(c 0.5, H_2O); nmr (DMSO-d_6) δ 8.87 (s, 1, H-5), 5.92 (d, 1, $J_{1',2'}$ = 3.5 Hz, H-1'), 4.50-3.75 (m, 3, H-2', H-3', and H-4'), 4.06 (q, 2, CH_2 of CH_2CH_3), 2.50-1.68 (m, 4, CH_2CH_2), 1.19 (t, 3, CH_3 of CH_2CH_3). *Anal.* ($C_{12}H_{18}N_4O_6$) C, H, N.

1-(5,6-Dideoxy-β-D-*ribo*-heptofuranosyluronamide)-1,2,4-triazole-3-carboxamide (13). A solution of ethyl ester 12 (0.80 g, 2.55 mmol) in methanol saturated at 0° with NH_3 (70 ml) was kept at 25° for 5 days and at 50° for 6 hr. Evaporation of the solution gave a residue that was purified by chromatography on silica gel following the same procedure indicated for the ethyl ester. Elution of the column with $CHCl_3$ (100 ml), EtOAc (200 ml), and 4:1 EtOAc-MeOH (1 l.) provided 0.46 g (64%) of 13 as an amorphous solid. The product was dried over P_2O_5 at 110° for 2 hr to give an analytical sample: $[\alpha]_D$ −1.7° (c 1, H_2O); nmr (DMSO-d_6-D_2O) δ 8.81 (s, 1, H-5), 5.87 (d, 1, $J_{1',2'}$ = 3.5 Hz, H-1'), 3.80-4.55 (m, 3, H-2', H-3', and H-4'), 2.40-1.70 (m, 4, CH_2CH_2). *Anal.* ($C_{10}H_{15}N_5O_5$) C, H, N.

1-(5,6-Dideoxy-β-D-*ribo*-heptofuranosyluronic acid)-1,2,4-triazole-3-carboxamide (14). A solution of the ethyl ester 12 (0.94 g, 3.0 mmol) in a pH 10.7 buffer (Na_2CO_3-$NaHCO_3$) (125 ml) was maintained at 50° for 7 hr. The solution was neutralized with Dowex 50 (H^+) under stirring. The resin was filtered and the aqueous solution was freeze-dried. The lyophilized product (0.7 g, 81%), chromatographically homogenous, was dried over P_2O_5 at 110° for 2 hr to obtain an analytical sample: $[\alpha]_D$ −5.9° (c 1, H_2O); nmr (DMSO-d_6-D_2O) δ 8.74 (s, 1, H-5), 5.80 (d, 1, $J_{1',2'}$ = 3 Hz, H-1'), 4.53-3.80 (m, 3, H-2', H-3', and H-4'), 2.50-1.70 (m, 4, CH_2CH_2). *Anal.* ($C_{10}H_{14}N_4O_6 \cdot 0.5H_2O$) C, H, N.

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3-Substituted 5,7-Dimethylpyrazolo[1,5-*a*]pyrimidines, 3′,5′-Cyclic-AMP Phosphodiesterase Inhibitors. 1†

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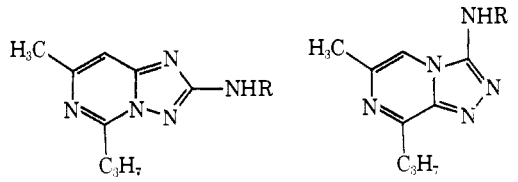
A series of 3-substituted 5,7-dimethylpyrazolo[1,5-*a*]pyrimidines has been synthesized and evaluated for their ability to inhibit the enzyme 3′,5′-cyclic-AMP phosphodiesterase that was isolated and purified from rabbit kidney, rabbit lung, and beef heart. The 3-bromo, 3-chloro, 3-iodo, and 3-acetyl derivatives have been found to be more potent than theophylline in their ability to inhibit these 3′,5′-cAMP phosphodiesterases.

