room. Rats were trained on a fixed-ratio 32 (FR32) schedule.

Drugs. Drugs were administered in a volume of 0.1 mL of physiological saline per 100 g of body weight. LSD tartrate was obtained from the National Institute on Drug Abuse. All other drugs were used as the hydrochlorides.

Data Analysis. The mean percent responding on the LSD-appropriate lever was calculated for each treatment group. These data were used to construct dose–response curves and, where complete generalization occurred (greater than 85% responding on the drug lever), an ED_{50} was calculated by the method of Litchfield and Wilcoxon.[19]

(19) Litchfield, J. T.; Wilcoxon, F. *J. Pharmacol. Exp. Ther.* **1949**, *96*, 99.

Acknowledgment. This work was supported by funds from Grant DA02189 from the National Institute on Drug Abuse, Chemical Pharmacology Training Grant GM 709504 (R.A.O.), and Biomedical Research Support Grant 2-S07-RR05586-15. We acknowledge helpful technical assistance in the drug discrimination assays provided by Evita Bynum, Donna Maxwell, and Jenny Weeden.

Registry No. **2a**, 90791-20-1; **2a**·HCl, 90791-19-8; **2b**, 90791-22-3; **2b**·HCl, 90791-21-2; **3**, 90791-14-3; **3**·HCl, 90791-13-2; **4a**, 90791-15-4; **4b**, 90791-16-5; **5a**, 90791-17-6; **5b**, 90791-18-7; 2,4,5-trimethoxybenzaldehyde, 4460-86-0; cyclopropyldiphenylsulfonium tetrafluoroborate, 33462-81-6; 2,5-dimethoxy-4-methylbenzaldehyde, 4925-88-6.

Benzylamines: Synthesis and Evaluation of Antimycobacterial Properties

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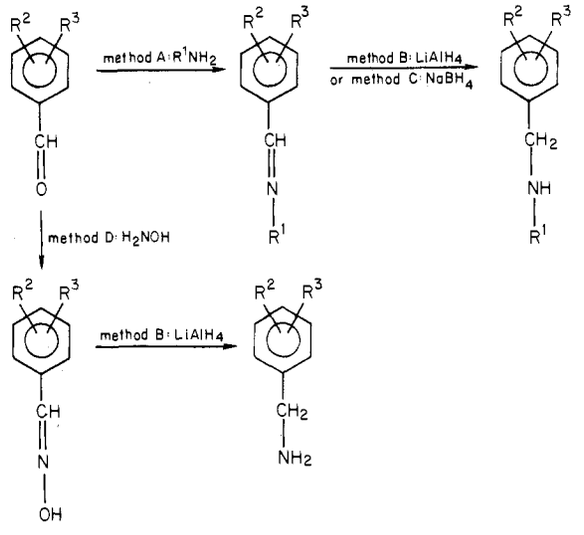
The synthesis of benzylamines with various *N*-alkyl chains and substituents in the aromatic system as well as their evaluation on *Mycobacterium tuberculosis H 37 Ra* are described. The most active compounds in this test, *N*-methyl-3-chlorobenzylamine (**19**, MIC 10.2 μg/mL), *N*-methyl-3,5-dichlorobenzylamine (**93**, MIC 10.2 μg/mL), and *N*-butyl-3,5-difluorobenzylamine (**103**, MIC 6.4 μg/mL), also exhibited a marked inhibitory effect on *Mycobacterium marinum* and *Mycobacterium lufu* used for the determination of antileprotic properties. The combinations of **93** with aminosalicylic acid, streptomycin, or dapsone exert marked supra-additive effects on *M. tuberculosis H 37 Ra*.

N-Alkylbenzylamines are compounds with a specific action against mycobacteria.[1] They lack any activity against fungi and Gram-positive and Gram-negative bacteria.[2] Structural manipulations like the replacement of one methylene hydrogen by an alkyl group (1-phenyl-1-(alkylamino)alkane type),[1] the connection of two *N*-alkylbenzylamines in this position (*N,N'*-dialkyl-1,2-diphenylethylenediamine type),[1] the shortening or lengthening of the distance between the nitrogen function and the aromatic system (**119**, **120**),[46] or the transformation of the secondary amino group into a tertiary one[1] led to a loss of antimycobacterial activity. However, primary benzylamines showed an inhibitory effect on mycobacteria (Tables I–III). The degree of the antimycobacterial activity of *N*-alkylbenzylamines is influenced by the length of the *N*-alkyl chain. *N*-Butylbenzylamine (**5**) proved to be the most active compound in a series of ring unsubstituted benzylamines[1] (Table I). Ramification of the *N*-alkyl chain in the α-position to the nitrogen atom led to a loss of efficacy as shown by comparison of the activities of compounds **14**, **23**, and **46** with those of **13**, **22**, and **45** (Table II). An unequivocal correlation between the length of the *N*-alkyl chain and the antimycobacterial activity was not found (Table I). The introduction of halogen, especially of fluorine, into the meta position of the most active unsubstituted compound, *N*-butylbenzylamine, enhanced its antimycobacterial activity (*N*-butyl-3-fluorobenzylamine hydrochloride (**15**), MIC 30 μg/mL *M. tuberculosis H 37 Rv*,[1] MIC 25.6 μg/mL *M. tuberculosis H 37 Ra* (Table II), MIC 8 μg/mL *M. tuberculosis H 37 Rv* (INH resistant),[3] MIC 32 μg/mL *M. tuberculosis H 37 Rv* (thiosemicarbazone resistant)[3]).

Scheme I



The in vivo activity of **15** in the *M. tuberculosis H 37 Rv* infected mouse was comparable with that of streptomycin.[3] Other substituents did not considerably increase the efficacy of *N*-butylbenzylamine.[1] 4-(Aminomethyl)-2-hydroxybenzoic acid (HOMO-PAS) and its *N*-alkyl derivatives were not capable of inhibiting the growth of *M. tuberculosis*.[4] These results are in contrast to the findings of Kuhn et al.,[5] who described an effect of HOMO-PAS

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[‡] Max-von-Pettenkofer-Institut für Hygiene und Medizinische Mikrobiologie der Universität München.

(1) Ruckdeschel, G.; Stransky, D.; Schönenberger, H. *Pharmazie* **1976**, *31*, 374.
(2) Ruckdeschel, G.; Stransky, D.; Schönenberger, H. *Pharmazie* **1977**, *32*, 119.
(3) Otten, H., unpublished results.
(4) Meindl, W.; von Angerer, E.; Ruckdeschel, G.; Schönenberger, H. *Arch. Pharm. (Weinheim, Ger.)* **1982**, *315*, 941.

