Heart rate was recorded electronically from the blood pressure pulse. Isoproterenol was injected at 0.5 μg/kg iv and the resultant hypotension and tachycardia were computed. Test compounds were administered cumulatively until nearly complete inhibition of isoproterenol effects was achieved.

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Adrenergic Agents. 6.[1] Synthesis and Potential β-Adrenergic Agonist Activity of Some Meta-Substituted *p*-Hydroxyphenylethanolamines Related to Salbutamol

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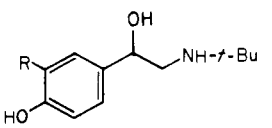
Salbutamol, an adrenergic receptor agonist with selectivity for tracheobronchial vs. cardiac muscle, differs from the catecholamine *N*-*tert*-butylnorepinephrine in that it bears a hydroxymethyl, rather than a phenolic, group in the meta position. In a search for new bronchodilating agents with minimal cardiovascular side effects, a series of derivatives, in which this *m*-hydroxymethyl group is modified, was prepared. These compounds were examined for potential bronchodilator activity in an in vitro test that measures relaxation of guinea pig tracheal smooth muscle. Potential cardiac stimulant activity was evaluated in vitro by monitoring changes in the rate of contraction of spontaneously beating guinea pig right atria. Although many of these compounds retained a high degree of potency, all were less effective than salbutamol in the tracheal test. Several of the derivatives, notably ones bearing 1-hydroxyethyl (**1d**), 1,2-dihydroxyethyl (**1f**), 1-hydroxy-2-methoxyethyl (**1g**), and 2-hydroxy-1-methoxyethyl (**1h**) substituents in place of the parent's *m*-hydroxymethyl group, however, were considerably more selective for tracheobronchial vs. cardiac muscle in the in vitro tests utilizing guinea pig tracheal and right atrial muscle.

Structural modifications of the meta substituent in *p*-hydroxyphenylethanolamines have produced many potent and selective β-adrenoreceptor agonists, some of which are therapeutically effective bronchodilators. In previous publications, we described the synthesis and β-adrenoreceptor agonist activity of carbuterol (**1a**)[2] and sulfonterol (**1b**)[3] which, among others, belong to this class of chemical compounds. Salbutamol (**1c**),[4] an orally effective bronchodilator in the clinic,[5] was one of the first

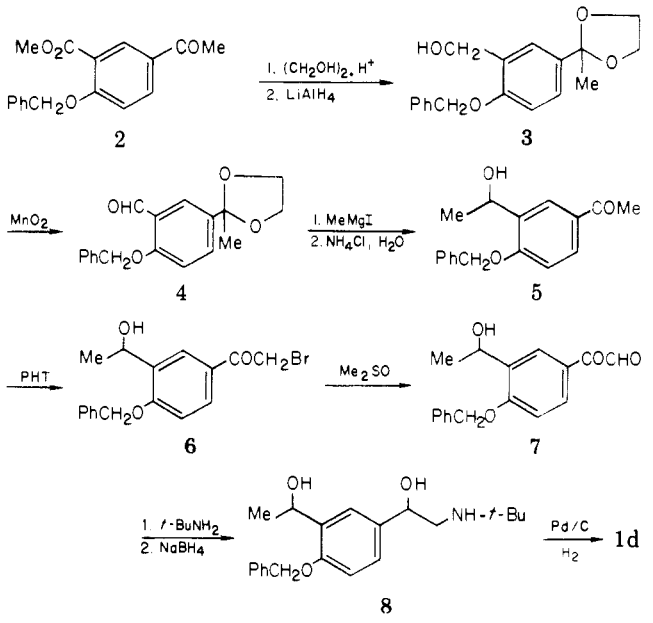


1a, R = H_2NCONH	**1f**, R = $HOCH_2CH(OH)$
b, R = $MeSO_2CH_2$	**g**, R = $MeOCH_2CH(OH)$
c, R = $HOCH_2$	**h**, R = $HOCH_2CH(OMe)$
d, R = $MeCH(OH)$	**i**, R = $MeSO_2CH_2CH(OH)$
e, R = $Me_2C(OH)$	**j**, R = t-$BuNHCH_2CH(OH)$

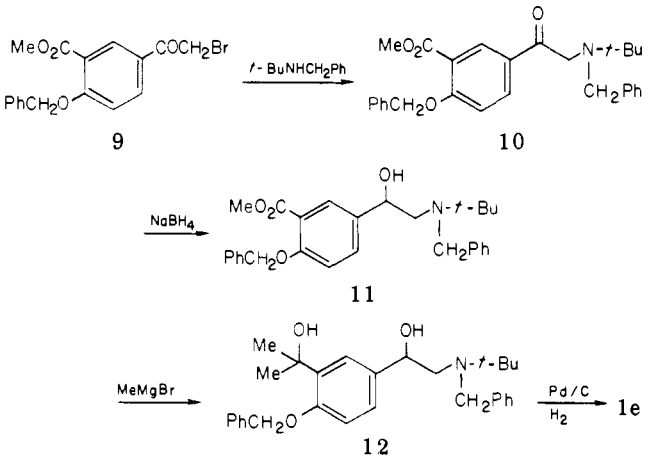
compounds to demonstrate that replacing the *m*-hydroxyl group of catecholamines with a hydroxymethyl group can improve the selectivity for tracheobronchial vs. cardiac muscle. In vitro studies in guinea pig tracheal and right atrial preparations show that sulfonterol has a much larger separation ratio[6] than salbutamol.[3] It seems plausible that modification of the *m*-hydroxymethyl group of salbutamol might further improve the selectivity. In the present article are described the synthesis and results of preliminary pharmacological examination for β-adrenoreceptor agonist activity of several compounds **1d–j** of this type.

Chemistry. Synthesis of the 1-hydroxyethyl derivative **1d** is outlined in Scheme I. Acylation of methyl salicylate with $AcCl–AlCl_3$ followed by benzylation afforded **2** in a more direct method than that previously reported.[4] The ketal derived from **2** was reduced with $LiAlH_4$ to give the hydroxyketal **3** which was oxidized to the aldehyde **4** with MnO_2. Treatment of **4** with MeMgI followed by hydrolysis of the ketal group during the work-up led to the secondary alcohol **5**. Formation of the ethanolamine side chain was

Scheme I



Scheme II

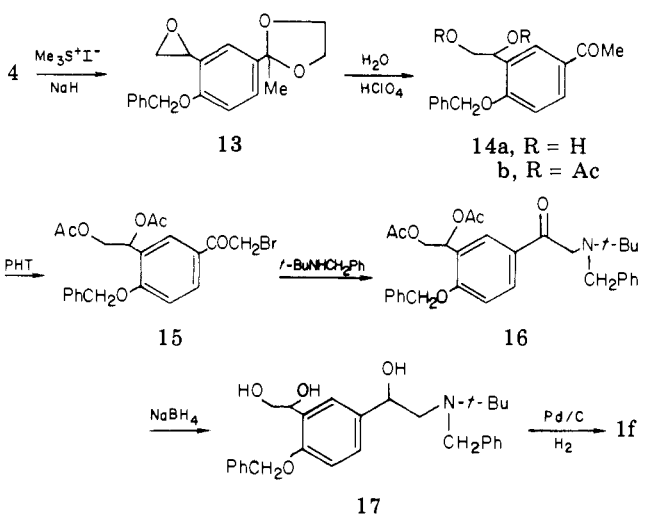


completed by one of the conventional methods.[7] Bromination of **5** with pyrrolidinone hydrotribromide (PHT) followed by Me_2SO oxidation[8] of the resulting phenacyl bromide **6** gave the glyoxal **7**, which was selectively aminated with *tert*-butylamine. The resulting ketoimine was reduced with $NaBH_4$ to give **8** which was hydrogenolyzed under catalytic conditions to afford **1d**.

