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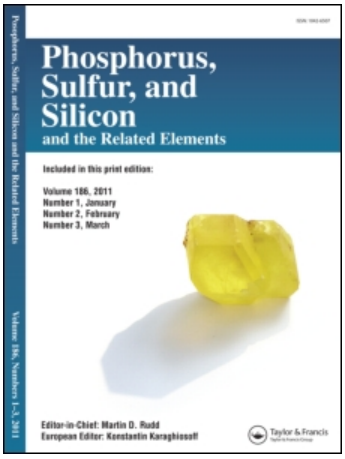

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The Reaction of 4-Phenyl-3-Thiosemicarbazide With β-Bifunctional Compounds: Novel Synthesis of Pyridine And Pyrazole Derivatives

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THE REACTION OF 4-PHENYL-3-THIOSEMICARBAZIDE WITH β-BIFUNCTIONAL COMPOUNDS: NOVEL SYNTHESIS OF PYRIDINE AND PYRAZOLE DERIVATIVES

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The 4-phenyl-3-thiosemicarbazide **1** reacted with acetoacetanilide derivatives **2a–c**, benzoyl acetonitrile **14** to afford the condensed products **3a–c** and **15** respectively. The reactivity of the reaction products toward different chemical reagents to form heterocyclic and fused heterocyclic ring systems has been studied.

Key words: 4-Phenyl-3-thiosemicarbazide, pyridine, pyrazole, pyridazine.

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INTRODUCTION

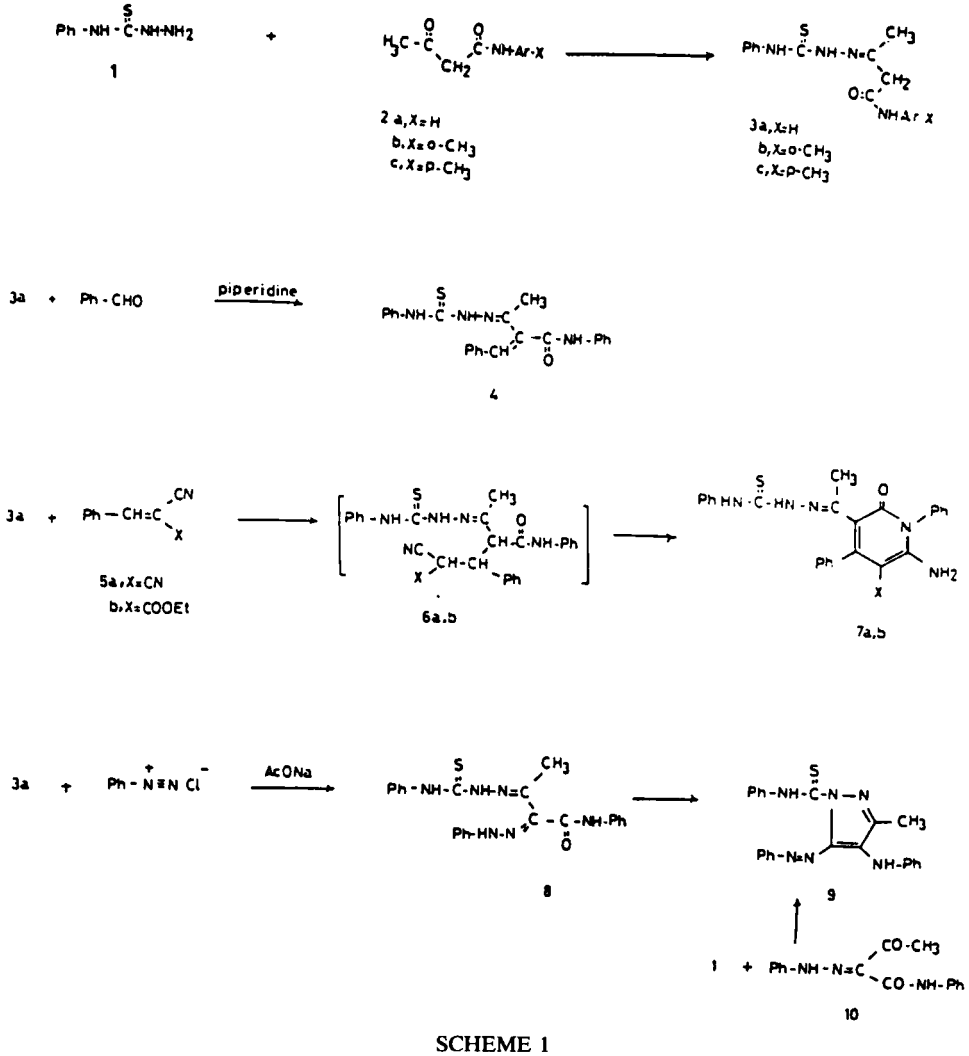
Thiosemicarbazides are versatile reagents which have recently been used as synthetic intermediates for a large number of heterocyclic and fused heterocyclic compounds.[1–4] The reactivity of 4-phenyl-3-thiosemicarbazide towards ketones, cyanomethylene reagents and dimeric adducts attracted our attention in recent years. The results showed the formation of thiazole, pyrazole, pyridine and 1, 3, 4-thiadiazine derivatives.[5,6]

