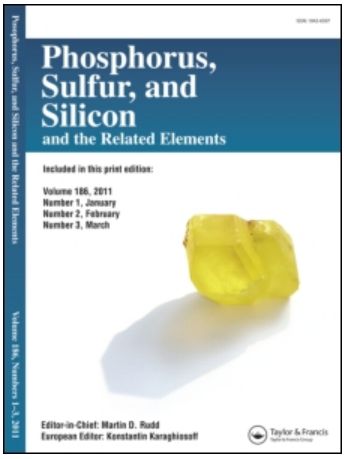

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SYNTHESIS OF FUSED AND SPIRO HETEROCYCLIC COMPOUNDS DERIVED FROM 3,5-PYRAZOLIDINEDIONE DERIVATIVES

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SYNTHESIS OF FUSED AND SPIRO HETEROCYCLIC COMPOUNDS DERIVED FROM 3,5-PYRAZOLIDINEDIONE DERIVATIVES

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The reaction of compound **1** with triethyl orthoformate afforded **2**, which in turn reacted with CS_2 and active methlyene compounds or malononitrile to give dithiolane and 4-malononitrile methylene derivatives **3,4**, respectively. Treatment of compound **4** with active methylene compounds afforded spiro cyclopentene derivatives $\mathbf{5_{a-c}}$. Compound **1** was reacted with bromomalononitrile or $CS_2$and halocompounds to afford furo-, thieno- and dithiolano-pyrazole derivatives **6–11**, respectively. The reaction of compound **12** with phenacyl bromide or benzylidenemalononitrile furnished oxathiol-2-ylidene and pyridinethione derivatives **13,14**, respectively. The dibromo derivative **16** was reacted with CS_2 and active methylenes or malononitrile to obtain spiro dithietanes $\mathbf{17_{a-e}}$ and 4-dicyano-methlyene derivative **22**, respectively. Compounds **17** underwent a cycloaddition reaction with thioglycolic acid, N-phenylbenzohydrazindoyl bromide, 2,5-dimethylfuran and 1- phenyl-3,5-pyrazolidinedione to give cycloadducts **18–21**, respectively. Treatment of *o*-aminothiophenol or *o*-phenylenediamine with the dicyano compound **22** leads to the formation of spiro thiazepine or spiro diazine derivatives $\mathbf{23_{a,b}}$. The arylidene derivatives **24** was reacted with S,S-acetals, N,S-acetals or ammonium dithiocarbamate to afford dithiane, oxazine or pyrazolodithiocarbamate derivatives **25–29**, respectively. Chemoselective cyclization of compound **29** with H_2SO_4, NaOH or MeI gave compounds **30–32**, respectively. Benzopyrano derivatives **34,36** were obtained through the reaction of compound **1** with a mixture of thiourea, triethyl orthoformate and ethyl cyanoacetate or with cyanoketene S,S diacetals, respectively.

Keywords: Dithiolanes; Pyridinethione; Dithiane; Thiazepine and PTC

The 3,5-pyrazolinediones have become of increasing importance in recent years owing to the medical use of 4-butyl-1,2-diphenyl-3,5-pyrazolinedione (butazalidin) in the treatment of rheumatoid arthritis.[1–3] In connection with our previous work[4–6] on the application of phase-transfer catalysis in

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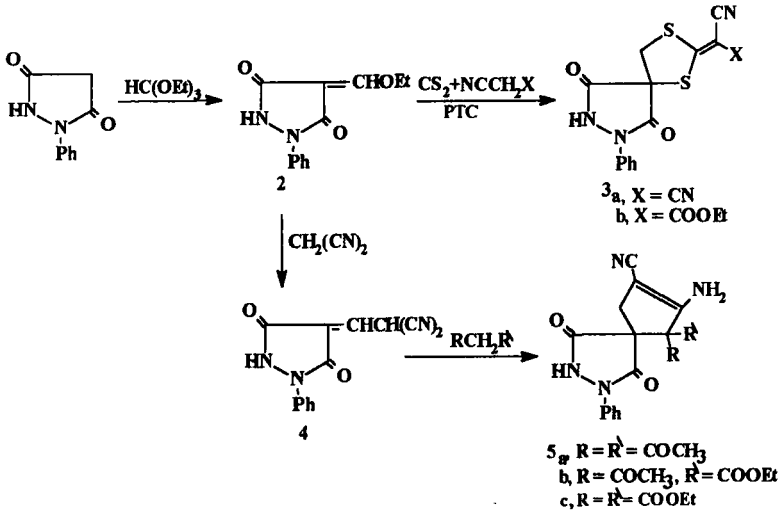
heterocyclic synthesis, we report the synthesis of fused and spiro heterocyclic compounds containing a pyrazole moiety.

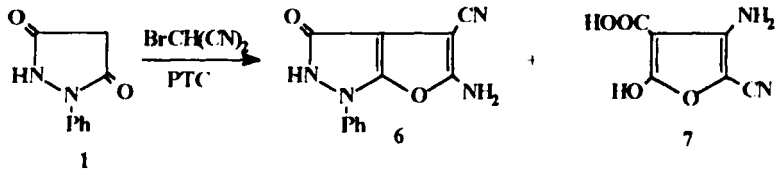
The reaction of 1-phenyl-3,5-pyrazolinedione[7] (**1**) with triethyl orthoformate afforded the corresponding 4-ethoxymethylene derivative **2**, which in turn reacted with CS_2 and active methlyenes (e.g, malononitrile or ethyl cyanoacetate) under solid-liquid, phase-transfer catalysis conditions [dioxane/K_2CO_3/tetrabutylammonium bromide (TBAB)] to give the spiro dithiolane derivatives $\mathbf{3_{a,b}}$, respectively. Also, compound **2** was allowed to react with malononitrile to obtain the corresponding 4-malononitrilemethylene derivative **4** in moderate yield. The latter was an excellent precursor for the synthesis of spiro cyclopentene derivatives $\mathbf{5_{a-c}}$ when reacted with acetylacetone, ethyl acetoacetate or diethylmalonate, respectively. IR and ^{1}H NMR spectra of compounds **2–5** were consistent with the proposed structures (cf. Table I, Scheme 1).



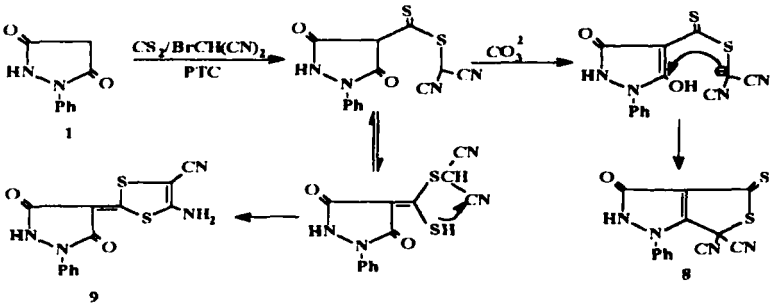
SCHEME 1

Treatment of compound **1** with bromomalononitrile under PTC conditions led to the corresponding 5-amino-4-cyano-1-phenylfuro(2,3-c)pyrazolin-3-one (**6**) and 4-amino-5-cyano-2-hydroxy-3 furancarboxylic acid (**7**). The mechanism of formation of compound **6** was assumed to involve

