[CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, RADIUM INSTITUTE, UNIVERSITY OF PARIS]

Compounds of Potential Interest for the Chemotherapy of Leprosy

N. P. BUU-HOÏ, N. D. XUONG, AND N. B. TIEN

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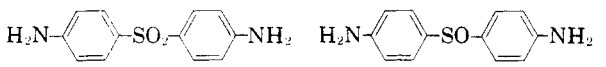
A large number of new derivatives of 4,4′-diaminodiphenylsulfoxide, thiosemicarbazide, and isonicotinylhydrazine have been prepared for investigation as possible antileprotic agents.

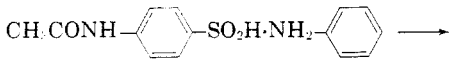
Although all the drugs which have been used with success in the chemotherapy of leprosy possess tuberculostatic activity to a greater or lesser degree, the reverse is not true, and all outstanding tuberculostats are not good leprostatic agents in man.[1] This fact justifies special investigations in the domain of the chemotherapy of leprosy which would not necessarily duplicate those undertaken with reference to tuberculosis.

Among the most efficient leprostatic compounds, sulfones[2] and thiosemicarbazones[3] rank particularly high. Of the sulfone type, the most frequently employed is 4,4′-diaminodiphenylsulfone (I), which, however, presents severe drawbacks on account of its pronounced toxicity. It was thought that 4,4′-diaminodiphenylsulfoxide (II), a compound of

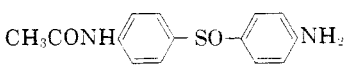


I II

equal antibacterial activity but notably less toxic, might be more promising for the treatment of leprosy, and this has subsequently proved to be the case.[4] This prompted an investigation of its synthesis and of its derivatives, and the most convenient method for preparing the mother substance (II) was found to be a Hinsberg rearrangement[5] of aniline 4-acetaminophenylsulfinate (III), followed by acid hydrolysis of the resulting 4-amino-4′-acetaminodiphenylsulfoxide (IV); the substance obtained in this way is easier to purify than the one prepared *via* 4,4′-diaminodiphenylsulfide,[6] and melts

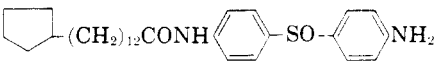


III



IV

considerably higher. Various other 4-amino-4′-acylaminodiphenylsulfoxides were prepared by reacting one mole of the corresponding acyl chloride with one mole of compound II in pyridine; by-products of this reaction were the corresponding 4,4′-diacylaminodiphenylsulfoxides (Table I). The lipid-soluble 4-amino-4′-dihydrochaulmoogrylaminodiphenylsulfoxide (V) is a compound of particular interest because of the antileprotic activity



V

of dihydrochaulmoogric acid itself. Another feature of such monoacyl derivatives of II is the theoretical possibility of resolving them into optically active enantiomorphs, in view of the successful resolution of the similarly built 4-amino-4′-methyldiphenylsulfoxide by Harrison, Kenyon, and Phillips.[7]

In the thiosemicarbazone group, compounds with higher leprostatic activity than the currently used *p*-acetaminobenzaldehyde thiosemicarbazone (Tibione) might be expected to be encountered among thiosemicarbazones with more pronounced lipid-solubility and antifungal properties, since the leprosy bacillus is known to have a neural habitat and to be more closely related to fungi than is the tubercle bacillus.[8] Compounds showing these desired features were vanillalacetone and bromovanillalacetone thiosemicarbazones (VI) and (VII), in line with the high antifungal activity of vanillin and bromovanillin thiosemicarbazones reported by Perry.[9] In the same group, veratralacetone, piperonalacetone, *p*-hydroxybenzalacetone, and 4-hydroxy-2-methylbenzalacetone thiosemicarbazones were also prepared. The 4-hydroxy-2-methylbenzaldehyde used for the preparation of 4-hydroxy-2-methylbenzalacetone was conveniently obtained by demethylation of the methyl ether with pyridine hydrochloride; benzylation and *p*-chlorobenzylation yielded 4-benzyloxy- and 4-(*p*-chlorobenzyl)-oxy-2-methylbenzaldehyde, whose thiosemicarbazones were prepared, in view of the considerable tuberculostatic activity of *p*-benzyloxybenzalde-

(1) See for instance, Burger, *Medicinal Chemistry*, Vol. II, p. 839 (Interscience Publishers Inc., New York, 1951).

