was hydrogenated at room temperature and atmospheric pressure until there was no further uptake of hydrogen. The mixture was filtered and the filtrate was evaporated to dryness. The residue was dissolved in EtOAc (200 mL) and the solution was extracted with 2 N Na_2CO_3 (200 mL) and then washed with H_2O (200 mL). The EtOAc phase was dried ($MgSO_4$) and evaporated under reduced pressure and the residue was crystallized from a mixture of equal volumes of EtOAc and petroleum ether (bp 80–100 °C): yield 24 g (33.7%); mp 94–06 °C. Anal. ($C_{10}H_{13}O_2N$) C, H, N.

Method F. 4-Acetamidomethyl-2-chlorophenol. A mixture of 3-chloro-4-hydroxybenzylamine hydrochloride (4.9 g, 0.025 mol), H_2O (50 mL), NaOH (1.0 g, 0.025 mol), and acetic anhydride (10.0 mL, 0.1 mol) was heated on a steam bath for 4 h. The mixture was evaporated to dryness and the residue was dissolved in 2 N NaOH (25 mL) and then poured onto a mixture of ice and 11 N HCl (10 mL). The mixture was filtered and the solid residue washed with water and dried: yield 4.4 g (90%); mp 150 °C. Anal. ($C_9H_{10}ClNO_2$) C, H, N.

***N*-(4-Allyloxybenzyl)propionamide.** A mixture of 4-propionamidomethylphenol (7.1 g, 0.04 mol), allyl bromide (3.52 mL, 0.04 mol), acetone (100 mL), and K_2CO_3 (5.52 g, 0.04 mol) was heated under reflux with stirring for 6 h. The mixture was then filtered and evaporated to dryness under reduced pressure and the residue was stirred with ether (50 mL) and 1 N NaOH (50 mL). The ether phase was separated, dried ($MgSO_4$), and evaporated under reduced pressure. The residue was crystallized from petroleum ether (bp 80–100 °C): yield 2.7 g (31%); mp 80–82 °C. Anal. ($C_{13}H_{17}NO_2$) C, H, N.

2-Allyl-4-propionamidomethylphenol. *N*-(Allyloxybenzyl)propionamide (2.5 g, 0.011 mol) was heated at 220 °C for 40 min, cooled, and dissolved in 1 N NaOH (20 mL). The solution was extracted twice with ether (20 mL), and the aqueous phase was acidified and extracted twice with ether (25 mL). The ether extracts were dried ($MgSO_4$) and evaporated under reduced pressure and the solid residue was crystallized from petroleum ether (bp 80–100 °C): yield 1.5 g (62%); mp 86–88 °C. Anal. ($C_{13}H_{17}NO_2$) C, H, N.

2-*n*-Propyl-4-propionamidomethylphenol. A mixture of 2-allyl-4-propionamidomethylphenol (2.2 g, 0.01 mol), EtOH (50 mL), and 5% Pd/C (0.3 g) was hydrogenated at atmospheric pressure and room temperature until there was no further uptake of hydrogen. The mixture was filtered, the filtrate was evaporated to dryness, and the residue crystallized from a mixture of equal volumes of EtOAc and petroleum ether (bp 60–80 °C): yield 1.6 g (72%); mp 117–118 °C. Anal. ($C_{13}H_{19}NO_2$) C, H, N.

3-Chloro-4-hydroxybenzylamine Hydrochloride. A solution of 4-hydroxybenzylamine (8.0 g, 0.05 mol) in HOAc (200 mL) was cooled to 10 °C and a rapid stream of anhydrous Cl_2 was passed through the solution for 10 min. The mixture was filtered and the solid residue was washed with ether: yield 4.5 g (46%); mp 244–246 °C. Anal. ($C_7H_9Cl_2NO$) C, H, N.

3-Bromo-4-hydroxybenzylamine Hydrobromide. A solution of 4-hydroxybenzylamine (8.0 g, 0.05 mol) in HOAc (400 mL) was cooled to 10 °C and a solution of Br_2 (2.75 mL, 0.05 mol) in HOAc (100 mL) was added dropwise, with stirring, over 30 min. The mixture was evaporated under reduced pressure to a volume of 300 mL and cooled until the product crystallized. The mixture was filtered and the solid residue was crystallized from a mixture of equal volumes of ethanol and ether: yield 4.0 g (28%); mp 262 °C dec. Anal. ($C_7H_9Br_2NO$) C, H, N.