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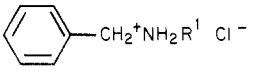
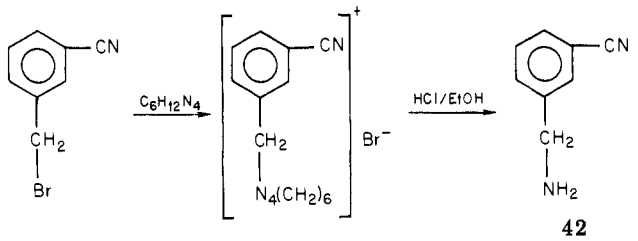
Table I. Tuberculostatic *N*-Alkylbenzylamine Hydrochlorides



compd	R^1	synth method[a]	yield,[b] %	mp,[c] °C	formula[d]	MIC,[e] μg/mL
1[f]	H			262–263	C_7H_9N·HCl	76.8
2[g]	CH_3	A, B	45	178	$C_8H_{11}N$·HCl	102.4
3[h]	C_2H_5	A, B	65	182	$C_9H_{13}N$·HCl	204.8
4[i]	C_3H_7	A, B	73	184	$C_{10}H_{15}N$·HCl	51.2
5[k]	C_4H_9	A, B	52	237	$C_{11}H_{17}N$·HCl	51.2
6[l]	C_5H_{11}				$C_{12}H_{19}N$·HCl	153.6
7[l]	C_6H_{13}				$C_{13}H_{21}N$·HCl	>256.0
8[l]	C_7H_{15}				$C_{14}H_{23}N$·HCl	>256.0
9[l]	C_8H_{17}				$C_{15}H_{25}N$·HCl	>256.0

[a] Capital letters refer to synthetic methods A and B in the Experimental Section. [b] No effort was made to optimize yields. [c] All compounds were crystallized from MeOH/ether. [d] All compounds were analyzed for C, H, and N within ±0.40% of the calculated values. [e] Minimum inhibitory concentration for growth inhibition of *M. tuberculosis H 37 Ra*. [f] Compound was purchased from EGA Steinheim, West Germany. [g] See ref 7. [h] See ref 8. [i] See ref 9. [k] See ref 10. [l] See ref 11.

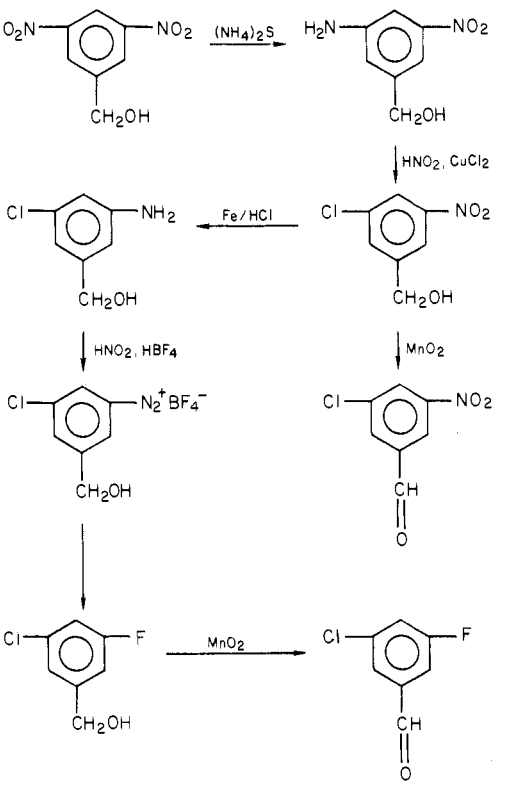
Scheme II



42

on *M. tuberculosis* type *gallinaceus* Stamm Stein. The marked in vitro activity of **15** and of other *N*-alkylbenzylamines against *M. marinum*[2] indicates the possibility of a leprostatic activity of these compounds, which can be determined using *M. marinum* infected mice.[6]

Scheme III

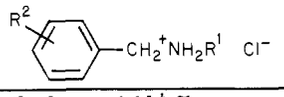


These findings prompted us to study the structure–activity relationship in the class of benzylamines in detail hoping to find drugs that can be used in combination with dapsone (DDS) or other antimycobacterial compounds in the therapy of leprosy. By appropriate variation of the *N*-alkyl chain and introduction of ring substituents, compounds with a strong activity against various mycobacteria were obtained (Tables II and III).

Chemistry. The synthesis of the benzylamines except compound **42** started from the substituted benzaldehydes. They were converted into the corresponding imines with alkylamines (method A) or into oximes with NH_2OH (method D). The oximes were reduced with $LiAlH_4$

(5) Kuhn, R.; Zilliken, F.; Trischmann, H. *Chem. Ber.* **1950**, *83*, 304.
(6) Freerksen, E.; Rosenfeld, M. *Z. Tropenmed. Parasitol.* **1973**, *24*, 17.
(7) Emde, H. *Arch. Pharm. (Weinheim, Ger.)* **1909**, *247*, 351.
(8) Kraft, F. *Ber. Dtsch. Chem. Ges.* **1890**, *23*, 2780.
(9) Shapiro, S. L.; Parrino, V. A.; Freedman, L. *J. Am. Chem. Soc.* **1959**, *81*, 3728.
(10) Einhorn, A.; Pfeiffer, H. *Justus Liebigs Ann. Chem.* **1900**, *310*, 225.
(11) Eder, M. Ph.D. Thesis, University of Munich, 1962.
(12) von Braun, J.; Michaelis, R. *Justus Liebigs Ann. Chem.* **1933**, *507*, 1.
(13) von Braun, J.; Kühn, M.; Weismantel, J. *Justus Liebigs Ann. Chem.* **1926**, *449*, 249.
(14) Pallos, F. M.; Brokke, M. E.; Arnekley, D. R. Ger. Offen. 2218097, 1972.
(15) Schönenberger, H.; Thies, H.; Rappl, A. *Arch. Pharm. (Weinheim, Ger.)* **1967**, *300*, 483.
(16) Kindler, K. *Arch. Pharm. (Weinheim, Ger.)* **1927**, *265*, 389.
(17) Yokohama, M.; Kawano, S.; Sugiyama, K. Eisai Co. Ltd., Japan 15674, 1961.
(18) Wellcome Foundation Ltd., Brit. 881625, 1961.
(19) Ehrlich, F. *Ber. Dtsch. Chem. Ges.* **1901**, *34*, 3366.
(20) von Braun, J.; Michaelis, R.; Spänig, H. *Chem. Ber.* **1937**, *70*, 1241.
(21) Tiffeneau, M. M. *Bull. Soc. Chim. Fr.* **1911**, *9*, 825.
(22) Baltzly, R.; Phillips, A. P. *J. Am. Chem. Soc.* **1949**, *71*, 3421.
(23) Holmes, E. L.; Ingold, C. K. *J. Chem. Soc.* **1925**, *127*, 1800.
(24) Freifelder, M.; Yew Hay, N. *J. Pharm. Sci.* **1965**, *54*, 1204.
(25) Elslager, E. F.; Johnson, J. L.; Werbel, L. M. *J. Med. Chem.* **1981**, *24*, 140.
(26) DeBrunner, R. E.; Blake, E. S.; Webster, J. A. Monsanto Co., Belg. 672659, 1966.
(27) Brabander, H. J.; Wright, W. B. *J. Org. Chem.* **1967**, *32*, 4053.
(28) Métayer, M.; Dat-Xuong, N. *Bull. Soc. Chim. Fr.* **1954**, *21*, 615.
(29) Surrey, A. R.; Rukwid, M. K. *J. Am. Chem. Soc.* **1955**, *77*, 3798.
(30) Sharadamma, H. S.; Maddi, G. B.; Kulkarni, S. N.; Sathir, P. B.; Nargund, K. S. *J. Karnatak Univ.* **1957**, *2*, 19.
(31) Angyal, S. J.; Morris, P. J.; Rassack, R. C.; Waterer, J. A. *J. Chem. Soc.* **1949**, 2704.
(32) Biel, J. H.; Nuhfer, P. A.; Drukker, A. E.; Mitchell, T. F.; Conway, A. C.; Horita, A. *J. Org. Chem.* **1961**, *26*, 3338.
(33) Wilcox, M. Fr. Demande 2295011, 1976.
(34) Marhold, A.; Klanke, E. Ger. Offen. 2526652, 1976.

