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New Synthesis of 2-Substituted Imidazo[2,1-b]thiazoles and their Antimicrobial Activities

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Abstract 4,5-Diphenyl-2-mercaptoimidazole (I) was reacted with hydrazidoyl halides IIa-d to give the S-alkyl derivatives IIIa-d. Cyclization of IIIa-d afforded imidazo[2,1-b]-thiazole derivatives VIa,b and VII. Treatment of I with α-chloroethylacetoacetate (IV) gave ethyl 2-(4,5-diphenyl-2-imidazolinylthio)-3-keto-butyrate (V). Compound V coupled with benzenediazonium chloride to give the corresponding phenylhydrazo compound IIId. On heating V with polyphosphoric acid, cyclization took place and 2-acetyl-5,6-diphenyl-imidazo[2,1-b]thiazol-3-one (VIII) was obtained. The compound VIII was condensed with aromatic aldehydes to yield the cinnamoyl derivatives IXa,b. The antimicrobial activities of compounds IIIa-d, V, VIa, VII were examined.

Keywords 4,5-Diphenyl-2-mercaptoimidazole, α-chloroethylacetoacetate, hydrazidoyl halides, antimicrobial activities.

A number of 2 (3H)-imidazole thiones have found an application in clinical medicine due to their pronounced antithyroid activity[1,2]. On the other hand thiazole compounds possess considerable fungicidal action[3], antibacterial activity[4-6] and anticonvalusant activity[7-9]. This work was done with the aim of synthesis of several new condensed heterocyclic compounds containing both imidazole and thiazole moieties to study their antimicrobial activity.

Chemistry

In this work, it is found that reaction of 4,5-diphenyl-2-mercaptoimidazole (I) with hydrazidoyl halides, IIa-d is a logic and easy way for the synthesis of imidazothiazole derivatives of potential biological and medicinal activities. Thus it has been found that I reacted with each of IIa-d to yield 1-(4,5-diphenyl imidazol-2-yl-thio)-1-phenylhydrazone glyoxal derivatives, IIIa-d. The structures, III were supported by elemental analyses and spectral data. The IR spectrum of IIId, as an example, showed bands at 1720 cm^{-1} (C=O) and 3380, 3260 cm^{-1} (2NH) and its UV spectrum showed a strong maximum at 430 nm which is in agreement with the hydrazone structure[10]. Compound IIId could be synthesized via another route by the reaction of I with α-chloroethylacetoacetate (IV) to give ethyl 2-(4,5-diphenyl-2-imidazolylinylthio)-3-keto-butyrate (V). Japp-Klingemann reaction of V with benzenediazonium chloride in presence of ethanol and sodium acetate afforded IIId.

