# Polycyclic Pyridazines. II [3]. Synthesis of Pyrazolo[4',3':5,6]pyrido[2,3-*d*]pyridazine Derivatives from Dimethyl Pyrazolo[3,4-*b*]pyridazine-5,6-dicarboxylates as the Key Intermediates

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The synthesis of the novel pyrazolo[4',3':5,6]pyrido[2,3-*d*]pyridazine ring system and some of its derivatives has been accomplished such as 4-amino-1-phenyl-5,8-dioxo-, 4-amino-5,8-dioxo-, 1-phenyl-5,8-dioxo-, 5,8-dioxo-, 5,8-dichloro-1-phenyl-, 5-ethoxy-1-phenyl- and 8-ethoxy-1-phenylpyrazolo[4',3':5,6]pyrido[2,3-*d*]pyridazines.

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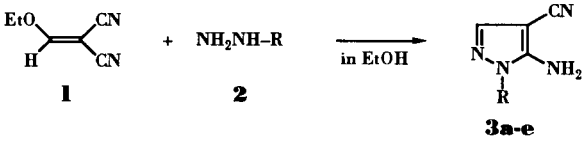
In continuation of our research program for the synthesis of tricyclic pyridazine-containing ring systems [3] we now report the synthesis of derivatives of the novel 1*H*-pyrazolo[4',3':5,6]pyrido[2,3-*d*]pyridazine ring system.

The required starting materials are the previously known 5-amino-4-cyano-1-substituted pyrazoles **3a-e** [4,5] prepared by allowing ethoxymethylenepropanedinitrile (**1**) to react with the appropriately substituted hydrazines **2** (Scheme 1).

Scheme 1




**1** **2** **3a-e**

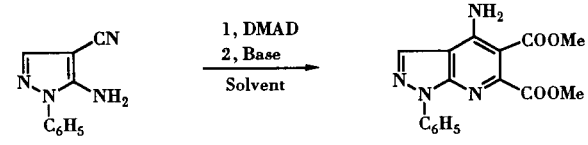
**a**, R = H
**b**, R = Me
**c**, R = $C_6H_5$
**d**, R = $COC_6H_5$
**e**, R = $SO_2$-$C_6H_4$-Me(*p*)

In order to prepare the key intermediates, the reaction of 5-amino-4-cyano-1-phenylpyrazole (**3c**) with dimethyl acetylenedicarboxylate (DMAD) [6-9] in the presence of base was selected as the model procedure to provide dimethyl 4-amino-1-phenylpyrazolo[3,4-*b*]pyridine-5,6-dicarboxylate (**4a**). Our first attempt afforded **4a** in only 17% yield, therefore we report in Table 1 the several sets of conditions which finally allowed the isolation of **4a** in 31% yield (run # 7).

The reaction of 5-amino-1-benzoyl-4-cyanopyrazole (**3d**) with DMAD in the presence of potassium carbonate as the base and DMSO as the solvent gave dimethyl 4-amino-1-benzoylpyrazolo[3,4-*b*]pyridine-5,6-dicarboxylate (**4b**) tautomeric with the 4-imino form **4b'** in 11% yield (Scheme 2).

Table 1

Synthesis of 5-Amino-4-cyano-1-phenylpyrazole [a]

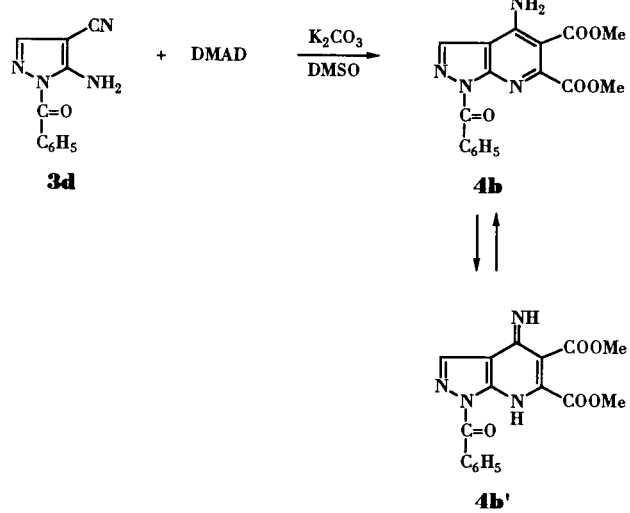



**3c** **4a**

| Run | Base | Solvent | Reaction time, hours | Reaction temperature | Yield [b] |
|---|---|---|---|---|---|
| 1 | $Na_2CO_3$ | DMF | 20 | 0° → rt | <1% |
| 2 | NaOH | DMSO | 20 | 0° → rt | 0% |
| 3 | $K_2CO_3$ | DMSO | 6 | 120° | 17% |
| 4 | $K_2CO_3$ | DMSO | 20 | 120° | 5% |
| 5 | $K_2CO_3$ | DMSO | 20 | rt | 13% |
| 6 | $K_2CO_3$ | DMSO | 40 | rt | 21% |
| 7 | $K_2CO_3$ | DMSO | 60 | rt | 31% |
| 8 | none | DMSO | 15 | 120-130° | 0% [c] |
| 9 | none | DMSO | 24 | rt | 0% |

[a] All reactions were carried out in a system of **3c** (100 mmoles), DMAD (150 mmoles), base (400 mmoles), in DMF or DMSO. [b] Yield after recrystallization from methanol. [c] Unknown product.

