Synthesis of Unsymmetrical 2,4-Dialkylpyrazolo[1,5-*a*]-1,3,5-triazines

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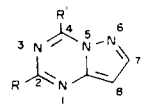
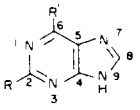
Received March 1, 1974

The reaction of 3-aminopyrazole with imidate esters such as ethyl acetimidate, gave *N*-(pyrazol-3-yl)acetamidine (**1**) rather than the isomeric 2-acetamidoyl-3-aminopyrazole. Ring closure of **1** with orthoesters such as ethyl propionimidate, afforded unsymmetrically substituted 2,4-dialkylpyrazolo[1,5-*a*]-1,3,5-triazines such as 4-ethyl-2-methylpyrazolo[1,5-*a*]-1,3,5-triazine (**3**). The structure of **1** was confirmed by several alternate syntheses. The unique feature of this two-step synthetic approach to the synthesis of pyrazolo[1,5-*a*]-1,3,5-triazines is that it is a convenient method of preparing fused triazines based on available pyrazoles rather than the less accessible dialkyltriazines.

In conjunction with our program on the synthesis of purine-like heterocycles, (1-3) we wished to prepare a series of 2,4-dialkylpyrazolo[1,5-*a*]-1,3,5-triazines.

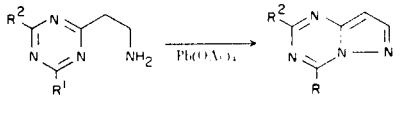


2,4-dialkylpyrazolo[1,5-*a*]-1,3,5-triazine

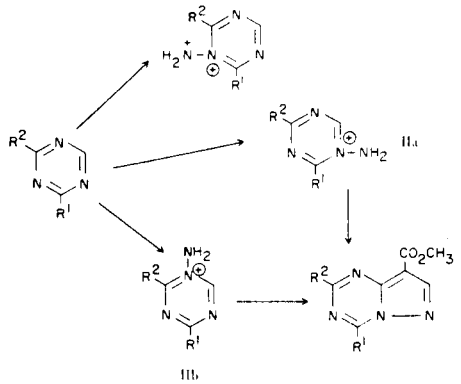


2,6-dialkylpurine

Of several possible approaches, the two most logical routes to the synthesis of this ring system would be either through the 2,4-dialkyl-1,3,4-triazine derivatives or through 3-aminopyrazole derivatives. It might be possible to cyclize the unreported 6-aminoethyl-2,4-dialkyl-1,3,5-triazines (I)



I



IIa

IIb

with lead tetraacetate, in analogy to the synthesis of pyrazolo[1,5-*a*]pyridines, as reported by Kirchner (4). Alternatively, the synthesis might be conducted *via* the reaction of the unreported 1-amino-2,4-dialkylpyridinium salts (II) with methylpropiolate, in comparison to the synthesis of pyrazolo[1,5-*a*]pyridine reported by Potts (5a) and by Boekelheide (5b). The chief problems anticipated from these approaches, other than the synthesis of the unreported starting materials, is that in each case, two isomers would be possible if R^1 was not the same as R^2.

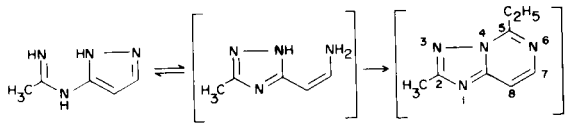
Instead of building up the pyrazolo[1,5-*a*]-1,3,5-triazine ring from the triazines, we took the alternative approach and built up the ring system from 3-aminopyrazole. The novelty of this approach was that a stepwise reaction of 3-aminopyrazole with the appropriate reagents allowed the introduction of almost any desired alkyl group or functional group into either the 2-position or the 4-position of the pyrazolo[1,5-*a*]-1,3,5-triazine ring system. In preliminary communications (6a-c), we described a modification of the classical Pinner (15) reaction whereby 3-aminopyrazole reacted with ethyl acetimidate to afford *N*-(pyrazol-3-yl)acetamidine (**1**). Thus when **1** was cyclized with triethyl orthacetate (Scheme I) 2,4-dimethylpyrazolo-[1,5-*a*]-1,3,5-triazine (**2**) was obtained (6a). In an analogous manner, *N*-(pyrazol-3-yl)acetamidine (**1**) was condensed with triethyl orthopropionate to yield 4-ethyl-2-methylpyrazolo[1,5-*a*]-1,3,5-triazine (**3**).