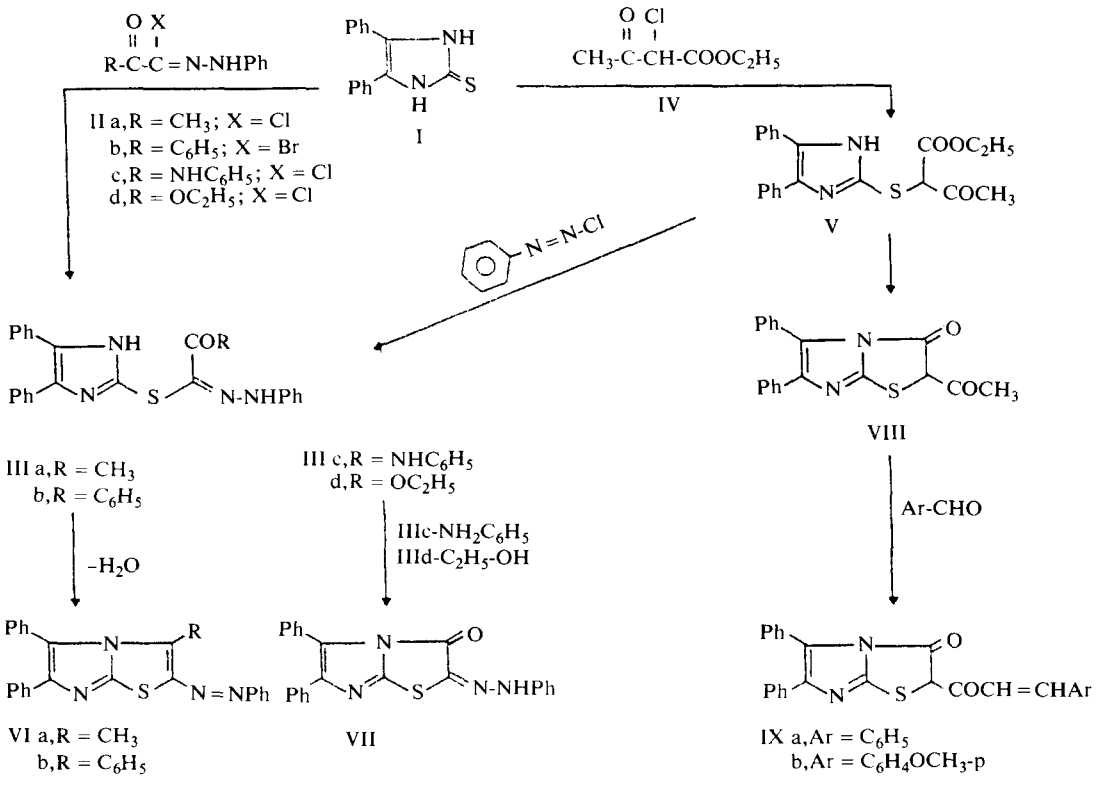
When compounds IIIa,b were heated separated with polyphosphoric acid, 2-phenylazo imidazo-[2, 1-b]thiazole derivatives, VIa,b were obtained. On the other hand, IIIc was converted into 5,6-diphenyl-2-phenylhydrazono-3-oxoimidazo[2,1-b]-thiazole (VII) via elimination of $PhNH_2$ by refluxing its ethanolic solution in presence of triethylamine solution. The same product VII was also obtained from IIId via loss of C_2H_5OH.

When compound V was heated with polyphosphoric acid, 2-acetyl-5, 6-diphenyl imidazo[2,1-b]-thiazol-3-one (VIII) was obtained. Compound VIII reacted with aromatic aldehydes at 140 °C in presence of catalytic amount of piperidine to give 2-cinnamoyl derivatives IXa,b

Antimicrobial Activity

Table III shows the effect of compounds IIIa-d, V, VIa, VII and VIII on the micro-organisms tested. All the compounds were inactive against *Fusarium oxysporum*.

It is of interest to note that the most active compound is VII followed by compounds VIa and VIII which are slightly less active. Compounds IIIa-d



show a moderate activity presumably due to the presence of the phenylhydrazo group (=N-NHPh). On the other hand introduction of a phenyl group instead of a methyl group as in IIIb decreased the activity of IIIa. The activity increased after cyclization of IIIa,c to VIa and VII respectively, thus indicating that the presence of the combined imidazothiazole ring together with phenylhydrazo group gives maximum activity.

EXPERIMENTAL METHODS

All m.p. 's are uncorrected. The IR spectra were recorded (KBr) on a Pye Unicam SP-1000 spectrophotometer. ^1H NMR were obtained on a Varian EM-390-90MHz spectrometer with $SiMe_4$ as internal standard. Elemental analyses were done by the microanalytical laboratory at Cairo University.

General synthetic procedure for IIIc,d and V

A solution of 4,5-diphenyl-2-mercaptoimidazole I(0.01 mole) in ethanol (30 m*l*) containing sodium ethoxide (0.011 mole) was treated with each of hydrazidoyl chlorid derivatives (IIc,d)[11] and *α*-chloroethylacetoacetate (IV) (0.01 mole) and the whole was stirred at room temperature for 3 hours. The reaction mixture was left overnight and the solid obtained was filtered off washed with water and then crystallised from ethanol to give a yellow crystal of IIIc,d and a pale yellow crystal of V.

Prparation of IIIa,b

A solution of 4,5-diphenyl-2-mercaptoimidazole (I) (0.01 mole) and each of hydrazidoyl halides derivatives (IIa,b)[11,12] (0.011 mole) in absolute ethanol (30 m*l*) and triethylamine (3 drops) was heated to boiling under reflux for one hour, then cooled. The solid products obtained were filtered, and crystallized from ethanol as yelllow crystals of IIIa,b.

