nofuranosyl)adenine, identical in all respects to the sample previously described.[2]

Supplementary Material Available: Table IV containing ^{1}H NMR spectral data for 2′- and 3′-*O*-acyl and 2′,3′- and 3′,5′-di-*O*-acyl compounds (1 page). Ordering information is given on any current masthead page.

References and Notes

(1) (a) For a preliminary account, see D. Baker, T. H. Haskell, and S. R. Putt, "Abstracts of Papers", 174th National Meeting of The American Chemical Society, Chicago, Ill., Aug., 1977, MEDI-27. The compounds herein are described in the following patents: D. C. Baker, U.S. Patents 4048432 and 4055718; D. C. Baker and T. H. Haskell, U.S. Patent 4055717. (b) To whom correspondence should be addressed at the Department of Chemistry, The University of Alabama, University, Alabama 35486.
(2) D. C. Baker, T. H. Haskell, and S. R. Putt, *J. Med. Chem.*, **21**, 1218 (1978).
(3) (a) The aqueous solubility for 1 is 0.4 mg/mL of the nucleoside hydrate, corresponding to a concentration of 1.4 μmol/mL; (b) J. D. Connor, L. Sweetman, S. Corey, M. S. Stuckey, and R. A. Buchanan, in "Adenine Arabinoside, An Antiviral Agent", D. Pavan-Langston, R. A. Buchanan, and C. A. Alford, Eds., Raven Press, New York, N.Y., 1975, pp 177-196.
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(8) D. C. Baker and T. H. Haskell, *J. Med. Chem.*, **18**, 1041 (1975).
(9) E. J. Corey and A. Venkateswarlu, *J. Am. Chem. Soc.*, **76**, 1030 (1972).
(10) (a) K. K. Ogilvie, *Can. J. Chem.*, **52**, 3799 (1974); (b) E. Volkin and W. E. Cohn, *Methods Biochem. Anal.*, 1, 304 (1954).
(11) G. H. Dodd, B. T. Golding, and P. V. Ioannou, *J. Chem. Soc., Perkin Trans. 1*, 2273 (1976).
(12) J. Nuesch and H. Bickel, U.S. Patent 3304236 (1976).
(13) The aqueous solubility of 9-(2,3,5-tri-*O*-acetyl-β-D-arabinofuranosyl)adenine is 3.5 mg/mL (8.9 μmol/mL) at pH 7; the 2′,3′,5′-tri-*O*-propionyl analogue falls to 0.23 mg/mL (0.60 μmol/mL).
(14) H. M. Kalckar, *J. Biol. Chem.*, **167**, 461 (1947).
(15) Interestingly, it is to be pointed out that the in vitro antiviral activities (see Table II) for the 3′-*O*-monoacyl analogues **6a–c** were found to be quite high, even for the branched-chain example **6c** whose di-*O*-acyl counterparts **4c** and **5c** were inactive.
(16) B. Lukas, W. Wiesenda, and K. H. Schonidir, *Arch. Gesamte Virusforsch.*, 44, 153 (1974).
(17) J. J. Furth and S. S. Cohen, *Cancer Res.*, **27**, 1528 (1967).
(18) B. J. Sloan, unpublished data.
(19) Details are available upon request from the author.
(20) Tetrabutylammonium fluoride is conveniently prepared by neutralization of 0.1 M tetrabutylammonium hydroxide at 0 °C with concentrated hydrofluoric acid, followed by lyophilization to give a white, flaky solid that may be stored up to a few hours in vacuo.

New Bronchodilators. Synthesis and Bronchodilating Activity of Some 3-(Alkoxymethyl)-α-(N-substituted aminomethyl)-4-hydroxybenzyl Alcohols

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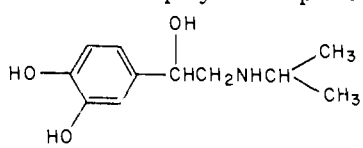
A series of 3-(alkoxymethyl)-α-(N-substituted aminomethyl)-4-hydroxybenzyl alcohols was synthesized as potential bronchodilators. The ability to prevent effects against histamine-induced bronchoconstriction in guinea pigs was studied to determine their bronchodilating activity. Introduction of a methoxymethyl group in place of the *m*-hydroxyl group of β-adrenergic catecholamines afforded compounds especially effective in delaying histamine-induced bronchoconstriction in guinea pigs. Appropriate N-substitution also enhanced the potency of these catecholamine analogues. 4-Hydroxy-3-(methoxymethyl)-α-[*N*-[4-(methoxymethyl)-α-methylphenyl]aminoethyl]benzyl alcohol hemifumarate (**3r**) was the most potent compound in this series.

β-Adrenergic receptors are classified into two types, β_1 and β_2.[1-3] The β_1 receptors mediate stimulation of cardiac muscle, relaxation of intestinal muscle, and glycogenolysis, while β_2 receptors mediate relaxation of bronchial, vascular, and uterine muscle and lipolysis. Isoproterenol (1) is a



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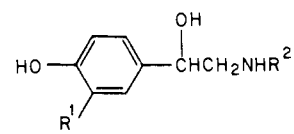
potent β-adrenergic stimulant which is widely used clinically as a bronchodilator in respiratory disorders. However, 1 stimulates both β_1 and β_2 receptors, and clinical application of 1 frequently causes adverse reactions such as palpitation, tachycardia, cardiac necrosis, and tremor. In addition, 1 has disadvantages of being short acting and low in activity by oral application owing to rapid conversion to ineffective metabolites,[4-7] *O*-sulfate and *m*-OMe derivatives. Numerous attempts have been made for structural modification of 1 to separate the bronchodilating effect from these side effects. The compounds **2a–d** in



2a,[8] $R^1 = CH_2OH$; $R^2 = t$-Bu
b,[9] $R^1 = NHSO_2Me$; $R^2 = i$-Pr
c,[10] $R^1 = NHCONH_2$; $R^2 = t$-Bu
d,[11] $R^1 = CH_2SO_2Me$; $R^2 = t$-Bu

which the *m*-phenolic OH was replaced with various substituents were reported[8-11] as improved bronchodilators with bronchial selectivity and oral activity.

In order to investigate the effect of introducing more lipophilic moieties into the meta position for bronchodilating activity, we prepared a series of 3-(alkoxymethyl)-α-(*N*-alkylaminomethyl)-4-hydroxybenzyl alcohols (**3a-i**) in which the meta substituents of 1 and **2a–d** were replaced by alkoxymethyl groups and examined their

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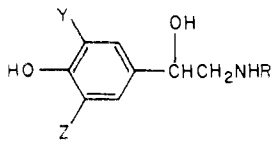
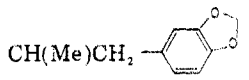


3, Y, Z = H, CH_2OMe, CH_2OEt, $CH_2O(CH_2)_2OMe$, $CH_2O(CH_2)_2OEt$, $CH_2O(CH_2)_2OH$
R = *i*-Pr, *t*-Bu, $C(Me)_2CH_2C_6H_5$, $CH(Me)CH_2C_6H_5$, $CH(Me)CH_2C_6H_4OH$, $CH(Me)CH_2C_6H_4OMe$,



activity. It was proved by the screening test that methoxymethyl and ethoxymethyl groups have a favorable property as the meta substituent. Several *N*-aralkyl analogues (**3l-r**) bearing a methoxymethyl or ethoxymethyl group at the meta position were prepared, and the effect of the *N*-aralkyl group on the activity was investigated.