It was conceivable that 3-aminopyrazole reacted with ethyl acetimidate to yield 2-acetimidoyl-3-aminopyrazole rather than *N*-(pyrazol-3-yl)acetamidine (**1**). The condensation of 2-acetimidoyl-3-aminopyrazole with triethyl ortho-

propionate would then have led to 2-ethyl-4-methylpyrazolo[1,5-*a*]-1,3,5-triazine (**4**) rather than 4-ethyl-2-methylpyrazolo[1,5-*a*]-1,3,5-triazine (**3**).

However, we did synthesize 2-ethyl-4-methylpyrazolo-[1,5-*a*]-1,3,5-triazine (**4**) *via* an alternate route. Thus 3-aminopyrazole was reacted with ethyl propionimidate to yield *N*-(pyrazol-3-yl)propionamidine (**5**). When **3** was cyclized with triethyl orthoacetate, the product obtained was **4**. However, one could still argue that the intermediate obtained from the condensation of ethyl propionimidate with 3-aminopyrazole was *N*-(pyrazol-3-yl)propionamidine, which would then cyclize with triethyl orthoacetate to yield 4-ethyl-2-methylpyrazolo[1,5-*a*]-1,3,5-triazine (**3**).

At this point, the possibility of a well documented (7) type of rearrangement should be discussed in conjunction with the intermediates formed from 3-aminopyrazole and ethyl acetimidate. It is conceivable that if 3(2-aminovinyl)-5-methyl-1,2,4-triazole had been the product formed from the reaction, cyclization with triethyl orthopropionate

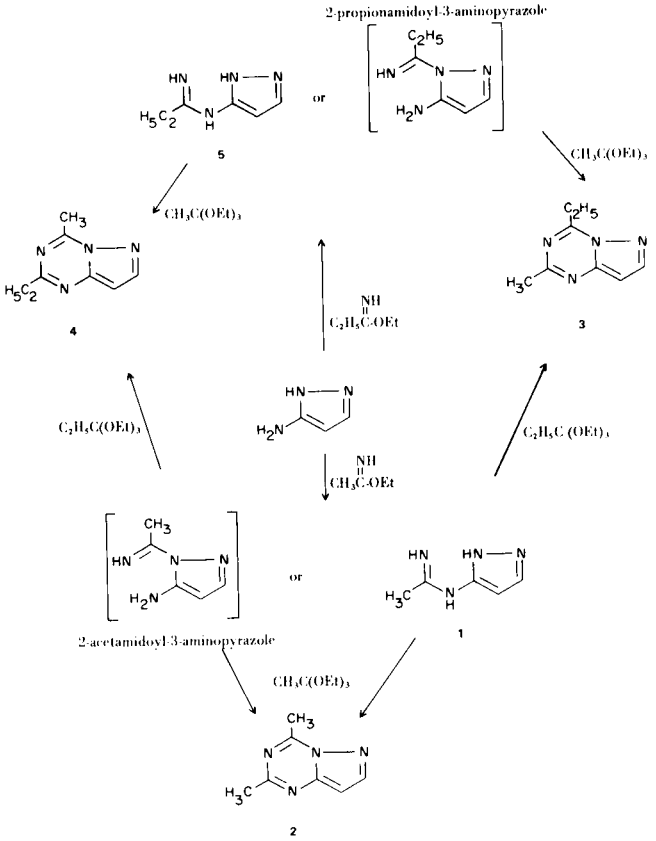


1 3-(2-aminovinyl)-5-methyl-1,2,4-triazole 5-ethyl-2-methyl-1,2,4-triazolo[1,5-*c*]pyrimidine

would have yielded 5-ethyl-2-methyl-1,2,4-triazolo[1,5-*c*]-pyrimidine. However, we felt that this possibility was too remote. The pmr spectrum of all the 2,4-dialkylpyrazolo-[1,5-*c*]pyrimidines exhibit doublets at δ 6.50 and δ 8.10 (in parts per million, measured in deuterochloroform with TMS as a standard) with a coupling constant of J = 2.5 Hz. Substituted triazolo[1,5-*c*]pyrimidines have been reported in the literature (8), and our own observations (9) of the pmr data of this heterocyclic system indicate that 5-ethyl-2-methyl-1,2,4-triazolo[1,5-*c*]pyrimidine was not the product of this synthetic route.

