Synthesis of 1*H*-Pyrazolo[3,4-*e*]-*s*-triazolo[3,4-*c*]-*as*-triazines, 8*H*-Pyrazolo[3,4-*e*]tetrazolo[5,1-*c*]-*as*-triazine and 1,7-Dihydro-8*H*-pyrazolo[3,4-*e*]-*as*-triazine Derivatives

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3-Hydrazino-7-methyl-5-phenyl-5*H*-pyrazolo[3,4-*c*]-*as*-triazine **1** underwent ring closure and/or condensation reaction with formic acid, acetic acid, acetic anhydride and benzoyl chloride to afford 1*H*-pyrazolo-[3,4-*d*]-*s*-triazolo[3,4-*c*]-*as*-triazines **2, 5** and **7a** and/or *N*-acyl derivatives **3, 4** and **6**. *N*-Acyl derivatives **3** and **6** underwent cyclisation reaction on treatment with phosphoryl chloride to give **5** and **7a**. 3-Methyl-1-phenyl-8-aryl-1*H*-pyrazolo[3,4-*e*]-*s*-triazolo[34,-*c*]-*as*-triazines **7** were also prepared by the reaction of the hydrazono derivatives **8** wit thionyl chloride. On treatment of **1** with nitrous acid gave the 8*H*-pyrazolo[3,4-*e*]tetrazolo-[5,1-*c*]-*as*-triazine **9**. Compound **1** underwent ring closure with carbon disulphide or ethyl chloroformate to 1,7-dihydro-8*H*-pyrazolo[3,4-*e*]-*s*-triazolo[3,4-*c*]-*as*-triazine derivatives **10** and **12**. Reaction of **1** with ethyl acetoacetate or acetylacetone gave 3-pyrazolo derivatives **13** and **14**.

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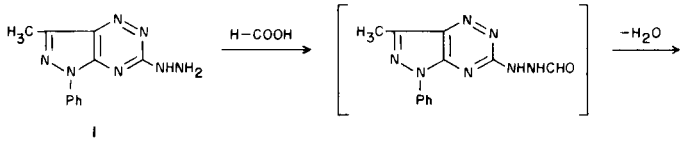
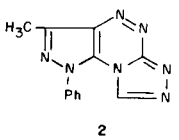
The broad utility of heterocyclic hydrazines as starting materials for the preparation of several condensed systems containing triazole and tetrazole nuclei has received increasing attention [2-10]. From this view it was of interest to examine the chemistry of 3-hydrazino-7-methyl-5-phenyl-5*H*-pyrazolo[3,4-*e*]-1,2,4-triazine (**1**) [11].

3-Hydrazino-7-methyl-5-phenyl-5*H*-pyrazolo[3,4-*e*]-1,2,4-triazine (**1**) readily underwent ring closure with formic acid to give 3-methyl-1-phenyl-1*H*-pyrazolo[3,4-*e*][1,2,4]triazolo[3,4-*c*][1,2,4]triazine (**2**). The reaction proceeds through N^2-acylation followed by thermal cyclisation at N-4 of the triazine ring to form the angular structure **2** as cited in the literature [2,3,12,13]. The chemical structure of **2** was confirmed by analytical and spectroscopic data.

