ACTA CHEMICA SCANDINAVICA 14 (1960) 1025–1030

Potential Chemotherapeutics

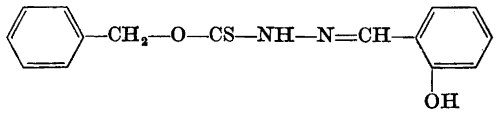
I. Hydrazine Derivatives, Structurally Related to 1-Benzoxythiocarbo-2-salicylidene Hydrazine

KURT SKAGIUS

Research Laboratories, A.B. Pharmacia, Uppsala, Sweden

Structural analogues (fortyone in all), of 1-benzoxythiocarbo-2-salicylidene hydrazine were prepared for antibacterial screening. The substances prepared are aldo- and ketohydrazones of oxycarbo-, oxythiocarbo- and dithiocarbohydrazines and their S- or N-alkylated derivatives.

In 1949 Wangel [1] published a study of some oxythiocarbohydrazides and their hydrazone derivatives. Since these compounds by analogy to the thiosemicarbazones were of interest as potential tuberculostatics, they were subjected to a bacteriologic screening procedure [2]. It was found, in continuation of this work, that the salicylaldehyde hydrazone of benzoxythiocarbohydrazide (I) showed a powerful activity against staphylococci and streptococci *in vitro*. In order to elucidate the structure-activity relation, a series of related substances were synthesized and tested against a number of microorganisms *in vitro*. The results of this investigation will be published elsewhere.

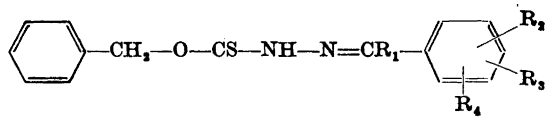


(I)

Firstly, the salicylidene residue of compound (I) was replaced by a number of aromatic aldehyde and ketone residues (Table 1), containing

a) a hydroxyl group in the 2-position of the benzene nucleus and various substituents in other positions
b) a substituted hydroxyl group in the 2-position
c) a hydroxyl group in the 4-position
d) other substituents than hydroxyl in the 2-position.

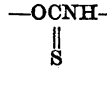
Table 1. Benzoxythiocarbohydrazones of aromatic aldehydes and ketones.



Compound No.	Code No. Ph 762/x	R_1	R_2	R_3	R_4	M. p.
1	38	H	2—OH	5—CH_3	H	179 —180
2	48	H	2—OH	5—$C(CH_3)_2CH_2—C—(CH_3)_3$	H	148 —149
3	12	H	2—OH	4—OH	H	
4	28	H	2—OH	5—Br	H	187.5 decomp.
5	50	H	2—OH	3—OCH_3	H	146 —148.5
6	21	H	2—OCH_3	H	H	119 —120.5
7	15	H	2—$OCOCH_3$	H	H	116 —118.5
8	55	CH_3	2—OH	H	H	133 —134
9	80	CH_3	2—OH	4—CH_3	H	155.5—157
10	75	CH_3	2—OH	4—CH_3	5—Cl	179 —180.5
11	81	C_2H_5	2—OH	H	H	119.5—121
12	84	C_2H_5	2—OH	5—CH_3	H	169.5—170.5
13	79	*n*-C_4H_9	2—OH	H	H	156 —157
14	83	*n*-C_4H_9	2—OH	5—CH_3	H	96.5— 98
15	73	*n*-C_5H_{11}	2—OH	5—CH_3	H	114 —115.5
16	78	C_6H_5	2—OH	5—Cl	H	161.5—163
17	76	C_6H_5	2—OH	5—CH_3	H	115 —117
18	77	$C_6H_5CH_2$	2—OH	5—CH_3	H	145 —147
19	9	H	4—OH	H	H	156 —157 decomp.
20	1	H	4—OH	3—OCH_3	H	146 —147 decomp.
21	49	H	2—NH_2	H	H	149 —151
22	41	H	2—NO_2	H	H	117 —119

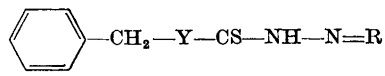
Since a hydroxyl group in the 2-position of the benzal residue seemed to be essential for the antistaphylococcal action, some benzoxythiocarbo- and benzyldithiocarbohydrazones of aldehydes and ketones, containing an aromatic hydroxyl group, an enolizable carbonyl group or an aliphatic hydroxyl group in the critical position were also prepared (Table 2).