Table II. Tuberculostatic Monosubstituted *N*-Alkylbenzylamine Hydrochlorides

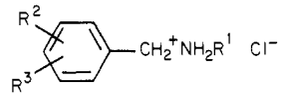


compd	R^1	R^2	synth method[a]	yield,[b] %	mp, °C	formula[f]	MIC,[g] μg/mL
10[h]	H	3-F			273[c]	C_7H_8FN·HCl	51.2
11	CH_3	3-F	A, B	56	206[c]	$C_8H_{10}FN$·HCl	19.2
12	C_2H_5	3-F	A, B	64	203[c]	$C_9H_{12}FN$·HCl	51.2
13	C_3H_7	3-F	A, B	70	217–218[c]	$C_{10}H_{14}FN$·HCl	25.6
14	i-C_3H_7	3-F	A, B	67	173[e]	$C_{10}H_{14}FN$·HCl	>256.0
15[i]	C_4H_9	3-F				$C_{11}H_{16}FN$·HCl	25.6
16	C_5H_{11}	3-F	A, B	58	260[c]	$C_{12}H_{18}FN$·HCl	51.2
17[h]	H	3-Cl			227[c]	C_7H_8ClN·HCl	17.9
18[k]	CH_3	2-Cl	A, B	64	134[c]	$C_8H_{10}ClN$·HCl	>256.0
19[k]	CH_3	3-Cl	A, B	60	170[c]	$C_8H_{10}ClN$·HCl	10.2
20[l]	CH_3	4-Cl	A, B	45	198[c]	$C_8H_{10}ClN$·HCl	>256.0
21[m]	C_2H_5	3-Cl	A, B	54	180[c]	$C_9H_{12}ClN$·HCl	25.6
22[m]	C_3H_7	3-Cl	A, B	64	210[c]	$C_{10}H_{14}ClN$·HCl	17.9
23	i-C_3H_7	3-Cl	A, B	50	179[e]	$C_{10}H_{14}ClN$·HCl	>256.0
24[i]	C_4H_9	2-Cl				$C_{11}H_{16}ClN$·HCl	>256.0
25[i]	C_4H_9	3-Cl				$C_{11}H_{16}ClN$·HCl	64.0
26[n]	C_4H_9	4-Cl	A, B	71	246[c]	$C_{11}H_{16}ClN$·HCl	>256.0
27	C_5H_{11}	3-Cl	A, B	55	240[c]	$C_{12}H_{18}ClN$·HCl	51.2
28[o]	H	3-Br	D, B	45	216[c]	C_7H_8BrN·HCl	32.0
29[k]	CH_3	3-Br	A, B	50	156[c]	$C_8H_{10}BrN$·HCl	19.2
30[p]	CH_3	4-Br	A, B	47	219[c]	$C_8H_{10}BrN$·HCl	>256.0
31[q]	C_2H_5	2-Br	A, B	67	138[c]	$C_9H_{12}BrN$·HCl	>256.0
32[r]	C_2H_5	3-Br	A, B	43	171[c]	$C_9H_{12}BrN$·HCl	64.0
33	C_3H_7	3-Br	A, B	50	199[c]	$C_{10}H_{14}BrN$·HCl	51.2
34[i]	C_4H_9	2-Br				$C_{11}H_{16}BrN$·HCl	>256.0
35[i]	C_4H_9	3-Br				$C_{11}H_{16}BrN$·HCl	38.4
36[i]	C_4H_9	4-Br				$C_{11}H_{16}BrN$·HCl	>256.0
37[h]	H	3-I				C_7H_8IN·HCl	179.2
38	CH_3	3-I	A, B	64	179[c]	$C_8H_{10}IN$·HCl	153.6
39	C_2H_5	3-I	A, B	69	195[c]	$C_9H_{12}IN$·HCl	>256.0
40	C_3H_7	3-I	A, B	51	193[c]	$C_{10}H_{14}IN$·HCl	256.0
41[i]	C_4H_9	3-I	A, B	63	190[c]	$C_{11}H_{16}IN$·HCl	204.8
42[s]	H	3-CN		54	220[d]	$C_8H_8N_2$·HCl	128.0
43[t]	CH_3	3-CN	A, C	67	156[c]	$C_9H_{10}N_2$·HCl	51.2
44	C_2H_5	3-CN	A, C	70	171[c]	$C_{10}H_{12}N_2$·HCl	102.4
45	C_3H_7	3-CN	A, C	75	210[c]	$C_{11}H_{14}N_2$·HCl	76.8
46	i-C_3H_7	3-CN	A, C	67	203[c]	$C_{11}H_{14}N_2$·HCl	>256.0
47	C_4H_9	3-CN	A, C	56	210[c]	$C_{12}H_{16}N_2$·HCl	51.2
48	C_5H_{11}	3-CN	A, C	70	198–199[c]	$C_{13}H_{18}N_2$·HCl	76.8
49[h]	H	4-OCH_3				$C_8H_{11}NO$·HCl	>256.0
50[u]	CH_3	4-OCH_3	A, B	57	171[c]	$C_9H_{13}NO$·HCl	>256.0
51[v]	C_2H_5	4-OCH_3	A, B	47	179[d]	$C_{10}H_{15}NO$·HCl	>256.0
52	C_3H_7	4-OCH_3	A, B	45	194[e]	$C_{11}H_{17}NO$·HCl	>256.0
53[h]	H	3-NO_2				$C_7H_8N_2O_2$·HCl	179.2
54[w]	CH_3	3-NO_2	A, C	63	183[d]	$C_8H_{10}N_2O_2$·HCl	256.0
55	C_2H_5	3-NO_2	A, C	59	241[d]	$C_9H_{12}N_2O_2$·HCl	>256.0
56	C_3H_7	3-NO_2	A, C	63	242[d]	$C_{10}H_{14}N_2O_2$·HCl	>256.0
57	i-C_3H_7	3-NO_2	A, C	50	223[d]	$C_{10}H_{14}N_2O_2$·HCl	>256.0
58[i]	C_4H_9	3-NO_2			200[c]	$C_{11}H_{16}N_2O_2$·HCl	>256.0
59	C_5H_{11}	3-NO_2	A, C	55	211[d]	$C_{12}H_{18}N_2O_2$·HCl	>256.0
60[x]	H	3-CF_3	D, B	52	176[c]	$C_8H_8F_3N$·HCl	>256.0
61[y]	CH_3	3-CF_3	A, B	37	171[c]	$C_9H_{10}F_3N$·HCl	>256.0
62[z]	C_2H_5	3-CF_3	A, B	62	189–190[c]	$C_{10}H_{12}F_3N$·HCl	>256.0
63[aa]	C_3H_7	3-CF_3	A, B	64	210[c]	$C_{11}H_{14}F_3N$·HCl	>256.0
64	i-C_3H_7	3-CF_3	A, B	57	169–171[c]	$C_{11}H_{14}F_3N$·HCl	>256.0
65	C_4H_9	3-CF_3	A, B	65	184[c]	$C_{12}H_{16}F_3N$·HCl	>256.0
66	C_5H_{11}	3-CF_3	A, B	41	180–181[c]	$C_{13}H_{18}F_3N$·HCl	>256.0
67[x]	H	4-CF_3	D, B	30	276[c]	$C_8H_8F_3N$·HCl	>256.0
68	CH_3	4-CF_3	A, B	44	205–207[c]	$C_9H_{10}F_3N$·HCl	>256.0
69	C_2H_5	4-CF_3	A, B	46	249[c]	$C_{10}H_{12}F_3N$·HCl	>256.0
70	C_3H_7	4-CF_3	A, B	37	247–249[c]	$C_{11}H_{14}F_3N$·HCl	>256.0
71	C_4H_9	4-CF_3	A, B	48	254[c]	$C_{12}H_{18}F_3N$·HCl	>256.0

[a] Capital letters refer to synthetic methods A–D in the Experimental Section. [b] Yield of the pure product; the yields refer to the methods mentioned under synthetic methods; no effort was made to optimize yields. [c] Recrystallization solvents were MeOH/ether. [d] These compounds were crystallized from EtOH. [e] The compound was crystallized from acetonitrile. [f] All compounds were analyzed for C, H, and N within ±0.4% of the calculated values. [g] Minimum inhibitory concentration for growth inhibition of *M. tuberculosis H 37 Ra*. [h] Compounds were purchased from EGA Steinheim, West Germany. [i] See ref 1. [k] See ref 12. [l] See ref 13. [m] See ref 14. [n] See ref 15. [o] See ref 16. [p] See ref 17. [q] See ref 18. [r] See ref 9. [s] See ref 19. [t] See ref 20. [u] See ref 21. [v] See ref 22. [w] See ref 23. [x] See ref 24. [y] See ref 25. [z] See ref 26. [aa] See ref 27.