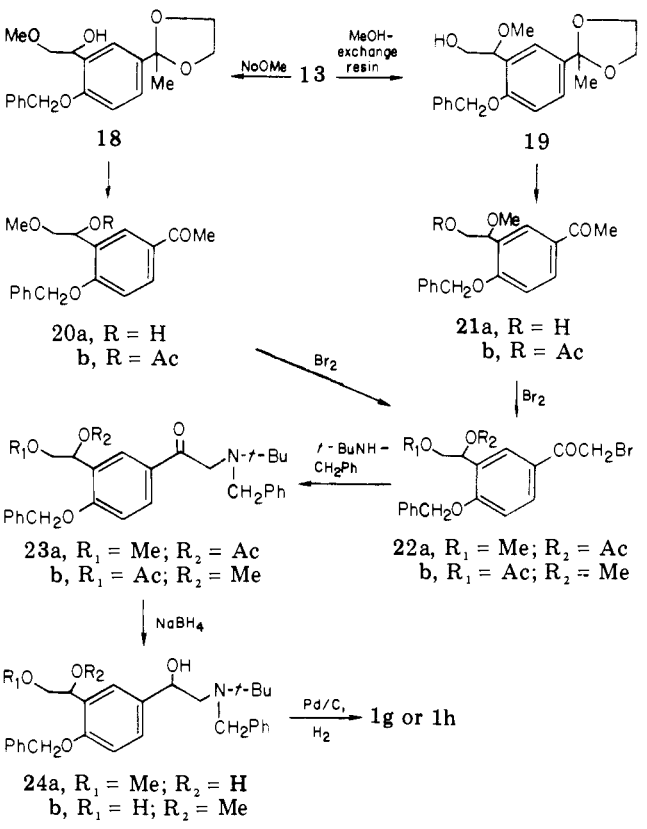
The tertiary alcohol **1e** was prepared from the phenacyl bromide **9**[4] (Scheme II). Treatment of **9** with *tert*-butylbenzylamine gave the amino ketone **10** which was reduced to the amino alcohol **11** by $NaBH_4$ with retention of the ester function. Reaction of the ester **11** with excess MeMgBr led to the tertiary alcohol **12**. Removal of the benzyl-protecting group by catalytic hydrogenolysis gave **1e**.

The synthetic route to the *m*-glycolyl analogue **1f** of salbutamol is outlined in Scheme III. Treatment of the aldehyde **4** with dimethylsulfonium methylide[9] gave the epoxide **13**. Acid-catalyzed hydrolysis of the epoxide concomitantly regenerated the keto group to give the glycol **14a**. Bromination of **14a** produced a mixture of products (TLC) which was difficult to separate. To circumvent this problem, **14a** was first converted to the diacetate **14b** which was brominated with PHT to afford the phenacyl bromide **15**. Amination of **15** with *tert*-butylbenzylamine followed by reduction of the resulting amino ketone **16** with $NaBH_4$

Scheme III



Scheme IV



was accompanied by acetate hydrolysis to give the amino alcohol **17** which was catalytically hydrogenolyzed to afford **1f**.

Synthesis of **1g** and **1h** via the epoxide **13** is outlined in Scheme IV. Reaction of styrene oxide with a nucleophile is known to give a mixture of two products as a result of nonselective attack of the nucleophile on either the α- or β-carbon atom.[10] Thus, treatment of **13** with NaOMe gave a mixture of **18** and **19**. These two alcohols were not separable using various TLC systems; however, the NMR spectrum of the mixture showed a quartet at δ 4.80 and a multiplet at δ 5.20 (the combined signals integrated for one proton in an approximate 3:2 ratio), suggesting the presence of **18** and **19**. The assignment of the signal at δ 4.80 to the CHOMe in **19** and that at δ 5.20 to CHOH in **18** was deduced subsequently from analysis

Table I. Pharmacological Testing Data

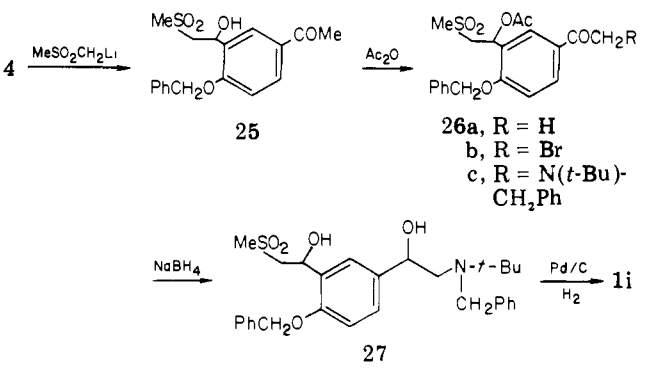
Compd	Guinea pig tracheal test,[a,b] ED_{50} (molar concn) (95% confidence limits)	Guinea pig atrial rate,[a] ED_{25} (molar concn) (95% confidence limits)	Intrinsic act. (α) in atrial test[c]	Separation ratio[d]
1d	1.8×10^{-8} ($0.7\text{-}4.6 \times 10^{-8}$)	$\sim 5.2 \times 10^{-6}$	0.3	289
1e	1.1×10^{-5}, 30%	5.6×10^{-5}, 8%		
1f	9.9×10^{-8} ($4.9\text{-}20.0 \times 10^{-8}$)	$\sim 3.0 \times 10^{-5}$	0.3	303
1g	5.3×10^{-7}[e] ($1.9\text{-}14.9 \times 10^{-7}$)	1.2×10^{-4}, 23%		~236[f]
1h	$\sim 3.4 \times 10^{-7}$[g]	1.1×10^{-4}, 0%		>320[f]
1i	1.2×10^{-5}, 34%	1.4×10^{-5}, 0%		
1j	1.5×10^{-5}[e] ($0.3\text{-}7.6 \times 10^{-5}$)	9.2×10^{-5}, 14%		>6[f]
Isoproterenol (IP)	7.1×10^{-9} ($5.2\text{-}9.9 \times 10^{-9}$)	3.4×10^{-9} ($2.6\text{-}4.6 \times 10^{-9}$)	1	0.48
N-tert-Butylnorepinephrine (BNE)	1.3×10^{-9} ($0.93\text{-}1.8 \times 10^{-9}$)	7.1×10^{-9} ($5.3\text{-}10.0 \times 10^{-9}$)	1	5.5
1c (salbutamol)	1.1×10^{-8} ($0.4\text{-}3.5 \times 10^{-8}$)	3.1×10^{-7} ($0.7\text{-}14.0 \times 10^{-7}$)	0.7	28