HBr elimination followed by a nucleophilic attack of the OH group at the cyano group with cyclization. The formation of **7** was due to the heterolytic cleavage of unreacted 3,5-pyrazolinedione into malonic acid and phenylhydrazine. The acid was attacked *in situ* by unreacted bromomalononitrile to give **7**.[8]



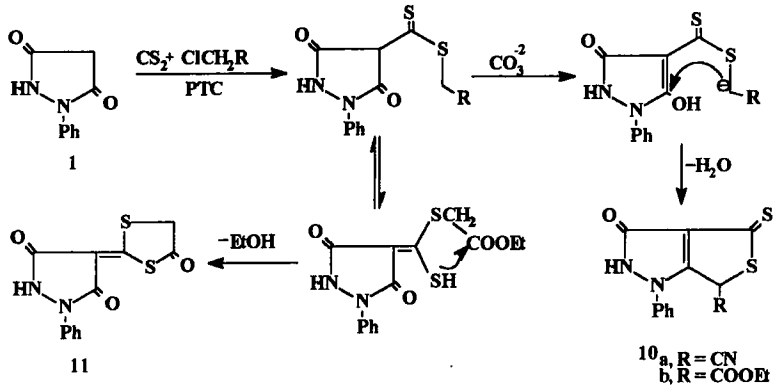
On reacting compound **1** with CS_2 and bromomalononitrile (1:1:1 molar ratio) under PTC conditions,[8] the corresponding 6,6-dicyano-1-phenyl-4H-thieno(3,4-c)pyrazolin-3-one (**8**) and 1-phenyl-4[4-amino-5-cyano-1,3-dithiolane-2-ylidene]pyrazolin-3,5-dione (**9**), respectively, were obtained (cf. Table I, Scheme 2).[8]



SCHEME 2

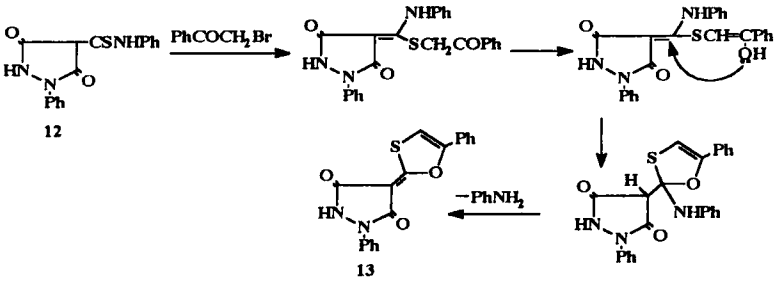
Compound **1** was treated with CS_2 and an active halocompound (e.g, chloroacetonitrile or ethyl chloroacetate) in 1:1:1 molar ratio under PTC conditions,[8] to give the corresponding 6-cyano(carbethoxy)-4,6-dihydro-1-phenylthieno(3,4-c)pyrazolino-4-thioxo-3-one ($\mathbf{10}_{a,b}$) and 1-phenyl-4[5-oxo-1,3-dithiolane-2-ylidene]pyrazolin-3,5-dione (**11**), respectively. The reaction pathway was assumed to involve the addition of the active CH_2 group of compound **1** to CS_2 to give the intermediate product which underwent intramolecular cyclization via nucleophilic attack of

RCH^-: atom onto tautomeric C-OH with elimination of a H_2O molecule to give compounds $\mathbf{10_{a,b}}$, or, via nucleophilic addition of SH group onto the carbonyl ester with elimination of ethanol molecule, to give compound **11** (cf. Table I, Scheme 3).[8]



SCHEME 3

1-Phenyl-4-phenylthiocarbonyl-3,5-pyrazolinedione[9] (**12**) was treated with phenacyl bromide to get the 1,3-oxathiol-2-ylidene derivative **13**. The reaction mechanism is explained in Scheme 4.[10]



SCHEME 4

Treatment of **12** with benzylidenemalononitrile, furnished the corresponding spiro pyridine[11] derivative **14**. IR analysis showed absorption bands corresponding to NH_2 at 3330,3240 cm^{-1} and CN at 2220 cm^{-1}, respectively.

TABLE I Analytical and Spectral Data of the New Compounds

M.P (°C)[a] Crystallization Solvent	Yield (%)	Mole. Form. (Mol. wt.)	Analytical Data[b] Cal./Found IR (Cm^{-1})[c] ^{1}H-NMr				IR (Cm^{-1})[c]	^{1}H-NMr ∂(ppm)[d]
			C	H	N	S		
Ethanol	66	$C_{12}H_{12}N_2O_3$ (232.24)	62.06 62.40	5.20 5.33	12.06 12.42		3175(NH), 2980(CH_{aliph}), 1720,1690 (CO).	8.1 (s, 1H, =CH), 7.8–7.2(m,6H arom.+NH), 3.8 – 3.6(q, 2H, Ch 1.3–1.0 (t, 3H, CH_3).
Ethanol	90	$C_{13}H_8N_4O_2S_2$ (316.36)	49.35 49.09	2.54 2.21	17.71 17.60	20.27 20.37	3143(NH), 2210(CN), 1720,1690 (CO).	7.6–7.1(m,6H, arom. + NH), 3.2 SCH_2).
Benzene	34	$C_{16}H_{13}N_3O_4S_2$ (375.42)	51.18 51.43	3.49 3.70	11.12 11.39	17.08 17.31	3221(NH). 1740(CO_{ester}), 1719, 1620 (CO).	7.8–7.2(m,6H,arom.+NH),4.4 4 2H, $CH_{2\ ester}$), 3.5 (s, 2H, SCH_2 1.0 (t,3H, CH_3)
Ethanol	29	$C_{20}H_{12}N_4O_2$ (252.23)	61.90 61.61	3.19 3.48	22.12 22.60		3328(NH), 2220(CN), 1711,1687 (CO).	8.7(s, 1H,=CH), 8.0– 7.8(m,6H,arom.+NH), 4.0(s,1H
Benzene	40	$C_{18}H_{16}N_4O_4$ (328.33)	65.84 65.61	4.91 4.72	17.16 17.36		3340, 3249, 3310 (NH,NH_2), 2220 (CN), 1720–1669 (CO).	7.8–7.3(m,6H,arom.+NH),6.1– 5.7(br,2H,NH_2), 3.3 (s,2H, CH_2 2.3(s,6H,2CH_3).
Dioxane	60	$C_{19}H_{18}N_4O_5$ (372.30)	61.24 61.00	4.87 4.50	15.04 15.39		3300,3211,3140(NH,NH_2), 2180(CN) 1740(CO_{ester}), 1711,1680(CO).	8.7–8.0(m,6H, arom. +NH), 6.1 5.7(br,2H,NH_2), 4.1- 3.8(q,2H,CH_{2ester}), 3.5(s,2H,CH 2.3(s,3H, CH_3), 1.3- 1.0 (t, 3H,
Acetic acid	69	$C_{20}H_{20}N_4O_6$ (412.4)	58.24 58.59	4.88 4.63	13.58 13.81		3310,3218,3110(NH,NH_2), 2110(CN) 1735(CO_{ester}), 1690–1670 (CO).	8.7–8.1(m,6H, arom. +NH), 6.0 5.8(br,2H,NH_2), 4.2- 3.9(q,4H,2 3.6(s,2H,CH_2), 1.3–1.0 (t, 6H, 2