(method B) and the imines with $LiAlH_4$ (method B) or $NaBH_4$ (method C), depending on the substituents in the aromatic system (Scheme I). For the synthesis of compound **42**, 3-(bromomethyl)benzonitrile was treated with

Table III. Tuberculostatic Disubstituted *N*-Alkylbenzylamine Hydrochlorides



compd	R^1	R^2	R^3	synth method[a]	yield,[b] %	mp,[c] °C	formula[d]	MIC,[e] μg/mL
72[f]	H	2-Cl	4-Cl	D, B	50	260	$C_7H_7Cl_2N$·HCl	>256.0
73[g]	CH_3	2-Cl	4-Cl	A, B	64	185–186	$C_8H_9Cl_2N$·HCl	>256.0
74[h]	C_2H_5	2-Cl	4-Cl	A, B	51	185	$C_9H_{11}Cl_2N$·HCl	>256.0
75[h]	C_3H_7	2-Cl	4-Cl	A, B	47	155	$C_{10}H_{13}Cl_2N$·HCl	>256.0
76[i]	C_4H_9	2-Cl	4-Cl	A, B			$C_{11}H_{15}Cl_2N$·HCl	>256.0
77[k]	H	2-Cl	5-Cl	D, B	62	250–253	$C_7H_7Cl_2N$·HCl	76.8
78	CH_3	2-Cl	5-Cl	A, B	58	171	$C_8H_9Cl_2N$·HCl	>256.0
79	C_2H_5	2-Cl	5-Cl	A, B	56	185–186	$C_9H_{11}Cl_2N$·HCl	>256.0
80	C_3H_7	2-Cl	5-Cl	A, B	56	202	$C_{10}H_{13}Cl_2N$·HCl	>256.0
81	C_4H_9	2-Cl	5-Cl	A, B	53	182	$C_{11}H_{15}Cl_2N$·HCl	>256.0
81[l]	H	2-Cl	6-Cl	D, B	57	235	$C_7H_7Cl_2N$·HCl	>256.0
83[m]	CH_3	2-Cl	6-Cl	A, B	42	198	$C_8H_9Cl_2N$·HCl	>256.0
84[n]	C_2H_5	2-Cl	6-Cl	A, B	62	207	$C_9H_{11}Cl_2N$·HCl	>256.0
85[n]	C_3H_7	2-Cl	6-Cl	A, B	48	212	$C_{10}H_{13}Cl_2N$·HCl	>256.0
86[i]	C_4H_9	2-Cl	6-Cl	A, B			$C_{11}H_{15}Cl_2N$·HCl	>256.0
87[f]	H	3-Cl	4-Cl	D, B	40	234	$C_7H_7Cl_2N$·HCl	>256.0
88[h]	CH_3	3-Cl	4-Cl	A, B	54	228	$C_8H_9Cl_2N$·HCl	>256.0
89[h]	C_2H_5	3-Cl	4-Cl	A, B	73	230	$C_9H_{11}Cl_2N$·HCl	>256.0
90[h]	C_3H_7	3-Cl	4-Cl	A, B	67	232	$C_{10}H_{13}Cl_2N$·HCl	>256.0
91[i]	C_4H_9	3-Cl	4-Cl	A, B			$C_{11}H_{15}Cl_2N$·HCl	>256.0
92[k]	H	3-Cl	5-Cl	D, B	45	264	$C_7H_7Cl_2N$·HCl	20.4
93	CH_3	3-Cl	5-Cl	A, B	79	194	$C_8H_9Cl_2N$·HCl	10.2
94	C_2H_5	3-Cl	5-Cl	A, B	67	248	$C_9H_{11}Cl_2N$·HCl	17.9
95	C_3H_7	3-Cl	5-Cl	A, B	77	264	$C_{10}H_{13}Cl_2N$·HCl	20.4
96	C_4H_9	3-Cl	5-Cl	A, B	75	248	$C_{11}H_{15}Cl_2N$·HCl	64.0
97	C_5H_{11}	3-Cl	5-Cl	A, B,	47	232	$C_{12}H_{17}Cl_2N$·HCl	128.0
98	C_7H_{15}	3-Cl	5-Cl	A, B	47	183	$C_{14}H_{21}Cl_2N$·HCl	153.6
99	H	3-F	5-F	D, B	41	270	$C_7H_7F_2N$·HCl	57.6
100	CH_3	3-F	5-F	A, B	49	231	$C_8H_9F_2N$·HCl	32.0
101	C_2H_5	3-F	5-F	A, B	47	209–210	$C_9H_{11}F_2N$·HCl	44.8
102	C_3H_7	3-F	5-F	A, B	48	249	$C_{10}H_{13}F_2N$·HCl	19.2
103	C_4H_9	3-F	5-F	A, B	50	281	$C_{11}H_{15}F_2N$·HCl	6.4
104	C_5H_{11}	3-F	5-F	A, B	45	277	$C_{12}H_{17}F_2N$·HCl	32.0
105	H	3-Cl	5-F	D, B	41	211	C_7H_7ClFN·HCl	32.0
106	CH_3	3-Cl	5-F	A, B	23	150	C_8H_9ClFN·HCl	19.2
107	C_2H_5	3-Cl	5-F	A, B	45	193	$C_9H_{11}ClFN$·HCl	32.0
108	C_3H_7	3-Cl	5-F	A, B	51	249	$C_{10}H_{13}ClFN$·HCl	25.6
109	C_4H_9	3-Cl	5-F	A, B	47	261	$C_{11}H_{15}ClFN$·HCl	19.2
110	CH_3	3-Cl	5-NO_2	A, C	51	173–175	$C_8H_9ClN_2O_2$·HCl	128.0
111	C_2H_5	3-Cl	5-NO_2	A, C	63	237	$C_9H_{11}ClN_2O_2$·HCl	102.4
112	C_3H_7	3-Cl	5-NO_2	A, C	45	245	$C_{10}H_{13}ClN_2O_2$·HCl	102.4
113	C_4H_9	3-Cl	5-NO_2	A, C	49	256	$C_{11}H_{15}ClN_2O_2$·HCl	204.8
114[o]	H	3-CF_3	4-Cl	D, B	35	224	$C_8H_7ClF_3N$·HCl	>256.0
115	CH_3	3-CF_3	4-Cl	A, B	30	179	$C_9H_9ClF_3N$·HCl	>256.0
116	C_2H_5	3-CF_3	4-Cl	A, B	47	176	$C_{10}H_{11}ClF_3N$·HCl	>256.0
117	C_3H_7	3-CF_3	4-Cl	A, B	50	206	$C_{11}H_{13}ClF_3N$·HCl	>256.0
118	C_4H_9	3-CF_3	4-Cl	A, B	57	179	$C_{12}H_{15}ClF_3N$·HCl	>256.0

