Adrenergic Agents. 8.[1] Synthesis and β-Adrenergic Agonist Activity of Some 3-*tert*-Butylamino-2-(substituted phenyl)-1-propanols

Timothy Jen, James S. Frazee, Mark S. Schwartz, Karl F. Erhard, Carl Kaiser,*

Department of Chemistry

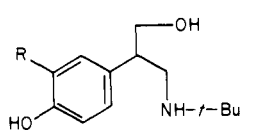
Donald F. Colella, and Joe R. Wardell, Jr.

Department of Biological Sciences, Research and Development Division, Smith Kline & French Laboratories, Philadelphia, Pennsylvania 19101. *Received October 28, 1976*

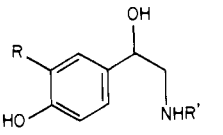
Replacement of the benzylic hydroxyl group of *N-tert*-butylnorepinephrine with a hydroxymethyl substituent affords a propanolamine homologue which retains a high degree of β-adrenergic agonist activity. As modification of the meta substituent of catecholic ethanolamines, such as *N-tert*-butylnorepinephrine, often provides compounds that exert a more pronounced effect in relaxing tracheobronchial smooth muscle (β_2-adrenergic agonist) than in stimulating cardiac muscle (β_1-adrenergic response), a series of 3-*tert*-butylamino-2-(3-substituted 4-hydroxyphenyl)-1-propanols was prepared. The 3-meta substituents included $HOCH_2$ (**1b**), H_2NCONH (**1c**), $MeSO_2NH$ (**1d**), H (**1e**), and NH_2 (**1f**). These phenylpropanolamine derivatives were compared with their phenylethanolamine counterparts in in vitro tests that measure the ability of these compounds to relax spontaneously contracted guinea pig tracheal smooth muscle (a measure of potential bronchodilating activity) and to increase the rate of contraction of a spontaneously beating guinea pig right atrial preparation (an indicator of potential cardiac stimulating activity). In these tests all of the propanolamine derivatives included in the study were less potent than their ethanolamine relatives. In both series replacement of the catecholic *m*-hydroxyl group with the indicated substituents usually resulted in compounds with increased selectivity for tracheobronchial vs. cardiac muscle.

The influence of structure upon the biological activity of adrenergic catecholamines has been extensively investigated.[2-5] The nature of the amino substituent influences selectivity for α- and β-adrenoreceptors,[6] whereas modification of the meta catecholic hydroxyl often has a pronounced effect on selectivity of the compound for β_1- and β_2-adrenoreceptors.[4,5,7] The benzylic hydroxyl group has been implicated in the reaction of molecules of this kind with postulated adrenoreceptors involving adenylate cyclase[5,8-10] as well as in other models[11,12] which rationalize the β-adrenergic actions of phenylethanolamines. Its presence in the proper configuration seems essential for potent β-adrenergic agonist activity.[13-18] Removal of isoproterenol's benzylic hydroxyl markedly reduces β-adrenergic agonist activity,[19,20] whereas replacement with a carbonyl group[21] results in a compound with little, or no, apparent activity of this kind in various tests for adrenergic agonist activity.[4,22-24] Replacement of this hydroxyl group with a methyl ether[25] also results in a significant reduction in β-adrenoreceptor agonist activity.[26] Even addition of a methyl group to the benzylic position of *N-tert*-butylnorepinephrine, i.e., to form a tertiary carbinol,[27] results in a pronounced decrease in β-adrenergic agonist potency.[28]

Conversely, in some instances alteration of the benzylic hydroxyl group results in compounds that retain a high order of β-adrenergic agonist activity. For example, replacement of the benzylic hydroxyl group of epinephrine by an amino group provides a pressor agent[29] having a positive inotropic effect on isolated frog heart.[30] Also, the hydroxymethyl homologue **1a** of *N-tert*-butylnorepinephrine (**2a**) retains a marked β-adrenergic agonist potency.[31] Our laboratory testing results showed that this phenylpropanolamine **1a** was about 0.2 times as potent as isoproterenol (**2f**) in an in vitro test[23,32] for relaxation of guinea pig tracheal smooth muscle. In a similar test that measures changes in the rate of contraction of spontaneously beating guinea pig right atria,[23] **1a** also displayed a high order of potency (Table I). Although **1a** was more selective for β_2-adrenoreceptors than for β_1-adrenoreceptors, it was significantly less selective than salbutamol (**2b**),[33] carbuterol (**2c**),[23] soterenol (**2d**),[11] and sulfonterol (**2g**).[34] In our continuing search[1] for new selective bronchodilators it was of interest to determine if modification of the meta catecholic hydroxyl group would have a pronounced effect on selectivity in the phenylpropanolamine series **1**, as it does in the phenylethanolamine series **2**. For this reason, the *m*-hydroxyl group of the catecholic phenylpropanolamine **1a** was replaced by various functionalities that increase β_2- vs. β_1-adrenoreceptor agonist selectivity in the phenylethanolamine series **2**. The synthesis and results of in vitro testing in the

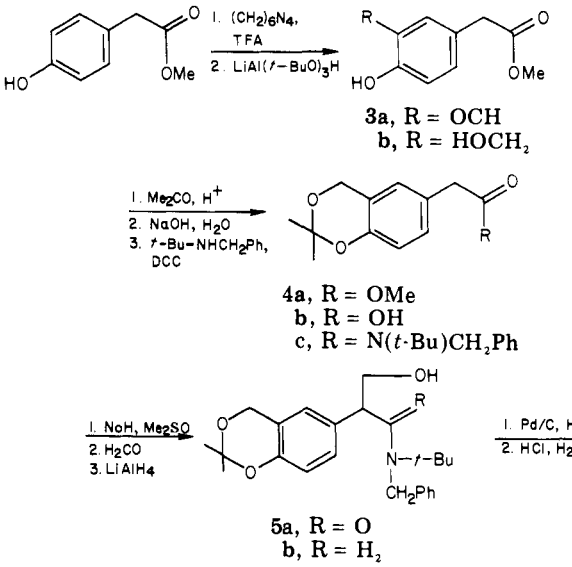


1a, R = HO
b, R = $HOCH_2$
c, R = H_2NCONH
d, R = $MeSO_2NH$
e, R = H
f, R = H_2N