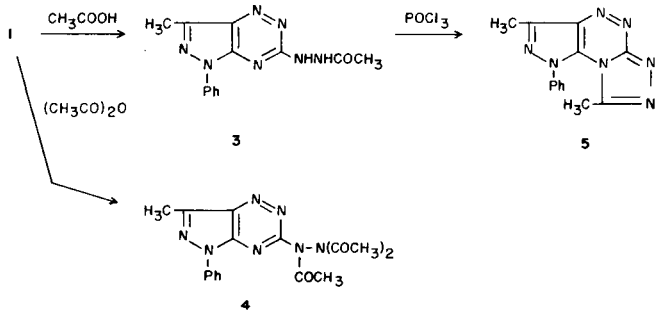


1



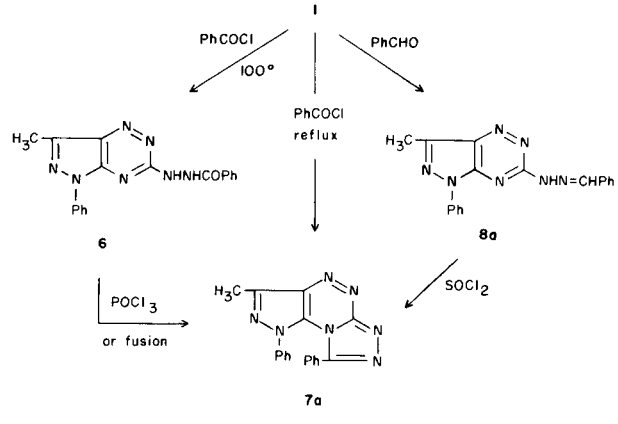
2

Attempts to synthesise 3,8-dimethyl-1-phenyl-1*H*-pyrazolo[3,4-*e*][1,2,4]triazolo[3,4-*c*][1,2,4]triazine (**5**) by refluxing **1** with acetic acid or acetic anhydride were unsuccessful and instead of the target compound **5**, 2-acetyl- and 1,2,2-triacetyl-1-(7-methyl-5-phenyl-5*H*-pyrazolo[3,4-*e*]-1,2,4-triazin-3-yl)hydrazines **3, 4** were obtained. The monoacetyl derivative **3** underwent ring closure with phosphoryl chloride [4] in boiling xylene to **5**. The chemical structure of **3, 4** and **5** was deduced from their analytical and spectroscopic data.



3 4 5

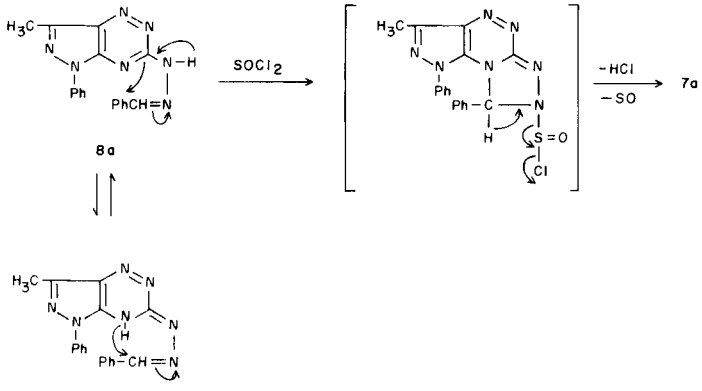
On heating **1** with excess benzoyl chloride at 100° gave 2-benzoyl-1-(7-methyl-5-phenyl-5*H*-pyrazolo[3,4-*e*]-1,2,4-triazin-3-yl)hydrazine (**6**) was obtained which subsequently cyclised to 3-methyl-1,8-diphenyl-1*H*-pyrazolo[3,4-*e*][1,2,4]-triazolo[3,4-*c*][1,2,4]triazine (**7a**) by using phosphoryl chloride [5] in boiling xylene or by fusion. Furthermore, the cyclised product **7a** was also obtained directly by refluxing the hydrazino derivative **1** with excess benzoyl chloride [2]. The chemical structure of **6** and **7a** was confirmed by analytical and spectroscopic data.



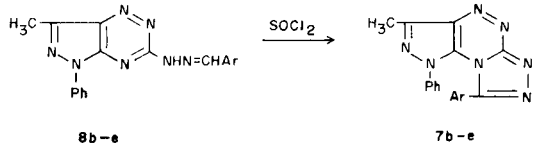
6 8a 7a

An alternative route for the synthesis of **7a** involved the reaction of benzaldehyde(7-methyl-5-phenyl-5*H*-pyrazolo-[3,4-*e*]-1,2,4-triazin-3-yl)hydrazone (**8a**) [11] with thionyl chloride at reflux for 3 hours. It was found that, the product obtained by this method was identical in all aspects (mp, mmp, ir and pmr) with those obtained by the above methods.