[a] Capital letters refer to synthetic methods A–D in the Experimental Section. [b] Yields of the pure product; the yields refer to the methods mentioned under synthetic method; no effort was made to optimize yields. [c] All compounds were crystallized from MeOH/ether. [d] All compounds were analyzed for C, H, and N within ±0.4% of the calculated values. [e] Minimum inhibitory concentration for growth inhibition of *M. tuberculosis H 37 Ra*. [f] See ref 28. [g] See ref 29. [h] See ref 9. [i] See ref 1. [k] See ref 30. [l] See ref 31. [m] See ref 32. [n] See ref 33. [o] See ref 34.

hexamethylenetetramine. The ammonium salt was decomposed with HCl/EtOH (Scheme II). 3,5-Difluorobenzoic acid was synthesized according to Roe and Little.[35] The reduction with $LiAlH_4$ yielded 3,5-difluorobenzyl alcohol,[36] which was oxidized into the 3,5-difluorobenzaldehyde[37] with use of MnO_2. The synthesis of 3-chloro-5-nitrobenzaldehyde[38] and 3-chloro-5-fluorobenzaldehyde started from 3,5-dinitrobenzyl alcohol (Scheme III). This compound was partially reduced with $(NH_4)_2S$ to give 3-amino-5-nitrobenzyl alcohol, which was converted into 3-chloro-5-nitrobenzyl alcohol by the Sandmeyer reaction. The latter was oxidized with MnO_2 to form 3-chloro-5-nitrobenzaldehyde[38] or reduced with Fe/HCl to give 3-amino-5-chlorobenzyl alcohol; the amino group was replaced by a fluoro atom by thermal decomposition of the diazonium tetrafluoroborate to afford 3-chloro-5-fluorobenzyl alcohol. Oxidation with MnO_2 yielded 3-chloro-5-fluorobenzaldehyde.

Biological Properties. The first step to improve the efficacy of benzylamines against mycobacteria concerned the kind and position of substituents at the aromatic ring. We chose substituents that differ considerably in their lipophilic (π) and electronic (σ) parameters: F, Cl, Br, I, CF_3 ($+\pi/+\sigma$); OH, OCH_3, NH_2 ($-\pi/-\sigma$); CH_3 ($+\pi/-\sigma$); NO_2, CN ($-\pi/+\sigma$) (see ref 1 and Table II). None of the compounds with substituents in the ortho and para positions was more active than the corresponding unsubstituted primary and secondary benzylamines; most of the

(35) Roe, A.; Little, W. F. *J. Org. Chem.* **1955**, *20*, 1577.
(36) Punja, N. Eur. Pat. Appl. 31 199, 1981.
(37) Prudchenko, A. T. *Izv. Sib. Otd. Akad. Nauk. SSSR, Ser. Khim. Nauk.* **1970**, *6*, 95.
(38) Butler, G. B.; Carter, M. E. *J. Am. Chem. Soc.* 1950, *72*, 2303.

Table IV. Antimycobacterial Activity of the Benzylamines **19**, **93**, and **103** (MIC μg/mL)[40]

compd	*M. tuberculosis*[a,c] *H 37 Rv*	*M. avium*[a,c] *SN 304*	*M. marinum*[a,c] *SN 1254*	*M. smegmatis*[a,c] *ATCC 607*	*M. lufu*[b,d] *L 209*
19	12.0	16.0	24.0	32.0	32.0–64.0
93	3.0	4.0	4.0	32.0	4.0
103	4.0	3.0	6.0	32.0	8.0

[a] Lockeman medium with 5% bovine serum. [b] Dubos medium with 5% bovine serum. [c] For test method, see ref 2. [d] For test method, see ref 39.

compounds have to be considered as inactive (MIC > 250 μg/mL, ref 1 and Table II). We suppose that substitution in the ortho and para position leads to a strong steric hindrance of the benzylamine receptor interaction. Accordingly, the benzylamines with F, Cl, Br, NO_2, and CH_3 residues in the aromatic ring exhibited the highest activity for the meta isomers (ref 1 and Table II). Only primary and secondary benzylamines bearing the $+\pi/+\sigma$ substituents F, Cl, and Br in the 3-position exceeded the antimycobacterial activity of the corresponding unsubstituted compounds (Tables I and II). The influence of the N-alkyl chain length (one to five C atoms) on the activity was relatively weak (Table II). However, their analogues with branched *N*-alkyl chains in the α-position to the nitrogen atom lacked any antimycobacterial effects (Table II). The most active compounds were *N*-methyl-3-fluorobenzylamine hydrochloride (**11**, MIC 19.2 μg/mL, *M. tuberculosis H 37 Ra*), *N*-methyl-3-chlorobenzylamine hydrochloride (**19**, MIC 10.2 μg/mL, *M. tuberculosis H 37 Ra*), and *N*-methyl-3-bromobenzylamine hydrochloride (**29**, MIC 19.2 μg/mL, *M. tuberculosis H 37 Ra*). In the series of benzylamines with the most interesting $+\pi/+\sigma$ substituents in the 3-position, the following order of activity was observed: Cl > F > Br > I > CF_3. The 3-I-substituted benzylamines are already less active than the corresponding unsubstituted compounds (Tables I and II). 3-CF_3-substituted benzylamines are inactive at a concentration of 256 μg/mL (Table II). The σ values of the halogen residues are comparable to each other, but the π values increase in the order F << Cl < Br < I. Therefore, the rise of activity by replacing F by Cl in the 3-position of benzylamines can be explained by the higher lipophilicity of the latter. The drop of activity observed in the even more lipophilic 3-bromo- and 3-iodobenzylamines can be interpreted by the increasing substituent volume (F < Cl < Br < I << CF_3), which presumably hinders the drug–receptor interaction. The same considerations apply for 3-(trifluoromethyl)benzylamines. Owing to these findings, the lipophilic/hydrophilic substituent effect seems to be most important for the binding to the receptor. This assumption is also supported by the fact that a substitution by the $-\pi/+\sigma$ residues CN and NO_2 in the 3-position of benzylamines does not improve significantly the antimycobacterial activity (Tables I and II). The steric hindrance of the drug–receptor interaction caused by the substituent volume of CN and NO_2 corresponds with that of analogous 3-bromobenzylamines.

In order to improve the activity of 3-halobenzylamines, a second substituent (F, Cl, CF_3, NO_2) was introduced into the aromatic ring. Except for 2,5-dichlorobenzylamine (**77**, MIC 76.8 μg/mL, *M. tuberculosis H 37 Ra*), only 3,5-derivatives were active among the isomeric dichlorobenzylamines (Table III). The MIC values of the homologous *N*-alkyl-3,5-dichlorobenzylamines were nearly identical with those of the analogous *N*-alkyl-3-chlorobenzylamines (Tables II and III). The most active compound of this series is *N*-methyl-3,5-dichlorobenzylamine hydrochloride (**93**, MIC 10.2 μg/mL, *M. tuberculosis H 37 Ra*). The lengthening of the *N*-alkyl chain beyond one C atom results in a decrease of activity (Table III). An improvement of biological activity caused by a rise of the lipophilic character of the molecule is obviously nullified by an increase in steric hindrance of the drug–receptor interaction. The study of further derivatives was therefore restricted to the 3,5-substituted series. The most active compound among these was *N*-butyl-3,5-difluorobenzylamine hydrochloride (**103**, MIC 6.4 μg/mL, *M. tuberculosis H 37 Ra*); the lower homologues were even less active than the 3,5-dichloro analogues (Table III). Apparently a lengthening of the *N*-alkyl chain can compensate the reduction of lipophilicity when the Cl atoms are replaced by F atoms. These considerations are supported by results obtained with the homologous *N*-alkyl-3-chloro-5-fluorobenzylamines which were equally active. In the class of 3-chloro-5-nitrobenzylamines, no derivatives with a high antimycobacterial activity were found. They were somewhat better than 3-nitrobenzylamines but much less active than 3-chlorobenzylamines. These structure–activity studies demonstrate that electronic substituent effects are less important than lipophilic and steric ones. The high structural specificity of benzylamines is in accordance with their pronounced and specific antimycobacterial activity.

