(Ethanol), Schmp. 174–176°, Ausb. 1.1 g (78 %). $C_{24}H_{22}O_{10}$Ber. C 61.3 H 4.71 Mol.-Masse 470.4; Gef. C 61.4 H 4.72 Mol.-Masse 470 (ms). – IR (KBr): 1740, 1660, 1640, 1610 cm^{-1}. – ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.45, 1.57 (2 tr, je 3H, J = 7Hz), 2.9, 4.17, 4.4 (3s, je 3H), 4.45, 4.63 (2q, je 2H, J = 7Hz), 7.07, 7.67 (2d, je 1H, J = 2Hz).

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[Ph 772]

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Some Reactions of 2-Aryl-4-chloromethyl-1,3,4-thiadiazoline-5-thiones

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Some 2-aryl-1,3,4-thiadiazoline-5-thiones **1** react with formaldehyde to give the compounds **2**, which react with thionyl chloride to afford the compounds **3**. The latter react with phenols, thiophenol and related compounds giving **4**. With amines, **3** yield the 2-aryl-4-alkyl(aryl)aminomethyl-1,3,4-thiadiazoline-5-thiones **7**. Some of the compounds described were screened bacteriologically.

Einige Reaktionen von 2-Aryl-4-chlormethyl-1,3,4-thiadiazolin-5-thionen

Einige 2-Aryl-1,3,4-thiadiazolin-5-thione **1** reagieren mit Formaldehyd zu **2**, dieses reagiert mit Thionylchlorid zu **3**. Verbindung **3** reagiert mit Phenolen, Thiophenol und verwandten Verbindungen zu **4**. Mit Aminen gibt **3** 2-Aryl-4-alkyl(oder aryl)aminomethyl-1,3,4-thiadiazolin-5-thione **7**. Einige ausgewählte Verbindungen wurden auf ihre Aktivität gegen Bakterien untersucht.

Some 5-mercapto-1,3,4-thiadiazoles are valuable pharmaceutical intermediates. They have a depressant effect on the central nervous system[1] and show antituberculous activity[2–5]. This induced the authors to prepare some of their derivatives and to test their biological activity.

2-Phenyl-1,3,4-thiadiazoline-5-thione **(1a)** was reported[5–7] to react with formaldehyde to give the 4-hydroxymethyl derivative **2a** which reacts with thionyl chloride to afford the 4-chloromethyl derivative **3a**. In the present investigation, the substituted phenyl derivatives **3b, c** were similarly prepared from **1b, c** and some reactions of **3a–c** were tried.

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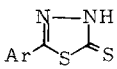
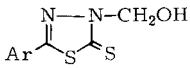
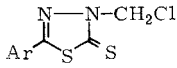


1



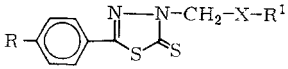
2



3

1–3	a	b	c
Ar	C_6H_5	4-Cl-C_6H_4	4-CH_3-C_6H_4

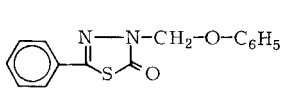
By refluxing 2-aryl-4-chloromethyl-1,3,4-thiadiazoline-5-thiones **3a–c** with some phenols, thiophenol and related compounds namely, 2-mercaptobenzothiazole and 8-hydroxyquinoline in anhydrous benzene, the ethers and thioethers **4a–h** were obtained.



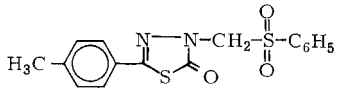
4

4	R	R^1	X
a	H	C_6H_5	O
b	Cl	C_6H_5	O
c	H	2,4-$(NO_2)_2$-C_6H_3	O
d	H	C_6H_5	S
e	CH_3	C_6H_5	S
f	H	2-benzothiazolyl	S
g	Cl	2-benzothiazolyl	S
h	CH_3	8-quinolyl	O

Oxidation of **4a, e** with potassium permanganate in acetic acid afforded the corresponding oxidation products **5** and **6**.