[a] Experimental procedure performed as described previously.[2] Where ED's were not determined results are given as percent response at the indicated concentration. [b] The intrinsic activity, α, i.e., maximum effect of test compound divided by the maximum effect induced by papaverine, is equal to 1 for all compounds for which ED_{50}'s were obtained unless otherwise indicated. [c] Determined as indicated in footnote *b* but related to maximum isoproterenol-induced response. [d] Guinea pig atrial test ED_{25} divided by tracheal test ED_{50}. [e] $\alpha = 0.9$. [f] An absolute separation ratio could not be calculated as the highest concentration tested produced an increase in atrial rate that was less than 25%. [g] $\alpha = 0.7$.

of the NMR spectra of pure **20a** and **21a** which were characterized by their corresponding acetates **20b** and **21b**. Acid-catalyzed hydrolysis of the mixture of **18** and **19** gave a mixture of **20a** and **21a** which showed two TLC spots having close R_f values. As attempts to separate these components by column chromatography were unsuccessful, the mixture of **18** and **19** was tritylated. Only the primary alcohol **19** reacted to give the corresponding nonpolar trityl ether which was readily removed from the unreacted secondary alcohol **18** by column chromatography. Acid-catalyzed cleavage of the ketal group of **18** gave pure **20a** which was acetylated to form the acetate **20b**. The NMR spectrum of **20b** showed a one-proton quartet at δ 6.44 corresponding to the CHOAc signal. This assignment is based on the large downfield shift due to the benzylic nature of the proton whereas the chemical shift of the CH_2OAc signal of the isomer **21b** was in the anticipated range. These results support the structural assignment of **20a**, whose CHOH signal appears as a multiplet at δ 5.28, and thus form the basis for assigning the signal at δ 5.20 to CHOH in the spectrum of the mixture of **18** and **19** as previously stated. Transformation of **20b** to **1g** was accomplished by bromination, amination, hydrolytic reduction, and catalytic hydrogenolysis, involving intermediates **22a–24a**. In this sequence bromination with Br_2, rather than PHT, gave a cleaner product. For the preparation of the isomer **1h**, a variation of the initial step of the above reaction sequence was undertaken (Scheme IV). The epoxide **13** was subjected to methanolysis in the presence of an acidic ion-exchange resin (Dowex 50)[11] followed by acid-catalyzed cleavage of the ketal, giving the expected product **21a** exclusively. Acetylation of **21a** gave the acetate **21b**. The structural assignments of **21a** and **21b** were supported by NMR spectral data. The CHOMe signal of **21a** was a quartet at δ 4.87, whereas the CHOMe and CH_2OAc signals of **21b** were found at δ 4.91 (triplet) and 4.21 (doublet), respectively. These data further support the previous structural assignments in the isomeric series. Transformation of **21b** to **1h** was achieved by the usual methods via intermediates **22b**, **23b**, and **24b**.

Synthesis of **1i** is outlined in Scheme V. The aldehyde **4** was treated with methylsulfonylmethyllithium followed by acid-catalyzed cleavage of the ketal group to give the methylsulfonylmethyl derivative **25**. Acetylation of **25** gave the acetate **26a**. Transformation of **26a** to **1i** was undertaken by conventional methods involving intermediates **26b**, **26c**, and **27**.

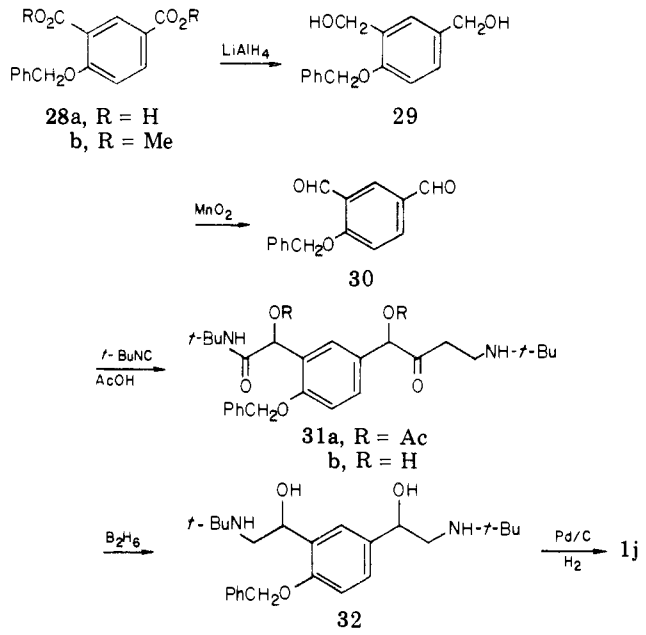
Scheme V



The synthetic route to **1j** is outlined in Scheme VI. The diacid **28a** was first esterified to the dimethyl ester **28b** which was reduced to the diol **29** with $LiAlH_4$. Oxidation of the diol to the dicarboxyaldehyde **30** was effected by activated MnO_2. Reaction of **30** with *tert*-butyl isocyanide in the presence of acetic acid (Passerini reaction)[12] gave the bis(acetoxyacetamide) **31a** which was hydrolyzed in acid to the bis(hydroxyacetamide) **31b**. Treatment of **31b** with diborane gave the bis(ethanolamine) **32**. The final product **1j** was obtained by catalytic hydrogenolysis of **32**.

Pharmacological Results and Discussion. The potential bronchodilator activity of the new analogues of salbutamol, **1d–j**, was evaluated in vitro by measuring their ability to relax a spontaneously contracted guinea pig tracheal chain preparation.[13] Cardiac stimulant potential was evaluated in vitro by changes induced in the contraction rate of spontaneously beating guinea pig right atria.[14] Comparison of the ED_{50} for tracheal relaxation with the ED_{25} for atrial stimulation offers an index of the selectivity of the compound for tracheobronchial vs. cardiac muscle and is referred to as the separation ratio.[6] Pharmacological testing data for **1d–j** and several standard

Scheme VI



28a, R = H
b, R = Me

29

30

31a, R = Ac
b, R = H

32

β-adrenergic agonists are presented in Table I. The relative potency of the present series of compounds and the standards in the tracheal chain preparation is ranked in the following decreasing order: BNE > IP > **1c** ≥ **1d** > **1f** > **1g** ≃ **1h** >> **1j** ≥ 1i ≈ 1e. The separation ratio of the compounds is similarly ranked as follows: **1h** >> **1f** > **1d** ≃ **1g** > **1c** > **1j** > BNE > IP. The separation ratios of 1e and 1i are not available because of their insufficient potency in both tests. Interpretation of these data should be exercised with caution because the stereochemistry of the present series of compounds is unknown. Except for 1e, these analogues are probably mixtures of diastereoisomers. As, with the exception of **1j**, the second asymmetric center was introduced near the final stage of the synthetic route, it may be assumed that the racemic diastereoisomeric pairs are present in nearly equal quantities. Further, the effect of stereoconfiguration of the α-carbon in the meta substituent on β-adrenoreceptor agonist activity is not known.

