The Synthesis and Chemical Reactions of Certain Pyrazolo[1,5-*a*]-1,3,5-triazines (1)

Joze Kobe, Roland K. Robins, and Darrell E. O'Brien

ICN Pharmaceuticals, Inc., Nucleic Acid Research Institute,
2727 Campus Drive, Irvine, California 92664

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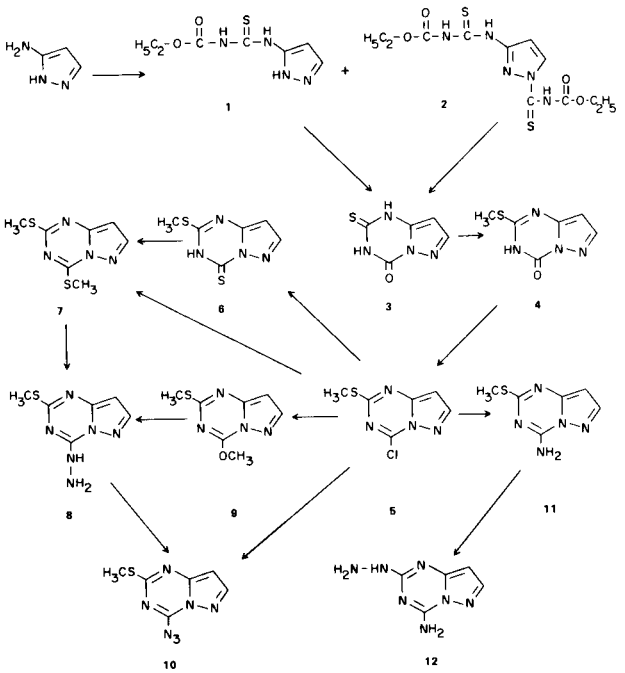
3-Aminopyrazole was utilized as a starting material for the preparation of certain pyrazolo-[1,5-*a*]-1,3,5-triazines. 4-Chloro-2-methylthiopyrazolo[1,5-*a*]-1,3,5-triazine was prepared and used for studies of nucleophilic displacement reactions, and it has been found that both the chloro and methylthio groups may be displaced by nucleophiles. By modifications of these procedures we have prepared the adenine, hypoxanthine, and xanthine analogs of the pyrazolo-[1,5-*a*]-1,3,5-triazine ring system. Electrophilic substitution occurs in the 8-position of this ring system. The methyl group was introduced into the 4-position by a novel ring opening and ring closing of the 1,3,5-triazine ring.

In a program that is concerned with the synthesis and pharmacological activities of certain nitrogen bridgehead compounds, we have investigated the pyrazolo[1,5-*a*]-1,3,5-triazine ring system. Derivatives of this ring system may be considered as isomeric with the corresponding purines and might be expected to inhibit various nucleic acid enzyme systems. In this study, we will report the synthesis and chemical properties of certain derivatives of this ring system.

The first derivative of this ring system, 2,4-diamino-7-phenylpyrazolo[1,5-*a*]-1,3,5-triazine, was prepared by the ring closure of 3-amino-5-phenylpyrazole with cyanoguanidine (2). The ready availability of 3-aminopyrazole (3), which might be visualized as an amidine in a typical *s*-triazine ring closure procedure (4), suggests that this pyrazole intermediate would serve as an excellent starting material for the preparation of pyrazolo[1,5-*a*]-1,3,5-triazines. The reaction of 3-aminopyrazole with ethoxycarbonyl isothiocyanate has been recently reported to yield *N*-carbethoxy-N^1-(pyrazol-3-yl)thiourea (**1**) which was ring closed by pyridine to yield 4-oxo-2-thioxo-1*H*,3*H*-pyrazolo[1,5-*a*]-1,3,5-triazine (**3**) in good yields (5).

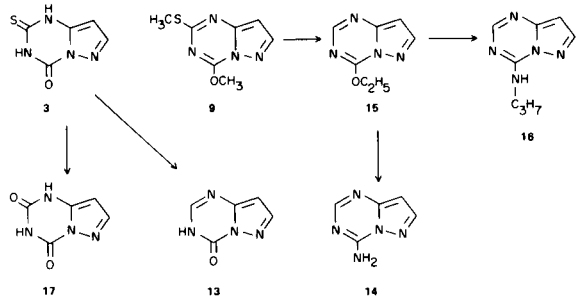
In our laboratories, the treatment of 3-aminopyrazole with ethoxycarbonyl isothiocyanate gave the expected *N*-carbethoxy-N^1-(pyrazol-3-yl)thiourea (**1**) as well as a low yield of *N*-carbethoxy-N^1-(1-carbethoxythiocarbamoylpyrazol-3-yl)thiourea (**2**). The identification of this *bis*-substituted product **2** was based on elemental analysis and pmr spectral data. Both **1** and **2** when treated with 2*N* sodium hydroxide at room temperature afforded 4-oxo-2-thioxo-1*H*,3*H*-pyrazolo[1,5-*a*]-1,3,5-triazine (**3**) which was identical in all respects to the product obtained by Capuano and Schrepfer (5).

Methylation of 4-oxo-2-thioxo-1*H*,3*H*-pyrazolo[1,5-*a*]-1,3,5-triazine (**3**) with methyl iodide gave a 90% yield of 2-methylthio-4-oxo-3*H*-pyrazolo[1,5-*a*]-1,3,5-triazine (**4**). The treatment of **4** with phosphorus oxychloride afforded 4-chloro-2-methylthiopyrazolo[1,5-*a*]-1,3,5-triazine (**5**) in good yield. The chloro derivative **5** proved to be a most versatile intermediate in the preparation of other derivatives of the pyrazolo[1,5-*a*]-1,3,5-triazine ring system.