2a, R = HO; R' = *t*-Bu
b, R = $HOCH_2$; R' = *t*-Bu
c, R = H_2NCONH; R' = *t*-Bu
d, R = $MeSO_2NH$; R' = *i*-Pr
e, R = H; R' = *i*-Pr
f, R = HO; R' = *i*-Pr
g, R = $MeSO_2CH_2$; R' = *t*-Bu

Scheme I

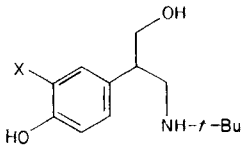


3a, R = OCH
b, R = $HOCH_2$

4a, R = OMe
b, R = OH
c, R = N(*t*-Bu)CH_2Ph

5a, R = O
b, R = H_2

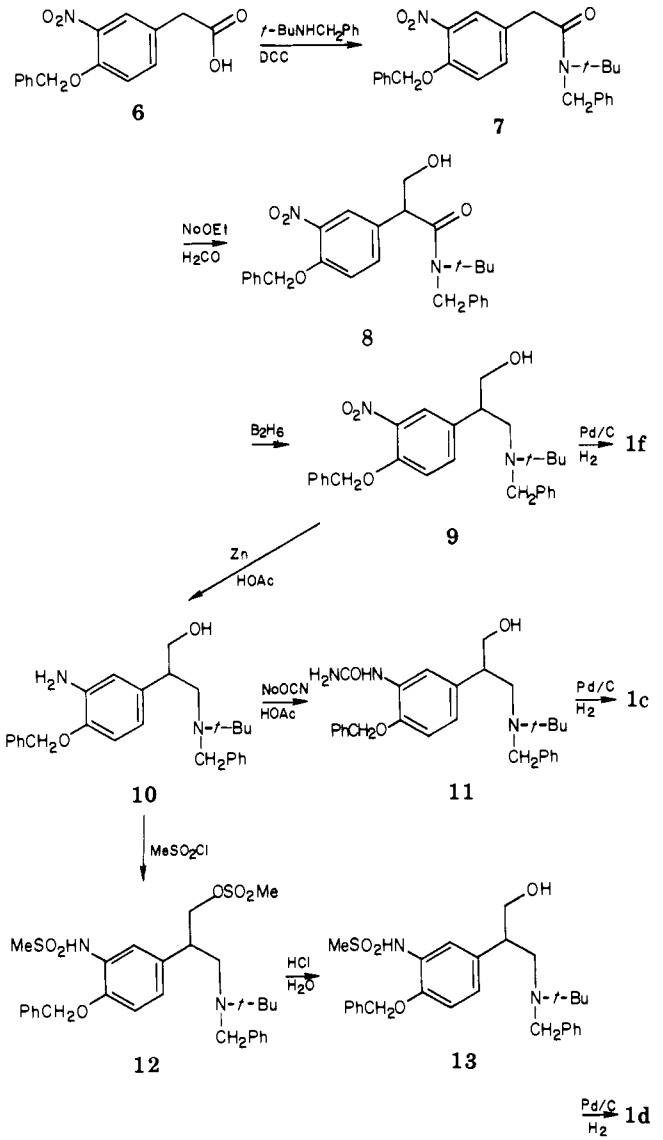
Table I. 3-*tert*-Butylamino-2-(3-substituted 4-hydroxyphenyl)-1-propanols and Related Phenylethanolamines



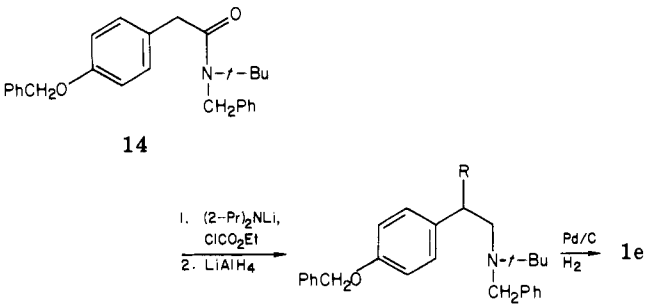
No.	X	Mp, °C	Recrystn solvent	Yield, %	Formula[a]	Guinea pig tracheal test,[b,c] ED_{50} (molar concn) (95% confidence limits)	Guinea pig atrial rate,[b,d] ED_{25} (molar concn) (95% confidence limits)	Intrinsic act.,[e] α, in atrial test	Separation ratio[f]
1a	HO[g]					3.3×10^{-8} ($2.0\text{-}5.4 \times 10^{-8}$)	9.6×10^{-8} ($3.3\text{-}26.0 \times 10^{-8}$)	1	2.9
1b	$HOCH_2$	*h*		83	$C_{14}H_{23}NO_3 \cdot HCl$	4.6×10^{-6}[i] ($1.6\text{-}13.0 \times 10^{-6}$)	$\sim 4.7 \times 10^{-5}$	0.25	10
1c	H_2NCONH	158 dec	EtOH-Et_2O[j]	82	$C_{14}H_{23}N_3O_3 \cdot 0.5C_4H_4O_4$[k,l]	5.2×10^{-7}[i] ($2.0\text{-}14.0 \times 10^{-7}$)	9.3×10^{-6} ($1.6\text{-}53.0 \times 10^{-6}$)	0.3	18
1d	$MeSO_2NH$	130–136	EtOH	82	$C_{14}H_{24}N_2O_4S \cdot HCl$[m]	6.0×10^{-7} ($3.6\text{-}10.1 \times 10^{-7}$)	1.1×10^{-5}, 18%		>18[n]
1e	H	206–211	EtOH-Et_2O	57	$C_{13}H_{21}NO_2 \cdot 0.5C_4H_4O_4$[k]	4.1×10^{-6} ($1.9\text{-}8.5 \times 10^{-6}$)[o]	$\sim 9.8 \times 10^{-5}$	0.3	24
1f	H_2N	99–101	MeOH-EtOAc	29	$C_{13}H_{22}N_2O_2 \cdot 2HCl$[p]	9.6×10^{-7} ($5.3\text{-}17.0 \times 10^{-7}$)	1.3×10^{-6} ($0.8\text{-}2.0 \times 10^{-6}$)	0.7	1.4
2a	(*N*-*tert*-butylnorepinephrine[q])					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
2b	(salbutamol[q])					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
2c	(carbuterol[q])					1.9×10^{-8} ($0.8\text{-}5.0 \times 10^{-8}$)	6.4×10^{-7} ($3.4\text{-}12.3 \times 10^{-7}$)	0.5	34
2d	(soterenol[q])					2.6×10^{-8} ($0.97\text{-}6.9 \times 10^{-8}$)	7.6×10^{-8} ($1.0\text{-}59.0 \times 10^{-8}$)	0.7	3
2e[q]						$\sim 1.1 \times 10^{-7}$[o]	$\sim 7.7 \times 10^{-8}$	0.3	0.7
2f	(isoproterenol[q])					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

