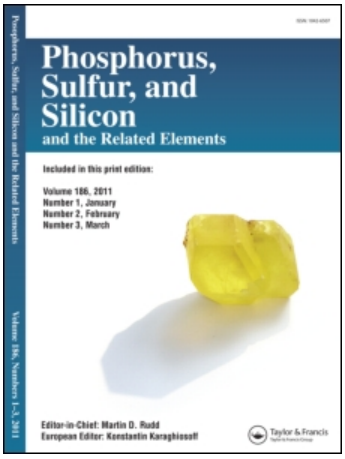

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STUDIES WITH POLYFUNCTIONALLY SUBSTITUTED HETEROAROMATICS: A NEW ROUTE TO POLYFUNCTIONALLY SUBSTITUTED ANNELATED MERCAPTOPHTHALAZINES

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STUDIES WITH POLYFUNCTIONALLY SUBSTITUTED HETEROAROMATICS: A NEW ROUTE TO POLYFUNCTIONALLY SUBSTITUTED ANNELATED MERCAPTOPHTHALAZINES

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The thieno[3,4-d]pyridazine derivatives **1a, b** reacted with acrylonitrile to afford the mercaptophthalazine derivatives **6a, b**. The latter products reacted with acrylonitrile again to afford **11a, b**. With maleic anhydride and N-phenylmaleimide they afforded **13a–d** respectively. Nitration and bromination of **6a, b** gave **14a, b** and **15a, b**. Cycloaddition reactions of the latter products with acrylonitrile and maleimides were studied.

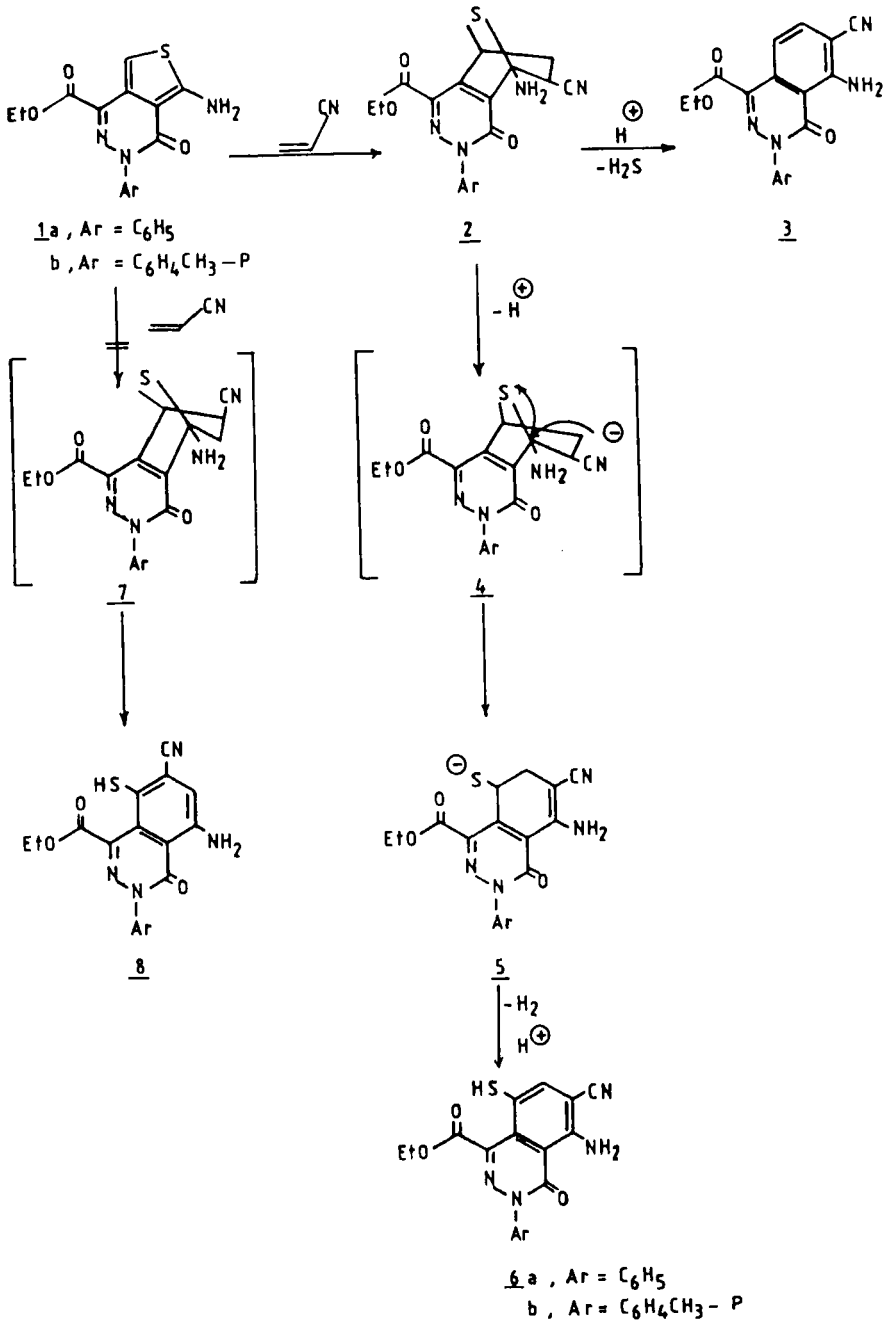
Key words: Mercaptophthalazines, heteroaromatics, biological activity, pyridazines.

