Novel Heterocyclic Nitrofurfural Hydrazones. In Vivo Antitrypanosomal Activity

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Hydrazine derivatives of several pyrazolo[1,5-*a*]pyrimidines (A), pyrazolo[1,5-*a*]-1,3,5-triazines (B), *s*-triazolo-[1,5-*a*]pyrimidines (C), and imidazo[1,2-*a*]pyrimidines (D) were synthesized and condensed with 5-nitrofurfural in order to obtain the corresponding nitrofurfural hydrazones of each heterocycle (**1d–14d**). Each compound was screened for in vitro activity against *Trypanosoma cruzi*. The compounds were then tested in vivo against experimental infections of *T. cruzi* in laboratory (C_3H/He strain) mice. An interesting structure–activity relationship was uncovered, revealing that 5-methyl-7-(5-nitrofurfurylidenehydrazino)pyrazolo[1,5-*a*]pyrimidine (**2d**) greatly increased the mean survival time (IMST) of mice with terminal infections. Subtle alterations in the structure of **2d**, such as the substitution of a 5-hydrogen for the 5-methyl group (**1d**) or the substitution of the 3-hydrogen by the water-soluble 3-sulfonic acid (**3d**) or 3-sodium sulfonate (**4d**), resulted in a drastic loss of in vivo and in vitro activity.

The seriousness of widespread trypanosomal infections, such as Chagas disease,[1,2] caused by the protozoan *Trypanosoma cruzi*, has prompted a continuing search for useful chemotherapeutic agents. The discovery of nitrofurfural[3] and its antimicrobial and antiparasitic properties,[4–6] followed by the establishment of the requirement of a –CH=NNH group[7] attached to the nucleus of the nitrofuran ring, provided a basis for our work.

Since the main problem of nitrofurfural hydrazones has been the inevitable toxicity to the host, we explored the possibility of synthesizing derivatives containing a carrier molecule of low toxicity. Our success[8–12] with the biological activity of certain heterocycles isomeric or isosteric with the purines led to the present study.

We explored the following as "carrier molecules": pyrazolo[1,5-*a*]pyrimidines[8,9] (A), pyrazolo[1,5-*a*]-1,3,5-triazines[10,11] (B), *s*-triazolo[1,5-*a*]pyrimidines[12] (C), and imidazo[1,2-*a*]pyrimidines[13,14] (D) (Scheme I).

Chemistry. The heterocyclic hydrazines, such as substituted and unsubstituted 7-hydrazinopyrazolo-[1,5-*a*]pyrimidines (A, **1c–10c**), 7-hydrazino-*s*-triazolo-[1,5-*a*]pyrimidines (C, **12c**), and 5-hydrazinoimidazo-[1,2-*a*]pyrimidines (D, **13c, 14c**), were prepared by treating the active chloro heterocycle precursors (**1b–10b, 12b–14b**) with hydrazine.

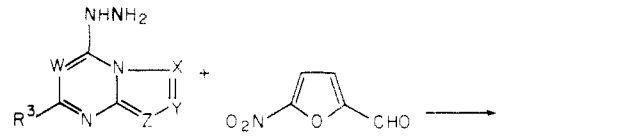
The chloro compounds (**1b–10b, 12b–14b**) were, in turn, synthesized via a procedure reported by Makisumi[15] for the preparation of 5-methyl-7-chloropyrazolo[1,5-*a*]pyrimidine (**2b**). The corresponding "hydroxy" precursors[16] (A, **1a–10a**; C, **12a**; and D, **13a–14a**), in this case 7-hydroxy-5-methylpyrazolo[1,5-*a*]pyrimidine[15] (**2a**), were chlorinated with phosphorus oxychloride (Scheme II).

Two of the chloro heterocycles, namely 3,5,7-trichloropyrazolo[1,5-*a*]pyrimidine (**10b**) and 3-bromo-7-chloro-5-methylpyrazolo[1,5-*a*]pyrimidine (**6b**), were synthesized via electrophilic substitution, employing *N*-chlorosuccinimide (NCS) on 5,7-dichloropyrazolo-[1,5-*a*]pyrimidine (**9b**) and *N*-bromosuccinimide (NBS) on 7-chloro-5-methylpyrazolo[1,5-*a*]pyrimidine (**2b**), respectively. The confirmation of the position of electrophilic attack has been discussed in our previous work.[8] Chlorination of 5,7-dihydroxypyrazolo[1,5-*a*]pyrimidine (**9a**) with $POCl_3$ resulted in dichlorination, giving **9b**.

