Synthesis of Heterocycles. Part VI [1]. Synthesis and Antimicrobial Activity of Some 4-Amino-5-aryl-1,2,4-triazole-3-thiones and their Derivatives

N. F. Eweiss [2], A. A. Bahajaj* and E. A. Elsherbini

Department of Chemistry, University of Kuwait
Kuwait

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4-Amino-5-aryl-1,2,4-triazole-3-thiones I react with acid chlorides to yield 4-acylamino-5-aryl-1,2,4-triazole-3-thiones II. Compounds I also react with methylene iodide, chloroacetonitrile and methyl bromoacetate to give *bis*-(4-amino-5-aryl-1,2,4-triazol-3-ylthio)methanes III, 4-amino-5-aryl-3-cyanomethylthio-1,2,4-triazoles IV and 4-amino-5-aryl-3-carbomethoxymethylthio-1,2,4-triazoles V, respectively. Compounds V react with hydrazine hydrate to give the corresponding acid hydrazides VI which in turn condenses with acid chlorides and aldehydes to afford respectively 1-[(4-amino-5-aryl-1,2,4-triazol-3-ylthio)acetyl]-2-aroylhydrazines VII and aryl methylene (4-amino-5-aryl-1,2,4-triazol-3-ylthio)acethydrazones VIII. The antimicrobial activities of the above compounds were screened against different strains of bacteria and fungi.

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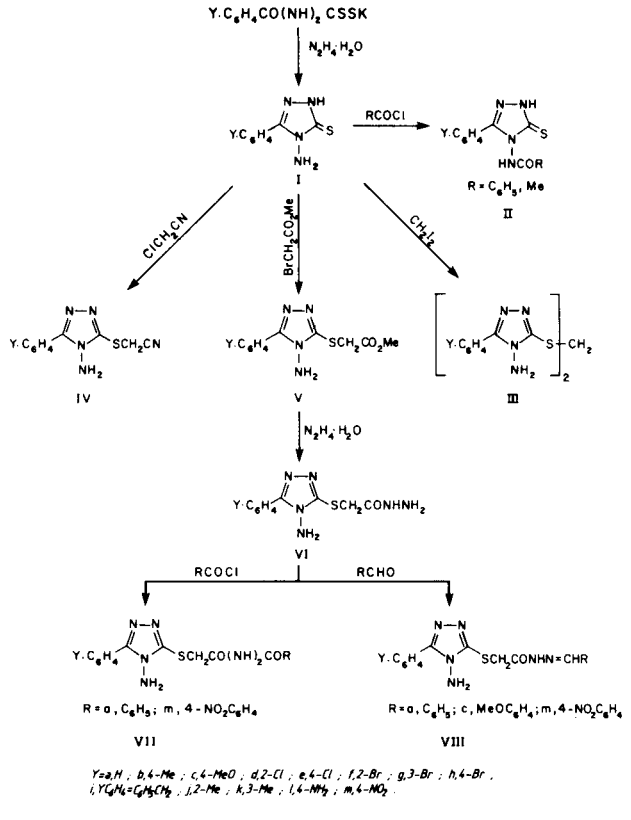
In continuation of our interest in the synthesis of heterocycles [1,3] and the antimicrobial activity of sulphur and nitrogen-containing organic compounds [4], we wish to report the synthesis of a series of 4-amino-5-aryl-1,2,4-triazole-3-thiones and their derivatives which were found to exhibit a wide range of biological and antimicrobial activities [5-12]. In this study we aimed to correlate the antimicrobial acitivity, if any, of triazoles I with different substituents at the phenyl group in position 5. Besides, masking either the amino or the mercapto group, one at a time, might demonstrate which could be involved in the antimicrobial activity. The synthesis and antimicrobial activity of some fused systems of I will be the subject of further work.

Results and Discussion.

A group of twelve 4-amino-5-aryl-1,2,4-triazole-3-thiones I were prepared by hydrazinolysis of the corresponding potassium 3-aroyldithiocarbazates with excess hydrazine hydrate (Scheme I) following Reid and Heindel procedure [13]. 4-Amino-1,2,4-triazole-3-thione was prepared according to the Beyer procedure [14]. The structure of I was confirmed from analytical (Table I) and spectral data (Table II). Thus their ir spectra showed stretching band in the regions 3280-3350 cm^{-1} and 1610-1635 cm^{-1} attributed to NH_2 and C=N respectively. Their nmr spectra showed a singlet at δ 5.14-5.87 ppm (2H, NH_2) and a singlet at δ 13.61-14.79 ppm (1H, SH or HNCS) reflecting the thiol-thione tautomeric forms [13,15]. The aromatic protons of the aryl group resonated as a multiplet at δ 6.93-8.27 ppm. It was suggested [16] that the cyclocondensation of the potassium 3-aroyldithiocarbazates to triazoles I upon treatment with hydrazine hydrate passes through an intermediate 1-aroylthiocarbohydrazide that undergoes simultaneous cyclization yielding I.

Reaction with Acid Chlorides.

The reaction of I with acid chlorides in pyridine at 0°

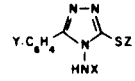


Scheme I

have been previously described by Kanaoka [17]. Thus treating triazoles I with acetyl chloride or benzoyl chloride afforded the corresponding 4-acylamino-5-aryl-1,2,4-triazole-3-thiones II. Their analytical (Table I) and spectral data (Table II) are in accordance with the structures ass-

Table I

Analytical Data of 4-Amino-5-acryl-1,2,4-triazole-3-thiones I and their Derivatives II-VIII