(2) For most recent results, see Lowe, *Leprosy Rev.*, **25**, 113 (1954).

(3) Sagher and Brand, *Internat. J. Leprosy*, **21**, 161 (1953); Lowe, *Leprosy Rev.*, **25**, 186 (1954).

(4) Buu-Hoï, *Intern. J. Leprosy*, **22**, 16 (1954); Buu-Hoï, Khuyen, and Xuong, *Bull. Acad. Nat. Méd. (Paris)*, **15/16**, 275 (1955).

(5) Hinsberg, *Ber.*, **41**, 113 (1908).

(6) Gazdar and Smiles, *J. Chem. Soc.*, **93**, 1835 (1908).

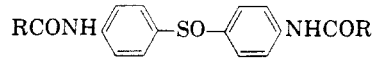
(7) Harrison, Kenyon, and Phillips, *J. Chem. Soc.*, 2079 (1926).

(8) See Khanolkar, *Indian Council for Med. Research, Special Report N° 19* (1951); Buu-Hoï, *Bull. Calcutta School Trop. Med.*, **3**, 133 (1955).

(9) Perry, *J. Am. Chem. Soc.*, **76**, 3591 (1954).

TABLE I

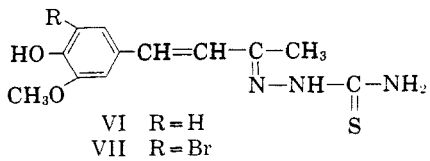
4,4'-DIACYLAMINODIPHENYLSULFOXIDES[a]



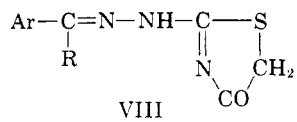
Acyl group R—CO—	Formula	M.P., °C.[b]	Analyses Calc'd C	Calc'd H	Found C	Found H
Propionyl	$C_{18}H_{20}N_2O_3S$	233	62.8	5.8	62.5	6.0
n-Butyryl	$C_{20}H_{24}N_2O_3S$	233	64.5	6.5	64.5	6.3
iso-Butyryl	$C_{20}H_{24}N_2O_3S$	268	64.5	6.5	64.4	6.3
n-Valeryl	$C_{22}H_{28}N_2O_3S$	226	66.0	7.0	65.7	7.1
n-Heptanoyl	$C_{26}H_{36}N_2O_3S$	220	68.4	7.9	68.5	8.1
n-Octanoyl	$C_{28}H_{40}N_2O_3S$	216	69.4	8.3	69.2	8.2
n-Decanoyl	$C_{32}H_{48}N_2O_3S$	210	71.1	8.9	71.3	8.8
n-Dodecanoyl	$C_{36}H_{56}N_2O_3S$	205	72.5	9.4	72.2	9.3
n-Tridecanoyl	$C_{38}H_{60}N_2O_3S$	200	73.1	9.6	73.0	9.6
n-Tetradecanoyl	$C_{40}H_{64}N_2O_3S$	194	73.6	9.8	73.6	9.9
Stearoyl	$C_{48}H_{80}N_2O_3S$	160	75.4	10.5	75.5	10.3
Behenoyl	$C_{56}H_{96}N_2O_3S$	181	76.7	11.0	76.9	11.1
β-Cyclohexylpropionyl	$C_{30}H_{40}N_2O_3S$	187	70.9	7.9	70.6	7.6
ω-Cyclopentyl-*n*-tridecanoyl	$C_{48}H_{76}N_2O_3S$	159–160	75.8	10.0	75.7	10.3
Benzoyl	$C_{26}H_{20}N_2O_3S$	272	70.9	4.5	71.2	4.6
Phenacetyl	$C_{28}H_{24}N_2O_3S$	224	71.8	5.1	71.5	5.2
Anisoyl	$C_{28}H_{24}N_2O_5S$	300	67.2	4.8	67.0	5.0
4-Methylbenzoyl	$C_{28}H_{24}N_2O_3S$	266	71.8	5.1	72.0	5.0
4-Bromobenzoyl	$C_{26}H_{18}Br_2N_2O_3S$	>330	52.2	3.0	51.9	2.9