The treatment of 4-chloro-2-methylthiopyrazolo[1,5-*a*]-1,3,5-triazine (**5**) with potassium hydrosulfide gave the corresponding 2-methylthio-4-thioxo-3*H*-pyrazolo[1,5-*a*]-

1,3,5-triazine (**6**). In an analogous manner, the reaction of **5** with methanethiol in the presence of base afforded 2,4-*bis*methylthiopyrazolo[1,5-*a*]-1,3,5-triazine (**7**). The latter compound, **7**, was also prepared by the methylation of 2-methylthio-4-thioxo-3*H*-pyrazolo[1,5-*a*]-1,3,5-triazine (**6**). When 2,4-*bis*methylthiopyrazolo[1,5-*a*]-1,3,5-triazine (**7**) was treated with hydrazine hydrate at room temperature, 4-hydrazino-2-methylthiopyrazolo[1,5-*a*]-1,3,5-triazine (**8**) was obtained. Proof that the methylthio group at the 4 position of compound **7** was replaced by the hydrazino moiety was noted by the fact that hydrazine hydrate converted 4-methoxy-2-methylthiopyrazolo[1,5-*a*]-1,3,5-triazine (**9**) to the corresponding 4-hydrazino analog (**8**). 4-Methoxy-2-methylthiopyrazolo[1,5-*a*]-1,3,5-triazine (**9**) was prepared by the reaction of sodium methoxide with 4-chloro-2-methylthiopyrazolo[1,5-*a*]-1,3,5-triazine (**5**). The treatment of 4-hydrazino-2-methylthiopyrazolo[1,5-*a*]-1,3,5-triazine with nitrous acid afforded 4-azido-2-methylthiopyrazolo[1,5-*a*]-1,3,5-triazine (**10**) which was also obtained directly from 4-chloro-2-methylthiopyrazolo[1,5-*a*]-1,3,5-triazine (**5**) with sodium azide. The corresponding 4-amino-2-methylthiopyrazolo[1,5-*a*]-1,3,5-triazine (**11**) was prepared from the corresponding 4-chloro derivative **5** and aqueous ammonia at room temperature. In each of these nucleophilic displacement reactions the methylthio moiety at the 2 position remained unchanged. However, replacement of the 2-methylthio group could also be accomplished under more vigorous reaction conditions. The treatment of 4-amino-2-methylthiopyrazolo[1,5-*a*]-1,3,5-triazine (**11**) with hydrazine hydrate in refluxing ethanol gave 4-amino-2-hydrazinopyrazolo[1,5-*a*]-1,3,5-triazine (**12**).

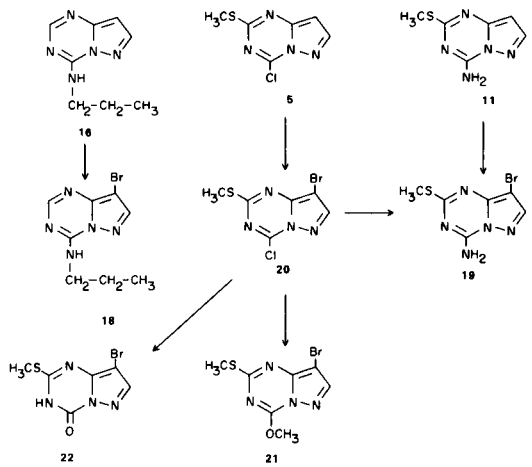


It was of interest to prepare several 4-substituted-pyrazolo[1,5-*a*]-1,3,5-triazines, in particular 4-oxo-3*H*-pyrazolo[1,5-*a*]-1,3,5-triazine (**13**) and 4-aminopyrazolo-[1,5-*a*]-1,3,5-triazine (**14**) which are the hypoxanthine and adenine analogs, respectively. Dethiation of 4-oxo-2-thioxo-1*H*,3*H*-pyrazolo[1,5-*a*]-1,3,5-triazine (**3**) with Raney nickel catalyst in dilute ammonia water gave a good yield of 4-oxo-3*H*-pyrazolo[1,5-*a*]-1,3,5-triazine (**13**). In an analogous manner, the dethiation of 4-methoxy-2-methylthiopyrazolo[1,5-*a*]-1,3,5-triazine (**9**) with Raney nickel catalyst in refluxing ethanol afforded 4-ethoxypyrazolo-[1,5-*a*]-1,3,5-triazine (**15**) (6). Refluxing a solution of **15** with an excess of aqueous ammonia in ethanol afforded the adenine analog 4-aminopyrazolo[1,5-*a*]-1,3,5-triazine (**14**) in 80% yields. In a similar manner, the treatment of **15** with *n*-propylamine in refluxing ethanol afforded the corresponding 4-*n*-propylaminopyrazolo[1,5-*a*]-1,3,5-triazine (**16**) in excellent yields.

The xanthine analog in the pyrazolo[1,5-*a*]-1,3,5-triazine ring system has also been prepared. The treatment of 4-oxo-2-thioxo-1*H*,3*H*-pyrazolo[1,5-*a*]-1,3,5-triazine with alkaline hydrogen peroxide readily afforded 2,4-dioxo-1*H*,3*H*-pyrazolo[1,5-*a*]-1,3,5-triazine (**17**). This product is identical in all respects to the product recently reported by Capuano and Schrepfer (5), who prepared **17** by alternative routes.