[a] Compounds for which formulas are given were analyzed for C, H, and N; analytical values were within ±0.4% of calculated values unless noted otherwise. All other compounds were prepared according to literature directions. [b] Performed as described previously.[23] [c] Intrinsic activity, α, i.e., maximum response of the compound divided by the maximum effect induced by papaverine is 1 for all compounds for which ED_{50} values were obtained unless otherwise indicated. [d] Where ED_{25} is not given results are presented as percent response at the indicated concentration. [e] Determined as indicated in footnote *b* but related to maximum isoproterenol-induced response. [f] Guinea pig atrial test ED_{25} divided by tracheal test ED_{50}. [g] Prepared according to patent directions;[31] HBr salt, mp 112–113 °C (reported 112–113 °C). [h] Amorphous solid of indefinite melting point. Prepared by addition of HCl to an Et_2O solution of base, followed by concentration at 78 °C (0.1 Torr). [i] α = 0.8. [j] Base had mp 128–131 °C (from MeOH-Et_2O). [k] Hemifumarate. [l] Anal. (calcd for 0.75 mol of H_2O) N: calcd, 11.91; found, 11.42. [m] Anal. calcd for 0.5 mol of H_2O; TLC [silica gel, MeOH-EtOAc (1:1)] showed only one spot. [n] A separation ratio could not be calculated as the highest concentration tested produced less than 25% increase in atrial rate. [o] α = 0.9. [p] C: calcd, 50.17; found, 49.69. *m/e* (M^+) 238. [q] See text for structure.

Scheme II



Scheme III



15a, R = CO_2Et
b, R = CH_2OH

guinea pig tracheal and right atrial tests for *m*-hydroxyl replaced analogues of **1a**, i.e., **1b–f**, are described in the present article.

Chemistry. The synthetic route to **1b** is outlined in Scheme I. Treatment of methyl 4-hydroxyphenylacetate[35] with hexamethylenetetramine in trifluoroacetic acid[36] afforded the aldehyde **3a** which was selectively reduced to the saligenin derivative **3b**. Protection of the hydroxyl groups as a cyclic ketal **4a** was accomplished by acid-catalyzed condensation of **3b** with acetone. Basic hydrolysis of the ester **4a** gave the acid **4b** which was converted to the amide **4c** by treatment with *tert*-butylbenzylamine in the presence of *N,N'*-dicyclohexylcarbodiimide (DCC). Hydroxymethylation of **4c** was accomplished by addition of the phenylacetamide anion (obtained by treatment with NaH–Me_2SO) to formaldehyde. The resulting hydroxypropionamide **5a** was reduced ($LiAlH_4$) to **5b** whose *N*-benzyl and ketal protective groups were removed by hydrogenolysis followed by aqueous acid hydrolysis to give the *m*-hydroxymethyl-substituted phenylpropanolamine **1b**.

Syntheses of **1c**, **1d**, and **1f** are outlined in Scheme II. Coupling of the acid **6**, obtained from methyl 4-hydroxy-3-nitrophenylacetate[37] via benzylation and ester hydrolysis, with *tert*-butylbenzylamine in the presence of DCC gave the amide **7**. Base-catalyzed formylation of **7** gave **8** which was reduced to the phenylpropanolamine **9** with diborane. Selective reduction of the nitro group in **9** by the action of zinc in acetic acid gave the aniline **10**. Treatment of **10** with sodium isocyanate in acetic acid produced the urea derivative **11** which upon catalytic hydrogenation gave the *m*-ureidophenylpropanolamine **1c**. Reaction of **10** with methylsulfonyl chloride resulted in **12**. Hydrolysis of **12** afforded **13** which was catalytically hydrogenolyzed to the *m*-methylsulfonamidophenylpropanolamine **1d**. Catalytic hydrogenation of **9** gave the *m*-aminophenylpropanolamine **1f**.

Synthesis of **1e** was performed as outlined in Scheme III. The amide **14**, obtained from 4-benzyloxyphenylacetic acid and *tert*-butylbenzylamine in the presence of DCC, was alkylated with ethyl chloroformate to give the ester **15a** which was reduced to **15b** by lithium aluminum hydride. Catalytic hydrogenolysis of **15b** afforded the *p*-hydroxyphenylpropanolamine **1e**.

Results and Discussion

The potential bronchodilator activity of the 3-*tert*-butylamino-2-phenyl-1-propanols, **1a–f**, was evaluated in vitro by measuring the ability of these substances to relax a spontaneously contracted guinea pig tracheal chain preparation.[23,31] Cardiac stimulant potential was evaluated in vitro by changes induced in the contraction rate of spontaneously beating guinea pig right atria.[23] Selectivity was calculated as a separation ratio, i.e., the ED_{25} in the atrial test divided by the ED_{50} in the tracheal test. Results of these in vitro studies for the present series (**1a–f**) as well as for related phenylethanolamines and several standards are presented in Table I.