Scheme 2

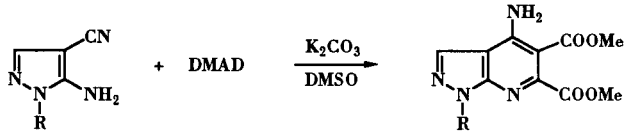



**3d** **4b** **4b'**

Thus to obtain 1-unsubstituted dimethyl pyrazolo[3,4-*b*]-pyridine-5,6-dicarboxylates we selected an electron-withdrawing substituent in the 1-position of the pyrazole ring. Therefore 5-amino-4-cyano-1-(*p*-toluenesulfonyl)pyrazole (**3e**) was allowed to react with DMAD in the presence of potassium carbonate with DMSO as the solvent at room temperature for 24 hours to obtain dimethyl 4-amino-1-(*p*-toluenesulfonyl)pyrazolo[3,4-*b*]pyridine-5,6-dicarboxylate in 38% yield from the basic solution. Upon acidification of the mother liquor dimethyl 4-amino-3-cyano-2-(*p*-toluenesulfonamido)pyridine-5,6-dicarboxylate (**5**) was obtained in 14% yield [10]. When the above sequence of reactions was carried out in a shorter period, the starting material, **3e**, was recovered. However, when **3e** was allowed to react with DMAD in the presence of potassium carbonate with DMSO as the solvent at room temperature for 48 hours, the product was dimethyl 4-(*p*-toluenesulfonylamido)-1-(*p*-toluenesulfonyl)pyrazolo[3,4-*b*]pyridine-5,6-dicarboxylate (**6**) in 51% accompanied by **5** in 16% yield [10]. Furthermore when **3e** was treated as above but at 120° for 6 hours, dimethyl 4-(*p*-toluenesulfonylamido)pyrazolo[3,4-*b*]-pyridine-5,6-dicarboxylate (**7**) was obtained in 23% yield together with **5** in 9% yield. Therefore the products of this cycloaddition reaction are variable depending upon the reaction conditions selected (Scheme 3). In Table 2 are summarized the results of the above reactions indicating the lack of reactivity of **3a** or **3b** (R = H or Me) and the need for an electron-withdrawing moiety at position 1 of

**Table 2**

**Synthesis of 1-Substituted 4-Amino-1*H*-pyrazolo-[3,4-*b*]pyridine-5,6-dicarboxylates [a]**

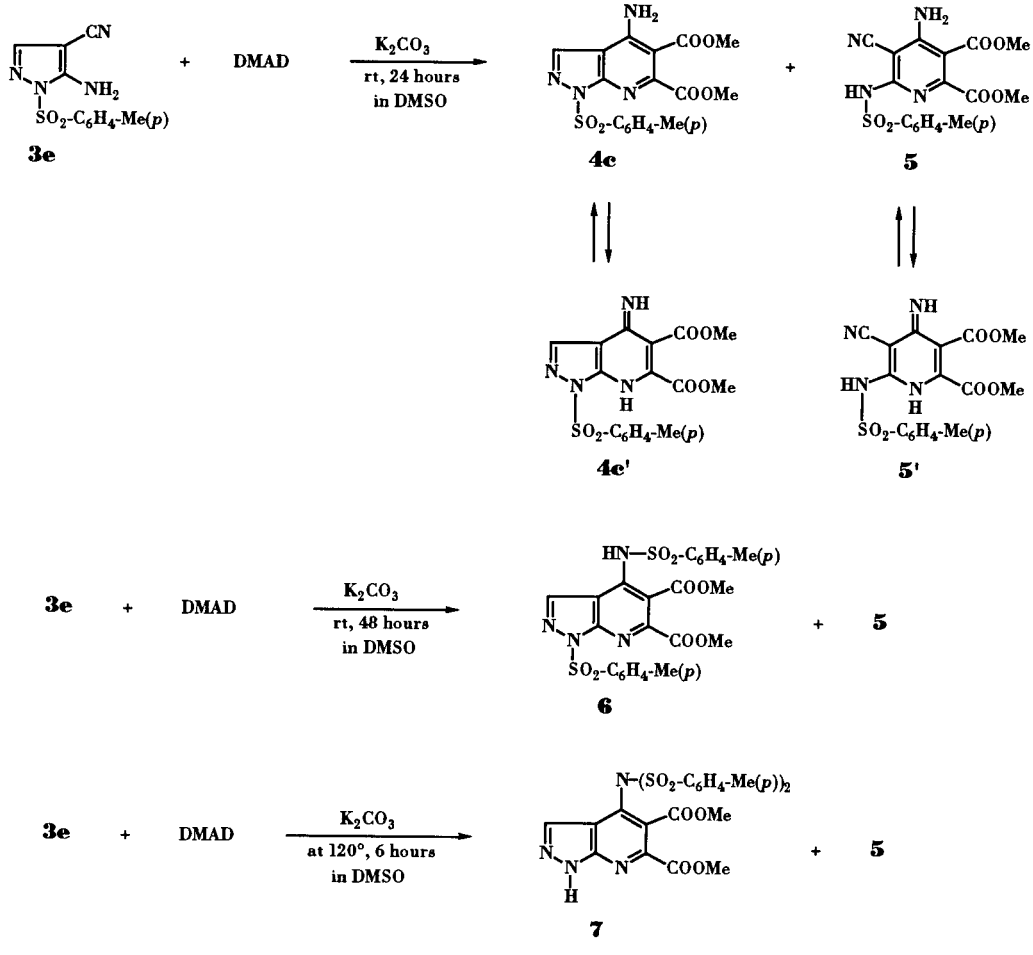



**3a-e** **5a-c**

| Entry | R | Reaction time, hours | Yield [b] |
|---|---|---|---|
| 1 | H | 48 | 0% [c] |
| 2 | Me | 48 | 0% [c] |
| 3 | $C_6H_5$ | 60 | 31% |
| 4 | $COC_6H_5$ | 15 | 11% |
| 5 | $SO_2$-$C_6H_4$-Me(*p*) | 24 | 38% |

[a] Reaction conditions, see Experimental. [b] Yield after recrystallization. [c] Unknown products.