The reaction of **8a** with thionyl chloride presumably proceeds through the following series of transformations.



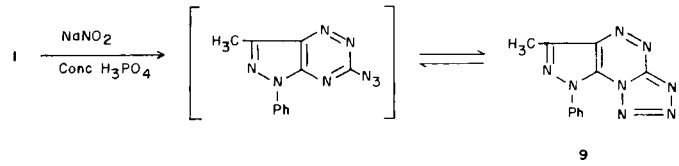
The latter procedure was applied to synthesise 3-methyl-1-phenyl-8-aryl-1*H*-pyrazolo[3,4-*e*][1,2,4]triazolo[3,4-*c*]-[1,2,4]triazines **7b-e**. The chemical structure of **7b-e** was confirmed on the basis of analytical data and ir spectra.



8b-e **7b-e**

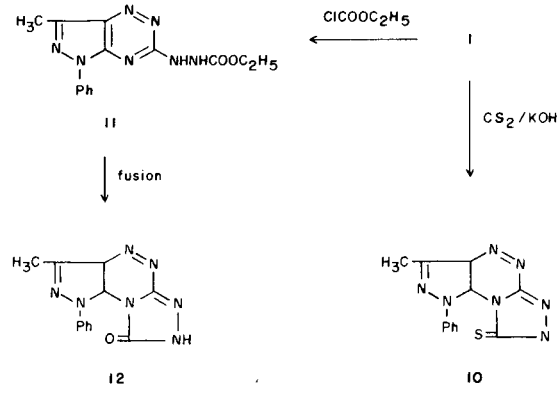
7b, Ar = C_6H_4Br-o, **c**, Ar = C_6H_4OH-o
d, Ar = $C_6H_4OCH_3$-p, **e**, Ar = $C_6H_4NO_2$-p

Treatment of **1** with nitrous acid gave, in nearly quantitative yield, the corresponding 6-methyl-8-phenyl-8*H*-pyrazolo[3,4-*e*]tetrazolo[5,1-*c*][1,2,4]triazine (**9**). The chemical structure of **9** was confirmed by its elemental analysis and spectroscopic data.



9

1,7-Dihydro-3-methyl-1-phenyl-8*H*-pyrazolo[3,4-*e*][1,2,4]-triazine-8-thione (**10**) was synthesised by refluxing **1** with carbon disulphide in alcoholic potassium hydroxide [4,5]. On the other hand, refluxing **1** with ethyl chloroformate in pyridine at 100°; alcoholic sodium hydroxide; sodium ethoxide or in benzene and triethylamine produced 2-ethoxycarbonyl-1-(7-methyl-5-phenyl-5*H*-pyrazolo[3,4-*e*]-1,2,4-triazin-3-yl)hydrazine (**11**). Fusion of **11** above its melting point for 10 minutes eliminates a molecule of alcohol giving 1,7-dihydro-3-methyl-1-phenyl-8*H*-pyrazolo[3,4-*e*]-[1,2,4]triazolo[3,4-*c*][1,2,4]triazin-8-one (**12**). The chemical structures of **10, 11** and **12** were established on the basis of elemental analyses and spectroscopic data.



