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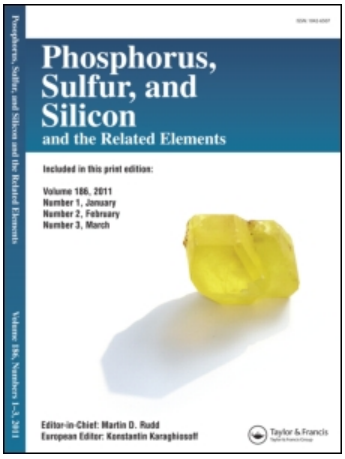

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SYNTHESIS AND BIOLOGICAL ACTIVITY OF SOME NEW BIS AZOLE AND AZINE DERIVATIVES

M. G. Assy[a]; M. M. Hassanien[a]; G. A. Ahmed[a]
[a] Chemistry Department, Faculty of Science, Zagazig University, Zagazig, A.R., Egypt

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SYNTHESIS AND BIOLOGICAL ACTIVITY OF SOME NEW BIS AZOLE AND AZINE DERIVATIVES

M. G. ASSY, M. M. HASSANIEN and G. A. AHMED
Chemistry Department, Faculty of Science, Zagazig University, Zagazig, A.R. Egypt

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Terphthaloyl isothiocyanate **1** was reacted with hydrazine hydrate to give triazole **3**. Addition of carbon nucleophile (ethyl cyanoacetate, crotonate, and/or enaminone) to **1** was described. Also the chemical transformation of pyrimidine **12** was reported.

Key words: Terphthaloyl isothiocyanate, triazole, pyrimidinethione.

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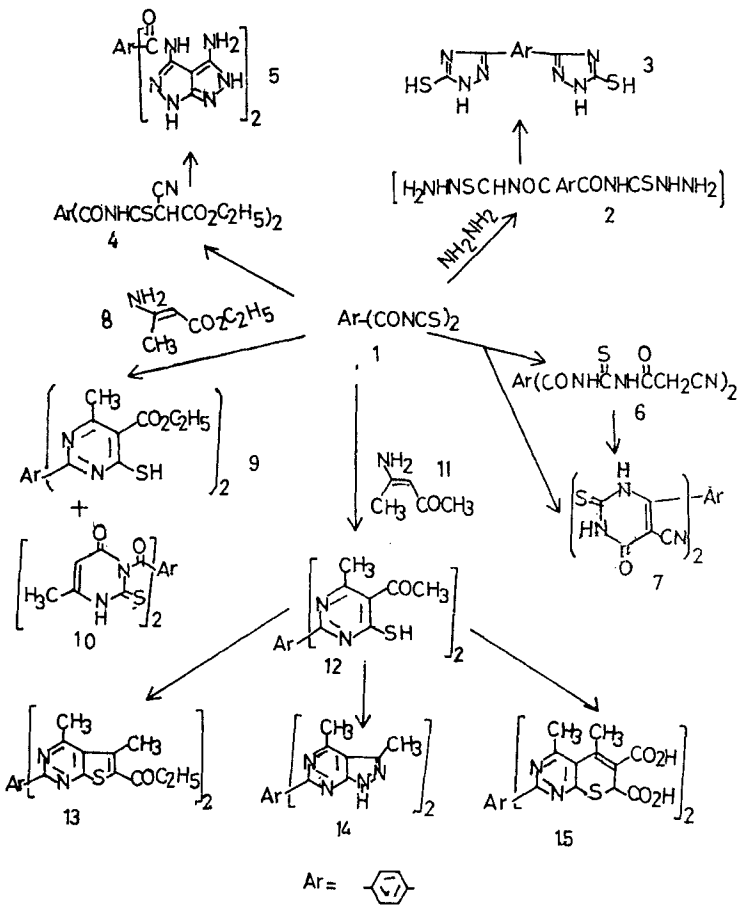
The wide spectrum of azoles and azines in medicine as hypoglycaemic agents, bactericides, fungicides, allergy inhibitors, antimalarials, analgesic and antispasmodic agents,[1–4] prompted us to synthesis some new azoles and azines with expected biological activity utilizing terphthaloyl isothiocyanate.

Aryol isothiocyanates are versatile building units that have been extensively utilized in organic synthesis.[5–8] Terphthaloyl isothiocyanate (**1**) was reacted with hydrazine hydrate to give bis 1,2,4 triazole derivative **3** presumably via the non-isolable thiosemicarbazide **2**. The addition of carbon and/or nitrogen nucleophiles to the isothiocyanate function of compound **1** was investigated, thus, the reaction of **1** with ethyl cyanoacetate gave thioamide **4**, hydrazinolysis of thioamide **4** yielded pyrazolopyrazole **5**. Condensation of compound **1** with cyanoacetamide afforded thiourea derivative **6** and pyrimidine **7**.[8] Thiourea derivative **6** was converted into pyrimidine **7** on treatment with sodium ethoxide at room temperature.

