (free ester carbonyl); pmr (TFA): 1.56 δ (ethyl-CH_3, triplet), 4.45 δ (methoxy, singlet), 4.7 δ (ethyl-CH_2, quartet), 7.9 δ (C_3-H, doublet), 9.4 δ (C_4-H, singlet), 12.1 δ (NH, doublet), J_{NH-3} = 2 Hz.

Anal. Calcd. for $C_{10}H_{11}N_3O_4$: C, 50.6; H, 4.6; N, 17.7. Found: C, 50.5; H, 4.6; N, 17.9.

(b) An attempt to dry wet **8** in a vacuum oven (75°, 25 torr) provided a moderate yield of **9**.

(c) 7-Methoxypyrrolo[2,3-*d*]pyridazine-1-carboxylic acid 5-oxide (**13**) (0.418 g., 0.002 mole) and absolute ethanol (30 ml.) saturated with anhydrous hydrogen chloride was refluxed one hour. The ethanol was evaporated under reduced pressure yielding 0.38 g. (80%) of **9** after recrystallization from chloroform (norite).

Ethyl 7-Methoxypyrrolo[2,3-*d*]pyridazine-2-carboxylate 5-Oxide (9) and Ethyl 7-Methoxypyrrolo[2,3-*d*]pyridazine-3-glyoxalate 5-Oxide (7).

A suspension of **8** (6 g., 0.0193 mole) and commercial absolute ethanol (500 ml.) was refluxed 10 hours and cooled overnight at 0°. Filtration yielded 2.4 g. (47%) of almost pure **7**. Evaporation of the filtrate under reduced pressure and recrystallization of the residue from chloroform (norite) afforded 2.3 g. (50%) of **9**.

Ethyl 7-Methoxy-3-nitropyrrolo[2,3-*d*]pyridazine-2-carboxylate 5-Oxide (10).

Compound **9** (8 g., 0.0338 mole) was added portionwise with stirring to 80 ml. of red fuming nitric acid (d. 1.56) at 0°. Stirring was continued for one hour at 0° and then the solution was poured over crushed ice (1000 g.). The bright yellow precipitate was filtered and washed thoroughly with water. Recrystallization from benzene-ethanol afforded 8.5 g. (89%) of **10**, m.p. 188-189° dec.; ir cm^{-1}: 3210 (s) (NH), 1710 (s), (C=O), 1550 (s) and 1290 (s) (-NO_2); pmr (TFA): 1.1 δ (ethyl-CH_3, triplet); 3.6-4.95 δ (ethyl-CH_2, methoxyl, multiplet), 7.36 δ and 7.55 δ (C_H-4, nitro ⇌ nitronic acid), 11.5 δ and 12.1 δ (-NH, nitro ⇌ nitronic acid).

Anal. Calcd. for $C_{10}H_{10}N_4O_6$: C, 42.6; H, 3.6; N, 19.8. Found: C, 42.8; H, 3.7; N, 19.9.

Ethyl 3-Amino-7-methoxypyrrolo[2,3-*d*]pyridazine-2-carboxylate 5-Oxide Hydrochloride (**15**).

Compound **10** (2.82 g., 0.01 mole), ethanol (650 ml.), and Raney nickel catalyst (*ca.* 6 ml. of the suspension) were stirred under a hydrogen atmosphere until the uptake of three equivalents of hydrogen was accomplished (*ca.* 10 minutes). The reaction mixture was filtered to remove the catalyst and the colorless filtrate was saturated with gaseous hydrogen chloride. Ether (800 ml.) was added to the ethanol solution and this was cooled overnight at 0°. Filtration of the resulting colorless precipitate afforded 1.7 g. of **15**. An additional 1.1 g. of product was obtained by taking the filtrate to dryness under reduced pressure. Recrystallization from ethanol and drying (0.1 torr, 100°) afforded 2.6 g. (90%) of colorless **15**, m.p. 187-188° dec.; pmr (DMSO-d_6): 1.37 δ (ethyl-CH_3, triplet), 3.95 δ (methoxy, singlet), 4.37 δ (ethyl-CH_2, quartet), 7.82 δ (C_4-H, singlet), 8.62 δ (NH_2, broadened singlet), *ca.* 11.3 δ (-NH, broad singlet).

