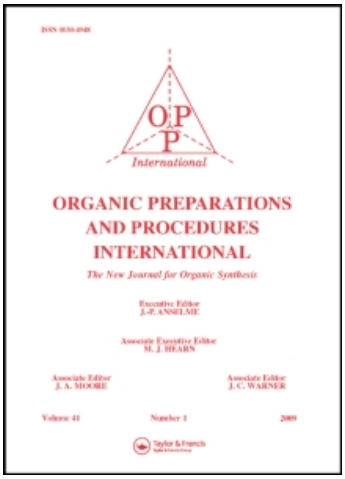

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REACTIONS WITH HETEROCYCLIC AMIDINES. SYNTHESIS OF SOME NEW AZOLYLTHIOUREA DERIVATIVES

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REACTIONS WITH HETEROCYCLIC AMIDINES. SYNTHESIS OF SOME NEW AZOLYLTHIOUREA DERIVATIVES

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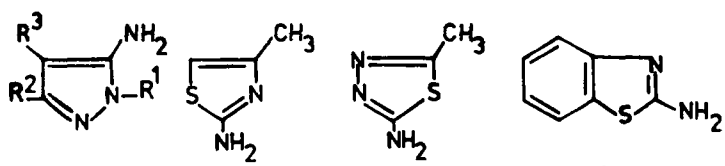
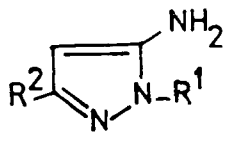
As a part of a program directed to the development of new procedures for the synthesis of azoles and fused azoles as potential CNS regulants and antimetabolites in purine biochemical reactions,[1] we became interested in the synthesis of some new derivatives of biological interest. We had previously reported the behavior of some 5-aminopyrazoles toward the action of isothiocyanates. The present paper describes the action of amino azole derivatives 1-4 toward benzoyl and ethoxycarbonyl isothiocyanates.



1 2 3 4

5-Aminopyrazole derivatives 1b-1h react with benzoyl and ethoxycarbonyl isothiocyanates to yield the corresponding azolylthiourea derivatives (7b-7h and 8b-8h) and not the isomeric 5-amino-4-thiocarbamoylpyrazole derivatives 6. The structures of the products were inferred from analytical and ^{1}H NMR data. This behavior is in contrast to the recently reported formation

of 5-amino-4-thiocarbamoyl pyrazole derivative 6a (R = C_6H_5) upon reaction of compound 1a with benzoyl isothiocyanate.[2] This observation prompted us to reinvestigate the reaction of 1a with benzoyl isothiocyanate, which afforded a product of mp. similar to that previously described; IR and ^1H NMR spectral data were also identical with those previously reported.



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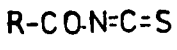
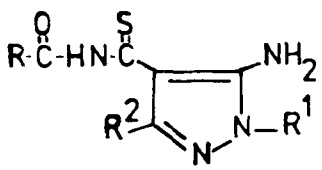


5

a) R = C_6H_5
b) R = OC_2H_5

a) R^1 = H R^2 = C_6H_5
b) R^1 = H R^2 = $C_6H_4CH_3$-p
c) R^1 = H R^2 = $C_6H_4OCH_3$-p
d) R^1 = H R^2 = C_6H_4Cl-p
e) R^1 = C_6H_5 R^2 = $C_6H_4CH_3$-p
f) R^1 = C_6H_5 R^2 = $C_6H_4OCH_3$-p
g) R^1 = C_6H_5 R^2 = C_6H_4Cl-p
h) R^1 = $C_6H_4NO_2$-p R^2 = C_6H_5



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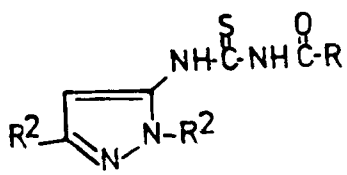
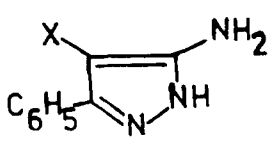


