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Synthesis of Some Heterocycles of Potential Biological Activity

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Abstract□A convenient method for the preparation of imidazobenzimidazole **3**, imidazoimidazole **5**, imidazotriazole **6** and pyrano [2, 3-c] oxazole **7** derivatives is described. This depends on interaction of 2-methyl-4-arylidene-2-oxazolin-5-ones **1** with o-diamines, thiosemicarbazide and/or ethylcyanoacetate. The effect of alcoholic potassium cyanide on oxazolinone **1** was studied. Antibacterial activity of the obtained products was studied.

Keywords□Imidazobenzimidazole, imidazoimdazole, benzothiazole, imidazotriazole, pyranooxyzole, antibacterial activity.

2-Oxazolin-5-ones are highly reactive reagents that have been extensively utilised in heterocyclic synthesis[1-4]. Also the interesting pharmacological activity of imidazoles[5], thiazoles[6], triazoles[7] and oxazoles[8] led us to study the synthesis and the various changes in the structures of these compounds, aiming to synthesize less toxic and more potent drugs utilizing some azlactones as the starting materials.

Thus, 2-methyl-4-arylidene-2-oxazolin-5-one **1a-d** reacted with *o*-phenylenediamine in refluxing ethanol and piperidine as catalyst to yield products, *via* one mole of water elimination. Structure **2** was established for these products on the basis of their elemental analysis, as well as their IR spectra which showed the amidic CO band ($\sim$1640 cm^{-1}) and the benzimidazole NH band at (3250 cm^{-1}). The ^{1}H-NMR data of the isolated products are in good agreement with structure **2** and indicate in addition to the aromatic and the methyl protons signals, signals for imidazole (NH) at δ 10.6 ppm (s, 1H), and amide proton (CONH) at δ 10.2 ppm (s, 1H) are found.

However, it has been found that in contrast to the previous results, **1a-d** were condensed with o-phenylenediamine in glacial acetic acid/sodium acetate as the reaction medium, to yield a product of condensation *via* two moles of water elimination. It seems logical to assume the imidazobenzimidazole structure **3** for these products on the basis of analytical data, IR spectra which revealed the presence of the correspondent band of C=N group at ($\sim$1630 cm^{-1}) and the absence of any bands corresponding to CO, NH_2 and $CONH_2$ groups. Also the ^{1}H-NMR spectral data of the isolated products was found to be in good agreement with structure **3**. Moreover, structure **2** was considered for the resulting products based on their chemical behaviour, *via* their cyclization to the corresponding imidazobenzimidazole derivatives **3a-d** in refluxing glacial acetic acid/ sodium acetate medium.

On the same bases the behaviour of o-aminothiophenol towards **1a-d** either in ethanol/piperidene or in glacial acetic acid/sodium acetate was also investigated. Evermore, the same benzothiazole derivatives having structure **4** were isolated. (mp., mix. mp.). Structure **4** was established on the basis of the elemental and spectral analysis. The IR spectral data which shows absorption bands at ($\sim$1645 cm^{-1}) and (3230 cm^{-1}) due to (-CONH-) group, also the ^{1}H-NMR spectrum data of **4b** which shows signals at δ 7.8-7.1 ppm (m, 9H, Ar-H and CH=C), δ 10.2 ppm (s, 1H, CONH) and δ 2.1 ppm (s, 3H, CH_3).

On the other hand, by reaction of **1a-d** with etylenediamine in glacial acetic acid/sodium acetate media, the corresponding imidazole derivatives **5a-d** were isolted in relative yields. Their structures were demonstrated by their elemental and spectral analyses. IR spectra of the isolated products shows the presence of (-CH_2-CH_2-) and (C=N) at 2900-2800 cm^{-1} and ($\sim$ 1630 cm^{-1}) respectively, also the ^{1}H-NMR spectrum of **5b** showed in addition to the aromatic protones signals, the presence of (-CH_2-CH_2-) protons signals at δ 3.8 ppm. The methanolate **9a-d** derivatives were also prepared. Structures **8** and **9** were established by elemental analyses, IR and ^{1}H-NMR spectral data which are in good agreement with structures **8** and **9**.