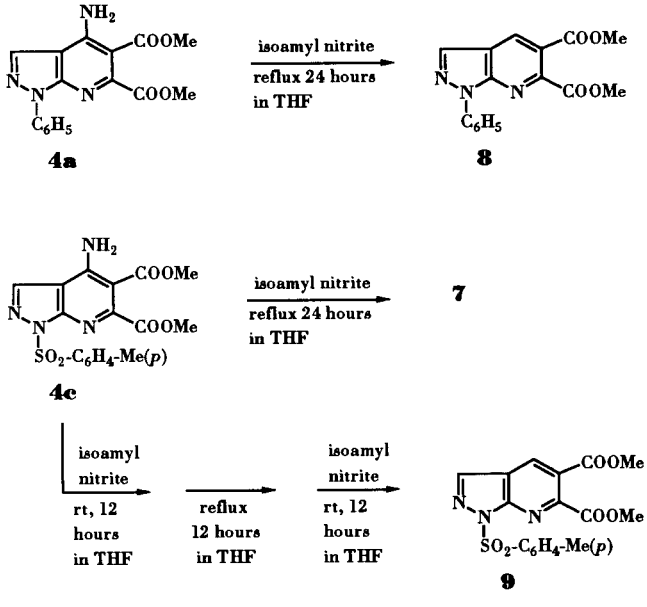
**Scheme 3**



the pyrazole ring for successful production of the key intermediates.

Dimethyl 4-amino-1-phenylpyrazolo[3,4-*b*]pyridine-5,6-dicarboxylate (**4a**) was smoothly deaminated by refluxing with isoamyl nitrite for 24 hours in THF. Dimethyl 1-phenylpyrazolo[3,4-*b*]pyridine-5,6-dicarboxylate (**8**) was obtained in 87% yield. Attempts to deaminate **4c** resulted in rearrangement to **7** when **4c** was allowed to react with isoamyl nitrite in THF under reflux for 24 hours. However, when **4c** and isoamyl nitrite in THF were stirred at room temperature for 12 hours, then refluxed for 12 hours, followed by additional isoamyl nitrite, then refluxed and stirred for an additional 24 hours, dimethyl 1-(*p*-toluenesulfonyl)pyrazolo[3,4-*b*]pyridine-5,6-dicarboxylate (**9**) was obtained in 78% yield (Scheme 4). These reactions illustrate the sensitivity of this deamination reaction to varying reaction conditions.