Electrophilic substitutions of certain pyrazolo[1,5-*a*]-1,3,5-triazines was next studied. It was expected that electrophilic substitution will occur at position 8 in the pyrazolo[1,5-*a*]-1,3,5-triazine ring system. This prediction is based on the fact that other nitrogen-bridgehead heteroaromatic systems involving the pyrazole moiety similarly undergo electrophilic substitution at this position (7,8). The treatment of 4-*n*-propylaminopyrazolo[1,5-*a*]-1,3,5-triazine (**16**) with *N*-bromosuccinimide in chloroform gave a good yield of 8-bromo-4-*n*-propylaminopyrazolo[1,5-*a*]-1,3,5-triazine (**18**). The site of electrophilic attack at position 8 was established, since the upfield proton at 6.48 δ (which is coupled to the proton at 8.19 δ; J = 2.4 Hz) found in 4-*n*-propylaminopyrazolo[1,5-*a*]-1,3,5-triazine (**16**) was absent in the bromo derivative **18**.

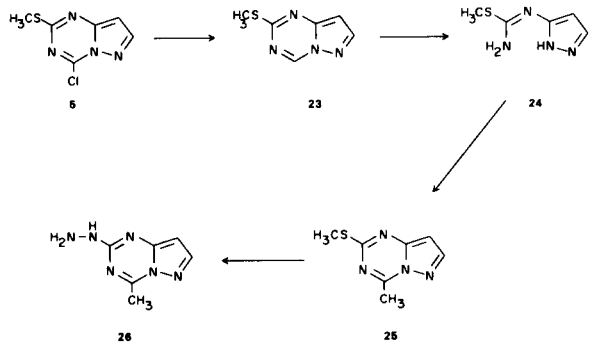
Similar bromination of 4-amino-2-methylthiopyrazolo-[1,5-*a*]-1,3,5-triazine (**11**) with *N*-bromosuccinimide gave 4-amino-8-bromo-2-methylthiopyrazolo[1,5-*a*]-1,3,5-triazine (**19**). The synthesis of **19** was also accomplished from 8-bromo-4-chloro-2-methylthiopyrazolo[1,5-*a*]-1,3,5-triazine (**20**) and ethanolic ammonia. The preparation of



20 was achieved in good yield by bromination of 4-chloro-2-methylthiopyrazolo[1,5-*a*]-1,3,5-triazine (**5**) with *N*-bromosuccinimide in refluxing chloroform. This bromination proceeds readily in good yield despite the electron withdrawing effect of the chloro substituent at position 4.

The nucleophilic displacement of the 4-chloro moiety of 8-bromo-4-chloro-2-methylthiopyrazolo[1,5-*a*]-1,3,5-triazine (**20**) was further demonstrated since **20** and 1.25 *N* sodium hydroxide at room temperature gave 8-bromo-2-methylthio-4-oxo-3*H*-pyrazolo[1,5-*a*]-1,3,5-triazine (**22**). Similarly sodium bicarbonate in refluxing methanol gave 8-bromo-4-methoxy-2-methylthiopyrazolo[1,5-*a*]-1,3,5-triazine (**21**) in good yield.

Reductive dehalogenation of 4-chloro-2-methylthiopyrazolo[1,5-*a*]-1,3,5-triazine (**5**) with palladium on charcoal catalyst in the presence of calcium oxide afforded 2-methylthiopyrazolo[1,5-*a*]-1,3,5-triazine (**23**) in 50-60% yield. The treatment of **23** with 0.5 *N* sodium hydroxide at room temperature resulted in opening of the 1,3,5-triazine ring to yield *S*-methyl-*N*-(pyrazol-3-yl)thiourea (**24**) in 70% yields. This thiourea derivative serves as an excellent starting material for the preparation of 4-alkyl derivatives of this ring system. Ring closure of *S*-methyl-*N*-(pyrazol-3-yl)thiourea (**24**) with refluxing triethyl orthoacetate afforded 4-methyl-2-methylthiopyrazolo[1,5-*a*]-1,3,5-triazine (**25**) in good yield. The treatment of **25** with hydrazine hydrate results in the displacement of the methylthio group and 2-hydrazino-4-methylpyrazolo-[1,5-*a*]-1,3,5-triazine was obtained.



It is interesting to point out that the pmr spectrum of **23** in DMSO-d_6 shows that the lowest field aromatic proton (at the 4 position), which occurs at 9.58 δ, is coupled to the least deshielded proton at position 8 ($J_{4,8}$ = 1.05 Hz). This results in long range splitting of the $H_{7,8}$ doublet at 6.56 δ. This long range coupling is similar to that reported recently for certain pyrazolo[1,5-*c*]pyrimidines (7). Such coupling was not observed with the H_2 proton of 4-ethoxypyrazolo[1,5-*a*]-1,3,5-triazine (**15**) and this long range coupling may be considered as a characteristic of the proton at the 4 position.

EXPERIMENTAL (9)

Reaction of 3-Aminopyrazole with Ethoxycarbonyl Isothiocyanate.

A solution of 3-aminopyrazole (2) (20.75 g., 0.25 mole) in 150 ml. of ethylacetate and 750 ml. of benzene was cooled to 5°. With good stirring, a solution of ethoxycarbonyl isothiocyanate (32.79 g., 0.25 mole) in 250 ml. of benzene was added dropwise to the cold solution. The addition was carried out during the period of 60 minutes keeping the temperature at 5 ± 2°. After the addition was complete, the mixture was allowed to stir at room temperature for 16 hours. The precipitated product was separated by filtration, dried, and recrystallized from ethyl acetate-*n*-hexane to afford 26.0 g. (49%) of analytically pure *N*-carbethoxy-*N'*-(pyrazol-3-yl)thiourea (**1**) that had a melting point of 158-159°. (Lit. (5) m.p. 163°).

