Synthesis of 1,3-Dialkylpyrazolo[1,5-*a*]-1,3,5-triazine-2,4-diones Isomers of 1,3-Dialkylxanthines

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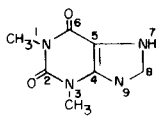
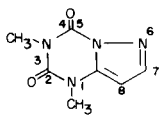
The synthesis of a new series of alkylxanthine analogs containing a bridgehead nitrogen atom is reported. 1,3-Dialkylpyrazolo[1,5-*a*]-1,3,5-triazine-2,4-diones, were prepared by the treatment of 3-methylpyrazolo[1,5-*a*]-1,3,5-triazine-2,4-dione (**3**) with the corresponding alkyl iodide. Similarly, the reaction of 3-methyl-7-phenylpyrazolo[1,5-*a*]-1,3,5-dialkyl-7-phenylpyrazolo[1,5-*a*]-1,3,5-triazine-2,4-diones. The starting materials, **3** and **17**, were prepared *via* the reaction of an appropriate 3-aminopyrazole with ethoxycarbonyl isothiocyanate. Several 8-bromo derivatives were prepared by direct bromination of the 1,3-dialkylpyrazolo[1,5-*a*]-1,3,5-triazine-2,4-diones.

Since the methylxanthines (1-3) caffeine and theophylline are now known to function as inhibitors of cyclic AMP phosphodiesterase (PDE), a number of substituted xanthine derivatives (4-6) have recently been examined for their ability to inhibit this enzyme isolated from various sources. In the course of our synthetic program on bridgehead nitrogen heterocycles as inhibitors of PDE (7), it became desirable to investigate the chemistry and biological properties of 1,3-dialkylpyrazolo[1,5-*a*]-1,3,5-triazine-2,4-diones. Structure **7** is of particular interest since it may be regarded as theophylline with the C_5 and N_9 atoms interchanged.



Theophylline



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Although the pyrazolo[1,5-*a*]-1,3,5-triazine ring system is closely related to the biologically important purines, it has been little explored. Recently, the synthesis of certain pyrazolo[1,5-*a*]-1,3,5-triazine including the isosteric xanthine analog pyrazolo[1,5-*a*]-1,3,5-triazine-2,4-dione (**10**) has been reported from this laboratory (8).

In the present work, 3-methylpyrazolo[1,5-*a*]-1,3,5-triazine-2,4-dione (**3**) was selected as a key intermediate for the synthesis of isosteric alkylxanthine derivatives. The treatment of 2-methylthiopyrazolo[1,5-*a*]-1,3,5-triazine-4-one (**1**) (8) with methyl iodide afforded 3-methyl iodide afforded 3-methyl-2-methylthiopyrazolo[1,5-*a*]-1,3,5-triazin-4-one (2). The structure of **2** was established by removal of the methylthio group with Raney nickel to 3-methylpyrazolo[1,5-*a*]-1,3,5-triazin-4-one (**4**). Compound **4** was identical in all respects to the product obtained by the facile cyclization of 3-amino-2-*N*-methylcarbamoylpyrazole (**5**) (9) with triethyl orthoformate. Alternatively, the direct methylation of pyrazolo[1,5-*a*]-1,3,5-triazin-4-one (**6**) (8) gave **4**. The action of hydrogen peroxide on **2** provided 3-methylpyrazolo[1,5-*a*]-1,3,5-triazine-2,4-dione (**3**) in good yield.

Compound 3-methylpyrazolo[1,5-*a*]-1,3,5-triazine-2,4-dione (**3**) obtained here served as a useful starting material for the synthesis of the desired xanthines. For example, reaction of **3** with methyl iodide gave an analog of theophylline, 1,3-dimethylpyrazolo[1,5-*a*]-1,3,5-triazine-2,4-dione (**7**). The same product was also obtained by the methylation of pyrazolo[1,5-*a*]-1,3,5-triazine-2,4-dione (**10**) (8) with methyl iodide. In an analogous manner, 1-ethyl-3-methylpyrazolo[1,5-*a*]-1,3,5-triazine-2,4-dione (**8**) and 3-methyl-1-*n*-propylpyrazolo[1,5-*a*]-1,3,5-triazine-2,4-dione (**9**) were similarly prepared by the treatment of **3** with the corresponding alkyl iodide.

As described in the recent report from this laboratory (8), electrophilic bromination of pyrazolo[1,5-*a*]-1,3,5-triazine ring system occurs at position 8. This treatment of 1,3-dimethylpyrazolo[1,5-*a*]-1,3,5-triazine-2,4-dione (**7**) with *N*-bromosuccinimide in chloroform to give 8-bromo-1,3-dimethylpyrazolo[1,5-*a*]-1,3,5-triazine-2,4-dione (11). The introduction of bromine at position 8 was desirable since the presence of such a bromine in the pyrazole ring had recently been shown to increase the PDE inhibitory properties of certain pyrazolo[1,5-*a*]pyrimidines.