The structure of the intermediate formed on condensing 3-aminopyrazole with ethyl alkylimidates was confirmed by an alternative synthetic route. When 3-amino-2-thiocarbamoyl-5-phenylpyrazole (10) (**11**) was refluxed with triethyl orthoacetate (Scheme 2), 2-methyl-7-phenylpyrazolo[1,5-*a*]-1,3,5-triazin-3*H*-4-thione (**12**) was obtained. This thione (**12**) was readily alkylated by methyl iodide to afford 2-methyl-4-methylthio-7-phenylpyrazolo-[1,5-*a*]-1,3,5-triazine (**13**). The 4-methylthio group of **13** was dethiated with Raney nickel to yield 2-methyl-7-phenylpyrazolo[1,5-*a*]-1,3,5-triazine (**7**). Alternatively *N*-(5-phenylpyrazol-3-yl)acetamidine (**6**) was refluxed with triethyl orthoformate, which gave **7** directly.

Additionally, *N*-(5-phenylpyrazol-3-yl)acetamidine (**6**) was condensed with carbon disulfide to afford 2-methyl-7-phenylpyrazolo[1,5-*a*]-1,3,5-triazin-3*H*-4-thione (**12**).



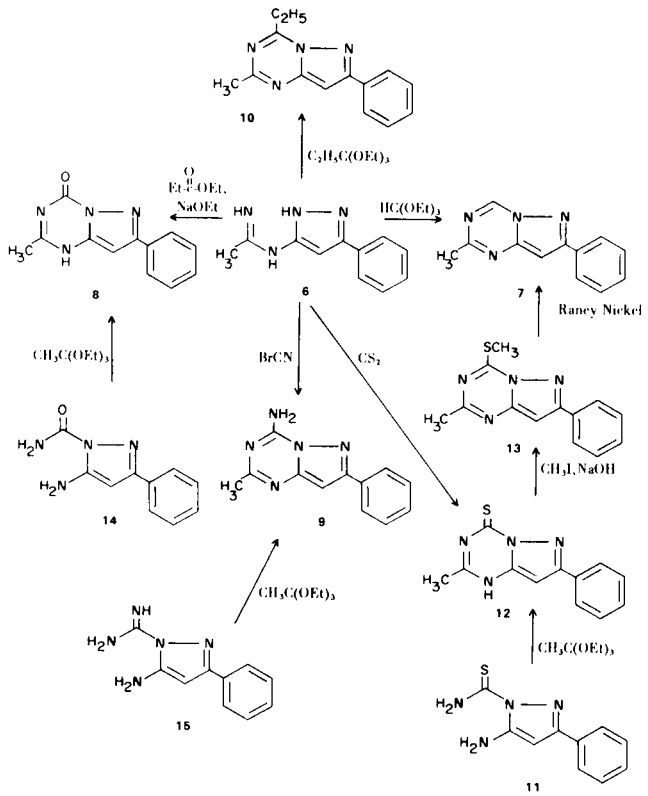
SCHEME I

There was no depression of melting point when the material (**12**) from this reaction was mixed with the thione (**12**) obtained from the cyclization of 3-amino-2-thiocarbamoyl-5-phenylpyrazole (**11**) with triethyl orthoacetate.

The utility of *N*-(5-phenylpyrazol-3-yl)acetamidine (**6**) as a synthetic intermediate was realized to even a greater extent. For example, **6** was also condensed with diethyl carbonate in the presence of ethanolic sodium methoxide to yield 2-methyl-7-phenylpyrazolo[1,5-*a*]-1,3,5-3*H*-4-one (**8**). The structure of **8** was confirmed when 3-amino-2-carbamoyl-5-phenylpyrazole (11) (**14**) was condensed with triethyl orthoacetate to yield the identical product, 2-methyl-7-phenylpyrazolo[1,5-*a*]-1,3,5-3*H*-4-one. The mixed melting point showed no depression when **8** from both routes was mixed.

