Synthesis and Some Reactions of 7-Methyl-5-phenyl-5*H*-pyrazolo[3,4-*e*]1,2,4-triazine-3-thiol

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The title compound II has been prepared by the reaction of 3-methyl-1-phenyl-4-oxo-5-pyrazolone with thiosemicarbazide in aqueous potassium carbonate. Alkylation of II on the sulfur atom in aqueous sodium hydroxide afforded the 3-alkylthio derivatives III. Interaction of II or III with different amines yielded the 3-amino derivatives IV. The 3-hydrazino derivative IVa condensed with aromatic aldehydes in ethanol or acetic acid giving the corresponding hydrazones V.

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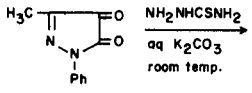
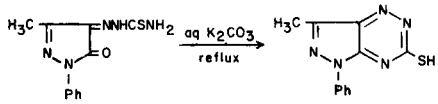
The chemistry of condensed heterocyclic systems especially containing the triazine moiety [2-10] has received much attention owing to the reported antibacterial, antiviral and antihypertensive activities [11-14]. In this work a series of unreported 3-substituted-7-methyl-5-phenyl-5*H*-pyrazolo[3,4-*e*]-1,2,4-triazines were prepared starting from 7-methyl-5-phenyl-5*H*-pyrazolo[3,4-*e*]-1,2,4-triazine-3-thiol (II) [15].

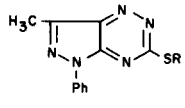
3-Methyl-1-phenyl-4-oxo-5-pyrazolone was allowed to react with thiosemicarbazide with stirring in aqueous potassium carbonate, cyclization occurred and 7-methyl-5-phenyl-5*H*-pyrazolo[3,4-*e*]-1,2,4-triazin-3-thiol (II) was obtained. The structure of I and II was elucidated on the basis of their analytical data and ir spectra. The ir spectrum of I showed absorption bands at 1670 cm^{-1} (C=O), 3180 cm^{-1} (NH), 3300-3420 cm^{-1} (NH_2) and 1330 cm^{-1} (C=S). The ir spectrum of II showed an absorption band at 2800 cm^{-1} (SH) and disappearance of the absorption band at 1670 cm^{-1} (C=O).





I II

Treatment of 7-methyl-5-phenyl-5*H*-pyrazolo[3,4-*e*]-1,2,4-triazine-3-thiol (II) with alkyl halides in aqueous sodium hydroxide resulting alkylation on the sulfur atom to give the corresponding alkylthio derivatives IIIa-d. Similarly, interaction of II with aralkyl and aryl halides yields the corresponding aralkyl and arylthio derivatives IIIe-i respectively.

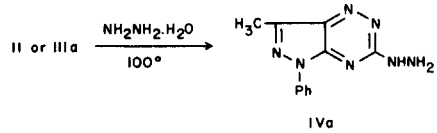


III

a, R = CH_3; b, R = C_2H_5; c, R = $C_4H_9(n)$; d, R = $CH_2C_6H_5$
e, R = $CH_2C_6H_4Cl(p)$; f, R = $CH_2CH_2C_6H_5$; g, R = $(CH_2)_3C_6H_5$
h, R = $CH_2COOC_2H_5$; i, R = $C_6H_3(NO_2)$-2,4

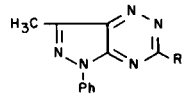
The structure of compounds IIIa-i was confirmed by elemental and ir analysis. The ir spectra of these compounds showed the disappearance of absorption band at 2800 cm^{-1} (SH) confirming *S*-alkylation. The ir spectrum of compound IIIh showed an absorption band at 1710 cm^{-1} (C=O).

3-Hydrazino-7-methyl-5-phenyl-5*H*-pyrazolo[3,4-*e*]-1,2,4-triazine (IVa) was prepared by the reaction of thiol II with excess 98% hydrazine hydrate at 100°. The structural assignments of IVa were based on elemental analysis and ir spectra. The ir spectrum showed an absorption broad band at 3220 and 3450 cm^{-1} (NH and NH_2). On the other hand, the structure of IVa has also been established by an unambiguous synthesis involving the reaction of thioalkyl derivative IIIa with excess 98% hydrazine hydrate at 100°. It was found that the product thus obtained by this method was identical (mp, mmp and ir) with a sample obtained by the above method.



