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A facile route for the synthesis of substituted pyrrolo[2,3-*d*]pyrimidine-2,4-diones from substituted 2-amino-3-cyano-4-methylpyrroles is reported.

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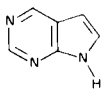
During the last decade, there has been considerable biological interest in the pyrrolo[2,3-*d*]pyrimidine (**1**) nucleus or 7-deazapurine. The first systematic investigations of this nucleus as a potential purine (**2**) antagonist were reported in 1959 and 1960 (2,3). Since that time, derivatives of this nucleus have been reported to have antibiotic and antitumor activity (4-6), central nervous system depressant properties (7), diuretic, cardiac, and



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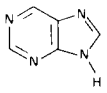

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central nervous system stimulating properties (8).

In 1911, Johnson (9) reported the first synthesis of **1**. Since that time, numerous methods of synthesis have been reported. These can be broadly divided into two general categories: one beginning with a pyrrole nucleus and the other method, which is more extensively reported, beginning with a properly substituted pyrimidine nucleus.

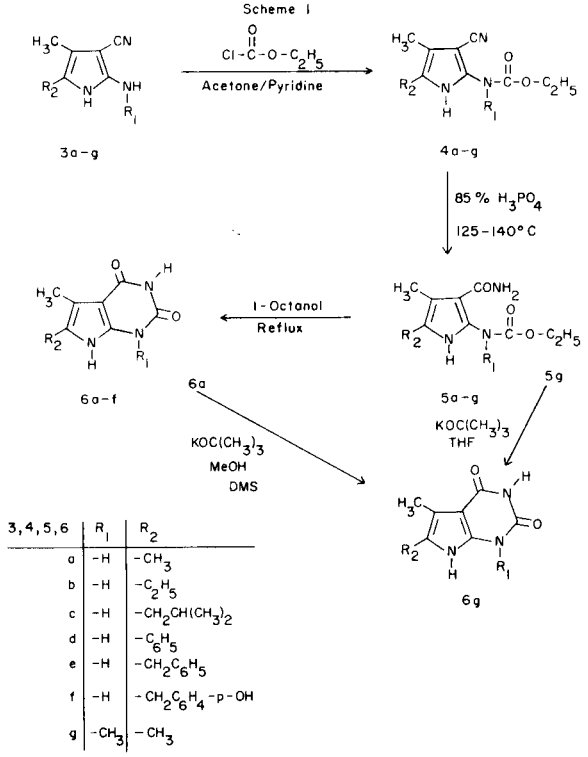
In the synthesis of pyrrolo[2,3-*d*]pyrimidines from pyrroles or analogs thereof, Morita, *et al.* (10), Richter and Ulrich (11), and Granik and Glushkov (12) have reported the synthesis of partially hydrogenated derivatives of **1** from 2-pyrrolidone, 1-methyl-2-pyrrolidone, and 2-ethoxy-3-carbethoxy-4,5-dihydropyrrole, respectively. Several methods of synthesis of substituted derivatives of **1** from 2-aminopyrroles have been described (13-17).

In the present work, an additional method of synthesis of substituted derivatives of **1** from substituted 2-amino-3-cyano-4-methylpyrroles (**3a-f**) (18-20) is reported. Acylation of **3a-f** with ethyl chloroformate, in anhydrous acetone using an equivalent of pyridine, gave the corresponding substituted 2-carbethoxyamido-3-cyano-4-methylpyrroles (**4a-f**) in excellent yields (Scheme I). Hydrolysis of the nitrile in compounds **4a-f** with 85% phosphoric acid gave the corresponding 2-carbethoxyamido-3-carbamyl-4-methylpyrroles (**5a-f**). The pyrrolo[2,3-*d*]pyrimidine-2,4-diones (**6a-f**) were obtained by thermal cyclization of **5a-f** in refluxing 1-octanol. Comparable ring closures have been reported by Cook and Smith (21), Shaw (22), and Hayao, *et al.*, (23).

In order to determine the site of methylation of **6a**, 2-methylamino-3-cyano-4,5-dimethylpyrrole (**3g**) (24) was acylated with ethyl chloroformate to yield 2-(*N*-carbethoxy-*N*-methyl)amino-3-cyano-4,5-dimethylpyrrole (**4g**). Hydrolysis of **4g** in 85% phosphoric acid gave 2-(*N*-carbethoxy-*N*-methyl)amino-3-carbamyl-4,5-dimethylpyrrole (5g). Cyclization of **5g** to yield 1,5,6-trimethylpyrrole[2,3-*d*]pyrimidine-2,4-dione (**6g**) was acccomplished with potassium *t*-butoxide in anhydrous tetrahydrofuran. An attempt to obtain **6g** from **5g** by the thermal process described for synthesis of **6a-f** was unsuccessful. Compound **6g** was obtained from 5,6-dimethylpyrrolo[2,3-*d*]pyrimidine-2,4-dione (**6a**) by treating the latter with potassium *t*-butoxide in absolute methanol followed by alkylation with dimethyl sulfate. Under comparable conditions, xanthine is methylated at the N_3 position which corresponds to the N_1 position of **6a**. Excess base and alkylating agent results in further alkylation of xanthine at the N_7 and N_1 positions (25).