5



6

The structure of the compounds **4, 5** and **6** was supported by the following assignments: (i) the IR spectra of **4a–h** showed absorption bands at 1215–1285 cm^{-1} which may be assigned to the N–CS–S group[8a] while compounds **5** and **6** showed instead a stretching frequency attributable to C=O at 1670 and 1680 cm^{-1}, resp. The spectrum of **6** showed also two bands at 1340 and 1155 cm^{-1} corresponding to the SO_2 group[8b].

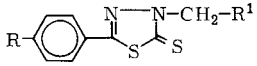
(ii) The UV spectra of **4a–h** showed the characteristic bands of the 4-substituted 1,3,4-thiadiazoles present in the thiono form at 336–344 nm (in accordance with literature data)[9], while those for **5** and **6** showed bands at 275 and 280 nm, corresponding to the absorption of the 1,3,4-thiadiazole ring present in the oxo-form[10,11].

(iii) The ^{1}H-NMR spectrum of **4e** showed the following signals: δ (ppm) = 2.5 (s, CH_3), 5.5 (s, CH_2) and 6.8–7.9 (m, 9H, aromatic). That of **4f** showed signals at: 5.7 (s, CH_2) and 7.0–8.1 (m, 9H aromatic). The signal for the CH_2 protons in **6** appeared as a singlet at 6.0.

(iv) The mass spectra of **4, 5** and **6** all showed molecular ions (M^+).

The ratio of relative abundance and the mass fragmentation of **4b** and **4g** are represented in Scheme 1.

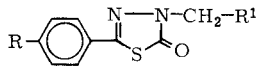
The reaction of **3a–c** with equimolecular amounts of different amines gave the corresponding 4-aminomethyl derivatives **7**.



7

7	R	R^1	7	R	R^1
a	H	$NHCH_3$	g	CH_3	morpholino
b	H	$N(CH_3)_2$	h	CH_3	NH-quinolyl(5)
c	H	NH-pyridyl(2)	i	Cl	NH-quinolyl(5)
d	H	piperidino	j	Cl	NH-pyridyl(2)
e	CH_3	NHC_6H_5	k	Cl	morpholino
f	CH_3	$NHCH_2C_6H_5$			

The structure of the products **7** is inferred beside elemental and spectral analyses form their reactions with hydrogen peroxide. Thus, treatment of **7a, e** with hydrogen peroxide in acetic acid gave the oxidation products **8a, b.**



8

8	R	R^1
a	H	$NHCH_3$
b	CH_3	NHC_6H_5

The IR spectra of compounds **7** showed stretching frequencies attributable to the N–CS–S group in the region 1230–1285 cm^{-1}, while that of **8a** showed the C=O absorption at 1645 cm^{-1} and that for **8b** at 1665 cm^{-1} (C=O). The UV spectra of compounds **7** showed the characteristic absorption bands of 4-substituted 1,3,4-thiadiazoles in the region of 337–340 nm[9], while those of **8a, b** showed the main absorption bands at 280 and 273 nm, resp.[10,11].

It is worthy to mention that the IR absorption bands for the NH group in **7a, f** and **8a** are very weak and appeared at lower values (2920–3080 cm^{-1}) due to the formation of a strong intramolecular hydrogen bonding[12].