RESULTS AND DISCUSSION

In continuation of this work we report here a new series of reactions involving the use of the title reagent in the synthesis of pyridine and pyrazole derivatives of potential biological activity.[7–10] The reaction of **1** with acetoacetanilide derivatives **2a–c** afforded the 4-phenyl-3-thiosemicarbazone derivatives **3a–c**. The structures of **3a–c** were established based on analytical and spectral data. The ^{1}H NMR spectrum of **3a** revealed the presence of a singlet at δ = 1.98 ppm for CH_3 group, a singlet at δ = 3.91 ppm for CH_2 group, a multiplet at δ = 7.32–7.45 ppm for two phenyl groups and three singlets (D_2O exchangeable) at δ = 8.92, 9.21 and 9.24 ppm for three NH groups. Further confirmation for the structures of **3a–c** was obtained through the study of the reactivity of **3a** towards some chemical

reagents. Compound **3a** reacted with benzaldehyde to afford the benzylidene derivative **4**. It reacted with cinnamonitrile derivatives like **5a, b** to afford the pyridine derivatives **7a, b**. The reaction takes place through the intermediate formation of **6a, b** followed by cyclization. The structures of **7a, b** were established based on analytical and spectral data. The IR spectrum of **7a** revealed the presence of NH_2 stretching at 3460–3355 cm^{-1} and one CN group stretching at 2220 cm^{-1}. ^1H NMR spectrum showed the presence of a singlet at δ = 2.21 ppm for the CH_3 group, a singlet at δ = 4.95 ppm (D_2O exchangeable) for the NH_2 group, a multiplet at δ = 7.32–7.45 ppm for three phenyl protons and two singlets at δ = 8.91 and 9.23 ppm (D_2O exchangeable) for two NH groups. The same arguments were used to confirm the structure of **7b**.

The reactivity of **3a** towards coupling reactions with diazonium salts was also studied. Thus, **3a** reacted with benzenediazonium chloride in alcoholic sodium



SCHEME 1

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acetate to afford the phenyl hydrazone derivative **8**. Compound **8** underwent ready cyclization in refluxing sodium ethoxide solution to afford the pyrazole derivative **9** through water elimination. The structure of compound **9** was established based on analytical and spectral data together with the synthesis via another reaction route (see Chart 1). The reaction of **3a** with phenylhdrazono acetoacetanilide **10** afforded the same product **9** (identical m.p. and mixed m.p.).

Compound **3a** reacted with the active methylene reagents like malononitrile **11a** and ethyl cyanoacetate **11b** to afford the benzene derivatives **13a** and **13b** respectively. Formation of **13a, b** is assumed to take place through the intermediate formation of **12a, b**. The structures of **13a, b** were established based on analytical and spectral data (cf. Tables I and II).

The reaction of **1** with benzoyl acetonitrile **14** yielded a product with molecular formula $C_{16}H_{14}N_4S$. Two possible isomeric structures **15** and **16** were considered.