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Adrenergic Agents. 7.[1] Synthesis and β-Adrenergic Agonist Activity of Several 2-Pyridylethanolamines

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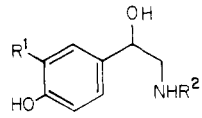
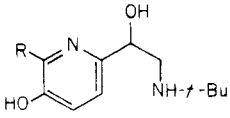
In a search for new selective bronchodilators, three 2-pyridylethanolamines, i.e., 2-*tert*-butylamino-1-(5-hydroxy-2-pyridyl)ethanol (**2b**), a related 6-methylsulfonylmethyl (**2c**), and a 6-methyl (**2d**) derivative, were prepared. These compounds were examined for potential bronchodilator activity in an in vitro test for relaxation of guinea pig tracheal tissue. Potential cardiac stimulant activity was evaluated in vitro by measuring changes in the rate of spontaneously beating guinea pig right atrial muscle. Comparison of potency in the tracheal test relative to that in the atrial procedure provides a measure of selectivity. Results of this study indicate that replacement of the phenyl ring of a para-hydroxylated phenylethanolamine with a 2-pyridyl system generally results in compounds which retain a high order of potency in the tracheal test; however, selectivity for tracheobronchial vs. cardiac tissue is markedly greater for the pyridyl derivatives. The α-picoline, 2-*tert*-butylamino-1-(5-hydroxy-6-methyl-2-pyridyl)ethanol (**2d**), which bears labile protons at a position meta to the ethanolamine side chain, was about equipotent with the corresponding 6-unsubstituted relative **2b**. The reason for the failure of these apparently appropriately located labile protons to enhance β-adrenoreceptor agonist activity is uncertain.

In previous publications, we described that replacing the *m*-hydroxyl group in isoproterenol with a ureido or methylsulfonylmethyl group led to potent and selective β_2-adrenergic receptor agonists as exemplified by carbuterol

(**1a**)[2] and sulfonterol (**1b**)[3] which are currently being examined for clinical bronchodilating activity. In an effort to obtain new bronchodilators with decreased cardiac-





1a, $R^1 = H_2NCONH$; $R^2 = t$-Bu
b, $R^1 = MeSO_2CH_2$; $R^2 = t$-Bu
c, $R^1 = HOCH_2$; $R^2 = t$-Bu
d, $R^1 = MeSO_2NH$; $R^2 = i$-Pr

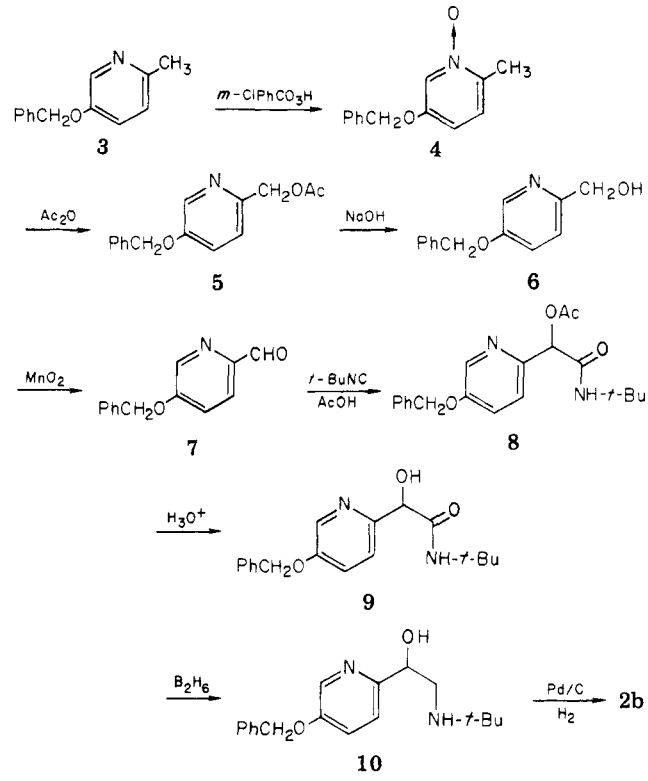
2a, R = $HOCH_2$
b, R = H
c, R = $MeSO_2CH_2$
d, R = Me

