[CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, RADIUM INSTITUTE, UNIVERSITY OF PARIS, FROM THE ANTIBIOTICS DEPARTMENT OF THE UNIVERSITY OF LIÈGE, AND FROM THE RESEARCH LABORATORIES OF THE "SOCIETE BELGE DE L'AZOTE", LIÈGE].

# SOME NEW TUBERCULOSTATIC THIOSEMICARBAZONES

NG. PH. BUU-HOÏ, M. WELSCH, G. DECHAMPS, H. LE BIHAN, F. BINON, AND NG. D. XUONG

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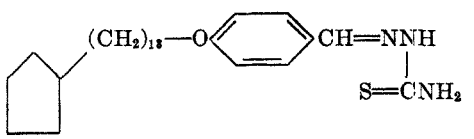
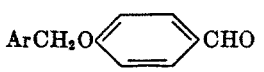
For several years, the announcement by Domagk and associates (1) that thiosemicarbazones of *para*-substituted benzaldehydes are active against *Mycobacterium tuberculosis* both *in vitro* and *in vivo*, has prompted an extensive search for more active and less toxic compounds of this type (2). Results in this field have thus far been somewhat disappointing, since many compounds, while displaying considerable activity *in vitro*, proved to be either far less effective *in vivo*, or so toxic as to preclude any clinical use. General toxicity and intolerance are frequently encountered in thiosemicarbazones of aldehydes derived from nitrogenous heterocycles, and this is most unfortunate because in these series several outstanding tuberculostatic compounds have been found (2, 3). Thus, nicotinylaldehyde thiosemicarbazone, which shows high activity in animals (3), could not be used in human therapy because of intolerance (communication from the Roussel Laboratories Ltd., England).

In view of the pronounced *in vitro* and *in vivo* tuberculostatic activity of *p*-anisaldehyde (2, 4) and *p*-ethoxybenzaldehyde thiosemicarbazones (2, 5), an investigation was carried out here to see whether, in the series of thiosemicarbazones derived from ethers of *p*-hydroxybenzaldehyde, there were compounds with even more favorable chemotherapeutic indices.

*p*-Hydroxybenzaldehyde and several of its mono- and di-halogenated derivatives were condensed in an alkaline medium with several alkyl and arylalkyl chlorides or bromides, to yield the corresponding *p*-alkyloxy- and *p*-arylalkyloxybenzaldehydes. The corresponding thiosemicarbazones are listed in Table I, along with the new thiosemicarbazones derived from halogenated *p*-hydroxybenzaldehydes. Of particular interest are long-chain compounds such as *p*-dihydrochaulmoogryloxybenzaldehyde thiosemicarbazone (I), which are readily soluble in lipids. In view of the mild tuberculostatic activity of *p*-hydroxypropiophenone, its thiosemicarbazone and those corresponding to some of its ethers have also been included in the present research, together with similar derivatives from a series of aromatic ketones and chalkones; these are listed in Table III.




I




II

The tuberculostatic activity was determined on a strain of *Myobacterium tuberculosis var. bovis* (strain B.C.G.); the medium was that of Dubos and Middlebrook (6). Results showed a considerable *in vitro* activity (one part in ten million)

in thiosemicarbazones of *p*-arylalkyloxybenzaldehydes of the type represented by formula (II) and in several thiosemicarbazones of aromatic ketones and chal-