M.P (°C)[a] Crystallization Solvent	Yield (%)	Mole. Form. (Mol. wt.)	Analytical Data[b] Cal./Found IR (Cm^{-1})[c] ^1H-NMr				IR (Cm^{-1})[c]	^1H-NMr ∂(ppm)[d]
			C	H	N	S		
Ethanol	80	$C_{12}H_8N_4O_6$ (240.22)	60.00 60.30	3.35 3.70	23.22 23.50		3370,3271,3150(NH,NH_2), 2210(CN) 1689(CO).	7.6–7.0 (m,6H,arom. +NH), 5.4 (br, 2H, NH_2).
Acetic acid	90	$C_6H_4N_2O_4$ (168.11)	42.86 42.60	2.90 2.59	16.66 16.88		3440,3320,3220(OH,NH_2), 2210(CN)	8.0(s,1H,COOH), 6.6–6.4(br,2H,NH_2),2.2(s,1H, OH).
Ethanol	70	$C_{13}H_6N_4OS_2$ (298.39)	52.33 52.11	2.02 2.31	18.77 18.91	21.49 21.65	3220(NH), 2210(CN), 1699(CO).	7.5–6.9 (m,6H,arom. + NH).
Benzene	93	$C_{13}H_8N_4O_2S_2$ (316.36)	49.35 49.59	2.54 2.70	17.71 17.98	20.27 20.49	3332,3211,3100(NH,NH_2). 2210(CN), 1720,1670(CO).	8.7–8.1(m,6H, arom. +NH),6.1-5.9(br,2H,NH_2).
Acetic acid	30	$C_{12}H_7N_2OS_2$ (241.27)	59.38 59.51	2.92 2.63	11.61 11.39	26.56 26.75	3120(NH),2210(CN),1680 (CO), 1140(CS).	8.4–7.7(m,6H, arom. +NH), 4.0 1H,CH).
DMF	75	$C_{14}H_{12}N_2O_3S_2$ (320.39)	52.48 52.51	3.77 3.51	8.74 8.44	20.01 20.27	3150(NH), 1740(CO_{ester}), 1685(CO).	8.7–8.1(m,6H, arom. +NH), 5.0(s,1H,CH), 4.4–4.1(q, 2H,2C 1.4–1.1 (t, 3H, $2CH_3$).
benzene	36	$C_{12}H_8N_2O_3S_2$ (292.34)	49.30 49.00	2.75 2.54	9.58 9.70	21.93 21.86	3210(NH), 1712,1678(CO).	8.4–7.9(m,6H,arom + NH), 4.2(s,2H,CH_3).
Dioxane	90	$C_{18}H_{12}N_2O_3S$ (336.37)	64.24 64.59	3.59 3.75	8.32 8.50	9.53 9.69	3170 (NH), 1710,1690 (CO). 1H,=CH).	8.0–7.2(m,11H,arom. + NH), 5.

M.P (°C)[a] Crystallization Solvent	Yield (%)	Mole. Form. (Mol. wt.)	Analytical Data[b] Cal./Found IR (Cm^{-1})[c] ^{1}H-NMr				IR (Cm^{-1})[c]	^{1}H-NMr ∂(ppm)[d]
			C	H	N	S		
Benzene	35	$C_{26}H_{19}N_5O_2S$ (435.53)	71.70 71.98	4.39 4.51	16.08 16.29	7.36 7.01	3310,3210,3110 (NH,NH_2), 2210(CN), 1719, 1690 (CO), 1028(CS).	8.0–7.2(m, 11H,arom. + NH), 6. 6.3(br,1H,CH) 5.0–4.7 (br, 2H.
Ethanol	58	$C_{17}H_{16}N_4OS$ (324.40)	62.94 62.70	4.97 4.70	17.27 17.49	9.88 9.57	3315,3211(2NH), 2210(CN), 1690(CO), 1065 (CS).	8.6–8.1 (m,7H, arom. + 2NH), 3 (m, 4H, $2CH_2$), 1.8–1.5(m,4H,2
Ethanol	55	$C_{19}H_{20}N_4OS$ (352.46)	64.74 64.50	5.71 5.59	15.89 15.70	9.09 9.30	3210,3121 (NH). 2210 (CN), 1681(CO) 1140(CS).	8.7–8.1 (m,7H, arom. + 2NH), 3 (m, 4H, $2CH_2$), 2.0–1.7 (m. 8H. $4CH_2$).
Benzene	60	$C_{15}H_{12}N_2O_4S_2$ (348.40)	51.71 51.52	3.47 3.45	8.04 8.49	18.40 18.70	3130 (NH), 1710–1680 (CO).	7.9–7.2 (m. 6H, arom. + NH), 2 6H, $2CH_3$)
Ethanol	30	$C_{17}H_{16}N_2O_6S_2$ (408.45)	49.99 49.71	3.94 3.74	5.03 5.30	11.51 11.39	3150 (NH), 1740(CO_{ester}), 1709,1679 (CO).	7.9–7.4 (m, 6H. arom. + NH), 4 4.1(q,4H, $2CH_2$),1.3- 1.1 (t, 6H, $2CH_3$).
Chloroform	41	$C_{16}H_{14}N_2O_5S_2$ (378.43)	50.78 50.60	3.72 3.95	7.40 7.19	16.94 16.60	3160(NH), 1730(CO_{ester}),1711,1669 (CO).	8.0–7.4 (m, 6H, arom. + NH), 4 4.0(q,2H, CH_2), 2.3(s,3H,CH_3), 1.1 (t, 3H, CH_3)
DMF	56	$C_{13}H_6N_4O_2S_2$ (284.34)	54.91 54.71	2.12 2.35	19.70 19.99	22.55 22.77	3170(NH), 2210(CN), 1710,1680(CO).	8.4–8.0 (m, 6H, arom. + NH).

M.P (°C)[a] Crystallization Solvent	Yield (%)	Mole. Form. (Mol. wt.)	Analytical Data[b] Cal./Found IR (Cm^{-1})[c] ^{1}H-NMr				IR (Cm^{-1})[c]	^{1}H-NMr ∂(ppm)[d]
			C	H	N	S		
Dioxane	70	$C_{15}H_{11}N_3O_4S_2$ (361.4)	49.85 49.63	3.06 3.30	11.62 11.44	17.74 17.59	3138 (NH), 2181 (CN), 1730(CO_{ester}), 1710,1669(CO).	8.0–7.2 (m, 6H, arom. + NH), 4 (q, 2H, CH_2), 1.3–1.0(t,3H,CH
Dioxane	56	$C_{17}H_{13}N_3O_5S$ (403.44)	50.61 50.33	3.24 3.10	10.41 10.63	15.89 15.72	3200(NH), 2189(CN),1740(CO_{ester}), 1720- 1671 (CO).	8.1–7.1 (m, 6H, arom. + NH), 4 (q, 2H, $CH_{2\ ester}$), 3.4(s,2H,SCI 1.3–1.0(t,3H,CH_3).
Chloroform	40	$C_{28}H_{24}N_5O_4S_2$ (555.63)	60.52 60.79	3.80 3.99	12.60 12.84	11.54 11.70	3120(NH), 2180(CN),1730(CO_{ester}), 1710,1689 (CO).	8.6–7.9 (m, 16H. arom. + NH), 3.9 (q, 2H, CH_2), 1.4–1.1(t,3H,
DMF	40	$C_{19}H_{14}N_4O_3S_2$ (410.47)	55.59 55.79	3.43 3.63	13.64 13.50	15.62 15.80	3120 (NH), 2890 (CH_{aliph}), 2216(CN), 1710,1689 (CO).	8.0–7.3 (m. 6H, arom. + NH), 5 (br, 2H, CH). 2.4 (s, 6H, 2 CH_3
Ethanol	90	$C_{24}H_{18}N_4O_5S_2$ (506.56)	56.90 56.69	3.58 3.75	11.06 11.40	12.65 12.69	3270,3119 (2NH), 2890 (CH_{aliph}), 1710–1685 (CO).	8.0–7.6(m, 12H, arom. + 2NH) 2.9(s,3H,CH_3), 2.3(s,3H,COCH
–7 Chloroform	95	$C_{24}H_{18}N_4O_7S_2$ (538.79)	53.50 53.30	3.36 3.49	10.39 10.48	11.90 11.77	3422(OH), 3230, 3190(2NH), 1739 (CO_{ester}), 1710–1675 (CO).	8.1 –7.5(m, 12H, arom. +2NH) 3.9(q,2H, CH_2), 2.6(s,1H,OH), 1.0 (t, 3H, CH_3).
Ethanol	35	$C_{23}H_{16}N_4O_6S_2$ (508.53)	54.32 54.58	3.71 3.61	11.01 11.49	12.61 12.81	3421(OH), 3210,3211(2NH), 1712-1680(CO).	8.0–7.6 (m, 7H.arom. + 2NH), 2.3(s,3H,CH_3), 2.0(s,1H, OH).