Recently Rose and coworkers[1-3],‡ have reported a number of triazolo[2,3-*c*]pyrimidines and triazolo[4,3-*c*]pyrazines which are capable of protecting animals from a histamine-induced bronchospasm. In particular, compounds **1b** and **2b** were found to be the most potent bronchodilators in these ring systems.[4] These workers point out the structural similarities of these compounds to theophylline (**3**). Inhibition of 3′,5′-cyclic-AMP phosphodiesterase (PDE) appears to be the underlying biochemical mechanism for the pharmacological effects of theophylline,[5] compounds **1** and **2**, and their derivatives.[6] 2-Amino-7-methyl-5-*n*-propyl-*s*-triazolo[2,3-*c*]pyrimidine (**1a**) has been found in our laboratories to be approximately equal to theophylline (**3**) in inhibiting the PDE isolated from rabbit lung; however, **1a** is only 0.2 as active as **3** in inhibiting PDE isolated from rabbit kidney. In an effort to discover more potent inhibitors of PDE, and possibly compounds with superior selective pharmacological activity, we have prepared a number of 3-substituted 5,7-dimethylpyrazolo[1,5-*a*]pyrimidines and evaluated these derivatives for their ability to inhibit PDE.

Chemistry. According to the procedure of Makisumi,[7] condensation of 3-aminopyrazole (**4a**) and 3-amino-4-carbethoxypyrazole (**4b**) with acetylacetone gave 5,7-dimethylpyrazolo[1,5-*a*]pyrimidine (**5a**) and the corresponding 3-carbethoxy derivative **5b**. We have also found that a similar condensation of 3-amino-4-cyanopyrazole[8] (**4c**) and 3-amino-4-pyrazolecarboxamide[8] (**4d**) yields the 3-cyano (**5c**) and the 3-carbamoyl (**5d**) derivatives in excellent yields. The catalytic reduction of 3-cyano-5,7-dimethylpyrazolo[1,5-*a*]pyrimidine (**5c**) with palladium on charcoal catalyst affords 3-aminomethyl-5,7-dimethylpyrazolo[1,5-*a*]pyrimidine (**5e**) which was isolated as the hydrochloride salt.

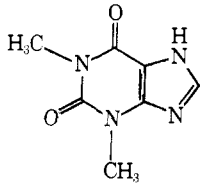
†A preliminary account of this work was presented at the Fifth International Congress on Pharmacology, San Francisco, Calif., July 1972.

‡These authors point out that the acetylamino derivative 1b is preferred for *in vivo* studies because of toxicological findings.



1a, R = H
b, R = $COCH_3$

2a, R = H
b, R = $COCH_3$

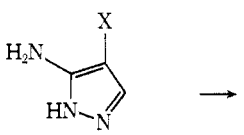


3

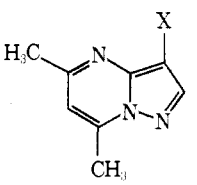
A literature survey revealed that relatively little is known about electrophilic substitution of 5,7-dialkylpyrazolo[1,5-*a*]pyrimidines. The parent compound, 5,7-dimethylpyrazolo[1,5-*a*]pyrimidine (**5a**), was brominated with *N*-bromosuccinimide to afford 3-bromo-5,7-dimethylpyrazolo[1,5-*a*]pyrimidine. The site of electrophilic attack at position 3 was established, since the upfield proton at δ 6.60 [which is coupled to the proton at δ 8.11 (J = 0.066 Hz)] found in 5,7-dimethylpyrazolo[1,5-*a*]pyrimidine (**5a**) was absent in the bromo derivative **5f**. The nmr spectrum of **5f** was essentially identical with the nmr spectrum of 3-cyano-5,7-dimethylpyrazolo[1,5-*a*]pyrimidine (**5c**) whose structure is known by the method of synthesis.

In an analogous fashion, treatment of **5a** with *N*-chlorosuccinimide afforded 3-chloro-5,7-dimethylpyrazolo[1,5-*a*]pyrimidine (**5g**). Similarly, treatment of **5a** with iodine monochloride afforded the corresponding 3-iodo-5,7-dimethylpyrazolo[1,5-*a*]pyrimidine (**5h**).

The parent heterocycle, 5,7-dimethylpyrazolo[1,5-*a*]pyrimidine (**5a**) gave the corresponding 3-acetyl derivative **5i** upon Friedel–Crafts acylation with acetyl chloride. It was also found that **5a** undergoes a Mannich reaction with dimethylamine and formaldehyde to afford 3-dimethylaminomethyl-5,7-dimethylpyrazolo[1,5-*a*]pyrimidine (**5j**).