7a-h R = C_6H_5
8a-h R = OC_2H_5



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a) X = Br b) X = SH

However, the peak at δ 8.18 in the ^1H NMR spectrum assigned to amino function seemed to be most likely for two different NH functions. ^{13}C NMR revealed that the pyrazole C-4 is coupled with a proton, thus excluding the possibility that the reaction

product is compound 6. Thus it is believed that the product previously described as 5-amino-4-thiocarbamoylpyrazole derivative 6a (R = C_6H_5) is really the thiourea derivative 7a. This assignment was further confirmed by the investigation of the chemical behavior of 7a. Bromination of 7a afforded the highly unstable 4-bromo derivative 10, which could be readily cyclized into the pyrazolo[3,4-d]thiazole derivative 11 upon heating in polar solvents.

In contrast to the observed formation of azolyl thioureas on treatment of 1 with isothiocyanates 5a and 5b, the 4-mercapto derivative 9b reacted with benzoyl isothiocyanate to yield directly the pyrazolo[3,4-d]thiazole derivative 11, which was identical with that previously reported.[3] The formation of the latter may be assumed to proceed either via route (a) or route (b) (Chart 1). It seemed most likely that the reaction proceeds via route (a) as 5-amino-4-bromo-3-phenylpyrazole (9a) and 5-amino-4-mercapto-3-phenylpyrazole (9b) afforded the same product on reaction with benzoyl isothiocyanate. Moreover, cyclization via route (b) would lead to the formation of some of the mercapto derivatives which could not be detected.

Similarly compound 12 reacted with benzoyl and ethoxycarbonyl isothiocyanate to afford the same and only product, of molecular formula $C_{16}H_{12}N_4S$. Two possible structures 13 and 14 were considered. Structure 13 was established for the reaction product by the results of the IR spectrum which revealed absorption bands characteristic for thiocarbonyl and NH groups (Chart 1 & 2). 2-Amino-4-methylthiazole (2) reacted with benzoyl isothiocyanate to afford the acyclic thiazol-2-yl deriva-

tive 15. Compound 15 could be smoothly cyclized into thiazolo-[2,3-a]-s-triazine derivative 16 upon treatment with sodium ethoxide.

In contrast to the behavior of 2, compound 3 reacted with benzoyl isothiocyanate to yield the benzoylamino derivative 17

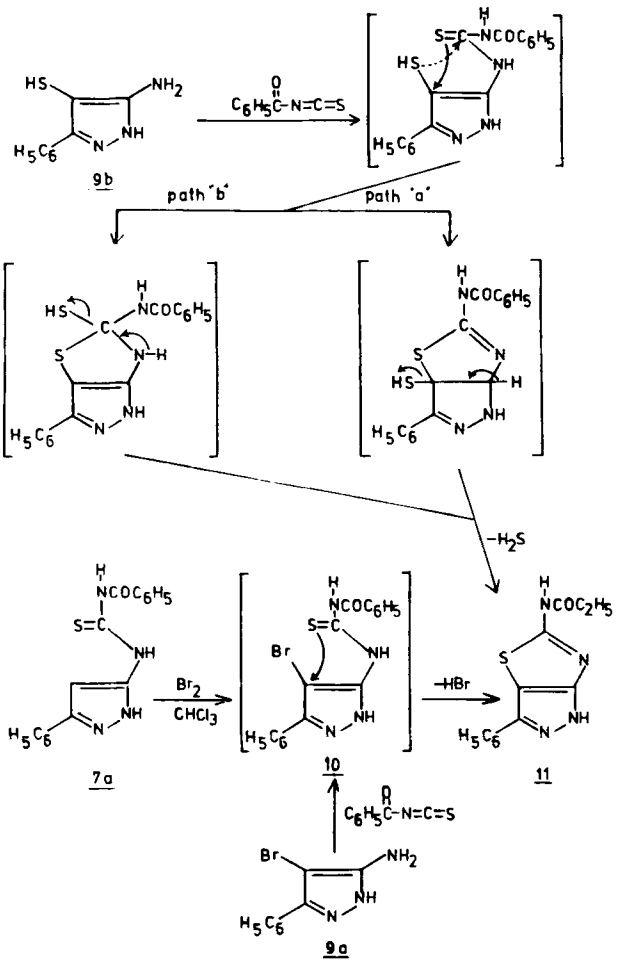

Chart 1

as the only isolable reaction product.[4] Compound 3 also reacted with ethoxycarbonyl isothiocyanate to yield the expected