Synthesis of Imidazo[2,1-b]thiazole derivatives, VIa,b and VIII

General procedure:

A mixture of each of 1 g of IIIa,b or V, and 5 g of polyphosphoric acid (prepared by dissolving 2.5g of phosphorous pentoxide in 2.5 m*l* of ortho-phosphoric acid) was heated at 100 °C for 1 hr and then at 120° for 20 minutes. After cooling, the reaction

Table I. Synthetic data of S-alkyl derivatives (IIIa-d and V), imidazo[2,1-b]thiazole derivatives (VIa,b, VII and VIII) and 2-cinnamoyl derivatives (IXa,b)

Compound	M.P (°C)	Yield (%)	Formula	Elemental Analysis (%) Calcd.				Found			
				C	H	N	S	C	H	N	S
IIIa	205	78	$C_{24}H_{20}N_4OS$	69.90	4.85	13.59	7.76	70.2	4.6	13.8	7.9
IIIb	186	75	$C_{29}H_{22}N_4OS$	73.41	4.64	11.81	6.75	73.6	4.8	12.0	6.6
IIIc	175	83	$C_{29}H_{23}N_5OS$	71.60	4.70	14.31	6.54	71.5	4.9	14.1	6.4
IIId	196-7	85	$C_{25}H_{22}N_4O_2S$	67.87	4.97	12.66	7.23	68.1	5.2	12.5	7.5
V	182	80	$C_{21}H_{20}N_2O_3S$	66.31	5.26	7.36	8.42	66.1	5.5	7.5	8.2
VIa	240	70	$C_{24}H_{18}N_4S$	73.09	4.56	14.21	8.12	73.3	4.3	14.5	8.3
VIb	210-12	68	$C_{29}H_{20}N_4S$	76.31	4.38	12.28	7.01	76.5	4.5	12.1	7.2
VII	260	72	$C_{23}H_{16}N_4OS$	69.69	4.04	14.14	8.08	69.5	4.2	14.0	7.9
VIII	225	75	$C_{19}H_{14}N_2O_2S$	68.26	4.19	8.38	9.58	68.5	4.0	8.5	9.7
IXa	170	70	$C_{26}H_{18}N_2O_2S$	73.93	4.26	6.63	7.58	73.7	4.5	6.5	7.8
IXb	187-8	79	$C_{27}H_{20}N_2O_3S$	71.68	4.42	6.19	7.07	71.5	4.6	6.0	7.3

Table II. The IR and ^{1}H-NMR spectra of the newly synthesized compounds

Compound	IR [cm^{-1}]	^{1}H-NMR [δ ppm]
IIIa	3390, 3280 (2NH); 1680 (C = O) and 1645 (C = N).	2.5(s,3H,CH_3); 7.3-7.6(m,15H, aromatic protons); 10.5,12.3(2s,2H,2NH exchangeable with D_2O).
IIIb	3400, 3320 (2NH); 1690 (C = O) and 1645 (C = N).	7.3-7.8(m,2OH, aromatic protons) and 10.8, 12.5(2s,2H,2NH).
IIIc	3390,3340,3280 (3NH); 1680 (C = O) and 1640 (C = N).	7.3-7.6(m,2OH, aromatic protons) and 9.9,10.5,12.1 (3s,3H,3NH exchangeable with D_2O).
IIId	3380, 3260 (2NH); 1720 (C = O) and 1645 (C = N).	1.7(t,3H,CH_2-$\underline{CH_3}$); 4.1(q,2H,$\underline{CH_2}$-CH_3); 7.2-7.5 (m,15H, aromatic protons) and 10.2,11.7(2s,2H,2NH).
V	3270 (NH), 1720, 1680 (2C = O) and 1640 (C = N)	1.6(t,3H,CH_2-$\underline{CH_3}$); 2.4(s,3H,$\underline{CH_3}$-CO); 3.7(s,1H, CH); 4.2(q,2H,$\underline{CH_2}$-CH_3); 7.2-7.5(m,10H, aromatic protons) and 10.3(s,1H,NH).
VIa	1640 (C = N) and 1620 (C = C).	2.5(s,3H,CH_3) and 7.3-7.6(m,15H, aromatic protons).
VII	3380 (NH); 1710 (C = O) and 1635 (C = N)	7.3-7.6(m,15H, aromatic protons) and 12.4(s,1H,NH).
VIII	1710, 1680 (2C = O) and 1640 (C = N).	2.5(s,3H,CH_3CO); 4.4(s,1H, thiazole H-2) and 7.2-7.6(m,10H, aromatic protons).
IXa	1710, 1670 (2C = O) and 1640 (C = N)	4.6(s,1H, thiazole H-2); 6.5,6.8(2d,2H, ylidenic CH protons) and 7.2-7.5(m,15H, aromatic protons).
IXb	1720, 1680 (2C = O) and 1640 (C = N).	3.8(s,3H,OCH_3); 4.8(s,1H, thiazole H-2); 6.6,6.8 (2d,2H, ylidenic CH protons) and 7.3-7.7 (m,14H, aromatic protons).

