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SYNTHESIS OF NEW DERIVATIVES OF 4-ACETYLSULPHANILO-HYDRAZIDE AND THEIR BACTARICIDIAL AND FUNGICIDIAL PROPERTIES

by

A.M. ABDEL-HALIM, R.M. ABDEL-RAHMAN, E.A. MOHAMED and M.E. HUSSEIN

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SYNTHESIS OF NEW DERIVATIVES OF 4-ACETYLSULPHANILO-HYDRAZIDE AND THEIR BACTERICIDAL AND FUNGICIDAL PROPERTIES

By

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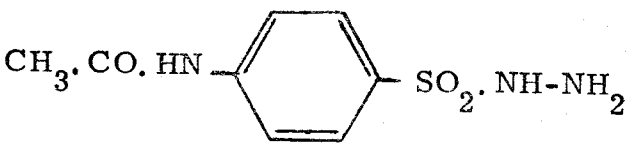
In a search for new bactericides and fungicides the following derivatives of sulphanilohydrazide have been prepared: Hydrazones from aromatic aldehydes and ketones; N'-aryl carbonyl derivatives; N'arylsulphonyl derivatives. In addition to various sulphones containing heterocyclic ring. Their antifungal and antibacterial activity has been evaluated, where compounds (Ic), (IIIg), (IIIg), IVc), (Va) and (VIb) were found to be the most effective ones.

HYDRAZONES have been found to possess antibacterial activity[1,2]. In addition they have also been reported to possess antifungal[3,4,5] as well as insecticidal activity[6,7,8,9]. On the other hand, it is known that compounds containing a sulphanilyl or potential sulphanilyl group act as antimetabolites competing with normal metabolites in bacterial growth[10,11].

On the grounds of these observations it was suggested in the present work to synthesize six series of new compounds from acetylsulphanilohydrazide (I) listed in the annexed Tables, as potential antibacterial or antifungal activity. The methods used were standard and are indicated in the experimental section.



(I)

* Faculty of Science, Al-Azhar University, Nasr-City, Cairo, A.R. Egypt.

BIOLOGICAL ACTIVITY

I- *Antibacterial Evaluation:*

The in vitro antibacterial activity of the acetylsulphanilohydrazide derivatives, in sterile dimethylsulphoxide (DMSO) as a solvent, was tested by the Oden *et al.*, method[12], and summarized in Tables 1-6. In these tests the response of the selected microorganisms, namely; *Bacillus subtilis* (B.s.), *Bacillus megaterium* (B.m.) *Bacillus cereus* (B.c.) and *Sarcina lutea* (S.l.) as Gram positive bacteria in addition to *Escherichia coli* (E.c) and *Pseudomonas aeruginose* (P.a.) as Gram negative bacteria, to these derivatives was readily demonstrated. In general, they have good broad-spectrum in vitro activity against *Bacillus megaterium* (Gram positive organism); fair broad-spectrum in vitro activity against *Bacillus cereus* (Gram positive organism) and *Pseudomonas aeruginosa* (Gram negative organism), but inactive against *Bacillus* subtilis (except for compounds; IIIg, VIb; VIc; VIIe and VIIf) *Sarcina lutea and Escherichia coli.*

The newly synthesized derivatives can be arranged according to their activity on each of the selected organisms as follows:

1- *Gram-positive Bacteria:*

a) *Bacillus subtilis;* VIIeVIIf=IIIg.

b) *Bacillus megaterium;* Va>IVb=Vb=VIIe=VIIg>IIb>IId >IVf>IIIe>IVa>IIa=IIf=IIIa,b=IIIc=VIId>IVd>IVe =VIa=VIc>IIe>IVb≃VIb>IVc.

c) *Bacillus cereus;* IIIg>IIId>IIIh=IVe=Vb=VIIf>IIa=IVb VIIg>VIId>IVd=Va>IIIb=IVa>IIb=IIc=IIf=IIIc= IVc=VIc.

d(*Sarcina lutea;* all the compounds were completely inactive.