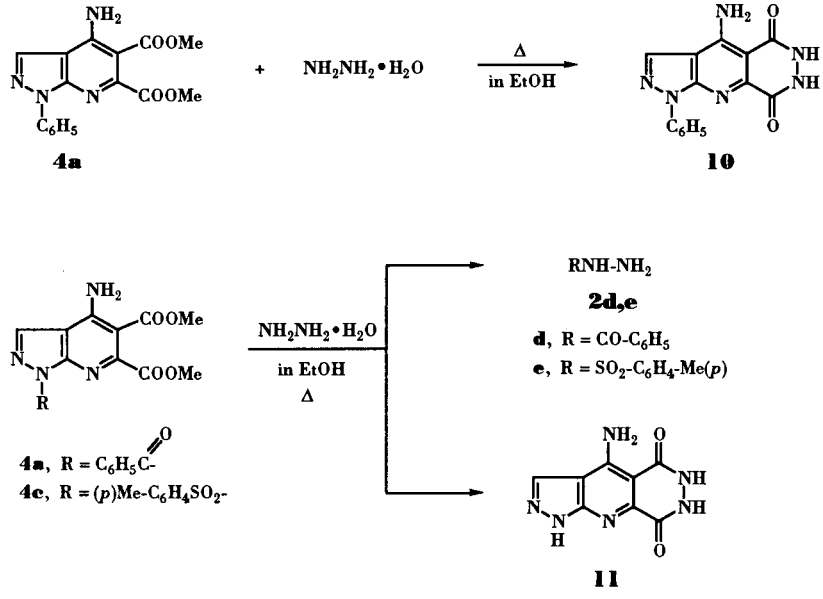
Scheme 4



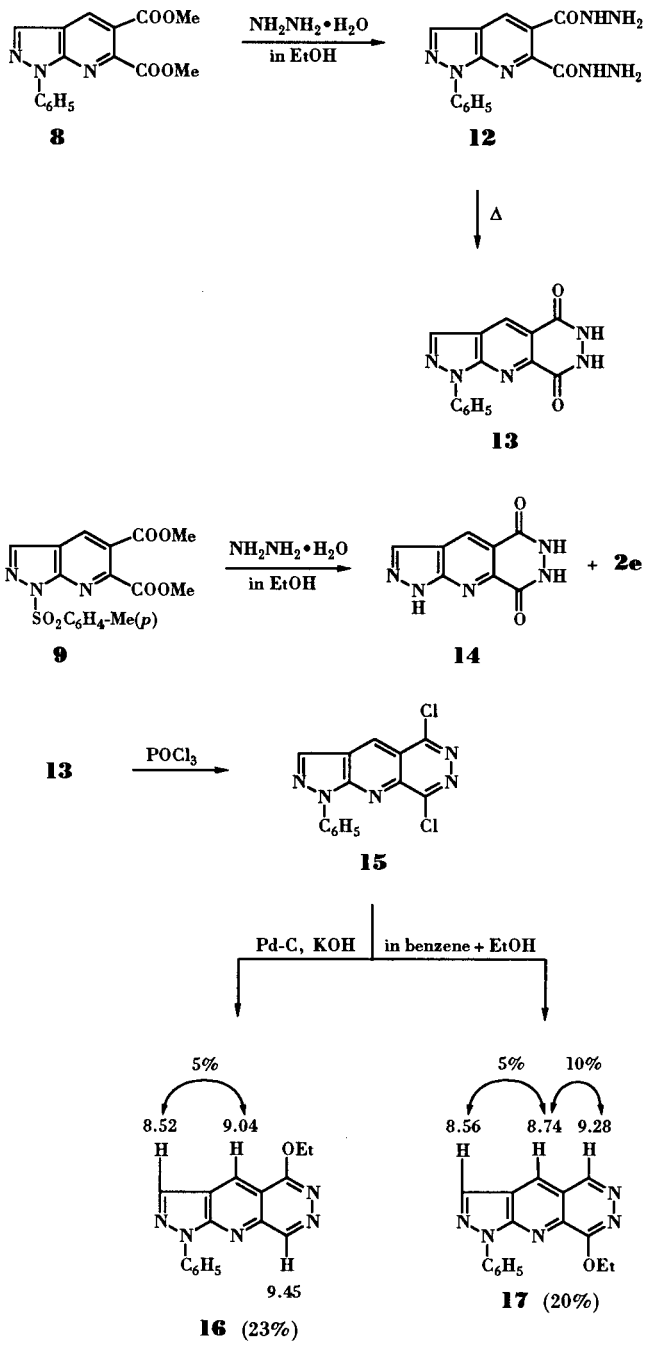

Dimethyl 4-amino-1-phenylpyrazolo[3,4-*b*]pyridine-5,6-dicarboxylate (**8**) was refluxed with hydrazine hydrate in ethanol followed by removal of the ethanol by distillation. The residue was heated at 250-280° for one hour affording 4-amino-1-phenylpyrazolo[4',3':5,6]pyrido[2,3-*d*]pyridazine-5,8(6*H*,7*H*)-dione (**10**) in 94% yield. To obtain 4-amino-1*H*-pyrazolo[4',3':5,6]pyrido[2,3-*d*]pyridazine-5,8(6*H*,7*H*)-dione (**11**) either **4b** or **4e** could serve as the starting substrate. The reaction of **4b** with hydrazine hydrate in ethanol under reflux conditions followed by removal of the ethanol and excess hydrazine by distillation provided a residue which upon heating for 20 minutes at 150-200° gave **11** in 71% yield. Under similar conditions **4c** provided **11** in 76% yield (Scheme 5).

When dimethyl 1-phenylpyrazolo[3,4-*b*]pyridine-5,6-dicarboxylate (**8**) was allowed to reflux with an excess of hydrazine hydrate in ethanol, 1-phenylpyrazolo[3,4-*b*]pyridine-5,6-biscarbohydrazide (**12**) was obtained in 72% yield as an analytically pure product. Upon heating **12** without solvent at 250-300° for one hour, 1-phenylpyrazolo[4',3':5,6]pyrido[2,3-*d*]pyridazine-5,8(6*H*,7*H*)-dione (**13**) was obtained in 90% yield. The reaction of dimethyl 1-(*p*-toluenesulfonyl)pyrazolo[3,4-*b*]pyridine-5,6-dicarboxylate (**9**) with excess hydrazine hydrate in ethanol under reflux conditions followed by removal of the hydrazine and ethanol by

Scheme 5



Scheme 6




distillation afforded a residue which upon heating at 150-200° gave 1*H*-pyrazolo[4′,3′:5,6]pyrido[2,3-*d*]pyridazine-5,8(6*H*,7*H*)-dione (**14**) in 93% yield accompanied by **2e** as a by-product.

The reaction of **13** with excess phosphorus oxychloride and dimethylaniline under reflux afforded 5,8-dichloro-1-phenylpyrazolo[4′,3′:5,6]pyrido[2,3-*d*]pyridazine (**15**) in 62% yield. Several attempts to catalytically dechlorinate **15** into 1-phenylpyrazolo[4′,3′:5,6]pyrido[2,3-*d*]pyridazine were uniformly unsuccessful under a variety of conditions. However reaction of **15** in ethanol-benzene (2:3) in the presence of Pd-C and potassium hydroxide under atmospheric hydrogen pressure for 72 hours afforded a mixture of two monoethoxy compounds. The monoethoxy compounds were readily separated by silica gel chromatography affording 5-ethoxy-1-phenylpyrazolo[4′,3′:5,6]pyrido[2,3-*d*]pyridazine (**16**) in 23% yield and 8-ethoxy-1-phenylpyrazolo[4′,3′:5,6]pyrido[2,3-*d*]pyridazine (**17**) in 20% yield. Compounds **16** and **17** were differentiated by nOe experiments.