Compound **6g** obtained by the two different methods exhibited identical nmr and infrared spectra. Within

Scheme I



3,4,5,6	R_1	R_2
a	-H	$-CH_3$
b	-H	$-C_2H_5$
c	-H	$-CH_2CH(CH_3)_2$
d	-H	$-C_6H_5$
e	-H	$-CH_2C_6H_5$
f	-H	$-CH_2C_6H_4$-p-OH
g	$-CH_3$	$-CH_3$

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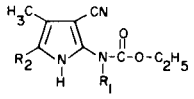
Table I

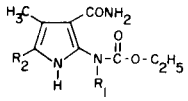
Substituted 2-Carbethoxyamido-3-cyano-4-methylpyrroles



Compound	R_1	R_2	Empirical Formula	Calcd., % C	H	N	Found., % C	H	N
4a	-H	$-CH_3$	$C_{10}H_{13}N_3O_2$	57.96	6.32	20.28	57.90	6.36	20.23
4b	-H	$-C_2H_5$	$C_{11}H_{15}N_3O_2$	59.71	6.83	18.99	59.68	6.83	18.97
4c	-H	$-CH_2CH(CH_3)_2$	$C_{13}H_{19}N_3O_2$	62.63	7.68	16.86	62.58	7.69	16.84
4d	-H	$-C_6H_5$	$C_{15}H_{15}N_3O_2$	66.90	5.61	15.60	66.77	5.67	15.57
4e	-H	$-CH_2C_6H_5$	$C_{16}H_{17}N_3O_2$	67.83	6.05	14.83	67.78	6.06	14.83
4f	-H	$-CH_2-C_6H_4-p-OH$	$C_{16}H_{17}N_3O_3$	64.20	5.72	14.04	64.38	5.76	13.95
4g	$-CH_3$	$-CH_3$	$C_{11}H_{15}N_3O_2$	59.71	6.83	18.99	59.77	6.86	18.91

Table II

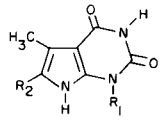
Substituted 2-Carbethoxyamido-3-carbamyl-4-methylpyrroles



Compound	R_1	R_2	Empirical Formula	Calcd., % C	H	N	Found., % C	H	N
5a	-H	$-CH_3$	$C_{10}H_{15}N_3O_3$	53.32	6.71	18.66	53.41	6.75	18.67
5b	-H	$-C_2H_5$	$C_{11}H_{17}N_3O_3$	55.22	7.16	17.56	55.09	7.19	17.52
5c	-H	$-CH_2CH(CH_3)_2$	$C_{13}H_{21}N_3O_3$	58.41	7.92	15.72	58.38	7.94	15.70
5d	-H	$-C_6H_5$	$C_{15}H_{17}N_3O_3$	62.71	5.96	14.62	62.66	5.97	14.63
5e	-H	$-CH_2C_6H_5$	$C_{16}H_{19}N_3O_3$	63.77	6.36	13.94	63.69	6.37	13.94
5f	-H	$-CH_2C_6H_4-p-OH$	$C_{16}H_{19}N_3O_4 \cdot 0.25H_2O$	59.71	6.11	13.06	59.79	6.11	13.06
5g	$-CH_3$	$-CH_3$	$C_{11}H_{17}N_3O_3$	55.22	7.16	17.56	55.11	7.22	17.51

Table III

Substituted 5-Methylpyrrolo[2,3-*d*]pyrimidine-2,4-diones



Compound	R_1	R_2	Empirical Formula	Calcd., % C	H	N	Found., % C	H	N
6a	-H	$-CH_3$	$C_8H_9N_3O_2$	53.63	5.06	23.45	53.86	5.15	23.19
6b	-H	$-C_2H_5$	$C_9H_{11}N_3O_2$	55.95	5.74	21.75	55.97	5.79	21.76
6c	-H	$-CH_2CH(CH_3)_2$	$C_{11}H_{15}N_3O_2$	59.71	6.83	18.99	59.66	6.84	18.96
6d	-H	$-C_6H_5$	$C_{13}H_{11}N_3O_2$	64.72	4.60	17.42	64.79	4.63	17.37
6e	-H	$-CH_2C_6H_5$	$C_{14}H_{13}N_3O_2$	65.87	5.13	16.46	65.74	5.19	16.36
6f	-H	$-CH_2C_6H_4-p-OH$	$C_{14}H_{13}N_3O_3 \cdot 0.4H_2O$	60.38	4.99	15.09	60.36	4.86	15.12
6g (a)	$-CH_3$	$-CH_3$	$C_9H_{11}N_3O_2 \cdot 0.5CH_3OH$	54.53	6.26	20.08	54.32	6.07	20.32
6g (b)	$-CH_3$	$-CH_3$	$C_9H_{11}N_3O_2 \cdot 0.4CH_3OH$	54.80	6.14	20.40	54.79	5.84	20.19

(a) Obtained from **5g**. (b) Obtained from **6a**.

experimental error, the R_f values for thin layer chromatography were the same. The strong affinity of **6g** to form a partial solvate with methanol is exemplified by the results of elemental analyses (Table III) and further supported by methanol absorption in the nmr spectrum.