TABLE I

THIOSEMICARBAZONES DERIVED FROM 4-SUBSTITUTED BENZALDEHYDES

| SUBSTITUTIONS | ACTIVITY[g] | FORMULA | M.P., °C. | ANALYSES | | | |
|---|---|---|---|---|---|---|---|
| | | | | Calc'd | | Found | |
| | | | | C | H | C | H |
| 4-Benzyloxy | ++++ | $C_{15}H_{15}N_3OS$ | 188 | 63.2 | 5.3 | 62.9 | 5.2 |
| 4-Chlorobenzyloxy | ++++ | $C_{15}H_{14}ClN_3OS$ | 194 | 56.3 | 4.4 | 56.4 | 4.2 |
| 4-Bromobenzyloxy | ++++ | $C_{15}H_{14}BrN_3OS$ | 187 | 49.5 | 3.8 | 49.0 | 3.9 |
| 4-Methylbenzyloxy[a] | ++++ | $C_{16}H_{17}N_3OS$ | 170 | 64.2 | 5.7 | 64.0 | 5.6 |
| 4-Ethylbenzyloxy[b] | ++++ | $C_{17}H_{19}N_3OS$ | 169 | 65.2 | 6.1 | 64.9 | 6.0 |
| 4-(2,4-Dimethylbenzyl)oxy | ++++ | $C_{17}H_{19}N_3OS$ | 154 | 65.2 | 6.1 | 65.3 | 6.3 |
| 4-Cinnamyloxy | ++++ | $C_{17}H_{17}N_3OS$ | 203 | 65.6 | 5.5 | 65.2 | 5.4 |
| 4-β-Phenylethoxy[c] | ++ | $C_{16}H_{17}N_3OS$ | 172 | 64.2 | 5.7 | 64.0 | 5.9 |
| 4-γ-Phenylpropyloxy | ++ | $C_{17}H_{19}N_3OS$ | 144 | 65.2 | 6.1 | 65.0 | 6.3 |
| 4-(1-Naphthomethyl)oxy[d] | ++++ | $C_{19}H_{17}N_3OS$ | 172 | 68.1 | 5.1 | 67.7 | 5.0 |
| 4-(1-β-Naphthylethyl)oxy[e] | +++ | $C_{20}H_{19}N_3OS$ | 173 | 68.8 | 5.4 | 68.5 | 5.6 |
| 4-*n*-Dodecyloxy[f] | + | $C_{20}H_{33}N_3OS$ | 114 | 66.1 | 9.1 | 66.0 | 9.4 |
| 4-*n*-Octadecyloxy[f] | + | $C_{26}H_{45}N_3OS$ | 118 | 69.8 | 10.1 | 69.5 | 10.2 |
| 4-Dihydrochaulmoogryl-oxy[f] | + | $C_{26}H_{43}N_3OS$ | 106 | 70.1 | 9.7 | 70.0 | 10.0 |
| 3-Chloro-4-hydroxy | +++ | $C_8H_8ClN_3OS$ | 237 (dec. >216) | 41.8 | 3.5 | 41.5 | 3.8 |
| 3-Chloro-4-benzyloxy | ++++ | $C_{15}H_{14}ClN_3OS$ | 180 | 56.3 | 4.4 | 56.1 | 4.5 |
| 3-Bromo-4-benzyloxy | ++++ | $C_{15}H_{14}BrN_3OS$ | 183 | 49.5 | 3.8 | 49.2 | 4.0 |
| 3,5-Dichloro-4-hydroxy | + | $C_8H_7Cl_2N_3OS$ | 260 (dec. >230) | 36.4 | 2.7 | 36.0 | 2.9 |
| 3,5-Dibromo-4-hydroxy | + | $C_8H_7Br_2N_3OS$ | 256 (dec. >235) | 27.2 | 2.0 | 26.9 | 2.3 |
| 3,5-Dibromo-4-benzyloxy | + | $C_{15}H_{13}Br_2N_3OS$ | 218 (dec. >190) | 40.6 | 2.9 | 40.4 | 3.2 |
| 3,5-Diiodo-4-hydroxy | 0 | $C_8H_7I_2N_3OS$ | 266 (dec. >230) | 21.5 | 1.6 | 21.2 | 2.0 |
| 3,5-Diiodo-4-benzyloxy | + | $C_{15}H_{13}I_2N_3OS$ | 214 (dec. >190) | 33.5 | 2.4 | 33.2 | 2.7 |
| 3-Methoxy-4-benzyloxy | +++ | $C_{16}H_{17}N_3O_2S$ | 166 | 61.0 | 5.4 | 60.8 | 5.6 |

[a] *p*-(4-Methylbenzyl)oxybenzaldehyde had b.p. 222–224°/13 mm. (Calc'd for $C_{15}H_{14}O_2$: C, 79.6; H, 6.2. Found: C, 79.3; H, 6.4.). [b] The liquid aldehyde had b.p. 233–234°/13 mm. (Calc'd for $C_{16}H_{16}O_2$: C, 80.0; H, 6.7. Found: C, 79.7; H, 6.9.). [c] The liquid aldehyde had b.p. 225°/13 mm. (Calc'd for $C_{15}H_{14}O_2$: C, 79.6; H, 6.2. Found: C, 79.6; H, 6.3.). [d] Aldehyde b.p. 278–279°/13 mm. (Calc'd for $C_{18}H_{14}O_2$: C, 82.4; H, 5.3. Found: C, 82.1; H, 5.1.). [e] Aldehyde b.p. 290–295°/13 mm. (Calc'd for $C_{18}H_{14}O_2$: C, 82.4; H, 5.3. Found: C, 82.1; H, 5.5.). [f] The three aldehydes were wax-like, low-melting substances. [g] ++++ corresponds to tuberculostatic activity at a concentration of $10^{-7}$, and + to an activity at a concentration of $10^{-4}$.

