Synthesis of some New Δ^2-Pyrazolines, Δ^2-Isoxazolines and 2-Thiopyrimidine Derivatives likely to Possess Antibacterial Activity

B.E. BAYOUMY, S. EL-BAHIE, M. EL-MOBAYED AND G.ABD EL-LATIF
Chemistry Department, Faculty of Science, Zagazig University, Zagazig, Egypt.

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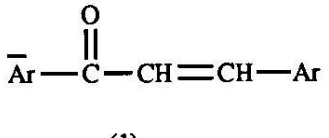
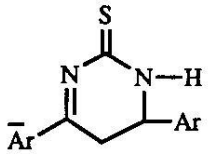
Summary: Benzalacetophenone derivatives (1) were allowed to react with thiourea to give tetrahydropyrimidine thione (2) which by reaction with acyl hydrazine or p-chlorobenzoyl hydrazine gave triazolopyrimidines (4) and (5) respectively. Compounds (1) were reacted with hydrazylamine hydrochloride or hydrazines to give the corresponding Δ^2-isoxazolines (8) and Δ^2-pyrazolines (9) respectively. The constitution of the novel compounds were proved by microanalysis, IR and mass spectral data.

Recently we have reported the synthesis of benzalacetophenone derivatives [1]. The importance of pyrazolines, isoxazolines and pyrimidine thiones in different biological and industrial aspects have led us to synthesize such new molecules [2,3].

In continuation of our studies on α,β-unsaturated carbonyl compounds [4,5], we repoet herein the synthesis of tetrahydropyrimidine thiones (2) *via* interaction of benzalacetophenone derivatives (1) with thiourea in the presence of sodium hydroxide.



(1)



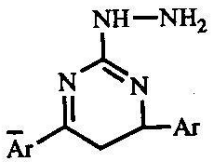
(2)

a, Ar = C_6H_4-Cl-P. ; b Ar = C_6H_4-NO_2-p.
; c, Ar = $C_6H_3(O_2CH_2)$-3,4
$\bar{Ar}$ = $C_6H_3(CH_3)_2$-2,5.

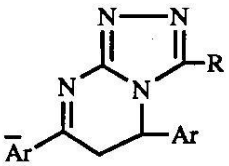
The structure of compound (2) was confirmed by their correct analytical data and IR spectra which showed strong absorption bands in the regions 1400-1450 cm^{-1} ($\nu C=S$) and 3250-3300 cm^{-1} (νNH).

The mass spectra of compound (2c) showed a molecular ion peak at m/z 338.

Compound (2c) was submitted to react with hydrazine hydrate in boiling ethanol to afford the hydrazinopyrimidine derivative (3). The IR spectrum of compound (3) showed absorption bands between 1595-1610 cm^{-1} ($\nu C=N$) and at 3240-3310 cm^{-1} (νNH).



(3)



(4)

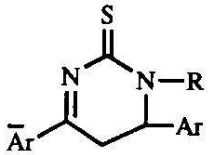
$\bar{Ar}$ = $C_6H_3(CH_3)_2$-2,5.
Ar = $C_6H_3(CH_2O_2)$-3,4.
R, a = CH_3; b = CC_6H_4-Cl-p.

Treatment of compound (3) with boiling acetic acid gave the triazolopyrimidine derivative (4a). Structure of compound (4a) was proved via its unambigueous synthesis by interaction of the pyrimidinethione (2) with acetylhydrazine in butanol.

On a similar basis, compound (2c) was allowed to react with p-chlorobenzoylhydrazine in

ethanol to give the triazolopyrimidine derivative (**4b**). The IR spectra of (**4a,b**) showed bands at 1610- 1600 cm^{-1} due to ($\nu C=N$).

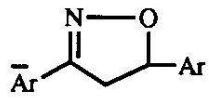
As a point of interest (**2a-c**) reacted with phenyl isocyanate in benzene and/or secondary amines (diethylamine, piperidine or morpholine) in aqueous formaldehyde and boiling ethanol to yield the pyrimidinethione derivatives (**5a-c**) and the Mannich base derivatives (**5c-f**). The structure of Mannich (**5c-f**) were inferred from their correct analytical data and their IR spectra, which exhibit strong absorption bands in the region 1430-1400 cm^{-1} ($\nu C=S$) and at 3300-3200 cm^{-1} (νNH).