The structural assignments were made on the basis of elemental analysis (Tables I-III), infrared spectra, nmr spectra, and thin-layer chromatography. This data is presented in the Experimental.

EXPERIMENTAL

Melting points were determined using a Thomas-Hoover capillary melting point apparatus or an Electrothermal capillary melting point apparatus, and are uncorrected. Infrared spectra were determined on a Beckman AccuLab 4 Grating Spectrophotometer using the potassium bromide technique. Nuclear magnetic resonance spectra were determined on a Hitachi Perkin-Elmer R24 High Resolution Spectrophotometer using tetramethylsilane as the internal reference. All thin layer chromatograms were performed on Eastman Chromatogram sheets, type 6060 (silica gel.). Elemental analyses were performed by Atlantic microlab, Inc., Atlanta, Georgia.

2-Carbethoxyamido-3-cyano-4,5-dimethylpyrrole (**4a**).

A solution of 2-amino-3-cyano-4,5-dimethylpyrrole (27.0 g., 0.2 mole) (**3a**) (18) in 200 ml. of acetone and pyridine (17.0 g., 0.22 mole) was stirred in an ice bath during the addition of ethyl chloroformate (24.0 g., 0.22 mole). The mixture was stirred at room temperature for 30 minutes and then poured over 500 g. crushed ice. After the ice had melted, the product was collected by filtration, resuspended in 300 ml. water, filtered again, and air dried. The crude product (35.4 g., 85.4%) was recrystallized from methanol-water (2:1) to yield light brown crystals (homogeneous on tlc-ethyl acetate, R_f = 0.62), m.p. 155-156°; ir (potassium bromide): 3400, 3250, 2910, 2220, 1720, 1615, 1460, 1240, 760 cm^{-1}; nmr (DMSO-*d*): δ 1.21 (t, 3H, $-OCH_2CH_3$), 1.98 (s, 3H, $-CH_3$ at C_4), 2.07 (s, 3H, $-CH_3$ at C_5), 4.1 (q, 2H, $-OCH_2CH_3$), 9.5 (broad s, 1H, -NHCO-), 11.05 (broad s, 1H, $-N_1H$).

2-Carbethoxyamido-3-cyano-4-methyl-5-ethylpyrrole (**4b**).

A solution of 2-amino-3-cyano-4-methyl-5-ethylpyrrole (29.8 g., 0.2 mole) (**3b**) (19) in 200 ml. of acetone and pyridine (17.0 g., 0.22 mole) was reacted with ethyl chloroformate (24.0 g., 0.22 mole) according to the procedure for **4a**. The crude product (38.1 g., 86.1%) was recrystallized from methanol-water (2:1) to yield light yellow crystals (homogeneous on tlc-ethyl acetate, R_f = 0.54), m.p. 114-115°; ir (potassium bromide): 3380, 3260, 2980, 2200, 1720, 1620, 1600, 1240, 770 cm^{-1}; nmr (DMSO-d_6): δ 1.05 (t, 3H, $-CH_2CH_3$), 1.22 (t, 3H, $-OCH_2CH_3$), 1.95 (s, 3H, $-CH_3$ at C_4), 2.42 (q, 2H, $-CH_2CH_3$), 4.11 (q, 2H, $-OCH_2CH_3$), 9.46 (broad s, 1H, -NHCO-), 11.03 (broad s, 1H, $-N_1H$).

2-Carbethoxyamido-3-cyano-4-methyl-5-isobutylpyrrole (**4c**).

A solution of 2-amino-3-cyano-4-methyl-5-isobutylpyrrole (35.5 g., 0.2 mole) (**3c**) (20) in 200 ml. of acetone and pyridine (17.0 g., 0.22 mole) was reacted with ethyl chloroformate (24.0 g., 0.22 mole) according to the procedure for **4a**. The crude product (45.0 g., 90.3%) was recrystallized from methanol-water (2:1) to yield a tan powder (homogeneous on tlc-ethyl acetate, R_f = 0.61), m.p. 85-86°; ir (potassium bromide): 3380, 3240, 3160, 2940, 2200, 1690, 1620, 1590, 1460, 1250, 600 cm^{-1}; nmr (DMSO-d_6): δ 0.82 (d, 6 H, $-CH_2CH(CH_3)_2$), 0.8-1.2 (m, 1H, $-CH_2CH(CH_3)_2$), 1.20 (t, 3H, $-OCH_2CH_3$), 1.92 (s, 3H, $-CH_3$ at C_4), 2.27 (d, 2H, $-CH_2CH_3(_2)$, 4.07 (q, 2H, $-OCH_2CH_3$), 9.38 (broad s, 1H, -NHCO-), 11.03 (broad s, 1H, $-N_1H$).