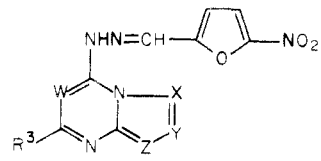
Since the conditions for sulfonation were quite harsh, and the labile 7-chloro substituent (pyrazolo[1,5-*a*]pyrimidines) is hydrolyzed quite easily, the sulfonation was carried out on 7-hydrazino-5-methylpyrazolo[1,5-*a*]pyrimidine (**2c**) to obtain 7-hydrazino-5-methylpyrazolo-[1,5-*a*]pyrimidine-3-sulfonic acid (**3c**).

The sodium salt of this acid (**4c**) was prepared by neutralization of **3c** with sodium hydroxide. The purpose for preparing **3c** and **4c** is that most of the hydrazones (**1d–14d**) had little or no aqueous solubility, which generated problems in the biological screens.

Scheme I. General Synthetic Route[a]

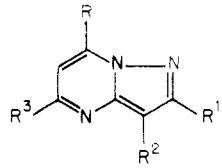


1c–14c



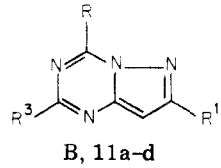
1d–14d

Ring systems referred to in text



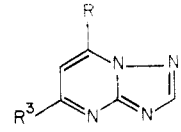
A, 1a-d–10a-d

X = N; Y = CH;
Z = CH, CR; W = CH



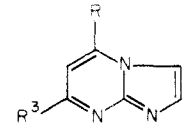
B, 11a-d

X = N; Y = CR;
Z = CH; W = N



C, 12a-d

X = Z = N; Y = CH;
W = CH



D, 13a-d, 14a-d

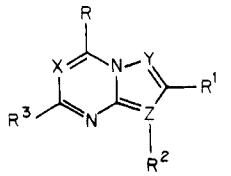
X = Y = CH; Z = N;
W = CH

[a] See Scheme II for preparation of hydrazines and intermediates. For R^1, R^2, and R^3 substituents, see Tables I and II.

Displacement of a bridgehead chloro substituent by hydrazine was not possible for the pyrazolo[1,5-*a*]-1,3,-5-triazines (B), since 4-chloropyrazolo[1,5-*a*]-1,3,5-triazine could not be prepared from 4-hydroxypyrazolo[1,5-*a*]-1,3,5-triazine. The difficulty was overcome by treating 2-methyl-4-methylthio-7-phenylpyrazolo[1,5-*a*]-1,3,5-pyrimidine (**11g**) with hydrazine to obtain 2-methyl-7-hydrazinopyrazolo[1,5-*a*]-1,3,5-triazine (**11f**). The synthesis of **11g** was accomplished by a variation of our recent work,[17] in which 3-amino-5-phenyl-2-*N*-thiocarbamoylpyrazole[18] was condensed with triethyl orthoacetate, affording 2-methyl-4-mercapto-7-phenylpyrazolo[1,5-*a*]-1,-3,5-triazine (**11h**). Alkylation of **11h** with methyl iodide gave **11g**.

In each case the hydrazino heterocycle (**1c–14c**) was

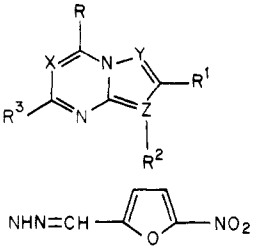
Table I. Physical Data of the Hydrazines



