

Mice infected with *E. coli* or *S. aureus* were medicated by the subcutaneous (sc) or oral (po) routes once (0.5 mL) at 0.5-h postinfection. Deaths were recorded daily for 7 days. Mice infected with *P. aeruginosa* were medicated sc (0.2 mL) at 0.5-, 4-, and 7-h postinfection. Deaths were recorded daily for 7 days.

Groups of 10 animals each for four or five dose levels were thus treated and the number of survivors in each group recorded. Nonmedicated control animals were included in each test. Fifty percent protective dose values (PD₅₀) were calculated by using probit analysis.¹⁸

Acknowledgment. We thank the Analytical Chemistry

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Department of this Institute for spectral measurements.

Registry No. 1, 75073-15-3; 2, 88569-30-6; 3, 88569-33-9; 4, 88569-34-0; 5, 88569-35-1; 6, 88569-38-4; 7, 88569-36-2; 8, 88569-45-3; 9, 88569-31-7; 10, 88569-39-5; 11, 88569-41-9; 12, 88569-44-2; 13, 88569-43-1; 14, 88569-47-5; 15, 88569-56-6; 16, 86393-37-5; 17, 88569-59-9; 18, 88569-68-0; 19, 88569-60-2; 20, 88569-61-3; 21, 88569-57-7; 22, 88569-62-4; 23, 88569-65-7; 24, 88569-67-9; 25, 88569-70-4; 26, 88569-53-3; 27, 88569-69-1; 28, 88569-77-1; 29, 88569-71-5; 30, 88569-73-7; 31, 88569-74-8; 32, 90584-37-5; 32 (free base), 89990-93-2; 33, 90584-38-6; 33 (free base), 89990-44-3; 34, 88569-72-6; 35, 88569-78-2; 36, 89990-96-5; 36 (free base), 88569-63-5; 1-(1-methylethyl)piperazine dihydrochloride, 88569-66-8; 1-propylpiperazine dihydrobromide, 64262-23-3; hexahydro-1*H*-1,4-diazepine, 505-66-8; hexahydro-4-methyl-1*H*-1,4-diazepine, 4318-37-0.

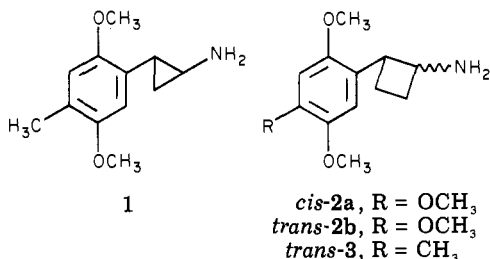
Synthesis and Evaluation of Substituted 2-Phenylcyclobutylamines as Analogues of Hallucinogenic Phenethylamines: Lack of LSD-like Biological Activity

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cis- and *trans*-2-(2,4,5-trimethoxyphenyl)cyclobutylamine and *trans*-2-(2,5-dimethoxy-4-methylphenyl)cyclobutylamine were synthesized as conformationally restricted analogues of hallucinogenic phenylisopropylamines. In rats trained to discriminate saline from LSD (0.08 mg/kg, ip) in a two-lever drug discrimination paradigm, no generalization of the LSD stimulus to the *cis* trimethoxy compound occurred at doses up to 20 mg/kg. For both of the *trans* compounds, partial generalization of the LSD cue occurred at doses of 5 mg/kg or greater. In contrast, complete generalization occurred with *trans*-2-(2,5-dimethoxy-4-methylphenyl)cyclopropylamine. The ED₅₀ for this compound and the doses of the *trans* cyclobutyl homologues at which significant drug-appropriate responding occurred indicate that the latter are on the order of 50–75 times less potent than the cyclopropylamine analogue. The lack of generalization to the cyclobutylamines indicates either that their discriminative stimulus properties differ from LSD or that they lack discriminative effects.