11 **12** **10**

The cyclic structure of compounds **2, 5, 7, 9, 10** and **12** comprised a longer wavelength band in the range (444-560 nm). This band does not appear in the spectra of the starting compound or the intermediates and corresponds to CT transition within the highly conjugated structure formed as a result of cyclization. The CT nature of this band is

Table I

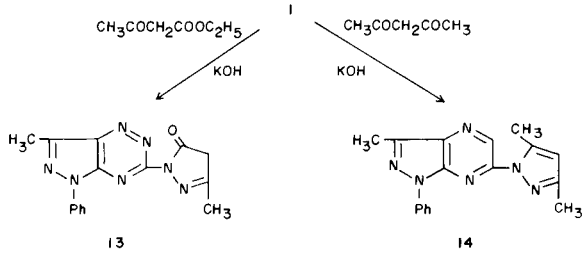
3-Methyl-8-aryl-1*H*-pyrazolo[3,4-*e*][1,2,4]triazolo[3,4-*c*][1,2,4]triazines **7b-e**

Compound No.	Mp (°C)	Yield (%)	Solvent of Crystallization [a]	λ max (Dioxane) (ε) nm	Molecular formula	Analysis (%) Calcd./(Found) C	H	N
7b	238-240	60	B	—	$C_{18}H_{12}N_7Br$ [b]	53.22	2.98	24.13
						(53.13)	(2.96)	(24.31)
7c	231-233	34	B	—	$C_{18}H_{13}N_7O$	62.97	3.82	28.56
						(63.05)	(4.00)	(28.38)
7d	250-252	70	B	286, 522 (46000), (1550)	$C_{19}H_{15}N_7O$	63.86	4.23	27.44
						(63.75)	(4.31)	(27.64)
7e	203-205	94	P	286, 344, 510 (35500), (19000), (1750)	$C_{18}H_{12}N_8O$	58.06	3.25	30.09
						(58.19)	(3.29)	(30.07)

[a] B = Benzene, P = Pyridine. [b] Calcd.: Br, 19.76%. Found: Br, 19.70%.

evidenced from its broadness as well as its sensitivity towards substitution (*cf.* Experimental).

Reaction of **1** with ethyl acetoacetate and/or acetylacetone in alcoholic potassium hydroxide led to the formation of 7-methyl-3-(3-methyl-2-pyrazolin-1-yl-5-one)-5-phenyl-5*H*-pyrazolo[3,4-*e*]-1,2,4-triazine and/or 7-methyl-3-(3,5-dimethylpyrazol-1-yl)-5-phenyl-5*H*-pyrazolo[3,4-*e*]-1,2,4-triazine (**13** and **14**) respectively. The chemical structures of **13** and **14** were confirmed by elemental analyses and ir spectra.



EXPERIMENTAL

All melting points are uncorrected. The ir spectra were recorded on a Perkin-Elmer 599 B spectrophotometer using the potassium bromide wafer technique. The pmr spectra were obtained on a Varian EM-360 (60 MHz) spectrometer. The uv spectra were recorded on a Varian-Cary 219 spectrophotometer.

3-Methyl-1-phenyl-1*H*-pyrazolo[3,4-*e*][1,2,4]triazolo[3,4-*c*][1,2,4]triazine (**2**).

3-Hydrazino-7-methyl-5-phenyl-5*H*-1,2,4-triazine (**1**) (0.3 g) was refluxed with formic acid (10 ml) for 5 hours. On cooling the reaction mixture and dilution with water, an orange precipitate was formed. The product was crystallised from benzene to give **2** as orange needles on 96% yield, mp 246-248°; ir (potassium bromide): showed no characteristic bands for NH and NH_2 groups; pmr (trifluoroacetic acid): δ 2.2 (s, CH_3, 3H), 6.5-7.3 (m, aromatic, 5H), 8.4 (s, CH=N, 1H); uv (dioxane): λ max 266 nm (ε 75000), 482 (2566).

Anal. Calcd. for $C_{12}H_9N_7$: C, 57.37; H, 3.61; N, 39.02. Found: C, 57.74; H, 3.81; N, 39.22.

2-Acetyl-1-(7-methyl-5-phenyl-5*H*-pyrazolo[3,4-*e*]-1,2,4-triazin-3-yl)hydrazine (**3**).