Compound	Y	X	Z	Mp °C (Lit mp)	Yield %	Molecular formula	C Calcd/ (Found)	H Calcd/ (Found)	N Calcd/ (Found)	S Calcd/ (Found)
Ia	H	H	H	203-204 (203-206) [13]	78	$C_8H_8N_4S$	49.97 (50.12)	4.20 (4.11)	29.15 (28.92)	16.68 (16.91)
Ib	4-Me	H	H	211-212 (213) [27]	63	$C_9H_{10}N_4S$	52.40 (52.26)	4.90 (4.87)	27.17 (26.99)	15.53 (15.49)
Ic	4-MeO	H	H	201 (205-206) [13]	59	$C_9H_{10}N_4OS$	48.63 (48.66)	4.54 (4.54)	25.21 (25.25)	14.42 (14.35)
Id	2-Cl	H	H	154-155 (152) [27]	72	$C_8H_7ClN_4S$ [a]	42.38 (42.21)	3.12 (3.02)	24.72 (24.82)	14.14 (14.06)
Ie	4-Cl	H	H	210-211	65	$C_8H_7ClN_4S$ [b]	42.38 (42.39)	3.12 (3.11)	24.72 (24.68)	14.14 (14.31)
If	2-Br	H	H	172-173	52	$C_8H_7BrN_4S$ [c]	35.43 (35.28)	2.61 (2.60)	20.67 (20.62)	11.82 (12.05)
Ig	3-Br	H	H	223-234	58	$C_8H_7BrN_4S$ [d]	35.43 (35.25)	2.61 (2.53)	20.67 (20.50)	11.82 (11.70)
Ih	4-Br	H	H	192-193	57	$C_8H_7BrN_4S$ [e]	35.43 (35.61)	2.61 (2.59)	20.67 (20.64)	11.82 (11.77)
Ii	[f]	H	H	179-180 (180) [27]	61	$C_9H_{10}N_4S$	52.40 (52.15)	4.90 (4.78)	27.17 (26.95)	15.53 (15.31)
Ij	2-Me	H	H	154-155	60	$C_9H_{10}N_4S$	52.40 (52.11)	4.90 (4.73)	27.17 (27.01)	15.53 (15.42)
Ik	3-Me	H	H	159-160	58	$C_9H_{10}N_4S$	52.40 (52.35)	4.90 (4.84)	27.17 (27.12)	15.53 (15.42)
Il	4-NH_2	H	H	260-261	50	$C_8H_9N_5S$	47.35 (47.21)	4.39 (4.31)	33.79 (33.56)	15.47 (15.41)
IIa	H	COMe	H	218-219 (218-219) [17]	60	$C_{10}H_{10}N_4OS$	51.04 (51.27)	4.25 (4.35)	23.82 (23.60)	13.62 (13.51)
IIh	4-Br	COMe	H	281-282	57	$C_{10}H_9BrN_4OS$ [g]	38.22 (38.23)	2.89 (2.87)	17.84 (17.69)	10.20 (10.15)
IIi	[f]	COMe	H	239-240	67	$C_{11}H_{12}N_4OS$	53.20 (53.12)	4.88 (4.94)	22.57 (22.75)	12.91 (13.00)
IIaa [h]	H	COC_6H_5	H	251-252 (255) [17]	89	$C_{15}H_{12}N_4OS$	60.79 (60.74)	4.09 (4.16)	18.91 (18.89)	10.82 (10.82)
IIga	3-Br	COC_6H_5	H	190-191	54	$C_{15}H_{11}BrN_4OS$ [i]	40.01 (40.16)	2.96 (2.81)	14.93 (14.87)	8.54 (8.68)
IIia	[f]	COC_6H_5	H	267-268	71	$C_{16}H_{14}N_4OS$	61.91 (61.78)	4.56 (4.64)	18.05 (17.96)	10.33 (10.38)
IIIa	H	H	[j]	178-179	45	$C_{17}H_{16}N_8S_2$	51.49 (51.46)	4.08 (4.03)	28.27 (28.20)	16.17 (16.33)
IIIb	4-Me	H	[j]	236-237	75	$C_{19}H_{20}N_8S_2$	53.74 (53.66)	4.76 (4.74)	26.40 (26.51)	15.10 (14.97)
IIIc	4-MeO	H	[j]	205-206	58	$C_{19}H_{20}N_8O_2S_2$	49.97 (49.94)	4.42 (4.43)	24.55 (24.60)	14.04 (14.02)
IIIe	4-Cl	H	[j]	238-239	65	$C_{17}H_{14}Cl_2N_8S_2$ [k]	43.87 (44.02)	3.04 (3.12)	24.08 (23.92)	13.78 (13.97)
IIIg	3-Br	H	[j]	194-195	61	$C_{17}H_{14}Br_2N_8S_2$ [l]	36.83 (36.71)	2.55 (2.52)	20.22 (20.03)	— —
IIIh	4-Br	H	[j]	236-237	54	$C_{17}H_{14}Br_2N_8S_2$ [m]	36.83 (36.78)	2.55 (2.56)	20.22 (20.24)	11.57 (11.43)
IIIi	[f]	H	[j]	178-179	61	$C_{19}H_{20}ON_8S_2$	53.74 (53.66)	4.76 (4.78)	26.40 (26.49)	15.10 (15.01)
IVa	H	H	CH_2CN	128-129	56	$C_{10}H_9N_5S$	51.92 (51.71)	3.93 (4.01)	30.29 (30.19)	13.86 (13.62)
IVb	4-Me	H	CH_2CN	182-183	62	$C_{11}H_{11}N_5S$	53.85 (53.77)	4.53 (4.64)	28.55 (28.46)	13.07 (12.92)
IVc	4-MeO	H	CH_2CN	140-141	63	$C_{11}H_{11}N_5OS$	50.55 (50.36)	4.25 (4.29)	26.81 (26.79)	12.27 (12.50)

Table I

(continued)

