1.6 mmol) in acetone (25 ml) with a solution of *d*-10-camphorsulfonic acid (0.37 g, 1.6 mmol) in acetone (25 ml) gave 0.7 g (91%) of **4a**·camsylate (crystals from acetone): mp 169–175°. Anal. ($C_{25}H_{38}N_2O_5S$) C, H, N, S. Treatment of a solution of **4b** (0.64 g, 2 mmol) in ethanol (5 ml) with 6 ml of an 0.6 *M* ethanolic solution of methanesulfonic acid furnished 0.72 g (80%) of **4b**·mesylate (white needles from ethanol): mp 117–118°. Anal. ($C_{18}H_{26}N_2O_2 \cdot 1.5CH_4O_3S$) C, H, N. Treatment of **4c** (0.33 g, 1.25 mmol) in acetone (20 ml) with a solution of anhydrous citric acid (0.24 g, 1.25 mmol) in acetone (20 ml), followed by crystallization of the resulting precipitate from acetone, yielded 0.535 g (95%) of **4c**·citrate (white crystals).

Administration of 4a–c. All pharmacologic tests were carried out using groups of ten Swiss–Webster Royal Hart male mice at each dose level, at doses of up to 300 mg/kg per group. The water soluble salts, prepared as described above, were administered po or ip as aqueous solutions (**4a,b**) and as a solution in 30% aqueous propylene glycol (**4c**).

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Adamantanamine Derivatives. Antimicrobial Activities of Certain Mannich Bases†

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A series of Mannich condensation products containing the β-(1-adamantylamino)propiophenone skeleton (type I) and the *o*-(1-adamantylaminomethyl)phenol skeleton (type II) was synthesized and tested for antimicrobial activity against certain bacteria and fungi by the agar diffusion and tube dilution methods. Type I compounds were more active than type II compounds and had a broad-spectrum effect on certain gram-negative and gram-positive bacteria, acid-fast bacteria, a yeast, and a mold.

Previous workers[1-3] have found that certain Mannich bases possessed in vitro antimicrobial activity. Chatten et al.[4] have shown that besides the difference in amine moieties, the substituents in phenyl ketones also exert an influence on activities. Also, Aldrich and workers[5] have reported the effect of structural variations of aminoadamantanes upon antiviral activity. These observations prompted the preparation and testing of the antimicrobial activity of substituted ketone and phenolic Mannich products containing 1-aminoadamantane as the amine moiety. The test organisms were chosen to represent the major types of organism associated with human disease, i.e., the gram-positive and gram-negative bacteria, the acid-fast bacteria, the yeasts, and the filamentous fungi.

Chemistry. Type I and type II Mannich products (Table I) were prepared by the standard Mannich reaction described in the Experimental Section. Compound **7**, which is not a Mannich base, was prepared by the condensation of 2-bromoacetophenone with 1-aminoadamantane.

The major difficulties encountered were poor yields, secondary condensations, and separation of products from unreacted materials, particularly the primary amine.

Microbiological Studies. The results of these studies are presented in Tables II and III as the averages of multiple determinations. The Me_2SO solvent controls did not produce any measurable inhibition of the test organisms. Replicate tests performed with a specific dilution of a test compound on any given day were in excellent agreement and results obtained with a specific dilution of

† This article is dedicated to Dr. Edward E. Smissman, who was an outstanding teacher and research scientist. His innovative philosophy regarding the teaching of medicinal chemistry and its research was given to posterity through his students, all of whom were close to him and loved him.

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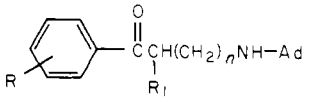
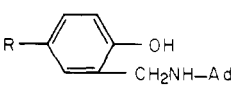
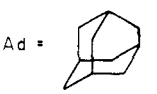
Table I. Mannich Condensation Products