The possible arrangements around the central carbon atom of the oxythiocarbamide group (II) is of special interest, since the action of many antibacterial agents is referred to their ability for chelate or complex formation with metal ions [3]. Substitution of the hydrogen atom in (II) with alkyl groups effectively blocks the possibility of salt formation, which would be the main contribution of the oxythiocarbohydrazide group to a chelate. Also, substitution of the sulfur atom by oxygen and the oxygen atom by sulfur or nitrogen would influence the enolizability of the hydrogen atom and the ability of chelate formation.



(II)

Table 2. Benzoxythiocarbo- and benzyldithiocarbohydrazones of various aldehydes and ketones.

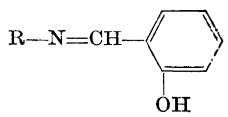


Compound No.	Code No. Ph 762/X	Carbonyl compound, corresponding to R	Y	M.p.
23	34	2-Hydroxy-1-napthaldehyde	O	151 –155
24	35	1-Hydroxy-2-napthaldehyde	O	170 –171
25	92	3-Hydroxypicolinealdehyde	O	168 decomp.
26	36	Dehydroacetic acid	O	125 –127
27	52	Dehydroacetic acid	S	138 –140
28	85	2-Acetyl-3-hydroxy-5-methyl-benzofurane	O	104 –105
29	94	3-Hydroxy-3-methylbutanone-2	O	136.5–138
30	40	Quinoline-2-aldehyde	O	147 –149
31	39	4-Pyridinealdehyde	O	144 decomp.
32	8	2-Thiophenealdehyde	O	107 –108

The N-methylated derivative of (I) was easily obtained from the sodium salt of benzoxythiocarbothioglycolic acid and salicylaldehyde methylhydrazone hydrochloride according to the method described by Wangel [1]. The S-methyl derivative was obtained by methylation of sodium benzoxythiocarbohydrazide with methyl iodide followed by hydrazone formation with salicylaldehyde. The oxycarbo- and dithiocarbohydrazides were prepared according to general principles [4,5], and the S-benzylthiocarbohydrazone from salicylidene hydrazine and S-benzylthiocarbonyl chloride, prepared from toluenethiol and phosgene.

Finally, some variations of the ester residue of the thiocarbonic acid ester grouping of (I) were carried out. These variations included the esters of 2-

Table 3. Acyl substituted salicylidenehydrazines.



Compound No.	Code No. Ph 762/X	R	M.p.
33	13	$C_2H_5OSCNH-$	167.5–169.5
34	31	$C_6H_5CH_2CH_2OCSNH-$	144 –145
35	45	$4-C_5H_4NCH_2OCSNH-$	176.5–177
36	37	$C_6H_5CH_2NHCSNH-$	195 –196
37	51	$C_6H_5CH_2SCSNH-$	179.5–180.5
38	29	$C_2H_5OCONH-$	126 –128
39	99	$C_6H_5CH_2SCONH-$	181.5–183
40	22	$C_6H_5CH_2OC(SCH_3)=N-$	87 – 89
41	97	$C_6H_5CH_2OCSN(CH_3)-$	139 –141.5

phenylethanol, ethanol, and 4-pyridylmethanol. The hydrazides were prepared from hydrazine hydrate and the potassium xanthates, obtained from potassium hydroxide, carbon disulphide and the alcohol in the usual way.