In our continuing studies to elucidate the structure-activity requirements of phenethylamine type hallucinogens, we reported that the cyclopropyl analogue 1 has potent hallucinogen-like activity in several animal models.^{1,2} Furthermore, it has been subsequently found that



racemic 1 is hallucinogenic in man, with an effective dose of the hydrochloride in the 16–20-mg range.³ The compound is therefore some 15–20 times more potent than mescaline. In contrast, 1 has relatively weak agonist activity in the rat fundus assay, when compared with its phenethylamine counterpart, 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM, STP).^{4,5} Since the p*K*_a of 1 is 8.11,⁵ while that of substituted amphetamines is about 9.6,⁶ it seems likely that the high in vivo activity

for 1 may be at least partially attributed to more favorable partitioning into the CNS, as a result of a higher fraction of the unionized form of the compound at physiological pH. Thus, higher concentrations of 1 in the brain could compensate for decreased efficacy at the receptor.

It is now fairly evident that addition of alkyl groups larger than methyl to the α side chain carbon of the substituted amphetamine type hallucinogens abolishes biological activity.^{4,7,8} It was therefore of interest to examine the cyclobutane homologues 2 and 3 for hallucinogen-like activity. In these compounds the ring of 1 has been expanded by one methylene unit. This would further test

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- (3) (a) Human activity for the hydrochloride of compound 1 was determined by Shulgin (personal communication) following procedures described in ref 3b. An active range (orally, in normal, adult volunteers) was 16–20 mg (with *n* = 7 and in 17 experimental trials). (b) Jacob, P., III; Shulgin, A. T. *J. Med. Chem.* 1983, 26, 746.
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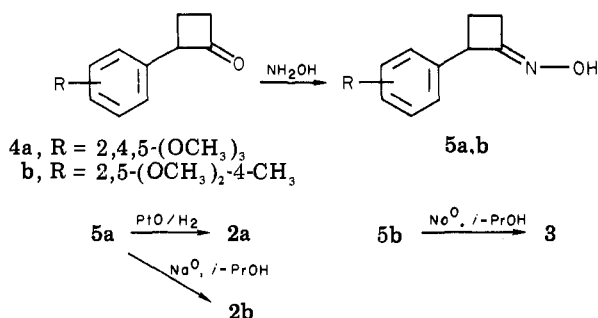
Table I. Results of Drug Discrimination Assay

compd	dose range, mg/kg	no. of doses	no. of test sessions per drug ^a	highest mean % LSD correct responses (dose, mg/kg) ^b	ED ₅₀ , mg/kg	95% ci
LSD ^c						
1	0.05–1.0	6	29	93 (0.75)	0.0077	0.0036–0.0162
2a	5–20	4	16	28 (15)	0.163	0.07–0.38
2b	4–20	5	16	44 (10)		
3	0.25–20	7	24	53 (10)		

^a Generally two to seven rats were tested at each dose. ^b Average LSD appropriate responding after saline never exceeded 15%. ^c The LSD data are taken from a previous report (ref 18); these data and those of ref 18 were obtained in one large randomized study so that LSD data are appropriate for both reports.

the limits of discrimination of steric bulk by the receptor and would establish whether the cyclopropane ring system is unique or whether larger carbocyclic systems should be examined. This report therefore describes the synthesis of components 2 and 3 and their evaluation in the two-lever drug discrimination assay using rats trained to discriminate injections of saline from LSD tartrate (0.08 mg/kg, ip). Evaluation of the cyclopropyl compound 1 in this assay is also reported, for comparison purposes.

Chemistry. The cyclobutylamines were prepared by the method previously described by Miller et al.⁹ Essentially, the appropriate aromatic aldehyde was allowed to react with diphenylsulfonium cyclopropylide. This afforded the phenylcyclobutanones 4, which were converted to their respective oximes 5. Catalytic reduction



of oxime 5a over Adam's catalyst yielded almost exclusively the cis amine 2a. Similar attempts to produce the cis amine from oxime 5b gave a compound that had the spectral properties of the expected cis compound but that slowly decomposed and could not be purified suitably for biological evaluation. Reduction of the oximes with sodium in 2-propanol gave predominantly the trans amines, which were purified as the hydrochlorides by repeated recrystallization. Analysis of the purity of the cis and trans amines was carried out by GLC analysis of the *N*-trifluoroacetyl amides, as described previously.⁹ Isomeric purity was greater than 99.5%.