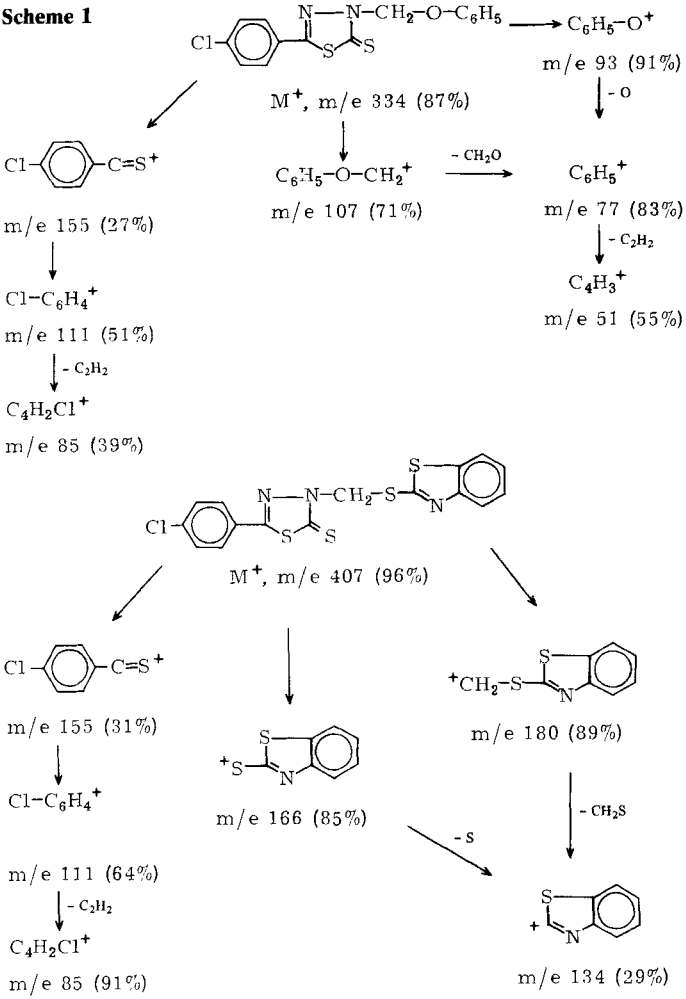
The NH group of **7e** and **8b** appeared, however, at 3315 and 3325 cm^{-1}, probably due to the presence of a phenyl group attached to the amino group which causes some attraction of the hydrogen atom towards the nitrogen atom, thus opposing the effect of hydrogen bonding with the oxo or the thioxo group[12] (Table 1).

The ^1H-NMR spectra of **7** and **8** are in accordance with the structures assigned and are listed in table 1. The mass spectra of **7** and **8** all showed molecular ions (M^+). The ratio of relative abundance and the mass fragmentations of **7g** is represented in Scheme 2.

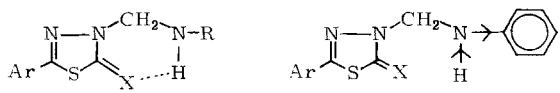
Biological Activity

Some of the above prepared compounds which were expected to have antimicrobial activity (containing pyridyl, quinolyl and 2-benzothiazolyl residues)[13] were screened against six organisms representative for Gram positive (1–3) and Gram negative (4–6)

Scheme 1



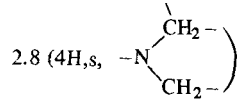
Scheme 2



7a/7f/8a **7e/8b**

bacteria using a modified cup-test assay technique[14, 15] (table 2). It appears that the compounds **4g, 7h** and **7i** are the most effective against all the tested organisms. These were followed by compounds **4f** and **4h** which failed to inhibit E. Coli and Salmonella species. Compounds **7c** and **7j** were found to be active only against the tested Gram positive organisms.