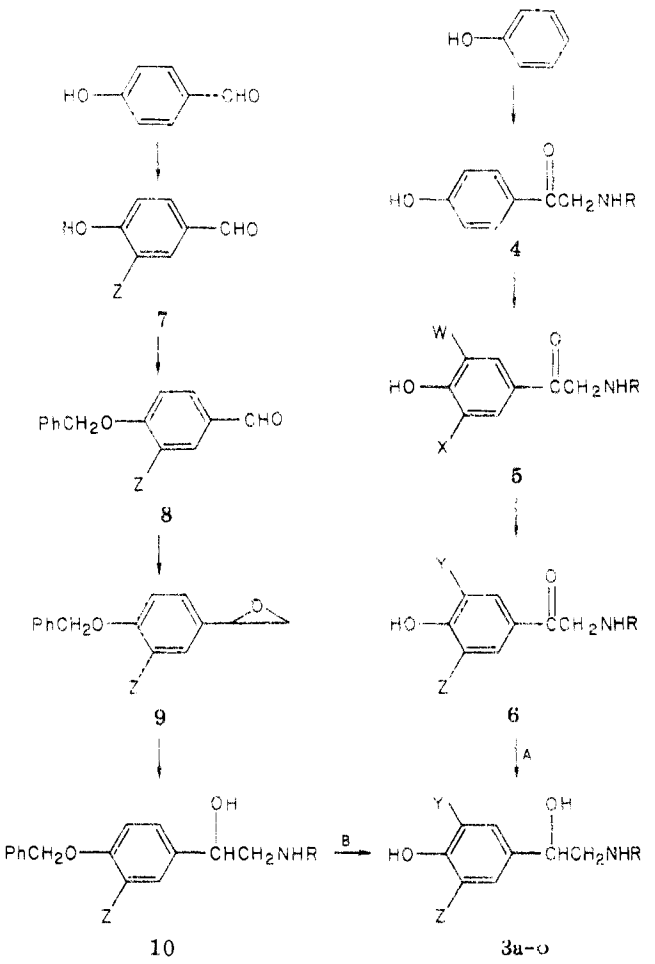
4-Hydroxy-3-(methoxymethyl)-α-[*N*-[4-(methoxymethyl)-α-methylphenethyl]aminomethyl]benzyl alcohol, which exhibited the most potent activity, was separated into the diastereoisomers **3r** and **3s**. Further, **3r** was resolved into its (-) and (+) enantiomers (*l*-**3r** and *d*-**3r**). Broncholytic potency of these isomers was investigated.

Chemistry. The compounds **3a-o** were prepared according to the procedure outlined in Scheme I. 2-(N-Substituted amino)-4-hydroxyacetophenones **4a-d** (Table I) were prepared by the modified Hoesch reaction[12] in moderate yields from phenol with the corresponding N-substituted glycinonitrile in the presence of anhydrous $AlCl_3$ and HCl in nitrobenzene. Chloromethylation of **4a-d** with equimolar formaldehyde and HCl gave 2-(*N*-substituted amino)-3′-(chloromethyl)-4′-hydroxyacetophenones **5a,b,e,f**. The reaction of **4a,b** with an excess of chloromethylating reagent gave the 3′,5′-bis(chloromethyl) analogues **5c,d** (Table II). 3′-(Chloromethyl) and 3′,5′-bis(chloromethyl) analogues **5** were converted to the corresponding 3′-(alkoxymethyl) derivatives **6** (Table III) by heating with various alcohols. The products **6a-o** were reduced to the desired products, 3-(alkoxymethyl)-α-(N-substituted aminomethyl)-4-hydroxybenzyl alcohols **3a-o** (Table IV), by catalytic hydrogenation (method A).

4-Hydroxy-3-(methoxymethyl)benzaldehyde (**7**) was prepared from 4-hydroxybenzaldehyde via the 3-(chloromethyl) derivative by the conventional method. Benzylation of **7** afforded 4-(benzyloxy)-3-(methoxymethyl)-benzaldehyde (**8**). The resulting **8** upon treatment with dimethylsulfonium methylide[13] in dimethylformamide gave 4-(benzyloxy)-3-(methoxymethyl)phenylethylene oxide (**9**). Reaction of the epoxide **9** with *tert*-butylamine gave 4-(benzyloxy)-α-(*tert*-butylaminomethyl)-3-(methoxymethyl)benzyl alcohol (**10**). The amine **10** showed two spots having close R_f values on TLC (SiO_2,$CHCl_3$). It is well known that the reaction of styrene oxide with a nucleophile gives a mixture of two products as a result of nonselective attack of the nucleophile on either the α- or β-carbon atom.[14] Thus, it appears that the treatment of **9** with *tert*-butylamine gave a mixture of the desired α-aminomethylbenzyl alcohol derivative **10** and the kinetically less favored isomer (β-aminophenethyl alcohol derivative). The NMR spectrum of the mixture showed a pair of singlets at δ 1.10 and 1.05 (the combined signals integrated for nine protons in an approximate 2:1 ratio), suggesting the presence of two types of *tert*-butyl groups in a different environment. Since attempts to separate these components by column chromatography were unsuccessful, the mixture was converted into the maleate to obtain pure **10** by fractional crystallization. Free amine **10** liberated from the maleate was debenzylated by catalytic hydrogenation to give α-aminomethylbenzyl alcohol derivative **3e** (method B). The melting point was undepressed on admixture with a sample (**3e**) prepared by method A. The NMR and IR spectra were compatible with the structure.

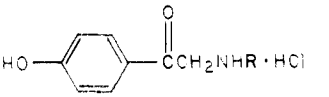
The compounds **3p-r** (Table IV) were prepared according to Scheme II. 4-Hydroxyacetophenone was

Scheme I



R = *i*-Pr, *t*-Bu, $CH(Me)CH_2C_6H_5$, $C(Me)_2CH_2C_6H_5$
W, X = H, CH_2Cl
Y, Z = H, CH_2OMe, CH_2OEt, $CH_2O(CH_2)_2OMe$, $CH_2O(CH_2)_2OEt$, $CH_2O(CH_2)_2OH$

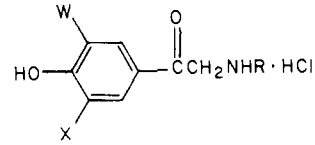
Table I. 2-(N-Substituted amino)-4-hydroxyacetophenone Hydrochlorides



compd	R	mp, °C	yield, %	recrystn solvent[a]	formula[b,c]
4a	*i*-Pr	263 dec	42	E	$C_{11}H_{15}NO_3$
4b	*t*-Bu	253-255	63	A + E	$C_{12}H_{17}NO_3$
4c	CH(Me)-CH_2Ph	224 dec	37	M	$C_{18}H_{19}NO_3$
4d	$C(Me)_2$-CH_2Ph	225-227	52	E	$C_{19}H_{21}NO_3$

[a] Abbreviations used are: A, acetone; E, ethanol; M, methanol. [b] HCl salt. [c] Anal. C, H, N.

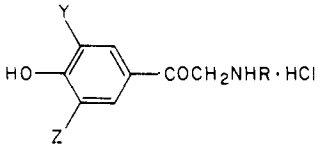
Table II. 2-(N-Substituted amino)-3′(5′)-(chloromethyl)-4′-hydroxyacetophenone Hydrochlorides



compd	R	W	X	mp, °C[a]	yield, %	formula[b,c]
5a	*i*-Pr	H	CH_2Cl	230 dec	77	$C_{12}H_{16}ClNO_2$
5b	*t*-Bu	H	CH_2Cl	>300	59	$C_{13}H_{18}ClNO_2$
5c	*i*-Pr	CH_2Cl	CH_2Cl	>300	86	$C_{13}H_{17}Cl_2NO_2$
5d	*t*-Bu	CH_2Cl	CH_2Cl	>300	75	$C_{14}H_{19}Cl_2NO_2$
5e	$CH(Me)CH_2Ph$	H	CH_2Cl	230 dec	73	$C_{18}H_{20}ClNO_2$
5f	$C(Me)_2CH_2Ph$	H	CH_2Cl	226 dec	62	$C_{19}H_{22}ClNO_2$

[a] Colorless crystalline powder recrystallized from methanol–hexane. [b] HCl salt. [c] Anal. C, H, N.

Table III. 2-(N-Substituted amino)-3′(5′)-(alkoxymethyl)-4′-hydroxyacetophenone Hydrochlorides



compd	R	Y	Z	mp, °C	yield, %	recrystn solvent[a]	formula[b,c]
6a	*i*-Pr	H	CH_2OMe	198 dec	69	M + S	$C_{13}H_{19}NO_3$
6b	*i*-Pr	H	CH_2OEt	131-132	94	M + S	$C_{14}H_{21}NO_3$
6c	*i*-Pr	H	$CH_2O(CH_2)_2OMe$	105-107	67	M + S	$C_{15}H_{23}NO_4$
6d	*i*-Pr	H	$CH_2O(CH_2)_2OEt$	101-104	36	E + S	$C_{16}H_{25}NO_4$
6e	*t*-Bu	H	CH_2OMe	>280	67	E + S	$C_{14}H_{21}NO_3$
6f	*t*-Bu	H	CH_2OEt	170-171	65	E + S	$C_{15}H_{23}NO_3$
6g	*t*-Bu	H	$CH_2O(CH_2)_2OMe$	155-156	76	M + S	$C_{16}H_{25}NO_4$
6h	*t*-Bu	H	$CH_2O(CH_2)_2OEt$	177-178	74	E + S	$C_{17}H_{27}NO_4$
6i	*t*-Bu	H	$CH_2O(CH_2)_2OH$	183-185	52	E + S	$C_{15}H_{23}NO_4$
6j	*i*-Pr	CH_2OMe	CH_2OMe	149 dec	37	M + S	$C_{15}H_{23}NO_4$
6k	*t*-Bu	CH_2OMe	CH_2OMe	200 dec	28	E + A	$C_{16}H_{25}NO_4$
6l	$CH(Me)CH_2Ph$	H	CH_2OMe	201 dec	54	M + S	$C_{19}H_{23}NO_3$
6m	$CH(Me)CH_2Ph$	H	CH_2OEt	176 dec	54	M + S	$C_{20}H_{25}NO_3$
6n	$C(Me)_2CH_2Ph$	H	CH_2OMe	203 dec	92	M + S	$C_{20}H_{25}NO_3$
6o	$C(Me)_2CH_2Ph$	H	CH_2OEt	178 dec	80	M + S	$C_{21}H_{27}NO_3$

[a] Abbreviations used are: A, acetone; E, ethanol; M, methanol; S, ethyl acetate. [b] HCl salt. [c] Anal. C, H, N.

