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3-(ETHOXYCARBONYL)-2-METHYLPYRROLE-5-CARBOXALDEHYDE AS A VERSATILE SYNTHONE FOR POTENTIAL ANTIBACTERIAL AGENTS

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تم فى هذا البحث تشييد العديد من مركبات الثيوسيمى كاربـازيدات محملـة علـى حلقـة البـيرول موضـع ٥. وقـد تـم حولقـة هـذه المركبـات إلـى مشـتقات الثيـازول ، والثيـازوليدينون ، وأخـيرا الثياديازول. وقد تم إثبات التركيب البنائى لهذه المركبات بالتحليل الدقى ودراسة أطيافهـا فـى الأشـعة تحت الحمراء والرنين النووى المغناطيسى وقياس أطياف الكتلة لبعضها. وقد تمت دراسة تأثير هذه المركبات ضد ميكروب باسيلس سيرس ، ستافيلوكوكس سابروفتيكا ، باسيلس بوتيدا ، أشرشـيا كولاى وغيرهم.

Reaction of 3-(ethoxycarbonyl)-2-methylpyrrole-5-carboxaldehyde with substituted thiosemicarbazides afforded the corresponding (thiocarbamoyl) hydrazones. The latter compounds underwent cyclization to thiazole, thiazolidinone, thiazinone and thiadizole derivatives under the proper reaction condition. All the prepared compounds were evaluated for this antimicrobial activity.

INTRODUCTION

Pyrrole derivatives possess antifungal[1,2] activity in addition to their antispasmodic and analgesic effects[3]. Thiazoles have antibacterial and tuberculastic activities[4] besides their action against nematodes, various yeasts and Fungi[5]. Also, thiazolidinones were found to possess different biological activities such as cyclooxygenase inhibitors[6], MAO inhibitors[7], CNS depressants[7], antihistaminics[8], antiarthritic[9] and antimicrobials[10]. Meanwhile, thiazines and thiadizoles were tested as oxytocin antagonists[11], antifungal, antibacterial and antinematodl agents[12,13]. In view of these observations, we synthesized various substituted thiazolines, thiazolidinones, thiadiazoles and thiazines attached to a pyrrole derivative (Scheme I) to be evaluated for their antibacterial and antifungal activities.

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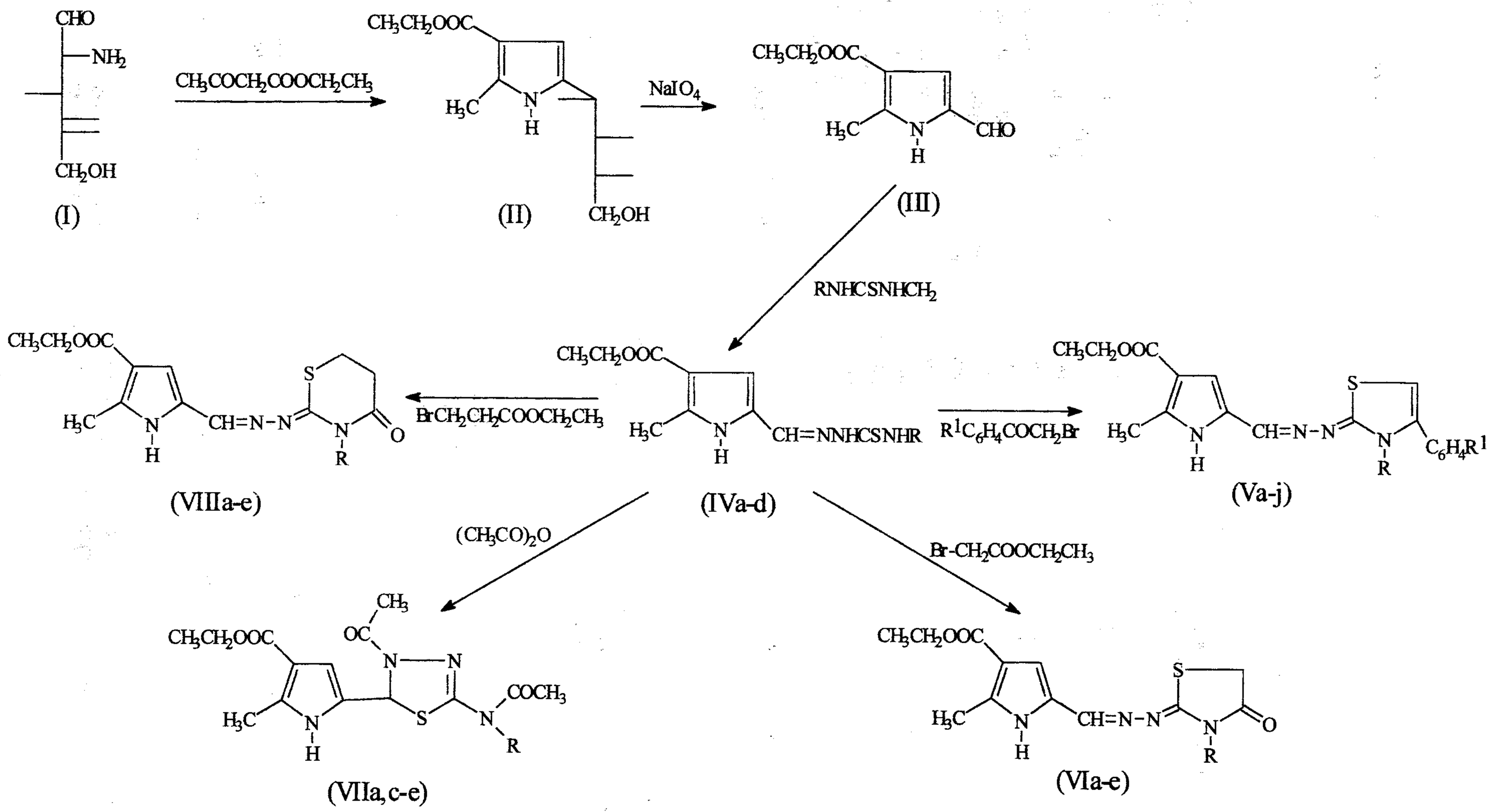
EXPERIMENTAL