Compound	Y	X	Z	Mp °C (Lit mp)	Yield %	Molecular formula	C Calcd/ (Found)	H Calcd/ (Found)	N Calcd/ (Found)	S Calcd/ (Found)
IVe	4-Cl	H	CH_2CN	153-154	65	$C_{10}H_8ClN_5S$ [n]	45.19 (45.30)	3.04 (3.17)	26.36 (26.17)	12.06 (11.97)
IVh	4-Br	H	CH_2CN	157-158	58	$C_{10}H_8BrN_5S$ [o]	38.72 (38.60)	2.60 (2.66)	22.58 (22.38)	10.34 (10.18)
IVi	[f]	H	CH_2CN	130-131	54	$C_{11}H_{11}N_5S$	53.85 (53.73)	4.53 (4.62)	28.55 (28.39)	13.07 (13.23)
Va	H	H	CH_2CO_2Me	176-177	80	$C_{11}H_{12}N_4O_2S$	49.98 (50.17)	4.59 (4.67)	21.20 (21.19)	12.13 (11.99)
Vb	4-Me	H	CH_2CO_2Me	225-226	87	$C_{12}H_{14}N_4O_2S$	51.77 (51.66)	5.08 (5.03)	20.13 (19.97)	11.63 (11.52)
Vc	4-MeO	H	CH_2CO_2Me	195-196	85	$C_{12}H_{14}N_4O_3S$	48.96 (49.07)	4.73 (4.66)	19.04 (19.20)	10.39 (10.35)
Ve	4-Cl	H	CH_2CO_2Me	202-203	78	$C_{11}H_{11}ClN_4O_2S$ [p]	44.22 (44.16)	3.72 (3.70)	18.76 (18.91)	10.73 (10.68)
Vg	3-Br	H	CH_2CO_2Me	112-113	73	$C_{11}H_{11}BrN_4O_2S$ [q]	38.49 (38.37)	3.24 (3.15)	16.33 (16.48)	9.34 (9.35)
Vi	[f]	H	CH_2CO_2Me	199-200	83	$C_{12}H_{14}N_4O_2S$	51.77 (51.94)	5.08 (5.20)	20.13 (19.97)	11.63 (11.59)
VIa	H	H	$CH_2CONHNH_2$	166-167	70	$C_{10}H_{12}N_6OS$	45.43 (45.53)	4.59 (4.63)	31.80 (31.68)	12.13 (11.94)
VIc	4-MeO	H	$CH_2CONHNH_2$	185-186	79	$C_{11}H_{14}N_6OS$	44.88 (44.74)	4.80 (4.83)	28.56 (28.49)	10.89 (10.78)
VIe	4-Cl	H	$CH_2CONHNH_2$	222-223	59	$C_{10}H_{11}ClN_6OS$ [r]	40.20 (40.32)	3.72 (3.66)	28.13 (28.00)	10.73 (10.56)
VIg	3-Br	H	$CH_2CONHNH_2$	175-176	68	$C_{10}H_{11}BrN_6OS$ [s]	34.99 (35.03)	3.24 (3.26)	24.49 (24.38)	9.34 (9.51)
VIi	[f]	H	$CH_2CONHNH_2$	138-139	65	$C_{11}H_{14}N_6OS$	47.46 (47.32)	5.08 (5.10)	30.20 (30.17)	11.52 (11.43)
VIIaa	H	H	$CH_2CO(NH)_2COC_6H_5$	204-205	65	$C_{17}H_{16}N_6O_2S$	55.41 (55.37)	4.39 (4.31)	21.81 (21.89)	8.70 (8.64)
VIIca	4-MeO	H	$CH_2CO(NH)_2COC_6H_5$	206-207	45	$C_{18}H_{18}N_6O_3S$	54.25 (54.23)	4.56 (4.65)	21.10 (21.07)	8.06 (7.99)
VIIem	4-Cl	H	$CH_2CO(NH)_2COC_6H_4$-4-NO_2	213-214	61	$C_{17}H_{14}ClN_7O_4S$ [t]	48.27 (48.30)	3.26 (3.19)	21.90 (21.76)	7.16 (7.22)
VIIIaa	H	H	$CH_2CONHN=CHC_6H_5$	196-197	71	$C_{17}H_{16}N_6OS$	57.93 (57.85)	4.54 (4.68)	23.85 (23.73)	9.10 (8.95)
VIIIac	H	H	$CH_2CONHN=CHC_6H_4$-4-MeO	201-202	89	$C_{18}H_{18}N_6O_2S$	56.52 (56.49)	4.75 (4.83)	21.98 (21.89)	8.38 (8.39)
VIIIam	H	H	$CH_2CONHN=CHC_6H_4$-4-NO_2	246-247	58	$C_{17}H_{15}N_7O_3S$	51.37 (51.25)	3.81 (3.91)	24.67 (24.52)	8.07 (7.96)
VIIIca	4-MeO	H	$CH_2CONHN=CHC_6H_5$	206-207	48	$C_{18}H_{18}N_6O_2S$	56.52 (56.53)	4.75 (4.82)	21.98 (21.85)	8.38 (8.27)
VIIIcm	4-MeO	H	$CH_2CONHN=CHC_6H_4$-4-NO_2	242-243	48	$C_{18}H_{17}N_7O_3S$	49.14 (49.28)	4.13 (4.11)	23.60 (23.53)	7.72 (7.49)
VIIIea	4-Cl	H	$CH_2CONHN=CHC_6H_5$	245-246	77	$C_{17}H_{15}ClN_6OS$ [u]	53.17 (52.99)	3.92 (3.98)	21.73 (21.62)	8.29 (8.17)
VIIem	4-Cl	H	$CH_2CONHN=CHC_6H_4$-4-NO_2	235-236	62	$C_{17}H_{14}ClN_7O_3S$ [n]	47.27 (47.39)	4.27 (4.17)	22.71 (22.56)	7.42 (7.29)