stimulating effects it was of interest to extend this finding to heterocyclic ethanolamines. One such agent, a pyridylethanolamine pyrbuterol (**2a**), has bronchodilator activity in humans.[4] Pharmacologically, **2a** is a potent and selective β_2-adrenoreceptor agonist,[5] having activity comparable to that of other widely studied bronchodilators, e.g., salbutamol (**1c**)[6] and soterenol (**1d**).[7-9] Structurally, pyrbuterol (**2a**) is a pyridine analogue of salbutamol (**1c**). A survey of the literature revealed only a limited number of other pyridylethanolamines. Certain chloro-substituted pyridylethanolamines are claimed to be potent β-adrenergic antagonists.[10] A series of 4-pyridylethanolamines possessed similar activity;[11] however, subsequent studies indicated that *N*-isopropyl-4-pyridylethanolamine had both β-adrenergic agonist and antagonist activities and that the corresponding 2- and 3-pyridylethanolamines were weak β-adrenoreceptor agonists.[12] A wide variety of other heterocyclic ethanolamines, e.g., pyrrole,[13] furan,[14,15] thiophene,[16] indole,[17,18] benzofuran,[17,19-21] benzothiophene,[22,23] chromone,[18,20,24a] isoquinoline,[18] quinoline,[24b] and phenanthridine[24b] derivatives, are predominantly β-adrenergic receptor antagonists.

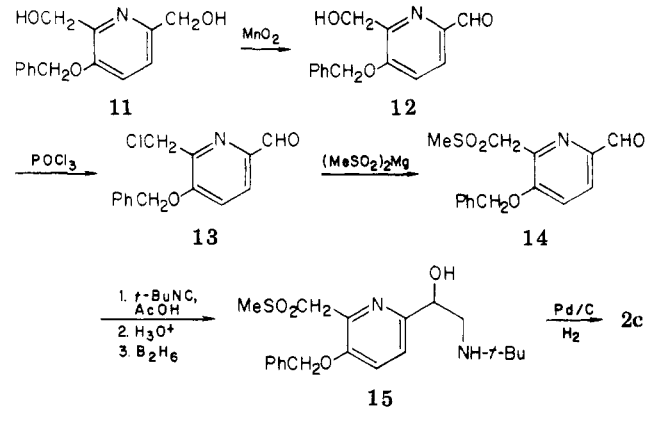
This survey suggests that additional 2- or 3-pyridylethanolamines would be rational targets as potential selective β_2-adrenoreceptor agonists. In the present study the synthesis of three 2-pyridylethanolamines related to pyrbuterol is described. These compounds were compared to their phenylethanolamine counterparts in an in vitro test for relaxation of guinea pig tracheal smooth muscle, a measure of potential bronchodilator activity. Potential cardiac stimulant activity was evaluated in vitro by measuring changes in the rate of contraction of spontaneously beating guinea pig right atria. The compounds studied were the analogue **2b** of pyrbuterol in which the 6 position, i.e., meta to the ethanolamine side chain of a 5-(para)-hydroxylated pyridine, was unsubstituted and ones in which this meta position was substituted with a methylsulfonylmethyl (**2c**, related to sulfonterol) or a methyl (**2d**) group. The latter compound is of particular interest as it provides a test of the concept[2] that a *labile* proton on the meta substituent of a para-hydroxylated arylethanolamine is required for potent adrenergic agonist activity. In **2d** the methyl group, as that in α-picoline, should be somewhat acidic.

Chemistry. Synthesis of the three new 2-pyridylethanolamines **2b–d** involved a similar sequence from requisite precursor pyridine-2-carboxaldehydes prepared by various methods as indicated in Schemes I–III. In each case, as illustrated in Scheme I, appropriate pyridine-2-carboxaldehydes, e.g., **7**, were condensed with *tert*-butyl isocyanide in a Passerini reaction[25] to give an acetoxyamide, e.g., **8**. Selective hydrolysis of these ester amides afforded corresponding hydroxyamides, e.g., **9**, which were sequentially reduced with diborane to the ethanolamines, e.g., **10**, and debenzylated to the 5-hydroxy-2-pyridylethanolamines **2b–d** by catalytic hydrogenolysis. Synthesis of **2b** is outlined in Scheme I. The pyridine *N*-oxide **4**,

Scheme I



Scheme II



obtained by *m*-chloroperbenzoic acid oxidation of **3**, underwent rearrangement[26] in acetic anhydride to give **5** which was hydrolyzed to the alcohol precursor **6** to the aldehyde **7**. Conversion of **7** to **2b** was achieved via the aforementioned general sequence.

The method employed to prepare **2c** is outlined in Scheme II. A modification (refluxing $CHCl_3$, 1.5 h) of the previously described procedure[5] was employed for conversion of **11** to **12**. Sequential chlorination of **12** to **13**, followed by methylsulfonylation gave the aldehyde **14** that was converted via **15** to **2c** by the general method outlined for conversion of pyridine-2-carboxaldehydes to 2-pyridylethanolamines.