In a previous publication[2] we described the efficacy of *N*-butyl-3-fluorobenzylamine hydrochloride (**15**) not only against *M. tuberculosis H 37 Ra* and *H 37 Rv* but also against mycobacteria of the Runyon groups I–III. These results prompted us to study the effect of the most active benzylamines **19**, **93**, and **103** on *Mycobacterium avium*, *Mycobacterium marinum*, *Mycobacterium smegmatis*, and *Mycobacterium lufu*, too. *M. lufu* resembles *Mycobacterium leprae* in its sensitivity pattern and is therefore used for tracing antileprotic compounds.[39] Especially **93** and **103** proved to be active against these bacteria except *M. smegmatis*, which was somewhat less sensitive (Table IV).

Benzylamines are predominantly bacteriostatic. Bactericidal effects are only observed in high concentrations (**93**: bactericidal concentrations ≥ 256 μg/mL, *M. tuberculosis H 37 Ra*). In contrast to isonicotinic acid hydrazide (isoniazid) (Figure 1), a development of resistance could not be stated during an experimental interval of 21 days (Figure 2). In order to find out a possible synergism, **93** was tested on *M. tuberculosis H 37 Ra* in combination with drugs used in the therapy of tuberculosis and leprosy (Table V). A moderate synergistic effect (1 > FIC ≥ 0.15) was observed in a combination with rifampicin, trimethoprim, and benzaldehyde thiosemicarbazone and a marked one (FIC < 0.15) with streptomycin sulfate, aminosalicylic acid, and dapsone (Table V and Figure 3). In a mixture of **93** with dapsone, which itself is only slightly inhibitory against *M. tuberculosis H 37 Ra* (32 μg/mL), $^1/_{64}$ of the MIC of each compound is sufficient for a complete growth inhibition. These results offer the possibility of combining benzylamines with drugs or combinations of drugs currently used similar to the preparation containing dapsone, isoniazid, prothionamide, and rifampicin, which was applied successfully in an eradication program for leprosy.

(39) Seydel, J. K.; Wempe, E. *Int. J. Lepr. Other Mycobact. Dis.* 1981, *50*, 20.

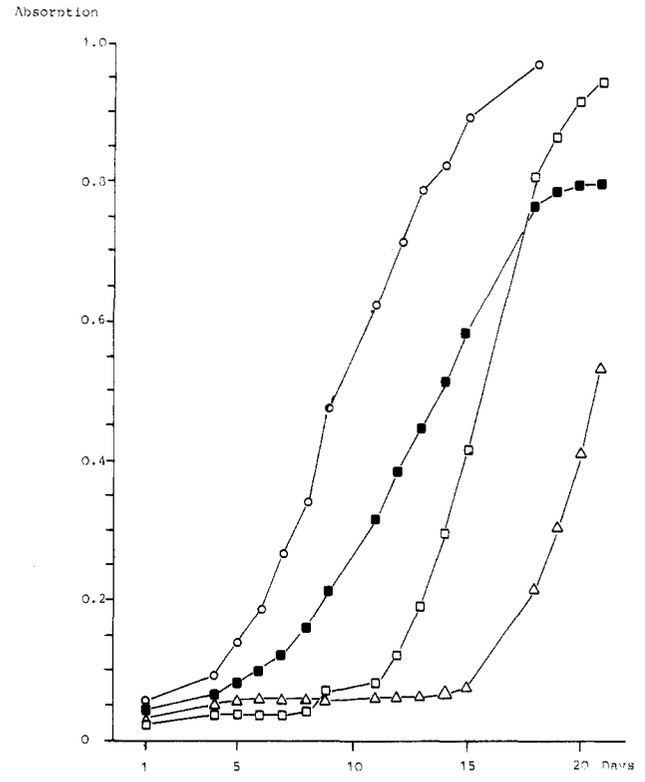


Figure 1. Growth inhibition of *M. tuberculosis H 37 Ra* by isonicotinic acid hydrazide, INH: 0.1 μg/mL (△), 0.05 μg/mL (□), 0.02 μg/mL (■); control (○); Middlebrook 7H9 medium (liquid); turbidimetric measurement at 546 nm.

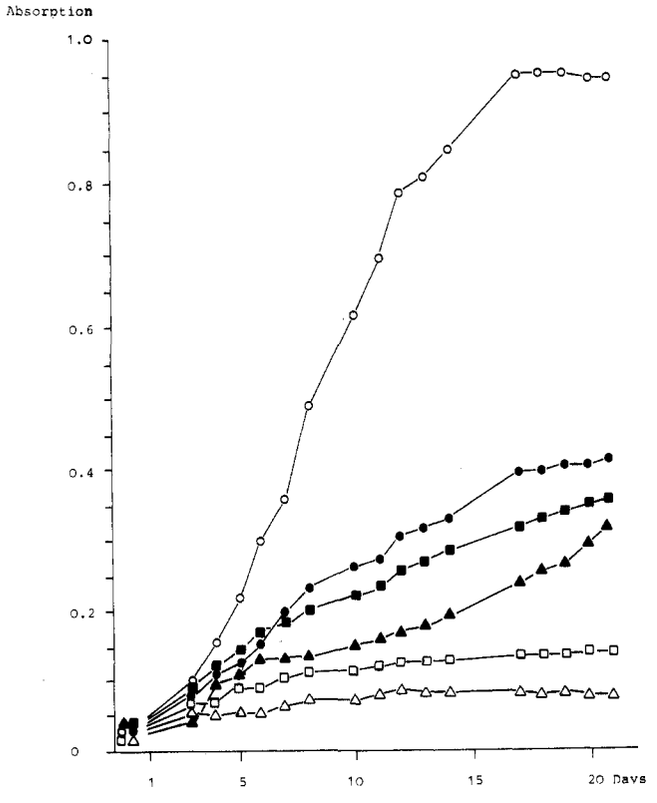


Figure 2. Growth inhibition of *M. tuberculosis H 37 Ra* by **93**. **93**: 32 μg/mL (△), 16 μg/mL (□), 8 μg/mL (▲), 4 μg/mL (■), 2 μg/mL (●); control (○); Middlebrook 7H9 medium (liquid); turbidimetric measurement at 546 nm.

Experimental Section

General Procedures. Melting points were determined on a Büchi 510 melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded with a Varian EM 360 A 60-MHz or a Varian EM 390, 90-MHz spectrometer in $CDCl_3$ or CD_3OD (internal standard Me_4Si; chemical shifts in ppm), and IR spectra were recorded with a Beckman Acculab 3 spectrometer. TLC of each compound was performed on Merck F 254 silica gel plates.

