143. *New Thiosemicarbazones and 4-Oxo-Δ^2-thiazolin-2-ylhydrazones.*

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A large number of thiosemicarbazones and 4-oxo-Δ^2-thiazolin-2-ylhydrazones, many derived from benzyloxybenzaldehydes, have been prepared for biological testing.

Owing to the varied medical potentialities of thiosemicarbazones,[1] and to the fact that some inhibit slightly the growth of Sarcoma 180 in mice (personal communication from Dr. Chester Stock, Sloan-Kettering Institute, New York) (annexed Table), the new

Thiosemicarbazone of :	Inhibitory dose (mg./kg./day)
p-(4-Methylbenzyloxy)benzaldehyde	10
p-(4-Chlorobenzyloxy)benzaldehyde	30
p-(4-Bromobenzyloxy)benzaldehyde	35
4-Methoxy-1-naphthaldehyde	250
4-(3-Phenylpropyloxy)benzaldehyde	10

thiosemicarbazones listed in Table 1 have been prepared. Table 2 records the new benzyloxybenzaldehydes prepared as intermediates. Some 4-oxo-Δ^2-thiazolin-2-ylhydrazones

[1] See, *inter al.*, Hoggarth *et al.*, *Brit. J. Pharmacol.*, 1949, **4**, 248; Donovick *et al.*, *J. Bacteriol.*, 1950, **59**, 667; Bavin *et al.*, *J. Pharm. and Pharmacol.*, 1950, **2**, 764; Buu-Hoï *et al.*, *J.*, 1952, 4590; 1953, 547; 1955, 1581; Domagk, *Naturwiss.*, 1946, **33**, 315; Behnisch *et al.*, *Angew. Chem.*, 1948, **60**, 113; Perry, *J. Amer. Chem. Soc.*, 1954, **76**, 3591; Buu-Hoï, *Internat. J. Leprosy*, 1954, **22**, 16; *Bull. Calcutta School Trop. Med.*, 1955, **3**, 133; Buu-Hoï *et al.*, *J. Org. Chem.*, 1953, **18**, 121.

TABLE 1. *Thiosemicarbazones.*[a]