type I, 1-8



type II, 9 and 10



No.	R	R_1	n	Mp,[a] °C	Yield,[b] %	Formula[c]	Crystn solvent	Analyses
1[d]	m-NO_2	H	1	188.5-189	22	$C_{19}H_{24}N_2O_3 \cdot HCl$	EtOH-hexane	C, H, N
2	p-F	H	1	196-197 (orange)	40	$C_{19}H_{24}FNO \cdot HCl$	$CHCl_3$-Me_2CO	C, H, N, F, Cl
3[e]	p-OH	H	1	232-233 (orange)	33	$C_{19}H_{25}NO_2 \cdot HCl$[f]	EtOH-hexane	C, H, N
4	m-Br	H	1	195-196	20	$C_{19}H_{24}BrNO \cdot HCl$	2-Propanol-hexane	H, N, Br, Cl; C[g]
5	p-NO_2	H	1	236-238[h]	36	$C_{19}H_{24}BrNO \cdot HCl$	MeOH-EtOAc	
6	p-Br	H	1	232-233	22	$C_{19}H_{24}BrNO \cdot HCl$	MeOH	C, H, N, Br, Cl
7[i]	H	H	0	259 dec	20	$C_{18}H_{23}NO \cdot HBr$	MeOH	C, H, N
8	H	CH_3	1	189-190[j]	24	$C_{20}H_{27}NO \cdot HCl$	MeOH-EtOAc	
9	C_6H_5			134.5-135	60	$C_{23}H_{27}NO$	2-Propanol	C, H, N
10	$C_6H_5N{=}N$-			187-188	30	$C_{23}H_{27}N_3O$	Diglyme	C, H, N

[a] Melting points were taken on a Hoover capillary melting point apparatus and are corrected. [b] Yields refer to purified compounds. [c] All compounds were anlyzed for C, H, N, and halogens where present. Analytical results obtained for these elements were within ±0.4% of calculated values unless otherwise indicated. [d] Difficult to isolate from the unreacted amine. Triturated in acetone before recrystallization. [e] Isolated from a tarry residue. [f] Water of crystallization (0.25 mol). [g] C: calcd, 57.19; found, 56.61. [h] Lit.[13] mp 233-235°; 82.4%. [i] Not a Mannich base. [j] Lit.[13] mp 188-189°; 52.4%.

any given compound on different days were generally in close agreement.

Infections caused by *Pseudomonas aeruginosa* are often difficult to treat chemotherapeutically because of the unusually high resistance of the organism to most antimicrobial drugs[6,7] and because resistance to other drugs may evolve rapidly.[7] Therefore, it was not surprising that this organism was unaffected by nearly all of the compounds studied, although it was slightly inhibited by compounds **5** and **6** at the highest concentrations studied. Similarly, *Aspergillus niger* was generally insensitive to these compounds but was inhibited most by compounds **5** and **6** and slightly by compounds **4** and **9**. Zones of inhibition of this organism were observed for several of the compounds early in the incubation period but the organism overgrew these areas within 48 hr.

In general, strain variation in sensitivity to these compounds was minimal for *Staphylococcus aureus* and *Escherichia coli* although strain 2 of *E. coli* was slightly more sensitive than the other two strains. Zones of inhibition of this strain comparable to those of strains 1 and 3 were observed at lower concentrations of the compounds or larger zones of strain 2 were observed if the same concentration was used for all strains (Table II).

The organisms most sensitive to these compounds were *S. aureus* and the *Mycobacterium* spp. and, in general, the gram-positive bacteria were more sensitive to these compounds than the gram-negative bacteria, the yeast, or the mold.

Because of the limited number of type II compounds and the low solubility of compound **10**, it is difficult to make meaningful comparisons, but, in general, type I compounds appeared to be much more effective in inhibiting the growth of these organisms than type II compounds. A notable exception is shown by the fact that compound **9** was the most effective compound against *Mycobacterium phlei* and *Mycobacterium smegmatis*.

Type I compounds appeared to have broad-spectrum effect on gram-negative and gram-positive bacteria, acid-fast bacteria, a yeast, and a mold, although the degree of inhibition varied.

The introduction of a methyl group in the α position to the carbonyl resulted in a decrease in activity as noted in compound **8** (Table II). Other workers have reported similar results.[4]

There was a general agreement between data obtained by the agar diffusion method and the tube dilution method. However, the p-NO_2-substituted compound was less effective against *M. smegmatis* in the tube dilution assay. Perhaps this was due to the Me_2SO carrier solvent, which was diluted in the tube dilution assay but was held constant in the agar diffusion method. The presence of a higher Me_2SO concentration might enhance penetration of the compound into the cell. Compound **9** was also tested by tube dilution against *M. smegmatis* and was shown to be the most effective compound tested against this organism.