R = $NHNH_2$

No.	R^3	R^2	R^1	Mp, °C	Yield, %	Mol formula (mol wt)	Class	Remarks
1c	H	H	H	215 dec	87.5	$C_6H_7N_5$ (149.156)	A	X = CH; Y = N; Z = CH
2c	CH_3	H	H	228-230 dec	95	$C_7H_9N_5$ (163.182)	A	X = CH; Y = N; Z = CH
3c	CH_3	SO_3H	H	>300	74	$C_7H_9N_5SO_3$ (242.24)	A	X = CH; Y = N; Z = CH
4c	CH_3	SO_3Na	H	>300	75	$C_7H_8N_5SO_3Na$ (264.23)	A	X = CH; Y = N; Z = CH
5c	CH_3	CO_2Et	H	215-217 dec	98.4	$C_{10}H_{13}N_5O_2$ (235.24)	A	X = CH; Y = N; Z = CH
6c	CH_3	Br	H	201-202 dec	90	$C_7H_8N_5Br$ (242.09)	A	X = CH; Y = N; Z = CH
7c	CH_3	C_6H_4-*p*-Cl	H	217-218 dec	85	$C_{13}H_{12}N_5Cl$ (273.73)	A	X = CH; Y = N; Z = CH
8c	CH_3	C_6H_5	H	189-190 dec	83	$C_{13}H_{13}N_5$ (239.27)	A	X = CH; Y = N; Z = CH
9c	Cl	H	H	202-204 dec	75	$C_6H_6N_5Cl$ (183.605)	A	X = CH; Y = N; Z = CH
10c	Cl	Cl	H	246-248 dec	87	$C_6H_5N_5Cl_2$ (218.05)	A	X = CH; Y = N; Z = CH
11c	CH_3	H	C_6H_5	>300	56	$C_{12}H_{12}N_6$ (240.27)	B	X = N; Y = N; Z = CH
12c	CH_3		H	260 dec	72	$C_6H_8N_6$ (164.174)	C	X = CH; Y = N; Z = N
13c	Cl		H	>300	95	$C_6H_6N_5Cl$ (183.605)	D	X = CH; Y = CH; Z = N
14c	CH_3		H	>300	76	$C_7H_9N_5$ (163.182)	D	X = CH; Y = CH; Z = N

Table II. Physical Data of the Hydrazones



R = NHN=CH-(furan)-NO_2

No.	R^3	R^2	R^1	Mp, °C	Mol formula (mol wt)	Class	Remarks
1d	H	H	H	263-264 dec	$C_{11}H_8N_6O_3$ (272.224)	A	X = CH; Y = N; Z = CH
2d	CH_3	H	H	265-267 dec	$C_{12}H_{10}N_6O_3$ (286.25)	A	X = CH; Y = N; Z = CH
3d	CH_3	SO_3H	H	>300	$C_{12}H_{10}N_6O_6S$ (366.316)	A	X = CH; Y = N; Z = CH
4d	CH_3	SO_3Na	H	>300	$C_{12}H_{11}N_6O_6SNa$ (388.305)	A	X = CH; Y = N; Z = CH
5d	CH_3	CO_2Et	H	258-259 dec	$C_{15}H_{14}N_6O_5$ (358.31)	A	X = CH; Y = N; Z = CH
6d	CH_3	Br	H	191-192 dec	$C_{12}H_9N_6O_3Br$ (365.158)	A	X = CH; Y = N; Z = CH
7d	CH_3	C_6H_4-*p*-Cl	H	142-143	$C_{18}H_{13}N_6O_2Cl$ (396.78)	A	X = CH; Y = N; Z = CH
8d	CH_3	C_6H_5	H	206-209 dec	$C_{18}H_{14}N_6O$ (362.34)	A	X = CH; Y = N; Z = CH
9d	Cl	H	H	264-265 dec	$C_{11}H_7N_6O_3Cl$ (306.673)	A	X = CH; Y = N; Z = CH
10d	Cl	Cl	H	118-120 dec	$C_{11}H_6N_6O_3Cl_2$ (341.12)	A	X = CH; Y = N; Z = CH
11d	CH_3	H	C_6H_5	244-246 dec	$C_{17}H_{13}N_7O_3$ (363.33)	B	X = N; Y = N; Z = CH
12d	CH_3		H	287-289	$C_{11}H_9O_3N_7$ (287.24)	C	X = CH; Y = N; Z = N
13d	Cl		H	>300	$C_{11}H_7N_6O_3Cl$ (306.673)	D	X = CH; Y = CH; Z = N
14d	CH_3		H	>300	$C_{12}H_{10}N_6O_3$ (286.25)	D	X = CH; Y = CH; Z = N

suspended or dissolved in methanol and stirred with 1 equiv of 5-nitrofurfural. Within 5–20 h, the corresponding nitrofurfural hydrazone (**1d–14d**) separated from the reaction mixture as an insoluble, highly colored (orange to deep red) precipitate. Physical constants of the 14 compounds screened for antitrypanosomal activity, as well as data for the intermediates, are listed in Tables I and II.