thiourea derivative 18 which could be readily cyclized into triazolyl aminothiaziazole derivative 19 upon treatment with hydrazine. Whereas compound 4 reacted with benzoyl isothiocyanate in refluxing acetone to yield the expected thiourea derivative 20, it reacted with ethoxycarbonyl isothiocyanate

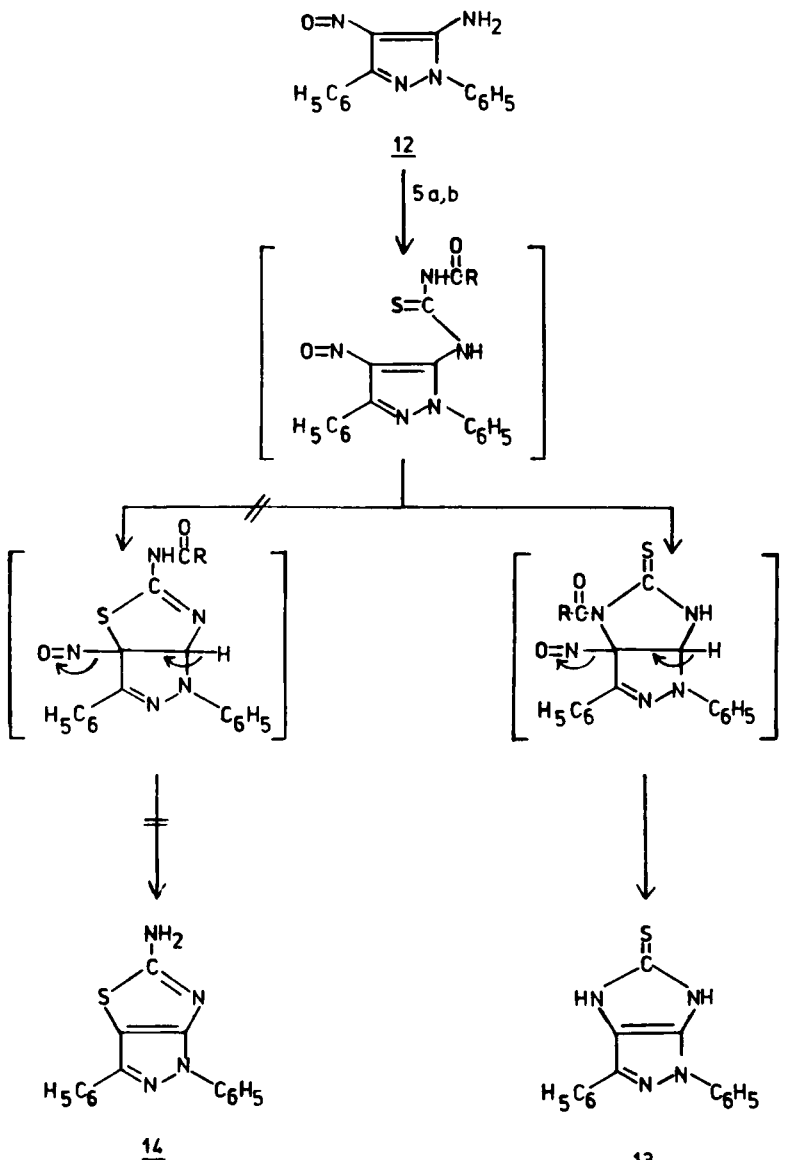

Chart 2

to yield ethoxycarbonylamino derivative 21 as the major product. It seems to us that most likely compounds 17 and 21 were formed via rearrangement of the initially formed ring N-thiocarbamoylated adduct as illustrated in Chart 3.