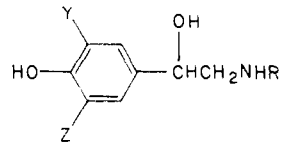
converted to 4-hydroxy-3-(methoxymethyl)acetophenone (**11**) via the 3-(chloromethyl) derivative[15] by a conventional method. Acetylation of **11** afforded the 4′-acetoxy derivative, which was brominated with bromine to give 2-bromo-4′-hydroxy-3′-(methoxymethyl)acetophenone (**13**). Treatment of **13** with 1-aryl-2-(*N*-benzylamino)propanes gave the corresponding amino ketones **14a–c**, which were hydrolyzed to 2-[*N*-benzyl-*N*-(α-methylarylethyl)-amino]-4′-hydroxy-3′-(methoxymethyl)acetophenones **15a–c** under mild acidic conditions. The compounds **15a–c** were reduced by catalytic hydrogenation to give the desired amino alcohols **3p–r** (method C). These compounds **3p–r** and **3l,m** have two asymmetric centers; therefore, they consist of two racemates (two pairs of enantiomers). Each compound **3p–r,l,m** was one of the two racemates, but the other racemate could not be isolated in the procedure described above. Another synthetic route for **3r** was investigated for the purpose of obtaining both diastereoisomers. The intermediate **11** was benzylated followed by bromination to give 4′-(benzyloxy)-2-bromo-3′-(methoxymethyl)acetophenone (**17**). Treatment of **17** with 2-(*N*-benzylamino)-1-(4-methoxyphenyl)propane gave the amino ketone **18**. The resulting amino ketone **18** was reduced with $NaBH_4$ to give the amino alcohol **19**, which showed two spots on TLC in an approximate 3:2 ratio. Since the compound **19** was presumed to be a mixture of diastereoisomers, an attempt was made to separate the two isomers **19a** and **19b** by selective crystallization. The hemifumarate of one of the isomers, **19a**, was obtained as crystals from a solution of the isomeric mixture **19** and fumaric acid, while the other isomer, **19b**, was obtained from the filtrate by conversion into the hydrochloride. The free amine **19b** was debenzylated by catalytic hydrogenation to give **3r**, which was identified by comparing its spectra (IR and NMR) and melting point with that of authentic **3r** prepared by method C. The free amine **19a** was hydrogenated to give **3s** (diastereoisomer of **3r**) in a similar manner as above.

Resolution of the racemate **3r** was examined. The free amine **3r** was treated with dibenzoyl-*d*-tartaric acid, and the resulting hemidibenzoyl *d*-tartrate was recrystallized to constant rotation. The resolved amine which was liberated from the salt was converted to the hydrochloride to give *d*-**3r**, while the levo isomer *l*-**3r** was obtained from the filtrate.

Results and Discussion

Bronchodilating activity was initially determined by protecting effect on the asthma-like syndromes in guinea pigs induced by a histamine moisture. Table V summarizes the activity of 17 compounds prepared in this study, in comparison with those of isoproterenol (**1**) and salbutamol (**2a**). In control animals, anoxia generally occurred within 5 min of histamine exposure, followed by

Table IV. 3-(Alkoxymethyl)-α-(N-substituted aminomethyl)-4-hydroxybenzyl Alcohols



compd	R	Y	Z	mp, °C	yield, %	recrystn solvent[a]	formula[b,c]	method
3a	*i*-Pr	H	CH_2OMe	159–160	82	M + S	$C_{13}H_{21}NO_3$	A
3b	*i*-Pr	H	CH_2OEt	138–139	78	M + S	$C_{14}H_{23}NO_3$	A
3c	*i*-Pr	H	$CH_2O(CH_2)_2OMe$	122–123	64	M + S	$C_{15}H_{25}NO_4$	A
3d	*i*-Pr	H	$CH_2O(CH_2)_2OEt$	118–119	69	M + S	$C_{16}H_{27}NO_4$	A
3e	*t*-Bu	H	CH_2OMe	202–203	76	E	$C_{14}H_{23}NO_3$	A
3f	*t*-Bu	H	CH_2OEt	188–189	67	E + S	$C_{15}H_{25}NO_3$	A
3g	*t*-Bu	H	$CH_2O(CH_2)_2OMe$	151–152	78	M + S	$C_{16}H_{27}NO_4$	A
3h	*t*-Bu	H	$CH_2O(CH_2)_2OEt$	161–162	75	E + S	$C_{17}H_{29}NO_4$	A
3i	*t*-Bu	H	$CH_2O(CH_2)_2OH$	136–137	61	M + S	$C_{15}H_{25}NO_4$	A
3j	*i*-Pr	CH_2OMe	CH_2OMe	144–146	88	M + S	$C_{15}H_{25}NO_4$	A
3k	*t*-Bu	CH_2OMe	CH_2OMe	146–147	79	M + S	$C_{16}H_{27}NO_4$	A
3l	$CH(Me)CH_2Ph$	H	CH_2OMe	163–164	41	M + S	$C_{19}H_{25}NO_3$	A
3m	$CH(Me)CH_2Ph$	H	CH_2OEt	168 dec	46	M + S	$C_{20}H_{27}NO_3$	A
3n	$C(Me)_2CH_2Ph$	H	CH_2OMe	184–186	85	M + S	$C_{20}H_{27}NO_3$	A
3o	$C(Me)_2CH_2Ph$	H	CH_2OEt	160–161	73	M + S	$C_{21}H_{29}NO_3$	A
3p	$CH(Me)CH_2C_6H_3$-3,4-OCH_2O	H	CH_2OMe	203 dec	38	E	$C_{20}H_{25}NO_5$[d]	C
3q	$CH(Me)CH_2C_6H_4$-4-OH	H	CH_2OMe	158–160	39	E	$C_{19}H_{25}NO_4$[d]	C
3r	$CH(Me)CH_2C_6H_4$-4-OMe	H	CH_2OMe	168–170	79	M	$C_{20}H_{27}NO_4$[e]	D
3s	$CH(Me)CH_2C_6H_4$-4-OMe	H	CH_2OMe	125–126	84	M	$C_{20}H_{27}NO_4$[e]	D
d-3r	$CH(Me)CH_2C_6H_4$-4-OMe	H	CH_2OMe	130.5–131		A	$C_{20}H_{27}NO_4$	
l-3r	$CH(Me)CH_2C_6H_4$-4-OMe	H	CH_2OMe	130.5–131.5		A	$C_{20}H_{27}NO_4$	

[a] Abbreviations used are: A, acetone; E, ethanol; M, methanol; S, ethyl acetate. [b] HCl salt unless otherwise indicated. [c] Anal. C, H, N. [d] Hemioxalate. [e] Hemifumarate.

Table V. Bronchodilating Activity (Inhibitory Effect on Histamine-Induced Asthma-like Syndromes in Guinea Pigs)

	onset time of asthma-like syndrome,[a] min.			
	anoxia: dose, mg/kg (po)		cough: dose, mg/kg (po)	
compd	1.25	5.0	1.25	5.0
saline	5.08		6.13	
3a		10.38		15.25
3b		9.23		14.03
3c		8.80		9.70
3e	17.17		20.00	
3f	14.55		14.85	
3g	6.75	13.80	7.88	15.18
3h	10.58	8.97	11.81	14.08
3i		4.98		5.97
3j	10.71		11.00	
3k	7.35		7.78	
3l		9.61		11.65
3m		12.57		13.92
3n		11.35		11.83
3o		15.98		16.08
3p	10.43		12.05	
3q	19.97		20.00	
3r	19.10		20.00	
isoproterenol	6.82	12.71	8.02	17.67
salbutamol	8.10	17.22	9.68	19.13

[a] Five animals were employed for each dose level.

cough response 1 or 2 min later. Most of the compounds tested were effective in delaying these toxic signs. Among the new compounds, **3r** and **3q** were the most active, and they were more potent than **1** or **2a**.