Aldehyde or ketone	M. p.	Formula	Found (%) C	Found (%) H	Reqd. (%) C	Reqd. (%) H
p-Fluorobenzaldehyde	180°	$C_8H_8N_3SF$	48·5	4·0	48·7	4·1
4-Methoxy-3-methylbenzaldehyde	194	$C_{10}H_{13}ON_3S$	53·6	6·0	53·8	5·8
4-Methoxy-2-methylbenzaldehyde	213	$C_{10}H_{13}ON_3S$	53·6	5·7		
2-Methoxy-5-methylbenzaldehyde	212	$C_{10}H_{13}ON_3S$	54·0	5·7		
p-(2-Chlorobenzyloxy)benzaldehyde	167	$C_{15}H_{14}ON_3SCl$	56·0	4·5	56·3	4·4
p-(2 : 4-Dichlorobenzyloxy)benzaldehyde	192	$C_{15}H_{13}ON_3SCl_2$	50·7	4·0	50·8	3·7
m-Benzyloxybenzaldehyde	157	$C_{15}H_{15}ON_3S$	63·0	5·1	63·2	5·3
m-(4-Chlorobenzyloxy)benzaldehyde	160	$C_{15}H_{14}ON_3SCl$	56·0	4·1	56·3	4·4
m-(4-Bromobenzyloxy)benzaldehyde	165	$C_{15}H_{14}ON_3SBr$	49·2	4·1	49·5	3·8
m-(4-Methylbenzyloxy)benzaldehyde	156	$C_{16}H_{17}ON_3S$	64·1	5·9	64·2	5·7
o-Benzyloxybenzaldehyde	160	$C_{15}H_{15}ON_3S$	63·3	5·2	63·2	5·3
o-(2-Chlorobenzyloxy)benzaldehyde	168	$C_{15}H_{14}ON_3SCl$	56·0	4·2	56·3	4·4
o-(4-Chlorobenzyloxy)benzaldehyde	225	$C_{15}H_{14}ON_3SCl$	56·1	4·1		
o-(2 : 4-Dichlorobenzyloxy)benzaldehyde	237	$C_{15}H_{13}ON_3SCl_2$	50·7	4·0	50·8	3·7
o-(4-Methylbenzyloxy)benzaldehyde	198	$C_{16}H_{17}ON_3S$	64·5	5·5	64·2	5·7
o-(4-Bromobenzyloxy)benzaldehyde	189	$C_{15}H_{14}ON_3SBr$	49·2	3·7	49·5	3·8
3-Formylpyrene [b]	270	$C_{18}H_{13}N_3S$	71·2	4·5	71·3	4·3
2-Benzyloxy-1-naphthaldehyde	210	$C_{19}H_{17}ON_3S$	68·0	5·3	68·1	5·1
3-Nitropropiophenone	199	$C_{10}H_{12}O_2N_4S$	47·5	4·8	47·6	4·8
4-Methylpropiophenone	146	$C_{11}H_{15}N_3S$	59·4	6·8	59·7	6·8
4-Bromopropiophenone	169	$C_{10}H_{12}N_3SBr$	41·8	4·1	42·0	4·2
3-Methyl-4-methylthiopropiophenone	152	$C_{12}H_{17}N_3S_2$	53·6	6·2	53·9	6·4
2-Propionylthiophen	128	$C_8H_{11}N_3S_2$	44·9	5·0	45·1	5·2
4-*iso*Propylpropiophenone	123	$C_{13}H_{19}N_3S$	62·8	7·5	62·7	7·6
4-Methyl-1-propionylnaphthalene	174	$C_{15}H_{17}N_3S$	66·1	6·5	66·4	6·3
2 : 4-Dimethoxyacetophenone	170	$C_{11}H_{15}O_2N_3S$	52·0	5·7	52·2	5·9
2 : 4-Dimethylacetophenone	158	$C_{11}H_{15}N_3S$	59·4	6·9	59·7	6·8
4-Iodoacetophenone	210	$C_9H_{10}N_3SI$	34·1	3·3	33·9	3·1
3-Bromo-4-methoxyacetophenone	208	$C_{10}H_{12}ON_3SBr$	39·5	4·0	39·7	4·0
2-Acetylphenanthrene	217	$C_{17}H_{15}N_3S$	69·8	5·0	69·6	5·1
3-Acetylphenanthrene	176	$C_{17}H_{15}N_3S$	69·5	5·2		
2-*n*-Decanoylfluorene	118	$C_{24}H_{31}N_3S$	73·0	8·0	73·3	7·9
6-Propionyltetralin	133	$C_{14}H_{19}N_3S$	64·4	7·2	64·4	7·3
Myristophenone	81	$C_{21}H_{35}N_3S$	70·1	9·6	69·8	9·7
2-Methoxy-6-phenylacetylnaphthalene	167	$C_{20}H_{19}ON_3S$	69·0	5·1	68·8	5·4
4-Phenoxyacetophenone	149	$C_{15}H_{15}ON_3S$	63·1	5·5	63·2	5·3
4-Phenylthiopropiophenone	129	$C_{16}H_{17}N_3S_2$	60·8	5·5	61·0	5·4
3-Acetyl-9-ethylcarbazole	203	$C_{17}H_{18}N_4S$	65·7	6·1	65·8	5·8
Methyl *cyclo*propyl ketone	107	$C_6H_{11}N_3S$	45·9	7·3	45·9	7·0
Octan-2-one	70	$C_9H_{19}N_3S$	53·9	9·5	53·7	9·5
Undecan-2-one	93	$C_{12}H_{25}N_3S$	59·0	10·1	59·2	10·3
5-Bromoisatin [c]	223	$C_9H_7ON_4SBr$	36·3	2·5	36·1	2·3

[a] The high-melting thiosemicarbazones generally decomposed at the m. p. [b] Bright yellow prisms. [c] Orange-yellow needles from acetic acid.