Reaction of terphthaloyl isothiocyanate (**1**) with crotonate **8** afforded pyrimidines **9**[9] and **10**[7] respectively. Addition of enaminone **11** to compound **1** gave 4-mercapto-5-acetylpyrimidine **12**.[9] Alkylation of **12** using ethyl bromoacetate yielded thienopyrimidine **13**. Hydrazinolysis of 4-mercapto-5-acetylpyrimidine **12** using hydrazine hydrate gave pyrazolopyrimidine **14**. The synthesis of thiopyranopyrimidine **15** was achieved by cyclocondensation of **12** with maleic acid.

The antimicrobial activity of terphthalyl derivatives **4** and **6** and compounds **12–15** has been tested against Escherichia coli NRRL B210. Bacillus mycoides NSSR 531, Bacillus subtilis NRRL B543, saccharonyces cerevisida NRRL Y 567 using disc diffusion method.[10,11] The results show that terphthalyl derivatives **4** and **6** possess no antimicrobial activity against these organisms but the introduction of heterocyclic moieties gives the terphthalyl derivatives a moderate antimicrobial activity expressed as 2 mm inhibition zones for compounds **12–15** against the four organisms.



COMPOUND 1

EXPERIMENTAL

All mp's are uncorrected IR spectra were recorded on a Pye Unicam spectrophotometer. ^{1}H-NMR spectra were measured on a Varian (EM-390) spectrophotometer. Microanalytical data were performed by the microanalytical data unit at Cairo University. Biological activity was carried out at Department of Botany, Faculty of Science, Zagazig University.

1. 1,2,4 Triazole-3-thiol **3**

A mixture of terphthaloyl isothiocyanate (**1**) [prepared by addition of **1** (0.01 mol) to a stirred NH_4SCN (0.025 mol) in acetone (20 ml) dropwise over 10 minutes, stirring continued for 1/2 h] and hydrazine hydrate (0.025 mol) in acetone (15 ml) was heated under reflux for one hour. The solid that separated was collected by filtration and crystallized from DMF into yellow crystals of **3** (Table I) yield 70%.

2. Thioamide **4**

A mixture of **1** (0.01 mol) and ethyl cyanoacetate (0.02 mol) in acetone (20 ml) was heated under reflux for 1 h. The solid obtained upon dilution with H_2O (20 ml) was collected by filtration and crystallized from ethanol to give colorless crystals of **4** (Table I) yield 70%.

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TABLE I

Compound	M.P.°C	Formula (MW)	Analysis Calc / Found %			
			C	H	N	S
3	> 300	$C_{10}H_8N_6S_2$ (276.33)	43.47 43.40	2.91 2.90	30.41 30.40	23.20 23.10
4	> 300	$C_{20}H_{18}N_4O_6S_2$ (474.50)	50.63 50.70	3.82 3.80	11.81 11.80	13.51 13.60
5	> 300	$C_{16}H_{14}N_{12}O_2$ (406.36)	47.29 47.30	3.47 3.40	41.36 41.40	- -
6	118-20	$C_{16}H_{12}N_6O_4S_2$ (416.43)	46.15 46.20	2.90 3.0	20.18 20.20	15.40 16.00
7	175-77	$C_{16}H_8N_6O_2S_2$ (380.39)	50.78 50.80	2.12 2.20	22.093 22.10	16.86 16.80
9	277-79	$C_{22}H_{22}N_4O_4S_2$ (470.56)	56.16 56.20	4.71 4.70	11.91 11.90	13.63 13.70
10	> 300	$C_{18}H_{14}N_4O_4S_2$ (414.45)	52.17 52.20	3.40 3.40	13.52 13.50	15.47 15.50
12	240	$4C_{20}H_{18}N_4O_2S_2$ (410.507)	58.52 58.50	4.42 4.50	13.65 13.70	15.62 15.60
13	> 300	$C_{28}H_{26}N_4O_4S_2$ (546.66)	61.52 61.50	4.79 4.80	10.25 10.25	11.73 11.80
14	210-12	$C_{20}H_{18}N_8$ (370.416)	64.85 64.80	4.90 4.00	30.25 30.30	- -
15	> 300	$C_{28}H_{22}N_4O_8S_2$ (606.62)	55.44 55.50	3.65 3.60	9.24 9.30	10.57 10.60

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3. Pyrazolo[3,4-C]pyrazole **5**

A mixture of **4** (0.01 mol) and hydrazine hydrate (0.025 mol) in ethanol (20 ml) was heated under reflux for 1 h. The solid separated upon cooling was filtered and crystallized from ethanol into colorless crystals of **5** (Table I) yield 50%.