INTRODUCTION

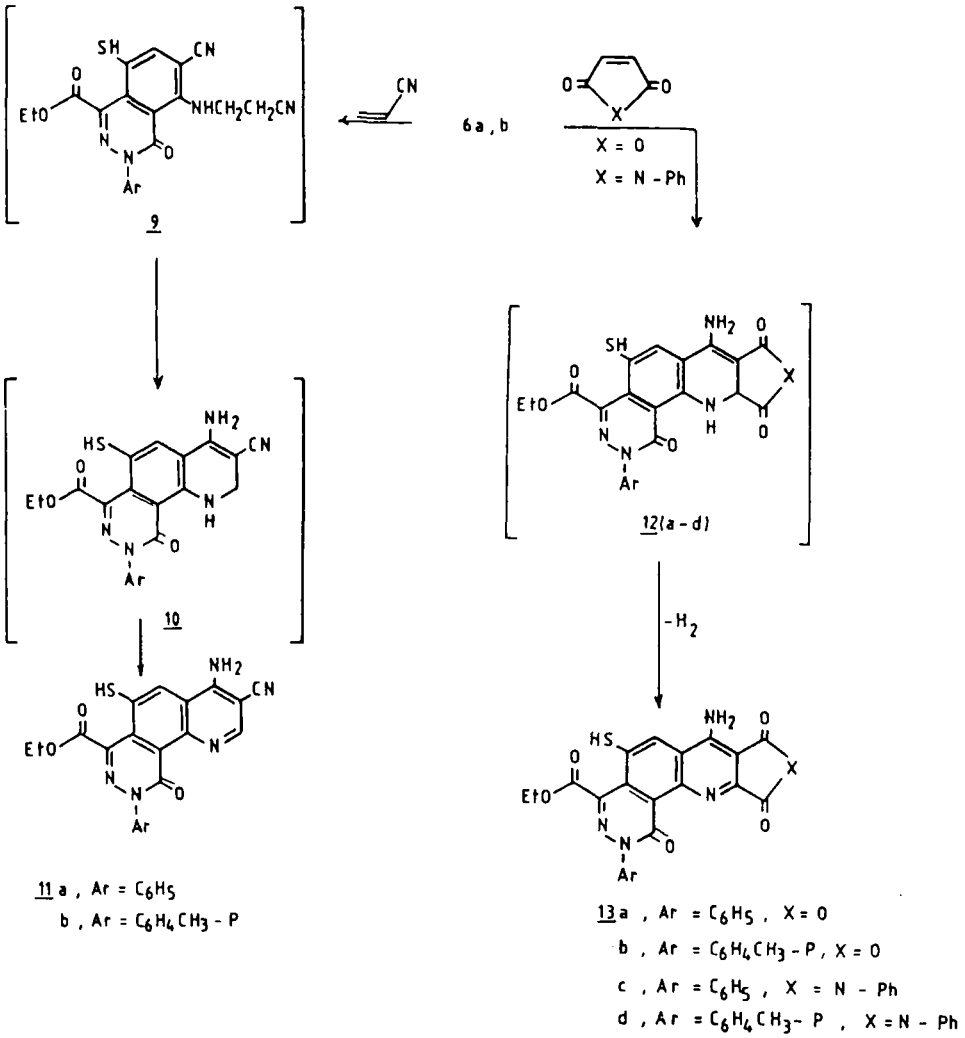
The biological and medicinal activities of pyridazines and condensed pyridazines has promoted recent interest in the chemistry of this class of compounds.[1–5] Although synthetic approaches to phthalazines are well documented,[6,7] none of them can be readily adopted for the synthesis of polyfunctionally substituted derivatives which look interesting as potential agrochemicals.[8–10] Recently, we reported a new convenient route to polyfunctionally substituted phthalazines via reacting ethyl thieno[3,4-d]-pyridazin-1-carboxylate **1a, b** with poor olefins, namely acrylonitrile and maleic anhydride in refluxing dioxane and acetic acid mixture.[11,12]

RESULTS AND DISCUSSION

In the present article, we report the results of our investigations exploring the potential of this synthetic approach. We have found that **1a** reacts with acrylonitrile in cold pyridine at room temperature to yield a 1:1 adduct for which structure **2** was assigned based on the analytical and spectral data. The ^{1}H NMR spectrum of the product revealed the presence of a triplet at δ = 1.0 ppm for CH_3, a triplet at δ = 1.25 ppm for CH, a multiplet at δ = 2.30 and 2.42 ppm for CH_2, a multiplet at δ = 3.75 ppm for CH, a quartet at δ = 4.32 ppm for CH_2, and a multiplet at δ = 3.35–3.60 ppm for C_6H_5 such data agree with structure **2**. Compound **2** has converted to the phthalazine derivative **3** when heated in refluxing dioxane solution in the presence of acetic acid. It was reported[12] that **2** was an intermediate in the convertion **1** to **3** but not isolated. Compounds **1a, b** reacted with acrylonitrile in