A mixture of **1** (0.3 g) and acetic acid (10 ml) was refluxed for 5 hours. On cooling the reaction mixture a yellow precipitate was formed. The product was crystallised from ethanol to give **3** as pale yellow needles in 79% yield, mp 250-252°; ir (potassium bromide): 3270, 3220 cm^{-1} (NH), 1670 (C=O); pmr (DMSO-d_6): δ 1.8 (s, $NCOCH_3$, 3H), 2.4 (s, CH_3, 3H), 6.8-7.7 (m, aromatic, 5H), 9.4 (s, NHNH, 2H), the latter signal disappeared on addition of deuterium oxide; uv (ethanol): λ max 260 nm (ε 16570), 334 (5000).

Anal. Calcd. for $C_{13}H_{13}N_7O$: C, 55.12; H, 4.63; N, 34.61. Found: C, 55.22; H, 4.73; N, 34.56.

1,2,2-Triacetyl-1-(7-methyl-5-phenyl-5*H*-pyrazolo[3,4-*e*]-1,2,4-triazin-3-yl)-hydrazine (**4**).

A mixture of **1** and acetic anhydride (10 ml) was refluxed for 5 hours. The reaction mixture was cooled and diluted with water whereby a yellow precipitate was formed. The product was crystallised from benzene to give **4** as a yellow powder in 73% yield, mp 140-142°; ir (potassium bromide): 1720 cm^{-1} (C=O); pmr (deuteriochloroform): δ 2.2 (s, N^1-$COCH_3$, 3H), 2.7 (s, N^2 $(COCH_3)_2$, 6H), 6.9-7.8 (m, aromatic, 5H); uv (ethanol): λ max 268 nm (ε 27000), 316 (7000), 360 sh (600).

Anal. Calcd. for $C_{17}H_{17}N_7O_3$: C, 55.58; H, 4.66; N, 26.69. Found: C, 55.59; H, 4.59; N, 27.00.

3,8-Dimethyl-1-phenyl-1*H*-pyrazolo[3,4-*e*][1,2,4]triazolo[3,4-*c*][1,2,4]triazine (**5**).

A mixture of **3** (0.5 g), dry xylene (5 ml) and phosphoryl chloride (1 ml) was refluxed for 8 hours. The cooled reaction mixture was diluted with petroleum ether (bp 60-80°) and the supernatant liquid decanted. The residue was dissolved in water, ammonium hydroxide and added and the precipitate was filtered off. The solid obtained was crystallised from ethanol to give **5** as red crsytals in 79% yield, mp 257-259°; ir (potassium bromide): no characterstic bands for NH and CO groups; pmr (trifluoroacetic acid): δ 2.3 (s, CH_3, 3H), 2.4 (CH_3-C=N, 3H), 6.7-7.4 (m, aromatic, 5H); uv (dioxane): λ max 268 nm (ε 42500), 498 (1600).

Anal. Calcd. for $C_{13}H_{11}N_7$: C, 58.86; H, 4.18; N, 36.96. Found: C, 59.01; H, 4.16; N, 36.88.

2-Benzoyl-1-(7-methyl-5-phenyl-5*H*-pyrazolo[3,4-*e*]-1,2,4-triazin-3-yl)hydrazine (**6**).

A mixture of **1** (0.3 g) and benzoyl chloride (5 ml) was heated on a water bath for 5 hours. The solid product thus obtained was filtered, washed with benzene and crystallised from ethanol to give 6 as yellow needles in 93% yield, mp 239-241°; ir (potassium bromide): 1650 cm^{-1} (C=O), 3200 (NH).

Anal. Calcd. for $C_{18}H_{15}N_7O$: C, 62.60; H, 4.38; N, 28.39. Found: C, 62.55; H, 4.44; N, 28.43.

3-Methyl-1,8-diphenyl-1*H*-pyrazolo[3,4-*e*][1,2,4]triazolo[3,4-*c*][1,2,4]triazine (**7a**). Method A.