Table V. Evaluation of the Synergistic Effect of **93** in Combinations with Various Drugs Used in the Therapy of Tuberculosis and Leprosy

drug	MIC,[a] μg/mL: method a[b]	MIC,[a] μg/mL: method b[c]	FIC_{index}[d]
isoniazid	0.030	0.100	1
tetracycline hydrochloride	7.680	2.000	1
ethionamide	6.400	1.000	1
capreomycin	4.470	0.500	1
streptomycin sulfate	7.680	0.100	0.125
ethambutol	1.000	5.000	1
aminosalicylic acid	0.025	0.050	0.0625
rifampicin	0.512	0.010	0.5
cycloserine	25.600	32.000	1
benzaldehyde thiosemicarbazone	0.179	0.100	0.25
dapsone	5.120	32.000	0.031
trimethoprim	179.000	256.000	0.5

[a] Minimum inhibitory concentration for growth inhibition of *M. tuberculosis H 37 Ra*. [b] Löwenstein–Jensen medium (solid) **93**: MIC 10.2 μg/mL. [c] Middlebrook 7H9 medium (liquid), turbidimetric measurement at 546 nm, **93**: MIC 16.0 μg/mL. [d] FIC: fractional inhibitory concentration; $FIC_{index} = FIC_A + FIC_B$; $FIC_A = MIC_{A'}/MIC_A$, FIC_B analogous; $MIC_{A'}$ = MIC of A in an A/B mixture, $MIC_{B'}$ analogous; A, **93** (μg/mL); B, drug (μg/mL). A and B were applied in equal fractions of their individual MICs, e.g., $MIC_A/32 + MIC_B/32$; synergism, $FIC_{index} \leq 0.5$; antagonism, $FIC_{index} \geq 2$; addition, $FIC_{index} = 1$.[41]

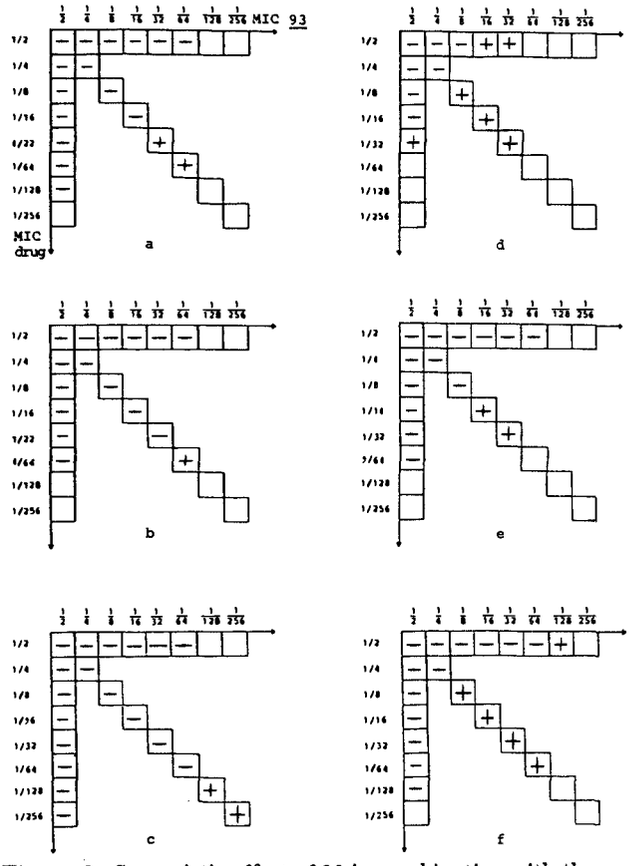


Figure 3. Synergistic effect of **93** in combination with the antimycobacterial drugs streptomycin sulfate (a), aminosalicylic acid (b), dapsone (c), rifampicin (d), benzaldehyde thiosemicarbazone (e), and trimethoprim (f) (Middlebrook 7H9 medium (liquid); turbidimetric measurement at 546 nm; *M. tuberculosis H 37 Ra*).

Elemental analyses were performed by the microlaboratory of the University of Regensburg. Analyses are indicated by the symbols of the elements and were within ±0.4% of the theoretical values. The structure of all compounds was confirmed by their ^{1}H NMR and IR spectra.

Method A. Preparation of the Imines. Alkylamines (0.03 mol) were slowly added to the benzaldehydes (0.025 mol) at room temperature. Heating to 80 °C is recommended in the synthesis of the *N*-methyl imines. After stirring for 1 h, the imine was extracted with $CHCl_3$. The extract was dried with Na_2SO_4 and the solvent was removed. The product was used without further purification.

Method B. Reduction of the Imines and the Oximes with $LiAlH_4$. A solution of the imine (0.02 mol) or the oxime (0.01 mol) in 30 mL of dry ether was added dropwise to a suspension of $LiAlH_4$ (0.38 g, 0.01 mol) in 20 mL of dry ether. After refluxing for 2 h, the reaction mixture was brought to room temperature and carefully hydrolyzed with water. The ether layer was separated and dried with Na_2SO_4. The hydrochlorides of the benzylamines were precipitated with ethereal HCl, collected by filtration, and recrystallized from MeOH/Et_2O, EtOH, or acetonitrile. For the reduction of the oximes, THF was preferred as the solvent.

Method C. Reduction of the Imines with $NaBH_4$. $NaBH_4$ (0.38 g, 0.01 mol) was added to the solution of the imine (0.02 mol) in 30 mL of dry MeOH. The mixture was refluxed for 1 h. After removal of the solvent, 10 mL of 6 N NH_4OH was added and the mixture was extracted with ether. The solution of the benzylamine was treated in the same way as in method B.

Method D. Synthesis of the Oximes. The solution of NH_2OH·HCl (6.95 g, 0.1 mol) and $KHCO_3$ (5.0 g, 0.05 mol) in water was slowly added to a solution of the benzaldehyde (0.1 mol) in EtOH. The oxime was collected by filtration or extracted with ether after removal of the EtOH. The product was used without further purification.

3-Cyanobenzylamine (42). 3-(Bromomethyl)benzonitrile (19.61 g, 0.1 mol) was dissolved in $CHCl_3$ and added to a solution of hexamethylenetetramine (14.02 g, 0.1 mol) in $CHCl_3$ at a temperature of 50 °C. After refluxing for 2 h, the precipitation of the quaternary salt was completed. The crystals were collected by filtration and dried. The quaternary salt (33.63 g, 0.1 mol) was dissolved in 34.0 mL of HCl (37%) and 55.0 mL of EtOH, and the solution was stirred for 30 min. After removal of diethylformal, EtOH, and water in vacuo, the procedure was repeated twice. Compound **42** was extracted with ether from the alkalized solution, and the hydrochloride was precipitated with ethereal HCl and recrystallized from EtOH.

3-Amino-5-nitrobenzyl Alcohol. The solution of $(NH_4)_2S$ used for this reaction was prepared by adding a solution of Na_2S·$9H_2O$ (96.0 g, 0.4 mol) in 250 mL of MeOH to a solution of NH_4Cl (85.6 g, 1.6 mol) in 250 mL of MeOH and separating the NaCl. This solution was added within 30 min to a solution of 3,5-dinitrobenzyl alcohol (39.6 g, 0.2 mol) in 700 mL of boiling MeOH and the mixture refluxed for 5 h. After the mixture was cooled to room temperature, the resulting precipitate of sulfur was removed. HCl (2 N) was added and the solvent was distilled off. After removal of the starting material with ether, the aqueous solution was alkalized and the product extracted with ether: yield 62%; mp 91.5 °C; ^{1}H NMR (CD_3OD) δ 4.57 (s, 2 H, CH_2), 6.93–7.53 (m, 3 H, aromatic H). Anal. ($C_7H_8N_2O_3$) C, H, N.

3-Chloro-5-nitrobenzyl Alcohol. 3-Amino-5-nitrobenzyl alcohol (16.8 g, 0.1 mol) was dissolved in 70 mL of HCl (15%). A solution of $NaNO_2$ (7.25 g, 0.105 mol) in water was added dropwise at a temperature of 0 °C. HCl (10%) was added to give a volume of 130 mL. This solution was mixed with a solution of copper salts prepared by dissolving $CuCl_2$ (20.2 g, 0.15 mol) and CuCl (0.12 g, 0.0012 mol) in 250 mL of HCl (12%). After stirring and heating to 60 °C for 1 h, the product crystallized and was purified by column chromatography: yield 54%; mp 78.5 °C; ^{1}H NMR ($CDCl_3$) δ 2.40 (s, 1 H, OH), 4.80 (s, 2 H, CH_2), 7.62–8.22 (m, 3 H, aromatic H). Anal. ($C_7H_6ClNO_3$) C, H, N.