Anal. Calcd. for $C_7H_{10}N_4O_2S$: C, 39.25; H, 4.71; N, 26.16; S, 14.94. Found: C, 38.98; H, 4.73; N, 26.18; S, 15.03.

The filtrate from the above reaction was evaporated to dryness, and the residue titurated with 25 ml. of ethyl acetate. This crude product weighed 20 g. and was composed of 2 major components as adjudged by thin layer chromatography on silica gel plates utilizing a solvent system of chloroform:ethyl acetate (9:1). A 1.8 g. sample of this crude product was subjected to column chromatography on 80 g. of silica gel and eluted with chloroform. Fractions from the 150-225 ml. elution afforded 1.15 g. of analytically pure *N*-carbethoxy-*N'*-(1-carbethoxythiocarbamoylpyrazol-3-yl)thiourea (**2**) that had a melting point of 146-148°.

Anal. Calcd. for $C_{11}H_{15}N_5O_4S_2$: C, 38.26; H, 4.38; N, 20.29; S, 18.53. Found: C, 38.06; H, 4.22; N, 20.12; S, 18.62.

Fractions from the 300-500 ml. elution afforded 400 mg. of analytically pure *N*-carbethoxy-*N'*-(pyrazol-3-yl)thiourea (**1**) with a melting point of 158-159°. The total yield of *N*-carbethoxy-*N'*-(pyrazol-3-yl)thiourea (**1**) was 59% and the yield of *N*-carbethoxy-*N'*-(1-carbethoxythiocarbamoylpyrazol-3-yl)thiourea (**2**) was 15%.

Preparation of 4-Oxo-2-thioxo-1*H*,3*H*-pyrazolo[1,5-*a*]-1,3,5-triazine (**3**).

Method A.

A solution of *N*-carbethoxy-*N'*-(pyrazol-3-yl)thiourea (**1**) (26.0 g., 0.121 mole) in 250 ml. of 2*N* sodium hydroxide was stirred at room temperature. This solution was acidified to *p*H 1 by the addition of 2*N* sulfuric acid. The light yellow product was separated by filtration, dried, and recrystallized from water to afford 19.3 g. (96%) of analytically pure 4-oxo-2-thioxo-1*H*,3*H*-pyrazolo[1,5-*a*]-1,3,5-triazine (**3**) that had a melting point of 297-299°. (Lit. (5) m.p. 298-300°).

Anal. Calcd. for $C_5H_4N_4OS$: C, 35.72; H, 2.40; N, 33.33; S, 19.10. Found: C, 35.72; H, 2.37; N, 33.49; S, 19.17.

Method B.

A solution of *N*-carbethoxy-*N'*-(1-carbethoxythiocarbamoylpyrazol-3-yl)thiourea (**2**) (250 mg., 0.72 mole) in 2 ml. of 2*N* sodium hydroxide was stirred overnight and the solution acidified to *p*H 1 by the addition of 2*N* sulfuric acid. The precipitated product, 60 mg. (45%) was identical in all respects to the product isolated by Method A.

Preparation of 2-Methylthio-4-oxo-3*H*-pyrazolo[1,5-*a*]-1,3,5-triazine (**4**).

A solution of 4-oxo-2-thioxo-1*H*,3*H*-pyrazolo[1,5-*a*]-1,3,5-triazine (**3**) (1.45 g., 8.65 mmoles) in 35 ml. of absolute ethanol

and 10 ml. of 1.73*N* sodium hydroxide solution was stirred at room temperature while methyl iodide (1.23 g., 8.65 mmoles) was added dropwise. Ten minutes after the addition was complete, the white sodium salt of the product began to precipitate. This mixture was stirred an additional 20 minutes and the sodium salt was separated by filtration. This sodium salt was dissolved in a minimum amount of water and acidified with 2*N* sulfuric acid. The precipitated product was separated by filtration, and recrystallization from aqueous ethanol afforded 1.4 g. (90%) of analytically pure product that had a melting point of 255-257°.

Anal. Calcd. for $C_6H_6N_4OS$: C, 39.56; H, 3.32; N, 30.76; S, 17.55. Found: C, 39.60; H, 3.34; N, 30.97; S, 17.76.

Preparation of 4-Chloro-2-methylthiopyrazolo[1,5-*a*]-1,3,5-triazine (**5**).

A mixture of 2-methylthio-4-oxo-3*H*-pyrazolo[1,5-*a*]-1,3,5-triazine (**4**) (15.0 g., 0.082 mole), 225 ml. of phosphorus oxychloride, and 5 ml. of *N,N*-dimethylaniline was heated at reflux for 2 hours, at which time a complete solution was obtained. The excess phosphorus oxychloride was removed *in vacuo* and the syrup residue was added slowly to crushed ice (750 g.) with good stirring. The light orange crystals were collected by filtration, washed with water, air dried, and recrystallized from *n*-heptane to yield 11.4 g. (70%) of analytically pure 4-chloro-2-methylthiopyrazolo[1,5-*a*]-1,3,5-triazine (**5**) that had a melting point of 130-132°.

Anal. Calcd. for $C_6H_5ClN_4S$: C, 35.89; H, 2.51; N, 27.93; S, 15.98; Cl, 17.67. Found: C, 35.63; H, 2.70; N, 27.71; S, 16.06; Cl, 17.43.

Preparation of 4-Methoxy-2-methylthiopyrazolo[1,5-*a*]-1,3,5-triazine (**9**).

