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Reactions with Heterocyclic Amidines (VI)[1]: Synthesis of some new sym. and assym. pyrazolotriazines and pyrazolo[4,5-e]pyrimidine derivatives

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Abstract□Several new pyrazolo[1,5-a]-S-triazine, pyrazolo[4,5-e]pyrimidine, pyrazolo [1,5-a]pyrimidine derivatives were synthesized *via* condensation of 3-antipyrinyl-5-amino-pyrazole (2) with β-bifunctional reagents. The azo analogues of pyrazolo[1,5-a] pyrimidines; *i.e* pyrazolo[5,1-c]-as-triazine and pyrazolo[5,1-c]-as-benzotriazine were synthesized by coupling of diazotized 2 with agents containing active hydrogen.

Key words□Antipyrine, fused pyrazole, isothiocyanates.

Schistosomiasis is considered to be one of the most difficult disease to treat[2-4]. Recently Senga *et al.*[5] have reported that certain pyrazolo [1,5-a] pyrimidines have considerable antischistosomal activity.

In conjunction with our current research with heterocyclic derivatives of antipyrine[6-10] we report the synthesis of several new pyrazolopyrimidines and their azo analogues as potential antischistosomal agents. The synthesized compounds possess antipyrinyl functional substituent and thus appear promising for utility in biological studies.

Acyl-, aroyl- and ethoxycarbonyl isothiocyanates are highly reactive compounds that have been extensively utilized in organic synthesis[11-13]. In the present work, it has been found that **1a** reacts with **2**[14] to yield a product of molecular formula $C_{17}H_{16}N_6OS$. Three isomeric structures seemed possible (cf. structures **4-6**). Structures **5** and **6** were readily ruled out as the ^{1}H-NMR of the reaction product revealed signals for the pyrazole H-4. Thus, structure **4** was established for the reaction product. Compound **4** can be assumed to formed *via* intermediacy of the thiourea derivative 3 which could not be isolated. Also compound **2** reacted with 1_{b-d} to yield the 5-amino-4-substituted thiocarbamoyl-3-antipyrinylpyrazoles (**7**). Structure **7** was prefered over possible isomeric **3** based on the presence of NH_2 function and also the absence of pyrazole H-4 proton in ^{1}H-NMR spectra[14] (cf. table II).

Contradiction of the behaviour of **1a** and **1b-d** toward **2** was totally determined by steric considerations and also due to maximum electron density at 4-position[15]

In contrast to **7a,b** compound **7c** cyclized readily to **8** on reflux in glacial acetic acid.

Compound **9**[16] was found inactive toward **1a-d** under the same previous conditions. On the other hand, **9** reacted with methyl acrylate to yield a product *via* methanol elimination for which structures **10** and **11** were considered. Structure **10** was supported for the reaction product based on similarity with the previous finding[6]. The same product could be also obtained from **9** and ethyl β-bromopropionate. In contrast to the reported[6] formation of pyrazolo[1,5-a]pyrimidines from **2** and cinnamonitriles, compound **9** recovered unchanged when refluxed with cinnamonitriles.

Again, steric considerations are the controlling factor in these reactions due to the presence of aryl-azo group at position 4 in the pyrazole ring.

Diazotized aminopyrazoles have been reported to react with active reagents to yield either azo derivatives or directly cyclize into pyrazolo[5,1-c]-as-triazines[17-19]. Thus diazotized **2** reacted with **12**[20] to yield **13** and with resorcinol afforded **14** which readily cyclized to **15** *via* water elimination on heating with glacial acetic acid. Structure **15** was established based on the absence of any absorption band corresponding to NH group in IR spectrum.