EXPERIMENTAL *

Hydrazones of the various acylhydrazides were prepared by heating the acylhydrazide and the carbonyl compound in a suitable solvent (ethanol, dioxane, or acetic acid) for a few minutes (if necessary, a few drops of HCl-MeOH were added), and the mixture was left to crystallize. The precipitate formed was recrystallized from dioxane, ethanol or acetic acid. The yields were usually satisfactory (70—90 %). The procedure is illustrated by the following two examples:

3-Hydroxypicolinealdehyde benzoxythiocarbohydrazone. 310 mg (2.5 mmole) of 3-hydroxypicolinealdehyde [6] and 460 mg (2.5 mmole) of benzoxythiocarbohydrazide were dissolved in 5 ml of hot ethanol. After a few minutes crystals appeared. About 15 ml of ethanol was then added and the mixture boiled until the precipitate dissolved. The solution was treated with charcoal, filtered and allowed to cool. The crystals were filtered off and dried. After recrystallization from ethanol, 0.6 g (80 %) of colourless crystals was obtained. The colour changes to yellow-brown in sunlight. The substance begins to melt at 168°C, after which it slowly solidifies and does not melt again below 200°C.

Benzoxythiocarbohydrazone of 3-methyl-3-hydroxybutanone-2. 9.1 g (50 mmole) of benzoxythiocarbohydrazide and 5.1 g (50 mmole) of the ketone were dissolved in about 50 ml of ethanol. The hot solution was treated with charcoal, filtered and the filtrate allowed to cool. After scratching, a slightly cream-coloured precipitate appeared. The crystals were filtered off and dried. After recrystallization from ethanol they melted at 136.5—138°C. Yield 9.8 g (74 %).

Benzylthiocarbonyl chloride. Under external cooling, 50 ml of a 12.5 % solution of phosgene in toluene was stirred in a three-necked flask and a mixture of 5 ml of pyridine and 7.5 ml of toluenethiol in about 50 ml of toluene was added. After one hour the pyridinium chloride was filtered off and the filtrate fractionated *in vacuo*. 8.0 g (70 %) of benzylthiocarbonyl chloride was obtained as an oil, which boiled at 122—123°/10 mm Hg.

1-(S-Benzylthiocarbonyl)-2-salicylidenehydrazine. 5 g (37 mmole) of salicylidenehydrazine were dissolved in dioxane and a solution of 7 g (37 mmole) of benzylthiocarbonyl chloride in ether was added. A colourless precipitate was immediately formed. A solution of 3 ml of pyridine in ether was added and the mixture heated on a steam bath for a few minutes. After cooling, the mixture was poured into water and the ether was allowed to escape. The precipitate was filtered off and dried. 9.2 g (87 %) of a colourless substance was obtained which, after several recrystallizations from ethanol and benzene, melted at 181.5—183°C.

1-Benzoxythiocarbo-1-methyl-2-salicylidenehydrazine. 10 g methylhydrazine sulphate were dissolved in 100 ml of 2 N acetic acid and 40 ml of 5 N sodium hydroxide was added. The solution was heated on a water bath and 11 ml of salicylaldehyde was added with stirring. After half an hour the oily layer was separated and the water layer extracted with ether. The combined organic layers were dried with anhydrous sodium sulphate and methanolic hydrogen chloride was added. Salicylidenemethylhydrazone hydrochloride was obtained as a pale yellow precipitate, which weighed 8.4 g after drying.

5.7 g (30 mmole) of the yellow salt was mixed with 15 ml of 2 N sodium hydroxide and 50 ml of ethanol and a solution of 7.5 g of benzoxythiocarbothioglycolic acid in 15 ml of 2 N sodium hydroxide and 50 ml of water was added. The yellow solution was left at room temperature for three days. The precipitate formed was filtered off and dried. Weight 7.4 g. After repeated recrystallizations from ethanol-dioxane and dioxane-water 4.6 g of 1-benzoxythiocarbo-1-methyl-2-salicylidenehydrazine was obtained. Mp 139—141.5°C.