TABLE 2. *Benzyloxybenzaldehydes.*

	M. p.	B. p./mm.	Formula	Found (%) C	Found (%) H	Reqd. (%) C	Reqd. (%) H
p-(2-Chlorobenzyloxy)benzaldehyde	50°	252°/25	$C_{14}H_{11}O_2Cl$	68·5	4·5	68·2	4·5
p-(2 : 4-Dichlorobenzyloxy)benzaldehyde	102	282/30	$C_{14}H_{10}O_2Cl_2$	59·6	3·6	59·8	3·6
m-Benzyloxybenzaldehyde	49	225/25	$C_{14}H_{12}O_2$	79·2	5·8	79·2	5·7
m-(4-Chlorobenzyloxy)benzaldehyde	[a]	248/18	$C_{14}H_{11}O_2Cl$	68·3	4·6	68·2	4·5
m-(4-Bromobenzyloxy)benzaldehyde	[b]	254/18	$C_{14}H_{11}O_2Br$	57·8	4·1	57·7	3·8
m-(4-Methylbenzyloxy)benzaldehyde	[c]	240/22	$C_{15}H_{14}O_2$	79·8	6·3	79·6	6·2
o-(2-Chlorobenzyloxy)benzaldehyde	70	246/25	$C_{14}H_{11}O_2Cl$	68·1	4·5	68·2	4·5
o-(4-Chlorobenzyloxy)benzaldehyde	82	—	$C_{14}H_{11}O_2Cl$	68·0	4·8	68·2	4·5
o-(4-Bromobenzyloxy)benzaldehyde	68	258/18	$C_{14}H_{11}O_2Br$	58·0	3·9	57·7	3·8
o-(2 : 4-Dichlorobenzyloxy)benzaldehyde	135	—	$C_{14}H_{10}O_2Cl_2$	60·1	3·9	59·8	3·6
o-(4-Methylbenzyloxy)benzaldehyde	[d]	228/13	$C_{15}H_{14}O_2$	79·8	6·3	79·6	6·2

[a] n_D^{27} 1·6032. [b] $n_D^{30·5}$ 1·6109. [c] n_D^{27} 1·5904. [d] n_D^{25} 1·5922.

are tuberculostatic *in vivo*;[2] several new ones are listed in Table 3; they include the 4-oxo-Δ^2-thiazolin-2-ylhydrazones of 2-, 3-, and 4-formylpyridine which yield highly tuberculostatic thiosemicarbazones.[3]

[2] Ratsimamanga *et al.*, *Bull. Soc. Chim. biol.*, 1952, **146**, 354.
[3] Levaditi, Girard, Vaisman, and Ray, *Compt. rend.*, 1950, **231**, 1174; Gardner, Smith, Wenis, and Lee, *J. Org. Chem.*, 1951, **16**, 1121.

TABLE 3. 4-*Oxo*-5-R-Δ^2-*thiazolin*-2-*ylhydrazones*.