Next, the ED_{50} value of **3r**, which was one of the most active compounds in this series, was determined by inhibitory effect on the histamine-induced increase in airway resistance. The compound **3r**, in a dose range of 1–10 μg/kg, dependently inhibited the increase in airway resistance, and the ED_{50} value (ip) of **3r** was 2.75 μg/kg. Relative potency of **3r** and its isomers was estimated by means of the parallel line assay.[16] The data are summarized in Table VI. The levo-isomer *l*-**3r** was approximately twice and the diastereoisomer **3s** was one-third times as potent as **3r**, respectively. On the other hand, the dextro isomer *d*-**3r** did not show the activity at a high dose of 1–3 mg/kg.

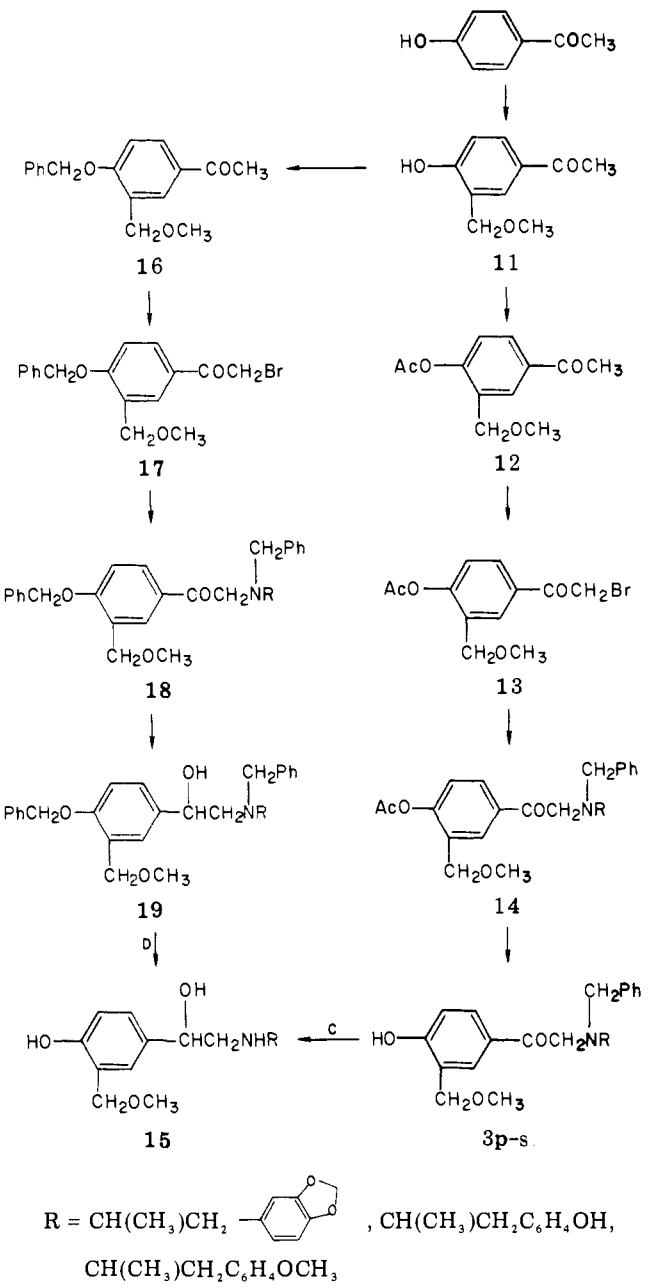
Table VI. Relative Bronchodilating Potency of 3r and Its Isomers (Inhibitory Effect on Histamine-Induced Increase in Airway Resistance)

compd	rel potency[a]
3r	1.0[b]
l-3r	1.89 (1.43–2.50)
d-3r	<0.001
3s	0.33 (0.23–0.49)

[a] Calculated by parallel line assay.[16] [b] ED_{50} (ip) 2.75 μg/kg.

Compounds **3a–d** in which the meta-phenolic hydroxyl group of **1** was replaced by various alkoxymethyl groups produced a great effect on the bronchodilating activity. The compound bearing a methoxymethyl group at the meta position, i.e., **3a**, was highly potent. Lengthening of the terminal alkyl in the alkoxymethyl group decreased activity, as in **3d**. As to the compounds **3e-i** in which the N-substituent of **3a–d** was converted into a *tert*-butyl group, the relationship between the structure of the meta substituent and the activity was also investigated. A structure–activity relationship similar to that described for **3a–d** was observed for **3e–i**, and the high potency was found in the compound bearing a methoxymethyl group at a meta position, i.e., α-(*N*-*tert*-butylaminomethyl)-4-hydroxy-3-(methoxymethyl)benzyl alcohol (**3e**). However,

Scheme II



it was found that the compound exhibited by the structure "**3e**" had been prepared by way of a different synthetic route by Collin and his associates.[17] According to their report, the compound **3e** did not show any β-adrenergic agonistic activity but rather a weak antagonistic activity. On the other hand, **3e** prepared in our study had bronchodilating activity, as shown in Table V. The reason for this discrepancy in the results of Collin et al. and ours still remains unknown.

The facts described above suggested that the methoxymethyl group has the most favorable property as the *meta* substituent. Thus, 3′,5′-bis(methoxymethyl) analogues **3j,k** in which two methoxymethyl groups were introduced into both of the meta positions were examined for their activity. Contrary to our expectations, introduction of an additional methoxymethyl group apparently decreased potency.

To investigate the effect of introducing an aromatic ring into an *N*-isopropyl or *tert*-butyl group on the activity, compounds in which *N*-alkyl substituents of **3a,b** and **3e,f** were replaced with an α-methylphenethyl (**3l,m**) or α,α-dimethylphenethyl (**3n,o**) group were examined for their activity. They showed a relatively high potency. Introduction of a benzene ring into the isopropyl group retained the potency, but similar *tert*-butyl derivatives were less effective. Moreover, in order to study substitution requirements in the aromatic ring of the α-methylphenethyl group, 3,4-methylenedioxy (**3p**), 4-hydroxy (**3q**), and 4-methoxy (**3r**), as well as unsubstituted (**3l**) derivatives, were examined. 4-Hydroxy and 4-methoxy derivatives **3q** and **3r** were the most potent. Compound **3r** exhibited a good bronchial selectivity and a long duration of action, and **3r** was selected as the best compound in this series (details of these examinations will be published elsewhere). With respect to the optical isomers of **3r**, bronchodilating activity exists only in the levo-isomer *l*-**3r**, and dextro-isomer *d*-**3r** may be inactive. The absolute configuration of the most active derivative **3r** is now under investigation by X-ray study relative to its enantiomer, *l*-**3r**·HBr.

On the basis of these results, compound **3r** seems to be worth further pharmacological and clinical study.

Experimental Section

Bronchodilating Activity. (1) Inhibitory Effect on Histamine-Induced Asthma-like Syndrome. Male guinea pigs weighing about 400 g were placed in a cylindrical box (15-cm radius and 56-cm high) and exposed for 20 min to a histamine atmosphere by nebulizing 0.1% histamine diphosphate solution at the rate of 0.5 mL/10 min. Bronchodilating activity was estimated from the delay in the appearance of toxic signs of anoxia and coughing. The test compound was given orally 30 min before the histamine exposure. Table V summarizes the bronchodilating activities of 17 new compounds prepared in this study.

(2) Inhibitory Effect on Histamine-Induced Increase in Airway Resistance. Male guinea pigs weighing 400–500 g were anesthetized with sodium pentobarbital (40 mg/kg, sc) and urethane (2.0 g/kg, ip). A Y-shaped glass cannula was inserted into the trachea and connected to a respirator (Harbard, Model 681). Artificial respiration was maintained at the rate of 65 rpm and 2–3 mL/100 g of body weight. A change in airway resistance was measured with a modified Konzett-Rössler's method.[18] An intravenous injection of histamine diphosphate in a dose of 10 μg/kg induced a sharp increase in airway resistance. The test compound was given intravenously 3 min before the histamine injection. Bronchodilating activity of **3r** and its isomers was determined in this assay. The ED_{50} value (iv) of **3r** was 2.75 μg/kg, and the relative potency of **3r**, *l*-**3r**, *d*-**3r**, and **3s** was estimated by the parallel line assay.[16] The results are summarized in Table VI.