Biological Methods. In vivo antitrypanosomal activities of compounds **1d–14d** were evaluated by intraperitoneal injection of 2×10^3 bloodstream forms of a Brazilian strain of *Trypanosoma cruzi*[19] into male C3H/He mice. Typically, all untreated mice infected with this organism demonstrated patent parasitemias in 10–14 days and died of a fulminating *T. cruzi* infection 19–26 days after inoculation. Activity was determined from mortality records and mean survival times of treated and untreated groups of mice. Results are presented in Table III.

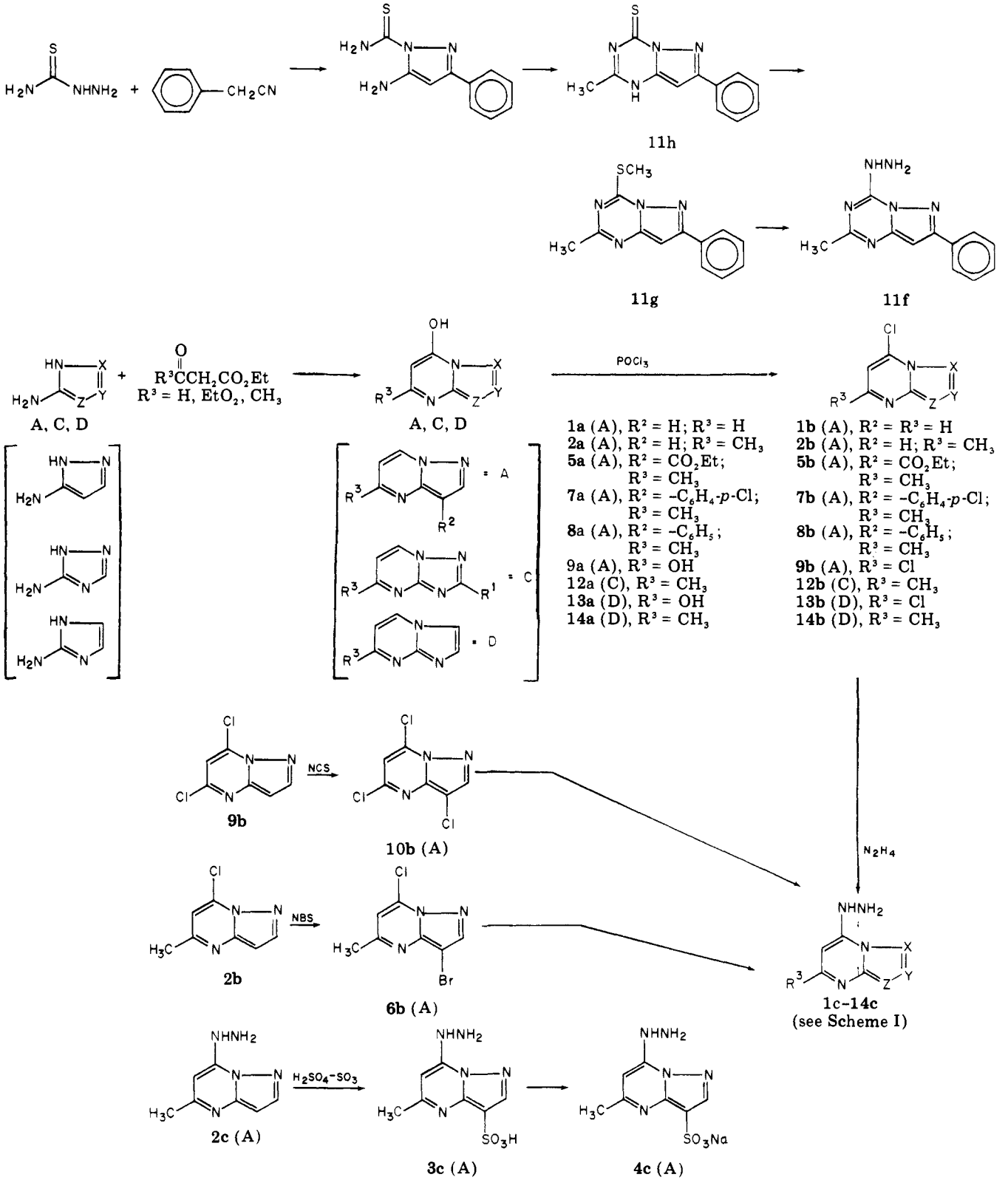
Compounds **1d–14d** were each micronized to a particle size of 0.5–2.0 μ and suspended in a vehicle containing 0.9% NaCl, 1.0% sodium carboxymethylcellulose, 0.5% Tween 80, and 0.05% antifoam B. The compounds were administered in this vehicle at a concentration whereby 0.01 ml/2 g of body weight provided the desired dose level of 100 mg/kg. Groups of seven mice were treated by gavage twice daily for 5 successive days beginning 3 days postinfection.