Examination of the pharmacological data outlined in Table I indicates that replacement of the benzylic hydroxyl group in phenylethanolamines by a hydroxymethyl group consistently diminishes potency in the guinea pig tracheal chain preparation. Thus, **1a** is only $^1/_{25}$th as potent as its phenylethanolamine counterpart, *N-tert*-butylnorepinephrine (**2a**). Similarly, **1b** is only $^1/_{420}$th as potent as its related phenylethanolamine salbutamol (**2b**), **1c** is about $^1/_{27}$th as potent as its homologue carbuterol **2c**, the propanol **1d** (an *N-tert*-butyl derivative) is about $^1/_{23}$rd as potent as its *N*-isopropyl relative soterenol (**2d**), **1e**, an *N-tert*-butyl derivative, is about $^1/_{37}$th as potent as the corresponding 4-hydroxyphenylethanolamine bearing an *N*-isopropyl substituent (**2e**), and **1f** is about $^1/_{46}$th as potent as its ethanolamine relative which has an $ED_{50} = 2.1 \times 10^{-8}$ M in the guinea pig tracheal test.[23]

The selectivity of the phenylpropanolamines **1**, in all instances, is greater than that of the prototype of β-adrenergic receptor agonists isoproterenol. Comparison of the separation ratios of the various derivatives of **1** with that of their phenylethanolamine relatives **2** bearing an

N-tert-butyl substituent, however, indicates that modification of the meta substituent generally induces less selectivity in the propanolamine series **1** than in the ethanolamine series **2**. For example, the separation ratios are **2a** > **1a**, **2b** > **1b**, **2** (X = NH_2, separation ratio = 5.2[23]) > **1f**, and **2c** > **1c**. Two exceptions were noted in the series. The *m*-methylsulfonamido-substituted propanolamine **1d** is more selective than its ethanolamine counterpart soterenol (**2d**). This may be rationalized somewhat by the fact that **1d** bears an *N-tert*-butyl substituent whereas soterenol (**2d**) has a secondary isopropylamino group. Also, *N-tert*-butyl-substituted *p*-hydroxyphenylpropanolamine **1e** has a considerably higher separation ratio than its *N*-isopropyl-substituted phenylethanolamine counterpart **2e**. It is also noteworthy that intrinsic activity (α) for the propanols **1** in the atrial test (Table I) is equal to or less than that of their corresponding ethanolamine derivatives **2**. This suggests enhanced tissue selectivity of the propanols **1** as compared to their ethanolamine relatives **2**.

Experimental Section

Melting points were determined in open capillary tubes using a Thomas-Hoover Uni-Melt apparatus; they were not corrected. 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 the calculated value. IR spectra were obtained using a Perkin-Elmer 727 IR spectrophotometer. NMR spectra were recorded with a Hitachi Perkin-Elmer R-24 spectrometer (Me_4Si). Mass spectra were obtained on a Hitachi Perkin-Elmer RMU-6E spectrometer. Although IR and NMR spectral data are reported only where considered significant, these spectra were obtained for all compounds described in the Experimental Section; they were judged to be consistent with the assigned structures.

Methyl 3-Formyl-4-hydroxyphenylacetate (3a). A solution of 2.0 g (0.012 mol) of methyl 4-hydroxyphenylacetate[35] in 15 mL of trifluoroacetic acid was refluxed with 1.68 g (0.012 mol) of hexamethylenetetramine for 18 h. The solution was evaporated and the residue was suspended in H_2O. After being made alkaline with Na_2CO_3, the mixture was extracted with EtOAc–Et_2O. The extract was washed with 1 N HCl, dried, and concentrated. The residue was passed through a Florisil column, using Et_2O–$CHCl_3$ (1:4) as the eluent, to give 1.2 g (52%) of a clear oil: TLC [silica gel, Et_2O–$CHCl_3$(1:4)] showed a single spot. NMR, IR, and mass spectral data supported the assigned structure.

Methyl 3-Hydroxymethyl-4-hydroxyphenylacetate (3b). To a solution of 6.1 g (31.4 mmol) of **3a** in 700 mL of THF at 0 °C was added 32 g of LiAl(*t*-BuO)$_3$H over a period of 15 min. After being stirred at 0 °C for 2 h, 100 mL of H_2O was added dropwise, and the mixture was adjusted to pH 5 with 12 N HCl. Additional H_2O (400 mL) was added, and the mixture was extracted with Et_2O. The extract was dried and concentrated. The residue was chromatographed on a silica gel column and eluted with Et_2O–hexane (1:1) until the less polar impurities were removed. Elution with Et_2O, evaporation of the eluate, and recrystallization of the residue from Et_2O–hexane gave 2.8 g (38%) of **3b**, mp 74–75 °C. Anal. ($C_{10}H_{12}O_4$) C, H.

Methyl 2,2-Dimethyl-1,3-benzodioxan-6-ylacetate (4a). To a solution of 2.7 g (13.8 mmol) of **3b** in 40 mL of Me_2CO was added three drops of 70% $HClO_4$ and the mixture was kept at 25 °C for 18 h over molecular sieves. The solution was diluted with Et_2O, washed with 5% Na_2CO_3 and brine, dried, and evaporated to give 3.1 g (95%) of an oil: TLC [silica gel, Et_2O–hexane (1:1)] showed a single spot.

2,2-Dimethyl-1,3-benzodioxan-6-ylacetic Acid (4b). A solution of 3.0 g (13.1 mmol) of **4a**, in 40 mL of MeOH and 8 mL of 2.5 N NaOH, was kept at 25 °C for 2 h. After evaporating the MeOH, the aqueous solution was stirred with C_6H_6 and the mixture was cautiously acidified with 3 N HCl. The C_6H_6 solution was washed with brine (until the washing became neutral), dried, and evaporated. The oily residue crystallized on trituration with hexane to give 1.65 g (57%) of crystals: mp 88–89 °C; TLC [silica gel, $CHCl_3$–Et_2O (1:1)] showed one spot. Anal. ($C_{12}H_{14}O_4$) C, H.