4a, X = H
b, X = $COOC_2H_5$
c, X = CN
d, X = $CONH_2$



5a, X = H
b, X = $COOC_2H_5$
c, X = CN
d, X = $CONH_2$
e, X = CH_2NH_2
f, X = Br
g, X = Cl
5h, X = I
i, X = $COCH_3$
j, X = $CH_2N(CH_3)_2$
k, X = NO_2
l, X = NH_2
m, X = $NHCOCH_3$

In a similar fashion, nitration of **5a** was accomplished at moderate temperature to yield 5,7-dimethyl-3-nitropyrazolo[1,5-*a*]pyrimidine (**5k**). This nitro derivative was catalytically reduced over palladium on charcoal to yield 3-amino-5,7-dimethylpyrazolo[1,5-*a*]pyrimidine (**5l**). Although this amino derivative could be purified for proper elemental analysis, it was highly colored due to air oxidation. Because of this discoloration we converted **5l** to 3-acetamido-5,7-dimethylpyrazolo[1,5-*a*]pyrimidine (**5m**).

Electrophilic substitution at position 3 in 5,7-dimethylpyrazolo[1,5-*a*]pyrimidine (**5a**) was not unexpected. The carbon-13 spectra of the closely related pyrazolo[1,5-*a*]pyridine ring system has been recently examined, and the results of this study indicate that position 3 appears at a high-field resonance position which has been correlated with ease of electrophilic substitution.[9]

Enzymology. 3′,5′-Cyclic-AMP phosphodiesterase (PDE) has been isolated and purified from three different tissues in the following manner. Homogenates of rabbit kidney and rabbit lung were made in sucrose–Tris–magnesium (0.25:0.05 (pH 7.4):0.01 *M*) buffer and were subjected to centrifugation at low speed to remove nuclei and cell debris. The supernatants were then centrifuged at 105,000g for 30 min. The 105,000g supernatants were then fractionated using $(NH_4)_2SO_4$. The precipitation which formed at 30% saturation was collected by centrifugation at 20,000g and dissolved in Tris (0.05 *M*, pH 7.4)–magnesium (0.01 *M*) buffer and dialyzed overnight against the same buffer. A second $(NH_4)_2SO_4$ fraction was obtained by raising the concentration of the first supernatant to 50%. These two $(NH_4)_2SO_4$ fractions as well as the supernatant from the 30–50% cut were then assayed for PDE activity using the ion-exchange method of Appleman.[10] The first fraction obtained from both kidney and lung tissue was found to contain a PDE with low affinity for 3′,5′-cyclic-AMP (high K_m). The second fraction was found to exhibit a biphasic curve when the Lineweaver–Burk method of analysis was used. This would indicate either the presence of two separate enzymes, one having a high and the other a low affinity for the enzymes, or one protein with two separate sites. Recent work by Appleman[10] has indicated that extracts of brain yield two separate enzymes (a high K_m and a low K_m) which can be separated by sepharose gel chromatography.

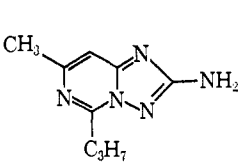
The inhibitory studies reported on in this paper were performed with the low affinity (fraction I, high K_m) enzyme obtained from rabbit kidney or rabbit lung and with the high affinity (fraction II, low K_m) enzyme obtained from rabbit lung and beef heart. I_{50} values were calculated from a plot of log [I] *vs.* per cent inhibition in experiments in which inhibitor concentration was varied over a wide range, at a constant 3′,5′-cyclic-AMP concentration of approximately 5×10^{-4} or 1.6×10^{-7} *M*. The relative inhibitory activity of each compound as compared with theophylline is expressed as an α value. This value is obtained by dividing the I_{50} value for theophylline in a particular experiment by the I_{50} value obtained for the particular compound being evaluated. The compounds were dissolved in water or Tris buffer (0.5 *M*, pH 7–10) with heating where necessary. In instances where buffer solution was used, there was no inhibition of the enzyme due to the presence of Tris buffer alone.