Results and Discussion

The testing data are summarized in Table I. In rats trained to discriminate saline from LSD (0.08 mg/kg), where LSD had an ED₅₀ of 0.0077 mg/kg (0.0036–0.0162 95% confidence interval (ci)), compound 1 had an ED₅₀ of 0.163 mg/kg (0.07–0.38 95% ci). By contrast, there was no significant generalization of the LSD stimulus to 3 at doses from 0.25 to 5 mg/kg. At 10 mg/kg, 3 produced an average of 53% responding on the LSD lever in five rats, while at 20 mg/kg behavioral disruption occurred in two of the four rats tested. The lack of a sufficient amount of compound 3 precluded the determination of a complete dose-response curve. However, the data indicate that 10

mg/kg may be near the ED₅₀, suggesting about a 50-fold difference in potency between 1 and 3. In man, 1 has clearly detectable clinical effects following an oral dose of 10 mg of the hydrochloride, while an effective intoxication is produced by doses of 16–20 mg. In contrast, 3 has no detectable effects in man following an oral dose of 25 mg of the hydrochloride.¹⁰

No significant LSD-appropriate responding was observed following administration of the cis compound 2a at doses up to 20 mg/kg, and no disruption occurred at the highest dose tested. Similar to 3, partial generalization occurred to the trans compound 2b. At 10 mg/kg, two of the seven rats tested selected the drug appropriate lever, while at 15 mg/kg one of the three rats tested selected the drug lever. This compound appeared to be slightly less potent than 3.

These data, in conjunction with earlier reports, from this laboratory and others,^{4,7,8} clearly indicate that the receptor systems involved in mediating the action of hallucinogenic phenethylamine derivatives cannot tolerate significant molecular bulk attached to the α side chain position. With one exception, where geminal α,α -dimethyls are incorporated into a cyclopropane ring,¹¹ nothing larger than a methyl is known to give active compounds. In that case it again is not clear to what extent the in vivo activity is related to distribution effects, due to the lower basicity of cyclopropylamines. On the basis of calculated solution conformations, we have previously suggested that the receptor may be viewed as a groove or slot or that some portion of the receptor may fold over the agonist molecule.¹²

Thus, we propose a view of the receptor involved in the action of hallucinogenic phenethylamines that would include a relatively planar region that could interact with one face of the hallucinogen molecule, presumably via a charge-transfer mechanism.¹³ Located in the vicinity of the amine binding site is an area of steric intolerance, possibly due to a groove or slot type geometry of the receptor. Steric bulk protruding beyond a radius of about 2 Å from the α side chain carbon apparently abolishes biological activity.

This conclusion parallels, in certain respects, the structure-activity relationships of dopamine agonists. Erhardt has postulated a steric boundary in the vicinity

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(10) Shulgin, A. T., personal communication. In one individual, compound 3 as the hydrochloride, in seven trials of single oral doses from 0.5 mg up to 25 mg, failed to produce any detectable central effects.

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of the amine binding site on the dopamine receptor that restricts the binding of agonists with α -alkyl substituents.¹⁴ Similar reasoning could be used in the present instance. If a serotonin receptor is primarily involved in the action of hallucinogens, this would indicate that the geometry of certain dopamine and serotonin receptors may be similar. However, the dopamine receptor evidently does not even accept compounds that incorporate the side chain into a cyclopropane ring, whereas 1 retains hallucinogenic potency.