In addition to the synthesis of 1,3-dialkylpyrazolo-[1,5-*a*]-1,3,5-triazine-2,4-diones, it was desirable to prepare certain 1,3-dialkyl-7-phenylpyrazolo[1,5-*a*]-1,3,5-triazine-2,4-diones to study the effect of the phenyl group on the biological activity of this group of compounds.

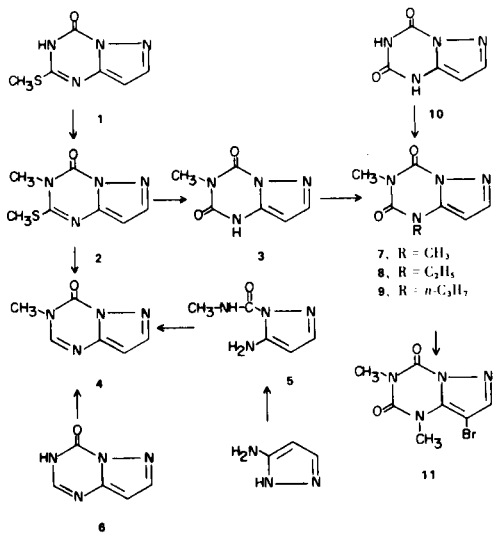
The required starting material, 3-*N*-carbethoxythiocarbonyl-5-phenylpyrazole (**12**) for the synthesis of 7-phenyl substituted derivatives was prepared in good yield by the treatment of 3-amino-5-phenylpyrazole (11) with ethoxycarbonyl isothiocyanate. The treatment of **12** with 2*N* sodium hydroxide at room temperature gave 7-phenyl-2-thiopyrazolo[1,5-*a*]-1,3,5-triazin-4-one (**13**). Compound **13** was converted to 7-phenylpyrazolo[1,5-*a*]-1,3,5-triazine-2,4-dione (**14**) by the action of hydrogen peroxide. The treatment of **13** with one mole of methyl iodide afforded 2-methylthio-7-phenylpyrazolo[1,5-*a*]-1,3,5-triazin-4-one (**15**). Further methylation of **15** with methyl iodide in dimethylformamide gave 3-methyl-2-methylthio-7-phenylpyrazolo[1,5-*a*]-1,3,5-triazin-4-one (**16**). Alternatively, compound **16** was prepared directly by methylation of **13** with excess methyl iodide. The action of hydrogen peroxide on **16** readily afforded the key intermediate, 3-methyl-7-phenylpyrazolo[1,5-*a*]-1,3,5-triazine-2,4-dione (**17**).

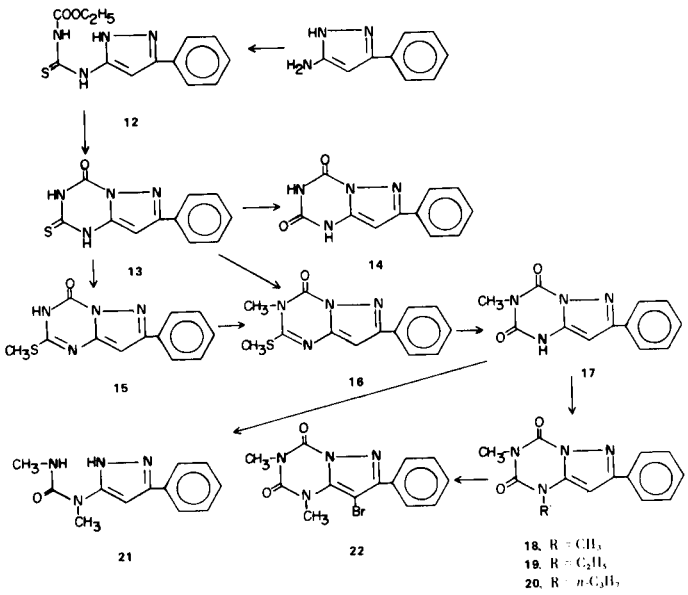
The treatment of **17** with excess methyl iodide at room temperature gave 1,3-dimethyl-7-phenylpyrazolo[1,5-*a*]-1,3,5-triazine-2,4-dione (**18**) which is identical in all respects to the product obtained by the methylation of **14** with methyl iodide. Analogously, the alkylation of **17** with ethyl or *n*-propyl iodide afforded 1-ethyl-3-methyl-7-phenylpyrazolo[1,5-*a*]-1,3,5-triazine-2,4-dione (**19**) and 3-methyl-1-*n*-propyl-7-phenylpyrazolo[1,5-*a*]-1,3,5-triazine-2,4-dione (**20**), respectively.

