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SOME SEMICARBAZIDE DERIVATIVES AND THEIR ANTIMICROBIAL ACTIVITY

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ABSTRACT

A number of arylsemicarbazide and arylthiosemicarbazide derivatives were synthesized. The antimicrobial activity of the prepared compounds was investigated.

INTRODUCTION

Various semicarbazides and thiosemicarbazides (1–5) and their cyclised products, triazoles, oxadiazoles and thiadiazoles (6–9) have been reported to possess antibacterial, antitubercular and antifungal activities. Based on these findings it was of interest to prepare some new arylsemicarbazide and arylthiosemicarbazide derivatives and to evaluate their antimicrobial activity in a trial to obtain new derivatives with higher activity than that of the parent compounds.

MATERIALS AND METHODS

The starting materials (Ia–h) were prepared according to the general method(10). Compounds (Va–c) were also prepared according to the general method (11, 12).

a) *Preparation of the arylsemicarbazide derivatives* (IIa–h):

To a solution of phenylisocyanate (2ml) in dry pure benzene (20 ml), acid hydrazide (0.01 mole) was added. The reaction mixture was refluxed for 4 hours. After cooling, the formed solid was filtered off and then recrystallized from ethanol. The physical and analytical data are presented in Table (1).

b) *Preparation of the arylthiosemicarbazide derivatives* (IIIa–h) and (IVa–e):

The procedure (a) was applied using phenylisothiocyanate or allylisothiosyanate instead of phenylisocyanate. The physical and

analytical data of compounds (IIIa–h) and (IVa–e) are presented in Table (1).

c) Reaction of acid chloride (VIa–h) *with phenylsemicarbazide* (*Va*) *and / or phenylthiosemicarbazide* (*Vb*):

Appropriate amounts of acid chloride (0.01 mole) and phenylsemicarbazide or phenylthiosemicarbazide (Va or Vb) (0.01 mole) were suspended in dry pure benzene (50 ml) containing 1 ml pyridine. The

Table (1). Physical and analytical data of the prepared compounds.

Compd. No.	Molecular Formula	M.P. °C	Yield (%)	Analysis Calculated / Found % C	H	N	S
IIa	$C_{14}H_{13}N_3O_2$	198	80	65.88	5.10	16.47	—
				65.77	5.01	16.61	—
b	$C_{15}H_{15}N_3O_2$	180	80	66.91	5.58	15.61	—
				66.61	5.62	15.61	—
c	$C_{15}H_{15}N_3O_2$	170	80	66.91	5.58	15.61	—
				67.02	5.61	15.70	—
d	$C_{15}H_{15}N_3O_2$	169	70	66.91	5.58	15.61	—
				67.21	5.72	15.52	—
e	$C_{14}H_{12}N_4O_4$	220	80	56.00	4.00	18.67	—
				56.15	4.10	18.72	—
f	$C_{15}H_{15}N_3O_3$	200	80	63.16	5.26	14.74	—
				63.82	5.31	14.62	—
g	$C_{15}H_{15}N_3O_2$	198	70	66.91	5.58	15.61	—
				66.80	5.50	15.30	—
h	$C_{13}H_{12}N_4O_2$	215	70	60.94	4.69	21.88	—
				60.64	4.81	22.00	—
IIIa	$C_{14}H_{13}N_3OS$	250	60	61.99	4.80	—	11.81
				61.27	5.26	—	12.00
b	$C_{15}H_{15}N_3OS$	230	60	63.16	5.26	—	11.23
				63.01	5.10	—	11.51
c	$C_{15}H_{15}N_3OS$	163	60	63.16	5.26	—	11.23
				63.70	5.50	—	11.61
d	$C_{15}H_{15}N_3OS$	170	60	63.16	5.26	—	—
				62.71	5.00	—	—
e	$C_{14}H_{12}N_4O_3S$	175	80	53.16	3.80	—	10.13
				53.40	3.90	—	10.01
f	$C_{15}H_{15}N_3O_2S$	196	75	59.80	4.98	—	10.63
				59.20	5.00	—	10.30
g	$C_{15}H_{15}N_3OS$	158	85	63.16	5.26	—	11.23
				62.90	5.10	—	11.10
h	$C_{13}H_{12}N_4OS$	188	80	57.35	4.41	—	11.76
				56.92	4.10	—	11.80
IVa	$C_{11}H_{13}N_3OS$	150	70	56.17	5.53	—	13.62
				56.25	5.21	—	12.85
b	$C_{12}H_{15}N_3OS$	170	70	57.83	6.02	—	12.85
				58.10	6.00	—	12.91
c	$C_{12}H_{15}N_3OS$	160	70	57.83	6.02	16.87	—
				57.92	6.20	16.72	—
d	$C_{12}H_{15}N_3OS$	145	80	57.83	6.02	—	12.85
				58.00	6.20	—	12.70
e	$C_{10}H_{12}N_4OS$	215	90	50.85	5.08	—	13.56
				51.03	5.07	—	13.26