When *N*-(5-phenylpyrazol-3-yl)acetamidine (**6**) was condensed with cyanogen bromide, the product obtained was identified as 4-amino-2-methyl-7-phenylpyrazolo[1,5-*a*]-1,3,5-triazine (**9**). This same 4-amino derivative (**9**) was prepared by cyclizing 3-amino-2-guanidinyl-5-phenylpyrazole (10) (**15**) with triethyl orthoacetate.

Finally, 4-ethyl-2-methyl-7-phenylpyrazolo[1,5-*a*]-1,3,5-triazine (**10**) was synthesized by cyclizing *N*-(5-phenylpyrazol-3-yl)acetamidine (**6**) with triethyl orthopropionate.



SCHEME 2

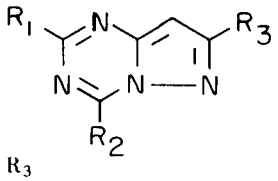
The pmr spectrum of **10** exhibited nearly identical data (chemical shift) for the 4-ethyl and 2-methyl signals, as the corresponding ethyl and methyl pmr spectrum of 4-ethyl-2-methylpyrazolo[1,5-*a*]-1,3,5-triazine (3).

Whereas it might be argued that the structural proofs of **10** and the starting material **6** do not conclusively support the structural conformation of the starting material **1** nor differentiate between **3** and **4**, the pmr data in Table I provides a sufficient basis for making this comparison. As can be seen in the Table, the chemical shifts for the methyl singlet at the 2-position and the ethyl quartet at the 4-position are identical (within experimental error) for both **3** and **10**, indicating that the phenyl ring at the 8-position of the ring system exerts virtually no effect on the chemical shifts of the alkyl groups at the 2- and 4-positions. A logical deduction from this pmr data and the synthetic sequence in Schemes 1 and 2, allows the reader to observe that ethyl acetimidate reacted with 3-aminopyrazole in the same manner as with 3-amino-5-phenylpyrazole. The only difficulty in demonstrating a more rigorous proof of the structure of **1** was that the unsubstituted (*e.g.*, without a phenyl substituent) analogs of **11**, **14** and **15** have never been reported and we were unable to synthesize them.

The synthesis of 2,4-dialkylpyrazolo[1,5-*a*]-1,3,5-triazines has been accomplished through a convenient two-step synthesis from readily available 3-aminopyrazole. The selection of the appropriate ethyl alkylimidates and triethyl orthoesters allows one to introduce practically any alkyl (or aryl) group into either the 2- or 4-positions of this ring system. The great utility of this synthetic scheme is that other dialkyl fused triazine systems may similarly be prepared starting from five membered heterocycles bearing an amino function adjacent to a ring nitrogen (NH). The extension of this general synthetic sequence is currently in progress in our laboratory and the results will be published shortly. Additionally, the utility of the intermediate *N*-(5-

TABLE I

Pmr Data for 2,4-Dialkylpyrazolo[1,5-*a*]-1,3,5-triazines (d)



Comp. No.	R_1	R_2	R_3	Chemical Shifts (b) C-2	C-4	C-7	C-8
2	CH_3	CH_3	H	2.70s	2.95s	6.49d (c)	8.11d (c)
3	CH_3	C_2H_5	H	2.70s	1.50t 3.30q	6.50d (c)	8.14d (c)
4	C_2H_5	CH_3	H	1.40t 3.30q	2.95s	6.25d (c)	8.12d (c)
7	CH_3	H	C_6H_5	2.70s	9.20s	------	6.85s
10	CH_3	C_2H_5	C_6H_5	2.67s	1.50t 3.34q	------	6.74s

(a) Chemical shifts measured in parts per million (δ) relative to TMS. (b) s = singlet, d = doublet, t = triplet, q = quartet. (c) Coupling constant $J_{7,8}$ = 2.0 Hz. (d) All samples run in deuteriochloroform.

Scheme 2, in which it is seen that an amino (**9**), oxo (**8**) or thio (**12**) group was also introduced into the pyrazolo[1,5-*a*]-1,3,5-triazine ring system. Thus it appears that this unique, convenient synthesis had wide applicability in preparing fused triazines and other related heterocyclic systems.