(5)

	$\bar{Ar}$	Ar	R
a	$C_6H_3(CH_3)_2$-2,5	C_6H_4-Cl-p.	CONHPh
b	"	$C_6H_3(CH_2O_2)$-3,4.	CONHPh
c	"	C_6H_4-Cl-p.	$CH_2\overset{+}{N}H(C_2H_5)_2Cl^-$
d	"	"	$CH_2\overset{+}{N}H(C_4H_8O)Cl^-$
e	"	$C_6H_3(CH_2O_2)$-3,4	"
f	"	"	$CH_2\overset{+}{N}H(C_4H_{10})Cl^-$

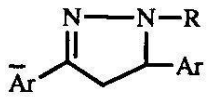
On the other hand, compound (**1a-c**) were condensed with hydroxylamine hydrochloride in boiling pyridine to product Δ^2-isoxazoline derivatives (**6**). The structure of (**6**) was inferred from their correct analytical data and their IR spectra which showed a strong absorption bands in the region 1630-1650 cm^{-1} attributable to ($\nu C=N$).



(6)

	$\bar{Ar}$	Ar
a.	$C_6H_3(CH_3)_2$-2,5	C_6H_4Cl-p.
b	,"	C_6H_4-NO_2-p.
c.	"	$C_6H_3(CH_2O_2)$-3,4.

Moreover, reaction of compounds (**1a-c**) with hydrazine hydrate and/or phenylhydrazine in boiling ethanol yielded the corresponding hydrazones which rearranged immediately to the isomericΔ^2-pyrazoline derivatives (**7**). The structure of the pyrazolines (**7**) from the formation of the colour test [6] for pyrazoline, their analytical data and their IR spectra which showed bands at 1640 cm^{-1} ($\nu C=N$) [7] and at 3300-3340 cm^{-1} attributable to (νNH). Also, the IR spectra for compouns (**7d-f**) showed strong absorption bands in the region 1610-1630 cm^{-1} ($\nu C=N$) and lacking any absorption for (νNH).

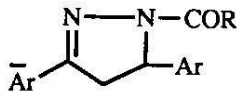


(7)

	$\bar{Ar}$	Ar	R
a	$C_6H_3(CH_3)_2$-2,5.	C_6H_4-Cl-p.	H
b	"	C_6H_4-NO_2-p.	H
c	"	$C_6H_3(CH_2O_2)$-3,4	H
d	"	C_6H_4-Cl-p.	C_6H_5
e	"	C_6H_4-NO_2-p.	C_6H_5
f	"	$C_6H_3(CH_2O_2)$-3,4	C_6H_5

Further, compounds (**1a-c**) were allowed to react with acylhydrazines in boiling ethanol gave N-acylpyrazoline (**8**).

The structure of compound (**8**) were proved by their correct analytical data, IR spectra which showed strong absorption bands in the region 1660-1640 cm^{-1} and at 1620-1630 cm^{-1} attributable to ($\nu C=O$) of sec. amide, and ($\nu C=N$). Chemically by boiling compound (**7a**) in gl. acetic acid gave compound (**8a**). Also the mass spectra of (**8c**) showed molecular ion peak at $M^+ = 336$.



(8)

	$\bar{Ar}$	Ar	R
a	$C_6H_3(CH_3)_2$-2,5	C_6H_4-Cl-p.	CH_3
b	"	C_6H_4-NO_2-p.	CH_3
c	"	$C_6H_3(CH_2O_2)$-3,4	CH_3
d	"	C_6H_4-Cl-p.	C_6H_5
e	"	C_6H_4-NO_2-p.	C_6H_5
f	"	$C_6H_3(CH_2O_2)$-3,4	C_6H_5
g	"	C_6H_4-Cl-p.	C_6H_4-Cl-p.
h	"	C_6H_4-NO_2-p.	C_6H_4-Cl-p.
i	"	$C_6H_3(CH_2O_2)$-3,4	C_6H_4-Cl-p.