M.P (°C)[a] Crystallization Solvent	Yield (%)	Mole. Form. (Mol. wt.)	Analytical Data[b] Cal./Found IR (Cm^{-1})[c] ^1H-NMr				IR (Cm^{-1})[c]	^1H-NMr ∂(ppm)[d]
			C	H	N	S		
Acetic acid	58	$C_{22}H_{14}N_6O_4S_2$ (490.52)	53.86 53.70	2.87 2.60	17.13 17.49	13.07 13.27	3454(OH),3215,3125 (2NH), 2150 (CN), 1711,1698(CO).	8.0–7.4 (m, 7H,arom. + 2NH), 2.4(s,1H,OH).
DMF	55	$C_{22}H_{13}N_5O_5S_2$ (491.50)	53.76 53.60	3.12 3.40	14.24 14.50	13.08 13.23	3310–3110(NH,NH_2), 2154(CN), 1709-1681(CO).	8.2–7.7 (m, 7H,arom. + 2NH),6 (br,2H, NH_2).
Dioxane	60	$C_{12}H_6N_4O_2$ (238.20)	60.50 60.33	2.53 2.33	23.52 23.67		3219(NH), 2219(CN), 1721,1687 (CO).	7.7–7.2 (m,6H,arom. + NH).
Benzene	30	$C_{18}H_{13}N_5O_2S$ (333.40)	64.84 64.61	3.93 3.64	21.00 21.30	9.61 9.39	3350–3130(NH,NH_2), 2117(CN), 1710, 1680(CO).	7.9–7.2 (m, 11H. arom. +2NH), 5.2(br,2H, $2NH_2$).
Benzene	41	$C_{18}H_{14}N_6O_2$ (346.35)	62.42 62.20	4.07 4.35	24.26 24.00		3360–3150 (NH,NH_2), 2161(CN), 1721 1679 (CO).	7.9–7.4 (m, 12H, arom. + 3NH) (s. 2H,NH_2)
Dioxane	56	$C_{20}H_{11}ClN_4OS_2$ (422.91)	56.80 56.61	2.62 2.35	13.24 13.59	15.16 15.37	3211(NH), 2181(CN), 1683 (CO).	8.4–7.9 (m, 10H, arom. +NH), 6.1(s,1H, CH).
Benzene	56	$C_{22}H_{16}ClN_3O_3S_2$ (470.05)	56.21 56.33	3.43 3.10	8.93 8.63	13.64 13.42	3216 (NH), 2161 (CN), 1743(CO_{ester}). 1687(CO).	8.1–7.8 (m, 10H, arom. +NH), 6.2(s,1H,CH), 4.0–3.8 (q, 2H, 1.3–1.1(t,3H,CH_3).
–5 Benzene	70	$C_{20}H_{11}N_5O_3S_2$ (433.47)	55.41 55.63	2.55 2.70	16.15 16.40	14.79 14.99	3210 (NH), 2141 (CN), 1669 (CO).	8.0–7.4 (m, 10H, arom. +NH), 6.3(s.1H, CH).

M.P (°C)[a] *rystallization Solvent*	*Yield (%)*	*Mole. Form. (Mol. wt.)*	*Analytical Data*[b] *Cal./Found IR (Cm^{-1})*[c] *^{1}H-NMr*				*IR (Cm^{-1})*[c]	*^{1}H-NMr ∂(ppm)*[d]
			C	*H*	*N*	*S*		
Ethanol	40	$C_{22}H_{16}N_4O_5S_2$ (480.52)	54.99 54.79	3.35 3.53	11.65 11.50	13.34 13.50	3210 (NH), 2141 (CN), 1739(CO_{ester}). 1689 (CO)	8.3–7.9 (m, 10H, arom. +NH), 6.0(s,1H,CH),4.1- 3.9 (q. 2H, C 1.3–1.1(t,3H,CH_3).
DMF	90	$C_{26}H_{16}ClN_5O_2$ (465.98)	67.01 67.39	3.46 3.75	15.02 15.30		3170 (NH),2113(CN),1685 (CO).	8.1–7.8 (m, 15H, arom. +NH). 1H. CH).8.1–7.8 (m, 15H, arom +NH). 6.0(s. 1H. CH).
7 Benzene	95	$C_{28}H_{21}ClN_4O_4$ (513.03)	65.55 65.30	4.12 4.49	10.92 10.78		3312(NH), 2100(CN), 1740(CO_{ester}), 1675(CO)	8.3–7.9 (m, 15H, arom. +NH),6 1H,CH),4.3- 4.0 (q, 2H, CH_2), 1.1(t,3H,CH_3)
Dioxane	35	$C_{28}H_{22}ClN_3O_4$ (500.04)	67.25 67.58	4.43 4.61	8.40 8.69		3310 (NH), 1689–1670 (CO),	8.0–7.5 (m, 15H,arom. + NH), 6.1(s,1H,CH), 2.4 (s,6H, 2COC
Dioxane	58	$C_{26}H_{16}N_6O_4$ (476.45)	65.54 65.70	3.87 3.60	17.63 17.49		3190 (NH),2133(CN),1695 (CO).	8.0–7.4 (m, 10H. arom. +NH), 6.3(s,1H, CH).
3 Benzene	55	$C_{28}H_{21}N_5O_6$ (523.51)	64.24 64.00	4.04 4.30	13.37 13.50		3312(NH), 2110(CN), 1740(CO_{ester}), 1695(CO)	8.3–7.9 (m, 10H, arom. +NH),6.5(s,1H,CH),4.2- 3.9 (q, CH_2), 14–1.2(t,3H,CH_3).
50 Ethanol	60	$C_{28}H_{22}N_4O_6$ (510.51)	65.87 65.72	4.34 4.55	10.97 10.73		3130 (NH), 1680–1666 (CO).	7.9–7.3 (m, 15H,arom. + NH), 6.4(s,1H.CH), 2.2 (s,6H; 2COC
Ethanol	30	$C_{23}H_{18}ClN_3O_2S_2$ (468.08)	59.01 59.31	3.87 3.64	8.97 8.70	13.70 13.59	3250,3143 (2NH),1710,1679 (CO). 1154(CS).	8.3(s,1H,NHPh), 7.9–7.4 (m, 1(arom. + 2NH). 6.1 (s, 1H, CH-A 6.5(d,1H,CH).