2-Carbethoxyamido-3-cyano-4-methyl-5-phenylpyrrole (**4d**).

A mixture of 2-amino-3-cyano-4-methyl-5-phenylpyrrole (39.4 g., 0.2 mole) (**3d**) (20) in 200 ml. of acetone and pyridine (17.0 g., 0.22 mole) was reacted with ethyl chloroformate (24.0 g., 0.22 mole) according to the procedure for **4a**. The crude product (52.1 g., 96.7%) was recrystallized from methanol to yield an off-white powder (homogeneous on tlc-ethyl acetate, R_f = 0.58), m.p. 165-166°; ir (potassium bromide): 3370, 3240, 2210, 1710, 1620, 1600, 1240, 760, 690 cm^{-1}; nmr (DMSO-d_6): δ 1.25 (t, 3H, $-OCH_2CH_3$), 2.24 (s, 3H, $-CH_3$ at C_4), 4.18 (q, 2H, $-OCH_2CH_3$), 7.4 (s, 5H, aromatic H's of phenyl), 9.75 (broad s, 1H, - NHCO-), 11.55 (broad s, 1H, $-N_1H$).

2-Carbethoxyamido-3-cyano-4-methyl-5-benzylpyrrole (**4e**).

A solution of 2-amino-3-cyano-4-methyl-5-benzylpyrrole (42.3 g., 0.2 mole) (**3e**) (20) in 200 ml. of acetone and pyridine (17.0 g., 0.22 mole) was reacted with ethyl chloroformate (24.0 g., 0.22 mole) according to the procedure for **4a**. The crude product (54.9 g., 96.9%) was recrystallized from methanol-water (2:1) to yield beige powdery crystals (homogeneous on tlc-ethyl acetate, R_f = 0.54), m.p. 133-134°; ir (potassium bromide): 3570, 3480, 3310, 2190, 1710, 1625, 1600, 1250, 1210, 760, 700 cm^{-1}; nmr (DMSO-d_6): δ 1.2 (t, 3H, $-OCH_2CH_3$), 1.97 (s, 3H, $-CH_3$ at C_4), 3.79 (s, 2 H, $-CH_2-C_6H_5$), 4.1 (q, 2H, - OCH_2CH_3), 7.17 (s, 5H, aromatic H's of benzyl), 9.52 (broad s, 1H, -NHCO-), 11.24 (broad s, 1H, $-N_1H$).

2-Carbethoxyamido-3-cyano-4-methyl-5-*p*-hydroxybenzylpyrrole (**4f**).

A solution of 2-amino-3-cyano-4-methyl-5-*p*-hydroxybenzylpyrrole (42.2 g., 0.18 mole) (**3f**) (20) in 200 ml. of acetone and pyridine (17.0 g., 0.22 mole) was reacted with ethyl chloroformate (24.0 g., 0.22 mole) according to the procedure for **4a**. The crude product (55.7 g., 100%) was recrystallized from methanol-water (2:1) to yield a tan powder (homogeneous on tlc-ethyl acetate, R_f = 0.51), m.p. 150-151°; ir (potassium bromide): 3570, 3480, 3320, 2190, 1710, 1625, 1250, 1210, 810, 760 cm^{-1}; nmr (DMSO-d_6): δ 1.2 (t, 3 H, $-OCH_2CH_3$), 1.98 (s, 3 H, $-CH_3$ at C_4), 3.58 (s, 2H, $-CH_2-C_6H_5$), 4.06 (q, 2H, $-OCH_2CH_3$), 6.78 (m, 4H, aromatic H's of *p*-hydroxybenzyl), 9.09 (s, 1H, phenolic -OH), 9.45 (broad s, 1H, -NHCO-), 11.13 (broad s, 1H, $-N_1H$).

2-(*N*-Carbethoxy-*N*-methyl)amino-3-cyano-4,5-dimethylpyrrole (**4g**).

A solution of 2-methylamino-3-cyano-4,5-dimethylpyrrole (12.5 g, 0.0838 mole) (**3g**) (24) in 75 ml. of acetone and pyridine (7.28 g., 0.092 mole) was stirred during the addition of ethyl chloroformate (10.0 g., 0.092 mole). The mixture was stirred together for 15 minutes, then refluxed for 30 minutes. The solvent was reduced to half volume *in vacuo*. The residue solution was poured over 300 g. crushed ice. After much stirring, a light tan precipitate was obtained. The precipitate was collected, washed with distilled water, and air dried. A 3.0 g. sample of the crude product (17.2 g., 92.8%) was recrystallized from ethanol-water (2:1) to yield 2.5 g. of an off-white powder (homogeneous on tlc-ethyl acetate, R_f = 0.55), m.p. 104-104.5°; ir (potassium bromide): 3300, 3000, 2830, 2220, 1800, 1730, 1620, 1260 cm^{-1}; nmr (DMSO-d_6): δ 1.19 (t, 3H, J = 4.8 Hz, $-OCH_2CH_3$), 1.97 (s, 3H, $-CH_3$ at C_4), 2.06 (s, 3H, $-CH_3$ at C_5), 3.15 (s, 3H, N-CH_3), 4.11 (q, 2H, J = 4.8 Hz, $-OCH_2CH_3$), 11.4 (broad s, 1H, N_1H).