				Found (%)		Reqd. (%)	
Prepd. from :	R	M. p.	Formula	C	H	C	H
p-Fluorobenzaldehyde	H	291°	$C_{10}H_8ON_3SF$	50·5	3·2	50·6	3·4
p-Fluorobenzaldehyde	Et	230	$C_{12}H_{12}ON_3SF$	54·0	4·8	54·3	4·5
p-Fluorobenzaldehyde	Pr^i	205	$C_{13}H_{14}ON_3SF$	56·0	5·1	55·9	5·0
p-Fluorobenzaldehyde	Pr^n	208	$C_{13}H_{14}ON_3SF$	56·1	5·3	55·9	5·0
p-Fluorobenzaldehyde	Bu^n	220	$C_{14}H_{16}ON_3SF$	57·5	5·6	57·3	5·5
p-Fluorobenzaldehyde	$Bu^i{\cdot}CH_2$	201	$C_{15}H_{18}ON_3SF$	58·3	6·0	58·6	5·9
p-Fluorobenzaldehyde	*n*-$C_{14}H_{29}$	158	$C_{24}H_{36}ON_3SF$	66·6	8·4	66·5	8·3
p-Fluorobenzaldehyde	*n*-$C_{16}H_{33}$	150	$C_{26}H_{40}ON_3SF$	67·7	9·0	67·7	8·7
4-Methoxy-3-methylbenzaldehyde	H	252	$C_{12}H_{13}O_2N_3S$	54·5	4·7	54·8	4·9
4-Methoxy-2-methylbenzaldehyde	H	262	$C_{12}H_{13}O_2N_3S$	54·7	5·0	54·8	4·9
2-Methoxy-5-methylbenzaldehyde	H	246	$C_{12}H_{13}O_2N_3S$	54·6	4·8	54·8	4·9
p-(2-Chlorobenzyloxy)benzaldehyde	H	236	$C_{17}H_{14}O_2N_3SCl$	56·4	4·1	56·7	3·9
p-(2 : 4-Dichlorobenzyloxy)benzaldehyde	H	253	$C_{17}H_{13}O_2N_3SCl_2$	52·0	3·3	51·8	3·3
m-Benzyloxybenzaldehyde	H	199	$C_{17}H_{15}O_2N_3S$	62·9	4·8	62·8	4·6
m-(4-Chlorobenzyloxy)benzaldehyde	H	220	$C_{17}H_{14}O_2N_3SCl$	56·5	3·8	56·7	3·9
m-(4-Bromobenzyloxy)benzaldehyde	H	228	$C_{17}H_{14}O_2N_3SBr$	50·2	3·8	50·5	3·5
m-(4-Methylbenzyloxybenzaldehyde	H	183	$C_{18}H_{17}O_2N_3S$	63·5	5·0	63·7	5·0
o-Benzyloxybenzaldehyde	H	212	$C_{17}H_{15}O_2N_3S$	62·8	4·4	62·8	4·6
o-(4-Chlorobenzyloxy)benzaldehyde	H	204	$C_{17}H_{14}O_2N_3SCl$	56·4	3·9	56·7	3·9
o-(4-Bromobenzyloxy)benzaldehyde	H	204	$C_{17}H_{14}O_2N_3SBr$	50·3	3·3	50·5	3·5
o-(2: 4-Dichlorobenzyloxy)benzaldehyde	H	200	$C_{17}H_{13}O_2N_3SCl_2$	51·5	3·2	51·8	3·3
o-(2-Chlorobenzyloxy)benzaldehyde	H	219	$C_{17}H_{14}O_2N_3SCl$	56·9	4·1	56·7	3·9
o-(4-Methylbenzyloxy)benzaldehyde	H	212	$C_{18}H_{17}O_2N_3S$	63·8	5·2	63·7	5·0
p-Anisaldehyde	Et	181	$C_{13}H_{15}O_2N_3S$	56·0	5·2	56·3	5·4
p-Anisaldehyde	Bu^n	160	$C_{15}H_{19}O_2N_3S$	59·3	6·0	59·0	6·2
p-Anisaldehyde	*n*-$C_{12}H_{25}$	128	$C_{23}H_{35}O_2N_3S$	66·3	8·5	66·2	8·4
p-Anisaldehyde	*n*-$C_{14}H_{29}$	116	$C_{25}H_{39}O_2N_3S$	67·7	8·9	67·4	8·8
p-Anisaldehyde	*n*-$C_{16}H_{33}$	108	$C_{27}H_{13}O_2N_3S$	68·6	9·4	68·5	9·1