REACTION SCHEME 1



REACTION SCHEME 2

refluxing pyridine to yield products of addition and hydrogen elimination. Two possible isomeric structures were assumed for the obtained molecular formula $C_{18}H_{14}N_4O_3S$. One may assume the formation of the cycloadducts **2** which are then attacked by base to yield the carbanion **4** which isomerized into **5** and aromatized via loss of hydrogen into the phthalazine derivatives **6a**, **b** (Scheme 1). Alternately one may assume formation of the adduct **7** which would yield **8** upon reaction with base. Structures **6a**, **b** were established for the reaction products based on synthesizing **6a** via heating compound **2** in pyridine (identical m.p. and mixed m.p.). Compounds **6a**, **b** reacted with polyfunctionally electrophiles in a manner expected for o-aminonitriles. The reaction of **6a**, **b** with acrylonitrile afforded **11a**, **b** via the intermediate formation of **9a**, **b** and **10a**, **b**. Structure of **11a**, **b** was established based on analytical and spectral data (Tables I and II). The IR spectrum of **11a**

TABLE I

Physical and analytical data of the newly prepared compounds

Compd. (colour)	solvent	m.p. (°C)	Yield (%)	Mol. formula (M. wt.)	Analysis (Calcd./Found) % C	H	N	S
6a	ethanol	170	74	$C_{18}H_{14}N_4O_3S$	59.0	3.8	15.3	8.7
(orange)				(366.38)	58.2	3.5	15.0	8.4
6b	ethanol	175	68	$C_{19}H_{16}N_4O_3S$	59.9	4.0	14.7	8.5
(orange)				(380.42)	59.8	4.0	14.7	8.3
3	benzene	205-7	50	$C_{18}H_{16}N_4O_3S$	58.6	4.4	15.2	8.7
(yellow)				(368.39)	58.6	4.3	15.0	8.5
11a	ethanol	210-12	75	$C_{21}H_{15}N_5O_3S$	60.4	3.6	16.1	7.7
(orange)				(417.74)	60.1	3.5	16.3	8.0
11b	ethanol	215-17	67	$C_{22}H_{17}N_5O_3S$	61.2	3.9	16.2	7.4
(orange)				(431.82)	61.2	3.7	16.0	7.2
13a	AcOH	200-2	70	$C_{22}H_{14}N_4O_6S$	57.1	3.0	12.1	6.9
(brown)				(450.32)	56.9	2.7	12.0	6.5
13b	ethanol	210-12	58	$C_{23}H_{16}N_4O_6S$	57.7	3.1	11.5	6.4
(brown)				(464.41)	57.7	3.1	11.5	6.4
13c	ethanol	220-23	71	$C_{28}H_{19}N_5O_5S$	62.5	3.6	13.0	5.9
(orange)				(537,42)	62.3	3.5	13.0	5.7
13d	ethanol	225-29	58	$C_{29}H_{21}N_5O_5S$	63.1	3.8	12.7	5.8
(orange)				(551.38)	62.9	3.7	12.4	5.6
14a	ethanol	184	78	$C_{18}H_{13}N_5O_5S$	52.5	3.2	17.0	7.8
(brown)				(411.34)	52.3	2.9	16.9	7.5
14b	ethanol	190	68	$C_{19}H_{15}N_5O_5S$	53.6	3.5	16.5	7.3
(brown)				(425.63)	53.4	3.3	16.2	7.0
14c	dioxane	140	80	$C_{18}H_{13}N_4O_3SBr$	48.5	2.9	12.6	7.2
(brown)				(445.41)	48.2	2.5	12.3	6.8
14d	methanol	145	80	$C_{19}H_{15}N_4O_3SBr$	49.7	3.3	12.2	7.0
(brown)				(459.39)	49.4	3.0	12.0	6.7
15a	ethanol	148	63	$C_{21}H_{14}O_5N_6S$	54.5	3.0	18.2	6.9
(Orange)				(462.41)	54.4	3.0	18.1	6.6
15b	ethanol	160	62	$C_{22}H_{16}O_5N_6S$	55.5	3.4	17.6	6.7
(orange)				(476.43)	55.4	3.1	17.5	6.5
15c	AcOH	110	57	$C_{21}H_{14}N_5O_3SBr$	50.8	2.8	14.1	6.4
(brown)				(496.41)	50.4	2.7	14.0	6.3
15d	AcOH	120	79	$C_{22}H_{16}N_5O_3SBr$	51.8	3.2	13.7	6.3
(yellow)				(510.39)	51.6	3.0	13.5	6.1
16a	ethanol	160	68	$C_{22}H_{13}N_5O_8S$	52.1	2.6	13.8	6.3
(yellow)				(507.29)	51.6	2.3	13.7	6.2
16b	ethanol	169	60	$C_{23}H_{15}N_5O_8S$	53.0	3.0	13.4	6.1
(orange)				(521.35)	52.8	3.2	13.1	6.0
16c	AcOH	172	64	$C_{22}H_{13}N_4O_6SBr$	48.8	2.4	10.4	5.9
(yellow)				(537.41)	48.5	2.2	10.2	5.7

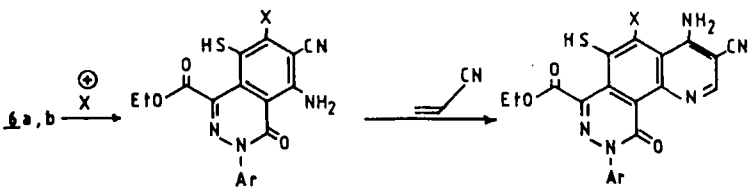
Table I (*Continued*)