IVa

3-Amino-7-methyl-5-phenyl-5*H*-pyrazolo[3,4-*e*]-1,2,4-triazines, IVb-f, were synthesized by fusion of II with aliphatic, aralkyl and aromatic amines. Similarly, heterocyclic secondary amines namely morpholine and piperidine reacted with II giving 3-(1-piperidinyl)- and 3-(4-morpholinyl)-7-methyl-5-phenyl-5*H*-pyrazolo[3,4-*e*]-1,2,4-triazines IVg,h, respectively.



IV

b, R = NHC_2H_5; c, R = $NHC_4H_9(n)$; d, R = $NHCH_2CH_2OH$
e, R = $NHCH_2C_6H_5$; f, R = NHC_6H_5; g, R = 1-piperdinyl;
h, R = 4-morpholinyl

The structure of compounds IVb-h was also confirmed by analytical data and ir spectra. The ir absorption spectra revealed an absorption band at 3220-3240 cm^{-1} (NH) and the disappearance of the absorption band at 2800 cm^{-1} (SH). The ir spectrum of compound IVd showed besides the foregoing NH absorption band, a band at 3360 cm^{-1} (OH).

Condensation of 3-hydrazino-7-methyl-5-phenyl-5*H*-pyrazolo[3,4-*e*]-1,2,4-triazine [16] (IVa) with aromatic aldehydes in alcohol or acetic acid proceeds smoothly to yield the corresponding 7-methyl-5-phenyl-5*H*-pyrazolo[3,4-*e*]-1,2,4-triazin-3-yl hydrazones Va-e. The structure of compounds Va-e was elucidated on the basis of their analytical and ir data. The ir absorption spectra showed the disappearance of the broad band at 3450 cm^{-1} (NH_2) and the existance of small band at 3220 cm^{-1} (NH).

Table 1

3-Substituted Thio-7-methyl-5-phenyl-5*H*-pyrazolo[3,4-*e*]-1,2,4-triazines III

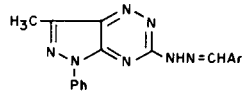
Compound No.	R	Mp (°C)	Yield (%)	Molecular formula	Analysis Calcd./(Found) (%) C	H	N	S
IIIa	$-CH_3$	117-119 (lit [15] 120-121°)	88	$C_{12}H_{11}N_5S$	56.01 (55.88)	4.31 (4.23)	27.22 (27.25)	12.46 (12.13)
b	$-C_2H_5$	89-91	75	$C_{13}H_{13}N_5S$	57.55 (57.47)	4.83 (4.81)	25.81 (26.01)	11.82 (11.91)
c	$-C_4H_9$-*n*	206-208	41	$C_{15}H_{17}N_5S$	60.18 (60.00)	5.72 (5.62)	23.39 (23.22)	10.71 (10.69)
d	$-CH_2C_6H_5$	153-155	73	$C_{18}H_{15}N_5S$	64.84 (64.78)	4.53 (4.50)	21.01 (21.11)	9.62 (9.34)
e	$-CH_2C_6H_4Cl$-*p*	160-161	84	$C_{18}H_{14}N_5SCl$ [a]	58.77 (58.84)	3.84 (3.91)	19.04 (18.88)	8.72 (9.04)
f	$-(CH_2)_2C_6H_5$	113-115	40	$C_{19}H_{17}N_5S$	65.68 (65.62)	4.93 (5.05)	20.16 (20.12)	9.23 (9.30)
g	$-(CH_2)_3C_6H_5$	105-107	43	$C_{20}H_{19}N_5S$	66.46 (66.53)	5.20 (5.42)	19.37 (19.27)	8.87 (8.68)
h	$-CH_2COOC_2H_5$	179-181	64	$C_{15}H_{15}N_5O_2S$	54.70 (54.70)	4.59 (4.61)	21.26 (21.27)	9.73 (9.62)
i	$-C_6H_3(NO_2)_2$-2,4	169-171	69	$C_{17}H_{11}N_7O_4S$	49.88 (49.70)	2.71 (2.65)	23.95 (24.09)	7.83 (8.26)

[a] *Anal.* Calcd. for Cl: 9.67%. Found: 9.69%.