Results and Discussion

Promising antitrypanosomal activity appeared to be restricted to the pyrazolo[1,5-*a*]pyrimidines **1d–10d** (class A). A number of derivatives of the pyrazolo[1,5-*a*]-1,3,-5-triazines (class B), triazolo[1,5-*a*]pyrimidines (class C), and imidazo[1,2-*a*]pyrimidines (class D) were synthesized but have not been included in Table III because they demonstrated no particular advantage over **11d** (B), **12d** (C), or **13d** and **14d** (D).

There were two major observations in regard to a

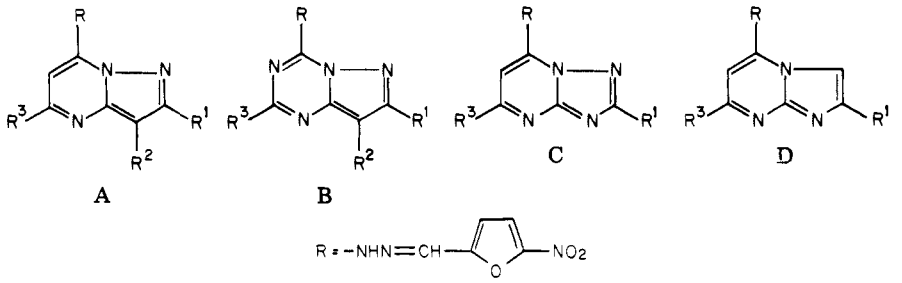
Scheme II. Synthesis of Hydrazine Derivatives and Other Intermediates



structure–activity relationship of the compounds of class A. First, substitution of a hydrogen (**1d**) for a methyl group (**2d**) at the C_5 position of the pyrazolo[1,5-*a*]pyrimidine ring resulted in a drastic loss of in vivo activity, although the in vitro activities of **1d** and **2d** were identical. Second, an increase of water solubility in this class did not enhance the efficacy of the compounds as antitrypanosomal agents. The 3-sulfonic acid (**3d**) and the sodium salt of the sulfonic acid (**4d**) were less effective than the water insoluble **2d** in both in vitro and in vivo tests.

Of the class A compounds, **2d** afforded the greatest increase in the survival time of infected mice (Table III). Unfortunately, parasitologic cures were not obtained by **2d**. Even at oral doses as high as 200 mg/kg four times daily for 5 days parasitemia would eventually occur and the mice succumbed to the infection. It should be noted that mice treated with this latter dose of **2d** exhibited a mild and transient weight loss as the only evidence of

Table III. Relative Efficacy of the Hydrazones 1d–14d against *T. cruzi* Infections in Mice



No.	Class[a]	R^3	R^2	R^1	In vitro[b] MIC/MLC[c]	In vivo IMST[d]
1d	A	H	H	H	10/10	<1.0
2d	A	CH_3	H	H	10/10	63.4[e]
3d	A	CH_3	SO_3H	H	>10/100	9.0
4d	A	CH_3	SO_3Na	H	>100	8.5
5d	A	CH_3	CO_2Et	H	10/10	1.3
6d	A	CH_3	Br	H	100/>100	21.9[e]
7d	A	CH_3	C_6H_4-*p*-Cl	H	1.0/3.2	20.5[e,f]
8d	A	CH_3	C_6H_5	H	<1.0/1.0	[g]
9d	A	Cl	H	H	<1.0/1.0	36.3[e]
10d	A	Cl	Cl	H	10/10	14.6
11d	B	CH_3	H	C_6H_5	1.0/3.2	24.9[e]
12d	C	CH_3		H	>100	4.3
13d	D	Cl		H	10/100	4.4
14d	D	CH_3		H	>100	[g]