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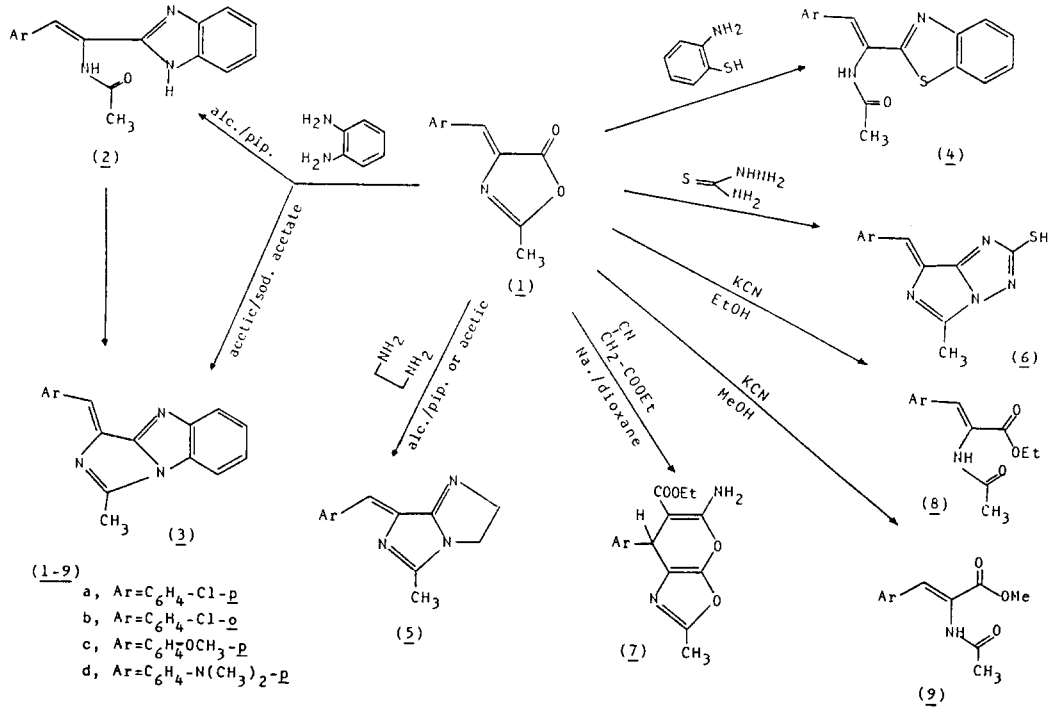

BACTERIOLOGICAL TESTING AND RESULTS

Four bacterial cultures selected at random for initial screening included both Gram-positive and Gram-negative bacteria of several genera having different nutritional requirements and metabolic activities. Several new compounds were tested *in vitro* at concentration 100 μg/m*l*. Data pertaining to the relation between structures and bacterial activity of the newly synthesized compounds are presented in Table I. It is to be noted first that most of listed compounds has marked activity against *Bacillus cereus*. Also it has been found that compound **4** and **6** shows the greatest antimicrobial activity.

EXPERIMENTAL METHODS

All melting points are uncorrected. IR spectra were recorded in KBr discs on a Pye Unicam SP-1100 spec trophotometer. ^{1}H-NMR spectra were measured in DMSO on a Varian EM 360 NMR Spectrometer (90 MHz), using TMS as internal standard and chemical shifts are expressed as δ ppm. Microanalysis were preformed by the microanalytical units at Cairo University and Assuit University.

Reaction of 2-oxazolin-5-ones (1) with o-phenylendiamine: Formation of 2-substituted benzimidazoles (2_{a-d})

Equimolar amounts of (**1a-d**) and *o*-phenylenediamine (0.01 mole) in ethanol (50 m*l*) was treated with few drops of piperidine. The reaction mixture was refluxed for 3 hours. The solid products were collected, crystallised from the proper solvent to give benzimidazoles (**2a-d**) (cf. Table II).

Formation of substituted imidazo benzimidazoles (3a-d)

(A) Equimolar amounts of (**1a-d**) and *o*-phenylenediamine (0.01 mole) in glacial acetic acid (30 m*l*) containing freshly fused sodium acetate (0.5g) was heated under reflux for 3 hours, the solvent was then removed *in vacuo* and the remaining products were triturated with little of water, the remaining solids were collected by filtration and crystallised from the proper solvent to give benzimidozole (**3a-d**) (cf Table II).

(B) Compound (**3a-d**) were also prepared *via* heating (**2a-d**) in refluxing glacial acetic acid (30 m*l*) containing freshly fused sodium acetate (0.5 gm) for one hour and the solid products so formed were collected by filtration and crystallised from the proper solvent, and identified (m.p. a,d mixed m.p.) as (**3a-d**) (cf. Table II).