2- *Gram-negative Bacteria:*

a) *Escherichia coli;* all the compounds were completely inactive

b) *Pseudomonas aeruginosa;* IVd>IIb=IIIa=IIIb=IIIc=IVa> IVb>IIIe

N^4-Acetyl-N′-phenylthioacetamido-sulphanilohydrazide (IIIg), N^4 acetyl-N′-methylsulphonyl sulphanilohydrazide (Va), N^4-acetyl-N′-cyanomethylcarbonyl sulphanilohydrazide (IVb), N^4-acetyl-N'-(p-aceta-

minobenzene sulphonyl) sulphanilohydrazide (Vb), 1-(N^4-acetylsulphanilyl)-3:5-diphenylpyrazole (VIIe) and 2-(N^4-acetylsulphanilyl)-4-phthalazin-1:4-dione (VIIg) were found to be the most potent among those tested.

II- *Antifungal Evaluation:*

The antifungal effectiveness of the newly synthesized compounds has been evaluated against two fungi; *Candida utilis* (C.u.) qnd *Aspergillus niger* (A.n.), some of the derivatives displayed broad in vitro activity (Tables 1-6), The compounds can be arranged according to their activity towards each fungus as follows:

a) *Candida utilis:*

VIb>IVB>IIIg=IIIh>IIb=VIId>IIa>VIIg>VIc=VIe>IVe>IIIe≃IIe=IVc>IIIb=Vb>IIc=IId=IIIa=IVf>IIf=IIIc=IIId=Va>IVa=IVd=VIa=VIIf.

b) *Aspergillus niger:*

IIIc>IVc=Va=VIIc>IIIg=VIIb>VIb>IId=IVe>VIIe>IIId=VIIf>IIa=VIIa>IIe>IIIe=VIIg.

The thio-p-cresol adduct of cinnamaldehyde-4-acetyl-sulphanilyl hydrazone (VIb), N^4-acetyl-N'-cyanomethylcarbonyl-sulphanilohydrazide (IVb), 1-(N^4-acetyl sulphanilyl)-3:5-dimethyl pyrazole (VIId), cinnamaldehyde-4-acetylsulphanilyl hydrazone (IIb), N^4-acetyl-N'-2- (p-aminophenyl)ethylidene-sulphanilohydrazide (IIIc), N^4-acetyl-N'-phenylacetamidosulphanilohydrazide (IIIg) and N^4-acetyl-N'-2- (p-toluenesulphonanilino) ethylidene sulphanilohydrazide (IIIh) were found to be the most effective compounds.

EXPERIMENTAL

Melting points were determined by using sealed tubes (to minimize decomposition).

N^4-Acetylsulphanilohydrazide (I) was prepared after the procedure described by Roth and Degering[13].

Tables (1) *and* (2): N^4-acetyl-N'- (primary alkylidene)- and -N'- arylidene)-sulphanilohydrazides (IIa-f), and N^4-acetyl-N'-secondary alkylidene-sulphanilohydrazides (IIIa-h) were synthesized by heating equimolecular proportions of acetylsulphanilohydrazide and the appropriate