***N*-Benzyl-*N-tert*-butyl-2,2-dimethyl-1,3-benzodioxan-6-ylacetamide (4c).** To a stirred solution of 1.44 g (6.5 mmol) of **4b** in 10 mL of MeCN was added 1.34 g (6.5 mmol) of *N,N'*-dicyclohexylcarbodiimide in 10 mL of MeCN. A precipitate was formed in a few minutes, then a solution of 10.6 g (6.5 mmol) of *tert*-butylbenzylamine in 5 mL of MeCN was added, and the mixture was stirred at 25 °C for 18 h. The precipitate was filtered and washed with Et_2O. The filtrate was evaporated to an oil which crystallized on trituration with Et_2O–hexane. TLC [silica gel, $CHCl_3$–Et_2O (1:1)] indicated the presence of impurities with higher and lower R_f values than the major component. The crude product was dissolved in CH_2Cl_2–hexane and chromatographed on a column of deactivated silica gel packed in hexane. The column was eluted with Et_2O–hexane (1:1). The first few fractions of the eluate removed the impurities of higher R_f values. Subsequent fractions eluted the major component. Evaporation of the solvent and trituration of the residue with Et_2O–hexane gave 1.62 g (68%) of crystals, mp 104–105 °C. Anal. ($C_{23}H_{29}NO_3$) C, H, N.

***N*-Benzyl-*N-tert*-butyl-3-hydroxy-2-(2,2-dimethyl-1,3-benzodioxan-6-yl)propionamide (5a).** To a stirred suspension of 176 mg of a 50% suspension of NaH in oil (3.7 mmol) in 25 mL of anhydrous Me_2SO was added 1.23 g (3.35 mmol) of **4c** and 5 drops of hexane. After being stirred for 10 min at 25 °C, the mixture was heated to 50 °C and then kept at ambient temperature until no further evolution of H_2 was evident. To this solution was added 0.3 g (10 mmol) of paraformaldehyde and the mixture was stirred at 25 °C for 15 min. An aliquot was analyzed by TLC [silica gel, Et_2O–hexane (1:1)] which indicated an approximate 1:1 mixture of product and **4c**. The mixture was heated at 60 °C for 30 min and TLC analysis suggested that the product was reverting to **4c**. It was cooled to 25 °C and additional portions of 0.3 g of paraformaldehyde and 176 mg of NaH were added. After stirring the mixture for 3 h at 25 °C, TLC indicated that the major component was **5a**. The mixture was poured into ice–H_2O. The precipitate was filtered, washed with H_2O, and dissolved in Et_2O. The Et_2O solution was washed with brine, dried, and evaporated. The gummy residue was chromatographed on a silica gel column packed with hexane. Elution with Et_2O–hexane (1:3) removed the starting material **4c** and a trace of impurities. The product **5a** was eluted with Et_2O–hexane (1:1). Evaporation of the eluate gave 0.65 g (49%) of colorless crystals, mp 137–138 °C. Anal. ($C_{24}H_{31}NO_4$) C, H, N.

3-(Benzyl-*tert*-butylamino)-2-(2,2-dimethyl-1,3-benzodioxan-6-yl)-1-propanol (5b). A stirred solution of 0.65 g (1.63 mmol) of **5a** in 120 mL of Et_2O was refluxed with 0.65 g of $LiAlH_4$ for 2 h. Excess $LiAlH_4$ was decomposed by cautious addition of saturated aqueous Na_2SO_4 solution. The mixture was stirred with $MgSO_4$ and filtered. After washing the filter cake with Et_2O, the filtrate was evaporated to give 0.55 g (90%) of a viscous oil which did not crystallize in various solvent systems. TLC analysis [alumina, Et_2O–hexane (1:1)] showed a single spot. The IR and mass (M^+ and fragments) spectral data supported the assigned structure.

4-Benzyloxy-3-nitrophenylacetic Acid (6). A stirred mixture of 48.7 g (0.231 mol) of methyl 4-hydroxy-3-nitrophenylacetate,[37] 30.8 g (0.243 mol) of $PhCH_2Cl$, 34.5 g (0.252 mol) of K_2CO_3, and 2 g of NaI in 50% aqueous Me_2CO (1 L) was refluxed for 18 h. It was poured into ice–H_2O. The mixture was washed with Et_2O, acidified, and extracted with Et_2O. The extract was dried and evaporated to give 67.7 g of a yellow crystalline solid. Recrystallization from EtOAc–hexane gave 50.4 g (73.3%) of crystals, mp 142–144 °C.

***N*-Benzyl-*N-tert*-butyl-4-benzyloxy-3-nitrophenylacetamide (7).** To a stirred solution of 8.3 g (0.02 mol) of **6** in 180 mL of MeCN was added 5.9 g (0.029 mol) of *N,N'*-dicyclohexylcarbodiimide in 35 mL of MeCN. The mixture was stirred for 5 min and then a solution of 5.2 g (0.032 mol) of *tert*-butylbenzylamine was added. After the mixture was stirred at 25 °C for 4 h, it was filtered and the filtrate was evaporated. The residue was dissolved in Et_2O, and the solution was washed with 2 N HCl, 5% $NaHCO_3$, and H_2O. The ethereal solution was dried and evaporated to give a yellow crystalline solid. Recrystallization from EtOH gave 7.7 g (61%) of crystals, mp 106–107 °C. Anal. ($C_{26}H_{28}N_2O_4$) C, H, N.