EXPERIMENTAL METHODS

Melting points are uncorrected. Infrared spectra were recorded using a Pye Unicam SP-1000 spectrophotometer. The ^{1}H-NMR spectra were measured

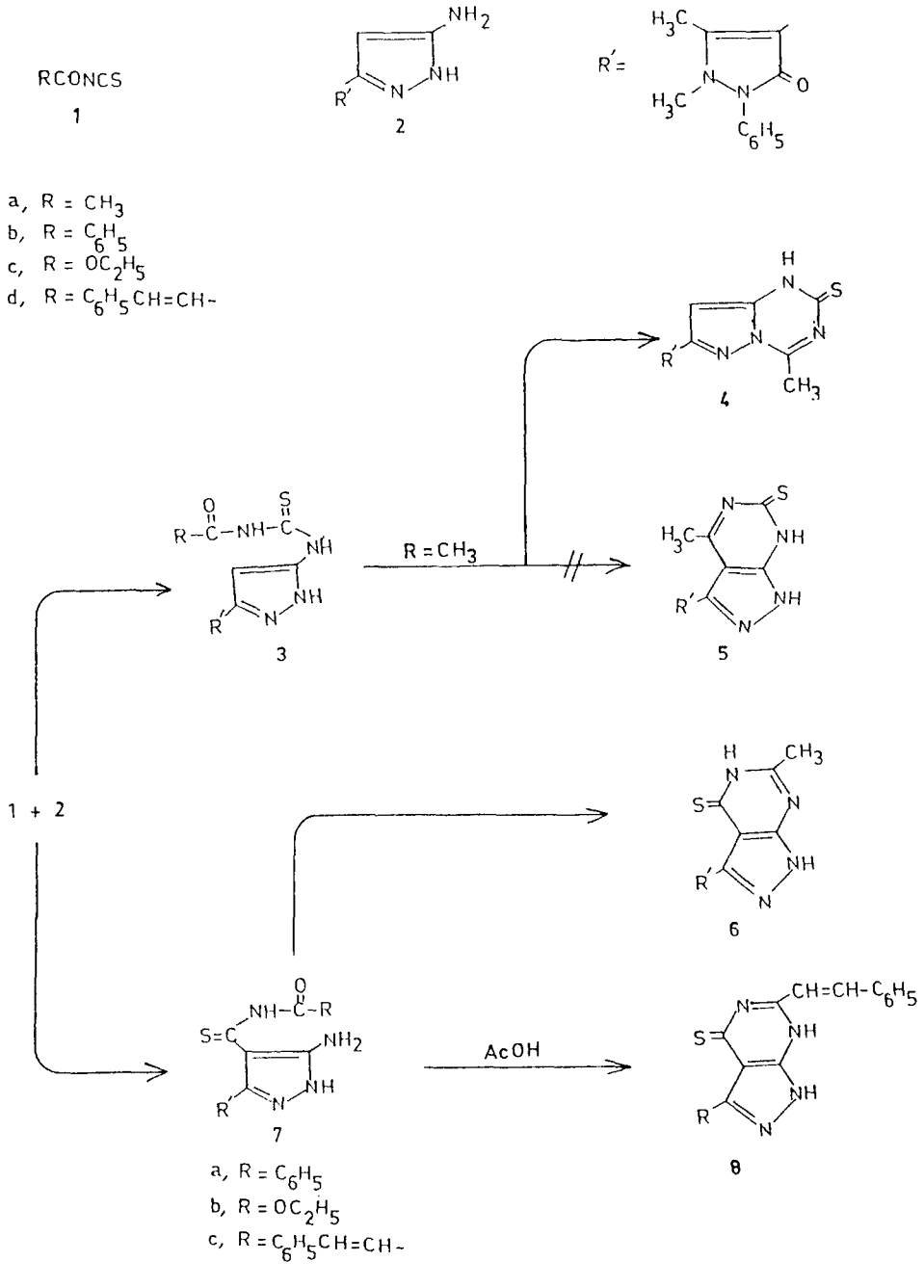
RCONCS
1
2
R′=
a, R = CH3
b, R = C6H5
c, R = OC2H5
d, R = C6H5CH=CH-
4
3
R = CH3
5
1 + 2
6
7
AcOH
8
a, R = C6H5
b, R = OC2H5
c, R = C6H5CH=CH-