Experimental Section

Melting points were taken on a Mel-Temp or Thomas-Hoover UniMelt apparatus and are uncorrected. IR spectra were obtained on a Beckman IR-33 instrument NMR spectra were recorded on a Varian FT-80, Bruker HX-90E, or Nicolet 470-MHz FT spectrometer. Chemical shifts are reported in δ values (ppm) relative to an internal standard of Me₄Si or DSS, depending on whether the sample was run in CDCl₃ or D₂O, respectively. Elemental analyses were performed by the microanalysis laboratory, Department of Chemistry, Purdue University, or by Galbraith Laboratories, Inc., Knoxville, TN.

2-(2,4,5-Trimethoxyphenyl)cyclobutanone (4a). To a stirred solution of 3.68 g (18.6 mmol) of 2,4,5-trimethoxybenzaldehyde and 5.80 g (18.6 mmol) cyclopropyldiphenylsulfonium tetrafluoroborate^{15,16} in 100 mL of dry THF, cooled to -15 °C, was added dropwise, with stirring, a slurry of 2.80 g (25 mmol) of potassium *tert*-butoxide in 50 mL of dry THF.⁹ Slow addition of the base was necessary to achieve optimum yields. After addition was complete the reaction was stirred an additional 30 min and 20 mL (20 mmol) of 1 N fluoroboric acid was added. The reaction mixture was allowed to warm to room temperature and was taken up into ether, and the ether solution was washed with successive portions of saturated NaHCO₃, brine, and water and was dried (MgSO₄). Filtration and concentration by rotary vacuum evaporation gave an oil which was adsorbed onto a pad of silica gel. Washing with petroleum ether removed the diphenyl sulfide and the ketone was eluted with ether. Concentration gave an oil, which slowly crystallized on standing to yield the cyclobutanone, 3.3 g (75%). An analytical sample was recrystallized from *i*-PrOH: mp 69–70.5 °C; IR (KBr) 1780 cm⁻¹ (C=O); NMR (CDCl₃) δ 6.70 (s, 1, Ar H), 6.54 (s, 1, Ar H), 4.45 (t, 1, Ar CH, $J = 9$ Hz), 3.87, 3.82, 3.77 (3 s, 9, OCH₃), 3.3–2.9 (m, 2, COCH₂), 2.6–2.1 (m, 2, CH₂). Anal. (C₁₃H₁₆O₄), C, H.

2-(2,5-Dimethoxy-4-methylphenyl)cyclobutanone (4b). Following a procedure similar to that above, a mixture of 2.39 g (13.3 mmol) of 2,5-dimethoxy-4-methylbenzaldehyde and 4.60 g (14.6 mmol) of cyclopropyldiphenylsulfonium tetrafluoroborate in 50 mL of dry THF was treated with a slurry of 1.80 g (16.1 mmol) of potassium *tert*-butoxide in 50 mL of dry THF at 0 °C. The reaction was stirred for 2 h after addition of the base and was then worked up as described above. Chromatography of the crude ketone over silica gel and elution with 7% ether in hexane gave the ketone as an oil which crystallized on standing: yield 2.45 g (84%); mp 64–65 °C; IR (CHCl₃) 1780 cm⁻¹ (C=O); NMR (CDCl₃) δ 6.70 (s, 1, Ar H), 6.60 (s, 1, Ar H), 4.41 (t, 1, Ar CH, $J = 8$ Hz), 3.74, 3.72 (2 s, 6, OCH₃), 3.10–2.99 (m, 2, COCH₂), 2.36–2.15 (m, 2, CH₂), 2.18 (s, 3, Ar CH₃). Anal. (C₁₃H₁₆O₃), C, H.