The reaction of 4-amino-1,5-dimethyl-2-phenylpyrazol 3-(2H)-one (22) with benzoyl and ethoxycarbonyl isothiocyanate are straight forward and affords the expected thiourea derivatives 23. The structure of compounds 23a and 23b are based on correct elemental analyses and spectroscopic data.

EXPERIMENTAL SECTION

All melting points are uncorrected. IR spectra were recorded (KBr) on pye-Unicam Sp-1100 spectrophotometer. ^{1}H NMR spectra were recorded on a Varian A-60 spectrometer using TMS as internal standard and chemical shifts are expressed as δ ppm. Analytical data were obtained from analytical data unit as Cairo University.

Reaction of Aminoazoles (1-4,8,11,12 and 22) with Isothiocyanates (5). General Procedure.- To a solution of 5 (prepared from 0.12 mole of NH_4SCN and the appropriate quantity of either benzoyl chloride or ethyl chloroformate as previously described[5]), 0.1 mol of the aminoazole in acetone (50 ml) was added. The reaction mixture was refluxed for 3 hrs and then evaporated in vacuo. The remaining product was washed with water several times, crystallized from the appropriate solvent (Tables 1 and 2).

Reaction of 18 with Hydrazine Hydrate.- A mixture of compound 18 (1 g.) and hydrazine hydrate (2 ml) was refluxed 2 hrs. in ethanol (20 ml). The reaction mixture was then allowed to cool and triturated with water. The solid product was crystallized from ethanol. Compound 19 was obtained in 60% yield as pale