Potassium 4-pyridylmethylxanthate. 32.7 g (330 mmole) of 4-pyridylmethanol was dissolved in a solution of 22 g of potassium hydroxide in 120 ml of water. 20 ml of carbon

* Microanalyses by Dr. Wolfgang Kirsten.

Table 4. Analytical data.

Compound No.	Formula	% C calc.	% C found	% H calc.	% H found	% N calc.	% N found	% S calc.	% S found
1	$C_{16}H_{16}N_2O_2S$	64.0	63.9	5.4	5.4	9.3	9.5	10.7	10.4
2	$C_{23}H_{30}N_2O_2S$	69.3	69.5	7.6	7.5	7.0	7.0	8.2	8.2
3	$C_{15}H_{14}N_2O_3S$	59.6	59.5	4.7	4.7	9.3	9.3	10.6	10.6
4	$C_{15}H_{13}N_2O_2SBr$	49.3	49.5	3.6	3.6	7.7	7.7	8.8	8.7
5	$C_{16}H_{16}N_2O_3S$	60.7	60.9	5.1	5.1	8.9	9.0	10.1	9.8
6	$C_{16}H_{16}N_2O_2S$	64.0	64.0	5.4	5.5	9.3	9.4	10.7	10.5
7	$C_{17}H_{16}N_2O_3S$	62.2	62.3	4.9	4.9	8.5	8.5	9.8	9.6
8	$C_{16}H_{16}N_2O_2S$	64.0	63.6	5.4	5.4	9.3	9.2	10.7	10.2
9	$C_{17}H_{18}N_2O_2S$	64.9	65.1	5.8	5.9	8.9	8.9	10.2	9.9
10	$C_{17}H_{17}N_2O_2SCl$	58.5	58.4	4.9	4.9	8.0	8.0	9.2	9.3
11	$C_{17}H_{18}N_2O_2S$	64.9	65.2	5.8	5.9	8.9	8.9	10.2	9.8
12	$C_{18}H_{20}N_2O_2S$	65.8	66.1	6.1	6.3	8.5	8.6	9.8	9.7
13	$C_{19}H_{22}N_2O_2S$	66.6	66.8	6.5	6.5	8.2	8.2	9.4	9.4
14	$C_{20}H_{24}N_2O_2S$	67.4	67.3	6.8	6.8	7.9	8.0	9.0	9.2
15	$C_{22}H_{28}N_2O_2S$	68.7	68.8	7.3	7.4	7.3	7.4	8.3	8.0
16	$C_{21}H_{17}N_2O_2SCl$	63.6	63.3	4.3	4.3	7.1	7.1	8.1	8.0
17	$C_{22}H_{20}N_2O_2S$	70.2	70.5	5.4	5.4	7.4	7.5	8.5	8.6
18	$C_{23}H_{22}N_2O_2S$	70.7	70.9	5.7	5.7	7.2	7.2	8.2	8.3
19	$C_{15}H_{14}N_2O_2S$	62.9	63.0	4.9	4.9	9.8	9.9	11.2	10.9
20	$C_{16}H_{16}N_2O_3S$	60.7	60.9	5.1	5.2	8.9	9.0	10.1	10.0
21	$C_{15}H_{15}N_3OS$	63.1	63.2	5.3	5.3	14.7	14.7	11.2	—
22	$C_{15}H_{13}N_3O_3S$	57.1	57.2	4.2	4.2	13.3	13.3	10.2	10.2
23	$C_{19}H_{16}N_2O_2S$	67.8	67.9	4.8	4.9	8.3	8.3	9.5	9.5
24	$C_{19}H_{16}N_2O_2S$	67.8	67.9	4.8	4.8	8.3	8.3	9.5	9.5
25	$C_{14}H_{13}N_3O_2S$	58.5	58.8	4.6	4.7	14.6	14.6	10.7	10.4
26	$C_{16}H_{16}N_2O_4S$	57.8	57.9	4.9	4.9	8.4	8.7	9.7	9.7
27	$C_{16}H_{16}N_2O_3S_2$	55.1	55.0	4.6	4.7	8.0	8.0	18.4	18.6
28	$C_{20}H_{20}N_2O_3S$	65.2	65.2	5.5	5.4	7.6	7.8	8.7	8.4
29	$C_{13}H_{18}N_2O_2S$	58.6	58.6	6.8	6.9	10.5	10.7	12.0	11.5
30	$C_{18}H_{15}N_3OS$	67.3	67.4	4.7	4.7	13.1	13.1	10.0	10.0
31	$C_{14}H_{13}N_3OS$	62.0	61.8	4.8	4.8	15.5	15.4	11.8	11.4
32	$C_{13}H_{12}N_2OS_2$	56.5	56.5	4.4	4.4	10.1	10.1	23.2	23.3
33	$C_{10}H_{12}N_2O_2S$	53.6	53.9	5.4	5.4	12.5	12.5	14.3	
34	$C_{16}H_{16}N_2O_2S$	64.0	63.9	5.4	5.4	9.3	9.3	10.7	10.4
35	$C_{14}H_{12}N_3O_2S$	58.7	58.3	4.2	4.6	14.7	14.7	11.2	10.8
36	$C_{15}H_{15}N_3OS$	63.1	63.4	5.3	5.2	14.7	14.8	11.2	11.2
37	$C_{15}H_{14}N_2OS_2$	59.6	59.5	4.7	4.7	9.3	9.4	21.2	21.3
38	$C_{10}H_{12}N_2O_3$	57.7	57.9	5.8	5.8	13.5	13.5	—	—
39	$C_{15}H_{14}N_2O_2S$	62.9	63.0	4.9	5.0	9.8	9.8	11.2	11.2
40	$C_{16}H_{16}N_2O_2S$	64.0	63.9	5.4	5.4	9.3	9.4	10.7	10.6
41	$C_{16}H_{16}N_2O_2S$	64.0	64.0	5.4	5.4	9.3	9.2	10.7	10.7