When methylation of **17** with methyl iodide in dimethylformamide was carried out at the reflux temperature, ring opening occurred and *N*-methyl-*N'*-(5-phenylpyrazol-3-yl)-methylurea (**21**) was isolated as the main product. The structure of **21** was readily determined on the basis of the nmr spectra (deuteriochloroform). Since characteristic methyl signal (adjacent NH) 3 protons were observed at δ 2.91 as doublet (J = 5 Hz), besides a singlet of *N*-methyl protons at δ 3.27. This excluded the possibility of 3-methylamino-2-*N*-methylcarbamoyl-5-phenylpyrazole as an alternative structure.

8-Bromo-1,3-dimethyl-7-phenylpyrazolo[1,5-*a*]-1,3,5-triazine-2,4-dione (**22**) was made by direct bromination of **18**.

The biological activity of the compounds described herein will be covered in a separate communication.





EXPERIMENTAL

Melting points were undertaken on a Thomas-Hoover melting point apparatus and are uncorrected. The nuclear magnetic resonance spectra were determined on a Hitachi Perkin-Elmer R-20A high resolution nuclear magnetic resonance spectrometer. The ultraviolet spectrophotometer. Elemental analyses were accomplished by the Heterocyclic Chemical Corp., Harrisonville, Missouri.

3-Methyl-2-methylthiopyrazolo[1,5-*a*]-1,3,5-triazin-4-one (**2**).

A mixture of 2-methylthiopyrazolo[1,5-*a*]-1,3,5-triazin-4-one (**1**) (8) (3.65 g., 20 mmoles) and anhydrous potassium carbonate (1.38 g., 10 mmoles) in 20 ml. of dimethylformamide was stirred at room temperature while methyl iodide (2.84 g., 20 mmoles) was added dropwise over a period of ten minutes. The resulting solution was stirred an additional 1 hour and then added to 80 ml. of water. The resulting precipitate was collected by filtration, air dried and recrystallized from ethyl acetate to give 3.30 g. (84%) of pure product as white crystals, m.p. 186-188°; λ max (ethanol): 208 nm (ε, 7,700), 222 nm (ε, 12,200), 282 nm (ε, 13,300); nmr (DMSO-d_6): δ 2.61 (s, 3, SCH_3), 3.51 (s, 3, NCH_3), 6.37 (d, 1, pyrazole proton $J_{7,8}$ = 1.8 Hz), 8.03 (d, 1, pyrazole proton $J_{7,8}$ = 1.8 Hz).

Anal. Calcd. for $C_7H_8N_4OS$: C, 42.86; H, 4.11; N, 28.56; S, 16.30. Found: C, 42.76; H, 3.85; N, 28.74; S, 16.12.

3-Methylpyrazolo[1,5-*a*]-1,3,5-triazine-2,4-dione (**3**).

A solution of **2** (1.45 g., 7.4 mmoles) in 15 ml. of 98% formic acid was cooled to 5°, and with good stirring 2.7 g. of 30% hydrogen peroxide was added dropwise over a period of 5 minutes. The temperature did not rise above 10° during the addition. When the addition was complete the reaction mixture was allowed to warm to room temperature (exothermic reaction to 40°). After the exothermic reaction had subsided the solution was stirred at room temperature for 1 hour. The solution was chilled (5°) and 1.15 g. (93%) of analytically pure product was separated by filtration, m.p. 350-352°; λ max (ethanol): 211 nm (ε, 7,100); nmr (DMSO-d_6): δ 3.27 (s, 3, NCH_3), 5.84 (d, 1, pyrazole proton $J_{7,8}$ = 2.1 Hz), 7.83 (d, 1, pyrazole proton $J_{7,8}$ = 2.1 Hz).

Anal. Calcd. for $C_6H_6N_4O_2$: C, 43.38; H, 3.64; N, 33.72. Found: C, 43.39; H, 3.53; N, 33.55.

3-Methylpyrazolo[1,5-*a*]-1,3,5-triazin-4-one (**4**).

Method A.

To a well washed (absolute ethanol) suspension of Raney nickel (11.5 g., W. R. Grace catalyst #28) in 50 ml. of absolute ethanol was added **2** (1.0 g., 5.1 mmoles). The mixture was stirred and heated at reflux for 1.5 hours. The hot suspension was filtered and the filtrate was allowed to cool. The crystalline product was separated by filtration, dired and recrystallized from ethyl acetate to afford 0.3 g. (40%) of analytically pure product as white crystals, m.p. 208-210°; uv λ max (ethanol): 205 nm (ε, 10,500), 262 nm (ε, 9,700); nmr (DMSO-d_6): δ 3.55 (s, 3, NCH_3), 655 (d, 1, pyrazole proton $J_{7,8}$ = 1.8 Hz), 8.09 (d, 1, pyrazole proton $J_{7,8}$ = 1.8 Hz).

Anal. Calcd. for $C_6H_6N_4O$: C, 48.00; H, 4.03; N, 37.32. Found: C, 48.02; H, 4.19; N, 37.30.

Method B.