EXPERIMENTAL

Melting points were recorded on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The pmr spectra were recorded on a Hitachi-Perkin Elmer model R-20A, 60 Mc instrument (tetramethylsilane was used as an internal standard) and all the samples were run in deuterochloroform (deuteriochloroform) unless otherwise noted. All ir spectra were recorded in potassium bromide discs with a Perkin-Elmer 257 instrument. All uv spectra were recorded in methanol solution on a Cary 15 instrument. Analyses for C, H and N for all compounds were performed by the Heterocyclic Chemical Corporation of Harrisonville, Missouri.

N-(Pyrazol-3-yl)propionamidine (**5**) Acetate.

A solution of 8.3 g. (0.1 mole) of 3-aminopyrazole (**9**) in 100 ml. of dry acetonitrile was treated (at room temperature) with 20.4 g. (0.2 mole) of ethyl propionimidate (10). To the resultant solution, 6.0 ml. (0.1 mole) of acetic acid was added. The reaction was mildly exothermic. The solution was stirred for 4-6 hours, whereupon a white precipitate formed. The precipitate was filtered, washed with 20 ml. ether, and dried *in vacuo* at 35° for 2-3 hours to afford 18 g. (95%) of analytically pure **5**, m.p. 115-116°. Recrystallization from methanol-ether did not raise the melting point.

Anal. Calcd. for $C_6H_{10}N_4 \cdot C_2H_4O_2$: C, 48.48; H, 7.07; N, 28.28. Found: C, 48.23; H, 7.16; N, 28.50.

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

A suspension of 3.7 g. (20 mmoles) of *N*-(pyrazol-3-yl)acetamidine (**1**) acetate (6a) in 25 ml. of triethyl orthopropionate (14) was refluxed for 4 hours during which time the solid dissolved. The resultant solution was cooled and evaporated *in vacuo* (50°/2 mm.) to yield a crude solid. The solid was recrystallized from petroleum ether (30°-60°) to yield 1.4 g. (85%) of **3** in the form of colorless needles, m.p. 78-79°. Pmr data for this compound are included in Table I; λ max (methanol): (*p*H 7) (ϵ x 10^3) 237 nm (7.32).

Anal. Calcd. for $C_8H_{10}N_4$: C, 59.25; H, 6.17; N, 34.56. Found: C, 59.27; H, 6.18; N, 34.61.

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

A suspension of 4.0 g. (0.02 mole) of *N*-(pyrazol-3-yl)propionamidine (**5**) acetate in 20 ml. of triethyl orthoacetate (14) was refluxed for 2-3 hours. The solution was evaporated (50°/2 mm.) to yield an oil. The oil was dissolved in petroleum ether (30-60°) at 30° and the solution was cooled at -4° for 24 hours. Filtration of the solid gave 3.1 g. (90%), m.p. 58-59°, as white needles. Pmr data for this compound are listed in Table I; λ max (methanol): (*p*H 7) (ϵ x 10^3) 237 nm (7.34).

Anal. Calcd. for $C_8H_{10}N_4$: C, 59.25; H, 6.17; N, 34.56. Found: C, 59.40; H, 6.31; N, 34.71.

N-(5-phenylpyrazol-3-yl)acetamidine (**6**) Acetate.

A suspension of 2.4 g. (0.015 mole) of 3-amino-5-phenylpyrazole (10) in 30 ml. of dry acetonitrile was treated with 1.9 g. (0.02 mole) of ethyl acetimidate at 25° with stirring. To this mixture, 0.9 ml. (0.015 mole) of acetic acid was added. The reaction was mildly exothermic (35°). The product precipitated as a white powder, upon stirring the resultant solution for 1 hour. The white solid was filtered, washed with acetonitrile, then with ether, and dried to yield 3.5 g. (90%) of **6**, m.p. 188-189°. Recrystallization from methanol-ether did not raise the melting point.

Anal. Calcd. for $C_{11}H_{12}N_4 \cdot C_2H_4O_2$: C, 59.98; H, 6.20; N, 21.53. Found: C, 60.13; H, 6.40; N, 21.89.

4-Ethyl-2-methyl-7-phenylpyrazolo[1,5-*a*]-1,3,5-triazine (**10**).