4-Chloro-2-methylthiopyrazolo[1,5-*a*]-1,3,5-triazine (**5**) (1.50 g., 7.5 mmoles) was added to a suspension of sodium bicarbonate (0.65 g., 0.0077 formula weights) in 25 ml. of methanol. The resulting mixture was refluxed for 2½ hours and then evaporated to dryness. The residue was covered with 10 ml. of cold water and the white crystalline product separated by filtration. Recrystallization from *n*-heptane afforded 1.1 g. (75%) of analytically pure 4-methoxy-2-methylthiopyrazolo[1,5-*a*]-1,3,5-triazine (**9**) that had a melting point of 127-129°.

Anal. Calcd. for $C_7H_8N_4OS$: C, 42.86; H, 4.11; N, 28.56; S, 16.36. Found: C, 42.63; H, 4.27; N, 28.74; S, 16.43.

Preparation of 2-Methylthio-4-thioxo-3*H*-pyrazolo[1,5-*a*]-1,3,5-triazine (**6**).

A solution of potassium hydrosulfide in ethanol was prepared by saturating a solution of potassium hydroxide (1.1 g., 0.02 formula weights) in 30 ml. of ethanol with anhydrous hydrogen sulfide. With good stirring, 4-chloro-2-methylthiopyrazolo[1,5-*a*]-1,3,5-triazine (**5**) (2.00 g., 0.01 mole) was added to the solution, and the resulting mixture heated at reflux for 1 hour. After cooling, the potassium salt of the product was separated by filtration, dissolved in 50 ml. of water. Acidification of this water solution with 2*N* sulfuric acid precipitated the desired product. Recrystallization from aqueous ethanol afforded 1.6 g. (80%) of analytically pure product, m.p. 264-266°.

Anal. Calcd. for $C_6H_6N_4S_2$: C, 36.37; H, 3.05; N, 28.28; S, 32.30. Found: C, 36.26; H, 3.03; N, 28.30; S, 32.45.

Preparation of 2,4-*Bis*methylthiopyrazolo[1,5-*a*]-1,3,5-triazine (**7**).

A solution of 2-methylthio-4-thioxo-3*H*-pyrazolo[1,5-*a*]-1,3,5-triazine (**6**) (1.15 g., 5.8 mmoles) in 10 ml. of 1.5*N* sodium hydroxide solution and 20 ml. of absolute ethanol was stirred at room temperature and treated with methyl iodide (0.825 g., 5.8 mmoles). After the addition was complete, the mixture was stirred at room temperature and then the product was separated by filtration. Recrystallization from aqueous ethanol afforded 1.0 g. (82%) of analytically pure 2,4-*bis*methylthiopyrazolo[1,5-*a*]-1,3,5-triazine (**7**), m.p. 133-135°.

Anal. Calcd. for $C_7H_8N_4S_2$: C, 39.62; H, 3.80; N, 26.41; S, 30.16. Found: C, 39.74; H, 3.88; N, 26.18; S, 30.31.

Preparation of 4-Hydrazino-2-methylthiopyrazolo[1,5-*a*]-1,3,5-triazine (**8**).

A solution of 2,4-*bis*methylthiopyrazolo[1,5-*a*]-1,3,5-triazine (**7**) (530 mg., 2.5 mmoles) and 0.15 ml. of 85% hydrazine hydrate in 10 ml. of absolute methanol was stirred at room temperature for 1 hour. At the end of this time, the mixture was chilled and the product separated by filtration. Recrystallization from methanol afforded 450 mg. (92%) of analytically pure 4-hydrazino-2-methylthiopyrazolo[1,5-*a*]-1,3,5-triazine (**8**) that had a melting point of 213-215°.

Anal. Calcd. for $C_6H_8N_6S$: C, 36.73; H, 4.11; N, 42.84; S, 16.31. Found: C, 36.71; H, 4.21; N, 42.57; S, 16.41.

4-Hydrazino-2-methylthiopyrazolo[1,5-*a*]-1,3,5-triazine (**8**) was obtained in 90% yields when 4-methoxy-2-methylthiopyrazolo-[1,5-*a*]-1,3,5-triazine (**9**) was treated with hydrazine in an analogous manner.

Preparation of 4-Azido-2-methylthiopyrazolo[1,5-*a*]-1,3,5-triazine (**10**).

Method A.

A suspension of 4-chloro-2-methylthiopyrazolo[1,5-*a*]-1,3,5-triazine (**5**) (1.00 g., 5 mmoles) and sodium azide (0.70 g., 0.0118 formula weights) in 20 ml. of water was stirred at room temperature for 2 hours. The white solid was collected by filtration and dried. This product was found to be sensitive to light with a deep yellow color developing. Recrystallization of this yellow product from aqueous ethanol afforded 950 mg. (92%) of analytically pure 4-azido-2-methylthiopyrazolo[1,5-*a*]-1,3,5-triazine (**10**) that was isolated as yellow crystals that had a melting point of 138-140°.

Anal. Calcd. for $C_6H_5N_7S$: C, 34.78; H, 2.43; N, 47.33; S, 15.45. Found: C, 34.64; H, 2.36; N, 47.07; S, 15.67.

Method B.

A solution of 4-hydrazino-2-methylthiopyrazolo[1,5-*a*]-1,3,5-triazine (**8**) (200 mg., 1.1 mmoles) in 1.6 ml. of 2*N* hydrochloric acid and 2.0 ml. of absolute ethanol was cooled to 8°. With good stirring, a solution of sodium nitrite (80 mg., 0.00116 formula weights) in 0.5 ml. of water was added dropwise over a period of 5 minutes. After the addition was complete, the mixture was stirred at room temperature for 1 hour and the solids collected by filtration. Recrystallization from aqueous ethanol afforded 200 mg. (95%) of analytically pure 4-azido-2-methylthiopyrazolo[1,5-*a*]-1,3,5-triazine (**10**) that was identical in all respects to the product obtained by Method A.