reaction mixture was refluxed for 3 hours. The solvent was evaporated and the obtained product was recrystallized from ethanol to give (IIa–h) and (IIIa–h). The physical and analytical data of these compounds are presented in Table (1).

d) *Reaction of acid chloride* (VIa–e) *with allylthiosemicarbazide* (Vc):

The procedure (c) was applied using allythiosemicarbazide instead of phenylthiosemicarbazide. The physical and analytical data of the obtained compounds (IVa–e) are presented in Table (1).

e) *Measurement of the antimicrobial activity*:

The preliminary screening tests were performed by the disc diffusion method(13). Whatman No. 1 filter paper discs were sterilized by autoclaving for 20 min. at 121°C. The sterile discs were impregnated with the tested compounds (300 μg / disc). The discs were placed on the surface of the cold solid medium in Petri–dishes, inoculated with the micro–organisms (c.f. Table 2), and then incubated at 5°C for 1 hour to permit good diffusion and then transferred to an incubator at 28°C for bacteria and at 37°C for yeast and fungus. The growth and inhibition zones were evaluated after 24 and 72 hours, respectively. The data obtained are given in Table (2).

Table (2). The preliminary screening of antimicrobial activity of some compounds.

Compd. No.	Micro–organism								
	1	2	3	4	5	6	7	8	9
IIa	++	++	+	++	—	++	—	++	+
b	—	—	—	—	—	—	—	—	—
c	—	—	—	—	—	—	—	—	—
f	—	—	—	—	—	—	—	—	—
g	—	—	—	—	—	—	—	—	—
h	—	—	—	—	—	—	—	—	—
IIIb	+	+	—	—	—	—	—	—	—
c	—	—	—	—	—	—	—	—	—
d	++	++	—	—	—	+	+	+	+
e	+++	++	+	+	+	+	+	—	+
f	+	+	+	++	++	++	+	+	+
h	++	+	++	+	—	—	—	+	+
IVb	++	+	—	—	—	+	+	+	+
c	—	—	—	—	—	—	—	—	—
d	—	—	—	—	—	—	—	—	—
h	+++	+++	+++	+	+	+	—	+	+

+++ = Highly active (inhibition zone 12–15 mm).
++ = Moderatly active (inhibition zone 9–12 mm).
+ = Slightly active (inhibition zone 6–9 mm).
— = Not sensitive.

The minimal inhibitory concentration (MIC) for the active compounds was also measured using the serial-tube dilution technique. Growth and inhibition was evaluated after 48 hours at 28°C for bacteria and after 48 hours at 37°C for *Candida albicans* (yeast) and 72 hours at 28°C for *Aspergillus niger* (fungus). The data are presented in Table (3).

Table (3). Minimal Inhibitory Concentration (MIC) of the active compounds.

Compd. No.	MIC (μg / ml) Micro-organism								
	1	2	3	4	5	6	7	8	9
IIa	100	100	>100	100	—	100	—	100	>100
IIId	100	100	—	—	—	>100	>100	>100	>100
IIIe	50	75	100	>100	>100	>100	>100	—	>100
IIIf	100	>100	>100	100	100	>100	>100	>100	>100
IIIh	100	>100	100	>100	—	—	—	>100	>100
IVb	75	100	—	—	—	>100	>100	>100	>100
IVh	75	75	75	100	100	>100	—	100	>100

Micro-organisms:

1- *Bacillus subtilis.* 2- *Staphylococcus aureus.*
3- *Citrobacter freundii.* 4- *Escherichia coli.*
5- *Pseudomonas aeruginosa.* 6- *Proteus mirabilis.*
7- *Klebseilla pneumonia.* 8- *Candida albicans.*
9- *Aspergillus niger.*

RESULTS AND DISCUSSION

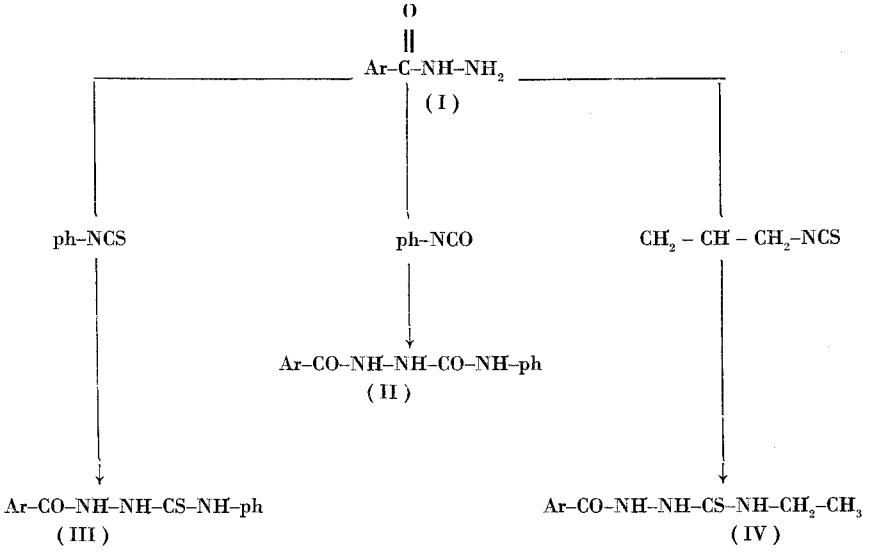
a) *Chemistry*

The reaction of phenylisocyanate with compounds (Ia-h) namely, benzoic, o, m, p-toluic, p-anisic, p-nitrobenzoic, phenylacetic or isonicotinic acid hydrazides in dry pure benzene and refluxing the mixture for 4 hours led to the formation of the corresponding arylsemicarbazide derivatives (IIa-h), respectively (c.f. Scheme 1). The structures of the obtained compounds were confirmed by IR and ^{1}HNMR spectra analysis, (c.f. Table 1). The IR spectrum of compound (IIa, as a random specimen) showed bands at 1670 cm^{-1} (N-CO-N), at 1650 cm^{-1} (ph-CO-N), at 1145, 710 cm^{-1} (N-C-N) and at 3200 cm^{-1} (NH). The ^{1}HNMR sepectrum of compound (IIa, in DMSO-d_2) revealed signals at δ = 7.25-7.65 ppm (10, m, two phenyl moieties) and at δ = 8.7-9.0 ppm (3H, b, 3NH).

The reaction of phenylisothiocyanate with the acid hydrazide derivatives (Ia-h) in refluxing benzene for 4 hours gave the corresponding arylthiosemicarbazide derivatives (IIIa-h), respectively (c.f. Scheme 1). The structures of these compounds were confirmed by IR and ^{1}HNMR spectra analysis, (c.f. Table 1). The IR spectrum of compound (IIIa,

as a random specimen) showed bands at 1500 cm^{-1} (N–CS–N) at 1100 and 730 cm^{-1} (N–C–N). The ^{1}HNMR spectrum of compound (IIIa, in DMSO–d_6) revealed signals at δ = 7.4–7.5 ppm (10, m, two phenyl moieties) and at δ = 7.9–8.0 ppm (3H, b, 3NH).

Similarly, allylisothiocyanata was allowed to react with acid hydrazide (Ia–e) in refluxing benzene for 4 hours to give the corresponding allylthiosemicarbazide derivatives (IVa–e), respectively (c.f. Scheme 1). The structures of these compounds were also confirmed (c.f. Table 1), by IR and ^{1}HNMR spectra analysis. The IR spectrum of compound (IVa) showed bands at 1500 cm^{-1} (N–CS–N) and at 1100, 730 cm^{-1} (N–C–N). The ^{1}HNMR spectrum of compound (IVa) in DMSO–d_6) revealed signals at δ = 8.0–8.2 ppm (3H, b, 3NH), at δ = 7.5–7.6 ppm (5H, m, phenyl moiety) at δ = 6.3 ppm (1H, m, C–CH–C), at δ = 6.4 ppm (2H, d, –C = CH_2) and at δ = 3.4 ppm (2H, d, N–CH_2–C).