Results and Discussion

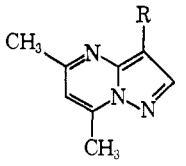
Thirteen derivatives of the pyrazolo[1,5-*a*]pyrimidine ring system have been evaluated for their ability to inhibit the low affinity PDE (fraction I, high K_m) enzyme obtained from rabbit kidney. The results of these studies are listed in Table I. Eight of these compounds have been found to be more potent inhibitors than compound **1a**. The parent compound of this series (**5a**) was approximately equal to 1a; however, the introduction of a cyano (**5c**), carbamoyl (5d), acetyl (**5i**), or dimethylaminomethyl (**5j**) moiety into the 3 position affords compounds that are more potent than **1a** but less potent than theophylline **3**. The introduction of a bromo (**5f**), chloro (**5g**), or iodo (**5h**) affords compounds that are 6–11 times more potent than **1a** and up to 2.2 times more potent than theophylline (3).

The eight compounds that were more active than **1a** as inhibitors of the PDE isolated from rabbit kidney have

Table I. 3-Substituted 5,7-Dimethylpyrazolo[1,5-*a*]pyrimidines as Inhibitors of 3',5'-Cyclic-AMP Phosphodiesterases (PDE) Isolated from Several Sources[a]



1a



5

Compd no.	R	α[b] (high K_m PDE) Rabbit kidney	α[b] (high K_m PDE) Rabbit lung	α[b] (low K_m PDE) Beef heart	α[b] (low K_m PDE) Rabbit lung
1a		0.2[c]	1.0[d]		
5a	H	0.22	0.3	0.2[e]	0.3[f]
5b	$CO_2C_2H_5$	0.14	ND[g]	0.4	0.6
5c	CN	0.88	0.68	0.4	0.6
5d	$CONH_2$	0.65	0.32	0.4	0.5
5e	CH_2NH_2	0.04	ND	ND	ND
5f	Br	2.20	2.40	1.7	0.7
5g	Cl	1.33	3.11	1.7	2.2
5h	I	1.23	3.55	1.5	3.5
5i	$COCH_3$	0.57	1.5	0.4	1.0
5j	$CH_2N(CH_3)_2$	0.61	0.57	0.3	0.3
5k	NO_2	0.17	ND	0.2	0.4
5l	NH_2	0.09	ND	ND	ND
5m	$NHCOCH_3$	0.04	ND	0.07	0.1

[a]Evaluation carried out in triplicate. [b]$\alpha = I_{50}$ (theophylline) $(M)/I_{50}$ (compound) (M). [c]I_{50} theophylline ranges from 1.6 to 3.2 $\times 10^{-4}$ *M*. [d]I_{50} theophylline ranges from 5.0 to 7.4 $\times 10^{-4}$ *M*. [e]I_{50} theophylline ranges from 0.9 to 2.0 $\times 10^{-4}$ *M*. [f]I_{50} theophylline ranges from 1.0 to 3.0 $\times 10^{-4}$ *M*. [g]Not determined.

been evaluated for their ability to inhibit the low affinity PDE (fraction I, high K_m) enzyme obtained from rabbit lung. The results of these studies are listed in Table I. Four of these compounds have demonstrated activity that is comparable to (or more potent than) compound **1a**. The 3-acetyl derivative **5i** displayed activity very similar to **1a**. The halogen derivatives **5f–h** displayed activity very similar to **1a**. The halogen derivatives **5f–h** are all considerably more potent than compound **1a** and are 2.5–3.5 times more potent than theophylline (**3**) as inhibitors of the PDE isolated from rabbit lung.

Because of the relatively low concentrations of cAMP found intracellularly, as well as the low concentrations of cAMP needed to exert nearly maximal effects on the enzyme protein kinase (10^{-7} *M*), it is more likely that the enzyme responsible for degradation of endogenous cAMP *in vivo* is the low K_m, high affinity form. We have therefore examined the ability of most of the derivatives reported on in this study to inhibit the low K_m cAMP PDE isolated from beef heart and rabbit lung.