A mixture of **6** (0.5 g), dry xylene and phosphoryl chloride was refluxed for 8 hours. The usual working up procedure gave **7** as red crystals in 84% yield, mp 258-260°; ir (potassium bromide): no absorption bands for NH and CO groups; pmr (trifluoroacetic acid): δ 2.3 (s, CH_3, 3H), 6.6-6.7 (m, 1-Ar-H, 8-Ar-H (2',3',5',6'), 9H), 9.0 (s, 8-Ar-H (4'), 1H); uv (dioxane): λ max 285 nm (ε 56000), 516 (2200).

Anal. Calcd. for $C_{18}H_{13}N_7$: C, 66.05; H, 4.00; N, 29.95. Found: C, 65.91; H, 3.87; N, 29.66.

Method B.

Compound **6** (1 g) was heated at 240-245° for 15 minutes on a sand bath. The solid mass was extracted with benzene-petroleum ether (bp 60-80°) mixture and the extract was concentrated and cooled whereby red crystals were separated. The product was collected and recrystallized from benzene to give **7a** as red crystals in 32% yield, mp 259-260°.

Method C.

Compound **1** (1 g) was refluxed with benzoyl chloride (10 ml) for 5 hours. Excess benzoyl chloride was distilled off under reduced pressure and the residue washed with hot petroleum ether (bp 60-80°). The product was collected and crystallised from benzene to give **7a** as red crystals in 37% yield, mp 258-260°.

Method D.

Benzaldehyde (7-methyl-5-phenyl-5*H*-pyrazolo[3,4-*e*]-1,2,4-triazin-3-yl)-hydrazone (**8a**) (0.5 g) and thionyl chloride were heated on a water bath for 3 hours. Excess thionyl chloride was removed by distillation and the residue washed with hot petroleum ether (bp 60-80°). The product was crystallised from benzene to give **7a** as red crsytals in 68% yield mp 258-260°. The reaction product was found to be identical with those formed by the above methods in all aspects.

3-Methyl-1-phenyl-8-aryl-1*H*-pyrazolo[3,4-*e*][1,2,4]triazolo[3,4-*c*][1,2,4]triazines **7b-e**. General Procedure.

A mixture of **8b-c** [11] (0.3 g) and thionyl chloride (10 ml) was heated on a water bath for 3 hours. Excess thionyl chloride was removed by distillation. The residue was triturated with petroleum ether (bp 60-80°) and the products were crystallised from the proper solvent to give **7b-e**

(Table I).

6-Methyl-8-phenyl-8*H*-pyrazolo[3,4-*e*]tetrazolo[5,1-*c*][1,2,4]triazine (**9**).

To compound **1** (0.25 g, 0.001 mole) in concentrated phosphoric acid (2 ml), sodium nitrite solution (1.5 ml, 0.005 mole) was added at 0° during 15 minutes with stirring. The mixture was stirred for a further 2 hours and the precipitate was filtered off and dried. The solid product was crystallised from methanol to give **9** as orange crystals in 96% yield, mp 138-140°; ir (potassium bromide): 1215 cm^{-1} (tetrazole ring) [10], no absorption band at 2120-2150 characteristic for azido group; pmr (DMSO-d_6): δ 2.6 (s, CH_3, 3H), 6.9-7.8 (m, aromatic, 5H); uv (ethanol): λ max 258 nm (ε 52500), 444 (1500).

Anal. Calcd. for $C_{11}H_8N_8$: C, 52.38; H, 3.20; N, 44.42. Found: C, 52.51; H, 3.37; N, 44.61.

1,7-Dihydro-3-methyl-1-phenyl-8*H*-pyrazolo[3,4-*e*][1,2,4]triazolo[3,4-*c*]-[1,2,4]triazine-8-thione (**10**).