Chemistry. Melting points are uncorrected. IR spectra were recorded as a Nujol mull using a Hitachi IR-215 spectrophotometer, and NMR spectra were determined on Hitachi R-25 spectrometer in $CDCl_3$ (unless otherwise noted) with added Me_4Si. Mass spectra were determined on a JEOL double-focusing mass spectrometer (JMS-01 SG), and the ionizing energy normally used was 75 eV. CD spectra were measured using 0.1% (w/v) solutions in a 2-mm cell with Jasco J-40A spectropolarimeters. Where analogues are represented by elemental symbols, the results of these elements fall within ±0.3% of the calculated values.

2-(N-Substituted amino)-4′-hydroxyacetophenones (4). Compounds **4a–d** (Table I) were prepared by a modified Hoesch reaction similar to that described for **4d** as follows. To a stirred mixture of 15.6 g (0.11 mol) of anhydrous $AlCl_3$ and 50 mL of nitrobenzene was added dropwise a solution of 9.4 g (0.05 mol) of *N*-(α,α-dimethylphenethyl)glycinonitrile[19] and 4.7 g (0.05 mol) of phenol in 20 mL of nitrobenzene under cooling. After the mixture was stirred at room temperature for 1 h, dry HCl gas was passed through the stirred mixture for 2 h. The resulting dark solution was warmed for 4 h at 60–70 °C under stirring. The solution was poured into ice–HCl. After the nitrobenzene layer was separated and removed, the acidic aqueous layer was washed with Et_2O. After the acidic aqueous layer was left standing overnight in a refrigerator, fine needles that precipitated were collected, washed with cold water, and dried. The crude product was recrystallized from EtOH to give 8.3 g (52%) of **2**-(α,α-

dimethylphenethylamino)-4′-hydroxyacetophenone hydrochloride (4d): mp 225–227 °C; IR 1675 cm^{-1} (C=O); NMR (Me_2SO-d_6) δ 4.60 (s, 2 H, $COCH_2N$), 3.12 (s, 2 H, CH_2Ph), 1.22 (s, 6 H, 2 CH_3).

2-(N-Substituted amino)-3′-(chloromethyl)-4′-hydroxyacetophenones (5). Compounds **5a,b,e,f** (Table II) were prepared by a method similar to that described for **5f** as follows. HCl gas was passed through a stirred mixture of 5.6 g (0.017 mol) of **4d**, 1.7 g (0.02 mol) of 37% aqueous HCHO solution, 2.8 g of $ZnCl_2$, 50 mL of AcOH, and 50 mL of concentrated HCl under stirring at room temperature. After the gas was saturated, the mixture was stirred for 3 h at 60–70 °C while passing HCl gas. The resulting clear solution was allowed to stand overnight. The crystalline mass that precipitated was collected and washed with Me_2CO. The crude product was recrystallized from MeOH–hexane to give 3.8 g (62%) of **3′-(chloromethyl)-2-(α,α-dimethylphenethylamino)-4′-hydroxyacetophenone hydrochloride (5f)**: mp 226 °C dec; IR 1650 cm^{-1} (C=O); NMR (Me_2SO-d_6) δ 4.65, 4.55 (pair of s, 4 H, CH_2Cl and $COCH_2N$), 3.05 (s, 2 H, CH_2Ph), 1.22 (s, 6 H, 2 CH_3).

2-(N-Substituted amino)-3′,5′-bis(chloromethyl)-4′-hydroxyacetophenones (5). Compounds **5c,d** (Table II) were obtained by a method similar to that described for **5c** as follows. To a stirred mixture of 6.8 g (0.03 mol) of **4a**, 7.3 g (0.09 mol) of 37% HCHO solution, and 300 mL of concentrated HCl, HCl gas was passed for 6 h at 80 °C. When the reaction mixture was cooled, crystals that precipitated were collected and washed with Me_2CO. The crude product was recrystallized from MeOH–hexane to give 8.4 g (86%) of **3′,5′-bis(chloromethyl)-4′-hydroxy-2-(isopropylamino)acetophenone hydrochloride (5c)**: mp >300 °C; IR 1660 cm^{-1} (C=O).

2-(N-Substituted amino)-3′(5′)-(alkoxymethyl)-4′-hydroxyacetophenones (6). Compounds **6a–o** (Table III) were prepared by a method similar to that described for **6n** or **6g** as follows. (a) A solution of 3.0 g of **5f** in 50 mL of MeOH was heated in an autoclave at 120–130 °C for 7 h. The reaction mixture was evaporated and the resulting crystalline residue was recrystallized from MeOH–EtOAc to give 2.6 g (92%) of **2-(α,α-dimethylphenethylamino)-4′-hydroxy-3′-(methoxymethyl)acetophenone hydrochloride (6n)**: mp 203 °C dec; IR 1670 cm^{-1} (C=O); NMR (Me_2SO-d_6) δ 4.66 (s, 2 H, $COCH_2N$), 4.40 (s, 2 H, CH_2OMe), 3.36 (s, 3 H, CH_2OCH_3), 3.14 (s, 2 H, CH_2Ph), 1.26 (s, 6 H, 2 CH_3). (b) A mixture of 2.9 g of **5c** and 50 mL of $CH_3OCH_2CH_2OH$ was refluxed for 6 h. The clear solution was evaporated to dryness under reduced pressure and the crystalline mass was recrystallized from MeOH–EtOAc to give 2.6 g (76%) of **2-(*tert*-butylamino)-4′-hydroxy-3′-(β-methoxyethoxymethyl)acetophenone hydrochloride (6g)**: mp 155–156 °C.

4-Hydroxy-3-(methoxymethyl)benzaldehyde (7). To a mixture of 50 mL of 37% HCHO solution and 180 mL of concentrated HCl, 20 g of *p*-hydroxybenzaldehyde was added in small portions at 40–50 °C with stirring. The suspension was stirred at 50 °C for 30 min to give a homogeneous light brown solution. After about 3 h of stirring the solution, a solid material began to precipitate. After the solution was left standing overnight, the crude material that precipitated was separated from the reaction mixture by filtration, washed with H_2O, and dried to give 19.5 g of crude 3-(chloromethyl)-4-hydroxybenzaldehyde.[20] A mixture of 19.5 g of the crude 3-(chloromethyl) derivative and 200 mL of MeOH was refluxed for 3 h. The reaction mixture was concentrated and the residue was poured into water. The oil that separated was extracted with Et_2O. The Et_2O extract was washed with H_2O, dried ($MgSO_4$), and evaporated. The oily residue obtained was distilled to give 17.2 g (63%) of **7**: bp 134–136 °C (1.5 mm); IR 3250 (OH), 1680 cm^{-1} (C=O); NMR δ 9.80 (s, 1 H, CHO), 8.90 (s, 1 H, OH), 4.65 (s, 2 H, CH_2OMe), 3.47 (3, 3 H, CH_2OCH_3); mass spectrum *m/e* 166 (M^+). Anal. ($C_9H_{10}O_3$) C, H.

4-(Benzyloxy)-3-(methoxymethyl)benzaldehyde (8). To a stirred and refluxing solution of 8.3 g (0.05 mol) of **7** and 3.5 g of KOH was added dropwise 10.3 g (0.06 mol) of benzyl bromide, and the mixture was stirred and refluxed for 3 h. The reaction mixture was concentrated under reduced pressure, and the resulting oil was dissolved in Et_2O. The Et_2O solution was washed with H_2O, dried ($MgSO_4$), and evaporated. The oily residue was distilled to give 10.5 g (82%) of **8**: bp 184–187 °C (0.7 mm); IR 1680 cm^{-1}; NMR δ 9.75 (s, 1 H, CHO), 5.05 (s, 2 H, OCH_2Ph), 4.45 (s, 2 H, CH_2OMe), 3.40 (s, 3 H, CH_3OCH_3). Anal. ($C_{16}H_{16}O_3$) C, H.