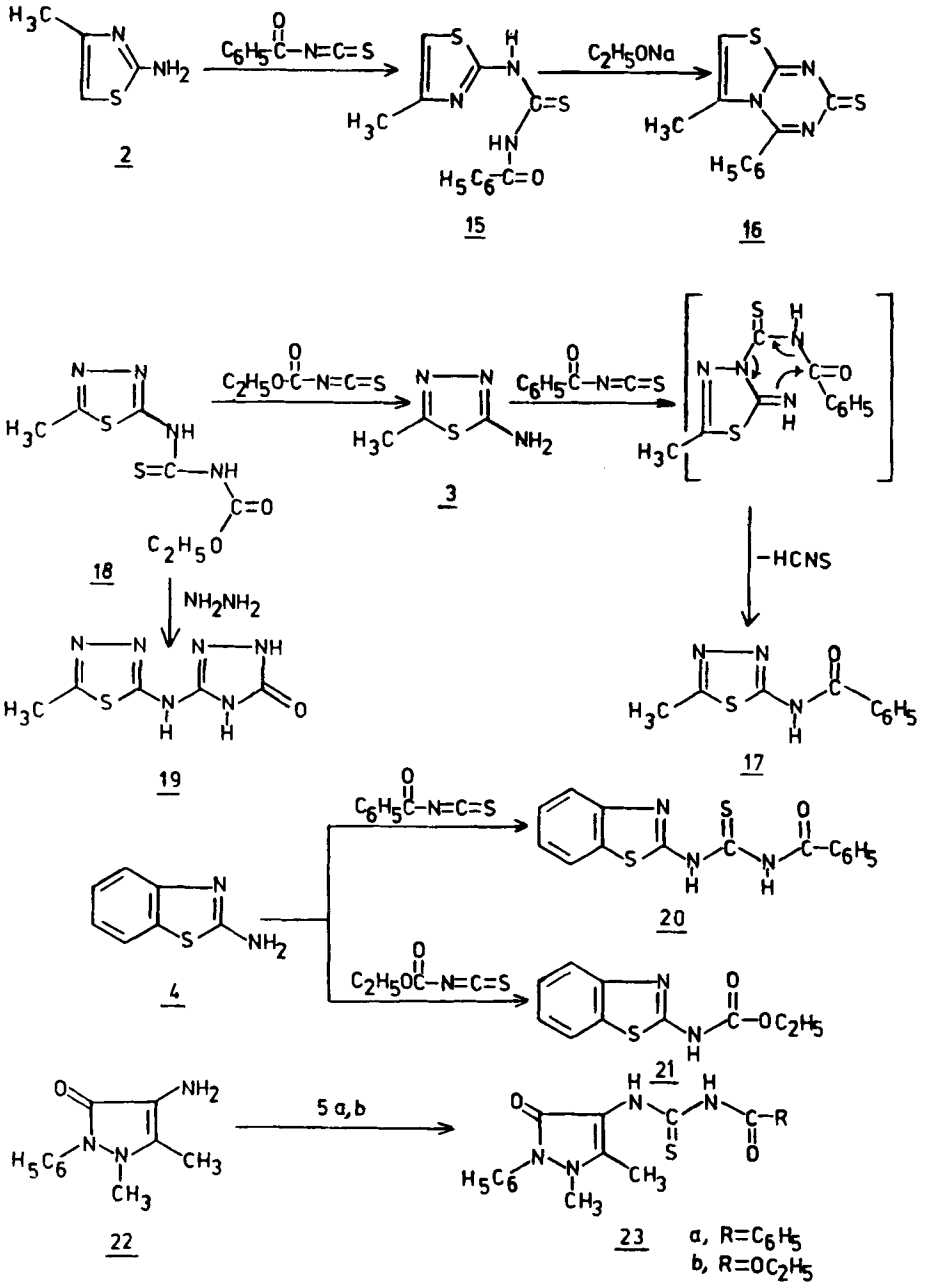

Chart 3

Table 1. List of New Thiourea Derivatives

Compd. No.	Crystal Solvent	mp. (C°)	Found/Calcd. C	Elemental Analysis H	N	S
7a	EtOH/Dioxan	242	63.2/63.4	4.3/4.3	17.1/17.4	9.8/9.9
7b	EtOH/DME	208	64.0/64.3	4.9/4.8	16.4/16.6	9.4/9.2
7c	EtOH/DMF	210	61.7/61.4	4.6/4.5	15.7/15.9	8.9/9.1
7d	EtOH/DMF	190	56.8/57.2	4.1/3.6	15.5/15.7	9.1/8.9
7e	EtOH	188	69.6/69.9	4.8/4.9	13.8/13.6	7.6/7.8
7f	EtOH	185	66.9/67.3	4.6/4.7	13.4/13.1	7.7/17.5
7g	EtOH	183	63.8/63.8	4.2/3.9	12.8/12.9	7.1/7.3
7h	EtOH/DMF	202	62.0/62.3	4.0/3.8	15.6/15.8	7.1/7.2
8a	EtOH	170	53.6/53.8	4.7/4.8	19.1/19.3	10.9/11.0
8b	EtOH	164	55.1/55.3	5.5/5.3	18.3/18.4	10.6/10.5
8c	EtOH	150	52.2/52.5	5.1/5.0	17.4/17.5	9.8/10.0
8d	EtOH	182	48.1/48.0	4.3/4.0	17.1/17.2	9.6/ 9.8
8e	EtOH	165	63.3/63.2	5.5/5.3	14.5/14.7	8.3/8.4
8f	EtOH	146	59.7/59.3	5.2/4.9	13.5/13.8	7.8/7.9
8g	EtOH	145	57.1/56.9	4.5/4.2	13.7/13.9	7.8/7.9
8h	EtOH	192	55.8/55.5	4.0/4.1	16.9/17.0	7.9/7.8
13	EtOH	135	65.5/65.7	4.1/4.1	18.9/19.1	10.7/10.9
15	EtOH	142	51.7/52.0	4.2/4.5	16.9/17.1	23.0/23.1
18	EtOH	189	33.8/34.1	4.4/4.1	22.5/22.7	25.8/26.1
20	EtOH/DMF	193	57.6/57.5	3.7/3.5	13.4/13.4	20.2/20.4
23a	EtOH/DMF	201	62.1/61.9	5.1/5.4	15.1/15.2	8.7/8.6
23b	EtOH	190	53.5/53.5	5.9/5.9	16.8/16.7	9.3/9.5