As illustrated in Scheme III, the aldehydic precursor (**17**) to **2d** was obtained by a three-step sequence involving hydroxymethylation of 3-hydroxy-2-methylpyridine, followed by benzylation of the 5-hydroxyl group to give **16** and oxidation of the latter alcohol. The aldehyde **17** was converted via **18** to **2d** by the general procedure outlined for conversion of precursor aldehydes to **2b** and **2c**.

Results and Discussion

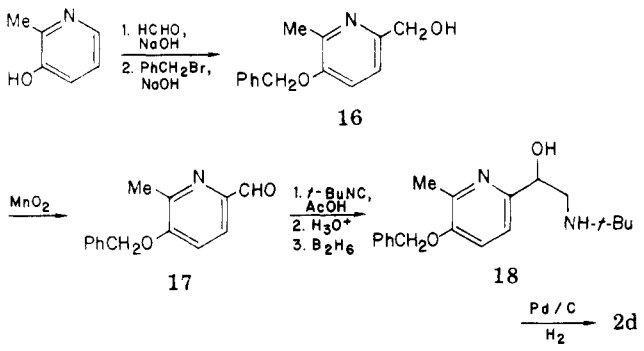
The potential bronchodilator activity of 2-pyridyl-

Table I. Pharmacological Testing Data of 2-Pyridylethanolamines and Related Compounds

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]
2a (pyrbuterol)[e]	2.8×10^{-9} ($0.96-8.4 \times 10^{-9}$)	1.2×10^{-7} ($0.2-7.9 \times 10^{-7}$)	0.8	43
2b	3.1×10^{-7} ($2.4-4.0 \times 10^{-7}$)	$\sim 1.7 \times 10^{-5}$, 7%		>182
2c	2.9×10^{-8} ($2.3-3.8 \times 10^{-8}$)	$\sim 9.9 \times 10^{-5}$, 13%		>3413
2d	2.8×10^{-7}[f] ($1.1-6.9 \times 10^{-7}$)	$\sim 1.0 \times 10^{-5}$	0.4	36
4-HOPhCH(OH)CH_2NH-*i*-Pr	$\sim 1.1 \times 10^{-7}$	$\sim 7.7 \times 10^{-5}$	0.8	~0.7
1b (sulfonterol)	1.7×10^{-8} ($0.8-3.6 \times 10^{-8}$)	2.8×10^{-5} ($0.3-23.4 \times 10^{-5}$)	0.3	1650
1c (salbutamol)	1.1×10^{-8} ($0.4-3.5 \times 10^{-8}$)	3.1×10^{-7} ($0.7-14.0 \times 10^{-7}$)	0.7	28
Isoproterenol	7.1×10^{-9} ($5.2-9.9 \times 10^{-9}$)	3.4×10^{-9} ($2.6-4.6 \times 10^{-9}$)	1	0.48

[a] See ref 2 for experimental procedure. Where ED values 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} values 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] Generously supplied by Pfizer Laboratories, to whom we are indebted. [f] $\alpha = 0.9$.

Scheme III



ethanolamines **2b–d** was evaluated in vitro by measuring their ability to relax a spontaneously contracted guinea pig tracheal chain preparation.[28] Cardiac stimulant potential was determined in vitro by changes induced in the rate of contraction of spontaneously beating guinea pig right atria.[29] Comparison of the ED_{50} in the tracheal chain test with the ED_{25} in the right atrial test provides an index of the potential selectivity of the compound for tracheobronchial vs. cardiac muscle and is referred to as the separation ratio. In Table I are presented the results of such testing of the 2-pyridylethanolamines **2a–d**, several phenyl analogues, i.e., *N*-isopropyl-4-hydroxy-β-phenylethanolamine, sulfonterol (**1b**), and salbutamol (**1c**), and the prototype of β-adrenergic agonists, isoproterenol.

These data permit comparison of the potential bronchodilator activity and the selectivity for tracheobronchial vs. cardiac muscle for a series of 2-pyridylethanolamines and their phenylethanolamine counterparts. Comparison of the pyridine **2b** with its phenyl counterpart, *N*-isopropyl-4-hydroxy-β-phenylethanolamine, is somewhat complicated as the N-substituents (*i*-Pr vs. *t*-Bu) are not identical; however, the potencies of these two compounds in the tracheal test are somewhat comparable; **2b** is about 0.3 times as potent as its phenyl relative; however, a significant difference is noted in their separation ratios; i.e., the pyridine derivative **2b** (separation ratio = >182) is considerably more selective than its phenyl analogue (separation ratio = 0.7). Both compounds are less potent in both the tracheal and atrial tests and have a higher separation ratio than isoproterenol.