Table 1. p-NH-Ac-C_6H_4-SO_2-NH-N=CHR

Compound	R	Solvent	M.P.°C	Yield %	Molecular formula	Analysis (Reqd/Found) %					In vitro Activity[a] (Mini-inhib. conc. ug/ml).							
						C	H	Cl	N	S	Gram positive bacteria				Gram-ve B.		Fungi	
											B.S.	H	B.c.	S.I.	E.c.	P.a.	C.u.	A.n.
IIa	-CH=CH=CH_3	AcOH	168–169	70	$C_{12}H_{15}N_3O_3S$	51.25	5.34	—	14.95	11.39	—	++	++	—	—	—	++++	++
						51.36	5.26		15.10	11.43		350	400				100	450
IIb	-CH=CH-C_6H_5	AcOH	174–175	75	$C_{17}H_{17}N_3O_3S$	59.48	4.96	—	12.25	9.33	—	+++	+	—	—	++	++++	—
						59.52	5.10		12.18	9.52		100	500			375	50	
IIc	-C_6H_4.Cl(o-)	AcOH	142–143	60	$C_{15}H_{14}Cl_2N_3O_3S$	51.28	3.99	10.11	11.97	9.12	—	++++	+	—	—	—	+	—
						51.39	4.12	10.17	11.86	9.28		150	500				450	
IId	-C_6H_3.Cl_2(2:4)	AcOH	220	70	$C_{15}H_{13}Cl_2N_3O_3S$	46.69	3.37	18.42	10.90	8.30	—	+++	—	—	—	—	+	+++
						46.72	3.26	18.40	10.96	8.42		175					450	300
IIe	-C_6H_4.$N(CH_3)_2$(p-)	AcOH	238–239	60	$C_{17}H_{20}N_4O_3S$	56.67	5.56	—	15.56	8.89	—	++	—	—	—	—	++	+
						56.82	5.46		15.64	9.00		450					450	475
IIf	-C_6H_4.OCH_3(p-)	AcOH	134–135	75	$C_{16}H_{17}N_3O_4S$	55.33	4.90	—	12.10	9.22	—	++	+	—	—	+	+	—
						55.18	4.96		12.16	9.36		350	500			500	475	

(—) inactive, (+) slightly active; (++) fairly active; (+++) moderately active; (++++) highly active.

B.s., Bacillus subrilis ATCC 7972; B.m. Bacillus iycoides USSR; B.c., Bacillus cereus IMRU; S.I., Sarcina lutea IMRU 14; E.c., Escherichia coli BPPO1; P.a., Pseudomonas areuginosa M_2; C.u., Candida utilis NRRLY 900; A.n., Aspergillus niger pp.

Table 2

p-NH.Ac.C_6H_4.SO_2.NH.N=C< (R, R_1)

(III)

Compound	R	R_1	Solvent	M.p.°C	Yield %	Molecular formula	Analysis (Reqd. / Found) % C	H	Cl	N	S	In vitro Activity (Mini-inhib-cons. ug / ml) Gram positive B: B.s.	B.m.	B.c.	S.l.	Gram–ve B: E.c.	P.a.	Fungi: C.u.	A.n.
IIIa	$-CH_3$	$-CH_2.CO.CH_3$	Benzene	203–205	80	$C_{13}H_{17}N_3O_4S$	50.16 50.20	5.47 5.38	—	13.51 13.64	10.29 10.43	—	++ 350	—	—	—	++ 375	+ 450	—
IIIb	$-CH_3$	$-C(CH_3)=N.OH$	Benzene	230–232	60	$C_{12}H_{16}N_4O_4S$	46.15 46.10	5.13 5.18	—	17.95 18.10	10.26 10.38	—	++ 350	+ 475	—	—	++ 375	+ 425	—
IIIc	$-CH_3$	$-C_6H_4.NH_2$(p-)	AcOH	217–218	85	$C_{16}H_{18}N_4O_3S$	55.49 55.53	5.20 5.11	—	16.19 16.30	9.25 9.40	—	++ 350	+ 500	—	—	++ 375	+ 475	++++ 25
IIId	$-CH_3$	$-C_6H_4.N{:}CH.CH.CH-C_6H_5$	(p-) Ethanol	205–207	60	$C_{25}H_{24}N_4O_3S$	65.22 65.30	5.22 5.34	—	12.17 12.32	6.96 7.15	—	— 300	+++ 300	—	+++	— 475	+ 475	++ 400
IIIe	$-CH_3$	$-C_6H_4.COOH$l(o-)	Methanol	249–250	89	$C_{17}H_{17}N_3O_5S$	54.40 54.48	4.53 4.60	—	11.20 11.35	8.53 8.37	—	+++ 250	—	—	—	++ 425	++ 425	+ 500
IIIf	$-C_6H_5$	$-CH_2.CO.C_6H_5$			80		63.49 63.64	4.83 4.86	—	9.66 9.79	7.36 7.22								
IIIg	$-CSH_3$	$-NH.C_6H_5$	Methanol	224–225	90	$C_{16}H_{18}N_4O_3S_2$	50.79 50.62	4.76 4.72	—	14.82 14.71	16.93 17.15	++ 375	—	++++ 25	—	—	—	++++ 25	+++ 150
IIIh	CH_3	$C_6H_4.NH.SO_2.C_6H_4.CH_3$	(p-) Benzene	117–118	90	$C_{23}H_{24}N_4O_5S_2$	55.20 55.31	4.80 4.91	—	11.20 11.33	12.80 12.96	—	—	++ 375	—	—	—	++++ 25	++ 450