2-(2,4,5-Trimethoxyphenyl)cyclobutanone Oxime (5a). A solution of the (trimethoxyphenyl)cyclobutanone 4a (3.3 g, 14 mmol), 8.0 g (115 mmol) of hydroxylamine hydrochloride, and 90 mL (112 mmol) of 5% NaOH in 75 mL of EtOH was heated at reflux for 2 h. The solution was cooled, adjusted to pH 6, and extracted with CHCl₃. The organic extract was washed with brine and dried (MgSO₄). Filtration and concentration yielded an oil which crystallized on standing. Recrystallization from EtOH–H₂O afforded 2.77 g (79%) of the crystalline oxime: mp 144–145 °C; IR (Nujol) 3440 (OH), 1690 cm⁻¹ (C=N); NMR (CDCl₃) δ 8.1 (br s, 1, OH), 6.98 (s, 1, Ar H), 6.55 (s, 1, Ar H), 4.57 (t, 1, Ar CH), 3.87, 3.83, 3.80 (3 s, 9, OCH₃), 3.2–1.8 (m, 4, CH₂). Anal. (C₁₃H₁₇NO₄) C, H, N.

2-(2,5-Dimethoxy-4-methylphenyl)cyclobutanone Oxime (5b). A procedure identical with that for 5a using the cyclobutanone 4b afforded the corresponding oxime in 80% yield, following recrystallization from EtOH–H₂O: mp 83–84 °C; IR (Nujol) 1700 cm⁻¹ (C=N); NMR (CDCl₃) δ 9.9 (br s, 1, OH), 6.66 (s, 1, Ar H), 6.62 (s, 1, Ar H), 4.76 (br s, 1, Ar CH), 3.78 (s, 6, OCH₃), 2.8–1.75 (m, 4, CH₂), 2.20 (s, 3, Ar CH₃). Anal. (C₁₃H₁₇NO₃) C, H, N.

***cis*-2-(2,4,5-Trimethoxyphenyl)cyclobutylamine Hydrochloride (2a).** A solution of oxime 5a (0.47 g, 1.87 mmol) in 50 mL of absolute EtOH, containing 1 mL of CHCl₃ and 50 mg of platinum oxide catalyst was shaken under 3 atm of H₂ in a Parr apparatus for 12 h.¹⁷ The catalyst was removed by filtration through a Celite pad. Concentration under reduced pressure yielded a white solid. Recrystallization from EtOH–ether gave the pure amine salt: 320 mg (66%); mp 219–220 °C dec; NMR (90 MHz, D₂O) δ 6.92 (s, 1, Ar H), 6.74 (s, 1, Ar H), 4.3–3.9 (m, 2, Ar CHCHN), 3.89, 3.85, 3.84 (3 s, 9, OCH₃), 2.8–1.9 (m, 4, CH₂); NMR (470 MHz, CDCl₃) δ 7.81 (br s, 3, NH₃), 6.76 (s, 1, Ar H), 6.43 (s, 1, Ar H), 3.87, 3.84, 3.79 (3 s, 9, OCH₃), 3.90–3.82 (m, 2, Ar CHCHN), 2.81 (m, 1, CH), 2.31 (m, 1, CH), 2.17 (m, 1, CH), 1.67 (m, 1, CH). Anal. (C₁₃H₂₀NO₃Cl) C, N, N.

***trans*-2-(2,4,5-Trimethoxyphenyl)cyclobutylamine Hydrochloride (2b).** To a refluxing solution of 1.2 g (4.8 mmol) of 5a in 120 mL of dry *i*-PrOH was added 4.3 g (187 mmol) of sodium metal, in small pieces over 30 min. After complete addition the solution was maintained at reflux for 1 h. The reaction was cooled, water was added, and the *i*-PrOH was removed under reduced pressure. The aqueous solution was extracted with CH₂Cl₂ and the organic layer was then extracted with 4 N HCl. Basification with NaOH liberated the free base, which was extracted into CH₂Cl₂. The organic solution was washed with H₂O, brine, and then dried (MgSO₄). Filtration and concentration yielded the free amine, which was converted to its hydrochloride salt with ether–HCl and recrystallized twice from EtOH–ether to yield 710 mg (55%) of the pure *trans* amine salt: mp 196–197 °C dec; NMR (470 MHz, CDCl₃) δ 8.63 (br s, 3, NH₃), 6.58 (s, 1, Ar H), 6.48 (s, 1, Ar H), 3.93, 3.85, 3.81 (3 s, 9 H, OCH₃), 3.86, 3.64 (2 m, 2, Ar CHCHN), 2.57 (q, 1, CH), 2.35 (m, 2, CH), 2.00 (q, 1, CH). Anal. (C₁₃H₂₀NO₃Cl) C, H, N.