4-(Benzyloxy)-3-(methoxymethyl)phenylethylene Oxide (9). To a stirred mixture of 5.2 g (0.02 mol) of **8**, 5.1 g (0.025 mol) of trimethylsulfonium iodide, and 70 mL of dimethylformamide, 1.2 g of NaH (in 50% mineral oil) was added in small portions at 5–10 °C under a N_2 stream. The reaction mixture was stirred at 45 °C for 3 h. The mixture was poured into water and the oil that separated was extracted with Et_2O. The Et_2O extract was washed with H_2O, dried ($MgSO_4$), and evaporated. The residue was washed with light petroleum to remove the mineral oil and distilled to give 4.3 g (79%) of **9** as a colorless liquid: bp 181–183 °C (0.5 mm); NMR δ 4.95 (s, 2 H, OCH_2Ph), 4.45 (s, 2 H, CH_2OMe), 3.64 (m, 1 H, methine of oxiran ring), 3.34 (s, 3 H, CH_2OCH_3), 2.94, 2.62 (pair of m, 2 H, methylene of oxiran ring); mass spectrum *m/e* 270 (M^+). Anal. ($C_{17}H_{18}O_3$) C, H.

4-(Benzyloxy)-α-(*tert*-butylaminomethyl)-3-(methoxymethyl)benzyl Alcohol (10). A solution of 13.5 g (0.05 mol) of **9** and 5.5 g (0.075 mol) of *t*-$BuNH_2$ in 200 mL of MeOH was refluxed for 4 h. The reaction mixture was concentrated and the residue was dissolved in Et_2O. The Et_2O solution was extracted with 10% HCl and the acidic extract was made alkaline with NaOH solution. The separated amine was extracted with Et_2O, and the extract was washed with H_2O and dried to give a crude product, which was distilled to give 14.6 g of **10**: bp 185–189 °C (1.0 mm); mass spectrum *m/e* 343 (M^+); NMR δ 1.10, 1.05 (the combined signals integrated for 9 H in an approximate 2:1 ratio). The NMR spectrum suggests the presence of two *t*-Bu groups in a different environment; TLC (SiO_2, 20% MeOH in $CHCl_3$) showed two spots having close R_f values. The free base of **10** was converted into the salt to remove the byproduct, and the maleate was recrystallized from MeOH–EtOAc to give 12.8 g (56%) of the pure maleate of **10**: mp 157–159 °C; IR 3300–3200 cm^{-1} (OH and NH); NMR δ 5.07 (s, 2 H, OCH_2Ph), 4.62 [m, 1 H, $CH(OH)$], 4.58 (s, 2 H, CH_2OMe), 3.42 (s, 3 H, CH_2OCH_3), 2.9–2.5 [m, 4 H, $C(OH)CH_2NH$], 1.10 (s, 9 H, N-*t*-Bu). Anal. ($C_{21}H_{29}NO_3 \cdot C_4H_4O_4$) C, H, N.

4-Hydroxy-3-(methoxymethyl)acetophenone (11). To a mixture of 54 mL of 37% HCHO solution and 170 mL of concentrated HCl, 21.4 g of *p*-hydroxyacetophenone was added at 50 °C with stirring. The suspended acetophenone gradually dissolved, and the reaction mixture became a clear scarlet solution. After the solution was stirred for 4 h at 50–55 °C, the precipitate was collected, washed thoroughly with H_2O, and dried to give 26.8 g of crude 3-(chloromethyl)-4-hydroxyacetophenone.[21] To a solution of 26.8 g of the crude 3-(chloromethyl) derivative in 120 mL of MeOH, 24.4 g of $NaHCO_3$ was added in small portions under stirring. The reaction mixture was stirred for 4 h and then filtered to remove the inorganic substance. The filtrate was diluted with 500 mL of H_2O and extracted with Et_2O. The Et_2O extract was washed with H_2O, dried ($MgSO_4$), and evaporated. The residue that crystallized on standing was recrystallized from toluene to give 25.0 g (88%) of **11** as needles: mp 87–88 °C; IR 1655 cm^{-1} (C=O); NMR (Me_2SO-d_6) δ 4.45 (s, 2 H, CH_2OCH_3), 3.35 (s, 3 H, CH_2OCH_3), 2.45 (s, 3 H, $COCH_3$). Anal. ($C_{10}H_{12}O_3$) C, H.

4-Acetoxy-3-(methoxymethyl)acetophenone (12). A mixture of 9.0 g of **11**, 2 mL of pyridine, and 20 mL of Ac_2O was refluxed for 6 h. After evaporation of the mixture under reduced pressure, the residue was dissolved in Et_2O. The Et_2O solution was washed with H_2O, dried ($MgSO_4$), and concentrated to an oil, and the product was purified by distillation to give 9.3 g (84%) of **12**: bp 138–141 °C (0.14 mm); IR 1760 (OAc), 1675 cm^{-1} (Ac); NMR δ 4.30 (s, 2 H, CH_2OMe), 3.30 (s, 3 H, CH_2OCH_3), 2.45 (s, 3 H, OAc), 2.18 (s, 3 H, $COCH_3$). Anal. ($C_{12}H_{14}O_4$) C, H.

4′-Acetoxy-2-bromo-3′-(methoxymethyl)acetophenone (13). To a cold stirred solution of 10.0 g (0.045 mol) of **12** in 200 mL of $CHCl_3$, a solution of 7.2 g (0.045 mol) of Br_2 in 70 mL of $CHCl_3$ was added dropwise at 5–10 °C at such a rate that the bromine color faded rapidly. After stirring for an additional 2 h, the reaction mixture was poured into 600 mL of ice–H_2O. The $CHCl_3$ layer was washed successively with H_2O, $NaHCO_3$ solution, and H_2O. After the extract was dried ($MgSO_4$) and evaporated, the residue was distilled to give 7.2 g (53%) of **13**: bp 173–175 °C (0.7 mm); IR 1760 (OAc), 1680 cm^{-1} (C=O); NMR δ 4.27 (s, 4 H,

$COCH_2Br$ and CH_2OMe), 3.24 (s, 3 H, CH_2OCH_3), 2.21 (s, 3 H, $OCOCH_3$). Anal. ($C_{12}H_{13}BrO_4$) C, H.

4′-Acetoxy-3′-(methoxymethyl)-2-[*N*-(4-methoxy-α-methylphenethyl)amino]acetophenone (14a). To a solution of 30.6 g (0.12 mol) of 1-(4-methoxyphenethyl)-2-(*N*-benzylamino)propane[22] in 150 mL of MeCN, a solution of 18.0 g (0.06 mol) of **13** was added dropwise with stirring at room temperature. After the addition was completed, the mixture was stirred for 10 h, and the resulting precipitate was filtered. The filtrate was evaporated under reduced pressure and the residue was dissolved in Et_2O. The Et_2O solution was washed with H_2O, dried ($MgSO_4$), and evaporated. The resinous residue, weighing 27.5%, could not be purified. This crude product (**14a**) was used directly without further purification.

In the same manner, **4′-acetoxy-2-[*N*-benzyl-*N*-[3,4-(methylenedioxy)-α-methylphenethyl]amino]-3′-(methoxymethyl)acetophenone (14b)** and **4′-acetoxy-2-[*N*-benzyl-*N*-[4-(benzyloxy)-α-methylphenethyl]amino]-3′-methoxymethyl)acetophenone (14c)** were prepared by the reaction of **13** with 1-[3,4-(methylenedioxy)phenyl]-2-(*N*-benzylamino)-propane and 1-[4-(benzyloxy)phenyl]-2-(*N*-benzylamino)propane, respectively.

2-[*N*-Benzyl-*N*-(α-methylarylethyl)amino]-4′-hydroxy-3′-(methoxymethyl)acetophenones (15). Compounds **15a–c** were prepared by a method similar to that described for **15a** as follows. A solution of 9.5 g of crude **14a** in 50 mL of 6 N HCl was stirred at 40 °C for 5 h, and the reaction mixture was made alkaline with NaOH solution under cooling. The basic solution was washed with Et_2O and then made acidic with HCl. The acidic solution was allowed to stand at 0 °C for 16 h, and the resulting crystalline powder was recrystallized from Me_2CO to give 6.7 g (71%) of **2-[*N*-benzyl-*N*-(4-methoxy-α-methylphenethyl)-amino]-4′-hydroxy-3′-(methoxymethyl)acetophenone hydrochloride (15a)**: mp 111.5 °C; IR 3400 (OH), 1660 cm^{-1} (C=O); NMR (Me_2SO-d_6) δ 4.43 (s, 2 H, CH_2OMe), 3.80 (s, 3 H, OCH_3), 3.41 (s, 2 H, NCH_2Ph), 3.40 (s, 3 H, CH_2OCH_3), 3.5–2.4 (m, 5 H, CH_2NCHCH_2), 1.30 (d, 3 H, $CHCH_3$); mass spectrum *m/e* 433 (M^+), 402. Anal. ($C_{27}H_{31}NO_4$·HCl), C, H, N. **2-[*N*-Benzyl-*N*-[3,4-(methylenedioxy)-α-methylphenethyl]amino]-4′-hydroxy-3′-(methoxymethyl)acetophenone hydrochloride (15b)**: yield 64%; mp 219 °C dec. Anal. ($C_{27}H_{29}NO_5$·H_2O·HCl) C, H, N. ($C_{27}H_{31}NO_4$·HCl), C, H, N. **2-[*N*-Benzyl-*N*-[(benzyloxy)-α-methylphenethyl]amino]-4′-hydroxy-3′-(methoxymethyl)acetophenone hydrochloride (15c)**: yield 62%; mp 108 °C. Anal. ($C_{33}H_{35}NO_4$·HCl) C, H, N.