Preparation of 4-Amino-2-methylthiopyrazolo[1,5-*a*]-1,3,5-triazine (**11**).

Heat was evolved when 4-chloro-2-methylthiopyrazolo[1,5-*a*]-1,3,5-triazine (**5**) (2.0 g., 10 mmoles) was added to a solution of 2.8 ml. of 28% ammonium hydroxide and 10 ml. of absolute ethanol. The resulting solution was stirred at room temperature for 15 hours and the white crystalline product was separated by filtration, triturated with water, and dried. Recrystallization

from aqueous ethanol afforded 1.61 g. (89%) of analytically pure 4-amino-2-methylthiopyrazolo[1,5-*a*]-1,3,5-triazine (**11**), m.p. 218-220°.

Anal. Calcd. for $C_6H_7N_5S$: C, 39.78; H, 3.89; N, 38.66; S, 17.66. Found: C, 39.85; H, 3.63; N, 38.70; S, 17.77.

Preparation of 4-Amino-2-hydrazinopyrazolo[1,5-*a*]-1,3,5-triazine (**12**).

A solution of 4-amino-2-methylthiopyrazolo[1,5-*a*]-1,3,5-triazine (**11**) (0.9 g., 5 mmoles) and 85% hydrazine hydrate (1.3 g.) in 50 ml. of absolute ethanol was refluxed for 24 hours, and then allowed to cool. The crystalline product was separated by filtration, dried, and recrystallized from ethanol to afford 0.7 g. (83%) of analytically pure 4-amino-2-hydrazinopyrazolo[1,5-*a*]-1,3,5-triazine (**12**) that had a melting point of 222-223°.

Anal. Calcd. for $C_5H_7N_7$: C, 36.36; H, 4.27; N, 59.37. Found: C, 36.25; H, 4.35; N, 59.51.

Preparation of 4-Oxo-3*H*-pyrazolo[1,5-*a*]-1,3,5-triazine (**13**).

Raney nickel (100 g., W. R. Grace catalyst No. 28) was added to a solution of 2-methylthio-4-oxo-3*H*-pyrazolo[1,5-*a*]-1,3,5-triazine (**3**) (12.0 g., 71.5 mmoles) in 550 ml. of 3% ammonium hydroxide. This suspension was stirred and heated at reflux for 1½ hours. The catalyst was separated by filtration of the hot suspension and washed with 200 ml. of hot water. The combined filtrate and wash solutions were evaporated to 60 ml. and acidified with 2*N* sulfuric acid. The precipitated product was separated by filtration, dried, and recrystallized from ethyl acetate to afford 5.8 g. (60%) of analytically pure 4-oxo-3*H*-pyrazolo-[1,5-*a*]-1,3,5-triazine (**13**) that had a melting point of 267-268° dec.

Anal. Calcd. for $C_5H_4N_4O$: C, 44.12; H, 2.96; N, 41.17. Found: C, 44.21; H, 3.02; N, 41.25.

Preparation of 4-Ethoxypyrazolo[1,5-*a*]-1,3,5-triazine (**15**).

To a well washed (absolute ethanol) suspension of Raney nickel (22 g., W. R. Grace catalyst No. 28) in 125 ml. of absolute ethanol was added 4-methoxy-2-methylthiopyrazolo[1,5-*a*]-1,3,5-triazine (**9**) (1.7 g., 8.6 mmoles), and this mixture was refluxed with stirring for 1 hour. The hot suspension was filtered and the solids washed with 100 ml. of hot ethanol. The combined ethanol washings and filtrate were evaporated to dryness at 35° *in vacuo*. Recrystallization of the residue from *n*-hexane afforded 700 mg. (50%) of analytically pure product that had a melting point of 50-52°; pmr (DMSO-d_6): δ 1.53 (t, 3), 4.8 (q, 2), 6.73 (d, J = 2.1 Hz, 1), 8.31 (d, J = 2.1 Hz, 1), and 8.41 ppm (s, 1).

Anal. Calcd. for $C_7H_8N_4O$: C, 51.21; H, 4.91; N, 34.13. Found: C, 50.90; H, 5.11; N, 34.32.

Preparation of 4-Aminopyrazolo[1,5-*a*]-1,3,5-triazine (**14**).

A mixture of 4-ethoxypyrazolo[1,5-*a*]-1,3,5-triazine (**15**) (300 mg., 1.8 mmoles) and 28% ammonium hydroxide (0.6 ml.) in 20 ml. of absolute ethanol was heated at reflux for 12 hours. At the end of this time, the solution was evaporated to dryness, and the residue recrystallized from absolute ethanol to afford 200 mg. (81%) of analytically pure 4-aminopyrazolo[1,5-*a*]-1,3,5-triazine (**14**) that had a melting point of 204-205°.

Anal. Calcd. for $C_5H_5N_5$: C, 44.44; H, 3.73; N, 51.83. Found: C, 44.29; H, 3.54; N, 52.04.

Preparation of 4-*n*-Propylaminopyrazolo[1,5-*a*]-1,3,5-triazine (**16**).

A solution of 4-ethoxypyrazolo[1,5-*a*]-1,3,5-triazine (**15**) (0.82 g., 5 mmoles) in 10 ml. of absolute ethanol was treated with *n*-propylamine (0.30 g., 5 mmoles). This solution was stirred at room temperature for 2 hours and then evaporated to dryness *in vacuo*. Recrystallization of the residue from an ethyl acetate-*n*-hexane mixture afforded 850 mg. (95%) of analytically pure 4-*n*-propylaminopyrazolo[1,5-*a*]-1,3,5-triazine (**16**) that had a melting point of 103-105°; pmr (DMSO-d_6): δ 0.95 (t, 3), 1.72 (m, 2), 3.55 (m, 2), 6.48 (d, J = 2.4 Hz, 1), 8.19 (d, J = 2.4 Hz, 1), 8.2 (s, 1), and 8.9 ppm (broad, 1).