General Method for the Preparation of Benzaldehydes. MnO_2 (21.7 g, 0.25 mol) and 200 mL of benzene were refluxed for 2 h in a Dean–Stark apparatus. Then the benzyl alcohol (0.05 mol) was added and the solution was refluxed for 24 h. The reaction mixture was filtered and the solvent was removed. The residue was recrystallized in an appropriate solvent and analyzed by ^{1}H NMR spectroscopy.[42]

3-Amino-5-chlorobenzyl Alcohol. Iron powder (2.24 g, 0.04 mol) was added to a solution of 3-chloro-5-nitrobenzyl alcohol (1.9 g, 0.01 mol) in 50 mL of EtOH. HCl gas was bubbled through this solution until the exothermic reaction ceased. After EtOH was replaced by water, the mixture was extracted with ether. After alkalization the aqueous layer was extracted with ether to afford the product: yield 81%; mp 86.5 °C; ^{1}H NMR ($CDCl_3$) δ 1.93 (s, 1 H, OH), 3.74 (s, 2 H, NH_2), 4.56 (s, 2 H, CH_2), 6.47–6.77 (m, 3 H, aromatic H).

3-Chloro-5-fluorobenzyl Alcohol. 3-Amino-5-chlorobenzyl alcohol (15.7 g, 0.1 mol) was dissolved in 92 mL of tetrafluoroboric acid (48%) and cooled to −5 °C. A solution of $NaNO_2$ (6.9 g, 0.1 mol) in water was added slowly. The diazonium salt was collected by filtration, washed with cold tetrafluoroboric acid, EtOH, and Et_2O, and dried in vacuo: yield 64%; decomposition temperature 100 °C; IR 2320 cm^{-1}; ($C_7H_6ClN_2OBF_4$). Small quantities of the diazonium tetrafluoroborate were decomposed in an oil bath. After addition of water, the product was extracted with Et_2O. The ethereal extract was washed with water and dried over Na_2SO_4. The solvent was removed and the product purified by column chromatography: yield 25%; bp 238 °C; ^{1}H NMR ($CDCl_3$) δ 2.24 (s, 1 H, OH), 4.63 (s, 2 H, CH_2), 6.82–7.18 (m, 3 H, aromatic H).

3-Chloro-5-fluorobenzaldehyde: yield 73%; mp 140 °C; ^{1}H NMR ($CDCl_3$) δ 7.25–7.73 (m, 3 H, aromatic H), 10.05 (s, 1 H, CHO).

Biological Methods. Preparation of Media. Löwenstein–Jensen medium and Middlebrook 7H9 broth were prepared according to Lennette et al.[45]

Determination of Tuberculostatic Activity. *M. tuberculosis H 37 Ra*, obtained from Max-von-Pettenkofer-Institut für Hygiene und Medizinische Mikrobiologie, University of Munich, were cultured in these media. The test tubes with Löwenstein–Jensen medium were inoculated with 10 μL of a suspension of *M. tuberculosis H 37 Ra* in physiological saline (E = 0.1; 18-mm cuvette, 546-nm filter, Eppendorf 1101 M spectrophotometer) and incubated for 21 days at 37 °C. MIC is defined as lowest concentration of compound used to prevent growth of *M. tuberculosis H 37 Ra*.

The test tubes with liquid Middlebrook 7H9 medium were inoculated with a suspension of *M. tuberculosis H 37 Ra* in 0.85% saline to give an extinction difference of 0.04 in the 18-mm culture tube (546-nm filter, Eppendorf 1101 M spectrophotometer) and incubated in a shaker (100 rpm, TR-1 and ITH-1, B. Braun-Melsungen) for 21 days at 37 °C. Extinctions were measured once a day, and an extinction below 0.15 after 21 days was regarded as no growth of *M. tuberculosis H 37 Ra*. Checkerboard titrations to determine the MIC of single drugs and their combinations in various ratios have been made in the usual manner.[41]

Determination of Bacteriostatic and Bactericidal Properties. *M. tuberculosis H 37 Ra* was cultured in tubes with Middlebrook 7H9 medium in the presence of compound **93** in three different concentrations (51.2, 102.4, and 256 μg/mL). After 14 days, Löwenstein–Jensen tubes were inoculated with 30 μL of the above-mentioned liquid cultures. In this way, the inhibitor concentrations were diminished below the MIC. Growth of bacteria 3 weeks later proved the survival of *M. tuberculosis H 37 Ra* in the liquid medium and indicated bacteriostatic activity.

Acknowledgment. We are indebted to Prof. Dr. J. K. Seydel and Dr. K.-J. Schaper, Borstel Research Institute,

(40) Seydel, J. K., unpublished results.
(41) Elion, G. B.; Singer, S.; Hitchings, G. H. *J. Biol. Chem.* **1954**, *208*, 477.
(42) Meindl, W. R. Ph.D. Thesis, University of Regensburg, 1983.
(43) von Braun, J.; Kruber, O. *Ber. Dtsch. Chem. Ges.* **1913**, *46*, 3470.
(44) Huisgen, R.; König, H. *Chem. Ber.* **1959**, *92*, 203.
(45) Lennette, E. H.; Spaulding, E. H.; Truant, J. P. "Manual of Clinical Microbiology", 2nd ed.; American Society for Microbiology: Washington, DC, 1974.
(46) *N*-Methyl-3-chloroaniline hydrochloride (**119**)[43] and *N*-methyl-3-chloro-β-phenylethylamine hydrochloride (**120**)[44] show a MIC > 256 μg/mL against *M. tuberculosis H 37 Ra* in Löwenstein–Jensen medium.

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Registry No. 1, 3287-99-8; 1 (base), 100-46-9; **2**, 13426-94-3; **2** (base), 103-67-3; **3**, 5417-36-7; **3** (base), 14321-27-8; **4**, 23510-22-7; **4** (base), 2032-33-9; **5**, 18618-49-0; **5** (base), 2403-22-7; **6**, 90389-36-9; **6** (base), 25468-43-3; **7**, 90389-37-0; **7** (base), 25468-44-4; **8**, 90389-38-1; **8** (base), 5730-02-9; **9**, 90389-39-2; **9** (base), 1667-16-9; **10**, 658-25-3; **10** (base), 100-82-3; **11**, 90389-40-5; **11** (base), 90389-84-7; **12**, 90389-41-6; **12** (base), 90389-85-8; **13**, 90389-42-7; **13** (base), 90389-86-9; **14**, 90389-43-8; **14** (base), 90389-87-0; **15**, 90389-44-9; **15** (base), 60509-34-4; **16**, 90389-45-0; **16** (base), 90389-88-1; **17**, 42365-42-4; **17** (base), 4152-90-3; **18**, 90006-43-2; **18** (base), 94-64-4; **19**, 90389-46-1; **19** (base), 39191-07-6; **20**, 65542-24-7; **20** (base), 104-11-0; **21**, 90389-47-2; **21** (base), 39180-82-0; **22**, 90389-48-3; **22** (base), 39190-98-2; 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3-chloro-5-fluorobenzaldehyde, 90390-49-1.

Supplementary Material Available: ^{1}H NMR data of compounds 11–14, 16, 18–23, 26–33, 38–48, 50–52, 54–57, 59–75, 77–85, 87–90, 92–118 (9 pages). Ordering information is given on any current masthead page.