Melting points were determined in Mel.Temp II apparatus and are uncorrected. The IR spectra were measured in Nujol mull on Beckman 4210 spectrophotometer. The ^{1}H-NMR spectra were recorded at 60 Mhz on a Varian EM-360L spectrometer, in DMSO-d_6 using tetramethyl-silane as internal standard (chemical shift in δ ppm). Mass spectra were taken with HP-MODEL 5988 spectrometer: inlet temperature Ca 300°C, ionization energy 70 eV. Microanalysis were performed by the Faculty of Science, Cairo University.

Substituted 3-(ethoxycarbonyl)-2-methyl-pyrrole-5-carboxaldehyde (thiocarbamoyl) hydrazones (IVa-d)

To a solution of 3-(ethoxycarbonyl)-2-methylpyrrole-5-carboxaldehyde[14] (III) (1.81 g, 0.01 mole) in ethanol (20 ml), the proper

Scheme I



R= $C_6H_4CH_3$(m), allyl, $CH_2C_6H_5$, C_6H_5, H

R^1= H, Br

thio-semicarbazide derivative (0.01 mole) was added. The reaction mixture was heated under reflux for 1 hr., cooled, the precipitate obtained was filtered off and recrystallized from ethanol, (Table 1). IR: 3466-3224, 3174-3104 (NH); 1750-1730 (C=O); 1620-1610 (C=N) and 1545-1520, 1330-1320, 1050-1040, 935-920 (N=C=S)[15] cm^{-1}.

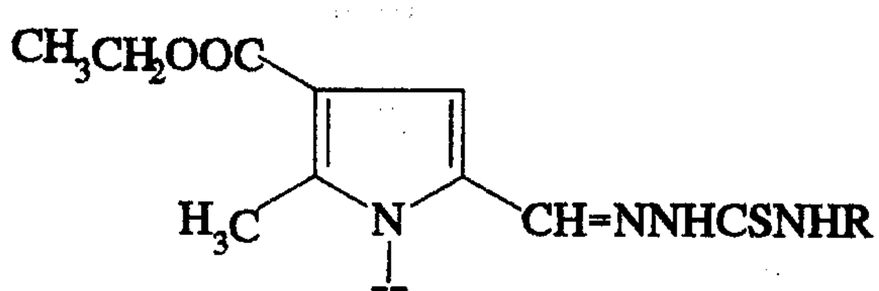
^{1}H-NMR of compound (IVa). 1.26 (t, 3H, $CH_2\underline{CH_3}$); 2.33 (s, 3H, pyrrole-3-CH_3); 2.52 (s, 3H, $C_6H_5\underline{CH_3}$); 4.15 (q, 2H, $\underline{CH_2}CH_3$); 6.65-7.40 (m, 5H, Ar-H); 7.85 (s, 1H, $\underline{CH}$-N); 9.75 (s, 1H, pyrrole-NH; deuterium exchangeable); 11.57 (s, 2H, 2NH; deuterium exchangeable).