Anal. Calcd. for $C_{10}H_{13}N_4O_4$·HCl: C, 41.6; H, 4.9; N, 19.4. Found: C, 41.7; H, 4.7; N, 19.7.

Pyrrolo[2,3-*d*]pyridazin-7(6*H*)one-2-carboxylic Acid 5-Oxide (**5**).

A suspension of **9** (1.25 g., 0.00528 mole) and 25% sodium hydroxide solution (15 ml.) was refluxed 2 hours. Acidification of the resulting solution with hydrochloric acid precipitated the white product. Recrystallization from ethanol-water afforded 0.65 g. (60%) of **5**, decomposes greater than 250°, decomposition point 295°.

Anal. Calcd. for $C_7H_5N_3O_4$·½H_2O: C, 41.1; H, 3.0; N, 20.6. Found: C, 41.4; H, 3.1; N, 20.3.

Ethyl 3-Formylpyrrolo[2,3-*d*]pyridazin-7(6*H*)one-2-carboxylate 5-Oxide (**14**).

A solution of **9** (2.37 g., 0.01 mole) and warm DMF (20 ml., 50°) was added dropwise to the previously prepared Vilsmeier reagent [phosphorus oxychloride (1.84 g., 0.012 mole) dropped into DMF (4 ml.) at 20°] in 15 minutes (temperature rises to *ca.* 50°). The deep red solution was allowed to stand one hour at 45-50° and then poured over crushed ice (40 g.) yielding a yellow precipitate. Sodium hydroxide solution (20 ml., 25%) was added and the solution was refluxed for 10 minutes. The resulting mixture was cooled to room temperature and adjusted to *ca.* *p*H 3 with concentrated hydrochloric acid. The white precipitate was filtered, washed with water and recrystallized from ethyl acetate-ethanol affording 1.5 g. (60%) of **14**, m.p. 319-320° dec.; pmr (TFA): 1.56 δ (ethyl-CH_3, triplet), 4.67 δ (ethyl-CH_2, quartet), 7.6 δ C_4-H, singlet), 12.3 δ (-NH, singlet).

Anal. Calcd. for $C_{10}H_9N_3O_5$: C, 47.8; H, 3.6; N, 16.8. Found: C, 48.1; H, 3.2; N, 17.1.

Ethyl 7-Methoxy-2-nitropyrrolo[2,3-*d*]pyridazine-3-glyoxalate 5-Oxide (**6**).

Compound **7** (1.8 g., 0.0068 mole) was added portionwise with stirring to red fuming nitric acid (15 ml., d. 1.56) at room temperature. The resulting solution was allowed to stand for 1.5 hours without cooling and then poured over crushed ice (75 g.). The yellow precipitate was filtered, washed with water and recrystallized several times from ethanol affording 1.5 g. (71%) of light yellow **6**, m.p. 217-218° dec., pmr (TFA): 1.07 δ (ethyl-CH_3, triplet), 3.74-4.33 δ (ethyl-CH_2 and methoxy, multiplet), 8.68 δ (C_4-H, singlet), 13.3 δ (-NH, singlet).

Anal. Calcd. for $C_{11}H_{10}N_4O_7$: C, 42.6; H, 3.3; N, 18.0. Found: C, 42.6; H, 3.2; N, 18.0.

Pyrrolo[2,3-*d*]pyridazin-7(6*H*)one-3-glyoxalic Acid 5-Oxide (**11**).

A solution of **7** (1.5 g., 0.00566 mole) and 48% hydrobromic acid (30 ml.) was refluxed 1.5 hours then poured over crushed ice (150 g.). The white precipitate was filtered and washed successively with boiling DMF, water, and ethanol affording 1.0 g. (79%) of faint yellow **11**. An analytical sample was obtained by precipitating the acid from its sodium salt with concentrated hydrochloric acid, m.p. > 320°; ir cm^{-1}: 3140 (m) (-NH), 3000-2500 (w) (chelated hydroxy and -OH of acid), 1700 (m) (acid carbonyl), 1665 (s) (lactam carbonyl).