Table-1: Physical and analytical data of synthetic compounds.

Com-pound	m.p.°C	Solvent	M.Formula M.Wt.	Analysis % Found/ Calc.			
				C	H	N	S
2a	180	Methanol	$C_{18}H_{17}ClN_2S$	65.71	5.68	8.51	9.63
			382.5	65.75	5.17	8.52	9.71
2b	170	Methanol	$C_{18}H_{17}N_3O_2S$	63.86	482	12.30	9.36
			339	63.12	4.98	12.31	9.38
2c	165	Ethanol	$C_{19}H_{18}N_2O_2S$	67.39	5.25	8.17	9.35
			338	67.45	5.32	8.28	9.46
3	172	Ethanol	$C_{19}H_{20}N_4O_2$	67.85	5.86	16.28	
			336	67.85	5.95	16.66	
4a	185	Methanol	$C_{21}H_{20}N_4O_2$	69.87	5.45	15.42	
			360	70.00	5.55	15.55	
4b	295	Methanol	$C_{26}H_{21}ClN_4O_2$	63.25	4.49	12.33	
			456.5	63.34	4.60	12.26	
5a	201	Benzene	$C_{25}H_{22}ClN_3OS$	66.75	4.86	9.27	7.97
			447.5	67.03	4.91	9.38	7.75
5b	220	Benzene	$C_{26}H_{23}N_3O_3S$	68.15	4.79	9.07	6.54
			457	68.27	4.99	9.19	7.00
5c	204	Ethanol	$C_{23}H_{29}Cl_2N_3S$	61.33	6.38	9.34	7.07
			524	61.46	6.45	9.35	7.12
5d	222	Ethanol	$C_{23}H_{17}Cl_2N_3OS$	60.91	3.66	9.21	6.55
			470	60.92	3.75	9.27	7.06
5e	211	Methanol	$C_{24}H_{23}ClN_3O_2S$	62.91	6.68	9.21	6.55
			452.5	62.95	6.12	9.18	6.99
5f	208	Methanol	$C_{25}H_{30}ClN_3OS$	65.76	6.53	9.17	6.89
			455.5	65.86	6.58	9.22	7.02
6a	205	Benzene	$C_{17}H_{16}ClNO$	71.39	5.55	4.87	
			285.5	71.45	5.60	4.90	
6b	185	Benzene	$C_{17}H_{16}N_2O_3$	68.83	5.36	9.42	
			296	68.91	5.40	9.45	
6c	164	Methanol	$C_{18}H_{17}NO_3$	73.41	5.71	4.65	
			295	73.22	5.76	4.74	
7a	180	Methanol	$C_{17}H_{17}ClN_2$	71.65	5.85	9.76	
			284.5	71.70	5.95	9.84	
7b	136	Methanol	$C_{17}H_{17}N_3O_2$	71.33	5.26	13.07	
			295	71.47	5.32	13.16	
7c	231	Ethanol	$C_{18}H_{18}N_2O_2n$	73.29	6.08	9.48	
			294	73.46	6.12	9.52	
7d	137	Methanol	$C_{23}H_{22}ClN_2$	76.22	5.76	7.68	
			361.5	76.34	6.08	7.74	
7e	148	Methanol	$C_{23}H_{21}N_3O_2$	74.28	5.61	11.26	
			371	74.39	5.66	11.32	
7f	166	Methanol	$C_{24}H_{22}N_2O_3$	77.69	5.81	7.53	
			370	77.83	5.94	7.56	
8a	196	Methanol	$C_{19}H_{19}ClN_2O$	69.76	5.80	8.42	
			326.5	69.83	5.81	8.57	
8b	232	Methanol	$C_{19}H_{19}N_3O_3$	67.56	5.61	12.35	
			337	67.62	5.63	12.46	
8c	186	Ethanol	$C_{20}H_{20}N_2O_3$	71.36	5.87	8.31	

Table-1: contd.