Transformation of the primary hydroxyl group in the meta substituent of salbutamol (**1c**) to the secondary alcohol 1d results in retention of a high degree of potency in the in vitro test for relaxation of guinea pig tracheal muscle and significantly increases the separation ratio. The marked decrease in β-adrenoreceptor agonist potency of the tertiary alcohol 1e is consistent with the observation[4] that the corresponding *N*-isopropyl homologue has weak β-adrenergic antagonist activity. In contrast to 1d, alteration of the *m*-hydroxymethyl group of salbutamol (**1c**) by addition of a second hydroxymethyl group, i.e., to give **1f**, results in a ninefold decrease in potency in the in vitro guinea pig tracheal chain test; however, the separation ratio of **1f** is about ten times greater than that of the parent. The two isomeric methoxy analogues **1g** and **1h** are also significantly less potent than salbutamol (**1c**) in the in vitro test for relaxation of guinea pig tracheal tissue; however, the separation ratio again is markedly increased. The structural hybrid of salbutamol (**1c**) and sulfonterol (**1b**), namely, 1i, is nearly devoid of β-adrenoreceptor agonist activity. Although many bis(phenylethanolamines), in which two phenylethanolamine portions are linked together between the two nitrogens by a polymethylene bridge, are potent β-adrenergic agents,[15] a congener **1j** bearing two ethanolamine chains had only weak adrenoreceptor agonist activity in the in vitro tests with guinea pig tracheal and right atrial tissue.

In summary, modification of the *m*-hydroxylmethyl group of the potent β-adrenoreceptor agonist salbutamol (**1c**) by monosubstitution on the methylene bridge of this meta functionality generally led to compounds having decreased potency in an in vitro test that measures relaxation of guinea pig tracheal muscle, a procedure that is generally predictive of potential bronchodilating activity in vivo. A similar result was noted for a congener **1h** bearing a 2-hydroxy-1-methoxyethyl group in the meta position. Despite loss of potency in this test, most of the compounds were more selective for airway smooth muscle than for cardiac muscle, as evaluated in an in vitro test that measures the compound's influence on the rate of contraction of spontaneously beating guinea pig atrial tissue. Among the relatives of salbutamol having an additional substituent on the *m*-methylene bridge, the methyl derivative 1d was the most promising candidate as a selective bronchodilator. It was about 0.6 times as effective as salbutamol in the in vitro assay for relaxation of guinea pig tracheal tissue and it was approximately ten times more selective for tracheal vs. cardiovascular tissue.

Experimental Section

Melting points were determined using a Thomas-Hoover capillary melting point apparatus. Boiling points and melting points are uncorrected. Microanalyses were determined by the Analytical and Physical Chemistry Section of Smith Kline & French Laboratories. Where analyses are reported by the symbols of elements, results were within ±0.4% of the calculated value. IR spectra were determined as Nujol mulls using a Perkin-Elmer 727 spectrophotometer. NMR spectra were recorded with a Perkin-Elmer R24 60-Hz spectrometer using Me_4Si as the internal reference and the indicated solvent at ambient temperature. Although IR and NMR data are reported only where considered significant, these spectra were obtained for all reported compounds and numbered intermediates and were evaluated as being consistent with the assigned structures. Mass spectral data were obtained with a Hitachi Perkin-Elmer RMU6E mass spectrometer.

Methyl 5-Acetylsalicylate. To a stirred solution of methyl salicylate (75 g, 0.5 mol) and acetyl chloride (40 g, 0.5 mol) in 600 mL of tetrachloroethylene at 0 °C was slowly added $AlCl_3$ (133 g, 1.0 mol), keeping the solution temperature below 25 °C. After being stirred for 4 h at 25 °C, the mixture was poured into ice–H_2O. The organic layer was separated, washed with H_2O and $NaHCO_3$ solution, and dried. The solvent was evaporated and the residue crystallized from hexane to give 55 g (57%) of colorless crystals, mp 60–62 °C (lit.[4] mp 55 °C).

2-(4-Benzyloxy-3-hydroxymethylphenyl)-2-methyl-1,3-dioxolane (3). A solution of 2[4] (54 g, 0.19 mol), 25 mL of ethylene glycol, and *p*-toluenesulfonic acid (2.0 g) in 500 mL of C_6H_6 was refluxed azeotropically for 18 h. The solution was washed with 5% Na_2CO_3 and H_2O and dried. The solvent was evaporated to give a yellow oil (ethylene ketal of 2). A solution of this oil in Et_2O (300 mL) was added to a stirred suspension of $LiAlH_4$ (7.0 g) in 500 mL of Et_2O. The mixture was refluxed for 2 h and stirred for 18 h at 25 °C. Excess $LiAlH_4$ was destroyed by the *cautious* dropwise addition of 14 mL of H_2O and 11.5 mL of 2.5 N NaOH. Insoluble material was removed by filtration. Evaporation of the filtrate gave 38.5 g (68%) of 3 as an oil: TLC (alumina, Et_2O) showed a single spot.

2-(4-Benzyloxy-3-formylphenyl)-2-methyl-1,3-dioxolane (4). A solution of 3 (13.5 g, 0.045 mol) in 350 mL of CH_2Cl_2 was stirred with activated MnO_2 (100 g) at 25 °C for 1 h. The mixture was filtered and the filtrate was evaporated to dryness. The crystalline residue was recrystallized from EtOH to give 12.0 g (89%) of 4: mp 78–80 °C; TLC (alumina, Et_2O–petroleum ether 2:3) showed a single spot. Anal. ($C_{18}H_{18}O_4$) C, H.

4-Benzyloxy-3-(1-hydroxyethyl)acetophenone (5). To a solution of MeMgI [prepared from Mg turnings (960 mg, 0.04 g-atom) and excess MeI] in 50 mL of Et_2O was added a solution of 4 (6.0 g, 0.02 mol) in 150 mL of Et_2O. The mixture was refluxed for 3 h and then stirred with saturated aqueous NH_4Cl. The Et_2O

solution was washed with H_2O, dried, and evaporated. The residue was recrystallized from $CHCl_3$–petroleum ether to give 3.5 g (65%) of **5**: mp 95–98 °C; TLC (alumina, Et_2O–petroleum ether 1:1) showed a single spot. Anal. ($C_{17}H_{18}O_3$) H; C: calcd, 75.53; found, 74.98.

4-Benzyloxy-α-bromo-3-(1-hydroxyethyl)acetophenone (6). A solution of **5** (12.8 g, 0.0475 mol), pyrrolidinone (4.46 g, 0.0525 mol), and pyrrolidinone hydrotribromide (26.0 g, 0.0525 mol) in 450 mL of tetrahydrofuran (THF) was refluxed for 3 h. Insoluble material was removed by filtration. The filtrate was concentrated to one-third of its volume and poured into 500 mL of ice–H_2O. The precipitated product was filtered, washed with H_2O, and dried. Recrystallization from Me_2CO–hexane gave 8.7 g (53%) of **6**: mp 136–137 °C; TLC (silica gel, Et_2O–petroleum ether 3:2) showed a single spot. Anal. ($C_{17}H_{17}BrO_3$) C, H.