M.P (°C)[a] Crystallization Solvent	Yield (%)	Mole. Form. (Mol. wt.)	Analytical Data[b] Cal./Found IR (Cm^{-1})[c] ^{1}H-NMr				IR (Cm^{-1})[c]	^{1}H-NMr ∂(ppm)[d]
			C	H	N	S		
Ethanol	41	$C_{23}H_{16}ClN_3OS_2$ (420.06)	65.76 65.50	3.83 3.65	10.00 10.30	15.26 15.40	3219(NH), 1669 (CO).	8.0–7.4 (m, 15H, arom. + NH), 1H, CH).
Benzene	56	$C_{23}H_{16}ClN_3OS_2$ (450.06)	61.38 61.61	3.58 3.35	9.33 9.59	14.42 14.67	3312(NH), 1699(CO).	8.4–8.0 (m, 15H, arom.), 6.7 (s, CH).
1,4-Dioxane	70	$C_{23}H_{16}ClN_3O_2S$ (434.00)	63.65 63.43	3.71 3.90	9.68 9.50	7.38 7.69	3200(NH), 1679(CO).	8.0–7.2 (m, 15H, arom. +NH). 6 1H. CH).
Methanol	56	$C_{11}H_{10}N_4O_2S$ (262.29)	50.37 50.63	3.84 3.60	21.36 21.53	12.22 12.42	3340–3100(NH,NH_2), 1710,1681 (CO) 1070(CS).	10.1(s,1H,NH), 9.3 (s, 1H, =CH 7.8 (m, 6H, arom. +$NH_{pyrazol}$), 6.6(br, 2H, NH_2).
Chloroform	40	$C_{15}H_{12}N_2O_5$ (300.27)	60.00 60.29	4.02 4.29	9.32 9.50		3120(NH), 1741(CO_{ester}), 1722 ($CO_{coumarin}$). 1687(CO).	9.0(s,1H,=CH), 8.0–7.9 (m, 6H, arom. + NH). 4.2–4.0 (q, 2H, C 1.3–1.0 (t, 3H, CH_3).
Benzene	43	$C_{14}H_{10}N_4O_2S$ (268.32)	62.66 62.41	3.75 3.56	20.88 20.67	11.94 11.76	3312(NH), 2170(CN),1695(CO)	10.0(s,1H,=NH), 8.0–7.7 (m, 6H arom. + $NH_{pyrazol}$), 2.2 (s, 3H, S
Dioxane	40	$C_{14}H_9N_3O_3S$ (299.31)	56.18 56.41	3.03 3.34	14.03 14.43	10.71 10.46	3210(NH), 2132(CN), 1713(CO_{ester}), 1677(CO)	7.8–7.3 (m, 6H, arom. +NH), 2. 3H, SCH_3)

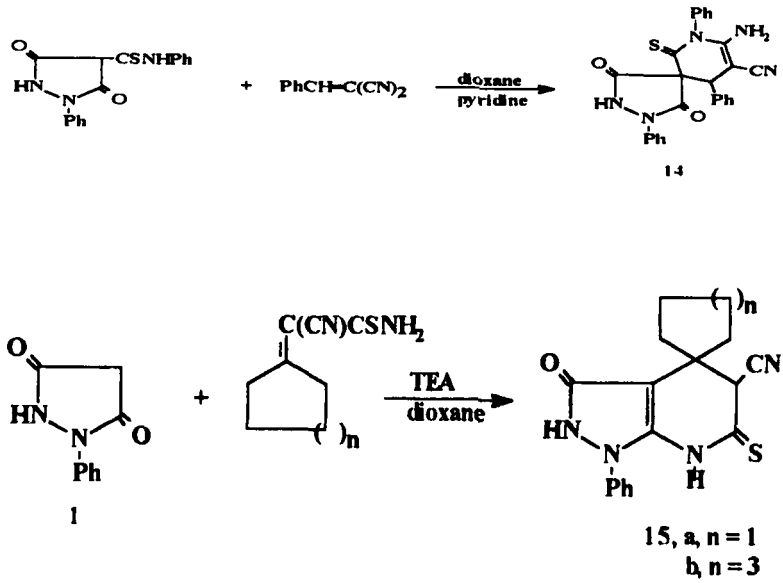
cted.

ory microanalysis obtained C; + 0.35, H; + 0.4, N; + 0.2, S; + 0.32

d by Nicolet FT-IR 710 spectrophotometer.

d by a varian EM 360 L spectrometer at 60 MHz using TMS as internal standard and DMSO d_6 as a solvent.

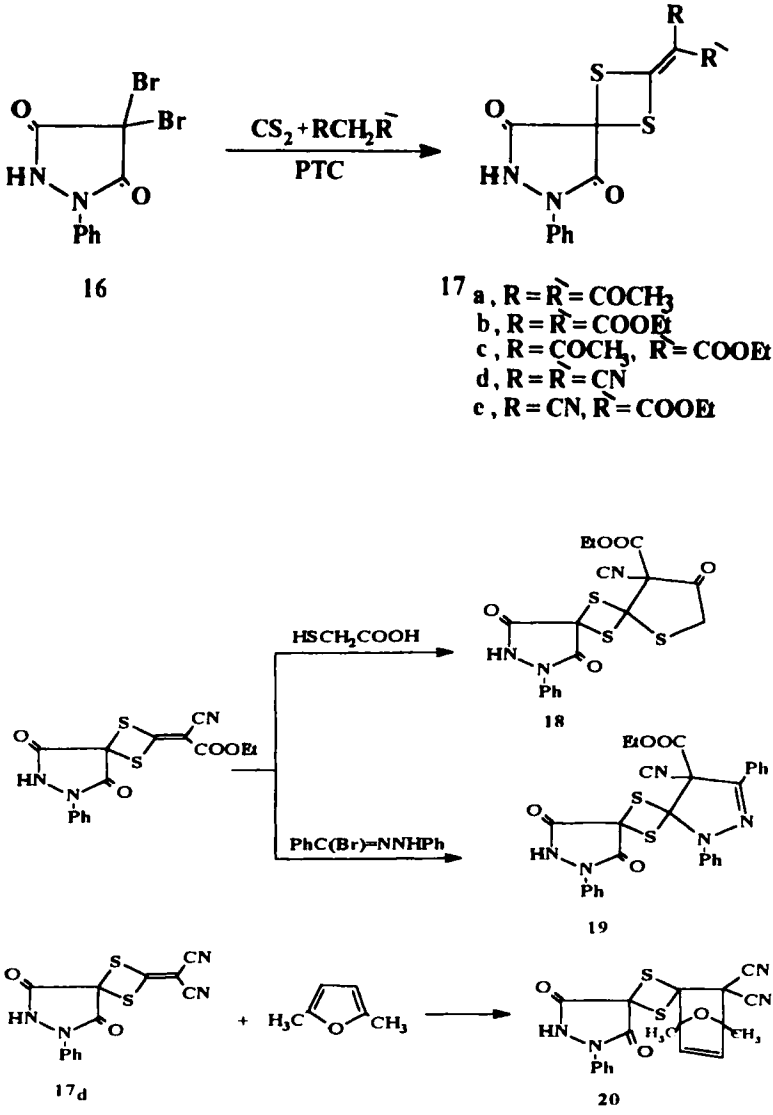
On refluxing compound **1** with cycloalkylidenecyanothioacetamide in dioxane in the presence of triethylamine as a base, the corresponding pyridinethione derivatives **15** were obtained.