(—) inactive; (+) slightly active; (++) fairly active; (+++) moderately active; (++++) highly active

B.s., Bacillus ATCC 7972; B.m., Bacillus mycoides USSR; B.c., Bacillus cereus IMRU; S.l., Sarcina lutea IMRU; E.c. Escherichia coli BPPOl; P.a., Pseudomonas aeruginosa M_2' C.u., Candida utilis NRRLY 900; A.n., Aspergillus niger PP.

aldehyde or ketone in ethanol, with or without sodium acetate as described by Cremylyn[14].

Tables (3, 4): N^4-acetyl-N′ (alkyl)-and-N′-arylcarbonyl-sulphanilohydrazides (IVa-f), and N^4-acetyl-N′-(alkyl)-and-N′-arylsulphonyl sulphanilohydrazides (Va and b) were obtained by treatment of acetyl sulphanilohydrazide with the appropriate acyl or sulphonyl chloride in a mixture of pyridine and dioxane at room temperature.

Table (5): N^4-acetyl-N'-(alkyl) -and-N'-arylsulphanilohydrazides (VIa, c) were prepared as follows.

i- *Formation of VIa*

A mixture of I (0.01 M), acrylonitrile (3ml.) and water (10 ml.) in pyridine (30 ml.) was heated under reflux for 2 hr., cooled, washed with dil. HCl and extracted with ether. The solid obtained after the removal of solvent was crystallized from benzene to give VIa

ii- *Formation of VIc*

A mixture of I (0.01 M), 3-chloro-5, 6-diphenyl-1, 2, 4-triazine (0.01 M) and triethylamine (0.01 M) in pyridine (15 ml.) was heated under reflux for 1 hr. The reaction mixture was cooled; washed with water and the organic layer was separated and dried over anhydrous sodium sulphate, filtered and evaporated to dryness to give VIc which recrystallized from petroleum ether 60–80 as brownish-yellow crystals.

Table (6): which includes the various heterocyclic sulphon derivatives, the method of preparation for each one is illustrated below:

i- *Formation of VIIa and b*:

A mixture of VIa or IVb (0.01 M) and 20 % HCl (40 ml.) was heated under reflux for 2 hr., cooled and filtered. The solid obtained was recrystallized from ethanol to give VIIa and b respectively.

ii) *Formation of VIIc:*

A suspension of IVc (2 gm.) in absolute ethanol (50 ml.) was heated under reflux for 2 hr., cooled, poured into cold water and the solid obtained was filtered and crystallized from ethanol to give VIIc as colourless crystals.

Table 3

p-NH.Ac.C_6H_4.SO_2.NH.NH.C(X)R

(IV)