MS: (m/z, %) for compound (IVa): M^+ (344.24); (237.34); (180.72); (165.42); (151.56); (135.31); (106.87); (91.100); (79.29); (51.18).

Substituted 3-(ethoxycarbonyl)-2-methyl-pyrrole-5-carboxaldehyde(3,4-disubstituted-2,3-dihydrothiazol-2-ylidene) hydrazones(Va-j)

A solution of the foregoing (thiocarbamoyl) hydrazones (IVa-e) (0.01 mole) in ethanol (40 ml) was treated with the equivalent amount of the proper phenacyl bromide (0.01 mole). The reaction mixture was heated under reflux for 1 hr. cooled and neutralized with a solution of sodium acetate (5 ml). The solid obtained was filtered off and recrystallized from ethanol, (Table 2).

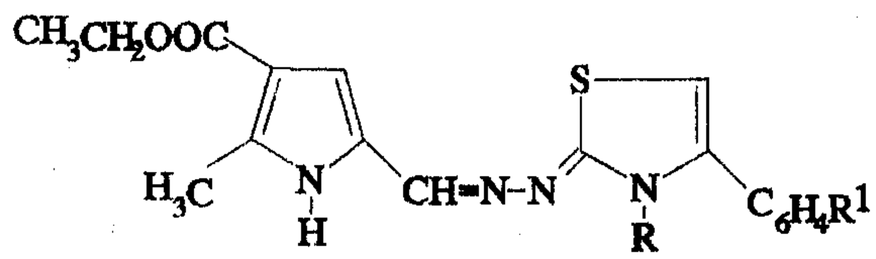
Table 1: Substituted 3-(ethoxycarbonyl)-2-methylpyrrole-5-carboxaldehyde-(thiocarbamoyl) hydrazones IVa-d.



H

Comp. No.	R	M.P. °C	Yield %	M. formula (M. wt.)	Analysis % (Calcd./Found)			
					C	H	N	S
IVa	$C_6H_4CH_3$(m)	119-20	65	$C_{17}C_{20}N_4O_2S$ (344.44)	59.28 59.40	5.85 5.60	16.27 16.40	9.31 9.20
b	CH_2-CH=CH_2	183-4	70	$C_{13}H_{18}N_4O_2S$ (294.37)	53.04 52.90	6.16 6.00	19.03 19.10	10.89 10.70
c	$CH_2C_6H_5$	213-4	74	$C_{17}H_{20}N_4O_2S$ (344.44)	59.28 58.90	5.85 6.00	16.27 16.00	9.31 9.40
d	C_6H_5	197-8	65	$C_{16}H_{18}N_4O_2S$ (330.41)	58.16 58.10	5.49 5.40	16.96 16.70	9.70 10.00

Table 2: Substituted 3-(ethoxycarbonyl)-2-methylpyrrole-5-carboxaldehyde-(3,4-H/ disubstituted-2,3-dihydrothiazol-2-ylidene) hydrazones IVa-j.