Compd. (colour)	solvent	m.p. (°C)	Yield	Mol. formula (M. wt.)	Analysis (Calcd./Found) % C	H	N	S
16d	AcOH	180	60	$C_{23}H_{15}N_4O_6SBr$	49.7	2.7	10.1	5.8
(orange)				(551.27)	49.5	2.5	9.9	5.6
16e	ethanol	150	60	$C_{28}H_{18}N_6O_7S$	57.7	3.1	14.4	5.5
(brown)				(582.38)	57.6	3.0	14.4	5.4
16f	ethanol	165	65	$C_{29}H_{20}N_6O_7S$	58.4	3.4	14.1	5.4
(yellow)				(596.44)	58.0	3.0	13.9	5.2
16g	AcOH	130	75	$C_{28}H_{18}N_5O_5SBr$	54.5	2.9	11.4	5.2
(brown)				(616.49)	54.3	2.7	11.0	5.0
16h	ethanol	150–52	70	$C_{29}H_{20}N_5O_5SBr$	55.2	3.2	11.1	5.1
(brown)				(630.42)	55.1	3.0	11.1	5.0
17a	ethanol	230–35	70	$C_{25}H_{18}N_4O_5$	66.2	3.9	12.3	
(orange)				(454.38)	65.9	3.6	12.0	
17b	ethanol	245–49	72	$C_{26}H_{20}N_4O_5$	66.7	4.3	11.9	
(orange)				(468.27)	66.5	4.2	11.7	
18a	ethanol	250–52	65	$C_{19}H_{13}N_3O_6$	60.2	3.4	11.2	
(yellow)	ethanol			(379.31)	60.0	3.2	11.0	
18b	ethanol	260–64		$C_{20}H_{15}N_3O_6$	61.2	3.8	10.8	
(yellow)				(393.40)	61.4	3.5	10.5	

revealed the presence of NH_2 stretching at 3464, 3323 cm^{-1}, SH stretching at 3300–3100, CN stretching at 2214 cm^{-1} and two C=O stretching at 1723, 1699 cm^{-1}. ^1H NMR spectrum of **11a** revealed the presence of a triplet at δ = 1.34 ppm for CH_3, a singlet at δ = 3.38 ppm for NH_2, a quartet at δ = 3.99 ppm, a multiplet at 7.33–7.38 ppm for C_6H_5, pyridine H-2, benzene H-2, and a singlet at δ = 8.21 for SH. Similarly, **6a**, **b** reacted with maleic anhydride and N-phenylmaleimide to yield the cycloadducts **13a**, **b** and **13c**, **d**. Structures of **13a**, **b** and **13c**, **d** were confirmed using the same methods used for establishing **11a**, **b**. Formation of **13a–d** is assumed to take place through the intermediate formation of **12a–d** (Scheme 2).

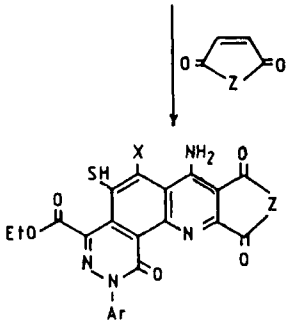
Compounds **6a**, **b** reacted with nitric acid to yield the nitro derivatives **14a**, **b** and with bromine to give the bromo derivatives **14c**, **d**. Structures **14a–d** were established based on analytical and spectral data (see experimental section). Compounds **14a–d** are capable of cyclo addition reactions, with acrylonitrile to give **15a–d** and with maleic anhydride to give **16a–d**. Similarly, **14a–d** reacted with N-phenylmaleimide to give the cycloadducts **16e–h**. Structures of **16a–h** were established based on analytical and spectral data (see Experimental section).

In contrast to the behaviour of **1a**, **b** with acrylonitrile, **1a** and **1b** reacted with N-phenylmaleimide to yield products of addition and hydrogen sulfide elimination which were formulated as **17a**, **b**. Structures of compounds **17a**, **b** were established based on analytical and spectral data (see Experimental section). Similarly, the reaction of **1a**, **b** with maleic anhydride afforded the furophthalazine derivatives

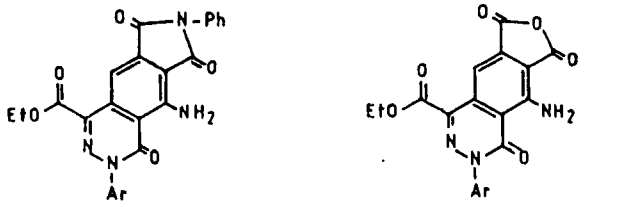


14 15

14, 15 a, Ar = C_6H_5 ; X = NO_2
b, Ar = $C_6H_4CH_3$-P ; X = NO_2
c, Ar = C_6H_5 ; X = Br
d, Ar = $C_6H_4CH_3$-P ; X = Br



16, a, Ar = C_6H_5 ; X = NO_2 ; Z = O
b, Ar = $C_6H_4CH_3$-P ; X = NO_2 ; Z = O
c, Ar = C_6H_5 ; X = Br ; Z = O
d, Ar = $C_6H_4CH_3$-P ; X = Br ; Z = O
e, Ar = C_6H_5 ; X = NO_2 ; Z = N-Ph
f, Ar = $C_6H_4CH_3$-P ; X = NO ; Z = N-Ph
g, Ar = C_6H_5 ; X = Br ; Z = N-Ph
h, Ar = $C_6H_4CH_3$-P ; X = Br ; Z = N-Ph