For those functional groups which had an adverse effect on the biological activity of these Mannich bases, it is tempting to incriminate steric effects, which could prevent these compounds from interacting with the receptor of the test organisms. However, the difference in potency ascribed to substituents at the various positions in the benzene ring may be due to physicochemical properties.[8]

Experimental Section

Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are corrected. Microanalyses were within ±0.4% of the theoretical values as performed by Midwest Microlab, Ltd., Indianapolis, Ind. 46226. Yields are based on pure compounds. Structures were characterized by ir and ^1H NMR spectra. Ir spectra were measured as KBr disks on a Beckman IR-20-A spectrophotometer. ^1H NMR spectra were performed on a Varian Associates T-60 spectrometer in either Me_2SO-d_6 or $CDCl_3$ with Me_4Si as an internal standard. All spectra were consistent with the assigned structures.

General Procedures. Synthesis of Mannich Bases Using Aryl Alkyl Ketone.[9] The appropriate ketone (0.05 mol), adamantanamine hydrochloride (0.05 mol), 37% formalin (0.07 mol), 1–2 ml of hydrochloric acid, and 4–8 ml of water were placed in a side-arm flask. The vessel was fitted with a reflux condenser, magnetic stirring bar, and side-arm stopper. The flask and contents were heated with stirring by partial immersion into an oil bath maintained at 100°. After heating under reflux for 4–17 hr the excess water was removed by aspiration through the side arm. The residue was placed in hot chloroform and the crystalline product was filtered, washed, and recrystallized from the appropriate solvent.

Synthesis of Mannich Bases Using Phenolic Derivatives.[10] To a mixture of the phenolic derivative (0.023 mol) and 37% formalin (0.025 mol) in ethanol was added adamantanamine (0.025 mol) which was heated under reflux for 4 hr. The solvent was removed in a rotating flash evaporator and the crude product was purified by recrystallization.

Preparation of Compound 7. A mixture of 2-bromoacetophenone (0.02 mol), adamantanamine (0.02 mol), and absolute ethanol was heated under reflux for 1 hr and the solvent was

Table II. Antimicrobial Activity of Certain Mannich Bases

Compd no.	Zone of inhibition, mm (concn, mg/0.1 ml)[a]									
	E. coli			*S. aureus*		*P. aeruginosa*	*M. phlei*	*M. smegmatis*	*A. niger*	*C. albicans*
	1	2	3	4	5	6	7	8	9	10
1	16.3 (2.0)	15.5 (1.0)	16.8 (2.0)	15.4 (0.1)	15.7 (0.1)	(4.0)	19.1 (0.5)	16.6 (0.5)	(2.0)	16.2 (2.0)
2	16.7 (1.0)	17.6 (0.5)	16.5 (1.0)	19.1 (1.0)	16.6 (1.0)	(4.0)	17.7 (0.5)	15.3 (0.5)	(4.0)	16.6 (0.5)
3	16.0 (2.0)	17.2 (2.0)	16.0 (2.0)	15.6 (0.5)	15.3 (0.5)	(4.0)	16.3 (0.5)	19.0 (1.0)	(4.0)	15.4 (4.0)
4	18.2 (1.0)	17.5 (0.5)	17.4 (1.0)	18.7 (0.1)	17.5 (0.1)	(4.0)	20.0 (0.25)	17.6 (0.25)	16.8 (4.0)	15.3 (0.1)
5	16.5 (2.0)	16.5 (1.0)	15.3 (1.0)	16.0 (0.1)	15.8 (0.1)	<14 (4.0)	19.4 (0.25)	17.4 (0.25)	15.2 (2.0)	16.4 (0.5)
6	17.8 (0.5)	15.6 (0.1)	15.3 (0.25)	16.6 (0.05)	17.0 (0.05)	<15 (4.0)	19.2 (0.25)	17.0 (0.25)	19.0 (2.0)	15.1 (0.1)
8	16.1 (2.0)	17.2 (2.0)	16.4 (2.0)	16.2 (2.0)	16.3 (2.0)	(4.0)	17.3 (0.5)	17.0 (0.5)	(4.0)	<15 (4.0)
9	15.6 (4.0)	15.1 (2.0)	15.0 (2.0)	17.3 (0.25)	16.8 (0.25)	(4.0)	18.9 (0.1)	18.7 (0.1)	<15 (4.0)	15.8 (2.0)
10	(0.5)	<15 (0.5)	(0.5)	<15 (0.25)	15.4 (0.25)	(0.5)	<15 (0.5)	15.5 (0.5)	(0.25)	<15 (0.5)

[a] Figures in parentheses represent lowest concentration producing a clear zone of inhibition 15 mm in diameter or larger or the highest concentration producing a zone of 15 mm or less.