Compound	m.p.°C	Solvent	M.Formula M.Wt.	Analysis % Found/ Calc. C	H	N	S
			336	71.42	5.95	8.33	
8d	150	Methanol	$C_{24}H_{21}ClN_2O$	79.41	5.67	7.69	
			388.5	79.44	5.79	7.72	
8e	236	Methanol	$C_{24}H_{21}N_3O_3$	72.07	5.18	10.50	
			399	72.18	5.26	10.52	
8f	230	Ethanol	$C_{25}H_{22}N_2O_3$	75.26	5.48	6.75	
			398	75.37	5.52	7.03	
8g	293	Ethanol	$C_{24}H_{23}Cl_2N_2O$	67.55	5.35	6.57	
			426	67.60	5.39	6.57	
8h	316	Ethanol	$C_{24}H_{23}ClN_3O_3$	65.92	5.17	9.57	
			436.5	65.97	5.26	9.62	
8i	297	Methanol	$C_{25}H_{24}ClN_2O_3$	68.69	5.42	6.40	
			435.5	68.83	5.51	6.42	

Experimental

All melting points reported are uncorrected. IR spectra (KBr) were run on a Unicam SP-200 G infrared spectrophotometer. The mass spectra were run at 70 eV on a Varian MAT 711 mass spectrometer.

Synthesis of tetrahydropyrimidine thione derivative (2)

A mixture of compound (**1a-c**) (0.01 mole), thiourea (0.01 mole) and potassium hydroxide (1 g. in 30 ml absolute ethanol was refluxed for 6 hrs. On concentration and cooling the separated products were filtered and crystallized from proper solvent to give tetrahydropyrimidine thiones (**2a-c**).

Synthesis of hydrazinopyrimidine derivatives (3)

A mixture of compound (**2c**) (0.01 mole) and hydrazine hydrate (0.01 mole) in 20 ml absolute ethanol was heated under reflux for 5 hrs. The reaction mixture was cooled and the precipitate product was collected and recrystallized to give compound (3) (Table 1).

Synthesis of triazolopyrimidine derivative (4a-b)

Method A

Compound (3) (0.01 mole) was heated under reflux in 15 ml acetic acid for 4 hrs. The reaction mixture was then cooled and the precipitated product was collected and recrystallized from suitable solvent to yield (**4a,b**)

Method B

A mixture of compound (2c) (0.01 mole) and acetylhydrazine (0.01 mole) in 20 ml absolute ethanol was refluxed for 6 hrs. The reaction mixture was cooled and the precipitate product was collected and recrystallized to give (**4a,b**) (Table 1).

Synthesis of pyrimidine thione derivatives (5a,b)

A solution of (**2a,b**) (0.01 mole) and phenyl isocyanate (0.01 mole) in 20 ml dry benzene was heated under reflux for one hour. The reaction mixture was then cooled and the white precipitate crystallized from suitable solvent to give (**5a,b**)

Synthesis of Mannich bases (5c-f)

A mixture of (**2a,b**) (0.01 mole), formaldehyde (0.01 mole) and secondary amine namely diethylamine, piperidine and/or morpholine (0.01 mole) in 30 ml ethanol was heated uneder reflux for 3 hrs. The reaction mixture was concentrated and cooled. The precipitate was collected and recrystallized from the proper solvent to give (**5c-f**) (Table 1).

Synthesis of Δ^2-isoxazoline derivatives (6a-c)

A mixture of (**1a-c**) (0.01 mole) and hydroxylamine hydrochloride (0.02 mole) in 30 ml ethanol was refluxed for 6 hrs. The reaction mixture was colled and poured into ice-cold water. The precipitate product was collected and recrystallized from suitable solvent to from the Δ^2-isoxazoline (6a-c) (Table-1).

Synthesis of Δ^2-pyrazoline (7a-f) and N- acyl-pyrazoline (8a-i)

A mixture of (**1a-c**) (0.01 mole) and hydrazine hydrate, phenylhydrazine and/or acylhydrazine (0.015 mole) in 30 ml ethanol was heated under reflux for 6 hrs. The precipitate obtained after cooling was crystallized from proper solvent to yield the pyrazoline (**7a-f**) and the N-acylpyrazoline (**8a-i**) (Table 1).

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