Table 2

3-Amino-7-methyl-5-phenyl-5*H*-pyrazolo[3,4-*e*]-1,2,4-triazines IV

Compound No.	R	Mp (°C)	Yield (%)	Molecular formula	Analysis Calcd./(Found) (%) C	H	N
IVb	$-NHC_2H_5$	197-198	37	$C_{13}H_{14}N_6$	61.40 (61.55)	5.55 (5.61)	33.05 (32.91)
c	$-NHC_4H_9$-*n*	202-204	42	$C_{15}H_{18}N_6$	63.81 (63.68)	6.43 (6.34)	29.76 (29.66)
d	$-NHCH_2CH_2OH$	224-225	47	$C_{13}H_{14}N_6O$	57.77 (57.59)	5.22 (5.12)	31.09 (31.16)
e	$-NHCH_2C_6H_5$	204-206 (lit [15] 208-209°)	42	$C_{18}H_{16}N_6$	68.34 (68.44)	5.10 (5.18)	26.56 (26.63)
f	$-NHC_6H_5$	225-227	42	$C_{17}H_{14}N_6$	67.54 (67.75)	4.67 (4.53)	27.80 (28.19)
g	1-piperidinyl	210-212	25	$C_{16}H_{18}N_6$	65.29 (65.38)	6.16 (6.27)	28.55 (28.47)
h	4-morpholinyl	185-187 (lit [15] 170°)	58	$C_{15}H_{16}N_6O$	60.80 (60.87)	5.44 (5.29)	28.36 (28.33)



V

a, Ar = C_6H_5; b, Ar = 2-BrC_6H_4; c, Ar = 2-HOC_6H_4; d, Ar = 4-$CH_3OC_6H_4$; e, Ar = 4-$NO_2C_6H_4$

EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded on a Perkin-Elmer 599 B spectrophotometer using the potassium bromide disc technique.

3-Methyl-1-phenyl-5-pyrazolone-4-thiosemicarbazone (I).

3-Methyl-1-phenyl-4-oxo-5-pyrazolone [17] (0.5 g, 0.0026 mole), thiosemicarbazide (0.27 g, 0.003 mole) and anhydrous potassium carbonate (0.55 g, 0.004 mole) were stirred in water (20 ml) for 1 hour at room temperature. The solid obtained (0.47 g, 82%) was crystallised from ethanol as red needles, mp 225-227° (lit [15] 250-251°).

Anal. Calcd. for $C_{11}H_{11}N_5SO$: C, 50.56; H, 4.24; N, 26.80; S, 12.27. Found: C, 50.51; H, 4.32; N, 26.77; S, 12.30.

7-Methyl-5-phenyl-5*H*-pyrazolo[3,4-*e*]-1,2,4-triazine-3-thiol (II).

3-Methyl-1-phenyl-4-oxo-5-pyrazolone (18.8 g, 0.1 mole), thiosemicarbazide (10.03 g, 0.11 mole) and anhydrous potassium carbonate (20.73 g, 0.15 mole) were stirred in water (500 ml) for 2 hours at room temperature and then refluxed for 5 hours. The mixture was cooled, filtered and the filtrate was acidified with acetic acid. The solid obtained was filtered off, washed with water and dried. The product 11.12 g (46%) was crystallised from ethanol into orange crystals mp 208-210°.

Anal. Calcd. for $C_{11}H_9N_5S$: C, 54.31; H, 3.73; N, 28.79; S, 13.18. Found: C, 54.41; H, 3.70; N, 28.77; S, 13.17.