[a] *Anal.* Calcd. Cl, 15.64. Found: Cl, 15.54. [b] *Anal.* Calcd. Cl, 15.64. Found: Cl, 15.58. [c] *Anal.* Calcd. Br, 29.47. Found: Br, 29.25. [d] *Anal.* Calcd. Br, 29.47. Found: Br, 29.52. [e] *Anal.* Calcd. Br, 29.47. Found: Br, 29.46. [f] Y-C_6H_4 = $C_6H_5CH_2$. [g] *Anal.* Calcd. Br, 25.43. Found: Br, 25.56. [h] Two letters after compound number: the first one indicates an aryl substituent in the triazole nucleus at position 5-, and the second one indicates an aryl substituent in other sites. [i] *Anal.* Calcd. Br, 21.31. Found: Br, 21.31. [j] For compounds of series III, Z [5] structure below where Y corresponds to the same in the Table. [k] *Anal.* Calcd. Cl 15.23. Found: C, 15.31. [l] *Anal.* Calcd. Br, 28.83. Found: Br, 28.65. [m] *Anal.* Calcd. Br, 28.83. Found: Br, 28.69. [n] *Anal.* Calcd. Cl, 13.35. Found: Cl, 13.21. [o] *Anal.* Calcd. Br, 25.76. Found: Br, 25.72. [p] *Anal.* Calcd. Cl, 11.86. Found: Cl, 11.79. [q] *Anal.* Calcd. Br, 23.28. Found: Br, 23.42. [r] *Anal.* Calcd. Cl, 11.86. Found: Cl, 11.68. [s] *Anal.* Calcd. for Br, 23.25. Found: Br, 23.15. [t] *Anal.* Calcd. Cl, 7.91. Found: Cl, 7.86. [u] *Anal.* Calcd. Cl, 9.16. Found: Cl, 9.14. [v] *Anal.* Calcd. Cl, 8.21. Found: Cl, 8.11.

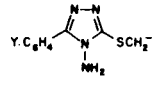
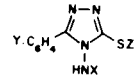


Table II

Spectral Data of 4-Amino-5-aryl-1,2,4-triazole-3-thiones I and their Derivatives II-VIII



Compound	Y	X	Z	ν (Potassium bromide) Cm⁻¹ N-H	C≡N	C=O	C=N	δ (Dimethylsulfoxide) (Multiplicity, assignment)
Ia	H	H	H	3300			1625	13.61 (s, 1H, SH), 8.01-7.39 (m, 5H, aromatic H), 5.14 (s, 2H, NH_2)
Ib	4-Me	H	H	3293			1635	13.96 (s, 1H, SH), 8.02-7.21 (m, 4H, aromatic H), 5.49 (s, 2H, NH_2), 2.41 (s, 3H, CH_3Ar)
Ic	4-MeO	H	H	3310			1610	13.91 (s, 1H, SH), 7.98-7.01 (m, 4H, aromatic H), 5.48 (s, 2H, NH_2), 3.78 (s, 3H, CH_3OAr)
Id	2-Cl	H	H	3330			1625	14.00 (s, 1H, SH), 8.23 (m, 4H, aromatic H), 4.84 (s, 2H, NH_2)
Ie	4-Cl	H	H	3265			1635	13.87 (s, 1H, SH), 8.11-7.62 (m, 4H, aromatic H), 5.70 (s, 2H, NH_2)
If	2-Br	H	H	3300			1630	14.73 (s, 1H, SH), 7.53 (m, 4H, aromatic H), 5.09 (s, 2H, NH_2)
Ig	3-Br	H	H	3300			1630	14.00 (s, 1H, SH), 8.27-7.45 (m, 4H, aromatic H), 5.61 (s, 2H, NH_2)
Ih	4-Br	H	H	3280			1630	13.79 (s, 1H, SH), 8.14-7.57 (m, 4H, aromatic H), 5.62 (s, 2H, NH_2)
Ii	[a]	H	H	3280			1635	13.61 (s, 1H, SH), 7.29 (s, 5H, aromatic H), 5.33 (s, 2H, NH_2), 4.01 (s, 2H, CH_2Ph)
Ij	2-Me	H	H	3290			1605	13.99 (s, 1H, SH), 7.52 (m, 4H, aromatic H), 5.51 (s, 2H, NH_2), 2.31 (s, 3H, CH_3Ar)
Ik	3-Me	H	H	3290			1640	14.79 (s, 1H, SH), 8.02 (m, 4H, aromatic H), 5.87 (s, 2H, NH_2), 2.31 (s, 3H, CH_3Ar)
Il	4-NH_2	H	H	3350			1610	13.92 (s, 1H, SH), 8.00 (m, 4H, aromatic H), 5.12 (s, 4H, NH_2)
IIa	H	COMe	H	3290, 3240		1680		13.64 (s, 1H, SH), 7.33 (m, 5H, aromatic H), 5.53 (s, 1H, NHCO), 2.02 (s, 3H, CH_3CO)
IIn	4-Br	COMe	H	3130		1680		14.21 (s, 1H, SH), 11.50 (s, 1H, N=COH), 7.79 (m, 4H, Ar), 2.02 (s, 3H, CH_3CO)
IIi	[a]	COMe	H	3130		1690		14.08 (s, 1H, SH), 11.52 (s, 1H, N=COH), 6.81 (m, 4H, Ar), 3.88 (s, 1H, NHCO) [b], 4.31 (s, 2H, CH_2Ph)
IIaa	H	COC_6H_5	H	3220, 3110		1690		14.28 (s, 1H, SH), 12.31 (s, 1H, N^{5}COH) [b], 8.03 (m, 10H, 2Ar), 3.51 (s, 1H, HNC=O) [b]
IIga	3-Br	COC_6H_5	H	3240		1680		14.18 (s, 1H, SH), 8.38 (m, 9H, 2Ar), 3.82 (s, 1H, NHCO) [b]
IIia	[a]	COC_6H_5	H	3280, 3150		1660		13.91 (s, 1H, SH), 11.92 (s, 1H, N=COH), 8.00-7.71 (m, 9H, Ar), 4.03 (s, 2H, CH_2Ar)
IIIa	H	H	[c]	3320, 3260			1620	8.02-7.51 (m, 10H, Ar), 6.09 (s, 4H, $2NH_2$), 5.00 (s, 2H, SCH_2)
IIIb	4-Me	H	[c]	3320, 3250			1620	7.91-7.38 (m, 8H, Ar) [d], 5.11 (s, 2H, SCH_2), 1.91 (s, 6H, $2CH_3$)
IIIc	4-MeO	H	[c]	3320, 3250			1615	7.92-7.00 (m, 8H, Ar), 6.09 (s, 4H, NH_2), 4.93 (s, 2H, SCH_2), 3.71 (s, 6H, $2CH_3O$)
IIIe	4-Cl	H	[c]	3320, 3250			1620	7.91 (m, 8H, Ar), 6.2 (s, 4H, $2NH_2$), 5.03 (s, 2H, SCH_2)
IIIg	3-Br	H	[c]	3320, 3270			1630	7.83 (m, 8H, Ar) [d], 5.17 (s, 2H, SCH_2)
IIIn	4-Br	H	[c]	3320, 3250			1625	8.01-7.72 (m, 8H, Ar), 6.19 (s, 4H, $2NH_2$), 5.01 (s, 2H, SCH_2)
IIIi	[a]	H	[c]	3320, 3260			1620	7.31 (s, 10H, Ar), 5.84 (s, 4H, $2NH_2$), 4.81 (s, 2H, SCH_2), 4.11 (s, 4H, $2CH_2Ar$)
IVa	H	H	CH_2CN	3350, 3140	2250		1650	8.46-8.01 (m, 5H, Ar), 6.48 (s, 2H, NH_2) [b], 4.51 (s, 2H, SCH_2)
IVb	4-Me	H	CH_2CN	3340, 3140	2250		1615	8.31-7.69 (m, 4H, Ar), 6.48 (s, 2H, NH_2) [b], 4.51 (s, 2H, SCH_2), 2.41 (s, 3H, CH_3Ar)
IVc	4-MeO	H	CH_2CN	3340, 3150	2260		1610	8.43-7.51 (m, 4H, Ar), 6.48 (s, 2H, NH_2), 4.51 (s, 2H, SCH_2), 4.03 (s, 3H, CH_3OAr)
IVe	4-Cl	H	CH_2CN	3310, 3190	2250		1630	8.32-7.58 (m, 4H, Ar), 6.48 (s, 2H, NH_2) [b], 4.48 (s, 2H, SCH_2)
IVh	4-Br	H	CH_2CN	3340, 3200	2260		1620	8.34 (m, 4H, Ar), 6.48 (s, 2H, NH_2), 4.48 (s, 2H, SCH_2)
IVi	[a]	H	CH_2CN	3300, 3200	2260		1620	7.83 (s, 5H, Ar), 6.48 (s, 2H, NH_2), 4.51 (s, 2H, SCH_2), 4.31 (s, 2H, CH_2Ar)