TABLE I

Physical and analytical data of the newly prepared compounds

Compd. (colour)	Solvent	m.p. (°C)	Yield (%)	Mol. Formula (M. wt.) (Mol. ion)	Analysis (Calcd / Found) % C	H	N	S
3a	EtOH	115	90	$C_{17}H_{18}N_4SO$	62.6	5.5	17.1	9.8
(yellow)				(326.21)	62.3	5.2	17.4	9.7
3b	Dioxane	170	78	$C_{18}H_{20}N_4SO$	63.5	5.9	16.5	9.0
(yellow)				(340.18)	63.4	5.7	16.5	9.4
3c	Dioxane	215	69	$C_{18}H_{20}N_4SO$	63.5	5.9	16.5	9.4
(orange)				(340.18)	63.5	5.6	16.4	9.0
4	EtOH	145	78	$C_{24}H_{22}N_4SO$	69.7	5.3	13.5	7.8
(brown)				(414.24)	69.8	5.0	13.9	7.7
7a	EtOH	175	66	$C_{27}H_{22}N_6SO$	67.8	4.6	17.6	6.7
(brown)				(478.22)(478)	67.5	4.5	17.4	6.5
7b	EtOH	223-5	75	$C_{29}H_{27}N_5SO_3$	66.3	5.1	13.3	6.1
(brown)				(525.22)(525)	66.0	5.0	13.6	6.5
8	EtOH	183	77	$C_{23}H_{22}N_6SO$	64.0	4.8	19.5	7.4
(red)				(430.23)	64.2	5.1	19.6	7.0
9	DMF	263-6	81	$C_{23}H_{20}N_6S$	67.0	4.8	20.4	7.8
(orang)				(411.22)	66.6	4.7	20.3	7.6
13a	EtOH	102	67	$C_{20}H_{18}N_6S$	64.2	4.8	22.4	8.5
(yellow)				(374.2)	64.0	4.5	22.0	8.4

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TABLE I (*Continued*)

Compd. (colour)	Solvent	m.p. (°C)	Yield (%)	Mol. Formula (M. wt.) (Mol. ion)	Analysis (Calcd / Found) % C	H	N	S
13b	EtOH	112	72	$C_{22}H_{23}N_5SO_2$	62.7	5.4	16.6	7.6
(orange)				(421.22)	62.5	5.1	16.9	7.7
15	Dioxane	163	78	$C_{16}H_{14}N_4S$	65.3	4.8	19.0	10.9
(yellow)				(294.16)	65.1	4.5	18.6	10.5
17	EtOH	125	70	$C_{22}H_{18}N_6S$	66.3	4.5	21.1	8.0
(orange)				(398.22)	66.2	4.7	21.5	7.6
18	DMF	>300	82	$C_{25}H_{20}N_5S$	71.1	4.7	16.5	-
(yellow)				(424.21)(424)	71.0	4.5	16.5	-
20	EtOH	181	66	$C_{17}H_{13}N_4S$	66.9	4.1	18.3	10.4
(paleyellow)				(305.17)(305)	66.7	4.3	18.2	10.3
16	Dioxane	232-5	72	$C_{16}H_{14}N_4S$	65.3	4.8	19.0	10.9
(yellow)				(294.16)	65.0	4.6	19.2	10.6
22a	EtOH	190	77	$C_{19}H_{13}N_7S$	61.4	3.5	26.4	8.6
(brown)				(371.19)	61.3	3.2	26.0	8.4
22b	EtOH	144	82	$C_{21}H_{18}N_6SO_2$	60.3	4.3	20.0	7.6
(yellow)				(418.21)	60.0	4.2	19.8	7.3
22c	Dioxane	176	71	$C_{21}H_{19}N_5SO_2$	62.2	4.7	17.3	7.9
(orange)				(405.21)	62.0	4.5	17.2	7.6

M^+ values found by mass spectroscopy.

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The possibility of the pyrazole derivative **16** was ruled out based on the IR spectrum of the reaction product which revealed the presence of only one CN group stretching and the absence of any NH_2 stretching which might be expected to appear if structure **16** is considered. The ^1H NMR spectrum of the reaction product revealed the presence of a singlet at δ = 4.21 ppm corresponding to the CH_2 group, a multiplet at δ = 7.32–7.38 ppm for two phenyl groups and two singlets at δ = 8.25 and 9.11 ppm for two NH groups. Further confirmation of the structure of **15** can be obtained from its reactions. Thus, **15** coupled with benzenediazonium chloride to yield **17**. The latter reacted with malononitrile to afford the pyridazine derivative **18**. The structure of **18** was established based on analytical and spectral data (cf. Tables I and II).

Compound **15** reacted with trichloroacetonitrile to afford the pyrazole derivative

20. The structure of **20** was confirmed by its mass spectrum which revealed m/e = 305 M^+ together with ^1H NMR which showed a singlet at δ = 5.21 ppm (D_2O exchangeable) for NH_2 group, a multiplet at δ = 7.32–7.46 ppm for two phenyl groups and a singlet at δ = 9.21 ppm (D_2O exchangeable) for NH groups. Formation of **20** is assumed to take place through the intermediate formation of the 1:1 adduct **19** followed by chloroform elimination (see Chart 2).