***N*-Benzyl-*N-tert*-butyl-2-(4-benzyloxy-3-nitrophenyl)-3-hydroxypropionamide (8).** A mixture of 13.5 g (0.0312 mol)

of 7, 1.2 g (0.039 mol) of paraformaldehyde, 3 mL of 0.5 N NaOEt in EtOH, and 30 mL of Me_2SO was heated at 80–90 °C for 18 h. Two additional portions of paraformaldehyde (1.2 and 2.4 g) were added after 3 and 6 h, respectively. The mixture was poured into ice–H_2O. The precipitate was extracted into $CHCl_3$. The $CHCl_3$ solution was dried and evaporated to give a yellow oil. Trituration of the oil with Et_2O gave 10.1 g (70%) of a white crystalline solid which showed only a trace of impurities by TLC analysis (alumina, $CHCl_3$). Recrystallization from EtOAc–hexane gave crystals, mp 111–112 °C. Anal. ($C_{27}H_{30}N_2O_5$) H, N; C: calcd, 70.11; found, 69.62.

3-(Benzyl-*tert*-butylamino)-2-(4-benzyloxy-3-nitrophenyl)-1-propanol (9). A stirred solution of 9.0 g (0.019 mol) of 8 in 300 mL of THF and 200 mL of 1.6 M BH_3 in THF was refluxed for 24 h. After the chilled mixture was treated with MeOH and ethereal HCl, it was concentrated. The residue was shaken with a mixture of aqueous Na_2CO_3 and $CHCl_3$. The $CHCl_3$ extract was dried and evaporated. The residue was chromatographed on an alumina column (eluted with $CHCl_3$) to give 6.9 g (79%) of an oil which was homogeneous by TLC [silica gel, MeOH–$CHCl_3$ (1:4)]. Treatment of the oil in MeOH–EtOAc with ethereal HCl gave **9**·HCl, mp 223–224 °C. Anal. ($C_{27}H_{32}N_2O_4$·HCl·0.25H_2O) C, H, N.

2-(3-Amino-4-benzyloxyphenyl)-3-(benzyl-*tert*-butylamino)-1-propanol (10). A solution of 2.8 g (6.25 mmol) of **9** in a mixture of 50 mL of AcOH and 20 mL of H_2O was stirred vigorously with 25 g of activated Zn dust at 25 °C for 40 min. The mixture was filtered and the filtrate was diluted with H_2O, basified, and extracted with a mixture of EtOAc and Et_2O. The extract was washed with H_2O, dried, and evaporated. The residue was passed through a neutral alumina column, using Et_2O–EtOAc (1:1) as the eluent, to give 1.5 g (58%) of a dark oil: TLC (silica gel, Et_2O) showed a single spot; NMR, IR, and mass spectral data supported the assigned structure.

3-Benzyl-*tert*-butylamino-2-(4-benzyloxy-3-ureidophenyl)-1-propanol (11). To a solution of 1.5 g (3.6 mmol) of **10** in a mixture of 20 mL of AcOH and 5 mL of H_2O at 45 °C was added a solution of 0.6 g of NaOCN in 10 mL of H_2O. After being stirred for 45 min at 50 °C, additional NaOCN (0.1 g) was added, and stirring was continued for 30 min. The solution was poured into 100 mL of H_2O, basified, and extracted with EtOAc. The extract was washed with H_2O, dried, and evaporated to give 1.0 g (63%) of crystals: mp 188–190 °C dec; TLC [alumina, MeOH–Et_2O (1:49)] showed a major component and a trace of two other components of lower R_f; NMR, IR, and mass spectral data supported the assigned structure.

3-Benzyl-*tert*-butylamino-2-(4-benzyloxy-3-methylsulfonamidophenyl)-1-propanol (13). A solution of 0.7 g (1.68 mmol) of **10** in 6 mL of pyridine was stirred with 0.29 mL (3.7 mmol) of methanesulfonyl chloride for 18 h at 25 °C. The mixture was poured into 100 mL of 1 N HCl and extracted with $CHCl_3$. The extract was dried and evaporated to give **12** as a gum (0.93 g). The gum in a mixture of 40 mL of EtOH and 12 mL of H_2O was refluxed with 2 mL of 12 N HCl for 18 h. The EtOH was evaporated, the aqueous solution was basified with 5% $NaHCO_3$, and the mixture was extracted with $CHCl_3$. The extract was dried and evaporated to give an oil which was chromatographed on neutral almina [eluent, Et_2O–hexane (3:1)] to give 0.44 g (53%) of **13**: TLC (alumina, Et_2O) showed a single spot; NMR, IR, and mass spectral data supported the assigned structure.

***N*-Benzyl-*N*-*tert*-butyl-2-(4-benzyloxyphenyl)acetamide (14).** A stirred solution of 1.21 g (5 mmol) of 4-benzyloxyphenylacetic acid[38] in 10 mL of MeCN at 25 °C was treated first with a solution of 1.03 g (5 mmol) of *N*,*N*′-dicyclohexylcarbodiimide in 3 mL of MeCN and then with a solution of 0.815 g (5 mmol) of *tert*-butylbenzylamine in 3 mL of MeCN. The mixture was stirred for 18 h and filtered. The filtrate was evaporated and the residue was taken up in Et_2O. The ethereal solution was washed with 1 N HCl and 5% $NaHCO_3$, dried, and evaporated. Crystallization of the residue from EtOH gave 1.60 g (83%) of crystals: mp 99–100 °C; TLC [silica gel, Et_2O–petroleum ether (1:1)] showed a single spot. Anal. ($C_{26}H_{29}NO_2$) C, H, N.

***N*-Benzyl-*N*-*tert*-butyl-2-carboethoxy-2-(4-benzyloxyphenyl)acetamide (15a).** To a stirred solution of lithium diisopropylamide [generated in situ from 2 mmol of *n*-BuLi and 2 mmol of $(2\text{-Pr})_2NH$ in 30 mL of THF at −15 °C] was added a solution of 387 mg (1 mmol) of **14** in 5 mL of THF. The mixture was allowed to warm to 25 °C and then excess $ClCO_2Et$ was added. After the mixture was stirred for 1 h, 5 mL of a saturated solution of NH_4Cl was added. The THF and excess $ClCO_2Et$ were evaporated and the aqueous mixture was extracted with Et_2O. The extract was washed with 1 N HCl and H_2O, dried, and evaporated. The oily residue was chromatographed on silica gel (eluted with $CHCl_3$) to give 360 mg (78%) of an oil: TLC [silica gel, $CHCl_3$ or Et_2O–petroleum ether (1:1)] showed a major component with a trace of a minor component of slightly higher R_f.