[a] Substituents are numbered R^1, R^2, and R^3 only for convenience; see Experimental Section for correct nomenclature. [b] Determined by serial dilution in liquid culture in the medium of L. G. Warren, *J. Parasitol.*, **46**, 529 (1960). [c] Minimum inhibitory concentration (MIC) and minimum lethal concentration (MLC) values expressed in μg/ml. [d] Increase in mean survival time (IMST) is expressed as percent increase beyond survival time of control mice; 100 mg/kg twice daily, by gavage. [e] $p < 0.05$ (Student's *t* test). [f] Intraperitoneal route. [g] Not determined.

toxicity, not observed at the standard dose of this and other pyrazolo[1,5-*a*]pyrimidine derivatives.

Experimental Section

Melting points are uncorrected and were taken in capillary tubes on a Hoover-Thomas apparatus. Spectra are not included in the Experimental Section, but uv data for all compounds were recorded on a Cary 15 in methanol; ir data were obtained in KBr disks and recorded on a Perkin-Elmer 257; and ^1H NMR spectra were obtained in deuteriochloroform, dimethyl-d_6 sulfoxide, or trifluoroacetic acid (depending on the solubility of each compound) and recorded on a Hitachi Perkin-Elmer 270 spectrometer.[8,11] Analyses for C, H, and N on each compound were within ±0.4% of the calculated values and were performed by Heterocyclic Chemical Corp. of Harrisonville, Mo., and Galbraith Laboratories, Inc., Knoxville, Tenn. Physical data not included in the Experimental Section are included in Tables I and II.

1(3)*H*-2-Methyl-7-phenylpyrazolo[1,5-*a*]-1,3,5-triazine-4-thione (11h). A suspension of 7.0 g (0.03 mol) of 3-amino-5-phenyl-2-*N*-thiocarbamoylpyrazole[17,18] in 50 ml of triethyl orthoacetate was refluxed for 5 h. The resultant solid was filtered, washed with EtOH, and then recrystallized from DMF to afford 5.5 g (50%) of the product as white needles, mp 318–320°. Anal. ($C_{12}H_{10}N_4S$) C, H, N.

2-Methyl-4-methylthio-7-phenylpyrazolo[1,5-*a*]-1,3,5-triazine (11g). A suspension of 5.0 g (0.021 mol) of **11h** in 100 ml of MeOH was stirred as 0.9 g (0.022 mol) of NaOH in 30 ml of H_2O was added. To this mixture was added 2.93 g (0.021 mol) of CH_3I and stirring was continued for 24 h at 25°. The solid was filtered and washed with water and then recrystallized from DMF to afford 5.5 g (76%) of the product as a white powder, mp 159–160°. Anal. ($C_{13}H_{12}N_4S$) C, H, N.

4-Hydrazino-2-methyl-7-phenylpyrazolo[1,5-*a*]-1,3,5-triazine (11f). A suspension of 5.0 g (0.02 mol) of **11g** in 150 ml of methanol was treated with 10 ml of 85% hydrazine hydrate at 25°, with stirring. The yellowish color of the solution was rapidly discharged and a flocculent white precipitate separated. The material was filtered, washed with water, and recrystallized from DMF to yield 2.5 g (30%) of the product, mp >300° dec. Anal. ($C_{12}H_{12}N$) C, H, N.

2-Methyl-4-(5-nitro-2-furfurylidene)hydrazino-7-phenylpyrazolo[1,5-*a*]-1,3,5-triazine (11d). A mixture of 1.4 g (5 mmol) of **11f** and 0.8 g (5 mmol) of 5-nitro-2-furfural in 100 ml of MeOH was stirred at 25° for 20 h. The light yellow mixture gradually became deep orange as the hydrazone formed. The precipitate was filtered, washed with MeOH, and dried to afford 2.1 g (93%) of the analytically pure product as a bright orange powder, mp 244–245°. Anal. ($C_{17}H_{13}N_7O_3$) C, H, N.

All of the other hydrazones listed in Table III (**1d–14d**) were prepared in an identical manner. Physical properties of these compounds are listed in Table II.