Comp. No.	X	R	Solvent	M.p.°C	Yield %	Molecular formula	Analysis (Reqd. / Found) %					In vitro Activity[a] (Mini. inhib. conc. ug / ml)							
							C	H	Cl	N	S	Gram+ve B.				Gram—ve B		Fungi	
												B.s.	B.m.	B.c.	S.l.	E.c.	P.a.	C.u.	A.n.
IVa	O	$-CH_3$	AcOH	199–200	90	$C_{10}H_{13}N_3O_3S$	47.06 47.18	5.10 5.16	—	16.47 16.61	12.55 12.65	—	+++ 300	+ 475	—	—	++ 375	+ 500	—
IVb	O	$-CH_2.CN$	Benzene	178–179	70	$C_{11}H_{12}N_4O_3S$	47.14 47.18	4.29 4.19	—	20.00 20.12	11.43 11.52	—	++++ 50	++ 400	—	—	++ 400	++++ 5	—
IVc	O	$-CH_2.CO.CH_3$	Benzene	139–140	70	$C_{12}H_{15}N_3O_4S$	48.49 48.54	5.05 5.16	—	14.14 14.16	10.77 10.84	—	+ 500	+ 500	—	—	—	++ 450	++++ 100
IVd	O	$-C_6H_5$	Benzene	224–225	85	$C_{15}H_{15}N_3O_3S$	56.78 56.74	4.73 4.64	—	13.25 13.30	10.10 10.40	—	++ 375	+ 450	—	—	+++ 300	+ 500	—
IVe	O	$-CH=CH-C_6H_5$	Benzene	150–151	80	$C_{17}H_{17}N_3O_3S$	59.48 59.64	4.96 4.82	—	12.25 12.32	9.33 9.48	—	++ 400	++ 375	—	—	—	++ 400	+++ 300
IVf	S	$-NH.C_6H_5$	Pet-ether (60–80)	210–211	85	$C_{15}H_{16}N_4O_3S$	54.22 54.26	4.82 4.80	—	16.87 16.80	9.64 9.82	—	+++ 200	—	—	—	—	+ 450	—

Table 4

p-NH-Ac-$C_6H_4.SO_2.NH.NH.SO_3$-R

(V)

Compound No.	R	Solvent	M.p.°C	Yield %	Molecular formula	Analysis (Reqd. / Found) %					In vitro Activity (Mini. inhib. conc. ug / ml)							
						C	H	Cl	N	S	Gram positive B				Gram ve B.		Fungi	
											B.s	B.m.	B.c.	S.l.	E.c.	P.a.	C.u.	A.n.
Va	$-CH_3$	AcOH	168–169	85	$C_9H_{13}N_3O_5S_2$	35.18 35.32	4.24 4.20	—	13.68 13.33	20.85 21.00	—	++++ 25	+ 450	—	—	—	+ 475	++++ 100
Vb	$-C_6H_4.NH.CO.CH_3$(p-)	Benzene	128–130	90	$C_{16}H_{18}N_4O_6S_2$	45.07 45.20	4.23 4.36	—	13.15 13.00	15.02 15.35	—	++++ 50	++ 375	—	—	—	+ 425	—

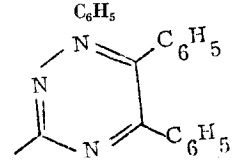
(—) inactive, (+) slight active; (++) fairly active; (+++) moderately active; (++++) highly active.

B.s., Bacillus subtilis ATCC 7972; B.m. Bacillus mycoides USSR; B.c., Bacillus cereus IMRU; S.I., Sarcine lutes IMRU 14; E.c., Escherichia coli BPPOl; P.s., .assudomonas aeruginosa M_2; C.u., Candida utilis NRRLY 900; A.n., Aspergillus niger pp.

Table 5

p-NH.Ac.C_6H_4.SO_2.NH.NH.R

(VI)

Compound No.	R	Solvent	M.p.°C	Yield %	Molecular formula	Analysis (Reqd./Found) %					In Vitro Activity[a] (Mini. inhibi. conc. ug/ml).							
						C	H	Cl	N	S	Gram+ve B.				Gram+veB		Fungi	
											B.s.	B.m.	B.c.	S.l.	E.c.	P.a.	C.u.	A.n.
VIa	-CH_2.CH_2.CN	Benzene	205–207	65	$C_{11}H_{14}N_4O_3S$	46.81 46.94	4.97 4.82	—	19.86 20.00	11.35 11.48	—	++ 400	—	—	—	++ 375	+ 500	—
VIb	-CH:CH.CH.S.C_6H_4.CH_3(p-) C_6H_5	pet-ether 60–80	115–117	90	$C_{24}H_{25}N_3O_3S_2$	61.67 61.54	5.35 5.49	—	8.99 9.12	13.70 13.92	+++ 150	+ 475	—	—	—	—	++++ 1	+++ 250
VIc		pet-ether 60–80	149–150	80	$C_{23}H_{20}N_6O_3S$	60.00 59.84	4.35 4.28	—	18.26 18.12	6.96 6.82	++ 400	++ 400	+ 500	—	—	—	+++ 350	—