Comp. No.	R	R^1	M.P. °C	Yield %	M. formula (M. wt.)	Analysis % (Calcd./Found)				
						C	H	N	S	Br
Va	$C_6H_4CH_3$(m)	H	184-5	61	$C_{25}H_{24}N_4O_2S$ (444.56)	67.54 67.70	5.44 5.71	12.60 12.20	7.21 7.00	
b	$C_6H_4CH_3$(m)	Br	144-5	78	$C_{25}H_{23}BrN_4O_2S$ (523.46)	57.36 57.20	4.43 4.40	10.70 10.60	6.13 6.10	15.26 15.00
c	CH_2-CH=CH_2	H	95-6	74	$C_{21}H_{22}N_4O_2S$ (394.50)	63.94 64.00	5.62 5.20	14.20 14.60	8.13 8.00	
d	CH_2-CH=CH_2	Br	121-2	73	$C_{21}H_{21}BrN_4O_2S$ (473.40)	53.28 53.00	4.47 4.70	11.83 11.40	6.77 7.00	16.87 16.90
e	$CH_2C_6H_5$	H	88-9	78	$C_{25}H_{24}N_4O_2S$ (444.56)	67.54 67.60	5.44 5.51	12.60 13.00	7.21 7.20	
f	$CH_2C_6H_5$	Br	73-4	84	$C_{25}H_{23}BrN_4O_2S$ (523.46)	57.36 56.90	4.43 4.34	10.70 11.00	6.13 6.10	15.26 15.50
g	C_6H_5	H	91-2	88	$C_{24}H_{22}N_4O_2S$ (430.53)	66.96 66.90	5.15 5.00	13.01 13.00	7.45 7.10	
h	C_6H_5	Br	97-8	72	$C_{24}H_{21}BrN_4O_2S$ (509.43)	56.59 56.90	4.16 3.80	10.00 10.40	6.29 6.10	15.68 15.50
i	H	H	186-7	75	$C_{18}H_{18}N_4O_2S$ (354.43)	61.00 61.00	5.12 4.80	15.81 15.40	9.05 9.40	
j	H	Br	119-20	78	$C_{18}H_{17}BrN_4O_2S$ (433.33)	49.89 50.10	3.95 4.30	12.93 12.60	7.40 7.80	18.44 18.80

IR: 3300-3240 (NH); 1730-1720 (C=O); 1580-1575 (C=N) in addition to the disappearance of N-C=S bands.

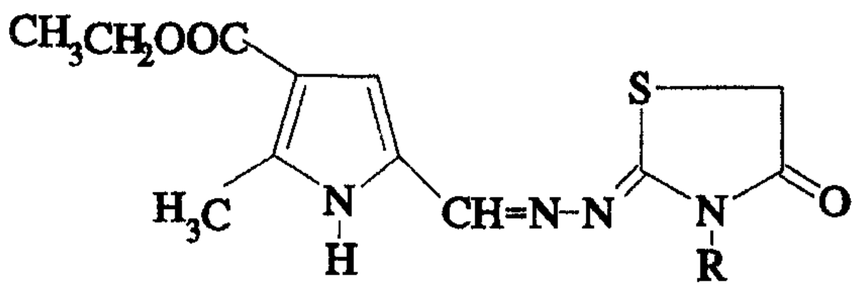
^{1}H-NMR of compound (Vf): 1.15 (t, 3H, $CH_2\underline{CH_3}$), 2.44 (s, 3H, pyrrole-3-CH_3); 4.03 (q, 2H, $\underline{CH_2}CH_3$); 5.26 (s, 2H, $\underline{CH_2}C_6H_5$); 6.44-7.70 (m, 11H, Ar-H); 10.65 (s, 1H, CH=N); 11.35 (s, 1H, NH; deuterium exchangeable). MS (m/z, %) for compound (Vb); M^+ 524, 522; (16,17); 432, 430 (7, 7.7); 386, 384; (68, 64); 376, 374; (22, 22); 346 (9); 269 (30; 174 (11); 134 (14); 91 (100); 65 (23).

Substituted 3-(ethoxycarbonyl)-2-methyl-pyrrole-5-carboxaldehyde-(3-substituted thiazolidin-4-on-2-ylidene) hydrazones (VIa-e)

A mixture of (IVa-e) (0.01 mole) in dry acetone (40 ml), ethyl bromoacetate (1.7 g, 0.01 mole) and anhydrous potassium carbonate (0.9 g, 0.01 mole) was heated under reflux for 30 min. Water was added and the produced precipitate was filtered off and recrystallized from ethanol, (Table 3). IR: 3340-3320 (NH); 1720 (C=O ester); 1715-1680 (C=O thiazolidinone); 1640-1630, 1600-1570; 1540-1515 (C=N, δ NH, C=C) cm^{-1}.