Chart 1

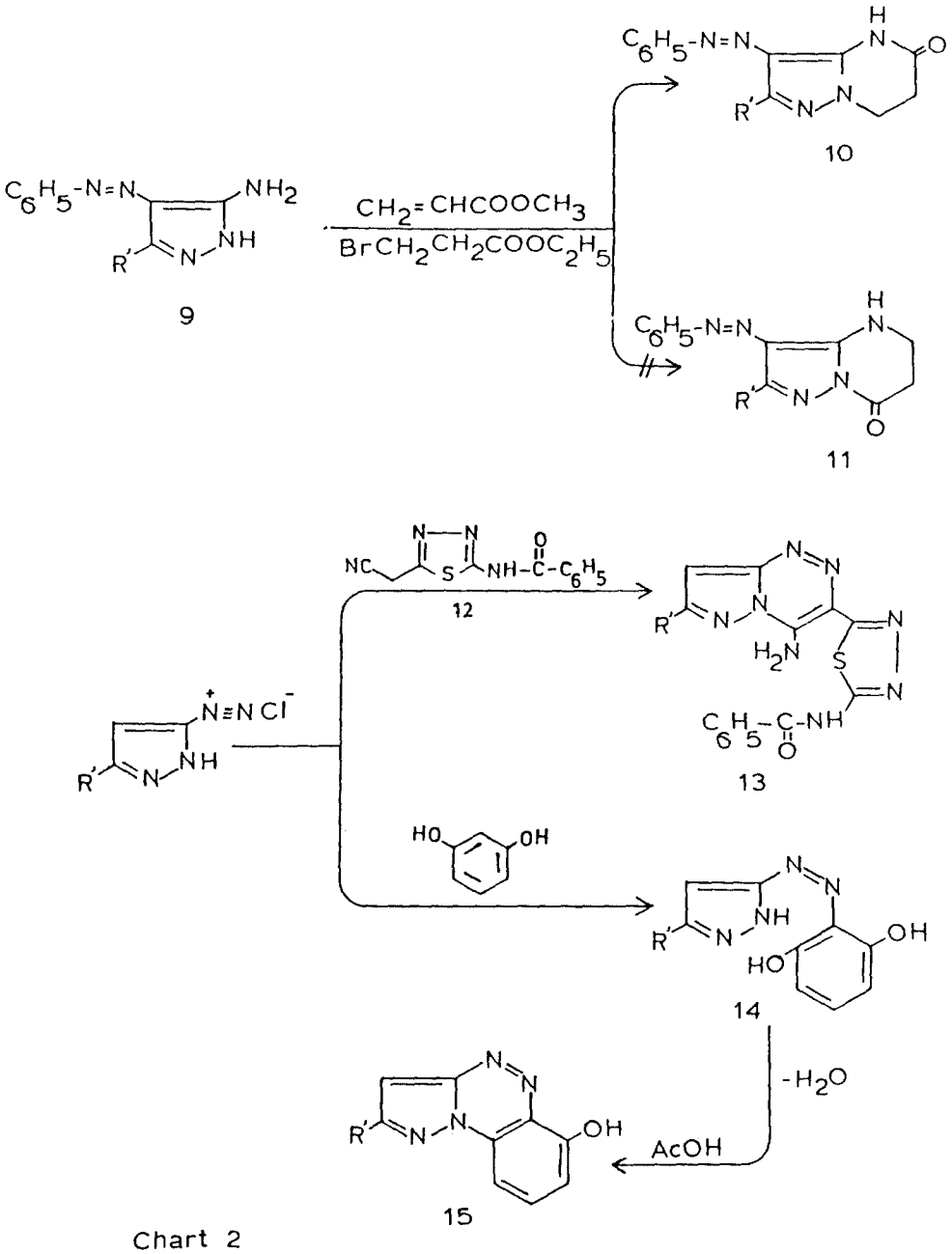
C6H5-N=N
NH2
NH
R'
N
9
CH2=CHCOOCH3
BrCH2CH2COOC2H5
C6H5-N=N
H
N
O
R'
N
N
10
C6H5-N=N
H
N
R'
N
N
O
11
NC
N
N
S
NH-C-C6H5
O
12
N≡N Cl
NH
R'
N
HO
OH
N
N
R'
N
NH2
S
N
C6H5-C-NH
O
13
N
N
R'
N
NH
HO
OH
14
-H2O
AcOH
N
N
R'
N
N
OH
15

