Potential Antiviral and Antituberculous Compounds. III

N-1-(4-Methoxy Naphthylidene/2-benzofurylidene)-N-4-(aryl) Thiosemicarbazides; 5-carboxymethyl, 3-aryl, Thiazolidine-2,4-dione Hydrazones; 3-aryl, Thiazolidine-2,4-dione Hydrazones and N-1-(4-methoxy Naphthylidene/2-benzofurylidene)-N-4-(aryl) Amino Guanidines

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Summary

With a view to study their antiviral and antitubercular activity, ten new 4-aryl substituted thiosemicarbazones of 2-formyl benzofuran and 4-methoxy naphthaldehyde have been prepared. The preparation of sixteen new hydrazones of 3-aryl, thiazolidine-2,4-dione and 5-carboxymethyl-3-aryl, thiazolidine-2,4-dione and ten new substituted guanidines has also been accomplished from these thiosemicarbazones.

The importance of thiosemicarbazones of aromatic and heterocyclic aldehydes and ketones as antiviral[1]) and antitubercular[2]) agents is well known. While studying these thiosemicarbazones, A. Krbavcic et al.[3]) observed that the incorporation of the thiosemicarbazone grouping into a cyclic component leads to a considerable enhancement of the antiviral activity. The high antiviral activity of the derivatives of 5-carboxymethyl thiazolidine-2,4-diones as compared to their precursor thiosemicarbazones from which they were obtained by maleic anhydride condensation, substantiates this theory. This encouraged us to prepare ten new thiosemicarbazones of 2-formyl benzofuran and 4-methoxy naphthaldehyde by condensing these two with different 4-aryl-thiosemicarbazides. These thiosemicarbazones were then condensed both with maleic anhydride and with monochloracetic acid in order to incorporate the thiosemicarbazone grouping in a

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[1]) D. Hamre et al., Proc. Soc. Exper. Biol. and Med. **73**, 275 (1950).
[2]) F. P. Doyle et al., J. chem. Soc. London **1956**, 2853.
[3]) A. Krbavcic et al., J. med. Chem., Vol. **9**, No. 3, 430 (1966).

ring and impart greater antiviral and antitubercular[4]) character to the molecule.

The antiviral[5]) and antituberculous[6]) activity of biguanides and guanidines encouraged us to obtain ten guanidines from our newly prepared thiosemicarbazones by the oxidation of the >C=S grouping into >C=NH.

The starting materials, 4-methoxy naphthaldehyde[7]) and 2-formyl benzofuran[8]) were prepared by the direct formylation of 1-methoxy naphthalene and benzofuran[9]) respectively with dimethyl formamide, in the presence of phosphorus oxychloride.

The antiviral and antitubercular activity of these compounds will be reported later on.

Table 1
N-1-(4-Methoxy naphthylidene / 2-benzofurylidene)-N-4-(aryl) thiosemicarbazides

$RCH{=}NNHCNHR'$ (S)

No.	R =	R'=	M.P. °C	% Yield (of theory)	Formula	% Nitrogen Found	% Nitrogen Calcd.
1.	4-Methoxy naphthyl	C_6H_5-	177	88	$C_{19}H_{17}N_3OS$[a]	12.65	12.53
2.	do.	o-$CH_3 \cdot C_6H_4$-	190	85	$C_{20}H_{19}N_3OS$[a]	11.79	12.03
3.	do.	p-$CH_3 \cdot C_6H_4$-	192	83	$C_{20}H_{19}N_3OS$[b]	12.10	12.03
4.	do.	p-$C_2H_5O \cdot C_6H_4$-	182	86	$C_{21}H_{21}N_3O_2S$[a]	11.14	11.08
5.	do.	p-Cl·C_6H_4-	203	85	$C_{19}H_{16}N_3OSCl$[b]	11.39	11.36
6.	2-Benzofuryl	C_6H_5-	192	70	$C_{16}H_{13}N_3OS$[c]	14.44	14.24
7.	do.	o-$CH_3 \cdot C_6H_4$-	202	70	$C_{17}H_{15}N_3OS$[d]	13.44	13.59
8.	do.	o-$C_2H_5O \cdot C_6H_4$-	182	72	$C_{18}H_{17}N_3O_2S$[c]	12.49	12.39
9.	do.	n-C_6H_{11}-	185	74	$C_{16}H_{19}N_3OS$[c]	13.75	13.95
10.	do.	p-Cl·C_6H -	201	80	$C_{16}H_{12}N_3OSCl$[c]	12.54	12.74

Crystallised from (a) acetone-ether, (b) ethanol, (c) acetone, (d) methyl ethyl ketone.