disulphide was added and the mixture was stirred at room temperature for 5 h. During the reaction the potassium salt of 4-pyridyl-methylxanthic acid precipitated. The salt was filtered off and dried. Weight 17 g. The mother liquor was concentrated *in vacuo* to about 1/5 of its original volume and chilled strongly. A further 17 g of the salt was obtained, washed with acetone and dried.

4-Pyridylmethoxythiocarbohydrazide. 17.8 g (80 mmole) of potassium pyridylmethyl-xanthate were dissolved in 30 ml of water and 5 ml of hydrazine hydrate was added. The mixture was left at room temperature for 18 h. The crystalline precipitate was filtered off, washed with water and recrystallized from ethanol. 10 g (67 %) of the hydrazide was obtained as colourless shells, which turned slightly reddish in the air. Mp 142.5—143°C. (Found: C 45.9; H 5.0; N 22.9. Calc. C 45.8; H 5.0; N 23.0.)

Acknowledgements. The author is deeply indebted to Mr. Niels Elming of A/S Pharmacia, Copenhagen, Denmark, who kindly supplied a sample of 3-hydroxypicolinealdehyde, and to Mr. S. O. Hall of this laboratory for help with the experimental work.

REFERENCES

1. Wangel, J. *Arkiv Kemi* **1** (1949) 431.
2. Wangel, J. *Kemisk maanedsblad* **39** (1958) 73.
3. Weinberg, E. D. *Bacteriol Rev.* **21** (1957) 46.
4. Stollé, R. and Benrath, A. *J. prakt. Chem.* (2) **70** (1904) 276.
5. Busch, M. and Starke, M. *J. prakt. Chem.* (2) **93** (1916) 59.
6. Elming, N. *Acta Chem. Scand.* **11** (1957) 1496.

Received February 13, 1960.