kones. In *in vivo* tests performed on guinea pigs, *p*-benzyloxybenzaldehyde thiosemicarbazone showed promising activity, accompanied by a remarkably low

degree of toxicity (7). *p*-Cinnamyloxybenzaldehyde thiosemicarbazone was also found active both *in vitro* and *in vivo*, but was toxic, and produced convulsions in animals treated. *p*-Benzyloxybenzaldehyde thiosemicarbazone is now undergoing extensive clinical tests in tuberculosis and leprosy. It is noteworthy that homonuclear disubstitution, such as in the case of thiosemicarbazones derived

TABLE II

4-KETO-2-THIAZOLINYLHYDRAZONES OF FORMULA III

| RADICALS R, $R_1$, AND $R_2$ | FORMULA | M.P., °C. | ANALYSES | | | |
|---|---|---|---|---|---|---|
| | | | Calc'd | | Found | |
| | | | C | H | C | H |
| R = Benzyl, $R_1$ = $R_2$ = H[a] | $C_{17}H_{15}N_3O_2S$ | 239 | 62.8 | 4.6 | 62.4 | 4.6 |
| R = 4-Methylbenzyl, $R_1$ = $R_2$ = H | $C_{18}H_{17}N_3O_2S$ | 246 | 63.7 | 5.0 | 63.4 | 5.1 |
| R = 2,4-Dimethylbenzyl, $R_1$ = $R_2$ = H | $C_{19}H_{19}N_3O_2S$ | 236 | 64.6 | 5.4 | 64.3 | 5.2 |
| R = 4-Chlorobenzyl, $R_1$ = $R_2$ = H | $C_{17}H_{14}ClN_3O_2S$ | 247 | 56.7 | 3.9 | 56.5 | 4.1 |
| R = 4-Bromobenzyl, $R_1$ = $R_2$ = H | $C_{17}H_{14}BrN_3O_2S$ | 235 | 50.5 | 3.5 | 50.2 | 3.6 |
| R = γ-Phenylpropyl, $R_1$ = $R_2$ = H | $C_{19}H_{19}N_3O_2S$ | 169 | 64.6 | 5.4 | 64.4 | 5.7 |
| R = Benzyl, $R_1$ = H, $R_2$ = Cl | $C_{17}H_{14}ClN_3O_2S$ | 254 | 56.7 | 3.9 | 56.3 | 3.6 |
| R = Benzyl, $R_1$ = H, $R_2$ = Br | $C_{17}H_{14}BrN_3O_2S$ | 260 | 50.5 | 3.5 | 50.2 | 3.4 |
| R = Benzyl, $R_1$ = H, $R_2$ = I | $C_{17}H_{14}IN_3O_2S$ | 227 (dec. >216) | 45.2 | 3.1 | 45.0 | 3.0 |
| R = Benzyl, $R_1$ = $R_2$ = Br | $C_{17}H_{13}Br_2N_3O_2S$ | 268 (dec. >260) | 42.2 | 2.7 | 41.9 | 2.8 |
| R = Benzyl, $R_1$ = $R_2$ = I | $C_{17}H_{13}I_2N_3O_2S$ | 266 (dec. >240) | 35.4 | 2.3 | 35.1 | 2.6 |
| R = $R_1$ = H, $R_2$ = Cl | $C_{10}H_8ClN_3O_2S$ | 264 | 44.5 | 3.0 | 44.3 | 3.2 |
| R = H, $R_1$ = $R_2$ = Cl | $C_{10}H_7Cl_2N_3O_2S$ | 321 (dec. >300) | 39.5 | 2.3 | 39.2 | 2.5 |
| R = H, $R_1$ = $R_2$ = Br | $C_{10}H_7Br_2N_3O_2S$ | 316 (dec. >300) | 30.5 | 1.8 | 30.2 | 2.1 |
| R = H, $R_1$ = $R_2$ = I | $C_{10}H_7I_2N_3O_2S$ | 275–277 (dec. >200) | 24.6 | 1.5 | 24.3 | 1.8 |