7-Hydrazino-5-methylpyrazolo[1,5-*a*]pyrimidine (2c). A solution of 8.15 g (0.05 mol) of 7-chloro-5-methylpyrazolo[1,5-*a*]pyrimidine[15] in 200 ml of EtOH was treated with 20 ml of 85% hydrazine hydrate at room temperature with stirring. The product precipitated almost immediately and was filtered, washed with EtOH, air-dried, and recrystallized from DMF to afford 8.5 g (75%) of the product as a white powder, mp 228–230° dec. Anal. ($C_7H_9N_5$) C, H, N.

Compounds **1c** and **5c–10c** were prepared in an identical manner and their properties are listed in Table I.

7-Hydrazino-5-methylpyrazolo[1,5-*a*]pyrimidine-3-sulfonic Acid (3c) and the Sodium Sulfonate Salt 4c. Powdered **2c** (1.63 g, 0.01 mol) was added cautiously to 10 ml of 98% fuming sulfuric acid at 0–10°, with stirring. The solution was allowed to warm to room temperature gradually and stirring was continued for 72 h. The solution was then poured over 100 g of crushed ice, stirring manually with a glass rod. The cold solution was neutralized with cold 6 N NaOH (pH 7.2) whereupon a voluminous white precipitate formed. The product was filtered, washed with 10 ml of ice H_2O, and dried. Recrystallization from DMF afforded 1.8 g (74%) of the product **3c**, mp >300° dec. Anal. ($C_7H_9N_5O_3S$) C, H, N.

The sodium sulfonate salt **4c** was prepared by dissolving 1 g of **3c** in 1 equiv of sodium carbonate in 20 ml of H_2O. The H_2O was evaporated slowly in a crystallizing dish to afford 1 g (75%) of **4c** as white cubettes, mp >300° dec. Anal. ($C_7H_8N_5O_3SNa\cdot H_2O$) C, H, N.

7-Hydrazino-5-methyl-*s*-triazolo[1,5-*a*]pyrimidine (12c) was prepared in an identical manner as **2c**, from hydrazine and 7-chloro-5-methyl-*s*-triazolo[1,5-*a*]pyrimidine:[20,21] colorless needles from H_2O; yield 85%; mp 260° dec. Anal. ($C_6H_8N_6$) C, H, N.

5-Methyl-7-(5-nitro-2-furfurylidene)hydrazino-*s*-triazolo[1,5-*a*]pyrimidine (12d) was prepared from **12c** in the same manner as **2d** was prepared from **2c**: yield 75%. Anal. ($C_{11}H_9O_3N_7$) C, H, N.

5-Hydrazino-7-methylimidazo[1,2-*a*]pyrimidine (14c) was prepared in 76% yield, mp >300°, from 5-chloro-7-methylimidazo[1,2-*a*]pyrimidine (**14b**), which was not stable enough to be analyzed but was prepared from 5-hydroxy-7-methylimidazo[1,2-*a*]pyrimidine[22] by the method used for the preparation of **2b**[15] and **12b**.[20] Anal. ($C_7H_9N_5$) C, H, N.

5-Hydrazino-7-chloroimidazo[1,2-*a*]pyrimidine (13c) was prepared in 95% yield from 5,7-dichloroimidazo[1,2-*a*]pyrimidine[13] to yield a product with mp >300°. Anal. ($C_6H_6N_5Cl$) C, H, N.

7-Methyl-5-(5-nitro-2-furfurylidene)hydrazinoimidazo[1,2-*a*]pyrimidine (14d) was prepared from **14c** as described for **11d** (see Table II). Likewise, **7-chloro-5-(5-nitro-2-furfurylidene)hydrazinoimidazo[1,2-*a*]pyrimidine (13d)** was prepared in the same manner from **13c** (see Table II).

3-Bromo-7-chloro-5-methylpyrazolo[1,5-*a*]pyrimidine (6b). A solution of 16.8 g (0.1 mol) of 7-chloro-5-methylpyrazolo[1,5-*a*]pyrimidine[15] in 200 ml of methylene chloride was cooled to 15° and 16.0 g (0.2 mol) of bromine in 50 ml of methylene chloride was added dropwise, with stirring. The yellowish hydrobromide salt of the product separated as a paste. The mixture was allowed to warm to room temperature and was then filtered, washed well with ether, and air-dried. The yellow HBr salt was then dissolved in 100 ml of H_2O, neutralized with $NaHCO_3$ solution, and extracted into fresh methylene chloride. The organic solvent was evaporated to afford a white solid which was recrystallized from EtOH to yield 18.0 g (78%) of the product as white needles, mp 100–102°. Anal. ($C_7H_5N_3ClBr$) C, H, N.