A mixture of **1** (0.3 g), methanol (20 ml), potassium hydroxide (0.1 g) and carbon disulphide (1ml) was refluxed for 4 hours. The reaction mixture was filtered, concentrated and neutralised with acetic acid whereby a dark green material was precipitated. The product was crystallised from xylene to give **10** in 57% yield, mp > 300°; ir (potassium bromide): 1275 cm^{-1} (C=S), 3100 (NH); uv (ethanol): λ max 248 nm (ε 11750), 286 (20500), 404 (600), 560 (475).

Anal. Calcd. for $C_{12}H_9N_7S$: C, 50.87; H, 3.20; N, 34.61; S, 11.32. Found: C, 50.69; H, 3.11; N, 34.65; S, 11.39.

2-Ethoxycarbonyl-1-(7-methyl-5-phenyl-5*H*-pyrazolo[3,4-*e*]-1,2,4-triazin-3-yl)hydrazine (**11**).

A mixture of **1** (0.3 g) and ethyl chloroformate (0.22 ml) was heated in pyridine (20 ml) on a water bath for 8 hours. The reaction mixture was cooled and acidified with dilute acetic acid whereby a yellow precipitate was formed. The product was crystallised from ethanol to give **11** as yellow needles in 62% yield, mp 204-205°; ir (potassium bromide): 3320, 3220 cm^{-1} (NH), 1750 (C=O); uv (ethanol): λ max 260 nm (ε 17250), 334 (5312).

Anal. Calcd. for $C_{14}H_{15}N_7O_2$: C, 53.67; H, 4.83; N, 31.29. Found: C, 53.76; H, 4.63; N, 31.25.

1,7-Dihydro-3-methyl-1-phenyl-8*H*-pyrazolo[3,4-*e*][1,2,4]triazolo[3,4-*c*]-[1,2,4]triazin-8-one (**12**).

Compound **11** (0.3 g) was heated on a sand bath at 205-210° for 10 minutes. The resulting material was crystallised from benzene to give **12** as violet product in 78% yield, mp 268-270°; ir (potassium bromide): 3180 cm^{-1} (NH), 1710 (C=O); pmr (trifluoroacetic acid): δ 2.05 (s, CH_3, 3H), 6.5-7.2 (m, aromatic, 5H), 9.1 (s, NH, 1H); uv (ethanol): λ max 226 nm (ε 8750), 264 (17500), 325 sh (450), 532 (625).

Anal. Calcd. for $C_{12}H_9N_7O$: C, 53.93; H, 3.39; N, 36.69. Found: C, 53.80; H, 3.56; N, 36.51.

7-Methyl-3-(3-methyl-2-pyrazolin-1-yl-5-one)-5-phenyl-5*H*-pyrazolo[3,4-*e*]-1,2,4-triazine (**13**).

Compound **1** (0.3 g), ethyl acetoacetate (0.16 ml) and potassium hydroxide (0.1 g) in ethanol (20 ml) were refluxed for 3 hours. The reaction mixture was cooled and neutralized with acetic acid whereby a yellow material was precipitated. The product was crystallised from ethanol to give **13** as yellow crystals in 77% yield, mp 254-256°; ir (potassium bromide): 1660 cm^{-1} (C=O).

Anal. Calcd. for $C_{15}H_{13}N_7O$: C, 58.63; H, 4.26; N, 31.90. Found: C, 58.71; H, 4.36; N, 31.73.

7-Methyl-3-(3,5-dimethylpyrazol-1-yl)-5-phenyl-5*H*-pyrazolo[3,4-*e*]-1,2,4-triazine (**14**).

The above method was employed using acetylacetone instead of ethyl acetoacetate. The product was crystallised from ethanol to give **14** as greenish yellow powder in 53% yield, mp 136-138°; ir (potassium bromide): no absorption bands due to NH or NH_2 groups.

Anal. Calcd. for $C_{16}H_{15}N_7$: C, 62.94; H, 4.95; N, 32.11. Found: C, 62.91; H, 5.14; N, 32.09.

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