## EXPERIMENTAL

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. The ir spectra were recorded on a Beckman FT-1100 spectrometer as potassium bromide pellets and frequencies are expressed in $cm^{-1}$. The $^1H$ nmr spectra were obtained on a JEOL FX-90Q and on a Varian EM-360A spectrometer in the solvent indicated with TMS as the internal standard and chemical shifts are reported in ppm ($\delta$) and J values are in Hz. For compounds **16** and **17** the $^1H$ and $^{13}C$ nmr spectra were acquired on a Bruker AMX 360 MHz nmr spectrometer operating at an observation frequency of 360.13 MHz for $^1H$ and 90.56 for $^{13}C$. The $^1H$ spectra were recorded at 16K data points and zero-filled to 32K data points. All $^1H$ chemical shifts are referenced to TMS which was used as an internal standard. The $^{13}C$ spectra were recorded at 64K data points and zero-filled to 128K data points. All $^{13}C$ chemical shifts were referenced to the center peak of the 1:1:1 multiplet of deuteriochloroform which was assigned a value of 77.00 ppm. The nOe-difference experiments were acquired at 4K data points and the reference spectrum was acquired with the presaturation transmitter set greater than 1500 Hz away from any observed resonances. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ. The high resolution mass spectrum was acquired by the Midwest Center for Mass Spectroscopy at the University of Nebraska-Lincoln, using a Kratos MS-50 mass spectrometer which has Nier-Johnson geometry.

Dimethyl 4-Amino-1-phenylpyrazolo[3,4-*b*]pyridine-5,6-dicarboxylate (**4a**).

To a stirred mixture of 9.2 g (50 mmoles) of **3c**, 13.8 g (100 mmoles) of anhydrous potassium carbonate and 300 ml of dimethyl sulfoxide, a solution of 10.0 g (71 mmoles) of dimethyl acetylenedicarboxylate (DMAD) in 20 ml of dimethyl sulfoxide (DMSO) was added dropwise during 30 minutes with ice-water cooling. Stirring was continued for an additional 60 hours at room temperature. The color of the reaction mixture changed from brown to dark greenish brown. The reaction mixture was poured into 1500 ml of ice-water and stirred for 30 minutes. The dark brown solid that appeared was collected by filtration. After drying in air, the product was suspended in 20 ml of methanol. The white crystalline product that appeared was collected by filtration and recrystallized from methanol to give 3.50 g (31%) of colorless prisms, mp 178-180°; ir: 3473, 3352 ($NH_2$), 1707, 1700 (CO), 1630, 1585 $cm^{-1}$; $^1H$ nmr (deuteriochloroform): $\delta$ 3.88 (s, 3H, OMe), 3.96 (s, 3H, OMe), 6.99 (bs, 1H, NH), 7.26-7.59 (m, 3H, phenyl-H), 8.13-8.23 (m, 2H, phenyl-H), 8.15 (s, 1H, 3-H).

*Anal.* Calcd. for $C_{16}H_{14}N_4O_4$: C, 58.89; H, 4.32; N, 17.17. Found: C, 59.05; H, 4.43; N, 17.08.

Dimethyl 4-Amino-1-benzoylpyrazolo[3,4-*b*]pyridine-5,6-dicarboxylate (**4b**).

To a stirred mixture of 1.06 g (5.0 mmoles) of **3d**, 4.0 g of anhydrous potassium carbonate and 100 ml of DMSO, a solution of 1.0 g (7.1 mmoles) of DMAD in 2 ml of DMSO was added dropwise during 10 minutes with cooling in a water bath. Stirring was continued for an additional 15 hours at room temperature. The color of the reaction mixture changed from brown to dark greenish brown. The reaction mixture was poured into 200 ml of ice-water and stirred for 30 minutes. The grey solid that appeared was collected by filtration. After drying in air, the product was suspended in 5 ml of methanol. The white crystalline product was collected by filtration and recrystallized from methanol to give 0.183 g (0.37 mmole, 11%) of colorless needles, mp 194-196°; ir: 3258 (NH), 1754, 1720, 1702 (CO) $cm^{-1}$; $^1H$ nmr (deuteriochloroform): δ 3.82 (s, 3/2H, OMe), 3.98 (s, 3/2H, OMe), 4.02 (s, 3/2H, OMe), 4.08 (s, 3/2H, OMe), 7.50-7.80 (m, 3H, phenyl-H), 8.05-8.30 (m, 2H, phenyl-H), 8.96 (s, 1H, 3-H).

*Anal.* Calcd. for $C_{17}H_{14}N_4O_5$: C, 57.63; H, 3.98; N, 15.81. Found: C, 57.51; H, 4.01; N, 15.66.

Dimethyl 4-Amino-1-(*p*-toluenesulfonyl)pyrazolo[3,4-*b*]pyridine-5,6-dicarboxylate (**4c**) and Dimethyl 4-Amino-3-cyano-2-(*p*-toluenesulfonylamido)pyridine-5,6-dicarboxylate (**5**).

To a stirred mixture of 5.24 g (20 mmoles) of **3e**, 8.0 g of anhydrous potassium carbonate and 200 ml of DMSO, a solution of 3.5 g (24.6 mmoles) of DMAD in 10 ml of DMSO was added dropwise during 30 minutes with ice-water cooling. Stirring was continued an additional 24 hours at room temperature. The color of the reaction solution turned from brown to dark green. The reaction mixture was poured into 500 ml of ice-water and stirred for 30 minutes. The gray solid that appeared was collected by filtration. After drying in air, the product was suspended in 10 ml of methanol. The white crystalline product was collected by filtration and recrystallized from methanol to give 3.11 g (7.53 mmoles, 38%) of colorless needles of **4c**, mp 220-222° [10].

The filtrate was acidified with 10% hydrochloric acid solution. The resulting precipitate was collected by filtration and recrystallized from methanol to give 1.15 g (2.85 mmoles, 14%) of colorless needles of **5**, mp 243-245° [10].