Table II

(continued)

Compound	Y	X	Z	ν (Potassium bromide) Cm⁻¹ N-H	C=O	C=N	δ (Dimethylsulfoxide) (Multiplicity, assignment)
Va	H	H	CH_2CO_2Me	3250, 3120	1740	1640	7.89-7.51 (m, 5H, Ar), 6.09 (s, 2H, NH_2), 4.11 (s, 2H, SCH_2), 3.81 (s, 3H, CH_3CO_2)
Vb	4-Me	H	CH_2CO_2Me	3250, 3120	1740	1640	7.91-7.33 (m, 4H, Ar), 6.09 (s, 2H, NH_2), 4.12 (s, 2H, SCH_2), 3.81 (s, 3H, CH_3CO_2), 2.42 (s, 3H, CH_3Ar)
Vc	4-MeO	H	CH_2CO_2Me	3250, 3120	1740	1640	7.93-7.01 (m, 4H, Ar), 6.09 (s, 2H, NH_2), 4.11 (s, 2H, SCH_2), 3.81 (s, 3H, CH_3CO_2), 3.61 (s, 3H, CH_3OAr)
Ve	4-Cl	H	CH_2CO_2Me	3260, 3140	1735	1640	8.13-7.62 (m, 4H, Ar), 6.19 (s, 2H, NH_2), 4.11 (s, 2H, SCH_2), 3.81 (s, 3H, CH_3CO_2)
Vg	3-Br	H	CH_2CO_2Me	3270, 3150	1730	1640	7.83 (m, 4H, Ar), 6.18 (s, 2H, NH_2), 4.11 (s, 2H, SCH_2), 3.81 (s, 3H, CH_3CO_2)
Vi	[a]	H	CH_2CO_2Me	3250, 3120	1740	1640	7.52 (s, 5H, Ar), 6.09 (s, 2H, NH_2), 4.11 (s, 2H, SCH_2), 4.21 (s, 2H, CH_2Ar), 3.81 (s, 3H, CH_3CO_2)
VIa	H	H	$CH_2CONHNH_2$	3320, 3190	1680	1600	9.81 (s, 1H, HNCO), 8.01-7.47 (m, 5H, Ar), 6.06 (s, 2H, NH_2) 4.29 (s, 2H, $CONNH_2$) [b], 3.81 (s, 2H, SCH_2)
VIb	4-Me	H	$CH_2CONHNH_2$	3310, 3250	1690	1600	9.83 (s, 1H, HNCO), 8.00-7.12 (m, 4H, Ar), 6.19 (s, 2H, NH_2), 4.31 (s, 2H, $CONHNH_2$) [b], 4.13 (s, 2H, SCH_2), 3.61 (s, 3H, CH_3OAr)
VIe	4-Cl	H	$CH_2CONHNH_2$	3300, 3190	1700	1615	9.81 (s, 1H, HNCO), 8.03-7.51 (m, 4H, Ar), 6.11 (s, 2H, NH_2), 4.18 (s, 2H, $CONNH_2$) [b], 3.81 (s, 2H, SCH_2)
VIg	3-Br-H		$CH_2CONHNH_2$	3300, 3180	1670	1600	9.49 (s, 1H, HNCO), 8.01 (m, 4H, Ar), 6.20 (s, 2H, NH_2), 4.31 (s, 2H, $CONNH_2$), 3.89 (s, 2H, SCH_2)
VIi	[a]	H	$CH_2CONHNH_2$	3320, 3190	1680	1600	9.13 (s, 1H, HNCO), 7.48 (s, 5H, Ar), 5.91 (s, 2H, NH_2), 4.19 (s, 2H, $CONNH_2$), 4.11 (s, 2H, SCH_2), 3.71 (s, 2H, CH_2Ar)
VIIaa	H	H	$CH_2CO(NH)_2COC_6H_5$	3300, 3200	1670	1610	11.18 (s, 1H, HNCO), 10.91 (s, 1H, HNCOR'), 8.39-7.41 (m, 10H, 2Ar), 6.28 (s, 2H, NH_2), 4.18 (s, 2H, SCH_2)
VIIca	4-MeO	H	$CH_2CO(NH)_2COC_6H_5$	3320, 3260	1695	1640	10.81 (s, 1H, HNCO), 10.74 (s, 1H, NHCOR'), 7.91-7.12 (m, 9H, 2Ar), 6.21 (s, 2H, NH_2), 4.11 (s, 2H, SCH_2), 3.92 (s, 3H, CH_3OAr)
VIIem	4-Cl	H	$CH_2CO(NH)_2COC_6H_4$-4-NO_2	3380, 3280	1690	1600	11.28)s, 1H, HNCO), 10.93 (s, 1H, NHCOR'), 8.21-7.58 (m, 8H, 2Ar), 6.18 (s, 2H, SCH_2), 4.11 (s, 2H, SCH_2)
VIIIaa	H	H	$CH_2CONHN=CHC_6H_5$	3300, 3190	1670	1600	12.31 (s, 1H, HNCO), 8.01-7.49 (m, 10H, 2Ar), 6.48 (s, 2H, NH_2), 4.48 (s, 2H, SCH_2), 4.09 (s, 1H, N=CH)
VIIIac	H	H	$CH_2CONHN=CHC_6H_4$-4-MeO	3340, 3180	1670	1600	12.01 (s, 1H, HNCO), 7.93-6.92 (m, 9H, 2Ar), 6.11 (s, 2H, NH_2), 4.39 (s, 2H, SCH_2), 4.01 (s, 1H, N=CH), 3.71 (s, 3H, CH_3OAr)
VIIIam	H	H	$CH_2CONHN=CHC_6H_4$-4-NO_2	3300, 3290	1680	1610	12.38 (s, 1H, HNCO), 8.11-7.49 (m, 9H, 2Ar), 6.19 (s, 2H, NH_2), 4.46 (s, 2H, SCH_2), 4.13 (s, 1H, N=CH)
VIIIca	4-MeO	H	$CH_2CONHN=CHC_6H_5$	3310, 3200	1680	1610	12.00 (s, 1H, HNCO), 8.21-7.19 (m, 9H, 2Ar), 6.29 (s, 2H, NH_2), 4.48 (s, 2H, SCH_2), 4.13 (s, 1H, N=CH), 3.92 (s, 3H, CH_3OAr)
VIIIcm	4-MeO	H	$CH_2CONHN=CHC_6H_4$-4-NO_2	3320, 3290	1670	1600	12.18 (s, 1H, HNCO), 8.31-7.19 (m, 8H, 2Ar), 6.28 (s, 2H, NH_2), 4.51 (s, 2H, SCH_2), 4.11 (s, 1H, N=CH), 3.92 (s, 3H, CH_3OAr)
VIIIea	4-Cl	H	$CH_2CONHN=CHC_6H_5$	3300, 3190	1670	1600	12.21 (s, 1H, HNCO), 8.09-7.58 (m, 9H, 2Ar), 6.18 (s, 2H, NH_2), 4.51 (s, 2H, SCH_2), 4.11 (s, 1H, N=CH)
VIIIem	4-Cl	H	$CH_2CONHN=CHC_6H_4$-4-NO_2	3300, 3180	1690	1610	11.68 (s, 1H, HNCO), 8.11-7.48 (m, 8H, 2Ar), 6.21 (s, 2H, NH_2), 4.51 (s, 2H, SCH_2), 4.13 (s, 1H, N=CH)