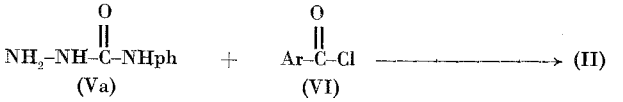


I, II and III, a, Ar = ph
b, Ar = C_6H_4–CH_3 (o)
c, Ar = C_6H_4–CH_3 (m)
d, Ar = C_6H_4–CH_3 (p)
e, Ar = C_6H_4–NO_2 (p)
f, Ar = C_6H_4–OCH_3 (p)
g, Ar = CH_2–C_6H_5
h Ar = C_5H_4N

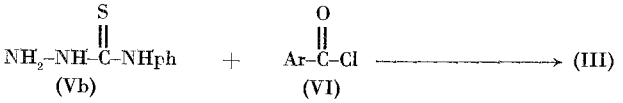
IV, a, Ar = ph
b, Ar = C_6H_4–CH_3 (m)
c, Ar = C_6H_4–CH_3 (p)
d, Ar = CH_2–C_6H_5
e, Ar = C_5H_4N

Scheme (I)

On the other hand, the arylsemicarbazide and arylthiosemicarbazide derivatives (IIa–h and IIIa–h) could be prepared through the reaction of the acid chloride (VIa–h) with phenylsemicarbazide (Va) or phenylthiosemicarbazide (Vb), respectively (c.f. Scheme 2). The M.P.s of these compounds and those prepared in method (a) are undepressed when mixed together. Also allylthiosemicarbazide derivatives (IVa–e) could be prepared by the reaction of the acid chloride (VIa–e) with allylthiosemicarbazide (Vc), respectively (c.f. Scheme 2).



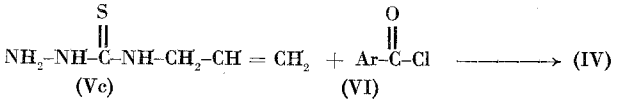
(Va) (VI) (II)



(Vb) (VI) (III)

II, III & VI, a, Ar = ph

b, Ar = C_6H_4–CH_3 (o).
c, Ar = C_6H_4–CH_3 (m).
d, Ar = C_6H_4–CH_3 (p).
e, Ar = C_6H_4–NO_2 (p).
f, Ar = C_6H_4–OCH_3 (p).
g, Ar = CH_2–C_6H_5
h, Ar = C_5H_4N



(Vc) (VI) (IV)

IV and VI, a, Ar = ph

b, Ar = C_6H_4–CH_3 (m)
c, Ar = C_6H_4–CH_3 (p)
d, Ar = CH_2–C_6H_5
e, Ar = C_5H_4N

Scheme (2)

b) *Biological data*

The prepared compounds were tested for two strains of Gram-positive bacteria *(Bacillus subtilis* and *Staphylococcus aureus)* and five strains of Gram-negative bacteria *(Citrobacter freundii, Escherichia coli, Pseudomonas aeruginosa, Proteus mirabilis* and *Klebseilla pneumonia)*, one strain of yeast *(Candida albicans)* and one strain of fungus

(Aspergillus niger). Table (2) presents the preliminary screening test of the prepared compounds. From the data obtained, it is clear that compounds IIa, IIId, IIIe, IIIf, IIIh, IVb and IVh possess remarkable activity towards Gram–positive and Gram–negative bacteria, whereas the other compounds are inactive. Table (3) presents the results of the minimal inhibitory concentrations of the active compounds. From the results, it is clear that compounds IIIe, IVb and IVh possess high activity (less than 100 μg / ml medium) towards Gram–positive bacteria. Compounds IIa, IIIf and IVh possess moderate activity (100 μg / ml medium) towards Gram–negative bacteria. On the other hand, all the previous compounds possess slight activity (more than 100 μg / ml medium) towards yeast and fungus.

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