Reaction of Alkyl, Aralkyl and Aryl Halides With II. Formation of IIIa-i. General Procedure.

Alkyl, aralkyl and/or aryl halide (0.11 mole) was added during 2-5 minutes to a stirred solution of II in sodium hydroxide solution (1*N*; 0.115 mole). The mixture was stirred for further ½ to 4 hours. The solid which separated was filtered, washed with water and dried. The products were crystallised from ethanol as yellow crystals. The results are summarized in Table 1.

3-Hydrazino-7-methyl-5-phenyl-5*H*-pyrazolo[3,4-*e*]-1,2,4-triazine IVa.

A mixture of II (2.5 g, 0.01 mole) and hydrazine hydrate (10 ml, 98%) was heated on a water bath for 5 hours, whereby yellow crystals separated out. The product was collected, washed with alcohol and dried. The product (2 g, 81%) was crystallised from ethanol as yellow needles to give IVa, mp 199-200°. This compound was also obtained by heating IIIa (0.47 g, 0.001 mole) with excess hydrazine hydrate (2 ml, 98%) on a water bath for 8 hours. It was identical in all respects with the above one, but in 64% yield.

Anal. Calcd. for $C_{11}H_{11}N_7$: C, 54.76; H, 4.60; N, 40.64. Found: C, 54.68; H, 4.51; N, 40.75.

Reaction of Aliphatic, Aralkyl and Aromatic Amines With II. Formation of IVb-h. General Procedure.

A mixture of II (1 g, 0.004 mole) and appropriate amine (3 ml) was heated at 170-180° for 4 hours. On cooling and dilution with ethanol, yellow crystals separated out. For the low boiling point amines the mixture was heated on a water bath for 8 hours and the excess amine was evaporated completely. The deposited product was crystallised from ethanol as yellow crystals. The results are summarized in Table 2.

Reaction of IVa With Aromatic Aldehydes. Formation of Va-e. General Procedure.

A mixture of IVa (0.01 mole) and aromatic aldehyde (0.011 mole) was refluxed in ethanol or acetic acid (30 ml) for 3 hours. The precipitate was filtered off, dried and crystallised from the proper solvent. The results are summarized in Table 3.

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Table 3

7-Methyl-5-phenyl-5*H*-pyrazolo[3,4-*e*]-1,2,4-triazin-3-yl Hydrazones V

Compound No. [a]	Ar	Mp (°C)	Yield %	Molecular formula	Analysis Calcd./(Found) (%) C	H	N
Va	C_6H_5	281-283	76	$C_{18}H_{15}N_7$	65.64 (65.71)	4.59 (4.40)	29.77 (29.82)
b	*o*-BrC_6H_4	281-282	83	$C_{18}H_{14}N_7Br$ [b]	52.96 (52.79)	3.46 (3.35)	24.02 (23.85)
c	*o*-HOC_6H_4	295-297	91	$C_{18}H_{15}N_7O$	62.60 (62.54)	4.38 (4.29)	28.39 (28.41)
d	*p*-$CH_3OC_6H_4$	271-273	87	$C_{19}H_{17}N_7O$	63.50 (63.48)	4.77 (4.76)	27.28 (27.09)
e	*p*-$NO_2C_6H_4$	289-290	90	$C_{18}H_{14}N_8O_2$	57.75 (57.59)	3.77 (3.60)	29.93 (30.03)

[a] Solvent of crystallization: Va, Dioxane; Vb, Toluene; Vc, Pyridine; Vd, Dioxane; Ve, Dimethylformamide. [b] *Anal.* Calcd. for Br: 19.57%. Found: 19.36%.

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[16] Further investigation on the synthesis of 6-methyl-8-phenyl-8*H*-pyrazolo[3,4-*e*]tetrazolo[5,1-*c*]-1,2,4-triazine and 3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*e*]-1,2,4-triazolo[3,4-*c*]-1,2,4-triazine derivatives using 3-hydrazino-7-methyl-5-phenyl-5*H*-pyrazolo[3,4-*e*]-1,2,4-triazine is in progress and the results will be reported in a further communication.

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