17 a ; Ar = C_6H_5
b ; Ar = $C_6H_4CH_3$-P

18 a ; Ar = C_6H_5
b ; Ar = $C_6H_4CH_3$-P

REACTION SCHEME 3

18a, b. The difference in behaviour of **1a, b** with acrylonitrile and maleic anhydride or N-phenylmaleimide can be rationalized by the fact that the hydrogen atom at α-position to cyano function in adduct **2** is not hindered and can be easily attacked by the base while hydrogens in adducts resulting from reaction with maleic an-

TABLE II

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

Compd. No.	I.R. cm^{-1} (selected bands)	^{1}H NMR (ppm)
6a	3460, 3323 (NH_2), 3065 (aromatic CH), 2977, (CH_3), 2221 (CN), 1725, 1680 (2 C=O).	1.25 (t, 3H, J= 8.1 Hz, CH_3), 2.48 (s, 2H, NH_2), 4.40 (q, 2H, J= 8.1 Hz, CH_2), 7.20 (s, 1H, SH), 7.31-7.62 (m, 6H, C_6H_5, benzene H-5).
6b	3450, 3330 (NH_2), 2215 (CN), 1732, 1712 (2 C=O), 1665 (C=N).	1.28 (t, 3H, J= 8.0 Hz, CH_3), 1.44 (s, 3H, CH_3), 2.50 (s, 2H, NH_2), 4.42 (q, 2H, J= 8.0 Hz, CH_2), 7.22 (s, 1H, SH), 7.30-7.63 (m, 5H, C_6H_4, benzene H-5).
3	3464, 3323 (NH_2), 2211 (CN), 1725, 1680 (2 C=O).	1.0 (t, 3H, J= 7.89 Hz, CH_3), 1.25 (t, 1H, CH), 2.30, 2.42 (m, 2H, CH_2), 3.75 (m, 1H, CH), 4.32 (q, 2H, CH_2), 3.35-3.60 (m, 5H, C_6H_5).
11a	3464, 3323 (NH_2), 3300-3100 (SH), 2214 (CN) 1723, 1699 (2 C=O).	1.34 (t, 3H, J= 7.0 Hz, CH_3), 3.38 (s, 2H, NH_2), 3.99 (q, 2H, J= 7.0 Hz, CH_2), 7.33-7.38 (m, 7H, C_6H_5, pyridine H-2, benzene H-2), 8.21 (s, br, 1H, SH).
11b	3462, 3425 (NH_2), 2217 (CN), 1729, 1690 (2 C=O).	1.39 (t, 3H, J= 7.7 Hz, CH_3), 2.20 (s, 3H, CH_3), 3.01 (q, 2H, J= 7.7 Hz, CH_2), 3.36 (s, 2H, NH_2), 7.32-7.38 (m, 6H, C_6H_4, pyridine H-2, benzene H-2)
13a	3463, 3429 (NH_2), 1731, 1700-1680 (4 C=O).	1.23 (t, 3H, J=7.89 Hz, CH_3), 2.52 (s, 2H, NH_2), 4.43 (q, 2H, J= 7.89 Hz, CH_2), 7.32-7.58 (m, 6H, C_6H_5, benzene H-5).
13b	3550, 3447 (NH_2), 1737 1685 (2 C=O), 1615 (C=N).	1.29 (t, 3H, J= 7.77 Hz, CH_3), 1.49 (s, 3H, CH_3), 2.51 (s, 2H, NH_2), 4.39 (q, 2H, J= 7.77 Hz, CH_2), 7.33-7.62 (m, 5H, C_6H_5, benzene H-5).
13c	3429, 3323 (NH_2), 1720, 1680-1670 (4 C=O), 1621 (C=N).	1.40 (t, 3H, J= 8.0 Hz, CH_3), 2.65 (s, 2H, NH_2), 4.63 (q, 2H, J= 8.0 Hz, CH_2), 7.34-7.37 (m, 11H, $2C_6H_5$, benzene H-5), 8.21 (s, br, 1H, SH).
13d	3550, 3424 (NH_2), 1737, 1690-1680 (4 C=O), 1614 (C=N).	1.42 (t, 3H, J= 7.8 Hz, CH_3), 1.50 (s, 3H, CH_3), 2.46 (s, 2H, NH_2), 4.59 (q, 2H, J= 7.8 Hz, CH_2), 7.38-7.39 (m, 10H, C_6H_5, C_6H_4, benzene H-5), 8.21 (s, 1H, SH).
14a	3450, 3400 (NH_2), 1739 1684 (2 C=O), 1620 (C=N).	1.39 (t, 3H, J= 8.2 Hz, CH_3), 2.55 (s, 2H, NH_2), 4.22 (q, 2H, J= 8.2 Hz, CH_2), 7.32-7.48 (m, 5H, C_6H_5), 7.62 (s, br, 1H, SH).
14b	3450, 3400 (NH_2), 2220 (CN), 1739, 1684 (2 C=O).	1.40 (t, 3H, J= 7.90 Hz, CH_3), 2.02 (s, 3H, CH_3), 2.66 (s, 2H, NH_2), 4.22 (q, 2H, J= 7.90 Hz, CH_2), 7.30-7.38 (m, 4H, C_6H_4), 8.10 (s, br, 1H, SH).
14c	3450, 3320 (NH_2), 2220 (CN), 1720, 1690-1680 (2 C=O).	1.45 (t, 3H, J= 8.0 Hz, CH_3), 2.10 (s, 2H, NH_2), 4.24 (q, 2H, J= 8.0 Hz, CH_2), 7.23 (s, 1H, SH), 7.45 (m, 5H, C_6H_5).