Boiling of **15** in dimethylformamide containing a catalytic amount of triethylam-

TABLE II

I.R. and ^1H NMR data of the newly prepared compounds

Compd. No.	I. R cm^{-1} (KBr) Selected bands	^1H NMR (δ ppm)
3a	3450-3380 (3NH); 3050 (CH aromatic); 2980, 2875 (CH_3, CH_2), 1680 (C=0); 1660 (C=N), 1220 (C=S).	1.98 (s, 3H, CH_3); 3.91 (s, 2H, CH_2); 7-32-7.35 (m, 10H, $2C_6H_5$); 8.92; 9.21, 9.24 (3s, 3H, 3NH).
3b	3450-3380 (3NH); 3050 (CH aromatic), 2980, 2875 ($2CH_3$, CH_2), 1680 (C=0), 1660 (C=N), 1220 (C=S).	1.98, 2.01 (2s, 6H, $2CH_3$), 3.91 (s, 2H, CH_2), 7.32-7.54 (m, 9H, C_6H_5, C_6H_4); 8.94, 9.25, 9.25 (3s, 3H, 3NH).
3c	3440-3390 (3NH); 3045 (CH aromatic); 2980, 2920 (CH_3, CH_2), 1680 (C=0); 1660 (C=N), 1220 (C=S).	1.99, 2.04 (2s, 6H, $2CH_3$); 3.94 (s, 2H, CH_2), 7.34- 7.42 (m, 9H, C_6H_5, C_6H_4), 8.96, 9.27, 9.30 (3s, 3H, 3NH).
4	3460-3355 (3NH); 3045 (CH aromatic); 2970 (CH_3), 1685 (C=0); 1655 (C=N), 1635 (C=C), 1210 (C=S).	1.98 (s, 3H, CH_3), 6.92 (s, 1H, CH=C), 7.33- 7.45 (m, 15H, $3C_6H_5$),8.92, 9.32, 9.41 (3s, 3H, 3NH).
7a	3460-3355(NH_2,2NH);3045(CH aromatic); 2980 (CH_3), 2220 (CN), 1690 (C=0); 1650 (C=N), 1635 (C=C), 1200 (C=S).	2.21 (s, 3H, CH_3); 4.95 (s, 2H, NH_2), 7.32- 7.45 (m, 15H, $3C_6H_5$), 8.91, 8.23 (2s, 2H, 2NH).
7b	3440-3370(NH_2,NH); 3050 (CH aromatic); 2975 (CH_3), 1690, 1685 (2C=0), 1650 (C=N); 1635 (C=C), 1220 (C=S)	1.32 (t, 3H, J=8.12 H_2, CH_3); 2.21 (s, 3H, CH_3), 4.21 (q, 2H, J=8.12 H_2, CH_2), 5.21 (s, 2H, NH_2), 7.33- 7.48 (m, 15H, $3C_6H_5$), 8.39, 9.33 (2s, 2H, 2NH).
8	3440-3410 (4NH); 3045 (CH aromatic); 1680 (C=0); 1660 (C=N), 1210 (C=S).	2.19 (s, 3H, CH_3), 7.32- 7.45 (m, 15H, $3C_6H_5$), 7.89, 8.21- 9.29 (m, 4H, 4NH).
9	3410-3380 (2NH); 3050 (CH aromatic); 2975 (CH_3), 1655 (C=N), 1210 (C=S).	2.21 (s, 3H, CH_3), 7.32- 7.52 (m, 15H ,$3C_6H_5$), 8.92, 9.36 (2s, 2H, 2NH).