[a] Y. $C_6H_4=C_6H_5CH_2$. [b] Broad. [c] Same as in [j] Table I. [d] Solvent deuterated trifluoroacetic acid.

igned. The ir spectra of compounds II showed a strong sharp band in the 1660-1690 cm^{-1} characteristic of ν C=O of secondary amides [18a] and two bands at 3100-3300 cm^{-1} which stand for ν N-H and ν O-H forms. Besides, their nmr spectra showed singlet at δ 12.31 ppm (1H) and at δ 5.53 ppm (1H) attributed to the HOC=N and HNC=O tautomeric forms. All members of II showed a singlet at δ 13.64-14.28 ppm (1H, HNC=S). The *N*-acetyl derivatives showed also a singlet at δ ppm (3H, CH_3CO).

Reaction with Methylene Iodide.

Triazoles I reacted with excess methylene iodide in aqueous potassium hydroxide giving rise to *bis*(4-amino-5-aryl-1,2,4-triazol-3-ylthio)methanes III in 45-75% yield. Tables I and II list the analytical and spectral data, respectively, of compounds III. The diagnostic features in their nmr spectra are the presence of the methylene singlet at δ 4.92-5.17 ppm (2H, SCH_2S), the amino singlet at δ 5.84-6.09 ppm integrating to four protons, and that it is

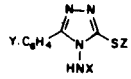
devoid of the SH singlet present in the original triazoles I. Beside the mass spectra of one example IIIi gave a parent peak M^+ [m/e = 456 (100%)].

Reaction with Chloroacetonitrile.

Heating an alcoholic solution of I with chloroacetonitrile for four hours afforded 4-amino-5-aryl-3-cyanomethylthio-1,2,4-triazoles IV [9]. The structures of IV were confirmed by analytical (Table I) and spectral data (Table II). Their ir spectra showed a sharp band at 2230-2260 cm^{-1} characteristic of the stretching frequency of nitriles [18b], whereas the nmr spectra of IV showed a singlet at δ 4.51 ppm (2H, CH_2CN) and broad singlet at δ 6.48 ppm (2H, NH_2).