2-Carbethoxyamido-3-carbamyl-4,5-dimethylpyrrole (**5a**).

A suspension of 2-carbethoxyamido-3-cyano-4,5-dimethylpyrrole (15.0 g., 0.72 mole) (**4a**) in 200 ml. of 85% phosphoric acid was submerged in a preheated oil bath. The mixture was heated until a solution was achieved, about 6 minutes at 128 to 134°. The reaction vessel was cooled under running water, and its contents were poured over 500 g. crushed ice. After the ice had melted, the product was collected by filtration, washed with distilled water, and air dried. The crude product (15.6 g., 96.2%) was boiled in 100 ml. absolute ethanol, to remove any unreacted starting material, to yield pink, powdery crystals (homogeneous on tlc-ethyl acetate, R = 0.46), m.p. > 350°; ir (potassium bromide): 3530, 3360, 3340, 3270, 1705, 1635, 1590, 1220, 1080 cm^{-1}; nmr (DMSO-d_6): δ 1.22 (t, 3H, J = 4.8 Hz, $-OCH_2CH_3$), 2.04 (s, 6H, $-CH_3$'s at C_4 and C_5), 4.24 (q, 2H, $-OCH_2CH$), 6.54 (broad s, 2H, $-CONH_2$), 10.1 (broad s, 1H, -NHCO-), 10.6 (broad s, 1H, $-N_1H$).

2-Carbethoxyamido-3-carbamyl-4-methyl-5-ethylpyrrole (**5b**).

A suspension of 2-carbethoxyamido-3-cyano-4-methyl-5-ethylpyrrole (22.1 g., 0.1 mole) (**4b**) in 100 ml. of 85% phosphoric acid was hydrolyzed according to the procedure for the synthesis of **5a**. The temperature of the oil bath ranged from 130 to 140°. The crude product (23.2 g., 96.9%) was washed three times with cold methanol to yield a light pink powder (homogeneous on tlc-ethyl acetate, R_f = 0.51), m.p. 180-182°; ir (potassium bromide): 3460, 3340, 2980, 1705, 1660, 1635, 1615, 1590, 1230, 1080 cm^{-1}; nmr (DMSO-d_6): δ 1.03 (t, 3H, $-CH_2CH_3$), 1.23 (t, 3H, $-OCH_2CH_3$), 2.07 (s, 3H, $-CH_3$ at C_4), 2.46 (q, 2H, $-CH_2CH_3$), 4.11 (q, 2H, $-OCH_2CH_3$), 6.61 (broad s, 2H, $-CONH_2$), 10.02 (broad s, 1H, -NHCO-), 10.46 (broad s, 1H, $-N_1H$).

2-Carbethoxyamido-3-carbamyl-4-methyl-5-isobutylpyrrole (**5c**).

A suspension of 2-carbethoxyamido-3-cyano-4-methyl-5-isobutylpyrrole

(12.5 g., 0.05 mole) (**4c**) in 100 ml. of 85% phosphoric acid was hydrolyzed according to the procedure for the synthesis of **5a**. The temperature of the oil bath ranged from 113 to 130° over the course of the reaction. The crude product (12.4 g., 92.7%) was recrystallized three times from ethanol to yield white powdery crystals (homogeneous on tlc-ethyl acetate, R_f = 0.44), m.p. 159-160°; ir (potassium bromide): 3415, 3290, 3170, 2950, 1685, 1640, 1580, 1240, 1080 cm^{-1}; nmr (DMSO-d_6): δ 0.84 (d, 6H, $CH_2CH(CH_3)_2$), 0.8-1.2 (m, 1H, $CH_2CH(CH_3)_2$), 1.24 (t, 3H, $-OCH_2CH_3$), 2.07 (s, 3H, $-CH_3$ at C_4), 2.34 (d, 2H, $-CHCH(CH_3)_2$), 4.14 (q, 2H, $-OCH_2CH_3$), 6.60 (broad s, 2H, $-CONH_2$), 10.02 (broad s, 1H, -NHCO-), 10.42 (broad s, 1H, $-N_1H$).

2-Carbethoxyamido-3-carbamyl-4-methyl-5-phenylpyrrole (**5d**).