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TABLE II (*Continued*)

Compd. No.	I. R cm^{-1} (KBr) Selected bands	^1H NMR (δ ppm)
13a	3450-3370(NH_2,4NH),3050(CH aromatic), 2225 (CN), 1630 (C=C), 1205 (C=S).	5.21 (s, 2H, NH_2); 7.31-7.52 (m, 12H, $2C_6H_5$, benzene H_4,6), 7.91-8.22, 9.23 (m, 4H, 4NH).
13b	3460-3380(NH_2,4NH);3050(CH aromatic); 2980, 2870 (CH_3, CH_2), 1695 (C=0); 1620 (C=C), 1200 (C=S).	1.36 (t, 3H, J=7.95 H_2, CH_3), 4.24 (q, 2H, J=7.95 H_2, CH_2), 5.21 (s, 2H, NH_2),7.32-7.52 (m, 12H, $2C_6H_5$, benzene H_4,6), 8.2-8.49 (m, 4H, 4NH).
15	3420-3360 (2NH); 3045 (CH aromatic); 2220 (CN), 1660 (C=N), 1205 (C=S).	4.21 (s, 2H, CH_2), 7.32-7.38 (m, 10H, $2C_6H_5$), 8.25, 9.11 (2s, 2H, 2NH).
17	3450-3360 (3NH); 3050 (CH aromatic); 2220 (CN), 1655 (C=N), 1210 (C=S)	7.22-7.36 (m, 15H, $3C_6H_5$), 7.92-8.19 (m, 3H, 3NH).
18	3460-3320(NH_2,3NH);3050(CH aromatic); 2220 (CN), 1685 (exocyclic C=N); 1660 (C=N), 1635 (C=C), 1200 (C=S).	5.38 (s, 2H, NH_2), 7.32-7.38 (m, 15H, $3C_6H_5$), 8.33, 9.32, 9.35 (3s, 3H, 3NH).
20	3450-3320(NH_2,NH);3050(CH aromatic); 2225 (CN), 1660 (C=N), 1205 (C=S).	5.21 (s, 2H, NH_2), 7.32-7.46 (m, 10H, $2C_6H_5$), 9.21 (s, 1H, NH).
16	3440-3310(NH_2,NH); 3050 (CH aromatic); 1635 (C=C), 1195 (C=S).	4.58 (s, 2H, NH_2), 7.32-7.51 (m, 11H, $2C_6H_5$, Pyrazole H-4), 8.23 (s, 1H, NH)
22a	3435 (NH); 3040 (CH aromatic); 2225, 2220 (2CN), 1650 (C=N), 1630 (C=C), 1200 (C=S).	5.81 (s, 1H, CH), 7.30-7.52 (m, 11H, $2C_6H_5$, Pyrazole H-4), 9.02 (s, 1H, NH)
22b	3450 (NH); 3050 (CH aromatic); 2225, 2220 (CN), 1690 (C=0); 1660 (C=N), 1625 (C=C), 1195 (C=S).	1.36 (t, 3H, J=8.01 Hz, CH_3), 4.45 (s, 1H, CH), 7.32-7.49 (m, 11H, $2C_6H_5$, Pyrazole H-4), 8.24 (s, 1H, NH).
22c	3450 (NH); 3050 (CH aromatic); 2965 (CH_3), 1695, 1680 (2C=0), 1650 (C=N), 1620 (C=C), 1200 (C=S).	2.21, 2.35 (2s, 6H, $2CH_3$), 5.21 (s, 1H, CH), 7.32-7.52 (m, 11H, $2C_6H_5$, Pyrazole H-4).

ine afforded the pyrazole derivative, **16**. The hydrochloride salt of **16** reacted with sodium nitrite to yield the nonisolatable diazonium salt **21** which, in turn, coupled in situ with the active methylene reagents, **11a–c**, to afford the corresponding