[4]) O. F. PAVLENKO, Farm. Zhur (Kiev), No. **4**, 3 (1959).
[5]) N. ISHIDA et al., J. Antibiotics (Japan), Ser. A **15**, 168 (1962).
[6]) V. GRINSTEINS and A. VEVERIS, Latvijas PSR Zinatnu Akad. Vestis. Kim. Ser. **4**, 45 (1963).
[7]) N. P. BUU HOI and D. LEVIT, J. chem. Soc. London **1955**, 2776.
[8]) V. T. SUU et al., Bull. Soc. chim. France **1962**, 1875.
[9]) A. ROSSING, Berichte **17**, 2990 (1884).

Experimental

N-1-(4-Methoxy naphthylidene/2-benzofurylidene)-N-4-(aryl)-thiosemicarbazides

Equimolar amounts of the corresponding aldehyde and the appropriate 4-aryl thiosemicarbazide were refluxed in 95% ethanol for half to one hour on a steam bath. The crystalline thiosemicarbazone, which separated out during the reaction, was filtered after cooling. It was then crystallised from a suitable solvent (Table 1).

5-Carboxymethyl-3-aryl-thiazolidine-2,4-dione hydrazones

Equimolar amounts of the corresponding thiosemicarbazone and maleic anhydride were suspended in either benzene or toluene and the mixture refluxed for 2—3 hours. The excess solvent was distilled off, the product filtered after cooling, dried and crystallised from a suitable solvent (Table 2).

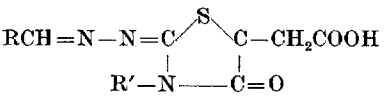
3-Aryl-thiazolidine-2,4-dione hydrazones

A suspension of the appropriate thiosemicarbazone (0.01 mol) with monochloracetic acid (0.015 mol) in ethanol or acetic acid was refluxed for 4—5 hours in the presence of anhydrous sodium acetate (0.02 mol). The solvent was then completely removed and the residue washed with water, filtered, dried and crystallised from a suitable solvent (Table 3).

N-1-(4-Methoxy naphthylidene/2-benzofurylidene)-N-4-(aryl) amino guanidines

The appropriate thiosemicarbazone (0.01 mol), yellow lead oxide (0.022 mol) and strong ethanolic ammonia (20 ml) were heated in a sealed tube on a water bath for 3—4 hours.

Table 2
5-Carboxymethyl-3-aryl, thiazolidine-2,4-dione hydrazones

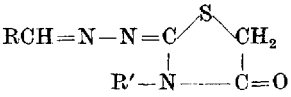


No.	R =	R'=	M.P. °C	% Yield (of theory)	Formula	% Nitrogen Found	% Nitrogen Calcd.
1.	4-Methoxy naphthyl	C_6H_5-	221	75	$C_{23}H_{18}N_3O_4S^a$	9.51	9.72
2.	do.	o-$CH_3 \cdot C_6H_4$-	186	79	$C_{24}H_{20}N_3O_4S^b$	8.96	9.41
3.	do.	p-$CH_3 \cdot C_6H_4$-	229	65	$C_{24}H_{20}N_3O_4S^a$	9.31	9.41
4.	do.	p-$C_2H_5O \cdot C_6H_4$-	236 dec.	72	$C_{25}H_{22}N_3O_5S^c$	8.78	8.82
5.	dc.	p-Cl·C_6H_4-	204	60	$C_{23}H_{17}N_3O_4SCl^c$	9.41	9.00
6.	2-Benzofuryl	C_6H_5-	243	62	$C_{20}H_{14}N_3O_4S^a$	10.36	10.71
7.	do.	n-C_6H_{11}-	188	59	$C_{20}H_{20}N_3O_4S^c$	10.09	10.55
8.	do.	p-Cl·C_6H_4-	222	57	$C_{20}H_{13}N_3O_4SCl^c$	9.67	9.84

Crystallised from (a) acetone, (b) benzene-petrol ether, (c) acetone-ether.