Pyrbuterol (**2a**),[5] a 2-pyridylethanolamine bearing a hydroxymethyl group in a position meta to the ethanolamine side chain, is about 2.5 times more potent than isoproterenol and about four times more potent than its phenylethanolamine counterpart salbutamol (**1c**) in the in vitro test for relaxation of guinea pig tracheal tissue. Again, the pyridine derivative (**2a**) is more selective than isoproterenol (separation ratio = 43 vs. 0.48) for guinea pig tracheal vs. right atrial muscle. It is also somewhat more selective than its phenyl relative **1c** (separation ratio = 43 vs. 28). Comparison of the pyridine derivative **2c**, bearing a methylsulfonylmethyl group in the position meta to the ethanolamine side chain, with its phenyl counterpart **1b** once again indicates that the pyridine retains a high order of potency in the tracheal test (**2c** is about 0.6 times as potent as sulfonterol) and again the separation ratio is greater for the pyridine than for its phenyl relative. In fact, the large separation ratio of **2c** (>3413) exceeds that of the other compounds in Table I; a 25% increase in the rate of contraction of isolated spontaneously beating guinea pig right atria was not attained at the highest concentration tested.

Comparison of the α-picoline derivative **2d** with its phenyl counterpart was not made. It is significant, however, that **2d**, which bears a methyl group in the position meta to the ethanolamine side chain, was approximately equipotent in the tracheal test with **2b**, which is unsubstituted in the meta position. These results suggest that the labile protons of the α-picoline are unable to simulate the *m*-hydroxymethyl substituent of **2a** or the methylsulfonylmethyl substituent of **2c**. The reason for this is not certain. Perhaps the protons of the α-picoline **2d** are insufficiently labile to be effective or perhaps the biological influence of the meta substituent is not strictly dependent upon the presence of a labile proton.

In summary, our study indicates that replacement of the phenyl ring of a para-hydroxylated phenylethanolamine with a pyridine ring generally results in retention, or even enhancement, of potency in an in vitro test that measures relaxation of guinea pig tracheal tissue. Such modification, however, results in an increased selectivity for tracheobronchial vs. cardiac tissue. One of the compounds, a 2-pyridylethanolamine relative (**2c**) of the phenylethanolamine sulfonterol (**1b**), was very potent in the tracheal test and showed an extremely high separation ratio. The α-picoline derivative **2d**, which bears an activated methyl group (i.e., acidic protons) in the position

meta to the ethanolamine side chain, was about equipotent with the related meta-unsubstituted compound **2b**. The implication of this observation is not clear.

Experimental Section

Melting points were determined in open capillary tubes using a Thomas-Hoover Uni-Melt apparatus and are uncorrected. Elemental analyses were performed by the Analytical and Physical Chemistry Section of Smith Kline & French Laboratories. Where analyses are reported by symbols of elements, results were within ±0.4% of calculated value. Mass spectra were obtained on a Hitachi Perkin-Elmer RMU-6E spectrometer. NMR spectra were recorded with either a Perkin-Elmer R-24 or R-32 spectrometer (Me_4Si). Although IR and NMR spectral data are reported only where considered significant, these spectra were obtained for all numbered or named compounds and were judged to be consistent with the assigned structures.

5-Benzyloxy-2-methylpyridine *N*-Oxide (4). A solution of **3**[30] (38.1 g, 0.192 mol) in 1 L of $CHCl_3$ was stirred at 25 °C with 85% *m*-chloroperbenzoic acid (42.7 g, 0.211 mol) for 1 h. The solution was washed with 5% Na_2CO_3 and H_2O, dried, and evaporated to give 39.8 g (97%) of colorless crystals: TLC [silica gel, MeOH–Et_2O (1:4)] showed a single spot. A sample recrystallized from Me_2CO–petroleum ether had mp 87–89 °C. Anal. ($C_{13}H_{13}NO_2$) C, H, N.

2-Acetoxymethyl-5-benzyloxypyridine (5). To 80 mL of stirred Ac_2O at 135 °C was slowly added **4** (39.8 g, 0.185 mol). After being stirred at 135 °C for 30 min, the solution was poured into ice–H_2O (500 mL) and stirring was continued for 2 h. The aqueous solution was extracted with a mixture of EtOAc and Et_2O. The extract was washed with H_2O, dried, and concentrated. The dark residue was chromatographed on an alumina column. Elution with Et_2O and evaporation of the solvent gave 25.0 g (52%) of **5** as an oil: TLC [silica gel, Et_2O–petroleum ether (1:1)] showed a single spot.