Using PTC technique, 4,4-dibromo-1-phenylpyrazolinedione[12](**16**) was treated with CS_2 and active methylenes, namely, acetylacetone, diethylmalonate, ethyl acetoacetate, malononitrile or ethyl cyanoacetate, to afford the corresponding dithietane[13] derivatives $\mathbf{17}_{a\text{-}e}$, respectively. IR spectra of compounds $\mathbf{17}_{a\text{-}e}$ showed the absorption bands corresponding to C=O and CN groups, and ^{1}H NMR spectra were consistent with the proposed structures. (cf. Table I).

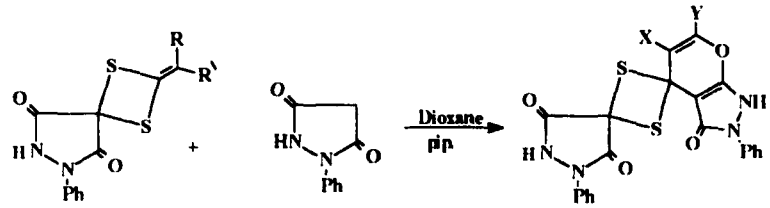
The reaction of compound $\mathbf{17}_e$ with thioglycolic acid or N-phenylbenzohydrazindoyl bromide gave the spiro derivatives of thiazolidinone **18** and diazine **19**, respectively. When compound $\mathbf{17}_d$ was reacted with 2,5-dimethylfuran, the corresponding spiro bicyclo[2,2,1]hexene **20** was obtained in low yield (cf. Table I, Scheme 5).

Moreover, compounds $\mathbf{17}_{a\text{-}e}$ were reacted with 1-phenyl-3,5-pyrazolinedione (**1**) in dioxane in the presence of triethylamine as a base and gave the corresponding spiro-γ pyrans $\mathbf{21}_{a\text{-}e}$, respectively. IR spectra of compounds **21** showed the absorption bands corresponding to NH, NH_2, CN and C=O



SCHEME 5

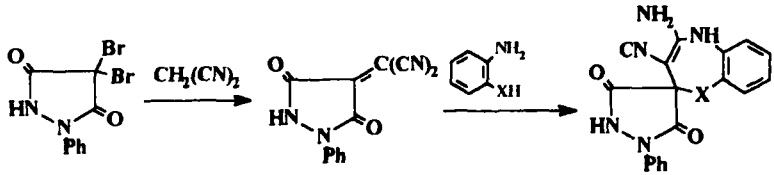
groups, and the ^{1}H NMR were in agreement with the proposed structures (cf. Table I).



17a, R = R' = $COCH_3$
b, R = R' = COOEt
c, R = $COCH_3$, R' = COOEt
d, R = R' = CN
e, R = CN, R' = COOEt

21a, X = $COCH_3$, Y = CH_3
b, X = COOEt, Y = OH
c, X = $COCH_3$, Y = OH
d, X = CN, Y = OH
e, X = CN, Y = NH_2

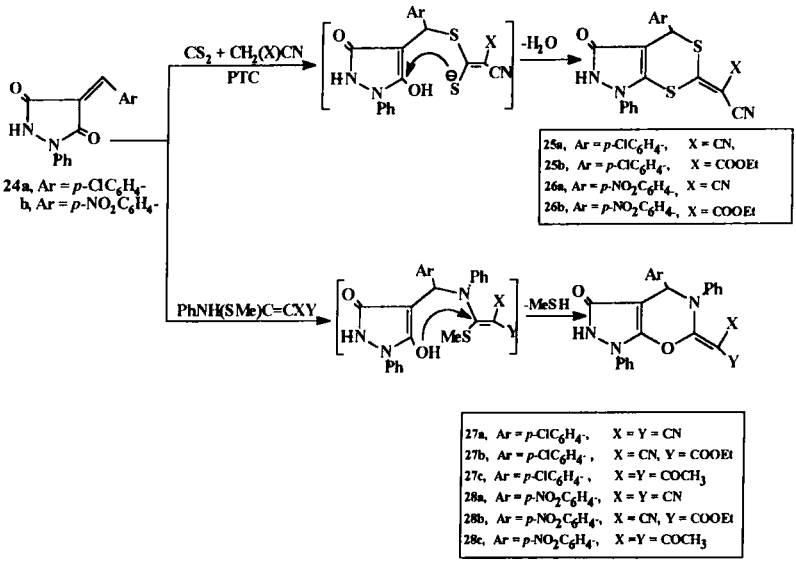
On refluxing compound **16** with malononitrile in ethanol furnished the derivative **22**. IR analysis showed an absorption band corresponding to CN groups at 2210 cm^{-1}. Treatment of *o*-aminophenol or *o*-phenylenediamine with the dicyano compound **22** led to the formation of spiro thiazepine or spiro diazine derivatives $\mathbf{23_{a,b}}$, respectively, instead of 4-benzothiazole or benzimidazole derivatives.[14] IR spectra of compounds showed an absorption bands corresponding to NH_2 and CN groups at (3327,3213 cm^{-1}) and 2210 cm^{-1}, respectively (cf. Table I, Scheme 6).



16 22 23a, X = S
b, X = NH

SCHEME 6

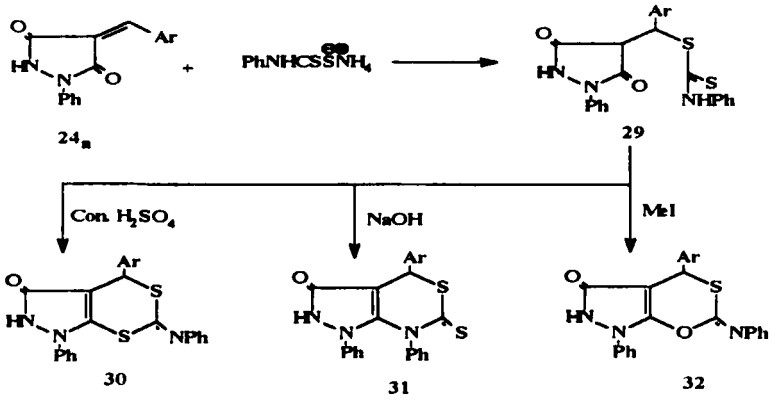
4-Arylidene-1-phenyl-3,5-pyrazolinediones[15] ($\mathbf{24_{a,b}}$) were reacted with S,S-acetals[16] or N,S-acetals[16] to give pyrazolino(1,3)dithiane $\mathbf{25_{a,b}}$, $\mathbf{26_{a,b}}$ and pyrazolino(1,3)oxazine $\mathbf{27_{a-c}}$, $\mathbf{28_{a-c}}$ derivatives, respectively. The reaction pathway was assumed to proceed via the addition of the SH group or the imino group to the ethylenic bond followed by elimination of H_2O or MeSH molecules (cf. Table I, Scheme 7).