4-Benzyloxy-α-*tert*-butylaminomethyl-3-(1-hydroxyethyl)benzyl Alcohol (8). A solution of **6** (2.0 g, 5.73 mmol) in 20 mL of Me_2SO was stirred at 25 °C for 72 h. The crystalline precipitate was filtered, washed with H_2O, and dried to give 1.2 g of the glyoxal **7**, mp 152–158 °C. A solution of **7** (1.0 g, 3.52 mmol) in 50 mL of EtOH and 20 mL of *tert*-butylamine was refluxed for 2 h. The solvent was evaporated to give 1.1 g of 4-benzyloxy-α-*tert*-butyliminomethyl-3-(1-hydroxyethyl)benzyl alcohol as an oil: TLC (alumina, Et_2O–$CHCl_3$ 1:1) showed a single spot; NMR and IR spectral data supported the assigned structure. A solution of the above product (1.1 g, 3.16 mmol) in 50 mL of EtOH was stirred with $NaBH_4$ (1.1 g) at 25 °C for 18 h. The solvent was evaporated and the residue was dissolved in EtOAc. The EtOAc solution was extracted with 0.5 N HCl. The aqueous extract was washed with Et_2O and made alkaline with 2.5 N NaOH, and the mixture was extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with H_2O, dried, and concentrated to give 0.85 g (43% overall) of **8** as an oil: TLC (silica gel, MeOH–$CHCl_3$–HCOOH 20:80:3) showed a single spot.

α-*tert*-Butylaminomethyl-4-hydroxy-3-(1-hydroxyethyl)benzyl Alcohol (1d). A solution of **8** (850 mg, 2.5 mmol) in 50 mL of EtOH was hydrogenated over 10% Pd/C (1.0 g) at 3.5 kg/cm^2 for 10 min at ambient temperature. The mixture was filtered and the filtrate was evaporated to dryness to give **1d** as an oil. A solution of this oil (640 mg) in 20 mL of 2-PrOH was treated with 138 mg (0.5 mol equiv) of fumaric acid in 10 mL of 2-PrOH and chilled. The crystalline salt was filtered and recrystallized from 2-PrOH to give 450 mg (49%) of **1d** hemifumarate 2-propanolate: mp 181–183 °C; TLC (silica gel, MeOH–$CHCl_3$–HCOOH 20:80:3) showed a single spot. Anal. ($C_{14}H_{23}NO_3 \cdot 0.5C_4H_4O_4 \cdot C_3H_7OH$) C, H, N.

α-(Benzyl-*tert*-butylamino)-4-benzyloxy-3-carbomethoxyacetophenone (10). A solution of **9**[4] (18.15 g, 0.05 mol) and *tert*-butylbenzylamine (16.3 g, 0.1 mol) in 100 mL of MeCN was refluxed for 2 h. After addition of 50 mL of Et_2O, the mixture was chilled and the precipitated solid was filtered. The filtrate was evaporated and the residue was chromatographed on an alumina column (eluted with Et_2O). The initial fractions were evaporated to give 12.0 g (54%) of **10** as an oil: TLC (alumina, Et_2O–petroleum ether 2:3) showed only one spot.

α-(*N*-Benzyl-*tert*-butylaminomethyl)-4-benzyloxy-3-carbomethoxybenzyl Alcohol (11). A solution of **10** (5.6 g, 0.013 mol) in 100 mL of EtOH was stirred with $NaBH_4$ (0.5 g, 0.13 mol) at 25 °C for 3 h and at 45 °C for 0.5 h. Excess $NaBH_4$ was decomposed by addition of 3 N HCl (5 mL), and the EtOH was evaporated. The aqueous solution of the residue was made alkaline with 2.5 N NaOH and the mixture was extracted with Et_2O–EtOAc. The extract was washed with H_2O, dried, and concentrated. The residual oil crystallized from $CHCl_3$–hexane to give 4.2 g (74%) of **11**, mp 96–98 °C. Anal. ($C_{28}H_{33}NO_4$) C, H, N.

α-(*N*-Benzyl-*tert*-butylaminomethyl)-4-benzyloxy-3-(1-hydroxy-1-methylethyl)benzyl Alcohol (12). A stirred solution of **11** (1.9 g, 4.25 mmol) in 300 mL of anhydrous THF was treated with 9 mL of a 3 M solution of MeMgBr in THF. After being stirred for 15 min at 25 °C, saturated aqueous NH_4Cl was added to the mixture. The organic solvent was evaporated and the aqueous residue was extracted with Et_2O. The extract was washed with H_2O, dried, and concentrated to give 1.53 g (83%) of **12** as an oil: TLC (alumina, Et_2O–petroleum ether 1:1) showed a single spot.

α-*tert*-Butylaminomethyl-4-hydroxy-3-(1-hydroxy-1-methylethyl)benzyl Alcohol (1e). A solution of **12** (500 mg, 1.12 mmol) in 100 mL of EtOH was hydrogenated over 10% Pd/C (100 mg) at 3.5 kg/cm^2 for 25 min at ambient temperature. The mixture was filtered and the filtrate was concentrated. The residue in 5 mL of EtOH was treated with fumaric acid (0.5 mol equiv) and 3 mL of Et_2O was added to precipitate the salt. Recrystallization from 2-PrOH gave 230 mg (64%) of **1e** hemifumarate, mp 176–178 °C. Anal. ($C_{15}H_{25}NO_3 \cdot 0.5C_4H_4O_4 \cdot 0.5H_2O$) C, H, N.

2-(4-Benzyloxy-3-epoxyethylphenyl)-2-methyl-1,3-dioxolane (13). A suspension of NaH (1.21 g, 0.05 mol) in 35 mL of anhydrous Me_2SO was stirred at 65 °C for 1 h under Ar. The now clear solution was diluted with 50 mL of anhydrous THF, chilled to −15 °C, and treated with a solution of trimethylsulfonium iodide (9.46 g, 0.046 mol) in 50 mL of anhydrous Me_2SO. After 3 min, a solution of **4** (13.8 g, 0.046 mol) in 75 mL of anhydrous THF was added; the mixture was allowed to warm to 25 °C and stirred for 18 h. The mixture was poured into ice–H_2O and extracted with Et_2O. The extract was washed with H_2O, dried, and evaporated. The oily residue was chromatographed on an alumina column (eluted with Et_2O–hexane 1:1). The initial fractions were evaporated to give 10.6 g (74%) of **13**: mp 40–42 °C; TLC (alumina, Et_2O–hexane 2:3) showed only one spot. Anal. ($C_{19}H_{20}O_4$) C, H.

4-Benzyloxy-3-(1,2-dihydroxyethyl)acetophenone (14a). A solution of **13** (8.8 g, 0.028 mol) in 100 mL of dioxane, 20 mL of H_2O, and 1.5 mL of $HClO_4$ was stirred at 25 °C for 15 min. The acidic solution was made alkaline with 50 mL of 5% Na_2CO_3 and the dioxane was evaporated. The aqueous mixture was extracted with EtOAc. The extract was washed with H_2O, dried, and concentrated. The solid residue was recrystallized from C_6H_6 to give 6.0 g (75%) of **14a**, mp 121–123 °C. Anal. ($C_{17}H_{18}O_4$) C, H.