Anal. Calcd. for $C_8H_5N_3O_5$: C, 43.2; H, 2.3; N, 18.9. Found: C, 43.4; H, 2.2; N, 18.8.

7-Methoxypyrrolo[2,3-*d*]pyridazine-2-carboxylic Acid 5-Oxide (**13**).

A suspension of **8** (2.7 g., 0.00868 mole) and concentrated hydrochloric acid (30 ml.) was refluxed 90 minutes and then poured over crushed ice. The white precipitate was filtered, washed with water, and recrystallized from DMF-water affording 1.3 g. (71%) of **13**; gradually decomposes greater than 200°, decomposition point, 262°; ir cm^{-1}: 2650 (m) (envelope from -OH), 1725 (s) (carbonyl); pmr (TFA): 4.47 δ (methoxy, singlet), 7.98 δ (C_3-H, doublet), 9.38 δ (C_4-H, singlet), 11.9 δ (NH, singlet).

Anal. Calcd. for $C_8H_7N_3O_4$: C, 45.9; H, 3.4; N, 20.1. Found: C, 46.0; H, 3.7; N, 20.2.

Compound **13** was also obtained in good yield by refluxing ethyl 7-methoxypyrrolo[2,3-*d*]pyridazine-2-carboxylate 5-oxide (**9**) and hydrochloric acid for 90 minutes.

3-Bromo-7-methoxypyrrolo[2,3-*d*]pyridazine-2-carboxylic Acid 5-Oxide (**12**).

To a stirred suspension of **13** (0.5 g., 0.00239 mole) and glacial acetic acid (10 ml.) was added bromine (0.421 g., 0.00239 mole) causing complete dissolution followed immediately by precipitation of the orange product. Stirring was continued at room temperature for 3 days. Addition of water (20 ml.) caused further precipitation of **12** which was filtered, washed with water, and purified by precipitation from its sodium salt with hydrochloride acid; 0.5 g. (68%) of faint yellow **12**; m.p. decomposes greater than 250°; ir cm^{-1}: 2600 (m) (envelope from -OH), 1715 (s) (C=O); pmr (TFA), 4.44 δ (methoxy, singlet), 9.27 δ (C_4-H, singlet), 12.0 δ (NH, singlet).

Anal. Calcd. for $C_8H_6BrN_3O_4$·H_2O: C, 31.4; H, 2.6; N, 13.7. Found: C, 31.3; H, 2.7; N, 13.7.

1,2-Bis(6-chloro-3-methoxy-4-nitro-1-oxido-5-pyridazinyl)ethane (**17**).

The procedure was the same as for the preparation of **8**. The dark green suspension obtained after 3 days stirring at room temperature was filtered, washed with ether, and the greenish-brown residue dissolved in water. Acidification with acetic acid to *ca.* *p*H 3 caused the precipitation of a yellow material which was collected and recrystallized from DMF-water (50% yield of **17**), m.p. 252° dec.; pmr (TFA): 2.8 δ (methylene, singlet), 3.78 δ (methoxyl, singlet).

Anal. Calcd. for $C_{12}H_{10}Cl_2N_6O_8$: C, 33.0; H, 2.3; N, 19.2. Found: C, 33.3; H, 2.5; N, 19.2.

Ethyl 6-Chloro-3-methoxy-5-pyridazinylpyruvate 1-Oxide (**18**).