[a] All these substances were prepared from chloroacetic acid, and recrystallized from ethanol, benzene, or acetic acid. Similar 4-keto-2-thiazolinylhydrazones bearing an alkyl substituent at the 2-position have been equally successfully prepared by replacing chloroacetic acid by various higher α-bromoacids.

from 3,5-dihalogenated-4-benzyloxybenzaldehydes of type (IV), resulted in a sharp decrease in tuberculostatic activity.

Condensation of α-halogenated fatty acids with thiosemicarbazones is known to result in 4-keto-2-thiazolinylhydrazones (8); although these heterocyclic compounds generally have but little tuberculostatic activity *in vitro*, *p*-ethoxybenzaldehyde 5-ethyl-4-keto-2-thiazolinylhydrazone has displayed a definite *in vivo* activity (5). In the present paper, the preparation of some 4-keto-2-thiazolinylhydrazones of the general formula III derived from the thiosemicarb-

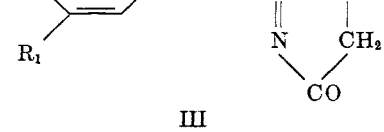
TABLE III

THIOSEMICARBAZONES DERIVED FROM VARIOUS AROMATIC KETONES

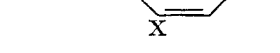
| PARENT KETONE | ACTIVITY | FORMULA | M.P., °C. | ANALYSES | | | |
|---|---|---|---|---|---|---|---|
| | | | | Calc'd | | Found | |
| | | | | C | H | C | H |
| 4-Hydroxypropiophenone | ++++ | $C_{10}H_{13}N_3OS$ | 200 (dec. >180) | 53.8 | 5.8 | 53.6 | 6.0 |
| 4-Isoamyloxypropiophenone[a] | | $C_{15}H_{23}N_3OS$ | 204–205 (dec. >176) | 61.4 | 7.8 | 61.1 | 7.8 |
| 4-Benzyloxypropiophenone | ++++ | $C_{17}H_{19}N_3OS$ | 200–202 (dec.) | N, 13.4 | | N, 13.2 | |
| 4-(*p*-Methylbenzyl)oxypropiophenone[b] | ++++ | $C_{18}H_{21}N_3OS$ | 209 (dec.) | N, 12.8 | | N, 12.4 | |
| 4-Benzyloxy-3-methoxyacetophenone[c] | ++++ | $C_{17}H_{19}N_3O_2S$ | 175 | 62.0 | 5.8 | 61.7 | 5.9 |
| 4-Acetylveratrole | ++++ | $C_{11}H_{15}N_3O_2S$ | 227 (dec. >210) | 52.2 | 5.9 | 51.9 | 6.3 |
| 4-Propionylveratrole | ++++ | $C_{12}H_{17}N_3O_2S$ | 160 (dec.) | 53.9 | 6.4 | 53.7 | 6.5 |
| Acetovanillone | +++ | $C_{10}H_{13}N_3O_2S$ | 209 (dec. >199) | 50.2 | 5.4 | 50.4 | 5.3 |
| 4-Benzyloxyacetophenone | ++++ | $C_{16}H_{17}N_3OS$ | 177 | 64.2 | 5.7 | 64.7 | 5.7 |
| 4-Chlorobenzalacetone[d] | ++++ | $C_{11}H_{12}ClN_3S$ | 188 | 52.1 | 4.7 | 52.0 | 4.5 |
| 2-Chlorobenzalacetone | +++ | $C_{11}H_{12}ClN_3S$ | 166 | 52.1 | 4.7 | 51.8 | 4.5 |
| 2,4-Dichlorobenzalacetone | +++ | $C_{11}H_{11}Cl_2N_3S$ | 196 | 45.8 | 3.8 | 45.6 | 4.1 |
| 3,4-Dichlorobenzalacetone | +++ | $C_{11}H_{11}Cl_2N_3S$ | 188 | 45.8 | 3.8 | 45.5 | 4.0 |
| Anisalacetone | ++++ | $C_{12}H_{15}N_3OS$ | 187 (dec. >180) | 57.8 | 6.0 | 57.6 | 6.3 |
| Anisal-4-acetoveratrone[a] | | $C_{19}H_{21}N_3O_3S$ | 167 | 61.5 | 5.7 | 61.1 | 5.9 |