Anal. Calcd. for $C_8H_{11}N_5$: C, 54.22; H, 6.26; N, 39.52. Found: C, 54.17; H, 6.32; N, 39.70.

Preparation of 2,4-Dioxo-1*H*,3*H*-pyrazolo[1,5-*a*]-1,3,5-triazine (**17**).

A solution of 4-oxo-2-thioxo-1*H*,3*H*-pyrazolo[1,5-*a*]-1,3,5-triazine (**3**) (1.68 g., 10 mmoles) in 80 ml. of 0.25*N* sodium hydroxide was cooled to 0°. With good stirring, 20 ml. of 30% hydrogen peroxide was added dropwise to the cool solution. The temperature was maintained at 0° during the addition, and after the addition was complete the solution was stirred at 0° for an additional 15 minutes. The slightly turbid solution was allowed to warm to room temperature and then acidified to *p*H 1 by the addition of 2*N* sulfuric acid. This acidic mixture was chilled and the precipitated product separated by filtration. Recrystallization from water afforded 1.10 g. (73%) of analytically pure 2,4-dioxo-1*H*,3*H*-pyrazolo[1,5-*a*]-1,3,5-triazine (**17**) that had a melting point of 328-330°. (Lit. (5) m.p. sinters at 330°).

Anal. Calcd. for $C_5H_4N_4O_2$: C, 39.48; H, 2.65; N, 36.84. Found: C, 39.37; H, 2.45; N, 36.82.

Preparation of 8-Bromo-4-*n*-propylaminopyrazolo[1,5-*a*]-1,3,5-triazine (**18**).

A solution of 4-*n*-propylaminopyrazolo[1,5-*a*]-1,3,5-triazine (**16**) (350 mg., 2 mmoles) in 5 ml. of chloroform was treated with *N*-bromosuccinimide (360 mg., 2 mmoles). The resultant mixture was heated at reflux for 5 minutes, stirred at room temperature for 2 hours, and finally chilled. The solids were removed by filtration and the filtrate washed with saturated sodium carbonate solution, dried over anhydrous sodium sulfate, and evaporated to dryness. The residue was recrystallized from *n*-hexane to afford 400 mg. (78%) of analytically pure product that had a melting point of 104-106°; pmr (DMSO-d_6): δ 0.95 (t, 3), 1.72 (m, 2), 3.55 (m, 2), 8.23 (s, 1), 8.32 (s, 1) and 9.0 ppm (broad, 1).

Anal. Calcd. for $C_8H_{10}BrN_5$: C, 37.51; H, 3.93; N, 27.34. Found: C, 37.59; H, 3.77; N, 27.44.

Preparation of 4-Amino-8-bromo-2-methylthiopyrazolo[1,5-*a*]-1,3,5-triazine (**19**).

A mixture of 4-amino-2-methylthiopyrazolo[1,5-*a*]-1,3,5-triazine (**11**) (0.9 g., 5 mmoles) and *N*-bromosuccinimide (0.9 g., 5.05 mmoles) in 30 ml. of chloroform was heated at reflux for 1 hour. This mixture was filtered while hot, and the separated solids were triturated with water and dried. Recrystallization from ethanol afforded 1.10 g. (85%) of analytically pure product that had a melting point of 268-270° dec.

Anal. Calcd. for $C_6H_6BrN_5S$: C, 27.70; H, 2.32; N, 26.93; S, 12.30; Br, 30.72. Found: C, 27.57; H, 2.28; N, 27.17; S, 12.30; Br, 30.99.

Preparation of 8-Bromo-4-chloro-2-methylthiopyrazolo[1,5-*a*]-1,3,5-triazine (**20**).

A mixture of 4-chloro-2-methylthiopyrazolo[1,5-*a*]-1,3,5-triazine (**5**), (1.6 g., 8 mmoles) and *N*-bromosuccinimide (1.42 g., 8 mmoles) in 15 ml. chloroform was refluxed for 10 minutes, at which time a complete solution was formed. The solution was stirred at room temperature for 2 hours, and the succinimide that precipitated was separated by filtration. The filtrate was extracted

with saturated sodium carbonate solution, and the chloroform layer evaporated to dryness. Recrystallization of the residue from a mixture of ethyl acetate-*n*-hexane afforded 1.7 g. (77%) of analytically pure 8-bromo-4-chloro-2-methylthiopyrazolo[1,5-*a*]-1,3,5-triazine (**20**) that had a melting point of 143-145°.

Anal. Calcd. for $C_6H_4BrClN_4S$: C, 25.78; H, 1.44; N, 20.04; S, 11.44. Found: C, 25.50; H, 1.33; N, 20.27; S, 11.22.

Preparation of 8-Bromo-4-methoxy-2-methylthiopyrazolo[1,5-*a*]-1,3,5-triazine (**21**).

A solution of 8-bromo-4-chloro-2-methylthiopyrazolo[1,5-*a*]-1,3,5-triazine (**20**) (2.79 g., 10 mmoles) and sodium bicarbonate (84 mg., 0.01 formula weights) in 200 ml. of methanol was stirred and heated at reflux for 1 hour. At the end of this time, the mixture was cooled, filtered, and the filtrate evaporated to dryness. Recrystallization of the residue from *n*-heptane afforded the analytically pure 8-bromo-4-methoxy-2-methylthiopyrazolo[1,5-*a*]-1,3,5-triazine (**21**) in 73% yield, m.p. 157-159°.