Table 2 . List of IR Data

Compd. No.	IR (K Br) cm^{-1}		Compd. No.	IR (K br) cm^{-1}	
7a	1670,3260-3380	(CO,NH)	8d	1710,3100-3250	(ester,NH)
7b	1675,3060-3180	(CO,NH)	8e	1715,3000-3200	(ester,NH)
7c	1670,3150-3370	(CO,NH)	8f	1715,3120-3280	(ester,NH)
7d	1665,3100-3350	(CO,NH)	8g	1715,3080-3200	(ester,NH)
7e	1662,3100-3350	(CO,NH)	8h	1730,3000-3220	(ester,NH)
7f	1672,3080-3300	(CO,NH)	13	1150,1590	(C=S, C=N)
7g	1665,3150-3310	(CO,NH)	15	1675,3100-3380	(CO,NH)
7h	1668,3100-3400	(CO,NH)	18	1721,2900-3000	(ester,NH)
8a	1735,3100-3300	(ester,NH)	20	1677,3100-3340	(CO,NH)
8b	1735,3000-3200	(ester,NH)	23a	1665,3050-3280	(CO,NH)
8c	1740,3100-3250	(ester,NH)	23b	1660,1720-3250	(CO,ester, NH)

Table 3. ^{1}H nmr Spectral Data

Compound Number	^{1}H NMR Peak (ppm)
8e	1.5 (t, 3H, CH_3), 2.65 (S, 3H, CH_3); 4.4 (q, 2H, CH_2), 7.23 (S, 1H, pyrazole C-4), 7.35-7.7 (m, 9H, aromatic), 12.0 (2S, 2H, 2 NH).
8f	1.6 (t, 3H, CH_3), 4.0 (S, 3H, CH_3O-), 4.4 (q, 2H, CH_2), 7.1 (S, 1H, pyrazole C-4), 7.2-8.0 (m, 9H, aromatic), 11.8 (25, 2H, 2NH).
8g	1.2 (t, 3H, CH_3), 4.18 (q, 2H, CH_2), 7.08 (S, 1H, pyrazole C-4), 7.3-7.9 (m, 9H, aromatic), 12.1 (2S, 2H, 2NH).
8h	1.29 (t, 3H, CH_2), 4.28 (q, 2H, CH_2), 7.15 (s, 1H, pyrazole C-4), 7.45-8.55 (m, 9H, aromatic), 11.6-11.8 (2S, 2H, 2NH).
18	1.7 (t, 3H, CH_3), 2.65 (S, 3H, CH_3), 4.2 (q, 2H, CH_2).
23a	2.16 (S, 3H, CH_3), 3.16 (S, 3H, N-CH_3), 7.4-7.66 (m, 1 OH, aromatic) and 7.91-8.08 (S, 2H, 2NH).
23b	1.2 (t, 3H, CH_3), 3.1 (S, 3H, CH_3), 3.23 (S, 3H, N-$CH)_3$, 4.15 (q, 2H, CH_2), 7.3 (S, 5H, C_6H_5), 11.3 (S, 1H, NH), 12.2 (S, 1H, NH).

yellow crystals, mp. > 260°.

IR: 1750 cm^{-1} (CO), 3300 cm^{-1} (NH).

Anal. Calcd. for $C_6H_6N_6OS$: C, 30.3; H, 3.0; N, 42.4; S, 16.1

Found: C, 30.2; H, 2.9; N, 42.1; S, 16.0

Reaction of 15 with 5% Sodium Ethoxide.- A solution of sodium ethoxide (prepared from sodium metal and the appropriate quantity of ethanol) was treated with compound 15. The reaction mixture was then refluxed for 3 hrs and evaporated. The remaining product was triturated with water and neutralized with dil. hydrochloric acid. The solid product was crystallized from ethanol/DMF mixture. Compound 16 was obtained in 40%

yield as colorless crystals, mp. 205°.

IR: 1500 cm^{-1} (C=N), 2890 cm^{-1} (CH).

Anal. Calcd. for $C_{12}H_9N_3S_2$: C, 55.5; H, 3.4; N, 16.2; S, 24.6

Found: C, 55.2; H, 3.4; N, 16.1; S, 24.3

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