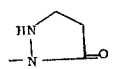
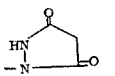
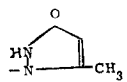
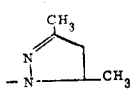
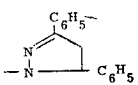
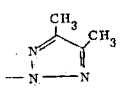
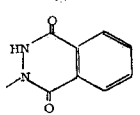
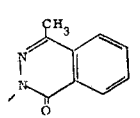
(--) inactive, (+) slightly active; (++) fairly active; (+++) moderately active; (++++) highly active.

B.s., Bacillus subtilis ATCC 7972; B.m. Bacillus mycoides USSR; B.c. Bacillus cereus IMRU; S.I., Sarcina lutea IMRU 14; E.c., Escherichia coli BPPOl; P.S., Pseudomonas seruginosa M_2; C.u., Candida utilis NRRLEY 900; A.n., Aspergillus niger pp.

Table 6

p-NH.Ac.C_6H_4.SO_2.R

(VII)

Compound No.	R	Solvent	M.p.°C	Yield %	Molecular formula	Analysis (Reqd. / Found) %					In vitra Activity[a] (Mini. inhib, canc. ug / ml.)							
						C	H	Cl	N	S	Gram+ve B.				Gram+ve B		Fungi	
											B.s.	B.m.	B.c.	S.l.	E.c.	P.a.	C.u.	A.n.
VIIa		AcOH	222–223	60	$C_{11}H_{13}N_3O_4S$	46.64 46.80	4.59 4.62	—	14.84 15.00	11.31 11.62	—	—	—	—	—	—	—	++ 450
VIIb		Methanol	285–287	70	$C_{11}H_{11}N_3O_5S$	44.44 44.32	3.70 3.78	—	14.14 14.36	10.77 10.92	—	—	—	—	—	—	—	+++ 150
VIIc		Ethanol	109–110	80	$C_{12}H_{13}N_3O_4S$	48.81 48.73	4.41 4.35	—	14.24 14.18	10.85 11.00	—	—	—	—	—	—	—	++++ 150
VIId		Ethanol	170–172	80	$C_{13}H_{16}N_3O_3S$	53.06 53.18	5.44 5.36	—	14.29 14.15	10.88 11.00	—	++ 350	++ 500	—	—	+++ 350	++++ 50	—
VIIe		Ethanol	185	85	$C_{23}H_{20}N_3O_3S$	66.03 65.87	4.79 4.86	—	10.05 10.20	7.66 8.84	+++ 100	++++ 50	++ 425	—	—	++++ 100	+++ 350	++ 375
VIIf		Ethanol	244–245	65	$C_{12}H_{14}N_4O_3S$	48.98 48.78	4.76 4.88	—	19.05 19.30	10.88 11.10	++ 375	—	++ 375	—	—	—	+ 500	++ 400
VIIg		AcOH	279–280	75	$C_{16}H_{13}N_3O_5S$	53.48 53.32	3.62 3.51	—	11.70 11.82	8.91 8.74	—	++++ 50	++ 400	—	—	—	+++ 300	+ 500
VIIh		Ethanol	224–225	70	$C_{17}H_{15}N_3O_4S$	57.14 57.10	4.20 4.32	—	11.77 11.64	8.96 8.82	—	+ 475	—	—	—	—	—	—

iii- *Formation of VIId-h:*

A mixture of I (0.01 M) and 1,3-diketone, namely; acetylacetone and benzoylacetone; 1:2-diketone, namely; biacetylmonoxime; acid anhydride namely; phthalic anhydride, or keto-acids, namely; o-acetobenzoic or o-benzoylbenzoic acid (0.015 M) in acetic acid (50-100 ml.) was hetaed under reflux for 2-4 hr., cooled, poured into water, filtered and the solid obtained was crystallized from the proper solvent to give the titled compounds.

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