A mixture of pyrazolo[1,5-*a*]-1,3,5-triazin-4-one (**6**) (8) (2.72 g., 20 mmoles) and anhydrous potassium carbonate (1.38 g., 10 mmoles) in 15 ml. of dimethylformamide was stirred at room temperature while methyl iodide (4.36 g., 30 mmoles) was added dropwise over a period of 5 minutes. After stirring 3 hours, the resulting solution was added to 60 ml. of water and then allowed to stand at 5° for 5 hours. The precipitate was collected by filtration, dried, and recrystallized from ethyl acetate to give 2.4 g. (80%) of pure product which is identical in all respects to the product prepared by Method A.

Method C.

A suspension of *N*-methyl-*N'*-(3-amino-2-pyrazolyl)urea (**5**) (300 mg., 2.14 mmoles) in 5 ml. of triethyl orthoformate was stirred and heated at 50° for 15 hours. At the end of this time the solution was evaporated to dryness *in vacuo*. The residue was purified by column chromatography on silica gel (10 ml.) utilizing chloroform as the solvent. Evaporation of the chloroform solution afforded 0.03 g. (9.4%) of pure crystals which is identical in all respects to the product prepared by Method A.

Reaction of 3-Aminopyrazole with Methyl Isocyanate.

A solution of 3-aminopyrazole (10) (8.3 g., 0.1 mole) in 30 ml. of ethyl acetate was cooled to -10° (ice-salt) and with good stirring methyl isocyanate (6.5 g., 0.116 mole) was added dropwise over a period of 30 minutes. After the addition was complete, the solution was stirred at -5° for 1 hour and then at room temperature for 16 hours. During this time a white crystalline product had separated. This product was collected by filtration and dried. Recrystallization from ethyl acetate gave 1.8 g. (9.6%) of pure *N*-methyl-*N'*-(1-*N*-methylcarbamoylpyrazol-3-yl)urea, m.p. 205-207°.

Anal. Calcd. for $C_7H_{11}N_5O_2$: C, 42.63; H, 5.62; N, 35.52. Found: C, 42.39; H, 5.86; N, 35.79.

The filtrate from the reaction mixture was evaporated to dryness *in vacuo*. The residue (10.8 g.) was purified by column chromatography on silica gel (100 g.) utilizing chloroform as the solvent. Fractions from 300-500 ml. elution were evaporated to afford 4.5 g. (32%) of pure 3-amino-1-*N*-methylcarbamoylpyrazole, m.p. 80-82°.

Anal. Calcd. for $C_5H_8N_4O$: C, 42.85; H, 5.75; N, 39.98. Found: C, 42.83; H, 5.86; N, 40.09.

Evaporation of the fractions from 700-1,000 ml. elution afforded 0.6 g. (4.3%) of analytically pure 3-amino-2-*N*-methylcarbamoylpyrazole (**5**), m.p. 63-65°.

Anal. Calcd. for $C_5H_8N_4O$: C, 42.85; H, 5.75; N, 39.98. Found: C, 42.98; H, 5.71; N, 40.05.

1,3-Dimethylpyrazolo[1,5-*a*]-1,3,5-triazine-2,4-dione (**7**).

Method A.

A mixture of **3** (1.66 g., 10 mmoles) anhydrous potassium carbonate (1.66 g., 12 mmoles) in 15 ml. of dimethylformamide was stirred at room temperature while methyl iodide (1.70 g., 12 mmoles) was added dropwise over a period of 5 minutes. The solution was heated at the reflux temperature for 5 hours and the reaction mixture was evaporated to dryness *in vacuo*. The resulting residue was dissolved in 20 ml. of water and the *p*H was adjusted to 4 by the addition of 2*N* hydrochloric acid. The solution was allowed to stand at room temperature for 5 hours, and the precipitate was collected by filtration to give 0.3 g. of starting material **3**.

The filtrate was extracted with chloroform (3 x 25 ml.). The chloroform extracts were combined and dried over anhydrous sodium sulfate. The chloroform solution was evaporated to dryness *in vacuo* and the resulting residue was covered with 30 ml. of petroleum ether (30-60°). After cooling at 5° for 5 hours, the crystalline product was collected by filtration, and then recrystallized from ethyl acetate to give 1.26 g. (70%) of pure product as colorless needles, m.p. 161-163° (lit. 161° (19)); uv λ max (ethanol): 212 nm (ε, 16,200), 234 nm (ε, 5,900) sh, 252 nm (ε, 6,400); nmr (DMSO-d_6): δ 3.31 (s, 3, NCH_3), 6.15 (d, 1, pyrazole proton, $J_{7,8}$ = 2.1 Hz), 7.89 (d, 1, pyrazole proton $J_{7,8}$ = 2.1 Hz).

Anal. Calcd. for $C_7H_8N_4O_2$: C, 46.66; H, 4.48; N, 31.10. Found: C, 46.63; H, 4.43; N, 31.05.

Method B.