4. Synthesis of thiourea **6** *and pyrimidine* **7**

A mixture of **1** (0.01 mol) and cyanoacetamide (0.02 mol) in acetone (20 ml) was heated under reflux for 1 h. The solid that separated upon dilution with water (20 ml) was filtered, then dissolved in ethanol and filtered, the residue crystallized from DMF, to give colorless crystals of **7** and the filtrate diluted with water, solid obtained by filtration was, crystallized from aqueous ethanol to give yellow crystals of **6** (Table I) yield ≈40–45%.

Conversion of thiourea **6** *into pyrimidine* **7**

A mixture of **6** (0.01 mol) and sodium ethoxide (0.025 mol) in ethanol (20 ml) was allowed to stand at room temperature overnight with stirring. The solid obtained upon addition HCl (10 ml, 50%) was filtered and recrystallized from ethanol to give colorless crystals of **7** yield 50%.

TABLE II

Compound	IR (υ Cm^{-1}) selected bands
3	3400 - 3200 (NH), 1590 (C=N), 1190 (C=S)
4	3400 - 3250 (NH), 2250 (CN), 1665 (CO)
5	3350 - 3200 (NH, NH_2), 1670 (CO)
6	3300 - 3200 (NH), 2230 (CN), 1670 (CO)
7	3340 - 3250 (NH), 2240 (CN), 1670 (CO)
14	33500 - 3200 (NH)
15	3500 - 3250 (OH), 1665, 1670 (2 CO)

TABLE III

Compound	^1H NMR (δ, DMSO)
4	1.7 (t, 3H, CH_3, j = 8.0 Hz), 4.2 (q,2H, CH_2, j = 6.1 Hz), 5(S, 1H, CH), 7.1, 8.1 (m, 4H, ArH's)
5	5(S, 2H, NH_2), 7.2 - 7.8 (m, 4H, ArH's) 8.1 - 9.0, 9.9 (2m, 3H, 3NH)
7	7.2 - 7.9 (m, 4H, ArH's), 8.1 (S, 2H, 2NH)
9	1.2 (t, 3H, CH_2 CH_3), 2.15 (S, 3H, CH_3), 4.2 (q, 2H, CH_2 CH_3), 7.1 - 7.2, 7.9 - 8.1 (m, 4H, ArH's), 10 (S, 1H, SH)
10	1.9 (s, 3H, CH_3), 5.5 (s, 1H, pyrimidine proton), 7.1 - 8.2 (m, 4H, ArH's), 8.7 (s, 1H, NH)
12	1.98(S, 3H, CH_3), 2.5 (S,3H, CH_3), 7.2 - 8.2 (m, 4H, ArH's), 9.2 (S, 1H, SH)
13	1.3 (t, 3H, CH_2,CH_3), 1.9 (S, 3H, CH_3), 2.4 (S, 3H, CH_3) 4.2 (q, 2H, CH_2CH_3), 7.1 - 7.5, 7.8 - 8.1 (m, 4H, ArH's).

5. *Ethyl 4-mercaptopyrimidines-carboxylate* **9** *and pyrimidinethione* **10**

A mixture of compound **1** (0.01 mol) and crotonate **8** (0.02 mol) in acetone was heated under reflux for 1 h. The solid obtained upon dilution with water (20 ml) was filtered, dissolved in ethanol and filtered. The residue was recrystallized from aqueous methanol to give yellow crystals of **9** and the filtrate diluted with water (20 ml), filtered, crystallized from aqueous methanol to give colorless crystals of **10** (Table I) yield ≈30%.

6. *4-Mercapto-5-acetylpyrimidine* **12**

A mixture of **1** (0.01 mol) and enaminone **11** (0.02 mol) in acetone (20 ml) was heated under reflux for 1/2 h. The yellow crystals that separated upon dilution with water (10 ml) recrystallized from ethanol to give yellow crystals of **12** (Table I) yield 75%.

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7. Thieno[2,3-d]pyrimidine **13**

A mixture of **12** (0.01 mol) ethyl bromoacetate (0.01 mol) and TEA (3 drops) in ethanol (15 ml) was heated under reflux. The solid obtained upon cooling was filtered and recrystallized from ethanol to give colorless crystals of **13** (Table I) yield 60%.

8. Pyrazolo[3,4-d]pyrimidine **14**

A mixture of **12** (0.01 mol) and hydrazine hydrate (0.015 mol) in ethanol (20 ml) was heated under reflux for 1/2 h. The colorless solid obtained upon cooling was collected by filtration and recrystallized from DMF to give **14** (Table I) yield 75%.

9. Thiopyrano[2,3-d]pyrimidine **15**

A mixture of **12** (0.01 mol) maleic acid (0.01 mol) and TEA (3 drops) in dry xylene (10 ml) was heated under reflux for 1 h. The solid obtained upon concentration and cooling was filtered and recrystallized from xylene to give colorless crystals of **15** (Table I) yield 60%.

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