4-(Benzyloxy)-3-(methoxymethyl)acetophenone (16). A mixture of 20 g (0.11 mol) of **11**, 15.5 g (0.12 mol) of benzyl chloride, 18.4 g (0.13 mol) of K_2CO_3, a small amount of KI, and 200 mL of EtOH was refluxed and stirred for 6 h. After cooling the mixture, the inorganic substances were filtered off, and the filtrate was evaporated to dryness. The residual oil was dissolved in Et_2O, and the Et_2O extract was washed with H_2O, dried ($MgSO_4$), and evaporated. The oily residue was crystallized from isopropyl ether to give 27.6 g (92%) of **16**: mp 42–45 °C; IR 1675 cm^{-1} (C=O); NMR δ 4.67 (s, 2 H, OCH_2Ph), 4.20 (s, 2 H, CH_2OMe), 3.25 (s, 3 H, CH_2OCH_3), 2.13 (s, 3 H, $COCH_3$); mass spectrum *m/e* 270 (M^+), 239, 238. Anal. ($C_{17}H_{18}O_3$) C, H.

4′-(Benzyloxy)-2-bromo-3′-(methoxymethyl)acetophenone (17). To a stirred solution of 30.2 g (0.11 mol) of **16** and 1.4 g of benzoyl peroxide in 200 mL of EtOH, 20.8 g (0.13 mol) of Br_2 was added dropwise at 25–30 °C. After the addition was completed, the reaction mixture was stirred for 1 h at room temperature. White leaflet crystals that precipitated were collected and washed with cold EtOH. The crude bromide was recrystallized from EtOH to give 29.7 g (76%) of **17**: mp 94–96 °C; IR 1680 cm^{-1} (C=O); NMR (Me_2SO-d_6) δ 5.23 (s, 2 H, OCH_2Ph), 4.75 (s, 2 H, CH_2OMe), 4.49 (s, 2 H, $COCH_2Br$), 3.34 (s, 3 H, CH_2OCH_3). Anal. ($C_{17}H_{17}BrO_3$) C, H.

4′-(Benzyloxy)-2-[*N*-benzyl-*N*-(4-methoxy-α-methylphenethyl)amino]-3′-(methoxymethyl)acetophenone (18). To a stirred solution of 51.1 g (0.2 mol) of 1-(4-methoxyphenyl)-2-(*N*-benzylamino)propane[22] in 50 mL of EtOAc, 34.9 g (0.1 mol) of **17** was added dropwise in a period of 1 h at room temperature, and then stirring was continued for another 2 h. The reaction mixture containing much precipitate was cooled to 10 °C and filtered. The filtrate was evaporated to dryness under reduced pressure and the pasty residue was dissolved in Et_2O. The Et_2O solution was washed with H_2O, dried ($MgSO_4$), and evaporated. The resulting pasty residue, weighing 46.8 g, showed one spot on TLC (SiO_2, 10% EtOAc in $CHCl_3$), but attempts to purify this material by distillation or crystallization were unsuccessful: IR 1670 cm^{-1} (C=O); NMR δ 4.94 (s, 2 H, OCH_2Ph), 4.40 (s, 2 H, CH_2OMe), 3.70 (s, 2 H, NCH_2Ph), 3.61 (s, 3 H, OCH_3), 3.32 (s, 3 H, CH_2OCH_3), 3.2–2.1 (m, 5 H, $COCH_2NCHCH_2$), 0.96 (d, 3 H, $CHCH_3$); mass spectrum *m/e* 523 (M^+), 432, 403, 402. Thus, crude **18** was used for the next reaction without further purification.

4-(Benzyloxy)-α-[*N*-benzyl-*N*-(4-methoxy-α-methylphenethyl)aminomethyl]-3-(methoxymethyl)benzyl Alcohol Hydrochloride (19). To a cold solution of 10.5 g of **18** in 100 mL of EtOH, 0.5 g of $NaBH_4$ was added with stirring and the mixture was refluxed for 1 h. After decomposition of the excess $NaBH_4$ by adding Me_2CO, the reaction mixture was evaporated under reduced pressure. The crude amine obtained was converted into the hydrochloride, and the salt was recrystallized from *i*-PrOH to give 7.3 g of **19**, mp 136–137 °C. The product showed two spots on TLC (SiO_2, ammonia-saturated isopropyl ether) in an approximate 3:2 ratio. This product was presumed to be a mixture of the diastereoisomers. Further purification could not be effected by several recrystallizations from *i*-PrOH.

Separation of a Mixture of Diastereoisomers (19) into 19a and 19b. A mixture of 10.5 g (0.02 mol) of crude **19** (free base) and 1.2 g (0.01 mol) of fumaric acid in 12 mL of *i*-PrOH was refluxed for 30 min, and then 12 mL of isopropyl ether was added to the solution. The resulting clear solution was allowed to stand overnight in a refrigerator. The precipitated crystalline mass was filtered and the filtrate was kept for another operation. The collected crystals were recrystallized from MeOH to give 4.8 g of **19a** hemifumarate, mp 143–145 °C. Anal. ($C_{34}H_{39}NO_4$·$C_2H_2O_2$) C, H, N. The free amine **19a** was liberated from **19a** hemifumarate by the usual way and used for spectroscopic measurements and the next hydrogenation step: IR 3260 cm^{-1} (OH); NMR δ 5.08 (s, 2 H, OCH_2Ph), 4.52 (s, 2 H, CH_2OMe), 4.50 [m, 1 H, $CH(OH)$], 3.80 (s, 5 H, OCH_3 and NCH_2Ph), 3.39 (s, 3 H, CH_2OCH_3), 3.5–2.2 (m, 5 H, CH_2NCHCH_2), 1.5–1.2 (deformed d, 3 H, $CHCH_3$).

The filtrate obtained above was evaporated to dryness and the residue was dissolved in H_2O. The aqueous solution was made alkaline with NaOH solution and the oil that separated was extracted with Et_2O. The Et_2O extract was washed with H_2O, dried ($MgSO_4$), and evaporated. The crude amine obtained was converted into the hydrochloride, and the salt was recrystallized from EtOH to give 4.1 g of **19b**·HCl, mp 169–172 °C. Anal. ($C_{34}H_{39}NO_4$·HCl) C, H, N. The free amine **19b** prepared from the hydrochloride by the usual way was used for spectroscopic measurements and the next hydrogenation step: IR 3250 cm^{-1} (OH); NMR δ 5.08 (s, 2 H, OCH_2Ph), 4.53 (s, 2 H, CH_2OMe), 4.50 [m, 1 H, $CH(OH)$], 3.76 (s, 5 H, OCH_3 and NCH_2Ph), 3.40 (s, 3 H, CH_2OCH_3), 3.5–2.1 (m, 5 H, CH_2NCHCH_2), 1.5–1.2 (deformed d, 3 H, $CHCH_3$).

3,5,N-Substituted 4-Hydroxy-α-aminomethylbenzyl Alcohols (3). Method A. Compounds **3a–o** (Table IV) were prepared by a method similar to that described for **3n** as follows. A mixture of 4.0 g of **6n** and 20 mL of MeOH was hydrogenated with 0.5 g of Raney Ni at 2.3 kg/cm^2 at ordinary pressure and temperature. The solution was filtered and the filtrate was evaporated to dryness in vacuo, giving a pale yellow gum which crystallized on standing. The crude product was recrystallized from MeOH–EtOAc to give 3.4 g (85%) of **α-[*N*-(α,α-dimethylphenethyl)aminomethyl]-4-hydroxy-3-(methoxymethyl)benzyl alcohol hydrochloride (3n)**: mp 184–186 °C; IR 3350, 3250 cm^{-1} (OH, NH); NMR (Me_2SO-d_6) δ 4.70 [m, 1 H, $CH(OH)$], 4.20 (s, 2 H, CH_2OMe), 3.16 (s, 3 H, CH_2OCH_3), 2.98 (s, 2 H, CH_2Ph), 2.75 (m, 2 H, $CHCH_2N$), 1.21 (s, 6 H, 2 CH_3); mass spectrum *m/e* 329 (M^+), 238, 188.