[a] Not tested; 4-isoamyloxypropiophenone formed from methanol colorless prisms, m.p. 35° (Calc'd for $C_{14}H_{20}O_2$: C, 76.3; H, 9.1. Found: C, 76.1; H, 9.1.). [b] *p*-(4-Methylbenzyl)-oxypropiophenone formed from methanol fine colorless prisms, m.p. 74° (Calc'd for $C_{17}H_{18}O_2$: C, 80.3; H, 7.1. Found: C, 80.2; H, 7.2.). [c] 4-Benzyloxy-3-methoxyacetophenone, prepared from acetovanillone, benzyl chloride, and potassium hydroxide, formed from ethanol colorless needles, m.p. 88° (Calc'd for $C_{16}H_{16}O_3$: C, 75.0; H, 6.3. Found: C, 75.0; H, 6.5.). [d] The high activity of thiosemicarbazones of arylideneacetones is reminiscent of that of cinnamaldehyde thiosemicarbazone.

azones listed in Table I is reported; these ketothiazolinylhydrazones, listed in Table II, showed however no important *in vitro* tuberculostatic activity.




III




IV

X = Br, I

In the course of the present work, it was found that *p*-hydroxybenzaldehyde could be conveniently prepared, at variance with the literature, by demethylation of anisaldehyde with pyridine hydrochloride.

## EXPERIMENTAL

*Preparation of p-benzyloxybenzaldehyde thiosemicarbazone.*[1] A mixture of 300 g. of anisaldehyde and 1000 g. of pyridine hydrochloride was refluxed for 30 minutes; the hot solution obtained was stirred in 5 l. of cold water, and the supernatant resinous material was removed by immediate filtration. The cold filtrate was extracted thoroughly with ether, the ethereal solution dried over sodium sulfate, the solvent removed, and the *p*-hydroxybenzaldehyde obtained was purified by vacuum-distillation and crystallization from benzene. Yield, 70–75% of a product, m.p. 115°. This aldehyde (196 g.) was dissolved in 1000 ml. of ethanol and 200 g. of a 50% aqueous solution of potassium hydroxide, and arylalkylated with 225 g. of benzyl chloride in the usual way. Yield, 230 g. of *p*-benzyloxybenzaldehyde, b.p. 217–219°/13 mm., m.p. 72° (9). A solution of 230 g. of this aldehyde in 100 ml. of ethanol was added in small portions to a boiling solution of 104 g. of thiosemicarbazide in 1000 ml. of ethanol. The mixture was refluxed for 15 minutes and filtered; the thiosemicarbazone which separated on cooling was collected and recrystallized from 1000 ml. of ethanol. Yield, 269 g. (86%). The other thiosemicarbazones were prepared in the same way.

*Substituted p-benzyloxybenzaldehydes. p-(4-Chlorobenzyl)oxybenzaldehyde*, prepared from 4-chlorobenzyl chloride, formed from methanol colorless needles, m.p. 76°, boiling at 234–235°/13 mm.

*Anal.* Calc'd for $C_{14}H_{11}ClO_2$: C, 68.1; H, 4.4.
Found: C, 68.0; H, 4.6.

*p-(4-Bromobenzyl)oxybenzaldehyde* formed from ethanol fine shiny colorless needles, m.p. 91°, b.p. 255–257°/13 mm.

*Anal.* Calc'd for $C_{14}H_{11}BrO_2$: C, 57.7; H, 3.8.
Found: C, 57.4; H, 3.6.

*p-(2,4-Dimethylbenzyl)oxybenzaldehyde*, prepared from the chloromethylated derivative of *m*-xylene, had b.p. 253–254°/13 mm., and formed from ligroin colorless leaflets, m.p. 60°.

*Anal.* Calc'd for $C_{16}H_{16}O_2$: C, 80.0; H, 6.7.
Found: C, 79.8; H, 6.9.

*3-Chloro-4-benzyloxybenzaldehyde.* Prepared from benzyl chloride and 3-chloro-4-hydroxybenzaldehyde, it formed from ethanol colorless prisms, m.p. 94°; 3-chloro-4-hydroxybenzaldehyde was prepared, at variance with the literature (10), by treating 4-hydroxybenzaldehyde with one or two moles of sulfuryl chloride in chloroform solution at room temperature followed by purification by vacuum-distillation.