Table III

Compd	MIC, μg/ml		
	E. coli	*S. aureus*	*M. smegmatis*
2	1000	500	250
4	500	125	125
5	500	125	500
6	500	125	125
9	*a*	*a*	62.5

[a] Not tested.

removed in a rotating evaporator. The crude reaction product was placed in MeOH–Et_2O and the crystalline material was filtered and purified by recrystallization.

Microbiological Assays. The following strains of microorganisms were used to study the antimicrobial activities of the compounds: *Escherichia coli* (ATCC 8739), *E. coli* (ATCC 11303), *E. coli* (ATCC 10586), *Staphylococcus aureus* (ATCC 10001), *S. aureus* (ATCC 10014), *Pseudomonas aeruginosa* (OU 10048), *Mycobacterium phlei* (ATCC 356), *M. smegmatis* (OU 10049), *Candida albicans* (CDC MI-023), *Aspergillus niger* (OU S-23).

C. albicans and *A. niger* were maintained on Sabouraud's dextrose agar (SDA) and *Mycobacterium* spp. were maintained on *Mycobacterium* defined test medium agar (MDTM).[11] All other organisms were maintained on nutrient agar (Difco). The organisms were transferred at weekly intervals on the appropriate media and stock cultures stored at 4°.

The compounds were tested by the quantitative method of Chatten et al.[4] using Schleicher and Schuell antibiotic disks (12.7 mm diameter), except that SDA and MDTM were used for *A. niger*, *C. albicans*, and the *Mycobacterium* spp., respectively.

Stock solutions of each compound were prepared in dimethyl sulfoxide (Me_2SO) and used for testing directly or after dilution with Me_2SO. A volume of 0.1 ml of solution was added per disk, and the disks were allowed to stand 30 min on a wire mesh screen before applying to the seeded agar plates (four disks per plate). In preliminary experiments, each compound was tested in the highest concentration possible in Me_2SO (usually 2–4 mg/0.1 ml). Me_2SO was used because of the poor solubility of the compounds in water or other common laboratory solvents. In the case of compound **10**, the highest concentration tested was 50 μg/0.1 ml because of its limited solubility in Me_2SO. Compound 7 was not tested because it is insoluble in Me_2SO.

Those compounds producing definite zones of inhibition in preliminary tests were diluted for quantitative tests. Two to four replicate samples of each dilution were tested in each experiment and at least two complete experiments were done on separate days with stock solutions prepared the same day.

The plates were incubated at 37° for 24 hr (48 hr for the *Mycobacterium* spp. and for *A. niger*). Zones of inhibition were measured to the nearest 0.1 mm with calipers. Replicate samples and results from experiments run on different days were generally in close agreement, and the results were averaged.

Minimum inhibitory concentrations (MIC) were determined by the tube dilution method.[12] In the case *M. smegmatis*, separate determinations were made in MDTM broth and agar because of the growth characteristics peculiar to this organism.

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2,3-Dihydroxyphenethanolamine as an Adrenergic Agent†

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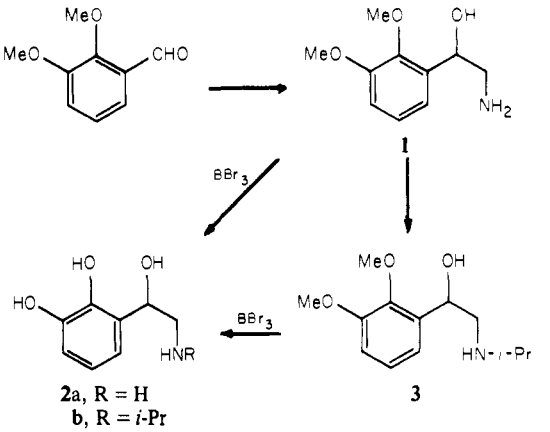
In an attempt to further define the role of the *m*-hydroxy group in adrenergic agents, 2,3-dihydroxyphenethanolamine hydrobromide and *N*-isopropyl-2,3-dihydroxyphenethanolamine hydrobromide were prepared. These agents are less active than norepinephrine in α- and β-adrenergic in vitro tests. The synthesis and conclusions from the tests are discussed.