p-Acetamidobenzaldehyde	H	342—345	$C_{12}H_{12}O_2N_4S$	51·8	4·3	52·2	4·3
p-Acetamidobenzaldehyde	Bu^n	218	$C_{16}H_{20}O_2N_4S$	57·5	6·1	57·8	6·0
p-Dimethylaminobenzaldehyde	H	251	$C_{12}H_{14}ON_4S$	55·0	5·0	55·0	5·3
p-Dimethylaminobenzaldehyde	Et	223	$C_{14}H_{18}ON_4S$	57·6	6·0	57·9	6·2
p-Dimethylaminobenzaldehyde	Bu^n	214	$C_{16}H_{22}ON_4S$	60·1	7·0	60·4	6·9
p-Dimethylaminobenzaldehyde	*n*-$C_{12}H_{25}$	153	$C_{24}H_{38}ON_4S$	67·2	9·0	67·0	8·8
p-Dimethylaminobenzaldehyde	*n*-$C_{14}H_{29}$	150	$C_{26}H_{42}ON_4S$	68·2	9·5	68·1	9·2
p-Dimethylaminobenzaldehyde	*n*-$C_{16}H_{33}$	145	$C_{28}H_{46}ON_4S$	69·4	9·6	69·1	9·5
Cinnamaldehyde	Et	232	$C_{14}H_{15}ON_3S$	61·2	5·3	61·5	5·5
Cinnamaldehyde	Bu^n	203	$C_{16}H_{19}ON_3S$	63·8	6·0	63·8	6·3
3-Formylpyrene	H	>310	$C_{20}H_{13}ON_3S$	69·7	3·6	70·0	3·8
3-Acetyl-9-ethylcarbazole	H	254	$C_{19}H_{18}ON_4S$	65·0	5·1	65·1	5·1
2-Acetylphenanthrene	H	>320	$C_{19}H_{15}ON_3S$	68·8	4·4	68·5	4·5
3-Acetylphenanthrene	H	>320	$C_{19}H_{15}ON_3S$	68·6	4·6	68·5	4·5
2-Propiothienone	H	245	$C_{10}H_{11}ON_3S_2$	47·6	4·2	47·4	4·3
2 : 4-Dimethoxyacetophenone	H	220	$C_{13}H_{15}O_3N_3S$	53·0	5·3	53·2	5·1
4-Bromopropiophenone	H	208	$C_{12}H_{12}ON_3SBr$	44·4	3·6	44·2	3·7
3-Bromo-4-methoxyacetophenone	H	239	$C_{12}H_{12}O_2N_3SBr$	42·4	3·5	42·1	3·5
4-Iodoacetophenone	H	247	$C_{11}H_{10}ON_3SI$	36·4	2·7	36·7	2·8
2 : 4-Dimethylacetophenone	H	237	$C_{13}H_{15}ON_3S$	59·5	5·5	59·8	5·7
4-Methylpropiophenone	H	221	$C_{13}H_{15}ON_3S$	59·4	5·8	59·8	5·7
4-Methyl-1-propionaphthone	H	238	$C_{17}H_{17}ON_3S$	65·5	5·8	65·6	5·5
2-Methoxy-6-phenylacetylnaphthalene	H	253	$C_{22}H_{19}O_2N_3S$	67·6	4·8	67·9	4·9
Citral	H	178	$C_{13}H_{19}ON_3S$	59·0	7·0	58·9	7·2
Citral	Et	149	$C_{15}H_{23}ON_3S$	61·2	7·8	61·4	7·8
Citral	Bu^n	147	$C_{17}H_{27}ON_3S$	63·3	8·4	63·6	8·4
Octan-2-one	H	122	$C_{11}H_{19}ON_3S$	54·5	7·7	54·8	7·9
Octan-2-one	Bu^n	89	$C_{15}H_{27}ON_3S$	60·5	9·0	60·6	9·1
Undecan-2-one	H	147	$C_{11}H_{25}ON_3S$	59·5	9·0	59·4	8·8
Undecan-2-one	Bu^n	84	$C_{18}H_{33}ON_3S$	63·9	9·6	63·7	9·7
2-Formylpyridine	H	264	$C_9H_8ON_4S$	N, 25·3		N, 25·5	
3-Formylpyridine	H	278	$C_9H_8ON_4S$	N, 25·1		N, 25·5	
4-Formylpyridine	H	271	$C_9H_8ON_4S$	N, 25·2		N, 25·5	