mixture was poured onto ice-cold water. The solid that separated was collected and crystallised from ethanol to give yellow crystals of VIa,b and VIII, respectively.

Table III. The antimicrobial activity of compounds IIIa-d, V, VIa, VII and VIII

Compound	*Eschesichia coli*	*Serratia sp.*	*Bacillus subtilis*	*Bacillus cereus*	*Candida utilis*	*Aspergillus terreus*	*Fusarium oxysporum*
IIIa	–	+ +	+	+	–	+	–
IIIb	–	+	+	–	–	+	–
IIIc	–	+	+	+ +	+ +	–	–
IIId	–	+ +	+ +	– +	+	+	–
V	–	+	–	– +	+	–	–
VIa	– +	+ + +	+	–	– +	+	–
VII	– +	+ + +	+ +	– +	+	+	–
VIII	– +	+ +	+	– +	+	– +	–

(–) no inhibition zone; (– +) slight inhibition zone; (+) moderate inhibition zone; (+ +) extensive inhibition zone; (+ + +) highly extensive inhibition zone.

Synthesis of 5,6-diphenyl-2-phenylhydrazoneimidazo[2,1-b]thiazol-3-one (VII)

A solution of each of IIIc or IIId (1 g) in ethanol (30 m*l*) containing 3 drops of triethylamine was refluxed for 2 hours and then evaporated under reduced pressure. The remaining solid product was collected and crystallized from ethanol to give the product, VII.

Preparation of IIId from V

1.8 g of V was suspended in 50 m*l* of ethanol containing 3 g of sodium acetate. The mixture was cooled in ice bath and treated with an equimolar amount of benzene diazonium chloride, left for 1 hr and then poured into cold water. The precipitate formed was collected, dried and crystallized from ethanol as yellow crystals of IIId.

2-(3-Aryl-2-propenoyl) 5,6-diphenylimidazole[2,1-b]thiazol-3-one (IXa,b)

A mixture of VIII (0.01 mole) and the appropriate aromatic aldehyde (0.01 mole) in presence of catalytic amount of piperdine was heated at 100° for 30 minutes and then at 140° for another 30 minutes, cooled and triturated with ethanol. The precipitate obtained was filtered and crystallized from acetic acid to give yellow crystals of IXa,b.

Antimicrobial Activity

The following microbial strains were used as target organisms. *Bacillus cereus* and *Bacillus subtilis* (gram +ve bacteria), *Escherichia coli, Serratia* sp. (gram –ve bacteria), *Candida utilis* (yeast), *Fusarium oxysporum, Aspergillus terrus* (Fungi).

The compounds under investigation were insoluble in water, therefore they were dissolved in acetone at the concentration of 500 μg ml^{-1}.

The antimicrobial effect of the compounds were determined by the whole plate method[13]. A spore suspension of the test organisms were prepared and inoculated onto the surface of the solidified plate medium (pH = 7). Incubation temperature was 35-37° for bacteria and 27-30°C for fungi and yeast. The toxicity was measured after 24 and 48 hrs for bacteria and 5-7 days for fungi and yeast and estimated based on the diameter of the inhibition zone formed. A control experiment with acetone was also performed.

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