A suspension of 2-carbethoxyamido-3-cyano-4-methyl-5-phenylpyrrole (13.5 g., 0.05 mole) (**4d**) in 250 ml. of 85% phosphoric acid was hydrolyzed according to the procedure for the synthesis of **5a**. The temperature of the oil bath ranged from 135 to 140° and total heating time was about 10 minutes. The crude product (14.0 g., 97.5%) was heated in ethanol to remove any unreacted starting material. A 1.1 g. sample was recrystallized from 300 ml. absolute ethanol to yield 0.9 g. beige powder (homogeneous on tlc-ethyl acetate, R_f = 0.53), m.p. > 350°; ir (potassium bromide): 3420, 3340, 3160, 2990, 1715, 1640, 1615, 1590, 1220, 765, 700 cm^{-1}; nmr (DMSO-d_6): δ 1.22 (t, 3H, $-OCH_2CH_3$), 2.26 (s, 3H, $-CH_3$ at C_4), 4.12 (q, 2H, $-OCH_2CH_3$), 6.75 (broad s, 2H, $-CONH_2$), 7.32 (s, 5H, aromatic H's of phenyl), 9.6 (broad s, 1H, -NHCO-), 10.8 (broad s, 1H, $-N_1H$).

2-Carbethoxyamido-3-carbamyl-4-methyl-5-benzylpyrrole (**5e**).

A suspension of 2-carbethoxyamido-3-cyano-4-methyl-5-benzylpyrrole (10.4 g., 0.037 mole) (**4e**) in 150 ml. of 85% phosphoric acid was hydrolyzed according to the procedure for **5a**. The temperature of the oil bath ranged from 133 to 135° over the course of the reaction. Total time of heating was 10 minutes. The crude product was washed with 100 ml. cold absolute methanol to remove any starting material. The product (8.3 g., 74.4%) was further purified by boiling in 100 ml. of absolute ethanol. One gram of the crude product was recrystallized twice from 100 ml. absolute ethanol to yield white crystals (homogeneous on tlc-ethyl acetate, R_f = 0.51), m.p. 196-197°, then resolidifies to yield a solid, m.p. > 350°; ir (potassium bromide): 3480, 3370, 3160, 1705, 1635, 1610, 1590, 1215 cm^{-1}; nmr (DMSO-d_6): δ 1.22 (t, 3H, $-OCH_2CH_3$), 2.14 (s, 3H, $-CH_3$ at C_4), 3.85 (s, 2H, $-CH_2-C_6H_5$), 4.12 (q, 2H, $-OCH_2CH_3$), 6.65 (s, 2H, $-CONH_2$), 7.15 (s, 5H, aromatic H's of benzyl), 10.09 (broad s, 1H, -NHCO-), 10.66 (broad s, 1H, $-N_1H$).

2-Carbethoxyamido-3-carbamyl-4-methyl-5-hydroxybenzylpyrrole (**5f**).

A suspension of 2-carbethoxyamido-3-cyano-4-methyl-5-*p*-hydroxybenzylpyrrole (15.0 g., 0.05 mole) (**4f**) in 150 ml. of 85% phosphoric acid was hydrolyzed according to the procedure for the synthesis of **5a**. The crude product (14.0 g., 88.2%) was recrystallized from ethanol to yield a beige powder (homogeneous on tlc-ethyl acetate, R_f = 0.55), m.p. > 350°; ir (potassium bromide): 3480, 3420, 3360, 3140, 1700, 1640, 1615, 1600, 1585, 1560, 1510, 1380, 1215 cm^{-1}; nmr (DMSO-d_6): δ 1.2 (t, 3H, $-OCH_2CH_3$), 2.09 (s, 3H, $-CH_3$ at C_4), 3.65 (s, 2H, $-CH_2-C_6H_4$-p-OH), 4.12 (q, 2H, $-OCH_2CH_3$), 6.61 (s, 2H, $-CONH_2$), 6.84 (m, 4H, aromatic H's of *p*-hydroxybenzyl), 9.03 (s, 1H, phenolic -OH), 10.0 (broad s, 1H, -NHCO-), 10.5 (broad s, 1H, $-N_1H$).

A solution of 2-(*N*-carbethoxy-*N*-methyl)amino-3-cyano-4,5-dimethylpyrrole (5.0 g., 0.023 mole) (**4g**) in 25 ml. of 85% phosphoric acid was heated in a boiling water bath for 3 minutes and then stirred for 5 minutes at room temperature. Crushed ice was added and, after 10 minutes of stirring, a beige precipitate formed. The precipitate was collected, washed with distilled water, and air dried. The crude product (3.0 g., 55.5%) was recrystallized from absolute ethanol to yield a white powder (homogeneous on tlc-ethyl acetate, R_f = 0.26), m.p. 215-216°; ir (potassium bromide): 3460, 3360, 3230, 1690, 1640, 1580, 1260, 1210 cm^{-1}; nmr (DMSO-d_6): δ 1.14 (t, 3H, J = 4.8 Hz, $-OCH_2CH_3$), 2.03 (s, 6H, $-CH_3$ at C_4 and C_5), 3.08 (s, 3H, $-NCH_3$), 4.05 (q, 2H, J = 4.8 Hz, $-OCH_2CH_3$), 6.45 (broad s, 2H, $-CONH_2$), 10.8 (broad s, 1H, $-N_1H$).

5,6-Dimethylpyrrolo[2,3-*d*]pyrimidine-2,4-dione (**6a**).