Table 3

3-Aryl, thiazolidine-2,4-dione hydrazones

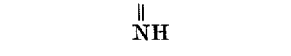


No.	R =	R′=	M.P. °C	% Yield (of theory)	Formula	% Nitrogen Found	% Nitrogen Calcd.
1.	4-Methoxy naphthyl	C_6H_5-	232	65	$C_{21}H_{17}N_3O_2S$[a]	11.40	11.20
2.	do.	o-$CH_3 \cdot C_6H_4$-	131	56	$C_{22}H_{19}N_3O_2S$[b]	11.22	10.79
3.	do.	p-$CH_3 \cdot C_6H_4$-	253	63	$C_{22}H_{19}N_3O_2S$[c]	10.60	10.79
4.	do.	p-$C_2H_5O \cdot C_6H_4$-	209	60	$C_{23}H_{21}N_3O_3S$[d]	9.90	10.02
5.	do.	p-Chloro·C_6H_4-	222	55	$C_{21}H_{16}N_3O_2SCl$[b]	10.42	10.25
6.	2-Benzofuryl	C_6H_5-	220	57	$C_{18}H_{13}N_3O_2S$[a]	12.60	12.54
7.	do.	n-C_6H_{11}-	172	63	$C_{18}H_{19}N_3O_2S$[a]	12.21	12.31
8.	do.	p-Chloro·C_6H_4-	236	59	$C_{18}H_{12}N_3O_2SCl$[c]	11.27	11.37

Crystallised from (a) acetone, (b) acetone-ether, (c) methylethyl ketone, (d) Methylethyl-ketone-Petrolether.

Table 4

N-1-(4-Methoxy naphthylidene / 2-benzofurylidene)-N-4-(aryl)-amino guanidines



No.	R =	R′=	M.P. °C	% Yield (of theory)	Formula	% Nitrogen Found	% Nitrogen Calcd.
1.	4-Methoxy naphthyl	C_6H_5-	158	50	$C_{19}H_{18}N_4O$[a]	17.73	17.61
2.	do	o-$CH_3 \cdot C_6H_4$-	191	47	$C_{20}H_{20}N_4O$[a]	16.83	16.86
3.	do.	p-$CH_3 \cdot C_6H_4$-	154	51	$C_{20}H_{20}N_4O$[b]	16.64	16.86
4.	do.	p-$C_2H_5O \cdot C_6H_4$-	176	52	$C_{21}H_{22}N_4O_2$[b]	15.07	15.47
5.	do.	p-Cl·C_6H_4-	191	42	$C_{19}H_{17}N_4OCl$[c]	15.75	15.88
6.	2-Benzofuryl	C_6H_5-	133	91	$C_{16}H_{14}N_4O$[d]	19.87	20.14
7.	do.	o-$CH_3 \cdot C_6H_4$-	118	43	$C_{17}H_{16}N_4O$[d]	19.27	19.17
8.	do.	o-$C_2H_5O \cdot C_6H_4$-	99	51	$C_{18}H_{18}N_4O_2$[d]	17.36	17.39
9.	do.	n-C_6H_{11}-	63	72	$C_{16}H_{20}N_4O$[d]	19.51	19.71
10.	do.	p-Cl·C_6H_4-	206	53	$C_{16}H_{13}N_4OCl$[c]	18.30	17.92

Crystallised from (a) acetone-ether, (b) ethanol, (c) acetone, (d) ethanol-water.

The precipitated lead sulphide was then filtered off and the desired guanidine obtained after evaporating the excess ethanol from the filtrate, was crystallised from a suitable solvent (Table 4).

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