Table II (*Continued*)

Compd. No.	I.R. cm^{-1} (selected bands)	^1H NMR (ppm)
14d	3500, 3440 (NH_2), 2217 (CN), 1730, 1680 (2 C=O).	1.45 (t, 3H, J= 7.81 Hz, CH_3), 2.01 (s, 3H, CH_3), 2.20 (s, 2H, NH_2), 4.28 (q, 2H, J= 7.81 Hz, CH_2), 7.31 (s, 1H, SH), 7.38-7.41 (m, 4H, C_6H_4).
15a	3457. 3350 (NH_2), 2221 (CN), 1735, 1680 (2 C=O), 1640 (C=N).	1.26 (t, 3H, J= 7.90 Hz, CH_3), 2.23 (s, 2H, NH_2), 4.42 (q, 2H, J= 7.90 Hz, CH_2), 7.31-7.38 (m, 5H, C_6H_5), 8.25 (s, br, 1H, SH).
15b	3500-3438 (2 NH_2), 2218 (CN), 1737, 1687 (2 C=O), 1630 (C=N).	1.30 (t, 3H, J= 7.99 Hz, CH_3), 2.02 (s, 3H, CH_3), 2.41 (s, 2H, NH_2), 4.22 (q, 2H, J= 7.99 Hz, CH_2), 7.32-7.36 (m, 5H, C_6H_5), 8.33 (s, br, 1H, SH).
15c	3554, 3429 (NH_2), 2217 (CN), 1737, 1683 (2 C=O), 1640 (C=N).	1.45 (t, 3H, J= 8.2 Hz, CH_3), 2.67 (s, 2H, NH_2), 4.58 (q, 2H, J= 8.20 Hz, CH_2), 7.35-7.38 (m, 6H, C_6H_5, quinoline H-2), 8.25 (s, 1H, SH).
15d	3530, 3440 (NH_2), 2220 (CN), 1720, 1668 (2 C=O), 1630 (C=N).	1.42 (t, 3H, J= 7.64 Hz, CH_3), 2.01 (s, 3H, CH_3), 2.88 (s, 2H, NH_2), 4.22 (q, 2H, J= 7.64, CH_2), 7.35-7.44 (m, 5H, C_6H_5, quinoline H-2), 8.26 (s,1H, SH).
16a	3500, 3400 (NH_2), 1738 1687-1660 (4 C=O), 1635 (C=N).	1.40 (t, 3H, J= 8.0 Hz, CH_3), 3.23 (s, 2H, NH_2), 4.42 (q, 2H, J= 8.0 Hz, CH_2), 7.22-7.40 (m, 5H, C_6H_5), 8.21 (s, 1H, SH).
16b	3454, 3323 (NH_2), 1737 1686 (4 C=O).	1.42 (t, 3H, J= 7.89 Hz, CH_3), 2.02 (s, 3H, CH_3), 3.31 (s, 2H, NH_2), 3.79 (q, 2H, J= 7.89 Hz, CH_2), 7.32-7.37 (m, 4H, C_6H_4), 8.21 (s, 1H, SH).
16c	3461, 3400 (NH_2), 1690 1685-1670 (4 C=O), 1630 (C=N).	1.42 (t, 3H, J= 7.69 Hz, CH_3), 3.23 (s, 2H, NH_2), 4.42 (q, 2H, J= 7.69 Hz, CH_2), 7.30-7.36 (m, 4H, C_6H_4), 8.32 (s, 1H, SH).
16d	3550, 3435 (NH_2), 1730 1695-1675 (4 C=O), 1635 (C=N).	1.39 (t, 3H, J= 8.02 Hz, CH_3), 2.02 (s, 3H, CH_3), 3.28 (s, 2H, NH_2), 4.40 (q, 2H, J= 8.02 Hz, CH_2), 7.31-7.35 (m, 4H, C_6H_4), 8.30 (s, 1H, SH).
16e	3540, 3471 (NH_2), 1726, 1720-1680 (4 C=O), 1630 (C=N).	1.48 (t, 3H, J= 8.0 Hz, CH_3), 3.89 (s, 2H, NH_2), 4.23 (q, 2H, J= 8.0 Hz, CH_2), 7.33-7.38 (m, 10H, $2C_6H_5$), 8.34 (s, br, 1H, SH).
16f	3450, 3440 (NH_2), 1730 1690-1670 (4 C=O), 1640 (C=N).	1.42 (t, 3H, J= 7.98 Hz, CH_3), 2.03 (s, 3H, CH_3), 3.78 (s, 2H, NH_2), 4.22 (q, 2H, J= 7.98 Hz, CH_2), 7.32-7.40 (m, 9H, C_6H_5, C_6H_4), 8.12 (s, br, 1H, NH).
16h	3550, 3444 (NH_2), 1737 1690-1670 (4 C=O).	1.41 (t, 3H, J= 8.0 Hz, CH_3), 2.01 (s, 3H, CH_3), 3.68 (s, 2H, NH_2), 4.21 (q, 2H, J= 8.0 Hz, CH_2), 7.30-7.36 (m, 9H, C_6H_5, C_6H_4), 8.09 (s, 1H, NH).
17a	3429, 3322 (NH_2), 1726 1690-1670 (4 C=O), 1656 (C=N).	1.43 (t, 3H, J= 7.82 Hz, CH_3), 4.01 (q, 2H, J= 7.82 Hz, CH_2), 4.34 (s, 2H, NH_2), 7.32-7.38 (m, 11H, $2C_6H_5$, benzene H-6).
17b	3429, 3320 (NH_2), 1726	1.45 (t, 3H, J= 8.23 Hz, CH_3), 2.03 (s, 3H, CH_3),