Chart 2

Table I. Characterization of Compounds 4-15

Compd.	m.p. (°C)	Yield(%) (solvent)	Formula (Mol. Wt.)	Calcd. / Found	Analysis (%) C	H	N	S
4	217	75 (C_2H_5OH)	$C_{17}H_{16}N_6OS$ (352.42)	Calcd.	57.98	4.56	23.81	9.32
				Found	57.94	4.58	23.85	9.10
7a	235	75 (C_2H_5OH)	$C_{22}H_{20}N_6O_2S$ (432.51)	Calcd.	61.31	4.58	19.68	8.25
				Found	61.10	4.66	19.43	8.41
7b	189	70 (C_2H_5OH)	$C_{18}H_{20}N_6O_3S$ (400.46)	Calcd.	54.21	5.23	20.76	8.15
				Found	53.99	5.03	20.99	8.01
7c	225	70 (Dioxane)	$C_{24}H_{22}N_6O_2S$ (458.55)	Calcd.	63.11	4.76	18.37	7.15
				Found	62.87	4.84	18.33	6.99
8	300	55 (DMF)	$C_{24}H_{20}N_6OS$ (440.53)	Calcd.	65.49	4.76	19.32	7.17
				Found	65.44	4.58	19.08	7.28
10	> 300	63 (C_2H_5OH)	$C_{23}H_{21}N_7O_2$ (427.95)	Calcd.	64.57	4.73	22.91	---
				Found	64.55	4.93	23.15	---
13	> 300	88 (Dioxane)	$C_{25}H_{20}N_{10}O_2S$ (524.55)	Calcd.	57.24	3.84	26.70	6.11
				Found	57.37	3.92	26.78	6.23
14	245	87 ($CHCl_3$)	$C_{20}H_{18}N_6O_3$ (390.4)	Calcd.	61.53	4.64	21.53	---
				Found	61.38	4.57	21.67	---
15	300	75 ($CHCl_3$)	$C_{20}H_{16}N_6O_2$ (372.38)	Calcd.	64.50	4.33	22.57	---
				Found	64.83	4.55	22.72	---

on a Varian EM-390 spectrometer (90 MHz) using TMS as internal standard and chemical shifts are expressed as δ values. Microanalytical data were obtained from the Microanalytical Data Unit at Cairo University.

3-Antipyrinyl-7-methyl-4, 5-dihydropyrazolo [1-5-a]-s-triazin-5-thione (4) and 5-amino-4-substituted thiocarbamoyl-3-antipyrinylpyrazole (7a-c).

General procedure: A suspension of 3-antipyrinyl-5-aminopyrazole (**2**) (0.01 mol) in acetone 50 m*l* was added to a solution of freshly prepared isothiocyanate (0.012 mol) (prepared in situe followed literature procedure[13] in 50 m*l* acetone. The reaction mixture was refluxed for 1h. and then evaporated under reduced pressure. The solid product, so formed, was filtered off, crystallized and identified (cf. Table I and II).

3-Antipyrinyl-6-(β-arylvinyl)-1,4,7-trihydropyrazolo [4,5-e] pyrimidin-4-thione (8).

Compound **7c** (0.01 mol) was refluxed for 1h in glacial acetic acid (30 m*l*). The solvent was evaporated in vacuo and the remaining reaction mixture was poured on cold water and neutralized with NH_4OH. The solid product, so formed, was filtered off, crystallized and identified as **8** (cf. Table I and II).

2-Antipyrinyl-3-phenylazo-4,5,6,7-tetrahydropyrazolo [1,5-a] pyrimidine (10):

A solution of **9** (0.01 mol) in pyridine (20 m*l*) was treated with (0.01 mol) of methyl acrylate. The reaction mixture was refluxed for 4h and the solvent was then removed in vacuo and the remaining solid product was triturated with hot ethanol, then filtered off and crystallized (cf. Table I and II).