Anal. Calcd. for $C_7H_7BrN_4OS$: C, 30.6; H, 2.55; N, 20.4. Found: C, 30.6; H, 2.55; N, 20.2.

Preparation of 8-Bromo-2-methylthio-4-oxo-3*H*-pyrazolo[1,5-*a*]-1,3,5-triazine (**22**).

A suspension of 8-bromo-4-chloro-2-methylthiopyrazolo[1,5-*a*]-1,3,5-triazine (**20**) (1.0 g., 3.58 mmoles) in 20 ml. of 1.25*N* sodium hydroxide was stirred at room temperature for 3 hours. At the end of this time, the solution was treated with decolorizing carbon and filtered. Acidification of the filtrate to *p*H 1 by the addition of concentrated hydrochloric acid precipitated the product. Recrystallization from aqueous ethanol afforded 400 mg. (43%) of analytically pure 8-bromo-2-methylthio-4-oxo-3*H*-pyrazolo[1,5-*a*]-1,3,5-triazine (**22**) that had a melting point of 360°.

Anal. Calcd. for $C_6H_5BrN_4OS$: C, 27.60; H, 1.90; N, 21.5. Found: C, 27.56; H, 1.90; N, 21.68.

Preparation of 2-Methylthiopyrazolo[1,5-*a*]-1,3,5-triazine (**23**).

A mixture of 4-chloro-2-methylthiopyrazolo[1,5-*a*]-1,3,5-triazine (**5**) (6.0 g., 30 mmoles), 5% palladium on charcoal catalyst (5.0 g.), and calcium oxide (1.2 g.) in 300 ml. of isopropyl alcohol was hydrogenated in a Parr apparatus at an initial pressure of 4 atmosphere of hydrogen. After hydrogen uptake had stopped (16 hours), the mixture was evaporated to dryness. The residue was extracted twice with 400 ml. of boiling *n*-heptane, and the combined *n*-heptane extracts on cooling deposited 2.1 g. of analytically pure 2-methylthiopyrazolo[1,5-*a*]-1,3,5-triazine (**23**) that had a melting point of 141-143°.

Evaporation of the *n*-heptane filtrate afforded 1.4 g. of crude product which was purified by column chromatography on silica gel (75 g.) utilizing chloroform as the solvent. Evaporation of the chloroform eluate afforded 700 mg. of analytically pure 2-methylthiopyrazolo[1,5-*a*]-1,3,5-triazine (**23**) that had a melting point of 141-143°. The total yield was 2.80 g. (56%); pmr (DMSO-d_6): δ 2.59 (s, 3), 6.56 (dd, $J_{7,8}$ = 2.28 Hz, $J_{4,8}$ = 1.05 Hz, 1), 8.31 (d, J = 2.28 Hz, 1) and 9.58 ppm (s, 1).

Anal. Calcd. for $C_6H_6N_4S$: C, 43.37; H, 3.64; N, 33.73; S, 19.26. Found: C, 43.11; H, 3.62; N, 33.49; S, 19.34.

Preparation of *S*-Methyl-*N*-[pyrazol-3-yl]thiourea (**24**).

A solution of 2-methylthiopyrazolo[1,5-*a*]-1,3,5-triazine (**23**) (830 mg., 5 mmoles) in 10 ml. of 0.5*N* sodium hydroxide was stirred at room temperature for 16 hours. The mixture was evaporated to dryness *in vacuo* at room temperature and the residue was extracted with hot ethyl acetate. On cooling, the ethyl acetate extract deposited 550 mg. (71%) of analytically pure *S*-methyl-*N*-[3-pyrazolyl]thiourea (**24**) that had a melting point of 92-94°.

Anal. Calcd. for $C_5H_8N_4S$: C, 38.46; H, 5.16; N, 35.88; S, 20.49. Found: C, 38.46; H, 5.18; N, 36.00; S, 20.55.

Preparation of 4-Methyl-2-methylthiopyrazolo[1,5-*a*]-1,3,5-triazine (**25**).

A solution of *S*-methyl-*N*-[3-pyrazolyl]thiourea (**24**) (200 mg., 1.28 mmoles) in 5 ml. of triethylorthoacetate was heated at reflux for 24 hours. At the end of this time, the solution was evaporated to dryness, and the residue recrystallized from *n*-hexane to afford 120 mg. (56%) of analytically pure 4-methyl-2-methylthiopyrazolo[1,5-*a*]-1,3,5-triazine (**25**) that had a melting point of 126-128°.

Anal. Calcd. for $C_7H_8N_4S$: C, 46.44; H, 4.48; N, 31.10; S, 17.76. Found: C, 46.53; H, 4.35; N, 31.23; S, 17.81.

Preparation of 2-Hydrazino-4-methylpyrazolo[1,5-*a*]-1,3,5-triazine (**26**).

A solution of 4-methyl-2-methylthiopyrazolo[1,5-*a*]-1,3,5-triazine (**25**) (400 mg., 2.38 mmoles) and 0.14 ml. of 85% hydrazine hydrate in 15 ml. of absolute ethanol was heated at reflux for 16 hours. Evaporation of this solution, and recrystallization of the residue from aqueous ethanol afforded 350 mg. (90%) of analytically pure 2-hydrazino-4-methylpyrazolo[1,5-*a*]-1,3,5-triazine (**26**) that had a melting point of 265-266°.

Anal. Calcd. for $C_6H_8N_6$: C, 43.89; H, 4.91; N, 51.20. Found: C, 43.92; H, 5.18; N, 51.25.

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