Table 1: *UV, IR and ^{1}H-NMR Spectral data for compounds* **7** *and* **8**

Compound	UV (nm) (main band)	IR (cm^{-1}) C=S	NH	aromatic	^{1}H-NMR δ (ppm) = R^1	R	$-CH_2-$
7a	340 (4.20)	1250	2920	7.2–7.6 (5H, m)	2.7 (1H,s,NH) 3.6 (3H,s,N–CH_3)	–	5.3(2H,s)
7d	339 (4.17)	1280	–	7.0–8.0 (5H,m)	1.5 (1H, d, $(-CH_2-)_3$) 2.8 (4H,s, 		5.1(2H,s)
7e	337 (4.01)	1265	3325	7.3–7.9 (9H,m)	2.1 (1H,s,NH)	2.4(3H,s)	5.8(2H,s)
7f	339 (4.15)	1230	3020	7.2–7.9 (9H,m)	2.0 (1H,s,NH) 5.8 (2H,s,N–CH_2-)	2.5(3H,s)	5.5(2H,s)
7h	340 (4.09)	1245	3300	7.1–8.2 (10H,m) (phenyl+quinolyl)	1.9 (1H,s,NH)	2.4(3H,s)	5.1(2H,s)
8a	280 (4.15)	1645 (C=O)	3030	7.2–7.7 (5H,m)	1.85 (1H,s,NH) 3.5 (3H,s,N–CH_3)	–	5.0(2H,s)
8b	273 (4.07)	1665 (C=O)	3315	7.1–8.0 (9H,m)	1.75 (1H,s,NH)	2.5(3H,s)	5.7(2H,s)

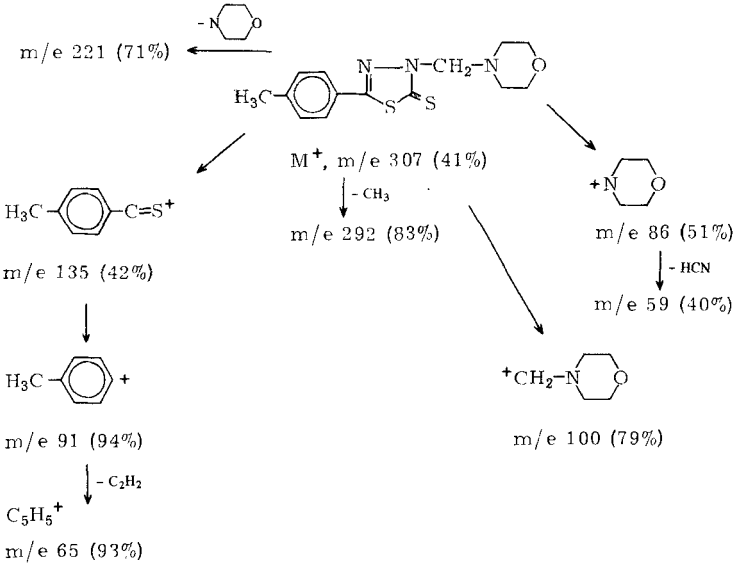


Table 2: *Effect strength of compounds on the individual bacteria*

Compound	Gram positive		Gram negative			
	1	2	3	4	5	6
4f	+++	++	+++	–	++	–
4g			complete inhibition			
4h	++++	++++	++++	–	++	–
7c	++	++	+++	–	–	–
7h	++	++	++++	++	++	+++
7i			complete inhibition			
7j	++	++	++	–	++	–

1. Micrococcus tetragonus
2. Staphylococcus citrus
3. Streptococcus faecalis
4. Salmonella species
5. Pseudomonas aeruginosa
6. Escherichia coli

Thanks are expressed to Dr. M. *Abdel-Hamid,* Microbiology Unit, National Research Centre, Cairo, Egypt, for help in the biological activity part.

Experimental Part

MP: uncorrected. *IR:* (KBr) Pye-Unicam SP 1200. *UV:* (EtOH) Pye-Unicam SP 8000. *^{1}H-NMR:* ($CDCl_3$) 60 MHZ Varian EM-360 (TMS). *MS:* 70 eV 7070 F.

Action of formaldehyde on compounds **1**

1 ml 40 % formaldehyde was added to 0.01 mole **1** in 10 ml ethanol and the mixture was refluxed for 3 h, concentrated, cooled and the solid obtained was crystallized from benzene to give compounds **2** in almost quantitative yield (table 3).