Dimethyl 1-(*p*-Toluenesulfonyl)-4-(*p*-toluenesulfonylamido)pyrazolo[3,4-*b*]pyridine-5,6-dicarboxylate (**6**) and **5**.

To a stirred mixture of 2.62 g (10 mmoles) of **3e**, 6.0 g of anhydrous potassium carbonate and 100 ml of DMSO, a solution of 2.0 g (14 mmoles) of DMAD in 5 ml of DMSO was added dropwise during 20 minutes with stirring at room temperature. Stirring was continued for an additional 48 hours at room temperature. The reaction mixture was poured into 500 ml of ice-water and stirred for 30 minutes. The yellowish solid that appeared was collected by filtration. The product was recrystallized from methanol to give 1.42 g (2.54 mmoles, 51%) of colorless prisms of **6**, mp 265-270°; ir: 3450 (NH), 1738, 1730 (CO) $cm^{-1}$; $^1H$ nmr (deuteriochloroform): δ 2.32 (s, 6H, 2 x *p*-Me), 3.68 (s, 3H, OMe), 3.87 (s, 3H, OMe), 7.23 (d, J = 8.2 Hz, 2H, phenyl-H), 7.37 (d, J = 8.5 Hz, phenyl-H), 7.67 (d, J = 8.2 Hz, 2H, phenyl-H), 7.92 (d, J = 8.5 Hz, 2H, phenyl-H), 8.62 (s, 1H, 3-H).

*Anal.* Calcd. for $C_{24}H_{22}N_4O_8S_2 \cdot H_2O$: C, 49.99; H, 4.19; N, 9.72; S, 11.22. Found: C, 49.82; H, 4.31; N, 9.65; S, 11.26.

The filtrate was acidified with 10% hydrochloric acid solution. The resulting precipitate was collected by filtration and recrystallized from methanol to give 0.648 g (1.6 mmoles, 16%) of **5** [10].

Dimethyl 4-[*N*,*N*-Bis(*p*-toluenesulfonylamido)]pyrazolo[3,4-*b*]pyridine-5,6-dicarboxylate (**7**) and **5**.

A mixture of 2.62 g (10 mmoles) of **3e**, 6.0 g of anhydrous potassium carbonate, 100 ml of DMSO and 2.0 g (14 mmoles) of DMAD was stirred at 120° for 6 hours. After cooling the reaction mixture was poured into 500 ml of ice-water and acidified with 10% hydrochloric acid. The gray solid that separated was collected by filtration. After drying in air the product was recrystallized from methanol to give 0.365 g (0.90 mmole, 9%) of colorless needles of **5**, mp 243-245 [10].

The mother liquor (about 10 ml) from the above crystallization was allowed to stand for 10 hours. The white needles which appeared were collected by filtration to give 0.642 g (1.13 mmoles, 23%) of colorless needles of **7**. An analytical sample was recrystallized from methanol to give **7** as colorless needles, mp 167-168°; ir: 3245 (NH), 1735, 1702 (CO) $cm^{-1}$; $^1H$ nmr (deuteriochloroform): δ 2.42 (s, 6H, 2 x *p*-Me), 3.87 (s, 3H, OMe), 4.04 (s, 3H, OMe), 7.24-7.52 (m, 4H, phenyl-H), 7.77 (d, J = 8 Hz, 2H, phenyl-H), 8.20 (d, J = 8 Hz, 2H, phenyl-H), 8.84 (s, 1H, 3-H).

*Anal.* Calcd. for $C_{24}H_{22}N_4O_8 \cdot 0.5H_2O$: C, 50.79; H, 4.08; N, 9.87; S, 11.30. Found: C, 50.67; H, 4.19; N, 9.60; S, 11.16.

Dimethyl 1-Phenylpyrazolo[3,4-*b*]pyridine-5,6-dicarboxylate (**8**).

A solution of 3.2 g (10 mmoles) of **4a** and 10 ml of isoamyl nitrite in 100 ml of absolute tetrahydrofuran (THF) was stirred for 5 hours at room temperature. After refluxing for 12 hours, 5 ml of isoamyl nitrite was again added and then the mixture was refluxed for 12 hours. After evaporation of the solvent and excess isoamyl nitrite, the residue was crystallized by the addition of 5 ml of methanol. The crystallized product was collected by filtration to give 2.70 g (8.68 mmoles, 87%). An analytical sample was recrystallized from methanol to give yellow needles, mp 125-127°; ir: 2954 (Me), 1748, 1725 (CO) $cm^{-1}$; $^1H$ nmr (deuteriochloroform): δ 3.95 (s, 3H, OMe), 4.02 (s, 3H, OMe), 7.32-7.62 (m, 3H, phenyl-H), 8.13-8.33 (m, 2H, phenyl-H), 8.30 (s, 1H, 3-H), 8.75 (s, 1H, 4-H).

*Anal.* Calcd. for $C_{16}H_{13}N_3O_4$: C, 61.73; H, 4.21; N, 13.50. Found: C, 61.55; H, 4.46; N, 13.42.

Dimethyl 1-(*p*-Toluenesulfonyl)pyrazolo[3,4-*b*]pyridine-5,6-dicarboxylate (**9**).