A suspension of pyrazolo[1,5-*a*]-1,3,5-triazine-2,4-dione (**10**) (8) (0.7 g., 4.6 mmoles) and anhydrous potassium carbonate (0.95 g., 6.9 mmoles) in 7 ml. of dimethylformamide was stirred at room temperature while methyl iodide (4.25 g., 30 mmoles) was added dropwise over a period of 5 minutes. A mixture was stirred at room temperature for 5 hours. At the end of this time the resulting solution was evaporated to dryness *in vacuo*. The residue was dissolved in 2*N* sulfuric acid. The acidic solution was extracted with chloroform (3 x 50 ml.) and the combined chloroform extracts were dried over anhydrous sodium sulfate. The chloroform solution was evaporated to dryness *in vacuo* and the residue was recrystallized from ethyl acetate to afford 0.5 g. (60%) of pure product which is identical in all respects to the product prepared by Method A.

1-Ethyl-3-methylpyrazolo[1,5-*a*]-1,3,5-triazine-2,4-dione (**8**).

A mixture of **3** (1.66 g., 10 mmoles) and anhydrous potassium carbonate (1.66 g., 12 mmoles) in 15 ml. of dimethylformamide was stirred at room temperature while ethyl iodide (1.87 g., 12 mmoles) was added dropwise over a period of 5 minutes. The

solution was heated at the reflux temperature for 5 hours. The reaction mixture was treated as described in the preparation of **7** (Method A) and recrystallized from a mixture of benzene and petroleum ether (30-60°) to give 0.95 g. (49%) of pure product as colorless needles, m.p. 161-162°; uv λ max (ethanol): 215 nm (ε, 10,400) 235 nm (ε, 5,500) sh, 252 nm (ε, 6,100); nmr (DMSO-d_6): δ 1.26 (t, 3, CH_3), 3.32 (s, 3, NCH_3), 3.95 (q, 2, NCH_2), 6.23 (d, 1, pyrazole proton, $J_{7,8}$ = 2.1 Hz), 7.90 (d, 1, pyrazole proton, $J_{7,8}$ = 2.1 Hz).

Anal. Calcd. for $C_8H_{10}N_4O_2$: C, 49.46; H, 5.20; N, 28.85. Found: C, 49.75; H, 5.36; N, 28.90.

3-Methyl-1-*n*-propylpyrazolo[1,5-*a*]-1,3,5-triazine-2,4-dione (**9**).

A mixture of **3** (1.66 g., 10 mmoles) and anhydrous potassium carbonate (1.66 g., 12 mmoles) in 15 ml. of dimethylformamide was stirred at room temperature while *n*-propyl iodide (2.04 g., 12 mmoles) was added dropwise over a period of 5 minutes. The solution was heated at the reflux temperature for 8 hours. The reaction mixture was treated as described in the preparation of **7** (Method A) and recrystallized from a mixture of benzene and petroleum ether (30-60°) to give 1.15 g. (56%) of pure product as colorless needles, m.p. 130-132°; uv λ max (ethanol): 215 nm (ε, 10,800), 234 nm (ε, 5,300) sh, 251 nm (ε, 5,300); nmr (DMSO-d_6): δ 0.95 (t, 3, CH_3), 1.70 (q, 2, CH_2), 3.30 (s, 3, NCH_3); 3.88 (t, 2, NCH_2), 6.23 (d, 1, pyrazole proton, $J_{7,8}$ = 2.1 Hz), 6.90 (d, 1, pyrazole proton, $J_{7,8}$ = 2.1 Hz).

Anal. Calcd. for $C_9H_{12}N_4O_2$: C, 51.90; H, 5.81; N, 26.90. Found: C, 51.85; H, 5.75; N, 26.89.

8-Bromo-1,3-dimethylpyrazolo[1,5-*a*]-1,3,5-triazine-2,4-dione (**11**).

A solution of **7** (1.8 g., 10 mmoles) and *N*-bromosuccinimide (1.78 g., 10 mmoles) in 30 ml. of chloroform was refluxed for 30 minutes. The mixture was stirred at room temperature for 2 hours and the solution was washed with saturated aqueous sodium bicarbonate (2 x 30 ml.) and then water (30 ml.). The chloroform solution was dried over anhydrous sodium sulfate, and evaporated to dryness *in vacuo*. The residue (oil) was triturated with petroleum ether (30-60°) and the resulting solid was collected by filtration. Recrystallization from a mixture of benzene and petroleum ether (30-60°) gave 1.85 g. (71%) of pure product, m.p. 188-190°; uv λ max (ethanol): 205 nm (ε, 7,600), 218 nm (ε, 11,900); nmr (DMSO-d_6): δ 3.29 (s, 3, NCH_3), 3.68 (s, 3, NCH_3), 8.00 (s, 1, 7H).

N-Carbethoxy-*N'*-(5-phenylpyrazol-3-yl)thiourea (**12**).