3-(1,2-Diacetoxyethyl)-4-benzyloxyacetophenone (14b). A solution of **14a** (7.2 g, 0.025 mol) in 40 mL of pyridine and 15 mL of Ac_2O was stirred at 25 °C for 18 h. The chilled solution was stirred with 10 mL of MeOH for 30 min and poured into H_2O. The mixture was extracted with Et_2O. The extract was washed with 1 N HCl and H_2O and dried. Evaporation of the solvent gave 8.9 g (95%) of **14b** as an oil: TLC (silica gel, Et_2O–petroleum ether 2:3) showed a single spot.

3-(1,2-Diacetoxyethyl)-4-benzyloxy-α-bromoacetophenone (15). A solution of **14b** (8.9 g, 0.024 mol), pyrrolidinone hydrotribromide (11.93 g, 0.024 mol), and 1.82 mL of pyrrolidinone in 250 mL of THF was refluxed for 2.5 h. The insoluble material was filtered. The filtrate was concentrated and poured into H_2O, and the mixture was extracted with Et_2O. The extract was dried and concentrated. The oily residue crystallized from Et_2O–petroleum ether to give 4.4 g (41%) of **15**, mp 80–82 °C. Anal. ($C_{21}H_{21}BrO_6$) C, H.

3-(1,2-Diacetoxyethyl)-α-benzyl-*tert*-butylamino-4-benzyloxyacetophenone (16). A solution of **15** (4.40 g, 9.8 mmol) and *tert*-butylbenzylamine (3.04 g, 18.6 mmol) in 50 mL of MeCN was refluxed for 3.5 h. To the chilled solution was added 100 mL of Et_2O, and the insoluble material was filtered. The filtrate was concentrated to leave a residue which was chromatographed on an alumina column (eluted with $CHCl_3$–hexane 3:2). The second fraction was evaporated to give **16** as an oil. The oil was dissolved in a small amount of EtOH–Et_2O and treated with ethereal HCl. The hygroscopic precipitate was filtered to give 2.1 g (38%) of **16**·HCl: TLC of the free base (silica gel, $CHCl_3$–Et_2O 3:2) showed a single spot.

α-(*N*-Benzyl-*tert*-butylaminomethyl)-4-benzyloxy-3-(1,2-dihydroxyethyl)benzyl Alcohol (17). A solution of **16**·HCl (2.0 g, 3.53 mmol) in 100 mL of EtOH was stirred with $NaBH_4$ (1.0 g, 0.03 mol) at 25 °C for 18 h and then evaporated. The residue was dissolved in EtOAc–H_2O. The EtOAc solution was separated, washed with H_2O, dried, and evaporated to give **17** as an oil. Treatment of **17** in 2-PrOH with fumaric acid (0.5 mol equiv) and addition of Et_2O to the solution precipitated **17** hemifumarate, mp 148–149 °C. Anal. ($C_{28}H_{35}NO_4 \cdot 0.5C_4H_4O_4 \cdot 0.5H_2O$) C, H, N.

α-*tert*-Butylaminomethyl-4-hydroxy-3-(1,2-dihydroxyethyl)benzyl Alcohol (1f). A solution of **17** (800 mg, 1.78 mmol) in 100 mL of EtOH was hydrogenated over 10% Pd/C (500 mg) at 3.5 kg/cm^2 for 25 min. The mixture was filtered and the filtrate

was evaporated to give **1f**. Treatment of **1f** in MeOH with fumaric acid (0.5 mol equiv) and addition of Et_2O precipitated the salt. Recrystallization from MeOH–Et_2O gave 480 mg (83%) of **1f** hemifumarate: mp 190–192 °C dec; mass spectral data supported the assigned structure. Anal. ($C_{14}H_{23}NO_4 \cdot 0.5C_4H_4O_4 \cdot 0.5H_2O$) C, H, N.

4-Benzyloxy-3-(1-hydroxy-2-methoxyethyl)acetophenone (20a). A solution of **13** (10.0 g, 32.1 mmol) and NaOMe (prepared from 2.5 g of Na) in 500 mL of MeOH was refluxed for 5 h and stirred at 25 °C for 18 h. The solution was evaporated and the residue was dissolved in Et_2O. The Et_2O solution was washed with H_2O, dried, and concentrated to give 10.0 g of a mixture of the ketals **18** and **19**. A solution of this mixture in 25 mL of pyridine was heated with freshly recrystallized trityl chloride (6.1 g, 0.022 mol) at 60–70 °C for 2.5 h and at 55–60 °C for 18 h. The solvent was evaporated and the residue was dissolved in a mixture of Et_2O and H_2O. The Et_2O solution was washed with H_2O, dried, and concentrated. The residue was chromatographed on a neutral alumina column. Initial fractions of the eluent (Et_2O–hexane 1:1) removed the trityl ether of **19** (as indicated by NMR spectral data) and other impurities. Elution with EtOAc and evaporation of the solvent gave the ketal **18** as indicated by TLC analysis (alumina, Et_2O–petroleum ether 3:2) and NMR and IR spectral data. A solution of the ketal **18** in THF was treated with 1 N HCl. The THF was evaporated, and the aqueous solution was extracted with Et_2O. The extract was dried and evaporated to give 1.43 g (15% from **13**) of **20a** as an oil: TLC (alumina, Et_2O–petroleum ether 3:2) showed a single spot.

3-(1-Acetoxy-2-methoxyethyl)-4-benzyloxyacetophenone (20b). A solution of **20a** (4.3 g, 14.3 mmol) in 60 mL of pyridine and 5 mL of Ac_2O was stirred at 25 °C for 18 h. After addition of 10 mL of MeOH to the chilled solution, it was stirred for 30 min and poured into H_2O. The mixture was extracted with Et_2O. The extract was washed with 1 N HCl and H_2O and dried. After evaporation of the solvent, the residue was chromatographed on a silica gel column and eluted with Et_2O. Evaporation of the eluate and recrystallization of the residue from $CHCl_3$–hexane gave 3.3 g (67%) of **20b**, mp 83–84 °C. Anal. ($C_{20}H_{22}O_5$) C, H.

4-Benzyloxy-3-(2-hydroxy-1-methoxyethyl)acetophenone (21a). A solution of **13** (10.0 g, 0.032 mol) in 700 mL of anhydrous MeOH was stirred vigorously with Dowex 50[11] (70 g, previously washed with 3 N HCl, H_2O, and MeOH and dried in vacuo at 95 °C for 6 h) for 5 min. The resin was removed by filtration and the filtrate was evaporated to dryness. The residue was dissolved in EtOAc and the solution was shaken v'gorously with 1 N HCl. The organic solution was washed with H_2O, dried, and concentrated. Trituration of the residue with Et_2O gave 10.6 g of **21a** as a solid: TLC (alumina, Et_2O–petroleum ether 2:3) showed a single spot. A sample recrystallized from CH_2Cl_2–hexane had mp 78–80 °C. Anal. ($C_{18}H_{20}O_4$) C, H.

3-(2-Acetoxy-1-methoxyethyl)-4-benzyloxyacetophenone (21b). The alcohol **21a** was acetylated in a manner similar to that described for the preparation of **20b** to give **21b** in 60% yield after recrystallization from Me_2CO–hexane: mp 67–70 °C. Anal. ($C_{20}H_{22}O_5$) C, H.