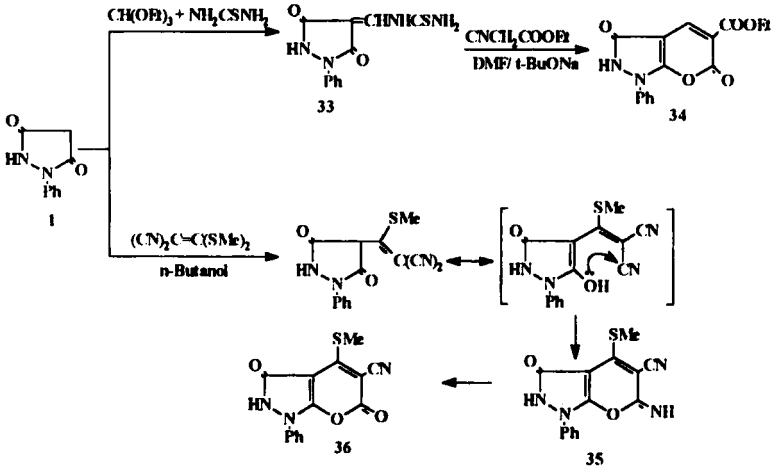
SCHEME 7

Compound $\mathbf{24_a}$ was reacted with ammonium N-phenyldithiocarbamate[17] to give [1-phenyl- 3,5-dioxo-2H-pyrazol-4-yl]-*p*-chlorophenylmethyl-N-phenyldithiocarbamate (**29**), which in turn underwent intramolecular chemoselective heterocyclization with conc. H_2SO_4, NaOH or CH_3I to afford pyrazolino(1,3)dithiane **30**, pyrazolino(1,3)thiazine **31** or pyrazolino(1,3)oxathiine **32**, respectively (cf. Table I, Scheme 8).

Reacting compound **1** with a mixture of thiourea and triethyl orthoformate gave the corresponding 4-ureidomethylene derivative **33**, which in turn reacted with ethyl cyanoacetate in the presence sodium t-butoxide[18] to furnish 3-carbethoxypyrano[2,3-c]ryrazolin-6-one (**34**). Reacting compound **1** with cyanoketene S,S diacetals,[16]afforded 3-cyano-4-thiomethyl-6-iminopyranopyrazoline derivative **35**. This product was treated with dil HCl to give pyrano[2,3-c]pyrazolin-7-one **36** (cf. Table I, Scheme 9).



SCHEME 8



SCHEME 9

EXPERIMENTAL

Synthesis of compound 2

To a solution of compound **1** (0.01 mol) in acetic anhydride (10 ml) was added triethyl orthoformate (0.01 mol). The reaction mixture was refluxed

for 5 h and then was evaporated in *vacuo*, and the residual solid was washed with water and crystallized from ethanol (cf. Table I).

Synthesis of compounds 3, 17_{a-e}, $25_{a,b}$ and $26_{a,b}$

A mixture of a proper active methylene (0.02 mol), CS_2 (0.02 mol), anhydrous potassium carbonate (3 gm), a catalytic amount of TBAB, and dioxane (20 ml) was stirred for 40 minutes at 60°C. To the dianionic ambident was added compound **2, 16** or $\mathbf{24_{a,b}}$ (0.02 mol). The reaction mixture was stirred for 6 hr at 40 °C, filtered off, and the organic layer was washed with water, dried over anhydrous sodium sulphate and evaporated in vacuo. The residual separated solid was collected by filtration and crystallized from the suitable solvent (cf. Table I, Scheme 1, 7).

Synthesis of compounds 4

A mixture of compound **2** (0.01 mol) and malononitrile (0.01 mol) in dioxane (20 ml) was refluxed for 3 h. The solvent was concentrated and the precipitated product was filtered off and crystallized from ethanol (cf. Table I).

Synthesis of compounds 5. (general procedure)

To a stirred solution of compound **4** (0.01 mol) and triethylamine (0.01 mol) in dioxane (30 ml) was added acetylacetone, ethyl acetoacetate and/or diethylmalonate (0.01 mol). The reaction mixture was refluxed for 2 h and then was evaporated in *vacuo*, and the remaining product was triturated with water. The residual solid was crystallized from the suitable solvent (cf. Table I, Scheme 1).

Synthesis of compounds 6,7

A mixture of compound **1** (0.01 mol), anhydrous potassium carbonate (3 g), a catalytic amount of TBAB, and dioxane (20 ml) was stirred for 50 minutes at 45 °C. The formed dianionic ambident was treated with bromomalononitrile (0.01 mol). The reaction mixture was stirred for 9 hr at 65°C. At the end of the reaction *(TLC)*, the reaction mixture was filtered off, and the organic layer was washed with water, dried over anhydrous sodium sulphate, and evaporated in *vacuo*. The residual solid was crystal-

lized from benzene to give compound **6** (Table I). Compound **7** was obtained by dissolving the carbonate in water (60 ml) and acidification with HCl.

Synthesis of compounds 8–11

A mixture of compound **1** (0.01 mol), CS_2 (0.015 mol), anhydrous potassium carbonate (3 g), a catalytic amount of TBAB, and dioxane (20 ml) was stirred for 20 minutes at 40 °C. To the reaction mixture was added bromomalononitrile, chloroacetonitrile or ethyl chloroacetate (0.01 mol). The reaction mixture was stirred for 6 hr at 65°C. At the end of the reaction (*TLC*), the organic layer was washed with water, dried over anhdrouse sodium sulphate, and evaporated in *vacuo*. The residual solid was crystallized from the suitable solvent to give compounds **8,10** respectively (Scheme 2,3). Compounds **9,11** precipitated during the course of the reaction. They were separated by dissolving the carbonate layer in water (60 ml) and crystallized from benzene (cf. Table I, Scheme 2,3).

Synthesis of compound 13

An equimolar amount (0.02 mol) of compound **11**, sodium ethoxide and phenacyl bromide in ethanol (20 ml) was stirred for 6 h at room temperature. The reaction mixture was concentrated, the precipitate was filtered off, washed with water and crystallized from dioxane (cf. Table I, Scheme 4).

Synthesis of compound 14

To a solution of compound **11** (0.01 mol) in dioxane (20 ml) was added benzylidine-malononitrile (0.01 mol) and a catalytic amount of pyridine. The reaction mixture was refluxed for 5 h, the solvent was evaporated in *vacuo*, and the remaining product was triturated with water. The residual solid was crystallized from benzene (cf. Table I).

Synthesis of compounds 15a,b. (general procedure)

To a solution of compound **1** (0.01 mol) in dioxane (20 ml) was added cycloalkylidenecyanothioacetamide (0.01 mol). The reaction mixture was

treated with few drops of triethylamine, refluxed for 5 h and evaporated in *vacuo*. The residual solid was crystallized from ethanol (cf. Table I).

Synthesis of compound 18

To a stirred solution of compound $\mathbf{17_d}$ (0.01 mol) in pyridine (30 ml) was added thioglycolic acid (0.014 mol). The reaction mixture was refluxed for 12 h and evaporated in *vacuo*. The remaining product was triturated with water, and the residual solid was crystallized from dioxane (cf. Table I, Scheme 5).

Synthesis of compound 19

To a solution of compound $\mathbf{17_d}$ (0.01 mol) in dioxane (20 ml) was added N-phenylbenzohydrazidoyl bromide (0.01 mol) and triethylamine (0.01 mol). The reaction mixture was refluxed for 5 h and evaporated in *vacuo*. The residual solid washed with water, and crystallized from chloroform (cf. Table I, Scheme 5).