It was hoped that a compound could be found that was more potent than theophylline for the enzyme from one tissue (heart) but less active than theophylline against the enzyme isolated from a second tissue (lung). As shown in Table I the 3-halogeno derivatives were all more potent than theophylline against the heart enzyme. Compound **5f**, 3-bromo-5,7-dimethylpyrazolo[1,5-*a*]pyrimidine (ICN-3009) was approximately 70% more effective than theophylline against the heart enzyme, but was 30% less active than theophylline against the lung enzyme. It is noteworthy to mention that we have reported that 3-bromo-5,7-dimethylpyrazolo[1,5-*a*]pyrimidine (**5f**, ICN-3009) was capable of producing an immediate and somewhat prolonged increase in the cardiac output of anesthesized dogs that had received an intravenous infusion at a dose level of 4 mg/kg.[11] Infusion of ICN-3009 into anesthesized dogs over a period of 1 hr at greater than three times this dose (14 mg/kg) showed little or no effect on respiration and no significant alteration of serum glucose, free fatty acid, or adrenal corticosteroid levels.

Experimental Section§

5,7-Dimethylpyrazolo[1,5-*a*]pyrimidine-3-carbonitrile (5c). A solution of 3-amino-4-cyanopyrazole[8] (**4c**, 7.25 g, 0.067 mol), acetylacetone (7.00 g, 0.07 mol), and piperidine (10 drops) in 100 ml of EtOH was heated at reflux. After refluxing 6 hr the solution was allowed to cool slowly, whereupon crystallization occurred. The product was separated by filtration and recrystallized from EtOH to afford 6.00 g (52%) of analytically pure product: mp 165–167°; ir (KBr) 2250 cm^{-1} (CN); nmr ($CDCl_3$) four singlets in a ratio of 3:3:1:1 at δ 2.69 (CH_3), 2.82 (CH_3), 2.82 (CH_3), 6.85 (H at 6 position), and 8.33 (H at position 2). *Anal.* ($C_9H_8N_4$) C, H, N.

5,7-Dimethylpyrazolo[1,5-*a*]pyrimidine-3-carboxamide (5d). A mixture of 3-amino-4-pyrazolecarboxamide hemisulfate[8] (**4d**, 1.00 g, 5.7 mmol), acetylacetone (0.60 g, 6.0 mmol), and piperidine (1.5 g) in 40 ml of EtOH was heated at reflux. After refluxing 16 hr the solution was allowed to cool. The crystalline product was recrystallized from EtOH to yield 0.90 g (83%) of analytically pure product: mp 247–248° dec; ir (KBr) 1665 cm^{-1} ($CONH_2$); nmr (DMSO-d_6) singlets in a ratio of 3:3:1:2:1, with chemical shifts of δ 2.62 (CH_3), 2.75 (CH_3), 7.1 and 8.52 (ring protons), and 7.50 (br, NH_2 of amide). *Anal.* ($C_9H_{10}N_4O$) C, H, N.

3-Aminomethyl-5,7-dimethylpyrazolo[1,5-*a*]pyrimidine Hydrochloride (5e). To a solution of the carbonitrile derivative **5c** (1.00 g) in 150 ml of EtOH was added 5 ml of HCl (12 *N*) and 0.25 g of 10% Pd/C catalyst. The resulting mixture was hydrogenated at room temperature for 16 hr. The mixture was filtered through Celite and evaporated to dryness at reduced pressure. The gummy semisolid was dissolved in water (25 ml), made basic by the addition of NaOH solution (1 *N*), and extracted into $CHCl_3$ (2 × 10 ml). The $CHCl_3$ solution, after drying, was chromatographed on basic alumina. Evaporation of the $CHCl_2$ eluent afforded a colorless solid (mp 119–120°) that rapidly became colored. The hydrochloride of **5e** was obtained in 55% yield by dis-

§Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Infrared and nuclear magnetic resonance spectra were determined on a Perkin-Elmer 257 grating infrared spectrophotometer and on a Hitachi Perkin-Elmer R-20A high-resolution nuclear magnetic resonance spectrophotometer, respectively. All hydrogenations were carried out on a Parr hydrogenator at room temperature and at a starting pressure of 42 lb/in.^{2} of hydrogen. All samples displayed a single spot on thin-layer chromatography and were analyzed by the Heterocyclic Chemical Corp. of Harrisonville, Mo. Where analyses are indicated only by symbols of the elements or functions, analytical results obtained for those elements or functions were within ±0.4% of the theoretical values.

solving the solid in Et_2O and adding HCl gas: mp 265–267° dec. *Anal.* ($C_9H_{12}N_4$·HCl) C, H, N.