3-(1-Acetoxy-2-methoxyethyl)-4-benzyloxy-α-bromoacetophenone (22a). A solution of **20b** (2.9 g, 8.49 mmol) in 200 mL of $CHCl_3$ was stirred with Br_2 (0.478 mL, 9.34 mmol) for 30 min. The $CHCl_3$ solution was washed with H_2O and 5% $NaHCO_3$, dried, and evaporated. The residue crystallized from $CHCl_3$–hexane to give 3.0 g (84%) of **22a**: mp 91–93 °C; TLC (silica gel, Et_2O–petroleum ether 1:1) showed one major component with a trace of impurity of higher R_f.

3-(2-Acetoxy-1-methoxyethyl)-4-benzyloxy-α-bromoacetophenone (22b). The alcohol **21b** was brominated in a manner similar to that described for the preparation of **22a** to give **22b** in 61% yield after recrystallization from Et_2O–petroleum ether: mp 79–80 °C. Anal. ($C_{20}H_{21}BrO_5$) C, H.

3-(1-Acetoxy-2-methoxyethyl)-α-benzyl-*tert*-butylamino-4-benzyloxyacetophenone (23a). A solution of **22a** (3.0 g, 7.13 mmol) and *tert*-butylbenzylamine (2.21 g, 13.56 mmol) in 50 mL of MeCN was refluxed for 4 h. The solvent was evaporated, and the residue was taken up in Et_2O. The Et_2O solution was washed with H_2O, dried, and treated with ethereal HCl. The Et_2O was decanted from the precipitated gummy HCl salt, and the gum was dissolved in H_2O. The aqueous solution was washed with Et_2O and made alkaline with 2.5 N NaOH, and the mixture was extracted with Et_2O. The extract was washed with H_2O, dried, and evaporated to give 2.23 g (62%) of **23a**: TLC (silica gel, Et_2O–$CHCl_3$ 1:4) showed only one spot.

3-(2-Acetoxy-1-methoxyethyl)-α-(benzyl-*tert*-butylamino)-4-benzyloxyacetophenone (23b). A solution of **22b** (4.7 g, 11.16 mmol) and *tert*-butylbenzylamine (2.86 g, 17.5 mmol) in 35 mL of MeCN was refluxed for 5 h and stirred at 25 °C for 18 h. After addition of 150 mL of Et_2O, the mixture was chilled and the precipitated solid was removed by filtration. The filtrate was evaporated and the residue was chromatographed on a silica gel column (eluted with Et_2O–$CHCl_3$ 1:9). The initial fractions were evaporated to dryness to give 1.6 g (29%) of **23b** as an oil: TLC (silica gel, Et_2O–$CHCl_3$ 2:3) showed a single spot.

α-(*N*-Benzyl-*tert*-butylaminomethyl)-4-benzyloxy-3-(1-hydroxy-2-methoxyethyl)benzyl Alcohol (24a). A solution of **23a** (2.2 g, 4.37 mmol) in 70 mL of EtOH was treated with $NaBH_4$ (2.5 g, 0.067 mol) at 25 °C for 18 h. After evaporating the solvent, the residue was dissolved in a mixture of 50 mL of MeOH and 10 mL of 20% K_2CO_3. After the solution was refluxed for 30 min, the MeOH was evaporated and the mixture was extracted with EtOAc. The extract was washed with H_2O, dried, and concentrated. The residue was chromatographed on a silica gel column. Elution with Et_2O and evaporation of the eluate gave 1.4 g (69%) of **24a**: TLC (silica gel, Et_2O) showed a single spot.

α-(*N*-Benzyl-*tert*-butylaminomethyl)-4-benzyloxy-3-(2-hydroxy-1-methoxyethyl)benzyl Alcohol (24b). A solution of **23b** (1.6 g, 3.18 mmol) in 100 mL of MeOH was stirred with $NaBH_4$ (1.6 g, 0.042 mol) at 25 °C for 18 h, and then it was evaporated. The residue was dissolved in EtOAc and the solution was washed with H_2O, dried, and concentrated. The residue was chromatographed on a neutral alumina column. Initial fractions of eluents (Et_2O and EtOAc) were discarded. Evaporation of later fractions (MeOH–EtOAc 1:19) gave 0.7 g (48%) of **24b** as an oil: TLC (alumina, MeOH–$CHCl_3$ 1:19) showed a single spot; mass spectral data supported the assigned structure.

α-*tert*-Butylaminomethyl-4-hydroxy-3-(1-hydroxy-2-methoxyethyl)benzyl Alcohol (1g). A solution of **24a** (1.0 g, 2.16 mmol) in 120 mL of EtOH was hydrogenated over 1.0 g of 10% Pd/C at 3.5 kg/cm^2 for 10 min. The filtrate was concentrated, treated with ethereal HCl, and diluted with Et_2O. The precipitated HCl salt was recrystallized from EtOH–Et_2O to give 0.45 g (65%) of **1g**·HCl, mp 194–195 °C. Anal. ($C_{15}H_{25}NO_4 \cdot HCl$) C, H, N.

α-*tert*-Butylaminomethyl-4-hydroxy-3-(2-hydroxy-1-methoxyethyl)benzyl Alcohol (1h). Compound **24b** was hydrogenated in a manner similar to that described for the preparation of **1g** to give 94% yield of **1h** as an oil. Treatment of **1h** in MeOH with fumaric acid (0.5 mol equiv) and addition of Et_2O to the solution precipitated **1h** hemifumarate: mp 230 °C dec; mass spectral data supported the assigned structure. Anal. ($C_{15}H_{25}NO_4 \cdot 0.5C_4H_4O_4 \cdot 0.75H_2O$) C, H, N.

4-Benzyloxy-3-(1-hydroxy-2-methylsulfonylethyl)acetophenone (25). A solution of dimethyl sulfone (10.0 g, 0.106 mol) in 150 mL of anhydrous THF was refluxed with *n*-BuLi (0.074 mol) for 1 h and cooled to 25 °C. A solution of **4** (20.0 g, 0.067 mol) in 150 mL of anhydrous THF was added. After being stirred for 30 min, 50 mL of H_2O and 50 mL of 2 N HCl were added to the solution. The THF was evaporated and the aqueous mixture was extracted with EtOAc. The extract was washed with H_2O, dried, and evaporated to dryness. The solid residue was recrystallized from EtOH to give 16.4 g (70%) of **25**, mp 136–138 °C. Anal. ($C_{18}H_{20}O_5S$) C, H.

3-(1-Acetoxy-2-methylsulfonylethyl)-4-benzyloxyacetophenone (26a). The alcohol **25** was acetylated in a manner similar to that described for the preparation of **20b** to give **26a** in 89% yield after recrystallization from Me_2CO–hexane, mp 117–120 °C. Anal. ($C_{20}H_{22}O_6S$) C, H.

3-(1-Acetoxy-2-methylsulfonylethyl)-4-benzyloxy-α-bromoacetophenone (26b). The acetate **26a** was brominated in a manner similar to that described for the preparation of **22a** to give **26b** in 56% yield after two recrystallizations from Me_2CO: mp 155–157 °C. Anal. ($C_{20}H_{21}BrO_6S$) C, H.