3-Benzyl-*tert*-butylamino-2-(4-benzyloxyphenyl)-1-propanol (15b). To a stirred suspension of 4.0 g of $LiAlH_4$ in 110 mL of Et_2O was slowly added a solution of 4.0 g (8.7 mmol) of **15a** in 150 mL of Et_2O. After stirring the mixture for 2 h, 8 mL of H_2O and 6.4 mL of 2.5 N NaOH were added dropwise with *caution*. The mixture was filtered and the filtrate was evaporated. The residue was dissolved in Et_2O and dried. Treatment of the Et_2O solution with ethereal HCl precipitated the HCl salt. Recrystallization from EtOH–Et_2O gave 2.2 g (57%) of colorless crystals, mp 133–136 °C. Anal. ($C_{27}H_{33}NO_2$·HCl) C, H, N. The free base **15b** was regenerated by basifying an aqueous solution of the HCl salt and extracting the mixture with EtOAc. The extract was dried and evaporated to give **15b**.

Hydrogenation of 3-(Benzyl-*tert*-butylamino)-2-(substituted phenyl)-1-propanols. A mixture of 2.0 mmol of the appropriate 3-(benzyl-*tert*-butylamino)-2-(substituted phenyl)-1-propanol (**5b**, **9**·HCl, **11**, **13**, or **15b**), 0.5 g of 10% Pd/C, and 100 mL of EtOH was hydrogenated on a Parr apparatus at ambient temperature until H_2 uptake was completed (15 min to 1 h). The mixture was filtered and the filtrate was concentrated in vacuo. The compound **5b** gave 3-*tert*-butylamino-2-(2,2-dimethyl-1,3-benzodioxan-6-yl)-1-propanol as a gum; TLC (alumina, Et_2O) showed one major component plus several trace impurities. NMR, IR, and mass spectral data were consistent with the structure. Hydrolysis of the 1,3-benzodioxanyl derivative to **1b** (Table I) was achieved by allowing a solution of the gum in H_2O–EtOH–HCl to stand at 25 °C for 5 min. The product was isolated by concentration of the solution. Other 3-*tert*-butylamino-2-(substituted phenyl)-1-propanol salts **1c–f** were obtained by concentration of the filtrate and treating a solution of the residue in the recrystallization solvent with the appropriate acid (Table I).

References and Notes

(1) For paper 7, see T. Jen, J. S. Frazee, M. S. Schwartz, C. Kaiser, D. F. Colella, and J. R. Wardell, Jr., *J. Med. Chem.*, preceding paper in this issue.
(2) R. B. Barlow "Introduction to Chemical Pharmacology", Methuen, London, 1964, p 282.
(3) P. Pratesi and E. Grana, *Adv. Drug Res.*, **2**, 127 (1965).
(4) A. M. Lands and T. G. Brown, Jr., "Drugs Affecting the Peripheral Nervous System", Vol. 1, A. Burger, Ed., Marcel Dekker, New York, N.Y., 1967, p 399.
(5) R. T. Brittain, D. Jack, and A. C. Ritchie, *Adv. Drug Res.*, **5**, 197 (1970).
(6) R. P. Ahlquist, *Am. J. Physiol.*, **153**, 586 (1948).
(7) A. M. Lands and T. G. Brown, *Proc. Soc. Exp. Biol. Med.*, **116**, 331 (1964).
(8) B. Belleau, "Ciba Foundation Symposium on Adrenergic Mechanisms", J. R. Vane, G. E. W. Wolstenholme, and M. O'Connor, Ed., Churchill, London, 1960, p 223.
(9) B. M. Bloom and I. M. Goldman, *Adv. Drug Res.*, **3**, 121 (1966).
(10) B. Belleau, *Ann. N.Y. Acad. Sci.*, **139**, 580 (1967).
(11) A. A. Larsen, W. A. Gould, H. R. Roth, W. T. Comer, R. H. Uloth, K. W. Dungan, and P. M. Lish, *J. Med. Chem.*, **10**, 462 (1967).
(12) A. A. Larsen, *Nature (London)*, **224**, 25 (1969).
(13) E. E. Swanson, C. C. Scott, H. M. Lee, and K. K. Chen, *J. Pharmacol. Exp. Ther.*, **79**, 329 (1943).
(14) F. P. Luduena, E. Ananenko, O. H. Siegmund, and L. C. Miller, *J. Pharmacol. Exp. Ther.*, **95**, 155 (1949).
(15) A. M. Lands, *Pharmacol. Rev.*, 1, 279 (1949).
(16) A. M. Lands and F. P. Luduena, *J. Pharmacol. Exp. Ther.*, **117**, 331 (1956).