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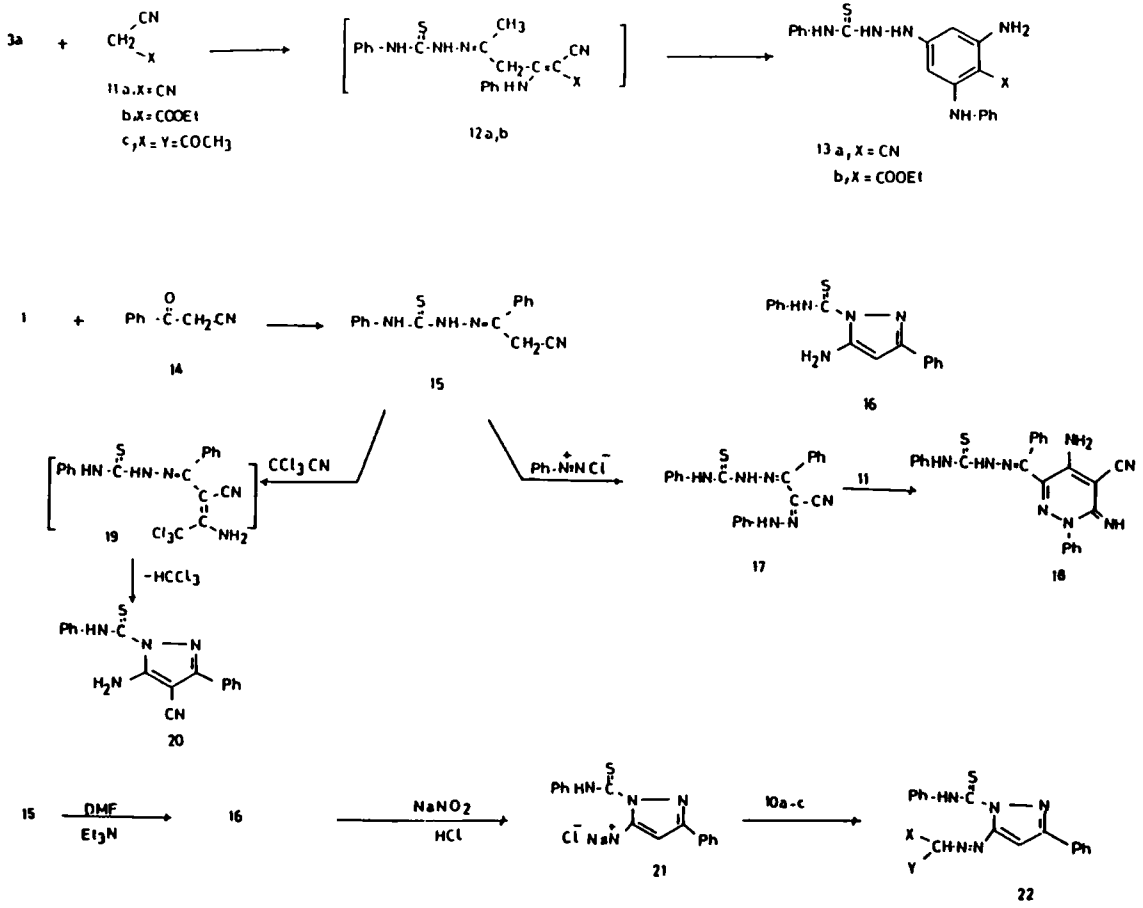

SCHEME 2

coupling products, **22a–c**, respectively (see Chart 2). The structures of **22a–c** were established based on analytical and spectral data (cf. Tables I and II).

EXPERIMENTAL

All melting points are uncorrected. IR spectra (KBr disks) were recorded on a Pye Unicam SP-100 Spectrophotometer. ^{1}H NMR spectra (DMSO as the solvent) were obtained on a Varian A-90 spectrometer using TMS as internal standard; chemical shifts are expressed as δ (ppm). Mass spectra were obtained with a LKB 9000 S spectrometer. Analytical data were obtained from the Microanalytical Data Unit at Cairo University.

Acetoacetanilide-β-(4'-phenyl-3'-thiosemicarbazone) Derivatives **3a–c**: General procedure: To solution of **1** (0.01 mol) in ethanol, there was added each of the acetoacetanilide derivatives **2a–c** (0.01 mol). The reaction mixture was heated under reflux for 6 h. The solid product, formed in each case upon cooling, was collected by filtration.

2-Benzalacetoacetanilide-3-(4'-phenyl-3'-thiosemicarbazone) **4**: To a solution of **3a** (0.01 mol) in ethanol (30 ml) containing piperidine (0.5 ml), there was added benzaldehyde (0.01 mol). The reaction mixture was heated under reflux for 3 h. The solid product, formed upon dilution with water containing few drops of hydrochloric acid, was collected by filtration.

6-Amino-3-acetyl-(4'-phenyl-3'-thiosemicarbazone)-5-cyano-1,4-diphenyl-2-oxo-pyridine **7a** *and 6-Amino-3-acetyl-(4'-phenyl-3'-thiosemicarbazone)-5-ethoxycarbonyl-1,4-diphenyl-2-oxo-pyridine* **7b**. To a solution of **3a** (0.01 mol) in absolute ethanol (20 ml) containing triethylamine (0.5 ml), there were added each of **5a** (0.01 mol) or **5b** (0.01 mol). The reaction mixture was heated under reflux for 3 h. The solid product, formed upon dilution with ice/water, was collected by filtration.