A suspension of 2-carbethoxyamido-3-carbamyl-4,5-dimethylpyrrole (9.0 g., 0.04 mole) (**5a**) in 200 ml. of 1-octanol was refluxed with stirring until a clear solution was achieved. A precipitate formed after refluxing for a short period of time. This suspension was refluxed for an additional 15 minutes, then 180 ml. of the 1-octanol was removed by distillation at atmospheric pressure. The thick residue was cooled to room temperature, diluted with anhydrous diethyl ether (100 ml.) and the insoluble precipitate collected by filtration. The produce was washed with ether to remove 1-octanol. The orange-pink powder (6.8 g., 94.8%) was analytically pure (homogeneous on tlc-ethyl acetate, R_f = 0.18), m.p. > 350°; ir (potassium bromide): 3150, 3060, 2905, 1720, 1685, 1670, 1655, 1460, 750 cm^{-1}; nmr (DMSO-d_6): δ 2.07 (s, 6H, $-CH_3$'s at C_5 and C_6), 10.15 (broad s, 1H, $-N_1H$), 10.7 (broad s, 1H, $-N_7H$), 10.95 (broad s, 1H, $-N_3H$).

5-Methyl-6-ethylpyrrolo[2,3-*d*]pyrimidine-2,4-dione (**6b**).

A suspension of 2-carbethoxyamido-3-carbamyl-4-methyl-5-ethylpyrrole (15.0 g., 0.05 mole) (**5b**), in 200 ml. of 1-octanol was refluxed according to the procedure for the synthesis of **6a**. After the reflux period, the thick suspension was cooled to room temperature. The solid was removed by filtration and washed with diethyl ether. The pale pink powder (8.0 g., 69.0%) was analytically pure (homogeneous on tlc-ethyl acetate, R_f = 0.30), m.p. > 350°; ir (potassium bromide): 3150, 3060, 2960, 2915, 1720, 1690, 1670, 1640, 1450, 755 cm^{-1}; nmr (DMSO-d_6): δ 1.0 (t, 3H, $-CH_2CH_3$), 2.02 (s, 3H, $-CH_3$ at C_5), 2.45 (q, 2H, $-CH_2CH_3$), 10.05 (broad s, 1H, $-N_1H$), 10.6 (broad s, 1H, $-N_7H$), 11.1 (broad s, 1H, $-N_3H$).

An additional 2.8 g. of product was obtained by removing 180 ml. of 1-octanol from the filtrate, overall yield 93.2%.

5-Methyl-6-isobutylpyrrolo[2,3-*d*]pyrimidine-2,4-dione (**6c**).

A suspension of 2-carbethoxyamido-3-carbamyl-4-methyl-5-isobutylpyrrole (14.2 g., 0.054 mole) (**5c**) in 200 ml. of 1-octanol was refluxed according to the procedure for the synthesis of **6a**. Octanol (78 ml.) was removed by distillation and the thick suspension was cooled to room temperature. The precipitate was collected by filtration, washed with diethyl ether, and air dried The white powder (11.2 g., 93.8%) was analytically pure (homogeneous on tlc-ethyl acetate, R_f = 0.26), m.p. > 350°; ir (potassium bromide): 3160, 3060, 2960, 2920, 2820, 1710, 1665, 1620, 1440, 710 cm^{-1}; nmr (DMSO-d_6): δ 0.85 (d, 6H, $-CH_2CH(CH_3)_2$), 0.8-1.2 (m, 1H, $-CH_2CH(CH_3)_2$), 2.07 (s, 3H, $-CH_3$ at C_5), 3.28 (d, 2H, $-CH_2CH(CH_3)_2$), 10.18 (broad s, 1H, $-N_1H$), 10.63 (broad s, 1H, $-N_7H$), 11.08 (broad s, 1H, $-N_3H$).

5-Methyl-6-phenylpyrrolo[2,3-*d*]pyrimidine-2,4-dione (**6d**).

A suspension of 2-carbethoxyamido-3-carbamyl-4-methyl-5-phenylpyrrole (9.0 g., 0.031 mole) (**5d**) in 200 ml. of 1-octanol was refluxed according to the procedure for the synthesis of **6a**. The mixture was refluxed for 45 minutes; however, a clear solution was never obtained. Octanol (152 ml.) was removed by distillation, and the thick suspension was cooled to room temperature. The precipitate was collected by filtration, washed with diethyl ether, and air dried. The green-tan powder (6.7 g., 89.6%) was analytically pure (homogeneous on tlc-ethyl acetate, R_f = 0.21), m.p. > 350°; ir (potassium bromide): 3160, 3040, 1705, 1665, 1600, 1560, 1525, 1490, 1440, 1280, 1125, 705, 665, 620 cm^{-1}; nmr (DMSO-d_6): δ 2.3 (s, 3H, $-CH_3$ at C_5), 7.3 (s, 5H, aromatic H's of phenyl), 10.38 (broad s, 1H, $-N_1H$), 10.84 (broad s, 1H, $-N_7H$), 11.25 (broad s, 1H, $-N_3H$).