To a suspension of 3-amino-5-phenylpyrazole (11) (4.77 g., 30 mmoles) in 30 ml. of ethyl acetate and 150 ml. of benzene, ethoxycarbonyl isothiocyanate (3.93 g., 30 mmoles) in 50 ml. of benzene was added dropwise over a period of 30 minutes, and then at room temperature for 3 hours. The product began to precipitate after 30 minutes. The precipitated product was collected by filtration, washed with benzene to give 6 g. of pale yellow crystals. The filtrate was evaporated to dryness *in vacuo* and 30 ml. of ethyl acetate was added to the residue. The separated product was collected by filtration to give 1.7 g. of pale yellow crystals, total yield 7.7 g. (86%). Recrystallization from benzene gave colorless crystals, m.p. 195-196°; uv λ max (ethanol): 210 nm (ε, 17,400) 244 nm (ε, 33,000), 277 nm (ε, 20,700); nmr (DMSO-d_6): 1.32 (t, 3, CH_3), 4.27 (q, 2, OCH_2), 7.35-7.88 (m, 6, phenyl protons and pyrazole proton), 11.55 (bs, 1, NH), 12.35 (bs, 1, NH), 13.42 (bs, 1, NH).

Anal. Calcd. for $C_{13}H_{14}N_4O_2S$: C, 53.76; H, 4.86; N, 19.29. Found: C, 53.59; H, 4.81; N, 19.49.

7-Phenyl-2-thiopyrazolo[1,5-*a*]-1,3,5-triazin-4-one (**13**).

A mixture of **12** (5.8 g., 20 mmoles) and 50 ml. of 2*N* sodium hydroxide was stirred at room temperature for 16 hours. The reaction mixture was acidified (*p*H 2) by the addition of 2*N* sulfuric acid. The precipitated product was collected by filtration, washed with water and ethanol, and dried to give 3.5 g. (71%) of white crystals. Recrystallization from a mixture of dimethylformamide and water afforded pure product as white powder, m.p. 304-305°; nmr (DMSO-d_6): δ 6.44 (s, 1, pyrazole proton), 7.40-8.10 (m, 5, C_6H_5), 14.80 (b, 2, two of NH).

Anal. Calcd. for $C_{11}H_8N_4OS$: C, 54.07; H, 3.30; N, 22.93. Found: C, 54.23; H, 3.53; N, 22.71.

7-Phenylpyrazolo[1,5-*a*]-1,3,5-triazine-2,4-dione (**14**).

A solution of **13** (2.44 g., 10 mmoles) in 100 ml. of 0.25 *N* sodium hydroxide was cooled to 0°. With good stirring, 40 ml. of 30% hydrogen peroxide was added dropwise to the cold solution. The temperature was maintained at 0° for an additional 15 minutes. The solution was allowed to warm to room temperature and then acidified to *p*H 1 by the addition of 2*N* sulfuric acid. The acidic solution was chilled and the precipitated solid was collected and recrystallized from a mixture of dimethylformamide and water to give 1.3 g. (57%) of pure product as white powder, m.p. 327-329°; nmr (DMSO-d_6): δ 6.36 (s, 1, 8H), 7.40-8.10 (m, 5, C_6H_5), 11.75 (bs, 1, NH), 12.13 (bs, 1, NH).

Anal. Calcd. for $C_{11}H_8N_4O_2$: C, 57.88; H, 3.54; N, 24.55. Found: C, 57.89; H, 3.68; N, 24.71.

2-Methylthio-7-phenylpyrazolo[1,5-*a*]-1,3,5-triazin-4-one (**15**).

A solution of **13** (7.32 g., 30 mmoles) in 100 ml. of ethanol and sodium hydroxide (2.4 g.) in 50 ml. of water was stirred at room temperature while methyl iodide (4.25 g., 30 mmoles) was added dropwise. After 10 minutes, the addition was completed and the sodium salt of the product began to precipitate. The mixture was stirred an additional 30 minutes and the salt was separated by filtration. The salt was dissolved in a minimum amount of water and acidified by the addition of 2*N* sulfuric acid. The precitated product was collected by filtration and recrystallized from ethanol to give 3.6 g. (47%) of pure product as white powder, m.p. 249-251°; uv λ max (ethanol): 210 nm (ε, 35,600); nmr (DMSO-d_6): δ 2.60 (s, 3, NCH_3), 6.89 (s, 1, 8H), 7.40-8.10 (m, 5, C_6H_5).

Anal. Calcd. for $C_{12}H_{10}N_4OS$: C, 55.78; H, 3.90; N, 21.69. Found: C, 55.80; H, 3.95; N, 21.66.

3-Methyl-2-methylthio-7-phenylpyrazolo[1,5-*a*]-1,3,5-triazin-4-one (**16**).

Method A.