5-Benzyloxy-2-pyridinemethanol (6). A solution of **5** (25.0 g, 0.098 mol) in 200 mL of EtOH and 50 mL of H_2O was refluxed with NaOH (7.0 g, 0.175 mol) for 4 h. The solution was evaporated and the residue was taken up in a mixture of EtOAc and Et_2O. The solution was washed with H_2O, dried, and concentrated. The solid residue was recrystallized from Me_2CO–hexane to give 14.5 g (69%) of **6**, mp 66–68 °C. Anal. ($C_{13}H_{13}NO_2$) C, H, N.

5-Benzyloxy-2-pyridinecarboxaldehyde (7). A well-stirred mixture of 14.0 g (0.065 mol) of **6** and 140 g of activated MnO_2 in 700 mL of $CHCl_3$ was refluxed for 5 min. The mixture was filtered and the filtrate was evaporated. The residue was recrystallized from EtOH to give 9.1 g (66%) of colorless crystals, mp 68–70 °C. Anal. ($C_{13}H_{11}NO_2$) C, H, N.

2-Acetoxy-2-(5-benzyloxy-2-pyridyl)-*N*-*tert*-butylacetamide (8). A solution of 4.22 g (0.02 mol) of **7**, 1.66 g (0.04 mol) of *tert*-butyl isocyanide, and 2.4 g (0.04 mol) of AcOH in 100 mL of $CHCl_3$ was heated under reflux for 5 h. After being washed with 5% $NaHCO_3$, the solution was dried and concentrated. The yellow residue was crystallized from hexane to give 4.7 g (66%) of colorless crystals, mp 65–71 °C. TLC (silica gel, Et_2O) showed only one spot.

2-(5-Benzyloxy-2-pyridyl)-*N*-*tert*-butyl-2-hydroxyacetamide (9). A solution of 4.0 g (11.2 mmol) of **8** in a mixture of 40 mL of MeOH, 40 mL of H_2O, and 20 mL of 2.5 N HCl was heated under reflux for 1.5 h. The MeOH was distilled and the aqueous solution was made alkaline with 10 N NaOH. The resulting mixture was extracted with EtOAc. The extract was washed with H_2O, dried, and concentrated to afford 3.5 g (99%) of colorless crystals, mp 73–74 °C, after recrystallization from Me_2CO–petroleum ether; TLC (silica gel, Et_2O) showed a single spot.

1-(5-Benzyloxy-2-pyridyl)-2-*tert*-butylaminoethanol Hydrochloride (10·HCl). To 45 mL of a 1 M solution of BH_3 in THF was added a solution of 3.3 g (10.5 mmol) of **9** in 100 mL of THF. After being refluxed for 1 h, the solution was concentrated. To the residue was added *cautiously* ice and 1 N HCl. The acidic solution was washed with Et_2O, it was made alkaline by addition of 10 N NaOH, and then the mixture was extracted with EtOAc. After the extract was dried, it was concentrated to leave a yellow liquid. To a solution of the liquid in a small volume of EtOH was added a solution of HCl in Et_2O. The precipitated **10**·HCl was recrystallized from EtOH to give 1.0 g (26%) of colorless crystals, mp 210–212 °C. TLC of the base derived from **10**·HCl [silica gel, MeOH–Et_2O (1:4)] gave only one spot. Anal. ($C_{18}H_{24}N_2O_2$·2HCl) C, H, N.

5-Benzyloxy-6-chloromethyl-2-pyridinecarboxaldehyde (13). To a stirred solution of 5.86 g (0.24 mol) of **12**, prepared from **11** by modification (1.5 h reflux in $CHCl_3$) of the procedure of Barth,[5] in 100 mL of EtOAc was added 4.06 g (0.027 mol) of $POCl_3$. The mixture was heated under reflux for 20 min. The progress of the reaction was monitored by TLC [silica gel, Et_2O–hexane (1:1)]. Additional $POCl_3$ (0.4 mL) was added and heating was continued for an additional 30 min (a brown tar began to develop at this point). After being cooled, the mixture was diluted with twice its volume of Et_2O and washed with 5% $NaHCO_3$ and a saturated aqueous solution of NaCl. The Et_2O solution was dried, treated with decolorizing C, filtered, and concentrated to leave 4.3 g of a liquid, which was shown by TLC (previously described system) to contain a trace of **12**. Crystallization from 2-PrOH gave 2.75 g (47%) of crystals, mp 72–73 °C. Anal. ($C_{14}H_{12}ClNO_2$) C, H, N.