3-Bromo-5,7-dimethylpyrazolo[1,5-*a*]pyrimidine (5f). To a solution of 5,7-dimethylpyrazolo[1,5-*a*]pyrimidine[7] (**5a**, 2.0 g, 13.6 mmol) in $CHCl_3$ (25 ml) was added NBS (2.42 g, 13.6 mmol). This mixture was heated on the steam bath for 10 min and then allowed to cool at room temperature. The clear yellow solution was then added to an ice-cold solution of potassium hydroxide (50 ml, 2 *N*) with good stirring. The $CHCl_3$ layer was dried over Na_2SO_4 and then chromatographed on basic alumina. Evaporation of the $CHCl_3$ eluent afforded a white solid which was further purified by recrystallization from petroleum ether (bp 30–60°) to give 1.7 g (56%) of analytically pure product: mp 115–116°; nmr ($CDCl_3$) four singlets in a ratio of 3:3:1:1 at δ 2.60 (CH_3), 2.72 (CH_3), 6.62 (H at 6 position), and 8.10 (H at 2 position). *Anal.* ($C_8H_8N_3Br$) C, H, N. The spectrum of the starting material **5a** exhibited peaks at δ 2.56 (CH_3 at C_7), 2.73 (CH_3 at C_5), 6.58 (C_6-H), 6.60 (C_3-H), and 8.11 (C_2-H) (the protons at C_2 and C_3 were coupled, J = 0.066 Hz).

3-Chloro-5,7-dimethylpyrazolo[1,5-*a*]pyrimidine (5g). In a manner similar to the preparation of **5f**, the treatment of **5a** (1.20 g, 8.15 mmol) with NCS (1.33 g, 10.0 mmol) afforded 963 mg (65%) of analytically pure product: mp 89–90°. *Anal.* ($C_8H_8N_3Cl$) C, H, N.

5,7-Dimethyl-3-iodopyrazolo[1,5-*a*]pyrimidine (5h). A solution of ICl (5.0 g, 27 mmol) in $CHCl_3$ (50 ml) was added to a stirred solution of **5a** (2.96 g, 20 mmol) in $CHCl_3$ (50 ml). Within a few minutes, the mixture became warm and crystals of the hydrochloride salt of **5h** began to separate. The mixture was warmed on the steam bath for 2–3 min to complete the reaction and then refrigerated overnight. The yellow hydrochloride salt was separated by filtration, washed with Et_2O, and air-dried. The yellow solid, which weighed 4.4 g, was dissolved in water (100 ml) and this solution was made alkaline by the addition of NaOH solution (2.5 *N*). The alkaline solution was extracted with $CHCl_3$ (3 × 25 ml), and the $CHCl_3$ extracts were dried over Na_2SO_4. The $CHCl_3$ extract was chromatographed on basic alumina and the $CHCl_3$ eluent evaporated to dryness. The residue was recrystallized from petroleum ether (bp 30–60°) to afford 2.02 g (37%) of analytically pure product: mp 120–122°. *Anal.* ($C_8H_8N_3I$) C, H, N.

3-Acetyl-5,7-dimethylpyrazolo[1,5-*a*]pyrimidine (5i). With good stirring, a solution of $SnCl_4$ (5.21 g, 20 mmol) in CH_2Cl_2 (10 ml) was added dropwise to a solution of **5a** (2.94 g, 20 mmol) and acetyl chloride (1.56 g, 20 mmol) in CH_2Cl_2 (10 ml). After the addition was complete, the mixture was heated at reflux for 12 hr, cooled, and then added to dilute HCl (100 ml, 3 *N*). The organic layer was separated and the acidic solution extracted with CH_2Cl_2 (2 × 20 ml). The combined CH_2Cl_2 extracts were dried over Na_2SO_4 and evaporated to dryness. The residue was dissolved in benzene and chromatographed on basic alumina, and the benzene eluent was evaporated to dryness. Recrystallization of the crystalline residue from a benzene–heptane mixture afforded 2.32 g (61%) of analytically pure product: mp 179–180°. *Anal.* ($C_{10}H_{11}N_3O$) C, H, N.