A mixture of **15** (2.58 g., 10 mmoles) and anhydrous potassium carbonate (0.69 g., 5 mmoles) in 15 ml. of dimethylformamide was stirred at room temperature while methyl iodide (2.84 g., 20 mmoles) was added dropwise over a period of 10 minutes. After the mixture was stirred for 30 minutes, 100 ml. of water was added and allowed to stand at 5° for 1 hour. The precipitated product was collected by filtration, washed with water, dried to give 2.45 g. (90%) of white powder. Recrystallization from dimethylformamide gave pure product as white crystals, m.p. 208-209°; nmr (DMSO-d_6): δ 2.62 (s, 3, NCH_3), 3.61 (s, 3, SCH_3), 6.86 (s, 1, 8H), 7.40-8.10 (m, 5, phenyl protons).

Anal. Calcd. for $C_{13}H_{12}N_4OS$: C, 57.32; H, 4.44; N, 20.57. Found: C, 57.35; H, 4.44; N, 20.47.

Method B.

A mixture of **13** (3.42 g., 14 mmoles) and anhydrous potassium carbonate (2.76 g., 20 mmoles) in 20 ml. of dimethylformamide was stirred at room temperature for 2 hours. At the end of this time, 500 ml. of water was added to the reaction mixture and precipitated product was collected by filtration, washed with water and dried to give 2.75 g. (72%) of pure product as white crystals which is identical in all respects to the product prepared by Method A.

3-Methyl-7-phenylpyrazolo[1,5-*a*]-1,3,5-triazine-2,4-dione (**17**).

A mixture of **16** (3.81 g., 14 mmoles) and 30 ml. of 98% formic acid was cooled at 5°, and with good stirring 30% hydrogen peroxide (4.5 g.) was added dropwise over a period of 5 minutes. The temperature did not rise above 10° during the addition. When the addition was complete the reaction mixture was allowed to warm to room temperature (exothermic reaction to 60°). After the exothermic reaction had subsided, the precipitate began to separate and the mixture was stirred at room temperature for 1 hour. The reaction mixture was chilled, and precipitate was collected by filtration, washed with water and dried to give 2.63 g. (78%) of dimethylformamide and ethanol gave pure product as white crystals, m.p. 324-325°; uv λ max (ethanol): δ 208 nm (ε, 23,700), 228 nm (ε, 21,100), 259 nm (ε, 22,300); nmr (DMSO-d_6 and sodium deuteroxide); 3.30 (s, 3, NCH_3), 6.00 (s, 1, 8H), 7.35-8.00 (m, 5, C_6H_5).

Anal. Calcd. for $C_{12}H_{10}N_4O_2$: C, 59.50; H, 4.17; N, 23.14. Found: C, 59.49; H, 4.17; N, 23.24.

1,3-Dimethyl-7-phenylpyrazolo[1,5-*a*]-1,3,5-triazine-2,4-dione (**18**).

A mixture of **17** (2.42 g., 10 mmoles) and anhydrous potassium carbonate (2.07 g., 15 mmoles) in 30 ml. of dimethylformamide was stirred at room temperature while methyl iodide (7.1 g., 50 mmoles) was added dropwise over a period of 10 minutes. The mixture was stirred for 5 hours at room temperature. At the end of this time, the reaction mixture was poured into 200 ml. of ice-water and allowed to stand at 5° for 5 hours. The precipitated product was collected by filtration and recrystallized from a mixture of dimethylformamide and ethanol to give 2.0 g. (78%) of pure product as colorless needles, m.p. 241-243°; uv λ max (ethanol): 208 nm (ε, 24,500), 231 nm (ε, 23,200), 259 nm (ε, 22,700); nmr (deuteriotrifluoroacetic acid): δ 3.52 (s, 3, NCH_3), 3.67 (s, 3, NCH_3), 6.70 (s, 1, 8H), 7.47-7.94 (m, 5, C_6H_5).

Anal. Calcd. for $C_{13}H_{12}N_4O_2$: C, 60.92; H, 4.73; N, 21.87. Found: C, 60.93; H, 4.85; N, 21.81.

Method B.

A mixture of **14** (0.57 g., 2.5 mmoles) and anhydrous potassium carbonate (0.41 g., 3 mmoles) in 5 ml. of dimethylformamide was stirred at room temperature while methyl iodide (1.42 g., 10 mmoles) was added dropwise over a period of 5 minutes. After the mixture was stirred for hours, the resulting solution was poured in 100 ml. of water and then allowed to stand at 5° for 5 hours. The precipitated crystals were collected by filtration and recrystallized from dimethylformamide and ethanol to give 0.25 g. (39%) of pure product which was identical in all respects to the product prepared by Method A.

1-Ethyl-3-methyl-7-phenyl[1,5-*a*]-1,3,5-triazine-2,4-dione (**19**).