(17) F. P. Luduena, L. Von Euler, B. F. Tullar, and A. M. Lands, *Arch. Int. Pharmacodyn. Ther.*, 111, 392 (1957).
(18) F. P. Luduena, *Arch. Int. Pharmacodyn. Ther.*, **137**, 155 (1962).
(19) A. M. Lands, V. L. Nash, H. M. McCarthy, H. R. Granger, and B. L. Dertinger, *J. Pharmacol. Exp. Ther.*, **90**, 110 (1947).
(20) A. M. Lands, V. L. Nash, B. L. Dertinger, H. R. Granger, and H. M. McCarthy, *J. Pharmacol. Exp. Ther.*, **92**, 369 (1948).
(21) H. D. Moed, J. Van Dijk, and H. Niewand, *Recl. Trav. Chim. Pays-Bas*, **74**, 919 (1955).
(22) H. Langecker and H. Friebel, *Arch. Exp. Pathol. Pharmakol.*, **226**, 493 (1955).
(23) C. Kaiser, D. F. Colella, M. S. Schwartz, E. Garvey, and J. R. Wardell, Jr., *J. Med. Chem.*, **17**, 49 (1974).
(24) In the in vitro test for relaxation of a guinea pig tracheal chain preparation[23] *N-tert*-butyladrenalone[21] produced only a 11% response at a concentration of 6.3×10^{-5} M.
(25) R. A. Heacock, O. Hutzinger, and B. D. Scott, *Can. J. Chem.*, **43**, 2437 (1965).
(26) 4-[2-(Isopropylamino)-1-methoxyethyl]pyrocatechol hydrochloride[25] had an $ED_{50} = \sim 1.6 \times 10^{-6}$ M in the in vitro guinea pig tracheal chain test[23] and an $ED_{25} = \sim 3.0 \times 10^{-7}$ M in the in vitro guinea pig right atrial test.[23]
(27) G. P. Bettinetti, U. Conte, A. LaManna, and P. Pratesi, *Farmaco, Ed. Sci.*, **23**, 1011 (1968); *Chem. Abstr.*, **70**, 28525u (1969).
(28) This compound, 3,4-dihydroxy-α-(isopropylaminomethyl)-α-methylbenzyl alcohol,[27] had an $ED_{50} = \sim 3.4 \times 10^{-6}$ M in the in vitro guinea pig tracheal chain test[23] and in the in vitro guinea pig right atrial test[23] it produced an 18% response at a concentration of 6.3×10^{-5} M.
(29) G. Lehmann and L. O. Randall, *J. Pharmacol. Exp. Ther.*, **93**, 114 (1948).
(30) S. Ellis, *J. Pharmacol. Exp. Ther.*, **96**, 365 (1949).
(31) A. Ebnother and K. Hasspacher, U.S. Patent 3 804 899 (1974).
(32) R. W. Foster, *J. Pharm. Pharmacol.*, **18**, 1 (1966).
(33) D. T. Collin, D. Hartley, D. Jack, L. H. C. Lunts, J. C. Press, A. C. Ritchie, and P. Toon, *J. Med. Chem.*, **13**, 674 (1970).
(34) C. Kaiser, M. S. Schwartz, D. F. Colella, and J. R. Wardell, Jr., *J. Med. Chem.*, **18**, 674 (1975).
(35) S. Goodwin and B. Witkop, *J. Am. Chem. Soc.*, **79**, 179 (1957).
(36) W. E. Smith, *J. Org. Chem.*, **37**, 3972 (1972).
(37) T. Kametani, K. Fukumoto, and M. Ro, *Yakugaku Zasshi*, **84**, 532 (1964); *Chem. Abstr.*, **61**, 13359a (1964).
(38) J. W. Corse, R. G. Jones, Q. F. Soper, C. W. Whitehead, and O. K. Behrens, *J. Am. Chem. Soc.*, **70**, 2837 (1948).

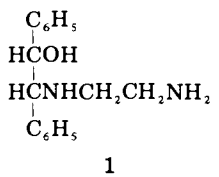
2-(2-Aminoethylamino)-1,2-diphenylethanol Derivatives, a New Class of Topical Antiinflammatory Agents

R. Ian Fryer,* Alfred Boris, James V. Earley, and Earl Reeder

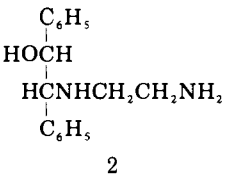
Chemical Research Division, Hoffmann-La Roche Inc., Nutley, New Jersey 07110. *Received February 23, 1977*

A number of analogues and derivatives of the title compound were synthesized and evaluated in a new test procedure used to detect topical antiinflammatory activity. Some general comments regarding observation on the structure–activity relationship of these compounds are made.

In connection with some unrelated work, one of us reported the synthesis of two novel isomeric diphenylethanol derivatives (compounds **1** and **2**) which were prepared by treatment of *trans*- and *cis*-stilbene oxide, respectively, with ethylenediamine.[1] Since it was known that the reaction of stilbene oxides with amines generally proceeds by a trans addition,[2] the erythro configuration was assigned to compound **1** and the threo configuration for compound **2**.



1

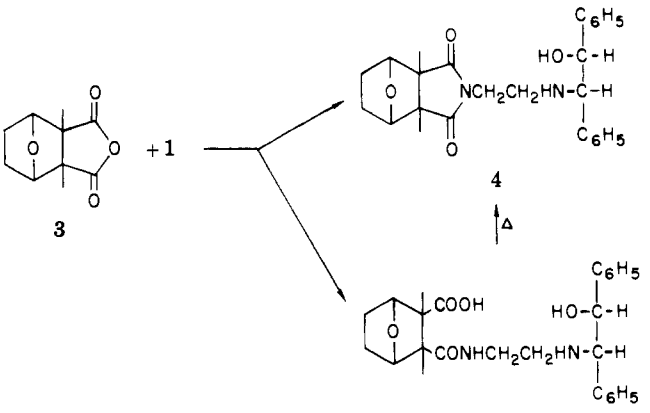


2

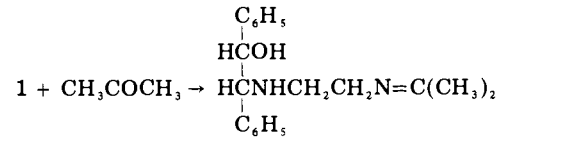
Both of these compounds were found to be active in a new topical antiinflammatory test developed in these laboratories.[3] While the topical activity parallels the activity of corticosteroids in this screen, these compounds do not show any systemic antiinflammatory activity and do not elicit any response against prostaglandin synthetase.

Discussion and Results

It was realized that the new topical antiinflammatory test procedures involved the admixture of the test compound with cantharidin **3** and acetone. Since both cantharidin and acetone are capable of reacting with compound **1**, perhaps casting doubt on the interpretation of the test results, the three possible reaction products from **1**, **3**, and acetone were prepared as shown below and tested for topical antiinflammatory activity.



3 **4** **5**



6

Testing results indicated that the imide **4** had no activity while the amide **5** was active. The imine **6** had an activity comparable to compound **1** (Table I). The possibility that the activity observed for the diphenylethanols was, in fact,