Table II (*Continued*)

Compd. No.	IR (cm^{-1}) (selected bands)	^1H NMR (ppm)
	1700-1670 (4 C=O), 1632 (C=N).	4.04 (q, 2H, J= 8.21 Hz, CH_2), 4.45 (s, 2H, NH_2), 7.34-7.37 (m, 10H, C_6H_5, C_6H_4, benzene H-6).
18a	3490, 3385 (NH_2), 1841, 1724-1670 (4 C=O), 1640 (C=N).	1.34 (t, 3H, J= 8.0 Hz, CH_3), 4.21 (q, 2H, J= 8.0 Hz, CH_2), 4.78 (s, 2H, NH_2), 7.34-7.46 (m, 6H, C_6H_5, benzene H-6).
18b	3433, 3328 (NH_2), 1830, 1730-1675 (4 C=O), 1625 (C=N).	1.41 (t, 3H, J= 8.04 Hz, CH_3), 2.05 (s, 3H, CH_3), 4.22 (q, 2H, J= 8.04 Hz, CH_2), 4.52 (s, 2H, NH_2), 7.33-7.40 (m, 5H, C_6H_4, benzene H-6).

hydride and N-phenylmaleimide the α-hydrogens are more sterically hindered. The resulting mercaptophthalazine derivatives are more sterically crowded compared to those resulting from the reaction with acrylonitrile like **6a**, **b** (Scheme 3).

EXPERIMENTAL

All melting points are uncorrected, IR spectra were recorded (KBr) on a Pye Unicam SP-1000 spectrophotometer. ^1H NMR spectra were recorded on a Varian EM-270 MHz spectrometer with DMSO as solvent and TMS as internal reference. Chemical shifts are expressed as δ units (ppm). Analytical data were obtained from the Microanalytical Data Centre at Cairo University, Egypt.

7-Thiabicyclo(2,2,1)hept-2-eno[2,3-d]pyridazine (**3**). To a solution of **1a** (0.01 mol) in pyridine (50 ml), acrylonitrile (0.01 mol) was added. The reaction mixture was stirred at room temperature for 24 h then evaporated in vacuo. The remaining product was triturated with benzene then collected by filtration.

5-Amino-6-cyano-1-ethoxycarbonyl-8-mercapto-4-oxo-3-phenylphthalazine (**6a**). *5-Amino-6-cyano-1-ethoxycarbonyl-8-mercapto-4-oxo-3-(4'-methylphenyl)phthalazine* (**6b**). *General procedure*: An equimolecular mixture of **1a** (0.01 mol) or **1b** (0.01 mol) and acrylonitrile (0.01 mol) in pyridine (40 ml) was heated under reflux for 5 h, then evaporated in vacuo. The remaining product was triturated with water containing few drops of hydrochloric acid and the solid product, formed, was collected by filtration.

7-Amino-8-cyano-1-ethoxycarbonyl-10-mercapto-3-phenylpyridazo[4,5-h]quinoline (**11a**). *7-Amino-8-cyano-1-ethoxycarbonyl-10-mercapto-3-(4'-methylphenyl)-pyridazo[4,5-h]quinoline* (**11b**). *General procedure*: To a solution of **6a** (0.01 mol) or **6b** (0.01 mol) in dioxane (50 ml) containing acetic acid (5 ml), acrylonitrile (0.01 mol) was added. The whole mixture was heated under reflux for 8 h. The solid product formed upon dilution with water was collected by filtration.

9-Amino-1-ethoxycarbonyl-11-mercapto-4,5,8-trioxo-3-phenylfuro[2,3-b]pyridazo[4,5-h]quinoline (**13a**). *9-Amino-1-ethoxycarbonyl-11-mercapto-4,6,8-trioxo-3-(4'-methylphenyl)furo[2,3-b]pyridazo[4,5-h]-quinoline* (**13b**). *General procedure*: The same experimental procedure described for the synthesis of **11a**, **b** was carried out with maleic anhydride instead of acrylonitrile.

9-Amino-1-ethoxycarbonyl-11-mercapto-4,6,8-trioxo-3,7-diphenylpyrrolo[2,3-b]pyridazo[r,5-h]quinoline (**13c**). *9-Amino-1-ethoxycarbonyl-11-mercapto-4,6,8-trioxo-3-(4'-methylphenyl)-7-phenylpyrrolo[2,3-b]pyridazo[4,5-h]quinoline* (**13b**). *General procedure*: The same experimental procedure described for the synthesis of **11a**, **b** was carried out with N-phenyl maleimide instead of acrylonitrile.

5-Amino-6-cyano-1-ethoxycarbonyl-4-oxo-8-mercapto-7-nitro-3-phenylpthalazine (**14a**). *5-Amino-6-cyano-1-ethoxycarbonyl-4-oxo-8-mercapto-7-nitro-3-(4'-methylphenyl)-phthalazine* (**14b**). *General procedure*: To a dry solid of **6a** (0.01 mol) or **6b** (0.01 mol), equimolecular mixture of concentrated

sulphuric acid and fuming nitric acid (0.02 mol) was added. The reaction mixture was heated in a boiling water bath for 10 min until all nitrogen dioxide fumes were evaporated. The solid product formed upon dilution with water was collected by filtration.