A mixture of **17** (2.42 g., 10 mmoles) and anhydrous potassium carbonate (2.07 g., 15 mmoles) in 30 ml. of dimethylformamide was stirred at room temperature while ethyl iodide (7.8 g., 50 mmoles) was added dropwise over a period of 10 minutes. After the mixture was stirred at room temperature for 5 hours, the solution was poured into 500 ml. of ice-water and allowed to stand at 5° for 5 hours. The precipitated product was collected by filtration, washed with water and then recrystallized from ethanol to give 2.2 g. (81%) of pure product as colorless needles, m.p. 182-183°; uv λ max (ethanol): 208 nm (ε, 24,400), 231 nm (ε, 24,400), 259 nm (ε, 22,600); nmr (DMSO-d_6): δ 1.30 (t, 3, CH_3), 3.32 (s, 3, NCH_3), 3.96 (q, 2, NCH_2), 6.78 (s, 1, 8H), 7.40-8.10 (m, 5, C_6H_5).

Anal. Calcd. for $C_{14}H_{14}N_4O_2$: C, 62.20; H, 5.23; N, 20.73. Found: C, 62.25; H, 5.49; N, 20.65.

3-Methyl-7-phenyl-1-*n*-propylpyrazolo[1,5-*a*]-1,3,5-triazine-2,4-dione (**20**).

A mixture of **17** (2.42 g., 10 mmoles) and anhydrous potassium carbonate (2.07 g., 15 mmoles) in 30 ml. of dimethylformamide was stirred at room temperature while *n*-propyl iodide (8.5 g., 50 mmoles) was added dropwise over a period of 10 minutes. After stirring at room temperature for 5 hours, the resulting solution was treated as described in the preparation of **20** (Method A) and recrystallized from ethanol to give 1.9 g. (67%) of pure product as colorless needles, m.p. 145-147°; uv λ max (ethanol): 207 nm (ε, 24,900), 230 nm (ε, 24,000), 258 nm (ε, 23,200); nmr (DMSO-d_6): δ 0.99 (t, 3, CH_3), 1.75 (q, 2, CH_2), 3.31 (s, 3, NCH_3), 3.90 (t, 2, NCH_2), 6.80 (s, 1, 8H), 7.40-8.10 (m, 5, C_6H_5).

Anal. Calcd. for $C_{15}H_{16}N_4O_2$: C, 63.35; H, 5.68; N, 19.70. Found: C, 63.01; H, 5.76; N, 19.61.

N-Methyl-*N'*-(5-phenylpyrazol-3-yl)methyl Urea (**21**).

A mixture of **17** (2.42 g., 10 mmoles) and anhydrous potassium carbonate (1.38 g., 10 mmoles) in 30 ml. of dimethylformamide was stirred at room temperature while methyl iodide (2.13 g., 15 mmoles) was added dropwise over a period of 5 minutes. The mixture was heated at reflux for 4 hours, and the solvent was removed *in vacuo*. The residue was added to 30 ml. of water and *p*H adjusted to 2 by the addition of diluted hydrochloride. The solution was extracted by chloroform (3 x 50 ml.) and the combined extracts were dried over anhydrous sodium sulfate. The chloroform solution was evaporated to dryness *in vacuo* and the residue was recrystallized from acetonitrile to afford 1.2 g. (52%) pure product as colorless needles, m.p. 164-165°; uv λ max (ethanol): 208 nm (ε, 20,300), 252 nm (ε, 19,600); nmr (deuteriochloroform): δ 2.91 (d, 3, $NHCH_3$ J = 5 Hz), 3.27 (s, 3, NCH_3), 6.18 (s, 1, pyrazole proton), 7.30-7.80 (m, 5, C_6H_5), 8.30 (b, 1, NH), 11.70 (b, 1, NH).

Anal. Calcd. for $C_{12}H_{14}N_4O$: C, 62.57; H, 6.13; N, 24.33. Found: C, 62.68; H, 6.13; N, 24.24.

8-Bromo-1,3-dimethyl-7-phenylpyrazolo[1,5-*a*]-1,3,5-triazine-2,4-dione (**22**).

A solution of **17** (1.28 g., 5 mmoles) and *N*-bromosuccinimide (0.89 g., 5 mmoles) in 50 ml. of chloroform was refluxed for 30 minutes. The reaction mixture was washed with saturated aqueous sodium bicarbonate (50 ml.) and then water (50 ml.). The chloroform solution was dried over anhydrous sodium sulfate and evaporated to dryness *in vacuo*. The resulting residue was recrystallized from ethanol to give 0.95 g. (57%) of pure product as colorless needles, m.p. 164-166°; uv λ max (ethanol): 212 nm (ε, 41,500), 232 nm (ε, 44,800), 259 nm (ε, 29,400) sh; nmr (deuteriochloroform): δ 3.49 (s, 3, NCH_3), 3.88 (s, 3, NCH_3), 7.35-7.95 (m, 5, C_6H_5).

Anal. Calcd. for $C_{13}H_{11}N_4O_2Br$: C, 46.57; H, 3.31; N, 16.71. Found: C, 46.71; H, 3.34; N, 16.95.

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