Employing the same apparatus and procedure as for the preparation of **8**, **1a** (6 g., 0.0343 mole), potassium ethoxide (3.2 g., 0.0377 mole) in a minimum amount of absolute ethanol, diethyl oxalate (10 g., 0.0686 mole), and absolute ether (600 ml.) was stirred under nitrogen for 2.5 hours. The heavy yellow potassium

enolate was filtered, washed with ether, air dried (quantitative yield), and dissolved in water (250 ml.). The *p*H was adjusted to *ca.* 4 with acetic acid and the resulting yellow solution was extracted with chloroform (3x, 75 ml.). The extracts were dried with sodium sulfate and the chloroform removed under reduced pressure yielding light yellow **18**. Recrystallization from benzene-isopropyl ether afforded 8.8 g. (94%) of **18**, m.p. 132-134° dec.; pmr (TFA): 1.53 δ (ethyl-CH_3, triplet), 4.2 δ (methoxy, singlet), 4.6 δ (ethyl-CH_2, quartet), 4.7 δ (methylene, singlet, one proton), 6.97 δ (C_4-H of keto tautomer, singlet, ½ proton), 7.4 δ (methine of enol tautomer, singlet, ½ proton), 8.41 δ (C_4-H of enol tautomer, singlet, ½ proton).

Anal. Calcd. for $C_{10}H_{11}ClN_2O_5$: C, 43.7; H, 4.0; N, 10.2. Found: C, 43.5; H, 3.8; N, 9.9.

6-Chloro-3-methoxy-4-nitro-5-styrylpyridazine 1-Oxide (**19**).

A solution of **2a** (4.0 g., 0.0182 mole), 50 ml. of methanol and 1.5 ml. of piperidine was stirred as benzaldehyde (3.9 g., 0.037 mole) in 20 ml. of methanol was added dropwise. This solution was stirred at reflux for 6 hours. The resulting yellow mixture was allowed to cool at 0° overnight causing the crude styryl derivative to precipitate. This was collected by filtration, washed successively with water and methanol, and recrystallized from acetone to give 4.2 g. (75%) of **19**, m.p. 187-188°; ir cm^{-1}: 1540 (s) and 1340 (s) (-NO_2); pmr (DMSO-d_6): 4.1 δ (methoxy, singlet), 7.13 δ (α and β styryl, singlet, two protons), 7.4-7.83 δ (phenyl, multiplet).

Anal. Calcd. for $C_{13}H_{10}ClN_3O_4$: C, 50.8; H, 3.3; N, 13.7. Found: C, 50.4; H, 3.3; N, 13.4.

4-Acetamido-3-methoxy-5-methylpyridazine 1-Oxide.

A mixture of **3** (1.0 g., 0.00645 mole) and 10 ml. of acetic anhydride was heated at 80° for 15 minutes and then poured over crushed ice. The resulting solution was neutralized with aqueous sodium carbonate, extracted with chloroform, and the combined dried extracts (magnesium sulfate) placed on a silica gel column (15 g.). The third fastest moving band was eluted with chloroform and collected. Evaporation of the chloroform *in vacuo* provided a white residue which was recrystallized from benzene-chloroform to give 0.32 (25%) of 4-acetamido-3-methoxy-5-methylpyridazine 1-oxide, m.p. 166-167°; pmr (deuteriochloroform): 2.23 δ (C_5-methyl, singlet), 3.94 δ (acetyl-CH_3, singlet), 7.87 δ (C_6-H, singlet), 8.70 δ (-NH, singlet).

Anal. Calcd. for $C_8H_{11}N_3O_3$: C, 48.7; H, 5.6; N, 21.3. Found: C, 48.6; H, 5.6; N, 21.4.

4-(α-Ethoxyethylideneamino)-3-methoxy-5-methylpyridazine 1-Oxide.

A small amount of 4-(α-ethoxyethylideneamino)-3-methoxy-5-methylpyridazine 1-oxide was obtained by employing the same procedure as for the preparation of **4** except that 24 hours of reflux was used, pmr (deuteriochloroform): 1.37 δ (ethyl-CH_3, triplet), 1.8 δ (acetimidate methyl, singlet), 2.1 δ (4-methyl, singlet), 4.0 δ (methoxyl, singlet), 4.32 δ (ethyl-CH_2, quartet), 7.91 δ (C_6-H, singlet).

Acknowledgement.

The authors wish to thank Dr. Leo Vernon, Director of the Research Division, Brigham Young University for research funds which have made this research possible, particularly for a Research Fellowship to Mr. P. Dan Cook. The authors are also indebted to the Department of Chemistry Budget Committee for allocation of funds for chemicals and supplies.

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