β-(4'-phenyl-3'-thiosemicarbazone)-α-phenylhydrazonoacetoacetanilide **8**. To a cold solution of **3a** (0.01 mol) in ethanol (40 ml) containing sodium acetate (3.0 g), benzenediazonium chloride (0.01 mol) [prepared by the addition of sodium nitrite (0.7 g in 5 ml water) solution to a cold solution (0.5°C) of aniline (0.01 mol) containing the appropriate amount of hydrochloric acid] was added with stirring. The reaction mixture was left at room temperature for 2 h and the solid product, so formed, was collected by filtration.

1-Phenylaminothioxo-4-phenylamino-5-phenylazo-3-methylpyrazole **9**. *Method A*: A solution of **8** (0.01 mol) in sodium ethoxide (0.01 mol) [prepared by adding sodium metal (0.01 mol) to absolute ethanol (40 ml)] was heated under reflux for 6 h. The solid product formed upon pouring into ice/water containing a few drops of hydrochloric acid (until pH = 6) was collected by filtration.

Method B: To a solution of **1a** (0.01 mol) in ethanol, **10** (0.01 mol) was added. The reaction mixture was heated under reflux for 6 h. The solid product, formed upon cooling, was collected by filtration.

1-Amino-2-cyano-3-phenylamino-5-(4'-phenyl-3'-thiosemicarbazone)-benzene **13a** *and 1-Amino-2-ethoxycarbonyl-3-phenylamino-5-(4'-phenyl-3'-thiosemicarbazone)-benzene* **13b**: General procedure: To a solution of **3a** (0.01 mol) in absolute ethanol (50 ml) containing triethylamine (0.5 ml), there was added either **11a** (0.01 mol) or **11b** (0.01 mol). The reaction mixture was heated after triturating, the remaining semisolid product with diethyl ether, was collected by filtration.

β-Phenyl-β-(4'-phenyl-3'-thiosemicarbazone)-propiononitrile **15**: To a solution of **1** (0.01 mol) in absolute ethanol (30 ml), there was added benzoylacetonitrile **14** (0.01 mol). The reaction mixture was heated under reflux for 4 h and the solid product, formed upon dilution with ice/water, was collected by filtration.

α-Phenylhydrazone-β-(4'-phenyl-3'-thiosemicarbazone)-propiononitrile **17**: The same experimental procedure described for the synthesis of **8** was carried out except for the use of **15** (0.01 mol) instead of **3a**.

4-Amino-5-cyano-6-imino-1-phenyl-3-[benzoyl-(4'-phenyl-3'-thiosemicarbazone)-benzene **18**: To a solution of **17** (0.01 mol) in dioxane (30 ml) containing triethylamine (0.5 ml), there was added malononitrile **11a** (0.01 mol). The reaction mixture was heated under reflux for 3 h and the solid product, formed upon dilution with water, was collected by filtration.

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5-Amino-4-cyano-3-phenyl-1-phenylaminothioxopyrazole **20**: To a solution of **14** (0.01 mol) in dioxane (30 ml) containing triethylamine (0.5 ml), there was added trichloroacetonitrile (0.01 mol). The reaction mixture was heated under reflux for 2 h. The solid product, which formed upon cooling, was collected by filtration.

5-Amino-3-phenyl-1-phenylaminothioxopyrazole **16**: A solution of **15** (0.01 mol) in dimethylformamide (30 ml) containing triethylamine (0.01 mol) was heated under reflux for 3 h. The remaining product, so formed, upon evaporation in vacuo was triturated with diethyl ether and the solid product, so formed, was collected by filtration.

3-phenyl-1-phenylaminothioxopyrazol-5-diazomalononitrile **22a**, *3-phenyl-1-phenylaminothioxopyrazol-5-diazoethyl cyanoacetate* **22b** *and 3-phenyl-1-phenylaminothioxopyrazol-5-diazoacetylacetone* **22c**. General procedure: Sodium nitrite (0.7 g in 5 ml water) was added, with stirring to a cold solution of **21** (0.01 mol) in hydrochloric acid (8 ml, 0.1 mol). The resulting diazonium salt was added, with stirring to a cold solution of each of **11a–c** (0.01 mol) in ethanol containing sodium acetate (6 g) with stirring. The reaction mixture was left at room temperature for 4 h and the resulting solid product, was collected by filtration.

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