Table I. Antimicrobial activity of compounds 2-7 against bacteria strains

Comp. in conc. 100 μg/ml	Inhibition zone [cm²]			
	Gram positive		Gram negative	
	Staphylococcus aureus	*Bacillus cereus*	*Escherichia coli*	*Serratia* sp.
2a	–	+	+	–
b	+	+ +	+	–
c	+	+ +	–	–
d	–	+	+	–
3a	+	+	+	+
b	+	+ + +	+ +	+
c	–	+ +	+	–
d	–	+ +	+	+ +
4a	+ +	+ + +	+ +	+
b	+ +	+ + +	+	–
c	+	+ +	+	+ +
d	+	+ +	–	–
5a	–	–	–	–
b	–	+	–	–
c	–	–	–	–
d	–	+	–	–
6a	+	+ + +	+ +	+
b	+	+ + +	+ +	+ +
c	+	+ +	+ +	+
d	+	+	+	–
7c	–	+	–	–
d	–	+	+ +	+

– <1 cm; + = 1 – 1.5 cm; + + = 1.5 – 2 cm; + + + >2 cm.

Formation of 2-substituted benzothiazole (4a-d)

Equimolar amounts of (**1a-d**) and *o*-aminothiophenol (0.01 mole) in ethanol in the presence of catalytic amount of piperdine (50 m*l*) or in glacial acetic acid (30 m*l*) containing freshly fused sodium acetate (0.5g) was heated under reflux for 2 hours then cooled and poured into water. The solid product was collected by filtration and crystallised from the proper solvent to give the benzothiazole derivatives (**4a-d**) (cf. Table II).

Formation of substituted imidazoimidazole (5a-d)

Equimolar amounts of (**1a-d**) and ethylenediamine (0.01 mole) in glacial acetic acid (30 m*l*) containing freshy fused sodium acetate (0.5g) was heated under reflux for 2 hours, then cooled and poured into water. The sloid product was collected and crystallised from the proper solvent to give the imidazoimidazole derivatives (**5a-d**) in relative yields. (cf. Table II).

Formation of the imidazotriazoles (6a-d)

A mixture of (**1**, 0.01 mole) and thiosemicarbazide (0.01 mole) in glacial acetic acid (30 m*l*) containing freshly fused sodium acetate (0.5g) was heated under reflux for 3 hours and then cooled, the solid product so formed was collected by filtration and crystallised from acetic acid to give imidazotrizoles (**6a-d**) (cf. Table II).

Formation of pyrano [2,3-c] oxazoles (7a-d)

Equimolecular amounts (0.01 mole) of **1a-d** ethyl cyanoacetate were heated under reflux in dioxane (50 m*l*) containing sodium metal (0.01 mole) for 6 hours. The mixture was then evaporated *in vacuo* and neutralized with HCl. The solid product, so formed, was collected by filtration and recrystallized from the appropriate solvent to give pyrano-[2,3-c] oxazolens (**7a-d**) (cf. Table II).

Reaction of 1 with potassium cyanide

A mixture of (**1**, 0.01 mole) and potassium cyanide (0.01 mole) in the least amount of water, was heated under reflux either in ethanol or methanol for 3 hours. The mixture was then evaporated and poured into water. The solid product was collected and crystallised from ethanol to give either the corresponding ethanolate (**8a-d**) or the methanolate (**9a-d**) respectively. (cf. Table II).

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Table II. Analytical data of the synthesized compounds