5-Benzyloxy-6-methylsulfonylmethyl-2-pyridinecarboxaldehyde (14). A mixture of 2.65 g (0.01 mol) of **13** in 120 mL of 2-PrOH and 13.5 g of $(MeSO_2)_2Mg$[3] (45% purity) in 120 mL of H_2O was stirred under reflux for 4 h. After evaporation of the 2-PrOH, the aqueous mixture was extracted with CH_2Cl_2. Concentration of the dried organic extract gave 2.0 g (66%) of colorless crystals, mp 103–104 °C. Anal. ($C_{15}H_{15}NO_4S$) C, H, N.

2-Acetoxy-2-(5-benzyloxy-6-methylsulfonylmethyl-2-pyridyl)-*N*-*tert*-butylacetamide. This compound was prepared from **14** in the same manner described for synthesis of **8** from **7**. In this instance the crude product was chromatographed on silica gel. After elution with Et_2O, the column was eluted with CH_2Cl_2. The CH_2Cl_2 eluent was concentrated to give 2.0 g of the product; TLC (silica gel, Et_2O) showed only one spot.

2-(5-Benzyloxy-6-methylsulfonylmethyl-2-pyridyl)-*N*-*tert*-butyl-2-hydroxyacetamide. This compound was prepared from 2-acetoxy-2-(5-benzyloxy-6-methylsulfonylmethyl-2-pyridyl)-*N*-*tert*-butylacetamide in the same manner as that described for conversion of **8** to **9**. The product was obtained (90% yield) as a gum; TLC (silica gel, Et_2O) showed a single spot identical with starting material in R_f value; the IR, NMR, and mass spectral data were consistent with the assigned structure.

1-(5-Benzyloxy-6-methylsulfonylmethyl-2-pyridyl)-2-*tert*-butylaminoethanol (15). This compound was prepared from 2-(5-benzyloxy-6-methylsulfonylmethyl-2-pyridyl)-*N*-*tert*-butyl-2-hydroxyacetamide in the same manner as that described for reduction of **9** to **10**. The crude base was triturated with Et_2O–hexane to give 48% of colorless crystals: mp (after being dried in vacuo for 18 h at 78 °C) 117–119 °C; TLC [alumina, $CHCl_3$–MeOH (19:1)] gave a single spot; IR, NMR, and mass spectral data were consistent with the assigned structure. Anal. ($C_{20}H_{28}O_4N_2S$·H_2O) C, N; H: calcd, 7.37; found, 6.87.

5-Benzyloxy-6-methyl-2-pyridinemethanol Hydrochloride (16·HCl). A mixture of 27.2 g (0.25 mol) of 3-hydroxy-2-methylpyridine, 10 g (0.25 mol) of NaOH, 100 mL of H_2O, and 22.5 mL (0.25 mol) of 40% formalin was refluxed for 2 h. An equal quantity of the formaldehyde solution was added and the mixture was refluxed for an additional 2 h. After acidification of the mixture with AcOH, the precipitate was filtered and washed with Me_2CO. The entire filtrate was concentrated, the residue was azeotroped with PhMe, and then the residue was dissolved in Me_2CO. The organic solution was dried, treated with decolorizing C, and concentrated to give 26.0 g (74%) of crude 5-hydroxy-6-methyl-2-pyridinemethanol, mp 151–153 °C (lit.[31] mp 153–154 °C). A stirred mixture of 26 g (0.187 mol) of this hydroxymethyl derivative, 7.48 g (0.187 mol) of NaOH in 20 mL of H_2O, and 32.0 g (0.187 mol) of benzyl bromide in 400 mL of Me_2CO and 100 mL of H_2O was heated under reflux for 5 h. The Me_2CO was evaporated and the resulting mixture was extracted with EtOAc. The EtOAc solution was washed with 0.5 N NaOH and extracted with 1.5 N HCl. The acid extract was made alkaline with 2.5 N NaOH and the mixture was extracted with EtOAc. After the extract was dried, it was treated with decolorizing C, filtered, and concentrated to give 32.2 g of a semisolid residue. A solution of the residue in MeOH was treated with ethereal HCl to give

colorless crystals, mp 198–200 °C. Anal. ($C_{14}H_{15}NO_2$·HCl) C, H, N.