[a] These compounds had no *in vitro* bacteriostatic activity on *M. tuberculosis* var. *hominis*, whilst the monoacyl derivatives were slightly active. [b] All m.p.s. uncorrected.

hyde thiosemicarbazone.[10] These various thiosemicarbazones condensed with chloroacetic acid to give the corresponding 4-oxo-Δ^2-thiazolin-2-ylhydrazones (VIII); it is recalled that acidomycin, an anti-



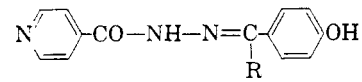
VI R = H
VII R = Br



VIII

biotic with the same heterocyclic arrangement, has recently been found active in leprosy.[11]

Isonicotinylhydrazine, although highly effective against tuberculosis and murine leprosy,[12] has proved disappointing in human leprosy,[13] a discrepancy which could perhaps in part be ascribed to its poor lipid solubility and rapid elimination. The isonicotinylhydrazones (IX) of a series of *p*-hydroxyphenyl alkyl ketones (Table V) were therefore prepared, and found to have enhanced lipid



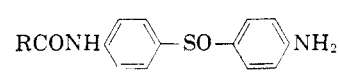
IX

solubility and a slower rate of resorption, as well as high tuberculostatic activity. Their usefulness in human leprosy is currently being assessed.

Biological tests. The mycobacteriostatic activity of the compounds described herein was determined on *Mycobacterium tuberculosis* var. *hominis* (strain H 37 Rv) in Dubos-Davis culture medium. The thiosemicarbazones of vanillalacetone and similar derivatives were tuberculostatic at concentrations of 10^{-6} to 10^{-7}; the isonicotinylhydrazones of *p*-hydroxyacetophenone and the next higher homologous ketones were active at a concentration of 10^{-7}. *In vivo* tests in mice showed these isonicotinylhy-

TABLE II

LIPID-SOLUBLE 4-ACYLAMINO-4'-AMINODIPHENYLSULFOXIDES



Acyl group R—CO—	Formula	M.P., °C.	Analyses Calc'd N	Found N
n-Octanoyl	$C_{20}H_{26}N_2O_2S$	165	7.8	8.0
n-Decanoyl	$C_{22}H_{30}N_2O_2S$	162	7.2	7.3
n-Undecanoyl	$C_{23}H_{32}N_2O_2S$	152–153	7.0	7.2
n-Tridecanoyl	$C_{25}H_{36}N_2O_2S$	159	6.5	6.6
n-Tetradecanoyl	$C_{26}H_{38}N_2O_2S$	154	6.3	6.5
Behenoyl	$C_{34}H_{54}N_2O_2S$	142–143	5.1	5.3
ω-Cyclopentyl-*n*-tridecanoyl	$C_{30}H_{44}N_2O_2S$	138–139	5.6	5.5

(10) Buu-Hoï, Welsch, Dechamps, Le Bihan, Binon, and Xuong, *J. Org. Chem.*, **18**, 121 (1953).

(11) Satani, Nishimura, Kono, Nojima, and Takahashi, *Intern. J. Leprosy*, **23**, 124 (1955).

(12) Cruickshank, *Lancet*, **264**, 624 (1953); Goulding, Robson, and Rees, *Lancet*, **264**, 423 (1953).

(13) See most recent results in Lowe, *Intern. J. Leprosy*, **23**, 181 (1955).