A solution of 4.04 g (10 mmoles) of **4c** and 15 ml of isoamyl nitrite in 100 ml of absolute THF was stirred for 12 hours at room temperature. After refluxing 12 hours, 10 ml of isoamyl nitrite was again added to the above reaction mixture. Refluxing and stirring was continued for 24 hours. After removal of the solvent by evaporation, the residue was crystallized by the addition of 5 ml of methanol. The crystalline product was collected by filtration to give 3.02 g (7.76 mmoles, 78%) of white crystals. An analytical sample was recrystallized from methanol to give colorless needles, mp 148-150°; ir: 1743, 1725 (CO) $cm^{-1}$; $^1H$ nmr (deuteriochloroform): δ 2.40 (s, 3H, *p*-Me), 3.98 (s, 3H, OMe), 4.09 (s, 3H, OMe), 7.40 (d, J = 8 Hz, 2H, phenyl-H), 8.19 (d, J = 8 Hz, 2H, phenyl-H), 8.41 (s, 1H, 4-H), 8.78 (s, 1H, 3-H).

*Anal.* Calcd. for $C_{17}H_{15}N_3O_6S$: C, 52.44; H, 3.88; N, 10.79; S, 8.23. Found: C, 52.49; H, 4.00; N, 10.82; S, 8.37.

4-Amino-1-phenylpyrazolo[4′,3′:5,6]pyrido[2,3-*d*]pyridazine-5,8-(6*H*,7*H*)-dione (**10**).

A solution of 0.326 g (1 mmole) of **4a** and 1.0 ml of hydrazine hydrate in 30 ml of ethanol was refluxed for 2 hours. After evaporation of the solvent and excess hydrazine hydrate, the residue

was heated at 250-280° for 1 hour. After cooling, the product was washed with methanol to give 0.275 g (0.935 mmoles, 94%) of a yellow powder. An analytical sample was recrystallized from a large amount of a mixture of methanol and benzene (1:1) to give yellow crystals, mp >300°; ir: 3400-2600 (br, NH or OH), 1676 (CO) $cm^{-1}$.

*Anal.* Calcd. for $C_{14}H_{10}N_6O$: C, 57.14; H, 3.43; N, 28.56. Found: C, 57.21; H, 3.39; N, 28.34.

4-Aminopyrazolo[4',3':5,6]pyrido[2,3-*d*]pyridazine-5,8(6*H*,7*H*)-dione (**11**).

Method A.

A solution of 354 mg (1 mmole) of **4b**, 0.5 ml of hydrazine hydrate in 50 ml of ethanol was refluxed for 2 hours. After evaporation of the solvent and the excess hydrazine hydrate, the residue was heated at 150-200° for 20 minutes. After cooling, the product was washed with 20 ml of ethanol. After removal of the ethanol, the residue was recrystallized from ethanol to give colorless leaflets, mp 111-115°, which was benzoic hydrazide (**2d**). The above yellow product was recrystallized from a large amount of benzene and methanol (1:1) to give 0.168 g (0.712 mmole, 71%) of yellow powder, **11**, mp >300°.

Method B.

Compound **11** (0.165 g, 0.756 mmole) was also prepared in 76% yield from **4c** (0.404 g, 1.0 mmole) and hydrazine hydrate (0.5 ml) in a similar manner to that described in the above reaction. In this case, *p*-toluenesulfonyl hydrazide (**2e**) was also obtained from the ethanol solution used for washing the reaction mixture. This compound had mp >300°; ir: 3300-2500 (br, NH or OH), 1670, 1635 (CO) $cm^{-1}$.

*Anal.* Calcd. for $C_8H_8N_6O_3$: C, 40.68; H, 3.41; N, 35.58. Found: C, 40.27; H, 3.66; N, 35.39.

1-Phenylpyrazolo[3,4-*b*]pyridine-5,6-biscarbohydrazide (**12**).

A solution of 1.55 g (50 mmoles) of **7** and 1.5 ml of hydrazine hydrate in 100 ml of ethanol was refluxed for 1 hour. After removal of the solvent and excess hydrazine hydrate, 20 ml of ethanol was added to the above residue. The product was collected by filtration to give 1.18 g (3.59 mmoles, 72%) of yellow crystals. This material was used in the next step without purification. An analytical sample was recrystallized from methanol to give golden yellow leaflets, mp 220-240° (color change); ir: 3312, 3188, 3180-2600 (br, NH or OH), 1635, 1630 (CO), 1577, 1491, 1476, 1406, 1358, 829, 681 $cm^{-1}$.

*Anal.* Calcd. for $C_{14}H_{13}N_7O_2$: C, 54.02; H, 4.21; N, 31.49. Found: C, 54.07; H, 4.38; N, 31.51.

1-Phenylpyrazolo[4',3':5,6]pyrido[2,3-*d*]pyridazine-5,8(6*H*,7*H*)-dione (**13**).

Compound **12** (1.0 g, 3.22 mmoles) was heated at 250-300° for 1 hour. After cooling, the product was washed with methanol to give 0.81 g (2.90 mmoles, 90%) of a pale yellow powder. An analytical sample was recrystallized from a large amount of benzene and methanol (1:1) to give a pale yellow powder, mp >300°; ir: 3200-2500 (br, NH or OH), 1628, 1622 (CO), 1617, 1610, 1589, 1558, 1499, 1412, 1278, 818, 797 $cm^{-1}$.

*Anal.* Calcd. for $C_{14}H_9N_5O_2$: C, 60.21; H, 3.25; N, 25.08. Found: C, 60.19; H, 3.42; N, 25.12.

1*H*-Pyrazolo[4',3':5,6]pyrido[2,3-*d*]pyridazine-5,8(6*H*,7*H*)-dione (**14**).