*Anal.* Calc'd for $C_{14}H_{11}ClO_2$: C, 68.2; H, 4.5.
Found: C, 68.0; H, 4.8.

*3-Bromo-4-benzyloxybenzaldehyde.* Prepared from 3-bromo-4-hydroxybenzaldehyde (11), it formed from ethanol silky colorless needles, m.p. 95°.

*Anal.* Calc'd for $C_{14}H_{11}BrO_2$: C, 57.7; H, 3.8.
Found: C, 57.5; H, 4.1.

*3,5-Dibromo-4-benzyloxybenzaldehyde* formed from ethanol silky pale yellow needles, m.p. 129°; the 3,5-dibromo-4-hydroxybenzaldehyde used had m.p. 184° [Lit. (11), m.p. 181°].

*Anal.* Calc'd for $C_{14}H_{10}Br_2O_2$: C, 45.4; H, 2.7.
Found: C, 45.0; H, 2.8.

*3,5-Diiodo-4-benzyloxybenzaldehyde* formed yellowish silky needles from ethanol, m.p. 97°; the 3,5-diiodo-4-hydroxybenzaldehyde was prepared, at variance with the literature (12), by treating 4-hydroxybenzaldehyde in ethanol solution with a mixture of iodine in excess, potassium iodate, and sulfuric acid; it was purified by recrystallization from ethanol.

[1] One of the referees drew our attention to Special Technical Report N° 25482 of the Department of Commerce (March 1951) in which *p*-benzyloxybenzaldehyde thiosemicarbazone was mentioned.

*Anal.* Calc'd for $C_{14}H_{10}I_2O_2$: C, 36.2; H, 2.2.
Found: C, 36.0; H, 2.0.

*4-n-Octadecyloxybenzaldehyde 5-ethyl-4-keto-2-thiazolinylhydrazone.* A suspension in acetic acid of 4-*n*-octadecyloxybenzaldehyde thiosemicarbazone was refluxed for six hours with the theoretical amount of α-bromo-*n*-butyric acid. After cooling, the precipitate was collected and recrystallized from acetic acid, giving colorless needles, m.p. 125°.

*Anal.* Calc'd for $C_{30}H_{49}N_3O_2S$: N, 8.2. Found: N, 8.0.

The *5-n-butyl-4-keto-2-thiazolinylhydrazone* of the same aldehyde, prepared from α-bromocaproic acid, formed from ethanol fine colorless needles, m.p. 105°.

*Anal.* Calc'd for $C_{32}H_{53}N_3O_2S$: N, 7.7. Found: N, 7.4.

*4-Benzyloxybenzaldehyde 5-isoamyl-4-keto-2-thiazolinylhydrazone* formed from ethanol colorless needles, m.p. 176°.

*Anal.* Calc'd for $C_{22}H_{24}N_3O_2S$: N, 10.7. Found: N, 10.3.

*Propioveratrone 4-keto-2-thiazolinylhydrazone* crystallized from acetic acid as colorless prisms, m.p. 211°; yield: 95%.

*Anal.* Calc'd for $C_{14}H_{17}N_3O_3S$: C, 54.7; H, 5.5.
Found: C, 54.8; H, 5.7.

*4-Benzyloxy-3-methoxyacetophenone 4-keto-2-thiazolinylhydrazone* crystallized from acetic acid as shiny, colorless prisms, m.p. 222°; yield, 98%.

*Anal.* Calc'd for $C_{19}H_{19}N_3O_3S$: C, 59.1; H, 5.2.
Found: C, 59.2; H, 5.4.

SUMMARY

1. A series of thiosemicarbazones of various derivatives of 4-hydroxybenzaldehyde, and of some structurally related ketones, has been prepared and tested as potential tuberculostatic substances.

2. Considerable *in vitro* tuberculostatic activity has been found in thiosemicarbazones of 4-arylalkyloxybenzaldehydes of the type represented by formula (II), in the thiosemicarbazone of 4-hydroxypropiophenone, and in the thiosemicarbazones of several other aromatic ketones.

PARIS (V^e), FRANCE
LIÈGE-RENORY, BELGIUM

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