Compound **9** was also obtained in 50% yield by the reaction of equimolecular amounts of **10** and ethyl β-bromopropionate in pyridine by the same previous treatment.

Coupling of diazotized 2 with active hydrogen reagents.

General Procedure: A cold solution of diazotized **2** (prepared from 0.01 mol of **2** and appropriate quantities of HCl and $NaNO_2$ as previously described[14] was added to a solution of **12** (0.01 mol) or resorcinol in 50 m*l* ethanol containing 3 g of sodium acetate. The reaction mixture was stirred for 2h, the solid product was crystallized and identified as **13** and **14** respectively (Table I and II).

4-(6-Hydroxypyrazolo [5,1-c] [1,2,4] benzotriazin-2-yl)-antipyrine (15).

A solution of **14** in glacial acetic acid (30 m*l*) was

Table II. Spectroscopic data of new compounds

Compd.	IR(cm^{-1})	^{1}H-NMR (δ ppm)
4	3420 (NH); 3020 (CH_3); 1680 (antipyrinyl CO), 1640 (C = S).	2.2 (s,3H,CH_3); 2.66 (s,3H,CH_3); 3.1 (s,3H, N-CH_3); 5.9 (s,1H, pyrazole H-4); 7.1-7.55 (m,6H,C_6H_5 + NH).
7a	3480-3100 (NH,NH_2); 2980 (CH_3); 1720 (CO); 1680 (antipyrinyl CO).	2.45 (s,3H,CH_3); 3.3 (s,3H, N-CH_3); 7.3-8.0 (m,10H,2C_6H_5); 11.3 (s,1H,NH); 13 (s,1H,NH).
7b	3480, 3300-3100 (NH,NH_2); 1720(CO); 1680 (antipyrinyl CO).	1.3 (t,3H,CH_3); 2.45 (s,3H,CH_3); 3.2 (s,3H,N-CH_3); 4.25 (q,2H, CH_2); 7.1 (s,2H,NH_2); 7.3-7.6 (m,5H,C_6H_5); 11.3 (s,1H,NH); 12 (s,1H,NH); 12.5 (s,1H,NH) (NH,NH_2, protons disappeared after D_2O).
7c	3480-3100 (NH,NH_2); 1710 (CO); 1680 (antipyrinyl CO).	2.6 (s,3H,CH_3); 3.2 (s,3H,N-CH_3); 7.0 (d, J = 15Hz,1H, ylidenic proton); 7.3-7.8 (m,10H,2C_6H_5); 7.7 (d, J = 15Hz,1H ylidenic proton).
8	3420-3050 (NH); 1680 (antipyrinyl CO); 1620 (C = C).	Insufficiently soluble in commonly available ^{1}H-NMR solvents.
10	3200-3100 (NH_2); 3050, 2925 (2CH_2); 1710 (azolyl CO); 1670 (antipyrinyl CO); 1620 (C = N); 1600 (N = N).	2.32 (s,3H,CH_3); 2.82 (t,2H,CH_2); 3.6 (s,3H,N-CH_3); 4.6 (t,2H,CH_2); 7.13-7.35 (m,8H, aromatic H); 7.4-7.8 (m,2H, ortho-H of N = N-C_6H_5).
13	3500-3100 (NH,NH_2); 1690 (amide CO); 1660 (antipyrinyl CO).	Insufficiently soluble in commonly available ^{1}H-NMR solvents.
14	3400-2400 (OH,NH); 1680 (antipyrinyl CO).	2.7 (s,3H,CH_3); 3.1 (s,3H,N-CH_3); 6.55 (s,1H, pyrazole H-4); 7.4-7.75 (m,9H, aromatic + pyrazole NH).
15	3200-2200 (OH); 1660 (antipyrinyl CO).	Insufficiently soluble in commonly available ^{1}H-NMR solvents.

refluxed for 4h. The solvent was concentrated to one third its original volume, the solid product, so formed, on cooling was collected by filtration and identified as **15** (Table I and II).

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