The tuberculostatic activities varied widely (determined on *Mycobacterium tuberculosis* var. *bovis*, strain B.C.G., in Dubos–Davis Tween–albumin medium). The most active compounds are reported in Table 4. Active ketone thiosemicarbazones were often structurally related to active aldehyde thiosemicarbazones. Some activity was also shown by 3-mercapto-5 : 6-dimethyl-1 : 2 : 4-triazine, prepared by condensation of thiosemicarbazide with diacetyl. 4-Oxo-Δ²-thiazolin-2-ylhydrazones were considerably less active than their active parent thiosemicarbazones. Most thiosemicarbazones rapidly

caused fatty degeneration and hæmorrhage in the liver of rats and mice, the 4-oxo-Δ²-thiazolin-2-ylhydrazones less so. In tests for antithyroid properties in rats, 3-mercapto-5 : 6-dimethyl-1 : 2 : 4-triazine had little effect compared with thiouracil at similar dose.

TABLE 4. *Thiosemicarbazones showing marked tuberculostatic activity* in vitro.[a, b]

Active at 1 : 10⁵	Active at 1 : 10⁶
9-Ethyl-3-formyl-6-nitrocarbazole	6-Bromo-9-ethyl-3-formylcarbazole
9-Formylanthracene	*p*-(2-Chlorobenzyloxy)benzaldehyde
3-Formylpyrene	Cinnamaldehyde
Methyl *cyclo*propyl ketone	*p*-(2 : 4-Dichlorobenzyloxy)benzaldehyde
7-Phenylheptatrienal	4-Methoxy-3-methylbenzaldehyde
5-Phenylpentadienal	**Active at 1 : 10—10⁷**
3-Phenylpropanol	3-Acetyl-9-ethylcarbazole
4-*n*-Tetradecanoylbenzene	*p*-Ethoxybenzaldehyde
Undecan-2-one	Piperonaldehyde
Active at 1 : 10⁵—10⁶	**Active at 1 : 10⁷**
5-Chloro-2-cinnamyloxybenzaldehyde	3-Formylphenothiazine
4-Methoxyacetophenone	

[a] Readings taken after 3 weeks' incubation. [b] The corresponding 4-oxo-Δ²-thiazolin-2-ylhydrazones did not show tuberculostatic activity at concentrations lower than 1 : 10⁴.

EXPERIMENTAL

Preparation of Thiosemicarbazones.—Thiosemicarbazones derived from aldehydes were prepared in 80—95% yield in the minimum volume of boiling ethanol and recrystallised from ethanol, benzene, or acetic acid. Thiosemicarbazones derived from ketones were prepared, generally in lower yield, in boiling alcohol containing a drop of acetic acid (30 min.).

Preparation of 4-Oxo-Δ²-thiazolin-2-ylhydrazones[4] *of Aldehydes and Ketones.*—A solution of the thiosemicarbazone (1 mol.) and chloroacetic acid or the appropriate α-bromo-acid (1 mol.) was refluxed with sodium acetate (1·5 mol.) for 1 hr. The resulting 4-oxo-Δ²-thiazolin-2-ylhydrazone was recrystallised from ethanol or acetic acid.

3-*Mercapto*-5 : 6-*dimethyl*-1 : 2 : 4-*triazine.*—A solution of diacetyl (8·6 g.) and thiosemicarbazide (9 g.) in ethanol was boiled for a few minutes, and the orange-yellow precipitate was collected after cooling, and recrystallised from ethanol. The *triazine* (12 g.) was soluble in aqueous alkali and decomposed at 191° (Found: N, 29·3. $C_5H_7N_3S$ requires N, 29·8%). It was tuberculostatic at concentrations of 1 : 10^5 to 10^6.

Preparation of Benzyloxybenzaldehydes.—Equimolecular amounts of the hydroxyaldehyde and the appropriate benzyl chloride were condensed in ethanolic sodium hydroxide. The products were distilled *in vacuo* and recrystallised from ligroin or methanol. 2-*Benzyloxy*-1-*naphthaldehyde* crystallised as yellowish needles, m. p. 126°, from ethanol (Found: C, 82·1; H, 5·5. $C_{18}H_{14}O_2$ requires C, 82·4; H, 5·3%); its iso*nicotinoylhydrazone* formed yellow prisms, m. p. 239°, from ethanol (Found: N, 11·2. $C_{24}H_{19}O_2N_3$ requires N, 11·0%), its *nicotinoylhydrazone*, shiny yellow leaflets, m. p. 210°, from ethanol (Found: N, 10·9%), and its 5-*chlorosalicyloylhydrazone*, colourless needles, m. p. 202°, from ethanol (Found: N, 6·7. $C_{25}H_{19}O_3N_2Cl$ requires N, 6·5%).

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[4] Wilson *et al.*, *J.*, 1922, **121**, 876; 1923, **123**, 799; 1926, 253; Chabrier *et al.*, *Bull. Soc. chim. France*, 1947, **14**, 797; 1950, **17**, 48.