TABLE III

NEW THIOSEMICARBAZONES

Oxo Compound	Formula	M.P., °C.	Analyses Calc'd N	Analyses Found N
Vanillalacetone[a]	$C_{12}H_{15}N_3O_2S$	167	15.8	15.8
5-Bromovanillalacetone	$C_{12}H_{14}BrN_3O_2S$	239	12.2	12.0
Veratralacetone	$C_{13}H_{17}N_3O_2S$	230	15.1	14.8
Piperonalacetone	$C_{12}H_{13}N_3O_2S$	199	16.0	15.7
4-Hydroxybenzalacetone	$C_{11}H_{13}N_3OS$	226	17.9	17.7
4-Hydroxy-2-methylbenzalacetone	$C_{12}H_{15}N_3OS$	220	16.9	17.1
4-Hydroxy-2-methylbenzaldehyde	$C_9H_{11}N_3OS$	249	20.1	20.0
4-Benzyloxy-2-methylbenzaldehyde	$C_{16}H_{17}N_3OS$	202	14.0	13.7
4-(*p*-Chlorobenzyloxy)-2-methylbenzaldehyde	$C_{16}H_{16}ClN_3OS$	214	12.6	12.5

[a] The solvated crystals which separated from ethanol melted at about 118–120°.

TABLE IV

NEW 4-OXO-Δ^2-THIAZOLIN-2-YLHYDRAZONES (VIII)[a]

Oxo compound	Formula	M.P., °C.	Analyses Calc'd N	Analyses Found N
Vanillalacetone	$C_{14}H_{15}N_3O_3S$	187	13.8	13.5
5-Bromovanillalacetone	$C_{14}H_{14}BrN_3O_3S$	208	10.9	10.7
Veratralacetone	$C_{15}H_{17}N_3O_3S$	216	13.2	12.9
Piperonalacetone	$C_{14}H_{13}N_3O_3S$	239	13.9	13.8
4-Hydroxybenzalacetone	$C_{13}H_{13}N_3O_2S$	257	15.3	15.0
4-Hydroxy-2-methylbenzalacetone	$C_{14}H_{15}N_3O_2S$	249	14.5	14.4
4-Hydroxy-2-methylbenzaldehyde	$C_{11}H_{11}N_3O_2S$	332	16.9	16.7
4-Benzyloxy-2-methylbenzaldehyde	$C_{18}H_{17}N_3O_2S$	257	12.4	12.1
4-(*p*-Chlorobenzyloxy)-2-methylbenzaldehyde	$C_{18}H_{16}ClN_3O_2S$	289	11.2	11.2

[a] These compounds showed *in vitro* tuberculostatic activity at concentrations equal or superior to 10^{-4}.

TABLE V

NEW ISONICOTINYLHYDRAZONES[a] OF ALDEHYDES AND KETONES

Oxo compound	Formula	M.P., °C.	Analyses Calc'd N	Analyses Found N
4-Hydroxy-2-methylbenzaldehyde	$C_{14}H_{13}N_3O_2$	307	16.5	16.3
4-Benzyloxy-2-methylbenzaldehyde	$C_{21}H_{19}N_3O_2$	214	12.2	12.3
4-(*p*-Chlorobenzyloxy)-2-methylbenzaldehyde	$C_{21}H_{18}ClN_3O_2$	216	11.1	11.0
4-Hydroxyacetophenone	$C_{14}H_{13}N_3O_2$	286	16.5	16.2
4-Hydroxypropiophenone	$C_{15}H_{15}N_3O_2$	247	15.6	15.3
3-Bromo-4-hydroxypropiophenone	$C_{15}H_{14}BrN_3O_2$	253	12.1	12.3
4-Methoxy-3-methylpropiophenone	$C_{17}H_{19}N_3O_2$	143	14.1	14.3
4-Hydroxyvalerophenone	$C_{17}H_{19}N_3O_2$	206	14.1	14.0
3-Fluoro-4-hydroxyvalerophenone	$C_{17}H_{18}FN_3O_2$	228	13.3	13.5
4-Hydroxycaprophenone	$C_{18}H_{21}N_3O_2$	205	13.5	13.6
4-Hydroxyenanthophenone	$C_{19}H_{23}N_3O_2$	203	12.9	13.1
4-Hydroxycaprylophenone	$C_{20}H_{25}N_3O_2$	206	12.4	12.3
4-Hydroxy-1-decanoylbenzene	$C_{22}H_{29}N_3O_2$	203	11.4	11.1
4-Methoxy-1-decanoylbenzene	$C_{23}H_{31}N_3O_2$	126	11.0	11.2
4-Hydroxypalmitophenone	$C_{28}H_{41}N_3O_2$	153	9.3	9.1
4-Hydroxybehenophenone	$C_{34}H_{53}N_3O_2$	131	7.9	7.6