A suspension of 3.0 g. (0.012 mole) of *N*-(5-phenylpyrazol-3-yl)-acetamidine (**6**) acetate in 10 ml. of triethyl orthopropionate (**14**) was refluxed for 16 hours. The solution was cooled to room temperature, then chilled at 0° for *ca.* 24 hours. The product crystallized out of the solution. This solid was filtered, washed with 20 ml. of dry ethyl ether, and dried to afford 1.85 g. (68%) of colorless plates, m.p. 135-136°. Recrystallization of this material brom benzene gave an analytically pure sample of **10**, m.p. 137-138°, as colorless prisms. Pmr data for this compound are included in Table I; λ max (methanol): (*p*H 7) (ϵ max x 10^3) 208 nm (19.32), 259 (28.56).

Anal. Calcd. for $C_{14}H_{14}N_4$: C, 70.55; H, 5.93; N, 23.51. Found: C, 70.53; H, 5.93; N, 23.58.

2-Methyl-7-phenylpyrazolo[1,5-*a*]-1,3,5-triazine-3H-4-one (**8**).

Method A.

A solution of 1.15 g. sodium metal was prepared in 30 ml. of absolute ethanol. To this solution was added 5 ml. of diethyl carbonate (14). After stirring the solution for 5 minutes, 1 g. (5 mmoles) of *N*-(5-phenylpyrazol-3-yl)acetamidine (**6**) acetate was added. The resultant mixture was refluxed for 2 hours. The solution was cooled and the product precipitated. The solid was filtered, washed with 10 ml. of ethanol, and then briefly dried by suction (Büchner funnel). The solid was suspended in 30 ml. of water and was then acidified (*p*H 3) with acetic acid. The mixture was allowed to stand for 3 hours at room temperature. Next, the precipitate was filtered, washed with 10 ml. of ethanol, and dried to yield 1.1 g. (80%) of colorless solid. The product was recrystallized from DMF-ethanol to give colorless prisms, m.p. 293-295°; λ max (methanol): (*p*H 7) (ϵ max x 10^3) 208 nm (16.95), 264 (16.05).

Anal. Calcd. for $C_{12}H_{10}N_4O$: C, 63.69; H, 4.46; N, 24.76. Found: C, 63.90; H, 4.50; N, 24.56.

Method B.

A suspension of 1.01 g. (5 mmoles) of 3-amino-2-carbamoyl-5-phenylpyrazole (11) (**14**) in 15 ml. of triethyl orthoacetate (**14**) was refluxed for 12 hours. The solution was cooled and the precitated product was collected by filtration. Recrystallization of this solid from DMF-ethanol gave 1.1 g. (92%) of colorless prisms, m.p. 293-295°. A mixed melting point of the products obtained from both methods showed no melting point depression. The ir and uv spectra for each sample were identical in all respects.

4-Amino-2-methyl-7-phenylpyrazolo[1,5-*a*]-1,3,5-triazine (**9**).

Method A.

A suspension of 6.03 g. (30 mmoles) of 3-amino-2-guanidinyl-5-phenylpyrazole (10) (**15**) in 50 ml. of triethyl orthoacetate was refluxed for 30 minutes. The solution was allowed to cool to room temperature, whereupon the product precipitated. The product was filtered and recrystallized from DMF-ethanol to yield 5.4 g. (59%) of **9** as colorless needles, m.p. 248-250°; λ max (methanol): (*p*H 7) (ϵ max) 213 nm (20.02), 252 (33.08).

Anal. Calcd. for $C_{12}H_{11}N_5$: C, 63.97; H, 4.93; N, 31.09. Found: C, 64.02; H, 5.19; N, 30.90.

Method B.

A suspension of 2.0 g. (10 mmoles) of *N*-(5-phenylpyrazol-3-yl)-acetamidine acetate (**6**) in 50 ml. methanol was treated with 1.1 g. (11 mmoles) of cyanogen bromide. The reaction was exothermic and the solution turned a dark color and began to reflux. The mixture was refluxed with external heating for 2-3 hours more. The cooled solution was evaporated and the crude product obtained as a residue was recrystallized from DMF-ethanol to yield 1.1 g. (42%) of colorless needles, m.p. 248-250°. A mixed melting point of the samples obtained from both methods exhibited no melting point depression. The spectra (ir, uv) of both samples were identical in all respects.

2-Methyl-7-phenylpyrazolo[1,5-*a*]-1,3,5-triazine-3*H*-4-thione (**12**).