Action of thionyl chloride on compounds **2**

5 ml thionyl chloride were added to 0.01 mole of the compounds **2**, the mixture was heated on a water-bath for 1 h, cooled and poured on 100 ml petroleum ether (40–60°). The formed precipitate was recrystallized from pet. ether (60–80°) to give compounds **3** (table 3).

Action of phenols and thiophenols on compounds **3**

A mixture of 0.01 mole **3a–c,** 0.013 mole appropriate phenol or thiophenol and 2 drops piperidine was refluxed in 20 ml anhydrous benzene for 3 h, concentrated and cooled. The solid products were crystallized from the proper solvent (table 3).

Oxidation of **4a** *and* **4e** *with potassium permanganate*

A solution of 0.46 g of potassium permanganate in 10 ml water was gradually added to a solution of 0.01 mole **4a** or **4e** in 20 ml acetic acid. The mixture was heated on a water bath for 1 h, concentrated, cooled and poured on cold water. The solid formed was crystallized to give **5** and **6** (table 3).

Action of amines on **3**

A mixture of 0.01 mole **3a–c** and 0.01 mole appropriate amine was refluxed in 20 ml anhydrous benzene for 3 h. The benzene was distilled off and the solid obtained crystallized to give **7a–k** (table 3).

Oxidation of **7a** *and* **7e** *with hydrogen peroxide*

100 ml 35 % H_2O_2 were added to 0.01 mole **7a** or **7e** in 20 ml acetic acid and the mixture was left for 2 days at room temp. The solid obtained, **8a** and **8b**, resp., were crystallized (table 3).

Table 3: *Analytical data*

Compound	m.p.°/ (Cryst. Solv.)	Yield %	Formula (Mol.Wt.)	Analyses: Calcd. Found C	H	N	S
2a	102 B	95	$C_9H_8N_2OS_2$ (224.30)	ref. 6,7)			
2b	110 B	94	$C_9H_7N_2OS_2Cl$ (258.75)	41.8 41.6	2.73 2.60	10.8 10.7	24.8 24.6
2c	125 B	94	$C_{10}H_{10}N_2OS_2$ (238.33)	50.4 50.3	4.23 4.12	11.8 11.8	26.9 27.0
3a	141 P	85	$C_9H_7N_2S_2Cl$ (242.75)	ref. 6,7)			
3b	135 P	87	$C_9H_6N_2S_2Cl_2$ (277.20)	39.0 39.1	2.18 2.10	10.1 9.9	23.1 22.9
3c	148 P	95	$C_{10}H_9N_2S_2Cl$ (256.78)	46.8 46.7	3.53 3.39	10.9 10.7	25.0 24.8
4a	163 E	80	$C_{15}H_{12}N_2OS_2$ (300.40)	60.0 60.0	4.03 4.12	9.3 9.2	21.3 20.9
4b	157 E	78	$C_{15}H_{11}N_2OS_2Cl$ (334.85)	53.8 54.0	3.31 3.14	8.4 8.3	19.2 19.0
4c	171 M	75	$C_{15}H_{10}N_4O_5S_2$ (390.40)	46.1 46.1	2.58 2.47	14.4 14.5	16.4 16.2
4d	110 M	70	$C_{15}H_{12}N_2S_3$ (316.47)	56.9 57.1	3.80 3.69	8.9 8.7	30.4 30.6
4e	104 P	69	$C_{16}H_{14}N_2S_3$ (330.50)	58.1 57.9	4.27 4.29	8.5 8.3	29.1 28.9
4f	141 P	67	$C_{16}H_{11}N_3S_4$ (373.54)	51.4 51.3	2.97 2.79	11.2 11.1	34.3 34.5
4g	134 M	71	$C_{16}H_{10}N_3S_4Cl$ (407.98)	47.1 47.5	2.47 2.78	10.3 10.2	31.4 31.2
4h	181 P	70	$C_{19}H_{15}N_3OS_2$ (365.48)	62.4 62.8	4.14 4.35	11.5 11.4	17.5 17.7