[a] Prepared by refluxing for a few hours in ethanol a solution of equimolecular amounts of isonicotinylhydrazine and the appropriate oxo compound; the product which precipitated on cooling or on dilution with water was recrystallized from methanol or ethanol. All the hydrazones were obtained in the form of colorless or pale yellow needles.

drazones to have much better chemotherapeutic indices than isonicotinic acid hydrazide itself; *p*-hydroxypropiophenone isonicotinylhydrazone, for instance, had a chemotherapeutic index of 48, whilst that of isonicotinic acid hydrazide is 9.4.

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TABLE VI

NEW NICOTINYLHYDRAZONES[a] OF ALDEHYDES AND KETONES

Oxo compound	Formula	M.P., °C.	Analyses Calc'd N	Analyses Found N
4-Hydroxy-2-methylbenzaldehyde	$C_{14}H_{13}N_3O_2$	272	16.5	16.4
4-Benzyloxy-2-methylbenzaldehyde	$C_{21}H_{19}N_3O_2$	144	12.2	12.0
4-(*p*-Chlorobenzyloxy)-2-methylbenzaldehyde	$C_{21}H_{18}ClN_3O_2$	180	11.1	11.0
4-Hydroxypropiophenone	$C_{15}H_{15}N_3O_2$	202	15.6	15.3
4-Hydroxyvalerophenone	$C_{17}H_{19}N_3O_2$	152	14.1	14.2
4-Hydroxyenenanthophenone	$C_{19}H_{23}N_3O_2$	155	12.9	12.6
4-Hydroxycaprylophenone	$C_{20}H_{25}N_3O_2$	148	12.4	12.5

[a] Prepared as for the isonicotinylhydrazones. As in previously investigated series [*cf.* Buu-Hoï, Xuong, Nam, Binon, and Royer, *J. Chem. Soc.*, 1358 (1953)], the *in vitro* tuberculostatic activities of the nicotinylhydrazones are considerably lower than those of their isomers.

EXPERIMENTAL (with Dr. L. Schembri)

Preparation of 4,4'-diaminodiphenylsulfoxide. A mixture of 1 part of 4-acetaminophenylsulfinic acid and 4 parts of aniline was heated at 125–150° for 48 hours with removal of water, some aniline hydrochloride being added as condensation catalyst. On cooling, the aniline in excess was removed by steam distillation, and the residue was hydrolyzed with hydrochloric acid. The 4,4'-diaminodiphenylsulfoxide hydrochloride which formed was purified by recrystallization from water; the free *base*, isolated after basification was recrystallized from aqueous ethanol. The yield was 10–15% of a white product melting at 184°; the substance obtained *via* 4,4'-diaminodiphenylsulfide[6] is generally gray and melts below 180°.