***trans*-3-(2,5-Dimethoxy-4-methylphenyl)cyclobutylamine Hydrochloride (3).** In a procedure analogous to that for 2b, 2.29 g (9.75 mmol) of the oxime 5b in 150 mL of dry *i*-PrOH was treated with 8 g (350 mmol) of sodium metal. A similar isolation procedure to that for 2b gave the hydrochloride salt, which was crystallized several times from absolute EtOH to afford 1.51 g (60%) of the salt: mp 198.5–200 °C; NMR (470 MHz, CDCl₃) δ 8.64 (br s, 3, NH₃), 6.64 (s, 1, Ar H), 6.52 (s, 1, Ar H), 3.90, 3.76 (2 s, 6, OCH₃), 3.89 (m, 1, CH), 3.64 (m, 1, CH), 2.58 (q, 1, CH), 2.35 (m, 2, CH), 2.17 (s, 3, Ar CH₃), 2.00 (q, 1, CH). Anal. (C₁₃H₂₀NO₂Cl) C, H, N.

Pharmacology. Animals. Sixteen male, Sprague–Dawley rats, weighing 200–240 g at the start of the experiment, were obtained from Murphy Breeding Labs, Inc., Plainfield, IN. Rats were housed in pairs in an environmentally controlled room at 22–24 °C and a 14/10 h light/dark cycle. Discrimination training was carried out as described previously,¹⁸ and rats were trained to discriminate intraperitoneal injections of saline from 0.08 mg/kg of LSD tartrate (NIDA). Rats were food deprived to allow for only about 1 g/day weight gain. Food (Lab Blox) was provided once daily, approximately 1 h after removal from the testing chambers.

Apparatus. Standard operant chambers (Coulbourn Instruments) within sound-attenuated, ventilated cubicles were used. Each chamber contained two response levers separated by a pellet delivery system through which 45 mg food pellets (Bioserv, dustless) were dispensed. Solid-state and computer-controlled programming and recording equipment was located in an adjacent

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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 ED₅₀ was calculated by the method of Litchfield and Wilcoxon.¹⁹

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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

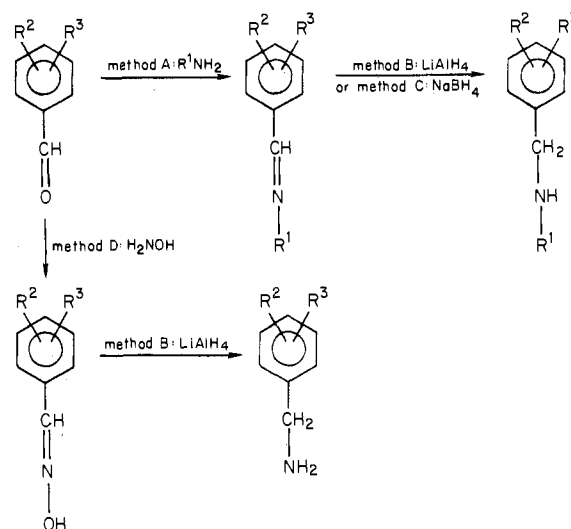
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The synthesis of benzylamines with various *N*-alkyl chains and substituents in the aromatic system as well as their evaluation on *Mycobacterium tuberculosis* H 37 Ra are described. The most active compounds in this test, *N*-methyl-3-chlorobenzylamine (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 aminosalicic 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),⁴⁰ or the transformation of the secondary amino group into a tertiary one¹ 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 benzylamines¹ (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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