Table III

Ultraviolet Absorption Spectral Data for 4-Amino-5-aryl-1,2,4-triazole-3-thiones and their Derivatives II,IV



Compound	Y	X	Z	λ max (Ethanol) nm (log ε)
Ia	H	H	H	276 (3.98) [a], 251 (4.30), 237 (4.16)
Ib	4-Me	H	H	275 (4.06) [a], 250 (4.33)
Ic	4-MeO	H	H	276 (4.52) [a], 256 (4.54)
Id	2-Cl	H	H	252 (4.38)
Ie	4-Cl	H	H	286 (3.98) [a], 252 (4.27)
If	2-Br	H	H	251 (4.26)
Ig	3-Br	H	H	276 (4.18) [a], 252 (4.42)
Ih	4-Br	H	H	285 (3.96) [a], 250 (4.12)
Ii	[b]	H	H	251 (4.32)
Ij	2-Me	H	H	276 (4.21) [a], 252 (4.52)
Ik	3-Me	H	H	280 (3.91) [a], 252 (4.25)
Il	4-NH_2	H	H	288 (4.29) [a], 260 (4.15)
IIa	H	COMe	H	251 (4.32)
IIh	4-Br	COMe	H	288 (4.03) [a], 253 (4.29)
IIi	[b]	COMe	H	278 (4.10) [a], 252 (4.26), 227 (4.05)
IIaa	H	COC_6H_5	H	255 (4.29), 223 (4.33)
IIga	3-Br	COC_6H_5	H	265 (4.09)
IIia	[b]	COC_6H_5	H	253 (4.16), 227 (4.06)
IVa	H	H	CH_2CN	263 (4.13)
IVb	4-Me	H	CH_2CN	256 (4.23)
IVc	4-MeO	H	CH_2CN	261 (4.25)
IVe	4-Cl	H	CH_2CN	263 (4.07)
IVh	4-Br	H	CH_2CN	266 (4.44)
IVi	[b]	H	CH_2CN	264 (4.12)

[a] Shoulder. [b] Y, $C_6H_4 = C_6H_5CH_2$.

Reaction with Methyl Bromoacetate and Subsequent Transformations.

Treatment of I with methyl bromoacetate in alcoholic sodium hydroxide solution afforded 4-amino-5-aryl-3-carbomethoxymethylthio-1,2,4-triazoles V in 73-87% yield. Their analytical and spectral data (Tables I and II) were in favour of the structure assigned. Thus their ir spectra showed a strong broad band in the region 1730-1740 cm^{-1} characteristic of the stretching frequency of the carbonyl group of esters and two strong bands in the region 3130-3250 cm^{-1} attributed to the stretching modes of the amino group [18c]. The nmr of V showed singlets at δ 4.11 ppm (2H, SCH_2), δ 3.81 ppm (3H, CH_3OCO), δ 6.09 ppm (2H, NH_2) and multiplet at δ 7.33-8.13 ppm due to aromatic protons. These carbomethoxymethylthio derivatives V were further treated with hydrazine hydrate in absolute ethanol to give (4-amino-5-aryl-1,2,4-triazol-3-ylthio)acethydrazides VI in 60-80% yields. Furthermore, VI was treated with aroyl chlorides to give 1-[(4-amino-5-aryl-1,2,4-triazole-3-ylthio)acetyl]-2-aroylhydrazines VII. Condensation of VI with aromatic aldehydes gave the corresponding arylmethylene-(4-amino-5-aryl-1,2,4-triazol-3-ylthio)acethydrazones VIII. The analytical data of compounds VI-VIII verify their structures and are given in Table I and their spectral data listed in Table II. The infrared spectra of the hydrazides VI showed a strong band in the region 1670-1690 cm^{-1} characteristic of ν C=O of secondary amides [18a]. The two bands in the region 3190-3320 cm^{-1} are the stretching modes of NH_2, HNCO and N=C-OH groups. The nmr spectra of VI showed a singlet at δ 9.13-9.81 ppm (1H, HNC=O or N=C-OH), a broad singlet at δ 4.29 ppm (2H) assigned to the hdyrazide NH_2 and a singlet at δ 5.96-6.18 ppm (2H, 4-NH_2). On the other hand, while the nmr spectra of VII and VIII lacked the characteristic of the NH_2 of the hydrazide group (*cf.* Series VI), it showed the pattern in accordance with the structure assigned to each series. Compound VII showed a singlet at δ 10.84-11.31 ppm (1H, HNCO) and a singlet at δ 10.68-10.82 ppm (1H, HNCOR). Compounds VIII showed in their nmr spectra a singlet at δ 11.72-12.38 ppm (1H, HNCO) and a singlet at δ 4.01-4.13 ppm (1H, N=CH). Besides, the 4-NH_2 and SCH_2 protons in VII and VIII resonated as singlets at δ 6.12-6.44 ppm and δ 4.11-4.24 ppm, respectively.

Electronic Spectra of Compounds I, II and IV.

Although many 4-amino-5-substituted-1,2,4-triazole-3-thiones, their amino and thiol derivatives have been synthesized earlier [14,20-26], yet no ultraviolet spectra were reported for these compounds. The ultraviolet absorption

spectra of compounds I, II and IV were determined in ethanol, a summary of the spectra data is listed in Table III. 4-Amino-1,2,4-triazole-3-thione show an absorption maximum at λ max 251 nm (log ε 4.13) due to n → II* transition. The introduction of a substituted phenyl group at position 5 of triazoles I results in appearance of a shoulder at λ max 275-288 nm (log ε 3.98-4.52) together with the absorption maxima at λ max 250-252 nm (log ε 4.12-4.54).

Compounds I with 4-Cl, 4-Br and 4-NH_2 phenyl substituents show a red shift of 10-12 nm in the shoulder which could be attributed to the extension of the chromophore situated *para* to the triazole nucleus. On the other hand, due to the steric inhibition of the 2-Cl and 2-Br phenyl substituents, this shoulder is obscurred reflecting the probable inability of the *ortho* substituted substituents to achieve complete coplanarity with the 1,2,4-triazole nucleus. A similar conclusion was also observed [27]. Moreover, this shoulder is not observed in 5-phenylmethyl Ii derivative which could be due to lack of extended conjugation of the phenyl and the triazole rings. This shoulder is assigned to II → II* transition. The electronic spectra of compounds II showed maximum absorption at λ max 251-255 nm (log ε 4.16-4.32). This band is not largely affected by the introduction of the acyl group except for compound II ga which showed 14 nm bathochromic shift of the absorption maximum. Compounds IIh and IIi showed a shoulder at λ max 288 nm (log ε 4.03) and λ max 278 nm (log ε 4.10) respectively. The ultraviolet spectra of compounds IV showed only one maximum absorption at λ max 261-266 nm (log ε 4.07-4.44). It seems that the introduction of the 3-cyanomethylthio group resulted in the disappearance of the shoulder present in I and also a red shift (11-15 nm) at λ max 251 nm. This bathochromic shift suggests that compounds I and IV exist predominantly in the thione form. This is what reproted with similar systems [28].