Method A.

A mixture of 4.36 g. (20 mmoles) of 3-amino-5-phenyl-4-thiocarbamoylpyrazole (10) (**11**) and 20 ml. of triethyl orthoacetate (14) was refluxed for 4 hours. The mixture was cooled to room temperature and the product was filtered. The solid was recrystallized from DMF to yield 2.4 g. (43%) of the title compound as a yellow-white powder, m.p. 313-315° dec.; λ max (methanol): (*p*H 7) (ε max x 10^3) 215 nm (16.94), 242 (22.02), 279 (18.87).

Anal. Calcd. for $C_{12}H_{10}N_4S$: C, 59.47; H, 4.16; N, 23.12. Found: C, 59.29; H, 4.35; N, 23.09.

Method B.

A suspension of 2.0 g. (10 mmoles) of *N*-(5-phenylpyrazol-3-yl)-acetamidine acetate (**6**) in 30 ml. of chloroform, was treated with 1.0 ml. of carbon disulfide. The resultant mixture was refluxed until the evolution of hydrogen sulfide ceased (*ca.* 7 hours). The red solution obtained was then evaporated (40°/15 mm.) to yield a red oil. The oil was triturated with methanol to yield a red-orange solid. The solid was filtered and recrystallized from DMF to yield 0.85 g. (32%) of a yellow white solid, m.p. 313-314° dec. A mixture of samples obtained from methods A and B exhibited no melting point depression. The spectra (ir, uv) of each sample were identical in all respects.

2-Methyl-4-methylthio-7-phenylpyrazolo[1,5-*a*]-1,3,5-triazine (**13**).

A suspension of 0.85 g. (0.35 mmole) of 2-methyl-7-phenylpyrazolo[1,5-*a*]-1,3,5-triazine-3*H*-4-thione (**12**) in 15 ml. of ethanol was treated with 0.2 g. of sodium hydroxide (pellets) dissolved in 5 ml. of water. The resultant solution was then treated with 0.49 g. (0.34 mmole) of methyl iodide, and the mixture was stirred for *ca.* 1 hour at room temperature. A solid precipitated and this was filtered to yield 0.6 g. of ivory-white product. The product was recrystallized from ethanol to yield 0.5 g. (65%) of an analytically pure sample of **13**, m.p. 159-160°; λ max (methanol): (*p*H 7) (ε max x 10^3) 208 nm (15.36, 246 (17.66), 273 (18.94).

Anal. Calcd. for $C_{13}H_{12}N_4S$: C, 60.90; H, 4.73; N, 21.86. Found: C, 61.13; H, 4.92; N, 21.97.

Method A.

A mixture of 2 g. (10 mmoles) of *N*-(5-phenylpyrazol-3-yl)-acetamidine acetate (**6**) and 20 ml. of triethyl orthoformate (14) was refluxed for 24 hours. The solution was allowed to cool to room temperature and a pale yellow precipitate formed. The precipitate was filtered, washed with ethyl ether and recrystallized from benzene to yield 2.1 g. (92%) of an ivory powder, m.p. 214-215°. Pmr data for this compound is listed in Table I; λ max (methanol): (*p*H 7) (ε max x 10^3) 209 nm (13.80), 257 (21.89).

Anal. Calcd. for $C_{12}H_{10}N_4$: C, 68.54; H, 4.80; N, 26.65. Found: C, 68.52; H, 4.81; N, 26.61.

Method B.

A suspension of 2.6 g. (10 mmoles) of 2-methyl-4-methylthio-7-phenylpyrazolo[1,5-*a*]-1,3,5-triazine (**13**) in 50 ml. of 5*M* ammonium hydroxide was refluxed with *ca.* 10 g. of Raney nickel catalyst (Grace W-26) for a period of 8 hours. The mixture was filtered hot and the precipitated catalyst was washed with 50 ml. boiling ethanol (with caution). The combined filtrate (and washings) was allowed to cool to room temperature, whereupon the product crystallized. The solid was recrystallized from benzene to afford 2.0 g. (85%) of pure **7**, m.p. 214-215°. A mixed melting point of the products prepared by both methods exhibited no depression. The spectra (ir, uv, pmr) for **7** prepared by both methods were shown to be identical in all respects.

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*Author to whom reprint requests should be directed.

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