5-Benzyloxy-6-methyl-2-pyridinecarboxaldehyde (17). A stirred mixture of 19.4 g (0.085 mol) of **16** (regenerated from **16**·HCl) and 100 g of MnO_2 in 800 mL of $CHCl_3$ was heated under reflux for 3 h. The mixture was filtered and the filtrate was evaporated to give a yellow liquid. The liquid was chromatographed on an alumina column, eluting with $CHCl_3$. Concentration of the $CHCl_3$ eluents gave a liquid, which was purified by crystallization of its HCl salt from EtOH–Et_2O. Reconversion of the salt to its base gave 6.5 g (34%) of crystalline solid, mp 62–63 °C. Anal. ($C_{14}H_{13}NO_2$) C, H, N.

2-Acetoxy-2-(5-benzyloxy-6-methyl-2-pyridyl)-*N*-*tert*-butylacetamide Hydrochloride. This compound was prepared from **17** in the same manner described for preparation of **8** from **7**. The HCl salt was prepared in MeOH–Et_2O, mp 135–137 °C. Anal. ($C_{21}H_{26}N_2O_4$·HCl) C, H, N.

2-(5-Benzyloxy-6-methyl-2-pyridyl)-*N*-*tert*-butyl-2-hydroxyacetamide was prepared from 2-acetoxy-2-(5-benzyloxy-6-methyl-2-pyridyl)-*N*-*tert*-butylacetamide hydrochloride in the same fashion as described for hydrolysis of **8** to **9**; this product (60% yield) had mp 140–141 °C, after trituration with Et_2O. Anal. ($C_{19}H_{24}N_2O_3$) H, N; C: calcd, 69.49; found, 68.94.

1-(5-Benzyloxy-6-methyl-2-pyridyl)-2-*tert*-butylaminoethanol (18). This compound was prepared from 2-(5-benzyloxy-6-methyl-2-pyridyl)-*N*-*tert*-butyl-2-hydroxyacetamide in a manner similar to the B_2H_6 reduction of **9** to **10**. The isolated base was extracted with Et_2O. Concentration of the Et_2O solution afforded a residue which after crystallization from cyclohexane–hexane gave 40% of crystals, mp 96–97 °C. The product was purified by recrystallization of its dihydrochloride from MeOH–Et_2O, mp 182.5–183.5 °C. Anal. ($C_{19}H_{26}N_2O_2$·2HCl·0.5H_2O) C, H, N.

Catalytic Hydrogenolysis of Benzyloxy Derivatives 2b–d. The following general procedure was employed for hydrogenolysis of the benzyloxy derivatives **10**, **15**, and **18**. A solution of 0.01 mol of the appropriate benzyloxy derivative (**10**, **15**, or **18**) in 100 mL of MeOH or EtOH and 0.5 g of 10% Pd/C (wetted with EtOAc) was hydrogenated on a Parr apparatus at ambient temperature and an initial H_2 pressure of 3.5 kg/cm^2. After H_2 uptake had slowed markedly (10–20 min), the mixture was filtered. Concentration of the filtrate from reduction of **10** gave 62% of **2-*tert*-butylamino-1-(5-hydroxy-2-pyridyl)ethanol (2b)** as a crystalline solid, mp 163–165 °C, after recrystallization from EtOH; TLC [silica gel, MeOH–Et_2O (1:2)] showed a single spot. Anal. ($C_{11}H_{18}N_2O_2$) C, H, N.

Concentration of the filtrate following hydrogenolysis of **15** gave a viscous noncrystalline material. A solution in MeOH was treated with 0.5 mol equiv of fumaric acid to give 60% of **2-*tert*-butylamino-1-(5-hydroxy-6-methylsulfonylmethyl-2-pyridyl-ethanol hemifumarate hemihydrate (2c** hemifumarate), mp 210–212 °C. Anal. ($C_{13}H_{22}N_2O_4$·0.5$C_4H_4O_4$·0.5H_2O) C, H, N.

The crystalline residue obtained upon concentration of the filtrate obtained after hydrogenolysis of **18** was dissolved in EtOH and treated with 1 mol equiv of fumaric acid; then Et_2O was added to give 45% of **2-*tert*-butylamino-1-(5-hydroxy-6-methyl-2-pyridyl)ethanol hemifumarate (2d** hemifumarate), mp 218 °C. Anal. ($C_{12}H_{20}N_2O_2$·0.5$C_4H_4O_4$) C, H, N.

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