Fortsetzung Tab. 3

Compound	m.p.°/ (Cryst. Solv.)	Yield %	Formula (Mol.Wt.)	Analyses: Calcd. Found C	H	N	S
5	145	75	$C_{15}H_{12}N_2O_2S$	63.4	4.25	9.9	11.3
	M		(284.34)	63.2	4.18	9.7	11.2
6	131	73	$C_{16}H_{14}N_2O_3S_2$	55.5	4.07	8.1	18.5
	M		(346.43)	55.8	4.40	8.3	18.3
7a	121	72	$C_{10}H_{11}N_3S_2$	50.6	4.67	17.7	27.0
	P		(237.35)	50.5	4.51	17.5	27.2
7b	60	71	$C_{11}H_{13}N_3S_2$	52.6	5.21	16.7	25.5
	M		(251.37)	52.7	5.14	16.6	25.3
7c	95	69	$C_{14}H_{12}N_4S_2$	56.0	4.03	18.7	21.3
	M		(300.41)	56.4	4.35	18.7	21.0
7d	119	75	$C_{14}H_{17}N_3S_2$	57.7	5.88	14.4	22.0
	D		(291.44)	57.9	5.71	14.2	22.2
7e	124	70	$C_{16}H_{15}N_3S_2$	61.3	4.82	13.4	20.5
	D		(313.45)	61.2	4.84	13.3	20.3
7f	128	81	$C_{17}H_{17}N_3S_2$	62.4	5.23	12.8	19.6
	E		(327.47)	62.6	5.17	13.0	19.4
7g	92	74	$C_{14}H_{17}N_3OS_2$	54.7	5.57	13.7	20.9
	M		(307.44)	54.6	5.43	13.5	21.0
7h	101	71	$C_{19}H_{16}N_4S_2$	62.6	4.42	15.4	17.6
	M		(364.49)	62.9	4.67	15.2	17.3
7i	108	65	$C_{18}H_{13}N_4S_2Cl$	56.2	3.40	14.6	16.7
	D		(384.91)	56.5	3.69	14.3	16.5
7j	96	72	$C_{14}H_{11}N_4S_2Cl$	50.2	3.31	16.7	19.2
	P		(334.85)	50.2	3.17	16.6	19.0
7k	94	68	$C_{13}H_{14}N_3OS_2Cl$	47.6	4.30	12.8	19.6
	P		(327.86)	47.8	4.13	12.7	19.4
8a	76	73	$C_{10}H_{11}N_3OS$	54.3	5.01	19.0	14.5
	P		(221.28)	54.2	5.16	18.8	14.6
8b	110	76	$C_{16}H_{15}N_3OS$	64.6	5.08	14.1	10.8
	P		(297.38)	64.4	5.00	14.0	10.6

B: benzene, P: petroleum ether (60/80°), E: ethanol, M: methanol, D: dioxan

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[Ph 773]

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Reaktionen von elektronenreichen Heterocyclen mit Orthocarbonsäure-Derivaten, 2. Mitt.[1)]

Säurekatalysierte Reaktionen von 3-substituierten Indolen mit Orthoameisensäuretriethylester

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Die methylsubstituierten Indole **1a** und **1b** reagieren mit dem im Medium erzeugten Diethoxycarbenium-Ion **(2b)** zu den Bi- bzw. Triindolylmethan-Derivaten **3, 4, 5** bzw. **7**. **5a** läßt sich präparativ zum heteroanalogen Triphenylmethan-Farbstoff **6a** oxidieren. Tryptamin **(8a)** wird durch **2b** ausschließlich formyliert. Blockierung der Aminnucleophilie in **8a** führt am Beispiel des N^{α}-Acetyltryptamins **(8b)** mit **2b** zum Triindolylmethan **10.**

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