^{1}H-NMR of compound (VIa) ($CDCl_3$): 2.28 (t, 3H, $CH_2\underline{CH_3}$); 2.37 (s, 3H, pyrrole-3-CH_3); 2.50 (s, 3H, $C_6H_5\underline{CH_3}$); 4.18 (q, 2H, $\underline{CH_2}CH_3$); 5.18 (s, 2H, $\underline{CH_2}C_6H_5$); 6.70-7.34 (m, 5H, Ar-H); 7.97 (s, 1H, NH).

Table 3: Substituted 3-(ethoxycarbonyl)-2-methylpyrrole-5-carboxaldehyde-(3-substituted thiazolidin-4-on-2-ylidene) hydrazones IVa-e.



Comp. No.	R	M.P. °C	Yield %	M. formula (M. wt.)	Analysis % (Calcd./Found)			
					C	H	N	S
VIa	$C_6H_4CH_3$(m)	60-2	70	$C_{19}C_{20}N_4O_3S$ (384.46)	59.36 59.60	5.24 5.00	14.57 14.90	8.34 8.60
b	CH_2-CH=CH_2	95-6	35	$C_{15}H_{18}N_4O_3S$ (334.40)	53.88 54.30	5.43 5.50	16.75 16.30	9.60 9.90
c	$CH_2C_6H_5$	129-30	75	$C_{19}H_{20}N_4O_3S$ (384.46)	59.36 59.00	5.24 4.80	14.57 14.50	8.34 8.00
d	C_6H_5	198-9	65	$C_{18}H_{18}N_4O_3S$ (370.43)	58.36 58.00	4.90 5.10	15.12 14.90	8.66 8.60
e	H	165-6	40	$C_{12}H_{14}N_4O_3S$ (294.33)	48.97 48.90	4.79 4.60	19.04 19.10	10.89 10.90

3-(Ethoxycarbonyl)-2-methyl-5-[3-acetyl-5-(N-substituted acetamido)-2,3-dihydro-1,3,4-thiadiazol-2-yl] pyrroles VIIa,c-e

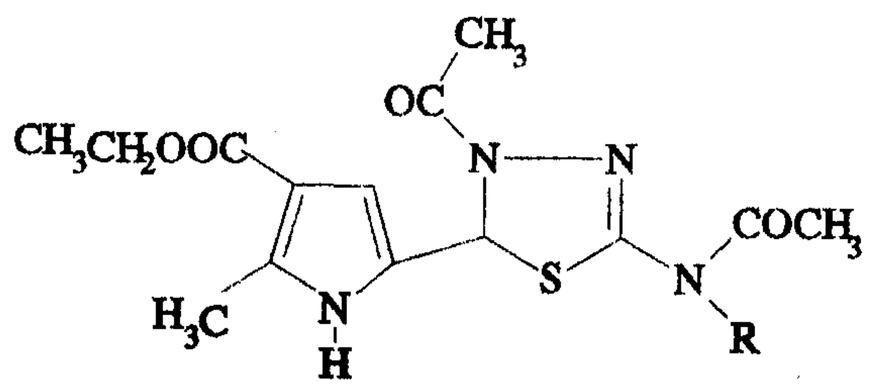
A mixture of the appropriate (thiocarbamoyl) hydrazones (IVa,c-e) (0.01 mole) and acetic anhydride (5 ml) was heated under reflux for 1 hr. The mixture was cooled and poured into crushed ice, the formed solid was filtered off, washed with water and recrystallized from ethanol, (Table 4). IR: 1735-1720 (C=O ester); 1680-1660 (C=O acetyl); 1640-1630 (C=N) cm^{-1}.

^{1}H-NMR of compound (VIIc): 1.15 (t, 3H, $CH_2\underline{CH_3}$); 1.74, 1.84 (two s, each 3H, $2\underline{CH_3}CO$); 2.30 (s, 3H, pyrrole-3-CH_3); 4.04 (q, 2H, $\underline{CH_2}CH_3$); 6.02 (s, 1H, thiadiazoline-2-H); 6.60-7.35 (m, 6H, Ar-H); 11.00 (s, 1H, NH; deuterium exchangeable).