Antimicrobial Activities of Compounds I-VIII.

The above compounds were tested for their antimicrobial activity by the agar dilution technique. The potassium 3-aroyldithiocarbazates and compounds I were studied in details [29] and it was found that the potassium 3-aroyldithiocarbazates show slight activity against *A. niger*. Compounds I showed a large activity against *C. albicans* and to a lesser extent against *S. aureus*. The activity of compounds I with the bromosubstituted phenyl group If-h is two to three times higher than that of the chloro substituted derivatives Id,e. Compounds of series II in which the amino group of triazoles I was modified and of series III-VIII with the thiol group of triazoles I modified were screened for their antimicrobial activity by the same method. The results [30] of these tests showed that compounds IIIga, IIIc, IVe are active against the fungi *C. albicans* and *A. niger* and that compounds IVc,e,h are active against the bacteria *S. aureus* and *M. phlei*.

EXPERIMENTAL

All melting points were determined on an electrothermal melting point apparatus, and are uncorrected. Elemental analyses were performed by Prof. Dipl.-Ing., Dr. H. Malissa and G. Reuter, West Germany. Spectra were recorded with Pye-Unicam SP 1000 and Perkin-Elmer 580B Infrared Spectrophotometers (potassium bromide water technique) and Pye-Unicam SP8-100 visible and ultraviolet spectrophotometer (in ethanol). The ^{1}H-nmr spectra were recorded on a varian T-60A spectrometer using tetramethylsilane (TMS) as an internal standard.

4-Amino-5-aryl-1,2,4-triazole-3-thiones I.

Following the method of Reid and Heindel [13], a mixture of potassium 3-aroyldithiocarbazate (0.1 mole), hydrazine hydrate (99%, 0.2 mole) and 10 ml of water was refluxed with stirring for 0.5-1.0 hour. The color of the reaction mixture changed to green, hydrogen sulfide evolved and a homogeneous solution resulted. Dilution with 500 ml of cold water and acidification with concentrated hydrochloric acid gave a white precipitate. This solid was filtered, washed three times with 50 ml of cold water and crystallized from ethanol (Table I).

4-Amino-1,2,4-triazole-3-thione.

This compound was prepared according to Beyer procedure [14]. A mixture of thiocarbazide (10.6 g, 0.1 mole) and 10 ml of 98-100% formic acid was refluxed for 5 min. A yellow solution was obtained which solidified upon cooling. The solid product was crystallized from diluted ethanol, yield 78%, mp 166-167° (lit [14] 167-168°); ir (potassium bromide): cm^{-1} 3280, 3180, 1630, 1540; nmr (dimethylsulfoxide-d_6): (multiplicity, assignment) 14.00 (s, 1H, HNC=S), 8.38 (s, 1H, triazole H), 5.60 (s, 2H, NH_2).

4-Acylamino-5-aryl-1,2,4-triazole-3-thiones II.

The triazole I (0.01 mole) in 20 ml of pyridine was treated dropwise with an equimolar amount of the acid chloride at 0°C. The mixture, after standing overnight, was heated for 5-6 hours at 130°, cooled, diluted with water then acidified with hydrochloric acid. The precipitate formed was filtered and crystallized from ethanol-water mixture (Table I).

Bis(4-amino-5-aryl-1,2,4-triazol-3-ylthio)methanes (III).

The triazole I (0.01 mole) and 5.6 g (0.01 mole) potassium hydroxide were dissolved in water (30 ml). To this solution methylene iodide (0.04 mole) was added. The mixture was refluxed until a white solid precipitated (*ca.* 0.5-1.0 hour). Refluxing was continued for another 30 minutes after which the reaction mixture was cooled and the precipitate filtered and crystallized from ethanol or dimethyl formamide-water mixture (Table I).

4-Amino-5-aryl-3-cyanomethylthio-1,2,4-triazoles IV.

The triazole I (0.01 mole) dissolved in 20-30 ml of absolute ethanol was mixed with 1.2 ml (0.02 mole) of chloroacetonitrile and heated for 4 hours. The solvent was evaporated and the residue dissolved in 25 ml of water. Neutralization with sodium carbonate gave a precipitate which was filtered, washed with cold water (2 × 20 ml), and crystallized from ethanol or ethanol-water mixture (Table I).

4-Amino-5-aryl-3-carbomethoxymethylthio-1,2,4-triazole V.

A solution of the triazoles I (0.01 mole) and 0.4 g (0.01 mole) of sodium hydroxide in 30 ml of absolute ethanol was refluxed for 0.5 hour. To this solution, methyl bromoacetate 1.53 g (0.01 mole) was added, and the resulting mixture refluxed for 4 hours. After cooling, the solution was poured on ice and the solid mass thus separated was crystallized from ethanol (Table I).

4-Amino-5-aryl-1,2,4-triazol-3-ylthio)acethydrazides VI.

A solution of V (0.01 mole) in 60-70 ml of absolute ethanol was refluxed

with 5 ml (0.01 mole) of hydrazine hydrate for 2 hours. The mixture was concentrated under vacuum. Upon cooling, a white solid separated which was then filtered and crystallized from ethanol (Table I).

1-[(4-Amino-5-aryl-1,2,4-triazol-3-ylthio)acetyl)-2-aroylhydrazines VII.

An ethanolic solution of the appropriate acid chloride (0.01 mole) was added to VI (0.01 mole) in 25 ml absolute ethanol. The mixture was refluxed for 5 hours. The solid material separated on cooling was filtered and crystallized from ethanol (Table I).

Arylmethylene(4-amino-5-aryl-1,2,4-triazol-3-ylthio)acethydrazones VIII.

A similar procedure was used as in the preparation of VII except using aromatic aldehydes instead of acid chlorides (Table I).

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