5-Amino-7-bromo-6-cyano-1-ethoxycarbonyl-4-oxo-8-mercapto-3-(4'-methylphenyl)phthalazine (**14d**). *General procedure*: To a solution of **6a** (0.01 mol) or **6b** (0.01 mol) in glacial acetic acid (50 ml), bromine (0.01 mol) in glacial acetic acid (5 ml) was added dropwise with continuous stirring at room temperature then left over night. The solid product formed upon dilution with ice/water mixture was collected by filtration.

8-Amino-7-cyano-1-ethoxycarbonyl-4-oxo-10-mercapto-9-nitro-3-phenylpyridazo[4,5-h]quinoline (**15a**). *8-Amino-7-cyano-1-ethoxycarbonyl-4-oxo-10-mercapto-9-nitro-3-(4'-methylphenyl)-pyridazo[4,5-h]quinoline* (**15b**). *General procedure*: The same experimental procedure described for the synthesis of **11a, b** was carried out with **14a, b** (0.01 mol) instead of **6a, b**.

8-Amino-9-bromo-7-cyano-1-ethoxycarbonyl-4-oxo-10-mercapto-3-phenylpyridazo[4,5-h]quinoline (**15c**). *8-Amino-9-bromo-7-cyano-1-ethoxycarbonyl-4-oxo-10-mercapto-3-(4'-methylphenyl)-pyridazo[4,5-h]quinoline* (**15d**). *General procedure*: The same experimental procedure described for the synthesis of **11a, b** was carried out with **14c, d** (0.01 mol) instead of **6a,b**.

9-Amino-1-ethoxycarbonyl-11-mercapto-10-nitro-3-phenyl-4,6,8-trioxofuro[2,3-b]pyridazo[4,5-h]quinoline (**16a**). *9-Amino-1-ethoxycarbonyl-11-mercapto-10-nitro-3-(4'-methylphenyl)-4,6,8-trioxofuro[2,3-b]pyridazo[4,5-h]quinoline* (**16b**). *9-Amino-10-bromo-1-ethoxycarbonyl-11-mercapto-3-phenyl-4,6,8-trioxofuro[2,3-b]pyridazo[4,5-h]quinoline* (**16c**). *9-Amino-10-bromo-1-ethoxycarbonyl-11-mercapto-3-(4'-methylphenyl)-4,6,8-trioxofuro[2,3-b]pyridazo[4,5-h]quinoline* (**16d**). *General procedure*: To a solution of each of **14a** (0.01 mol), **14b** (0.01 mol) or **14d** (0.01 mol) in dioxane (50 ml) containing acetic acid (5 ml), maleic anhydride (0.01 mol) was added. The reaction mixture was heated under reflux for 10 h then diluted with water. The oil product formed was extracted from chloroform and the solid product formed upon evaporation in vacuo was triturated with ethanol and collected by filtration.

9-Amino-1-ethoxycarbonyl-11-mercapto-10-nitro-3,7-diphenyl-4,6,8-trioxopyrrolo[2,3-b]pyridazo[4,5-h]quinoline (**16e**). *9-Amino-1-ethoxycarbonyl-11-mercapto-10-nitro-3-(4'-methylphenyl)-7-phenyl-4,6,8-trioxopyrrolo[2,3-b]pyridazo[4,5-h]quinoline* (**16f**). *9-Amino-10-bromo-1-ethoxycarbonyl-11-mercapto-3,7-diphenyl-4,6,8-trioxopyrrolo[2,3-b]pyridazo[4,5-h]quinoline* (**16g**). *9-Amino-10-bromo-1-ethoxycarbonyl-11-mercapto-3-(4'-methylphenyl)-7-phenyl-4,6,8-trioxophyrrolo[2,3-b]pyridazo[4,5-h]quinoline* (**16h**). *General procedure*: To a solution of each of **14a** (0.01 mol), **14b** (0.01 mol), **14c** (0.01 mol) or **14d** (0.01 mol) in dioxane (50 ml) containing sodium metal (0.01 mol), N-phenylmaleimide (0.01 mol) was added. The reaction mixture in each case was heated under reflux for 12 h. The solid product, formed upon dilution with cold water containing few drops of hydrochloric acid (until pH = 6) was collected by filtration.

5-Amino-1-ethoxycarbonyl-3,7-diphenyl-4,6,8-trioxopyrrolo[6,5-c]phthalazine (**17a**). *5-Amino-1-ethoxycarbonyl-7-phenyl-3-(4'-methylphenyl)-4,6,8-trioxopyrrolo[6,5-c]phthalazine* (**17b**). *5-Amino-1-ethoxycarbonyl-3-phenyl-4,6,8-trioxofuro[6,5-c]phthalazine* (**18a**). *5-Amino-1-ethoxycarbonyl-3-(4'-methylphenyl)-4,6,8-trioxofuro[6,5-c]phtalazine* (**18b**). *General procedure*: To a solution of each of **1a** (0.01 mol) or **1b** (0.01 mol) in dioxane (50 ml) containing acetic acid (5 ml) N-phenylmaleimide (0.01 mol) or maleic anhydride (0.01 mol) was added. The reaction mixture in each case was heated under reflux for 12 h and the solid product formed upon dilution with cold water was collected by filtration.

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