3-(1-Acetoxy-2-methylsulfonylethyl)-α-(benzyl-*tert*-butylamino)-4-benzyloxyacetophenone (26c). The bromo ketone **26b** was treated with *tert*-butylbenzylamine in a manner similar

to that described for the preparation of **23b**. The resulting oil was chromatographed on an alumina column. Elution with Et_2O gave **26c** as an oil: TLC (alumina, Et_2O–petroleum ether 1:1) showed a single spot. Treatment of a solution of **26c** in Et_2O with ethereal HCl precipitated 1.9 g (18%) of **26c**·HCl, mp 134 °C dec. Anal. ($C_{31}H_{37}NO_6S$·HCl·H_2O) C, H, N.

α-(*N*-Benzyl-*tert*-butylaminomethyl)-4-benzyloxy-3-(1-hydroxy-2-methylsulfonylethyl)benzyl Alcohol (27). The amino ketone **26c**·HCl was treated with $NaBH_4$ in a manner similar to that described for the preparation of **24a**. The crude product was chromatographed on an alumina column. Initial fractions of the eluent (Et_2O) removed impurities. Elution with MeOH–EtOAc (1:9) and evaporation of the solvent gave 0.24 g (16%) of **27** as an oil: TLC (alumina, Et_2O) showed a single spot.

α-*tert*-Butylaminomethyl-4-hydroxy-3-(1-hydroxy-2-methylsulfonylethyl)benzyl Alcohol (1i). The amino alcohol **27** (240 mg) was hydrogenated over 10% Pd/C at ambient temperature and an initial H_2 pressure of 3.5 kg/cm^2 to give 160 mg of **1i**. A solution of **1i** in EtOH was treated with fumaric acid (0.5 mol equiv). Addition of EtOAc precipitated the salt. Recrystallization from EtOH–EtOAc gave 100 mg (55%) of **1i** hemifumarate: mp 152 °C dec; mass spectral data supported the assigned structure. Anal. ($C_{15}H_{25}NO_5S$·0.5$C_4H_4O_4$·H_2O) C, H, N.

Dimethyl 4-Benzyloxyisophthalate (28b). A solution of **28a**[13] (2.0 g, 7.35 mmol) in 100 mL of MeOH and 0.1 mL of concentrated H_2SO_4 was refluxed for 18 h and then evaporated. The residue was dissolved in Et_2O. The Et_2O solution was washed with 5% $NaHCO_3$, dried, and concentrated. The residue was recrystallized from EtOH to give 1.2 g (55%) of **28b**: mp 103–104 °C; TLC (silica gel, Et_2O–petroleum ether 3:7) showed a single spot. Anal. ($C_{17}H_{18}O_5$) C, H.

4-Benzyloxyisophthalyl Alcohol (29). A suspension of $LiAlH_4$ (600 mg) in 30 mL of Et_2O was refluxed with a solution of **28b** (1.1 g, 3.67 mmol) in 30 mL of Et_2O and 5 mL of THF for 3 h. Excess $LiAlH_4$ was decomposed by *cautious* dropwise addition of 1.2 mL of H_2O and 1 mL of 2.5 N NaOH. Insoluble material was removed by filtration, and the filtrate was evaporated. The residue was recrystallized from Me_2CO–hexane to give 0.55 g (61%) of **29**: mp 90–92 °C; TLC (silica gel, Et_2O) showed a single spot. Anal. ($C_{15}H_{18}O_3$) C, H.

4-Benzyloxyisophthalaldehyde (30). A solution of **29** (300 mg, 1.23 mmol) in 50 mL of CH_2Cl_2 was refluxed with activated MnO_2 (3 g) for 1.5 h. After the mixture was filtered, the filtrate was evaporated to give 270 mg (92%) of crystalline **30**: mp 104–105 °C; TLC (silica gel, Et_2O–petroleum ether 2:3) showed a single spot. Anal. ($C_{15}H_{14}O_3$) C, H.

Bis[2,4-(2-*tert*-butylamino-1-hydroxyethyl)phenol] (1j). A solution of **30** (5.16 g, 0.0215 mol) in $CHCl_3$ (100 mL), AcOH (9 mL), and *tert*-butyl isocyanide (14 g) was refluxed for 48 h. The solution was washed with 5% $NaHCO_3$ and H_2O and dried. The solvent was evaporated and the residue was chromatographed on a silica gel column (eluted with Et_2O). Evaporation of the initial fractions gave 5.4 g of crude acetoxyamide **31a**.

A solution of crude **31a** (5.4 g) in 150 mL of MeOH and 45 mL of 2.5 N HCl was refluxed for 2.5 h, and the MeOH was then evaporated. The aqueous solution was extracted with Et_2O. The extract was washed with 5% $NaHCO_3$ and H_2O and dried. Evaporation of the solvent gave 3.7 g (39% from **30**) of the hydroxyamide **31b** as a foam: TLC (silica gel, Et_2O) showed a single spot.

To 90 mL of a 1 M solution of diborane in THF was added a solution of **31b** (3.7 g, 8.4 mmol) in 50 mL of THF. The mixture was refluxed for 2 h. The chilled solution was treated *cautiously* with 20 mL of MeOH and 20 mL of 3 N HCl, and the THF was evaporated. The aqueous solution was made alkaline with 2.5 N NaOH and extracted with Et_2O. The extract was treated with ethereal HCl, and the precipitated HCl salt was extracted into H_2O. The aqueous extract was washed with Et_2O, made alkaline with 2.5 N NaOH, and extracted with Et_2O. The extract was dried and evaporated to give 1.73 g (50%) of the ethanolamine **32** as an oil: TLC (silica gel, MeOH–Et_2O 1:19) showed a major component and two minor impurities.

A solution of **32** (1.2 g, 2.9 mmol) in 100 mL of EtOH was hydrogenated over 10% Pd/C (1.0 g) at 3.5 kg/cm^2 for 10 min. The mixture was filtered and the filtrate was evaporated. The residue in 30 mL of EtOH was treated with fumaric acid (1 mol equiv). The salt crystallized on dilution with EtOAc (20 mL) and cooling. Four recrystallizations from MeOH–EtOAc gave 0.24 g (19%) of **1j** hemifumarate: mp 243 °C dec; mass spectral data supported the assigned structure. Anal. ($C_{18}H_{32}N_2O_3$·$C_4H_4O_4$) H, N; C: calcd, 59.98; found, 61.37.

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Central Nervous System Activity of a Novel Class of Annelated 1,4-Benzodiazepines, Aminomethylene-2,4-dihydro-1*H*-imidazo[1,2-*a*][1,4]benzodiazepin-1-ones[1]

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The synthesis and CNS activity of a novel class of annelated 1,4-benzodiazepines, the aminomethylene-2,4-dihydro-1*H*-imidazo[1,2-*a*][1,4]benzodiazepines, are described. An investigation of the structure–activity relationships in the series derived from 8-chloro-2,4-dihydro-2-dimethylaminomethylene-6-phenyl-1*H*-imidazo[1,2-*a*][1,4]-benzodiazepin-1-one (**10**) led to the synthesis of a group of compounds with potent minor tranquillizer activity.

The 1,4-benzodiazepines are a remarkable class of compounds with potent minor tranquillizer, muscle-relaxant, anticonvulsant, and sedative–hypnotic activity, whose pharmacological and clinical eminence is attested