Comp.	M.P. °C Yield %	C.S.	Formula (Mol. Wt.)	Calc./Found %C	%H	%N	%Cl	%S
2a	233	E	$C_{17}H_{14}N_3OCl$	65.49	4.49	13.48		
	67		(311.5)	65.9	4.80	13.90		
b	207	A	$C_{17}H_{14}N_3OCl$	65.49	4.49	13.48		
	65		(311.5)	65.7	4.20	13.10		
c	241	B	$C_{18}H_{17}N_3O_2$	70.35	5.53	13.68		
	63		(307.0)	70.90	5.30	13.90		
d	259	E	$C_{19}H_{20}N_4O$	71.25	6.25	17.50		
	60		(320.0)	71.50	6.40	17.70		
3a	157	E	$C_{17}H_{12}N_3Cl$	69.51	4.09	14.31		
	66		(293.5)	69.40	4.30	14.60		
b	192	E	$C_{17}H_{12}N_3Cl$	69.51	4.09	14.31		
	70		(293.5)	69.8	4.40	14.70		
c	163	E	$C_{18}H_{15}N_3O$	74.74	5.19	14.53		
	65		(289.0)	74.50	5.00	14.90		
d	210	A	$C_{19}H_{18}N_4$	75.40	5.96	18.54		
	67			75.90	5.60	18.80		
4a	105	E	$C_{17}H_{13}N_2SOCl$	62.10	3.96	8.52	10.8	9.74
	70		(328.5)	62.40	3.70	8.80	10.3	10.20
b	123	E	$C_{17}H_{13}N_2SOCl$	62.10	3.96	8.52	10.8	9.74
	65		(328.5)	62.30	3.80	8.30	11.2	9.30
c	96	E	$C_{18}H_{16}N_2SO_2$	66.66	4.93	8.64		9.88
	63		(324.0)	66.80	4.60	8.90		9.50
d	149	E	$C_{19}H_{19}N_3SO$	67.65	5.63	12.46		9.49
	60		(337.0)	67.80	5.70	12.60		9.50
5a	137	E	$C_{13}H_{12}N_3Cl$	63.54	4.89	17.11		
	38		(245.5)	63.80	4.60	17.50		
b	120	E	$C_{13}H_{12}N_3Cl$	63.54	4.89	17.11		
	30		(245.5)	63.60	5.10	17.10		
c	110	E	$C_{14}H_{15}N_3O$	69.71	6.22	17.43		
	25		(241.0)	69.90	6.00	17.10		
d	142	E	$C_{15}H_{18}N_4$	70.87	7.09	22.05		
	30		(254.0)	71.20	7.10	21.70		
6a	215	A	$C_{12}H_9N_4SCl$	52.08	3.25	20.25		11.57
	69		(276.5)	52.30	3.10	20.00		11.06
b	230	A	$C_{12}H_9N_4SCl$	52.08	3.25	20.25		11.57
	66		(276.5)	52.40	3.50	20.30		11.90
c	206	A	$C_{13}H_{12}N_4OS$	57.35	4.41	20.59		11.76
	63		(272.0)	56.90	4.60	20.20		11.90
d	263	A	$C_{14}H_{15}N_5S$	58.95	5.26	24.56		11.23
	61		(285.0)	59.30	5.10	24.80		11.50
7a	169	E	$C_{16}H_{15}N_2O_4Cl$	57.40	4.48	8.37		
	67		(334.5)	57.70	4.20	8.80		
b	161	E	$C_{16}H_{15}N_2O_4Cl$	57.40	4.48	8.37		
	66		(334.5)	57.30	4.70	8.50		
c	135	E	$C_{17}H_{18}N_2O_5$	61.82	5.45	8.48		
	65		(330.0)	62.20	5.50	8.50		
d	187	E	$C_{18}H_{21}N_3O_4$	62.97	6.12	12.25		
	62		(343)	62.70	6.50	12.00		

Table II. Continued.

Comp.	M.P. °C Yield %	C.S.	Formula (Mol. Wt.)	Calc./Found %C	%H	%N	%Cl	%S
8a	142	E	$C_{13}H_{14}NO_3Cl$	58.31	5.23	5.23		
	60		(267.5)	58.50	5.40	5.30		
b	157	E	$C_{13}H_{14}NO_3Cl$	58.31	5.23	5.23		
	57		(267.5)	58.20	5.70	5.60		
c	132	E	$C_{14}H_{17}NO_4$	63.87	6.46	5.32		
	55		(263.0)	63.60	6.10	5.50		
d	181	E	$C_{15}H_{20}N_2O_3$	65.20	7.24	10.14		
	52		(276.0)	65.30	7.50	10.30		
9a	128	E	$C_{12}H_{12}NO_3Cl$	56.80	4.73	5.52		
	62		(253.5)	56.50	4.30	5.20		
b	122	E	$C_{12}H_{12}NO_3Cl$	56.80	4.73	5.52		
	58		(253.5)	56.5	4.80	5.30		
c	135	E	$C_{13}H_{15}NO_4$	62.65	6.02	5.62		
	56		(249.0)	62.30	6.30	5.70		
d	150	E	$C_{14}H_{18}N_2O_3$	64.12	6.87	10.68		
	55		(262.0)	64.40	6.40	10.90		

A, Acetic acid; B, Benzene; E, Ethanol

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