Method B. A mixture of 6.8 g (0.02 mol) of **10** (free amine) and 200 mL of MeOH was hydrogenated with 0.5 g of Pd/C (5%) at ordinary pressure and temperature. After filtration, the solution was evaporated under reduced pressure to afford a crystalline residue. The residue was recrystallized from isopropyl ether to give free amine of **3e**, mp 217–218 °C. The free amine was converted into the hydrochloride, and the salt was recrystallized from EtOH to give 5.1 g (88%) of **α-(*N*-*tert*-butylamino-**

methyl)-4-hydroxy-3-(methoxymethyl)benzyl alcohol hydrochloride (3e), mp 203–204 °C, undepressed on admixture with a sample of 3e prepared by method A: IR 3360, 3250 cm^{-1} (OH, NH); NMR (Me_2SO-d_6) δ 4.72 [m, 1 H, C*H*(OH)CH_2], 4.20 (s, 2 H, CH_2OMe), 3.14 (s, 3 H, CH_2OCH_3), 2.74 (m, 2 H, $CHCH_2N$), 1.11 (s, 9 H, 3 CH_3). These spectra were determined for the free base.

Method C. Compounds 3p–r (Table IV) were afforded by a method similar to that described for 3p as follows. A mixture of 5.0 g of 15b, 20 mL of H_2O, and 100 mL of MeOH was hydrogenated in the presence of 0.5 g of Pd/C (5%) at 2.5 kg/cm^2 and room temperature. After filtration of the mixture, the filtrate was evaporated to dryness and the residue was dissolved in water. The aqueous solution was washed with ether and made basic with NH_4OH to give an oil, which was extracted with Et_2O. The ethereal extracts were dried ($MgSO_4$) and evaporated. The resulting crude amine was converted into the hemioxalate, and the salt was recrystallized from MeOH–EtOAc to give 1.5 g of **4-hydroxy-3-(methoxymethyl)-α-[*N*-[3,4-(methylenedioxy)-α-methylphenethyl]aminomethyl]benzyl alcohol hemioxalate (3p)**, mp 203 °C dec. Anal. ($C_{20}H_{25}NO_5 \cdot CHO_2$) C, H, N. **4-Hydroxy-α-[*N*-(4-hydroxy-α-methylphenethyl)-aminomethyl]-3-(methoxymethyl)benzyl alcohol hemioxalate (3q)**: yield 39%; mp 158–160 °C. Anal. ($C_{19}H_{25}NO_4 \cdot CHO_2$) C, H, N. **4-Hydroxy-3-(methoxymethyl)-α-[*N*-(4-methoxy-α-methylphenethyl)aminomethyl]benzyl alcohol hemifumarate (3r)**: yield 41%; mp 172 °C dec; IR (KBr) 3420 cm^{-1} (OH, NH); NMR (Me_2SO-d_6) δ 4.70 (m, 1 H, C*H*OH), 4.38 (s, 2 H, CH_2OMe), 3.68 (s, 3 H, $ArOCH_3$), 3.28 (s, 3 H, CH_2OCH_3), 3.2–2.5 (m, 5 H, CH_2NCHCH_2), 1.00 (d, 3 H, $CHCH_3$); mass spectrum *m/e* 345 (M^+), 327 (M – 28), 314 (M – OCH_3), and 224 (M – $CH_2C_6H_4OCH_3$). Anal. ($C_{20}H_{27}NO_4 \cdot C_2H_2O_2$) C, H, N.

Method D. (a) A mixture of 5.3 g (0.01 mol) of **19b**, 0.5 g of Pd/C (5%), and 20 mL of MeOH was hydrogenated at ordinary pressure and temperature. The reaction mixture was filtered, and 0.58 g (0.005 mol) of fumaric acid was added to the filtrate. The mixture was heated and concentrated to one-third of its original volume. After addition of 20 mL of EtOAc, the mixture was allowed to stand overnight. The crystalline needles that precipitated were collected and recrystallized from MeOH to give 3.2 g (79%) of **3r** hemifumarate, mp 168–170 °C, undepressed on admixture with a sample of **3r** obtained by method C. The IR and NMR spectra of these two substances were identical: IR (KBr) 3420 cm^{-1} (OH, NH); NMR (Me_2SO-d_6) δ 4.69 (m, 2 H), 4.36 (s, 2 H), 3.68 (s, 3 H), 3.28 (s, 3 H), 3.2–2.4 (m, 5 H), 1.02 (d, 3 H).

(b) A mixture of 5.3 g (0.01 mol) of **19a**, 0.5 g of Pd/C (5%), and 20 mL of MeOH was hydrogenated at ordinary pressure and temperature. The mixture was treated as the procedure described for **3r**. The resulting free amine **3s** (diastereoisomer of **3r**) was converted into the hemifumarate, the salt was recrystallized from MeOH to give 3.4 g (84%) of **3s** hemifumarate: mp 125–126 °C; IR (KBr) 3350, 3270 cm^{-1} (OH, NH); NMR (Me_2SO-d_6) δ 4.80 (m, 1 H, C*H*OH), 4.38 (s, 2 H, CH_2OMe), 3.70 (s, 3 H, $ArOCH_3$), 3.30 (s, 3 H, CH_2OCH_3), 3.3–2.4 (m, 5 H, CH_2NCHCH_2), 1.06 (d, 3 H, $CHCH_3$). Anal. ($C_{20}H_{27}NO_4 \cdot C_2H_2O_2$) C, H, N.

Resolution of 3r. To a suspension of 25.0 g of **3r** hemifumarate in 20 mL of H_2O, an excess of NH_4OH was added. The resulting oil that liberated was extracted with Et_2O. The Et_2O extract was dried ($MgSO_4$) and evaporated to give 20.2 g of free base 3r. To a solution of 17.3 g (0.05 mol) of **3r** in 200 mL of EtOH, 9.4 g (0.025 mol) of dibenzoyl-*d*-tartaric acid monohydrate was added, and the mixture was heated to a clear solution, which was allowed to stand for 2 days to give a white crystalline powder. The crystals were filtered, and the filtrate was retained for another operation. The crystals were recrystallized from EtOH to give the hemidibenzoyl *d*-tartrate as colorless needles which was treated with NH_4OH to give the corresponding free base and the amine was converted into the hydrochloride. Three recrystallizations from Me_2CO gave pure *d*-**3r**·HCl: mp 130.5–131 °C; $[\alpha]^{25}_D$ +46.3° (*c* 2, EtOH); *CD* (c 0.1, 90% MeOH) $[\theta]_{300}$ 0, $[\theta]_{290}$ +305, $[\theta]_{285}$ +572, $[\theta]_{281}$ +753, $[\theta]_{280}$ +725, $[\theta]_{276}$ +763, $[\theta]_{270}$ +544, $[\theta]_{260}$ +219, $[\theta]_{250}$ +67. Anal. ($C_{20}H_{27}NO_4 \cdot HCl$) C, H, N.

The filtrate obtained above was evaporated and the residue was dissolved in H_2O. The solution was made basic with NH_4OH, and the resulting oil that liberated was extracted with Et_2O. The extracts were washed with H_2O, dried ($MgSO_4$), and evaporated. This crude amine so obtained was converted into the hydrochloride and the salt was recrystallized several times from Me_2CO to give pure *l*-**3r**·HCl: mp 130.5–131.5 °C; $[\alpha]^{25}_D$ -45.6° (*c* 2, EtOH); CD (c 0.1, 90% MeOH) $[\theta]_{300}$ 0, $[\theta]_{290}$ -305, $[\theta]_{285}$ -629, $[\theta]_{281}$ -763, $[\theta]_{280}$ -753, $[\theta]_{276}$ -801, $[\theta]_{270}$ -563, $[\theta]_{260}$ -229, $[\theta]_{250}$ -68. Anal. ($C_{20}H_{27}NO_4 \cdot HCl$) C, H, N.

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