3-Dimethylaminomethyl-5,7-dimethylpyrazolo[1,5-*a*]pyrimidine Dihydrochloride (5j). An aqueous solution of dimethylamine (4.0 ml, 40%) was added slowly to HOAc (4.5 ml) keeping the temperature below 10°. After the addition was complete, formalin solution (3.0 ml, 37%) was added to the solution. The resulting solution was allowed to stir for 20 min, and then **5a** (2.0 g, 13.6 mmol) was added in small portions. The resulting mixture was then stirred at room temperature for 12 hr and then added to cold NaOH solution (50 ml, 2.5 *N*). This basic mixture was then extracted with $CHCl_3$ (3 × 50 ml), and the combined $CHCl_3$ extracts were dried over Na_2SO_4 and evaporated to dryness. The resulting oil, which did not solidify, was dissolved in Et_2O and the dihydrochloride salt of the product was precipitated by adding dry HCl gas. This crude product was purified by recrystallization from EtOH–EtOAc to afford 1.2 g (31.6%) of analytically pure product: mp 194–195°; nmr (free amine, $CDCl_3$) seven singlets in a ratio of 3:3:3:3:2:1:1 at δ 2.21, 2.30 (NCH_3 groups), 2.59, 2.73 (CH_3), 3.70 (CH_2), 6.59 (H at 6 position), and 8.10 (H at 2 position). *Anal.* ($C_{11}H_{16}N_4$·2HCl) C, H, N.

5,7-Dimethyl-3-nitropyrazolo[1,5-*a*]pyrimidine (5k). 5,7-Dimethylpyrazolo[1,5-*a*]pyrimidine (**5a**, 1.0 g, 6.8 mmol) was dissolved in H_2SO_4 (10 ml) keeping the temperature below 5°. Fuming HNO_3 (4 ml, sp gr 1.5) was added dropwise to the cold H_2SO_4 solution, with good stirring. The temperature during this addition was maintained below 10°. After the addition was complete the solution was stirred at room temperature for 45 min and then added to 100 g of ice. The precipitated product was separated by filtration, washed well with H_2O, and dried. Recrystallization from CH_3OH afforded 0.75 g (57%) of analytically pure product: mp 156–157°; nmr ($CDCl_3$) singlets in a ratio of 3:3:1:1 at δ 2.80 (CH_3), 2.85 (CH_3), 7.04 (H at 6 position), and 8.76 (H at 2 position). *Anal.* ($C_8H_8N_4O_2$) C, H, N.

3-Amino-5,7-dimethylpyrazolo[1,5-*a*]pyrimidine (5l). To a solution of 5,7-dimethyl-3-nitropyrazolo[1,5-*a*]pyrimidine (**5k**, 5.0 g, 26 mmol) in EtOH (50 ml) was added HOAc (5 ml) and 0.25 g of 10% Pd/C catalyst. The resulting mixture was hydrogenated at room temperature for 16 hr. The mixture was filtered through Celite and evaporated to dryness at reduced pressure. The oil residue was dissolved in water (100 ml), made basic with NH_4OH, and then extracted into $CHCl_3$ (3 × 35 ml). The combined $CHCl_3$ extracts were dried over Na_2SO_4 and chromatographed on basic alumina. Evaporation of the $CHCl_3$ eluent afforded 2.7 g (64%) of red crystalline product: mp 133–135° dec. *Anal.* ($C_8H_{10}N_4$) C, H, N.

3-Acetamido-5,7-dimethylpyrazolo[1,5-*a*]pyrimidine (5m). 3-Amino-5,7-dimethylpyrazolo[1,5-*a*]pyrimidine (**5l**, 2.6 g, 16 mmol) in Ac_2O (50 ml) was heated on the steam bath for 10 min and then allowed to cool to room temperature. The crystalline product was separated by filtration, washed with H_2O, and dried. Recrystallization from H_2O afforded 2.6 g (80%) of analytically pure product: mp 175–176°. *Anal.* ($C_{10}H_{12}N_4O$) C, H, N.

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