This compound (94.1 mg, 93%) was synthesized from **9** (195 mg, 0.5 mmole) in a manner similar to that described for the preparation of **11**. An analytical sample was recrystallized from a mixture of benzene and methanol (1:1) to give a yellow powder, mp >300°; ir: 3454 (br, OH), 3200-2600 (br, NH or OH), 1697 (CO) $cm^{-1}$.

*Anal.* Calcd. for $C_8H_5N_5O_2$: C, 47.30; H, 2.48; N, 34.47. Found: C, 47.45; H, 2.56; N, 34.44.

5,8-Dichloro-1-phenylpyrazolo[4',3':5,6]pyridazine (**15**).

A mixture of 0.558 g (2.0 mmoles) of **13**, 13 ml of phosphorus oxychloride and 0.6 ml of *N,N*-dimethylaniline was refluxed for 2 hours. After cooling, the precipitate that appeared was collected by filtration and then washed with 10 ml of hexane to give 0.270 g (1.23 mmoles, 62%) of yellow crystals. An analytical sample was recrystallized from benzene to give yellow needles, mp 292-294°; ir: 1597, 1499, 1435, 1412, 751, 679 $cm^{-1}$; $^1H$ nmr (deuteriochloroform + trifluoroacetic acid, 10:1): $\delta$ 7.67 (s, 5H, phenyl-H), 9.05 (s, 1H, 4-H), 9.58 (s, 1H, 3-H).

*Anal.* Calcd. for $C_{14}H_7Cl_2N_5$: C, 53.19; H, 2.23; N, 22.15. Found: C, 53.14; H, 2.15; N, 22.04.

5- and 8-Ethoxy-1-phenylpyrazolo[4',3':5,6]pyrido[2,3-*d*]pyridazines **16** and **17**.

A mixture of 0.316 g (1.0 mmole) of **15**, 0.30 g of 10% Pd-C, 180 mg of potassium hydroxide, 200 ml of ethanol and 300 ml of benzene was stirred for 72 hours under hydrogen at room temperature. The catalyst was filtered off and the solvent was evaporated *in vacuo*. The residue was dissolved in 300 ml of hot benzene. Evaporation of the benzene afforded a mixture of the two isomers, **16** and **17** which were separated by silica gel chromatography. After elution with 200 ml of benzene, subsequent elution using a mixture of benzene and ethyl acetate (10:1) gave 0.0571 g (0.20 mmole, 20%) of yellow prisms, mp 226°. An analytical sample was recrystallized from benzene to give yellow prisms of **17**, mp 226-228°; ir: 1594, 1501, 1389, 1332 $cm^{-1}$; $^1H$ nmr (360 MHz, deuteriochloroform): $\delta$ 1.66 (t, J = 7.04 Hz, 3H, $OCH_2CH_3$), 4.85 (q, J = 7.05 Hz, 2H, $OCH_2CH_3$), 7.39 (t, J = 7.62 Hz, 1H, 4'-H), 7.60 (t, J = 7.92 Hz, 2H, 3' and 5'-H), 8.46 (d, J = 8.07 Hz, 2H, 2' and 6'-H), 8.56 (s, 1H, 8-H), 8.74 (s, 1H, 9-H), 9.28 (s, 1H, 1-H); $^{13}C$ nmr (360 MHz, deuteriochloroform): $\delta$ 14.42, 64.10, 119.72, 120.58, 120.84, 126.57, 129.26, 129.66, 135.05, 135.29, 139.03, 147.79, 150.78, 160.64.

*Anal.* Calcd. for $C_{16}H_{13}N_5O$: C, 65.97; H, 4.50; N, 24.04. Found: C, 65.97; H, 4.70; N, 24.18.

Subsequent elution using a mixture of benzene and ethyl acetate (10:4) afforded yellow needles, a substance which was recrystallized from a mixture of benzene and hexane to give 0.0657 g (0.23 mmole, 23%) of yellow needles of **16**, mp 223-225°; ir: 3037, 2980, 1599, 1502, 1437, 1396, 1335, 1126, 815, 753 $cm^{-1}$; $^1H$ nmr (360 MHz, deuteriochloroform): $\delta$ 1.59 (t, J = 7.1 Hz, 3H, $OCH_2CH_3$), 4.79 (q, J = 7.1 Hz, 2H, $OCH_2CH_3$), 7.38 (t, J = 7.4 Hz, 1H, 4'-H), 7.58 (t, J = 7.9 Hz, 2H, 3' and 5'-H), 7.84 (d, J = 7.8 Hz, 2H, 2' and 6'-H), 8.52 (s, 1H, 8-H), 9.04 (s, 1H, 9-H), 9.45 (s, 1H, 4-H); $^{13}C$ nmr (360 MHz, deuteriochloroform): $\delta$ 14.51, 64.10, 112.00, 120.50, 120.98, 126.58, 127.43, 129.17, 135.32, 138.87, 143.43, 149.88, 150.91, 160.47.

*Anal.* Calcd. for $C_{16}H_{13}N_5O$: C, 65.97; H, 4.50; N, 24.04. Found: C, 65.95; H, 4.57; N, 24.00.

Compounds **16** and **17** were differentiated using nOe-difference experiments. For **16** irradiation of the singlet at $\delta$ = 9.04

transferred a 5% nOe to the singlet at $\delta$ = 8.52 and none to the singlet at $\delta$ = 9.45 verifying the structure of **16**. For compound **17**, irradiation of the singlet at $\delta$ = 8.74 transferred 10% nOe to the singlet at $\delta$ = 9.28 and 5% nOe to the singlet at $\delta$ = 8.57 verifying the structure of **17**.

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