Substituted 3-(ethoxycarbonyl)-2-methyl-pyrrole-5-carboxaldehyde-3-(substituted-5, 6-dihydro thiazin-4-on-2-ylidene) hydrazones (VIIIa-e)

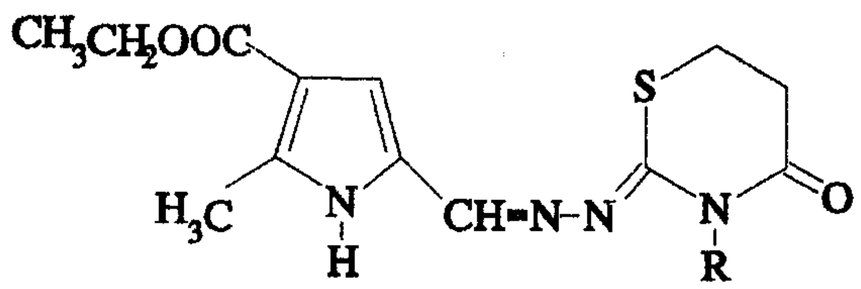
Ethyl B-bromopropionate (1.81 g, 0.01 mole) was added to a solution of the corresponding 3-(ethoxycarbonyl)-2-methyl-pyrrole-5-carboxaldehyde (thiocarbamoyl) hydrazones (IVa-e) (0.01 mole) in ethanol (20 ml). The reaction mixture was heated under reflux for 8 hr., cooled and poured into saturated potassium carbonate solution (5 ml). The precipitate separated out was filtered off and recrystallized from ethanol, (Table 5).
IR: 1720 (C=O ester); 1720-1690 (C=O thiazinone); 1620-1560, 1530 (C=N, δ NH, C=C) cm^{-1}.

Table 4: 3-(Ethoxycarbonyl)-2-methyl-5-[3-acetyl-5-(N-substituted acetamido)-2,3-dihydro-1,3,4-thiadiazol-2-yl] pyrroles VIIa,c-e.



Comp. No.	R	M.P. °C	Yield %	M. formula (M. wt.)	Analysis % (Calcd./Found)			
					C	H	N	S
VIIa	$C_6H_4CH_3$(m)	76-7	35	$C_{21}C_{24}N_4O_4S$ (428.51)	58.86 59.20	5.65 5.80	13.07 12.80	7.48 7.10
c	$CH_2CH_6H_5$	82-3	72	$C_{21}H_{24}N_4O_4S$ (428.51)	58.86 58.80	5.65 5.90	13.07 13.10	7.48 7.50
d	C_6H_5	159-60	69	$C_{20}H_{22}N_4O_4S$ (414.49)	57.96 58.40	5.35 5.50	13.52 13.50	7.74 7.20
e	H	234-5	70	$C_{14}H_{18}N_4O_4S$ (338.39)	49.69 49.80	5.36 5.10	16.65 16.90	9.48 9.40

Table 5: Substituted 3-(ethoxycarbonyl)-2-methylpyrrole-5-carboxaldehyde-(3-substituted-5,6-dihydro-1,3-thiazin-4-on-2-ylidene) hydrazones VIIIa-e.



Comp. No.	R	M.P. °C	Yield %	M. formula (M. wt.)	Analysis % (Calcd./Found)			
					C	H	N	S
VIIIa	$C_6H_4CH_3$(m)	83-4	65	$C_{20}C_{22}N_4O_3S$ (398.49)	60.28 60.00	5.56 5.16	14.06 14.10	8.05 8.00
b	CH_2-CH=CH_2	110-1	50	$C_{16}H_{20}N_4O_3S$ (348.43)	55.16 55.10	5.79 5.90	16.08 15.80	9.20 9.00
c	$CH_2C_6H_5$	108-9	65	$C_{20}H_{22}N_4O_3S$ (398.49)	60.28 60.40	5.56 5.80	14.06 14.10	8.05 8.00
d	C_6H_5	97-8	60	$C_{19}H_{20}N_4O_3S$ (348.46)	59.36 59.00	5.24 5.00	14.57 14.70	8.34 8.60
e	H	184-5	55	$C_{13}H_{16}N_4O_3S$ (308.36)	50.64 51.00	5.23 4.90	18.17 17.90	10.40 10.80