Synthesis of compound 20

A mixture of compound $\mathbf{17_c}$ (0.005 mol), 2,5-dimethylfuran (0.005 mol) and hydroquinone (0.002 g) in ethanol (30 ml) was refluxed for 13 h and evaporated in *vacuo*. The separated solid was washed with water and crystallized from DMF (cf. Table I, Scheme 5).

Synthesis of compounds 21a-e. (general procedure)

To a solution of compound $\mathbf{17_{a\text{-}e}}$ (0.01 mol) in dioxane (20 ml) was added 1-phenyl-3,5-pyrazolinedione (0.01 mol). The reaction mixture was treated with few drops of piperidine, refluxed for 5 h and evaporated in *vacuo*. The residual solid was crystallized from suitable solvent (cf. Table I).

Synthesis of compound 22

To a solution of compound **16** (0.01 mol) in ethanol (20 ml) was added malononitrile (0.01 mol). The reaction mixture was treated with catalytic

amount of triethylamine, refluxed for 0.5 h and evaporated in *vacuo*. The residual solid was washed with water and crystallized from dioxane (cf. Table I).

Synthesis of compounds $23_{a,b}$ (general procedure)

To a stirred solution of compound **22** (0.01 mol) in dioxane (30 ml) was added *o*-aminothiophenol (0.01 mol) or *o*-phenylenediamine (0.01 mol). The reaction mixture was refluxed for 4 h and evaporated in *vacuo*. The remaining product was triturated with petroleum ether (60–80°C), and the residual solid was crystallized from benzene (cf. Table I, Scheme 6).

Synthesis of compounds 27_{a-c} and 28_{a-c} (general procedure)

A mixture of compound $24_{a,b}$ (0.005 mol) and N,S-acetals (0.005 mol) in dioxane (30 ml) was refluxed until the evolution of MeSH ceased (~20 h) and then was evaporated in *vacuo*. The separated solid was washed with water and crystallized from the suitable solvent (cf. Table I, Scheme 7).

Synthesis of compound 29

To a stirred solution of compound 24_a (0.01 mol) in dioxane (30 ml) were added ammonium N-phenyldithiocarbamate (0.01 mol) and acetic acid (10 ml). The reaction mixture was refluxed for 5 h and evaporated in *vacuo*. The remaining product was triturated with water, and the residual solid was crystallized from ethanol (cf. Table I, Scheme 8).

Synthesis of compound 30

The compound **29** (0.01 mol) was separately treated dropwise with conc. H_2SO_4 (10 ml). The reaction mixture was poured into ice-water mixture (300 ml) and neutralized with ammonia. The precipitate was collected by filtration and crystallized from ethanol (cf. Table I, Scheme 8).

Synthesis of compound 31

To a stirred solution of compound **29** (0.01 mol) in ethanol (30 ml) was added sodium hydroxide solution (7 ml, 4%). The reaction mixture was

refluxed for 3h, cooled, poured into water, and brought to pH 5 with 5 N HCl. The precipitate was filtered and crystallized from benzene (cf. Table I, Scheme 8).

Synthesis of compounds 32

An equimolar mixture of compound **29** (0.005 mol) and methyl iodide (0.005 mol) in methanol (30 ml) was refluxed until the evolution of MeSH ceased (~20 h). The reaction mixture was treated with 5% aq NaOH (10 ml), and the precipitate was collected by filtration, washed with water and crystallized from dioxane (cf. Table I, Scheme 8).

Synthesis of compound 33

A mixture of compound **1** (0.005 mol), thiourea (0.005 mol), and triethyl orthoformate (0.005 mol) in gl acetic acid (10 ml) was refluxed for 3 h. The reaction mixture was cooled, and poured into ice-water mixture (200 ml). The residual solid was collected by filtration and crystallized from methanol (cf. Table I, Scheme 9).

Synthesis of compound 34

To a stirred solution of compound **33** (0.01 mol) in dry DMF (10 ml) were added ethyl cyanoacetate (0.01 mol) and sodium t-butoxide (0.01 mol in 5 ml t-butanol). The reaction mixture was stirred for 16 h and treated with 50% aq ethanol (10 ml). The solution was acidified with HCl to pH 2–3 with cooling. The residual solid was filtered and crystallized from chloroform (cf. Table I, Scheme 9).

Synthesis of compounds 35

An equimolar mixture (0.005 mol) of compound **29** and cyanoketene S,S-diacetals in n-butanol (30 ml) was refluxed until the evolution of MeSH ceased (~38 h). The reaction mixture was concentrated, and the precipitate solid was collected by filtration, washed with pet ether 40/60 °C, and crystallized from benzene (cf. Table I, Scheme 9).

Synthesis of compound 36

A solution of compound **35** (0.001 mol) in ethanol (20 ml) was treated with HCl (10 ml, 5%). The reaction mixture was refluxed for 2 h and then was poured into ice-water mixture (80 ml). The precipitate was collected by filtration and crystallized from dioxane (cf. Table I, Scheme 9).

References

1. W. Harlin, A. Linke and E. Messer, Deut. Arch. Klin. Med., **201**, 690(1955), C.A., **50**, 11519c (1956).
2. V. Pacobsky and V. Holecek; Casopis Lekaru Ceskych, **95**, 300(1956), C.A., **50**, 7306c(1956).
3. A.B. Stanfield, E.C. brodie and E.E. Yeoman, Proc. Soc. Exptl. Biol. Med., **83**, 254(1953), C.A., **47**, 10712d(1953).
4. A.M. El-Sayed and A. Khodairy, Synth. Comm., **28**(18), 3331(1998).
5. A.M. El-Sayed and A. Khodairy, Phosphorous, sulphur and Silicon, **132**, 41(1998).
6. H. Abdel- Ghany, H.M. Moustafa and A. Khodairy, Synth. Comm., **28**(18), 3431(1998).
7. D. Prelicz and B. Arct; Acta Pol. Pharm., **25**(2), 207(1968).
8. A.K. El. Shafei, H. Abdel- Ghany, A.A. Sultan and A.M.M. El-Saghier, Phosphorous, sulphur and Silicon, **73**, 15(1992).
9. B. Arct, L. Kasperek, D. Prelicz and L. Wyzgowska, Diss. Pharm. Pharmacol., **19**, 165(1967).
10. H.M. Hassaneen, N.M. Elwan, H.A. Abdelhadi and T.A. Abdellah, Sulfur Letters, **18**, 121 (1995).
11. K.B. Ogdanowicz- Szwed, N.K. Rasodanska, N. Lipowska, B. Rys, and A. Skonecka, Monatsheft fur Chemie, **124**, 721(1993).
12. Asher, Ber., 1018(1897).
13. H. Abdel-Ghany, Phosphorous, sulphur and Silicon, **122**, 173(1997).
14. S.A.M. Metwally, G.M. El- Naggar, M.I. Younis, T.I. El- Emary and M.H. El-Nagdi, Liebigs Ann. Chem., 1037(1989).
15. A. Mustafa, A. Sammour, M. Kira, M.K. Hilmy, M. Anwar and S.N. Nakhla, Arch. Pharm., **298**(8), 516(1965).
16. A. Kumar, H. Ila and H. Junjappa, Synthesis, 324 (1976).
17. L.S. Yadav, S. Saigal, S. Shukla and D.R. Pol, Ind. J. Chem., **37**(B), 306(1998).
18. V.K. Ahluwalia, V.K. Garg, A. Dahiya and M.D. Alauddin, Ind. J. Chem., **34**(B), 51(1995).