Numerous aromatic-substituted phenethylamines have been tested for adrenergic activity; however, the demonstrated dopaminergic activity of some phenethylamines[1] makes reexamination of aromatic substitution patterns in phenethanolamines of interest. To this end, a study of the previously unreported 2,3-dihydroxyphenethanolamines **2a,b** was undertaken. These compounds, like norepinephrine, are catechols and are capable of chelating divalent metal ions (considered important in interactions with the adrenergic receptor[2] and in storage at presynaptic sites[3]). Work with alkylsulfonamide substituents on the benzene ring of phenylethanolamines has been interpreted by Larsen and co-workers[4] as indicating the importance of an acidic group at the 3 position of the ring. Consistent with Larsen's proposal, 3,5-dihydroxyisoproterenol is a direct-acting β-adrenergic agonist.[5] Its ability to chelate metal ions has not been reported. The work of Rosen et al.[6] on frog erythrocytes supports the importance of the 3-hydroxy group for β-adrenergic agents. Kappe and Armstrong[7] determined that the first proton in a catechol is more acidic than in a simple phenol, suggesting that a hydroxy group in the 2 position of **2a,b** may simultaneously increase the activity and acidity of a 3-hydroxy-substituted compound.

Buck[8] reported a low-yield (5%) synthesis of 2,3-dimethoxyphenethanolamine (1) but did not describe its *O*-demethylation. The treatment of 2,3-dimethoxybenzaldehyde with trimethylsilyl cyanide (using the procedure of Evans and coworkers[9]) followed by reduction with $LiAlH_4$ afforded an improved yield (57%) of 1. Demethylation of 1 and 3 with BBr_3 to yield **2a,b**, respectively, was more satisfactory than reaction with HBr.

Standard procedures on three animals using isolated rat vas deferens preparations and blood pressure were employed in testing for adrenergic agonist activity.[10] Compound **2a** had a slow onset of action and was $^1/_{80}$th as potent as *l*-norepinephrine (13 μg/ml of **2a** was equipotent with 0.165 μg/ml of *l*-norepinephrine) in the vas deferens preparations. Treatment of the tissue with *l*-norepinephrine potentiated the contraction. Compound **2b** produced a decrease in blood pressure but was $^1/_{800}$th as potent as *dl*-isoproterenol (120 mg/kg of **2b** was equipotent with 0.150 mg/kg of *dl*-isoproterenol). Compound **2a** produced an increase in blood pressure but was $^1/_{100}$th as potent as *l*-norepinephrine (100 mg/kg of **2a** was equipotent with 1 mg/kg of *l*-norepinephrine).

Scheme I



When compound **2a** was tested at 1.0 m*M* concentration as a substrate for catechol *O*-methyltransferase by the procedure of Nikodejevic,[11] less than 5% methylation was detected. A tenfold excess of **2a** inhibited methylation of *l*-norepinephrine by about 25%.

It is tempting to rationalize the absence of direct adrenergic activity of **2a** in terms of two proposed models[2] for the adrenergic receptor. Chelation of a divalent metal ion has been suggested as important in adrenergic agonist–receptor interactions. However, lack of information about the microenvironment of the receptor makes quantitative measurement of agonist–metal association difficult to interpret. Chelation between catecholamines and magnesium in aqueous solution is difficult to demonstrate, even at a pH greater than 9;[3] yet, in *N,N*-dimethyllaurylamide (simulating a lipid environment) chelation can be detected.[12]

Using the spectrophotometric assay of Jameson[13] the data in Figure 1 indicate that **2a** can form a complex with Cu^{2+} similar to catechol and norepinephrine. This is an indication that 2,3-dihydroxyphenethanolamines are able to participate in chelation if it is necessary for adrenergic

† Dedicated to Dr. Edward E. Smissman who was chairman of this Department from 1960 to July 1974.