5-Methyl-6-benzylpyrrolo[2,3-*d*]pyrimidine-2,4-dione (**6e**).

A suspension of 2-carbethoxyamido-3-carbamyl-4-methyl-5-benzylpyrrole (18.1 g., 0.06 mole) (**5e**) in 200 ml. of 1-octanol was refluxed according to the procedure for the synthesis of **6a**. Octanol (145 ml.) was removed by distillation, and the thick suspension was cooled to room temperature. The precipitate was collected by filtration, washed with diethyl ether, and air dried. The light beige powder (14.0 g., 91.5%) was analytically pure (homogeneous on tlc-ethyl acetate, R_f = 0.16), m.p. > 350°; ir (potassium bromide): 3440, 3140, 1705, 1665, 1640, 1620, 1595, 1435, 1280, 1125, 700 cm^{-1}; nmr (DMSO-d_6): δ 2.15 (s, 3H, $-CH_3$ at C_5), 3.8

(s, 2H, -CH_2-C_6H_5), 7.15 (s, 5H, aromatic H's of benzyl), 10.21 (broad s, 1H, -N_1H), 10.8 (broad s, 1H, -N_7H), 11.15 (broad s, 1H, -N_3H).

5-Methyl-6-*p*-hydroxybenzyl[2,3-*d*]pyrimidine-2,4-dione (**6f**).

A suspension of 2-carbethoxyamido-3-carbamyl-4-methyl-5-*p*-hydroxybenzylpyrrole (9.7 g., 0.03 mole) (**5f**) in 100 ml. of octanol was refluxed according to the procedure of **6a**. Octanol (70 ml.) was removed by distillasiton, and the thick suspension was cooled to room temperature. The precipitate was collected by filtration, washed with diethyl ether, and air dried. The light brown powder (8.1 g., 99.5%) was analytically pure (homogeneous on tlc-ethyl acetate, R_f = 0.24), m.p. > 350°; ir (potassium bromide): 3360, 3140, 1720, 1710, 1660, 1590, 1540, 1475, 1440, 1120 cm^{-1}; nmr (DMSO-d_6): δ 2.1 (s, 3H, -CH_3 at C_5), 3.67 (s, 2H, -CH_2-C_6H_5), 6.5-7.0 (m, 4H, aromatic H's of *p*-hydroxybenzyl), 9.04 (s, 1H, phenolic -OH), 10.18 (broad s, 1 H, -N_1H), 10.7 (broad s, 1H, -N_7H), 11.12 (broad s, 1H, -N_3H).

1,5,6-Trimethylpyrrolo[2,3-*d*]pyrimidine-2,4-dione (**6g**).

Method A.

A suspension of 2-(*N*-carbethoxy-*N*-methyl)amino-3-carbamyl-4,5-dimethylpyrrole (2.4 g., 0.01 mole) (**5g**) in 50 ml. THF and potassium *tert*-butoxide (1.3 g., 0.012 mole) was refluxed for 6 hours. Distilled water was added and the dark solution was filtered. The filtrate was acidified with 10% hydrochloric acid. The THF was removed *in vacuo* and the resulting precipitate was washed with distilled water and air dried. The crude product (1.3 g., 67.4%) was boiled in absolute methanol and the suspension filtered. The cooled filtrate yielded a pink powder (homogeneous on tlc-ethyl acetate, R_f = 0.30), m.p. > 350°; ir (potassium bromide): 3200, 3140, 2920, 1700, 1690, 1620, 1560, 1540, 1330, 700 cm^{-1}; nmr (DMSO-d_6): δ 2.05 (s, 6H, -CH_3's at C and C_6), 3.22 (s, 3H, -CH_3 at N_1), 10.5 (broad s, 1H, -N_7H), 11.15 (broad s, 1H, -N_3H).

Method B.

A suspension of 5,6-dimethylpyrrolo[2,3-*d*]pyrimidine-2,4-dione (1.8 g., 0.01 mole) (**6a**) in 40 ml. absolute methanol and potassium *t*-butoxide (1.2 g., 0.011 mole) was stirred at room temperature for 1 hour. Dimethyl sulfate (1.4 g., 0.011 mole) was added and the mixture was refluxed overnight. Ice was added to the mixture and the product was collected, washed with distilled water, and air dried. The crude product (1.7 g., 88.1%) was boiled in absolute methanol and the suspension filtered. The cooled filtrate yielded a pink powder (homogeneous on tlc-ethyl acetate, R_f = 0.27), m.p. > 350°; ir (potassium bromide): 3200, 3140, 2920, 1700, 1690, 1620, 1560, 1540, 1330, 700 cm^{-1}; nmr (DMSO-d_6): δ 2.05 (s, 6H, -CH_3's at C_5 and C_6), 3.22 (s, 3H, -CH_3 at N_1), 10.5 (broad s, 1H, -N_7H), 11.15 (broad s, 1H, -N_3H).

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