Antimicrobial activity

Staphylococcus saprophyticus as (Gm +ve bacteria), *Pseudomonas putida*, *E. coli* as (Gm -ve bacteria), *Saccharomyces cerevisiae* Y-1347, *Saccharomyces uvarum*, *Aspergillus flavus* ATCC-5517 and *Aspergillus parasiticus* NRRL-2999 were used to determine antimicrobial activity, as measured by agar diffusion method[16]. Test compounds were dissolved in dimethylformamide to yield a concentration of 1 mg/ml of solution. Ampicillin and griseofulvin were used as standards for comparison of antibacterial and antifungal activities. The tests were carried out with 6 UL solutions of the tested compounds and the solvent served as the control. Sterile agar plates were inoculated with inoculum (1 ml/100 ml of agar). The nutrient agar plates for bacteria were incubated at 37±1°C for 24 hr. For fungi, sabouraud dextrose agar was used and cultures were incubated at 28±1°C for 72 hr. After incubation, the comparative zones of inhibition formed around the discs were measured. All the tests were done in triplicate and means values were recorded, (Table 6).

Table 6: Antimicrobial activity[a].

Compd. No.		Bacteria[a]			Fungi[b]			
IV	a	SS	PP	EC	EC	SU	AF	AP
	b	-	-	-	-	17	-	-
	c	-	-	-	-	-	-	-
	d	-	-	-	-	17	-	-
	e	-	-	0.06	38	17	-	-
V	a	-	-	-	40	24	-	-
	b	-	-	-	-	-	-	-
	c	-	0.06	0.06	-	-	-	-
	d	0.07	-	-	10	25	-	33
	e	-	0.0025	-	12	33	17	17
	f	-	-	-	15	35	18	23
	g	-	-	-	-	-	12	-
	h	-	-	-	-	21	-	-
	i	-	-	-	17	17	-	-
	j	1	-	-	17	-	-	-
VI	a	0.05	-	-	-	-	-	-
	b	1	1	0.02	-	15	-	-
	c	-	-	-	17	-	-	24
	d	-	0.02	0.05	-	-	16	33
	e	-	-	-	-	-	25	34
VII	a	-	-	-	-	-	-	25
	c	-	-	-	-	-	-	-
	d	-	-	-	-	-	-	-
	e	-	-	-	-	-	35	25
VIII	a	-	-	0.05	-	-	-	-
	b	0.05	-	-	20	26	-	33
	c	-	-	-	18	-	-	-
	d	0.01	-	-	19	-	-	-
	e	-	-	-	-	-	-	-
Ampicillin		4	4	4	-	-	-	-
Griseofulvin		-	-	-	38	38	35	34

a) MIC, b) Zones of inhibition (mm)
Saprophyticus; PP, *P. putida*; EC, *E. coli*; SC, *Sacch. cerevisiae*; SU, *Sacch. uvarum*; AF, *A. flavus*; AP, *A. parasiticus* NNRL-2999 b)-, showed no inhibition zone.

RESULTS AND DISCUSSION

3-(Ethoxycarbonyl)-2-methylpyrrole-5-carboxaldehyde[14] (III) which served as the starting material, was reacted with substituted thiosemicarbazides to yield 3-(ethoxycarbonyl)-2-methylpyrrole-5-carboxaldehyde (thiocarbamoyl) hydrazones (IVa-e) in good yields (Table 1). The mass spectrum of compound (IVa) was performed as a representative example of the thiocarbamoyl derivatives. It revealed a molecular ion peak at m/z 344 and the base peak at m/z 91 that is attributed to the tropylium ion. Compounds (IVa-e) underwent cyclization with phenacyl bromide derivatives to produce a series of substituted 3-(ethoxy-carbonyl)-2-methyl-

pyrrole-5-carboxaldehyde-(3,4-disubstituted-2,3 -dihydrothiazol-2-ylidene) hydrazones (Va-j) (Table 2). The structure of the foregoing compounds was supported by measuring the mass spectrum of compound (Vb), where it shows two molecular ion peak at m/z 523 and 525 respectively indicating the presence of bromine.

Antimicrobial testing revealed that some of the newly prepared compounds possess potent antimicrobial activity (Table 6). Compounds (Vd and VIIIc) showed better activity against Gam-positive and Gram-negative bacteria such as *Staphylococcus saprophyticus* and *Pseudomonas putida* and *Escherichia coli*, respectively. While compounds (IVe, Vf, VIIe and VIIIa) were highly active against *Saccharomyces cerevisiae* Y-1347 and *Saccharomyces uvarum*, the rest of the compounds exhibited either lower activity or no activity, (Table 6).

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