3-Ethoxycarbonyl-7-chloro-5-methylpyrazolo[1,5-*a*]pyrimidine (5b). A suspension of 3-ethoxycarbonyl-7-hydroxy-5-methylpyrazolo[1,5-*a*]pyrimidine[15] (2.3 g, 0.01 mol) in phosphorus oxychloride (30 ml) was refluxed for 30–40 min. The resultant clear red solution was partially distilled (rotovac, in vacuo at 40°) and the syrup remaining was cautiously poured over ice (50 g), with rapid stirring. The organic material was extracted immediately with methylene chloride (ether was inferior) and the solvent was washed ($NaHCO_3$ solution, twice) and dried (sodium sulfate). The methylene chloride extract was chromatographed on neutral alumina (100 g, Woelm grade I) with the same solvent. Evaporation of the appropriate solvent fraction gave 1.2 g (50%) of the product which was recrystallized from absolute EtOH as white plates, mp 120–121°. Anal. ($C_{10}H_{10}N_3O_2Cl$) C, H, N.

The other chloro heterocycles were prepared in the same manner.

7-Chloropyrazolo[1,5-*a*]pyrimidine (1b) was obtained in 52% yield from **1a**, mp 96–97° (EtOH). Anal. ($C_6H_4N_3Cl$) C, H, N.

7-Chloro-3-(4-chlorophenyl)-5-methylpyrazolo[1,5-*a*]pyrimidine (7b) was obtained in 43% yield from **7a**, mp 137–138° (EtOH). Anal. ($C_{12}H_9N_3Cl_2$) C, H, N.

5,7-Dichloropyrazolo[1,5-*a*]pyrimidine (9b) was obtained in 37% yield from **9a**,[14] mp 68–71° (EtOH). Anal. ($C_6H_3N_3Cl_2$) C, H, N.

7-Chloro-5-methyl-3-phenylpyrazolo[1,5-*a*]pyrimidine (8b) was prepared in 65% yield from **8a**, mp 151–152° (hexane–$CHCl_3$). Anal. ($C_{12}H_{10}N_3Cl$) C, H, N.

3,5,7-Trichloropyrazolo[1,5-*a*]pyrimidine (10b). A solution of 1.88 g (0.01 mol) of **9b** in 50 ml of $CHCl_3$ was treated with 1.5 g (0.01 mol plus slight excess) of *N*-chlorosuccinimide at 25°. The mixture was heated briefly on the steam bath until all the solids were dissolved and then the reaction was quenched by pouring the contents of the flask over ice. The $CHCl_3$ extract was washed with Na_2CO_3 solution (twice) and dried (sodium sulfate) and then chromatographed on neutral alumina (Woelm grade I) with the same solvent: yield 47%; mp 83–84° (EtOH). Anal. ($C_6H_2N_3Cl_3$) C, H, N.

3-(4-Chlorophenyl)-7-hydroxy-5-methylpyrazolo[1,5-*a*]pyrimidine (7a). A mixture of 3.87 g (20 mmol) of 3-amino-4-(4'-chlorophenyl)pyrazole,[23] 3.25 g (25 mmol) of ethyl acetoacetate, and 50 ml of glacial acetic acid was refluxed for 5 h. The resultant solution was evaporated in vacuo and the residue was taken up in boiling EtOH and allowed to cool, affording 4.8 g (92%) of the product as white needles, mp 210–212° (EtOH–DMF). Anal. ($C_{10}H_{10}N_3OCl$) C, H, N.

7-Hydroxy-5-methyl-3-phenylpyrazolo[1,5-*a*]pyrimidine (8a) was prepared in the same manner as **7a**, starting with 3-amino-4-phenylpyrazole.[23] The yield of **8a** was 98%; mp 291–293° dec (DMF–H_2O). Anal. ($C_{13}H_{11}N_3O$) C, H, N.

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