Acylation of 4,4'-diaminodiphenylsulfoxide. To a cooled solution of 4,4'-diaminodiphenylsulfoxide (1 mole) in anhydrous pyridine, the appropriate acid chloride (2 moles) was added portionwise with stirring, and the mixture was kept for 10 minutes at room temperature. Water was added, and the solid obtained after an overnight standing was collected, and crystallized from methanol or ethanol. The less-soluble portion consisted of the 4,4'-diacylaminodiphenylsulfoxide (yield 60–80%), and the mother liquors deposited on concentration small quantities of a more soluble fraction, consisting of the corresponding 4-acylamino-4'-diphenylsulfoxide. Each fraction was recrystallized until a constant m.p. was reached. All compounds in both series formed colorless needles; monoacylated compounds turned gray on exposure to air and light.

Vanillalacetone thiosemicarbazone. A solution of equimolecular amounts of vanillalacetone (m.p. 129°) and thiosemicarbazide in the minimum of ethanol was refluxed for 30 minutes with a few drops of acetic acid; the solid obtained on cooling was recrystallized from ethanol, giving shiny, pale yellow prisms; yield 98%.

The other thiosemicarbazones, listed in Table III, were prepared in the same way.

Vanillalacetone 4-oxo-Δ^2-thiazolin-2-ylhydrazone. A solution of equimolecular amounts of the foregoing thiosemicarbazone, chloroacetic acid, and sodium acetate in ethanol was refluxed for 2 hours. The precipitate obtained on cooling was recrystallized from acetic acid, giving a 95% yield of fine yellowish prisms.

The other 4-oxo-Δ^2-thiazolin-2-ylhydrazones (Table IV) were similarly prepared.

Preparation of 4-hydroxy-2-methylbenzaldehyde. A mixture of 178 g. of 4-methoxy-2-methylbenzaldehyde (prepared by the reaction of dimethylformamide on *m*-cresol methyl ether[14]) and 600 g. of redistilled pyridine hydrochloride was refluxed for 45 minutes, and the reaction product was treated with water after cooling. The demethylation product was taken up in ether and purified by vacuum-distillation. Yield 65–70% of the aldehyde, b.p. 205–207°/18 mm.

4-Benzyloxy-3-methylbenzaldehyde. A solution of 7 g. of the foregoing aldehyde and 3 g. of potassium hydroxide in ethanol was refluxed with 7 g. of benzyl chloride for 15 minutes. The alcohol was distilled, water was added, and the reaction product was taken up in benzene and purified by vacuum-distillation. Yield of aldehyde, b.p. 232–234°/19 mm. 9 g.; fine colorless needles from ligroin, m.p. 53°.

Anal. Calc'd for $C_{15}H_{14}O_2$: C, 79.6; H, 6.2. Found: C, 79.5; H, 6.1.

4-(p-Chlorobenzyloxy)-3-methylbenzaldehyde was similarly prepared from 7 g. of the hydroxy aldehyde, 3.5 g. of potassium hydroxide, and 9.5 g. of 4-chlorobenzyl chloride. Yield 10.5 g. of an aldehyde, b.p. 258–260°/19 mm., crystallizing from ethanol in fine colorless prisms, m.p. 60°.

Anal. Calc'd for $C_{15}H_{13}ClO_2$: C, 69.1; H, 4.8. Found: C, 68.8; H, 4.9.

4-Hydroxy-2-methylbenzalacetone. A solution of 5 g. of 4-hydroxy-2-methylbenzaldehyde in 25 ml. of acetone was treated with 15 ml. of a 10% aqueous solution of sodium hydroxide, and the mixture kept for 48 hours with frequent shaking. The acetone was distilled, and the residue was treated with water and acidified with acetic acid. The reaction product was taken up in ether and purified by vacuum-distillation. Yield 4.5 g. of a ketone, b.p. 251–252°/20 mm., crystallizing from aqueous ethanol in fine, colorless prisms, m.p. 130°. The other arylideneacetones were prepared in the same way.

Anal. Calc'd for $C_{11}H_{12}O_2$: C, 75.0; H, 6.8. Found: C, 75.1; H, 6.8.

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(14) Buu-Hoï, Xuong, Sy, Lejeune, and Tien, *Bull. soc. chim.*, **22**, 1594 (1955).